Supporting Information

A convenient, highly selective and eco-friendly N-Boc protection of pyrimidines under microwave irradiation

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General :

All commercially available chemicals were of reagent grade and used as received. The reactions were monitored by thin layer chromatography (TLC) analysis using silica gel plates (Kieselgel 60F254, E. Merck). Column chromatography was carried out on Silica Gel 60 M (0.040e0.063 mm, E. Merck). The ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian InovaUnity 400 spectrometer (400 MHz) in $CDCl_3$, shift values in parts per million relative to $SiMe_4$ as internal reference. High Resolution Mass spectra were performed on a Bruker maXis mass spectrometer. Sonication was performed on an Elmasonic P30H ultrasonic instrument with a frequency of 80 kHz and an effective power of 100 W. Microwave irradiations were performed in sealed vessels placed in a Biotage Initiator system using a standard absorbance level (300 W maximum power)

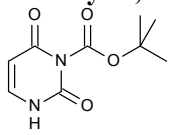
Synthesis and characterisation of compounds:

General procedure 1

To a solution of C5-substituted uracil (300 mg) in DEM (20 mL) were added Boc_2O (3 eq.) and DMAP (0.35 eq.). After microwave at 70°C during 5 minutes, the solution is evaporated under reduced pressure and the N1,N3-bis-

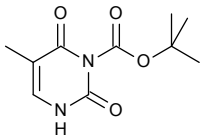
boc-uracil is used in the next step without further purification. The crude was then diluted in 5 mL of DEM/EtOH (9/1) with SiO_2 60% w/w under microwaves irradiation until the completion of the reaction. After evaporation of all the volatiles, the resulting N3-substituted uracil was purified by flash chromatography (ethyl acetate) to afford pure products as white solids.

***tert*-butyl-2,4-dioxopyrimidine-3-carboxylate** (5)



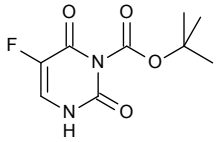
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.20 (dd, *J* = 7.8, 5.6 Hz, 1H), 5.76 (d, *J* = 7.8Hz, 1H), 1.60 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.84, 150.52, 147.52, 139.82, 102.18, 87.15, 27.49. HRMS calculated for $C_9H_{12}N_2O_4$ 212.0797, found 212.0791.

***tert*-butyl-5-methyl-2,4-dioxopyrimidine-3-carboxylate** (6)



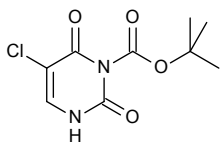
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.06 (d, *J* = 1.1 Hz, 1H), 1.91 (d, *J* = 1.1 Hz, 3H), 1.59 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.90, 150.80, 147.91, 136.10, 110.47, 86.97, 27.46, 12.27. HRMS calculated for $C_{10}H_{14}N_2O_4$ 226.0954, found 226.0953.

***tert*-butyl-5-fluoro-2,4-dioxopyrimidine-3-carboxylate** (8a)



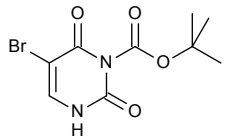
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 4.6 Hz, 1H), 1.61 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.91 (d, *J* = 23.2Hz), 149.10, 146.35, 140.50 (d, *J* = 232.22Hz), 124.11 (d, *J* = 33.1 Hz), 88.09, 27.46. ^{19}F NMR (376 MHz, $CDCl_3$) δ -165.17 (d, *J* = 4.6Hz). HRMS calculated for $C_9H_{12}N_2O_4$ 230.0703, found 230.0702.

***tert*-butyl-5-chloro-2,4-dioxopyrimidine-3-carboxylate** (8b)



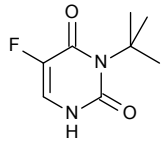
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 1.61 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.99, 149.52, 146.52, 136.72, 109.38, 88.02, 27.44. HRMS calculated for $C_9H_{12}N_2O_4$ 246.0407, found 246.0405.

***tert*-butyl-5-bromo-2,4-dioxopyrimidine-3-carboxylate** (8c)



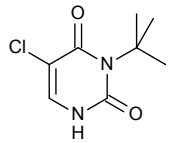
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 1.63 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.10, 149.99, 146.67, 139.76, 96.74, 88.03, 27.44. HRMS calculated for $C_9H_{12}N_2O_4$ 289.9902, found 289.9896.

5-fluoro-3-*tert*-butylpyrimidine-2,4-dione (14a)



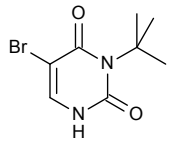
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.10 (d, J = 3.8 Hz, 1H), 1.75 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.39 (d, J = 24.0 Hz), 152.43, 140.85 (d, J = 232.5 Hz), 120.57 (d, J = 32.4 Hz), 63.84, 29.73. ^{19}F NMR (376 MHz, $CDCl_3$) δ -164.03 (d, J = 3.8 Hz). HRMS calculated for $C_9H_{12}N_2O_4$ 186.0805, found 186.0800.

5-chloro-3-*tert*-butylpyrimidine-2,4-dione (14b)



^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.29 (s, 1H), 1.70 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.08, 152.33, 133.89, 109.83, 63.79, 29.68. HRMS calculated for $C_9H_{12}N_2O_4$ 202.0509, found 212.0500.

5-bromo-3-*tert*-butylpyrimidine-2,4-dione (14c)

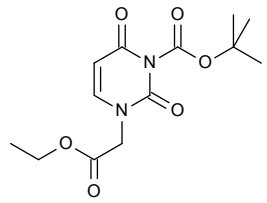


^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.45 (s, 1H), 1.71 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.17, 153.53, 137.35, 97.85, 63.86, 29.73. HRMS calculated for $C_9H_{12}N_2O_4$ 246.0004, found 246.0001.

General procedure 2

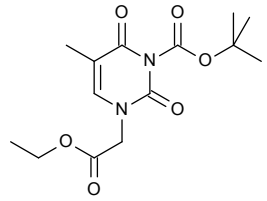
To a DMF (2 mL) solution of the substituted protected uracil (1 eq.) were added ethyl bromoacetate (1 eq.) and K_2CO_3 (1 eq.). The solution was stirred 20h at room temperature, and dissolved in 10 mL of EtOAc and 10 mL of NH_4Cl. The aqueous layer was extracted 3 times with 10 mL of EtOAc, and the organic layer was washed with H_2O (5 x 10 mL), and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford pure products as colorless oils.

***tert*-butyl-3-(2-ethoxy-2-oxoethyl)-2,6-dioxopyrimidine-1-carboxylate** (11)



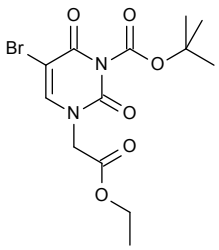
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.0 Hz, 1H), 5.74 (d, *J* = 8.0 Hz, 1H), 4.42 (s, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.56 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.94, 160.37, 148.94, 147.41, 143.44, 102.30, 86.95, 62.34, 48.73, 27.43, 13.95. HRMS calculated for $C_{13}H_{18}N_2O_6$ 298.1164, found 298.1165.

***tert*-butyl-3-(2-ethoxy-2-oxoethyl)-5-methyl-2,6-dioxopyrimidine-1-carboxylate** (12)



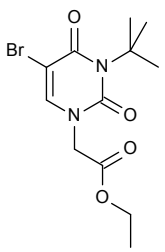
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 4.42 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.92 (s, 3H), 1.58 (s, 9H), 1.27 (q, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.28, 161.49, 148.98, 147.69, 139.54, 110.86, 86.78, 62.21, 48.69, 27.41, 14.06, 12.35. HRMS calculated for $C_{14}H_{20}N_2O_6$ 312.1321, found 312.1320.

***tert*-butyl-5-bromo-3-(2-ethoxy-2-oxoethyl)-2,6-dioxopyrimidine-1-carboxylate**



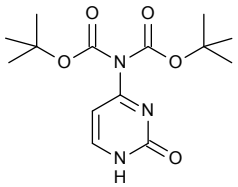
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 4.47 (s, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.59 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.69, 156.83, 148.26, 146.56, 142.96, 96.57, 87.69, 62.55, 49.01, 27.38, 14.07. HRMS calculated for $C_9H_{12}N_2O_4$ 376.0270, found 376.0264.

Ethyl-2-(5-bromo-3-*tert*-butyl-2,4-dioxopyrimidin-1-yl)acetate



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 4.35 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.67 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.32, 160.83, 151.30, 140.64, 97.51, 64.10, 62.14, 50.19, 29.59, 14.08. HRMS calculated for $C_9H_{12}N_2O_4$ 332.0371, found 332.0366.

N,N-di-*tert*-butoxycarbonyl-N-2-oxopyrimidin-4-yl (7)



To a DEM (20 mL) solution of cytosine (500 mg) were added Boc_2O (4 eq.) and DMAP (0.35 eq.). After microwave at 70°C for 7 minutes, the solution is concentrated in *vacuo*. The *tris*-boc-cytosine is dissolved in 5 mL of solvent, and stirred under variable conditions until the completion of the reaction. After the evaporation of all the volatiles, the crude product was purified by flash chromatography (eluting ethyl acetate) to afford **7** as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.01 (s, 1H), 7.68 (d, *J* = 7.1 Hz, 1H), 7.09 (d, *J* = 7.1 Hz, 1H), 1.53 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.67, 158.46, 149.44, 145.61, 96.72, 84.97, 27.71. HRMS calculated for $C_{14}H_{21}N_3O_5$ 311.1481, found 311.1481.

