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Design and synthesis of alepterolic acid and 5-fluorouracil conjugates as potential anticancer agents

Xin Jin, Tingting Yang, Chenlu Xia, Nina Wang, Zi Liu, Jianguo Cao, Liang Ma and Guozheng Huang

Contents

Experimental

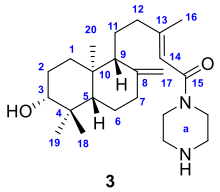
3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay

Primary human liver HL-7702 cells were purchased from SIBS (Shanghai Institutes for Biological Sciences, Shanghai, China) and MCF-7, A549, HeLa and PC-3 cells were from ATCC (American Type Culture Collection, Rockville, MD, USA). HL-7702, HeLa, and MCF-7 cells were incubated with Dulbecco's Modified Eagle's Medium (DMEM) and A549 cells were cultured in Roswell Park Memorial Institute (RPMI) 1640 medium and PC-3 cells were cultured in Han's F-12 medium supplemented with 10% heat-inactivated fetal bovine serum (FBS) and 1% antibiotics (Penicillin and streptomycin). All cells were cultured at 37 °C in 5% CO_2 atmosphere.

Cells were seeded in 96-well plates and incubated for overnight at 37 °C in 5% CO_2 atmosphere. Then various amounts of compounds were added to the wells and then incubated further for 72 h. After treatment, 20 μL of 5 mg/L^{-1} MTT was added to each well, and then incubated at 37 °C in 5% CO_2 atmosphere for another 2~5 h. Finally, 100 μL of dissolved solution (10% SDS+5% isobutanol +0.01mol/L HCl) was added to each well. After incubated for overnight at 37 °C, the plate was then measured at 570 nm with an enzyme-linked immunosorbent assay reader. All these tests were repeated in triplicate.

For treatment with inhibitors, MCF-7 cells were pretreated with inhibitor, Necrostatin-1 (10 μM) or Z-VAD-FMK (20 μM) for 1 h, and incubated with tested compounds for 48 h. The cell survival rate was measured by above MTT assay.

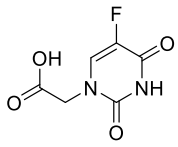
Synthesis of (*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-naphthalen-1-yl)-3-methyl-1-(piperazin-1-yl)pent-2-en-1-one (3)



3

To alepterolic acid **1** (320 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added *N*,*N*-diisopropylethylamine (194 mg, 1.5 mmol), HATU (456 mg, 1.2 mmol) and piperazine (172 mg, 2.0 mmol). The reaction was stirred at room temperature for 12 h. Then the mixture was quenched with water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (3 × 20 mL), brine (20 mL), and dried over Na_2SO_4. After the solvent was removed in vacuum, the crude product was purified by column chromatography (CH_2Cl_2 : MeOH=20: 1 to 10:1) to afford 314 mg of desired product as a white solid (yield of 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (d, *J* = 12.6 Hz, 1H, 14-H), 4.87 (s, 1H, 17-H), 4.51 (s, 1H, 17-H), 4.01 – 3.51 (m, 6H, 3×a-C$\underline{H}_2$), 3.25 (dd, *J* = 11.9, 4.2 Hz, 1H, 3-H), 3.17 (m, 2H, a-C$\underline{H}_2$), 2.42 (d, *J* = 17.0 Hz, 1H, 7-H), 2.27 (t, *J* = 15.3 Hz, 12-H), 2.02 – 1.92 (m, 2H, 7, 12-H), 1.90 (s, 3H, 16-C$\underline{H}_3$), 1.82 – 1.47 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.40 (qd, *J* = 12.9, 4.3 Hz, 1H, 6-H), 1.16 (t, *J* = 13.2 Hz, 1H, 1-H), 1.10 – 1.03 (m, 1H, 5-H), 1.00 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.69 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.32 (C-15), 153.83 (C-13), 147.82 (C-8), 116.34 (C-14), 106.96 (C-17), 78.89 (C-3), 56.04 (C-9), 54.77 (C-5), 39.57 (C-10), 39.27 (C-4), 38.82 (C-7), 38.30 (C-12), 37.22 (C-1), 28.45 (C-18), 28.00 (C-2), 24.12 (C-6), 21.72 (C-11), 18.95 (C-16), 15.56 (C-19), 14.66 (C-20).

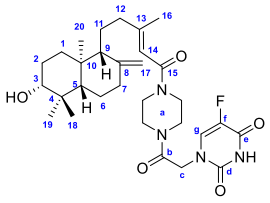
Synthesis of 2-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetic acid (4)



4

Potassium hydroxide (842 mg, 15 mmol) was added to 5-fluoropyrimidine-2,4(1*H*,3*H*)-dione (1.30 g, 10 mmol) in water (5 mL). The mixture was stirred at 60 °C for 30 min. Then, 2-bromoacetic acid (1.38 g, 10 mmol) in water (3 mL) was added dropwise. After two hours, the reaction was cooled to room temperature, and concentrated hydrochloric acid was added dropwise and regulated the pH to 5. The mixture is filtered and the residue was washed with cold water and ethanol, and then purified by crystallization to give 1.41 g (75%) of the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.26 (s, 1H), 11.95 (d, J = 5.1 Hz, 1H), 8.12 (d, J = 6.7 Hz, 1H), 4.40 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.79, 157.96 (d, J = 25.9 Hz), 150.16, 139.82 (d, J = 228.8 Hz), 131.04 (d, J = 33.9 Hz), 49.15.

Synthesis of 5-fluoro-1-(2-(4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)pyrimidine-2,4(1*H*,3*H*)-dione (5)



5

To a solution of 2-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetic acid (112.8 mg, 0.60 mmol) in dichloromethane (5 mL) was added *N*,*N*-diisopropylethylamine (96.9 mg, 0.75 mmol), HATU (228.1 mg, 0.60 mmol), and intermediate **4** (194.0 mg, 0.50 mmol). The mixture was stirred at room temperature for 6 hours. When TLC indicated complete conversion, the reaction was quenched with water, extracted with dichloromethane, and purified column chromatography (CH_2Cl_2: MeOH=30: 1 to 20: 1) to obtain 226.0 mg desired product as white solid (yield of 81%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.26 (d, J = 89.7 Hz, 1H, *NH*), 7.31 (d, J = 37.4 Hz, 1H, g-H), 5.74 (s, 1H, 14-H), 4.87 (s, 1H, 17-H), 4.56 (s, 2H, c-CH_2), 4.52 (s, 1H, 17-H), 3.80 – 3.45 (m, 8H, 4×a-CH_2), 3.25 (d, J = 10.8 Hz, 1H, 3-H), 2.41 (d, J = 12.8 Hz, 1H, 7-H), 2.26 (ddd, J = 13.2, 9.7, 3.0 Hz, 1H, 12-H), 1.94 (m, 2H, 7-H, 12-H), 1.90 (s, 3H, 16-CH_3), 1.82 – 1.49 (m, 7H, 1-H, 2-CH_2, 6-H, 9-H, 11-CH_2), 1.38 (td, J = 12.8, 3.7 Hz, 1H, 6-H), 1.19 – 1.13 (m, 1H, 1-H), 1.07 (d, J = 12.1 Hz, 1H, 5-H), 0.99 (s, 3H, 18-CH_3), 0.77 (s, 3H, 19-CH_3), 0.69 (s, 3H, 20-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.66 (C-15), 164.74 (b-C), 157.27 (d, J = 25.7 Hz, e-C), 152.26 (d-C), 149.79 (C-13), 147.86 (C-8), 140.46 (d, J = 237.3 Hz, f-C), 129.67 (d, J = 32.8 Hz, g-C), 116.46 (C-14), 106.96 (C-17), 78.89 (C-3), 56.06 (C-9), 54.83 (C-5), 48.39 (c-C), 39.56 (C-10), 39.27 (C-4), 38.78 (C-1), 38.32 (C-12), 37.27 (C-1), 28.46 (C-18), 27.99 (C-2), 24.13 (C-6), 21.73 (C-11), 18.99 (C-16), 15.56 (C-19), 14.66 (C-20).

General procedure for the synthesis of compounds 6a-q

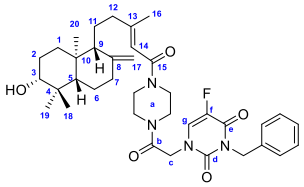
To intermediate **5** (11.2 mg, 0.02 mmol) in DMF (2 mL) was added potassium carbonate (5.5 mg, 0.04 mmol) and the corresponding benzylic bromide (0.03 mmol). The reaction was stirred at room temperature for 12 h. The mixture was then quenched with water and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with water (3 × 5 mL), brine (10 mL), and dried over Na_2SO_4. After the solvent was

removed in vacuum, the crude product was purified by column chromatography (CH_2Cl_2 : MeOH= 40: 1 to 30 :1) to afford desired products.

Analysis of NMR data of compounds 6a-q

We characterized the structure of obtained compounds by NMR and HRMS. The NMR peak assignments were conducted by the contrast between the signals of synthesized derivatives and alepterolic acid. The signals of four methylene groups on piperazine were located between ~δ 3.82 and ~δ 3.41 ppm as mutiplet, which corroborated the existence of the linker. As for the introduction of 5-FU and benzyl groups, signal of protons of methylene group linked to 5-fluorouracil fluctuated between ~δ 4.57 and ~δ 4.51 ppm and the signal of methylene group in benzyl groups of the products appeared between ~δ 5.64 and ~δ 5.06 ppm as singlets. This proved that the reaction proceeded smoothly according to the preset route. The signal of 3-OH in the synthesized compounds appeared at ~δ 3.25 or ~δ 3.24 ppm, usually as a doublet of doublets, just the same of alepterolic acid, which showed that the 3-OH was not affected in the whole process of the reactions. The signals of olefin hydrogens of the parent ring of alepterolic acid on the NMR spectra were similar to those of alepterolic acid and the signals of the four methyl groups remained unchanged as those in alepterolic acid. From the information furnished by ^{1}H NMR, it can be concluded that the frame of alepterolic acid except the carboxyl group did not take changes during the whole process of the reactions. The ^{13}C NMR data also consisted to the related structures. The ^{13}C NMR signals of the three carbon atoms closest to the fluorine atom on the fluorouracil ring produced different degrees of splitting as expected, which further confirmed the structure of all the products. The mass of the products showed molecular ion peaks corresponding to the molecular weight of the acquired structures.

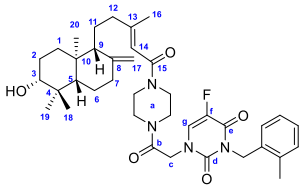
*3-Benzyl-5-fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-naphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)pyrimidine-2,4(1H,3H)-dione (**6a**)*



6a

11.0 mg, yield 85 %, light yellow solid, m.p.= 84-86 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.3 Hz, 1H, 2×Ph-H), 7.32 – 7.27 (m, 3H, 3×Ph-H), 7.23 (d, *J* = 10.3 Hz, 1H, g-H), 5.73 (s, 1H, 14-H), 5.12 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.54 (s, 2H, c-C$\underline{H}_2$), 4.52 (s, 1H, 17-H), 3.73 – 3.43 (m, 8H, 4×a-C$\underline{H}_2$), 3.24 (dd, *J* = 11.7, 4.1 Hz, 1H, 3-H), 2.41 (dt, *J* = 12.9, 3.2 Hz, 1H, 7-H), 2.26 (ddd, *J* = 14.0, 9.9, 3.9 Hz, 1H, 12-H), 1.98 – 1.92 (m, 2H, 7-H, 12-H), 1.91 (s, 3H, 16-C$\underline{H}_3$), 1.80 – 1.55 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.39 (qd, *J* = 13.0, 4.4 Hz, 1H, 6-H), 1.16 (td, *J* = 13.3, 3.6 Hz, 1H, 1-H), 1.07 (dd, *J* = 12.4, 2.7 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.69 (s, 3H, 20-C$\underline{H}_3$).^{13}C NMR (101 MHz, $CDCl_3$) δ 167.56 (C-15), 164.66 (b-C), 157.35(d, *J* = 25.2 Hz, e-C), 152.17 (d, J = 19.3 Hz, d-C), 150.30 (C-13), 147.82 (C-8), 140.12(d, *J* = 235.4 Hz, f-C), 135.97 (Ph-C), 129.06 (2×Ph-C), 128.62 (2×Ph-C), 128.03 (Ph-C), 127.61(d, *J* = 33.1 Hz, g-C), 116.31 (C-14), 106.91 (C-17), 78.80 (C-3), 56.01 (C-9), 54.73 (C-5), 49.16 (c-C), 45.29 (Ar-$\underline{C}H_2$), 39.52 (C-10), 39.23 (C-4), 38.78 (7-C), 38.26 (C-12), 37.19 (C-1), 28.42 (C-18), 27.96 (C-2), 24.08 (C-6), 21.68 (C-11), 18.92 (C-16), 15.53 (C-19), 14.62 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{37}H_{50}FN_4O_5$ $[M+H]^+$: 649.3760, observed 649.3737.

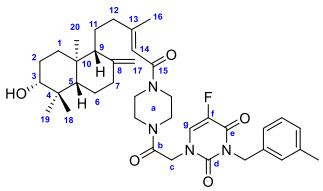
*5-Fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-naphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)-3-(2-methylbenzyl)pyrimidine-2,4(1H,3H)-dione (**6b**)*



6b

10.6 mg, yield 80 %, light yellow solid, m.p.= 114-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1H, g-H), 7.18 – 7.07 (m, 3H, 3×Ph-H), 7.06 – 6.99 (m, 1H, Ph-H), 5.73 (s, 1H, 14-H), 5.14 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.55 (s, 2H, c-C$\underline{H}_2$), 4.52 (s, 1H, 17-H), 3.77 – 3.41 (m, 8H, a-C$\underline{H}_2$), 3.24 (dd, *J* = 11.7, 3.9 Hz, 1H, 3-H), 2.43 (s, 3H, Ph-C$\underline{H}_3$), 2.43 (ddd, J = 12.8, 4.3, 2.4 Hz, 1H, 7-H), 2.35 – 2.21 (m, 1H, 12-H), 1.96 (m, *J* = 15.7 Hz, 2H, 7-H, 12-H), 1.91 (s, 3H, 16-C$\underline{H}_3$), 1.84 – 1.55 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.40 (qd, *J* = 13.0, 4.3 Hz, 1H, 6-H), 1.18 (d, *J* = 13.7 Hz, 1H, 1-H), 1.07 (dd, J = 12.5, 2.7 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.69 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.58 (b-C), 164.69 (C-15), 157.45 (d, *J* = 25.3 Hz, e-C), 152.34 (d-C), 150.43 (C-13), 147.87 (C-8), 140.16 (d, *J* = 235.7 Hz, f-C), 136.06 (Ph-C), 133.76 (Ph-C), 130.53 (Ph-C), 127.86 (Ph-C), 127.69 (d, *J* = 33.5 Hz, g-C), 126.27 (Ph-C), 126.17 (Ph-C), 116.36 (C-14), 106.95 (C-17), 78.88 (C-3), 56.07 (C-9), 54.80 (C-5), 49.31 (c-C), 42.79 (Ar-$\underline{C}H_2$), 39.57 (C-10), 39.28 (C-4), 38.84 (C-7), 38.31 (C-12), 37.24 (C-1), 28.45 (C-18), 28.01 (C-2), 24.13 (C-6), 21.74 (C-11), 19.48 (Ph-$\underline{C}H_3$), 18.95 (C-16), 15.55 (C-19), 14.66 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{38}H_{52}FN_4O_5$ $[M+H]^+$: 663.3916, observed 663.3893.

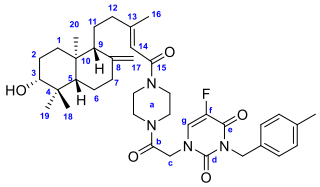
*5-Fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-naphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)-3-(3-methylbenzyl)pyrimidine-2,4(1H,3H)-dione (**6c**)*



6c

11.6 mg, yield 88 %, light yellow solid, m.p.= 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H, g-H), 7.23 (d, *J* = 8.6 Hz, 2H, 2×Ph-H), 7.18 (t, *J* = 7.4 Hz, 1H, Ph-H), 7.07 (d, *J* = 7.3 Hz, 1H, Ph-H), 5.73 (s, 1H, 14-H), 5.09 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.54 (s, 2H, c-C$\underline{H}_2$), 4.52 (s, 1H, 17-H), 3.74 – 3.48 (m, 8H, a-C$\underline{H}_2$), 3.24 (dd, *J* = 11.7, 4.4 Hz, 1H, 3-H), 2.41 (ddd, J = 12.8, 4.3, 2.4 Hz, 1H, 7-H), 2.31 (s, 3H, Ph-C$\underline{H}_3$), 2.29 – 2.22 (m, 1H, 12-H), 1.99 – 1.92 (m, 2H, 7-H, 12-H), 1.91 (d, *J* = 1.1 Hz, 3H, 16-C$\underline{H}_3$), 1.81 – 1.58 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.39 (qd, *J* = 12.9, 4.3 Hz, 1H, 6-H), 1.16 (td, *J* = 13.2, 3.8 Hz, 1H, 1-H), 1.07 (dd, *J* = 12.5, 2.7 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.69 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.59(b-C), 164.72 (C-15), 157.38 (d, *J* = 25.4 Hz, e-C), 152.31 (d-C), 150.34 (C-13), 147.86 (C-8), 140.20 (d, *J* = 235.7 Hz, f-C), 138.31 (Ph-C), 135.91 (Ph-C), 129.71 (Ph-C), 128.80 (Ph-C), 128.51 (Ph-C), 127.52 (d, *J* = 33.3 Hz, g-C), 126.10 (Ph-C), 116.35 (C-14), 106.94 (C-17), 78.86 (C-3), 56.06 (C-9), 54.79 (C-5), 49.12 (c-C), 45.30 (Ar-$\underline{C}H_2$), 39.56 (C-10), 39.27 (C-4), 38.82 (C-7), 38.30 (C-12), 37.23 (C-1), 28.45 (C-18), 28.00 (C-2), 24.12 (C-6), 21.73 (C-11), 21.50 (Ph-$\underline{C}H_3$), 18.94 (C-16), 15.54 (C-19), 14.65 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{38}H_{52}FN_4O_5$ $[M+H]^+$: 663.3916, observed 663.3895.

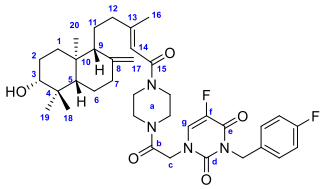
*5-Fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-naphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)-3-(2-methylbenzyl)pyrimidine-2,4(1H,3H)-dione (**6d**)*



6d

11.7 mg, yield 88 %, light yellow solid, m.p.= 113-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.8 Hz, 2H, 2×Ph-H), 7.21 (s, 1H, g-H), 7.10 (d, *J* = 7.7 Hz, 2H, 2×Ph-H), 5.74 (s, 1H, 14-H), 5.09 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.53 (s, 1H, 17-H), 4.52 (s, 2H, c-C$\underline{H}_2$), 3.76 – 3.48 (m, 8H, 4×a-C$\underline{H}_2$), 3.25 (dd, *J* = 11.7, 4.2 Hz,1H, 3-H), 2.42 (d, *J* = 12.8 Hz, 1H, 7-H), 2.30 (s, 3H, Ph-C$\underline{H}_3$), 2.26 (d, *J* = 12.0 Hz, 1H, 12-H), 1.96 (d, *J* = 17.0 Hz, 2H, 7-H, 12-H), 1.91 (s, 3H, 16-C$\underline{H}_3$), 1.82 – 1.55 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.40 (dd, *J* = 13.1, 4.3 Hz, 1H, 6-H), 1.17 (t, *J* = 12.8 Hz, 1H, 1-H), 1.07 (d, *J* = 12.3 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.78 (s, 3H, 19-C$\underline{H}_3$), 0.70 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.88 (C-15), 164.71 (b-C), 157.36 (d, J = 25.4 Hz, e-C), 152.33 (d, *J* = 5.9 Hz, d-C), 150.34 (C-13), 147.87 (C-8), 140.24 (d, *J* = 235.7 Hz, f-C), 137.83 (Ph-C), 133.08 (Ph-C), 129.31 (2×Ph-C), 129.20 (2×Ph-C), 127.51(d, *J* = 32.0 Hz, g-C), 116.38 (C-14), 106.95 (C-17), 78.89 (C-3), 56.08 (C-9), 54.81 (C-5), 49.15(c-C), 45.10 (Ar-C$\underline{H}_2$), 39.58 (C-10), 39.28 (C-4), 38.85 (7-C), 38.32 (C-12), 37.25 (C-1), 28.46 (C-18), 28.02 (C-2), 24.13 (C-6), 21.75 (C-11), 21.30 (Ph-C$\underline{H}_3$), 18.96 (C-16), 15.55 (C-19), 14.66 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{38}H_{52}FN_4O_5$ $[M+H]^+$: 663.3916, observed 663.3902.

