ChemistrySelect

Supporting Information

Synthesis, Spectroscopic Characterizations of Novel Norcantharimides, Their ADME Properties and Docking Studies Against COVID-19 M^{pro}

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Supporting Information

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Experimental Section

4.1. Material and Methods

The melting points (mp) of the synthesized compounds in open capillaries were determined using the Electrothermal 9100 device and were uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker 300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz, chemical shifts in ppm) in DMSO-d_6. Various abbreviations have been made to indicate the multiplicity: s, singlet; d, doublet; t, triplet; m is multiple; br, wide. The IR spectra (4000-400 cm^{-1}) were recorded on Thermo Scientific Nicolet İS5 (Diamond Crystal-ATR) FT-IR spectrometer. The elemental analyses (C, H, N and S) of the compounds were performed on Thermo Scientific Flash 2000 elemental analyzer. The reaction was monitored by thin layer chromatography (TLC) on aluminum plates coated with silica gel (Merck 60 F_{254}). The products were purified by column chromatography over silica gel (CC). All solvents were purchased from Merck and reagents were obtained from Aldrich Chem. Co. Solvents and reagents were used without further purification.

4.2.1. Synthesis of (3aR,4S,7R,7aS)-3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione (5,6-dehydronorcantharidin) (3)

5,6-dehydronorcantharidin (**3**), which is one of the important compounds of this study, was prepared by *exo*-selective cycloaddition or Diels-Alder reaction by the furan and maleic anhydride procedure of Kose et al. [1] The synthesis method of the 5,6-dehydronorcantharidin (**3**) was depicted schematically in Scheme 1. A solution of furan (40 mL, 550 mmol) and maleic anhydride (10 g, 102 mmol) was stirred for 24 h of heating under reflux. Then, thin-layer chromatography was used in 1:6 ethyl acetate/hexane to check the completeness of the reaction. After completion of the reaction, the solvent was removed on the rotary evaporator. The solvent was evaporated under vacuum. The white crude product (5,6-dehydronorcantharidin (**3**) was dried and recrystallized from ethyl acetate, yield 95%, mp:122-123 °C, lit mp:124-126 °C,[2-3] ^{1}H-NMR ($CDCl_3$): δ 6.58 (s, 2H), 5.46 (s, 2H), 3.18 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 170.0, 137.1, 82.5, 48.8.

4.2.2. Synthesis of (3aR,4S,7R,7aS)-2-amino-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (4)

Hydrazine hydrate (%80, 0.66 g, 10 mmol) was added into solution of 5,6-dehydronorcantharidin (**3**) (1.26 g, 10 mmol) in 30 mL of methanol.[16] The mixture was stirred in an oil bath under reflux for 16 hours. Then, thin-layer chromatography was used in 1:6 ethyl acetate/hexane to check the completeness of the reaction. The solvent was evaporated under vacuum. The crude product was dried and recrystallized from ethyl acetate. yield 90%, mp:144-145 °C. lit mp: 145-146 °C,[2-3] ^{1}H-NMR ($CDCl_3$): δ 6.49 (s, 2H), 5.20 (s, 2H), 2.97 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 177.4, 136.5, 84.1, 55.8.

4.2.3. General synthetic procedure of compounds 6a-f

Synthesis of novel Norcantharimide derivatives (**6a-f**) was carried out following the literature procedure. [4]

Compound **4** (1 eq. mol) was dissolved in 30 mL of dry THF. To the solution was added p-substituted benzoyl chloride (1.2 eq. mol) and triethyl amine (1.2 eq. mol). The mixture was stirred for half an hour in an ice bath and then at room temperature for 4 hours. The completion of the reaction was checked by thin-layer chromatography (chloroform-ethyl acetate 3:1). After completion of the reaction, the solvent was removed on the rotary evaporator. The reaction mixture was extracted with a mixture of ethyl acetate, water and brine. After separating the organic phase which was dried with sodium sulfate. Then the solvent was evaporated in a rotary evaporator and the product was dried and recrystallized from absolute ethyl alcohol.

4.2.4. Synthesis of *N*-((3aR,4S,7R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-epoxyisoindol-2-yl)-4-fluorobenzamide (6a)

Compound **6a** was synthesized according to the general synthesis procedure. Yield 61%; m.p. 172-175 °C; IR (ATR, ν_{max}/cm^{-1}): 3342 (NH), 3015 (Ar. CH), 2985 (Al. CH), 1718 (C=O), 1696 (C=O), 1593 (NH), 1115 (C-O); ^{1}H-NMR (300 MHz, ppm, DMSO-d_6): 11.33 (s, 1H, -NH); 7.98 (d, 2H); 7.39 (d, 2H); 6.60 (s, 2H); 5.26 (s, 2H); 3.17 (s, 2H). ^{13}C-APT NMR (100 MHz, DMSO-d_6): 173.9; 136.7; 131.1; 130.9; 116.4; 116.1; 80.9; 45.5. Anal. Calcd for $C_{15}H_{11}FN_2O_4$: C, 59.61; H, 3.67; N, 9.27, Found: C, 58.09; H, 3.78; N, 8.58.

4.2.5. Synthesis of 4-chloro-*N*-((3aR,4S,7R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-4,7-epoxyisoindol-2-yl) benzamide (6b)

Compound **6b** was synthesized according to the general synthesis procedure. Yield 60%; m.p. 182-184°C; IR (ATR, ν_{max}/cm^{-1}): 3337 (NH), 3014 (Ar. CH), 2987 (Al. CH), 1720 (C=O), 1693 (C=O), 1591 (NH), 1105 (C-O); ^{1}H-NMR (300 MHz, ppm, DMSO-d_6): 11.40 (s, 1H, -NH); 7.93 (d, 2H); 7.64 (d, 2H); 6.43 (s, 2H); 5.25 (s, 2H); 3.17 (s, 2H). ^{13}C-APT NMR (100 MHz, DMSO-d_6): 173.9; 164.2; 138.1; 136.8; 130.1; 129.4; 80.9; 45.5. Anal. Calcd for $C_{15}H_{11}ClN_2O_4$: C, 56.53; H, 3.48; N, 8.79, Found: C, 56.65; H, 3.55; N, 8.69.

