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Supporting Information

Straightforward Synthesis of Biologically Valuable Nonsymmetrical Malonamides Under Mild Conditions

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I. General Remarks

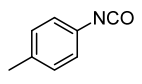
All reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. Petroleum ether (PE) used here refers to the 60–90 °C boiling point fraction of petroleum. Ethyl acetate is abbreviated as EA. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance/600 (^{1}H: 600 MHz, ^{13}C:150 MHz) or Bruker Avance/400 (^{1}H: 400 MHz, ^{13}C: 100 MHz at 25 °C) with tetramethylsilane as the internal standard. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, and m = multiplet), and coupling constants in Hertz (Hz). All high-resolution mass spectra (HRMS) were measured on a mass spectrometer by using electrospray ionization orthogonal acceleration time-of-flight (ESI-OA-TOF), and the purity of all samples used for HRMS (>95%) was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic analysis. Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All reactions were monitored by thin-layer chromatography (TLC) with GF254 silica gel-coated plates. Flash chromatography was carried out on SiO_2 (silica gel 200–300 mesh).

II. General Procedures

1. General Procedure for the Preparation of Reagents

Starting materials isocyanates **1** and β-ketoamides **2a-2l**, **2o**, **2q**, **2t** and **2u-2v** are obtained from commercial sources. Other starting materials **2** were synthesized following the literatures, and the procedures were described below.

Isocyanates



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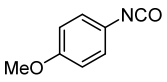

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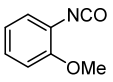

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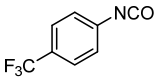

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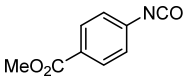
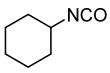


1e

1f

1g



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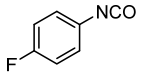
1i



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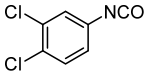

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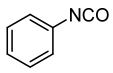

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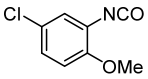

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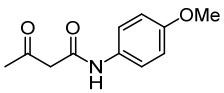
β-Ketoamides



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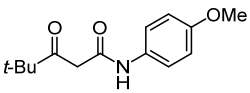

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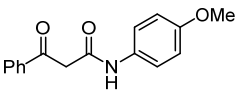

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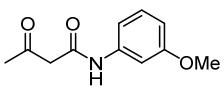

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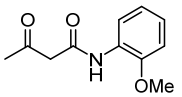

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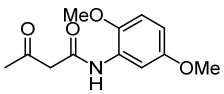

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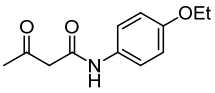

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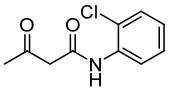

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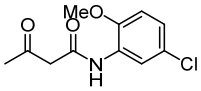

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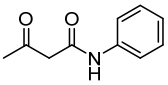

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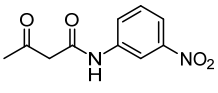

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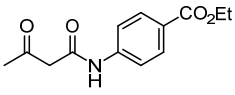

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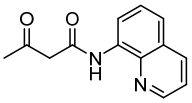

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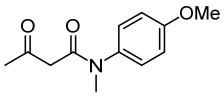

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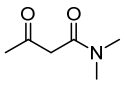

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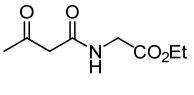

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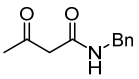

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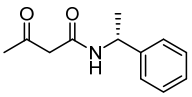

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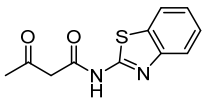

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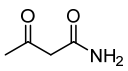

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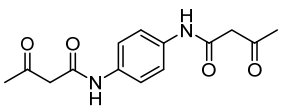

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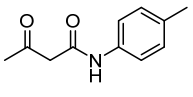

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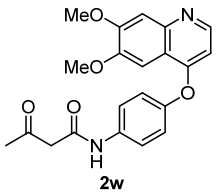

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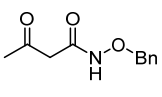

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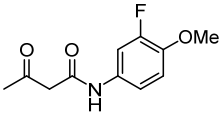

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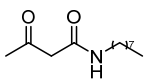
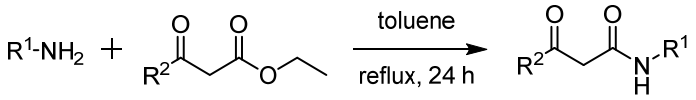


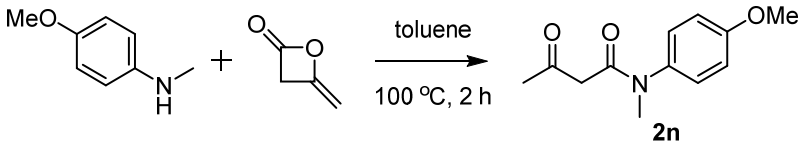
2z

Method A: Substrates **2b**, **2c**, **2l**, **2m**, **2s** and **2w** were synthesized according to the literature.[1]



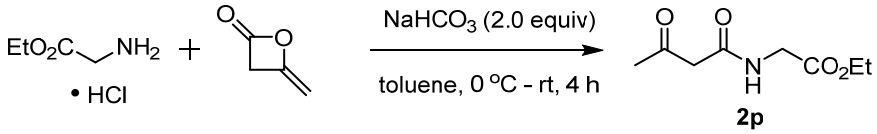
Anilines (1.0 equiv), β-ketoesters (1.1 equiv) and toluene (0.5 M) in an oven dried round bottom flask equipped with a magnetic stir bar. The resulting mixture was heated under reflux for 24 h. The reaction mixture was allowed to cool to ambient temperature and toluene was removed under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (PE / EA = 3:1) to afford the desired product **2b**, **2c**, **2l**, **2m**, **2s** and **2w**.

Method B: Substrates **2n**, **2x**, **2y** and **2z** were synthesized according to the literature.[2]



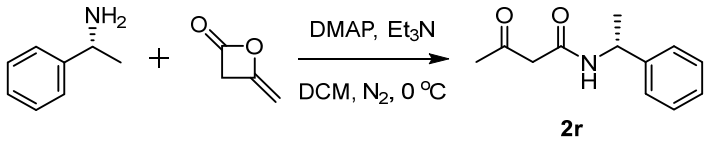
Diketene (1.1 equiv) was added to a magnetically stirred solution of the substituted anilines (1.0 equiv) in toluene (0.5 M), and the mixture was heated at 100 °C for 2 h. The reaction mixture was monitored by TLC. After completion of the reactions, the solution was evaporated under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (PE / EA = 3:1) to afford the desired product **2n**, **2x**, **2y** and **2z**.

Method C: The general procedure for the synthesis of **2p**.



Add glycine ethyl ester hydrochloride (1.0 equiv) and $NaHCO_3$ (2.0 equiv) to toluene (0.5 M) and stir at room temperature for 0.5 h, add diketene (1.1 equiv) at 0 °C and the mixture was heated at rt for 4 h. The reaction mixture was monitored by TLC. After completion of the reactions, the solution was evaporated under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (PE / EA = 1:1) to afford the desired product **2p**.

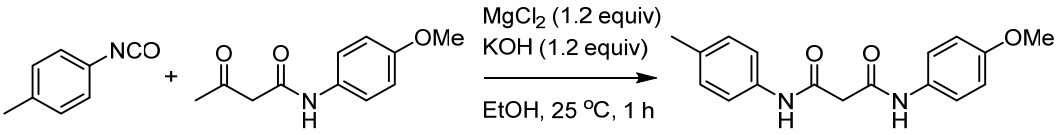
Method D: Substrates **2r** were synthesized according to the literature.[3]



4-Dimethylaminopyridine (0.45 equiv), triethylamine (1.0 equiv), and

(*R*)-1-phenylethan-1-amine (1.0 equiv) were dissolved in DCM (0.5 M), at 0 °C under an argon atmosphere. The reaction mixture was stirred for 10 min, then diketene (2.0 equiv) was added dropwise. After 4 h, the reaction was quenched with 5% aqueous KOH and extracted with DCM (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (PE / EA = 3:1) to afford the desired product **2r**.

2. General Procedure for the Synthesis of Nonsymmetrical Malonamides



1a **2a** **3a**

To a 15 mL tube was added **2a** (103.5 mg, 0.5 mmol), $MgCl_2$ (57 mg, 1.2 equiv), KOH (40 mg, 1.2 equiv, 85%+), EtOH (3 mL), and stirred at 25 °C for 0.5 h before **1a** (80 mg, 0.6 mmol) was added. Then the reaction mixture was stirred at 25 °C for 1 h (the whole process was closely monitored by TLC). After completion of the reactions, the solution was evaporated under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (EA : DCM : PE : Et_3N = 50 : 100 : 50 : 1) to give primary amide **3a** as white solid (135 mg, 91%).

3. General Procedure for the Gram-Scale Synthesis of **3s**

N^1,$N^{1'}$-(1,4-phenylene)bis(N^3-(*p*-tolyl)malonamide) (**3s**)：To a 250 mL round-bottom flask was added *N*,*N*'-(1,4-phenylene)bis(3-oxobutanamide) (**2u**) (5.52 g, 20 mmol), $MgCl_2$ (4.19 g, 2.2 equiv), KOH (2.90 g, 1.2 equiv, 85%+). Then the mixture was stirred well in EtOH (120 mL) at 25 °C for 0.5 h, then 1-isocyanato-4-methylbenzene (**1a**) (5.86 g, 44 mmol) was added and stir at room temperature for 4 h, After the completion of the reaction, 300 mL of distilled water was added to the reaction, suction filtered under reduced pressure and the crude product was washed with a large amount of water and dried in vacuum to give **3s** as a white solid (8.59 g, 94%).

4. General Procedure for the Synthetic Applications (**3ab** as the example)

Synthesis of **2w**: 4-((6,7-dimethoxyquinolin-4-yl)oxy) aniline (20 mmol, 1.0 equiv), ethyl acetoacetate (22 mmol, 1.1 equiv) and toluene (100 mL) in an oven dried round bottom flask (250 mL) equipped with a magnetic stir bar. The resulting mixture was heated under reflux for 24 h. The reaction mixture was allowed to cool to ambient temperature and toluene was removed under reduced pressure to give crude product **2w** (Figure S1).

To the crude product **2w** was added $MgCl_2$ (24 mmol, 1.2 equiv), KOH (24 mmol, 1.2 equiv, 85%+) and EtOH (120 mL) (Figure S2) and stirred well for 0.5 h (Figure S3) before 1-fluoro-4-isocyanatobenzene (**1j**) (24 mmol, 1.2 equiv) was added. Then the mixture stirred at 25 ºC for 3 hours (the whole process was closely monitored by TLC). After the completion of the reaction (Figure S4), the crude reaction mixture was purified by flash silica gel column chromatography (DCM : MeOH = 30 : 1) to give **3ab** as yellow solid (7.5 g, 79%) (Figure S5).

Figure S1 **Figure S2** **Figure S3** **Figure S4** **Figure S5**

Figure S1: The status of the completion of the reaction.

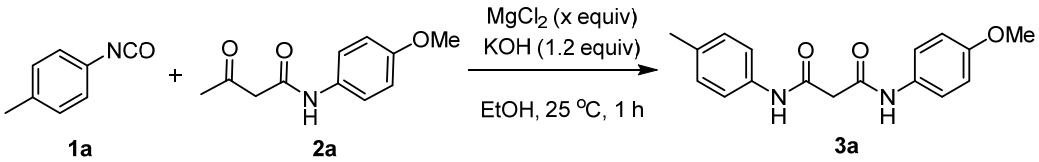
Figure S2: Add $MgCl_2$, KOH, and EtOH.

Figure S3: After stirring for 0.5 h.

Figure S4: The status of the completion of the reaction.

Figure S5: Product properties

III. Dosage Screening of $MgCl_2$



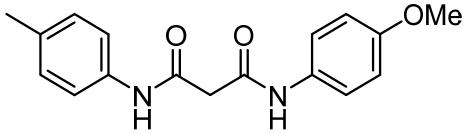
1a **2a** **3a**

Entry	$MgCl_2$ (x equiv)	Yield of **3a**/%
1	0.2	19[b]
2	0.5	45[c]
3	1.2	91[d]

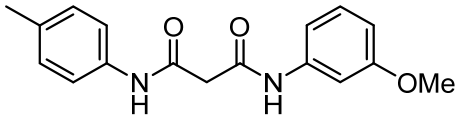
[a] Unless otherwise indicated, all reactions were conducted with **1a** (1.2 equiv), **2a** (0.5 mmol), KOH (1.2 equiv) in 3 mL of EtOH at 25 °C in 1 h. [b] 72% of **2a** was recovered. [c] 48% of **2a** was recovered. [d] Table 1, entry 1 in manuscript.

The experiment showed that 1.2 equivalent of $MgCl_2$ was necessary for the reaction, because we only got 19% and 45% product **3a**, respectively, when 0.2 and 0.5 equivalents of $MgCl_2$ were employed to the reaction, even if we prolonged the reaction time to 3 h.

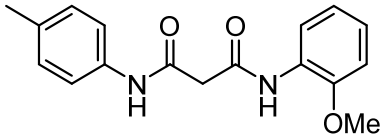
IV. Analytical Data of Compounds



***N*^{1}-(4-methoxyphenyl)-*N*^{3}-(*p*-tolyl)malonamide** (**3a**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and *N*-(4-methoxyphenyl)-3-oxobutanamide (**2a**) in presence of magnesium chloride and potassium hydroxide to afford **3a** as white solid (135 mg, 91%); Mp = 173-174 °C. **^{1}H NMR** (600 MHz, DMSO) δ 10.06 (s, 1H), 10.01 (s, 1H), 7.50 (dd, J = 15.6, 8.4 Hz, 4H), 7.11 (d, J = 7.8 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 3.72 (s, 3H), 3.41 (s, 2H), 2.25 (s, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 165.7, 165.4, 155.8, 136.9, 132.7, 132.6, 129.6, 121.1, 119.6, 114.3, 55.6, 46.2, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{17}H_{18}N_2NaO_3$ $[M+Na]^+$: 321.1210, found: 321.1201.

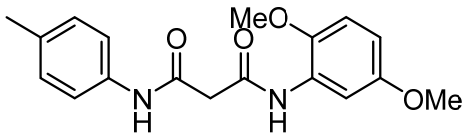


***N*^{1}-(3-methoxyphenyl)-*N*^{3}-(*p*-tolyl)malonamide** (**3b**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and *N*-(3-methoxyphenyl)-3-oxobutanamide (**2d**) in presence of magnesium chloride and potassium hydroxide to afford **3b** as white solid (127 mg, 85%); Mp = 175-177 °C. **^{1}H NMR** (600 MHz, DMSO) δ 10.16 (s, 1H), 10.08 (s, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.32 (s, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.12 (t, J = 8.4 Hz, 3H), 6.64 (d, J = 8.4 Hz, 1H), 3.73 (s, 3H), 3.45 (s, 2H), 2.25 (s, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 166.0, 165.6, 160.0, 140.6, 136.9, 132.8, 130.04, 129.6, 119.6, 111.8, 109.3, 105.4, 55.4, 46.4, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{17}H_{18}N_2NaO_3$ $[M+Na]^+$: 321.1210, found: 321.1205.

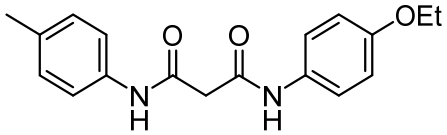


***N*^{1}-(2-methoxyphenyl)-*N*^{3}-(*p*-tolyl)malonamide** (**3c**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and *N*-(2-methoxyphenyl)-3-oxobutanamide (**2e**) in presence of magnesium chloride and potassium hydroxide to afford **3c** as white solid (138 mg, 93%); Mp = 171-172 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.12 (s, 1H), 9.68 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.09 – 7.03 (m, 2H), 6.93 – 6.89 (m, 1H), 3.85 (s, 3H), 3.58 (s, 2H), 2.25 (s, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 166.4, 165.7, 149.4, 136.7, 133.0, 129.6, 127.7, 124.6, 121.2, 120.8, 119.8, 111.5,

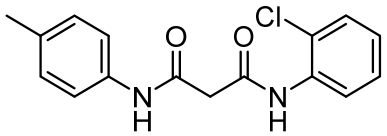
56.3, 45.5, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{17}H_{18}N_2NaO_3$ $[M+Na]^+$: 321.1210, found: 321.1209.



***N*^{1}-(2,5-dimethoxyphenyl)-*N*^{3}-(*p*-tolyl)malonamide** (**3d**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and *N*-(2,5-dimethoxyphenyl)-3-oxobutanamide (**2f**) in presence of magnesium chloride and potassium hydroxide to afford **3d** as white solid (146 mg, 90%); Mp = 146-147 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.13 (s, 1H), 9.71 (s, 1H), 7.84 (s, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.8 Hz, 1H), 6.62 (dd, J = 8.8, 2.8 Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.59 (s, 2H), 2.25 (s, 3H). **^{13}C NMR** (150 MHz, DMSO) δ 166.4, 165.7, 153.4, 143.4, 136.7, 133.0, 129.7, 128.6, 119.8, 112.3, 108.2, 107.7, 56.8, 55.8, 45.5, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{18}H_{20}N_2NaO_4$ $[M+Na]^+$: 351.1315, found: 351.1307.

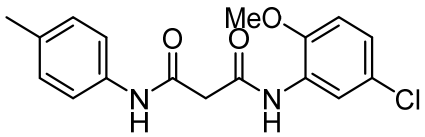


***N*^{1}-(4-ethoxyphenyl)-*N*^{3}-(*p*-tolyl)malonamide** (**3e**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and *N*-(4-ethoxyphenyl)-3-oxobutanamide (**2g**) in presence of magnesium chloride and potassium hydroxide to afford **3e** as white solid (135 mg, 87%); Mp = 218-220 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.05 (s, 1H), 10.00 (s, 1H), 7.51 – 7.47 (m, 4H), 7.11 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 9.2 Hz, 2H), 3.98 (q, J = 6.8 Hz, 2H), 3.41 (s, 2H), 2.25 (s, 3H), 1.30 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (150 MHz, DMSO) δ 165.8, 165.4, 155.0, 137.0, 132.7, 132.5, 129.6, 121.1, 119.5, 114.9, 63.5, 46.2, 20.9, 15.2. **HRMS** (ESI) (m/z) calculated for $C_{18}H_{20}N_2NaO_3$ $[M+Na]^+$: 335.1366, found: 335.1360.

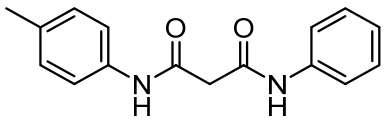


***N*^{1}-(2-chlorophenyl)-*N*^{3}-(*p*-tolyl)malonamide** (**3f**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and *N*-(2-chlorophenyl)-3-oxobutanamide (**2h**) in presence of magnesium chloride and potassium hydroxide to afford **3f** as white solid (142 mg, 95%); Mp = 186-188 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.15 (s, 1H), 10.03 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.52 – 7.48 (m, 3H), 7.36 – 7.31 (m, 1H), 7.19 – 7.12 (m, 3H), 3.60 (s, 2H), 2.26 (s, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 166.2, 166.1, 136.7, 135.3, 133.1, 129.9,

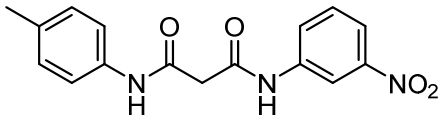
129.7, 128.0, 126.2, 125.2, 124.7, 119.8, 45.0, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{16}H_{15}ClN_2NaO_2$ $[M+Na]^+$: 325.0714, found: 325.0706.



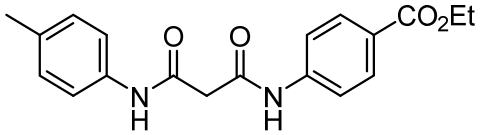
***N*^{1}-(5-chloro-2-methoxyphenyl)-*N*^{3}-(*p*-tolyl)malonamide** (**3g**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and *N*-(5-chloro-2-methoxyphenyl) -3-oxobutanamide (**2i**) in presence of magnesium chloride and potassium hydroxide to afford **3g** as white solid (150 mg, 91%); Mp = 189-190 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.13 (s, 1H), 9.88 (s, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.14 – 7.06 (m, 4H), 3.87 (s, 3H), 3.61 (s, 2H), 2.26 (s, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 166.3, 166.2, 148.0, 136.7, 133.0, 129.7, 129.0, 124.4, 123.7, 120.1, 119.8, 112.9, 56.8, 45.3, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{17}H_{17}ClN_2NaO_3$ $[M+Na]^+$: 355.0820, found: 355.0811.



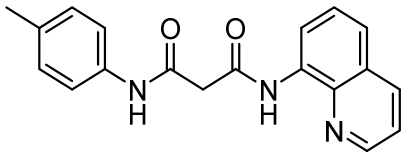
***N*^{1}-phenyl-*N*^{3}-(*p*-tolyl)malonamide** (**3h**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and 3-oxo-*N*-phenylbutanamide (**2j**) in presence of magnesium chloride and potassium hydroxide to afford **3h** as white solid (123 mg, 92%); Mp = 224-227 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.15 (s, 1H), 10.07 (s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.05 (t, J = 7.6 Hz, 1H), 3.45 (s, 2H), 2.25 (s, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 165.9, 165.7, 139.5, 136.9, 132.8, 129.6, 129.2, 123.9, 119.6, 119.5, 46.4, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{16}H_{16}N_2NaO_2$ $[M+Na]^+$: 291.1104, found: 291.1103.



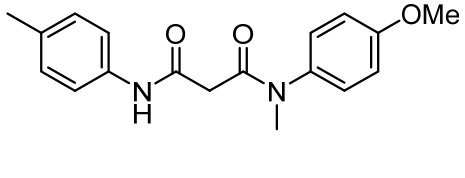
***N*^{1}-(3-nitrophenyl)-*N*^{3}-(*p*-tolyl)malonamide** (**3i**) : According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and *N*-(3-nitrophenyl)-3-oxobutanamide (**2k**) in presence of magnesium chloride and potassium hydroxide to afford **3i** as light yellow solid (117 mg, 75%); Mp = 196-197 °C. **^{1}H NMR** (600 MHz, DMSO) δ 10.70 (s, 1H), 10.13 (s, 1H), 8.65 (s, 1H), 7.94 – 7.91 (m, 2H), 7.63 (t, J = 8.4 Hz, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 3.51 (s, 2H), 2.25 (s, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 166.8, 165.3, 148.5, 140.5, 136.9, 132.9, 130.7, 129.6, 125.5, 119.6, 118.4, 113.6, 46.5, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{16}H_{15}N_3NaO_4$ $[M+Na]^+$: 336.0955, found: 336.0953.



ethyl 4-(3-oxo-3-(*p*-tolylamino)propanamido)benzoate (**3j**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and ethyl 4-(3-oxobutanamido) benzoate (**2l**) in presence of magnesium chloride and potassium hydroxide to afford **3j** as white solid (133 mg, 79%); Mp = 195-196 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.51 (s, 1H), 10.09 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 4.28 (q, J = 7.2 Hz, 2H), 3.50 (s, 2H), 2.25 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 166.6, 165.8, 165.4, 143.7, 136.9, 132.8, 130.8, 129.6, 124.9, 119.6, 118.9, 60.9, 46.5, 20.9, 14.7. **HRMS** (ESI) (m/z) calculated for $C_{19}H_{20}N_2NaO_4$ $[M+Na]^+$: 363.1315, found: 363.1313.

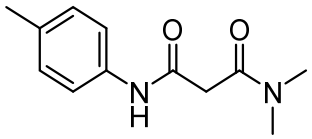


***N*^{1}-(quinolin-8-yl)-*N*^{3}-(*p*-tolyl)malonamide** (**3k**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and 3-oxo-*N*-(quinolin-8-yl)butanamide (**2m**) in presence of magnesium chloride and potassium hydroxide to afford **3k** as white solid (101 mg, 63%); Mp = 172-173 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.94 (s, 1H), 10.24 (s, 1H), 8.96 – 8.94 (m, 1H), 8.69 (d, J = 7.6 Hz, 1H), 8.41 – 8.39 (m, 1H), 7.68 – 7.62 (m, 2H), 7.58 (t, J = 8.0 Hz, 1H), 7.53 – 7.50 (m, 2H), 7.14 (d, J = 8.4 Hz, 2H), 3.77 (s, 2H), 2.25 (s, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 166.3, 166.0, 149.5, 138.6, 137.0, 136.7, 134.9, 133.1, 129.7, 128.3, 127.4, 122.6, 122.5, 119.9, 116.9, 46.2, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{19}H_{17}N_3NaO_2$ $[M+Na]^+$: 342.1213, found: 342.1208.

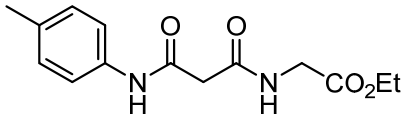


***N*^{1}-(4-methoxyphenyl)-*N*^{1}-methyl-*N*^{3}-(*p*-tolyl)malonamide** (**3l**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and *N*-(4-methoxyphenyl)-*N*-methyl-3-oxobutanamide (**2n**) in presence of magnesium chloride and potassium hydroxide to afford **3l** as white solid (131 mg, 84%); Mp = 136-137 °C. **^{1}H NMR** (400 MHz, DMSO) δ 9.78 (s, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 3.15 (s, 3H), 3.14 (s, 2H), 2.24 (s, 3H). **^{13}C NMR** (151 MHz,

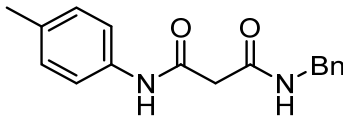
DMSO) δ 167.3, 165.6, 158.9, 136.9, 136.7, 132.6, 129.5, 129.0, 119.5, 115.2, 55.8, 43.5, 37.5, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{18}H_{20}N_2NaO_3$ $[M+Na]^+$: 335.1366, found: 335.1362.



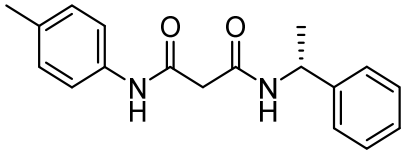
***N*^{1},*N*^{1}-dimethyl-*N*^{3}-(*p*-tolyl)malonamide** (**3m**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and *N*,*N*-dimethyl-3-oxobutanamide (**2o**) in presence of magnesium chloride and potassium hydroxide to afford **3m** as white solid (101 mg, 92%); Mp = 105-106 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.02 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 3.46 (s, 2H), 3.01 (s, 3H), 2.84 (s, 3H), 2.24 (s, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 167.6, 165.8, 137.1, 132.6, 129.6, 119.5, 43.2, 37.8, 35.4, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{12}H_{16}N_2NaO_2$ $[M+Na]^+$: 243.1104, found: 243.1101.



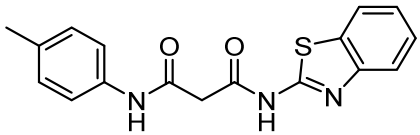
ethyl (3-oxo-3-(*p*-tolylamino)propanoyl)glycinate (**3n**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and ethyl (3-oxobutanoyl)glycinate (**2p**) in presence of magnesium chloride and potassium hydroxide to afford **3n** as white solid (131 mg, 95%); Mp = 107-108 °C. **^{1}H NMR** (400 MHz, DMSO) δ 9.99 (s, 1H), 8.48 (t, J = 5.6 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 7.6 Hz, 2H), 4.09 (qd, J = 7.2, 1.6 Hz, 2H), 3.88 (d, J = 5.6 Hz, 2H), 3.30 (s, 2H), 2.24 (s, 3H), 1.19 (td, J = 7.2, 1.6 Hz, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 170.2, 167.6, 165.6, 136.9, 132.8, 129.6, 119.6, 60.9, 44.7, 41.3, 20.9, 14.5. **HRMS** (ESI) (m/z) calculated for $C_{14}H_{18}N_2NaO_4$ $[M+Na]^+$: 301.1159, found: 301.1154.



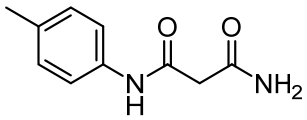
***N*^{1}-benzyl-*N*^{3}-(*p*-tolyl)malonamide** (**3o**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and *N*-benzyl-3-oxobutanamide (**2q**) in presence of magnesium chloride and potassium hydroxide to afford **3o** as white solid (132 mg, 94%); Mp = 184-185 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.02 (s, 1H), 8.55 (t, J = 5.6 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.34 – 7.28 (m, 4H), 7.26 – 7.22 (m, 1H), 7.11 (d, J = 8.4 Hz, 2H), 4.31 (d, J = 6.0 Hz, 2H), 3.29 (s, 2H), 2.25 (s, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 167.1, 165.9, 139.6, 136.9, 132.7, 129.6, 128.8, 127.7, 127.3, 119.6, 45.1, 42.7, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{17}H_{18}N_2NaO_2$ $[M+Na]^+$: 305.1260, found: 305.1256.



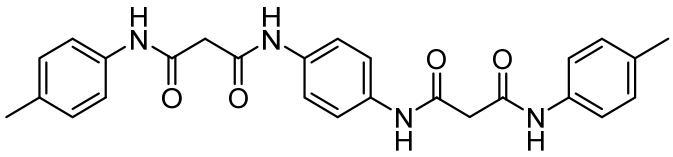
(R)-*N*^{1}-(1-phenylethyl)-*N*^{3}-(*p*-tolyl)malonamide (**3p**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and (R)-3-oxo-*N*-(1-phenylethyl)butanamide (**2r**) in presence of magnesium chloride and potassium hydroxide to afford **3p** as white solid (136 mg, 92%); Mp = 176-177 ºC. **^{1}H NMR** (400 MHz, DMSO) δ 9.99 (s, 1H), 8.52 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.35 – 7.30 (m, 4H), 7.24 – 7.20 (m, 1H), 7.10 (d, J = 8.0 Hz, 2H), 4.93 (p, J = 7.2 Hz, 1H), 3.27 (s, 2H), 2.24 (s, 3H), 1.37 (d, J = 7.2 Hz, 3H).**^{13}C NMR** (151 MHz, DMSO) δ 166.2, 165.9, 144.8, 136.9, 132.7, 129.6, 128.7, 127.1, 126.5, 119.5, 48.6, 45.1, 23.0, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{18}H_{20}N_2NaO_2$ $[M+Na]^+$: 319.1417, found: 319.1413.



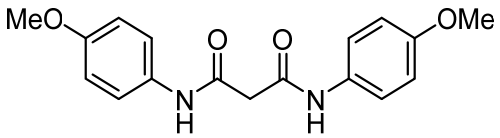
***N*^{1}-(benzo[*d*]thiazol-2-yl)-*N*^{3}-(*p*-tolyl)malonamide** (**3q**): According to the general procedure, combining 1-isocyanato-4-methylbenzene (**1a**) and *N*-(benzo[d]thiazol-2-yl)-3-oxobutanamide (**2s**) in presence of magnesium chloride and potassium hydroxide to afford **3q** as White solid (153 mg, 94%); Mp = 259-261 ºC. **^{1}H NMR** (600 MHz, DMSO) δ 12.42 (s, 1H), 10.16 (s, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.44 (t, J = 7.8 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 3.65 (s, 2H), 2.26 (s, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 167.1, 164.8, 158.2, 149.0, 136.8, 132.9, 131.9, 129.7, 126.6, 124.1, 122.2, 121.1, 119.6, 45.2, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{17}H_{15}N_3NaO_2S$ $[M+Na]^+$: 348.0777, found: 348.0773.



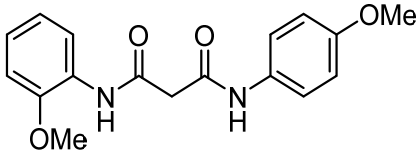
***N*^{1}-(*p*-tolyl)malonamide** (**3r**): According to the general procedure, combining 1-isocyanato-4 –methylbenzene (**1a**) and 3-oxobutanamide (**2t**) in presence of magnesium chloride and potassium hydroxide to afford **3r** as white solid (68 mg, 68%); Mp = 99-101 ºC. **^{1}H NMR** (600 MHz, DMSO) δ 9.98 (s, 1H), 7.49 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 3H), 3.19 (s, 2H), 2.24 (s, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 169.2, 166.0, 137.0, 132.7, 129.6, 119.5, 44.9, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{10}H_{12}N_2NaO_2$ $[M+Na]^+$: 215.0791, found: 215.0783.



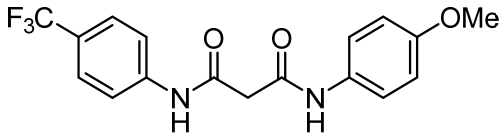
***N*^{1},*N*$^{1'}$-(1,4-phenylene)bis(*N*^{3}-(*p*-tolyl)malonamide)** (**3s**): According to the general procedure, combining isocyanatocyclohexane (**1a**) and *N*,*N*'-(1,4-phenylene)bis(3-oxobutanamide) (**2u**) in presence of magnesium chloride and potassium hydroxide to afford **3s** as white solid (8.59 g, 94%); Mp >320 ºC. **^{1}H NMR** (400 MHz, DMSO) δ 10.12 (s, 2H), 10.06 (s, 2H), 7.54 (s, 4H), 7.48 (d, J = 8.4 Hz, 4H), 7.11 (d, J = 8.4 Hz, 4H), 3.43 (s, 4H), 2.25 (s, 6H). **^{13}C NMR** (151 MHz, DMSO) δ 165.7, 165.7, 137.0, 135.0, 132.8, 129.6, 120.0, 119.6, 46.3, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{26}H_{26}N_4NaO_4$ $[M+Na]^+$: 481.1846, found: 481.1841.



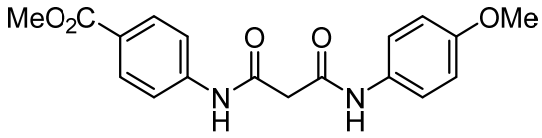
***N*^{1},*N*^{3}-bis(4-methoxyphenyl)malonamide** (**3t**): According to the general procedure, combining 1-isocyanato-4-methoxybenzene (**1b**) and *N*-(4-methoxyphenyl)-3-oxobutanamide (**2a**) in presence of magnesium chloride and potassium hydroxide to afford **3t** as white solid (149 mg, 95%); Mp = 230-232 ºC. **^{1}H NMR** (600 MHz, DMSO) δ 10.01 (s, 2H), 7.51 (d, J = 8.8 Hz, 4H), 6.90 – 6.87 (m, 4H), 3.72 (s, 6H), 3.40 (s, 2H). **^{13}C NMR** (151 MHz, DMSO) δ 165.5, 155.7, 132.6, 121.1, 114.3, 55.6, 46.1. **HRMS** (ESI) (m/z) calculated for $C_{17}H_{18}N_2NaO_4$ $[M+Na]^+$: 337.1159, found: 337.1159.



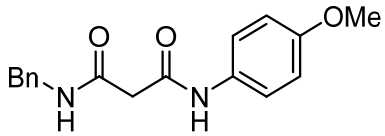
***N*^{1}-(2-methoxyphenyl)-*N*^{3}-(4-methoxyphenyl)malonamide** (**3u**): According to the general procedure, combining 1-isocyanato-3-methoxybenzene (**1c**) and *N*-(4-methoxyphenyl)-3-oxobutanamide (**2a**) in presence of magnesium chloride and potassium hydroxide to afford **3u** as white solid (141 mg, 90%); Mp = 120-122 ºC. **^{1}H NMR** (600 MHz, DMSO) δ 10.08 (s, 1H), 9.70 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 9.0 Hz, 2H), 7.08 – 7.04 (m, 2H), 6.92 – 6.89 (m, 3H), 3.85 (s, 3H), 3.72 (s, 3H), 3.56 (s, 2H). **^{13}C NMR** (151 MHz, DMSO) δ 166.2, 165.7, 155.9, 149.3, 132.3, 127.8, 124.6, 121.4, 121.1, 120.8, 114.4, 111.5, 56.3, 55.6, 45.3. **HRMS** (ESI) (m/z) calculated for $C_{17}H_{18}N_2NaO_4$ $[M+Na]^+$: 337.1159, found: 337.1153.