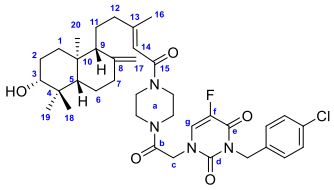
*5-Fluoro-3-(4-fluorobenzyl)-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)pyrimidine-2,4(1H,3H)-dione (**6e**)*



6e

10.9 mg, yield 82 %, light yellow solid, m.p.= 77-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.22 (s, 0H), 6.97 (t, *J* = 8.5 Hz, 2H), 5.74 (s, 1H, 14-H), 5.09 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.56 (s, 2H, c-C$\underline{H}_2$), 4.52 (s, 1H, 17-H), 3.81 – 3.41 (m, 8H, 4×a-C$\underline{H}_2$), 3.25 (dd, *J* = 11.8, 4.3 Hz, 1H, 3-H), 2.42 (ddd, J = 12.8, 4.3, 2.4 Hz, 1H, 7-H), 2.35 – 2.21 (m, 1H, 12-H), 1.95 (m, 2H, 7-H, 12-H), 1.91 (s, 3H, 16-C$\underline{H}_3$), 1.83 – 1.57 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.41 (qd, *J* = 13.0, 4.3 Hz, 1H, 6-H), 1.18 (td, J = 13.0, 3.5 Hz, 1H, 1-H), 1.07 (dd, J = 12.5, 2.7 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.70 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.77 (b-C), 164.65 (C-15), 162.58 (d, *J* = 246.5 Hz, Ph-C), 157.31 (d, *J* = 24.7 Hz, e-C), 152.40 (d-C), 150.84 (C-13),147.87 (C-8), 140.19 (d, *J* = 237.1 Hz, f-C), 131.85 (d, *J* = 3.2 Hz, Ph-C), 131.24 (d, *J* = 8.2 Hz, 2× Ph-C), 127.80 (d, *J* = 34.0 Hz, g-C), 116.36 (C-14), 115.49 (d, *J* = 21.4 Hz, 2×Ph-C), 106.95 (C-17), 78.89 (C-3), 56.08 (C-9), 54.81 (C-5), 49.34 (c-C), 44.63 (Ar-C$\underline{H}_2$), 39.57 (C-10), 39.28 (C-4), 38.86 (C-7), 38.32 (C-12), 37.26 (C-1), 28.46 (C-18), 28.02 (C-2), 24.13 (C-6), 21.75 (C-11), 18.98 (C-16), 15.55 (C-19), 14.66 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{37}H_{49}F_2N_4O_5$ $[M+H]^+$: 667.3666, observed 667.3655.

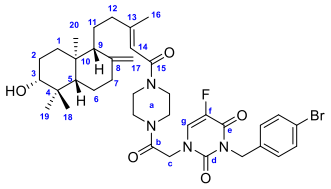
*3-(4-Chlorobenzyl)-5-fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)pyrimidine-2,4(1H,3H)-dione (**6f**)*



6f

11.6 mg, yield 85 %, light yellow solid, m.p.= 80-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 2H, 2×Ph-H), 7.29 – 7.25 (m, 3H, 2×Ph-H, g-H), 5.74 (s, 1H, 14-H), 5.08 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.55 (s, 2H, c-C$\underline{H}_2$), 4.52 (s, 1H, 17-H), 3.79 – 3.45 (m, 8H, 4×a-C$\underline{H}_2$), 3.25 (dd, *J* = 11.5, 2.6 Hz, 1H, 3-H), 2.41 (ddd, J = 12.8, 4.3, 2.4 Hz, 1H, 7-H), 2.35 – 2.21 (m, 1H, 12-H), 1.96 (m, *J* = 14.2 Hz, 2H, 7-H, 12-H), 1.91 (s, 3H, 16-C$\underline{H}_3$), 1.83 – 1.56 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.40 (qd, *J* = 13.0, 4.3 Hz, 1H, 6-H), 1.16 (td, *J* = 13.2, 3.7 Hz, 1H, 1-H), 1.06 (dd, J = 12.5, 2.7 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.69 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.42 (b-C), 164.41 (C-15), 157.12 (d, *J* = 25.0 Hz, e-C), 152.28 (d-C), 150.13 (C-13), 147.69 (C-8), 139.99 (d, *J* = 236.2 Hz, f-C), 134.28 (Ph-C), 133.85 (Ph-C), 130.56 (2×Ph-C), 128.65 (2×Ph-C), 127.62 (d, *J* = 33.2 Hz, g-C), 116.13 (C-14), 106.79 (C-17), 78.72 (C-3), 55.88 (C-9), 54.61 (C-5), 49.20 (c-C), 44.51 (Ar-$\underline{C}H_2$), 39.40 (C-10), 39.10 (C-4), 38.68 (C-7), 38.13 (C-12), 37.07 (C-1), 28.29 (C-18), 27.84 (C-2), 23.95 (C-6), 21.55 (C-11), 18.82 (C-16), 15.39 (C-19), 14.50 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{37}H_{49}FClN_4O_5$ $[M+H]^+$: 683.3370 observed 683.3353.

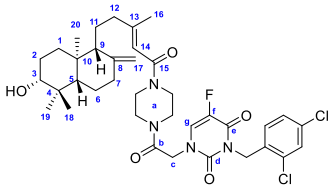
*3-(4-Bromobenzyl)-5-fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)pyrimidine-2,4(1H,3H)-dione (**6g**)*



6g

12.8 mg, yield 88 %, light yellow solid, m.p.= 94-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 2H, 2×Ph-H), 7.33 (d, *J* = 8.1 Hz, 2H, 2×Ph-H), 7.22 (s, 1H, g-H), 5.75 (s, 1H, 14-H), 5.07 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H,17 -H), 4.55 (s, 2H, c-C$\underline{H}_2$), 4.52 (s, 1H, 17-H), 3.79 – 3.45 (m, 8H, 4×a-C$\underline{H}_2$), 3.25 (d, *J* = 11.3 Hz, 1H, 3-H), 2.42 (d, *J* = 12.6 Hz, 1H, 7-H), 2.33 – 2.22 (m, 1H, 12-H), 2.00 – 1.93 (m, 2H, 7-H, 12-H), 1.92 (s, 3H, 16-H), 1.83 – 1.57 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.47 – 1.37 (m, 1H, 6-H), 1.17 (t, *J* = 13.0 Hz, 1H, 1-H), 1.07 (d, *J* = 12.3 Hz, 1H, 5-H), 0.99 (s, 3H, 18-H), 0.77 (s, 3H, 19-H), 0.70 (s, 3H, 20-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.55 (C-15), 163.85 (b-C), 157.27(d, *J* = 25.4 Hz, e-C), 152.38 (C-13), 150.30 (98-C), 147.88 (d-C), 145.13(d, *J* = 34.0 Hz, g-C), 140.15(d, *J* = 236.0 Hz, f-C), 134.98 (Ph-C), 131.78 (2×Ph-C), 131.02 (2×Ph-C), 122.19 (C-14), 116.34 (Ph-C), 106.95 (C-17), 78.89 (C-3), 56.08 (C-9), 54.80 (C-5), 49.29(d, *J* = 3.1 Hz, c-C), 44.73 (Ar-$\underline{C}H_2$), 39.58 (C-10), 39.28 (C-4), 38.86 (7-C), 38.32 (C-12), 37.25 (C-1), 28.46 (C-18), 28.02 (C-2), 24.13 (C-6), 21.75 (C-11), 18.98 (C-16), 15.55 (C-19), 14.66 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{37}H_{49}FBrN_4O_5$ $[M+H]^+$: 727.2865 observed 727.2853.

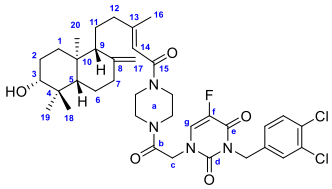
*3-(2,4-Dichlorobenzyl)-5-fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)pyrimidine-2,4(1H,3H)-dione (**6h**)*



6h

10.8 mg, yield 75 %, light yellow solid, m.p.= 102-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 2.0 Hz, 1H, Ph-H), 7.37 (d, *J* = 8.3 Hz, 1H, Ph-H), 7.30 (dd, *J* = 8.3, 2.1 Hz, 1H, Ph-H), 7.23 (s, 1H, g-H), 5.74 (s, 1H, 14-H), 5.06 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.55 (s, 2H, c-C$\underline{H}_2$), 4.52 (s, 1H, 17-H), 3.82 – 3.45 (m, 8H, 4×a-C$\underline{H}_2$), 3.24 (dd, *J* = 11.7, 4.4 Hz, 1H, 3-H), 2.41 (ddd, J = 12.8, 4.3, 2.4 Hz, 1H, 7-H), 2.33 – 2.21 (m, 1H, 12-H), 2.01 – 1.92 (m, 2H, 7-H, 12-H), 1.91 (s, 3H, 16-C$\underline{H}_3$), 1.83 – 1.54 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.40 (qd, *J* = 12.9, 4.2 Hz, 1H, 6-H), 1.13 (td, J = 13.0, 3.5 Hz, 1H, 1-H), 1.07 (dd, *J* = 12.5, 2.7 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.69 (s, 3H, 20-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.60 (b-C), 164.53 (C-15), 157.19 (d, *J* = 25.1 Hz, e-C), 152.45 (d-C), 150.25 (C-13), 147.88 (C-8), 140.11 (d, *J* = 236.5 Hz, f-C), 136.05 (Ph-C), 131.26 (Ph-C), 132.51 (d, *J* = 32.5 Hz, g-C), 130.62 (Ph-C), 128.77 (Ph-C), 128.02 (Ph-C), 127.70 (Ph-C), 116.32 (C-14), 106.94 (C-17), 78.89 (C-3), 56.08 (C-9), 54.81 (C-5), 49.28 (c-C), 44.24 (Ar-$\underline{C}H_2$), 39.58 (C-10), 39.28 (C-4), 38.86 (C-7), 38.32 (C-12), 37.25 (C-1), 28.46 (C-18), 28.02 (C-2), 24.14 (C-6), 21.75 (C-11), 18.96 (C-16), 15.55 (C-19), 14.66 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{37}H_{48}FCl_2N_4O_5$ $[M+H]^+$: 717.2980, observed 717.2960.

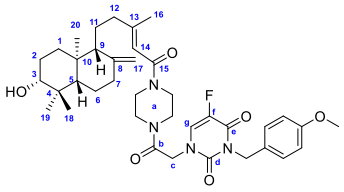
*3-(3,4-Dichlorobenzyl)-5-fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)pyrimidine-2,4(1H,3H)-dione (**6i**)*



6i

11.9 mg, yield 83 %, light yellow solid, m.p.= 87-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H, Ph-H), 7.29 (s, 1H, g-H), 7.16 (s, 1H, Ph-H), 6.99 (d, *J* = 8.4 Hz, 1H, Ph-H), 5.73 (s, 1H, 14-H), 5.22 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.56 (s, 2H, c-C$\underline{H}_2$), 4.51 (s, 1H, 17-H), 3.76 – 3.44 (m, 8H, 4×a-C$\underline{H}_2$), 3.24 (dd, *J* = 11.7, 4.4 Hz, 1H, 3-H), 2.41 (ddd, *J* = 12.7, 4.3, 2.3 Hz, 1H, 7-H), 2.35 – 2.21 (m, 1H, 12-H), 1.96 (m, *J* = 17.2 Hz, 2H, 7-H, 12-H), 1.91 (s, 3H, 16-C$\underline{H}_3$), 1.82 – 1.57 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.39 (qd, *J* = 13.0, 4.3 Hz, 1H, 6-H), 1.16 (td, *J* = 13.1, 3.8 Hz, 1H, 1-H), 1.07 (dd, *J* = 12.5, 2.7 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.69 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.53 (b-C), 164.49 (C-15), 157.22 (d, *J* = 25.6 Hz, e-C), 152.43 (d-C), 150.24 (C-13), 147.87 (C-8), 140.04 (d, *J* = 236.4 Hz, f-C), 133.91 (Ph-C), 131.84 (Ph-C), 129.60 (Ph-C), 128.43 (Ph-C), 128.26 (Ph-C), 128.09 (d, *J* = 33.8 Hz, g-C), 127.45 (Ph-C), 116.29 (C-14), 106.93 (C-17), 78.88 (C-3), 56.07 (C-9), 54.80 (C-5), 49.51 (c-C), 42.61 (Ar-$\underline{C}H_2$), 39.57 (C-10), 39.28 (C-4), 38.85 (C-7), 38.31 (C-12), 37.24 (C-1), 28.45 (C-18), 28.01 (C-2), 24.13 (C-6), 21.74 (C-11), 18.96 (C-16), 15.54 (C-19), 14.66 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{37}H_{48}FCl_2N_4O_5$ $[M+H]^+$: 717.2980, observed 717.2963.

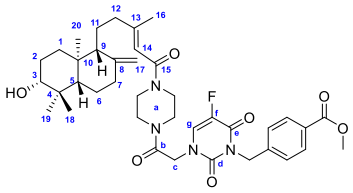
*5-Fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-naphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)-3-(4-methoxybenzyl)pyrimidine-2,4(1H,3H)-dione (**6j**)*



6j

11.5 mg, yield 85 %, light yellow solid, m.p.= 85-86 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 2H, 2×Ph-H), 7.20 (s, 1H, g-H), 6.84 – 6.80 (m, 2H, 2×Ph-H), 5.74 (s, 1H, 14-H), 5.06 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.53 (s, 2H, c-C$\underline{H}_2$), 4.52 (s, 1H, 17-H), 3.77 (s, 3H, Ph-OC$\underline{H}_3$), 3.74 – 3.48 (m, 8H, 4×a-C$\underline{H}_2$), 3.25 (dd, *J* = 11.8, 4.4 Hz, 1H, 3-H), 2.41 (ddd, J = 12.8, 4.3, 2.4 Hz, 1H, 7-H), 2.35 – 2.21 (m, 1H, 12-H), 1.99 – 1.93 (m, 2H, 7-H, 12-H), 1.91 (s, 3H, 16-C$\underline{H}_3$), 1.82 – 1.55 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.39 (qd, *J* = 13.0, 4.3 Hz, 1H, 6-H), 1.16 (td, *J* = 13.3, 3.7 Hz, 1H, 1-H), 1.07 (dd, *J* = 12.3, 2.6 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.70 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.62 (b-C), 164.74 (C-15), 159.45 (Ph-C), 157.37 (d, *J* = 25.1 Hz, e-C), 152.38 (d-C), 150.35 (C-13), 147.88 (C-8), 140.26 (d, *J* = 236.0 Hz, f-C), 130.87 (2×Ph-C), 128.29 (Ph-C), 127.41 (d, *J* = 33.2 Hz, g-C), 116.35 (2×Ph-C), 113.96 (C-14), 106.96 (C-17), 78.89 (C-), 78.89 (C-3), 56.07 (Ph-O$\underline{C}H_3$), 55.39 (C-9), 54.80 (C-5), 49.11 (c-C), 44.82 (Ar-$\underline{C}H_2$), 39.57 (C-10), 39.28 (C-4), 38.84 (C-7), 38.31 (C-12), 37.24 (C-1), 28.45 (C-18), 28.01 (C-2), 24.13 (C-6), 21.73 (C-11), 18.95 (C-16), 15.55 (C-19), 14.66 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{38}H_{52}FN_4O_6$ $[M+H]^+$: 679.3865, observed 679.3851.

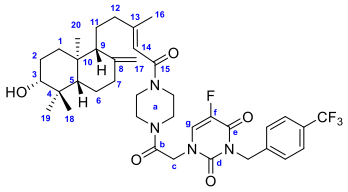
*Methyl 4-((5-fluoro-3-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)methyl)benzoate (**6k**)*



6k

9.9 mg, yield 70 %, light yellow solid, m.p.= 86-87 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 2H, 2×Ph-H), 7.47 (d, *J* = 7.9 Hz, 2H, 2×Ph-H), 7.34 (s, 1H, g-H), 5.73 (s, 1H, 14-H), 5.16 (s, 2H, Ar-C$\underline{H}_2$), 4.86 (s, 1H, 17-H), 4.57 (d, *J* = 8.6 Hz, 2H, c-C$\underline{H}_2$), 4.51 (s, 1H, 17-H), 3.89 (s, 3H, O=C-OC$\underline{H}_3$), 3.75 – 3.50 (m, 8H, 4×a-C$\underline{H}_2$), 3.24 (dd, *J* = 11.7, 4.3 Hz, 1H, 3-H), 2.41 (ddd, J = 12.8, 4.3, 2.4 Hz, 1H, 7-H), 2.35 – 2.21 (m, 1H, 12-H), 1.99 – 1.92 (m, 2H, 7-H, 12-H), 1.89 (s, 3H, 16-C$\underline{H}_3$), 1.80 – 1.51 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.41 (qd, *J* = 13.0, 4.3 Hz, 1H, 6-H), 1.15 (td, *J* = 13.1, 3.5 Hz, 1H, 1-H), 1.07 (dd, J = 12.5, 2.7 Hz, 1H, 5-H), 0.98 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.69 (s, 3H, 20-C$\underline{H}_3$).^{13}C NMR (151 MHz, $CDCl_3$) δ 167.69 (b-C), 166.92 (O=$\underline{C}$-OCH$_3$), 164.71 (C-15), 157.41 (d, *J* = 25.5 Hz, e-C), 152.12 (d-C), 150.37 (C-13), 147.85 (C-8), 141.02 (Ph-C), 140.05 (d, *J* = 235.4 Hz, f-C), 129.97 (2×Ph-C), 129.76 (Ph-C), 128.79 (2×Ph-C), 128.10 (d, *J* = 31.4 Hz, g-C), 116.42 (C-14), 106.94 (C-17), 78.86 (C-3), 56.05 (O=C-O$\underline{C}H_3$), 55.63 (C-9), 54.78 (C-5), 52.26 (c-C), 43.60 (Ar-$\underline{C}H_2$), 39.55 (C-10), 39.25 (C-4), 38.75 (C-7), 38.29 (C-12), 37.22 (C-1), 28.44 (C-18), 27.98 (C-2), 24.11 (C-6), 21.70 (C-11), 18.72 (C-16), 15.54 (C-19), 14.64 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{39}H_{52}FN_4O_7$ $[M+H]^+$: 707.3815, observed 707.3794.

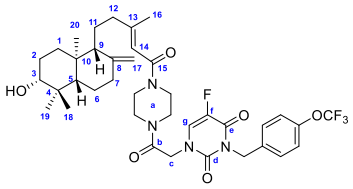
*5-Fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-naphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)-3-(4-(trifluoromethoxy)benzyl)-pyrimidine-2,4(1H,3H)-dione (**6l**)*



6l

12.9 mg, yield 90 %, light yellow solid, m.p.= 100-102 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 – 7.52 (m, 4H, 4×Ph-H), 7.24 (s, 1H, g-H), 5.74 (s, 1H, 14-H), 5.17 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (d, *J* = 1.7 Hz, 1H, 17-H), 4.55 (s, 2H, c-C$\underline{H}_2$), 4.52 (s, 1H, 17-H), 3.82 – 3.44 (m, 8H, 4×a-C$\underline{H}_2$), 3.24 (dd, *J* = 11.8, 4.3 Hz, 1H, 3-H), 2.41 (ddd, J = 12.8, 4.3, 2.4 Hz, 1H, 7-H), 2.31 – 2.23 (m, 1H, 12-H), 1.99 – 1.92 (m, 2H, 7-H, 12-H), 1.91 (d, *J* = 1.1 Hz, 3H, 16-C$\underline{H}_3$), 1.82 – 1.55 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.40 (qd, *J* = 13.0, 4.3 Hz, 1H, 6-H), 1.16 (td, *J* = 13.2, 3.7 Hz, 1H, 1-H), 1.07 (dd, *J* = 12.5, 2.7 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.70 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.63 (b-C), 164.55 (C-15), 157.28 (d, *J* = 25.3 Hz, e-C), 152.51 (d-C), 150.33 (C-13), 147.88 (C-8), 140.13 (d, *J* = 236.4 Hz, f-C), 139.84 (Ph-C), 130.28 (q, *J* = 32.3 Hz, Ph-C), 129.35 (2×Ph-C), 127.84 (d, *J* = 33.3 Hz, g-C), 125.66 (q, *J* = 3.4 Hz, 2×Ph-C), 124.15 (q, *J* = 272.1 Hz, Ph-$\underline{C}F_3$), 116.29 (C-14), 106.95 (C-17), 78.89 (C-3), 56.06 (C-9), 54.79 (C-5), 49.32 (c-C), 44.84 (Ar-$\underline{C}H_2$), 39.57 (C-10), 39.28 (C-4), 38.85 (C-7), 38.30 (C-12), 37.23 (C-1), 28.45 (C-18), 28.00 (C-2), 24.12 (C-6), 21.73 (C-12), 18.95 (C-16), 15.54 (C-19), 14.65 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{38}H_{49}F_4N_4O_5$ $[M+H]^+$: 717.3634 observed 717.3605.