4.2.6. Synthesis of 4-bromo-*N*-((3aR,4S,7R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-4,7-epoxyisoindol-2-yl)benzamide (6c)

Compound **6c** was synthesized according to the general synthesis procedure. Yield 65%; m.p. 174-176°C; IR (ATR, ν_{max}/cm^{-1}): 3340 (NH), 3010 (Ar. CH), 2985 (Al. CH), 1721 (C=O), 1694 (C=O), 1590 (NH), 1080 (C-O); ^{1}H-NMR (300 MHz, ppm, DMSO-d_6): 11.50 (s, 1H, -NH); 7.85 (d, 2H); 7.75 (d, 2H); 6.50 (s, 2H); 5.30 (s, 2H); 3.20 (s, 2H). ^{13}C-APT NMR (100 MHz, DMSO-d_6): 173.4; 163.8; 136.2; 131.8; 129.8; 129.7;126,6; 80.4; 45.0. Anal. Calcd for $C_{15}H_{11}BrN_2O_4$: C, 49.61; H, 3.05; N, 7.71, Found: C, 50.31; H, 3.00; N, 7.79,

4.2.7. Synthesis of *N*-((3aR,4S,7R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-4,7-epoxyisoindol-2-yl)-4-methylbenzamide (6d)

Compound **6d** was synthesized according to the general synthesis procedure. Yield 59%; m.p. 192-195°C; IR (ATR, ν_{max}/cm^{-1}): 3338 (NH), 3016 (Ar. CH), 2988 (Al. CH), 1721 (C=O), 1694 (C=O), 1593 (NH), 1110 (C-O); ^{1}H-NMR (300 MHz, ppm, DMSO-d_6): 11.18 (s, 1H, -NH); 7.83 (d, 2H); 7.63 (d, 2H); 6.60 (s, 2H); 5.25 (s, 2H); 3.15 (s, 2H); 2.98 (s, 3H). ^{13}C-APT NMR (100 MHz, DMSO-d_6): 174.0; 165.0; 143.8; 136.8; 129.7; 128.5; 128.2; 80.9; 45.5; 21.5. Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39, Found: C, 62.76; H, 4.92; N, 10.47.

4.2.8. Synthesis of *N*-((3aR,4S,7R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-4,7-epoxyisoindol-2-yl)-4-methoxybenzamide (6e)

Compound **6e** was synthesized according to the general synthesis procedure. Yield 57%; m.p. 169-171°C; IR (ATR, ν_{max}/cm^{-1}): 3334 (NH), 3020 (Ar. CH), 2980 (Al. CH), 1720 (C=O), 1695 (C=O), 1592 (NH), 1100 (C-O); ^{1}H-NMR (300 MHz, ppm, DMSO-d_6): 11.20 (s, 1H, -NH); 7.85 (d, 2H); 7.10 (d, 2H); 6.50 (s, 2H); 5.20 (s, 2H); 3.83 (s, 3H); 3.10 (s, 2H). ^{13}C-APT NMR (100 MHz, DMSO-d_6): 173.6; 164.0; 136.4; 136.3; 129.7; 122.3; 113.9; 80.4; 55.5; 44.5. Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91, Found: C, 62.25; H, 4.45; N, 7.66.

4.2.9. Synthesis of *N*-((3aR,4S,7R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-4,7-epoxyisoindol-2-yl)-4-nitrobenzamide (6f)

Compound **6f** was synthesized according to the general synthesis procedure. Yield 62%; m.p. 194-196°C; IR (ATR, ν_{max}/cm^{-1}): 3336 (NH), 3018 (Ar. CH), 2986 (Al. CH), 1723 (C=O), 1696 (C=O), 1598 (NH), 1090 (C-O); ^{1}H-NMR (300 MHz, ppm, DMSO-d_6): 11.67 (s, 1H, -NH); 8.40 (d, 2H); 8.15 (d, 2H); 6.61 (s, 2H); 5.27 (s, 2H); 3.19 (s, 2H); 2.98. ^{13}C-APT NMR (100 MHz, DMSO-d_6): 173.7; 165.0; 150.2; 136.8; 136.6; 129.7; 124.4; 80.9; 45.5. Anal. Calcd for $C_{15}H_{11}N_3O_6$: C, 54.72; H, 3.37; N, 12.76, Found: C, 56.16; H, 3.61; N, 10.88.