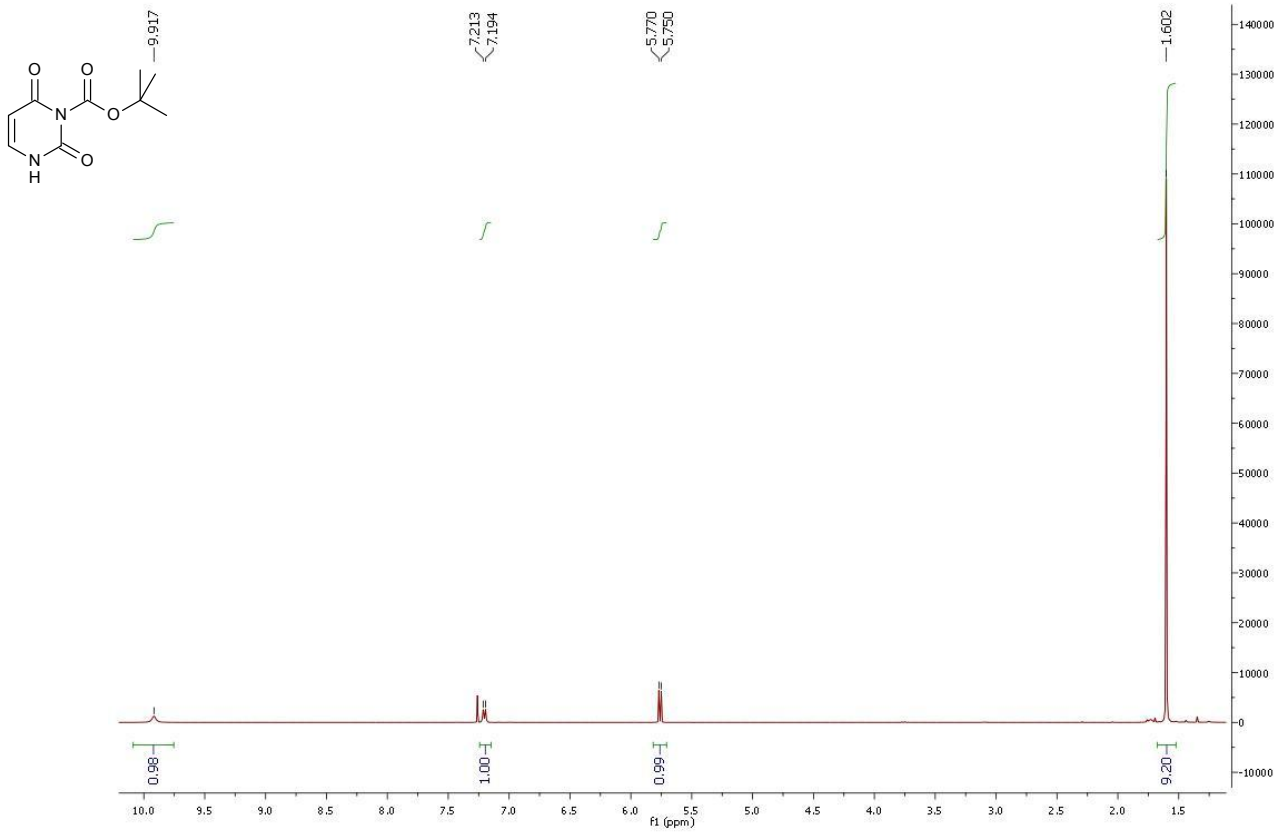


Figure 1: ^{1}H NMR compound **5**

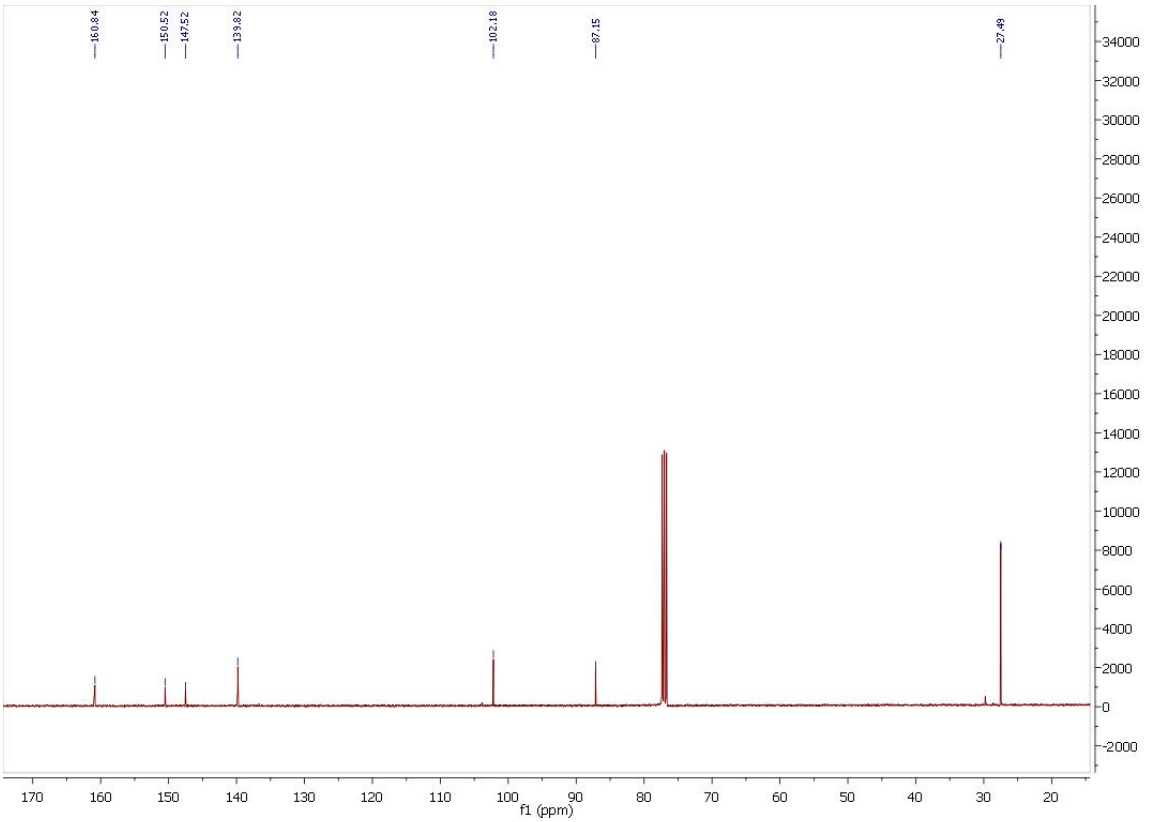


Figure 2: ^{13}C NMR compound **5**

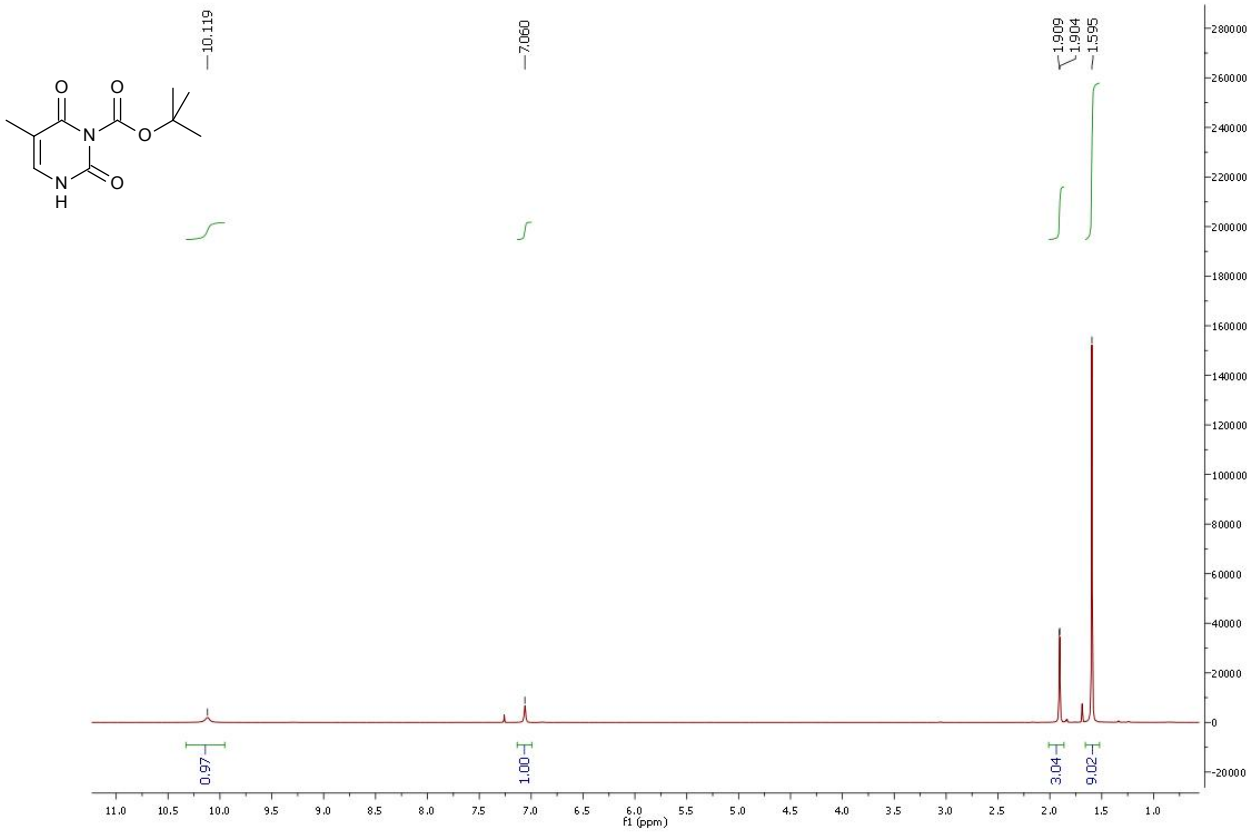


Figure 3 : ^{1}H NMR compound **6**

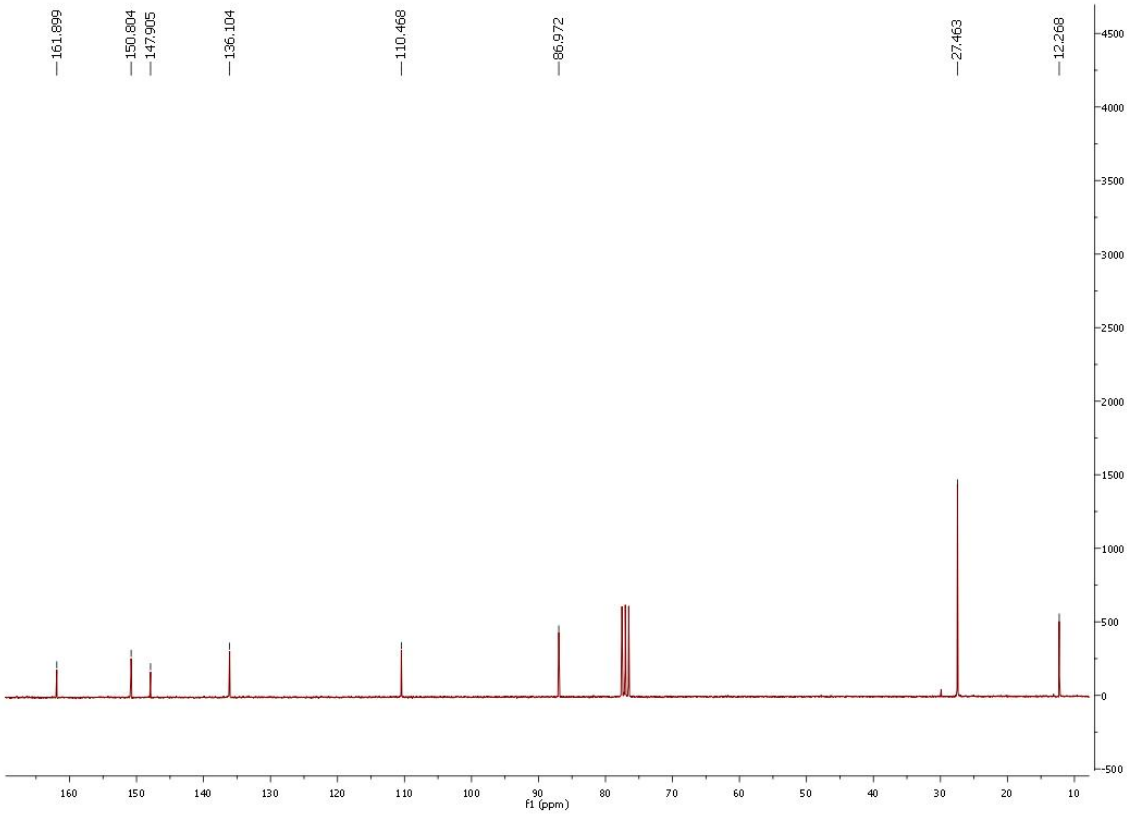


Figure 4: ^{13}C NMR compound **6**

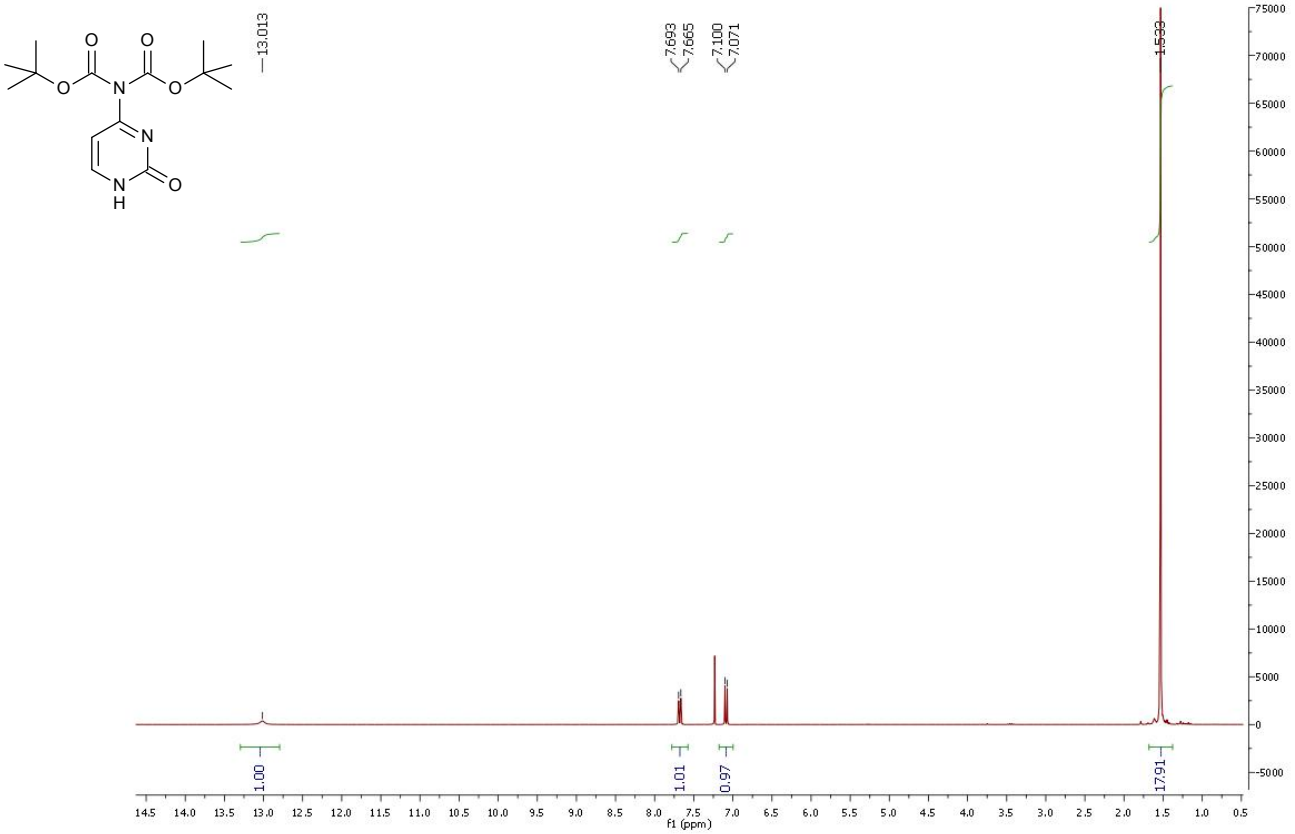


