Supporting Information

Dihydropyrimidine-2-thione derivatives as SARS-CoV-2 Main Protease inhibitors: SAR, lead optimization and in-vitro profiling

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Characterization data of Intermediate compounds

2.2.1. Ethyl 2-thioxo-6-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate (6a)

Cream white solid, Yield = 79%, m.p. 231-233 °C; R_f = 0.43; (n-hexane/EA; 3 : 1); HPLC purity = 97.2 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 12.7 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H, py-NH), 8.54 (s, 1H, py-NH), 7.74 (d, *J*= 8.1 Hz, -2H, ArH), 7.31 (d, *J*= 7.60 Hz, -2H, ArH), 5.28 (s, 1H, -CH), 3.9 (q, 2H, CH_2), 1.8 (t, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 132.5 (q, *J*= 36.6 Hz, -C-CF_3), 131.7 (q, *J*= 36.4 Hz, -C-CF_3), 122.4 (q, *J*= 273 Hz, -CF_3), 51.8, 14.3. Analysis calculated for $C_{15}H_{12}F_6N_2O_2S$; C, 45.23; H, 3.04; F, 28.62; N, 7.03; O, 8.03; S, 8.05; Found C, 45.04; H, 3.03; F, 28.62; N, 7.05; O, 8.03; S, 8.05; LCMS: m/z = 399.0 $[M + H]^+$

2.2.2. Ethyl 4-(4-nitrophenyl)-2-thioxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6b)

Brownish solid, Yield = 86%, m.p. 241-243 °C; R_f = 0.47; (n-hexane/EA; 3 : 1); HPLC purity = 97.8 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 9.7 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H, py-NH), 8.47 (s, 1H, py-NH), 7.81 (d, *J*= 7.6 Hz, -2H, ArH), 7.33 (d, *J*= 8.1 Hz, -2H, ArH), 5.24 (s, 1H, -CH), 3.7 (q, 2H, CH_2), 2.1 (t, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.7, 166.2, 148.0, 144.2, 134.3, 134.0, 133.4 (q, *J*= 36.3 Hz, -C-CF_3), 127.9, 124.9, 122.7, 102.2, 60.1, 51.6, 14.3. Analysis calculated for $C_{14}H_{12}F_3N_3O_4S$; C, 44.80; H, 3.22; F, 15.19; N, 11.20; O, 17.05; S, 8.54; Found C, 44.62; H, 3.23; F, 15.19; N, 11.23; O, 17.05; S, 8.54; LCMS: m/z = 376.0 $[M + H]^+$

2.2.3. Ethyl 4-(4-(methoxycarbonyl)phenyl)-2-thioxo-6-(trifluoromethyl)-1,2,3,4-tetra-hydropyrimidine-5-carboxylate (6c)

Greyish solid, Yield = 88%, m.p. 253-255 °C; R_f = 0.44; (n-hexane/EA; 3 : 1); HPLC purity = 98.6% (C18 RP, Acetonitrile / H_2O-80:20), T_R = 9.4 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H, py-NH), 8.51 (s, 1H, py-NH), 7.83 (d, *J*= 7.7 Hz, -2H, ArH), 7.35 (d, *J*= 7.9 Hz, -2H, ArH), 5.29 (s, 1H, -CH), 3.84 (s, 3H, OCH_3), 3.3 (q, 2H, CH_2), 2.6 (t, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.7, 168.0, 166.2, 146.0, 134.3, 134.0, 131.2 (q, *J*= 36.9 Hz, -C-CF_3), 130.4, 129.9, 126.9, 124.9, 103.0, 60.1, 52.1, 51.3, 14.3. Analysis calculated for $C_{16}H_{15}F_3N_2O_4S$; C, 49.48; H,

3.89; F, 14.68; N, 7.21; O, 16.48; S, 8.26; Found C, 49.67; H, 3.86; F, 14.68; N, 7.19; O, 16.48; S, 8.26; LCMS: m/z = 389.0 $[M + H]^+$

2.3.1 (2-Thioxo-6-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carbonyl)-L-glutamic acid (8a)

Pale green solid, Yield = 68%, m.p. 244-246 °C; R_f = 0.42; (DCM/MeOH; 5 : 1); HPLC purity = 97.5% (C18 RP, Acetonitrile / H_2O-80:20), T_R = 9.3 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H, COOH), 11.75 (s, 1H, COOH), 9.38 (s, 1H, py-NH), 8.41 (s, 1H, py-NH), 8.15 (s, 1H, py-NH), 7.81 (d, *J*= 8.2 Hz, -2H, ArH), 7.27 (d, *J*= 7.1 Hz, -2H, ArH), 5.44 (d, *J*= 3.36 Hz, 1H, -CH), 4.50-4.41 (m, 1H, glu), 2.25-2.19 (m, 2H, glu), 1.98-1.93 (m, 2H, glu). ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.6, 177.2, 174.3, 167.1, 143.0, 135.8, 135.2-134.2 (q, *J*= 32.2 Hz, -C-CF_3), 134.5-133.1 (q, *J*= 36.2 Hz, -C-CF_3), 128.7, 127.7, 126.5, 125.2, 124.7, 122.1 (q, *J*= 271.4 Hz, -CF_3), 94.8, 53.2, 52.0, 31.2, 26.8. Analysis calculated for $C_{18}H_{15}F_6N_3O_5S$; C, 43.29; H, 3.03; F, 22.83; N, 8.41; O, 16.02; S, 6.42; Found C, 43.42; H, 3.04; F, 22.83; N, 8.37; O, 16.02; S, 6.42; LCMS: m/z = 500.0 $[M + H]^+$

2.3.2. (2-Thioxo-6-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carbonyl)-L-aspartic acid (8b)

Off white solid, Yield = 64%, m.p. 242-244 °C; R_f = 0.43; (DCM/MeOH; 5 : 1); HPLC purity = 97.8 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 8.4 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H, COOH), 11.81 (s, 1H, COOH), 9.36 (s, 1H, py-NH), 8.40 (d, *J*= 6.16 Hz 1H, py-NH), 8.15 (d, *J*= 4.9Hz, -NH), 7.81 (d, *J*= 8.32 Hz, -2H, ArH), 7.27 (d, *J*= 8.23 Hz, -2H, ArH), 5.43 (d, *J*= 3.56 Hz 1H, -CH), 4.43-4.37 (m, 1H, glu), 3.53-2.33 (m, 2H, glu).^{13}C NMR (100 MHz, DMSO-d_6) δ 173.9, 173.4, 172.9, 165.9, 143.9, 135.9, 135.6, 133.3 (q, *J*= 36.1 Hz, -C-CF_3), 131.8 (q, *J*= 36.5 Hz, -C-CF_3), 128.7, 127.7, 126.5, 125.2, 124.7, 122.4 (q, *J*= 273.8 Hz, -CF_3), 95.0, 52.0, 50.5, 36.2. Analysis calculated for $C_{17}H_{13}F_6N_3O_5S$; C, 42.07; H, 2.70; F, 23.49; N, 8.66; O, 16.48; S, 6.61; Found C, 41.92; H, 2.71; F, 23.49; N, 8.70; O, 16.48; S, 6.61; LCMS: m/z=486.0 $[M + H]^+$

2.3.3 4-(2-Thioxo-6-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxamido)benzenesulfonic acid (8c)

White solid, Yield = 62%, m.p. 233-235 °C; R_f = 0.51; (n-hexane/EA; 3 : 1); HPLC purity = 97.7 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 12.4 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s,

1H, OH, sulpha), 9.36 (s, 1H, py-NH), 8.68 (s, -NH, sulpha), 8.15 (s, 1H, py-NH), 7.82 (d, *J*= 8.32 Hz, -2H, ArH, sulpha), 7.71 (d, *J*= 8.48 Hz, -2H, ArH), 7.40 (d, *J*= 8.48 Hz, -2H, ArH, sulpha), 7.26 (d, *J*= 8.32 Hz, -2H, ArH), 5.44 (d, *J*= 3.24 Hz, 1H, -CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 132.3 (q, *J*= 36.4 Hz, -C-CF_3), 131.4 (q, *J*= 36.1 Hz, -C-CF_3), 127.7, 126.5, 122.8 (q, *J*= 271.4 Hz, -CF_3). Analysis calculated for $C_{19}H_{13}F_6N_3O_4S_2$;C, 43.43; H, 2.49; F, 21.69; N, 8.00; O, 12.18; S, 12.20;Found C, 43.30; H, 2.50; F, 21.69; N, 8.02;O, 12.18;S, 12.20;LCMS:m/z=526.0$[M+H]^+$

2.3.4 (2-Thioxo-6-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carbonyl)-L-histidine (8d)

Light yellow solid, Yield = 66%, m.p. 244-246 °C; R_f = 0.41; (DCM/MeOH; 5 : 1); HPLC purity = 98.2 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 8.7 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H, COOH, His), 9.38 (s, 1H, py-NH), 8.68 (s, 1H, Imidazole, NH), 8.52 (s, 1H, CONH, His), 8.14 (s, 1H, py-NH), 7.92 (s, 1H, Imidazole, ArH), 7.75 (d, *J*= 8.8 Hz, -2H, ArH), 7.26 (d, *J*= 8.8 Hz, -2H, ArH), 7.10 (s, 1H, Imidazole, ArH), 5.42 (d, *J*= 4.76 Hz, 1H, -CH), 4.69-4.64 (m, 1H, $CHCH_2$, His), 3.28-3.21 (dd, 1H), 2.96-2.89 (dd, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 175.3, 173.7, 166.1, 143.9, 138.8, 135.9, 135.6, 135.2, 133.6 (q, *J*= 36.6 Hz, -C-CF_3), 132.7 (q, *J*= 36.8 Hz, -C-CF_3), 128.7, 127.7, 126.5, 125.2, 124.7, 123.0, 122.3 (q, *J*= 271.3 Hz, -CF_3), 94.9, 54.0, 52.0, 29.6. Analysis calculated for $C_{19}H_{15}F_6N_5O_3S$; C, 44.98; H, 2.98; F, 22.47; N, 13.80; O, 9.46; S, 6.32; Found C, 44.80; H, 2.97; F, 22.47; N, 13.86; O, 9.46; S, 6.32; LCMS: m/z = 508.0 $[M + H]^+$

2.3.5 (2-Thioxo-6-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carbonyl)-L-tyrosine (8e)

Light brown solid, Yield = 61%, m.p. 253-255 °C; R_f = 0.53; (n-hexane/EA; 3 : 1); HPLC purity = 98.4 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 12.4 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H, COOH, Tyr), 9.41 (s, 1H, py-NH), 9.26 (s, 1H, tyr-OH), 8.49 (s, 1H, py-NH), 8.14 (s, 1H, CO-NH), 7.70 (d, *J*= 7.84 Hz, -2H, ArH), 7.26 (d, *J*= 7.84 Hz, -2H, ArH), 7.06 (d, *J*= 8.04 Hz, 2H, Tyr-ArH), 6.78 (d, *J*= 8.04 Hz, 2H), 5.42 (s, *J*= 3.26 Hz 1H, -CH), 4.74-4.70 (m, 1H, $CHCH_2$ of Tyr), 3.20-3.16 (m, 1H, CH_2 of Tyr), 2.97-2.93 (m, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 174.9, 173.7, 166.1, 156.4, 143.9, 135.9, 135.6, 132.2 (q, *J*= 36.8 Hz, -C-CF_3), 131.4 (q, *J*= 36.3 Hz, -C-CF_3), 129.5, 129.0, 128.7, 127.7, 126.5, 125.2, 124.7, 123.0, 122.6 (q, *J*= 272.2 Hz, -CF_3), 94.9, 55.0, 52.0, 37.2. Analysis calculated for $C_{22}H_{17}F_6N_3O_4S$; C, 49.53; H, 3.21; F, 21.37; N,

7.88; O, 12.00; S, 6.01; Found C, 49.72; H, 3.21; F, 21.37; N, 7.86; O, 12.00; S, 6.01; LCMS: m/z = 534.0 $[M + H]^+$

2.3.6 (4-(4-Nitrophenyl)-2-thioxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carbonyl)-L-glutamic acid (8f)

Cream white solid, Yield = 72%, m.p. 199-200 °C; R_f = 0.43; (DCM/MeOH; 5 : 1); HPLC purity = 97.5 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 7.4 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H, COOH), 11.74 (s, 1H, COOH), 9.36 (s, 1H, py-NH), 8.44 (d, *J*= 4.4 Hz, 1H, py-NH), 8.26 (d, *J*= 8.72 Hz, -NH), 8.15 (s, 1H, -NH), 7.95 (d, *J*= 8.72 Hz, 2H, ArH), 5.45 (d, *J*= 3.52 Hz ,1H, -CH), 4.52-4.42 (m, 1H, glu), 2.31 (t, *J*= 7.56 Hz, 2H, glu), 2.00-1.92 (m, 2H, glu). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.3, 175.1, 173.7, 166.1, 148.4, 144.2, 135.9, 135.6, 132.4 (q, *J*= 36.1 Hz, -C-CF_3), 127.7, 124.7, 123.8, 94.9, 53.2, 51.9, 31.2, 26.8. Analysis calculated for $C_{17}H_{15}F_3N_4O_7S$; C, 42.86; H, 3.17; F, 11.96; N, 11.76; O, 23.51; S, 6.73; Found C, 42.99; H, 3.18; F, 11.96; N, 11.80; O, 23.51; S, 6.73; LCMS: m/z = 477.0 $[M + H]^+$

2.3.7 4-(4-(4-Nitrophenyl)-2-thioxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamido)benzenesulfonic acid (8g)

Light orange solid, Yield = 69%, m.p. 244-246 °C; R_f = 0.47; (DCM/MeOH; 5 : 1); HPLC purity = 98.2 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 8.1 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H, SO_2-OH), 9.46 (s, 1H, py-NH), 8.62 (s, 1H, py-NH), 8.48 (s, 1H, CO-NH), 8.34 (d, *J*= 8.3 Hz, 2H, ArH), 8.25 (d, *J*= 8.5 Hz, 2H, ArH), 7.88 (d, *J*= 7.9 Hz, 2H, ArH), 7.86 (d, *J*= 8.4 Hz, 2H, ArH), 5.44 (s, 1H, -CH). ^{13}C NMR (100 MHz, CDCl3) δ 173.7, 167.9, 148.5, 144.2, 140.7, 136.3, 135.8, 135.5, 132.7 (q, *J*= 36.4 Hz, -C-CF_3), 128.0, 127.7, 124.5, 123.8, 121.3, 100.0, 51.7. Analysis calculated for $C_{18}H_{13}F_3N_4O_6S_2$; C, 43.03; H, 2.61; F, 11.34; N, 11.15; O, 19.11; S, 12.76; Found C, 43.16; H, 2.62; F, 11.34; N, 11.10; O, 19.11; S, 12.76; LCMS: m/z = 503.0 $[M + H]^+$

2.3.8 (4-(4-(Methoxycarbonyl)phenyl)-2-thioxo-6-(trifluoromethyl)-1,2,3,4-tetrahydro-pyrimidine-5-carbonyl)-L-histidine (8h)

White solid, Yield = 76%, m.p. 253-255 °C; R_f = 0.42; (DCM/MeOH; 5 : 1); HPLC purity = 98.4 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 7.8 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (s, 1H, COOH, His), 9.36 (s, 1H, py-NH), 8.87 (s, 1H, Imidazole, NH), 8.48 (d, *J*= 4.4 Hz, 1H, CONH, His), 8.15 (s, 1H, py-NH), 8.03 (s, 1H, Imidazole, ArH), 7.92 (d, *J*= 7.76 Hz, -2H, ArH), 7.46 (d,

J= 7.76 Hz, -2H, ArH), 7.07 (s, 1H, Imidazole, ArH), 5.43 (d, *J*= 3.6 Hz, 1H, -CH), 4.36-4.31 (m, 1H, $CHCH_2$, His), 3.83 (s, 3H, $-OCH_3$), 3.48-3.40 (m, 2H, $CHCH_2$, His). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.3, 173.7, 168.0, 166.1, 146.8, 138.8, 135.9, 135.6, 135.2, 131.6 (q, *J*= 36.3 Hz, -C-CF_3), 130.4, 130.0, 126.9, 124.7, 118.8, 94.9, 54.0, 52.1, 51.5, 29.6. Analysis calculated for $C_{20}H_{18}F_3N_5O_5S$; C, 48.29; H, 3.65; F, 11.46; N, 14.08; O, 16.08; S, 6.44; Found C, 48.47; H, 3.64; F, 11.46; N, 14.02; O, 16.08; S, 6.44; LCMS: m/z = 498.1 $[M + H]^+$

2.4.1 (2-((2-Bromoacetyl)thio)-6-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,4 di-hydropyrimidine-5-carbonyl)-L-glutamic acid (10a)

Off white greenish solid, Yield = 61%, m.p. 232-234 °C; R_f = 0.49; (n-hexane/EA; 3 : 1); HPLC purity = 97.5 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 9.4 min. ^1H NMR (400 MHz, DMSO-d_6) δ 12.36 (s, 1H, COOH), 11.74 (s, 1H, COOH), 9.54 (s, 1H, py-NH), 8.45 (d, *J*= 4.79Hz, -NH), 7.74 (d, *J*= 8.12 Hz, -2H, ArH), 7.28 (d, *J*= 7.4 Hz, -2H, ArH), 5.31 (s, 1H, -CH), 4.71-4.63 (m, 2H, glu), 3.81 (s, 2H, CH_2), 2.26-2.24 (m, 2H, glu), 2.05-1.96 (m, 2H, glu). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.6, 175.3, 175.1, 164.6, 144.9, 142.4, 132.3, 132.8 (q, *J*= 36.9 Hz, -C-CF_3), 132.4 (q, *J*= 36.2 Hz, -C-CF_3), 130.6, 130.4, 127.5, 125.7, 125.2, 124.9, 122.1 (q, *J*= 272.4 Hz, -CF_3), 90.7, 57.2, 53.0, 33.9, 31.2, 26.8. Analysis calculated for $C_{20}H_{16}BrF_6N_3O_6S$; C, 38.73; H, 2.60; Br, 12.88; F, 18.38; N, 6.77; O, 15.47; S, 5.17; Found C, 38.59; H, 2.60; Br, 12.88; F, 18.38; N, 6.80; O, 15.47; S, 5.17; LCMS: m/z = 619.9 $[M + H]^+$

2.4.2 (2-((2-Bromoacetyl)thio)-6-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,4-di-hydropyrimidine-5-carbonyl)-L-aspartic acid (10b)

Off white greenish solid, Yield = 59%, m.p. 231-233 °C; R_f = 0.47; (n-hexane/EA; 3 : 1); HPLC purity = 97.8 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 11.4 min. ^1H NMR (400 MHz, DMSO-d_6) δ 12.41 (s, 1H, COOH), 11.81 (s, 1H, COOH), 9.52 (s, 1H, py-NH), 8.42 (d, *J*= 4.4Hz, -NH), 7.79 (d, *J*= 8.2 Hz, -2H, ArH), 7.33 (d, *J*= 7.7 Hz, -2H, ArH), 5.26 (s, 1H, -CH), 4.54-4.48 (m, 2H, glu), 3.76 (s, 2H, CH_2), 2.27-2.24 (m, 2H, glu). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.6, 173.5, 172.9, 164.1, 144.9, 142.4, 132.3, 132.0, 132.8 (q, *J*= 36.1 Hz, -C-CF_3), 131.5 (q, *J*= 36.2 Hz, -C-CF_3), 130.4, 127.5, 125.7, 125.2, 124.9, 122.7 (q, *J*= 273.1 Hz, -CF_3), 90.7, 57.2, 50.5, 36.2, 33.9. Analysis calculated for $C_{19}H_{14}BrF_6N_3O_6S$; C, 37.64; H, 2.33; Br, 13.18; F, 18.80; N, 6.93; O, 15.83; S, 5.29; Found C, 37.50; H, 2.31; Br, 13.18; F, 18.80; N, 6.95; O, 15.83; S, 5.29; LCMS: m/z = 605.9 $[M + H]^+$

2.4.3 4-(2-((2-Bromoacetyl)thio)-6-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,4-dihydropyrimidine-5-carboxamido)benzenesulfonic acid (10c)

Light Brownish solid, Yield = 57%, m.p. 247-249 °C; R_f = 0.49; (n-hexane/EA; 3 : 1); HPLC purity = 98.3 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 13.6 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H, OH, sulpha), 9.53 (s, 1H, py-NH), 8.66 (s, -NH, sulpha), 7.73 (d, *J*= 8.51 Hz, -2H, ArH, sulpha), 7.71 (d, *J*= 7.5 Hz, -2H, ArH), 7.35 (d, *J*= 7.7 Hz, -2H, ArH), 7.45 (d, *J*= 8.34 Hz, -2H, ArH, sulpha), 5.26 (s, 1H, -CH), 3.73 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.6, 166.1, 144.9, 142.4, 140.7, 136.3, 133.1, 132.8, 131.9 (q, *J*= 36.8 Hz, -C-CF_3), 131.3 (q, *J*= 36.3 Hz, -C-CF_3), 130.4, 128.0, 127.5, 125.7, 125.2, 124.7, 122.3 (q, *J*= 272.6 Hz, -CF_3), 121.3, 100.1, 57.2, 33.9. Analysis calculated for $C_{21}H_{14}BrF_6N_3O_5S_2$; C, 39.02; H, 2.18; Br, 12.36; F, 17.64; N, 6.50; O, 12.38; S, 9.92; Found C, 38.88; H, 2.19; Br, 12.36; F, 17.64; N, 6.52; O, 12.38; S, 9.92; LCMS: m/z = 645.9 $[M + H]^+$