References

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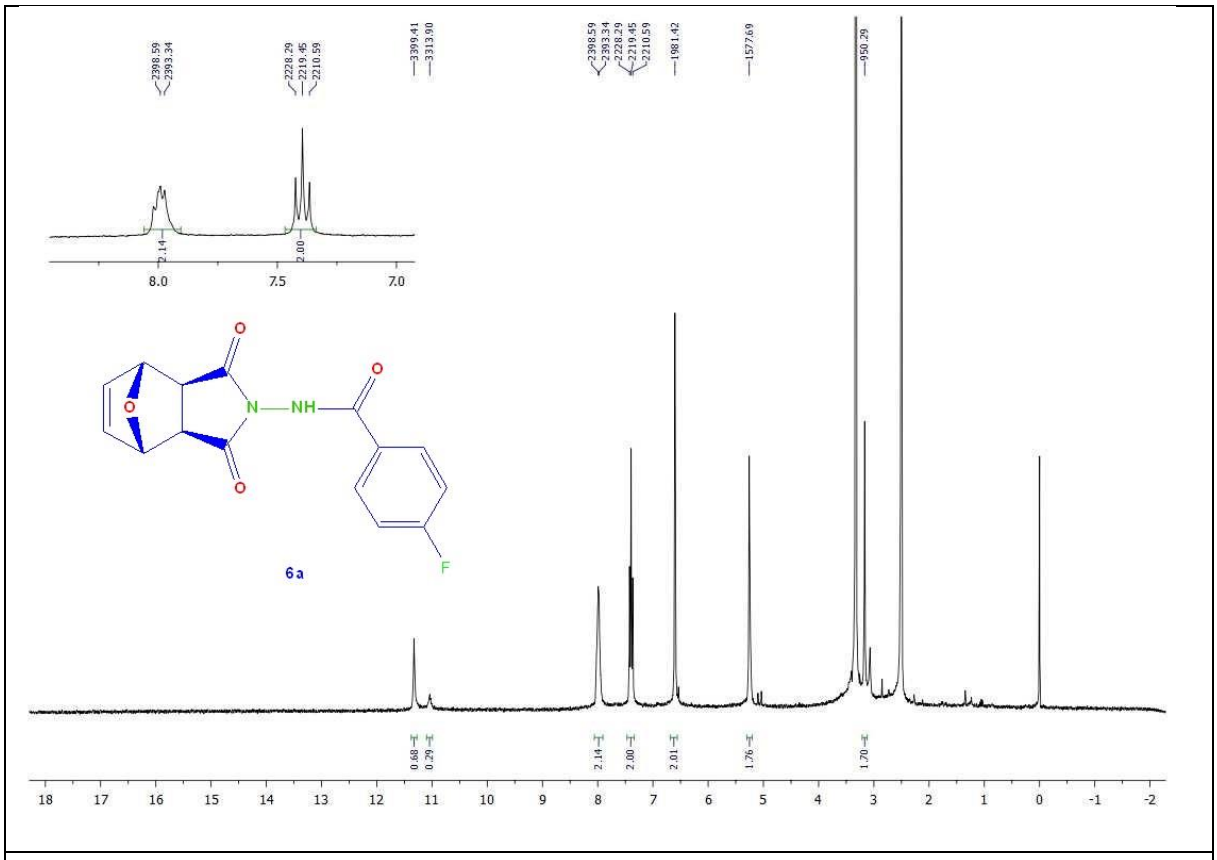
[4] Y. Yıldırır, O. Pamir, S. Yavuz, A. Disli, *J. Heterocycl. Chem.* **2013**, *50*, E93-E99.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