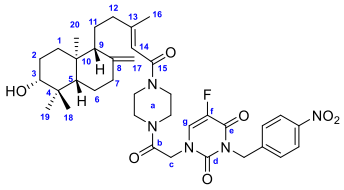
*5-Fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-naphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)-3-(4-trifluoromethoxybenzyl)-pyrimidine-2,4(1H,3H)-dione (**6m**)*



6m

11.7 mg, yield 80 %, light yellow solid, m.p.= 99-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H, 2×Ph-H), 7.24 (s, 1H, g-H), 7.18 – 7.10 (m, 2H, 2×Ph-H), 5.74 (d, *J* = 1.7 Hz, 1H, 14-H), 5.11 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.55 (s, 2H, c-C$\underline{H}_2$), 4.52 (s, 1H, 17-H), 3.63 (m, *J* = 46.9 Hz, 8H, 4×a-C$\underline{H}_2$), 3.25 (dd, *J* = 11.7, 4.4 Hz, 1H, 3-H), 2.41 (ddd, J = 12.8, 4.3, 2.4 Hz, 1H, 7-H), 2.33 – 2.21 (m, 1H, 12-H), 2.01 – 1.92 (m, 2H, 7-H, 12-H), 1.91 (s, 3H, 16-C$\underline{H}_3$), 1.83 – 1.55 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.40 (qd, *J* = 12.8, 4.3 Hz, 1H, 6-H), 1.16 (td, *J* = 13.1, 3.8 Hz, 1H, 1-H), 1.07 (dd, *J* = 12.6, 2.7 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.70 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.64 (b-C), 164.60 (C-15), 157.30 (d, *J* = 25.3 Hz, e-C), 152.41 (d-C), 150.34 (C-13), 150.25 (d, *J* = 249.4 Hz, Ph-C), 147.88 (C-8), 140.15 (d, *J* = 235.8 Hz, f-C), 134.88 (d, *J* = 39.4 Hz, Ph-C), 130.83 (2×Ph-C), 127.79 (d, *J* = 33.5 Hz, g-C), 120.49 (q, *J* = 246.4 Hz, Ph-O$\underline{C}F_3$,), 121.12 (2×Ph-C), 116.33 (C-14), 106.95 (C-17), 78.89 (C-3), 56.08 (C-9), 54.81 (C-5), 49.27 (c-C), 44.56 (Ar-$\underline{C}H_2$), 39.58 (C-10), 39.29 (C-4), 38.85 (C-7), 38.32 (C-12), 37.25 (C-1), 28.46 (C-18), 28.02 (C-2), 24.14 (C-6), 21.75 (C-11), 18.95 (C-16), 15.55 (C-19), 14.66 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{38}H_{50}F_4N_4O_6$ $[M+H]^+$: 733.3583 observed 733.3568.

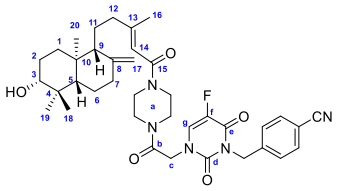
*5-Fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-naphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)-3-(4-nitrobenzyl)pyrimidine-2,4(1H,3H)-dione (**6n**)*



6n

12.2 mg, yield 88 %, light yellow solid, m.p.= 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.7 Hz, 2H, 2×Ph-H), 7.59 (d, *J* = 8.7 Hz, 2H, 2×Ph-H), 7.25 (s, 1H, g-H), 5.74 (s, 1H, 14-H), 5.21 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.56 (s, 2H, c-C$\underline{H}_2$), 4.51 (s, 1H, 17-H), 3.78 – 3.47 (m, 8H, 4×a-C$\underline{H}_2$), 3.24 (dd, *J* = 11.7, 4.4 Hz, 1H, 3-H), 2.41 (ddd, J = 12.8, 4.3, 2.4 Hz, 1H, 7-H), 2.33 – 2.22 (m, 1H, 12-H), 1.98 – 1.93 (m, 2H, 7-H, 12-H), 1.91 (s, 3H, 16-C$\underline{H}_3$), 1.82 – 1.55 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.38 (td, *J* = 13.0, 4.3 Hz, 1H, 6-H), 1.16 (td, *J* = 13.1, 3.6 Hz, 1H, 1-H), 1.07 (dd, *J* = 12.7, 2.7 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.69 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.63 (b-C), 164.44 (C-15), 157.21 (d, *J* = 25.5 Hz, e-C), 152.59 (d-C), 150.31 (C-13), 147.88 (Ph-C), 147.73 (C-8), 143.06 (Ph-C), 140.09 (d, *J* = 236.7 Hz, f-C), 129.85 (2×Ph-C), 128.04 (d, *J* = 33.1 Hz, g-C), 123.94 (2×Ph-C), 116.25 (C-14), 106.95 (C-17), 78.89 (C-3), 56.07 (C-9), 54.79 (C-5), 49.44 (c-C), 44.62 (Ar-$\underline{C}H_2$), 39.57 (C-10), 39.28 (C-4), 38.87 (C-7), 38.30 (C-12), 37.24 (C-1), 28.45 (C-18), 28.01 (C-2), 24.12 (C-6), 21.73 (C-11), 18.96 (C-16), 15.54 (C-19), 14.65 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{37}H_{49}FN_5O_7$ $[M+H]^+$: 694.3611, observed 694.3598.

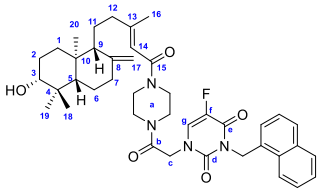
*4-((5-Fluoro-3-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-naphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)methyl)benzonitrile (**6o**)*



6o

11.6 mg, yield 86 %, light yellow solid, m.p.= 87-88 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H, 2×Ph-H), 7.55 – 7.50 (m, 2H, 2×Ph-H), 7.26 (s, 1H, g-H), 5.74 (s, 1H, 14-H), 5.16 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.56 (s, 2H, c-C$\underline{H}_2$), 4.51 (s, 1H, 17-H), 3.76 – 3.48 (m, 8H, a-C$\underline{H}_2$), 3.24 (dd, *J* = 11.8, 4.3 Hz, 1H, 3-H), 2.41 (ddd, *J* = 12.7, 4.2, 2.4 Hz, 1H, 7-H), 2.35 – 2.21 (m, 1H, 12-H), 1.98 – 1.93 (m, 2H, 7-H, 12-H), 1.91 (s, 3H, 16-C$\underline{H}_3$), 1.82 – 1.60 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.40 (qd, *J* = 13.0, 4.3 Hz, 1H, 6-H), 1.16 (td, *J* = 13.3, 3.7 Hz, 1H, 1-H), 1.07 (dd, *J* = 12.5, 2.7 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.69 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.65 (b-C), 164.49 (C-15), 157.23 (d, *J* = 25.6 Hz, e-C), 152.59 (d-C), 150.31 (C-13), 147.87 (C-8), 141.11 (Ph-C), 140.08 (d, *J* = 236.6 Hz, f-C), 132.53 (2×Ph-C), 129.68 (2×Ph-C), 128.01 (d, *J* = 33.1 Hz, g-C), 118.75 (Ph-$\underline{C}$N), 116.25 (C-14), 111.98 (Ph-C), 106.95 (C-17), 78.88 (C-3), 56.05 (C-9), 54.79 (C-5), 49.41 (c-C), 44.88 (Ar-$\underline{C}H_2$), 39.56 (C-10), 39.27 (C-4), 38.85 (C-7), 38.30 (C-12), 37.23 (C-1), 28.45 (C-18), 28.00 (C-2), 24.12 (C-6), 21.72 (C-11), 18.96 (C-16), 15.54 (C-19), 14.65 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{38}H_{49}FN_5O_5$ $[M+H]^+$: 674.3712, observed 674.3707.

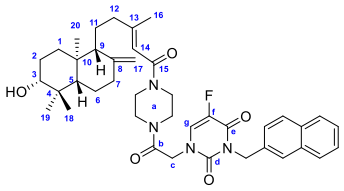
*5-Fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-naphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)-3-(naphthalen-1-ylmethyl)-pyrimidine-2,4(1H,3H)-dione (**6p**)*



6p

12.0 mg, yield 86 %, light yellow solid, m.p.= 103-104 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.5 Hz, 1H, Ph-H), 7.84 (dd, *J* = 8.1, 1.2 Hz, 1H, Ph-H), 7.75 (d, *J* = 8.1 Hz, 1H, Ph-H), 7.55 (ddd, *J* = 8.3, 6.7, 1.3 Hz, 1H, Ph-H), 7.49 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H, Ph-H), 7.38 (t, *J* = 7.7 Hz, 1H, Ph-H), 7.31 (s, 2H, Ph-H, g-H), 5.72 (s, 1H, 14-H), 5.64 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.51 (s, 3H, c-C$\underline{H}_2$, 17-H), 3.76 – 3.36 (m, 8H, 4×a-C$\underline{H}_2$), 3.24 (dd, *J* = 11.8, 4.3 Hz, 1H, 3-H), 2.41 (ddd, *J* = 12.8, 4.3, 2.4 Hz, 1H, 7-H), 2.35 – 2.21 (m, 1H, 12-H), 1.94 (m, *J* = 12.9, 6.3 Hz, 2H, 7-H, 12-H), 1.90 (s, 3H, 16-C$\underline{H}_3$), 1.81 – 1.54 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.39 (qd, *J* = 13.0, 4.1 Hz, 1H, 6-H), 1.15 (td, *J* = 13.3, 3.8 Hz, 1H, 1-H), 1.06 (dd, *J* = 12.5, 2.8 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.69 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.60 (b-C), 164.70 (C-15), 157.56 (d, *J* = 25.2 Hz, e-C), 152.29 (d-C), 150.47 (C-13), 147.87 (C-8), 140.14 (d, *J* = 235.8 Hz, f-C), 133.86 (Ph-C), 131.27 (Ph-C), 130.95 (Ph-C), 128.91 (Ph-C), 128.37 (Ph-C), 127.85 (d, *J* = 33.1 Hz, g-C), 126.51 (Ph-C), 125.92 (Ph-C), 125.41 (Ph-C), 124.83 (Ph-C), 123.34 (Ph-C), 116.36 (C-14), 106.95 (C-17), 78.87 (C-3), 56.06 (C-9), 54.78 (C-5), 49.36 (c-C), 42.88 (Ar-$\underline{C}H_2$), 39.56 (C-10), 39.26 (C-4), 38.81 (C-7), 38.29 (C-12), 37.22 (C-1), 28.44 (C-18), 27.99 (C-2), 24.11 (C-6), 21.71 (C-11), 18.93 (C-16), 15.54 (C-19), 14.64 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{41}H_{51}FN_4O_5$ $[M+H]^+$: 699.3916, observed 699.3896.

*5-Fluoro-1-(2-(4-((E)-5-((1R,4aS,6R,8aS)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-naphthalen-1-yl)-3-methylpent-2-enoyl)piperazin-1-yl)-2-oxoethyl)-3-(naphthalen-2-ylmethyl)-pyrimidine-2,4(1H,3H)-dione (**6q**)*

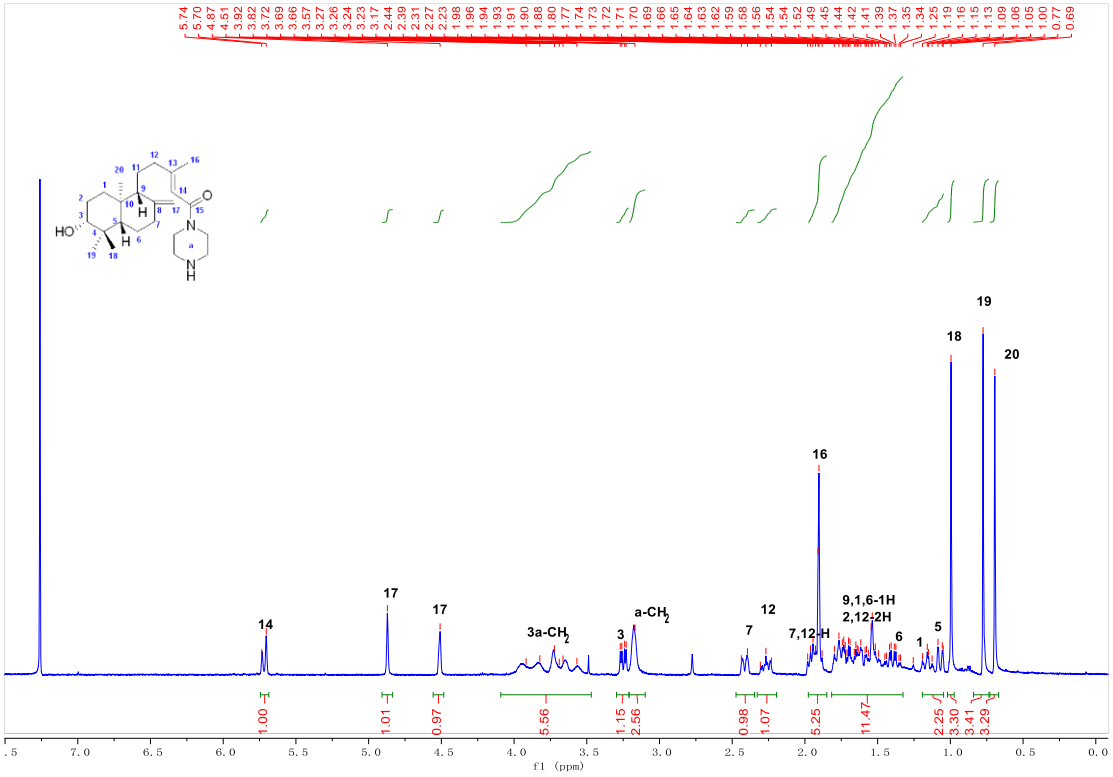


6q

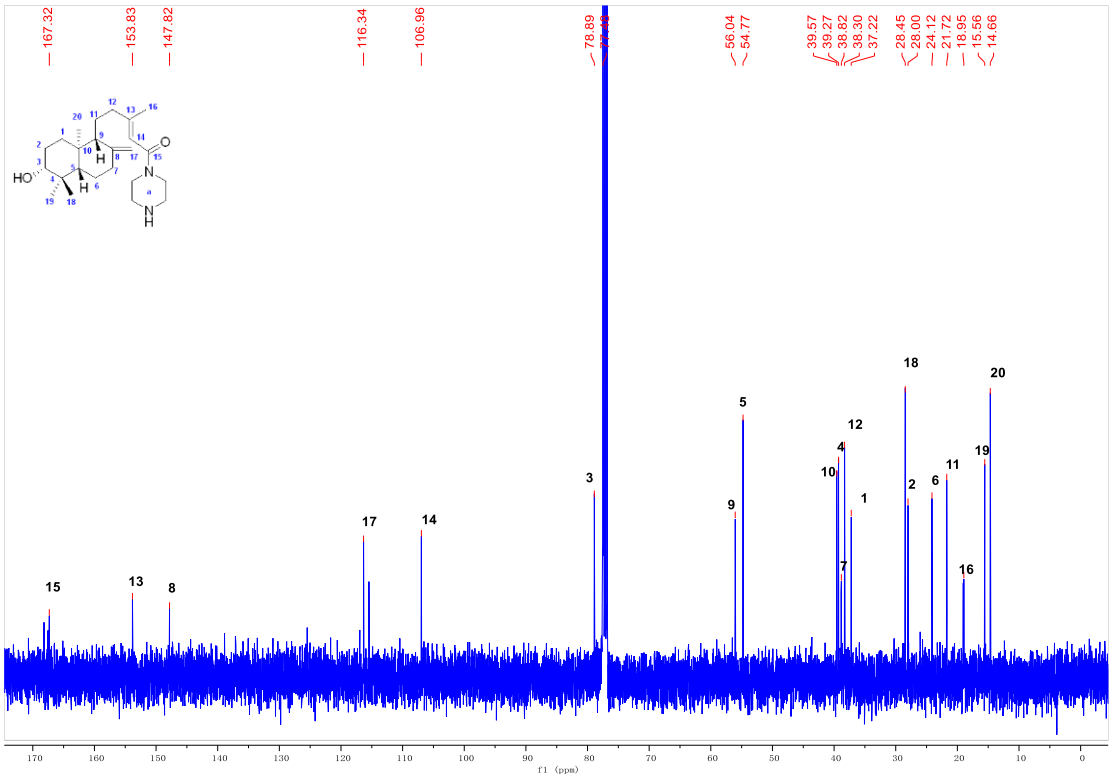
12.3 mg, yield 88 %, light yellow solid, m.p.= 101-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H, Ph-H), 7.79 (td, *J* = 8.6, 8.1, 4.6 Hz, 3H, 3×Ph-H), 7.59 – 7.52 (m, 1H, Ph-H), 7.48 – 7.41 (m, 2H, 2×Ph-H), 7.23 (s, 1H, g-H), 5.73 (s, 1H, 14-H), 5.29 (s, 2H, Ar-C$\underline{H}_2$), 4.87 (s, 1H, 17-H), 4.52 (s, 3H, c-C$\underline{H}_2$, 17-H), 3.78 – 3.45 (m, 8H, 4×a-C$\underline{H}_2$), 3.24 (dd, *J* = 11.7, 4.4 Hz, 1H, 3-H), 2.41 (ddd, J = 12.8, 4.3, 2.4 Hz, 1H, 7-H), 2.33 – 2.21 (m, 1H, 12-H), 2.00 – 1.91 (m, 2H, 7-H, 12-H), 1.91 (s, 3H, 16-C$\underline{H}_3$), 1.82 – 1.57 (m, 7H, 1-H, 2-C$\underline{H}_2$, 6-H, 9-H, 11-C$\underline{H}_2$), 1.39 (qd, *J* = 12.7, 4.2 Hz, 1H, 6-H), 1.16 (td, *J* = 13.1, 3.7 Hz, 1H, 1-H), 1.07 (dd, *J* = 12.6, 2.7 Hz, 1H, 5-H), 0.99 (s, 3H, 18-C$\underline{H}_3$), 0.77 (s, 3H, 19-C$\underline{H}_3$), 0.69 (s, 3H, 20-C$\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.43 (b-C), 164.51 (C-15), 157.28 (d, *J* = 25.2 Hz, e-C), 152.17 (d-C), 150.20 (C-13), 147.70 (C-8), 140.04 (d, *J* = 235.8 Hz, f-C), 133.27 (Ph-C), 133.16 (Ph-C), 132.89 (Ph-C), 128.22 (Ph-C), 128.10 (Ph-C), 127.95 (Ph-C), 127.56 (Ph-C), 127.49 (d, *J* = 33.0, g-C), 126.74 (Ph-C), 126.10 (Ph-C), 126.05 (Ph-C), 116.20 (C-14), 106.78 (C-17), 78.71 (C-3), 55.91 (C-9), 54.63 (C-5), 49.00 (c-C), 45.32 (Ar-$\underline{C}H_2$), 39.40 (C-10), 39.10 (C-4), 38.67 (C-7), 38.14 (C-12), 37.07 (C-1), 28.28 (C-18), 27.84 (C-2), 23.96 (C-6), 21.57 (C-11), 18.78 (C-16), 15.38 (C-19), 14.49 (C-20). (+) ESI-HRMS (m/z): calculated for $C_{41}H_{52}FN_4O_5$ $[M+H]^+$: 699.3916, observed 699.3906.

