

Supplementary Material

Design, synthesis and antimicrobial evaluation of novel 1-phenyl/hetaryl-4-aryloxy-3,5-bistrifluoromethyl-1H-pyrazole derivatives

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Experimental

Materials and methods

Melting point of the compounds were determined in open capillaries with an digital melting point apparatus (MEPA) and are uncorrected, the IR spectra of the compounds were recorded on Buck Scientific IR M-500 spectrophotometer using KBr pellets (ν_{\max} in cm^{-1}), ^1H and ^{13}C NMR spectra on a Bruker instrument at 400 and 100 MHz, respectively, using deuteriochloroform as a solvent. Chemical shifts are expressed in δ -scale downfield from TMS as an internal standard. ^{19}F NMR spectra were run on DPX 400 at 376 MHz, using deuteriochloroform as a solvent. The internal standard for ^{19}F spectra was fluorotrichloromethane, setting the CFCl_3 signal at δ 0.0. Mass analyses were performed at Sophisticated Analytical Instrument Facility, Panjab University, Chandigarh, India.

General synthetic procedure for 1-(4,6-dimethylpyrimidin-2-yl)-4-(2-(p-tolyl)hydrazono)-5-hydroxy-3,5-bistrifluoromethylpyrazoline **15a**

An ethanolic mixture of 1,1,1,5,5,5-hexafluoro-3-(p-tolyldiazenyl)pentane-2,4-dione **13a** (0.001 mol) 2-hydrazino-4,6-dimethylpyrimidine **14a** (0.001 mol) was refluxed on water bath. TLC of the reaction revealed complete consumption of reactants on 5-6 hr heating the reaction mixture at reflux temperature. The solvent was **removed in vacuo** and solid thus obtained was filtered, dried and recrystallized with ethanol to get final product bistrifluoromethylpyrazoline **15a**.

Compounds **15b-e** were also synthesized using the same procedure with respective starting materials as reactants.

General synthetic procedure for 1-Phenyl/benzothiazolyl/4,6-dimethylpyrimidine-3,5-bistrifluoromethyl-4-arylazopyrazoles **9a-f**, **10a-d** and **11a-b**.

An ethanolic mixture of 1,1,1,5,5,5-hexafluoro-3-arylazo-pentan-2,4-dione **13** (0.001 mol) and corresponding aryl/hetarylhydrazines (**14a-c**) (0.001 mol) in presence of catalytic amount of sulphuric acid was refluxed on water bath for 3-4 hr. Solvent was removed in vacuo and the solid thus obtained was filtered, dried and recrystallized with ethanol to get the corresponding

bistrifluoromethylpyrazoles (9/10/11)

1-(4,6-Dimethylpyrimidin-2-yl)-4-(2-(4-methylphenyl)hydrazono)-5-hydroxy-3,5-bistrifluoromethylpyrazoline 15a

M. Pt. 119°C, Yield 78%, IR (KBr, cm^{-1}): 3570, 3223, 2152, 1670, 1648, 1610; ^1H NMR (400 MHz, CDCl_3) δ : 9.33 (s, 1H, N-H); 7.13-7.16 (d, 2H, $J = 8.8\text{Hz}$, 2'', 6''-H); 7.06-7.09 (d, 2H, $J = 8.8\text{Hz}$, 3'', 5''-H); 6.75 (s, 1H, 5'-H); 2.63 (s, 1H, O-H); 2.49 (s, 6H, 4', 6'- CH_3); 2.33 (s, 3H, 4''- CH_3); ^{13}C NMR (100 MHz, CDCl_3): 157.81, 139.74, 133.25, 130.04, 126.79, 115.19, 114.22, 24.18, 20.89; MS (EI) m/z : calcd. for $\text{C}_{18}\text{H}_{16}\text{F}_6\text{N}_6\text{O}$: 447.1290 $[\text{M}+1]^+$; found: 447.1344; $[\text{M}+1]^+$; Elemental analysis: Calcd. for $\text{C}_{18}\text{H}_{16}\text{F}_6\text{N}_6\text{O}$: C, 48.44; H, 3.61; N, 18.83% Found: C, 48.37; H, 3.56; N, 18.80%.

4-(2-(4-Chlorophenyl)hydrazono)-1-(4,6-dimethylpyrimidin-2-yl)-5-hydroxy-3,5-bistrifluoromethylpyrazoline 15b

M. Pt. 124°C, Yield 80%, IR (KBr, cm^{-1}): 3563, 3213, 2151, 1668, 1642, 1603; ^1H NMR (400 MHz, CDCl_3) δ : 9.335 (s, 1H, N-H); 7.304 (d, 2H, $J = 8.4\text{Hz}$, 2'', 6''-H); 7.111 (d, 2H, $J = 8.4\text{Hz}$, 3'', 5''-H); 6.770 (s, 1H, 5'-H); 2.486 (s, 6H, 4', 6'- CH_3); ^{13}C NMR (100 MHz, CDCl_3): 168.45, 157.73, 140.69, 129.57, 128.50, 128.37, 124.64, 120.74, 118.04, 115.39, 115.36, 24.03; MS (EI) m/z : calcd. for $\text{C}_{17}\text{H}_{13}\text{ClF}_6\text{N}_6\text{O}$: 467.0477 $[\text{M}+1]^+$; found: 467.0459; $[\text{M}+1]^+$; 469.0448; $[\text{M}+1+2]^+$; Elemental analysis: Calcd. for $\text{C}_{17}\text{H}_{13}\text{ClF}_6\text{N}_6\text{O}$: C, 43.74; H, 2.81; N, 18.00% Found: C, 43.63; H, 2.70; N, 17.92%.

4-(2-(3-Chlorophenyl)hydrazono)-1-(4,6-dimethylpyrimidin-2-yl)-5-hydroxy-3,5-bistrifluoromethylpyrazoline 15c

M. Pt. 124°C, Yield 80%, IR (KBr, cm^{-1}): 3558, 3218, 2159, 1663, 1640, 1605; ^1H NMR (400 MHz, CDCl_3) δ : 9.906 (s, 1H, N-H); 7.546 (d, 1H, $J = 8.4\text{Hz}$, 6''-H); 7.319 (d, 1H, $J = 8.0\text{Hz}$, 4''-H); 7.288 (d, 1H, $J = 8.0\text{Hz}$, 2''-H); 6.966 (t, 1H, $J = 7.6\text{Hz}$, 5''-H); 6.76 (s, 1H, 5'-H); 2.614 (s, 1H, O-H); 2.479 (s, 6H, 4', 6'- CH_3); ^{13}C NMR (100 MHz, CDCl_3): 170.039, 168.485, 157.723, 138.350, 130.037, 129.428, 128.241, 123.568, 119.544, , 115.425, 114.942, 24.096; MS (EI) m/z : calcd. for $\text{C}_{17}\text{H}_{13}\text{ClF}_6\text{N}_6\text{O}$: 467.0477 $[\text{M}+1]^+$; found: 467.0459; $[\text{M}+1]^+$; 469.0448; $[\text{M}+1+2]^+$; Elemental analysis: Calcd. for $\text{C}_{17}\text{H}_{13}\text{ClF}_6\text{N}_6\text{O}$: C, 43.74; H, 2.81; N, 18.00% Found: C, 43.63; H, 2.70; N, 17.92%.

4-(2-(2-Chlorophenyl)hydrazono)-1-(4,6-dimethylpyrimidin-2-yl)-5-hydroxy-3,5-bistrifluoromethylpyrazoline 15d

M. Pt. 145°C, Yield 77%, IR (KBr, cm^{-1}): 3553, 3212, 2154, 1658, 1646, 1609; ^1H NMR (400 MHz, CDCl_3) δ : 9.33 (s, 1H, N-H); 7.281 (m, 1H, 4''-H); 7.185 (t, 1H, $J = 2.0\text{Hz}$, 4''-H); 7.01-7.05 (m, 2H, $J = 8.0\text{Hz}$, 3'', 5''-H); 6.77 (s, 1H, 5'-H); 2.49 (s, 6H, 4', 6'- CH_3); ^{13}C NMR (100

MHz, CDCl₃): 157.70, 143.20, 135.48, 130.59, 128.92, 120.697, 117.999, 115.42, 114.36, 112.42, 24.11; MS (EI) m/z: calcd. for C₁₇H₁₃ClF₆N₆O: 467.0477 [M+1]⁺; found: 467.0459; [M+1]⁺; 469.0448; [M+1+2]⁺; Elemental analysis: Calcd. for C₁₇H₁₃ClF₆N₆O: C, 43.74; H, 2.81; N, 18.00% Found: C, 43.63; H, 2.70; N, 17.92%.

1-(4,6-Dimethylpyrimidin-2-yl)-4-(2-phenylhydrazono)-5-hydroxy-3,5-bistrifluoromethylpyrazoline 15e

M. Pt. 105°C, Yield 85%, IR (KBr, cm⁻¹): 3555, 3216, 2157, 1660, 1641, 1611; ¹H NMR (400 MHz, CDCl₃) δ: 9.36 (s, 1H, N-H); 7.37-7.32 (m, 2H, 2'',6''-H); 7.19-7.16 (m, 2H, 3'',5''-H); 7.08-7.04 (m, 1H, 4''H); 6.76 (s, 1H, 5'-H); 2.48 (s, 6H, 4', 6'-CH₃); 1.61 (s, 1H, O-H); ¹³C NMR (100 MHz, CDCl₃): 157.77, 141.95, 129.49, 127.49, 123.50, 115.16, 114.18, 24.03; MS (EI) m/z: calcd. for C₁₇H₁₄F₆N₆O: 433.1133 [M+1]⁺; found: 433.1125; [M+1]; Elemental analysis: Calcd. for C₁₇H₁₄F₆N₆O: C, 47.23; H, 3.26; N, 19.44% Found: C, 47.18; H, 3.12; N, 19.38%.

1-(4,6-Dimethylpyrimidinyl)-4-(4-methylphenylazo)-3,5-bistrifluoromethylpyrazole 9a.

M. Pt. 125°C, Yield 85%, IR (KBr, cm⁻¹): 2155, 1664, 1638, 1613; ¹H NMR (400 MHz, CDCl₃) δ: 7.84-7.86 (d, 2H, J = 8Hz, 2'',6''-H); 7.53-7.55 (d, 2H, J = 8Hz, 3'',5''-H); 7.20 (s, 1H, 5'-H); 2.62 (s, 6H, 4', 6'-CH₃); 2.45 (s, 3H, 4''-CH₃); ¹³C NMR (100 MHz, CDCl₃): 169.96, 143.55, 129.93, 123.45, 120.88, 23.92, 21.76; ¹⁹F NMR (376 MHz, CDCl₃): -61.92, -55.60; MS (EI) m/z: calcd. for C₁₈H₁₄F₆N₆: 429.1184 [M+1]⁺; found: 429.1241 [M+1]⁺; Elemental analysis: Calcd. for C₁₈H₁₄F₆N₆: C, 50.47; H, 3.29; N, 19.62% Found: C, 50.32; H, 3.16; N, 19.45%.

1-(4,6-Dimethylpyrimidinyl)-4-(4-chlorophenylazo)-3,5-bistrifluoromethylpyrazole 9b.