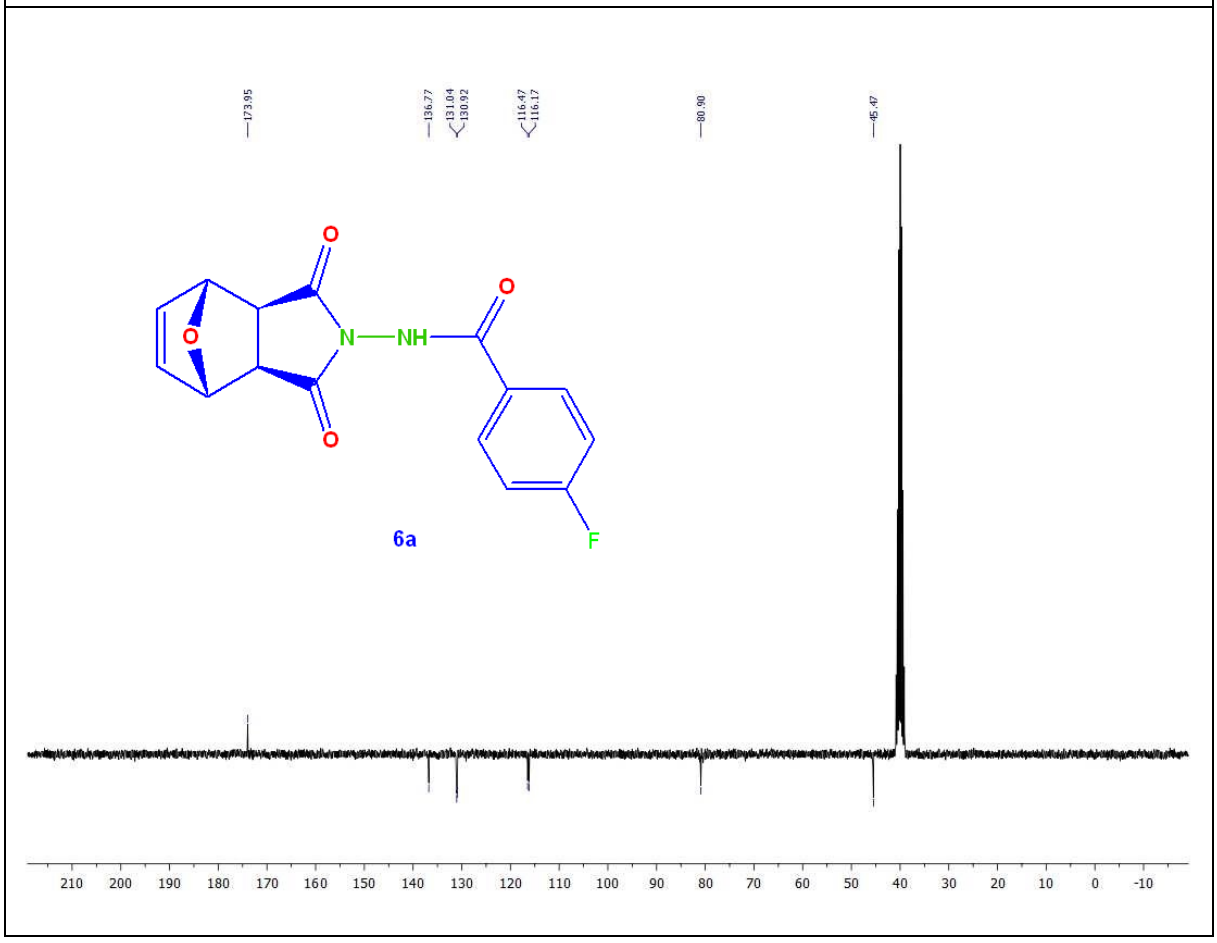
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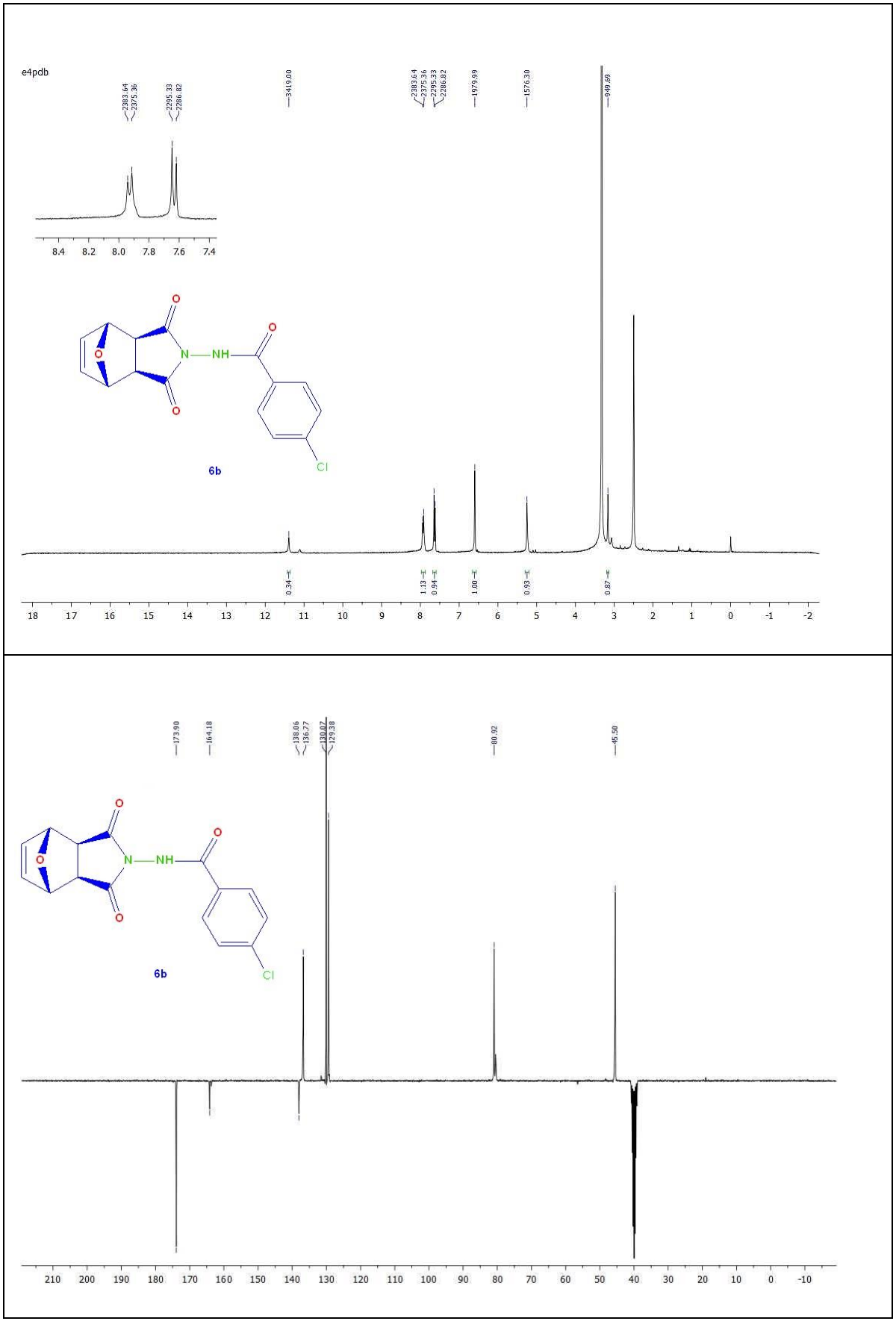
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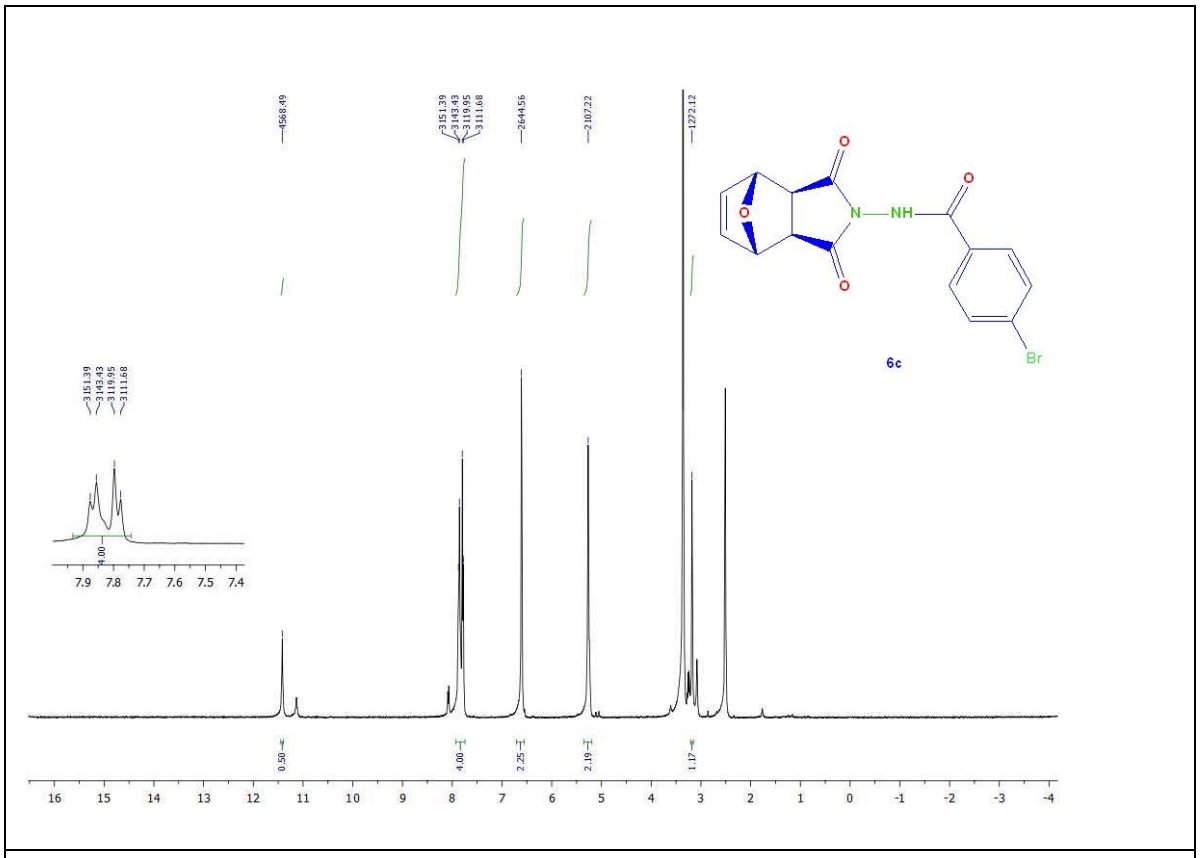