***N*^{1}-(4-methoxyphenyl)-*N*^{3}-(4-(trifluoromethyl)phenyl)malonamide** (**3v**): According to the general procedure, combining 1-isocyanato-4-(trifluoromethyl)benzene (**1d**) and *N*-(4-methoxyphenyl)-3-oxobutanamide (**2a**) in presence of magnesium chloride and potassium hydroxide to afford **3v** as white solid (150 mg, 85%); Mp = 233-234 ºC. **^{1}H NMR** (600 MHz, DMSO) δ 10.53 (s, 1H), 10.05 (s, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 3.72 (s, 3H), 3.48 (s, 2H). **^{19}F NMR** (565 MHz, DMSO) δ -60.32. ^{13}C NMR (101 MHz, DMSO) δ 166.7, 165.1, 155.8, 143.0, 132.6, 126.6 (q, $J_{C\text{-}F}$ = 3.4 Hz), 124.8 (q, $J_{C\text{-}F}$ = 269.4 Hz), 123.9 (q, $J_{C\text{-}F}$ = 31.8 Hz), 121.1, 119.5, 114.4, 55.6, 46.3. **HRMS** (ESI) (m/z) calculated for $C_{17}H_{15}F_3N_2NaO_3$ $[M+Na]^+$: 375.0927, found: 375.0925.

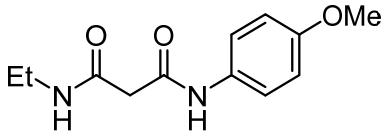


methyl 4-(3-((4-methoxyphenyl)amino)-3-oxopropanamido)benzoate (**3w**): According to the general procedure, combining methyl 4-isocyanatobenzoate (**1e**) and *N*-(4-methoxyphenyl)-3-oxobutanamide (**2a**) in presence of magnesium chloride and potassium hydroxide to afford **3w** as white solid (151 mg, 89%); Mp = 202-203 ºC. **^{1}H NMR** (600 MHz, DMSO) δ 10.51 (s, 1H), 10.05 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 3.82 (s, 3H), 3.72 (s, 3H), 3.49 (s, 2H). **^{13}C NMR** (151 MHz, DMSO) δ 166.6, 166.3, 165.1, 155.8, 143.8, 132.6, 130.8, 124.6, 121.1, 118.9, 114.4, 55.6, 52.4, 46.4. **HRMS** (ESI) (m/z) calculated for $C_{18}H_{18}N_2NaO_5$ $[M+Na]^+$: 365.1108, found: 365.1101.

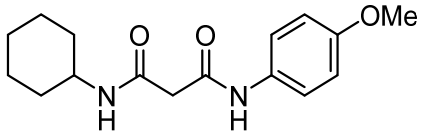


***N*^{1}-benzyl-*N*^{3}-(4-methoxyphenyl)malonamide** (**3x**): According to the general procedure, combining methyl (isocyanatomethyl)benzene (**1f**) and *N*-(4-methoxyphenyl)-3-oxobutanamide (**2a**) in presence of magnesium chloride and potassium hydroxide to afford **3x** as white solid (145 mg, 97%); Mp = 148-149 ºC. **^{1}H NMR** (400 MHz, DMSO) δ 9.98 (s, 1H), 8.56 (t, J = 5.6 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.35 – 7.29 (m, 4H), 7.26 – 7.22 (m, 1H), 6.89 (d, J = 8.8 Hz, 2H), 4.32 (d, J = 6.0 Hz, 2H), 3.72 (s, 3H), 3.29 (s, 2H). **^{13}C NMR** (151

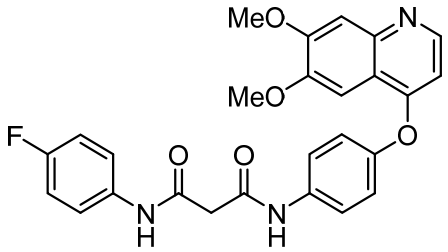
MHz, DMSO) δ 167.2, 165.7, 155.7, 139.7, 132.6, 128.8, 127.7, 127.3, 121.1, 114.3, 55.6, 45.0, 42.7. **HRMS** (ESI) (m/z) calculated for $C_{17}H_{18}N_2NaO_3$ $[M+Na]^+$: 321.1210, found: 321.1204.



***N*^{1}-ethyl-*N*^{3}-(4-methoxyphenyl)malonamide** (**3y**): According to the general procedure, combining isocyanatoethane (**1g**) and *N*-(4-methoxyphenyl)-3-oxobutanamide (**2a**) in presence of magnesium chloride and potassium hydroxide to afford **3y** as white solid (100 mg, 85%); Mp = 151-153 ºC. **^{1}H NMR** (400 MHz, DMSO) δ 9.94 (s, 1H), 8.03 (s, 1H), 7.48 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 9.2 Hz, 2H), 3.72 (s, 3H), 3.18 (s, 2H), 3.14 – 3.07 (m, 2H), 1.03 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 166.8, 165.7, 155.7, 132.6, 121.0, 114.3, 55.6, 44.9, 34.1, 15.1. **HRMS** (ESI) (m/z) calculated for $C_{12}H_{16}N_2NaO_3$ $[M+Na]^+$: 259.1053, found: 259.1046.

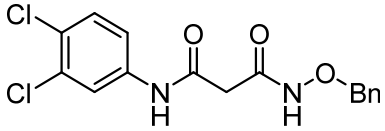


***N*^{1}-cyclohexyl-*N*^{3}-(4-methoxyphenyl)malonamide** (**3z**): According to the general procedure, combining isocyanatocyclohexane (**1h**) and *N*-(4-methoxyphenyl)-3-oxobutanamide (**2a**) in presence of magnesium chloride and potassium hydroxide to afford **3z** as white solid (127 mg, 87%); Mp = 162-163 ºC. **^{1}H NMR** (600 MHz, DMSO) δ 9.92 (s, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 7.2 Hz, 2H), 3.71 (s, 3H), 3.56 – 3.53 (m, 1H), 3.17 (s, 2H), 1.74 (d, J = 10.2 Hz, 2H), 1.67 (d, J = 13.2 Hz, 2H), 1.54 (d, J = 12.0 Hz, 1H), 1.29 – 1.23 (m, 2H), 1.19 – 1.13 (m, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 166.1, 165.8, 155.7, 132.6, 121.0, 114.3, 55.6, 48.1, 44.9, 32.8, 25.7, 24.9. **HRMS** (ESI) (m/z) calculated for $C_{16}H_{22}N_2NaO_3$ $[M+Na]^+$: 313.1523, found: 313.1514.

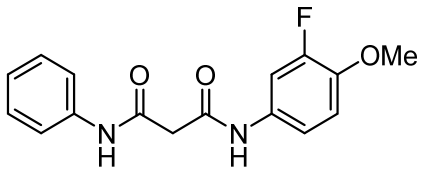


***N*^{1}-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-*N*^{3}-(4-fluorophenyl)malonamide(3ab):** According to the general procedure, combining 1-fluoro-4-isocyanatobenzene (**1j**) and *N*-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-3-oxobutanamide (**2w**) in presence of

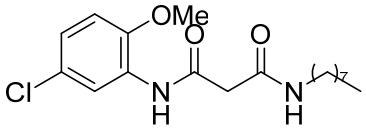
magnesium chloride and potassium hydroxide to afford **3ad** as yellow solid (206 mg, 87%); Mp = 119-121 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.36 (s, 1H), 10.28 (s, 1H), 8.46 (d, J = 5.2 Hz, 1H), 7.76 (d, J = 9.2 Hz, 2H), 7.66 – 7.62 (m, 2H), 7.51 (s, 1H), 7.39 (s, 1H), 7.25 (d, J = 8.8 Hz, 2H), 7.17 (t, J = 8.8 Hz, 2H), 6.45 (d, J = 5.2 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.50 (s, 2H). **^{19}F NMR** (376 MHz, DMSO) δ -119.17 (s).**^{13}C NMR** (151 MHz, DMSO) δ 165.8, 165.8, 160.4, 158.5 (d, $J_{C\text{-}F}$= 239.9 Hz), 153.0, 149.8, 149.8, 149.3, 146.9, 137.0, 135.9, 122.0, 121.3 (d, $J_{C\text{-}F}$ = 7.9 Hz), 121.3, 115.8 (d, $J_{C\text{-}F}$ = 22.2 Hz), 115.6, 108.3, 103.5, 99.6, 56.2, 56.2, 46.2. **HRMS** (ESI) (m/z) calculated for $C_{26}H_{23}FN_3O_5$ $[M+H]^+$: 476.1616, found: 476.1611.



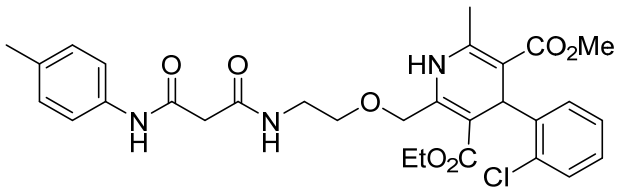
***N*^{1}-(benzyloxy)-*N*^{3}-(3,4-dichlorophenyl)malonamide** (**3ac**): According to the general procedure, combining 1,2-dichloro-4-isocyanatobenzene (**1k**) and *N*-(benzyloxy)-3-oxobutanamide (**2x**) in presence of magnesium chloride and potassium hydroxide to afford **3ac** as white solid (107 mg, 61%); Mp = 117-119 °C. **^{1}H NMR** (400 MHz, DMSO) δ 11.24 (s, 1H), 10.43 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.48 (dd, J = 8.8, 2.4 Hz, 1H), 7.42 – 7.34 (m, 5H), 4.82 (s, 2H), 3.16 (s, 2H). **^{13}C NMR** (101 MHz, DMSO) δ 166.0, 163.8, 139.4, 136.4, 131.5, 131.2, 129.3, 128.8, 128.8, 125.4, 120.8, 119.6, 77.4, 42.6. **HRMS** (ESI) (m/z) calculated for $C_{16}H_{14}Cl_2N_2NaO_3$ $[M+Na]^+$: 375.0274, found: 375.0270.



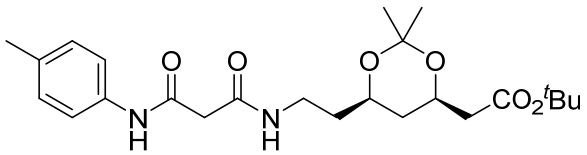
***N*^{1}-(3-fluoro-4-methoxyphenyl)-*N*^{3}-phenylmalonamide** (**3ad**): According to the general procedure, combining isocyanatobenzene (**1l**) and *N*-(3-fluoro-4-methoxyphenyl)-3-oxobutanamide (**2y**) in presence of magnesium chloride and potassium hydroxide to afford **3ad** as white solid (137 mg, 90%); Mp = 182-184 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.20 (s, 1H), 10.16 (s, 1H), 7.62-7.58 (m, 3H), 7.31 (t, J = 7.6 Hz, 2H), 7.28 – 7.25 (m, 1H), 7.12 (t, J = 9.6 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 3.80 (s, 3H), 3.45 (s, 2H). **^{19}F NMR** (376 MHz, DMSO) δ -133.82. **^{13}C NMR** (101 MHz, DMSO) δ 165.8, 165.7, 151.3 (d, $J_{C\text{-}F}$ = 242.3 Hz), 143.5 (d, $J_{C\text{-}F}$ = 10.8 Hz), 139.4, 132.9 (d, $J_{C\text{-}F}$ = 9.4 Hz), 129.2, 123.9, 119.5, 115.5 (d, $J_{C\text{-}F}$ = 3.4 Hz), 114.6 (d, J $J_{C\text{-}F}$ = 2.6 Hz), 108.0 (d, $J_{C\text{-}F}$ = 22.6 Hz), 56.6, 46.3. **HRMS** (ESI) (m/z) calculated for $C_{16}H_{15}FN_2NaO_3$ $[M+Na]^+$: 325.0959, found: 325.0954.



***N*^{1}-(5-chloro-2-methoxyphenyl)-*N*^{3}-octylmalonamide (3ae):** According to the general procedure to afford **3ae** as white solid (170 mg, 96%); Mp = 45-46 °C. **^{1}H NMR** (400 MHz, DMSO) δ 10.08 (s, 1H), 8.24 (d, J = 2.4 Hz, 1H), 8.17 (t, J = 5.2 Hz, 1H), 7.10 – 6.04 (m, 2H), 3.85 (s, 3H), 3.36 (s, 2H), 3.08 (q, J = 2.8 Hz, 2H), 1.41 (t, J = 6.4 Hz, 2H), 1.24 (s, 10H), 0.84 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 167.7, 166.2, 147.8, 129.1, 124.5, 123.5, 119.7, 112.8, 56.7, 43.9, 39.2, 31.7, 29.3, 29.2, 29.1, 26.8, 22.5, 14.4. **HRMS** (ESI) (m/z) calculated for $C_{18}H_{27}ClN_2NaO_3$ $[M+Na]^+$: 377.1602, found: 377.1592.

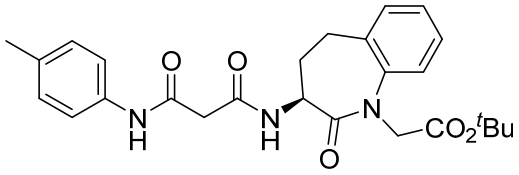


3-ethyl 5-methyl 4-(2-chlorophenyl)-6-methyl-2-((2-(3-oxo-3-(*p*-tolylamino)propanamido) ethoxy)methyl)-1,4-dihydropyridine-3,5-dicarboxylate (3af): According to the general procedure to afford **3af** as white solid (281 mg, 96%); Mp = 188-190 °C. **^{1}H NMR** (600 MHz, DMSO) δ 10.01 (s, 1H), 8.43 (s, 1H), 8.25 (t, J = 5.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.12–7.08 (m, 3H), 5.30 (s, 1H), 4.60 (dd, J = 51.0, 13.8 Hz, 2H), 4.00 – 3.90 (m, 2H), 3.54 – 3.50 (m, 5H), 3.35 – 3.34 (m, 2H), 3.27 (s, 2H), 2.28 (s, 3H), 2.24 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 167.6, 167.4, 166.8, 165.918, 146.3, 145.938, 145.4, 136.9, 132.7, 131.6, 131.5, 129.6, 129.4, 128.2, 127.9, 119.5, 102.8, 102.2, 69.7, 66.9, 59.9, 51.0, 45.1, 39.1, 37.2, 20.9, 18.7, 14.6. **HRMS** (ESI) (m/z) calculated for $C_{30}H_{34}ClN_3NaO_7$ $[M+Na]^+$:606.1977, found: 606.1967.

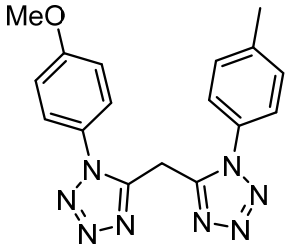


***tert*-butyl2-((4*R*,6*R*)-2,2-dimethyl-6-(2-(3-oxo-3-(*p*-tolylamino)propanamido)ethyl)-1,3-dioxan- 4-yl)acetate (3ag):** According to the general procedure to afford **3ag** as colorless oil (199 mg, 89%). **^{1}H NMR** (600 MHz, DMSO) δ 9.99 (s, 1H), 8.00 (t, J = 5.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 4.19 – 4.15 (m, 1H), 3.94 – 3.90 (m, 1H), 3.20 (s, 2H), 3.15 – 3.11 (m, 2H), 2.35 (dd, J = 15.0, 4.8 Hz, 1H), 2.24 (s, 3H), 2.21 (dd, J = 15.0, 7.8 Hz, 1H), 1.55 – 1.50 (m, 3H), 1.39 (s, 9H), 1.37 (s, 3H), 1.24 (s, 3H), 1.05 (dd, J = 24.0, 12.0

Hz, 1H). **^{13}C NMR** (151 MHz, DMSO) δ 170.1, 166.9, 165.9, 136.9, 132.7, 129.6, 119.5, 98.6, 80.2, 66.8, 66.5, 45.1, 42.7, 36.2, 36.0, 35.5, 30.4, 28.2, 20.9, 20.1. **HRMS** (ESI) (m/z) calculated for $C_{24}H_{36}N_2NaO_6$ $[M+Na]^+$:471.2466, found: 471.2452.



***tert*-butyl (*S*)-2-(2-oxo-3-(3-oxo-3-(*p*-tolylamino)propanamido)-2,3,4,5-tetrahydro-1*H*–benzo[*b*]azepin-1-yl)acetate (3ah):** According to the general procedure to afford **3ah** as white solid (214 mg, 92%); Mp = 94-96 ºC. **^{1}H NMR** (600 MHz, DMSO) δ 9.90 (s, 1H), 8.48 (s, 1H), 7.44 (d, J = 7.2 Hz, 2H), 7.36 – 7.32 (m, 3H), 7.23 (t, J = 7.2 Hz, 1H), 7.09 (d, J = 7.8 Hz, 2H), 4.58 (d, J = 17.4 Hz, 1H), 4.35 (d, J = 17.4 Hz, 1H), 4.28 (s, 1H), 3.27 – 3.20 (m, 3H), 2.65 (dd, J = 13.2, 6.6 Hz, 1H), 2.27 (d, J = 7.8 Hz, 1H), 2.24 (s, 3H), 2.05 – 1.99 (m, 1H), 1.36 (s, 9H). **^{13}C NMR** (151 MHz, DMSO) δ 171.1, 168.4, 166.5, 165.7, 141.3, 136.8, 135.8, 132.7, 129.8, 129.6, 128.3, 127.1, 123.3, 119.6, 81.7, 51.3, 49.5, 44.6, 35.5, 28.1, 27.9, 20.9. **HRMS** (ESI) (m/z) calculated for $C_{26}H_{31}N_3NaO_5$ $[M+Na]^+$: 488.2156, found: 488.2146.



1-(4-methoxyphenyl)-5-((1-(*p*-tolyl)-1*H*-tetrazol-5-yl)methyl)-1*H*-tetrazole (5):[4] Phosphorus oxychloride (1.53 g, 10 mmol) and NaN_3 (0.195 g, 3 mmol) were added to a vigorously stirred solution of amide 3a (0.298 g, 1 mmol) in 3 mL of acetonitrile. The mixture was refluxed for 8 h (the whole process was closely monitored by TLC). After the completion of the reaction, (the whole process was closely monitored by TLC). After the completion of the reaction, acetonitrile was evaporated, the residue was dissolved in water with ice, and the solution was neutralized with saturated soda solution. The precipitate that formed was filtered off. Liquid tetrazoles were extracted with methylene chloride, and the solvent was evaporated in a vacuum. The crude reaction mixture was purified by flash silica gel column chromatography. (PE : EA = 3 : 1) as eluent to give **5** as a yellow oil (184 mg, 53%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 – 7.45 (m, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.05 – 7.03 (m, 2H), 4.47 (s, 2H), 3.88 (s, 3H), 2.45 (s, 3 H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.4, 149.8, 149.7, 141.6, 130.7, 130.4, 126.8, 125.5, 125.0, 115.2, 55.8, 21.3, 19.2.

HRMS (ESI) (m/z) calculated for $C_{17}H_{16}N_8NaO$ $[M+Na]^+$: 371.1339, found: 371.1335.

V. References

(1) Tao, P.; Li, W.-L.; Zhang, J.; Guo, S.; Zhao, Q.; Wang, H.; Wei, B.; Liu, S.-J.; Zhou, X.-H.; Yu, Q.; Xu, B.-S.; Huang, W. *Adv. Funct. Mater*. **2016**, *26*, 881.

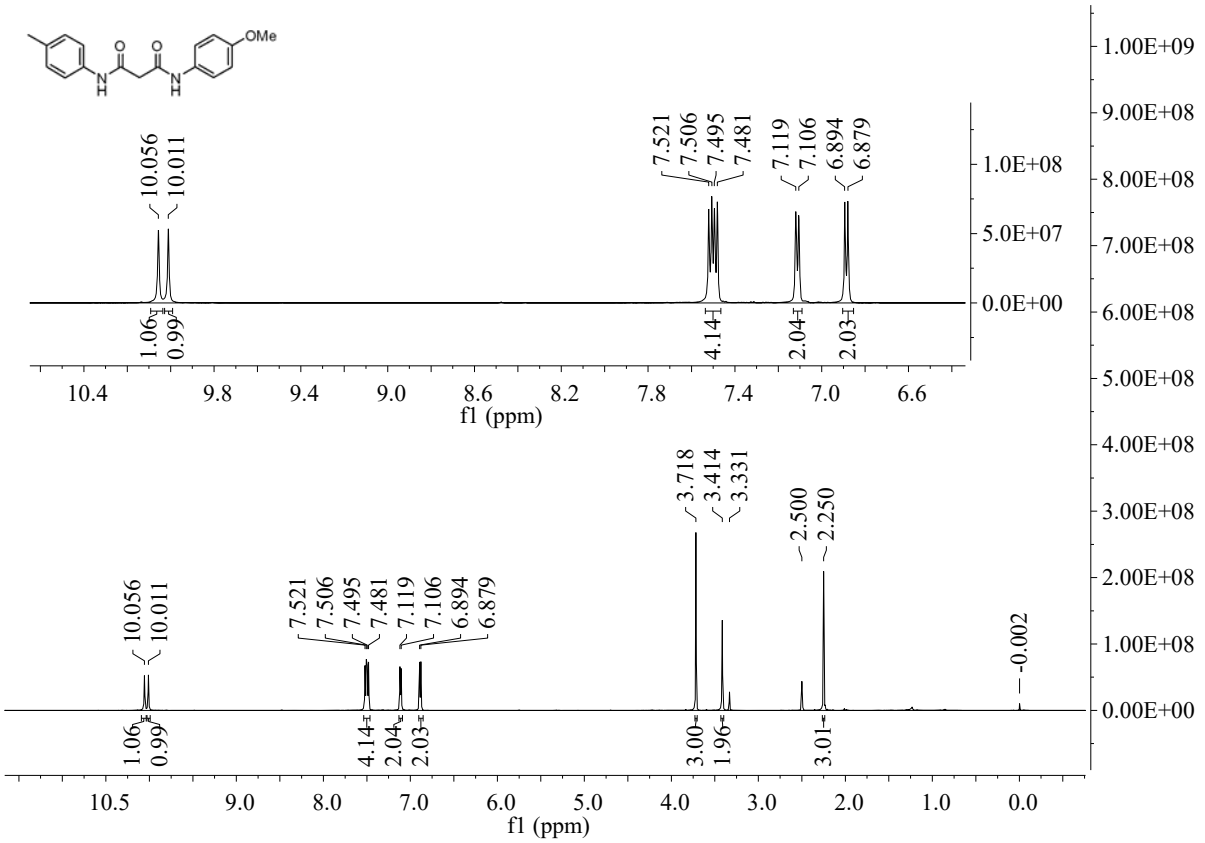
(2) Maiti, A.; Reddy, P. V. N.; Sturdy, M.; Marler, L.; Pegan, S. D.; Mesecar, A. D.; Pezzuto, J. M.; Cushman, M. *J. Med. Chem*. **2009**, *52*, 1873.

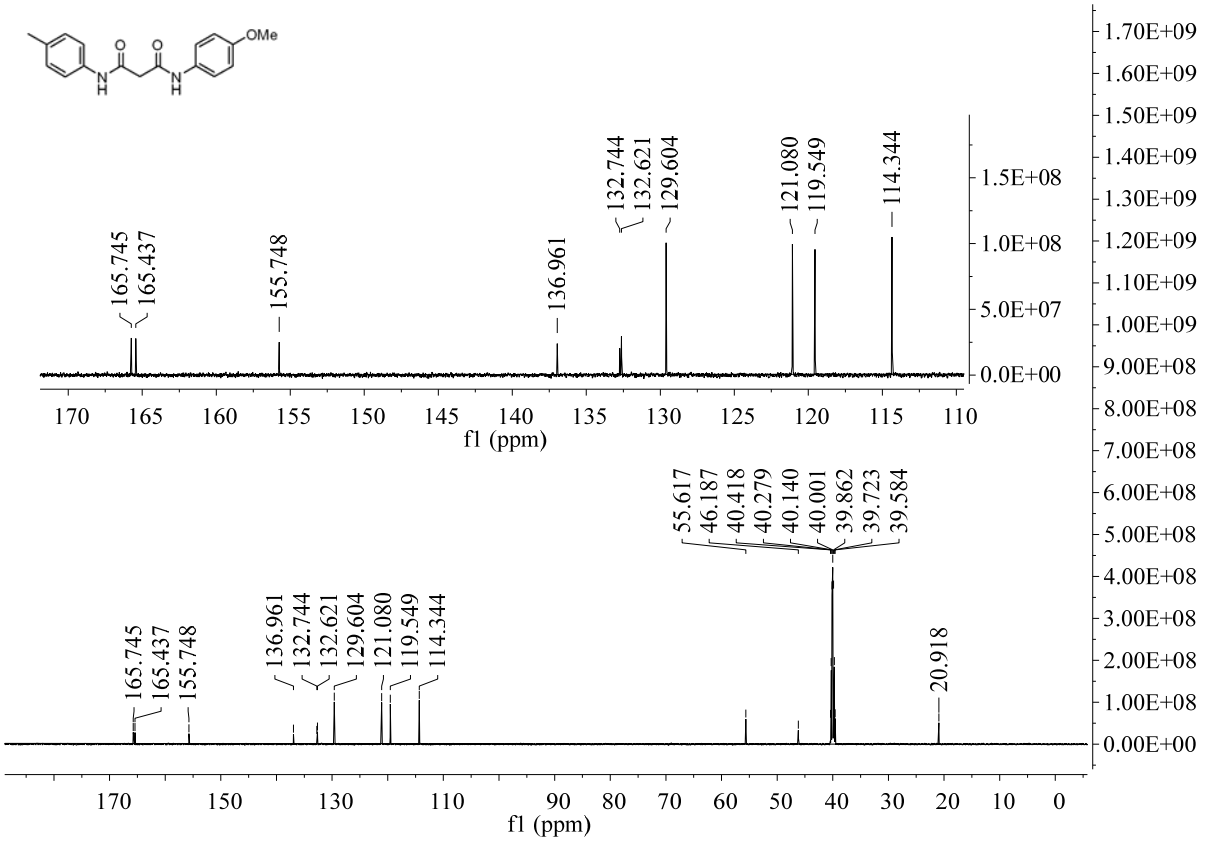
(3) Hudlicky, T.; Gillman, G.; Andersen, Catherine. *Tetrahedron Asymm.* **1992**, *3*, 281.

(4) Pokhodylo, N. T.; Shyyka, O. Ya.; Obushak, M. D. *Russ. J. Org. Chem.* **2020**, *56,* 802.

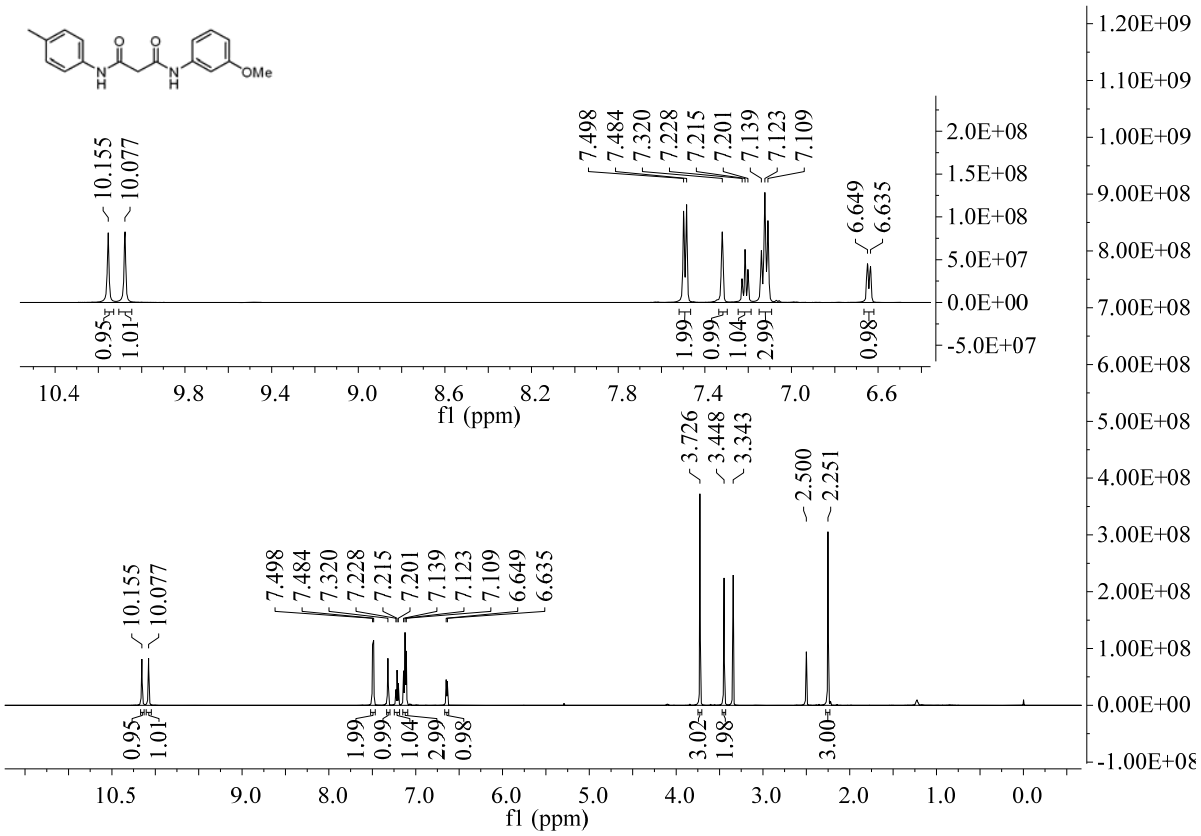
VI. ^{1}H and ^{13}C NMR Spectra

Compound **3a**





Compound **3b**


OMe
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10.077
7.498
7.484
7.320
7.228
7.215
7.201
7.139
7.123
7.109
6.649
6.635
0.95
1.01
1.99
0.99
1.04
2.99
0.98
f1 (ppm)
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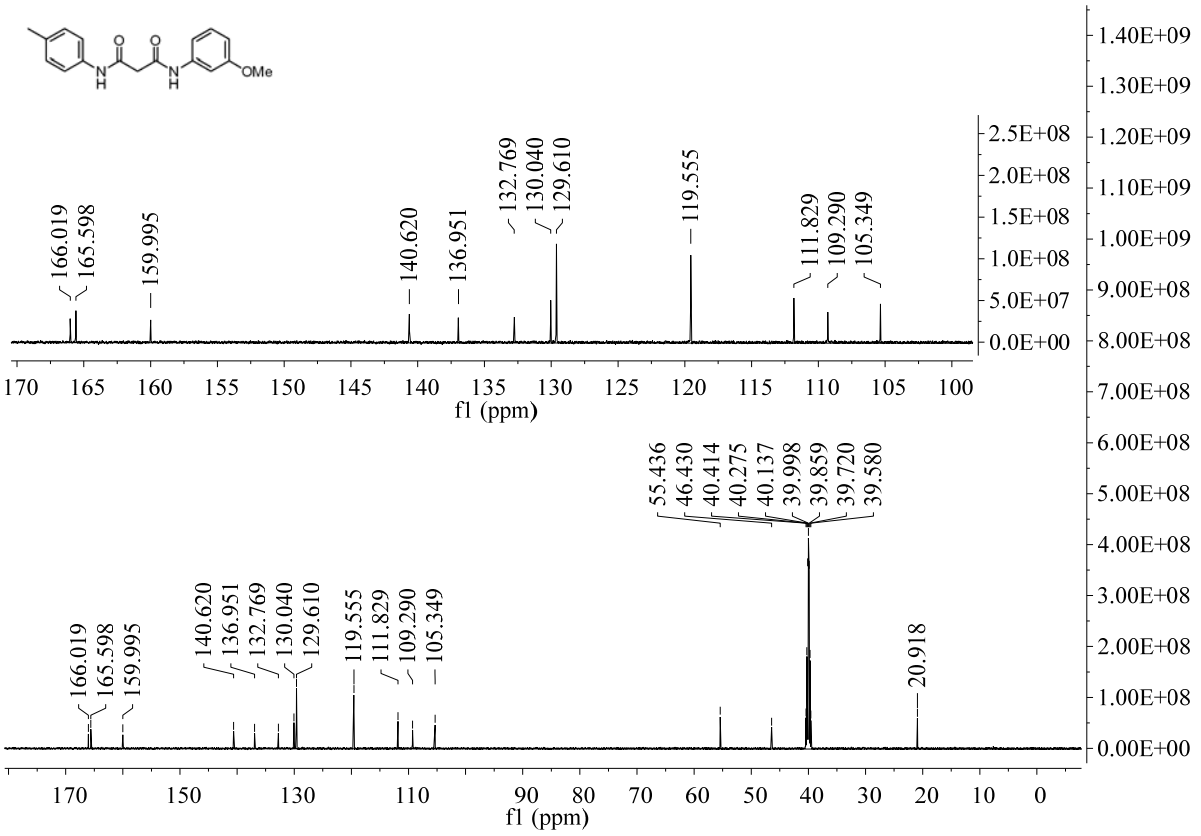
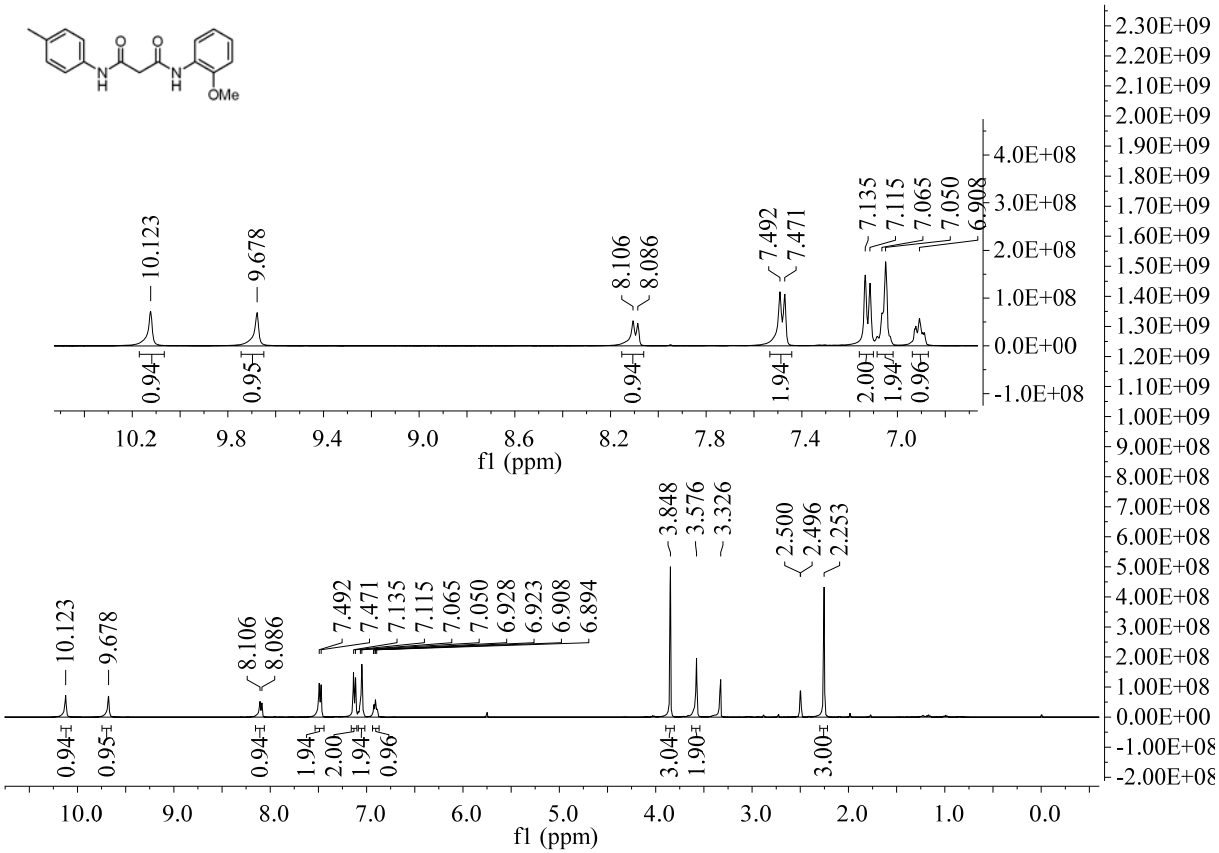
3.448
3.343
2.500
2.251
3.02
1.98
3.00