M. Pt. 154°C, Yield 87%, IR (KBr, cm⁻¹): 2152, 1667, 1637, 1618;; ¹H NMR (400 MHz, CDCl₃) δ: 7.88-7.90 (d, 2H, J = 8Hz, 2'',6''-H); 7.50-7.52 (d, 2H, J = 8Hz, 3'',5''-H); 7.21 (s, 1H, 5'-H); 2.63 (s, 6H, 4', 6'-CH₃); ¹³C NMR (100 MHz, CDCl₃): 177.87, 173.47, 170.03, 129.61, 124.63, 121.01, 23.92; ¹⁹F NMR (376 MHz, CDCl₃): -62.09, -55.61; MS (EI) m/z: calcd. for C₁₇H₁₁ClF₆N₆: 449.0638 [M+1]⁺; found: 449.0615 [M+1]⁺, 451.0626 [M+3]⁺; Elemental analysis: Calcd. for C₁₇H₁₁ClF₆N₆: C, 45.50; H, 2.47; N, 18.73% Found: C, 45.34; H, 2.31; N, 18.56%.

1-(4,6-Dimethylpyrimidinyl)-4-(3-chlorophenylazo)-3,5-bistrifluoromethylpyrazole 9c.

M. Pt. 145°C, Yield 84%, IR (KBr, cm⁻¹): 2159, 1658, 1642, 1619; ¹H NMR (400 MHz, CDCl₃) δ: 7.90-7.91 (s, 1H, 4''-H); 7.84-7.87 (s, 1H,

5''-H); 7.46-7.53 (m, 2H, 2'', 6''-H); 7.22 (s, 1H, 5'-H); 2.63 (s, 6H, 4', 6'-CH₃); ¹³C NMR (100 MHz, CDCl₃): 170.05, 153.27, 135.41, 132.49, 130.36, 122.61, 122.46, 121.05, 23.91; ¹⁹F NMR (376 MHz, CDCl₃): -62.14, -55.60 MS (EI) m/z: calcd. for C₁₇H₁₁ClF₆N₆: 449.0638 [M+1]⁺; found: 449.0615 [M+1]⁺, 451.0626 [M+3]⁺; Elemental analysis: Calcd. for C₁₇H₁₁ClF₆N₆: C, 45.50; H, 2.47; N, 18.73% Found: C, 45.34; H, 2.31; N, 18.56%.

1-(4,6-Dimethylpyrimidinyl)-4-(2-chlorophenylazo)-3,5-bistrifluoromethylpyrazole 9d.

M. Pt. 148°C, Yield 82%, IR (KBr, cm⁻¹): 2156, 1654, 1639, 1609; ¹H NMR (400 MHz, CDCl₃) δ: 7.72-7.74 (dd, 1H, J₁ = 8 Hz, J₂ = 1.6 Hz, 6''-H); 7.58-7.60 (dd, 1H, J₁ = 8 Hz, J₂ = 1.2 Hz, 3''-H); 7.43-7.47 (td, 1H, J₁ = 8 Hz, J₂ = 1.6 Hz, 4''-H); 7.33-7.37 (td, 1H, J₁ = 8 Hz, J₂ = 1.2 Hz, 5''-H); 7.21 (s, 1H, 5'-H); 2.63 (s, 6H, 4', 6'-CH₃); ¹³C NMR (100 MHz, CDCl₃): 170.03, 155.73, 148.95, 137.12, 133.34, 131.19, 127.28, 121.03, 117.39, 23.90; ¹⁹F NMR (376 MHz, CDCl₃): -62.33, -55.70; MS (EI) m/z: calcd. for C₁₇H₁₁ClF₆N₆: 449.0638 [M+1]⁺; found: 449.0615 [M+1]⁺, 451.0626 [M+3]⁺; Elemental analysis: Calcd. for C₁₇H₁₁ClF₆N₆: C, 45.50; H, 2.47; N, 18.73% Found: C, 45.34; H, 2.31; N, 18.56%.

1-(4,6-Dimethylpyrimidinyl)-4-(4-nitrophenylazo)-3,5-bistrifluoromethylpyrazole 9e.

M. Pt. 168°C, Yield 87%, IR (KBr, cm⁻¹): 2159, 1658, 1556, 1642, 1619, 1352; ¹H NMR (400 MHz, CDCl₃) δ: 8.40-8.42 (d, 2H, J = 8Hz, 2'', 6''-H); 8.06-8.08 (d, 2H, J = 8Hz, 3'', 5''-H); 7.24 (s, 1H, 5'-H); 2.64 (s, 6H, 4', 6'-CH₃); ¹³C NMR (100 MHz, CDCl₃): 170.15, 155.31, 152.86, 149.65, 124.90, 123.98, 121.22, 23.92; ¹⁹F NMR (376 MHz, CDCl₃): -62.65, -55.87; MS (EI) m/z: calcd. for C₁₇H₁₁F₆N₇O₂: 460.3124 [M+1]⁺; found: 460.3089 [M+1]⁺; Elemental analysis: Calcd. for C₁₇H₁₁F₆N₇O₂: C, 44.45; H, 2.41; N, 21.35% Found: C, 44.34; H, 2.28; N, 21.16%.

1-(4,6-Dimethylpyrimidinyl)-4-phenylazo-3,5-bistrifluoromethylpyrazole 9f.

M. Pt. 110°C, Yield 90%, IR (KBr, cm⁻¹): 2157, 1655, 1628, 1600; ¹H NMR (400 MHz, CDCl₃) δ: 7.94-7.97 (m, 2H, 2'', 6''-H); 7.53-7.55 (m, 3H, 3'', 4'', 5''-H); 7.21 (s, 1H, 5'-H); 2.63 (s, 6H, 4', 6'-CH₃); ¹³C NMR (100 MHz, CDCl₃): 169.92, 152.48, 132.55, 129.21, 123.34, 120.89, 23.85; ¹⁹F NMR (376 MHz, CDCl₃): -62.01, -55.60; MS (EI) m/z: calcd. for C₁₇H₁₂F₆N₆: 415.1028 [M+1]⁺; found: 415.1019 [M+1]⁺;

Elemental analysis: Calcd. for $C_{17}H_{12}F_6N_6$: C, 49.28; H, 2.92; N, 20.28% Found: C, 49.15; H, 2.81; N, 20.04%.

1-(6'-Methylbenzothiazol-2'-yl)-4-(4''-chlorophenylazo)-3,5-bistrifluoromethylpyrazole 10a.

M. Pt. 209°C, Yield 77%, IR (KBr, cm^{-1}): 1656, 1573, 1446, 1233, 1135; 1H NMR (400 MHz, $CDCl_3$) δ : 7.94–7.96 (d, 1H, $J = 8.0$ Hz, 4'-H); 7.89–7.91 (d, 2H, $J = 8.0$ Hz, 3'',5''-H); 7.70 (s, 1H, 7'-H); 7.51–7.53 (d, 2H, $J=8.0$ Hz, 2'',6''-H); 7.37–7.39 (d, 1H, $J=8.0$ Hz, 5'-H); 2.53 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 150.75, 148.2, 139.0, 137.1, 134.3, 129.6, 128.7, 124.6, 123.7, 121.2, 21.7; MS (EI) m/z : : calcd for $C_{19}H_{10}ClF_6N_5S$: 490.0250 $[M+1]^+$; found: 490.0239, $[M+1]^+$, 492.0234, $[M+1+2]^+$ (3:1); Elemental analysis: Calcd. for $C_{19}H_{10}ClF_6N_5S$: C, 46.59; H, 2.06; N, 14.30% Found: C, 46.12; H, 1.65; N, 13.73 %.

1-(6'-Methylbenzothiazol-2'-yl)-4-(3''-chlorophenylazo)-3,5-bistrifluoromethylpyrazole 10b.

M. Pt. 153°C, Yield 75%, IR (KBr, cm^{-1}): 1653, 1570, 1443, 1235, 1134; 1H NMR (400 MHz, $CDCl_3$) δ : 7.94–7.96 (d, 1H, $J = 8.0$ Hz, 4'-H); 7.90–7.91 (m, 1H, 6''-H); 7.85–7.88 (m, 1H, 3''-H); 7.70–7.71 (t, 1H, $J = 0.8$ Hz, 7'-H); 7.48–7.55 (m, 2H, 2'',4''-H); 7.37–7.40 (m, 1H, 5'-H); 2.53 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 153.1, 148.3, 137.1, 135.4, 134.4, 132.5, 130.5, 128.7, 123.8, 122.6, 122.5, 121.3, 21.7; MS (EI) m/z : calcd for $C_{19}H_{10}ClF_6N_5S$: 490.0250 $[M+1]^+$; found: 490.0239, $[M+1]^+$, 492.0234, $[M+1+2]^+$ (3:1); Elemental analysis: Calcd. for $C_{19}H_{10}ClF_6N_5S$: C, 46.59; H, 2.06; N, 14.30% Found: C, 46.21; H, 1.71; N, 13.90 %.

1-(6'-Methylbenzothiazol-2'-yl)-4-(2''-chlorophenylazo)-3,5-bistrifluoromethylpyrazole 10c.

M. Pt. 160°C, Yield 73%, IR (KBr, cm^{-1}): 1655, 1580, 1456, 1250, 1134; 1H NMR (400 MHz, $CDCl_3$) δ : 7.59–7.61 (d, 1H, $J=8.0$ Hz, 4'-H); 7.54–7.56 (m, 2H, 4'',5''-H); 7.33–7.36 (m, 1H, 7'-H); 7.28–7.32 (m, 1H, 6''-H); 7.22–7.25 (m, 1H, 3''-H); 6.96–7.03 (m, 1H, 5'-H); 2.45 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 161.7, 147.4, 137.9, 134.4, 130.4, 129.4, 129.0, 128.2, 128.0, 124.2, 123.9, 121.3, 120.5, 119.7, 115.0, 21.4; MS (EI) m/z : calcd for $C_{19}H_{10}ClF_6N_5S$: 489.0250; found: 491.0239 $[M+1]^+$, $[M+1]^+$, 492.0234, $[M+1+2]^+$ (3:1); Elemental analysis: Calcd. for $C_{19}H_{10}ClF_6N_5S$: C, 46.59; H, 2.06; N, 14.30% Found: C, 46.23; H, 1.77; N, 13.84 %.

1-(6'-Methylbenzothiazol-2'-yl)-4-(4''-bromophenylazo)-3,5-bistrifluoromethylpyrazole 10d.

M. Pt. 225°C, Yield 77%, IR (KBr, cm^{-1}): 1659, 1575, 1445, 1236, 1134; ^1H NMR (400 MHz, CDCl_3) δ : 7.94–7.96 (d, 1H, $J=8.0$ Hz, 4'-H); 7.81–7.83 (d, 2H, $J=8.0$ Hz, 3'',5''-H); 7.69–7.70 (m, 3H, $J=8.0$ Hz, 7',2'',6''-H); 7.37–7.39 (d, 1H, $J=8.0$ Hz, 5'-H); 2.53 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): 151.1, 148.2, 137.1, 134.3, 132.6, 128.7, 127.7, 124.8, 123.7, 121.2, 21.7; MS (EI) m/z : calcd for $\text{C}_{19}\text{H}_{10}\text{BrF}_6\text{N}_5\text{S}$: 535.9724 $[\text{M}+1]^+$; Found: 535.9708 $[\text{M}+1]$; 537.9699, $[\text{M}+1+2]^+$ (1:1); Elemental analysis: Calcd. for $\text{C}_{19}\text{H}_{10}\text{BrF}_6\text{N}_5\text{S}$: C, 42.71; H, 1.89; N, 13.11% Found: C, 42.32; H, 1.51; N, 12.77 %.

1-Phenyl-4-phenylazo-3,5-bistrifluoromethylpyrazole 11a.