Spectra

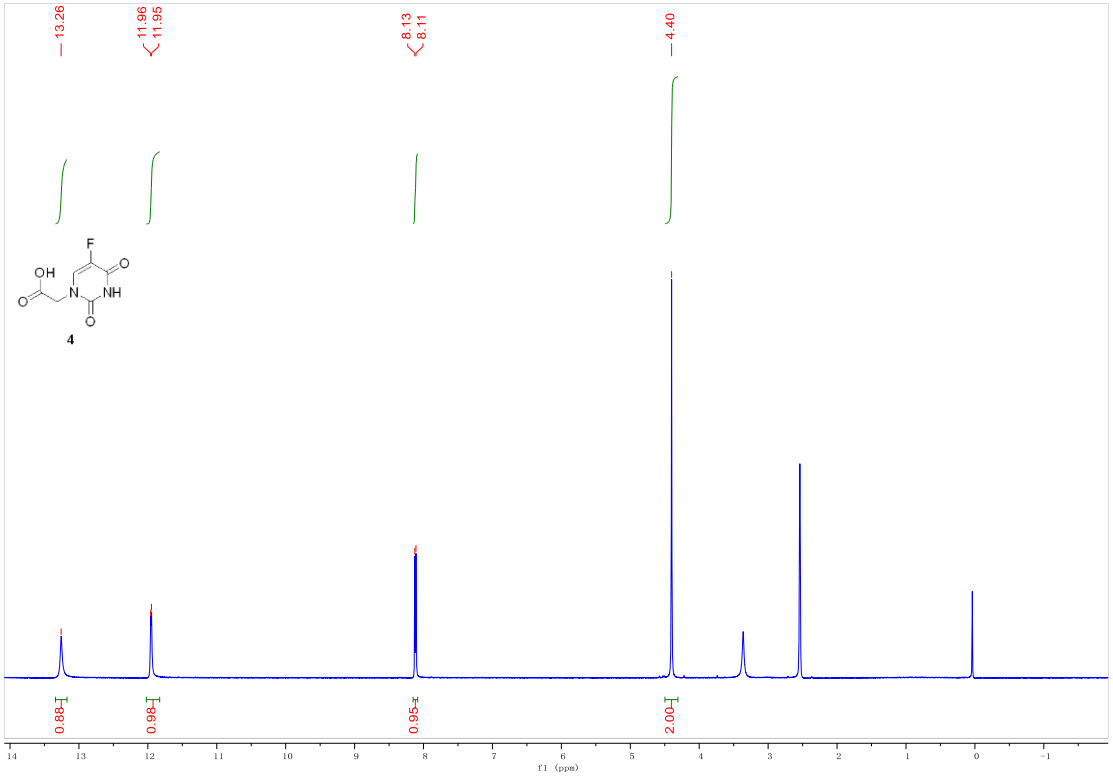
^{1}H NMR spectrum of compound **3**



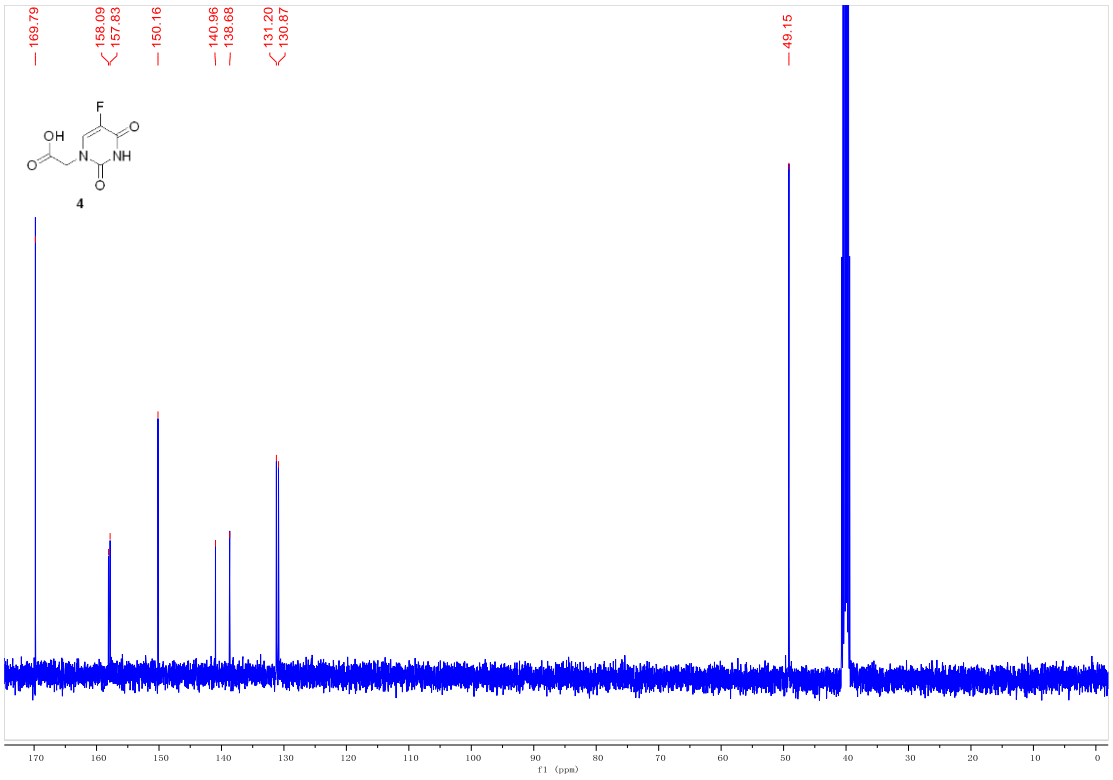
^{13}C NMR spectrum of compound **3**



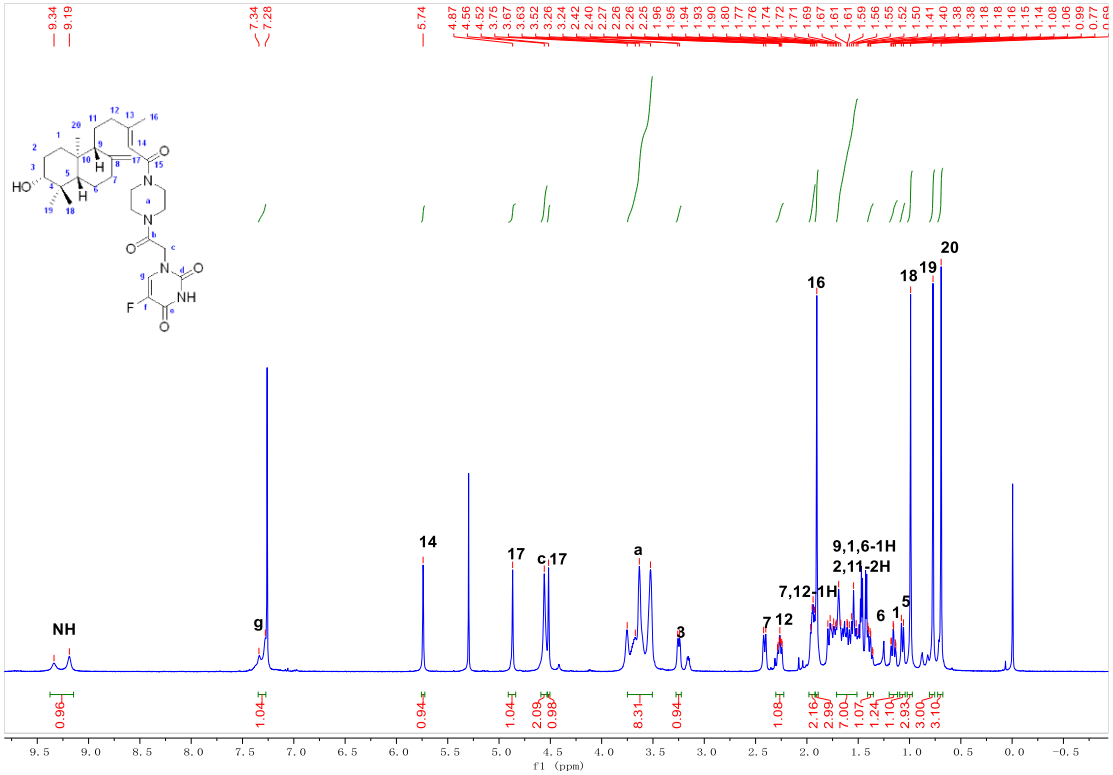
^{1}H NMR spectrum of compound **4**



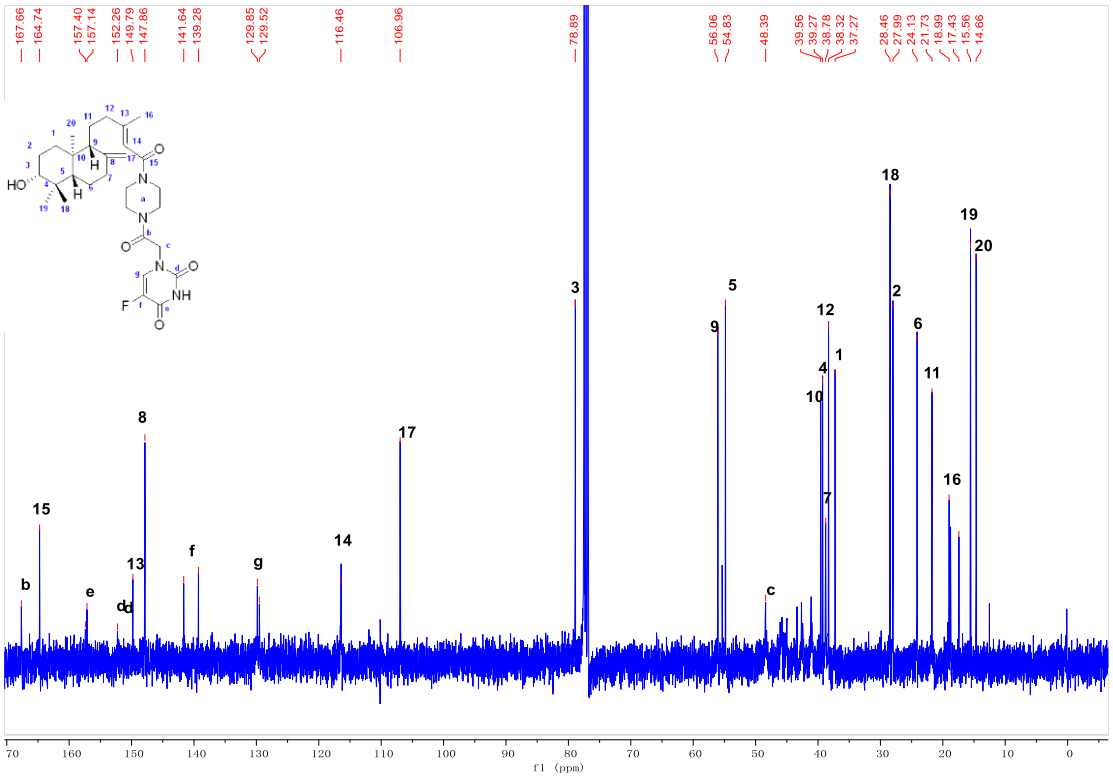
^{13}C NMR spectrum of compound **4**



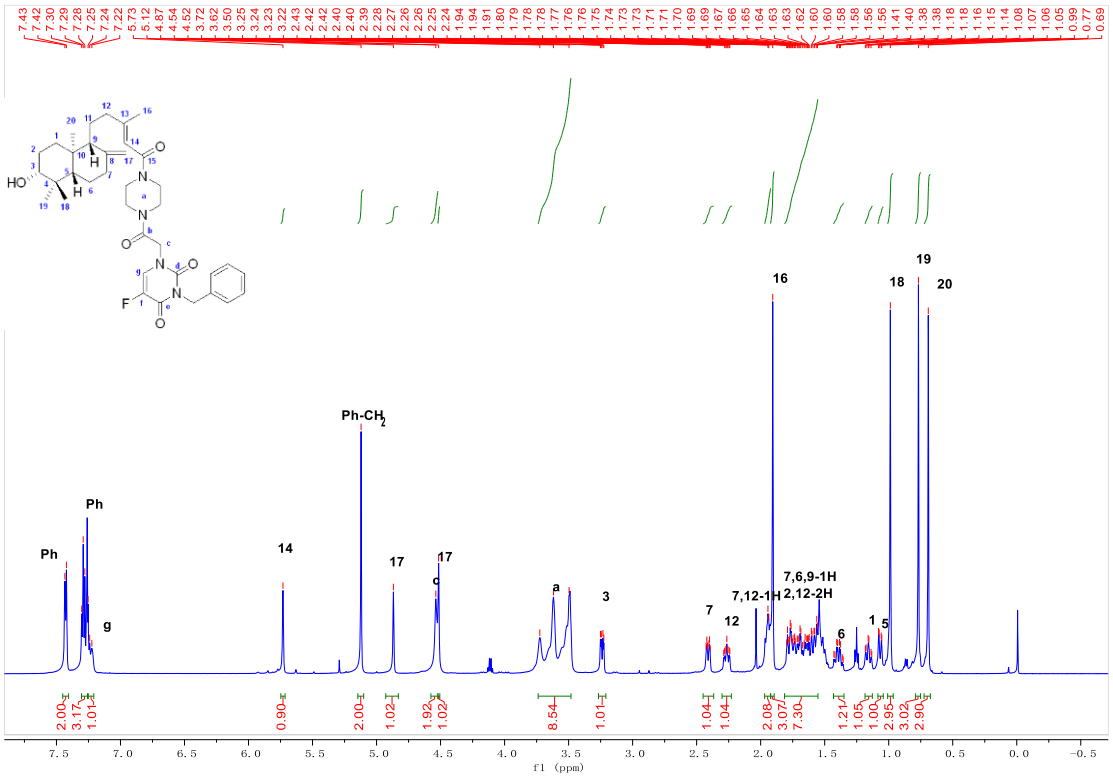
^{1}H NMR spectrum of compound **5**



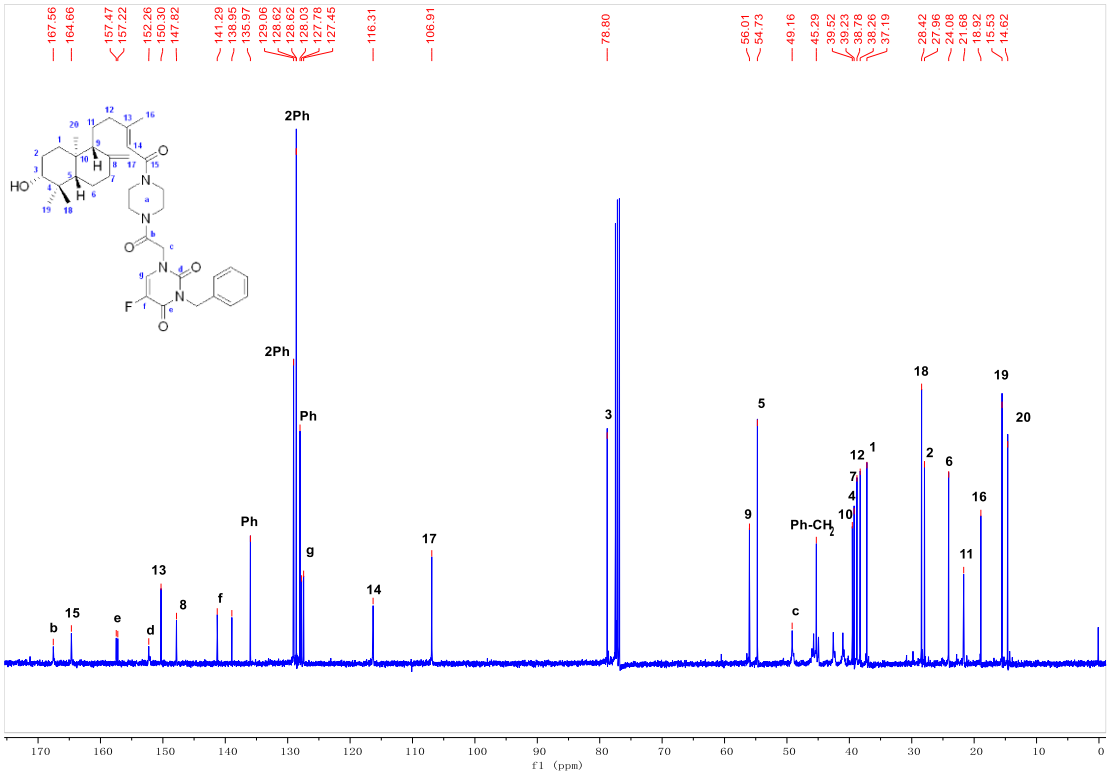
^{13}C NMR spectrum of compound **5**



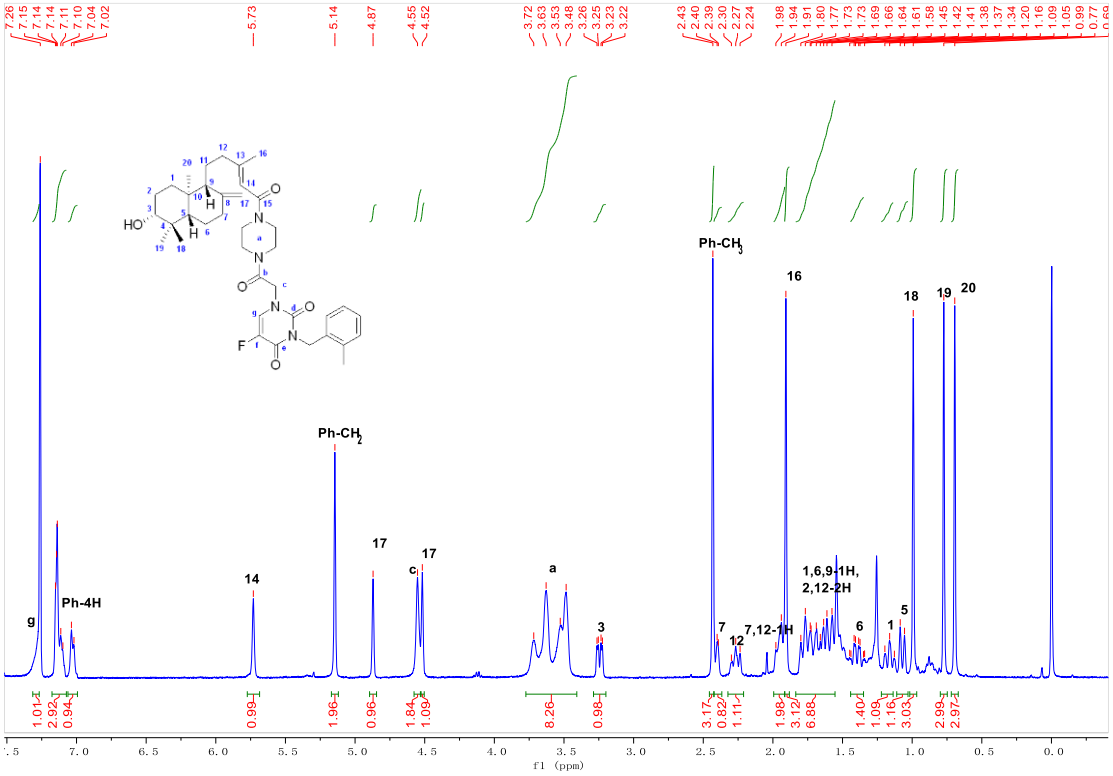
^{1}H NMR spectrum of compound **6a**



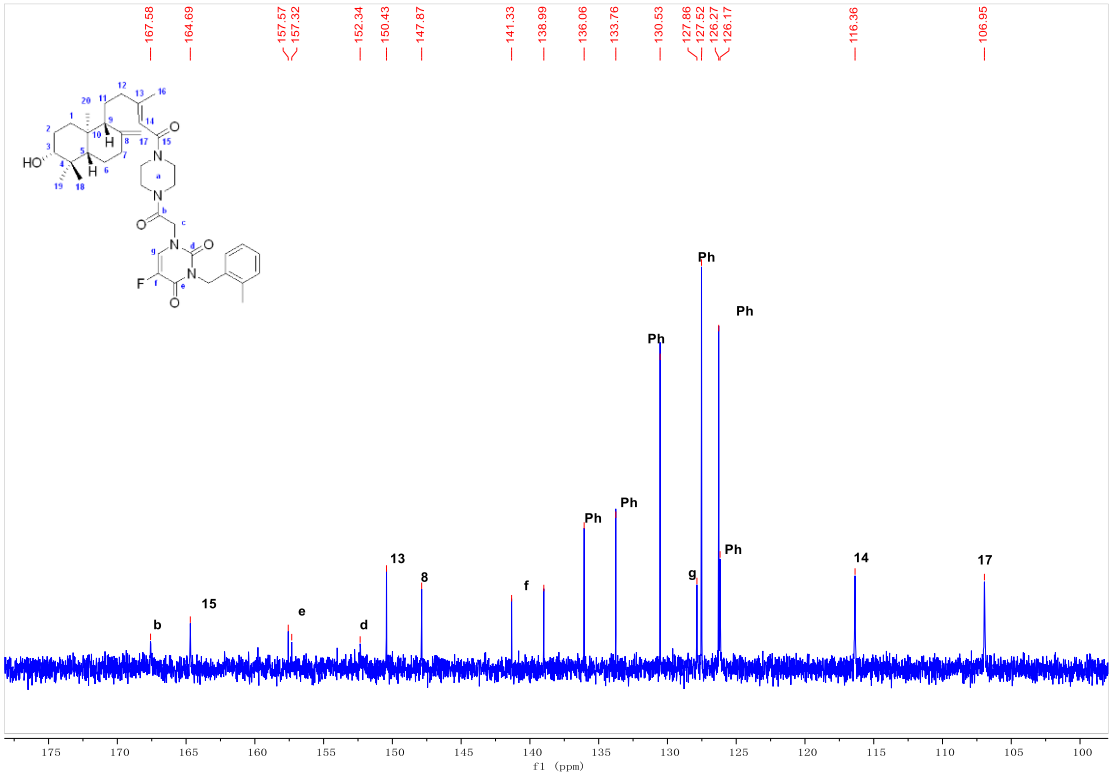