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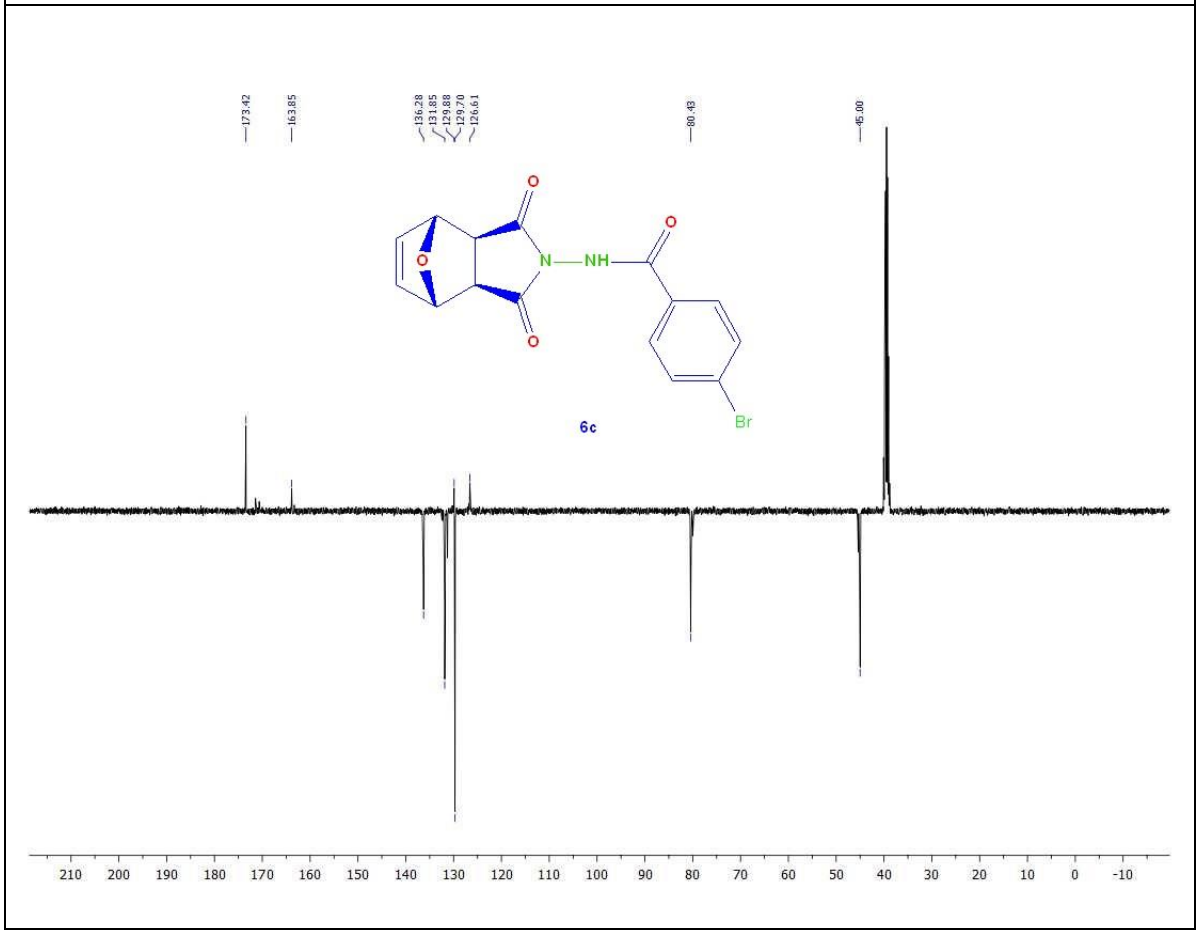
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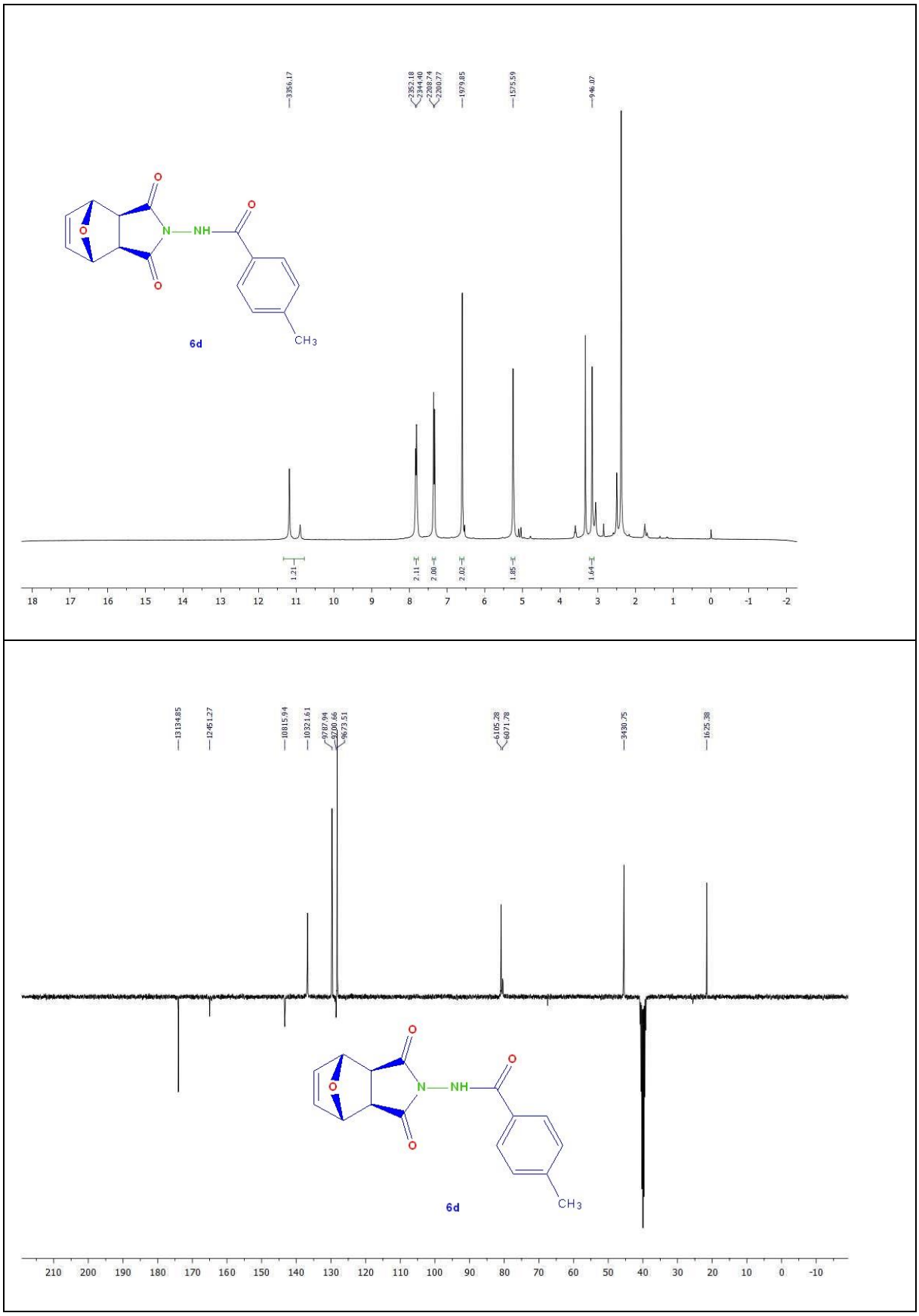
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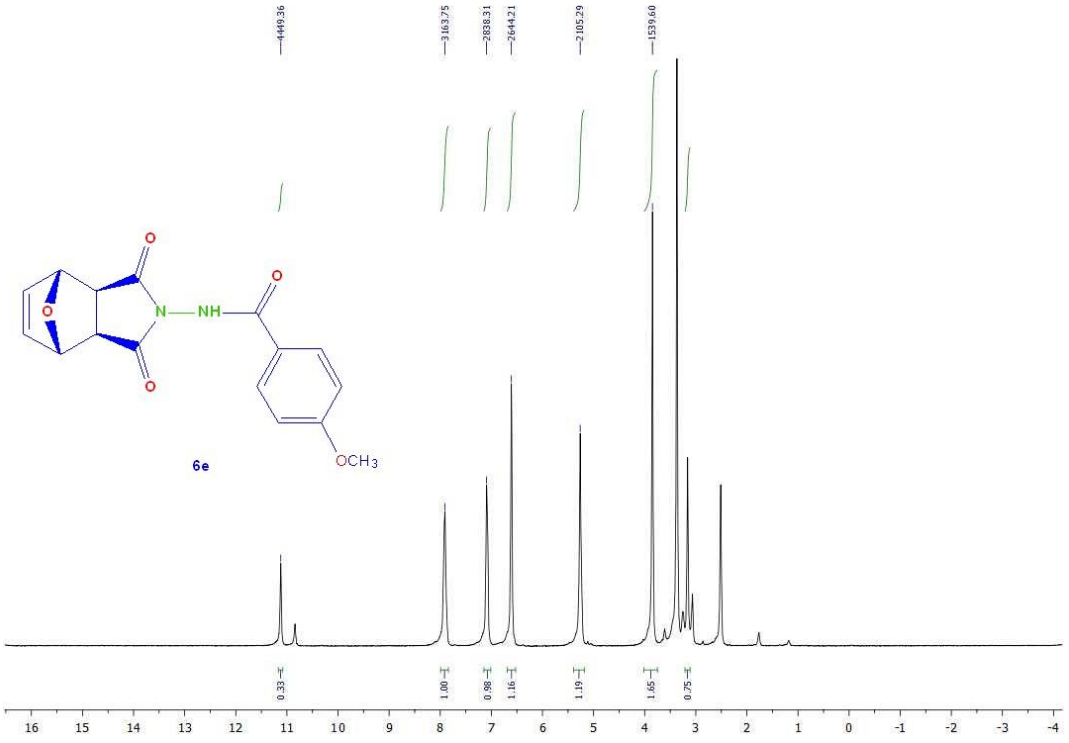