2.4.4 (2-((2-Bromoacetyl)thio)-6-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,4-dihydropyrimidine-5-carbonyl)-L-histidine (10d)

Light yellow solid, Yield = 62%, m.p. 261-263 °C; R_f = 0.48; (n-hexane/EA; 3 : 1); HPLC purity = 98.7 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 11.6 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H, COOH, His), 8.66 (s, 1H, Imidazole, NH), 8.52 (s, 1H, CONH, His), 7.92 (s, 1H, Imidazole, ArH), 7.71 (d, *J*= 7.6 Hz, -2H, ArH), 7.25 (d, *J*= 8.14 Hz, -2H, ArH), 7.13 (s, 1H, Imidazole, ArH), 5.23 (s, 1H, -CH), 3.74 (s, 2H, CH_2), 3.45-3.39 (m, 2H, $CHCH_2$, His), 4.34-4.31 (m, 1H, $CHCH_2$, His), 9.55 (s, 1H, py-NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.6, 175.3, 164.5, 144.9, 142.4, 138.8, 135.2, 132.7 (q, *J*= 36.4 Hz, -C-CF_3), 132.2 (q, *J*= 36.1 Hz, -C-CF_3), 132.0, 130.6, 130.4, 127.5, 125.7, 125.2, 124.9, 122.6 (q, *J*= 271.5 Hz, -CF_3), 118.8, 90.7, 57.2, 54.0, 33.9, 29.6. Analysis calculated for $C_{21}H_{16}BrF_6N_5O_4S$; C, 40.14; H, 2.57; Br, 12.72; F, 18.14; N, 11.15; O, 10.18; S, 5.10; Found C, 40.00; H, 2.58; Br, 12.72; F, 18.14; N, 11.19; O, 10.18; S, 5.10; LCMS: m/z = 628.0 $[M + H]^+$

2.4.5 (2-((2-Bromoacetyl)thio)-6-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,4-dihydro pyrimidine-5-carbonyl)-L-tyrosine (10e)

Off white solid, Yield = 58%, m.p. 227-239 °C; R_f = 0.41; (n-hexane/EA; 3 : 1); HPLC purity = 97.4 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 13.3 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H, COOH, Tyr), 8.53 (s, 1H, CO-NH), 9.28 (s, 1H, Tyr-OH), 9.58 (s, 1H, py-NH), 7.75

(d, *J*= 8.20 Hz, -2H, ArH), 7.33 (d, *J*= 7.1 Hz, -2H, ArH), 7.07 (d, *J*= 7.42 Hz, 2H, Tyr-ArH), 6.73 (d, *J*= 7.72 Hz, 2H, Tyr-ArH), 5.34 (s, 1H, -CH), 4.94-4.87 (m, 1H, $CHCH_2$ of Tyr), 3.84 (s, 2H, CH_2), 3.64 (dd, 1H, *J*= 12.07 Hz, *J*=9.64 Hz, 1H, CH_2 of Tyr). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.6, 174.9, 164.5, 156.4, 144.9, 142.4, 132.3, 132.1 (q, *J*= 36.5 Hz, -C-CF_3), 131.2 (q, *J*= 36.3 Hz, -C-CF_3), 130.6, 130.4, 129.6, 127.5, 125.7, 125.2, 124.9, 122.4 (q, *J*= 270.4 Hz, -CF_3), 115.8, 90.7, 57.2, 55.0, 37.2, 33.9. Analysis calculated for $C_{24}H_{18}BrF_6N_3O_5S$; C, 43.87; H, 2.76; Br, 12.21; F, 17.42; N, 6.45; O, 12.22; S, 4.90; Found C, 44.23; H, 2.76; Br, 12.21; F, 17.42; N, 6.39; O, 12.22; S, 4.90; LCMS: m/z = 654.0 $[M + H]^+$

2.4.6 (2-((2-Bromoacetyl)thio)-4-(4-nitrophenyl)-6-(trifluoromethyl)-1,4-dihydro pyrimidine - 5-carbonyl)-L-glutamic acid (10f)

Cream white solid, Yield = 69%, m.p. 194-196 °C; R_f = 0.49; (n-hexane/EA; 3 : 1); HPLC purity = 97.6 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 12.7 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.44 (s, 1H, COOH), 11.79 (s, 1H, COOH), 9.45 (s, 1H, py-NH), 8.46 (d, *J*= 4.51 Hz, -NH), 8.28 (d, *J*= 8.7 Hz, 2H, ArH), 7.91 (d, *J*= 8.4 Hz, 2H, ArH), 5.38 (s, 1H, -CH), 4.80-4.75 (m, 2H, glu), 3.05 (s, 2H, CH_2), 2.24-2.15 (m, 2H, glu), 2.03-1.93 (m, 2H, glu). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.6, 175.3, 175.1, 164.6, 147.4, 147.2, 144.9, 133.4 (q, *J*= 36.2 Hz, -C-CF_3), 132.7, 132.5, 127.9, 124.9, 122.8, 90.7, 57.4, 53.0, 33.9, 31.2, 26.8. Analysis calculated for $C_{19}H_{16}BrF_3N_4O_8S$; C, 38.21; H, 2.70; Br, 13.38; F, 9.54; N, 9.38; O, 21.43; S, 5.37; Found C, 38.07; H, 2.68; Br, 13.38; F, 9.54; N, 9.42; O, 21.43; S, 5.37; LCMS: m/z = 596.9 $[M + H]^+$

2.4.7 4-(2-((2-Bromoacetyl)thio)-4-(4-nitrophenyl)-6-(trifluoromethyl)-1,4-dihydro-pyri midine -5-carboxamido)benzenesulfonic acid (10g)

Off white solid, Yield = 66%, m.p. 254-256 °C; R_f = 0.45; (n-hexane/EA; 3 : 1); HPLC purity = 98.5 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 14.2 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H, SO_2-OH), 9.44 (s, 1H, py-NH), 8.44 (s, 1H, CO-NH), 8.37 (d, *J*= 8.3 Hz, 2H, ArH), 8.25 (d, *J*= 7.8 Hz, 2H, ArH), 7.85 (d, *J*= 7.2 Hz, 2H, ArH), 7.81 (d, *J*= 8.15 Hz, 2H, ArH), 5.43 (s, 1H, -CH), 3.14 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.6, 166.1, 147.3, 144.9, 140.7, 136.3, 133.1, 132.9, 131.3 (q, *J*= 36.4 Hz, -C-CF_3), 128.0, 124.7, 122.5, 121.3, 100.1, 57.4, 33.9. Analysis calculated for $C_{20}H_{14}BrF_3N_4O_7S_2$; C, 38.54; H, 2.26; Br, 12.82; F, 9.14; N, 8.99; O, 17.97; S, 10.29; Found C, 38.40; H, 2.25; Br, 12.82; F, 9.14; N, 9.02; O, 17.97; S, 10.29; LCMS: m/z = 622.9 $[M + H]^+$

2.4.8 (2-((2-Bromoacetyl)thio)-4-(4-(methoxycarbonyl)phenyl)-6-(trifluoromethyl)-1,2-dihydropyrimidine-5-carbonyl)-L-histidine (10h)

White solid, Yield = 68%, m.p. 263-265 °C; R_f = 0.45; (DCM/MeOH; 5 : 1); HPLC purity = 99.2 % (C18 RP, Acetonitrile / H_2O-80:20), T_R = 8.9 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H, COOH, His), 9.54 (s, 1H, py-NH), 8.66 (s, 1H, Imidazole, NH), 8.55 (s, 1H, CONH, His), 7.92 (s, 1H, Imidazole, ArH), 7.73 (d, *J*= 7.7 Hz, 2H, ArH), 7.29 (d, *J*= 7.9 Hz, 2H, ArH), 7.13 (s, 1H, Imidazole, ArH), 5.23 (s, 1H, -CH), 4.36-4.31 (m, 1H, $CHCH_2$, His), 3.75 (s, 3H, -OCH_3), 3.73 (s, 2H, CH_2), 3.45-3.43 (m, 2H, -$CHCH_2$, His). ^{13}C NMR (100 MHz, DMSO-d_6) δ 186.3, 175.3, 172.1, 169.0, 166.6, 139.5, 139.2, 138.8, 135.1, 132.4 (q, *J*= 36.7 Hz, -C-CF_3), 132.3, 130.9, 128.6, 121.7, 118.8, 86.7, 77.4, 53.6, 52.1, 33.8, 29.6. Analysis calculated for $C_{22}H_{19}BrF_3N_5O_6S$; C, 42.73; H, 3.10; Br, 12.92; F, 9.22; N, 11.33; O, 15.52; S, 5.18; Found C, 42.86; H, 3.11; Br, 12.92; F, 9.22; N, 11.36; O, 15.52; S, 5.18, LCMS: m/z = 618.0 $[M + H]^+$