^{13}C NMR spectrum of compound **6a**



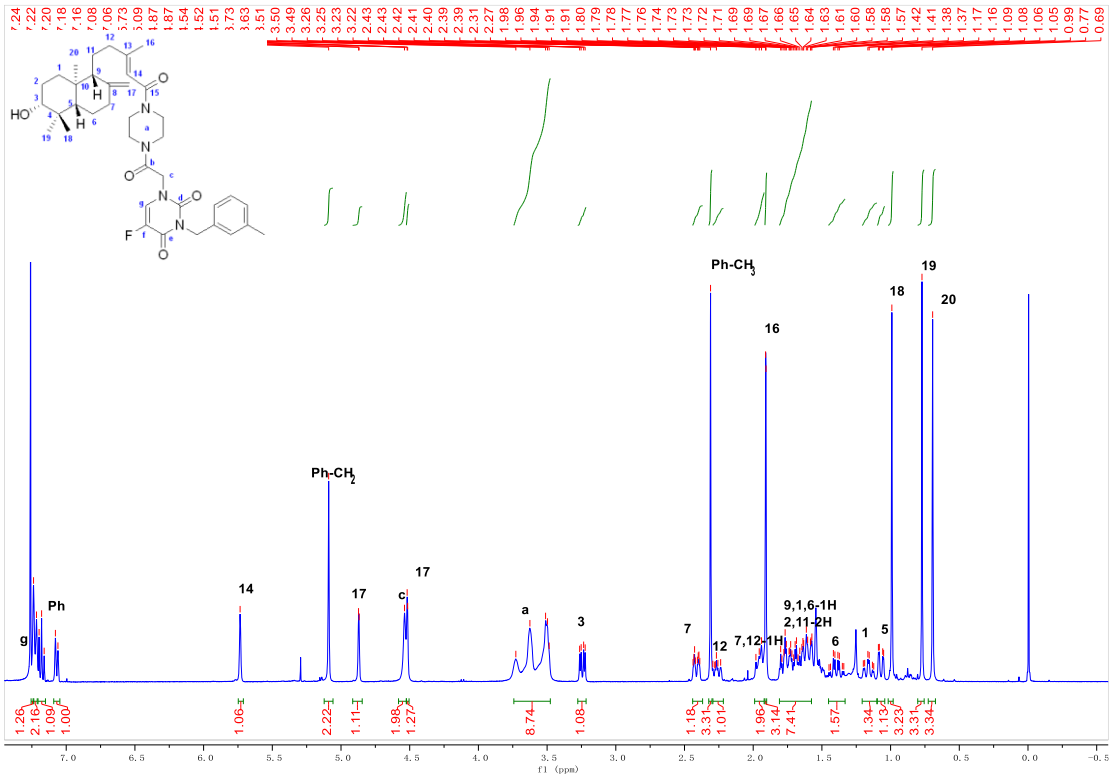
^{1}H NMR spectrum of compound **6b**



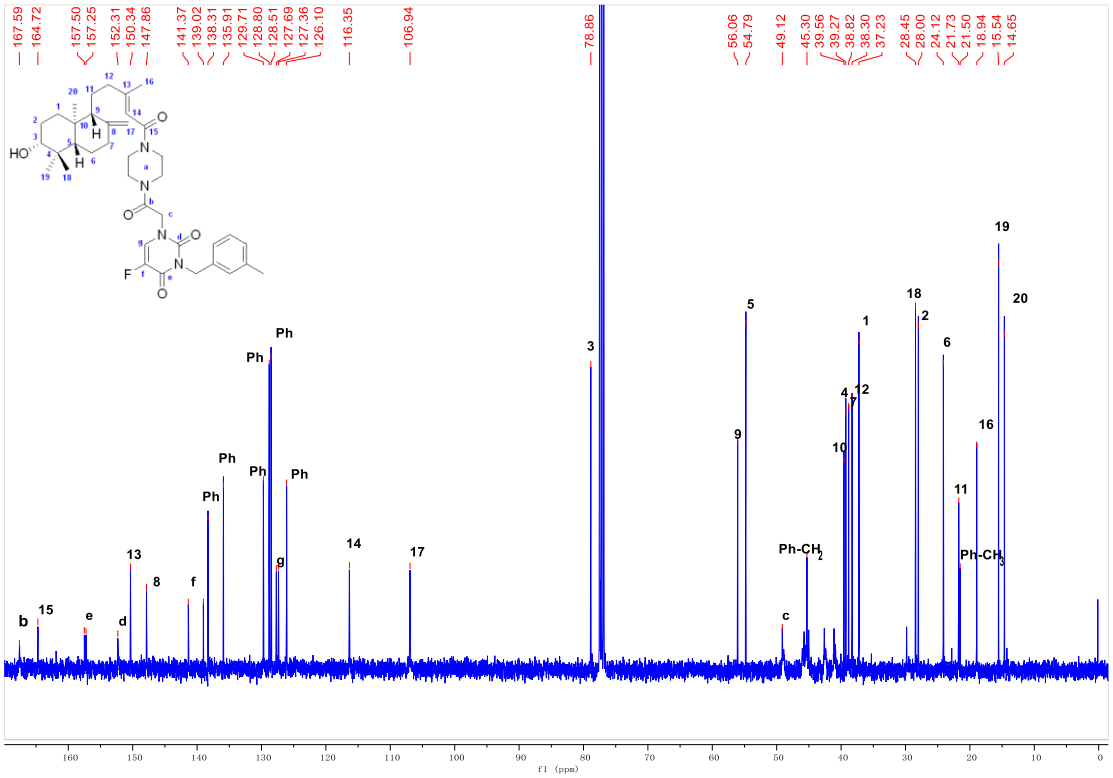
^{13}C NMR spectrum of compound **6b**



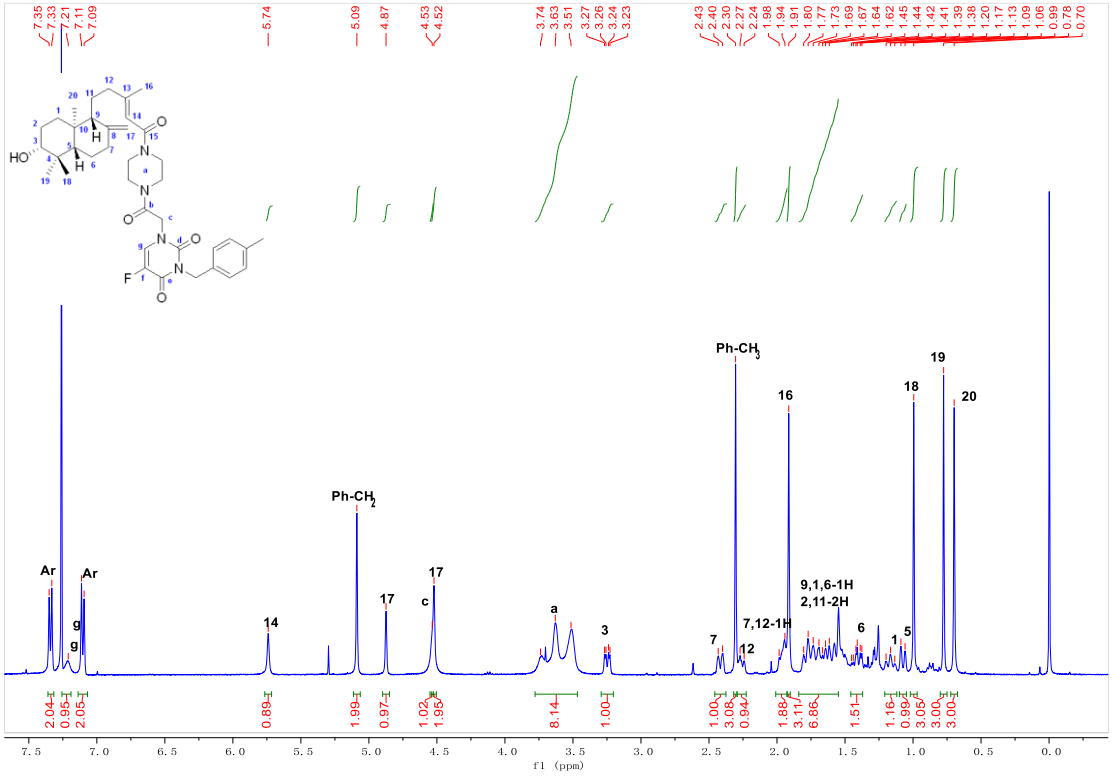
^{1}H NMR spectrum of compound **6c**



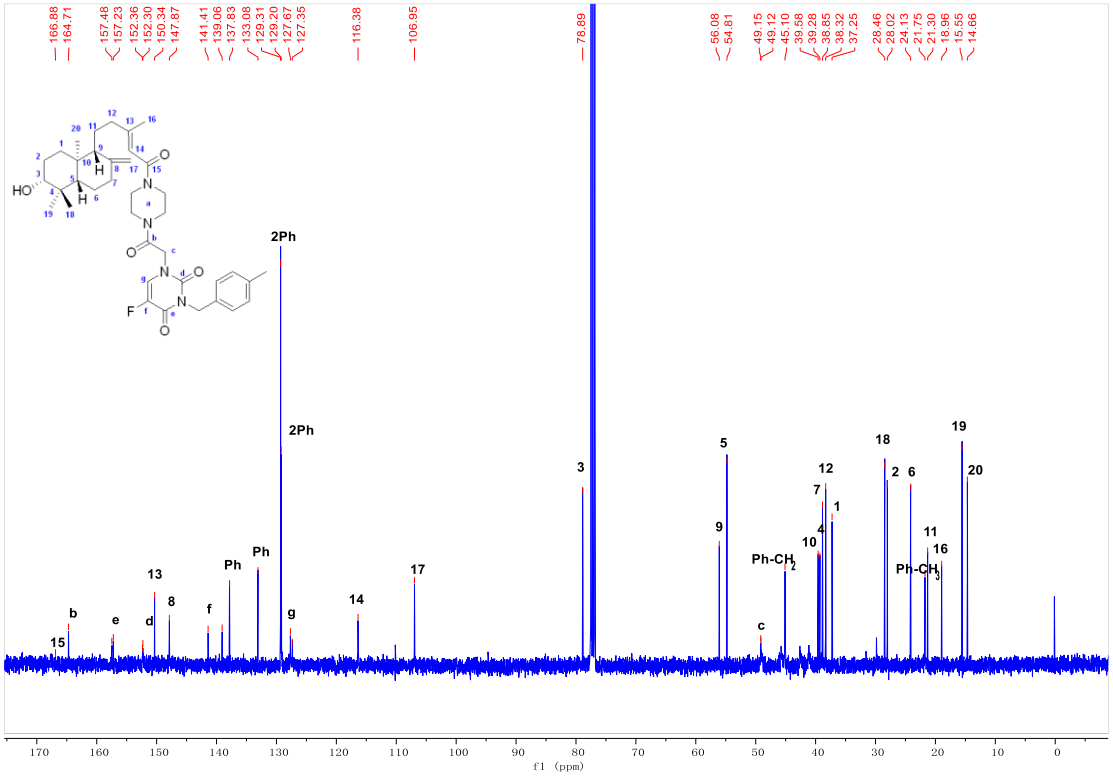
^{13}C NMR spectrum of compound **6c**



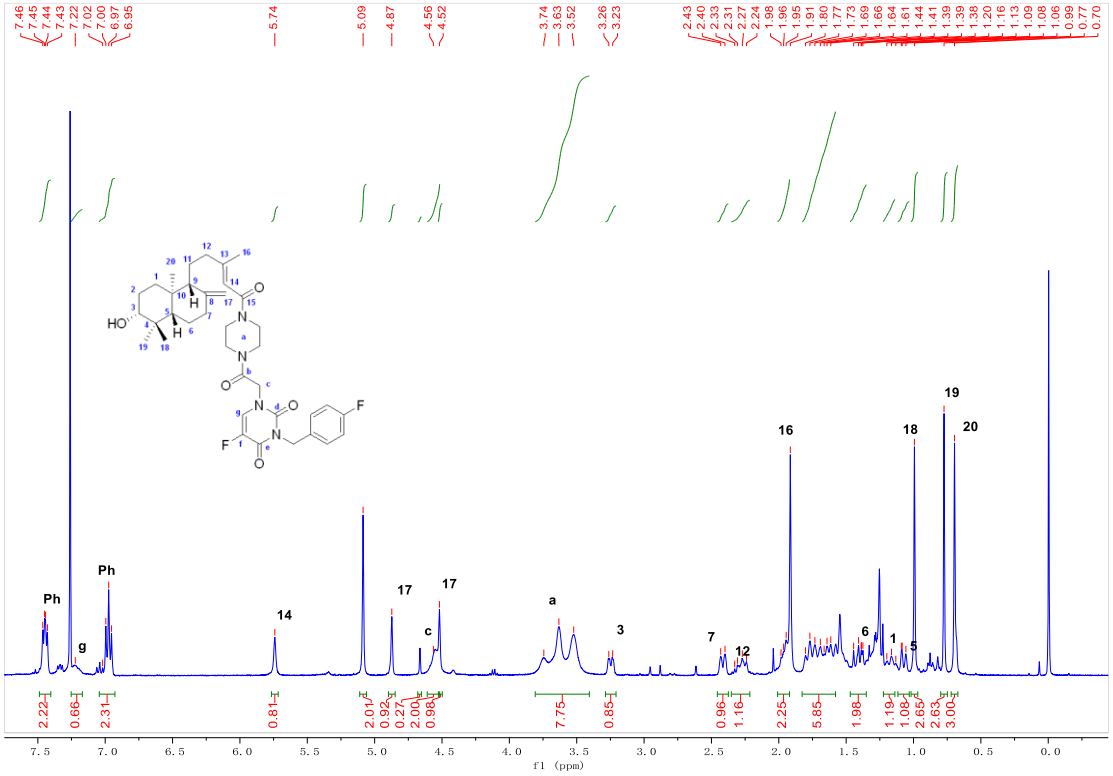
^{1}H NMR spectrum of compound **6d**



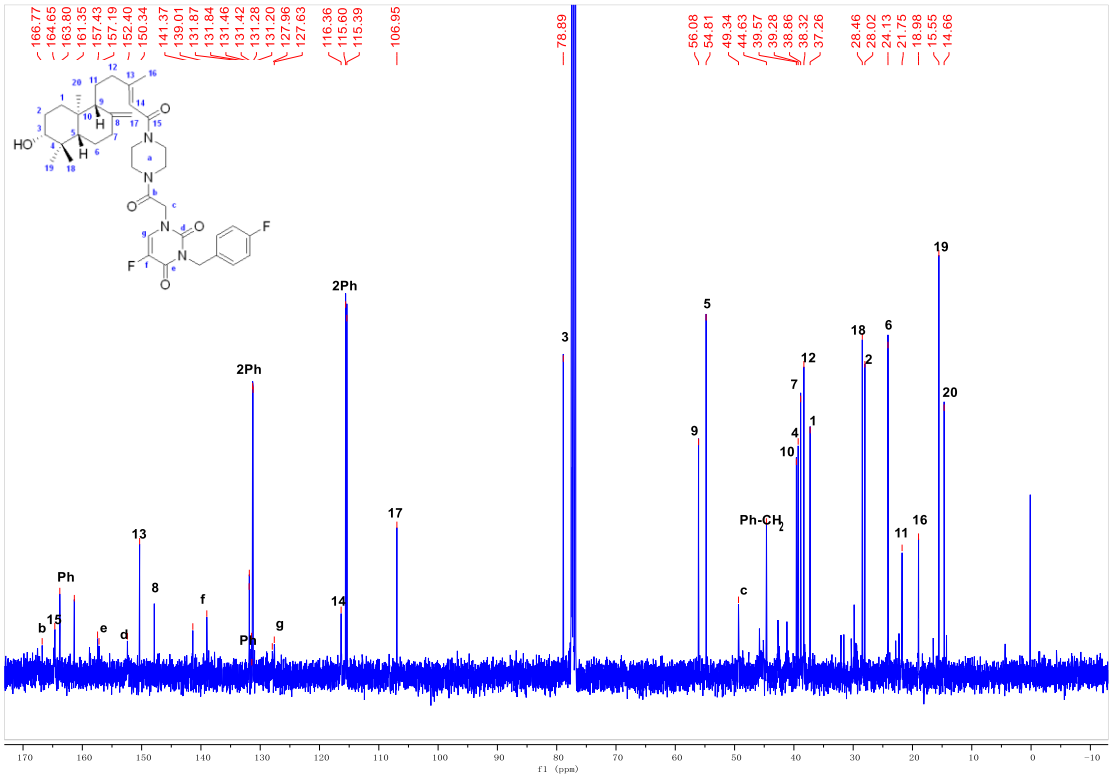
^{13}C NMR spectrum of compound **6d**



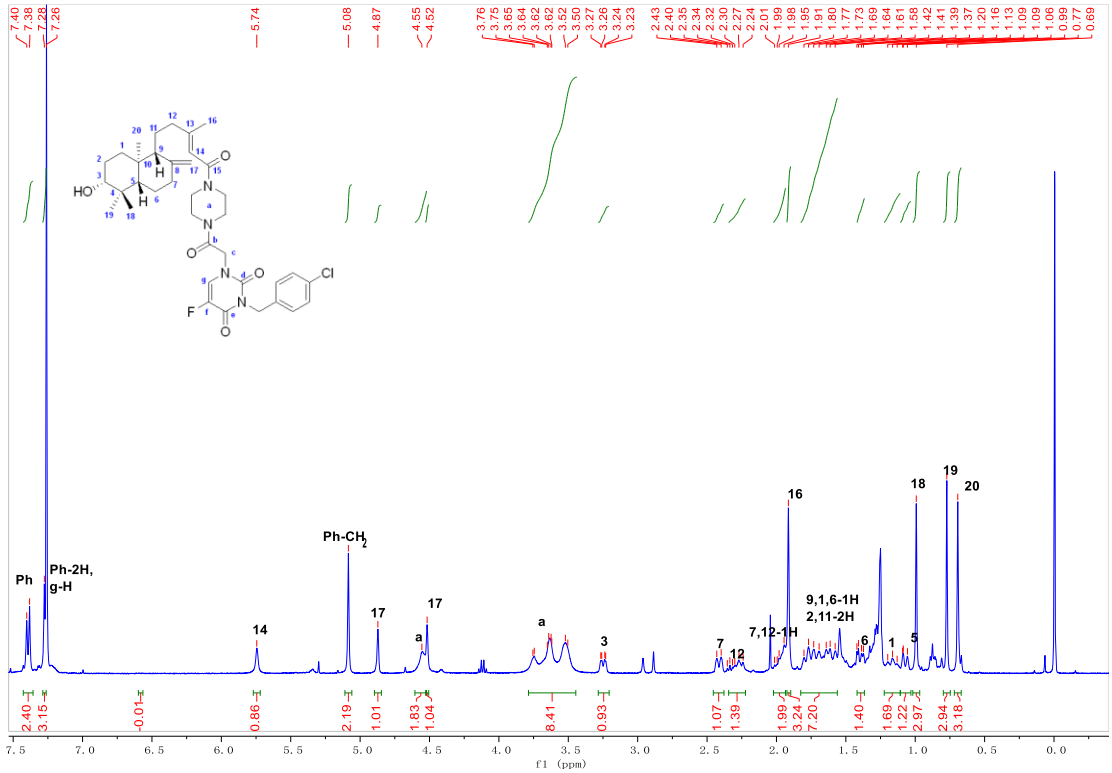
^{1}H NMR spectrum of compound **6e**



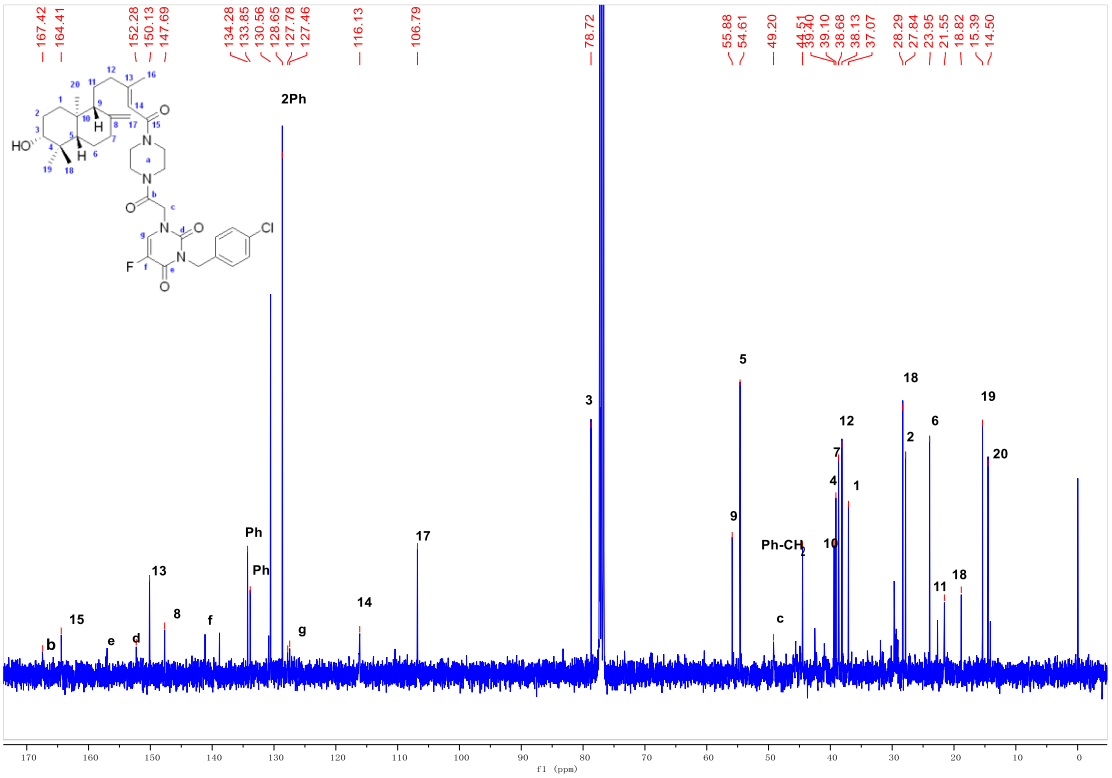