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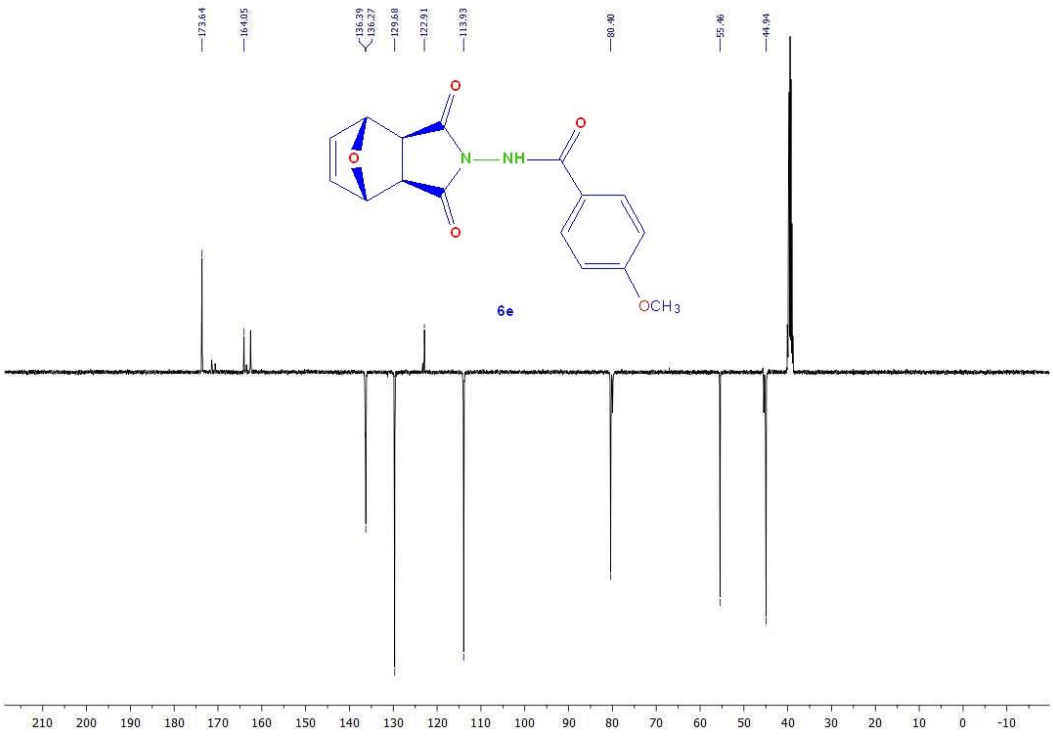
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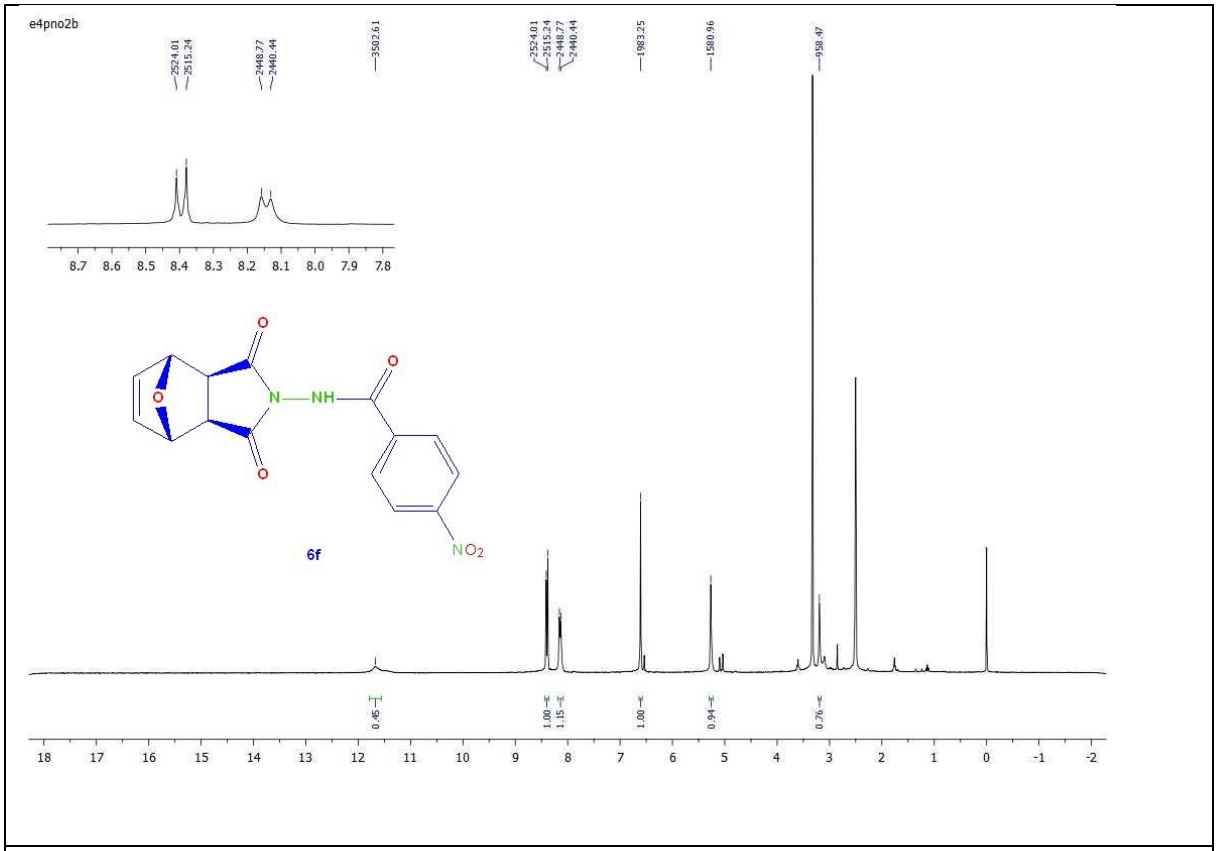