Figure 5: ^{1}H NMR compound **7**

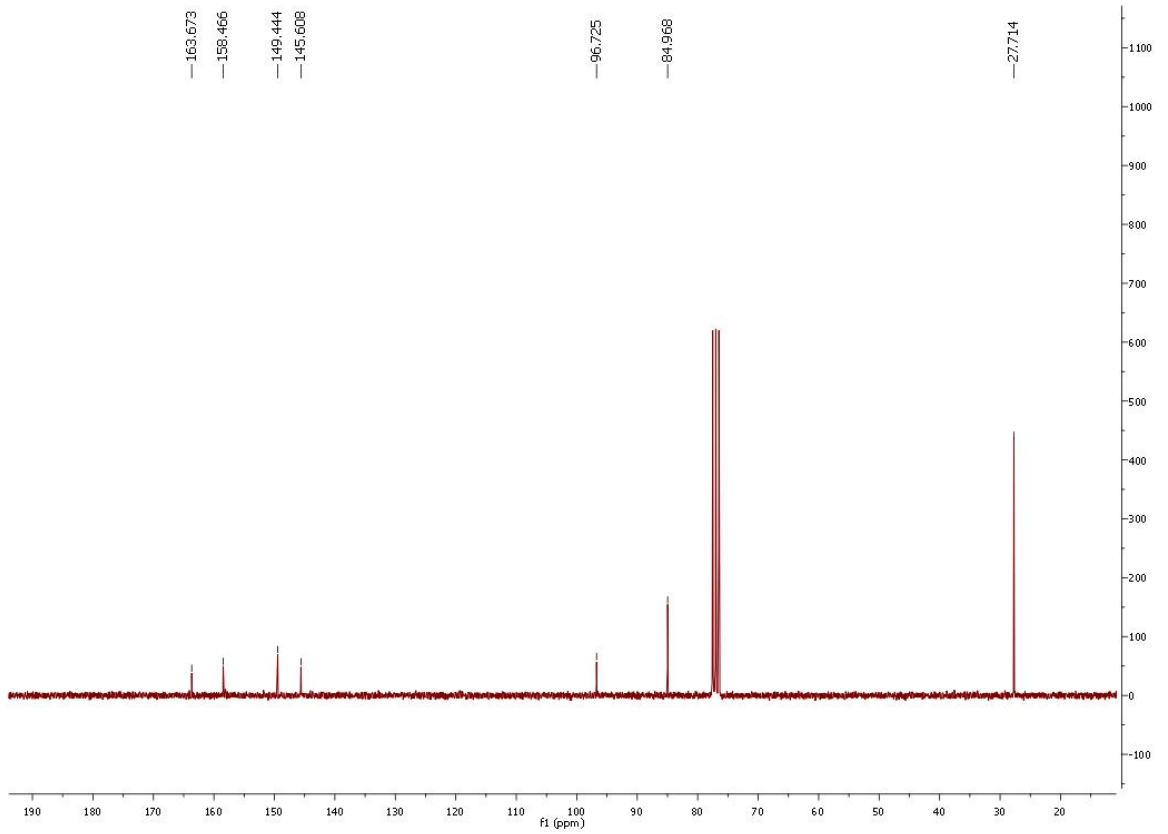


Figure 6: ^{13}C NMR compound **7**

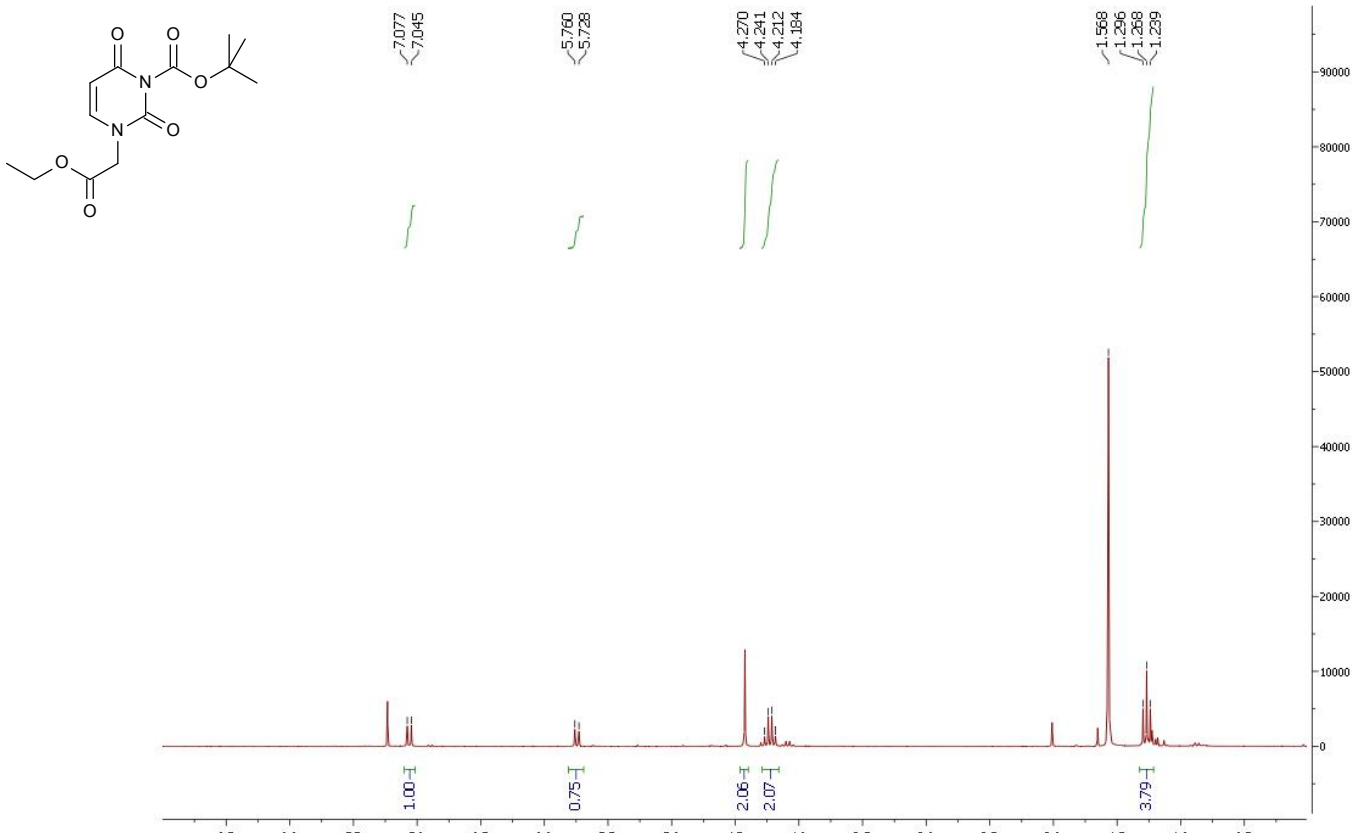


Figure 7: ^{1}H NMR compound **11**

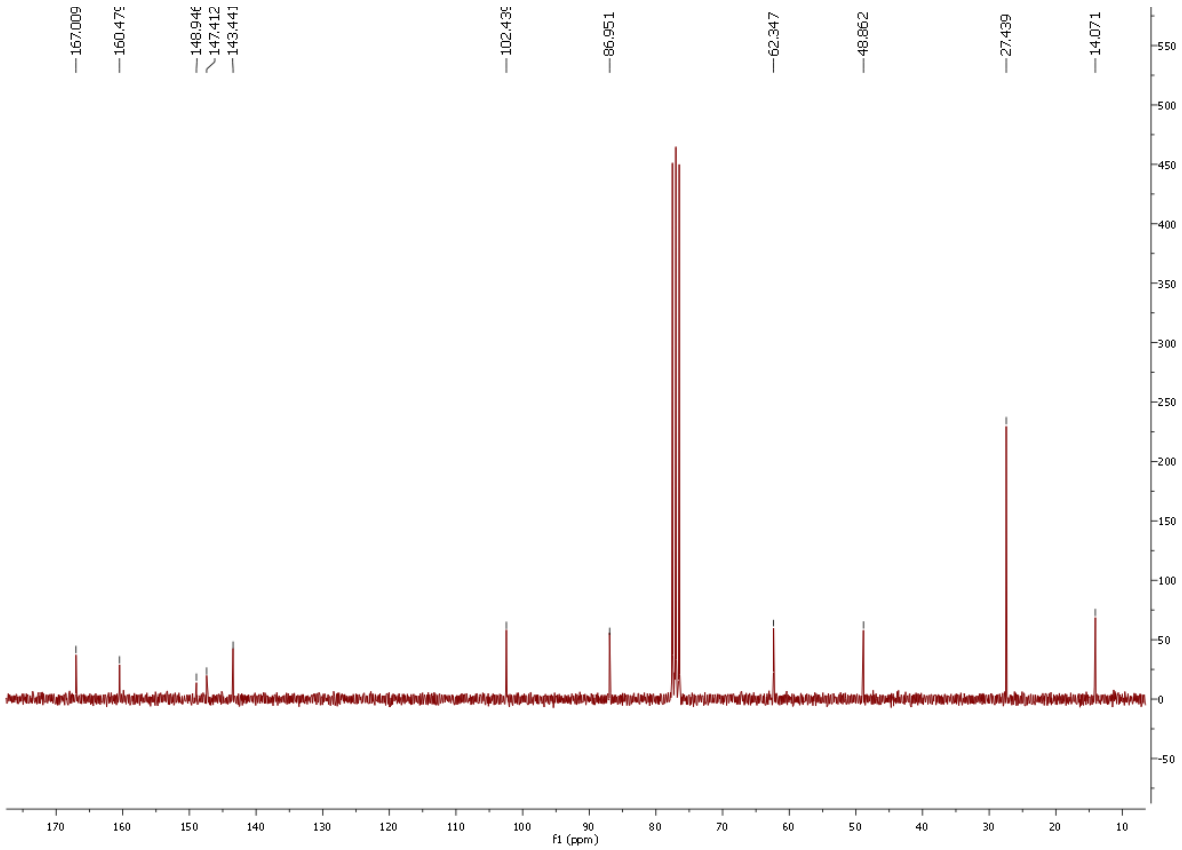


Figure 8: ^{13}C NMR compound **11**

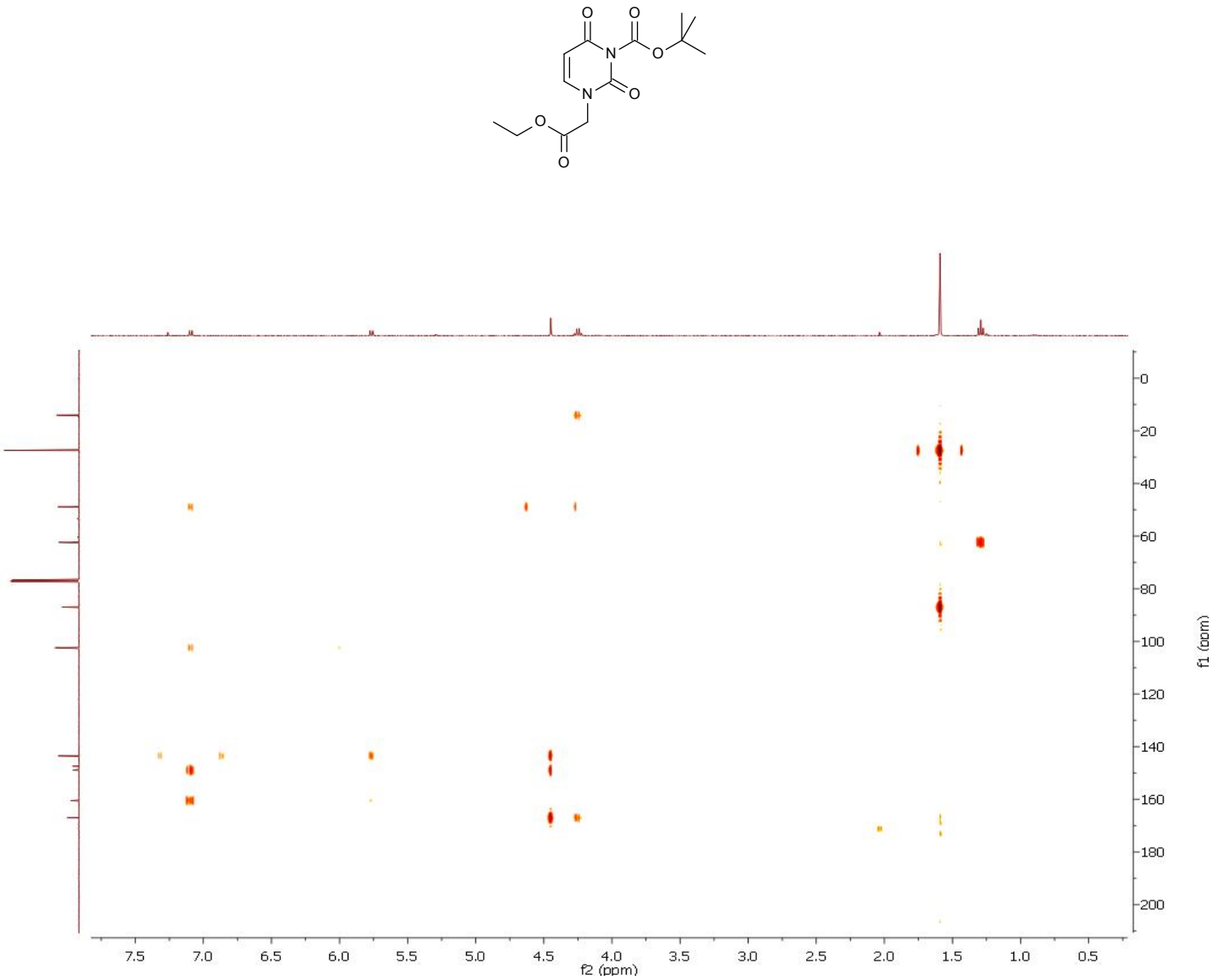


Figure 9: HMBC compound **11**