M. Pt. 108°C, Yield 81%, IR (KBr, cm^{-1}): 1650, 1565, 1438, 1220; ^1H NMR (400 MHz, CDCl_3) δ : 7.59–7.62 (m, 3H, 2',6',4'-H), 7.34–7.37 (m, 2H, 2'',6''-H), 7.19–7.24 (m, 4H, 3',5',3'',5''-H), 7.00–7.03 (m, 1H, 4''-H); ^{13}C NMR (100 MHz, CDCl_3): 152.8, 142.8, 138.9, 130.6, 130.1, 129.7, 129.5, 129.2, 129.1, 127.1, 126.5, 125.9, 123.1; MS (EI) m/z : calcd for $\text{C}_{17}\text{H}_{10}\text{F}_6\text{N}_4$: 385.0810 $[\text{M}+1]^+$; Found: 385.0770 $[\text{M}+1]^+$; Elemental analysis: Calcd. for $\text{C}_{17}\text{H}_{10}\text{F}_6\text{N}_4$: C, 53.13; H, 2.62; N, 14.585% Found: C, 52.81; H, 2.29; N, 13.87 %.

1-Phenyl-4-(4-methylphenylazo)-3,5-bistrifluoromethylpyrazole 11b.

M. Pt. 125°C, Yield 75%, IR (KBr, cm^{-1}): 1696, 1589, 1389, 1227, 1134; ^1H NMR (400 MHz, CDCl_3) δ : 7.82–7.84 (d, 2H, $J = 8.0$ Hz, 3'',5''-H); 7.51–7.56 (m, 5H, 2',3',4',5',6'-H); 7.31–7.33 (d, 2H, $J = 8.0$ Hz, 2'',6''-H); 2.44 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): 150.82, 143.43, 138.65, 134.25, 130.05, 129.95, 129.48, 129.45, 129.43, 126.0, 123.36, 123.33, 123.30, 21.7; MS (EI) m/z : calcd for $\text{C}_{18}\text{H}_{12}\text{F}_6\text{N}_4$: 400.0966 $[\text{M}+1]^+$; found: 399.0954 $[\text{M}+1]^+$; Elemental analysis: Calcd. for $\text{C}_{18}\text{H}_{12}\text{F}_6\text{N}_4$: C, 54.28; H, 3.04; F, N, 14.07% Found: C, 53.91; H, 2.89; N, 13.69 %.

Biological activity**Materials and methods**

The chemicals and materials like Dimethylsulphoxide (DMSO), ethidium bromide (EtBr), ethylenediaminetetraacetic acid (EDTA) were directly purchased from Sigma Aldrich, USA. Stock solutions of the compounds, with concentration of 20 mg/ml, in DMSO were

prepared. The solutions were stored in brown containers in a refrigerator. All the gel electrophoresis experiments were carried out in TAE buffer (0.04 M Trisborate, 0.114% acetic acid and 50 mM EDTA, pH 8.0).

Antimicrobial activity

Antimicrobial study of the tested compounds was assessed by Minimum Inhibitory Concentration (MIC) through serial dilution method³¹. The microorganisms like *Pseudomonas argunosa* (ATCC 15442), *Bacillus cereus* (ATCC 11770), *Escherichia coli* (MTCC 143), *Listeria monocytogenes* (MTCC 657), *Salmonella typhi* (MTCC 733), *Staphylococcus aureus* (ATCC 6538P), and *Shigella flexneri* (ATCC 9199) and one fungal strain *Candida albicans* (MTCC 183) were used for investigating the antimicrobial potential of compounds. The standard drugs used for the antibacterial and antifungal activities were amoxycillin and Fluconazole respectively. Colonies of microorganisms were picked off freshly from isolation plate and were inoculated in corresponding tubes containing 5 ml of brain heart infusion broth. This broth was incubated for 6 h at 37°C. The Mc Farland No. 5 standard was prepared by adding 0.05 mL of 1% w/v BaCl₂.2H₂O in Phosphate Buffered saline (PBS) to 9.95 ml of 1% v/v H₂SO₄ in PBS. The growth of all the cultures was adjusted to Mc Farland No. 5 turbidity standard using sterile PBS to achieve 10⁸ cfu/ml suspension. The working inoculums of aforementioned different microorganisms containing 10⁵ cfu/ml suspension was prepared by diluting the 10⁸ cfu/ml suspension, 10³ times in Brain heart infusion broth.

Toxicity Studies

Cell culture: Mouse Fibroblast cells were cultured in Dulbecco's Modified Eagle Medium (DMEM). The cells were supplemented with 10% foetal serum albumin along with 50 µg per mL of penicillin and streptomycin each. However, Plant Seed Germination cells were cultured in Roswell Park Memorial Institute medium (RPMIM). These lymphocytic leukemia cell lines were also supplemented with 10% foetal serum albumin and 1% of gentamycin. All the cell lines were kept in an incubator containing 5% CO₂ at 37°C for 5-10 minutes.

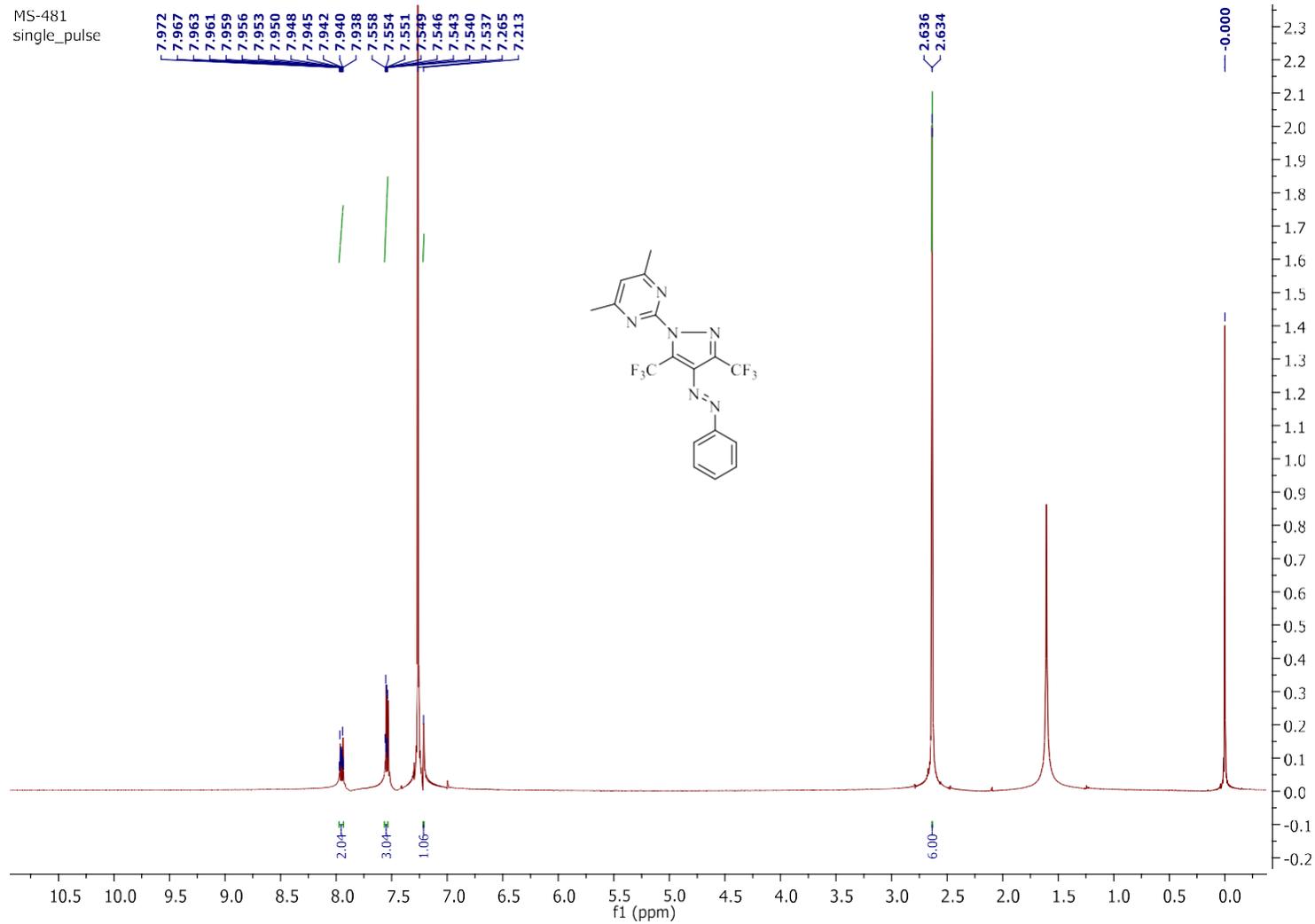
Cell viability assay: The cells under consideration were seeded in a 96-well plate at a density of 10⁵ per ml and were grown throughout the night. The cells were treated with test compounds at a concentration of 1mg/ml and were incubated for 24 h at 37°C, 5% CO₂ in

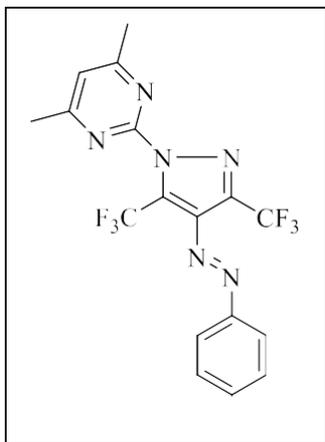
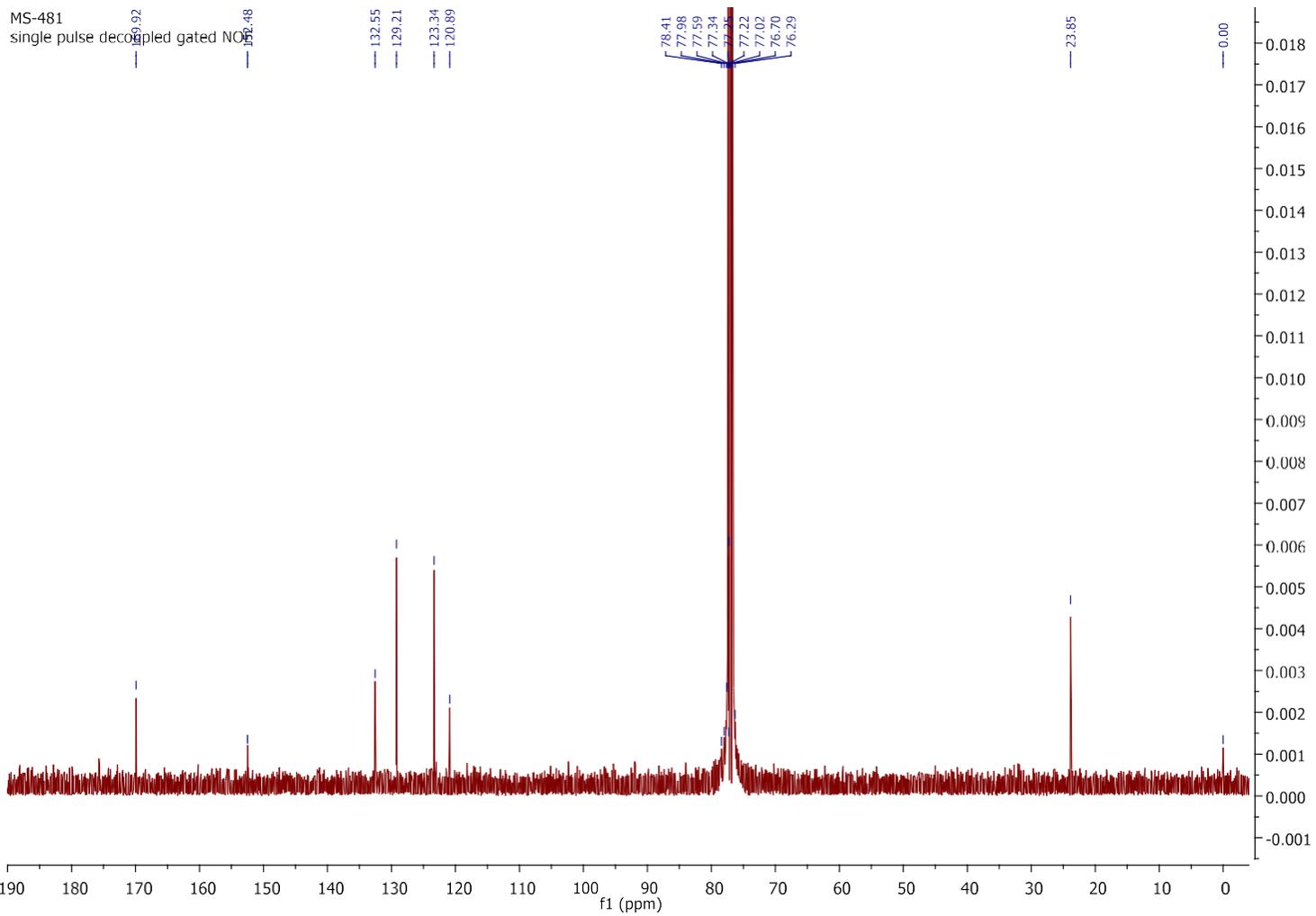
air. The cell viability assay was performed with MTT cell proliferation kit from American Type Culture Collection (ATCC) (#30-1010K). At the end, 10 μ L of MTT reagent was added to the well followed by placing the cells back in incubator for another 4 h. Subsequently, the absorbance at 570 nm was measured using a UV–visible spectrophotometer. MTT assays were repeated in three separate experiments. Data was processed for calculation of % cell survival with help of following formula:

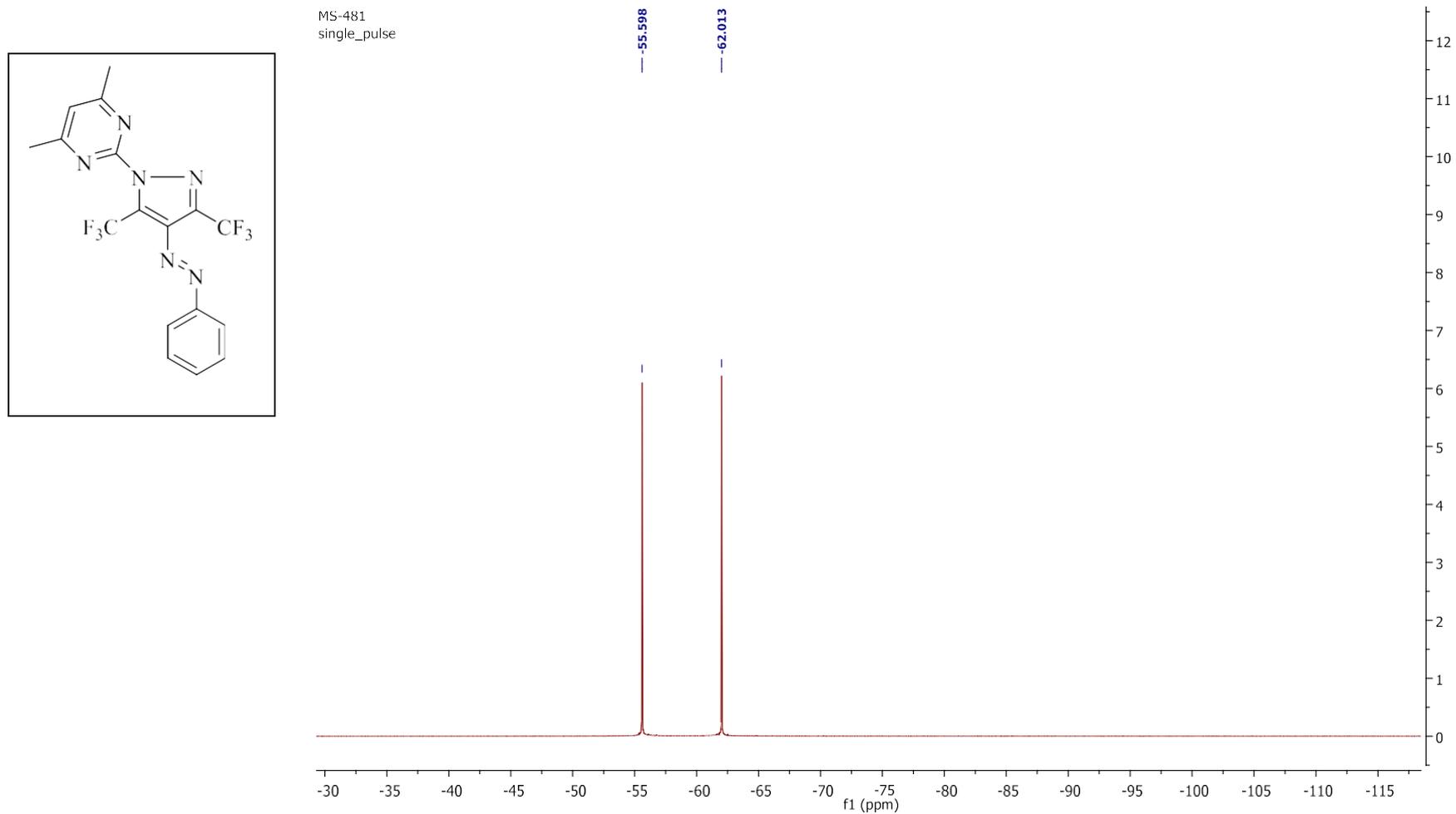
$$\% \text{ Cell survival} = (100/A_t \times A_s)$$

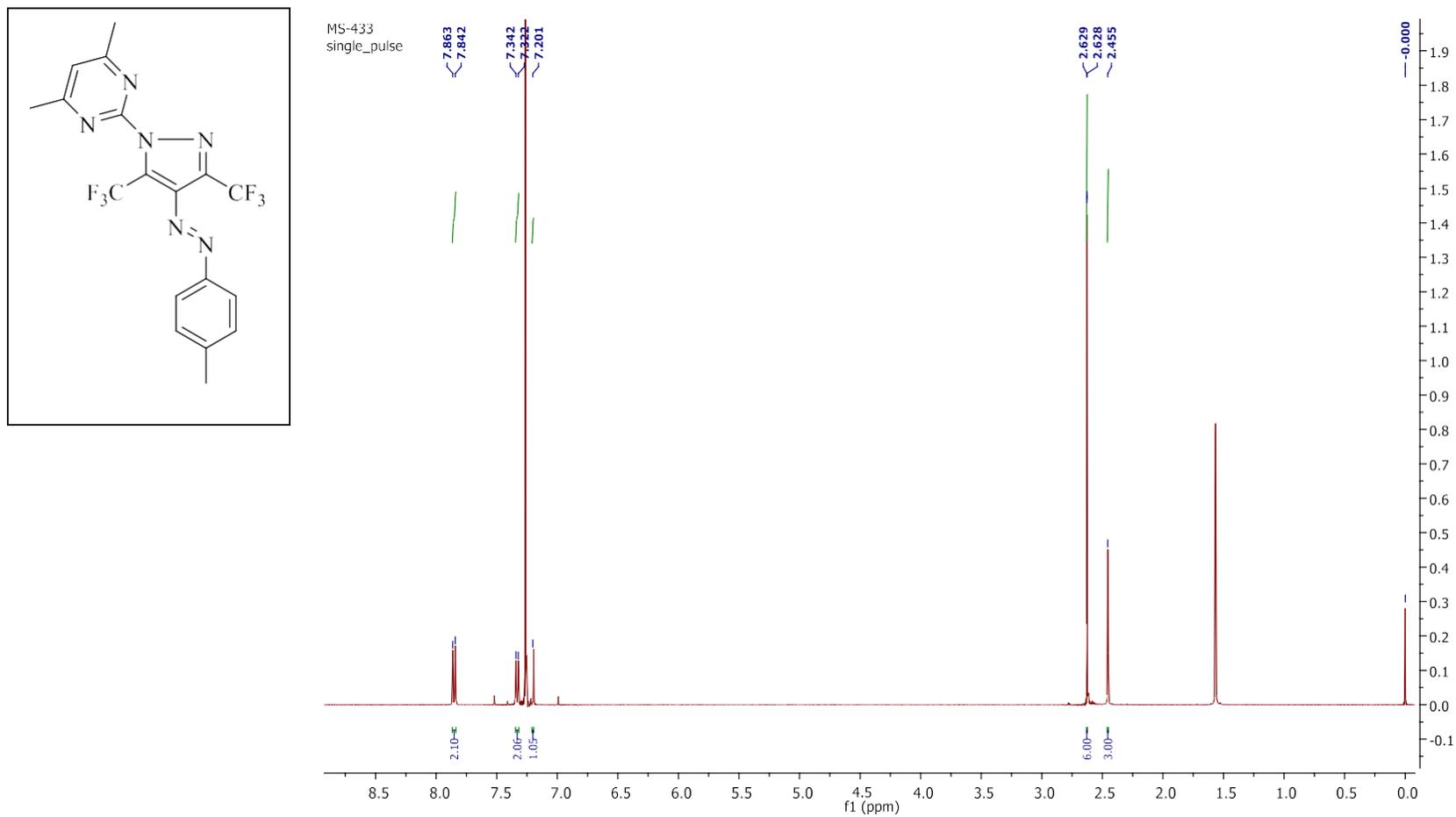
At- Absorbance of wells treated with test compounds.