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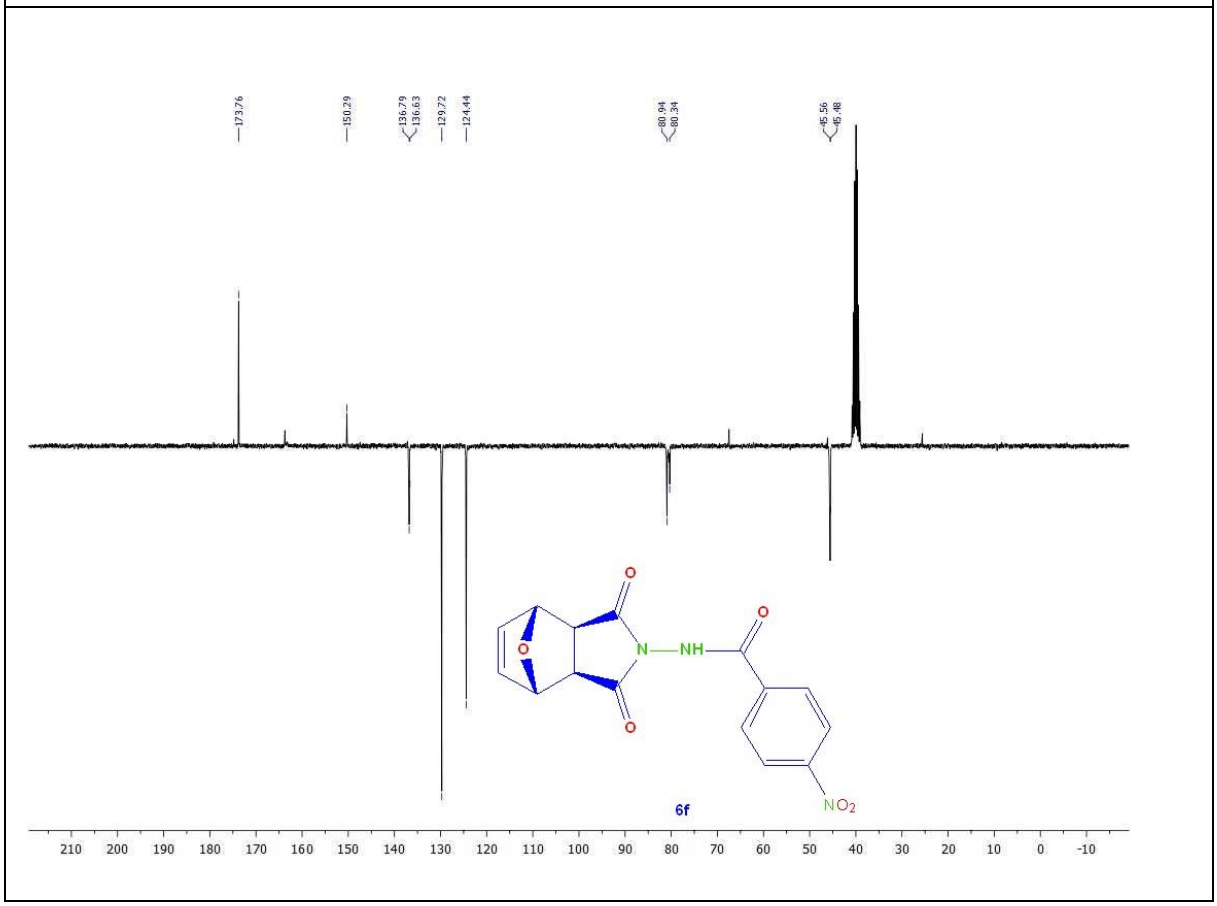
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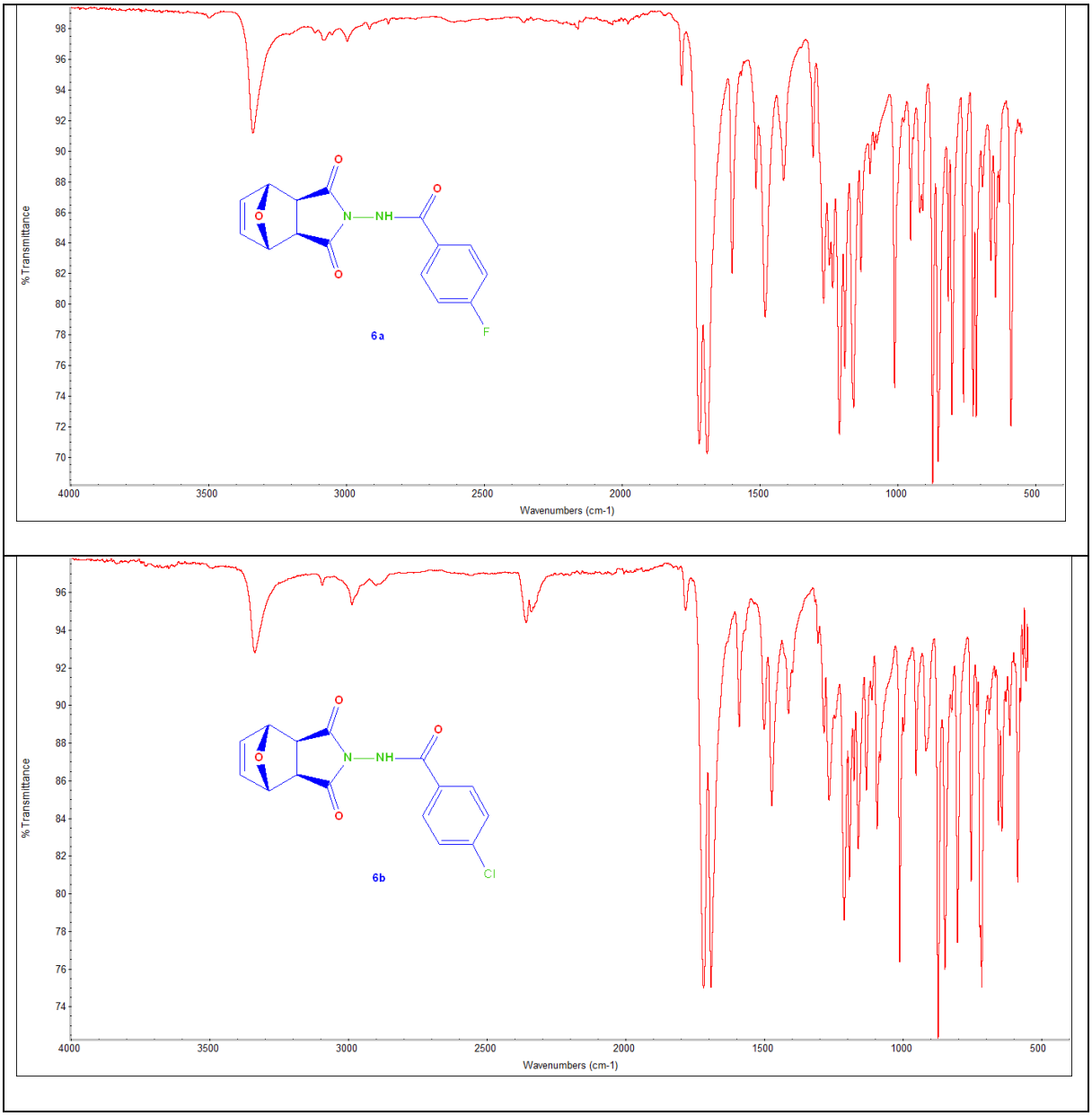
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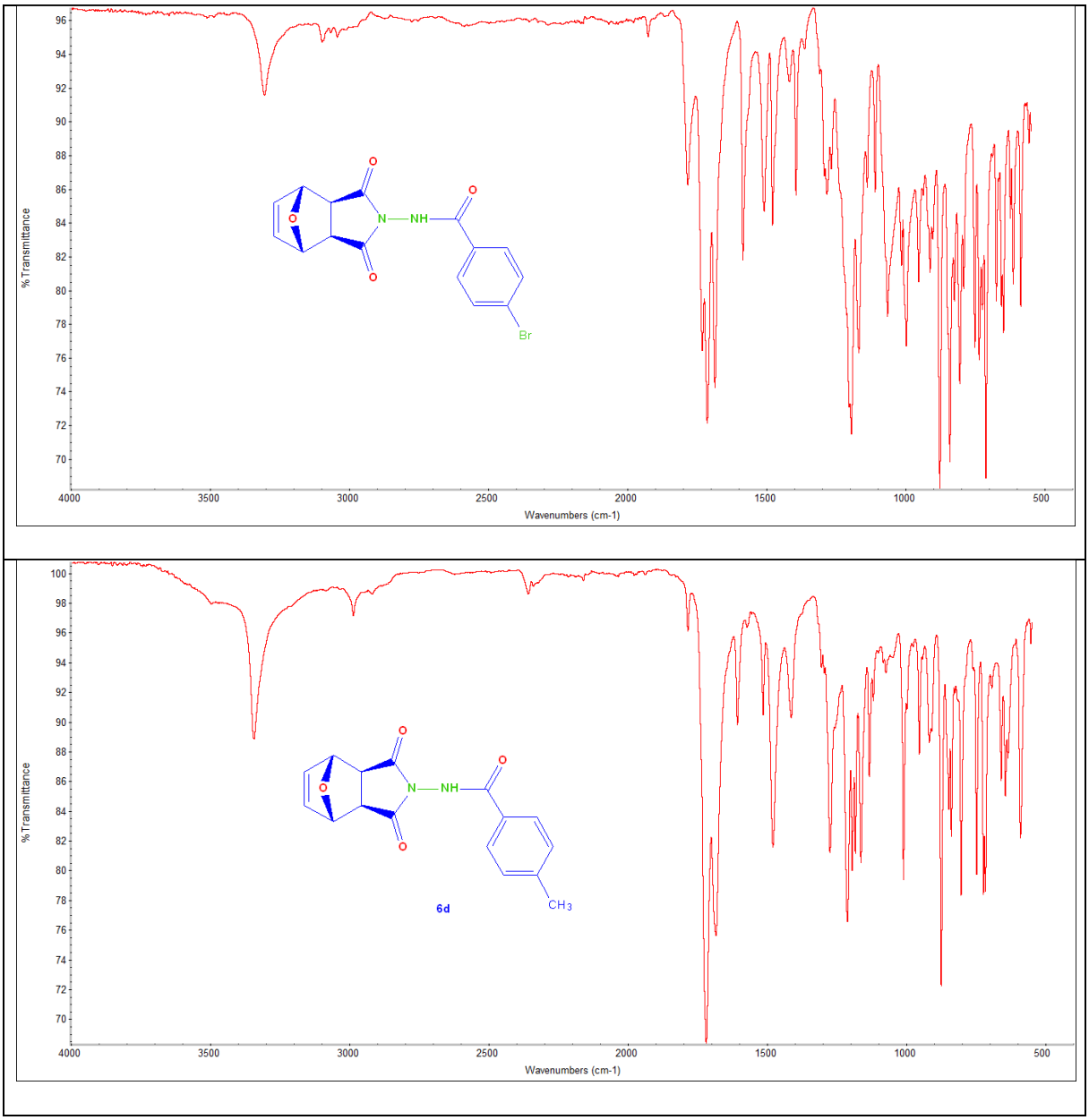