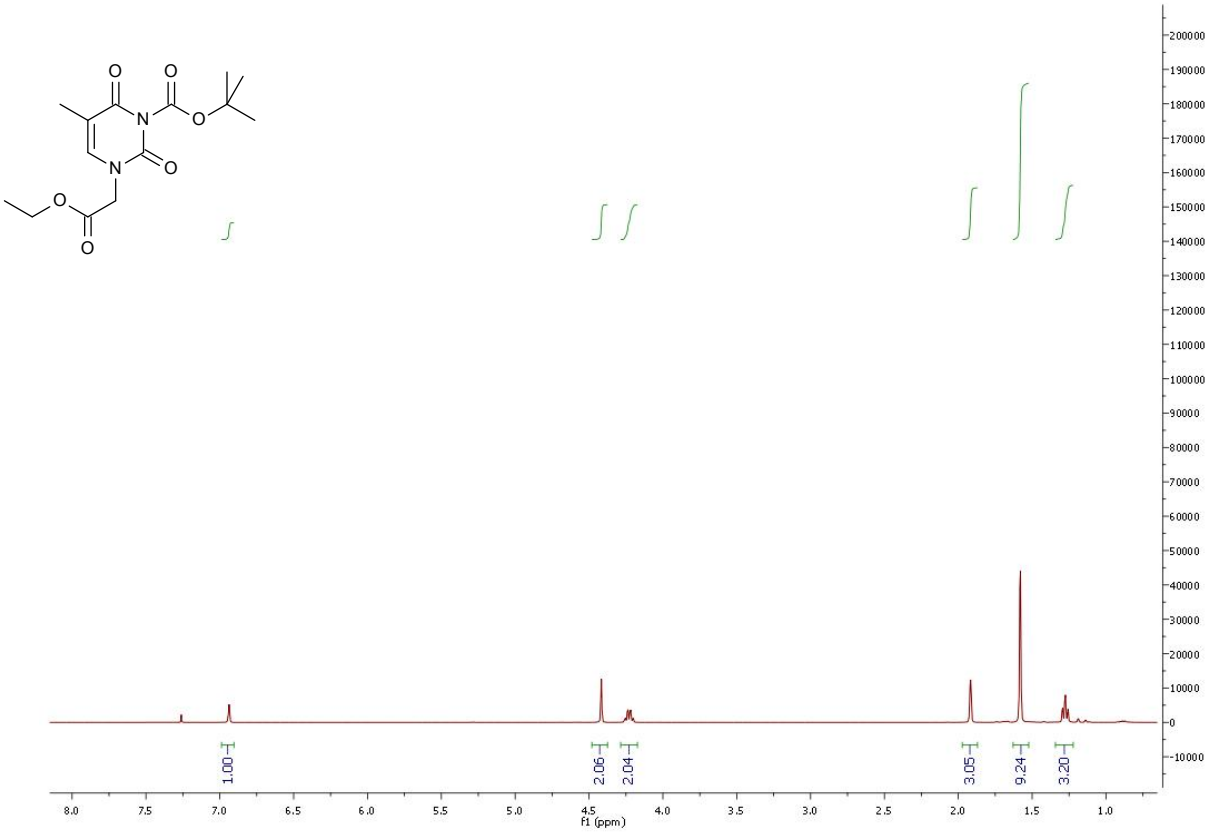


Figure 10: ^{1}H NMR compound **12**

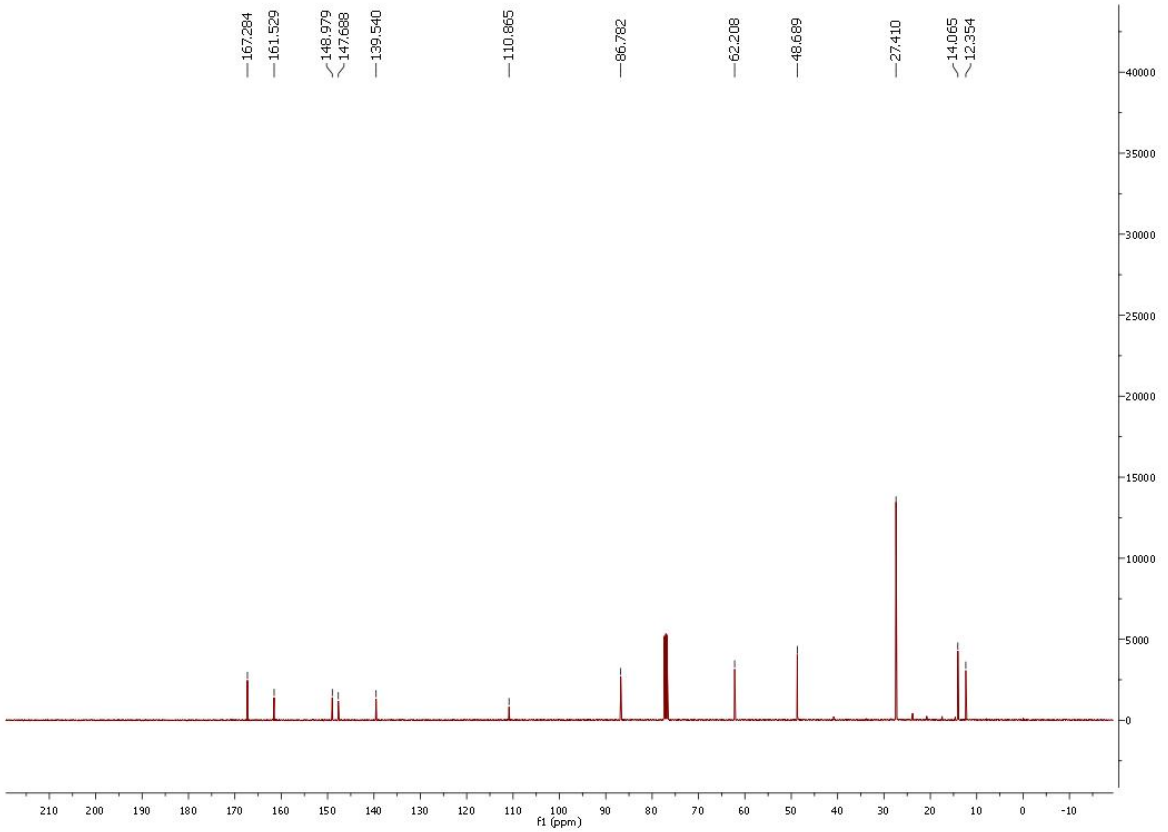


Figure 11: ^{13}C NMR compound **12**

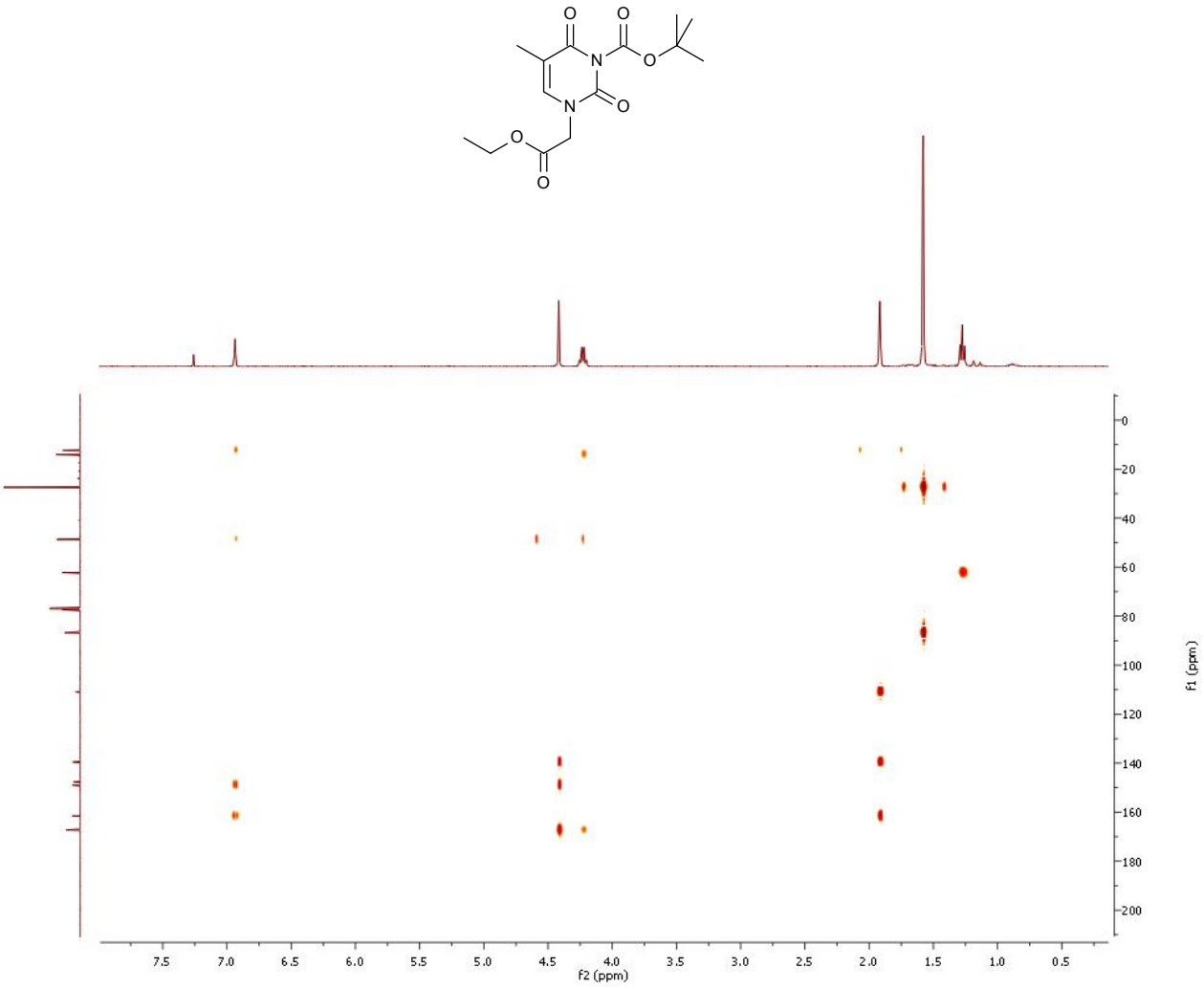


Figure 12: HMBC compound **12**

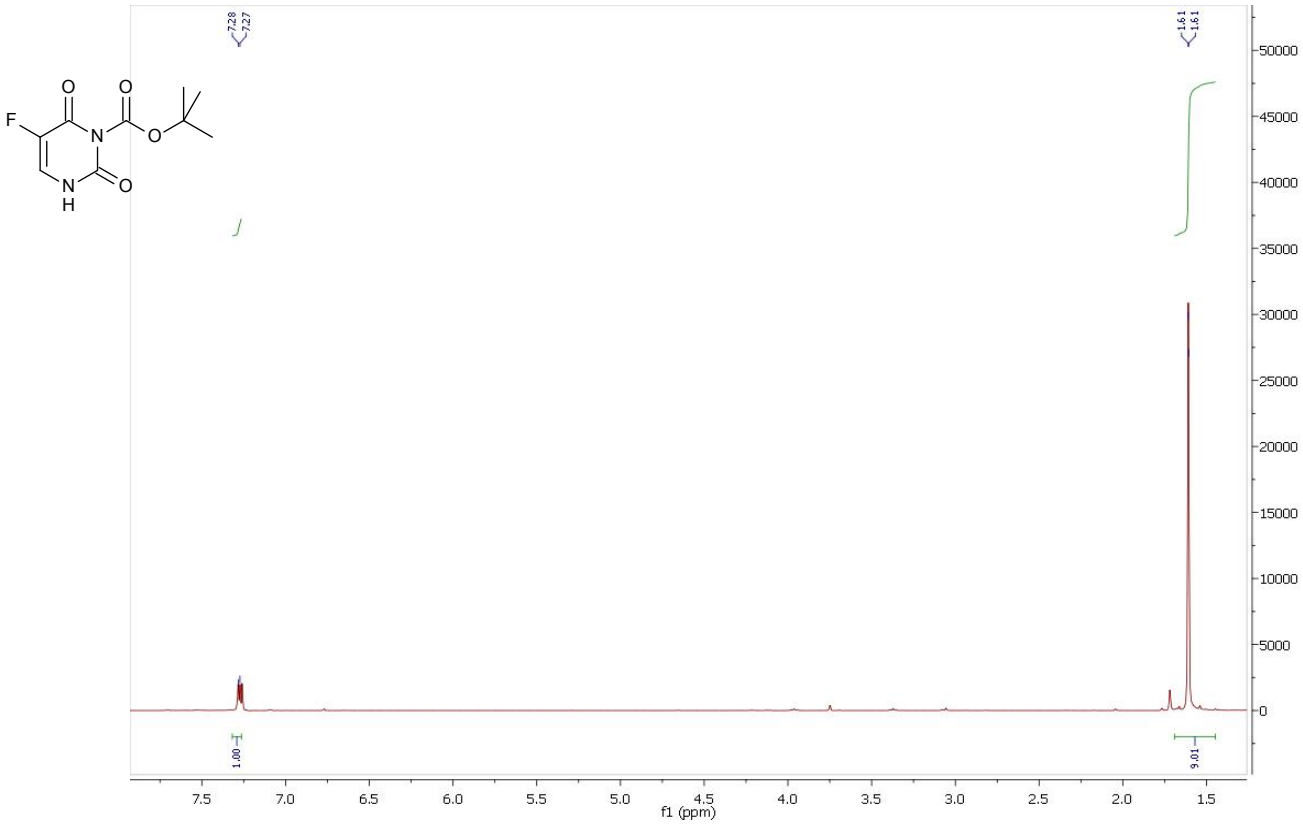


Figure 13: ^{1}H NMR compound **8a**

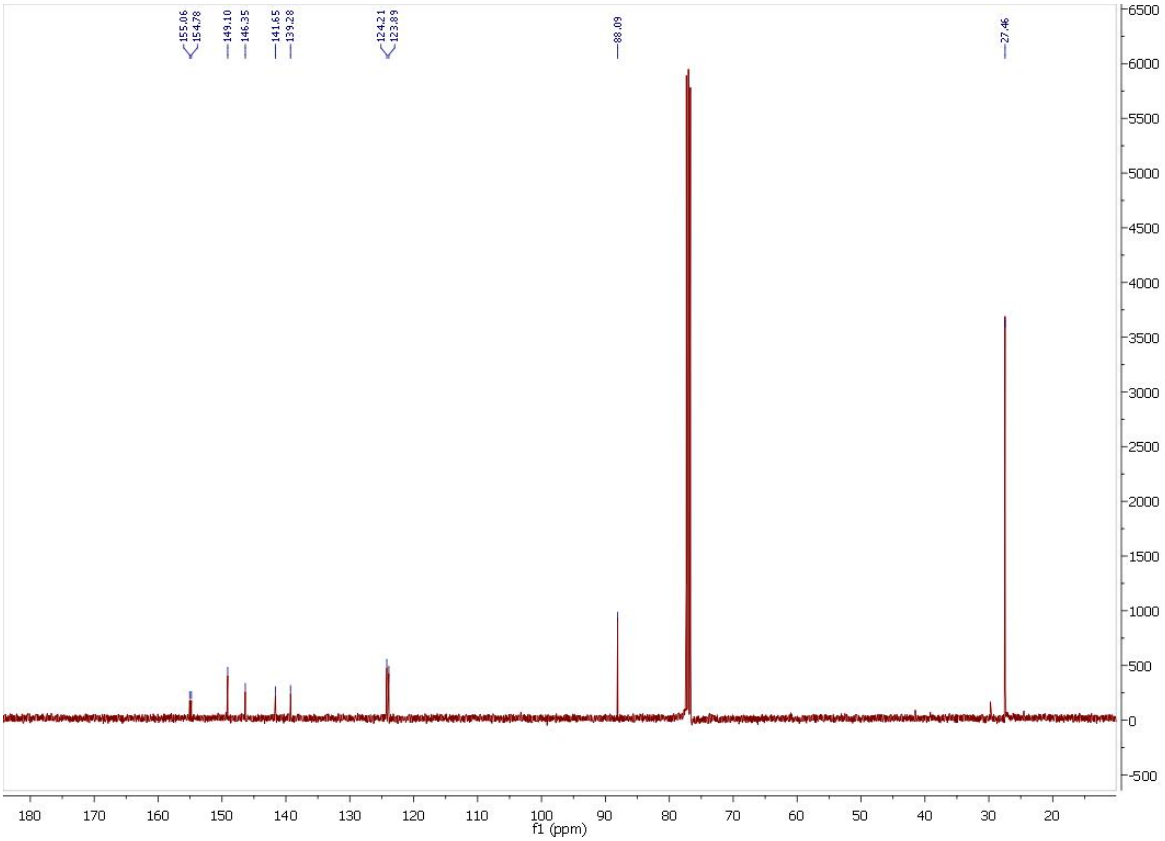