^{13}C NMR spectrum of compound **6e**



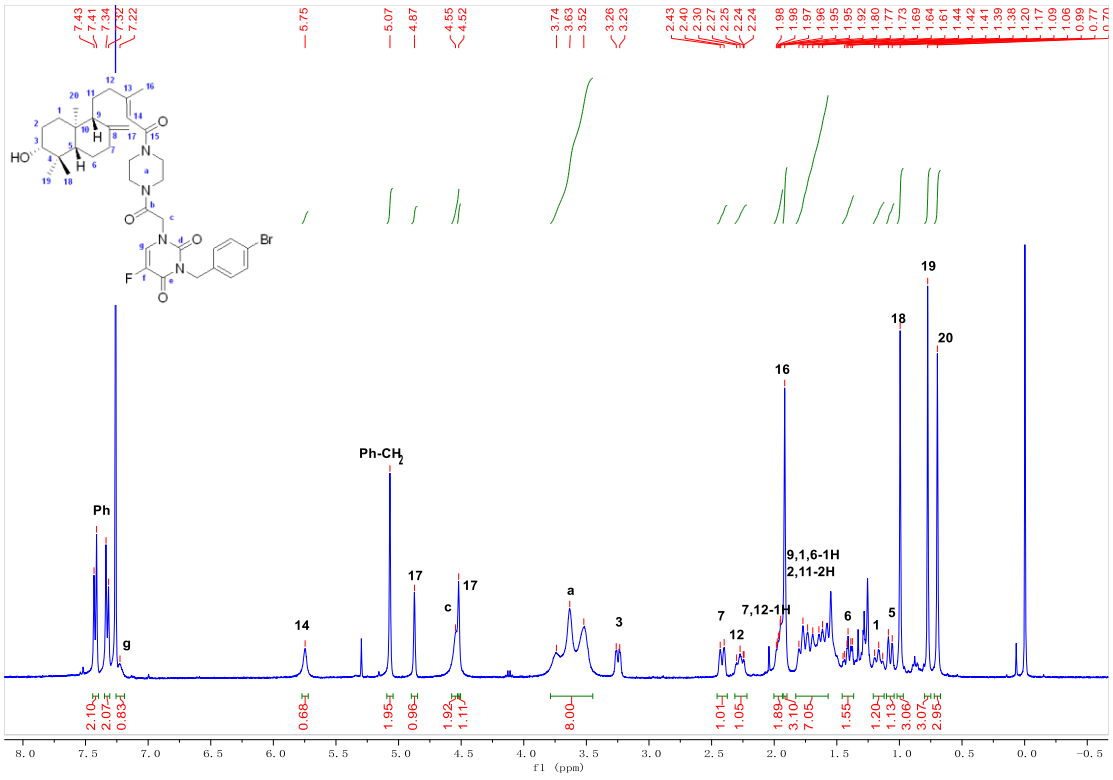
^{1}H NMR spectrum of compound **6f**



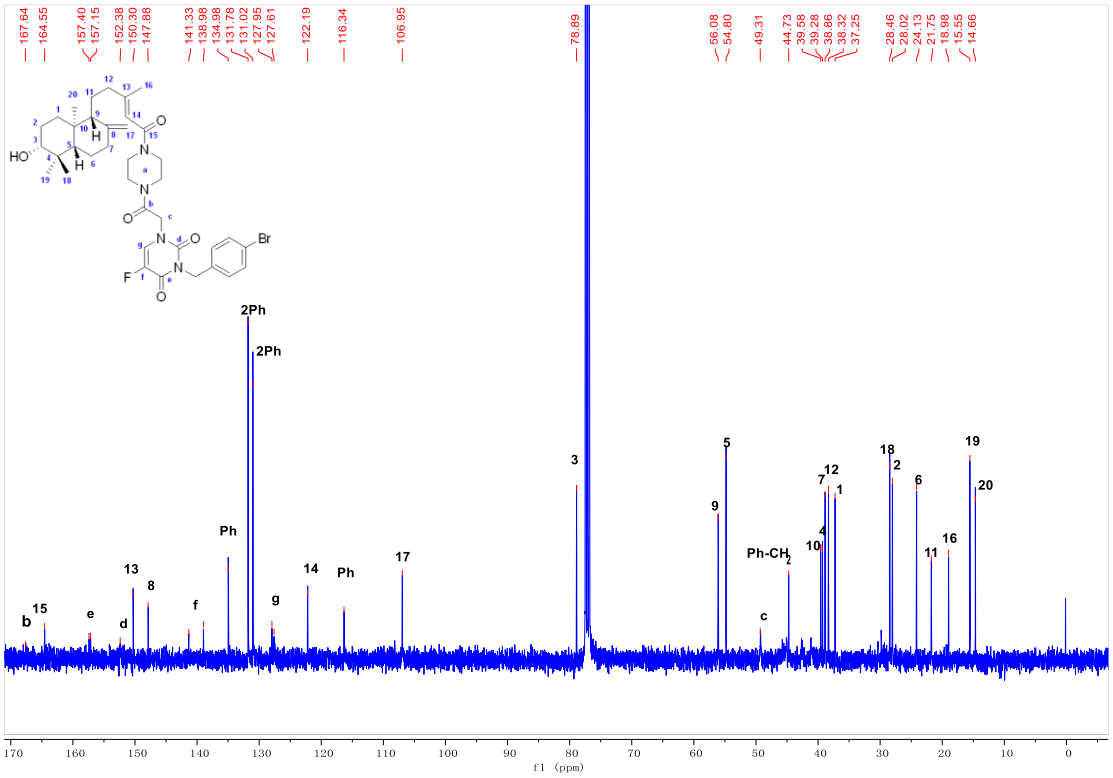
^{13}C NMR spectrum of compound **6f**



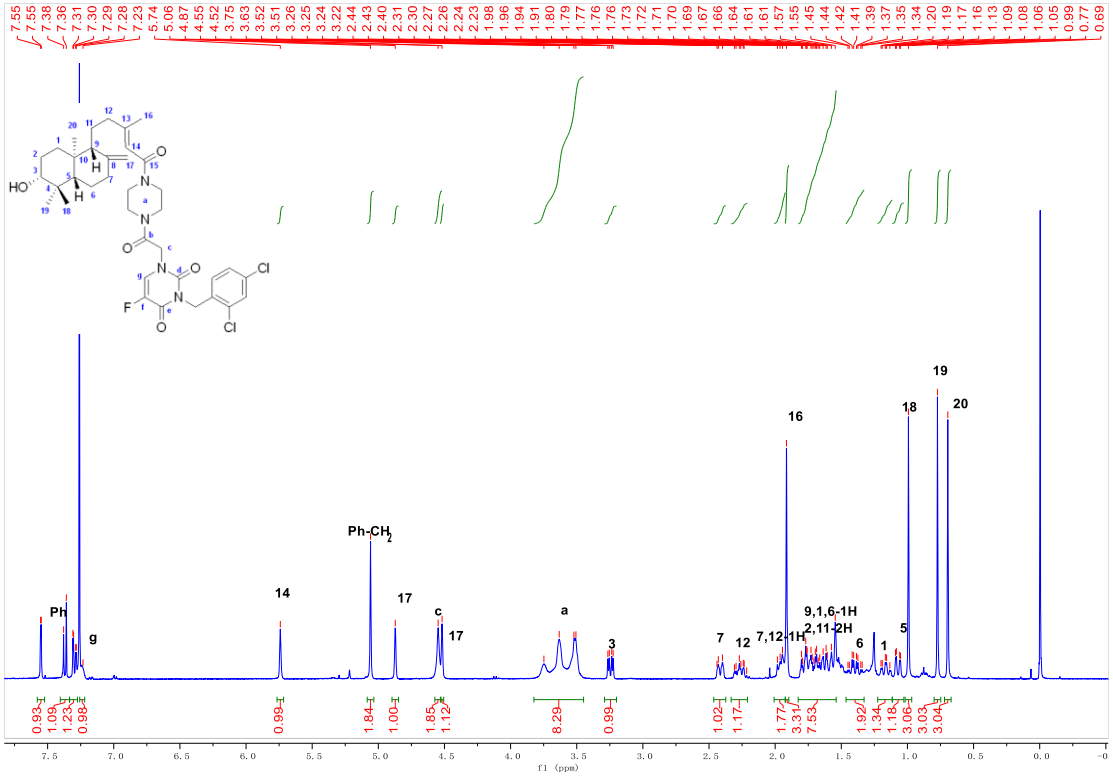
^{1}H NMR spectrum of compound **6g**



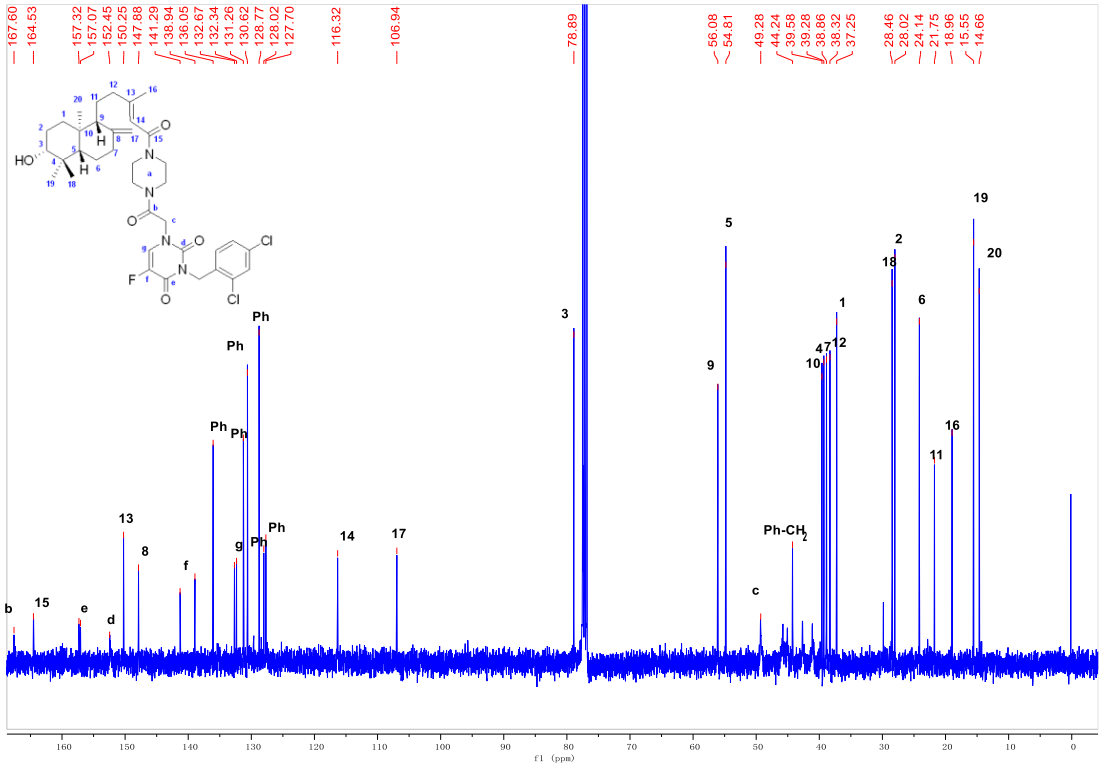
^{13}C NMR spectrum of compound **6g**



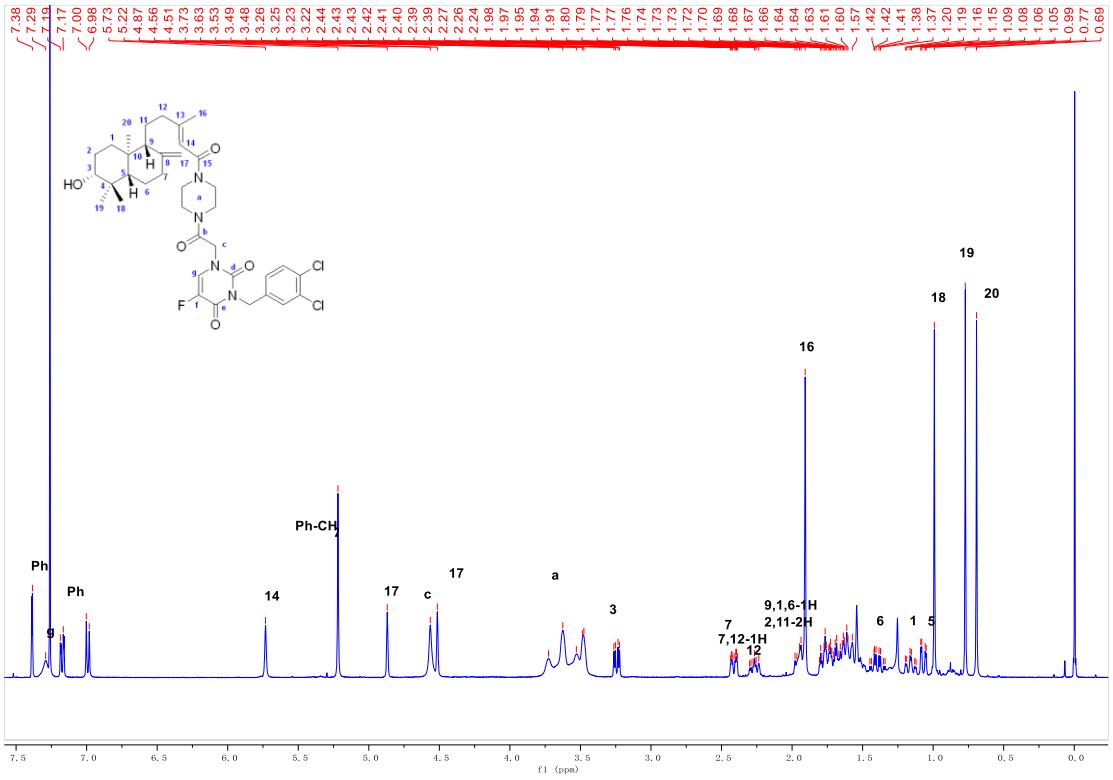
^{1}H NMR spectrum of compound **6h**



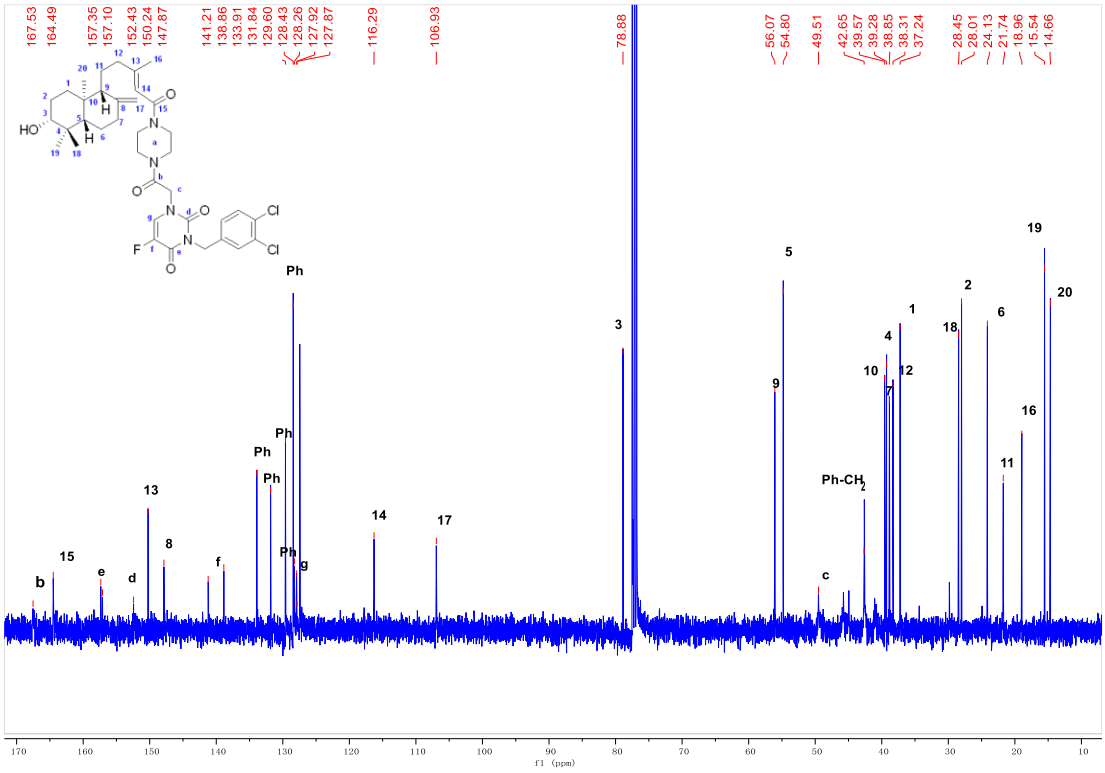
^{13}C NMR spectrum of compound **6h**



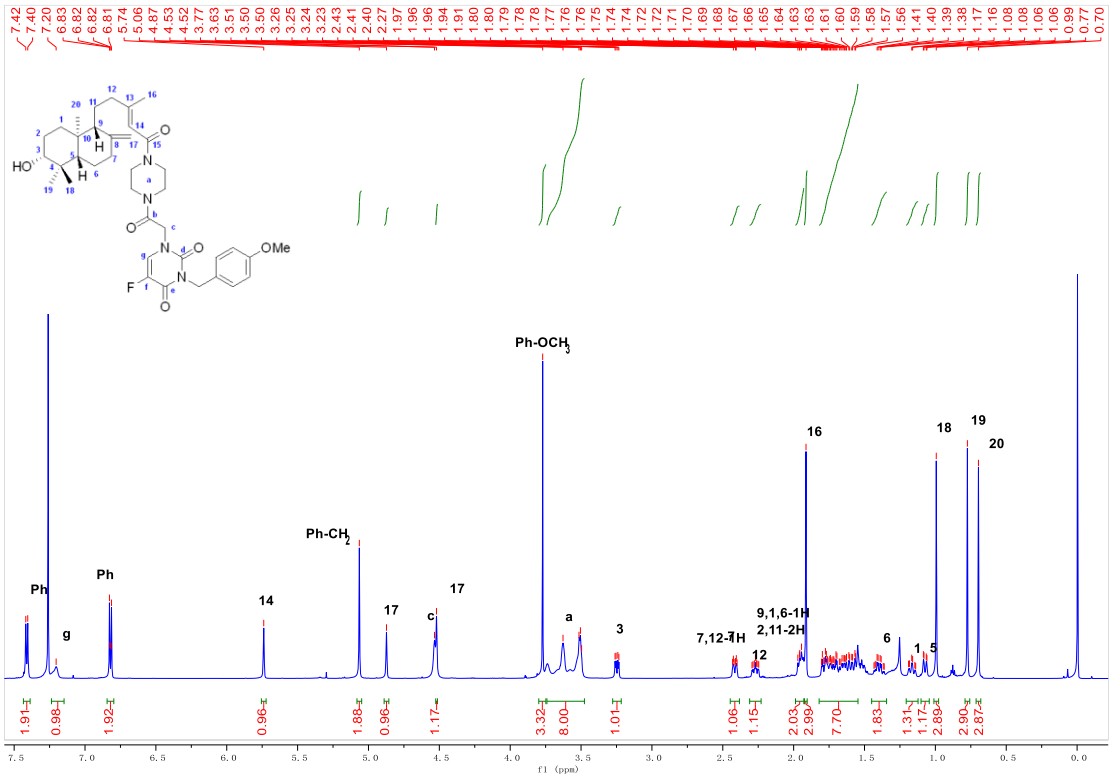
^{1}H NMR spectrum of compound **6i**