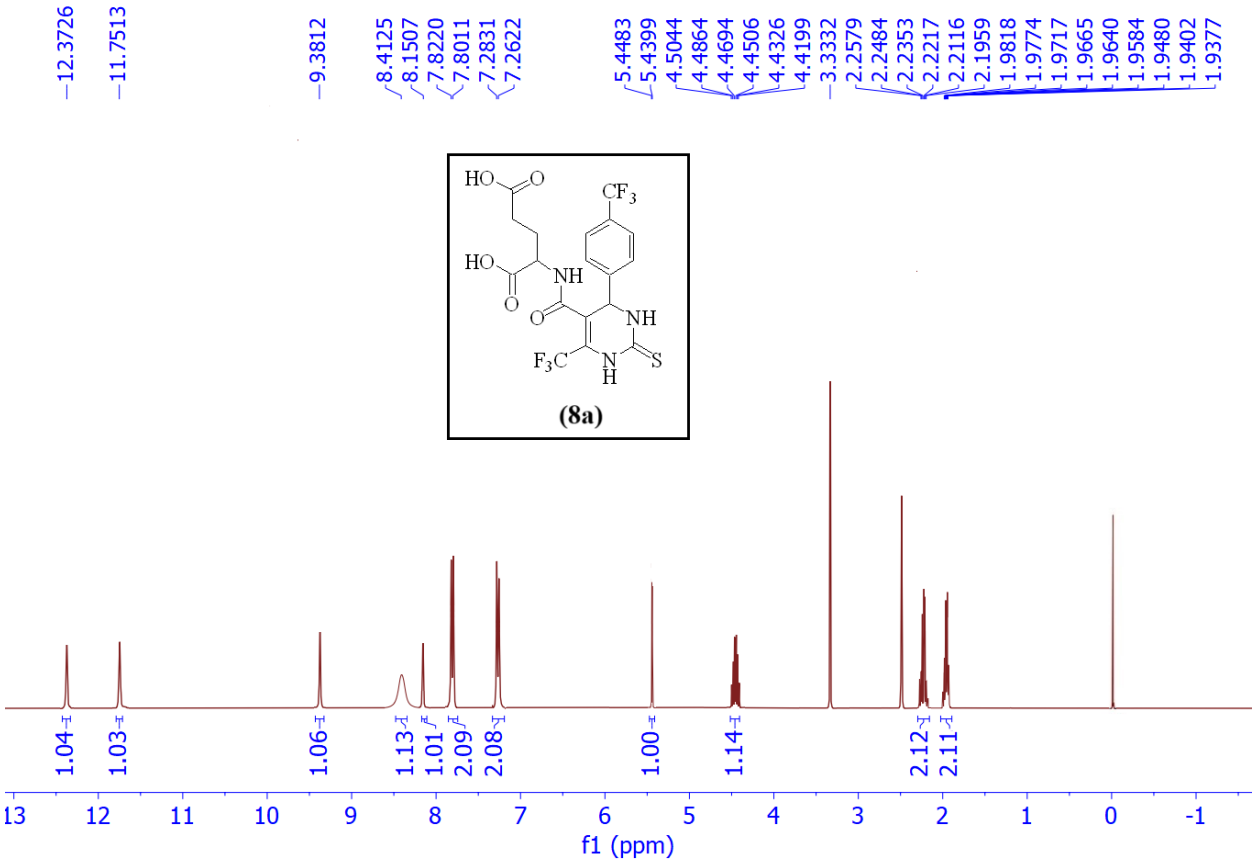

Figure S-1: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **8a**

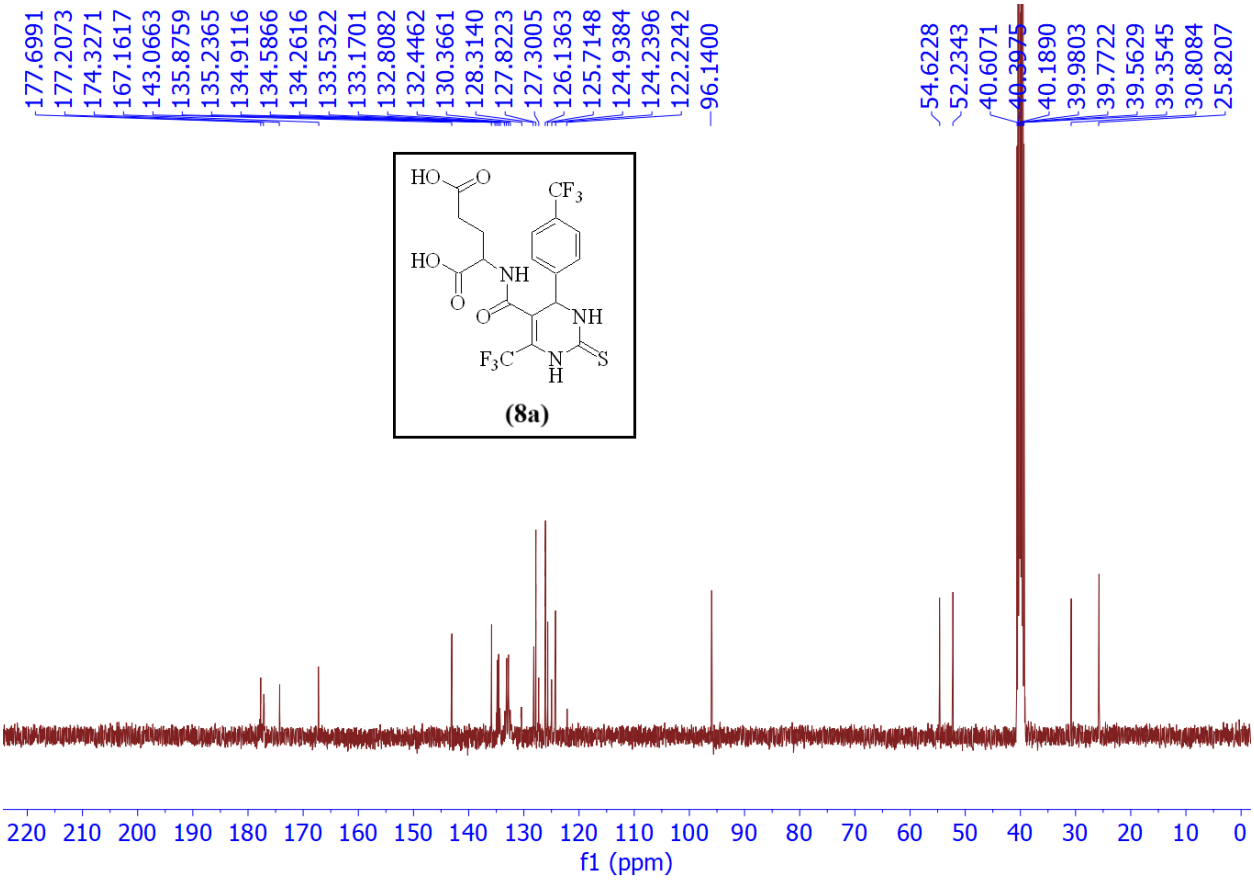

Figure S-2: ^{13}C NMR (100 MHz, DMSO-d_6) of compound **8a**

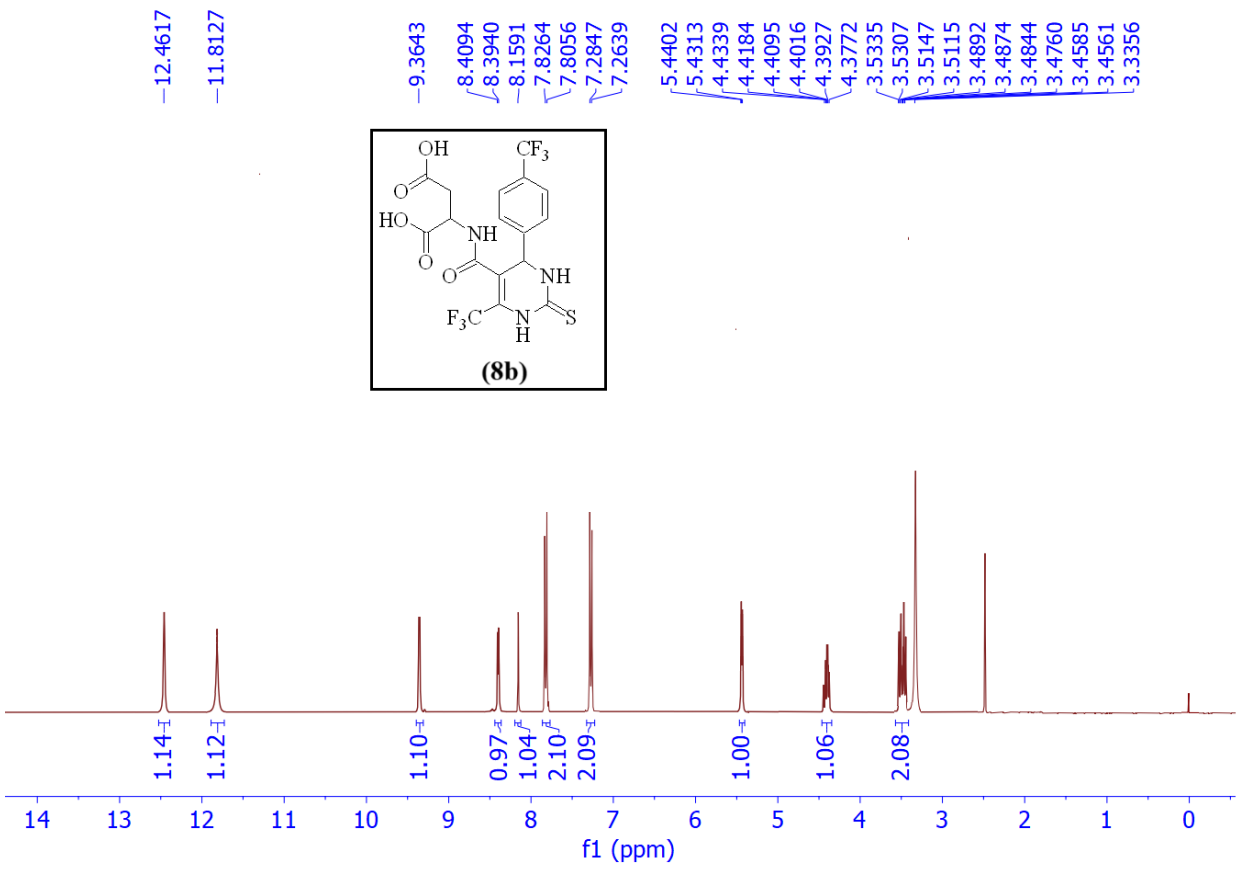

Figure S-3: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **8b**

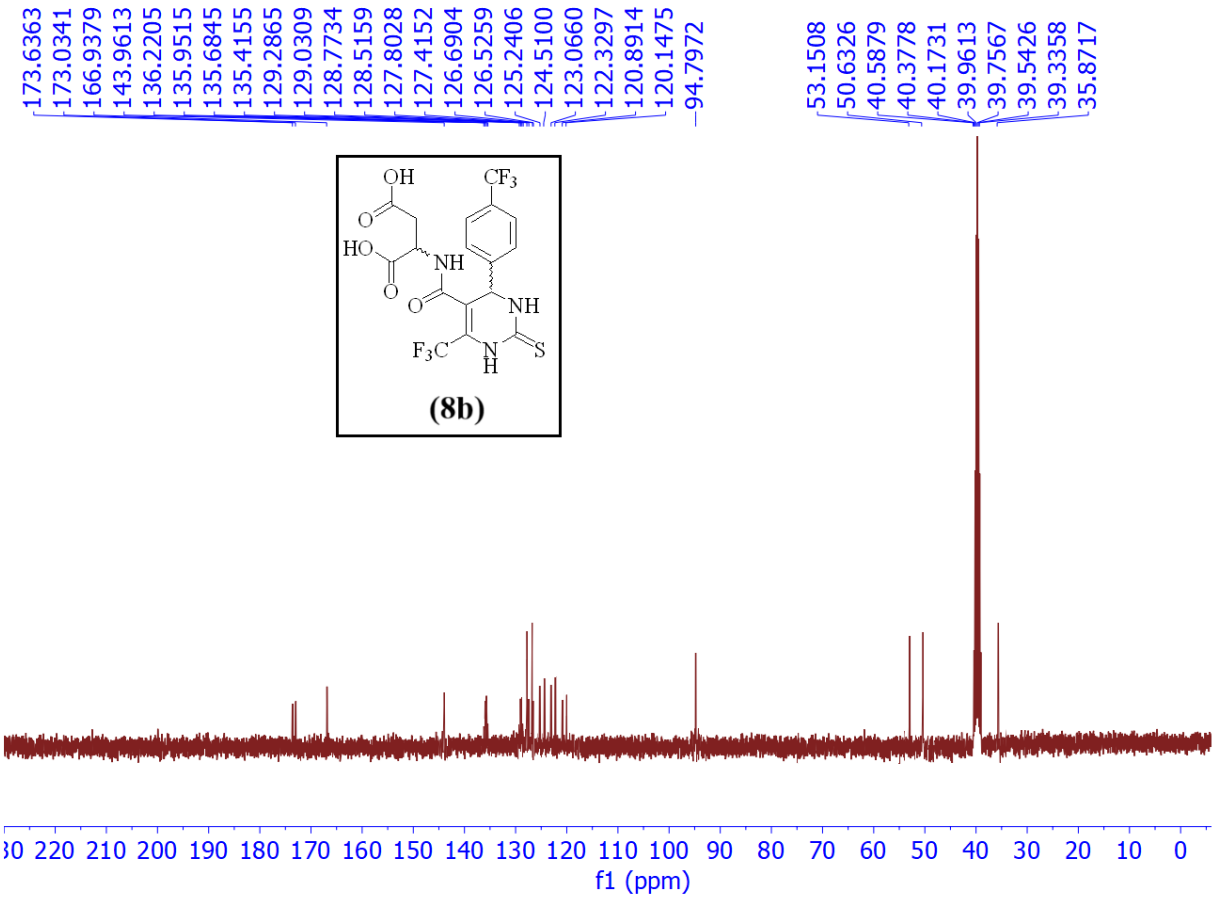

Figure S-4: ^{13}C NMR (100 MHz, DMSO-d_6) of compound **8b**

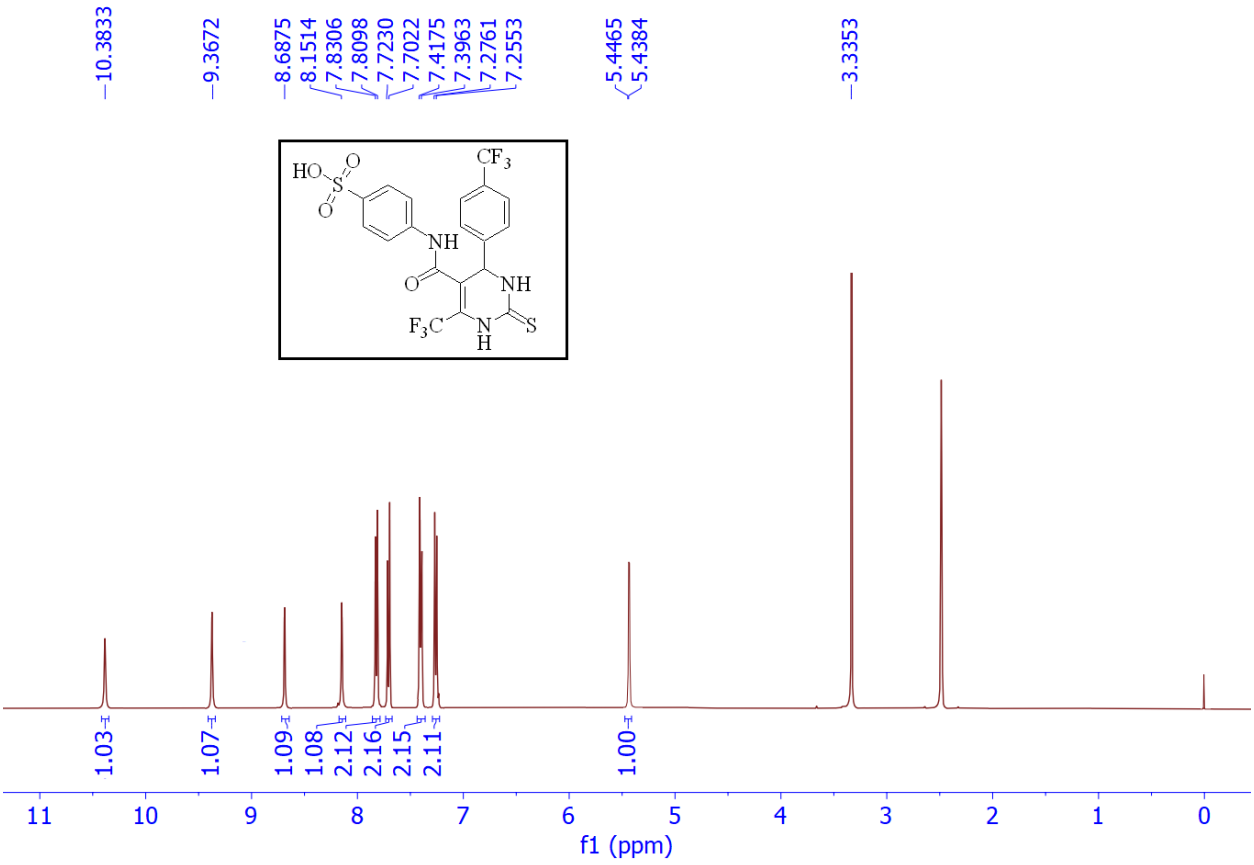

Figure S-5: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **8c**

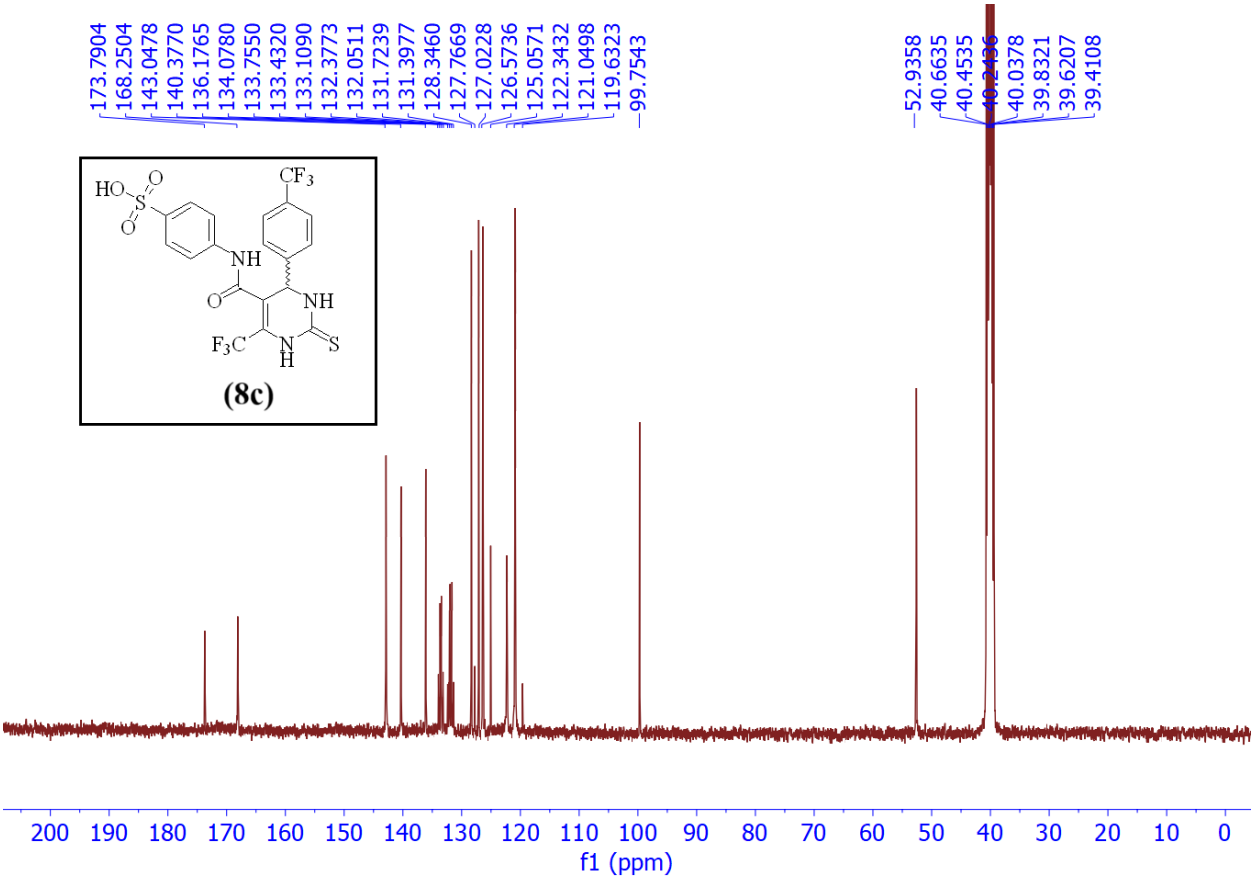

Figure S-6: ^{13}C NMR (100 MHz, DMSO-d_6) of compound **8c**

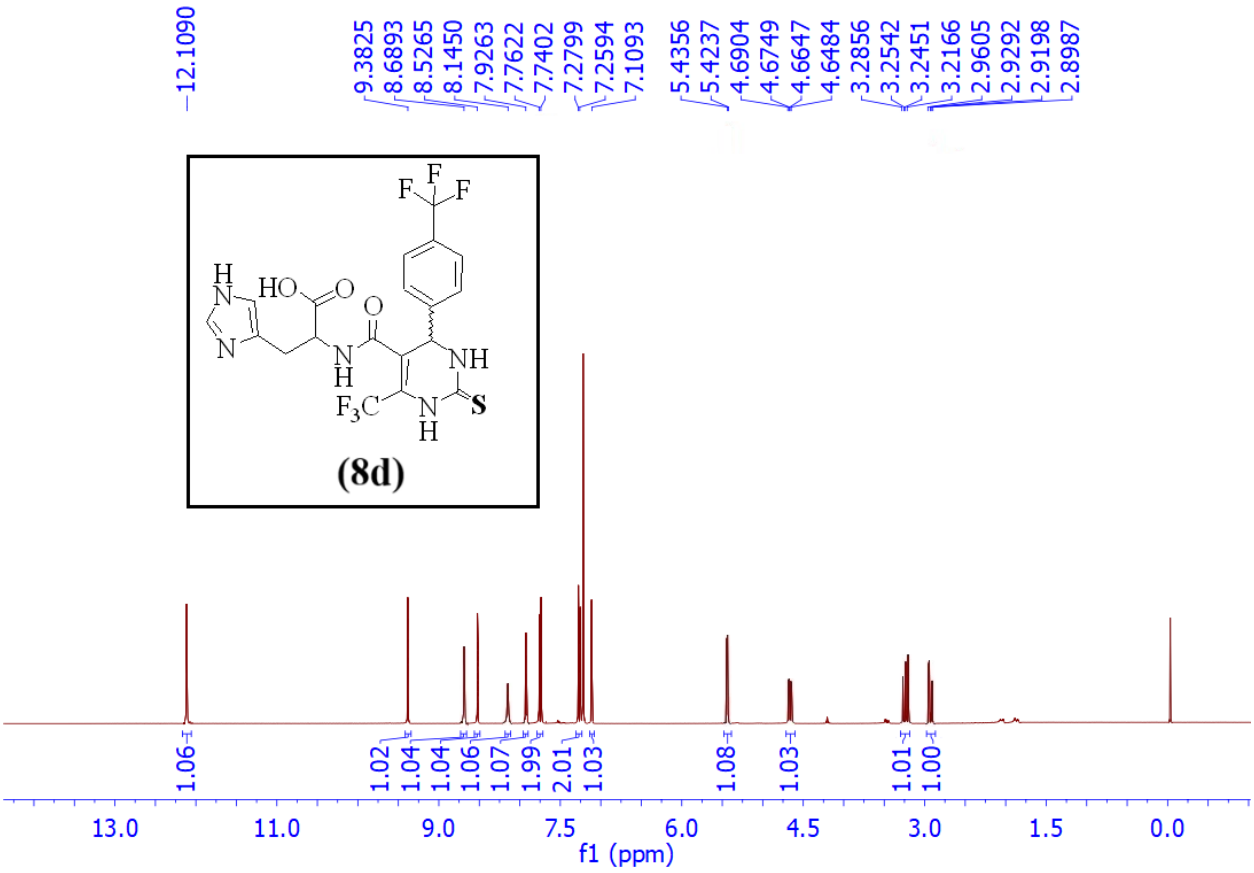