Figure 14: ^{13}C NMR compound **8a**

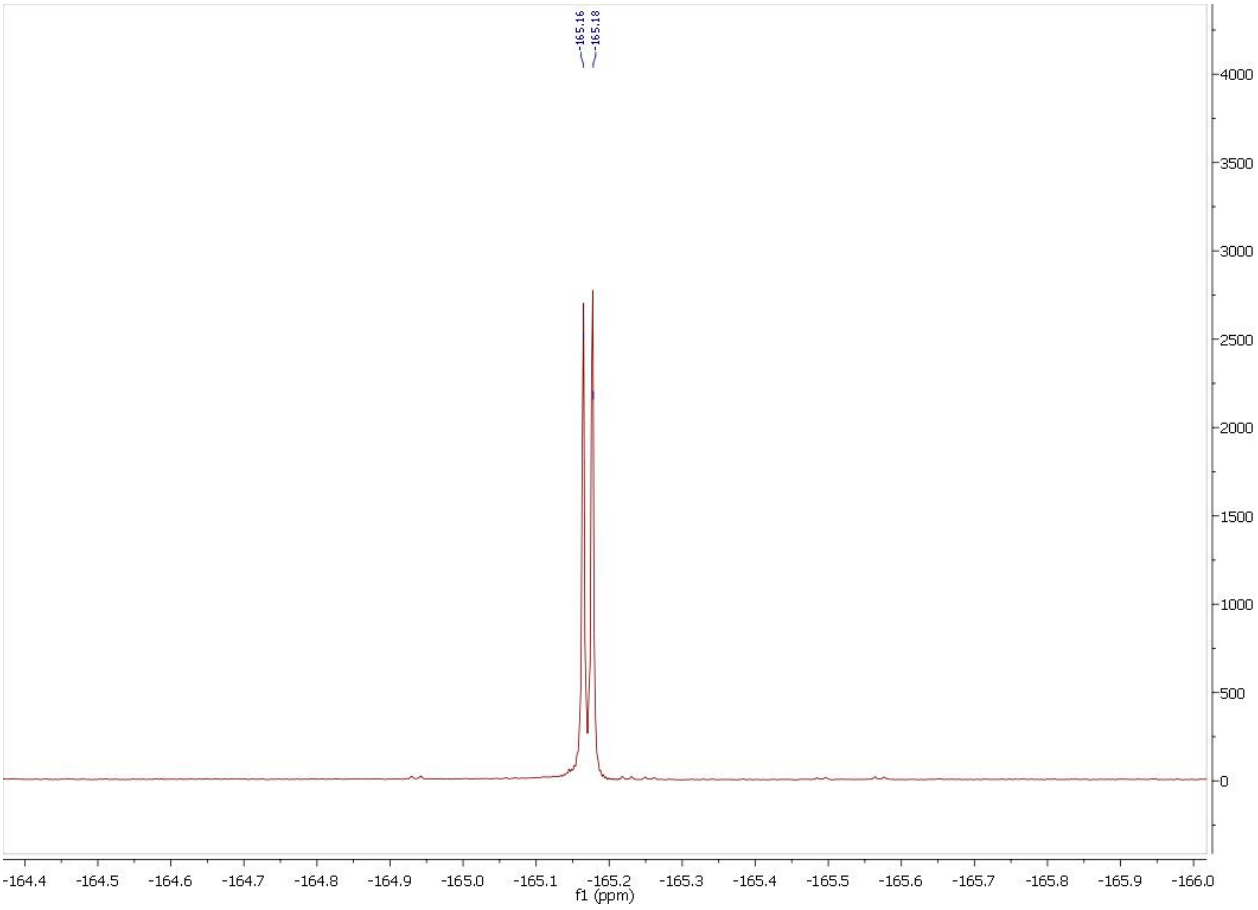


Figure 15: ^{19}F NMR compound **8a**

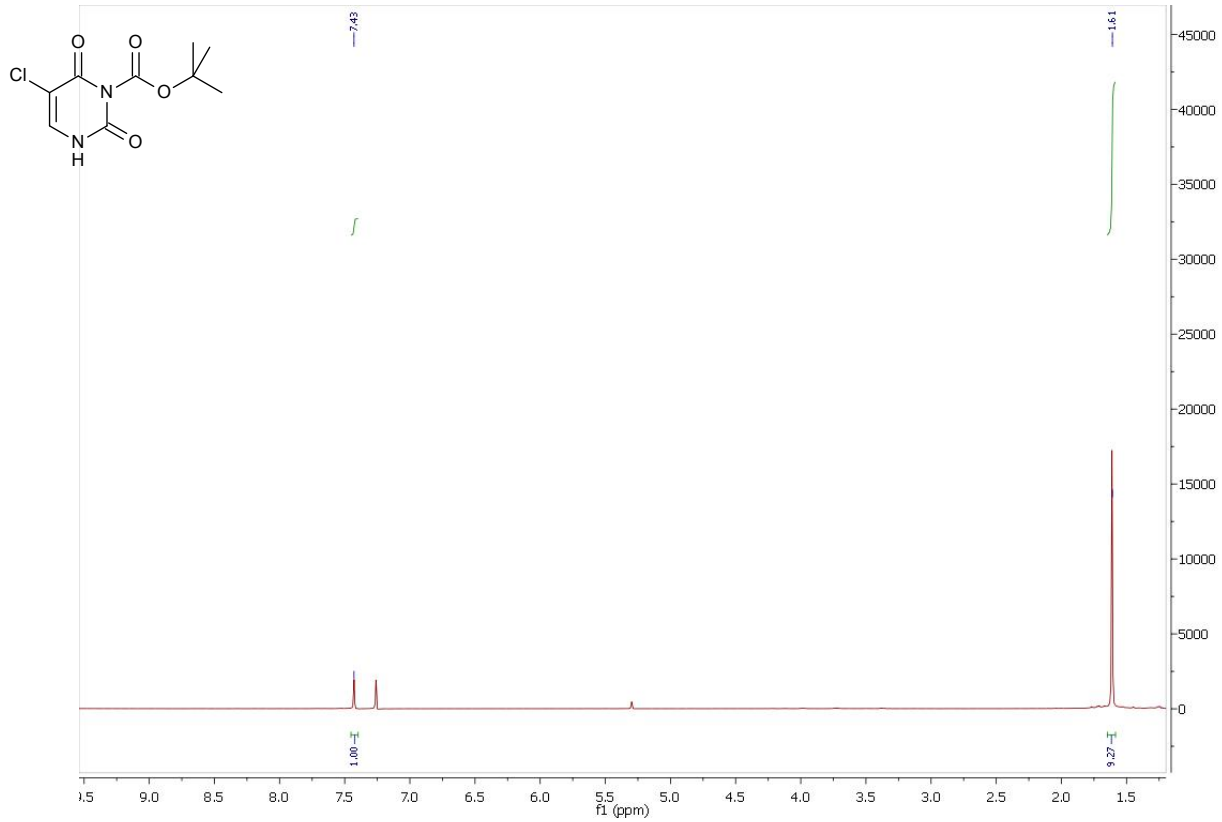


Figure 16: ^{1}H NMR compound **8b**

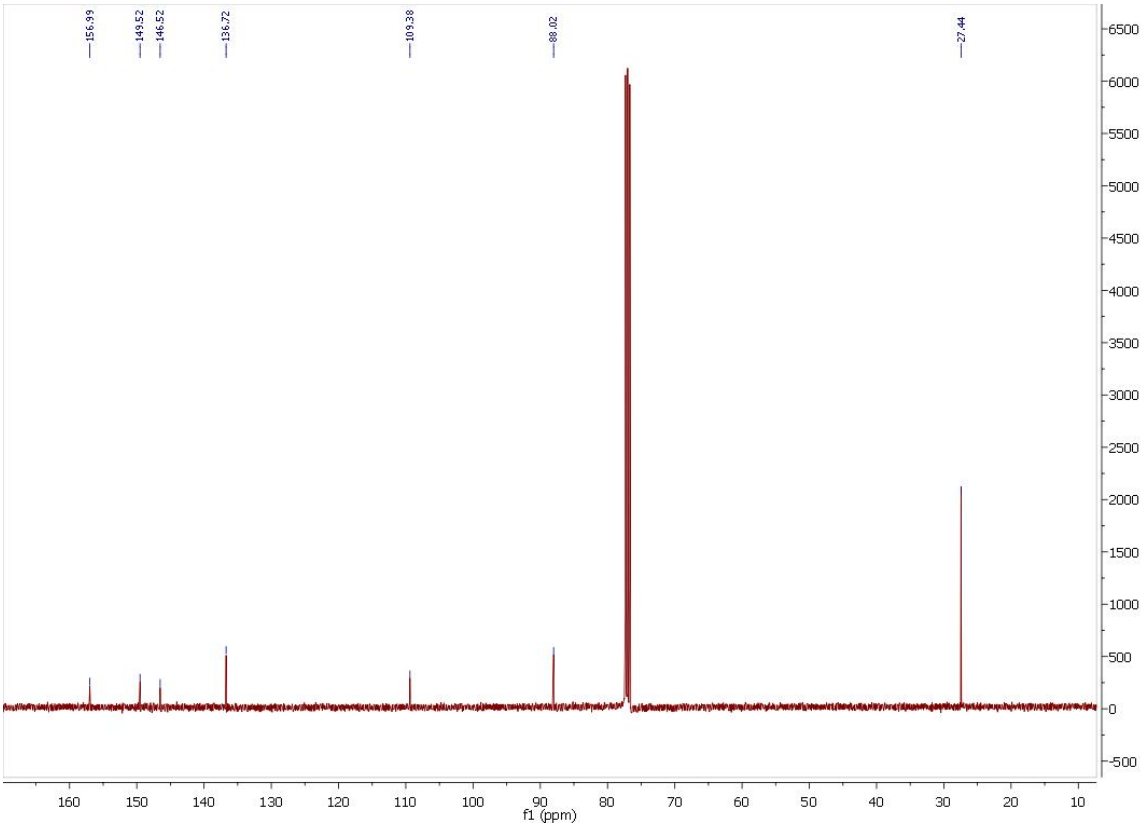


Figure 17: ^{13}C NMR compound **8b**

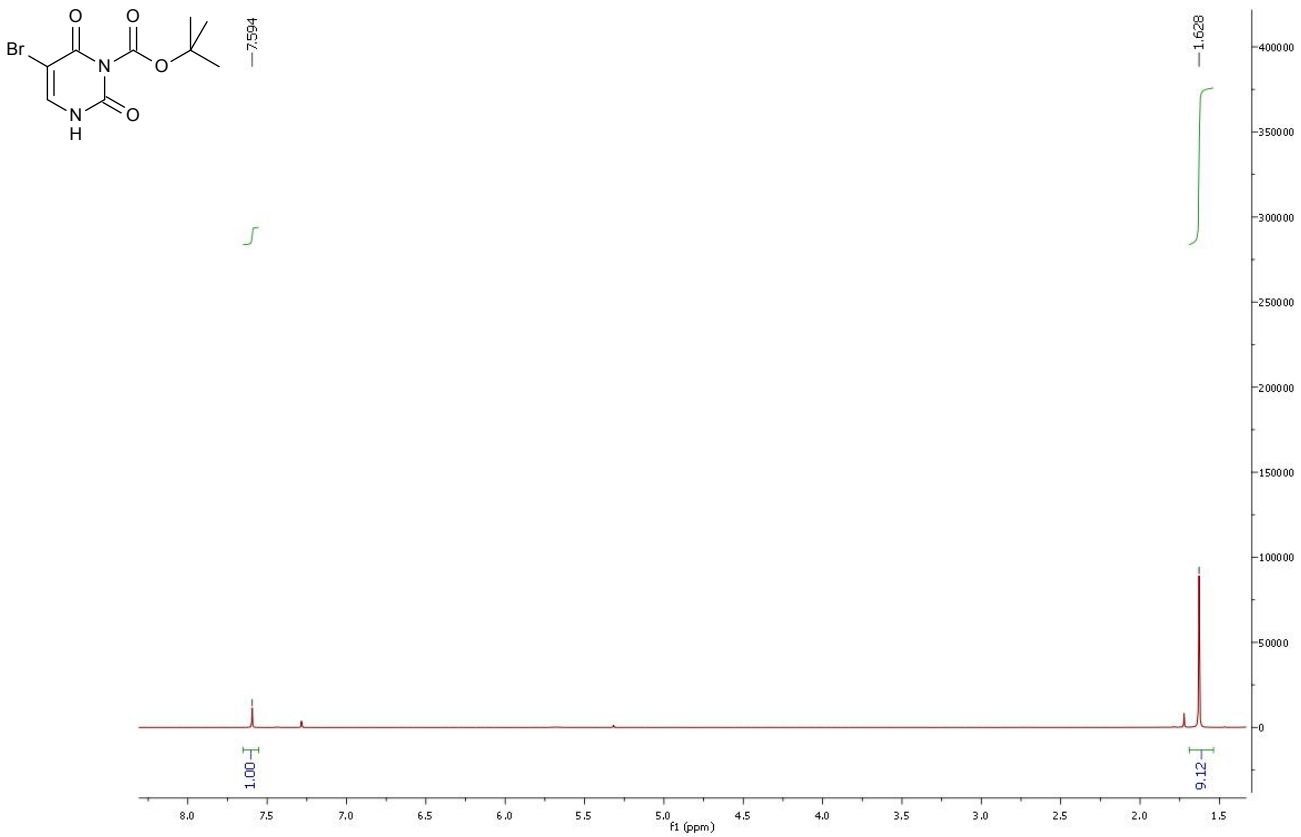