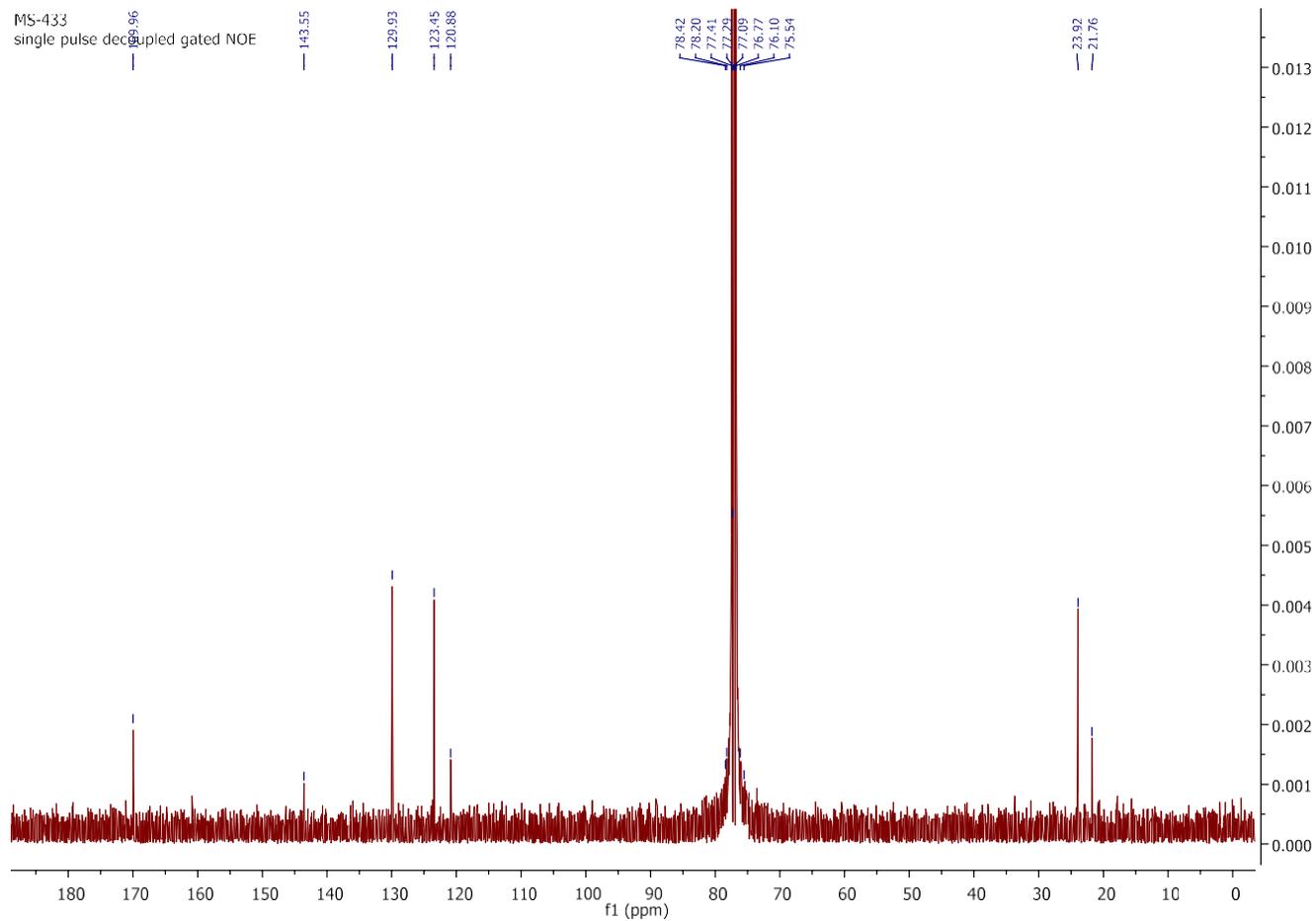
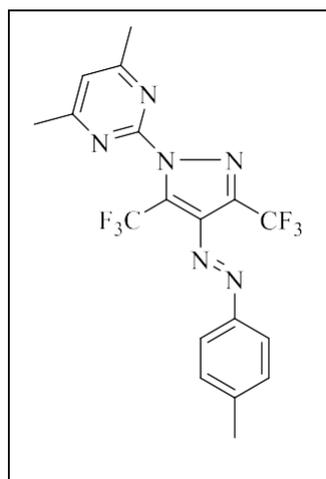
As-Absorbance of wells treated with solvent control.

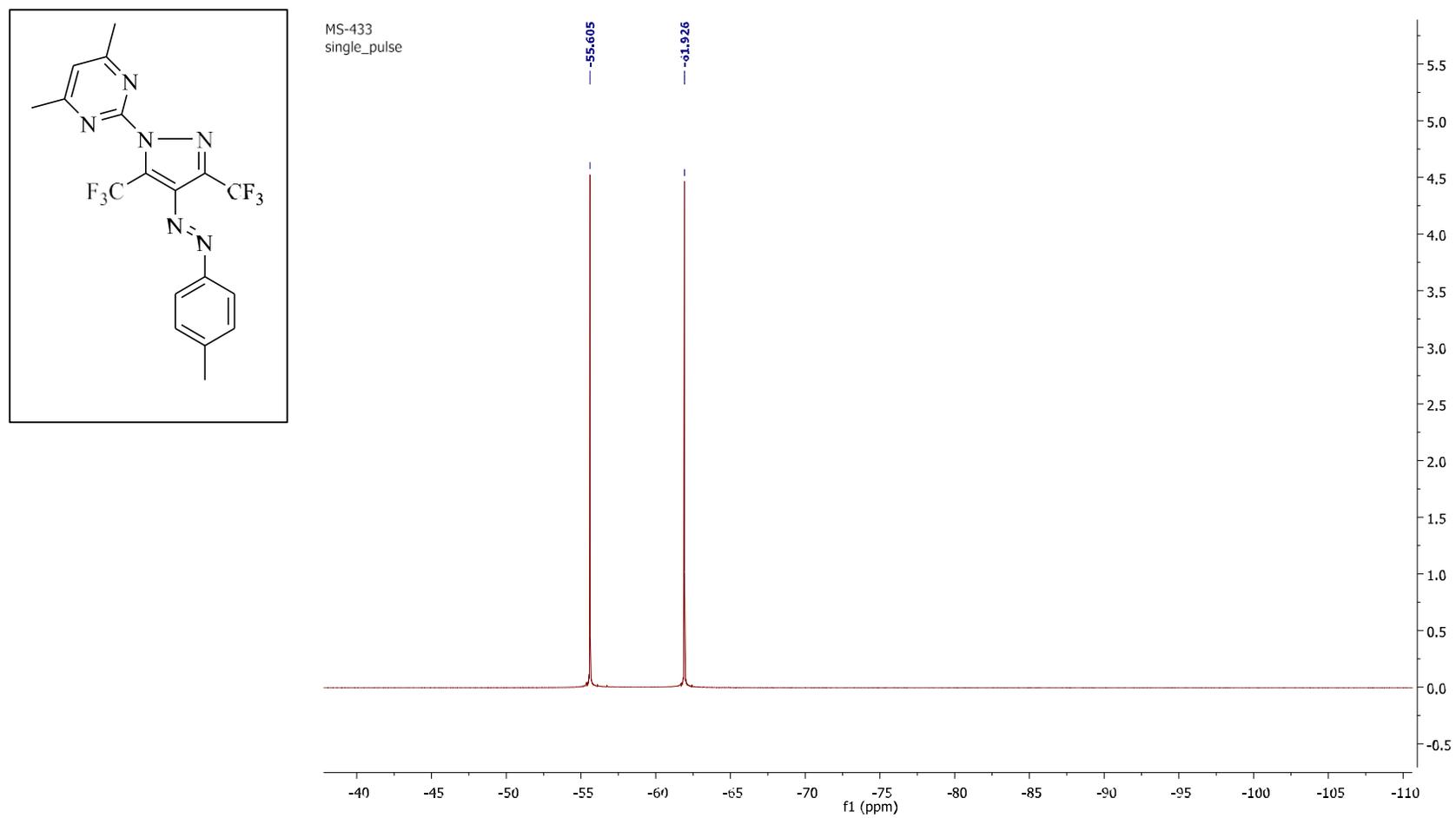




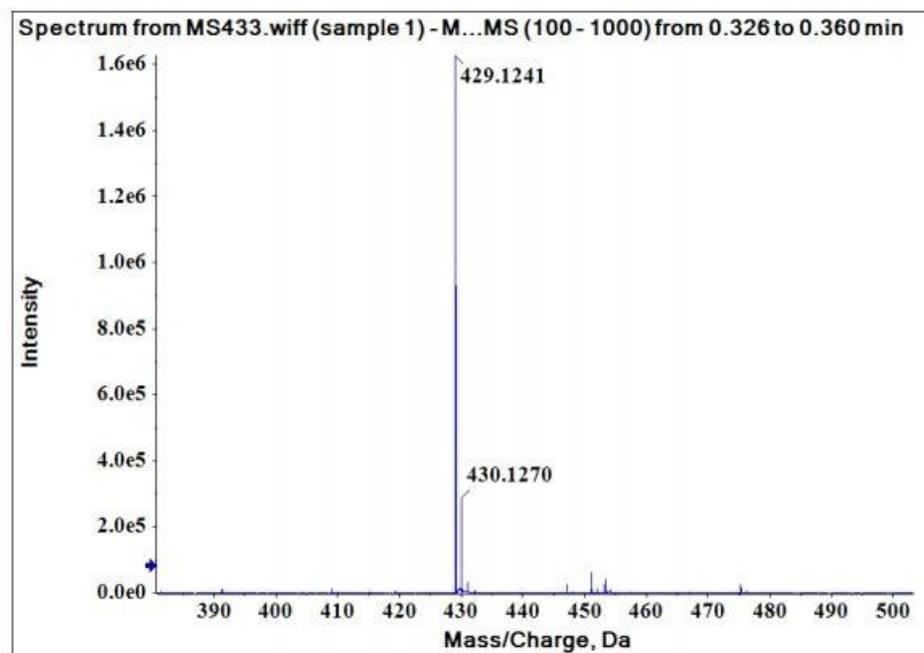
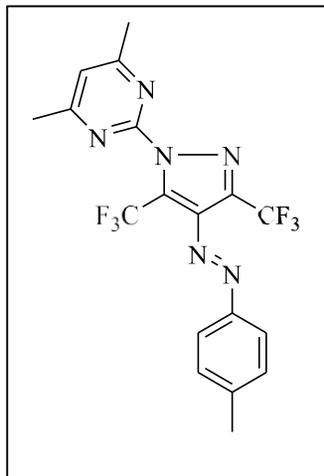
^{19}F -NMR spectra of 1-(4,6-dimethylpyrimidinyl)-4-Phenylazo-3,5-bistrifluoromethylpyrazole

¹H-NMR spectra of 1-(4,6-dimethylpyrimidinyl)-4-(4-methylphenylazo)-3,5-bistrifluoromethylpyrazole