Figure S-7: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **8d**

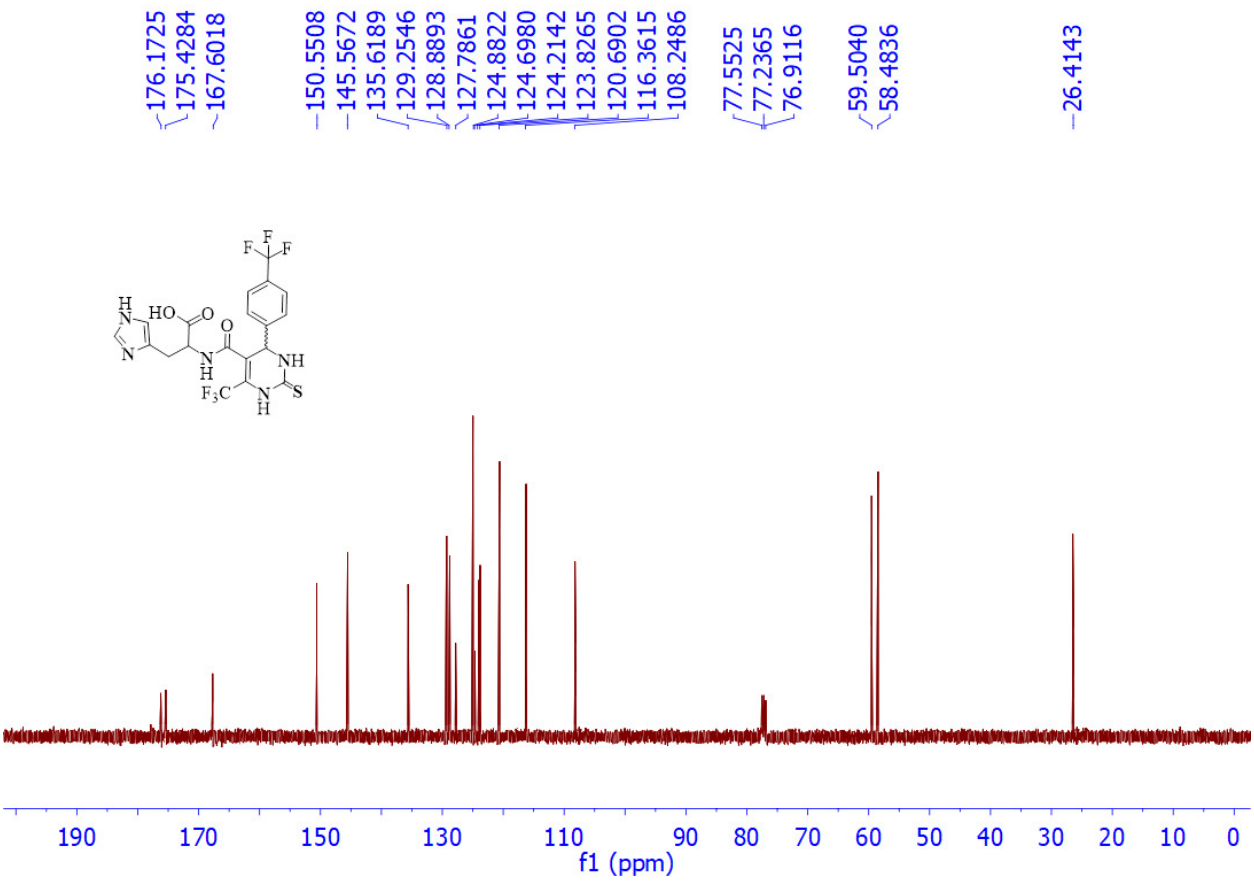

Figure S-8: ^{13}C NMR (100 MHz, $CDCl_3$) of compound **8d**

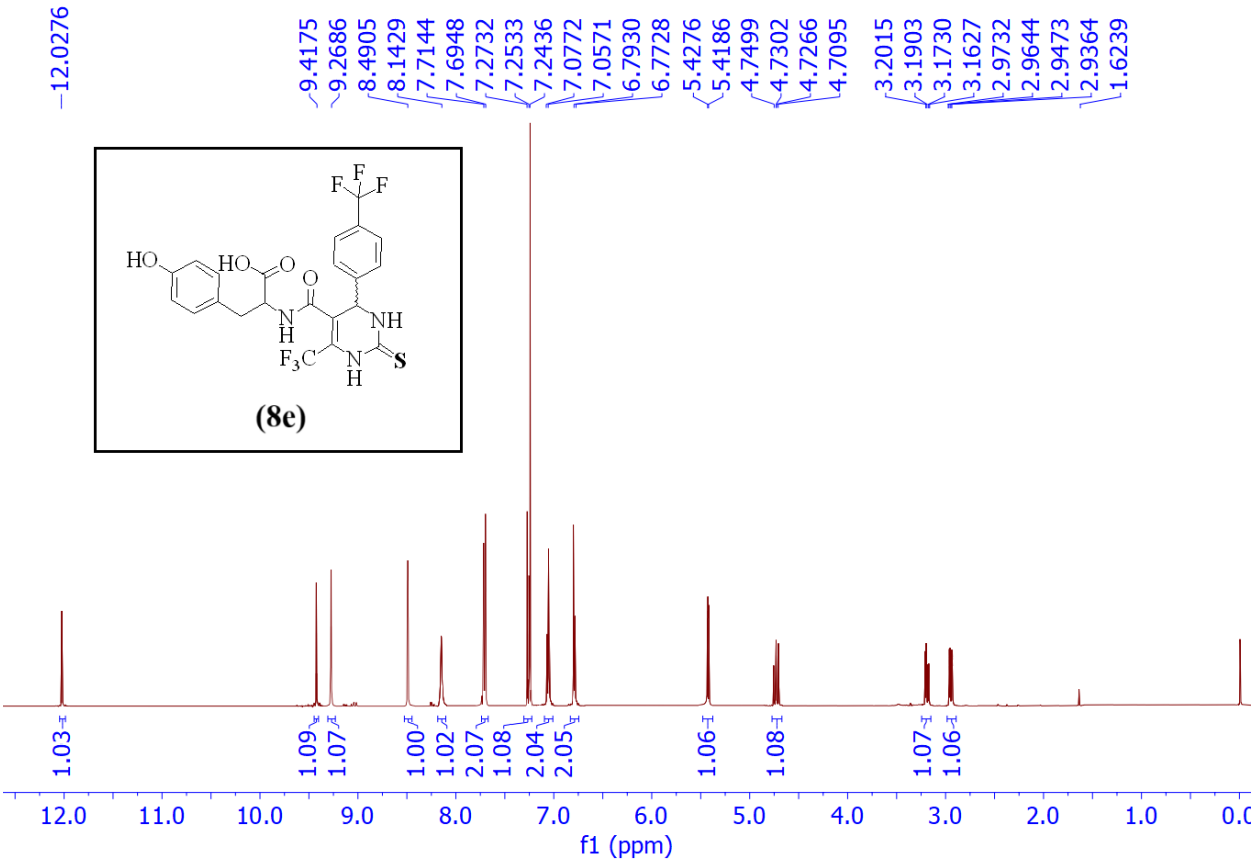

Figure S-9: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **8e**

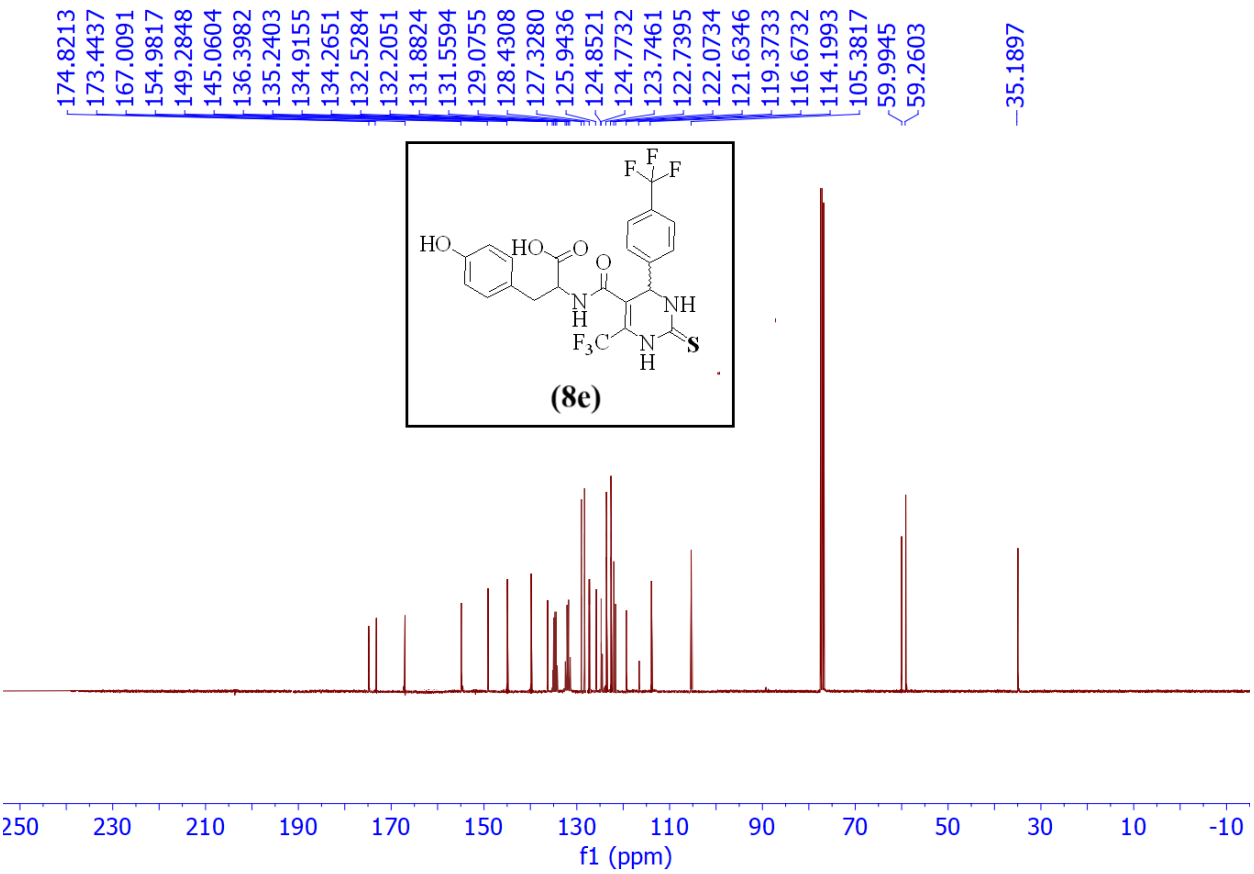

Figure S-10: ^{13}C NMR (100 MHz, $CDCl_3$) of compound **8e**

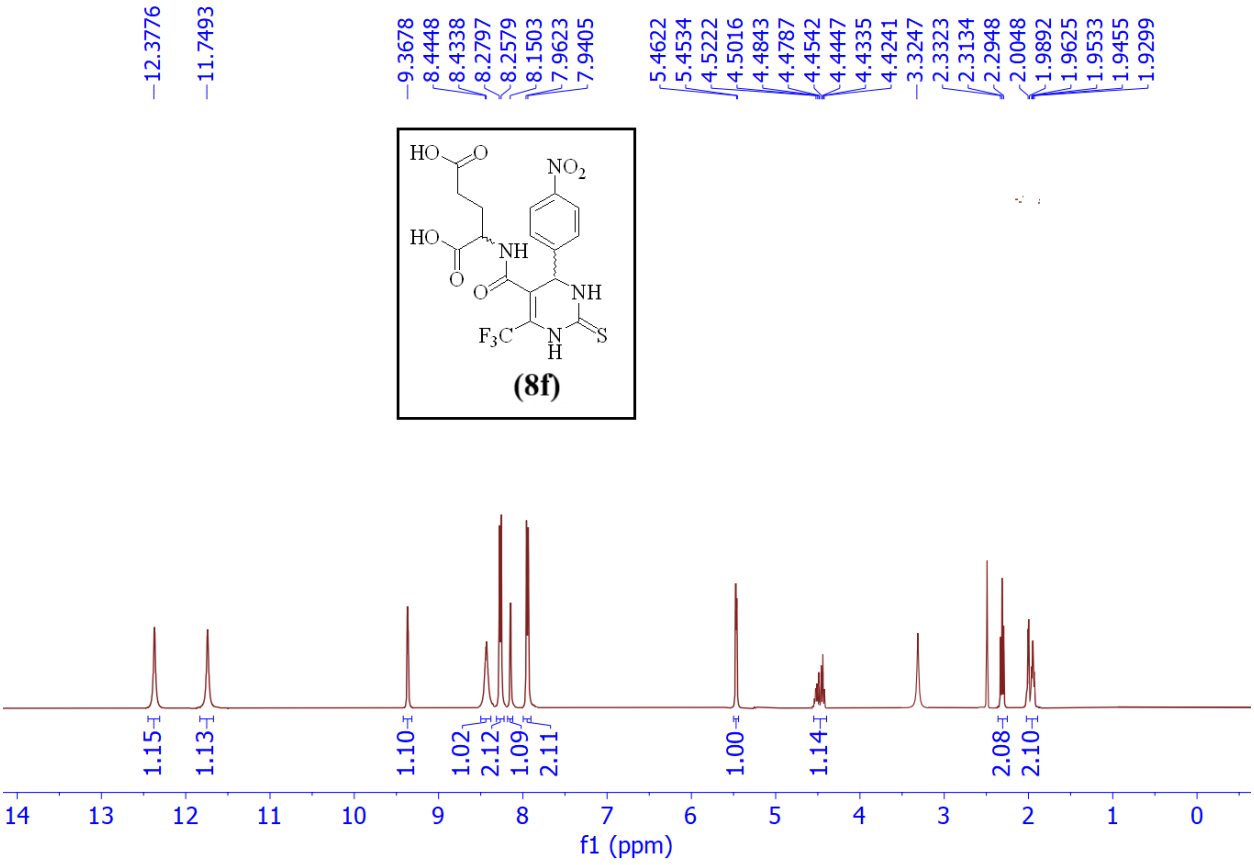

Figure S-11: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **8f**

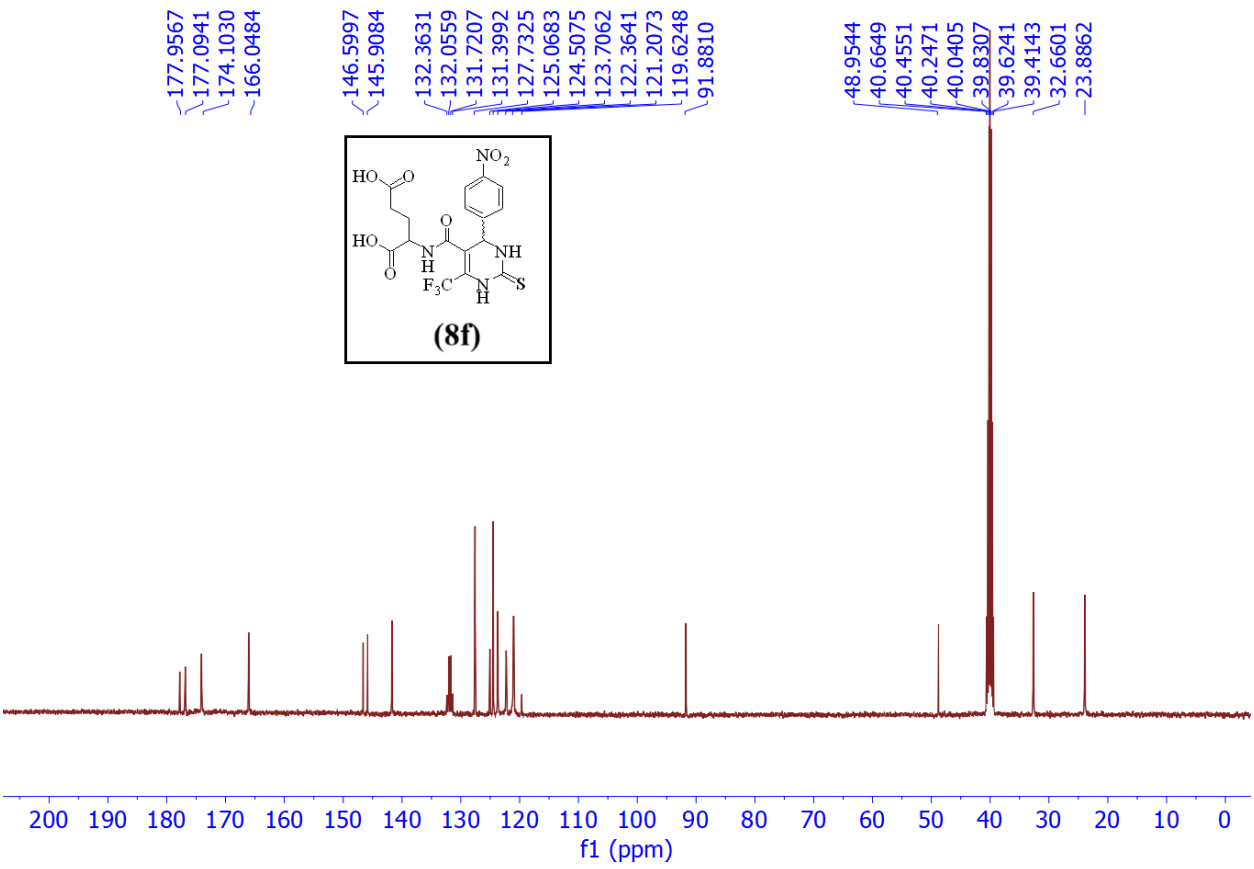

Figure S-12: ^{13}C NMR (100 MHz, DMSO-d_6) of compound 8f

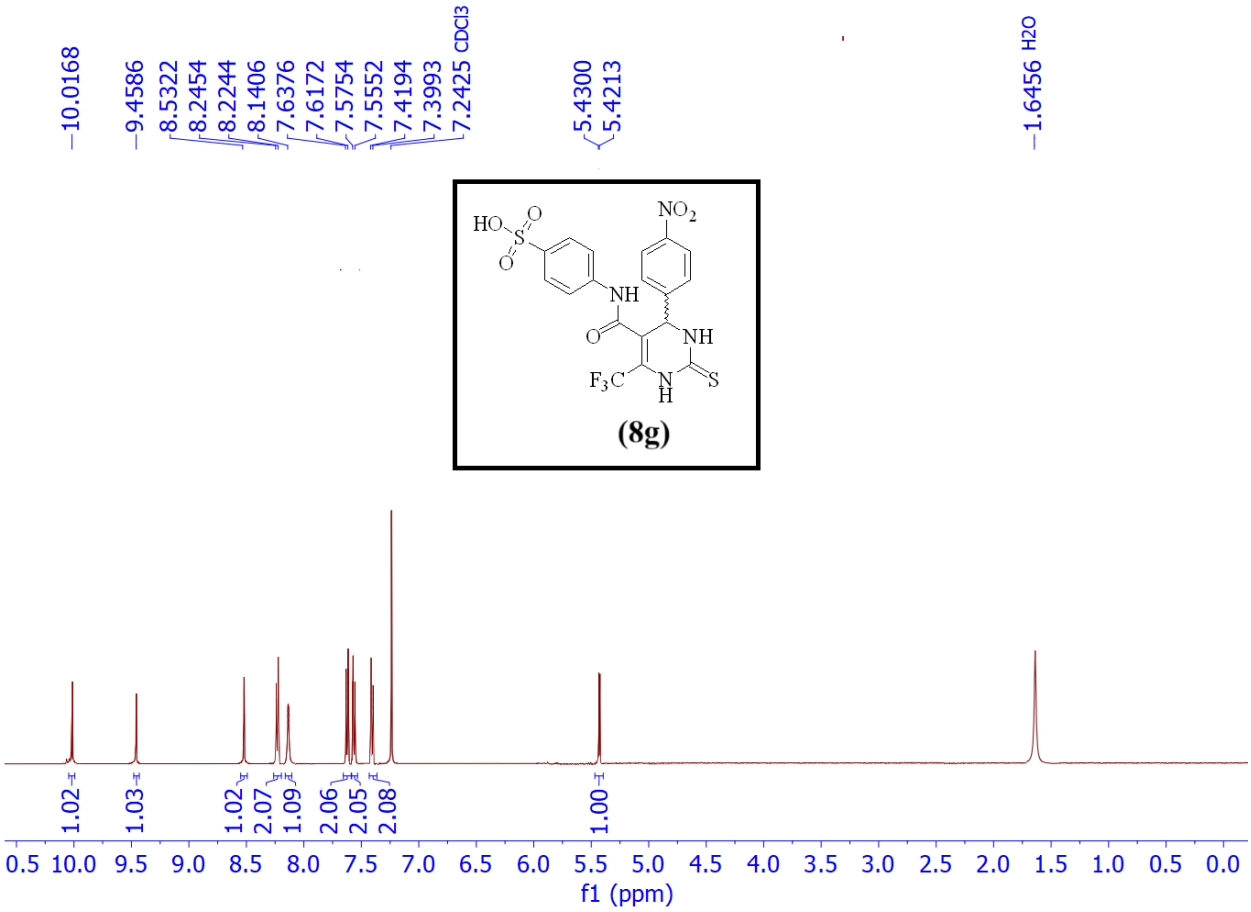

Figure S-13: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **8g**

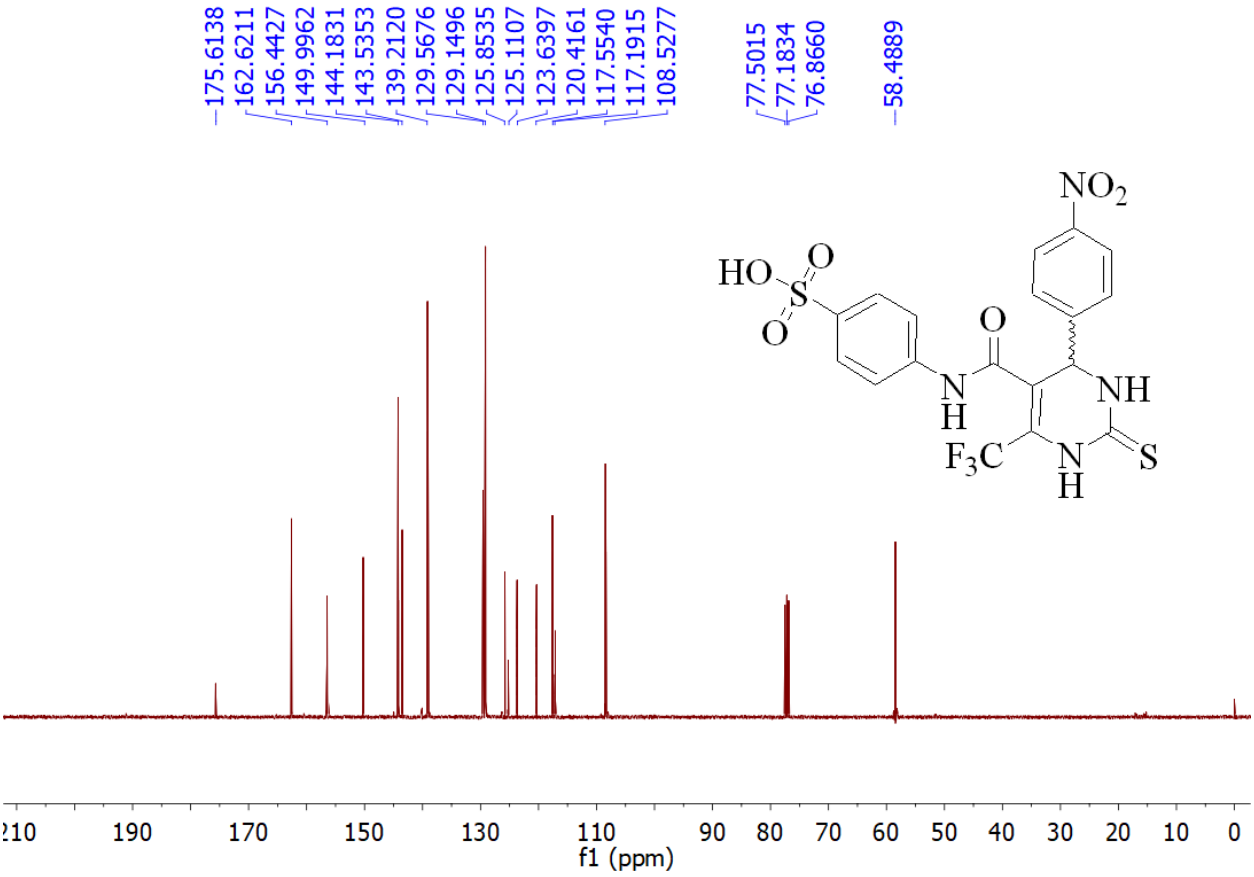