OMe
166.019
165.598
159.995
140.620
136.951
132.769
130.040
129.610
119.555
111.829
109.290
105.349
f1 (ppm)
55.436
46.430
40.414
40.275
40.137
39.998
39.859
39.720
39.580
20.918

Compound **3c**


OMe
10.123
9.678
8.106
8.086
7.492
7.471
7.135
7.115
7.065
7.050
6.908
0.94
0.95
0.94
1.94
2.00
1.94
0.96
f1 (ppm)
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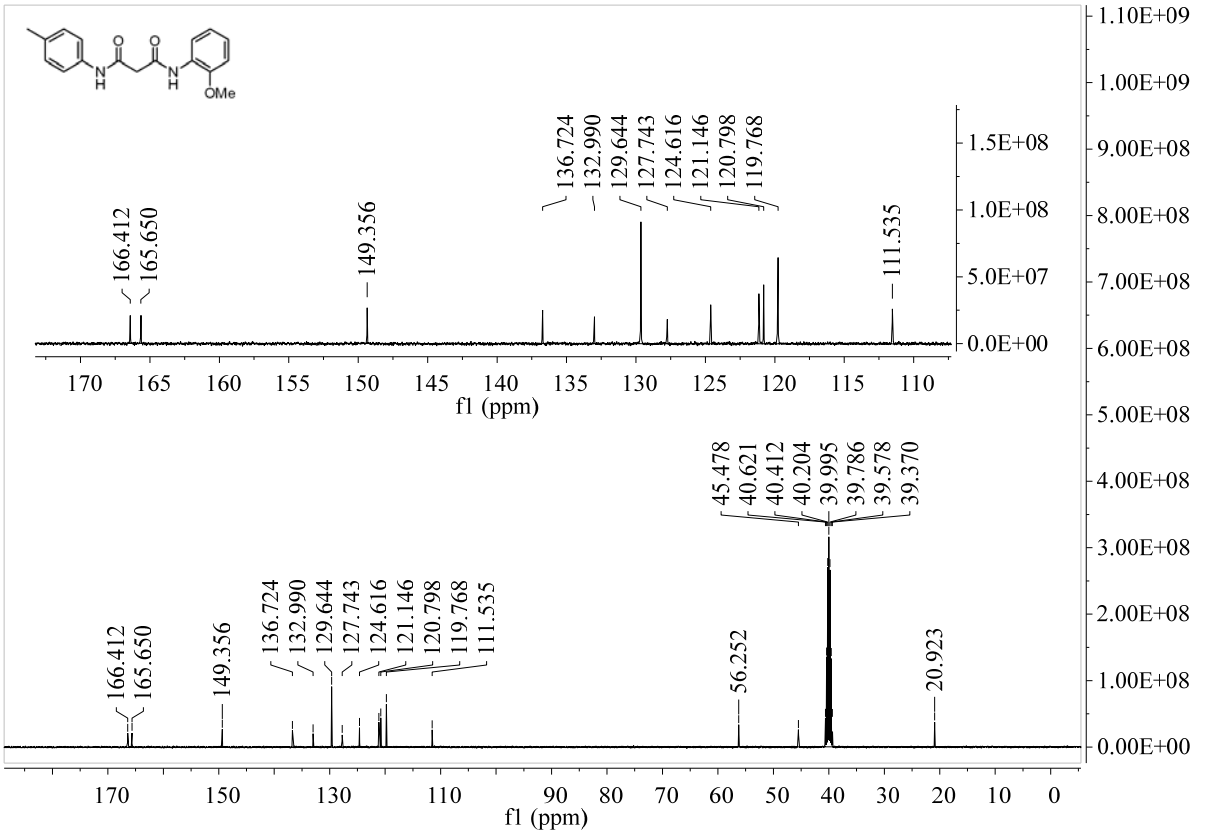
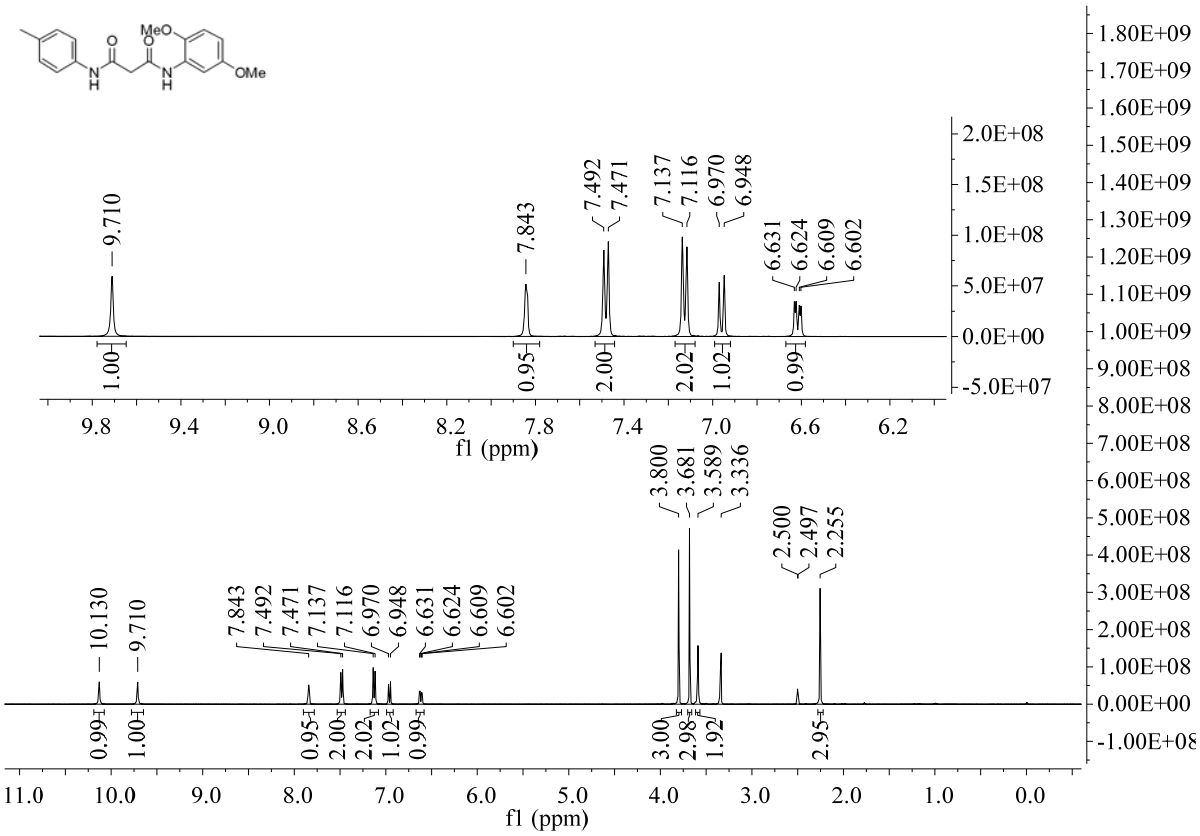
3.576
3.326
2.500
2.496
2.253
6.928
6.923
6.894
3.04
1.90
3.00


OMe
166.412
165.650
149.356
136.724
132.990
129.644
127.743
124.616
121.146
120.798
119.768
111.535
f1 (ppm)
45.478
40.621
40.412
40.204
39.995
39.786
39.578
39.370
56.252
20.923

Compound **3d**


MeO
OMe
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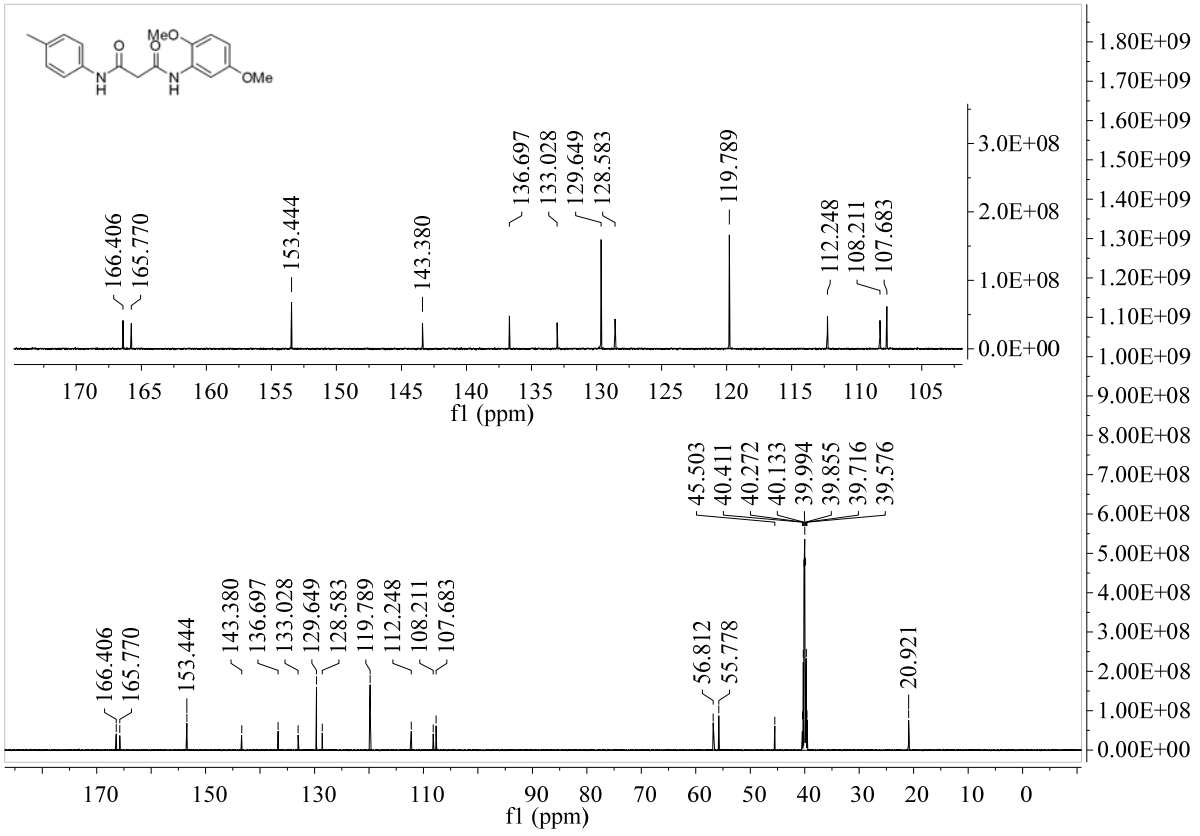
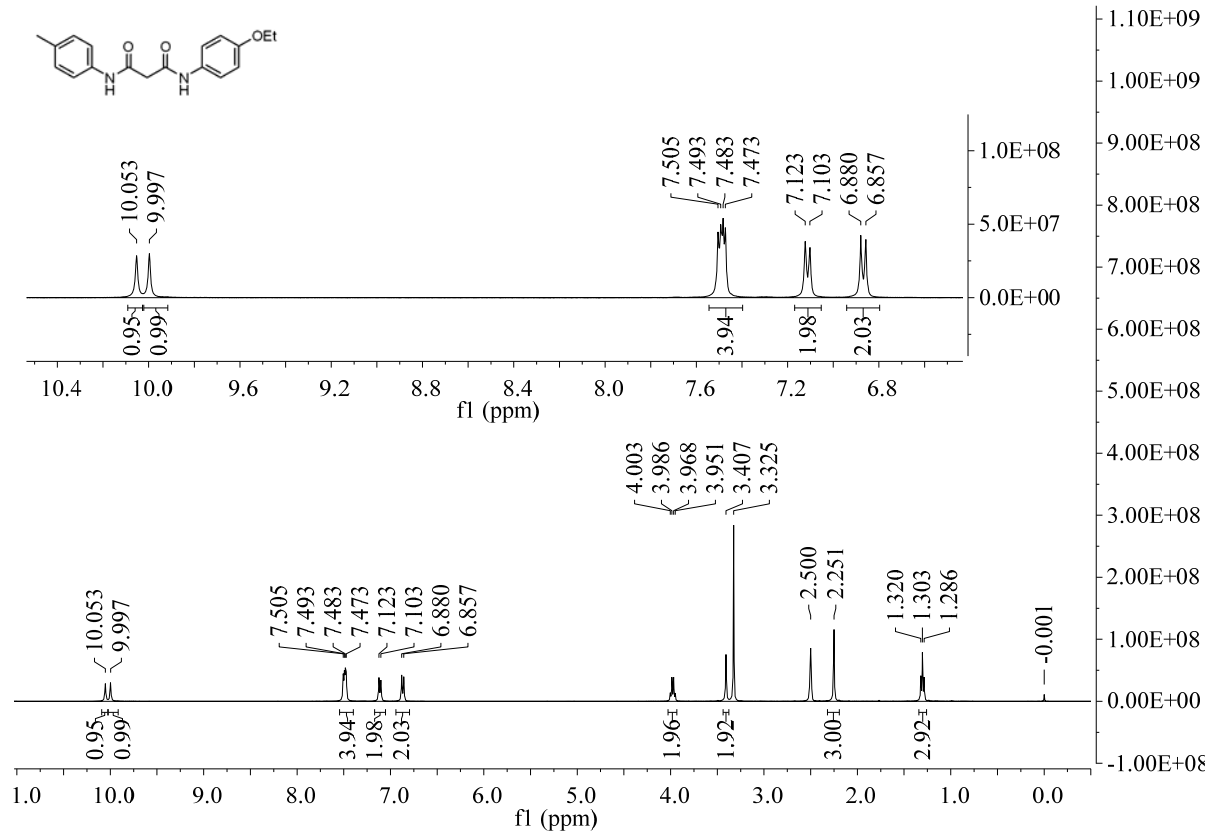
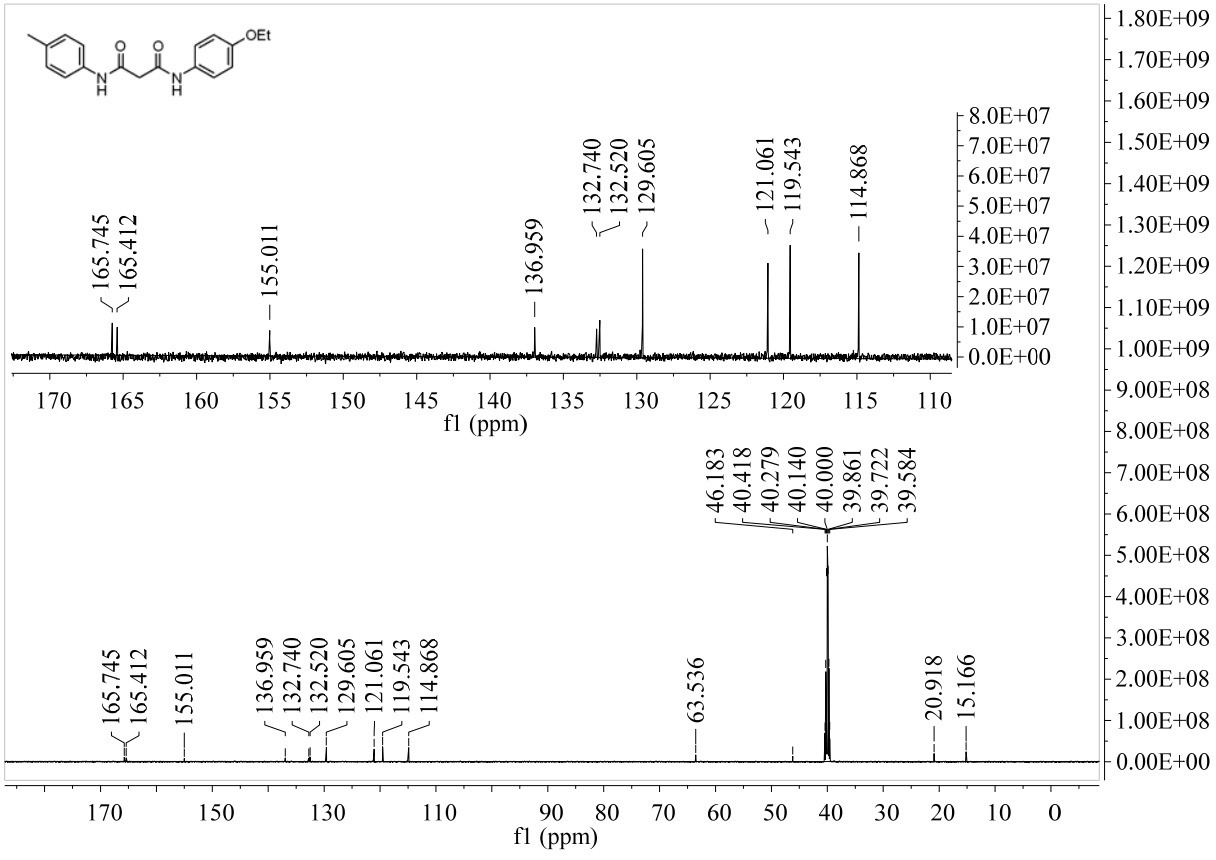
7.843
7.492
7.471
7.137
7.116
6.970
6.948
6.631
6.624
6.609
6.602
1.00
0.95
2.00
2.02
1.02
0.99
f1 (ppm)
10.130
3.800
3.681
3.589
3.336
2.500
2.497
2.255
0.99
1.00
0.95
2.00
2.02
1.02
0.99
3.00
2.98
1.92
2.95

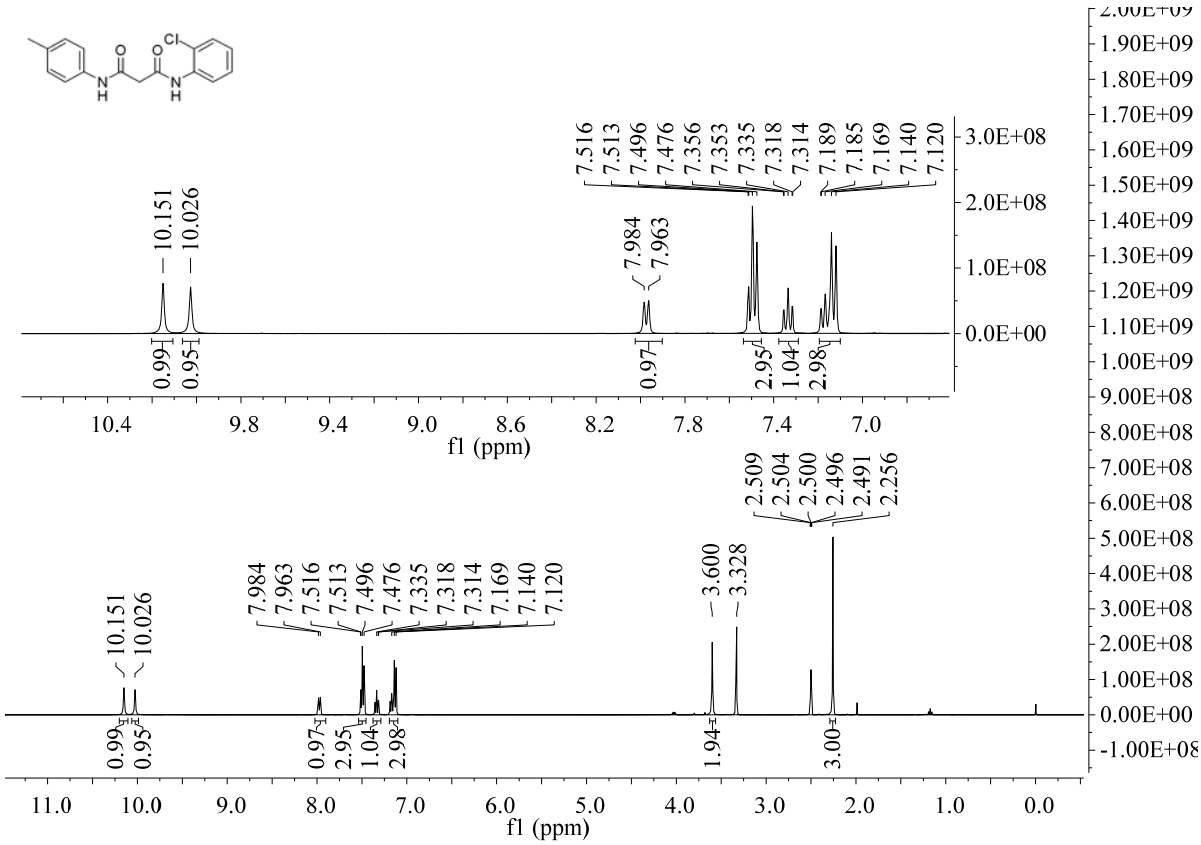

MeO
OMe
166.406
165.770
153.444
143.380
136.697
133.028
129.649
128.583
119.789
112.248
108.211
107.683
f1 (ppm)
45.503
40.411
40.272
40.133
39.994
39.855
39.716
39.576
56.812
55.778
20.921

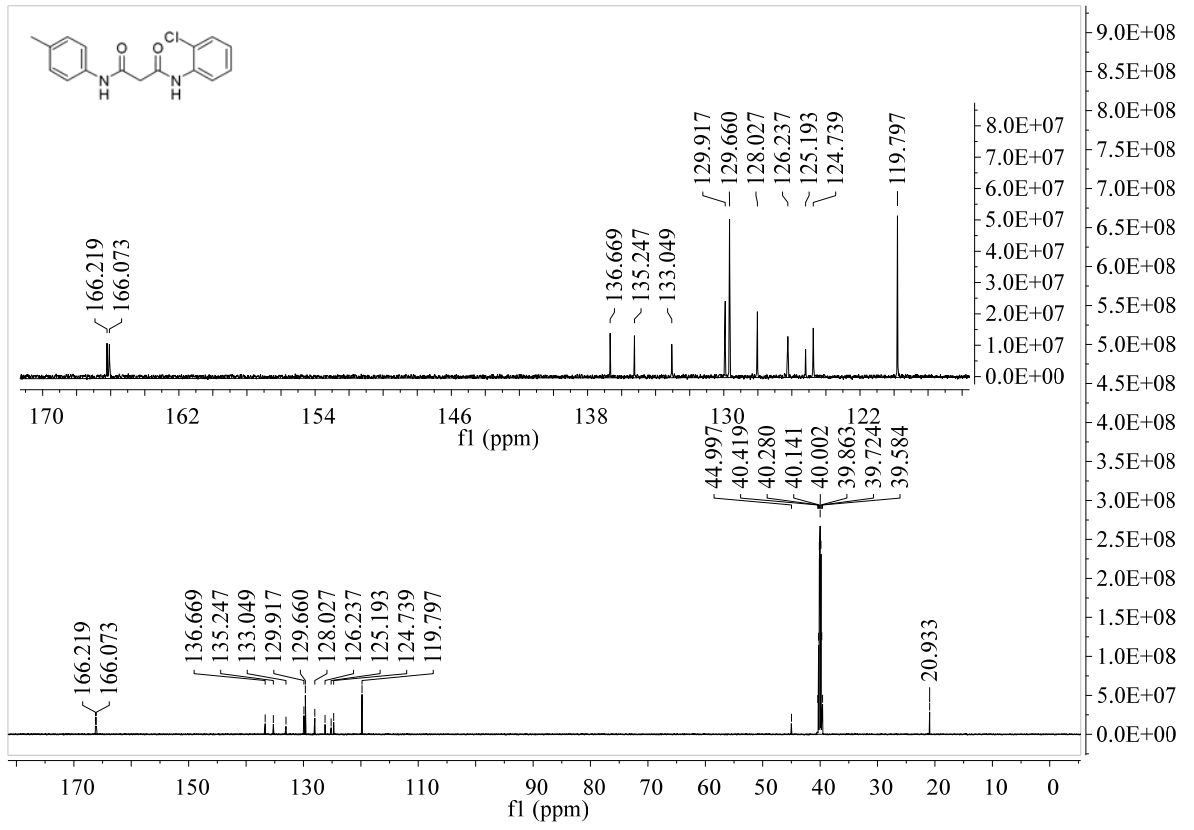
Compound **3e**


OEt
10.053
9.997
7.505
7.493
7.483
7.473
7.123
7.103
6.880
6.857
0.95
0.99
3.94
1.98
2.03
fl (ppm)
4.003
3.986
3.968
3.951
3.407
3.325
2.500
2.251
1.320
1.303
1.286
-0.001
1.96
1.92
3.00
2.92

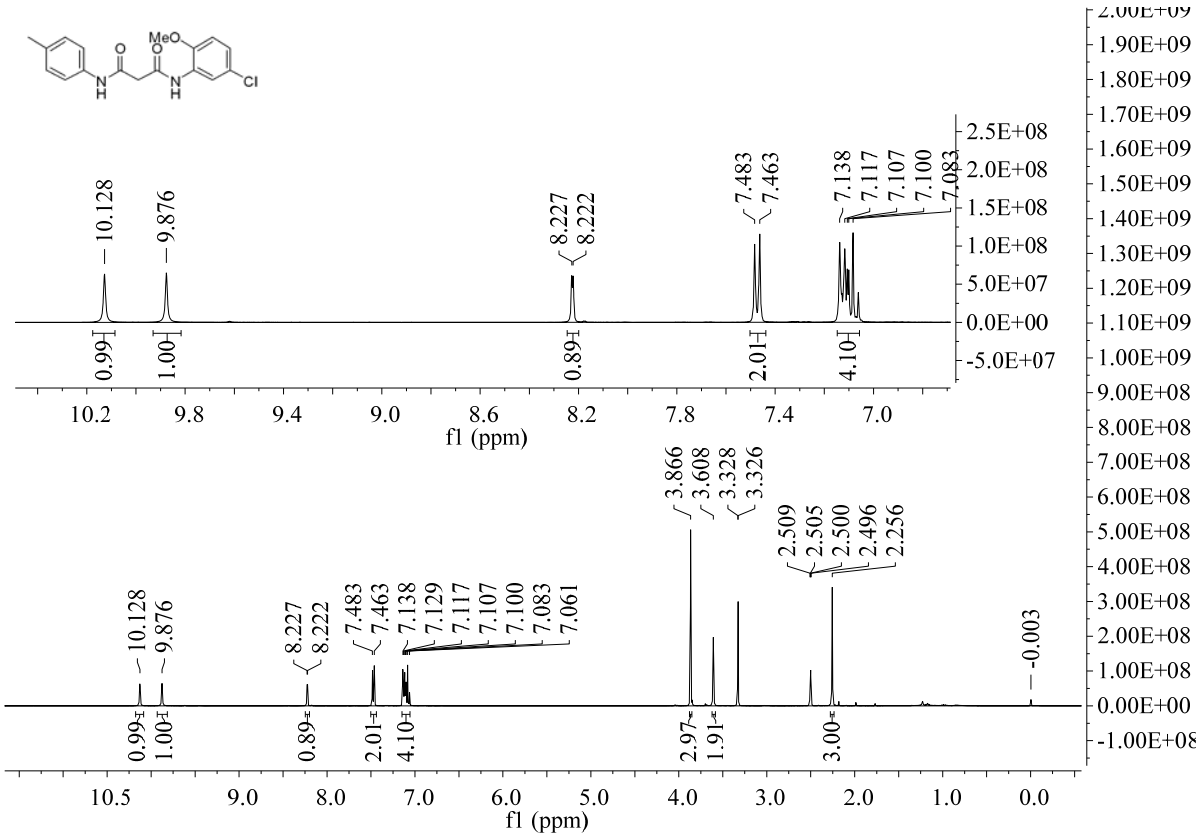

OEt
165.745
165.412
155.011
136.959
132.740
132.520
129.605
121.061
119.543
114.868
fl (ppm)
46.183
40.418
40.279
40.140
40.000
39.861
39.722
39.584
63.536
20.918
15.166

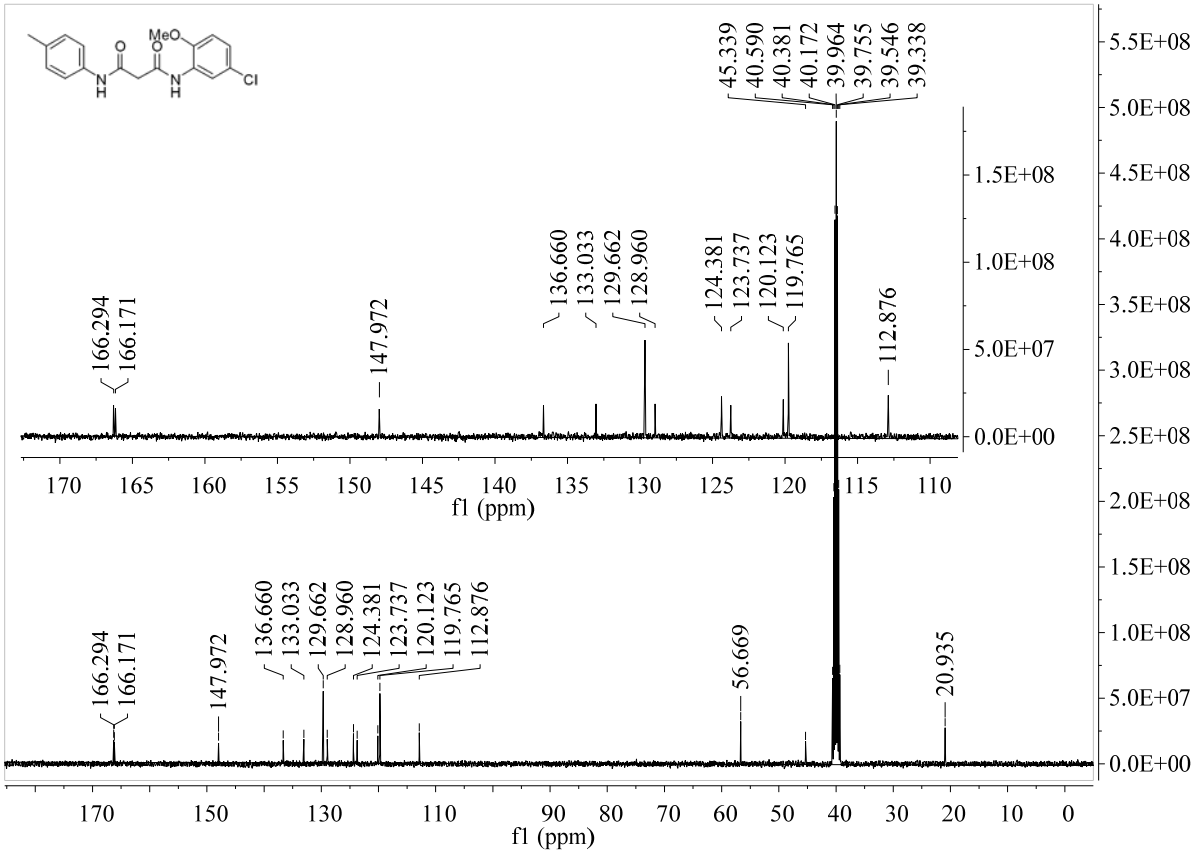
Compound **3f**


10.151
10.026
7.984
7.963
7.516
7.513
7.496
7.476
7.356
7.353
7.335
7.318
7.314
7.189
7.185
7.169
7.140
7.120
0.99
0.95
0.97
2.95
1.04
2.98
fl (ppm)
2.509
2.504
2.500
2.496
2.491
2.256
3.600
3.328
1.94
3.00

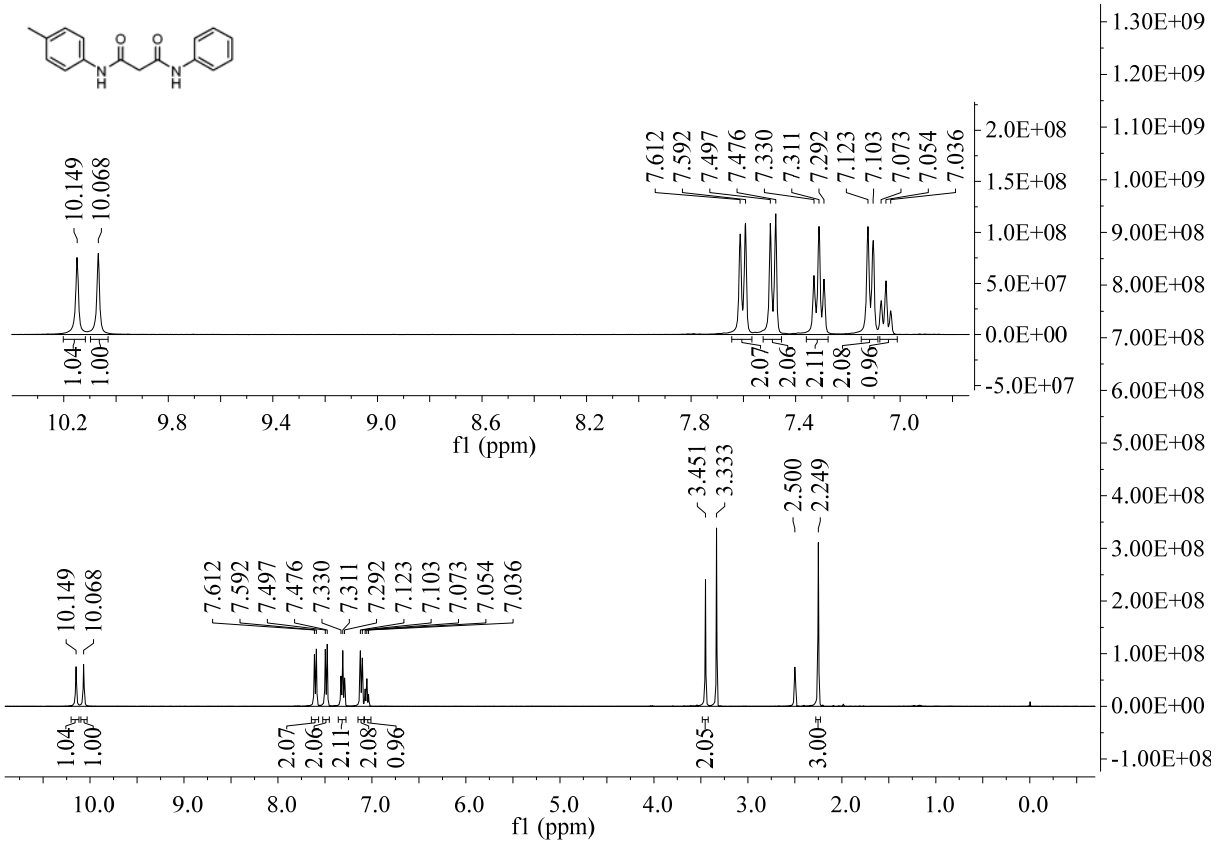

166.219
166.073
136.669
135.247
133.049
129.917
129.660
128.027
126.237
125.193
124.739
119.797
fl (ppm)
44.997
40.419
40.280
40.141
40.002
39.863
39.724
39.584
20.933