Figure 18: ^{1}H NMRcompound **8c**

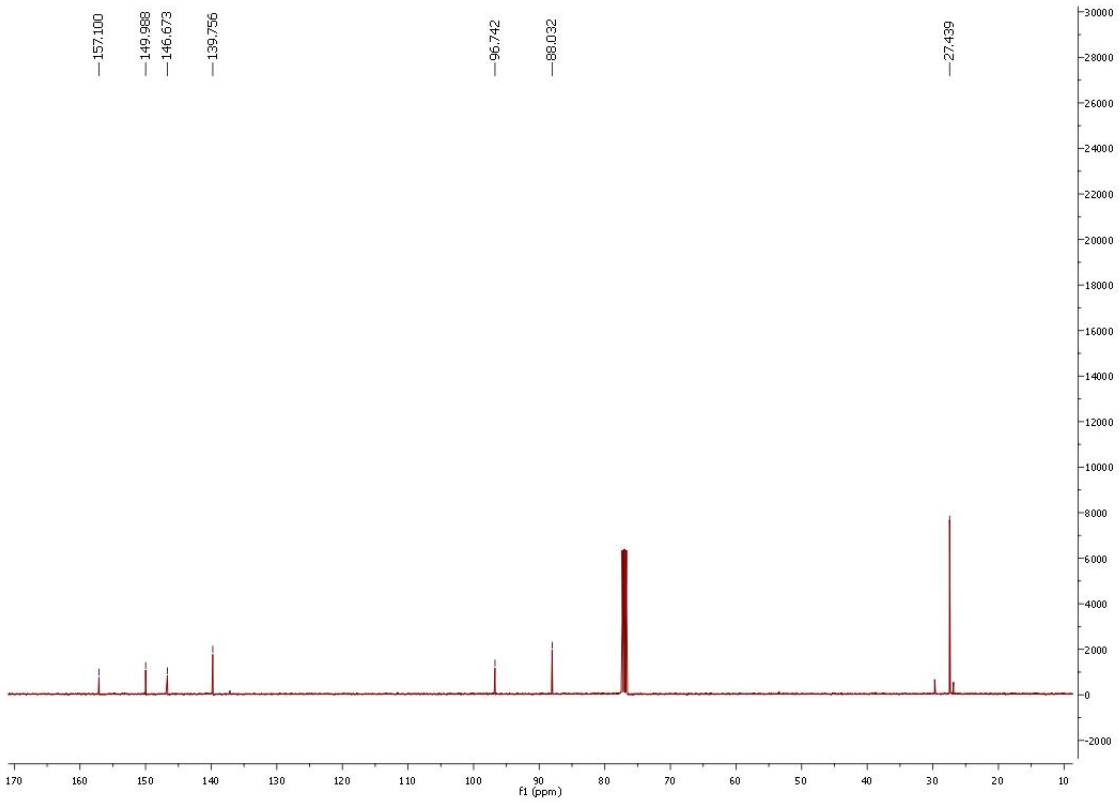


Figure 19: ^{13}C NMR compound **8c**

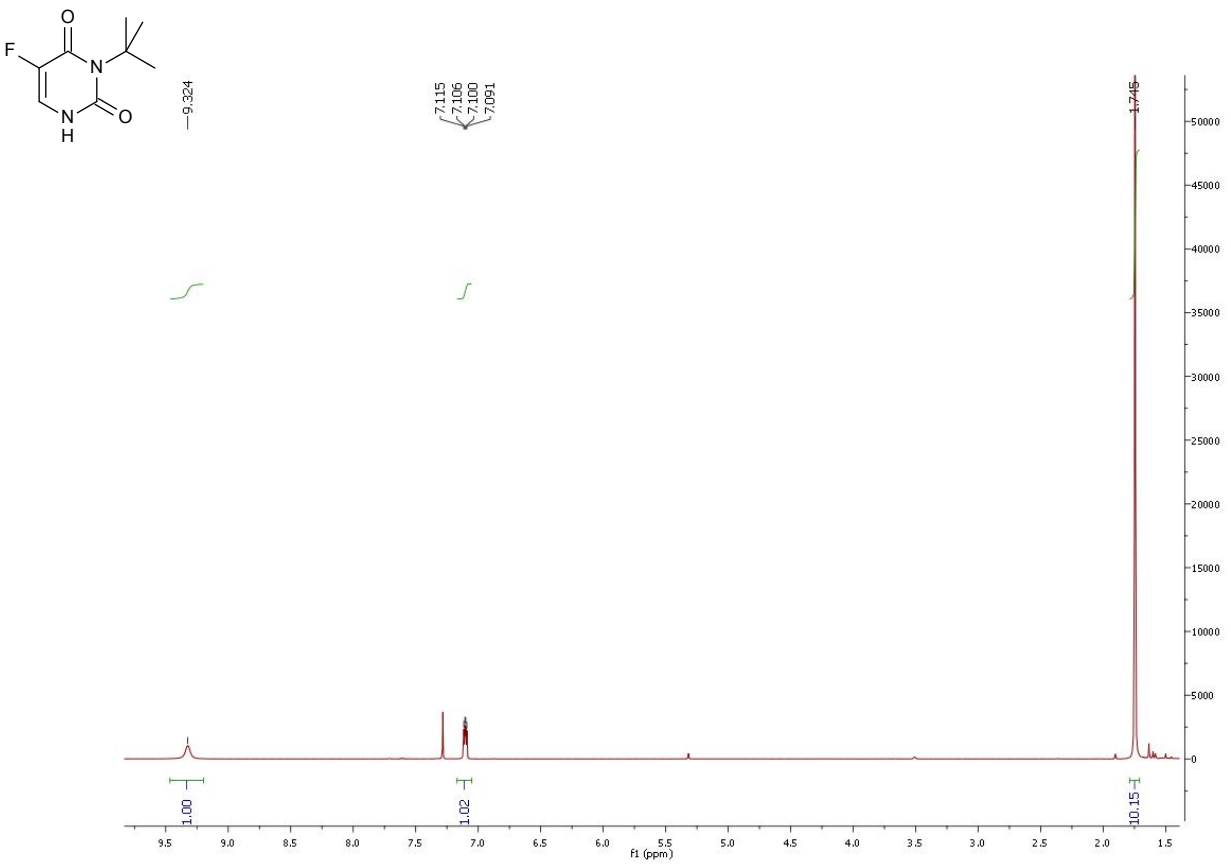


Figure 20: ^{1}H NMR compound **14a**

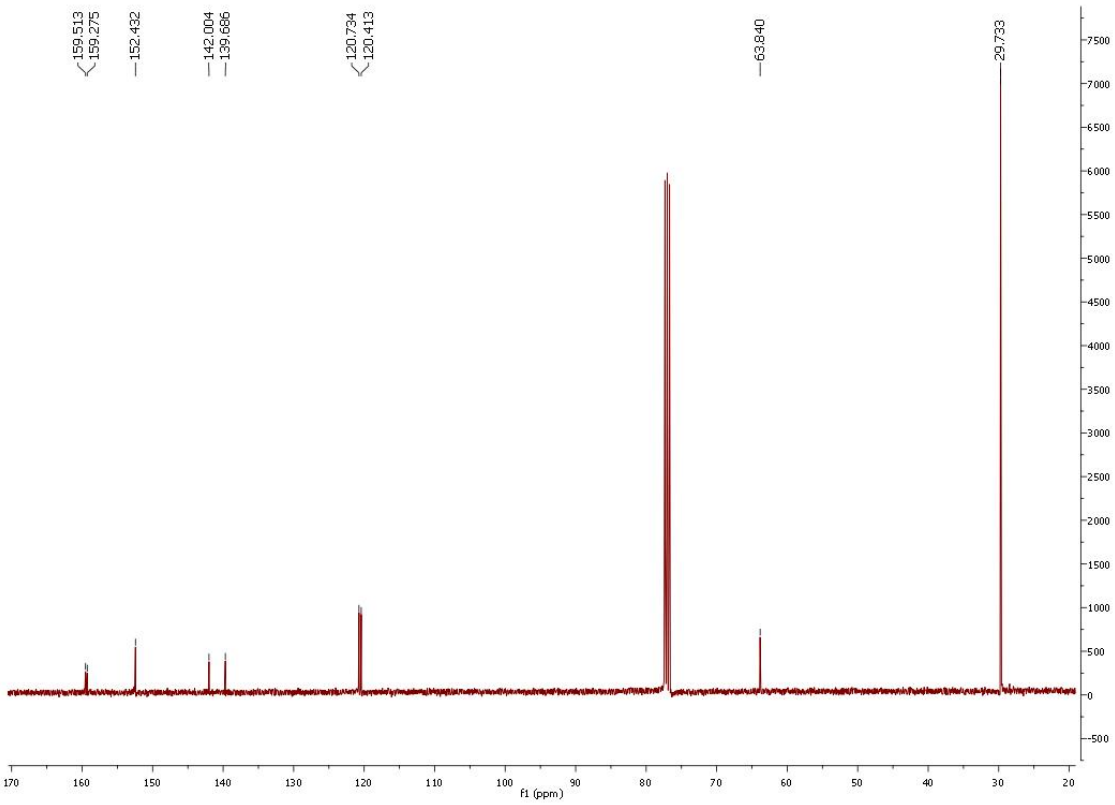


Figure 21: ^{13}C NMR coumpound **14a**

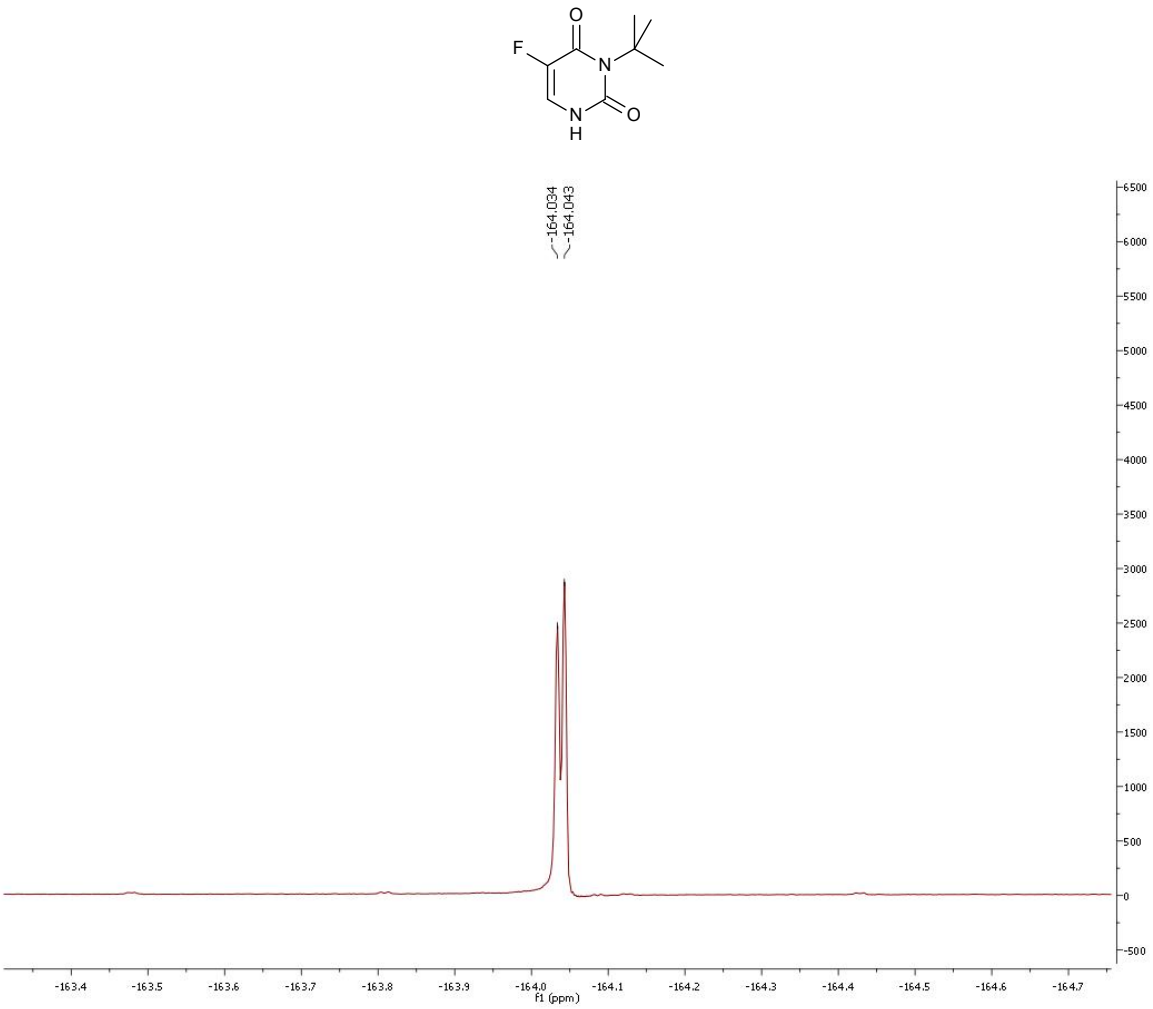
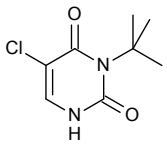