Figure S-14: ^{13}C NMR (100 MHz, $CDCl_3$) of compound **8g**

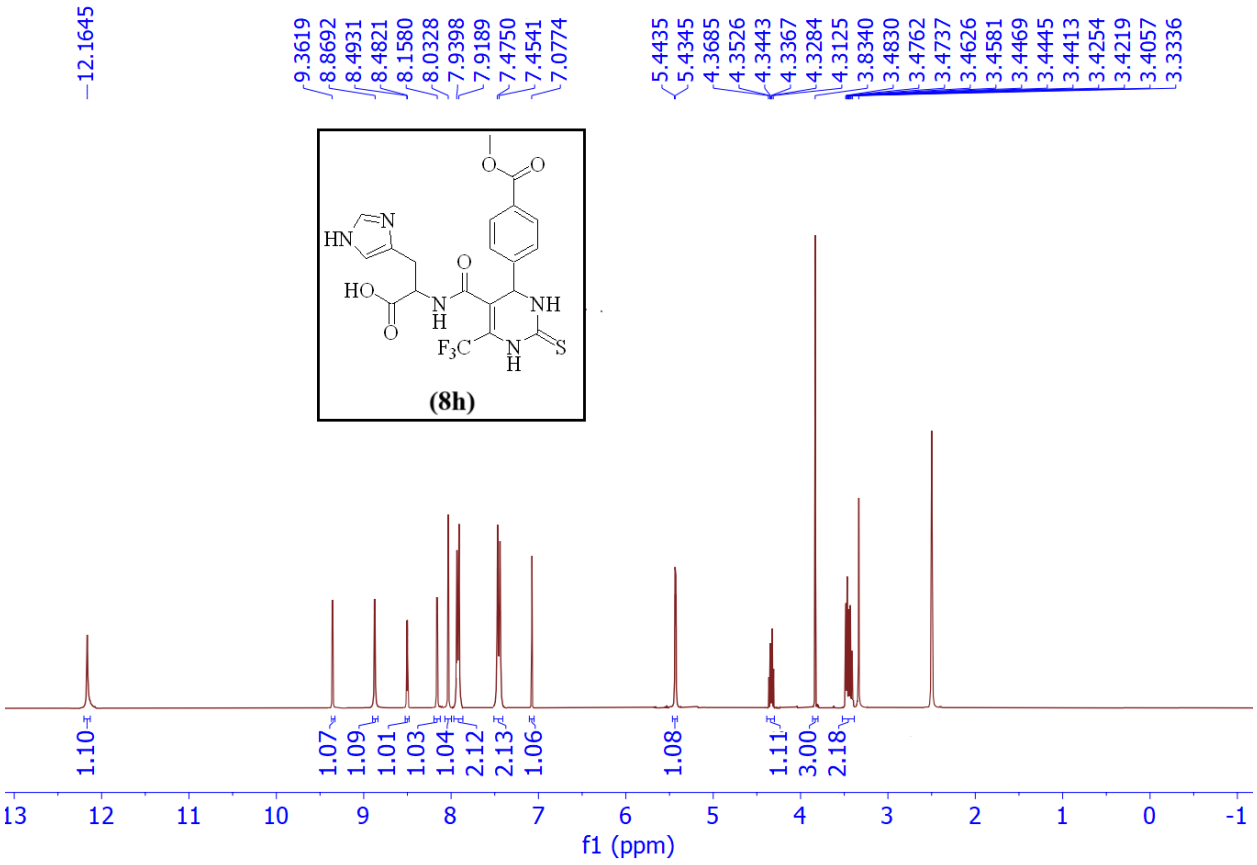

Figure S-15: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **8h**

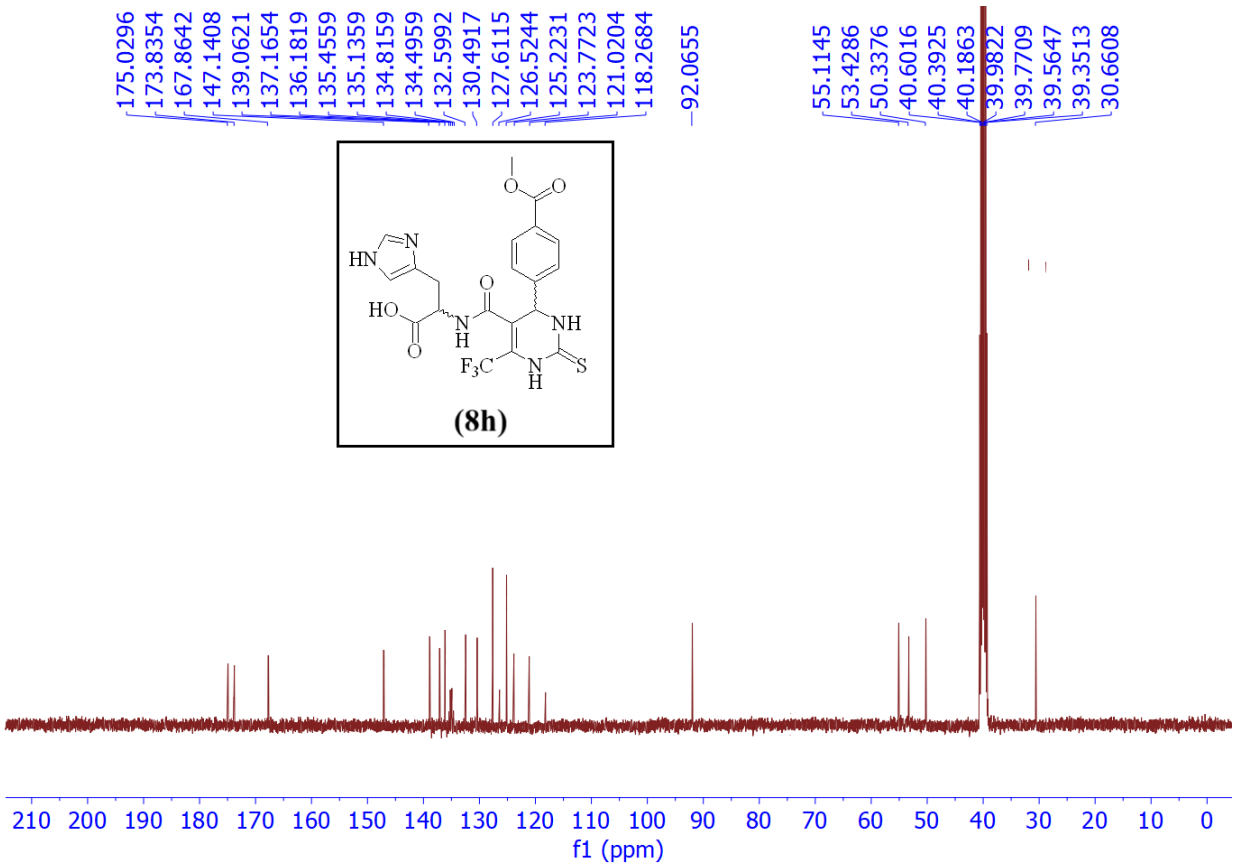

Figure S-16: ^{13}C NMR (100 MHz, DMSO-d_6) of compound **8h**

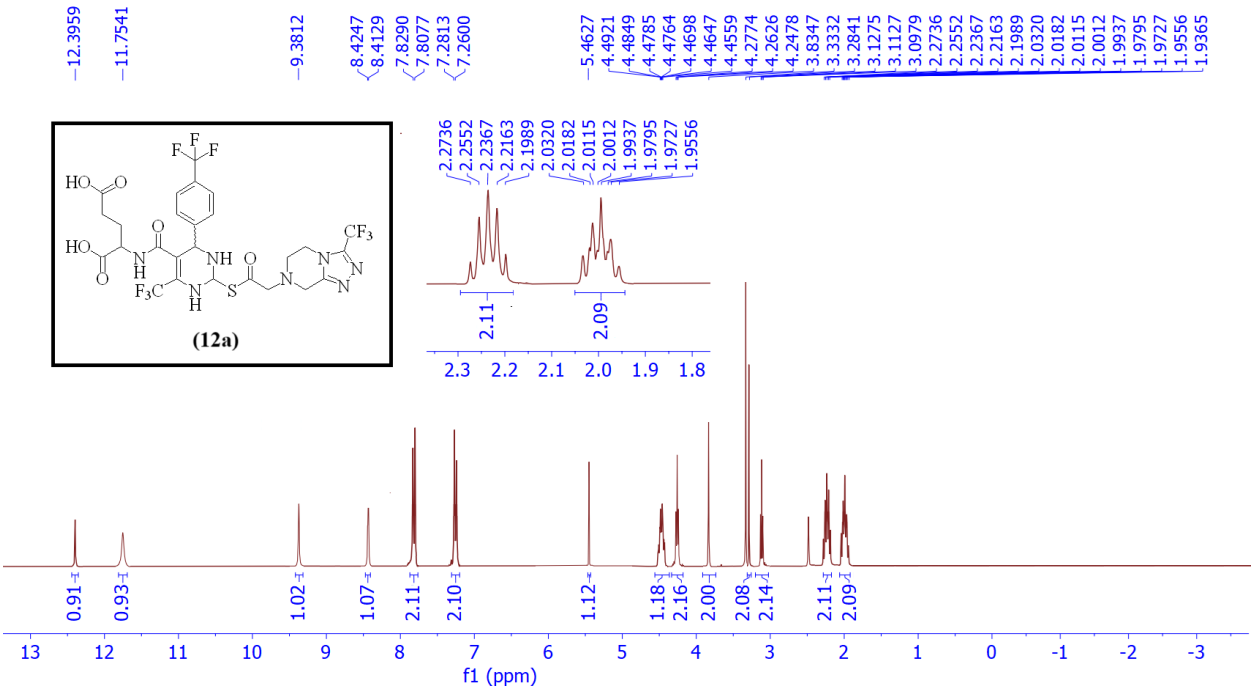

Figure S-17: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **12a**

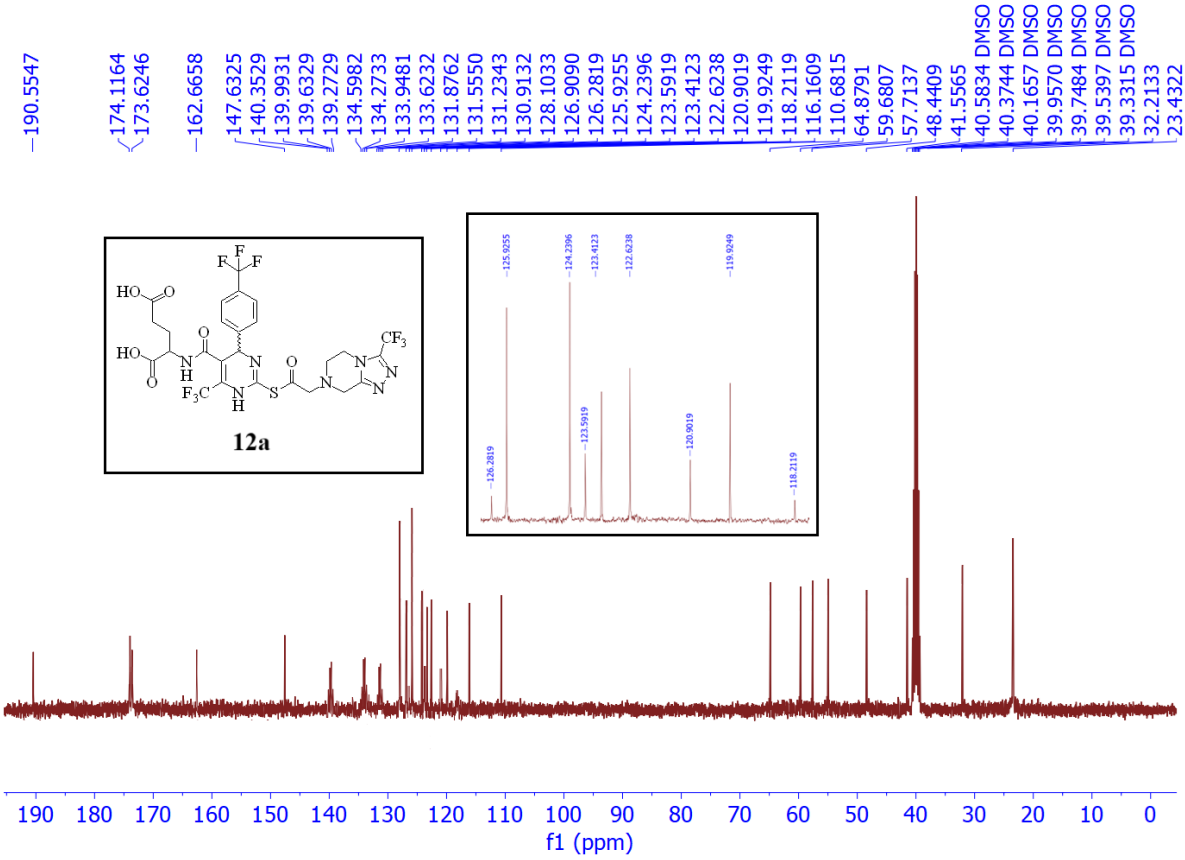

Figure S-18: ^{13}C NMR (100 MHz, DMSO-d_6) of compound **12a**

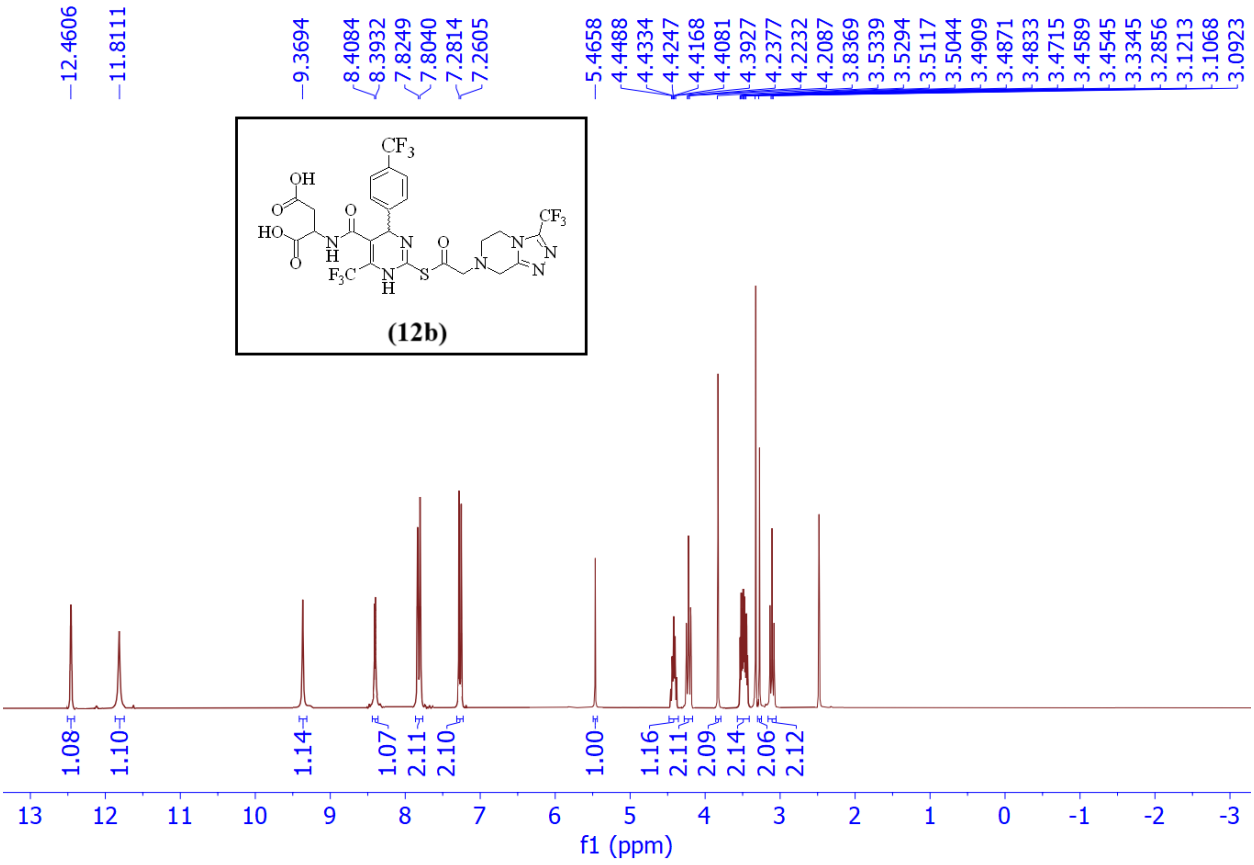

Figure S-19: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **12b**

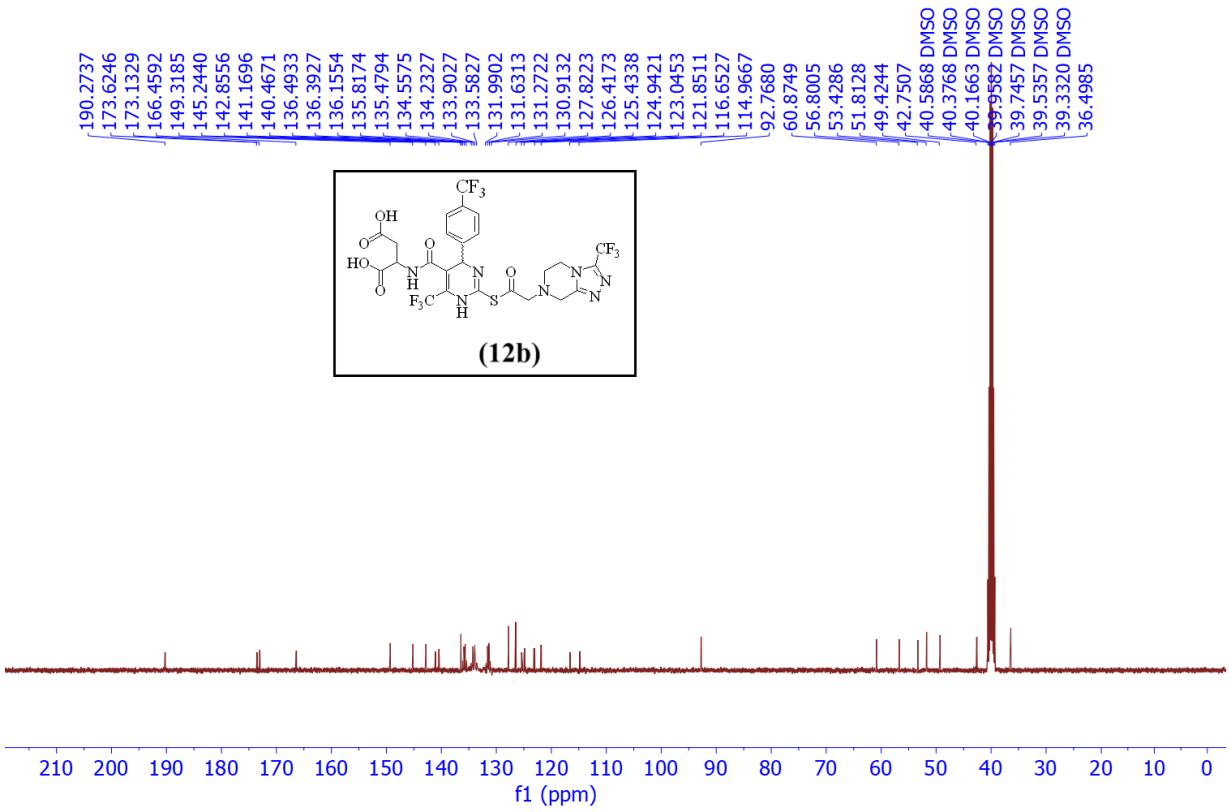

Figure S-20: ^{13}C NMR (100 MHz, DMSO-d_6) of compound **12b**