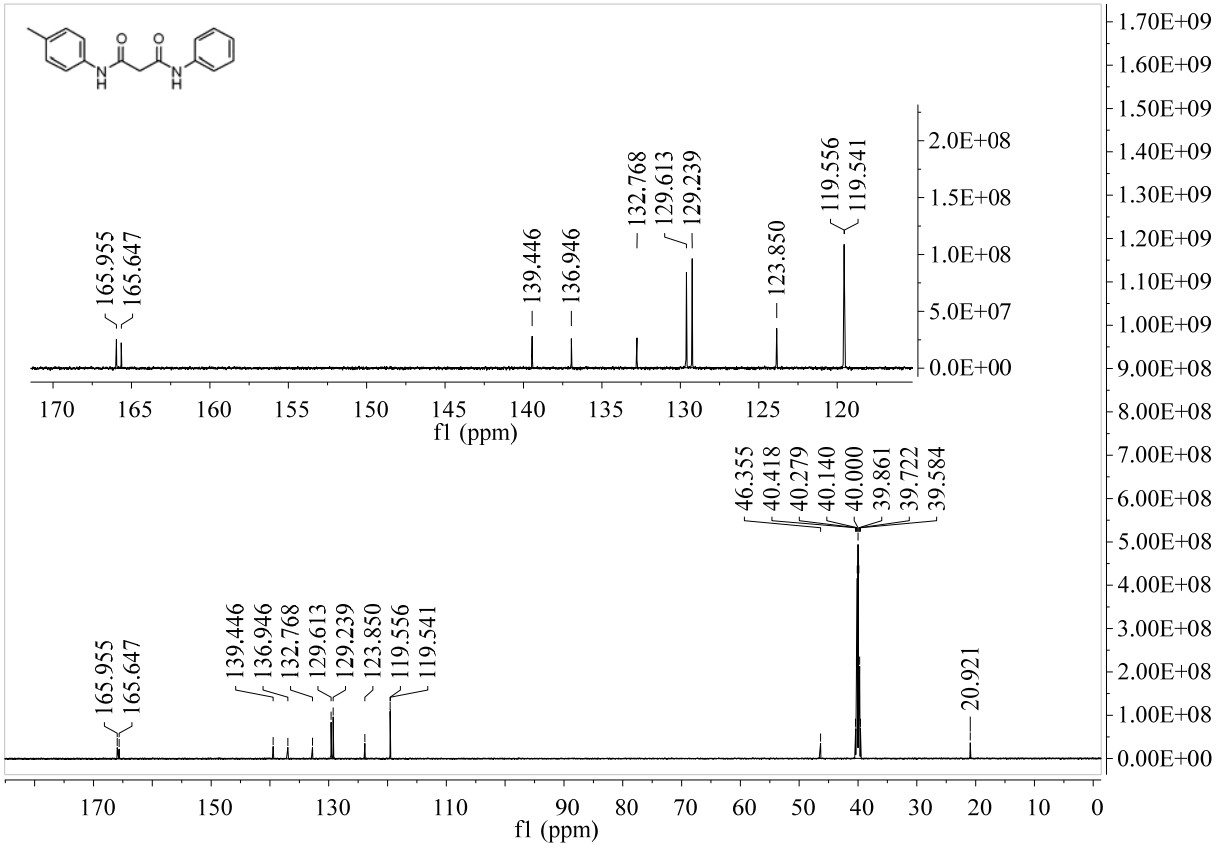
Compound **3g**


10.128
9.876
8.227
8.222
7.483
7.463
7.138
7.117
7.107
7.100
7.083
0.99
1.00
0.89
2.01
4.10
f1 (ppm)
3.866
3.608
3.328
3.326
2.509
2.505
2.500
2.496
2.256
7.129
7.061
-0.003
2.97
1.91
3.00

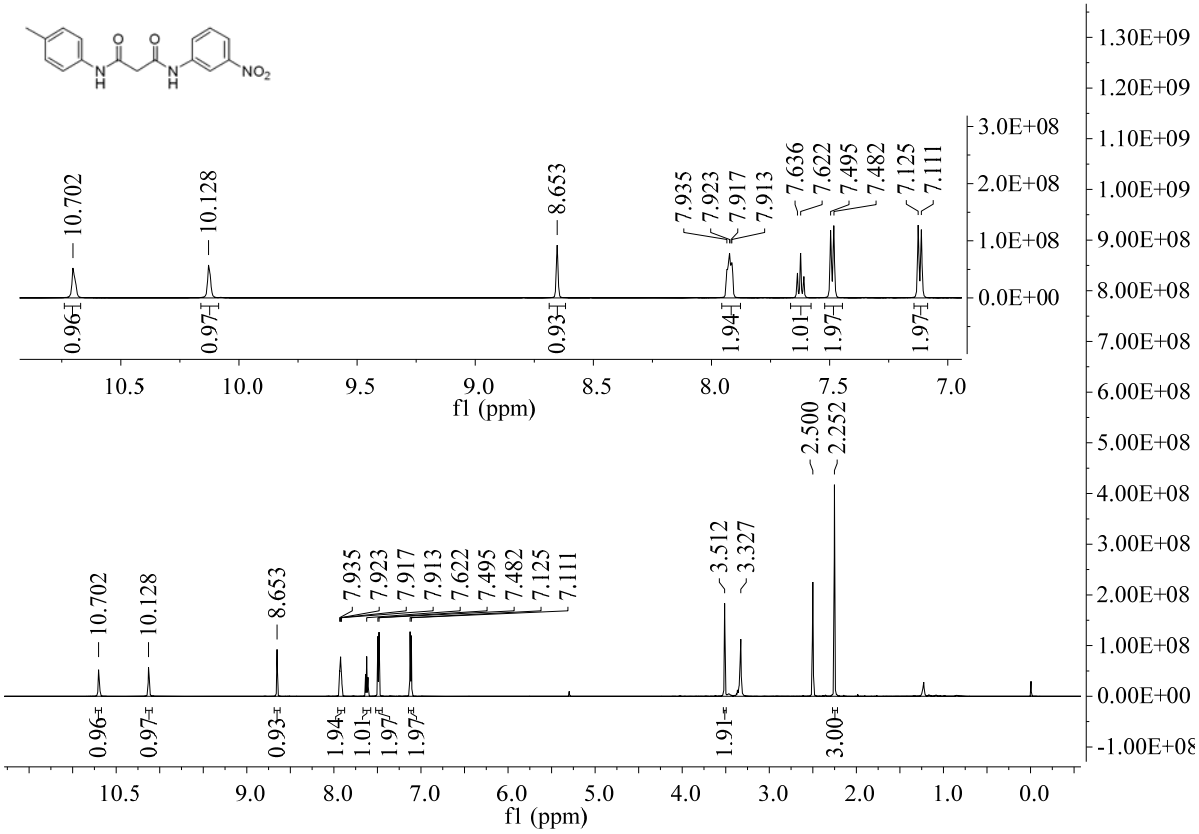

45.339
40.590
40.381
40.172
39.964
39.755
39.546
39.338
166.294
166.171
147.972
136.660
133.033
129.662
128.960
124.381
123.737
120.123
119.765
112.876
f1 (ppm)
56.669
20.935

Compound **3h**


10.149
10.068
7.612
7.592
7.497
7.476
7.330
7.311
7.292
7.123
7.103
7.073
7.054
7.036
1.04
1.00
2.07
2.06
2.11
2.08
0.96
f1 (ppm)
3.451
3.333
2.500
2.249
2.05
3.00
f1 (ppm)


165.955
165.647
139.446
136.946
132.768
129.613
129.239
123.850
119.556
119.541
f1 (ppm)
46.355
40.418
40.279
40.140
40.000
39.861
39.722
39.584
20.921
f1 (ppm)

Compound **3i**


10.702
10.128
8.653
7.935
7.923
7.917
7.913
7.636
7.622
7.495
7.482
7.125
7.111
0.96
0.97
0.93
1.94
1.01
1.97
1.97
f1 (ppm)
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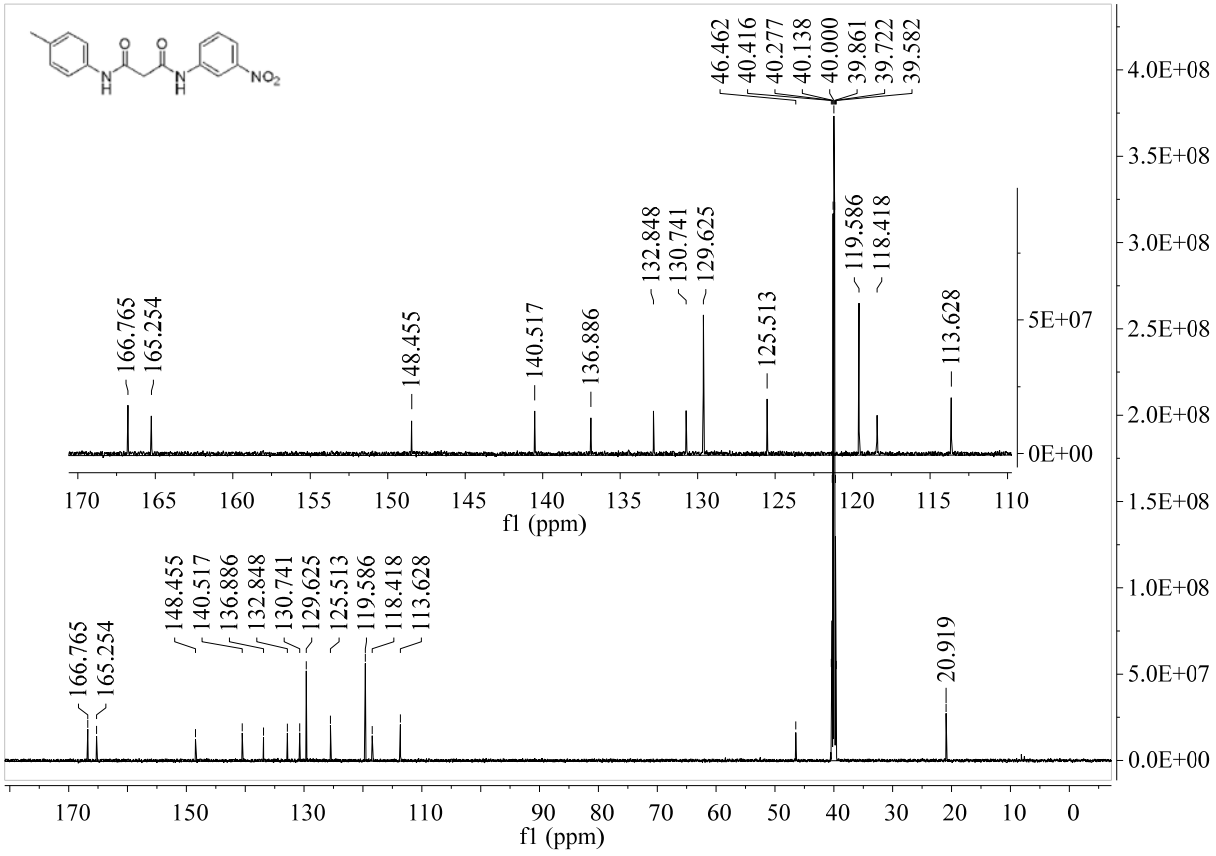
2.252
3.512
3.327
1.91
3.00


46.462
40.416
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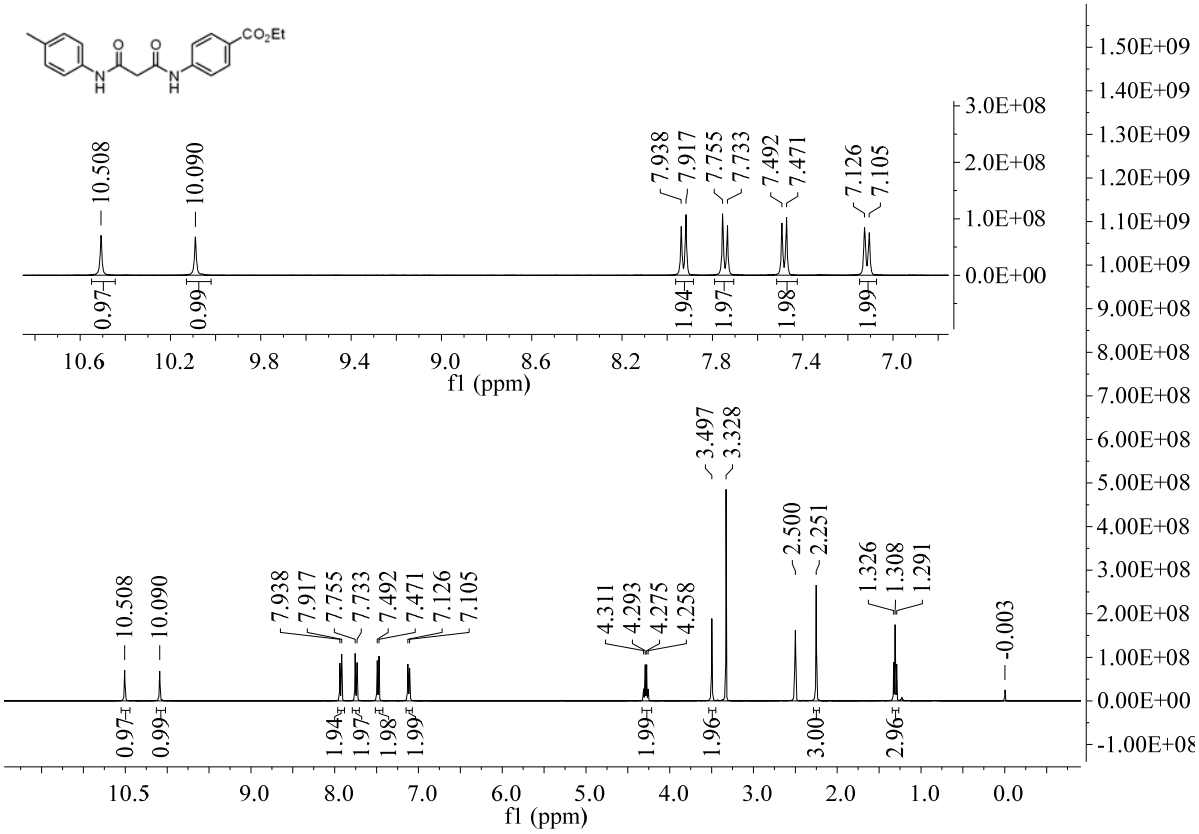
40.000
39.861
39.722
39.582
166.765
165.254
148.455
140.517
136.886
132.848
130.741
129.625
125.513
119.586
118.418
113.628
20.919
f1 (ppm)

Compound **3j**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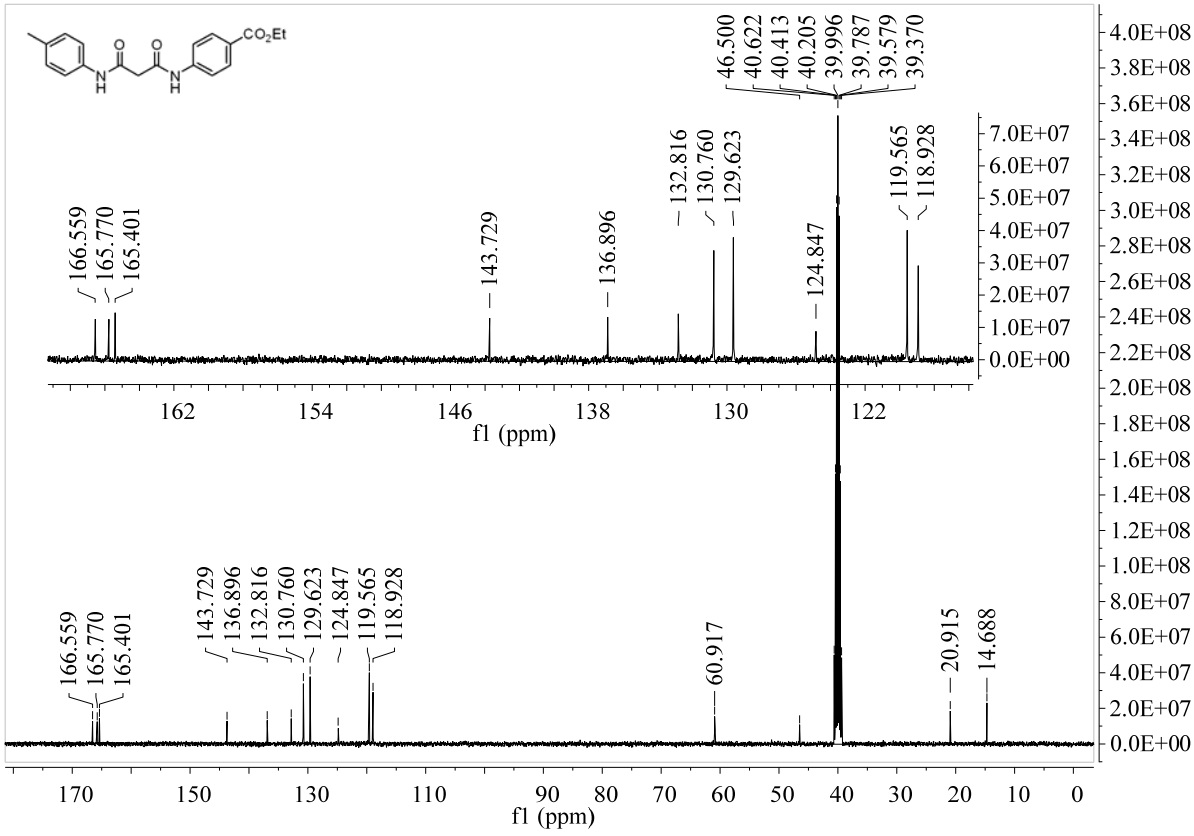
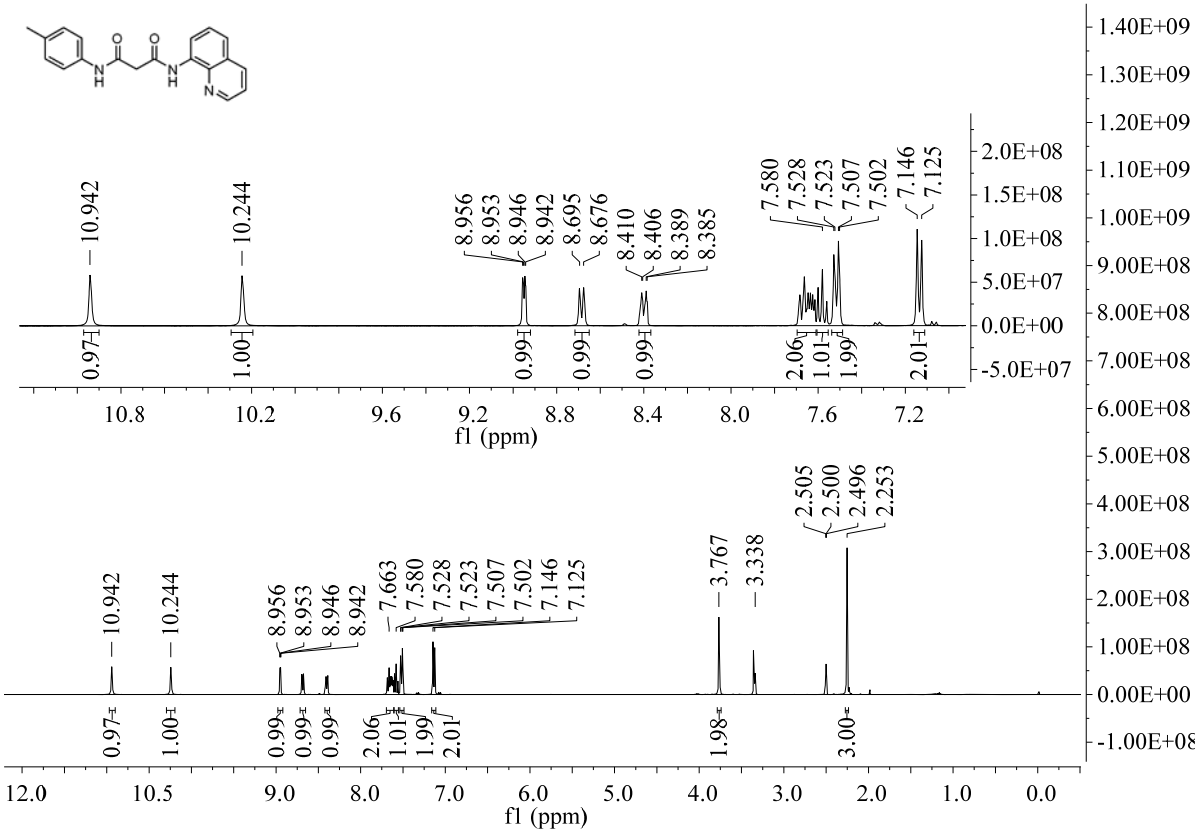
7.755
7.733
7.492
7.471
7.126
7.105
4.311
4.293
4.275
4.258
3.497
3.328
2.500
2.251
1.326
1.308
1.291
-0.003
0.97
0.99
1.94
1.97
1.98
1.99
1.96
3.00
2.96
fl (ppm)


46.500
40.622
40.413
40.205
39.996
39.787
39.579
39.370
166.559
165.770
165.401
143.729
136.896
132.816
130.760
129.623
124.847
119.565
118.928
60.917
20.915
14.688
fl (ppm)

Compound **3k**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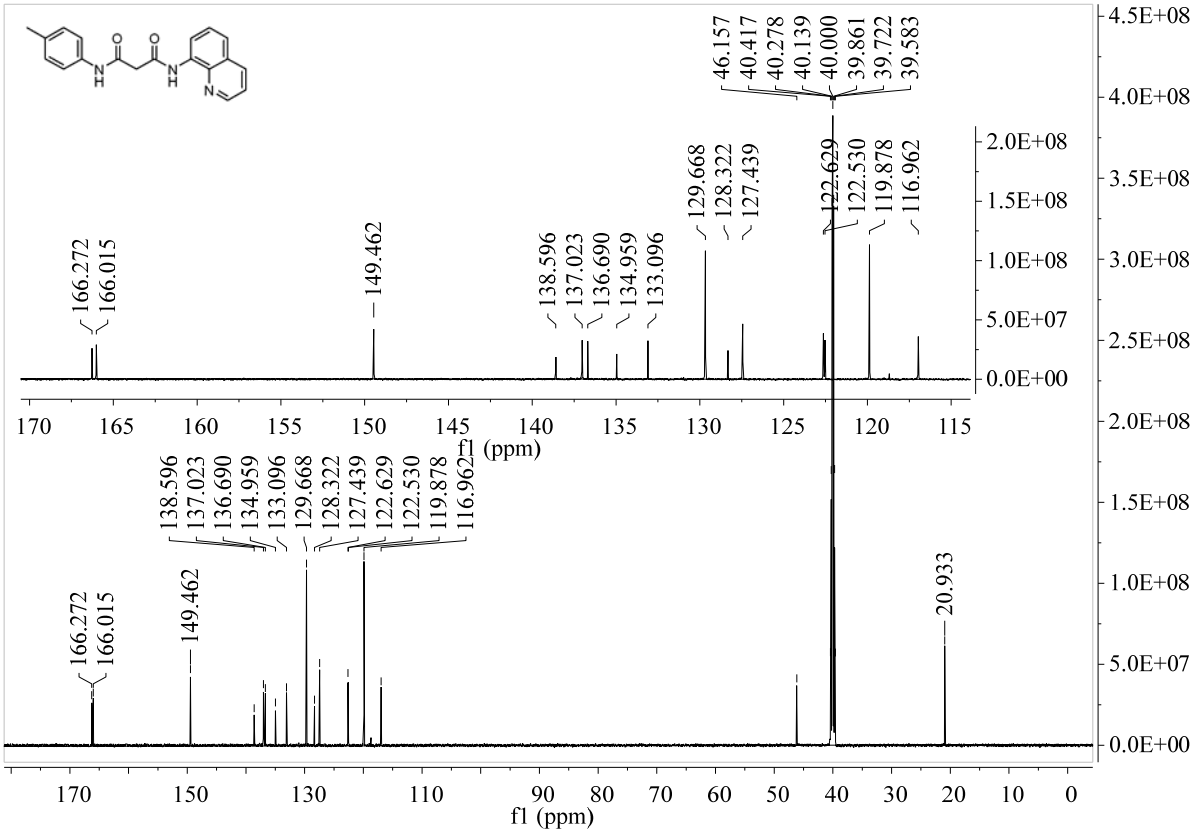
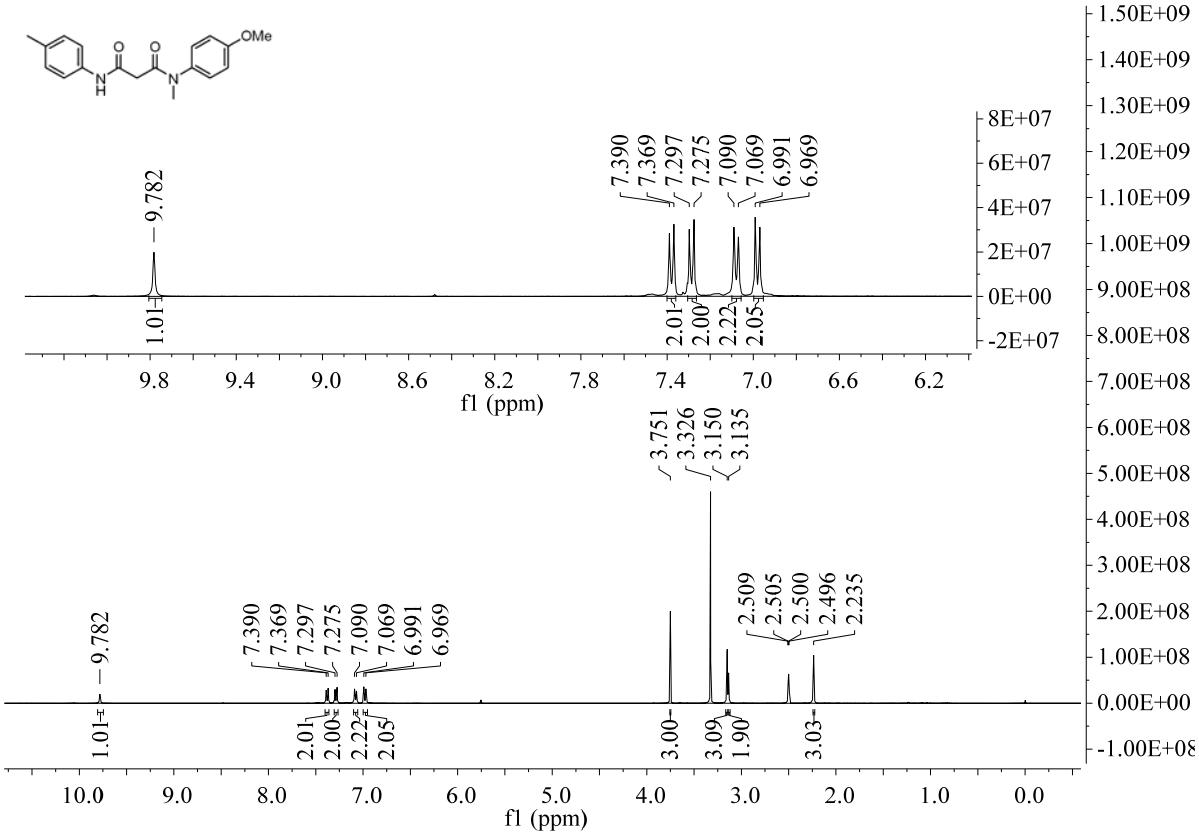
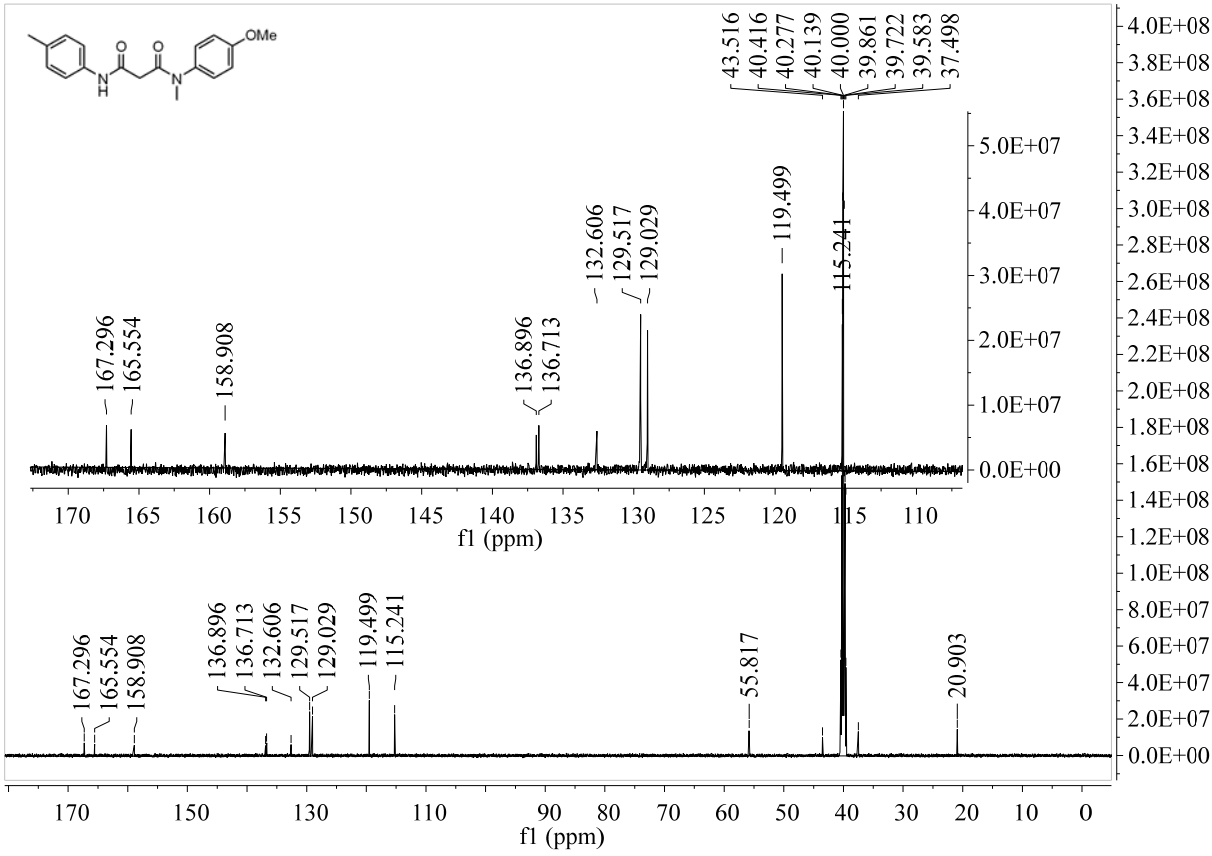
8.953
8.946
8.942
8.695
8.676
8.410
8.406
8.389
8.385
7.580
7.528
7.523
7.507
7.502
7.146
7.125
0.97
1.00
0.99
0.99
0.99
2.06
1.01
1.99
2.01
f1 (ppm)
10.942
10.244
8.956
8.953
8.946
8.942
7.663
7.580
7.528
7.523
7.507
7.502
7.146
7.125
3.767
3.338
2.505
2.500
2.496
2.253
0.97
1.00
0.99
0.99
0.99
2.06
1.01
1.99
2.01
1.98
3.00
f1 (ppm)

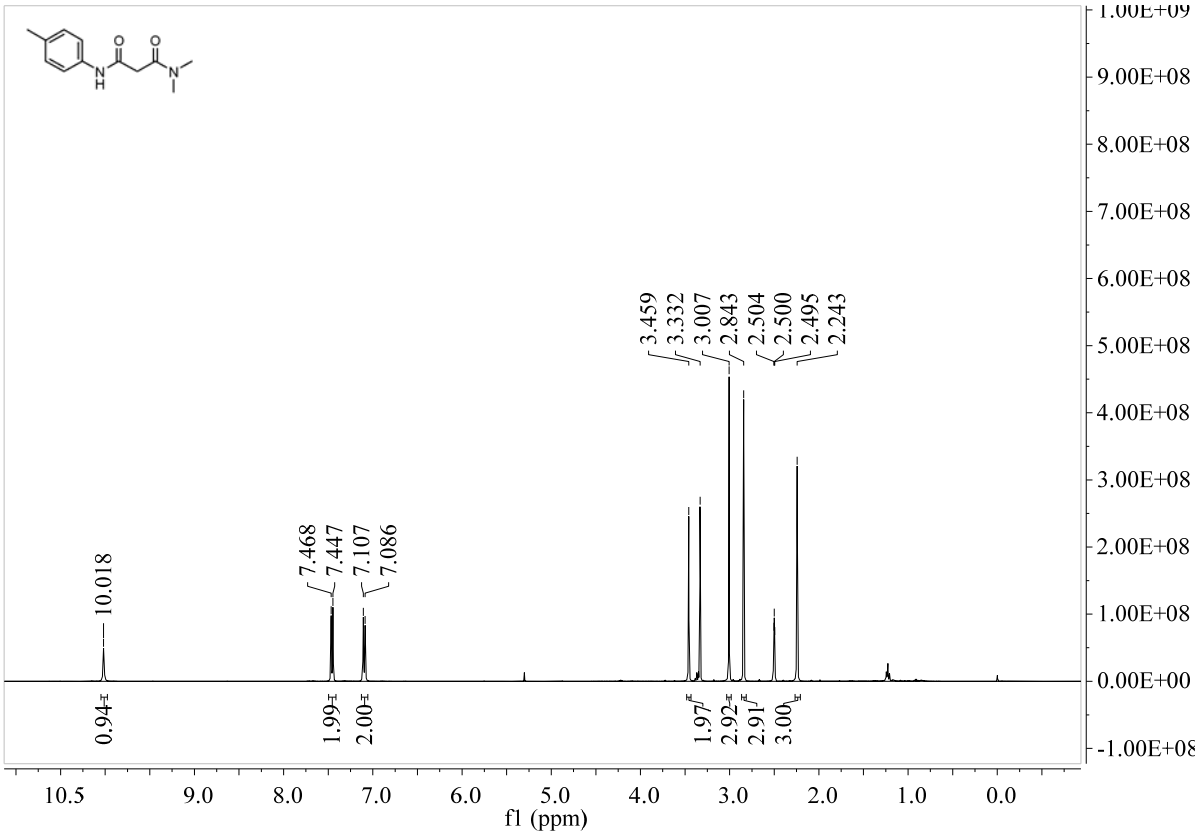

166.272
166.015
149.462
138.596
137.023
136.690
134.959
133.096
129.668
128.322
127.439
122.629
122.530
119.878
116.962
46.157
40.417
40.278
40.139
40.000
39.861
39.722
39.583
f1 (ppm)
166.272
166.015
149.462
138.596
137.023
136.690
134.959
133.096
129.668
128.322
127.439
122.629
122.530
119.878
116.962
20.933
f1 (ppm)

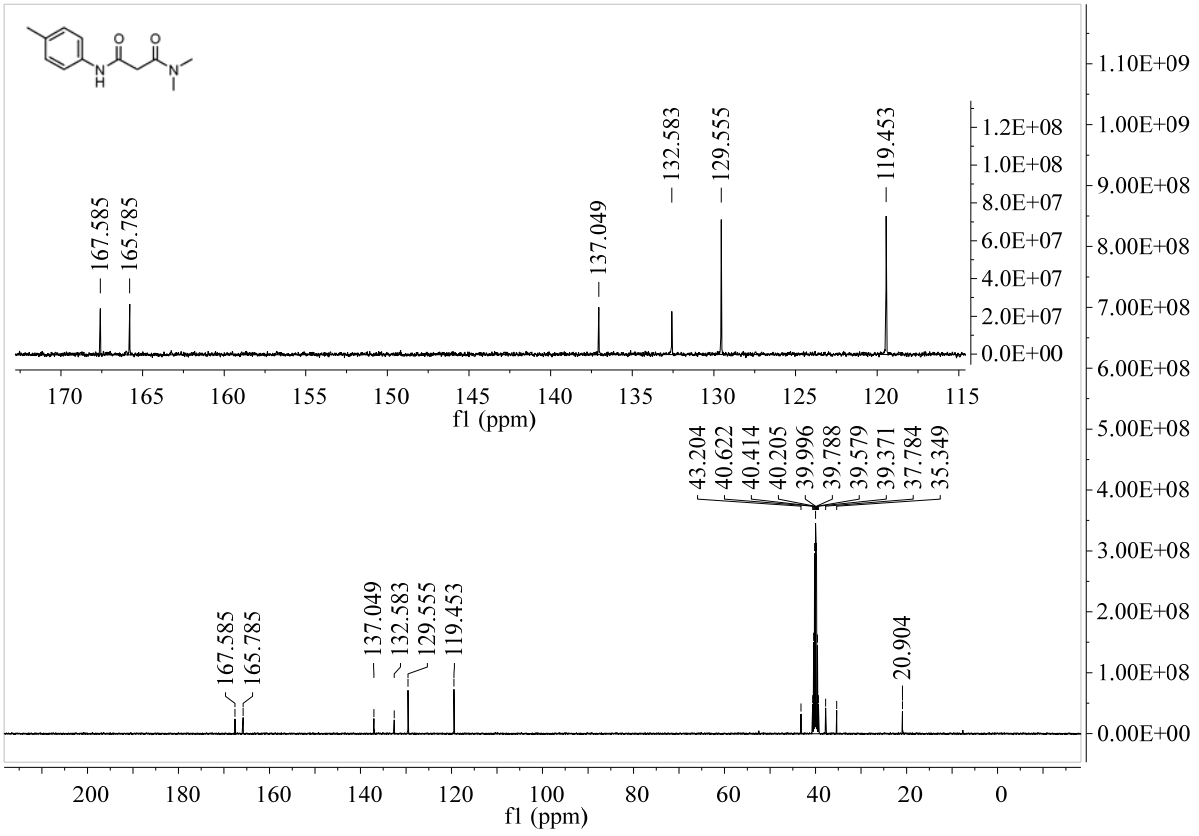
Compound **3l**


OMe
9.782
7.390
7.369
7.297
7.275
7.090
7.069
6.991
6.969
1.01
2.01
2.00
2.22
2.05
f1 (ppm)
3.751
3.326
3.150
3.135
2.509
2.505
2.500
2.496
2.235
3.00
3.09
1.90
3.03