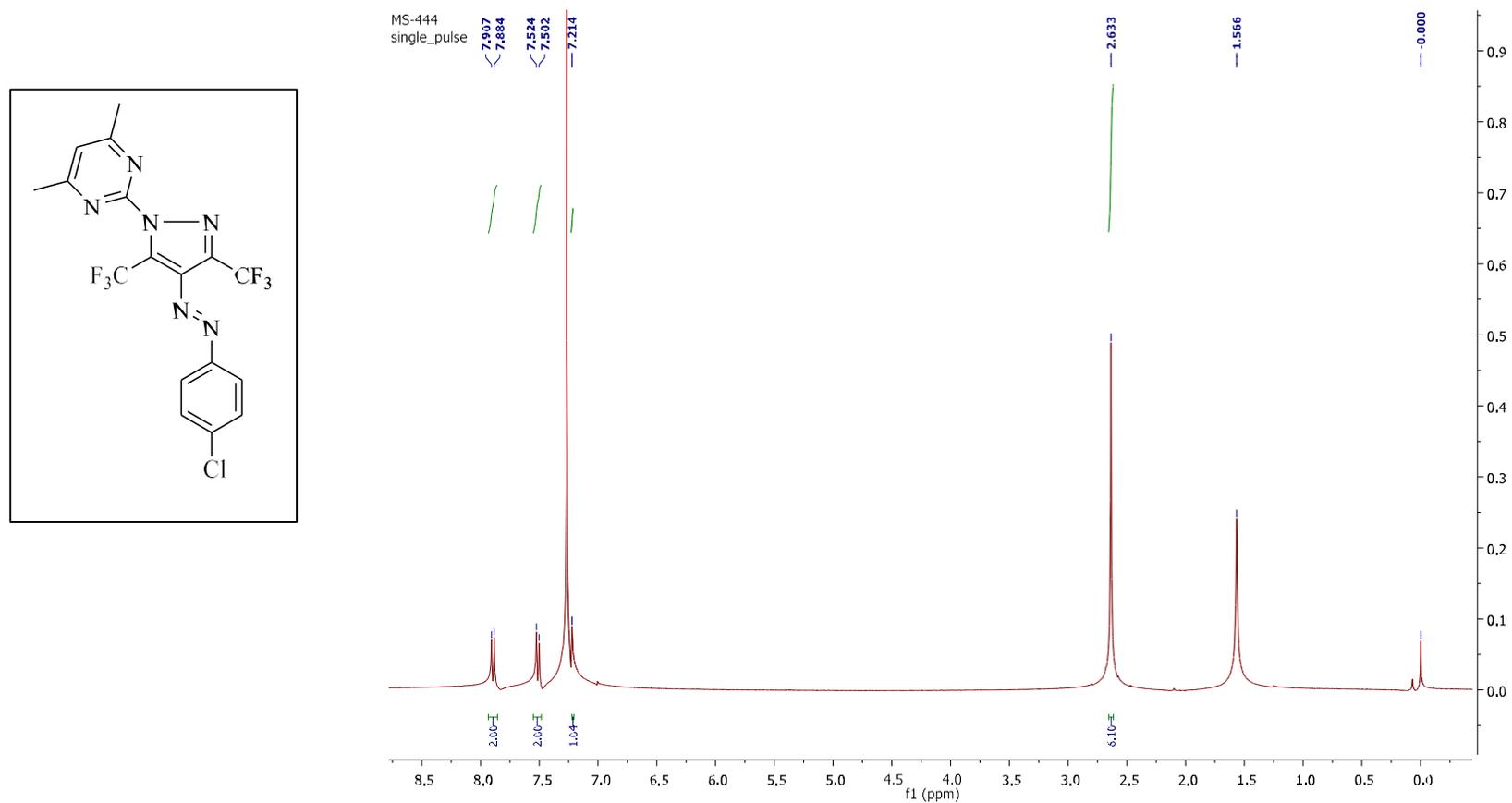
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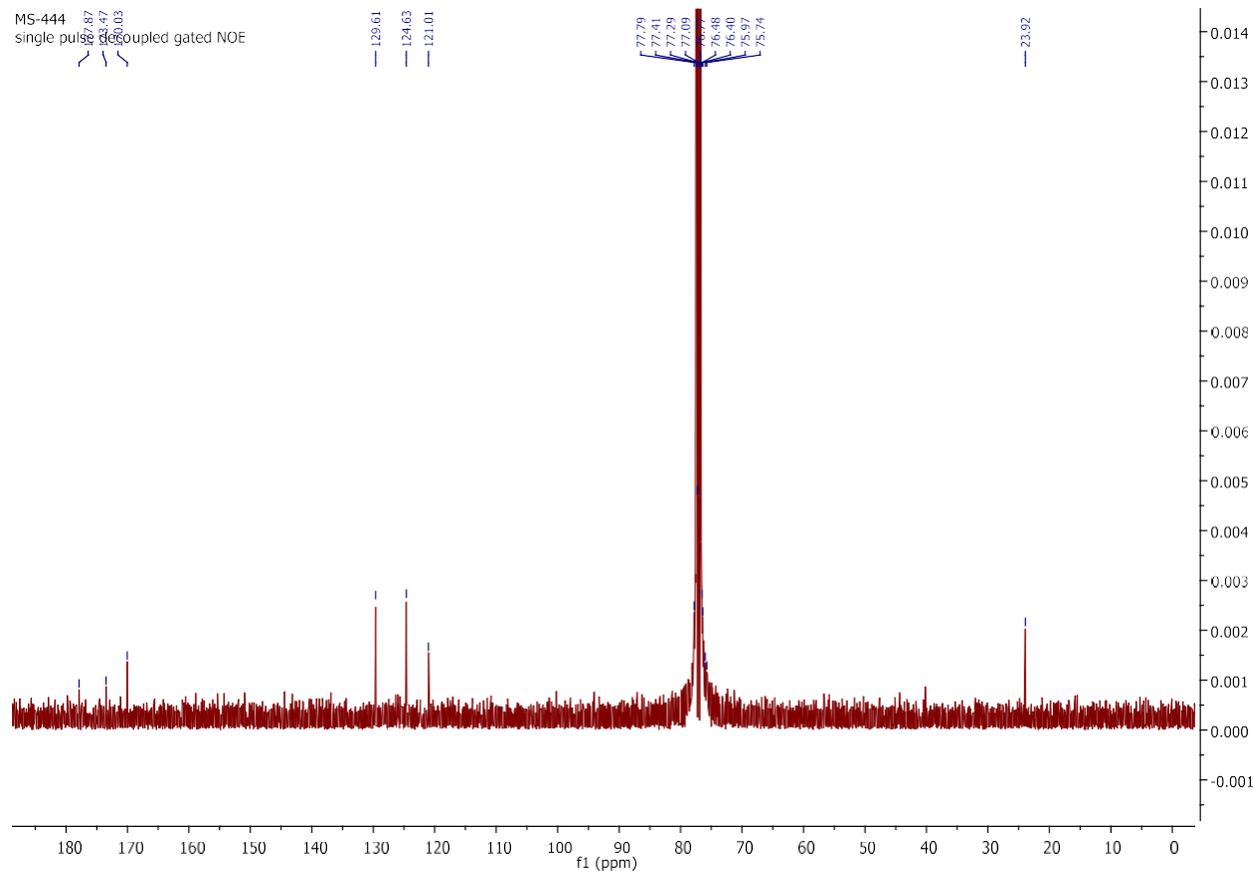
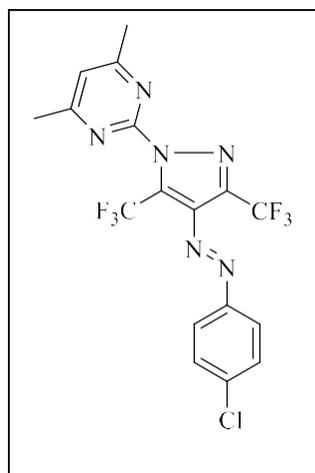
^{19}F -NMR spectra of 1-(4,6-dimethylpyrimidinyl)-4-(4-methylphenylazo)-3,5-bistrifluoromethylpyrazole

Mass spectra of 1-(4,6-dimethylpyrimidinyl)-4-(4-methylphenylazo)-3,5-bistrifluoromethylpyrazole



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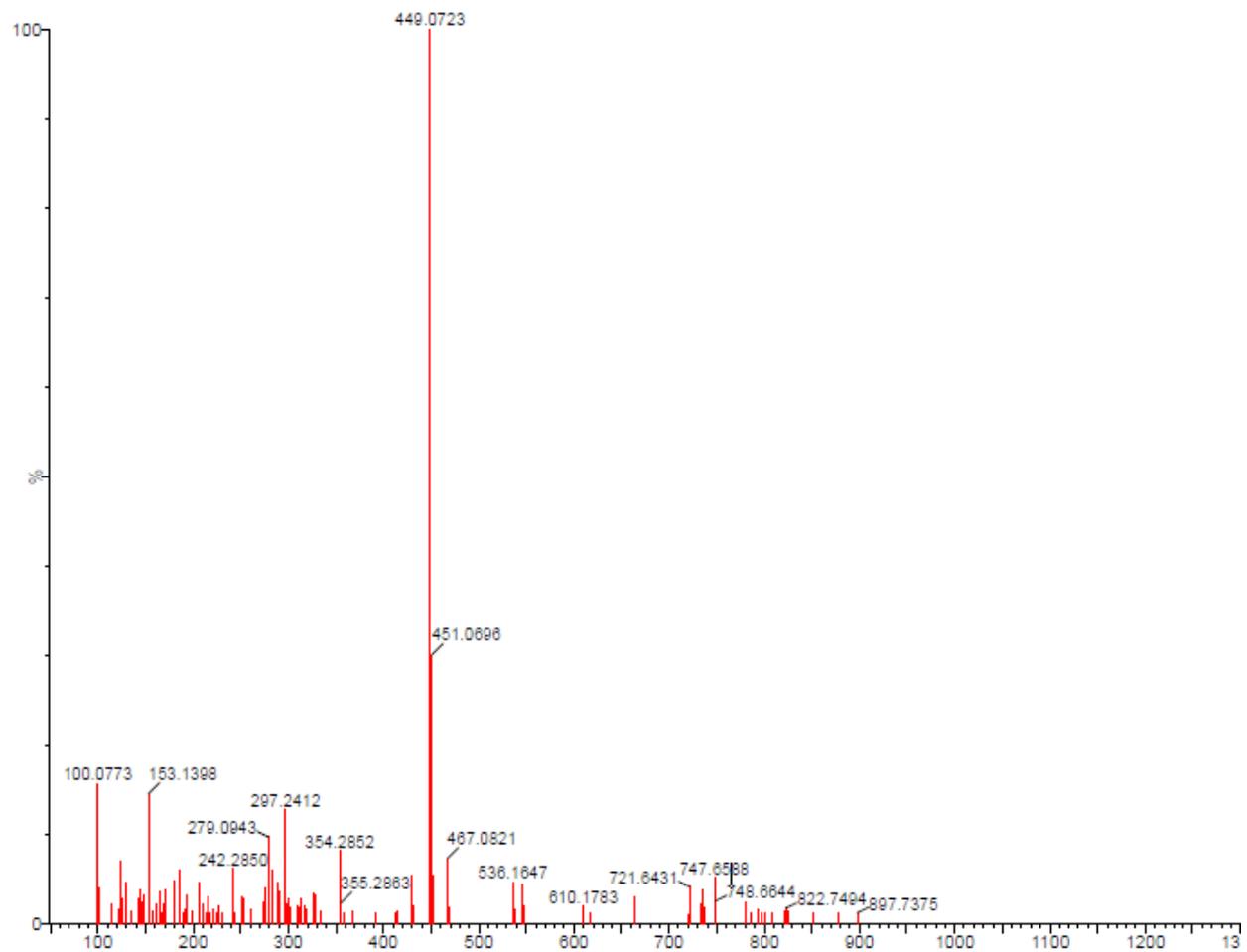
$^1\text{H-NMR}$ spectra of 1-(4,6-dimethylpyrimidinyl)-4-(4-chlorophenylazo)-3,5-bistrifluoromethylpyrazole