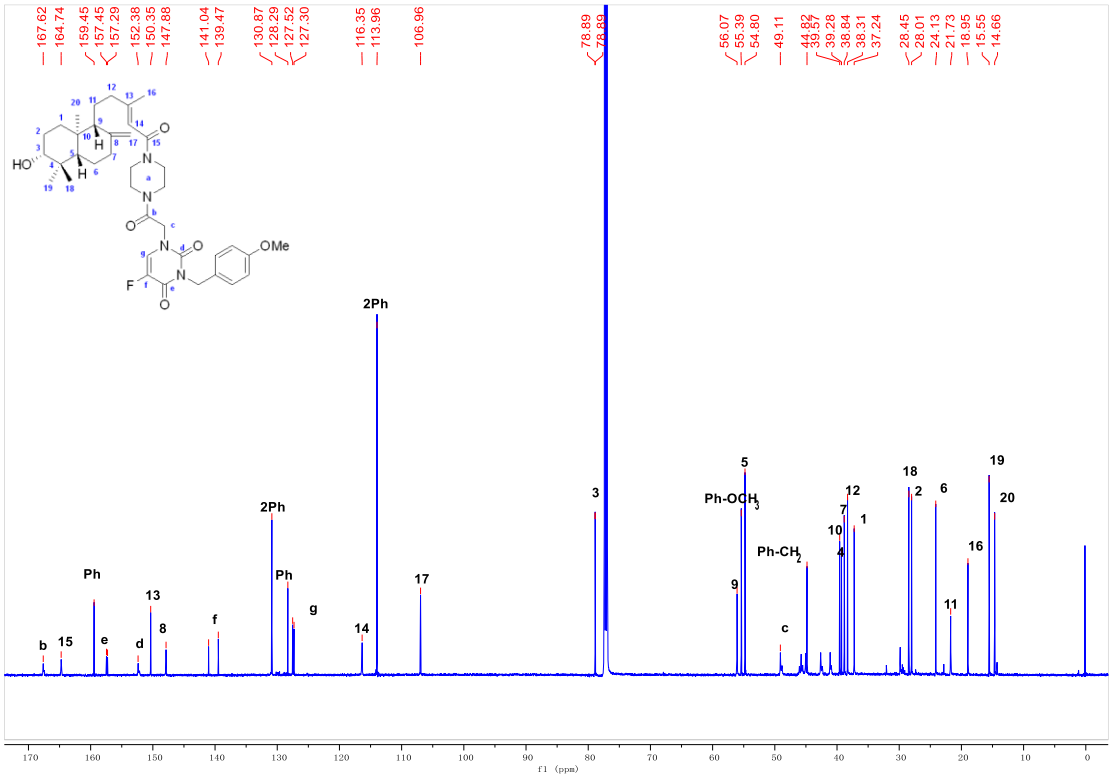
^{13}C NMR spectrum of compound **6i**



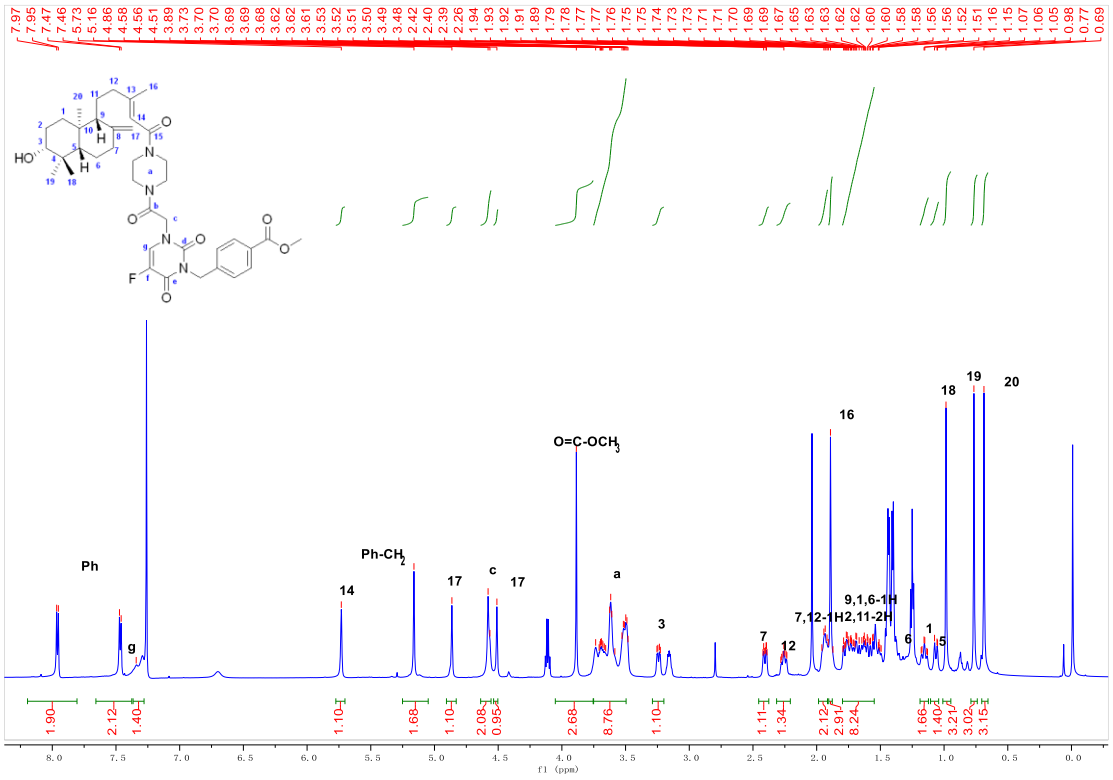
^{1}H NMR spectrum of compound **6j**



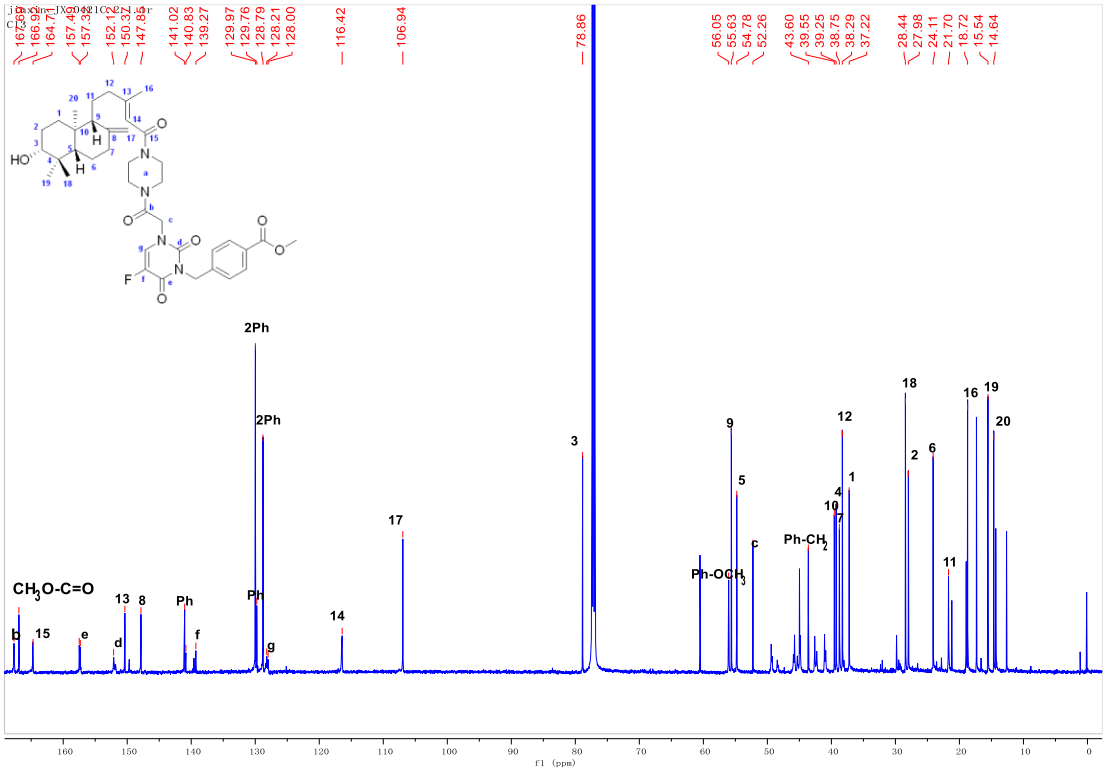
^{13}C NMR spectrum of compound **6j**



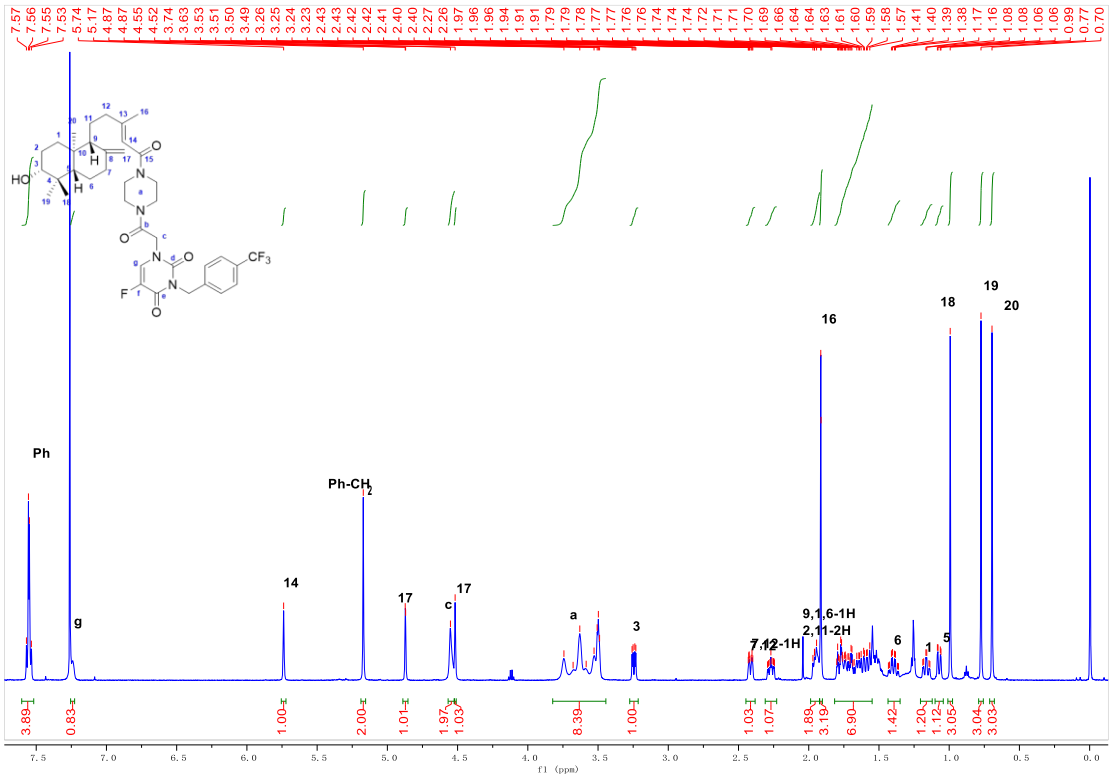
^{1}H NMR spectrum of compound **6k**



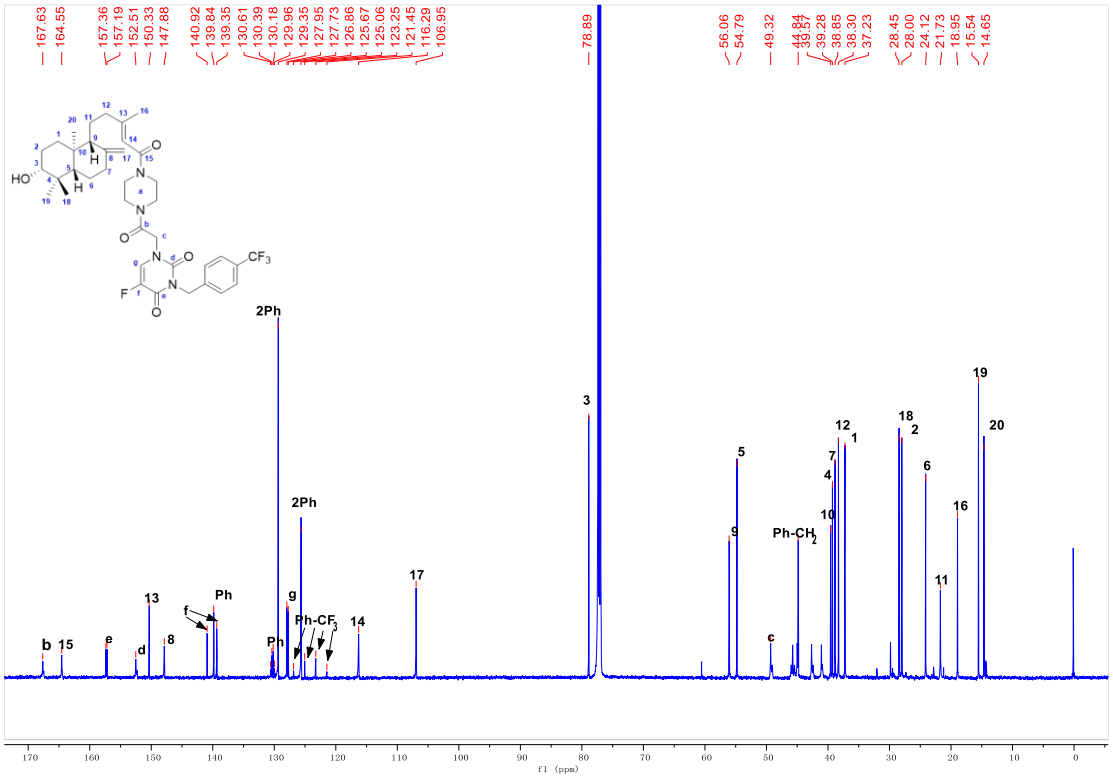
^{13}C NMR spectrum of compound **6k**



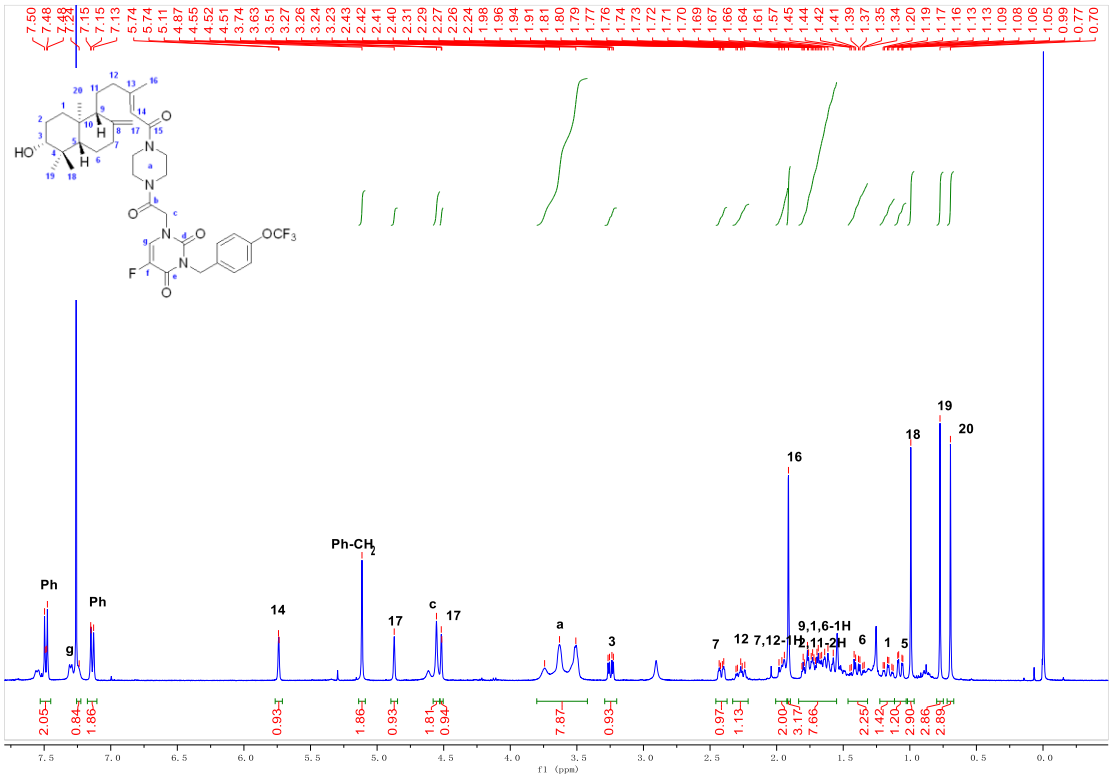
^{1}H NMR spectrum of compound **6l**



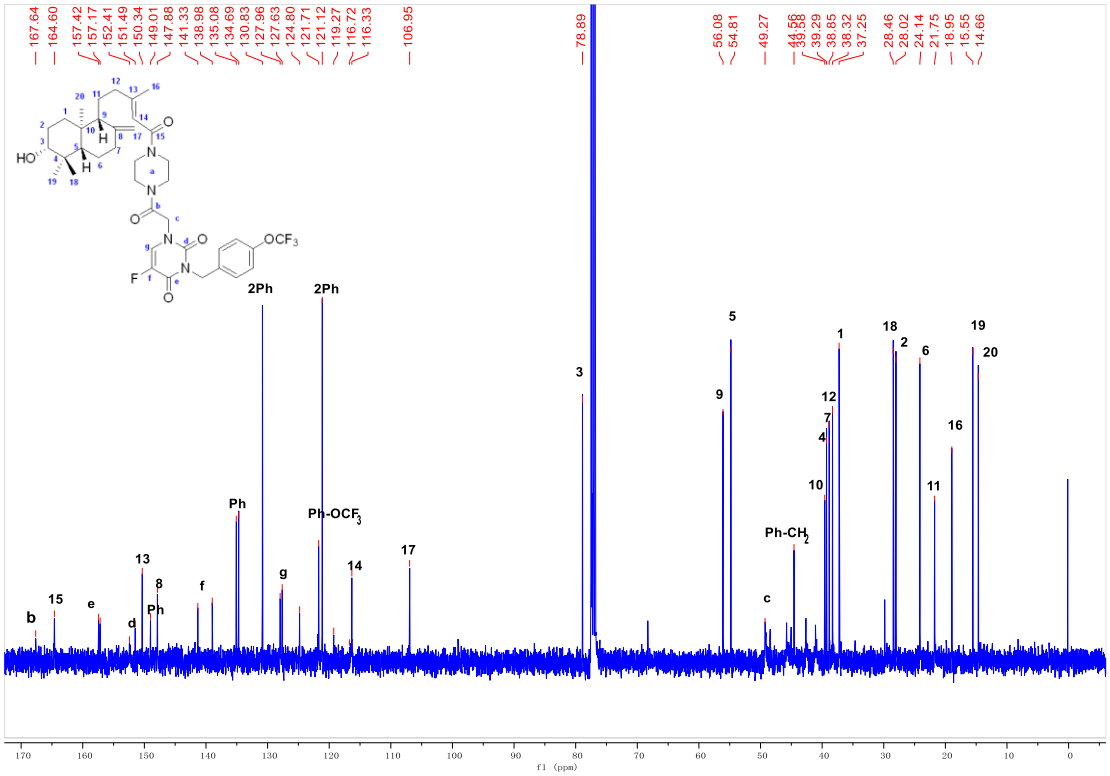
^{13}C NMR spectrum of compound **6l**



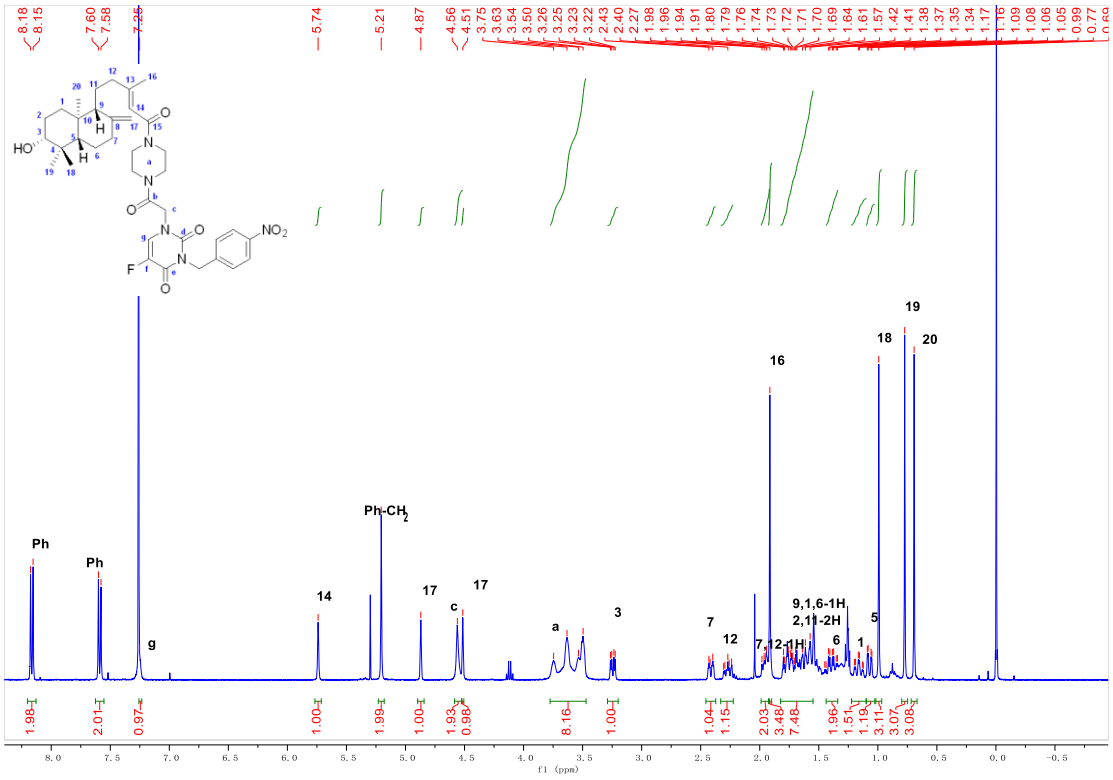
^{1}H NMR spectrum of compound **6m**