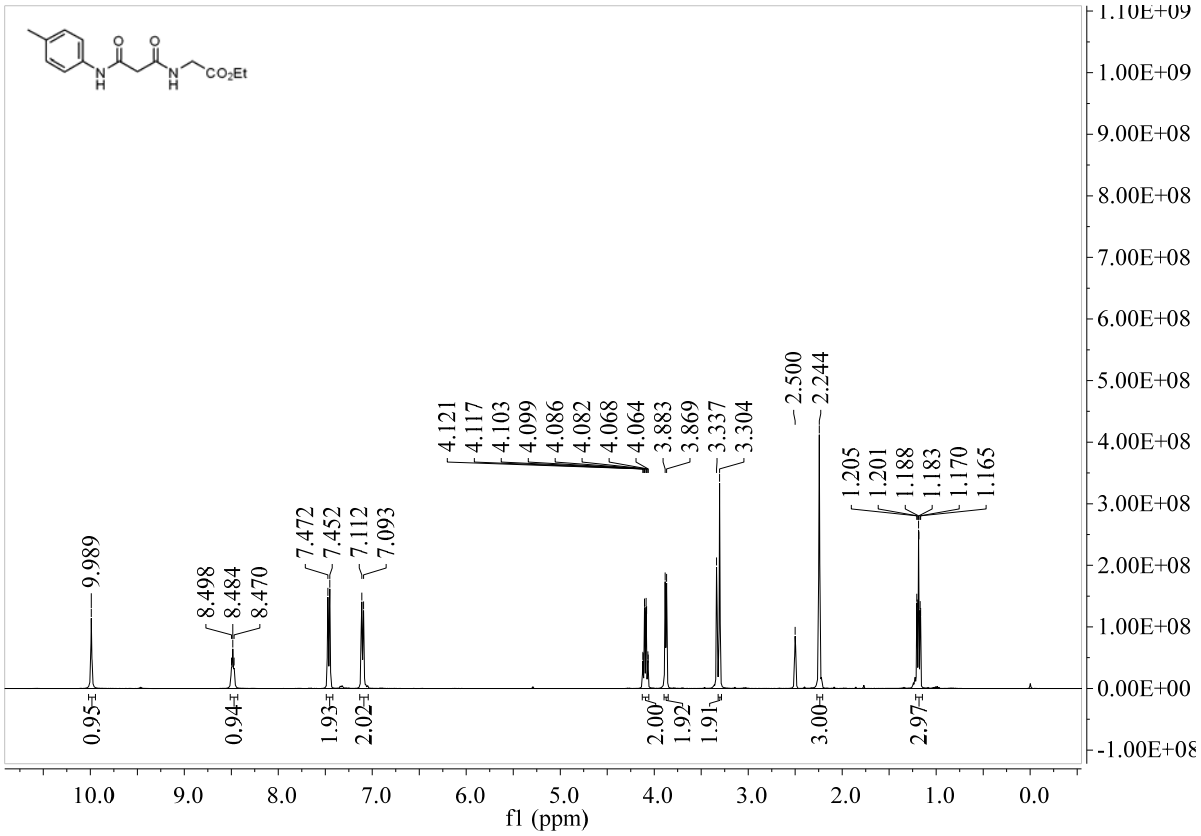

OMe
43.516
40.416
40.277
40.139
40.000
39.861
39.722
39.583
37.498
167.296
165.554
158.908
136.896
136.713
132.606
129.517
129.029
119.499
115.241
55.817
20.903
f1 (ppm)

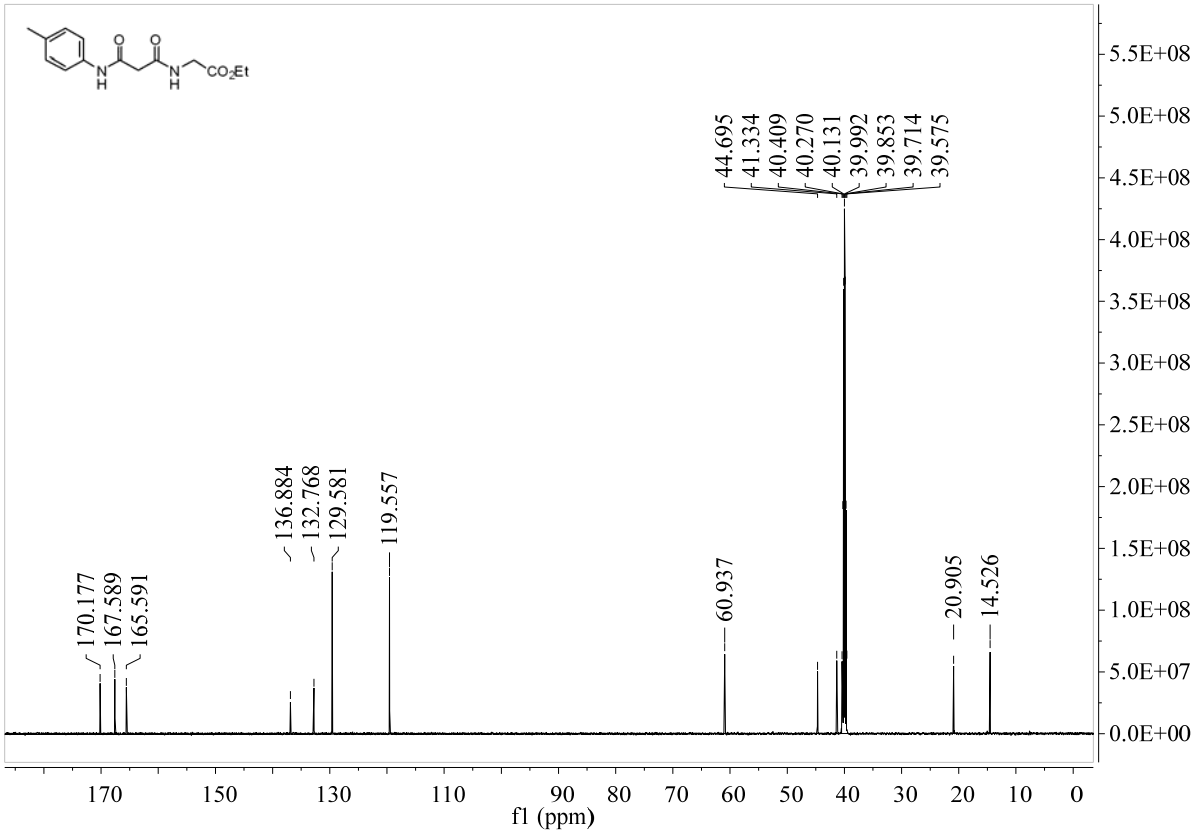
Compound **3m**


10.018
7.468
7.447
7.107
7.086
3.459
3.332
3.007
2.843
2.504
2.500
2.495
2.243
0.94
1.99
2.00
1.97
2.92
2.91
3.00
f1 (ppm)

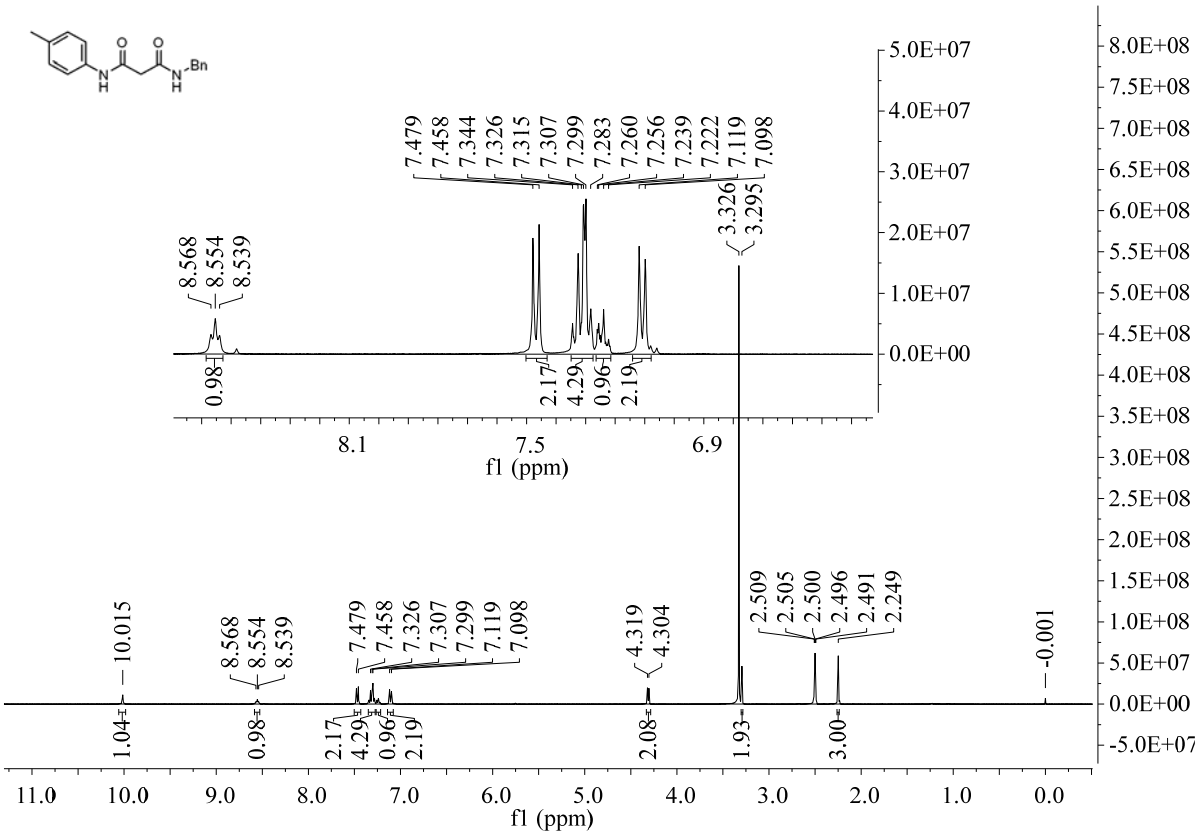

167.585
165.785
137.049
132.583
129.555
119.453
43.204
40.622
40.414
40.205
39.996
39.788
39.579
39.371
37.784
35.349
20.904
f1 (ppm)

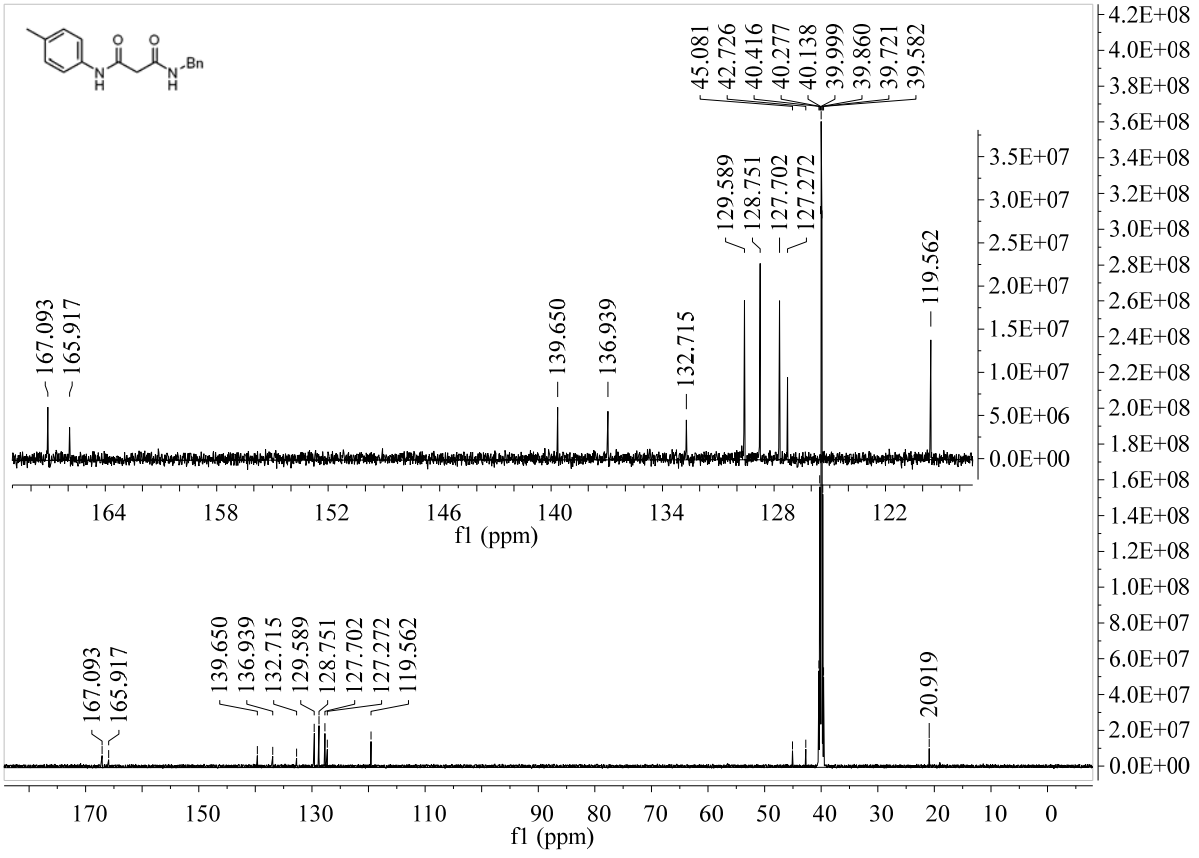
Compound **3n**


9.989
8.498
8.484
8.470
7.472
7.452
7.112
7.093
4.121
4.117
4.103
4.099
4.086
4.082
4.068
4.064
3.883
3.869
3.337
3.304
2.500
2.244
1.205
1.201
1.188
1.183
1.170
1.165
0.95
0.94
1.93
2.02
2.00
1.92
1.91
3.00
2.97
f1 (ppm)

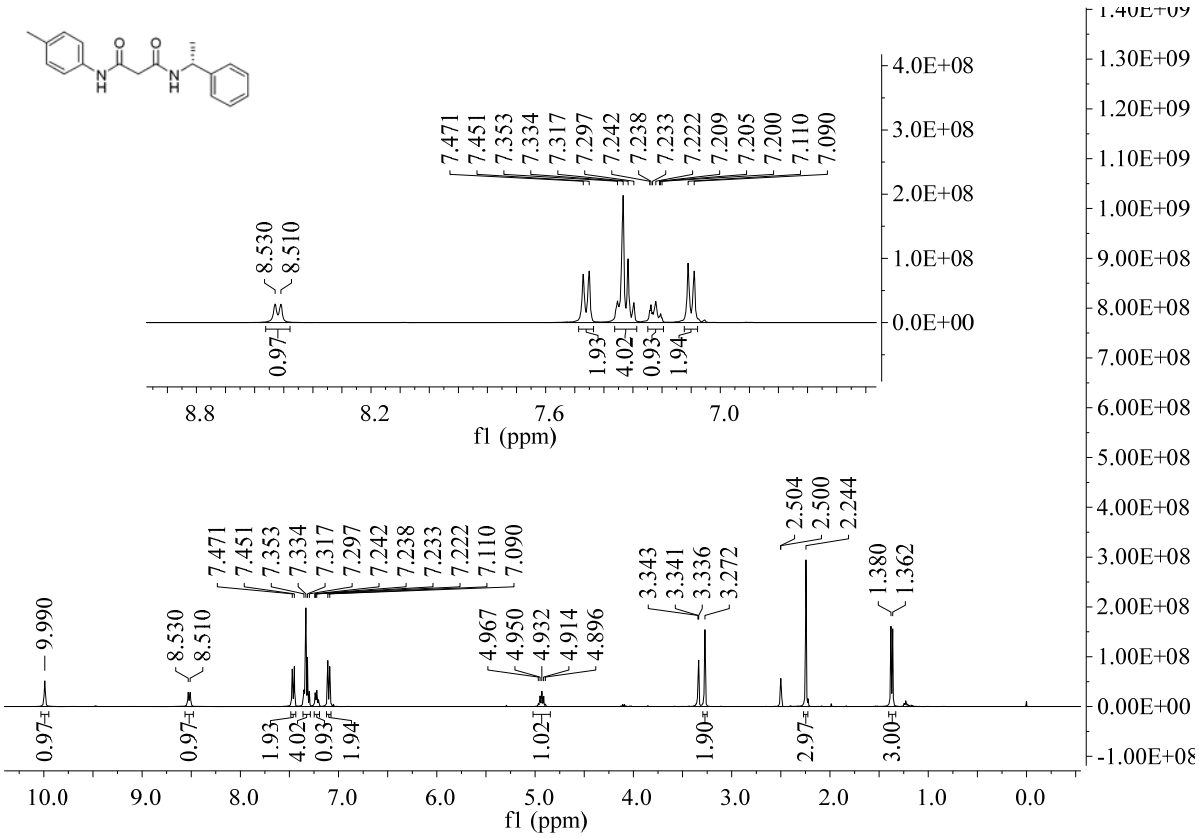

170.177
167.589
165.591
136.884
132.768
129.581
119.557
60.937
44.695
41.334
40.409
40.270
40.131
39.992
39.853
39.714
39.575
20.905
14.526
f1 (ppm)

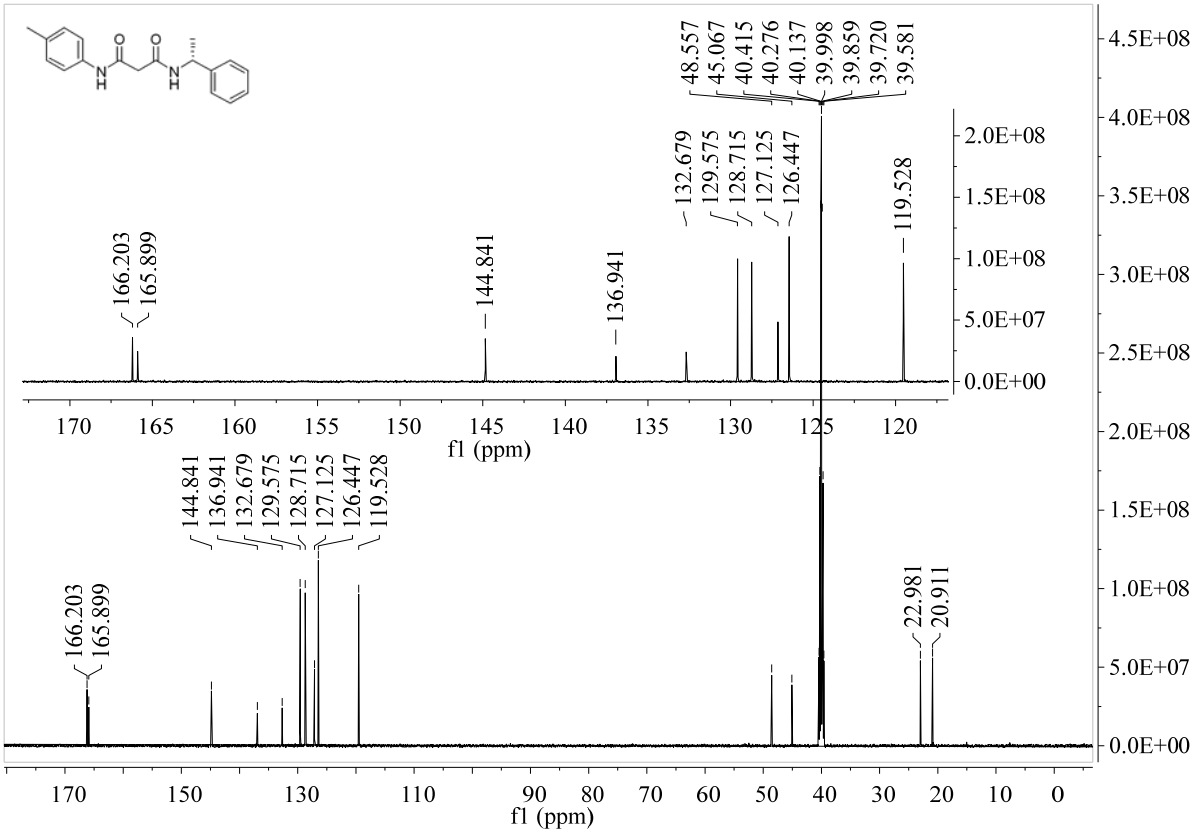
Compound **3o**


8.568
8.554
8.539
7.479
7.458
7.344
7.326
7.315
7.307
7.299
7.283
7.260
7.256
7.239
7.222
7.119
7.098
3.326
3.295
0.98
2.17
4.29
0.96
2.19
f1 (ppm)
10.015
4.319
4.304
2.509
2.505
2.500
2.496
2.491
2.249
-0.001
1.04
2.08
1.93
3.00

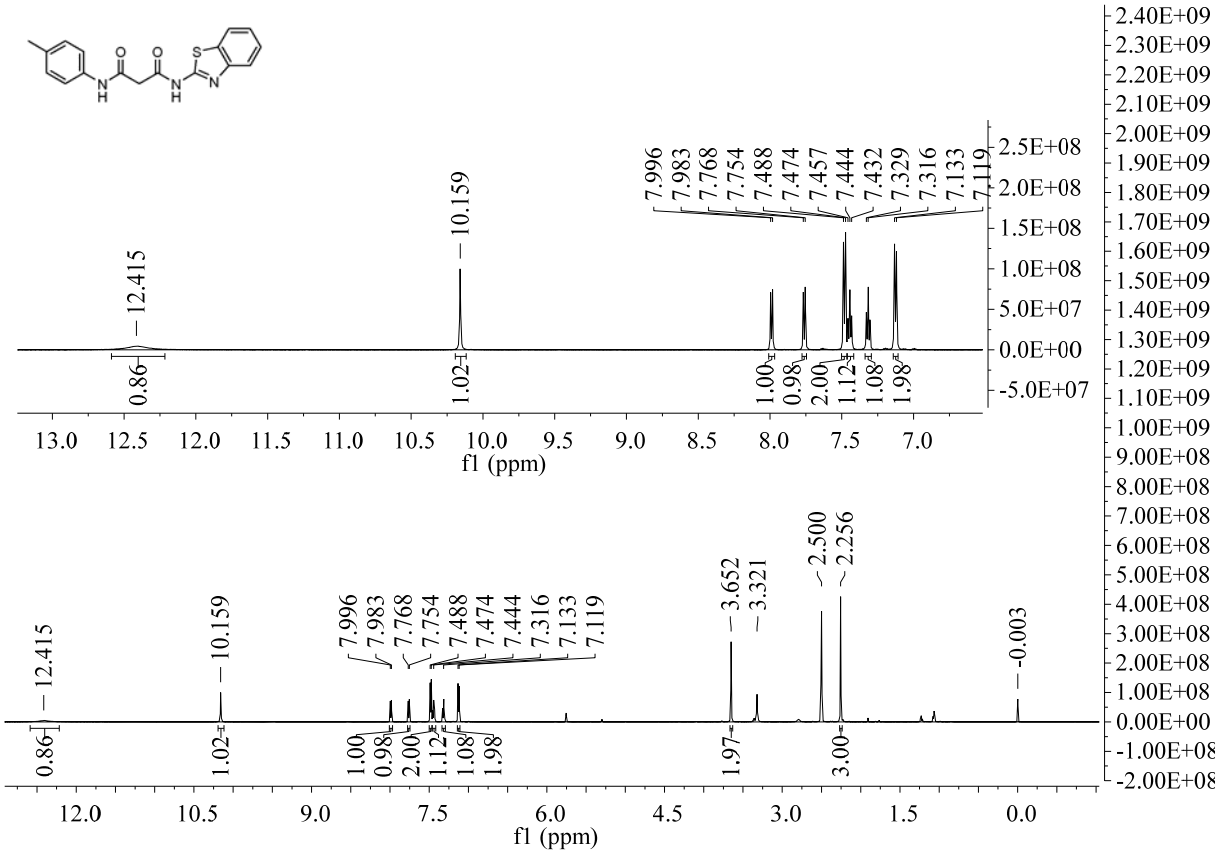

45.081
42.726
40.416
40.277
40.138
39.999
39.860
39.721
39.582
129.589
128.751
127.702
127.272
167.093
165.917
139.650
136.939
132.715
119.562
20.919
f1 (ppm)

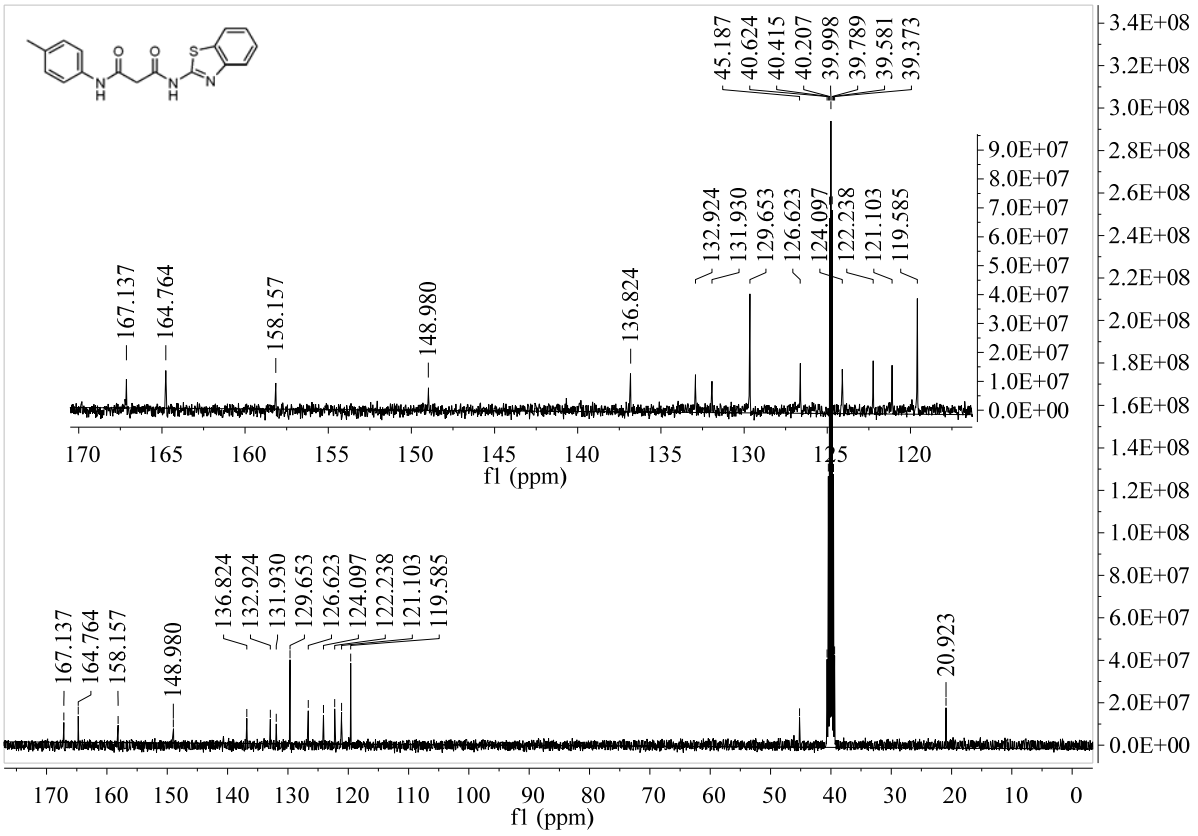
Compound **3p**


7.471
7.451
7.353
7.334
7.317
7.297
7.242
7.238
7.233
7.222
7.209
7.205
7.200
7.110
7.090
8.530
8.510
0.97
1.93
4.02
0.93
1.94
fl (ppm)
9.990
4.967
4.950
4.932
4.914
4.896
3.343
3.341
3.336
3.272
2.504
2.500
2.244
1.380
1.362
1.02
1.90
2.97
3.00

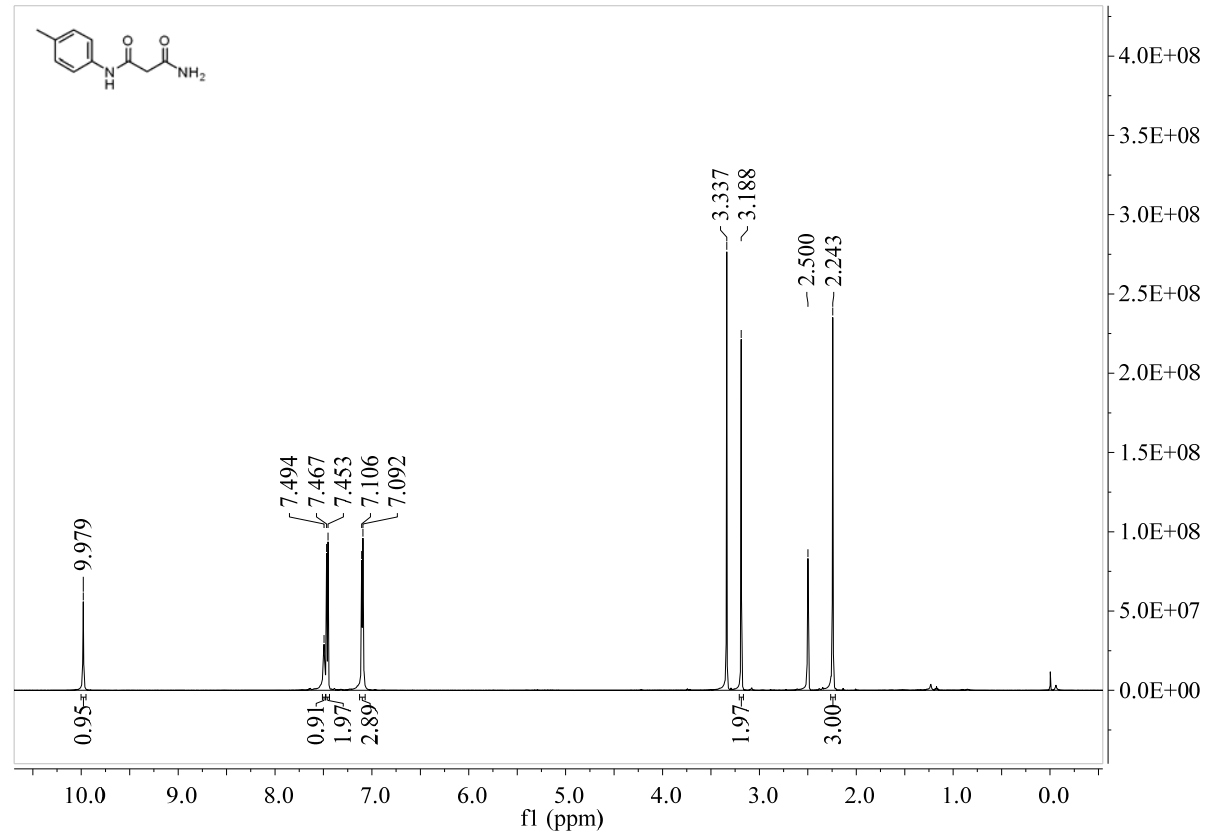

48.557
45.067
40.415
40.276
40.137
39.998
39.859
39.720
39.581
132.679
129.575
128.715
127.125
126.447
119.528
166.203
165.899
144.841
136.941
fl (ppm)
22.981
20.911

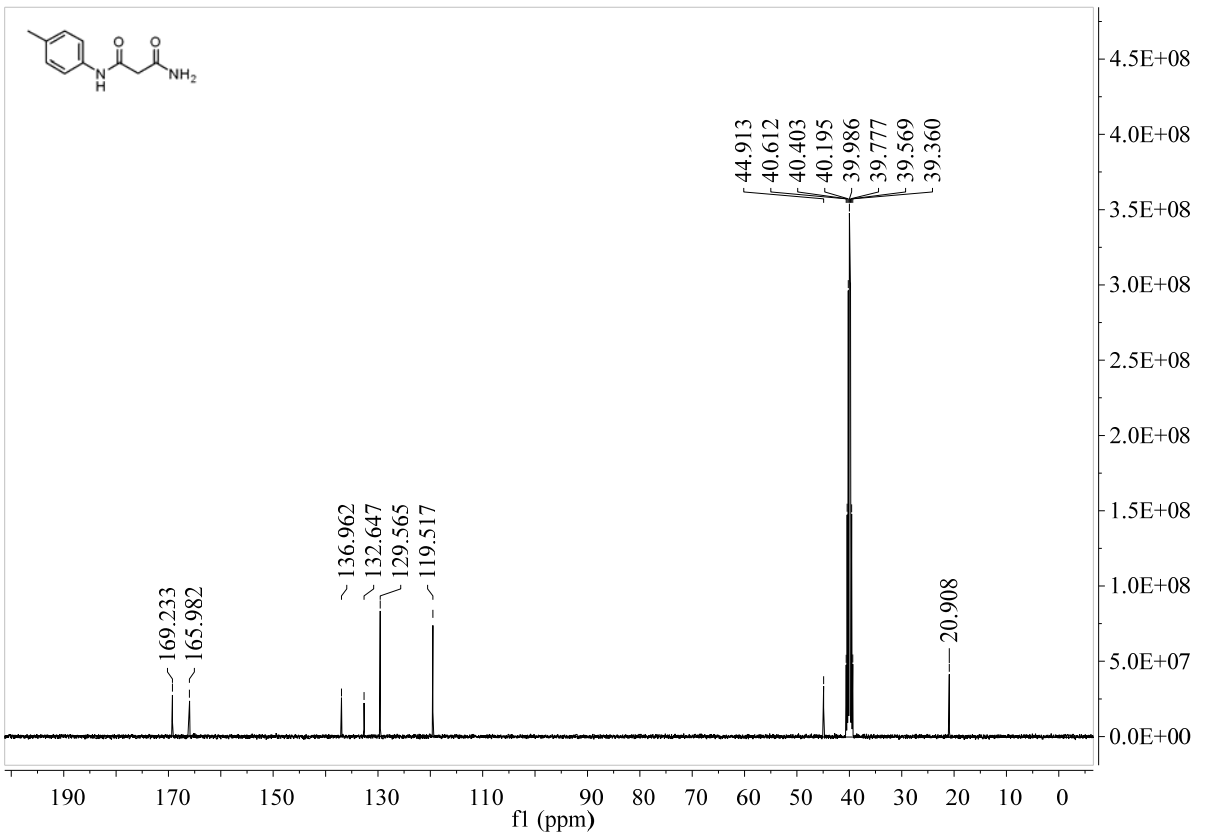
Compound **3q**


12.415
10.159
7.996
7.983
7.768
7.754
7.488
7.474
7.457
7.444
7.432
7.329
7.316
7.133
7.119
0.86
1.02
1.00
0.98
2.00
1.12
1.08
1.98
f1 (ppm)
3.652
3.321
2.500
2.256
-0.003
1.97
3.00