Figure 22: ^{19}F NMR compound **14a**



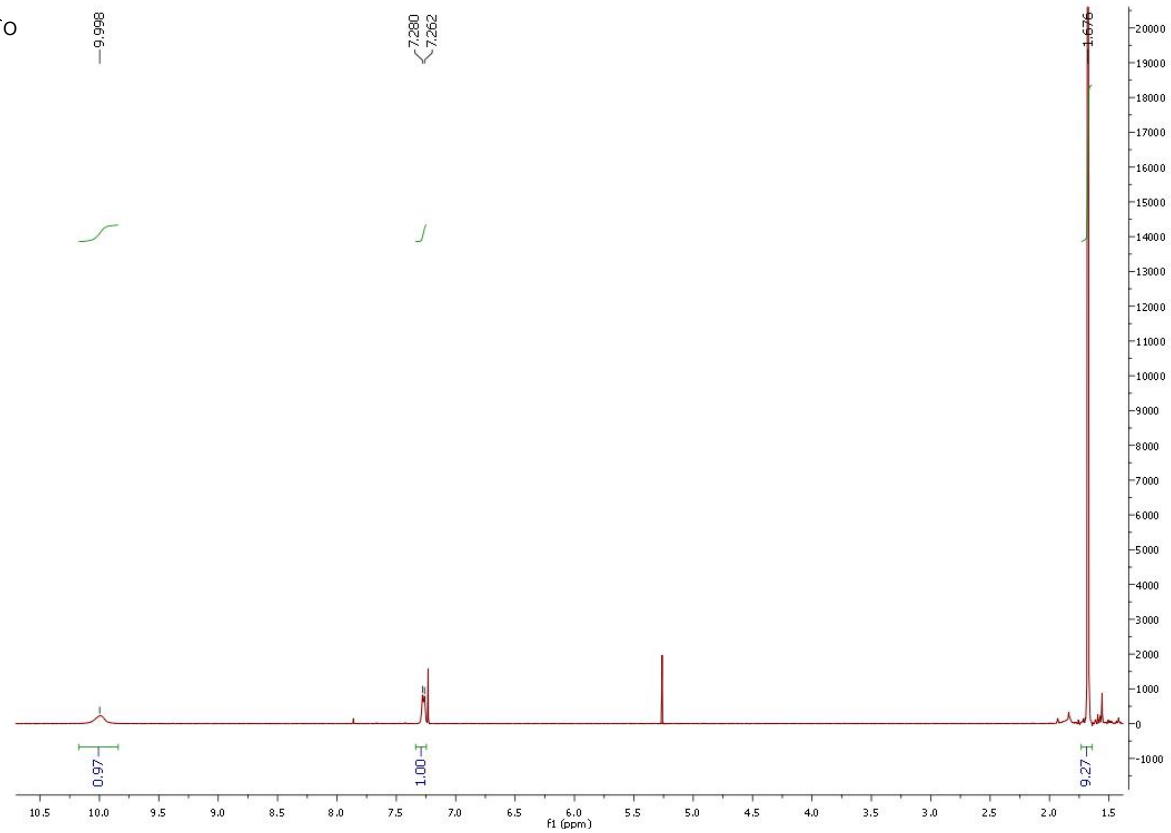


Figure 23: ^{1}H NMR compound **14b**

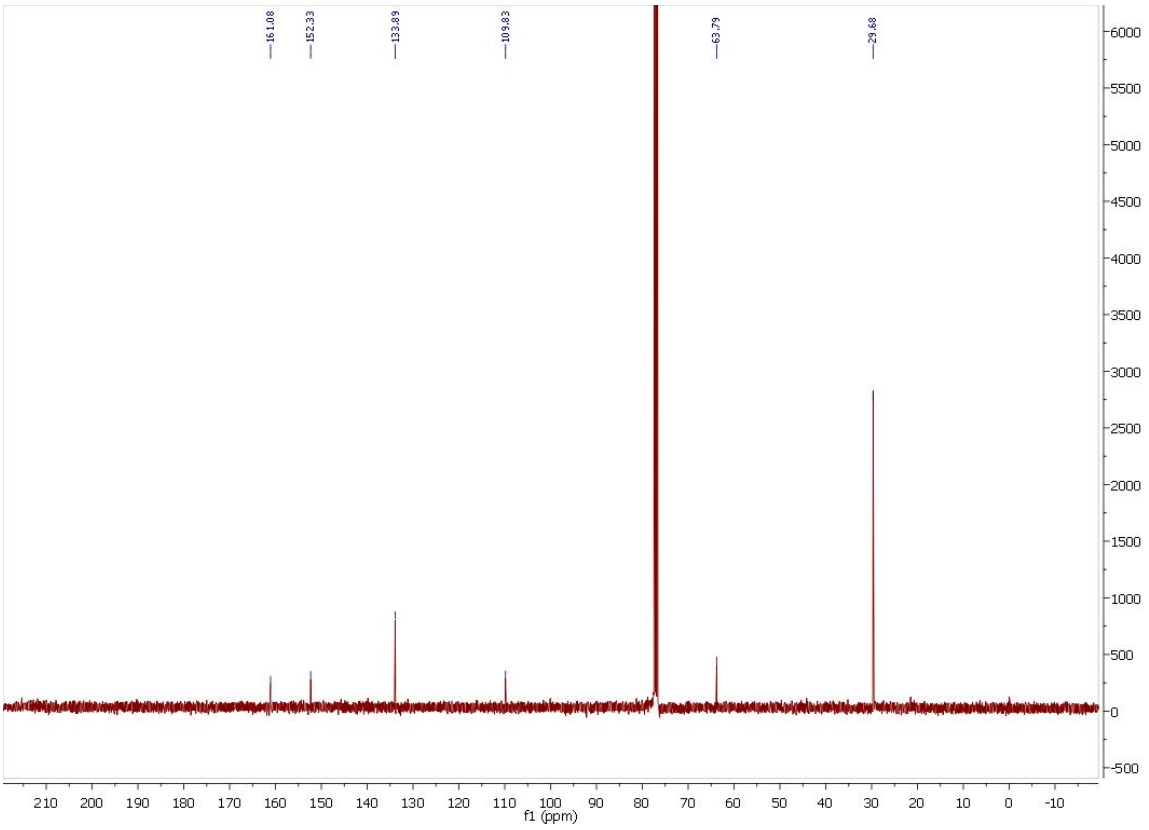


Figure 24: ^{13}C NMR compound **14b**

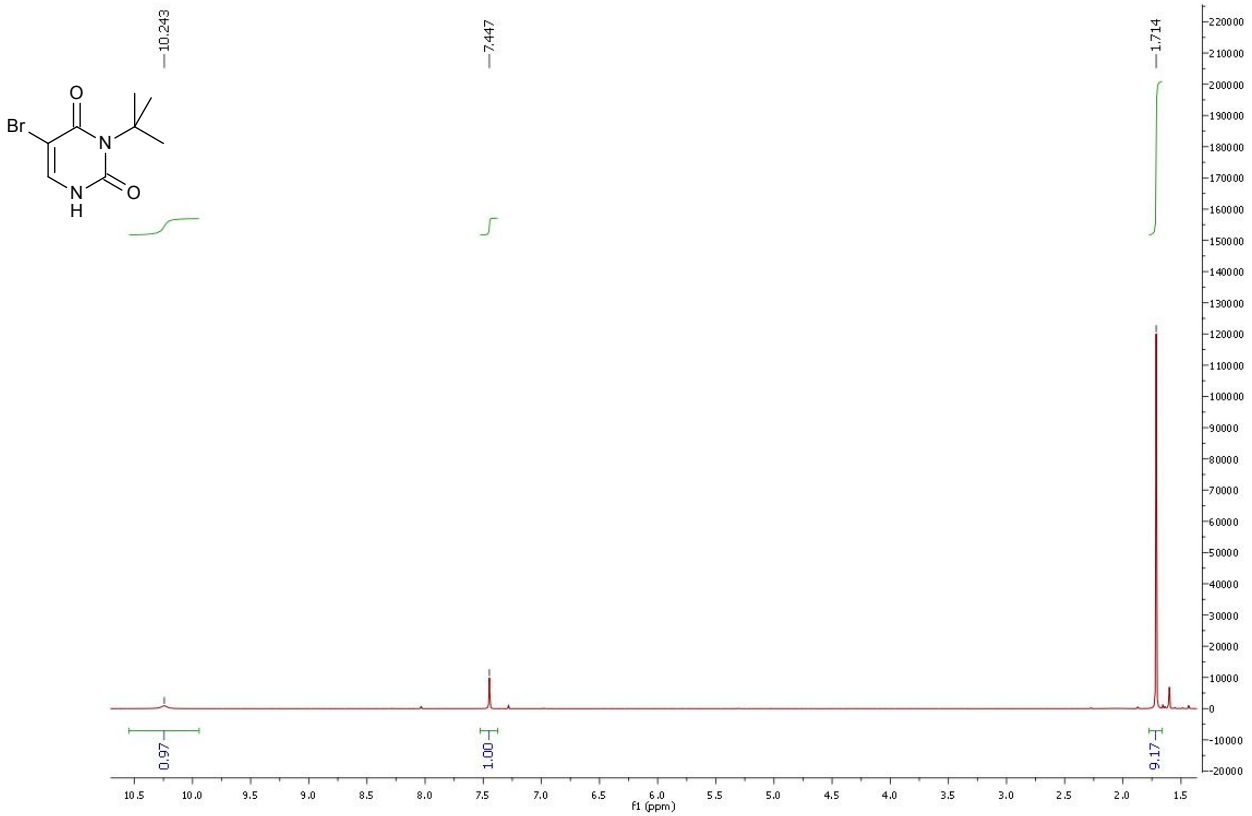


Figure 25: ^{1}H NMR compound **14c**

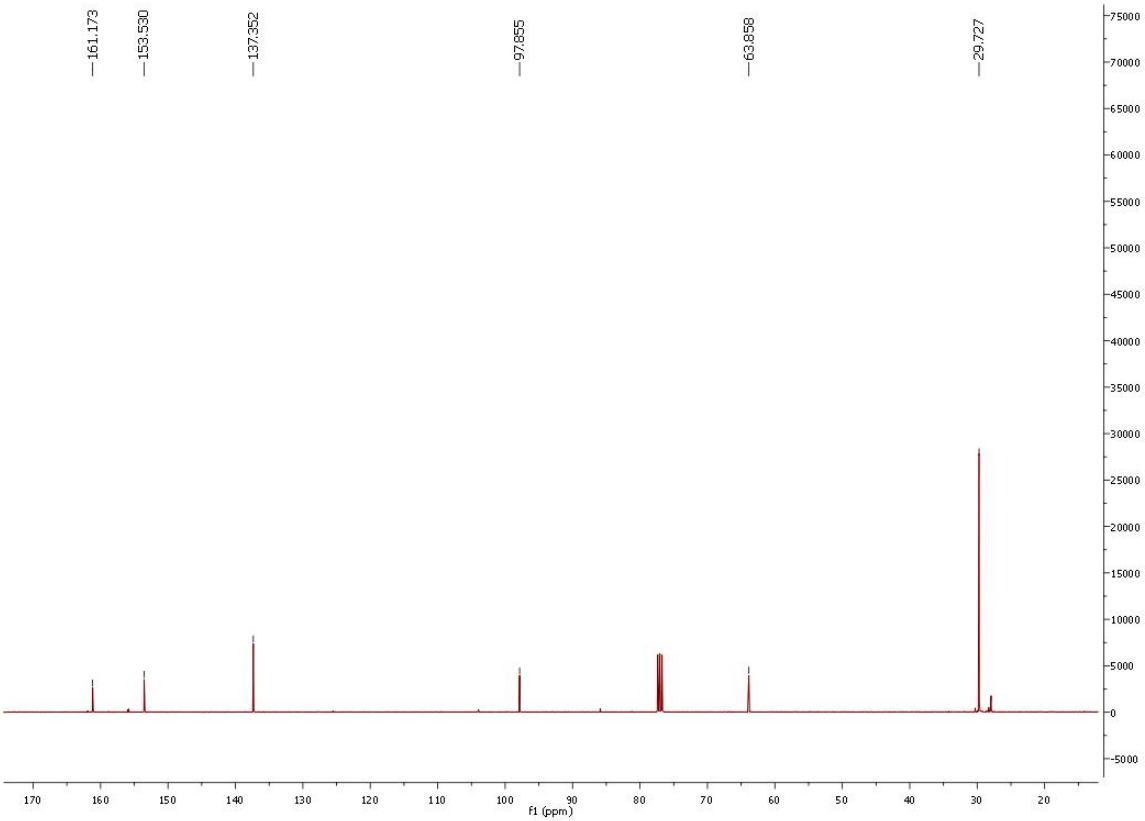