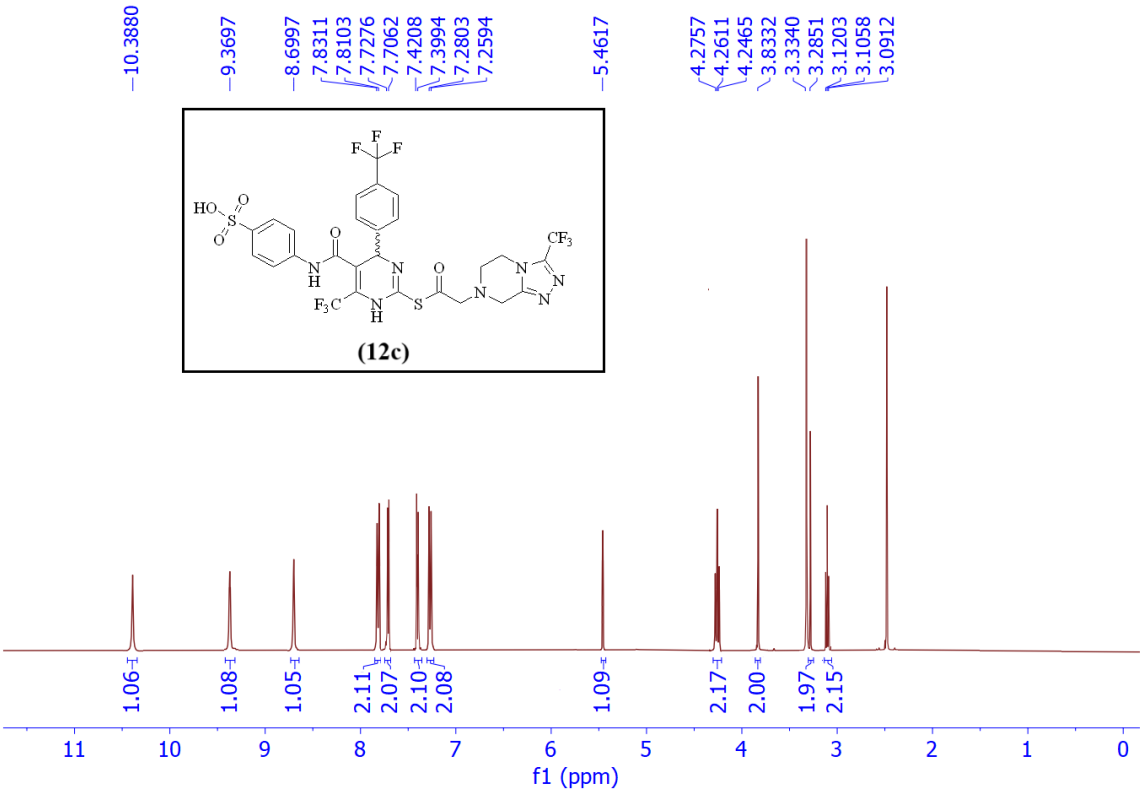

Figure S-21: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **12c**

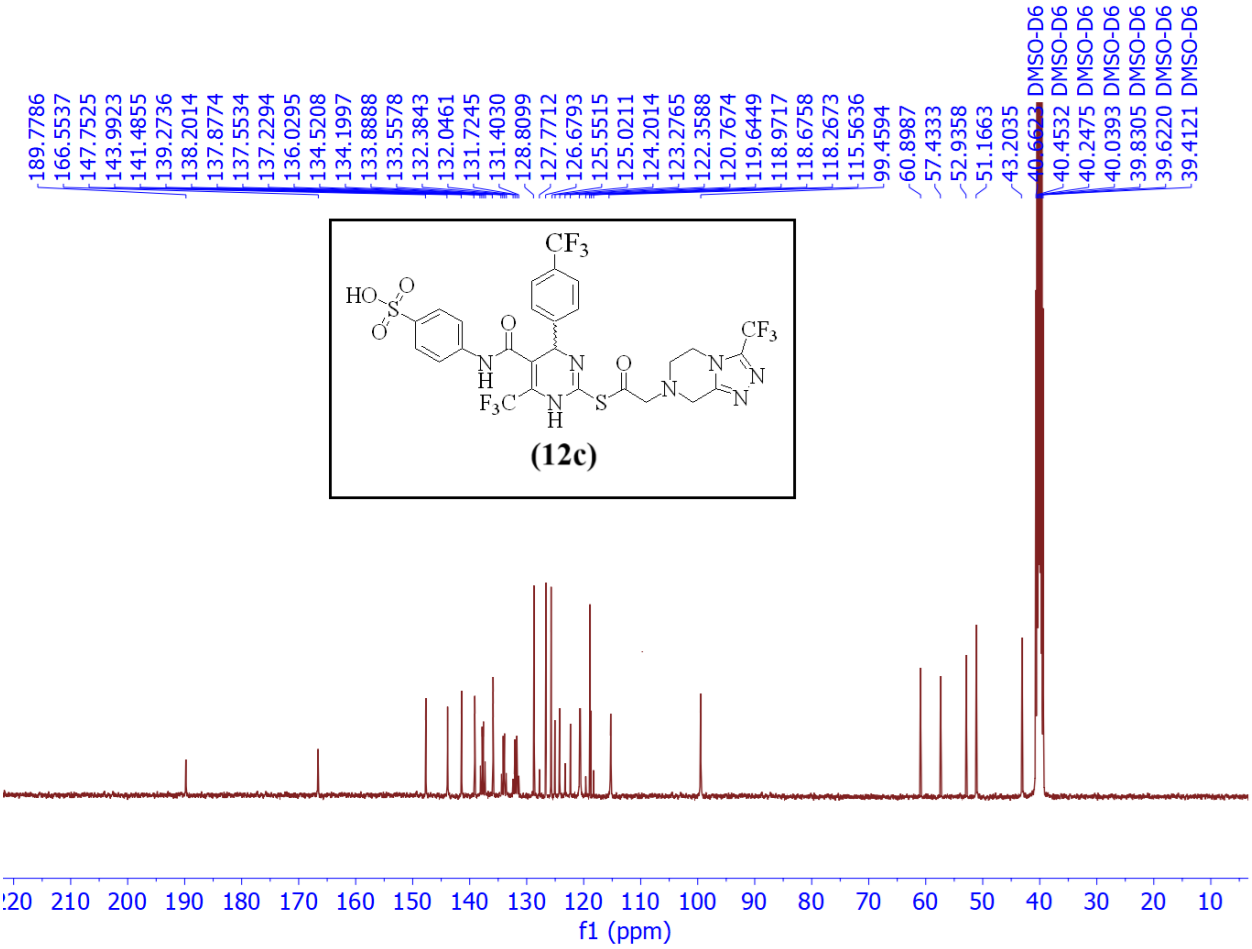

Figure S-22: ^{13}C NMR (100 MHz, DMSO-d_6) of compound **12c**

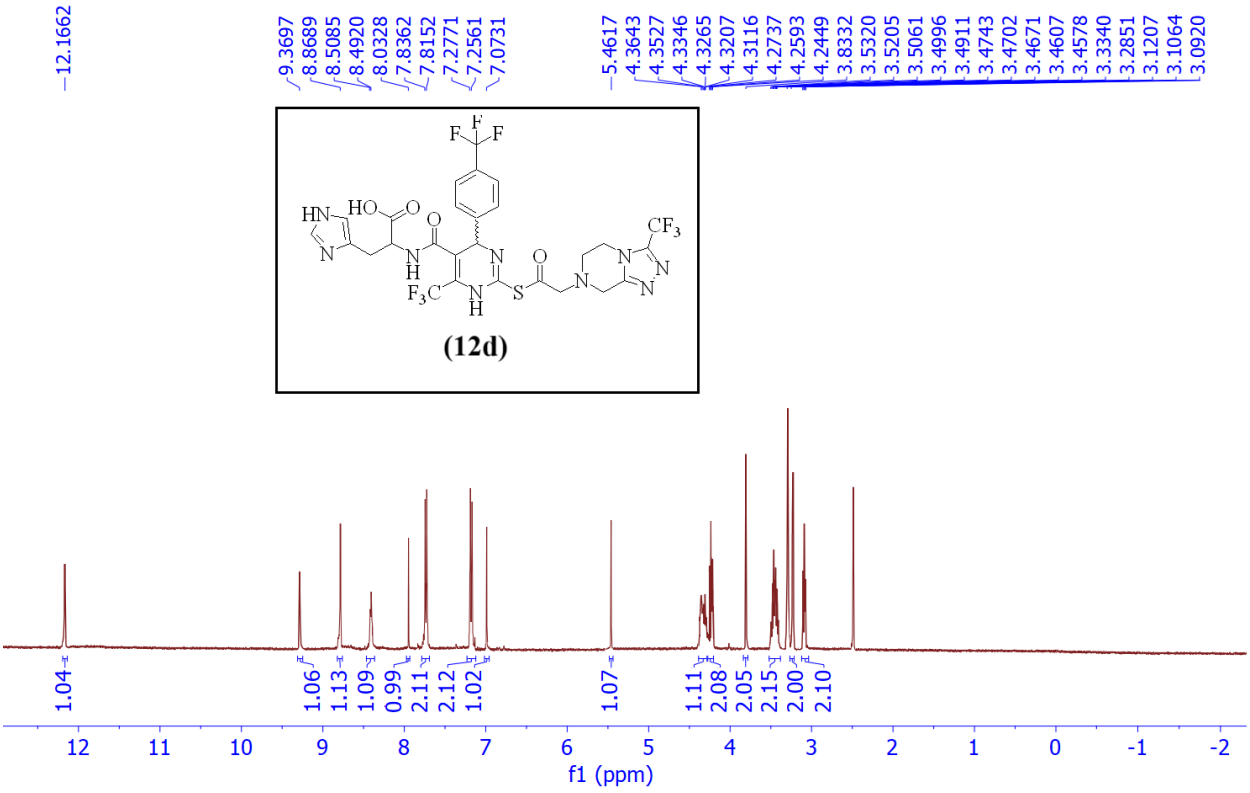

Figure S-23: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **12d**

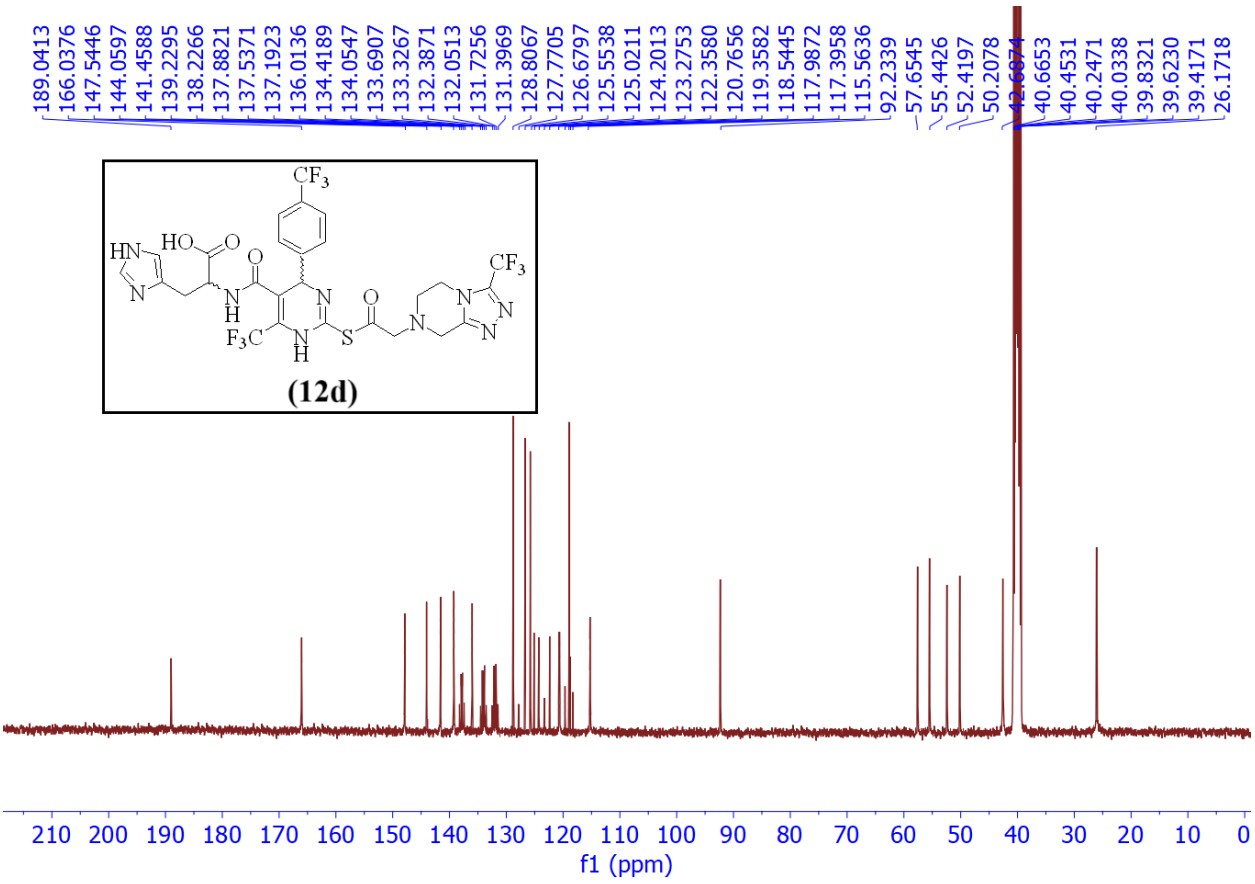

Figure S-24: ^{13}C NMR (100 MHz, DMSO-d_6) of compound **12d**

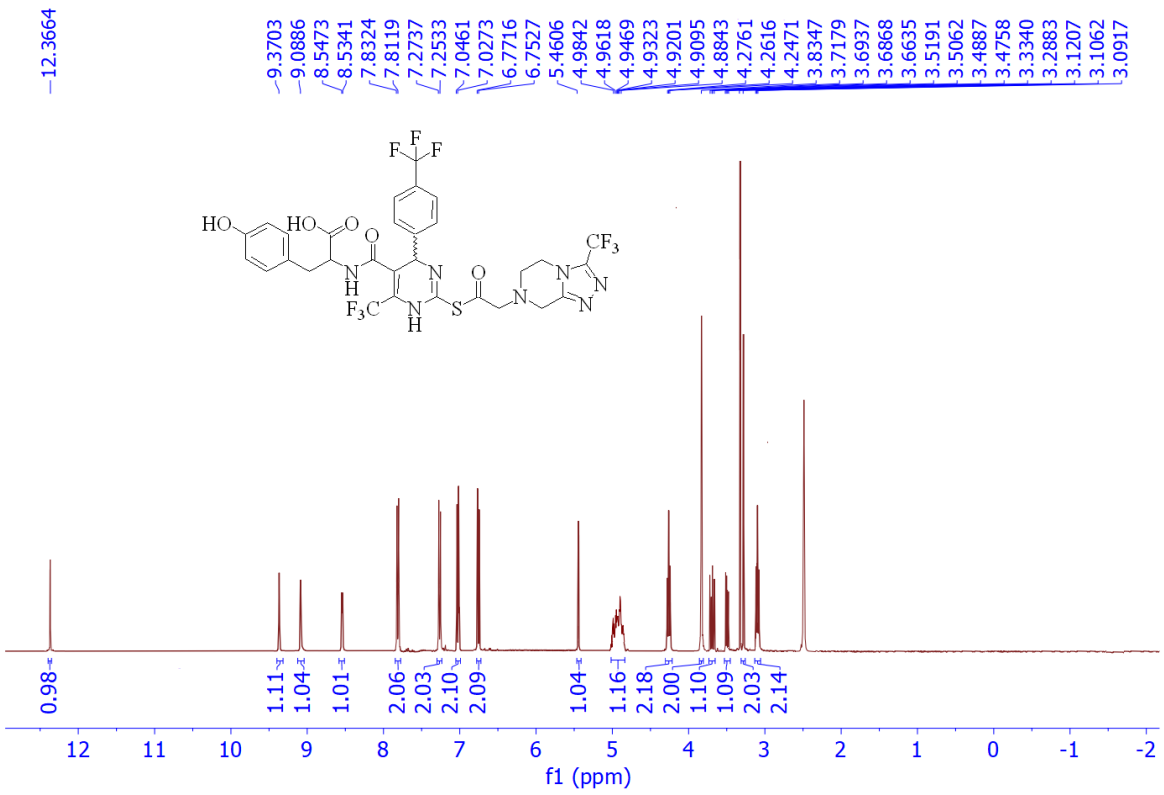

Figure S-25: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **12e**

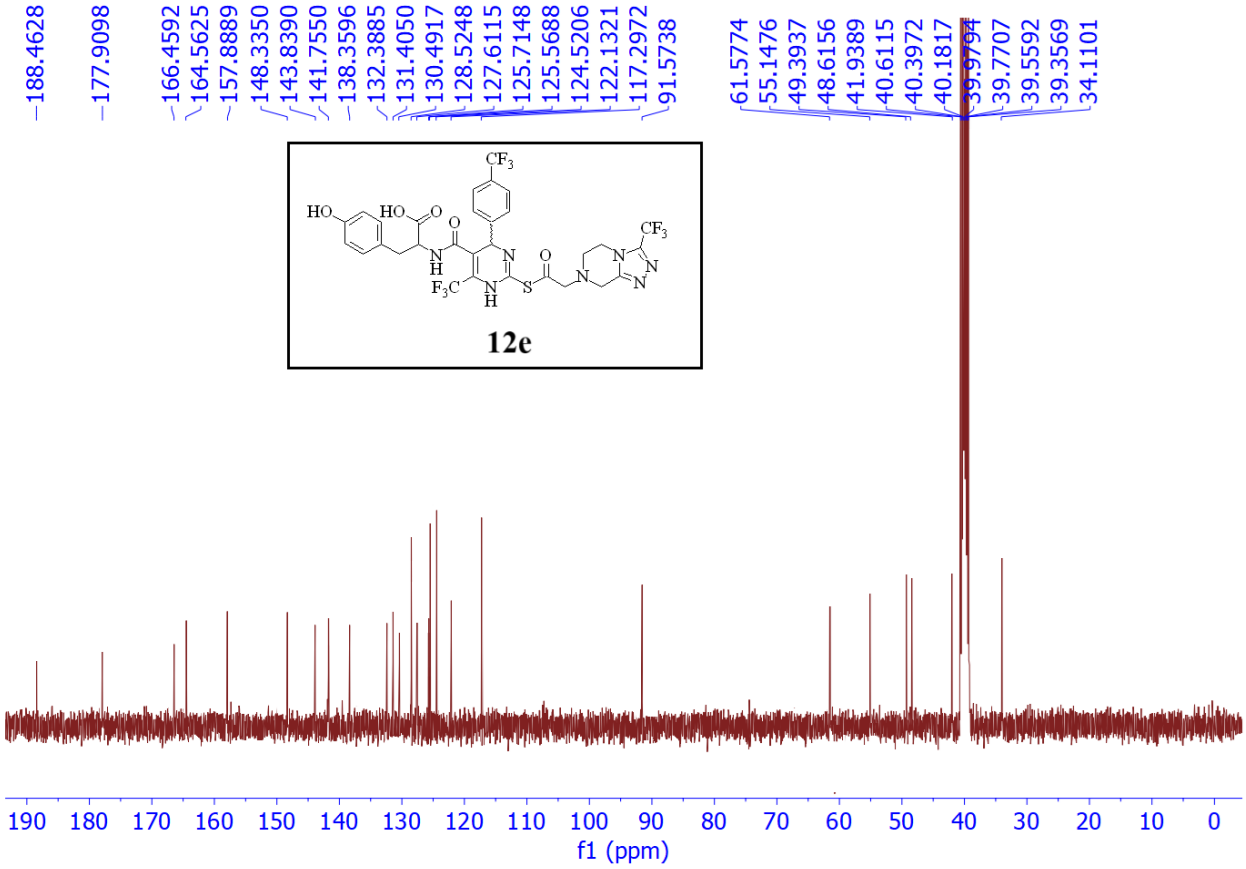

Figure S-26: ^{13}C NMR (100 MHz, DMSO-d_6) of compound **12e**

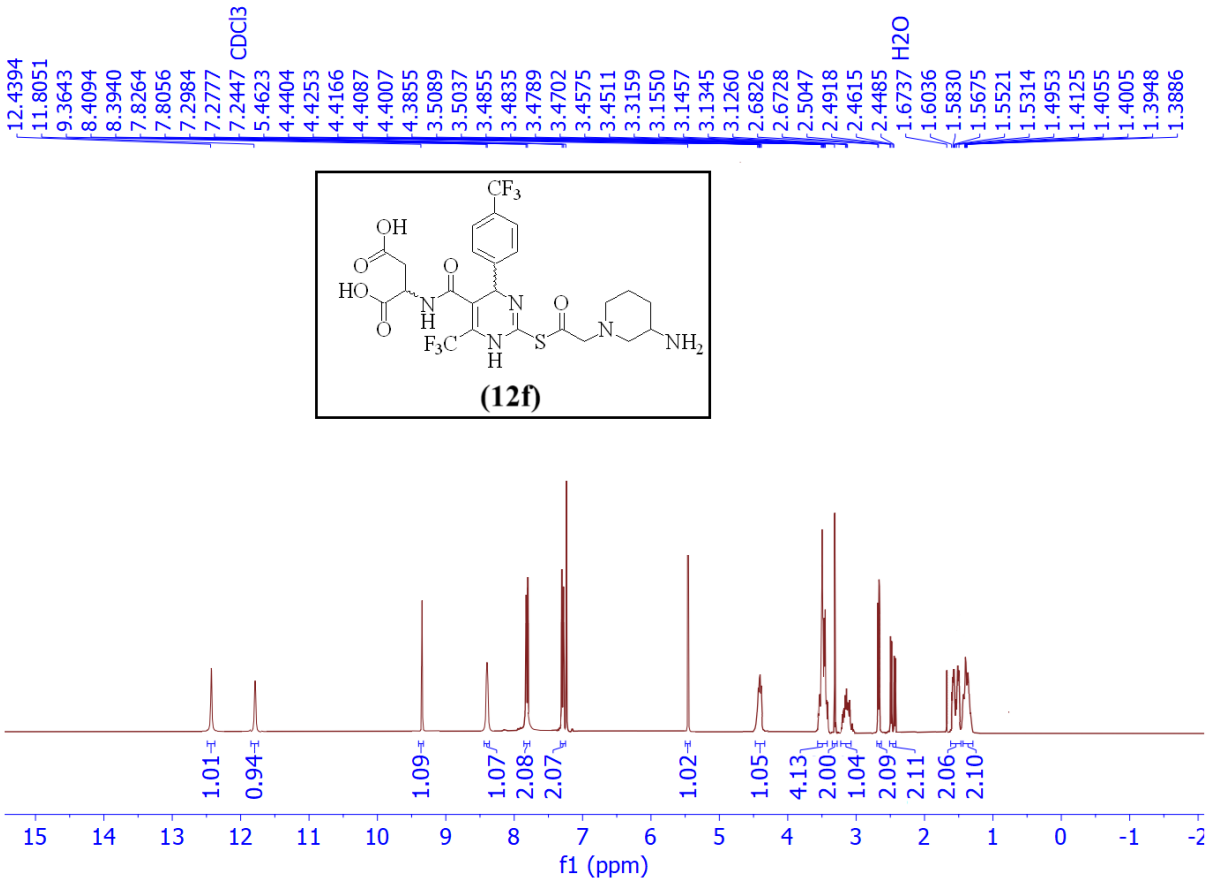