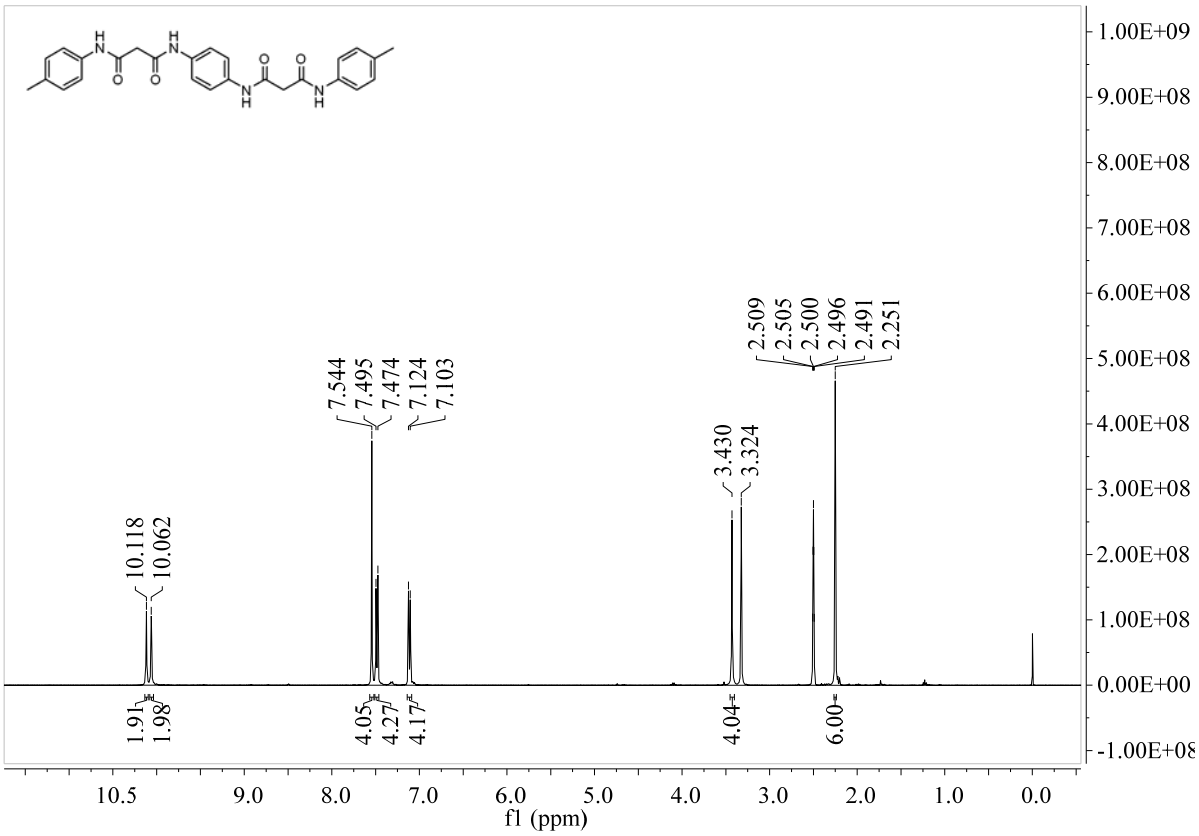

45.187
40.624
40.415
40.207
39.998
39.789
39.581
39.373
167.137
164.764
158.157
148.980
136.824
132.924
131.930
129.653
126.623
124.097
122.238
121.103
119.585
20.923
f1 (ppm)

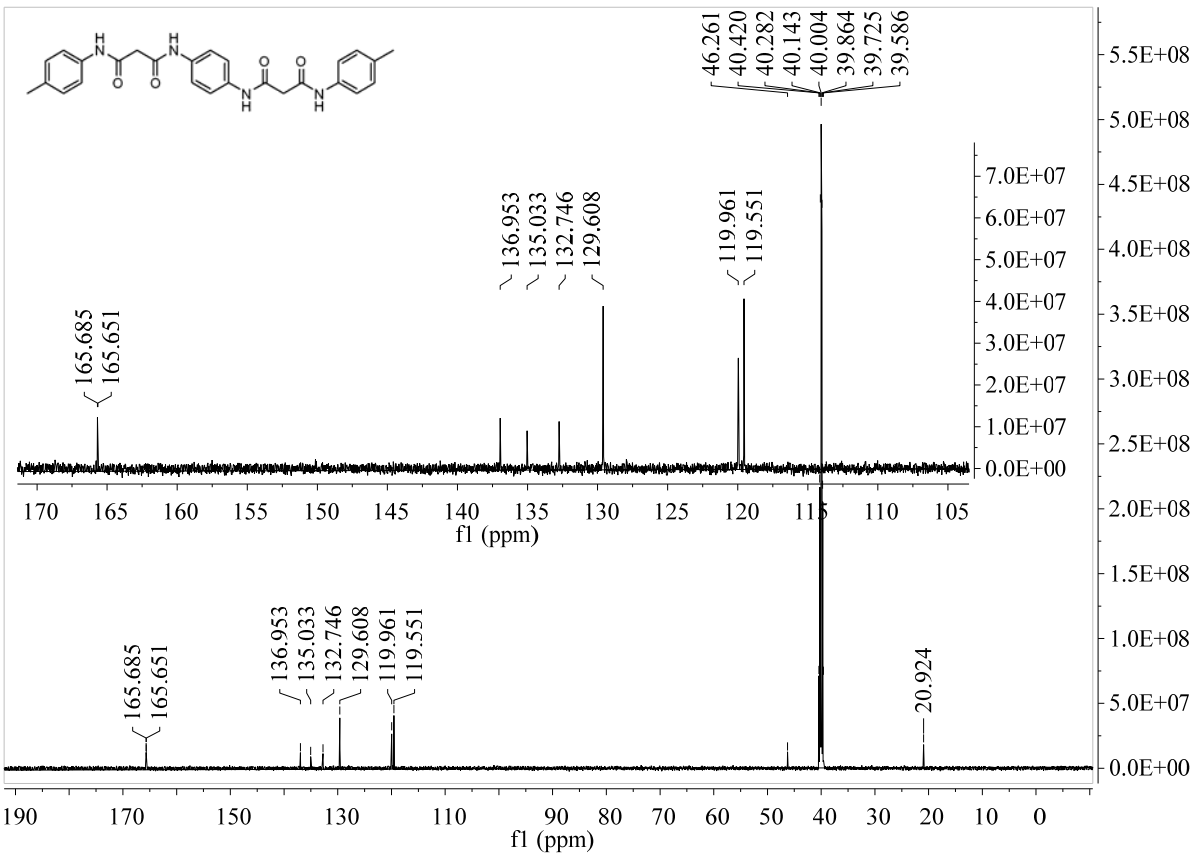
Compound **3r**


9.979
7.494
7.467
7.453
7.106
7.092
3.337
3.188
2.500
2.243
0.95
0.91
1.97
2.89
1.97
3.00
f1 (ppm)

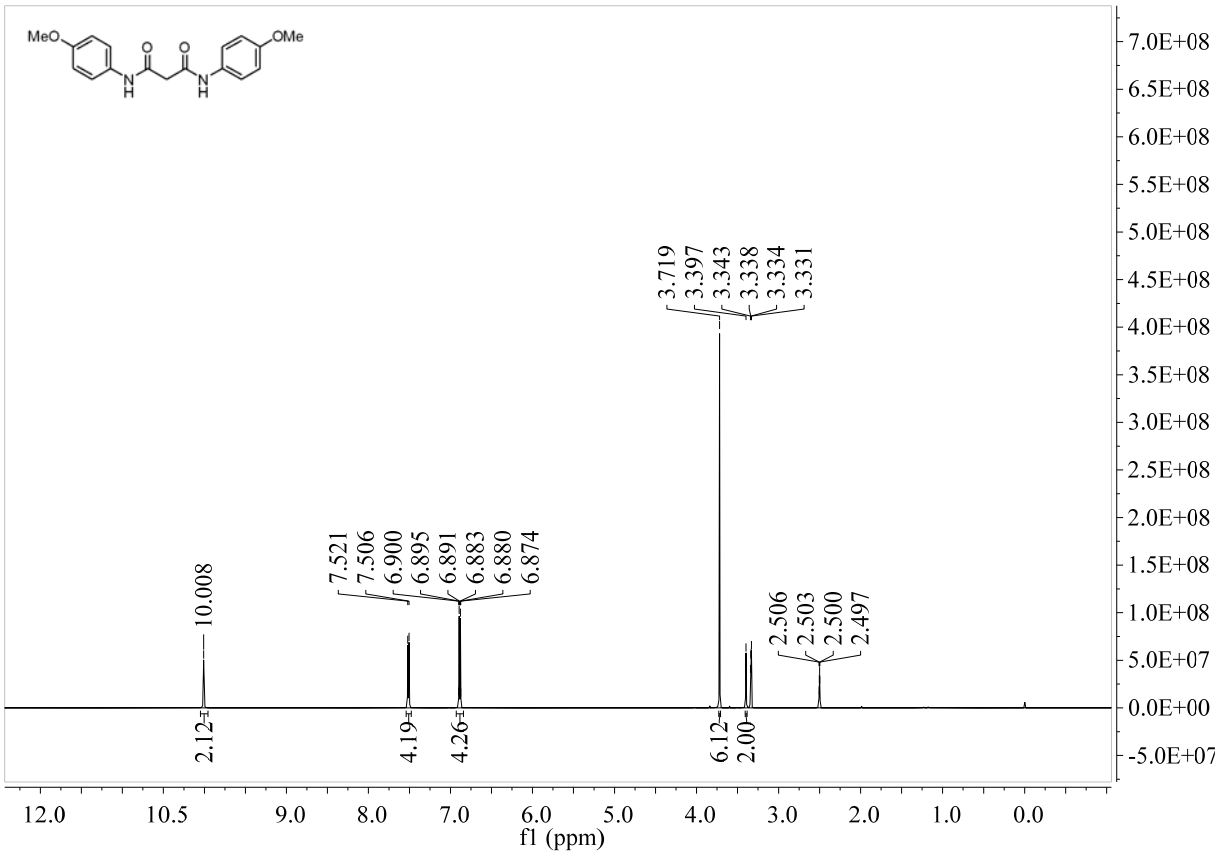

169.233
165.982
136.962
132.647
129.565
119.517
44.913
40.612
40.403
40.195
39.986
39.777
39.569
39.360
20.908
f1 (ppm)

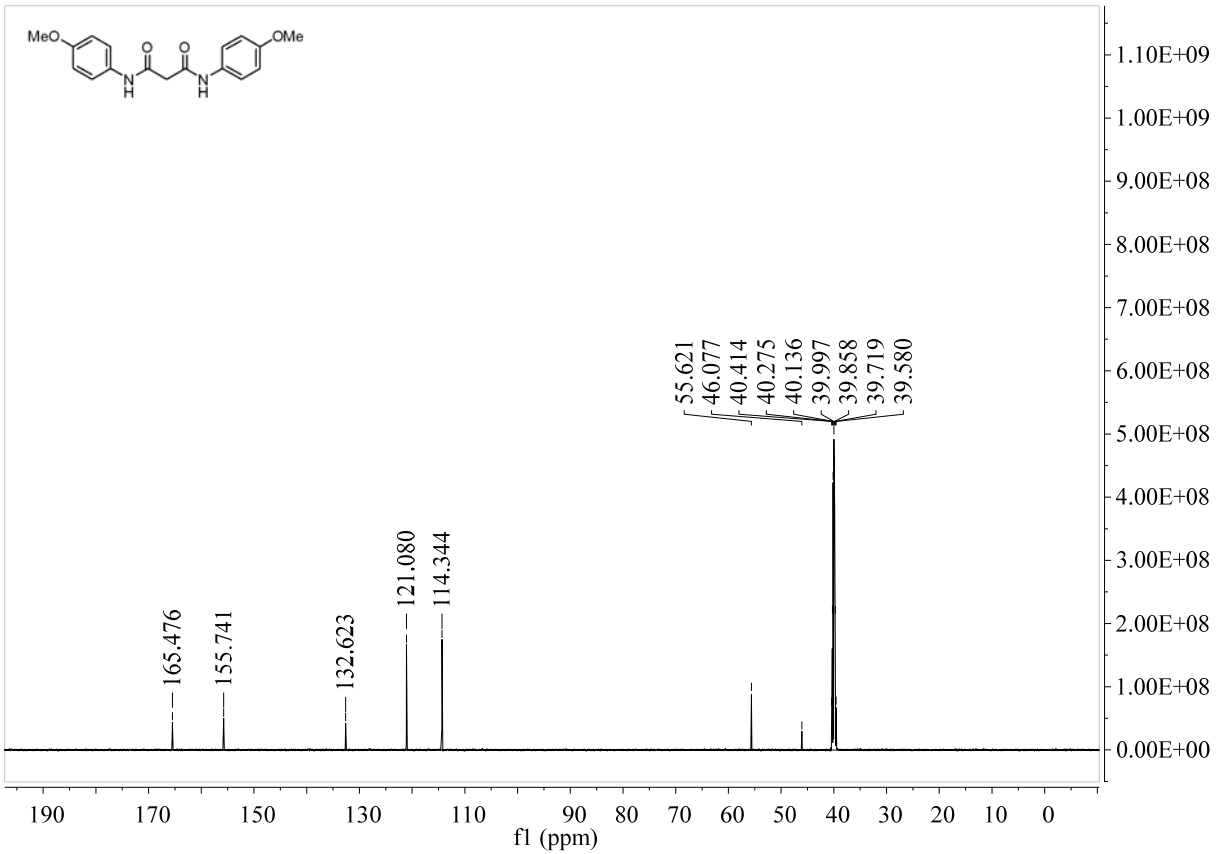
Compound **3s**


10.118
10.062
7.544
7.495
7.474
7.124
7.103
3.430
3.324
2.509
2.505
2.500
2.496
2.491
2.251
1.91
1.98
4.05
4.27
4.17
4.04
6.00
f1 (ppm)

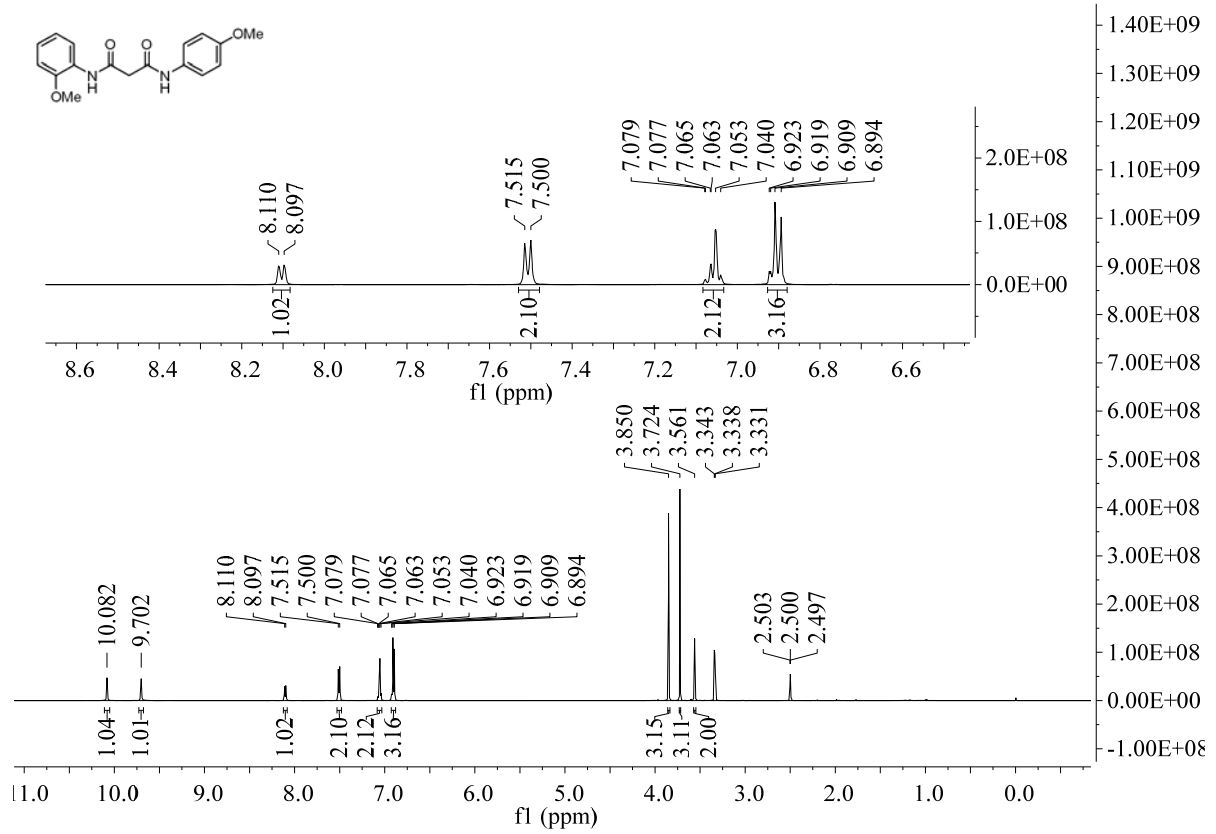

165.685
165.651
136.953
135.033
132.746
129.608
119.961
119.551
46.261
40.420
40.282
40.143
40.004
39.864
39.725
39.586
20.924
f1 (ppm)

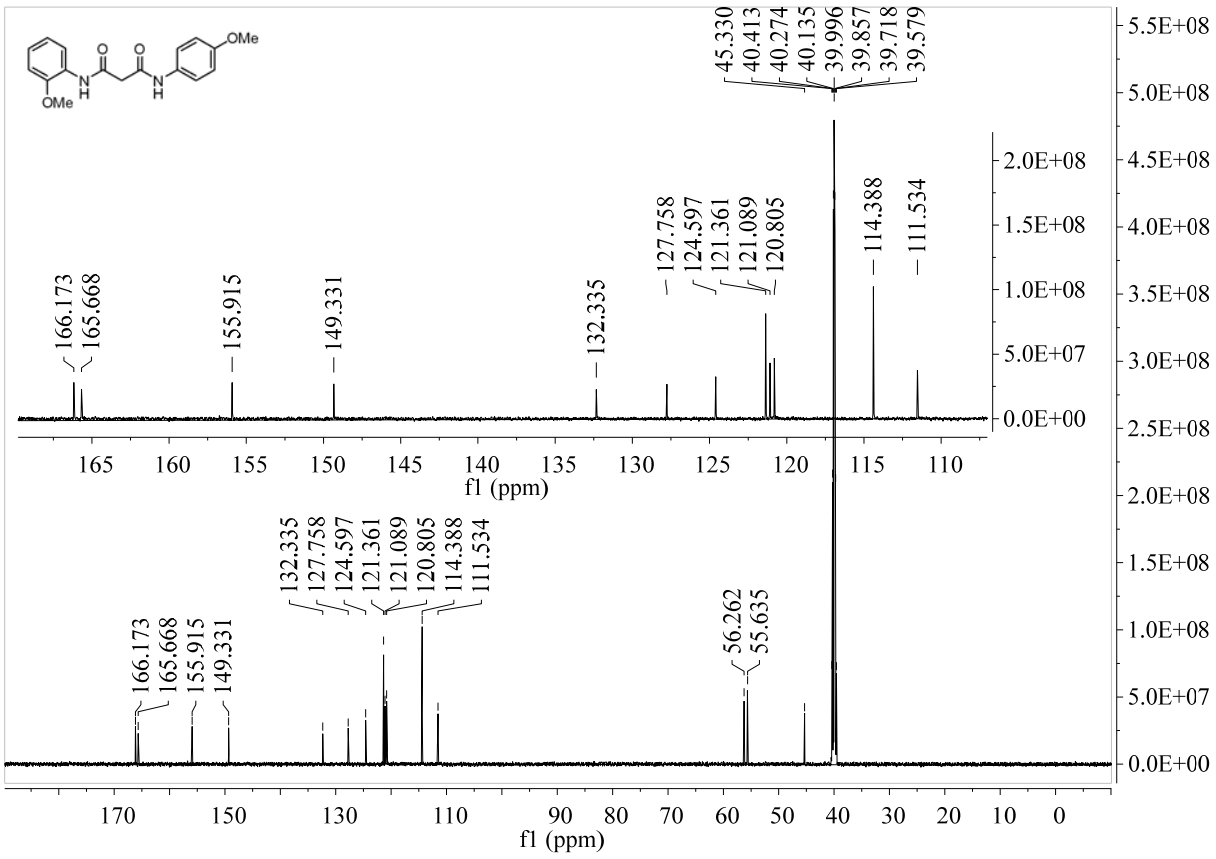
Compound **3t**


MeO
OMe
10.008
7.521
7.506
6.900
6.895
6.891
6.883
6.880
6.874
3.719
3.397
3.343
3.338
3.334
3.331
2.506
2.503
2.500
2.497
2.12
4.19
4.26
6.12
2.00
f1 (ppm)

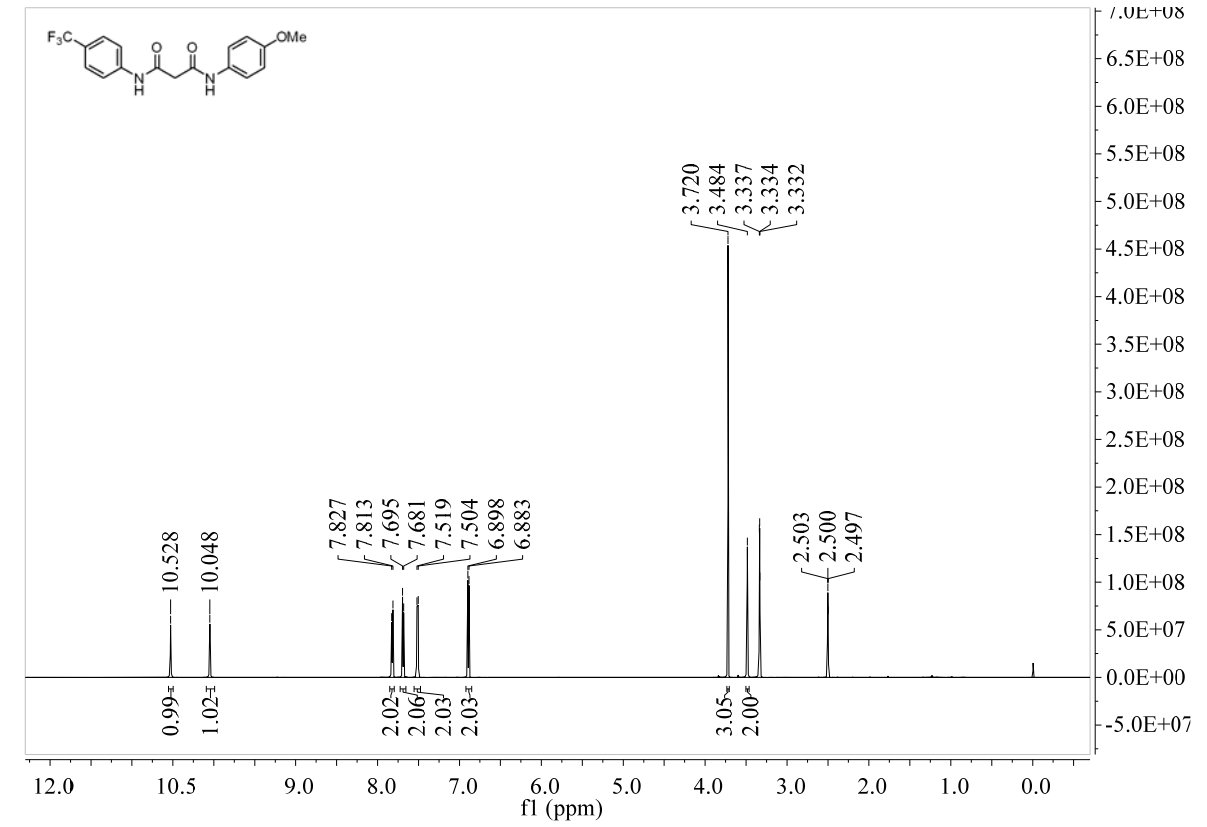

MeO
OMe
165.476
155.741
132.623
121.080
114.344
55.621
46.077
40.414
40.275
40.136
39.997
39.858
39.719
39.580
f1 (ppm)

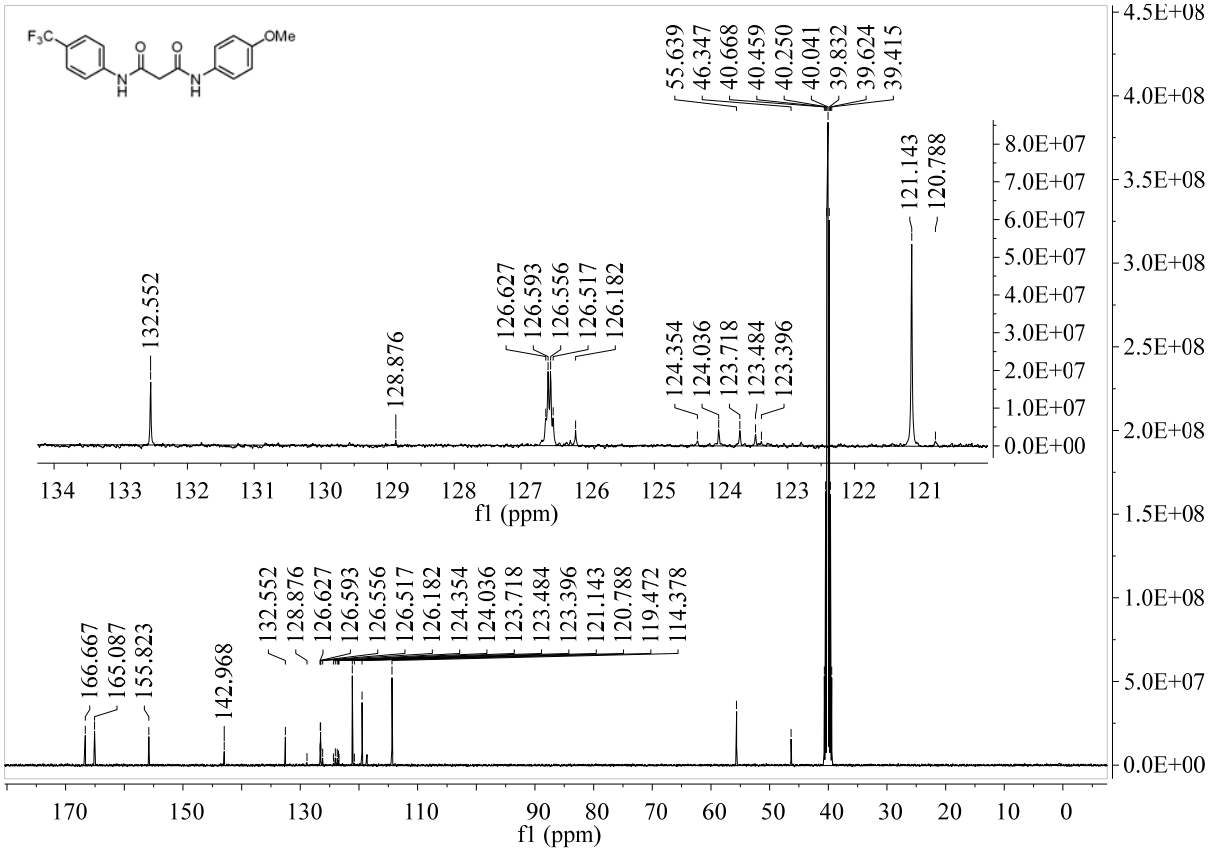
Compound **3u**


OMe
OMe
8.110
8.097
7.515
7.500
7.079
7.077
7.065
7.063
7.053
7.040
6.923
6.919
6.909
6.894
1.02
2.10
2.12
3.16
f1 (ppm)
3.850
3.724
3.561
3.343
3.338
3.331
10.082
9.702
2.503
2.500
2.497
1.04
1.01
1.02
2.10
2.12
3.16
3.15
3.11
2.00
f1 (ppm)

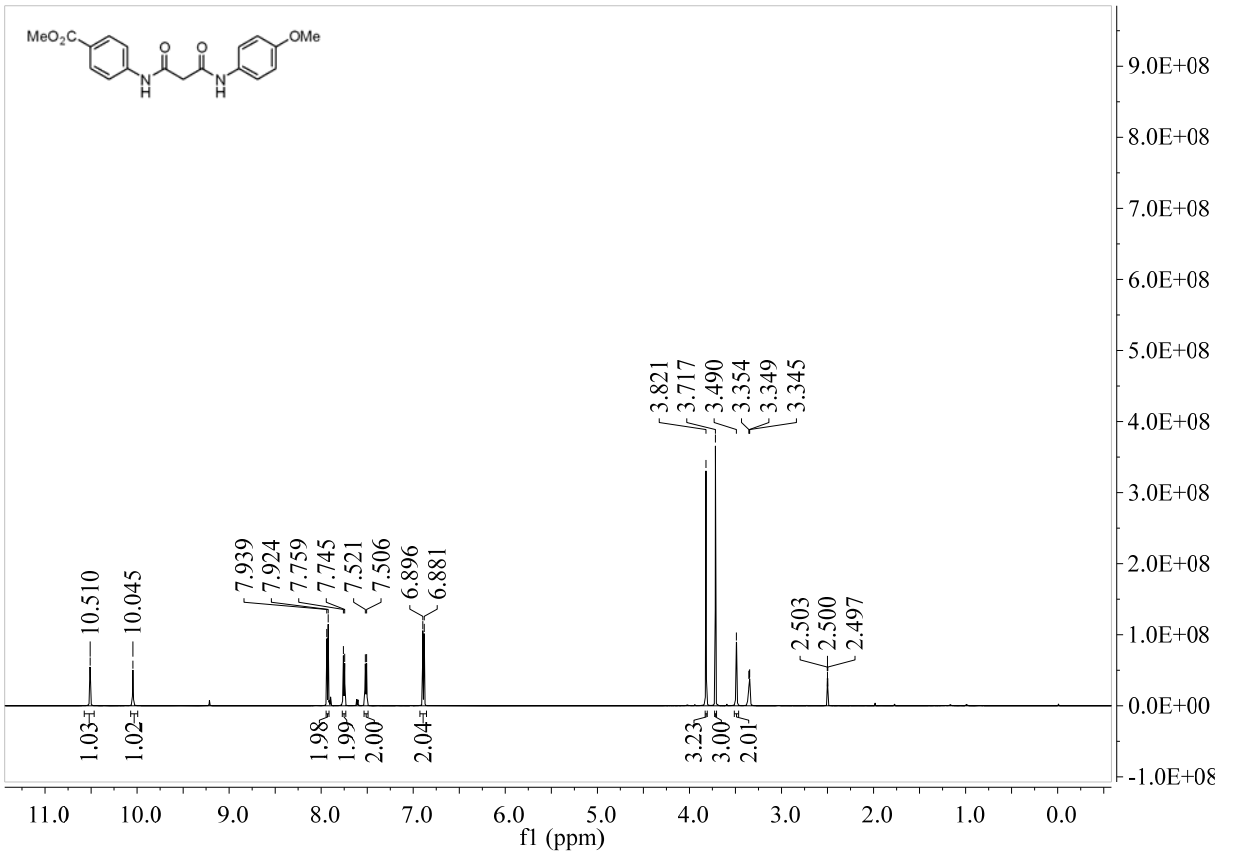

OMe
OMe
45.330
40.413
40.274
40.135
39.996
39.857
39.718
39.579
166.173
165.668
155.915
149.331
132.335
127.758
124.597
121.361
121.089
120.805
114.388
111.534
f1 (ppm)
56.262
55.635
f1 (ppm)

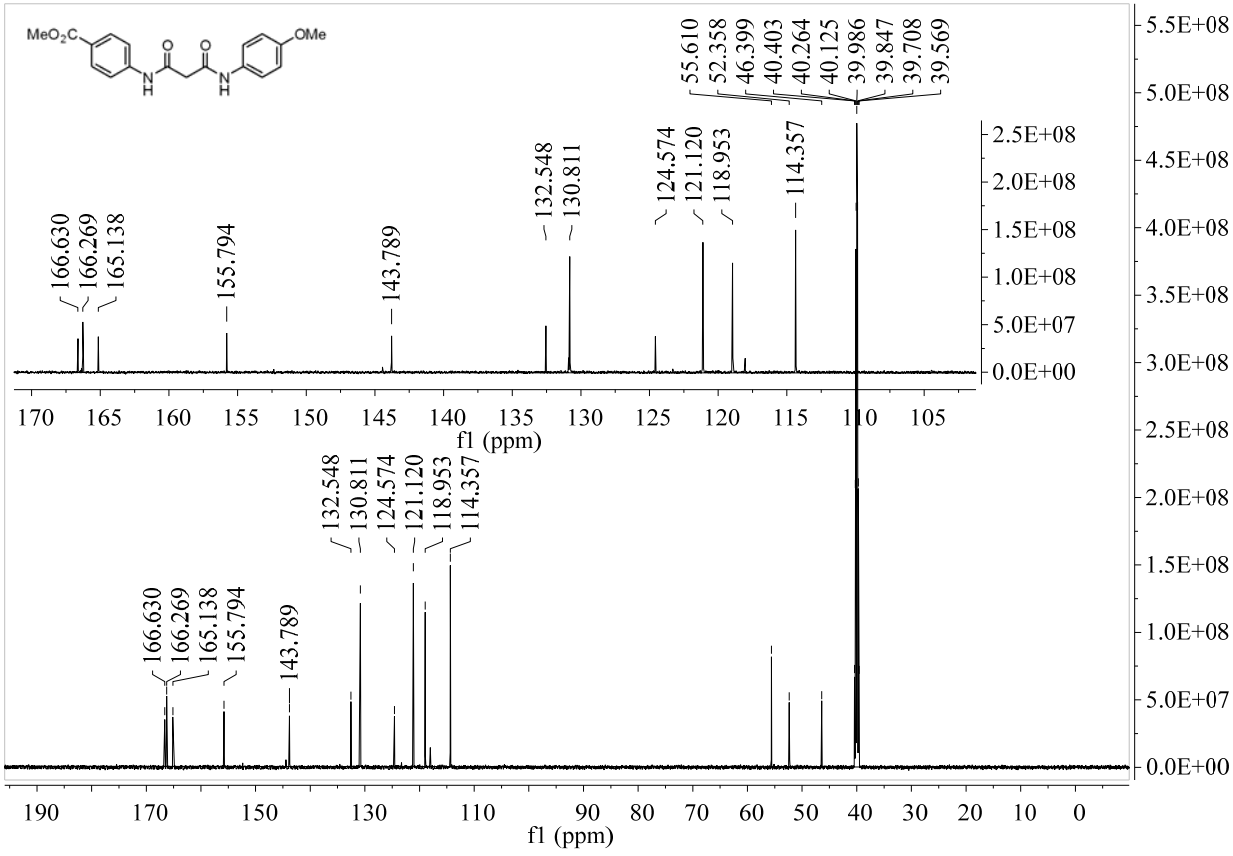
Compound **3v**


F3C
OMe
10.528
10.048
7.827
7.813
7.695
7.681
7.519
7.504
6.898
6.883
3.720
3.484
3.337
3.334
3.332
2.503
2.500
2.497
0.99
1.02
2.02
2.06
2.03
2.03
3.05
2.00
f1 (ppm)

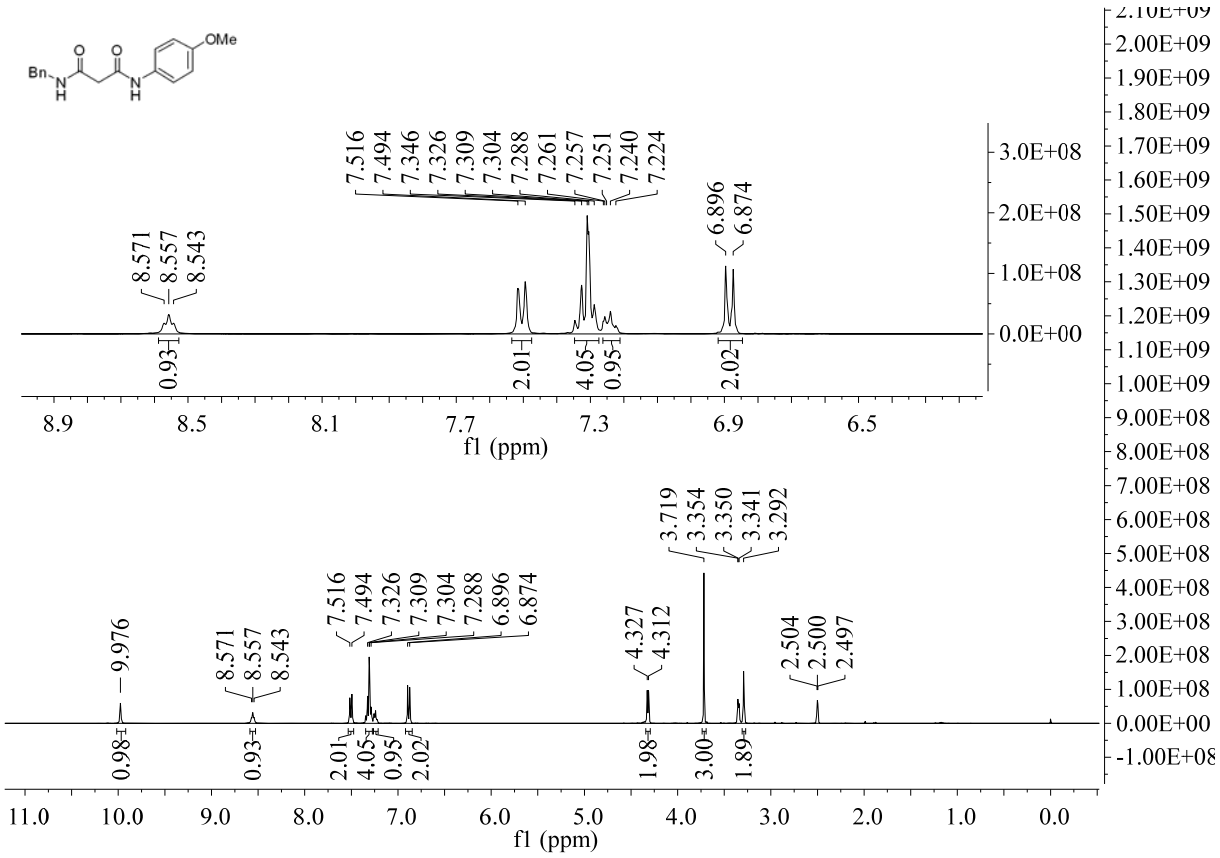

F3C
OMe
55.639
46.347
40.668
40.459
40.250
40.041
39.832
39.624
39.415
132.552
128.876
126.627
126.593
126.556
126.517
126.182
124.354
124.036
123.718
123.484
123.396
121.143
120.788
f1 (ppm)
166.667
165.087
155.823
142.968
132.552
128.876
126.627
126.593
126.556
126.517
126.182
124.354
124.036
123.718
123.484
123.396
121.143
120.788
119.472
114.378
f1 (ppm)