Figure 26: ^{13}C NMR compound **14c**

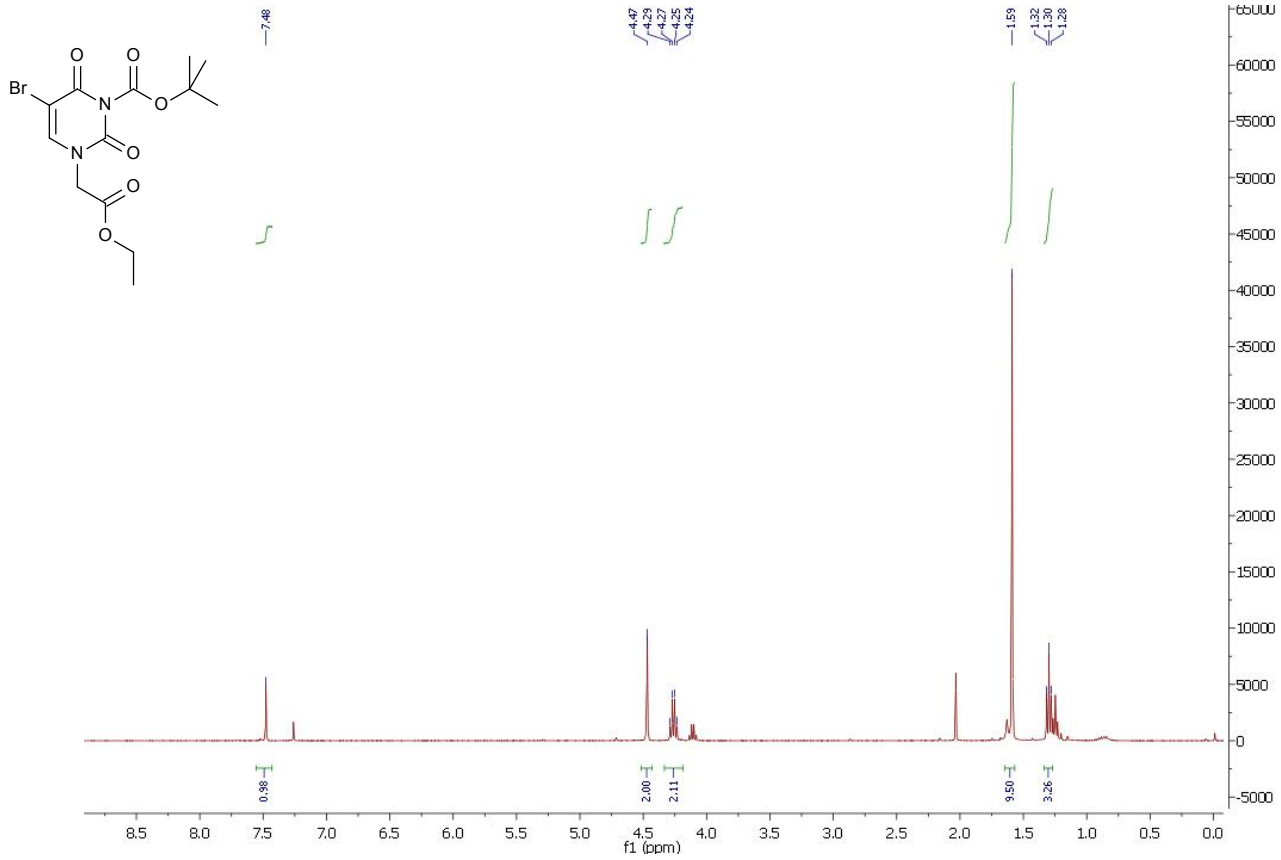


Figure 27: ^{1}H NMR

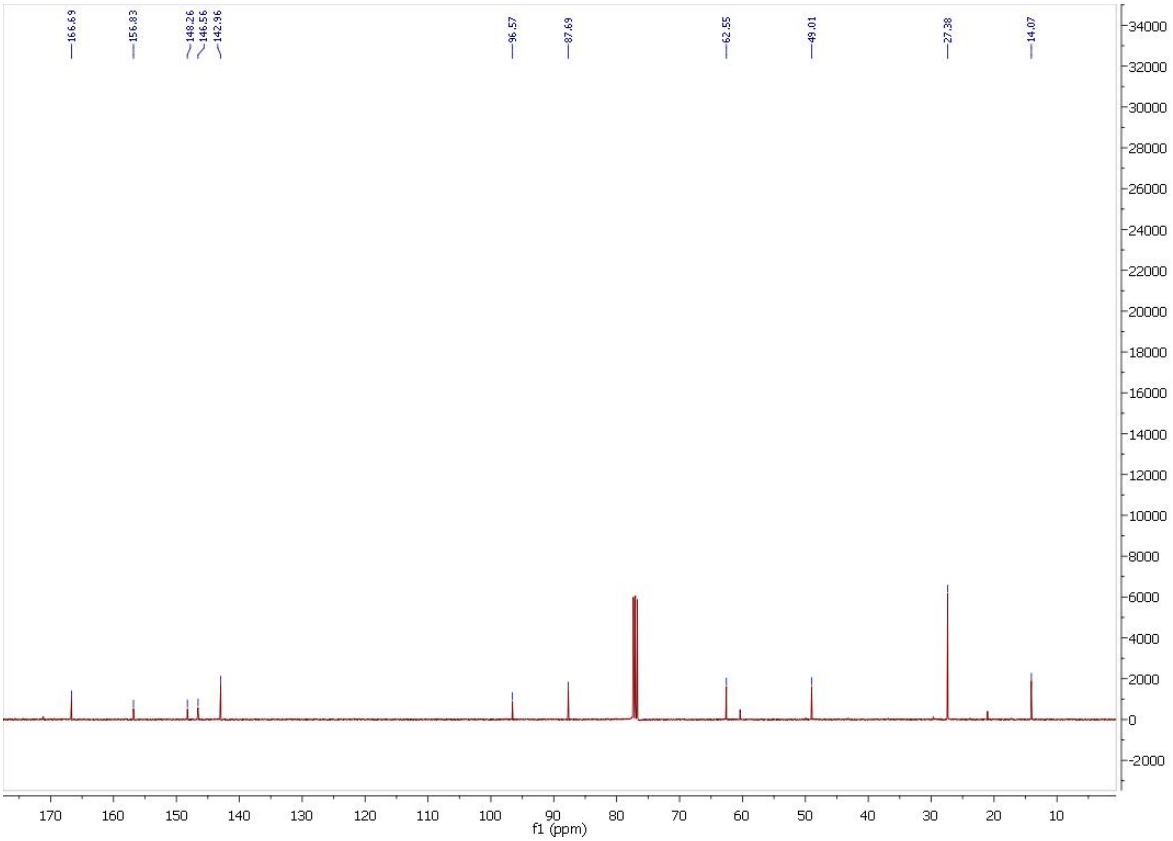


Figure 28: ^{13}C NMR

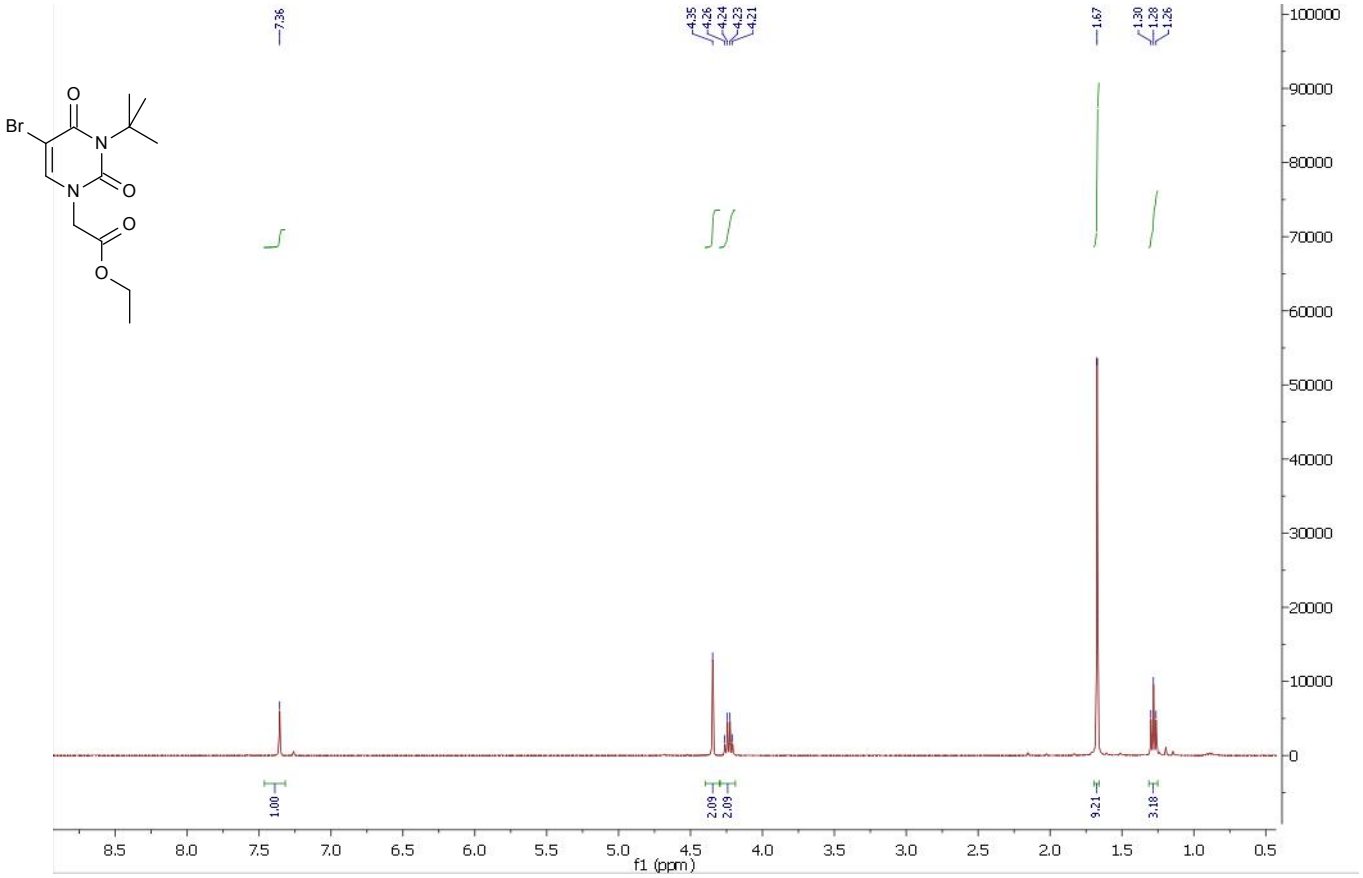


Figure 29: ^{1}H NMR

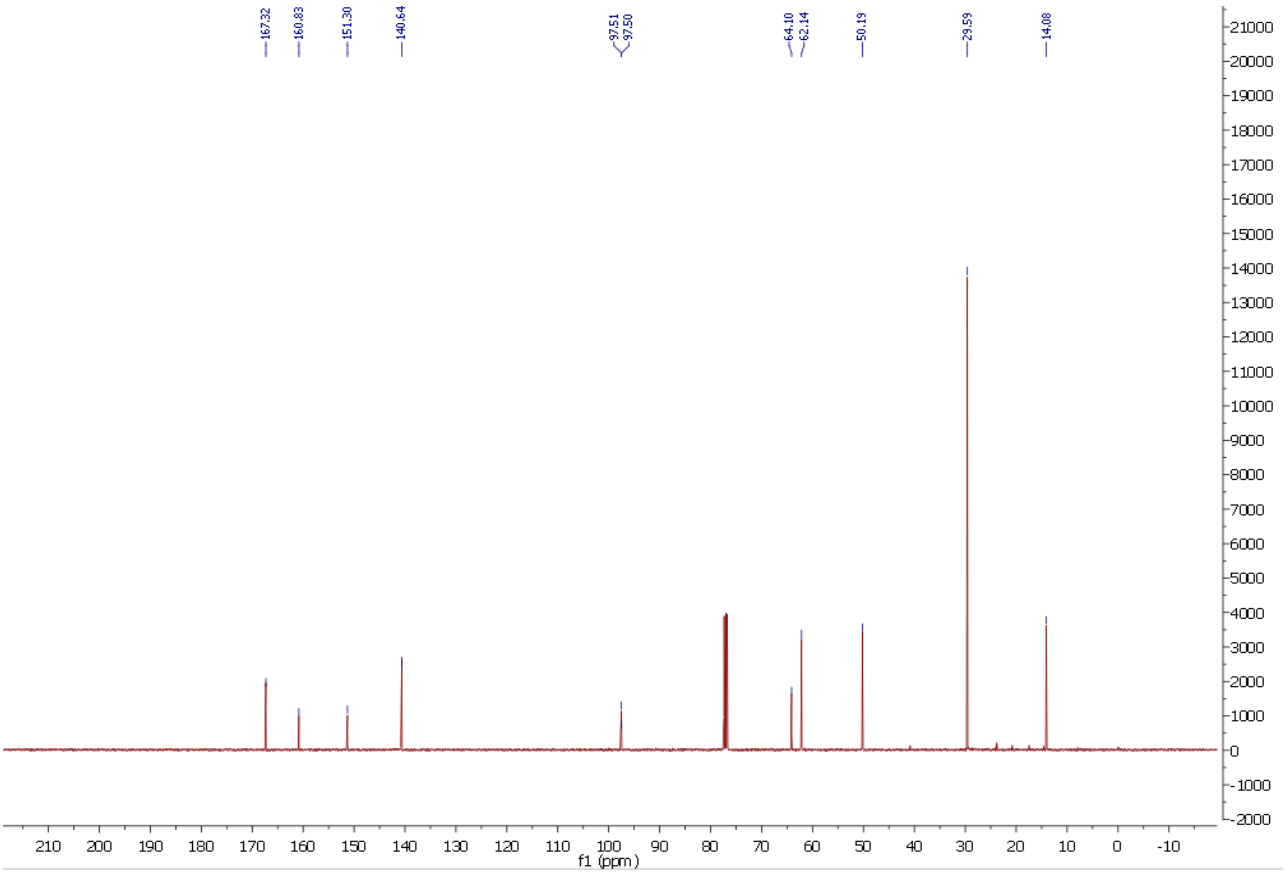


Figure 1: ^{13}C NMR