Figure S-27: ^{1}H NMR (400 MHz, $CDCl_3$) of compound **12f**

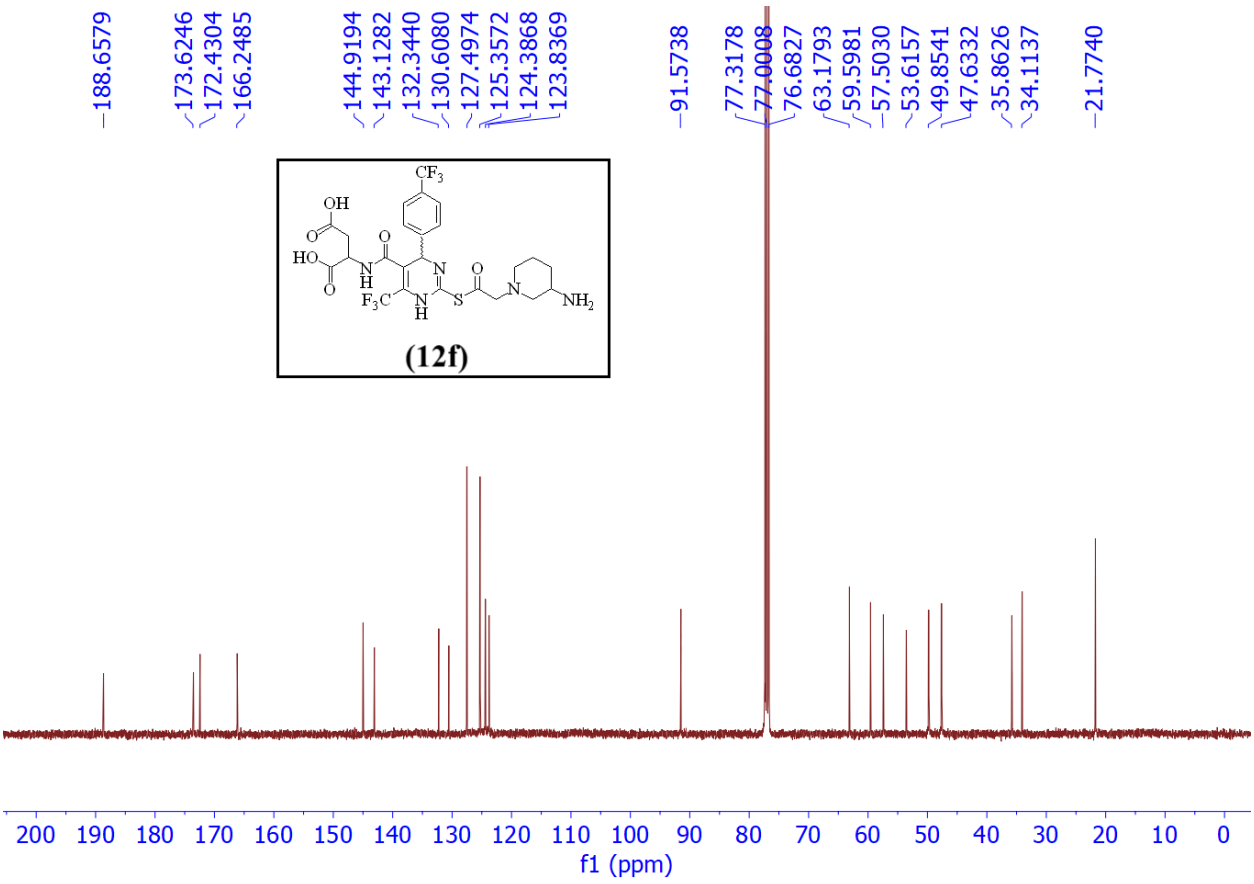

Figure S-28: ^{13}C NMR (100 MHz, $CDCl_3$) of compound **12f**

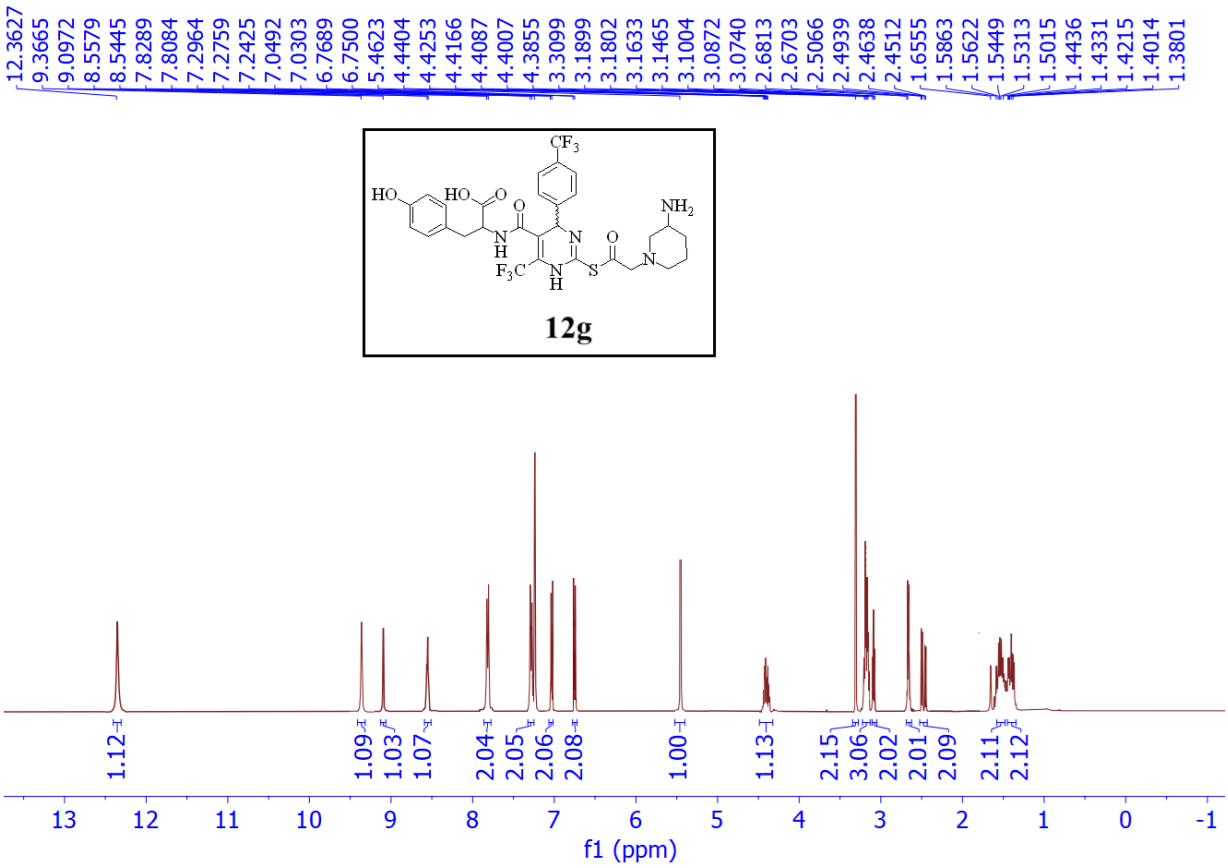

Figure S-29: ^{1}H NMR (400 MHz, $CDCl_3$) of compound **12g**

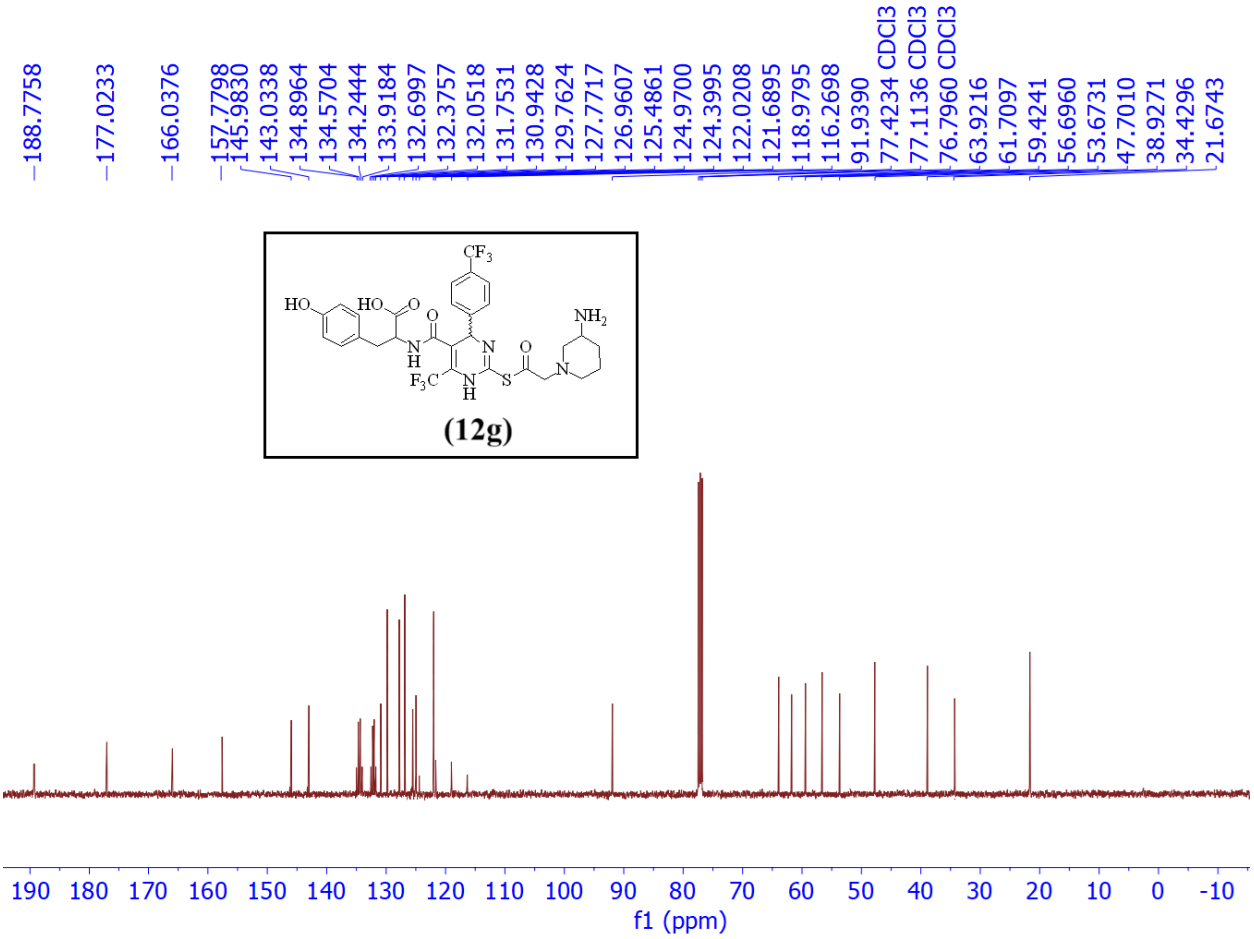

Figure S-30: ^{13}C NMR (100 MHz, $CDCl_3$) of compound **12g**

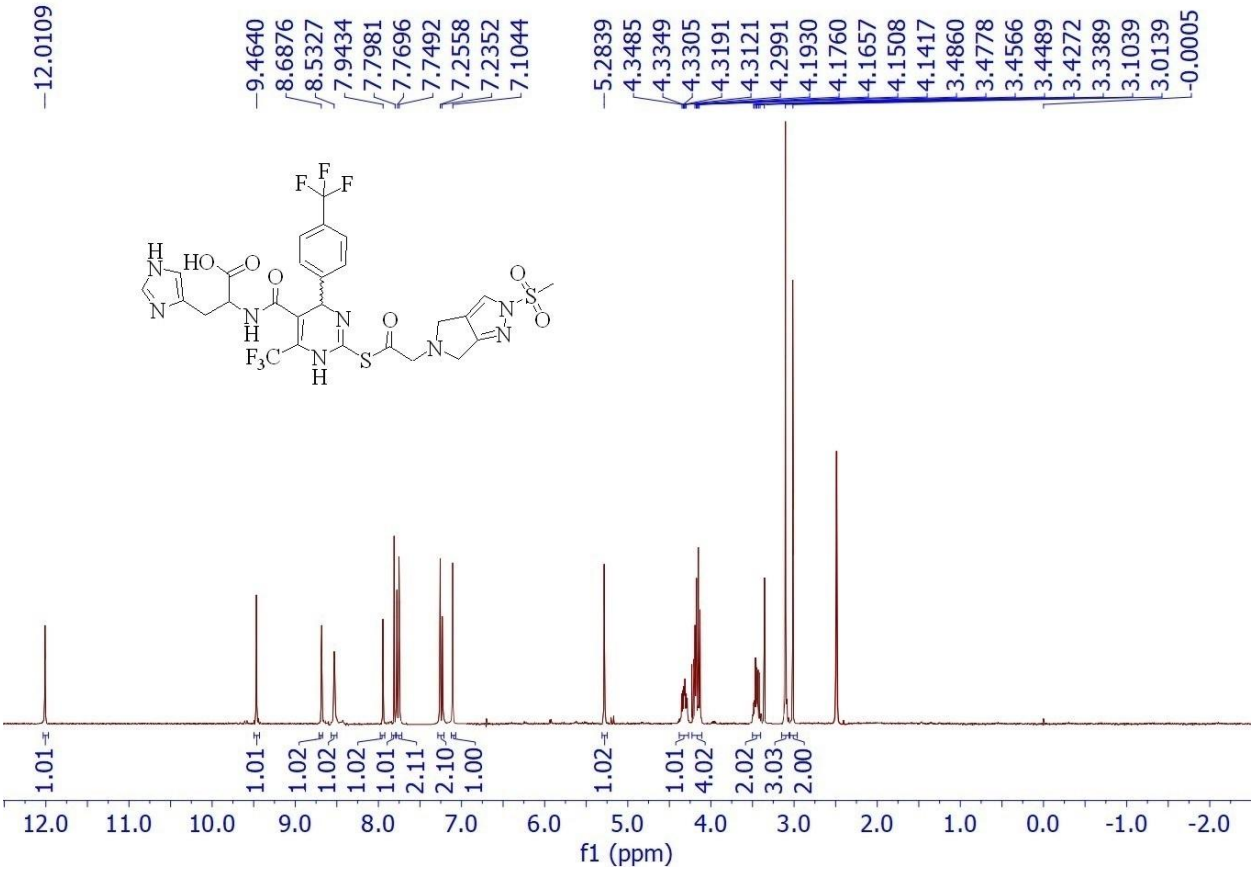

Figure S-31: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **12h**

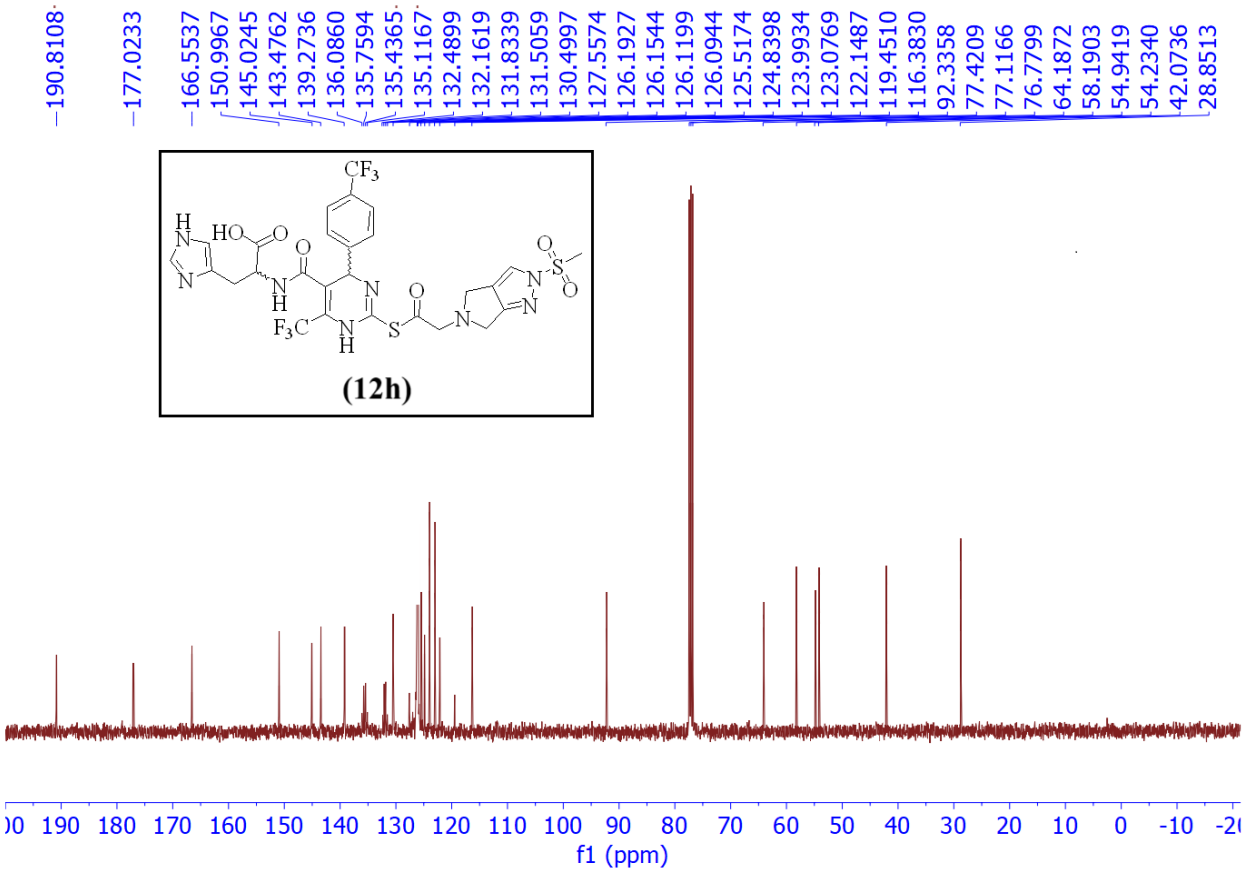

Figure S-32: ^{13}C NMR (100 MHz, $CDCl_3$) of compound **12h**

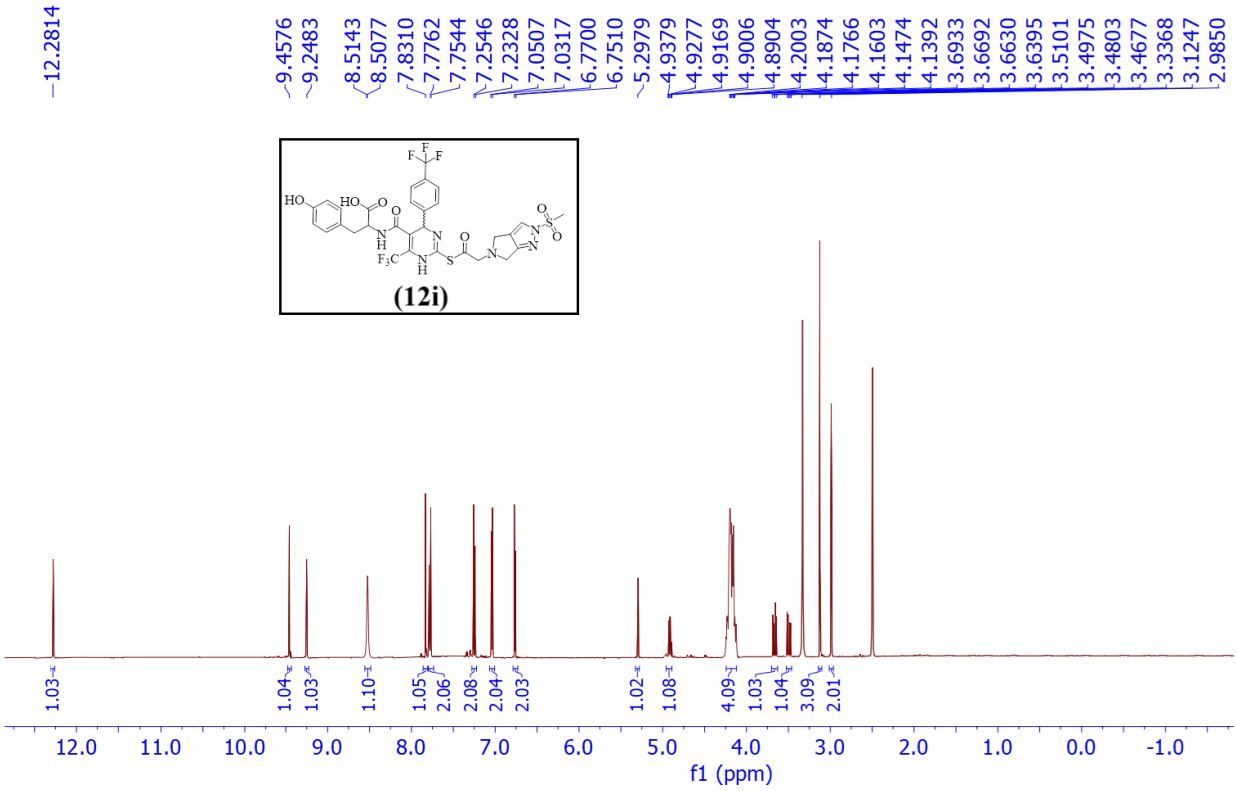

Figure S-33: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **12i**

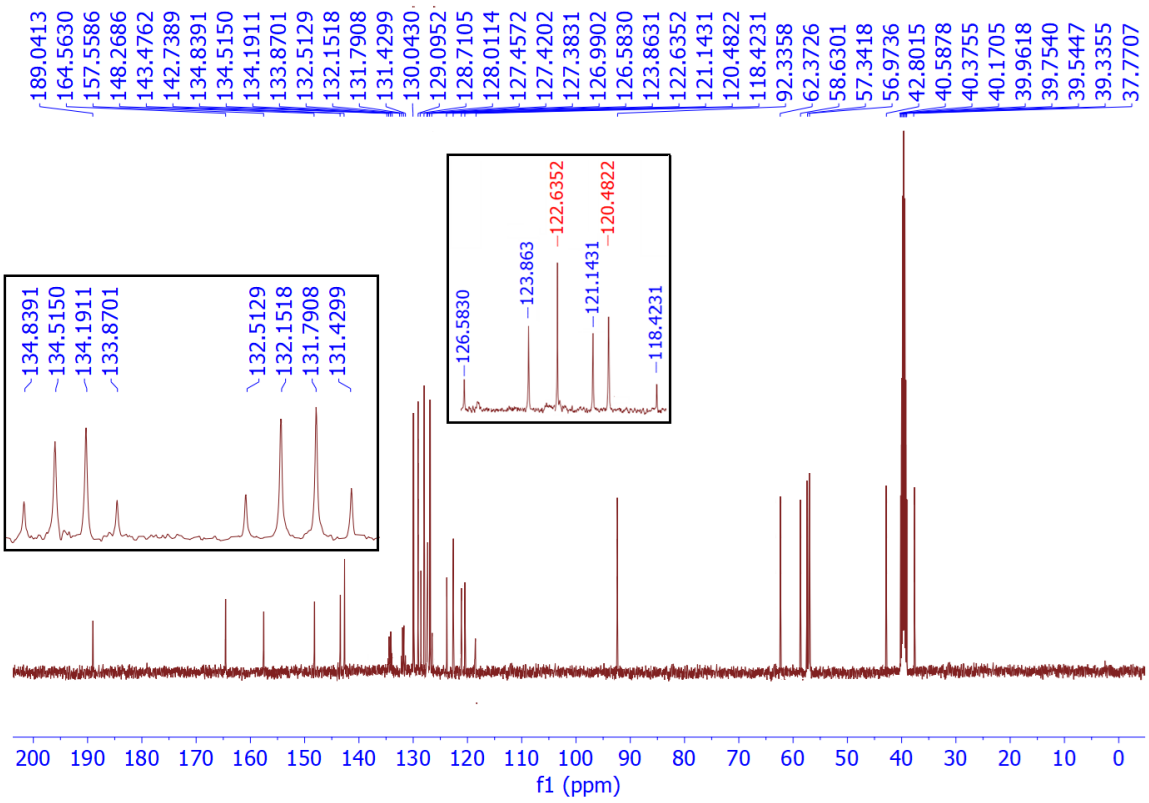