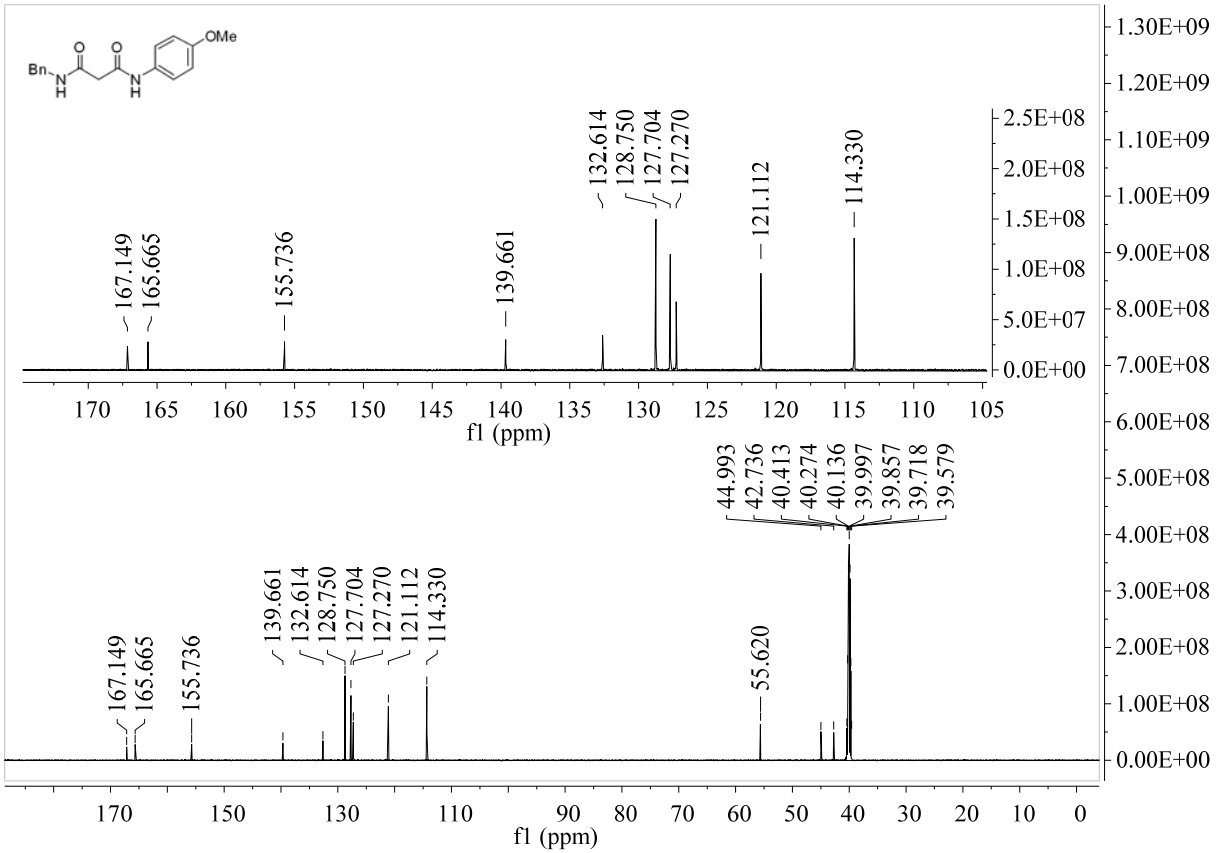
Compound **3w**


MeO2C
OMe
10.510
10.045
7.939
7.924
7.759
7.745
7.521
7.506
6.896
6.881
3.821
3.717
3.490
3.354
3.349
3.345
2.503
2.500
2.497
1.03
1.02
1.98
1.99
2.00
2.04
3.23
3.00
2.01
f1 (ppm)

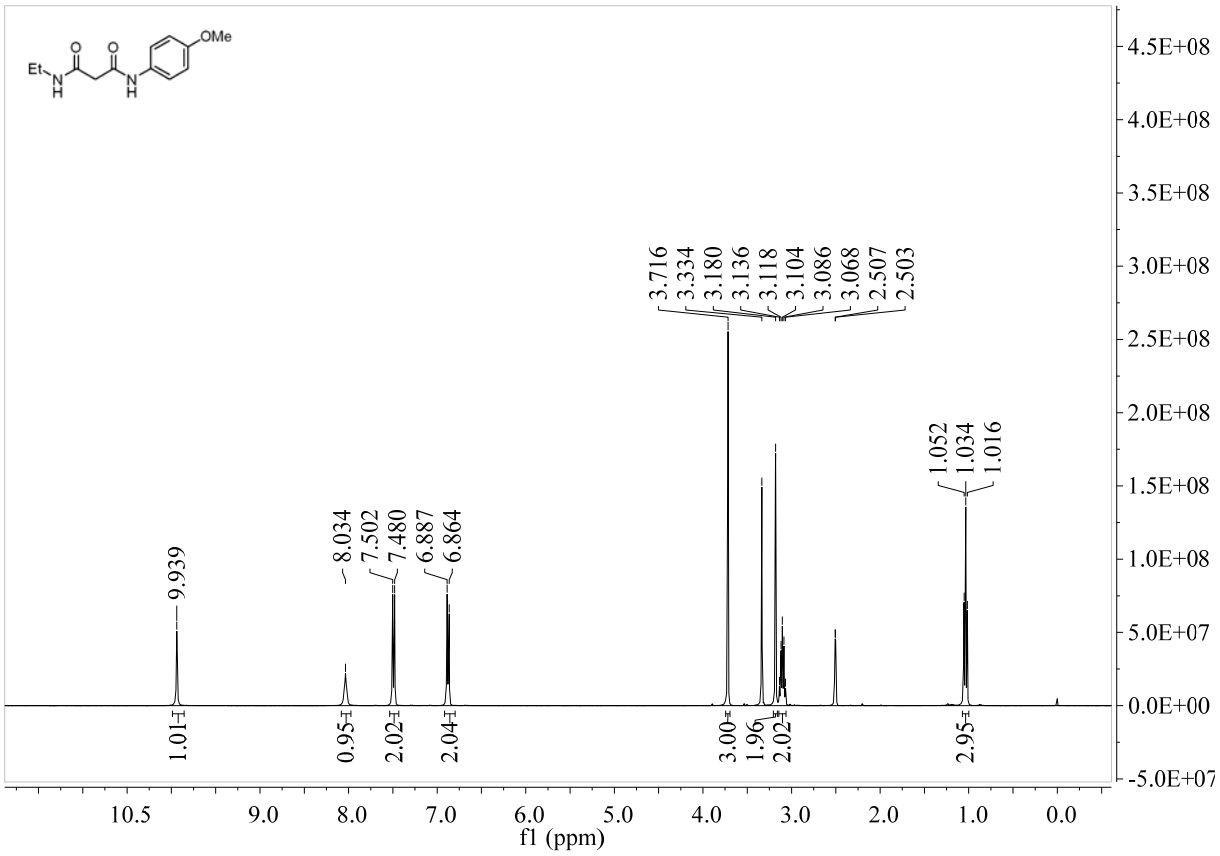

MeO2C
OMe
166.630
166.269
165.138
155.794
143.789
132.548
130.811
124.574
121.120
118.953
114.357
55.610
52.358
46.399
40.403
40.264
40.125
39.986
39.847
39.708
39.569
f1 (ppm)

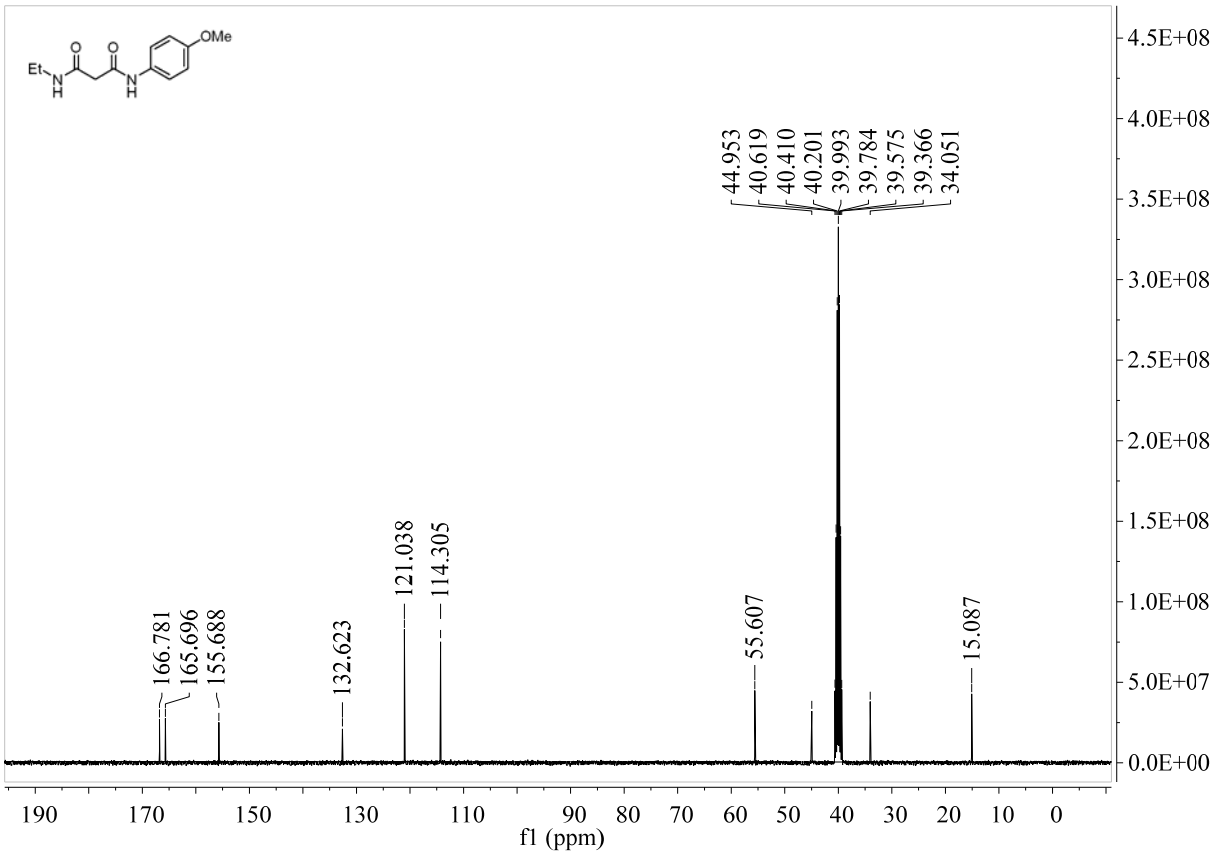
Compound **3x**


OMe
Bn
8.571
8.557
8.543
7.516
7.494
7.346
7.326
7.309
7.304
7.288
7.261
7.257
7.251
7.240
7.224
6.896
6.874
0.93
2.01
4.05
0.95
2.02
f1 (ppm)
9.976
3.719
3.354
3.350
3.341
3.292
4.327
4.312
2.504
2.500
2.497
0.98
1.98
3.00
1.89

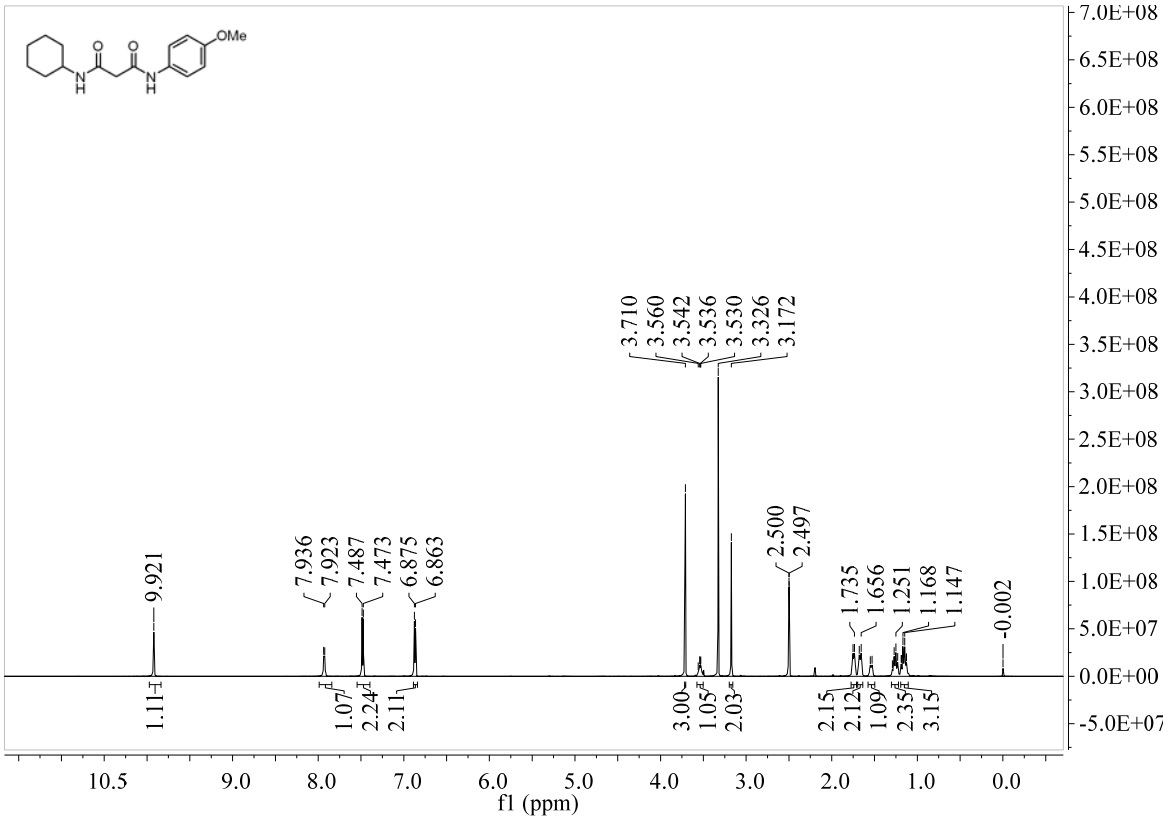

OMe
Bn
167.149
165.665
155.736
139.661
132.614
128.750
127.704
127.270
121.112
114.330
f1 (ppm)
44.993
42.736
40.413
40.274
40.136
39.997
39.857
39.718
39.579
55.620

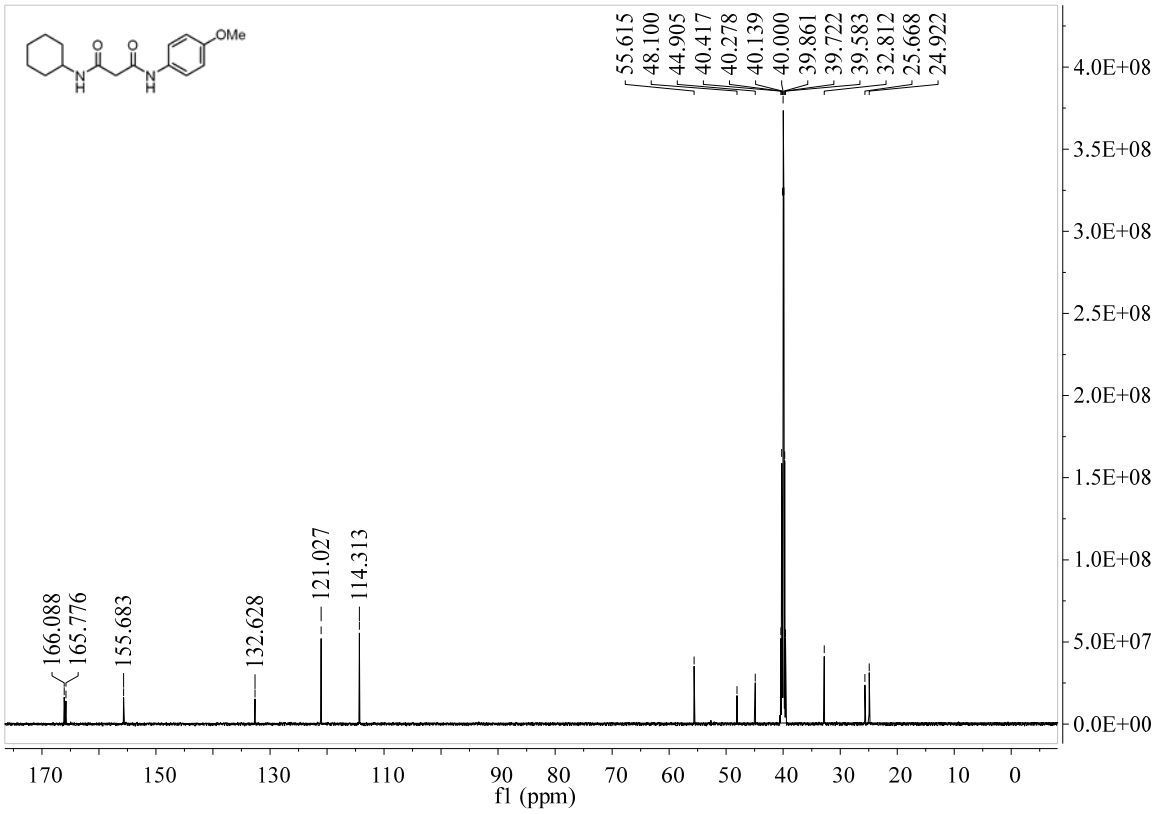
Compound **3y**


OMe
Et
9.939
8.034
7.502
7.480
6.887
6.864
3.716
3.334
3.180
3.136
3.118
3.104
3.086
3.068
2.507
2.503
1.052
1.034
1.016
1.01
0.95
2.02
2.04
3.00
1.96
2.02
2.95
f1 (ppm)

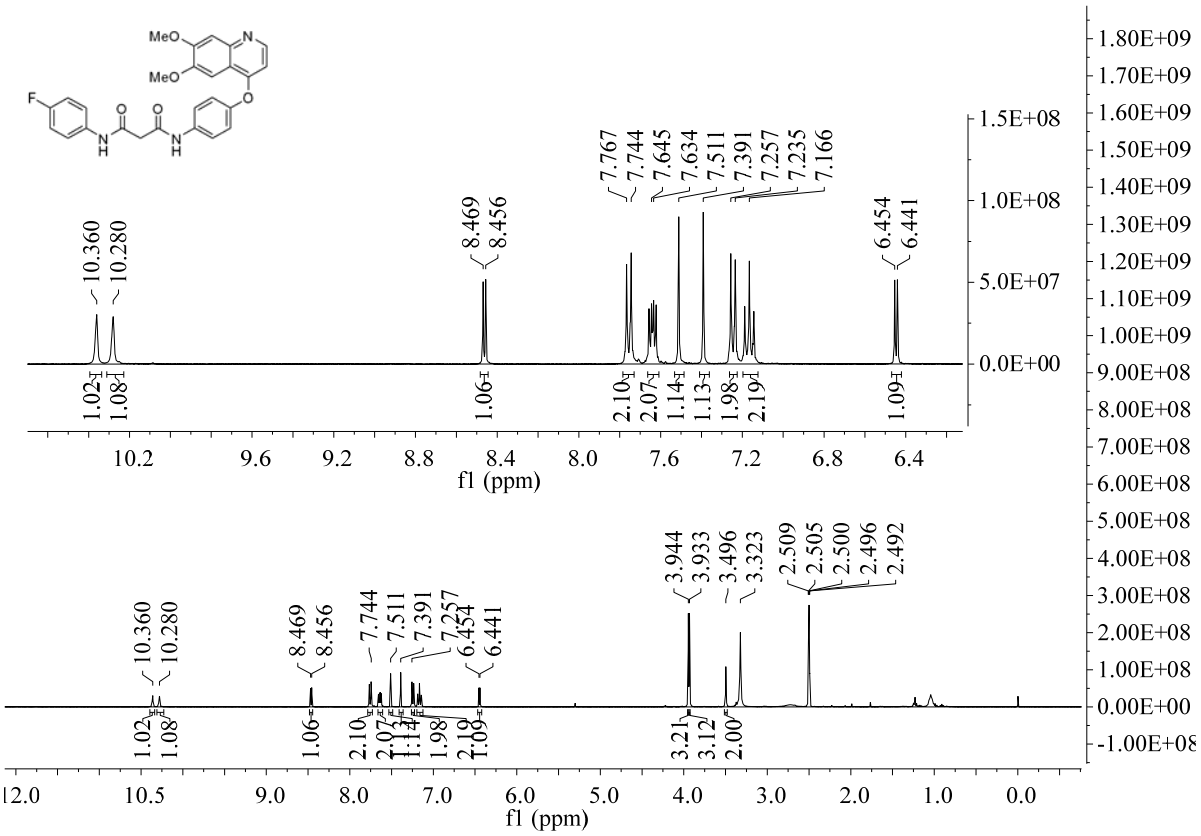

OMe
Et
166.781
165.696
155.688
132.623
121.038
114.305
55.607
44.953
40.619
40.410
40.201
39.993
39.784
39.575
39.366
34.051
15.087
f1 (ppm)

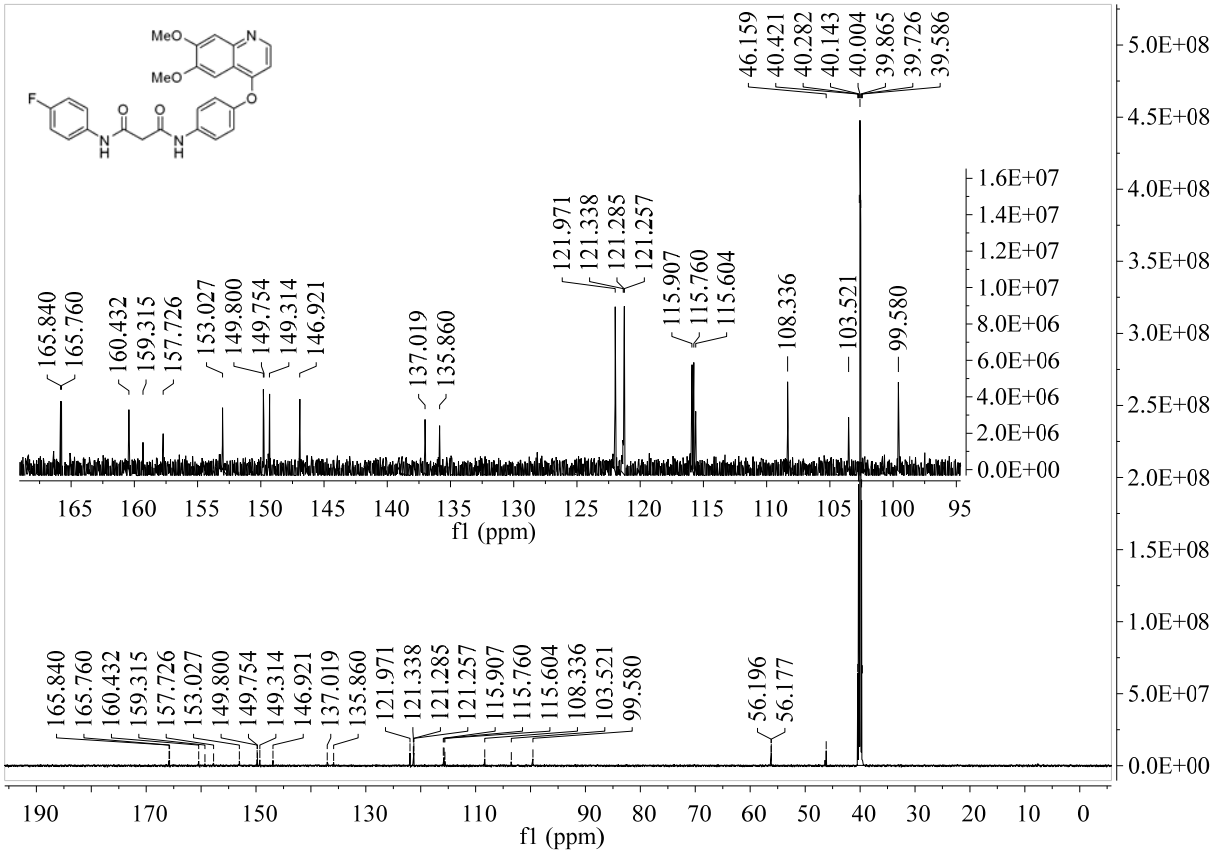
Compound **3z**


OMe
9.921
7.936
7.923
7.487
7.473
6.875
6.863
3.710
3.560
3.542
3.536
3.530
3.326
3.172
2.500
2.497
1.735
1.656
1.251
1.168
1.147
-0.002
1.11
1.07
2.24
2.11
3.00
1.05
2.03
2.15
2.12
1.09
2.35
3.15
f1 (ppm)

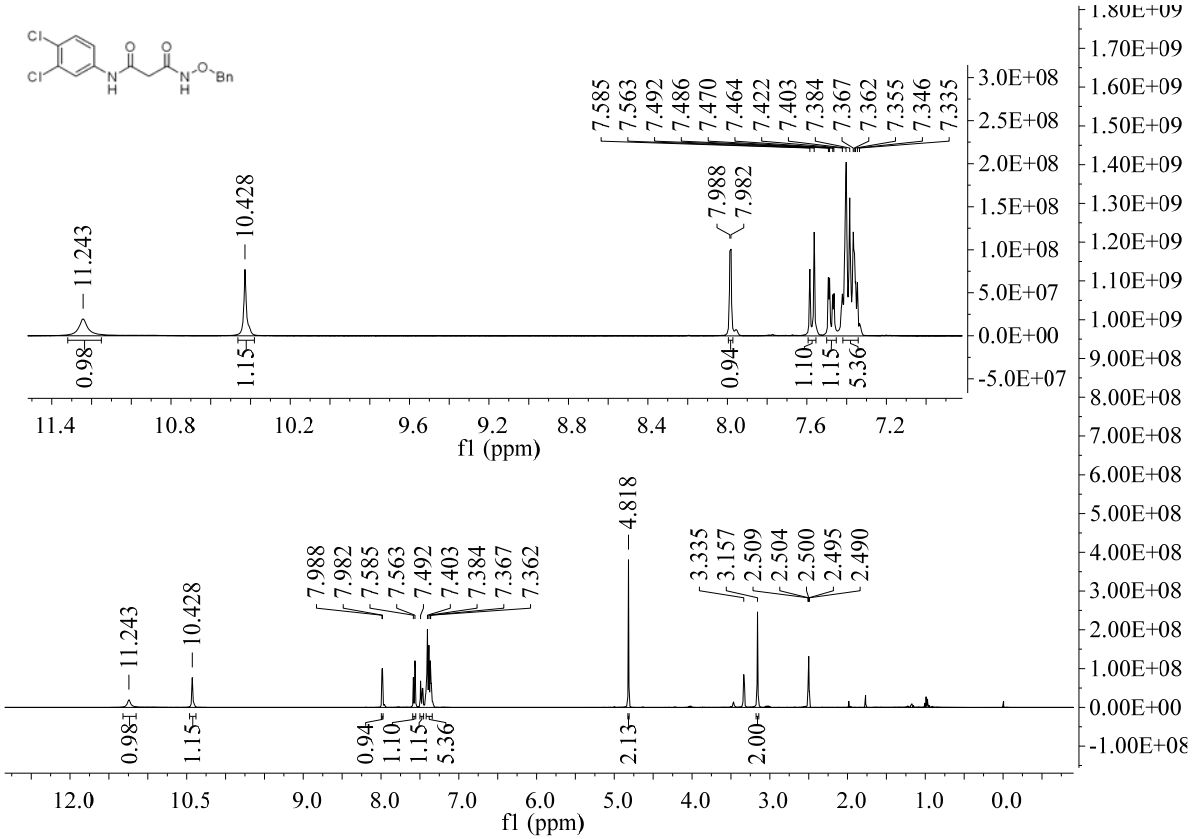

OMe
166.088
165.776
155.683
132.628
121.027
114.313
55.615
48.100
44.905
40.417
40.278
40.139
40.000
39.861
39.722
39.583
32.812
25.668
24.922
f1 (ppm)