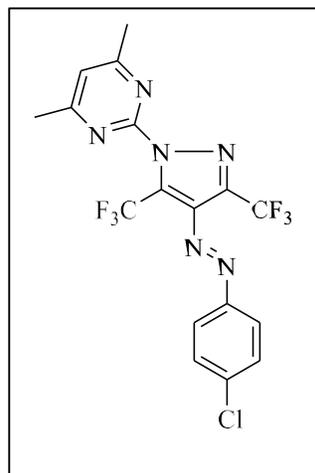
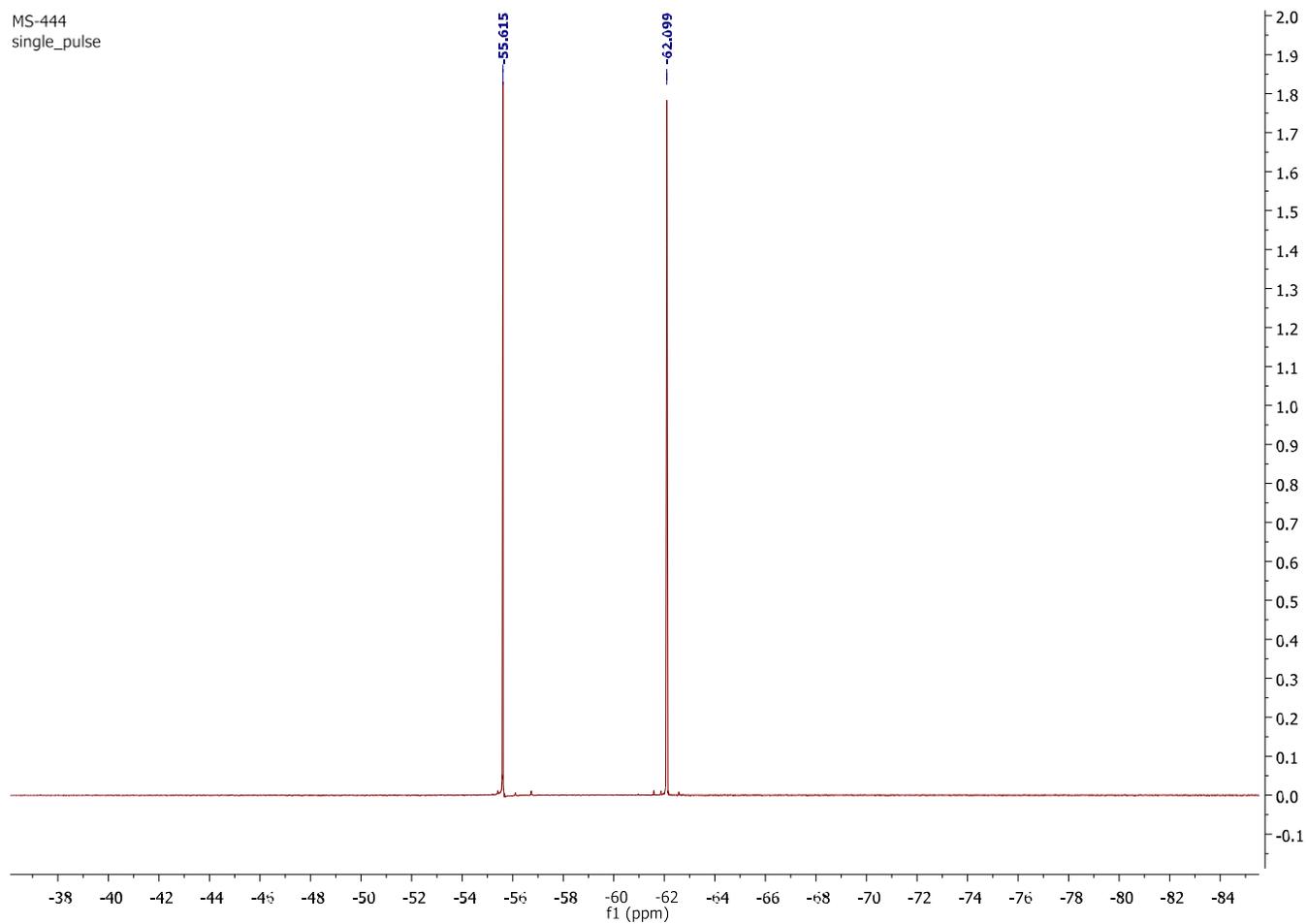
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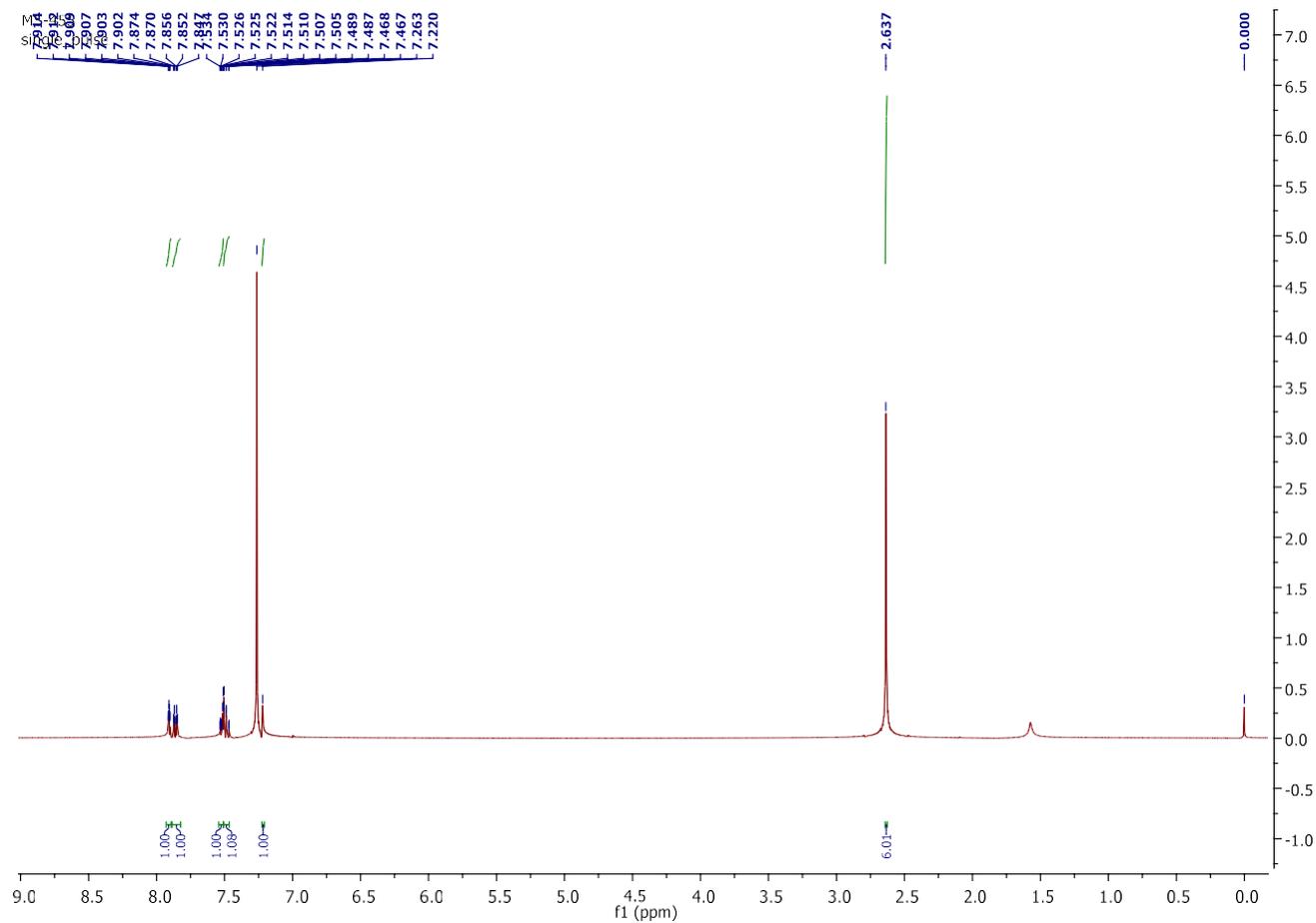
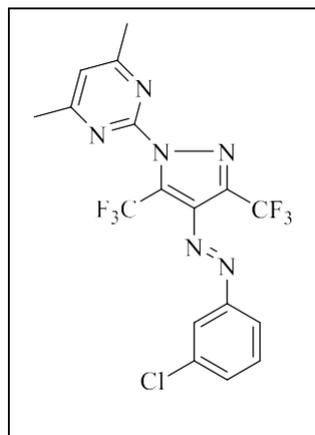
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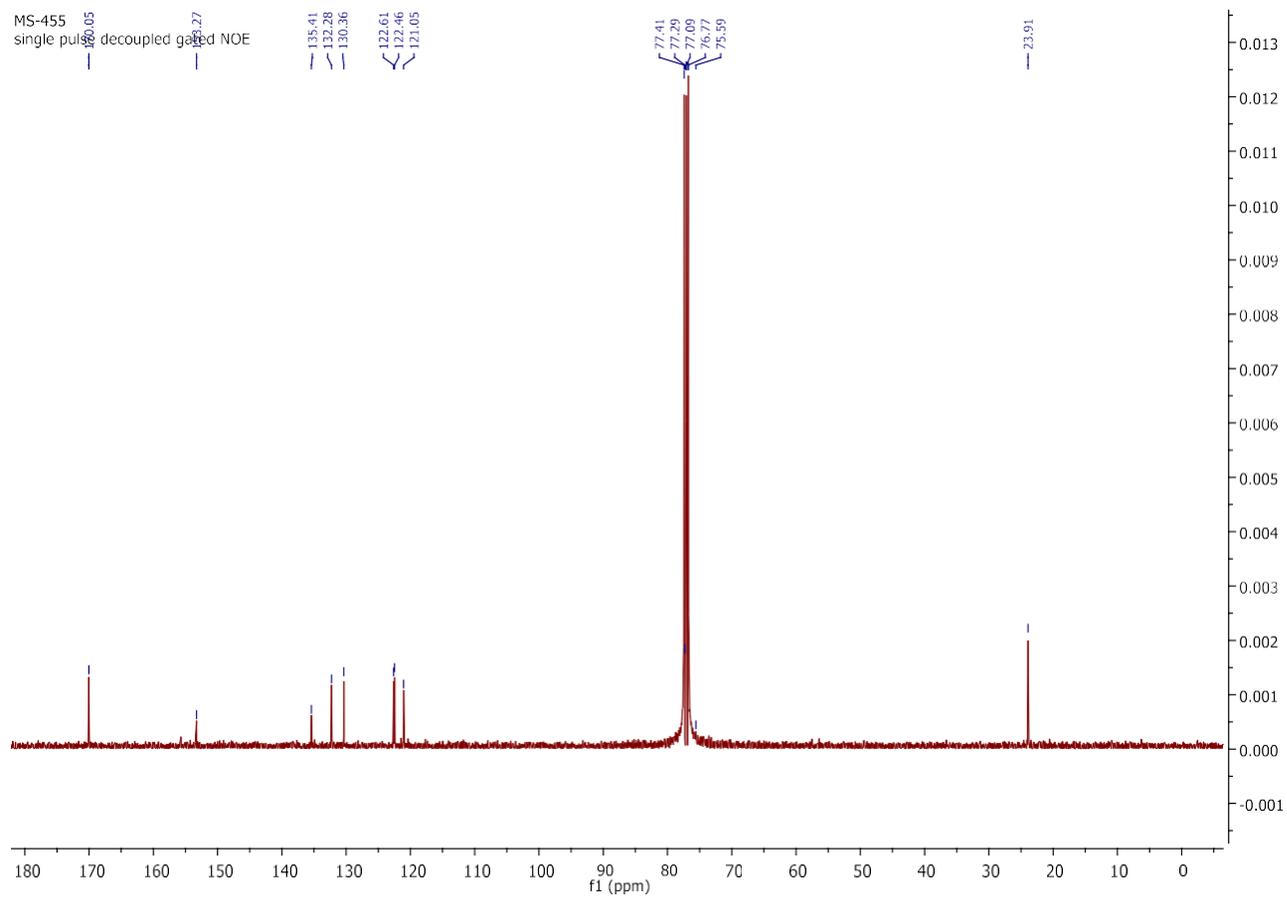
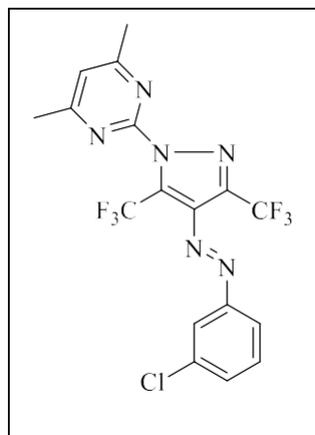