Figure S-34: ^{13}C NMR (100 MHz, DMSO-d_6) of compound **12i**

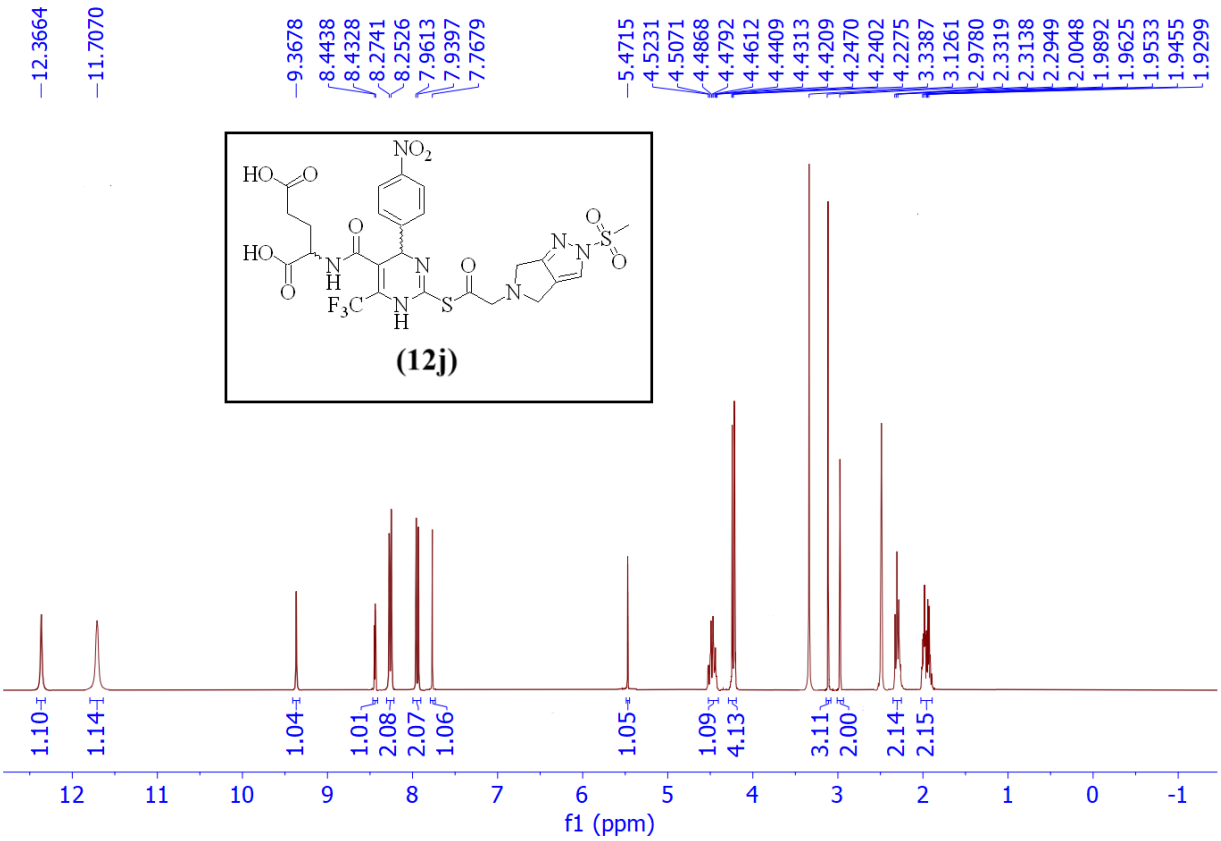

Figure S-35: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **12j**

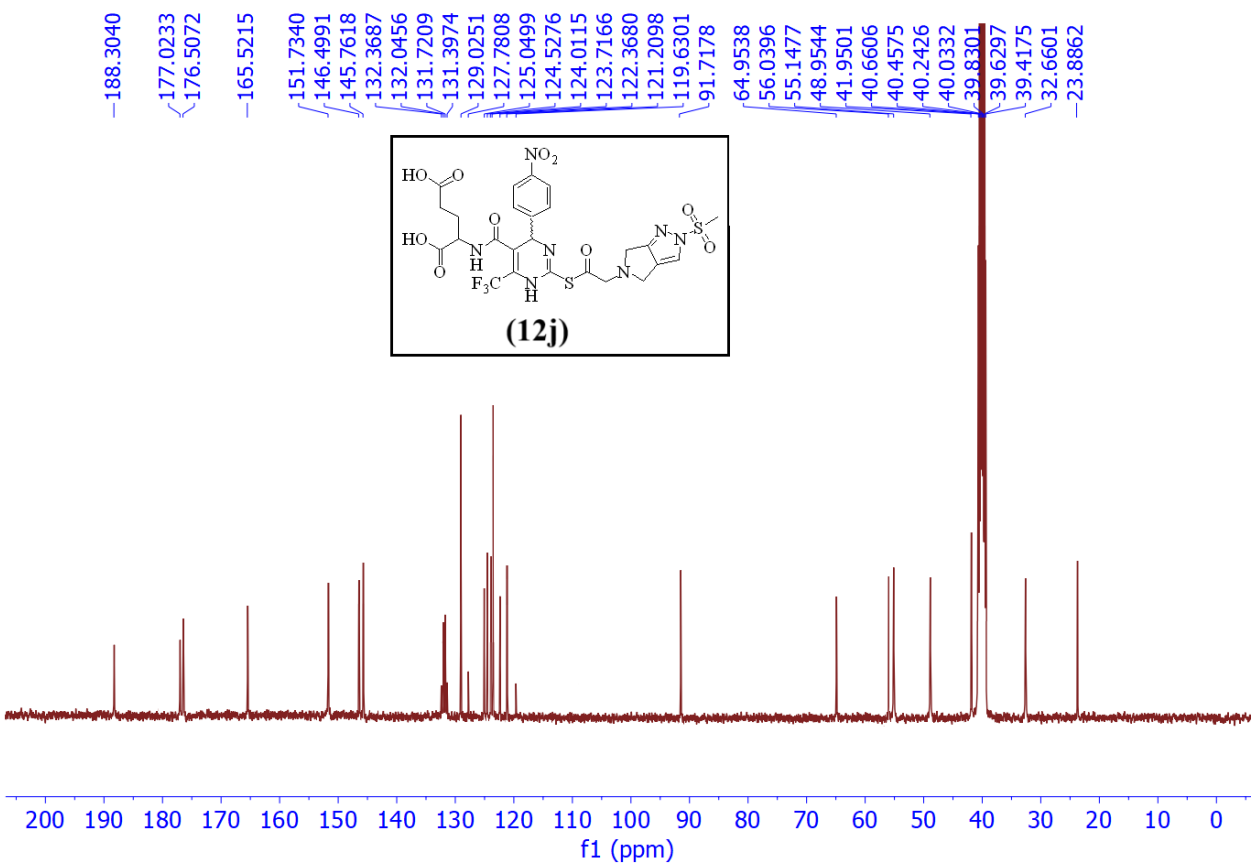

Figure S-36: ^{13}C NMR (100 MHz, DMSO-d_6) of compound **12j**

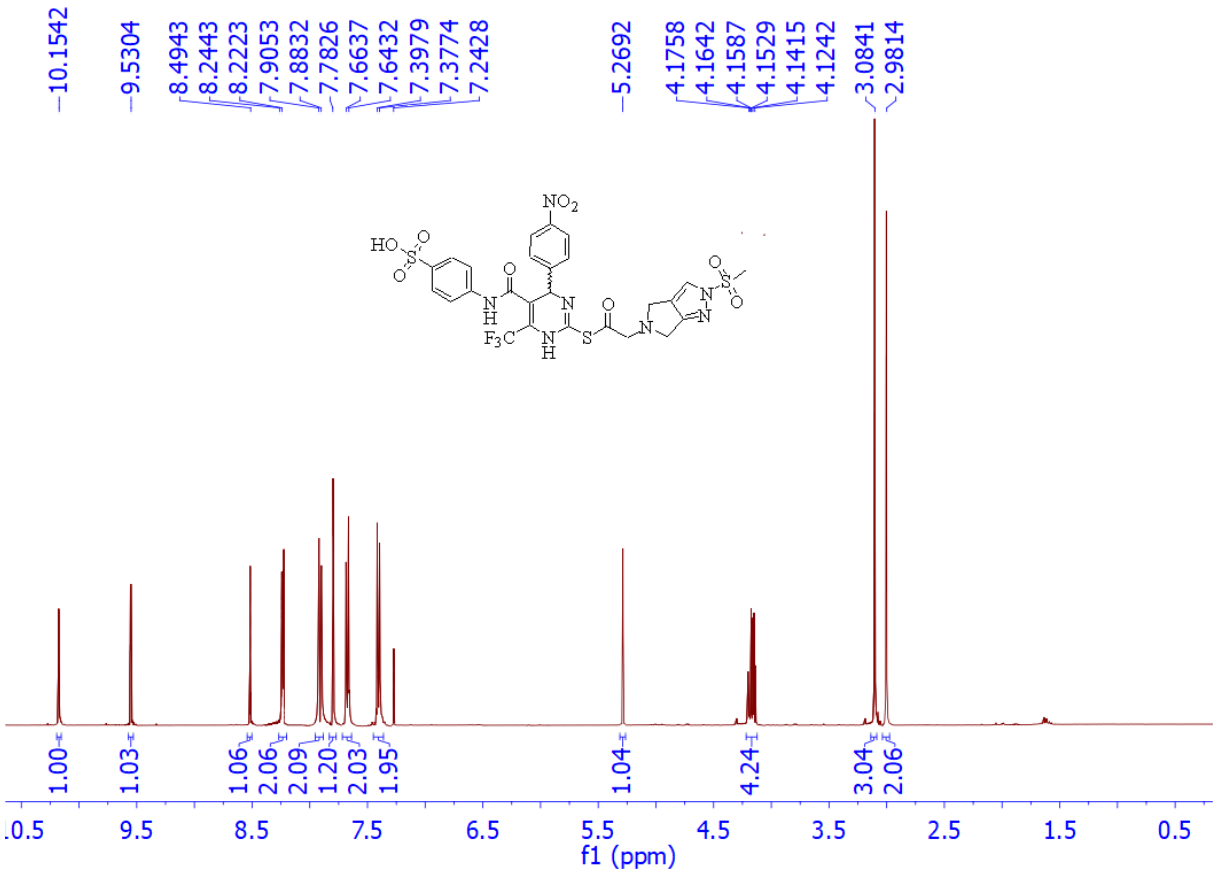

Figure S-37: ^{1}H NMR (400 MHz, $CDCl_3$) of compound **12k**

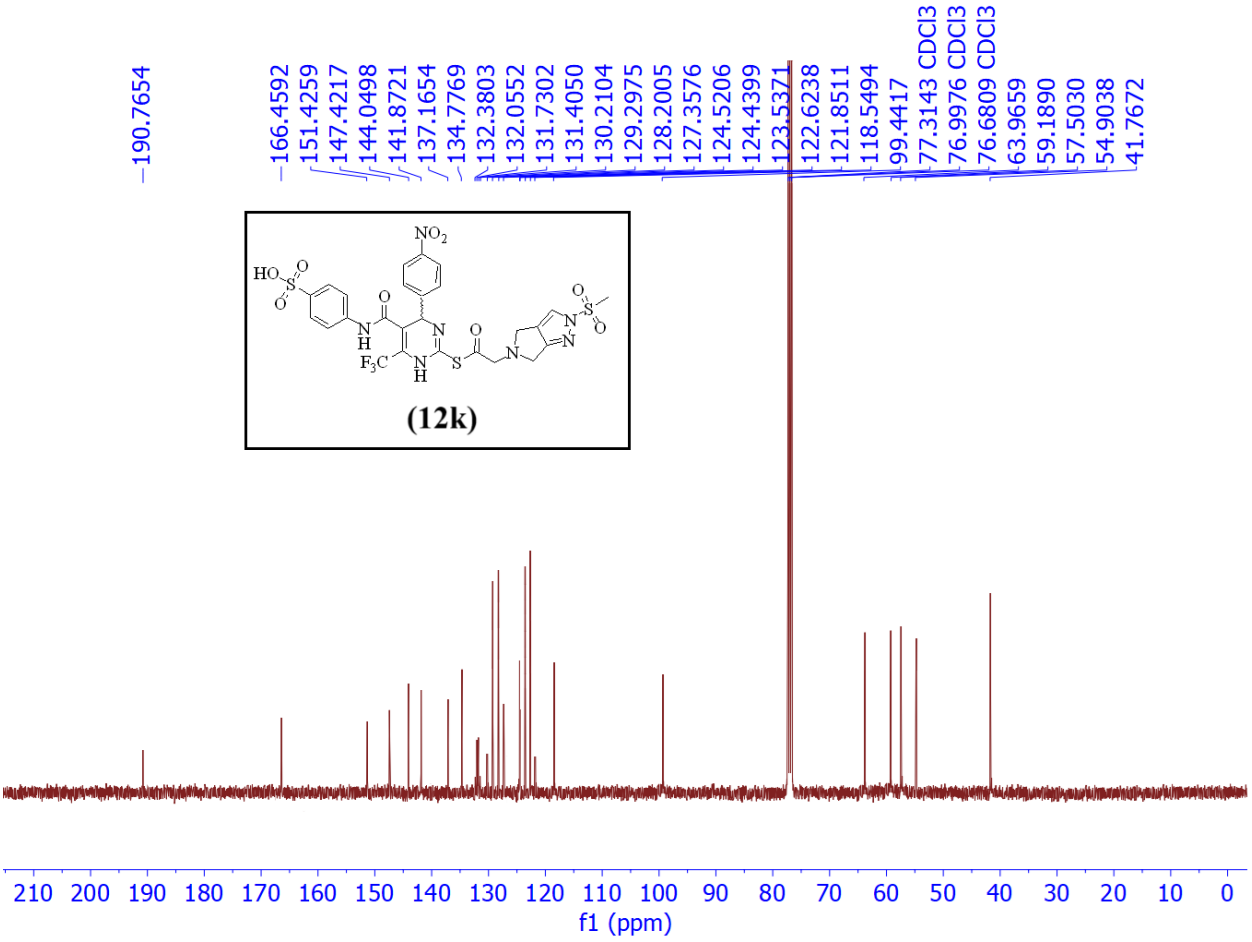

Figure S-38: ^{13}C NMR (100 MHz, $CDCl_3$) of compound **12k**

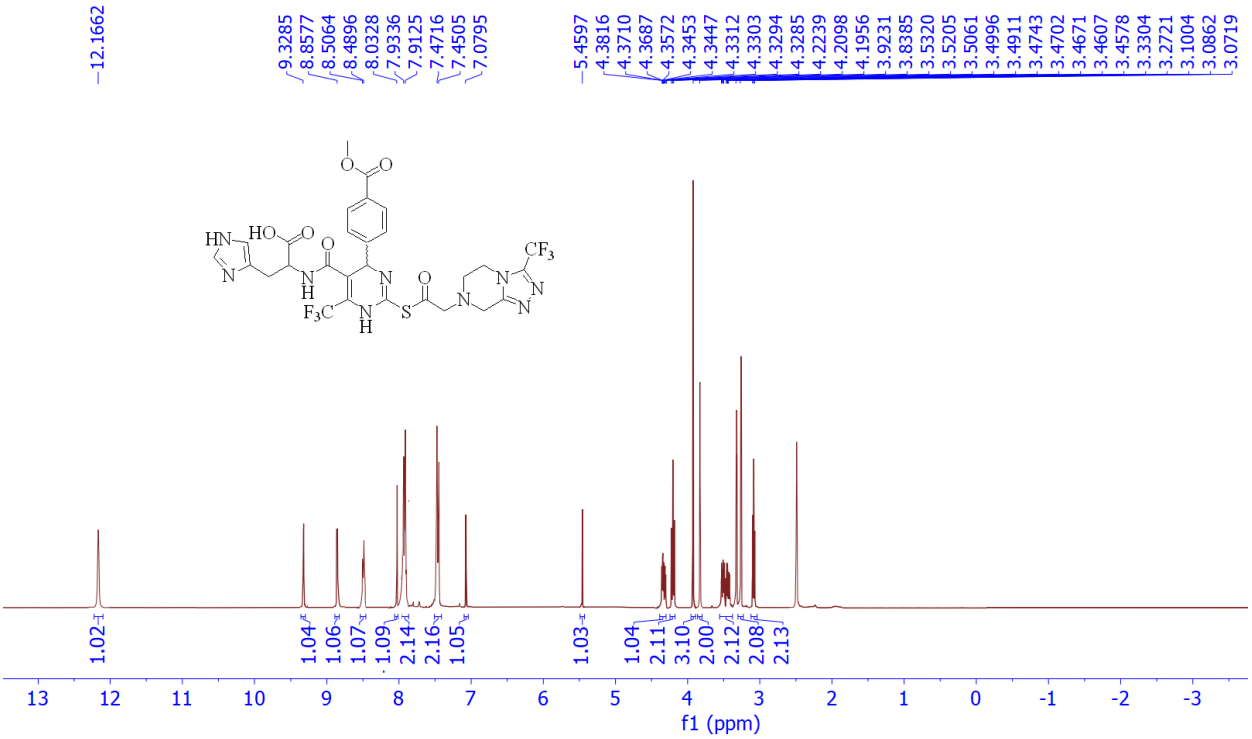

Figure S-39: ^{1}H NMR (400 MHz, DMSO-d_6) of compound **12l**

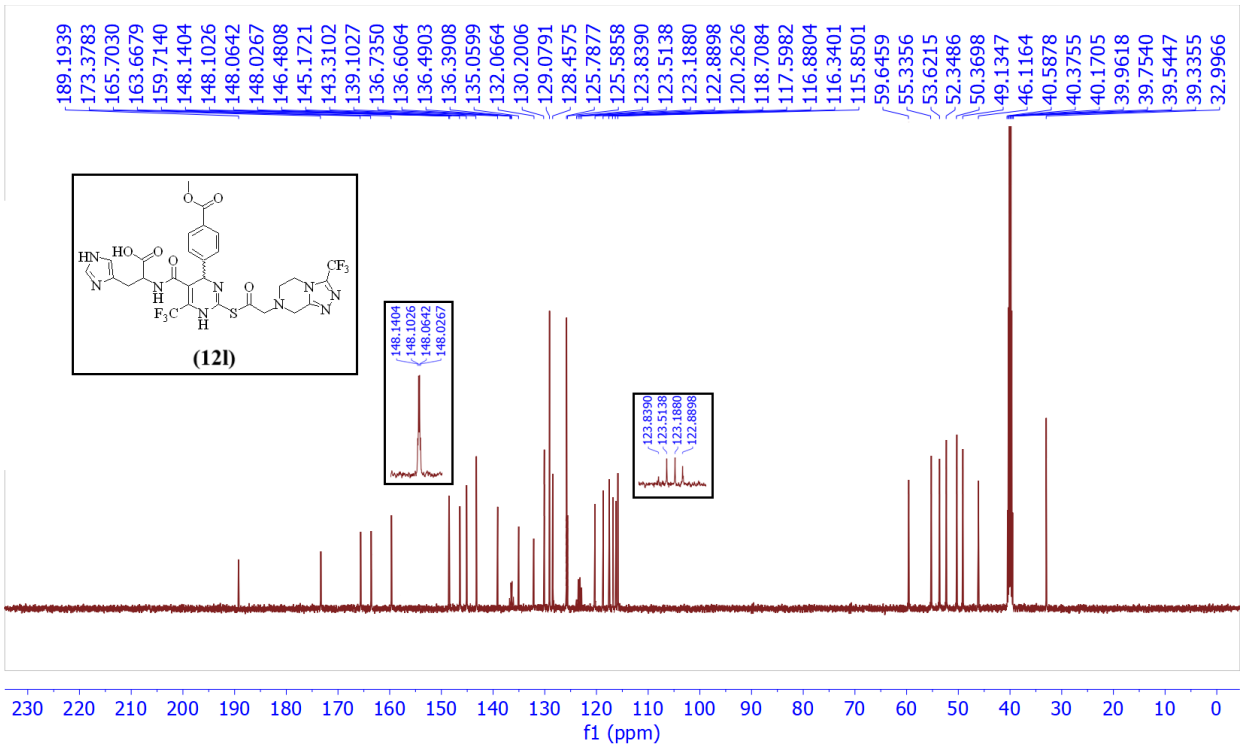

Figure S-40: ^{13}C NMR (100 MHz, DMSO-d_6) of compound **12l**