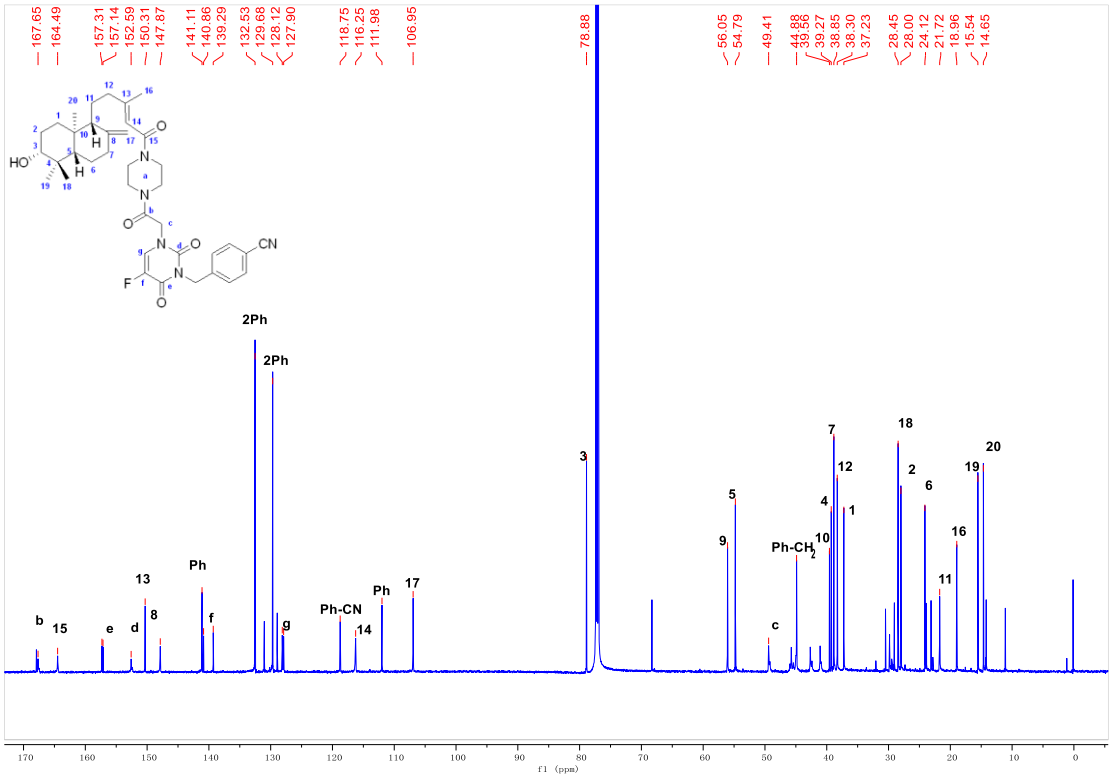
^{13}C NMR spectrum of compound **6m**



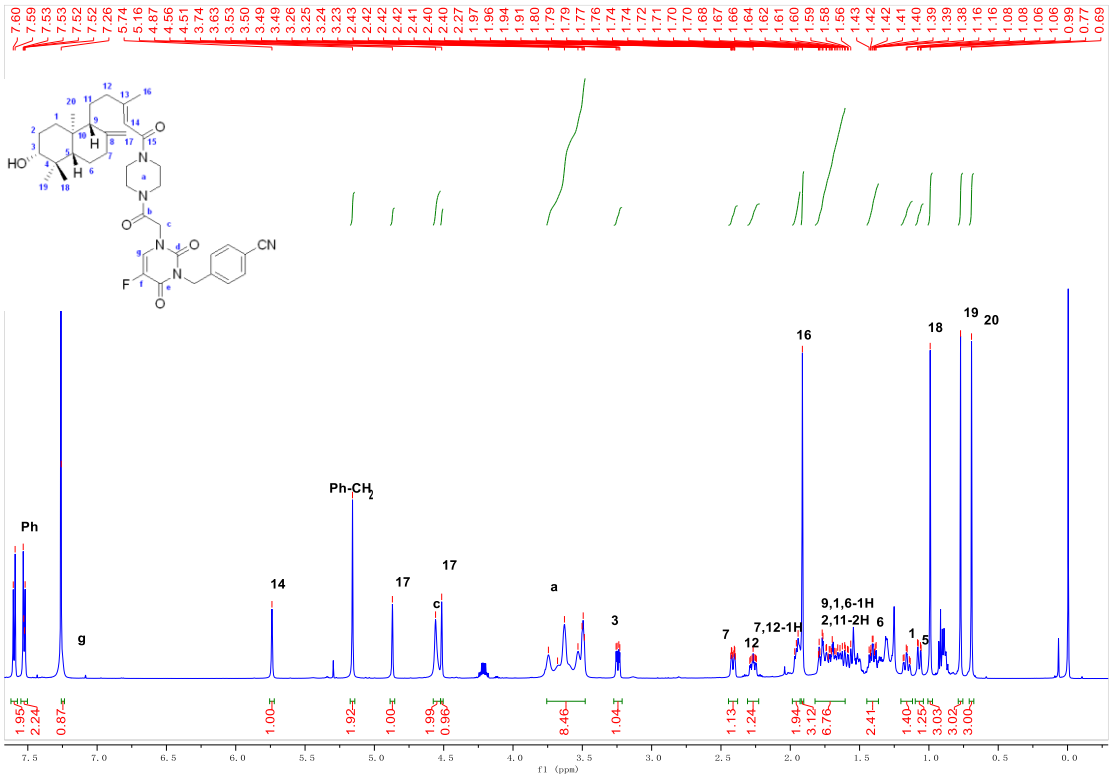
^{1}H NMR spectrum of compound **6n**



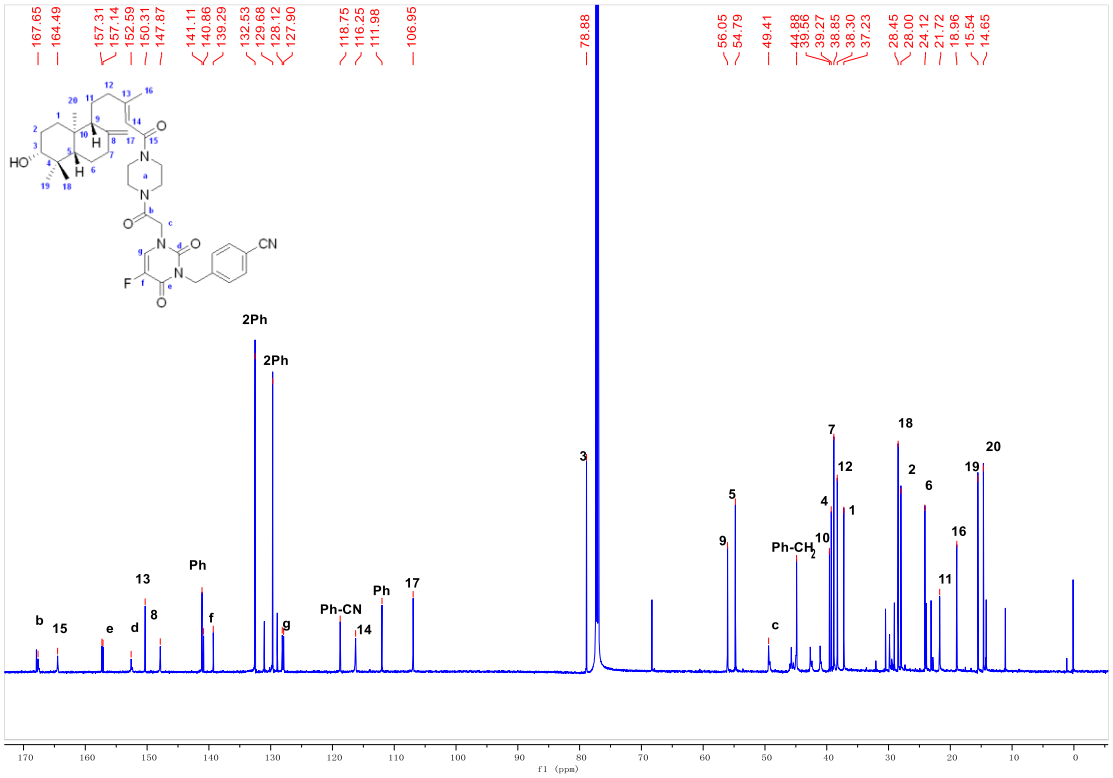
^{13}C NMR spectrum of compound **6n**



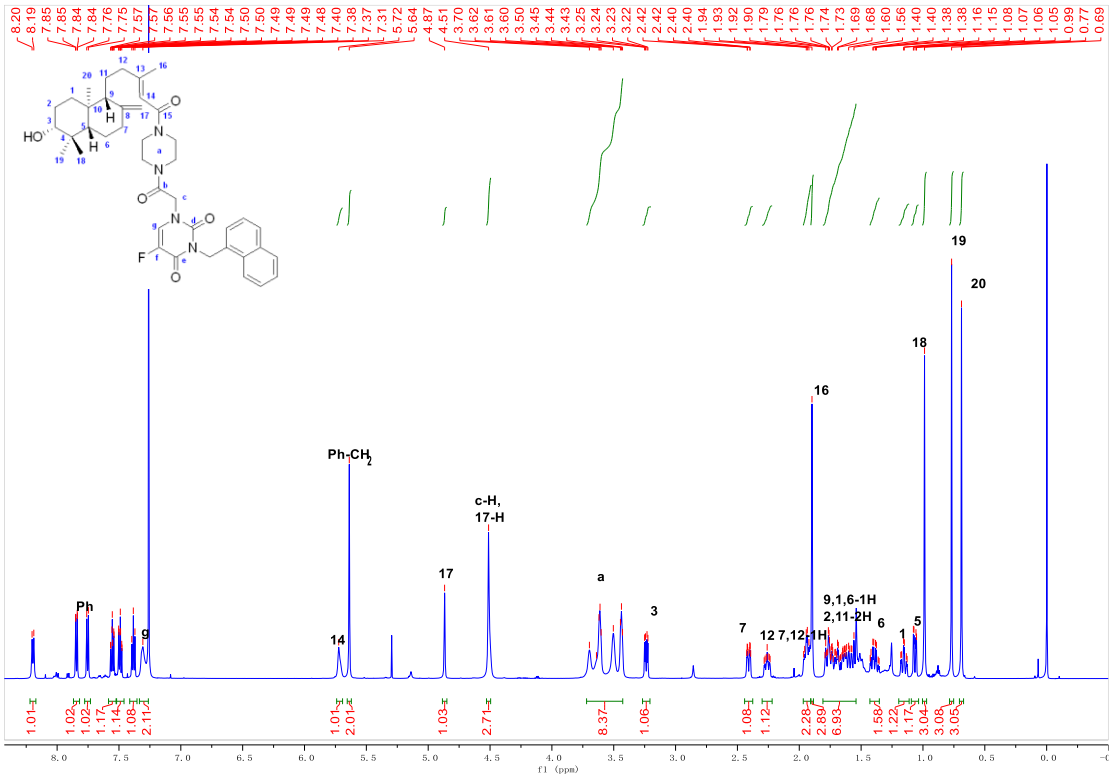
^{1}H NMR spectrum of compound **6o**



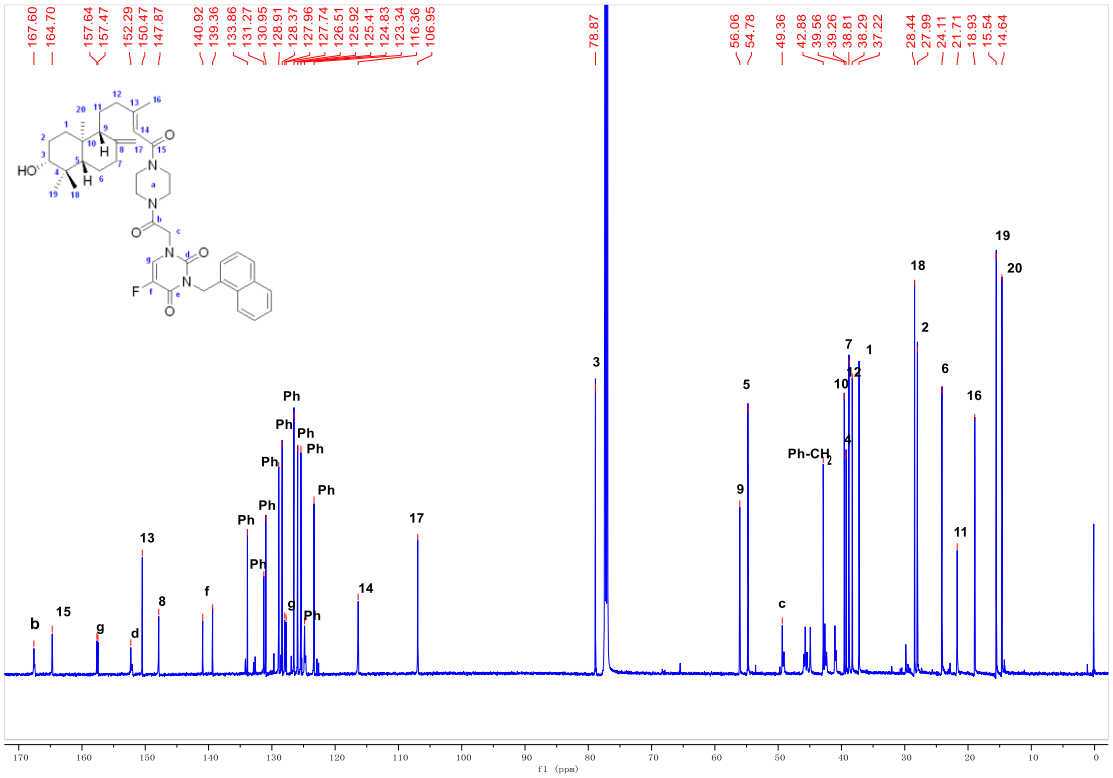
^{13}C NMR spectrum of compound **6o**



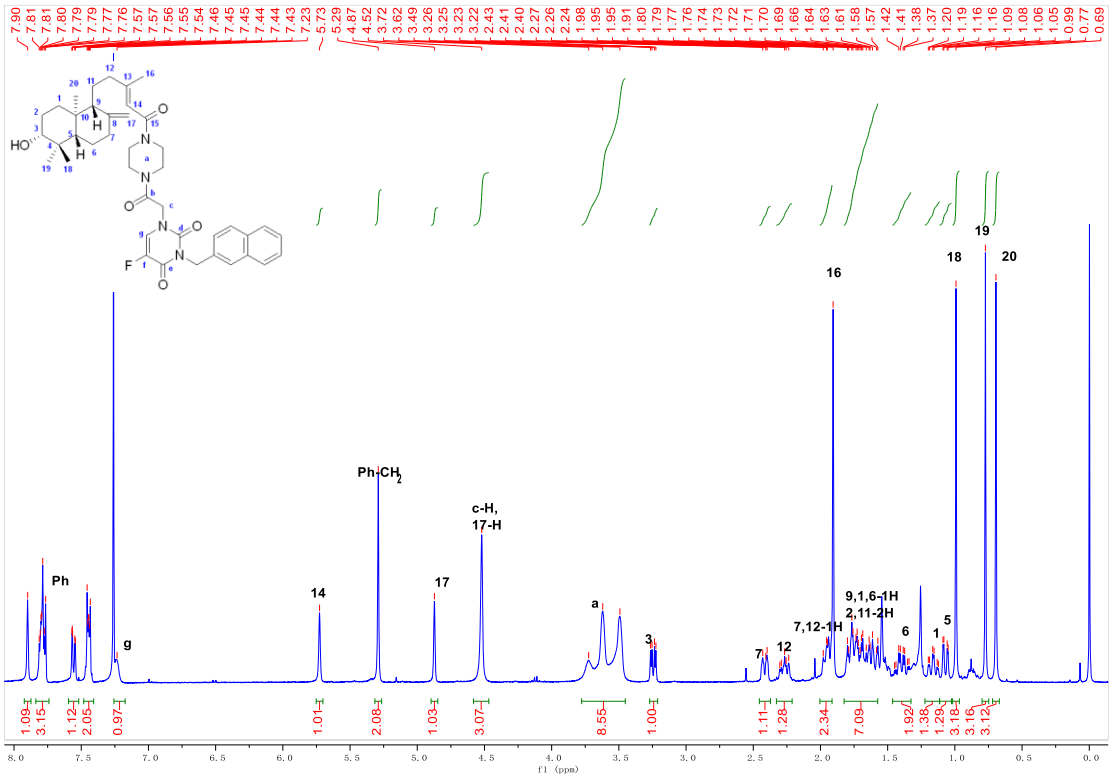
^{1}H NMR spectrum of compound **6p**



^{13}C NMR spectrum of compound **6p**



^{1}H NMR spectrum of compound **6q**



^{13}C NMR spectrum of compound **6q**