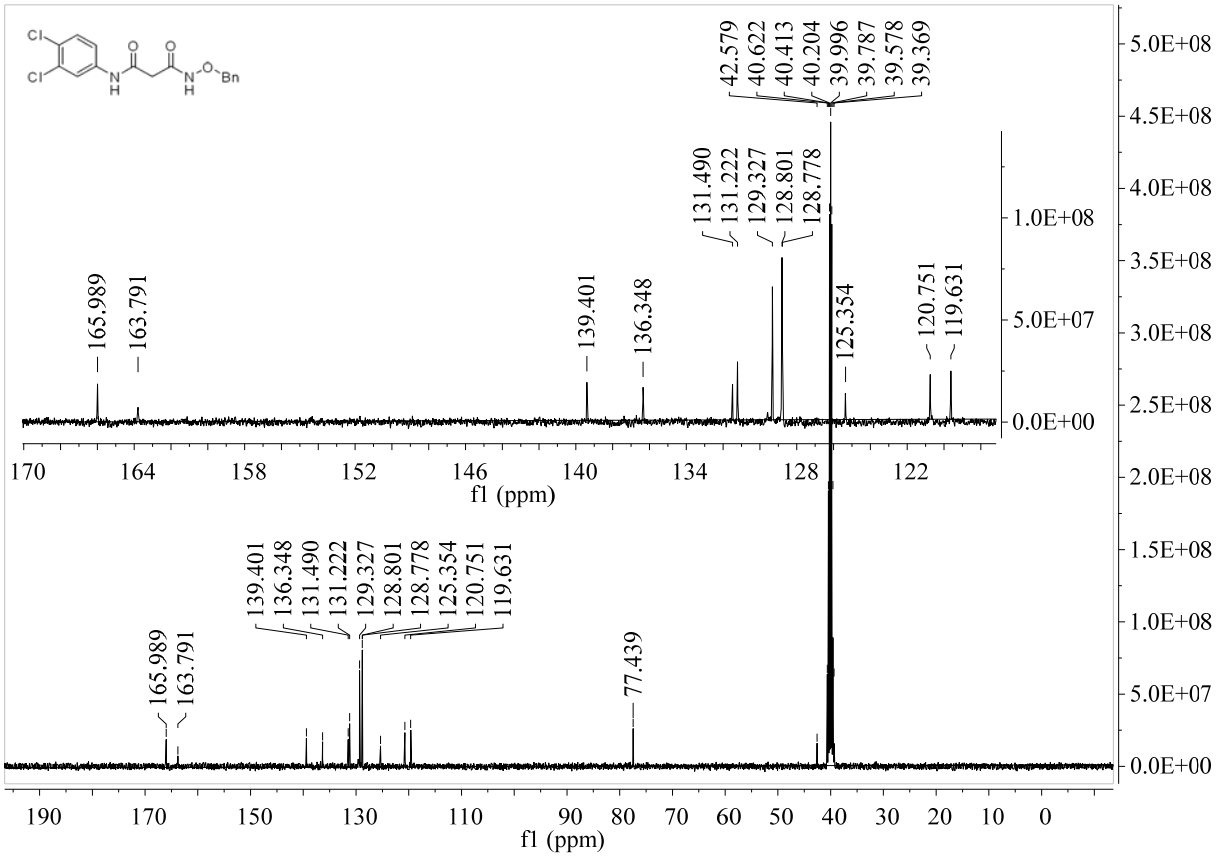
Compound **3ab**



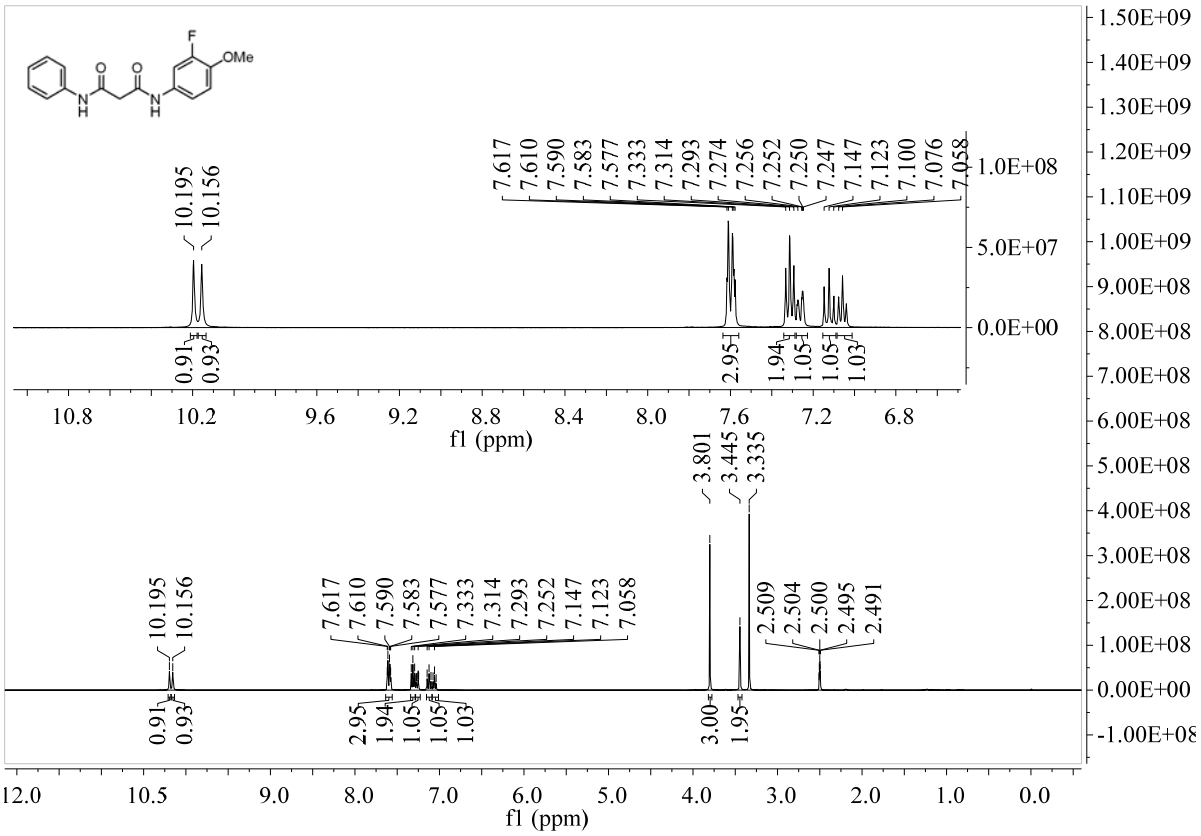


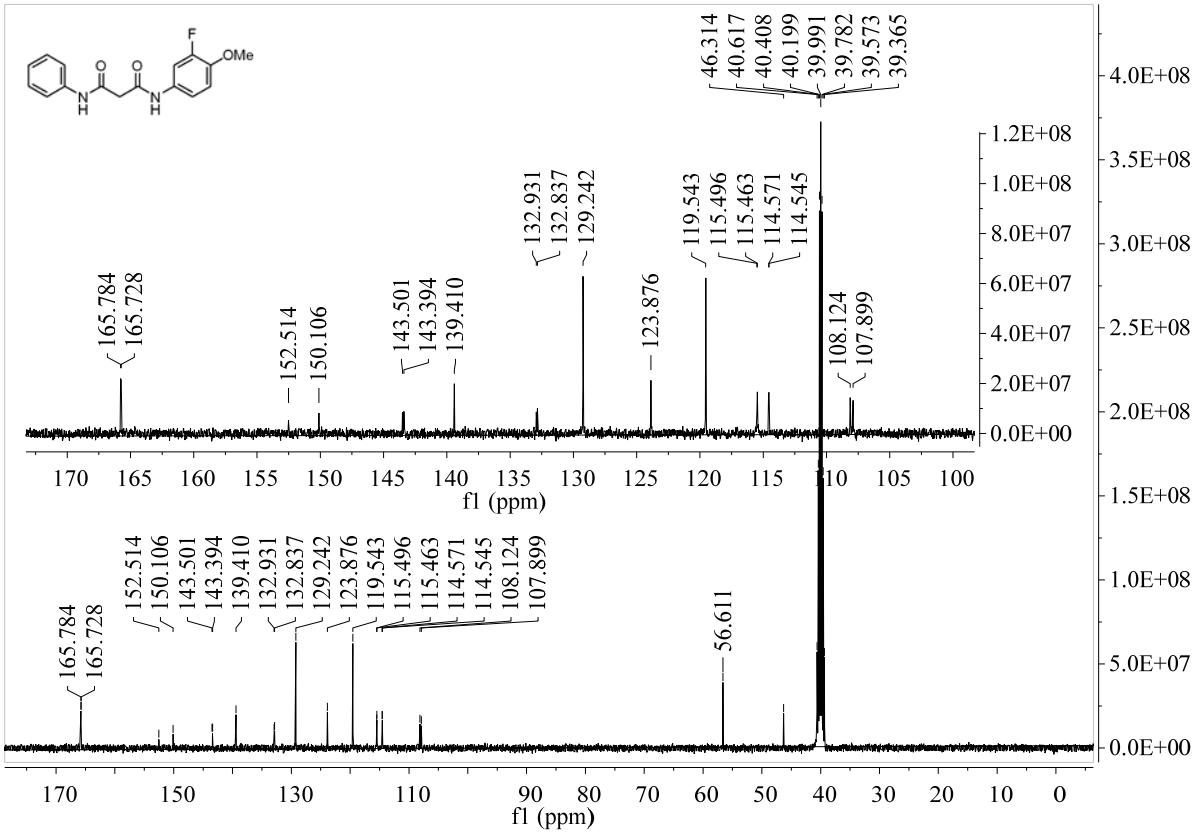
Compound **3ac**



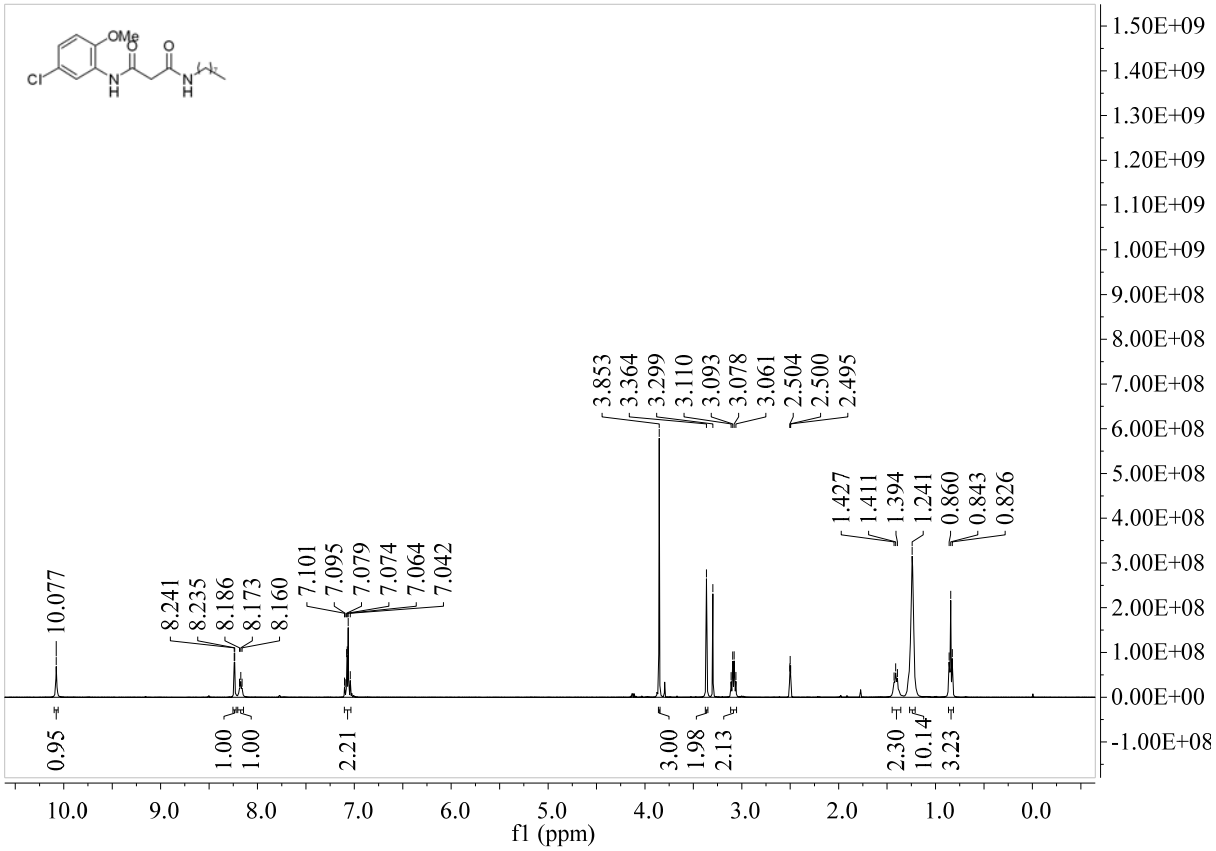


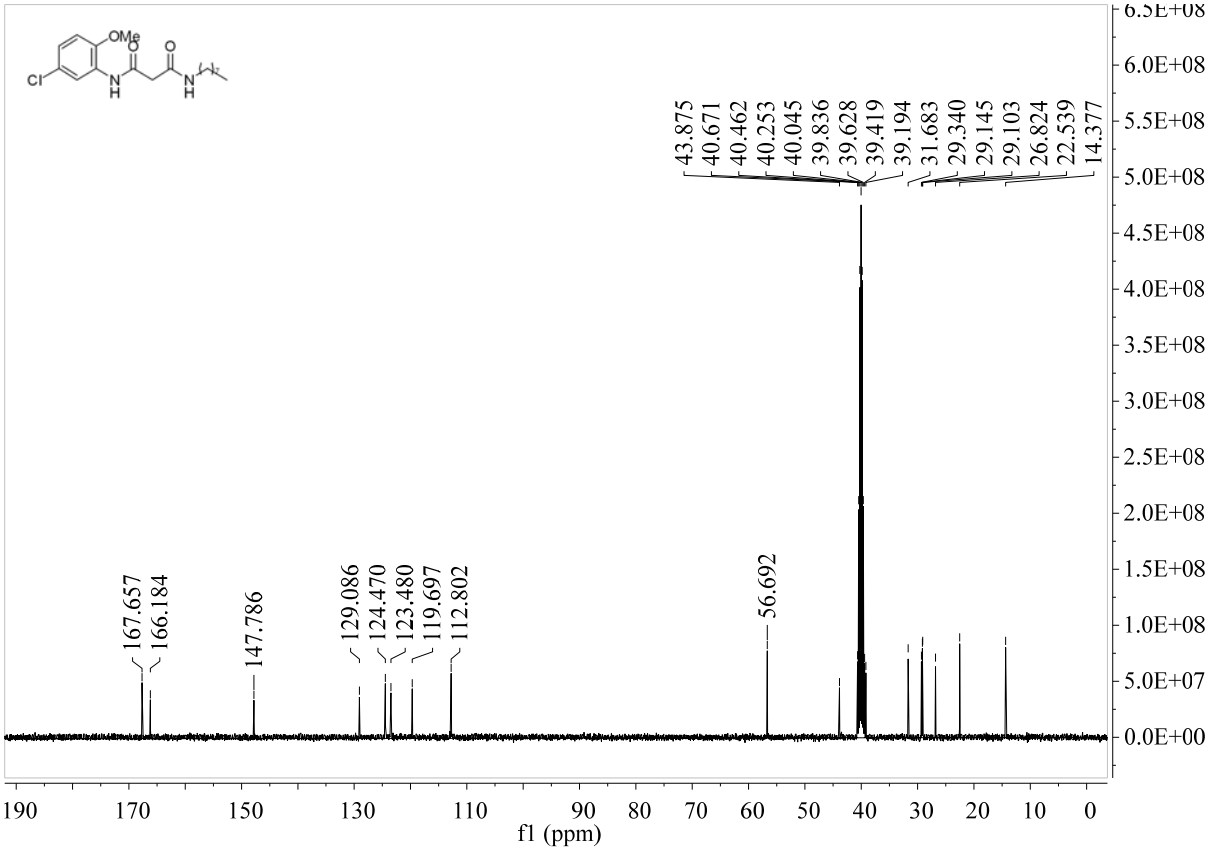
Compound **3ad**



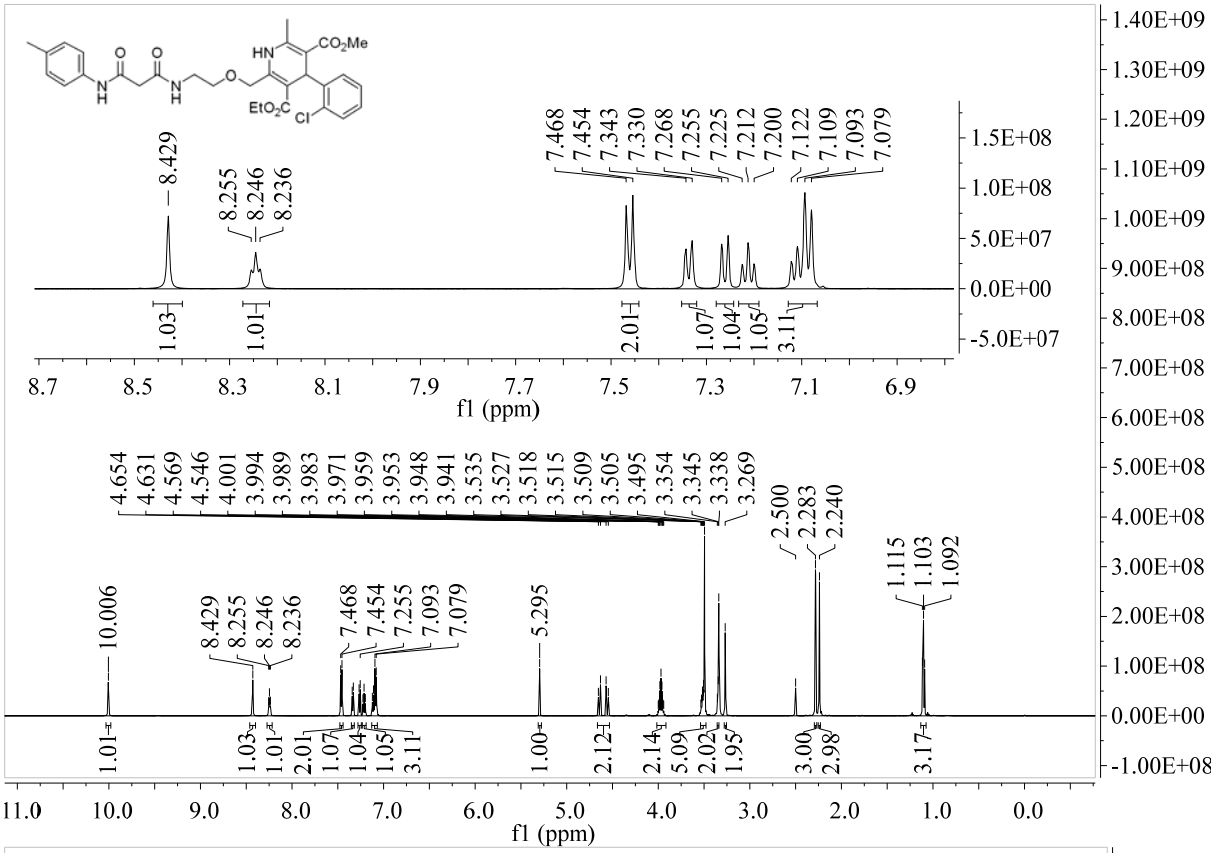


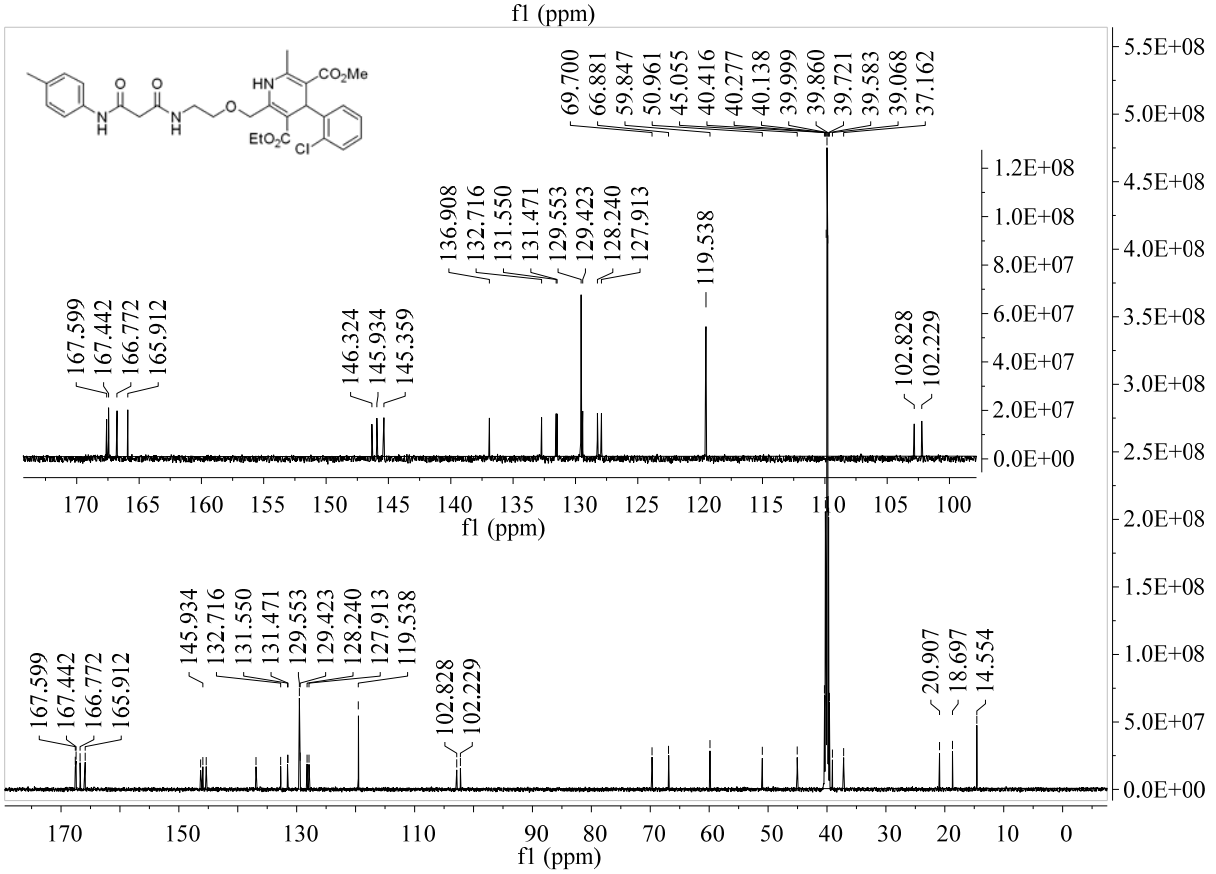
Compound **3ae**



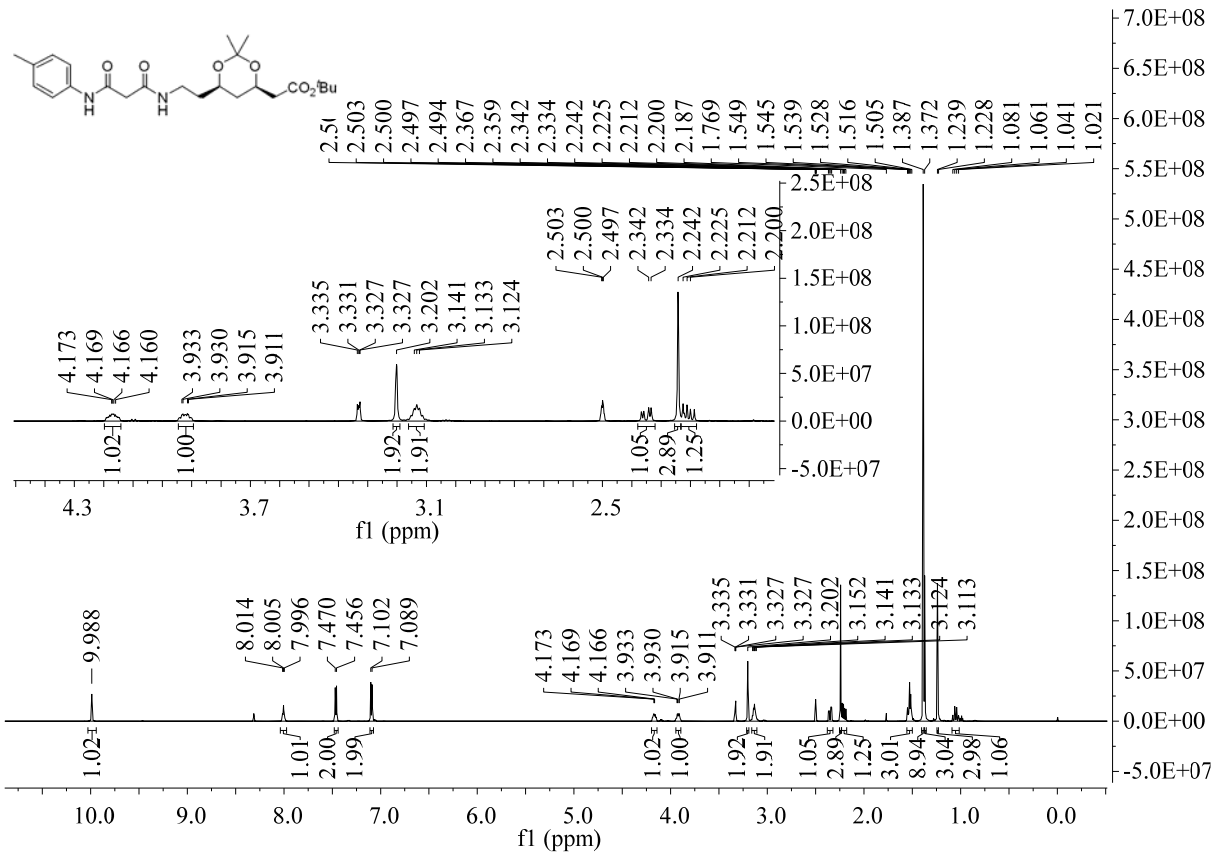


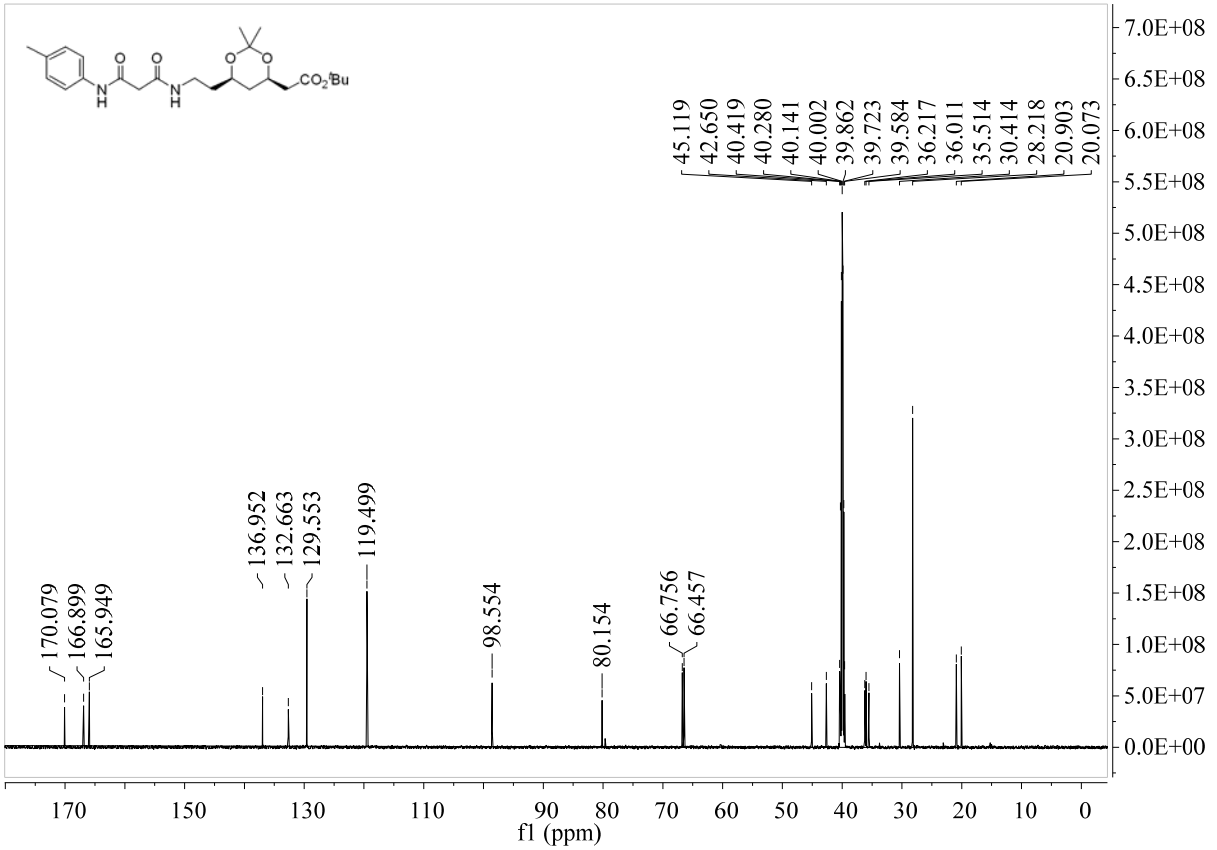
Compound **3af**



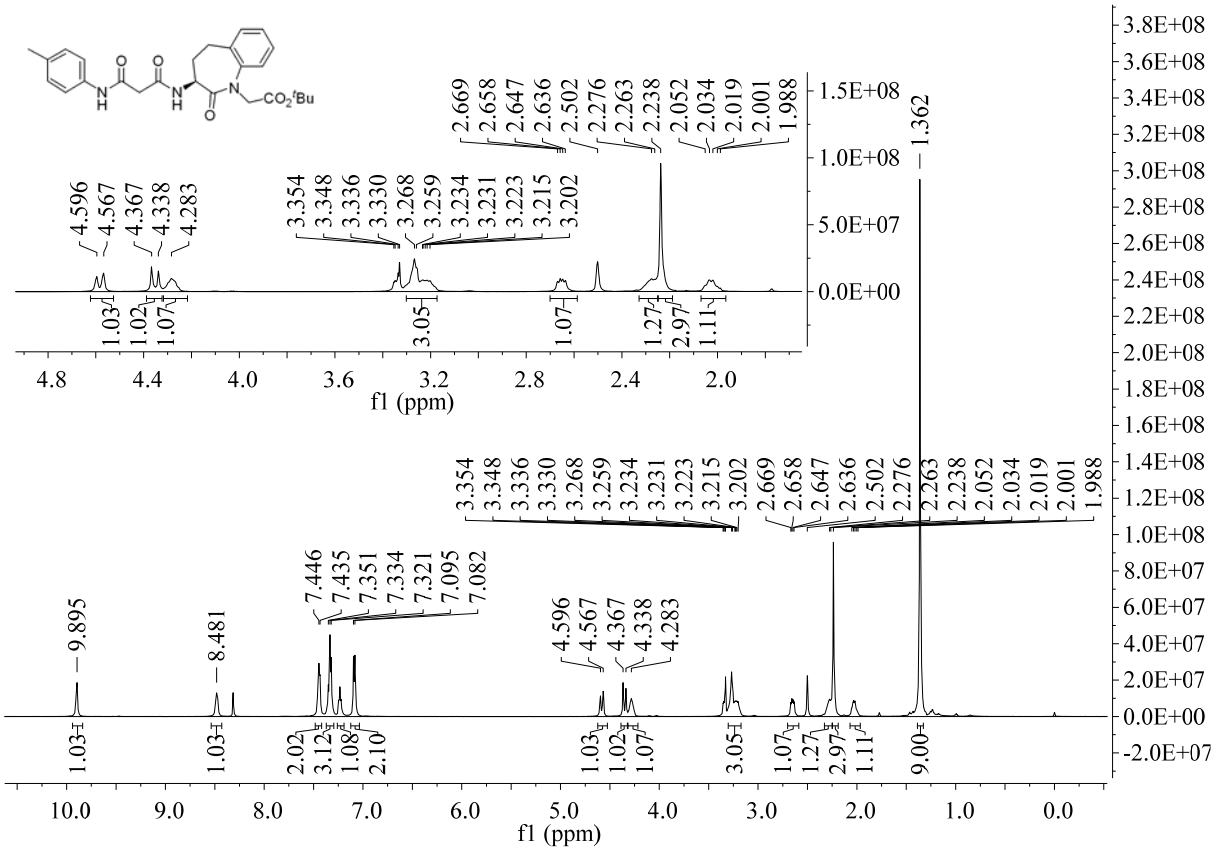


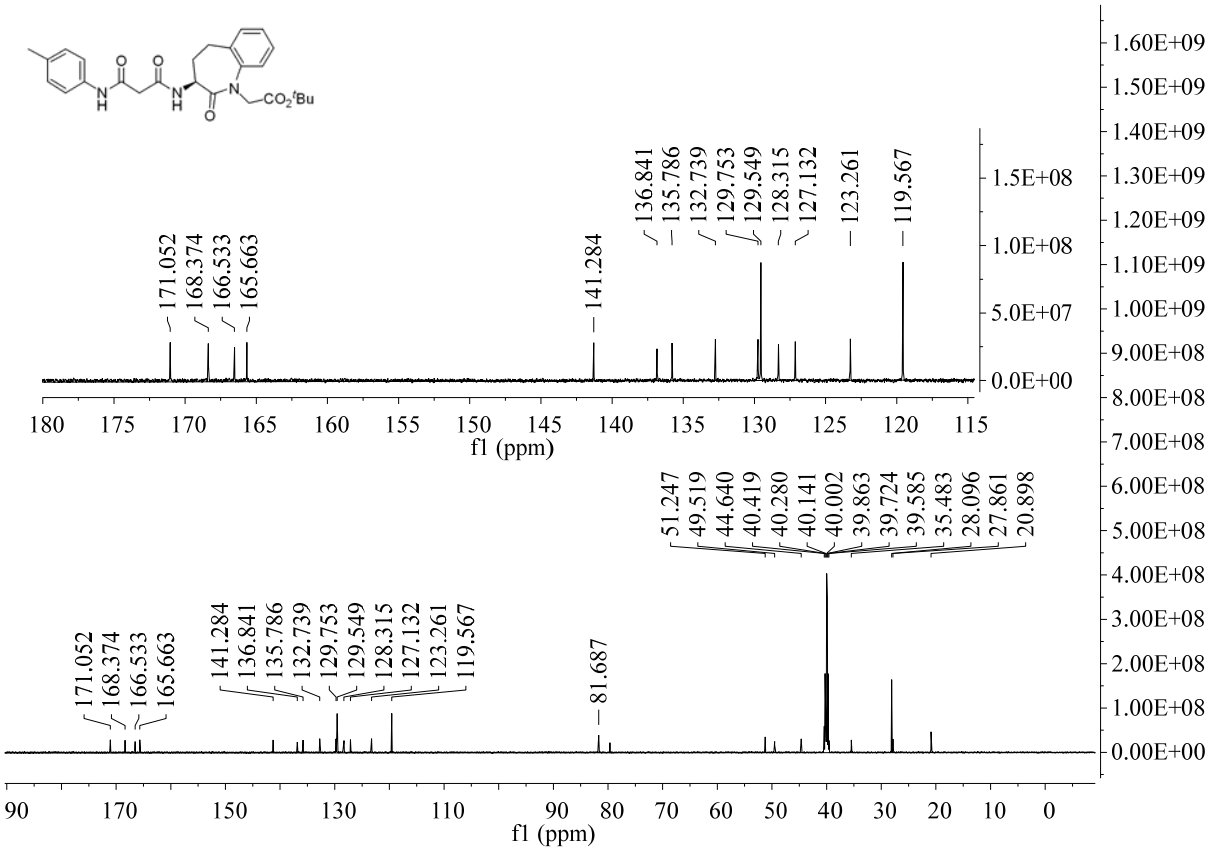
Compound **3ag**



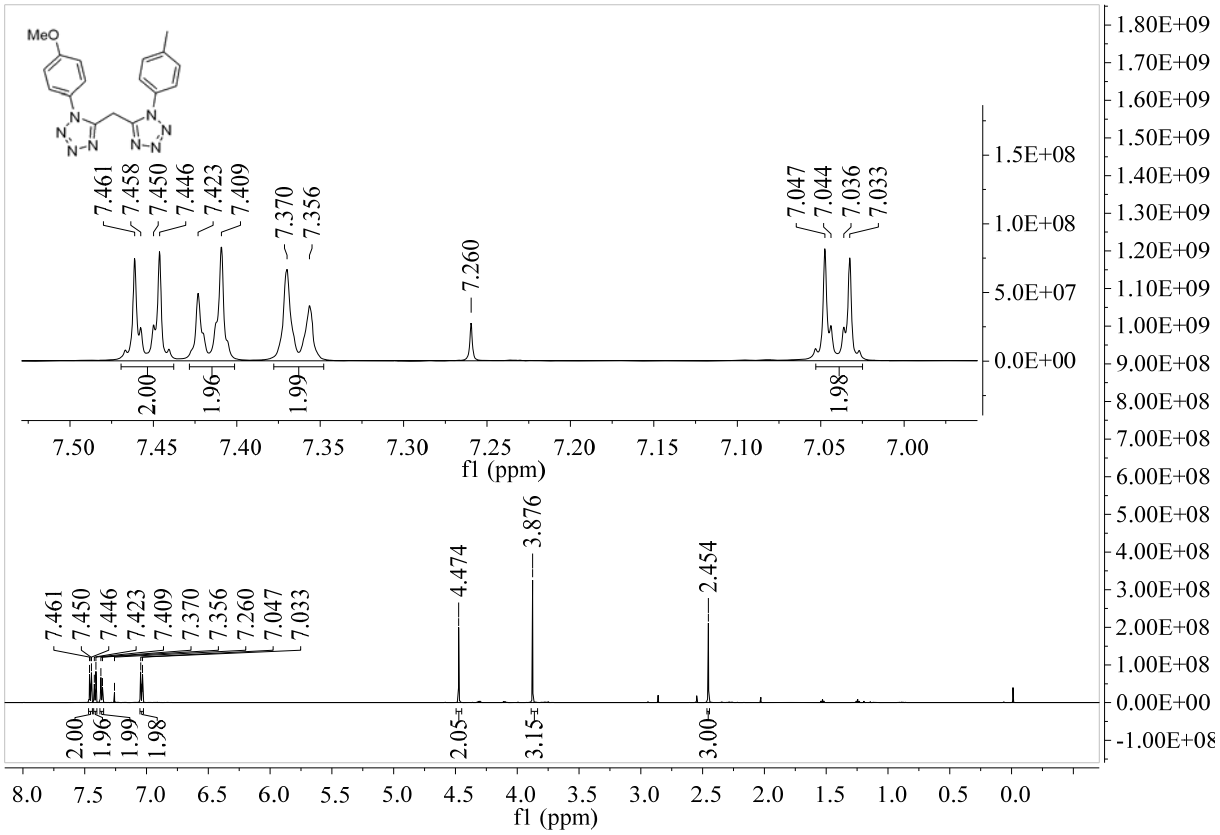


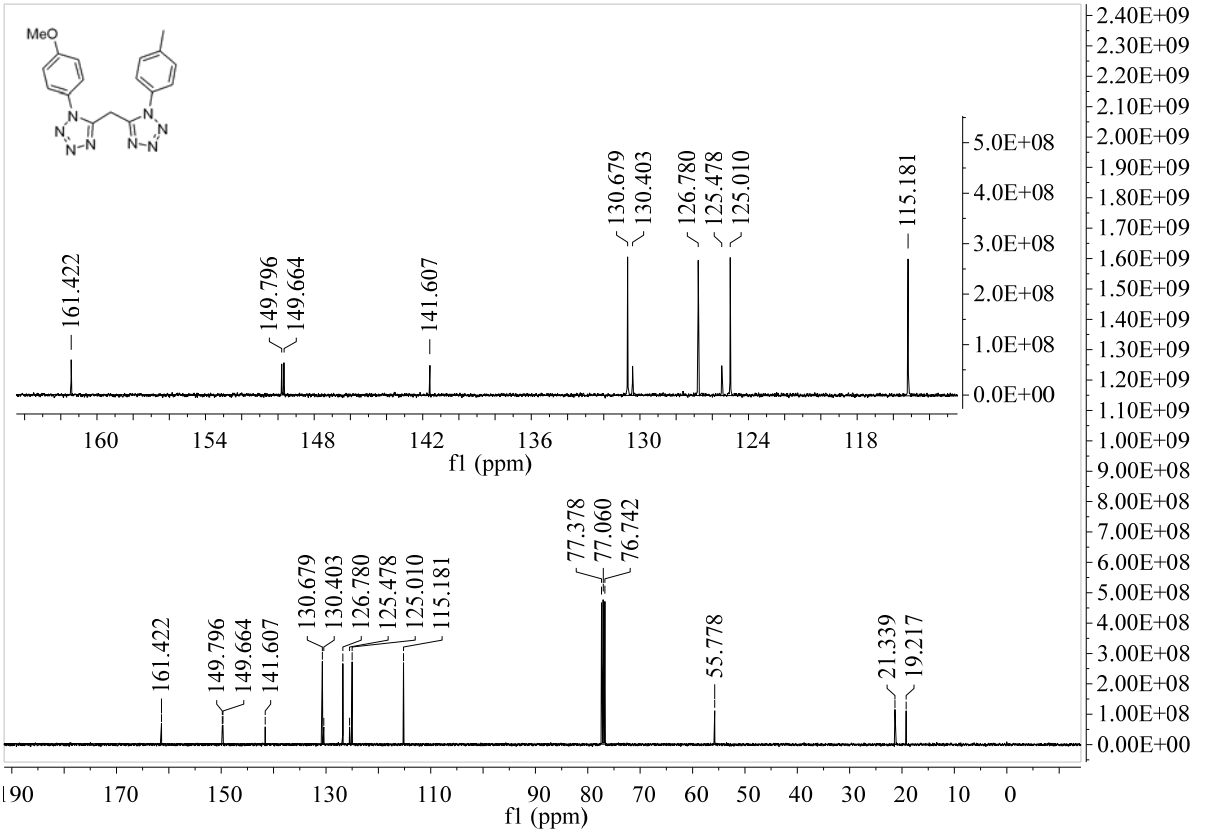
Compound **3ah**





Compound **5**


MeO
7.461
7.458
7.450
7.446
7.423
7.409
7.370
7.356
7.260
7.047
7.044
7.036
7.033
2.00
1.96
1.99
1.98
fl (ppm)
4.474
3.876
2.454
2.05
3.15
3.00
fl (ppm)


MeO
161.422
149.796
149.664
141.607
130.679
130.403
126.780
125.478
125.010
115.181
fl (ppm)
77.378
77.060
76.742
55.778
21.339
19.217
fl (ppm)