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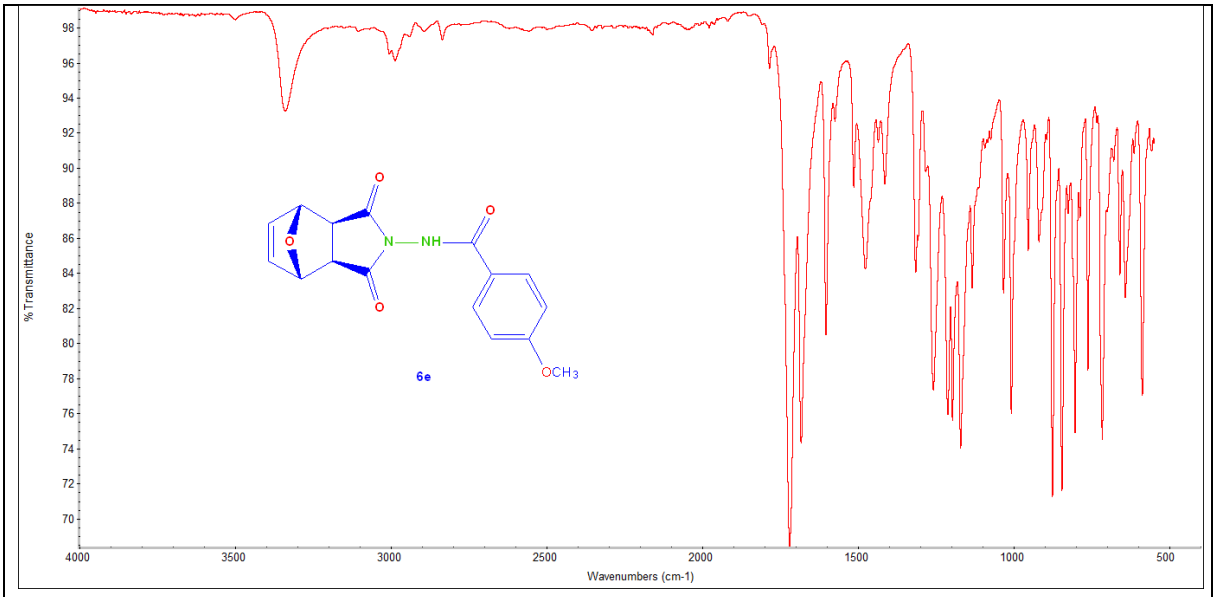
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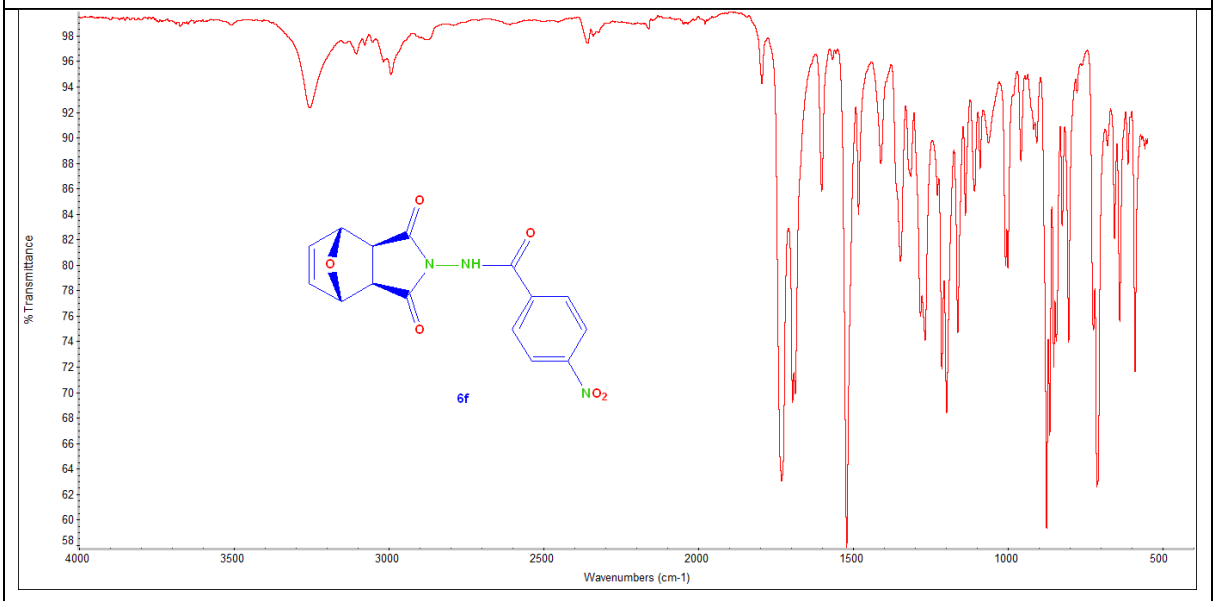
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