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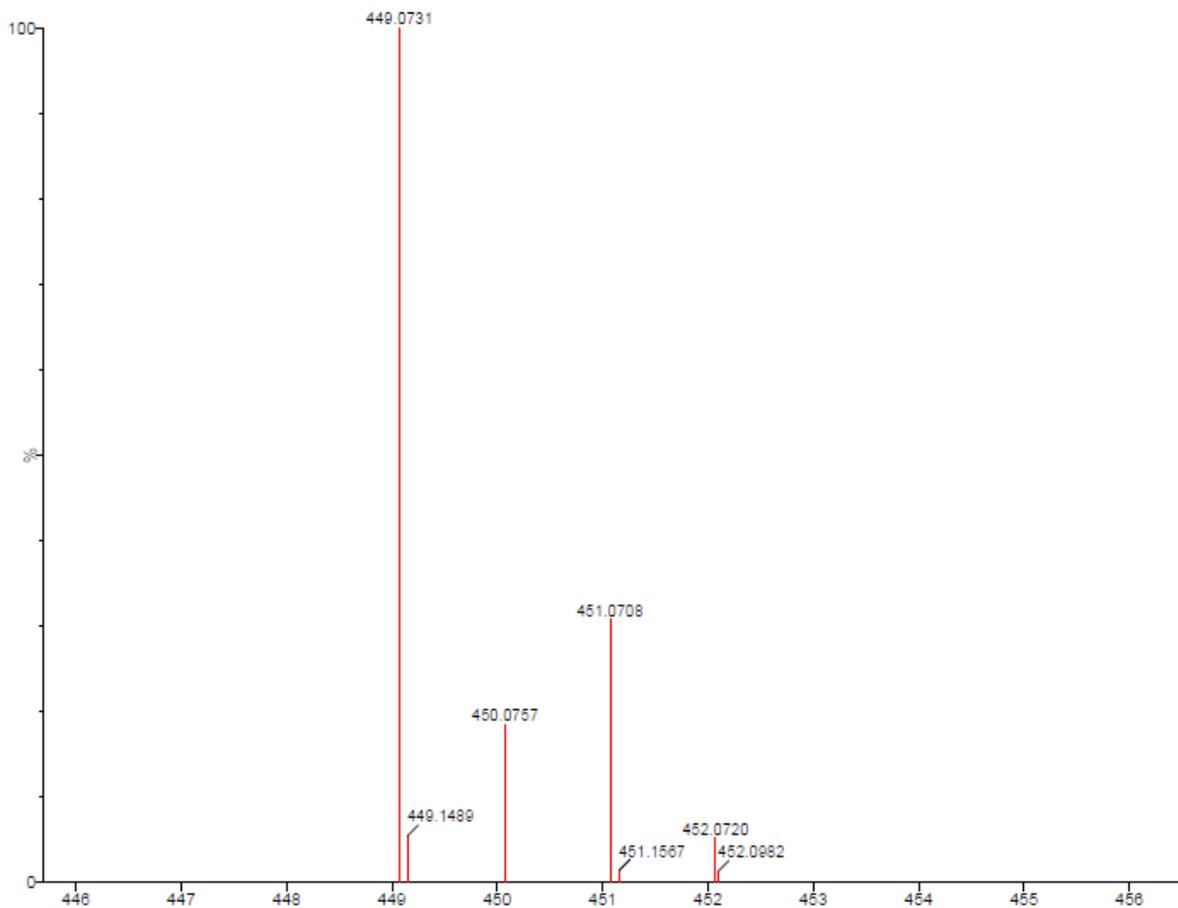
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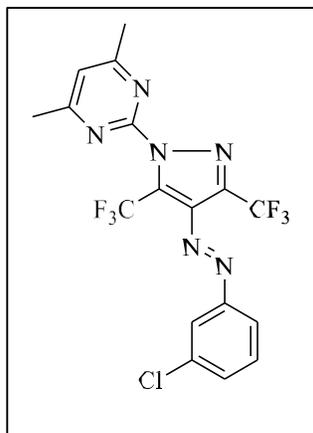
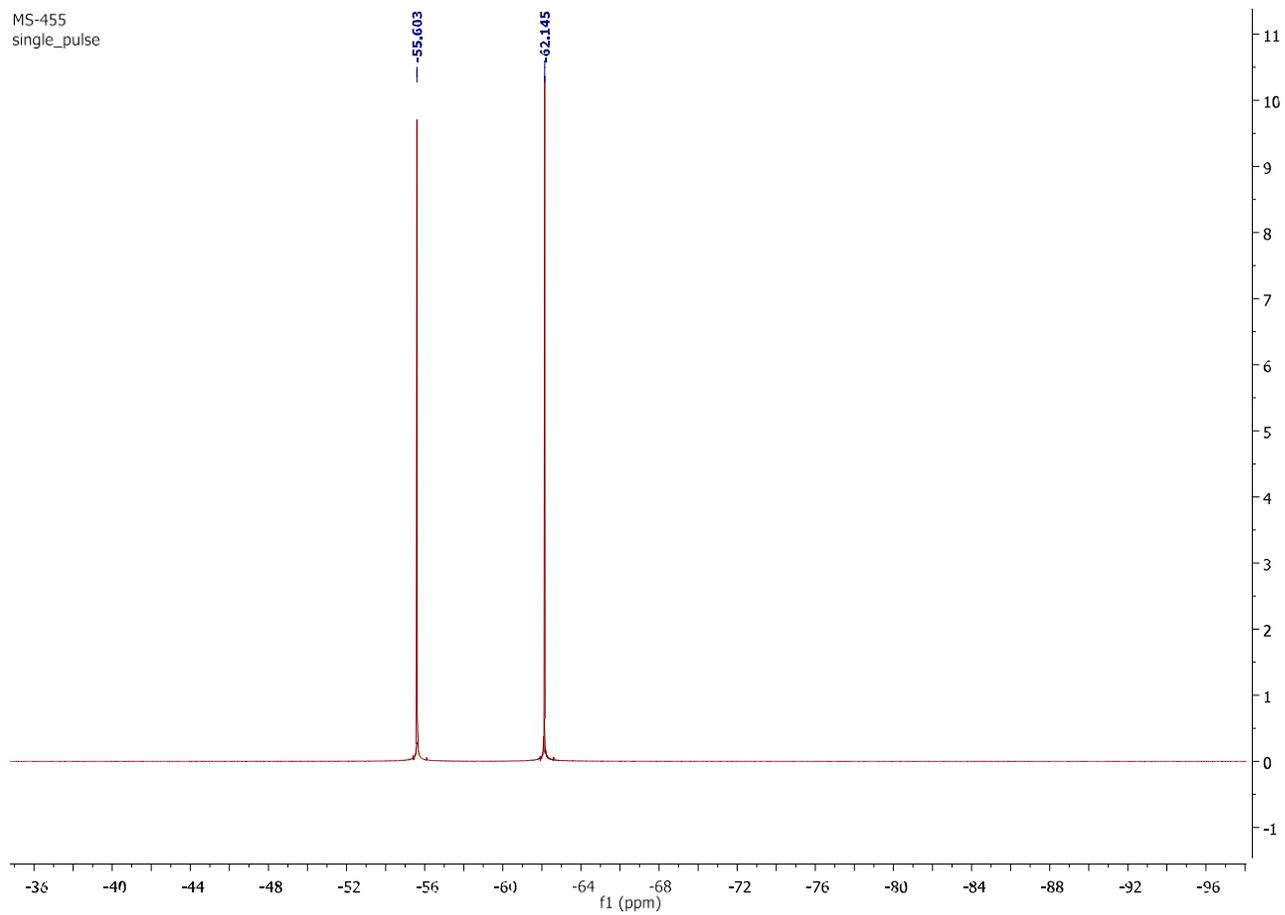
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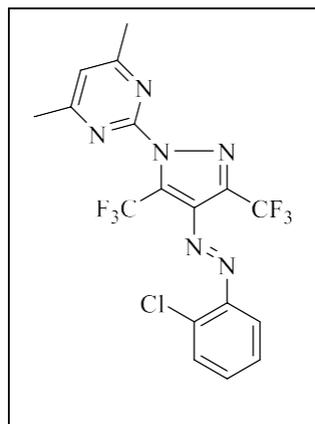
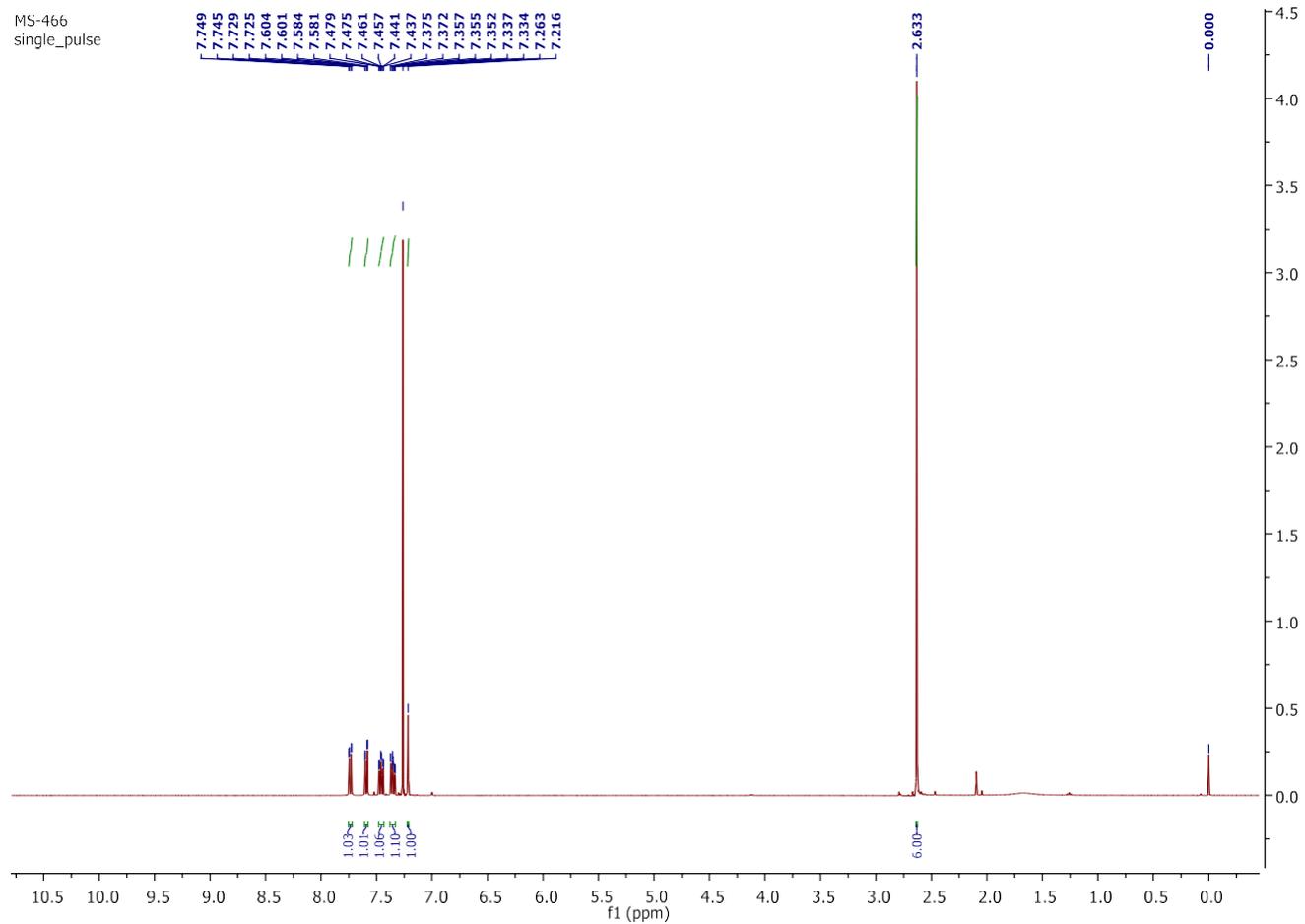
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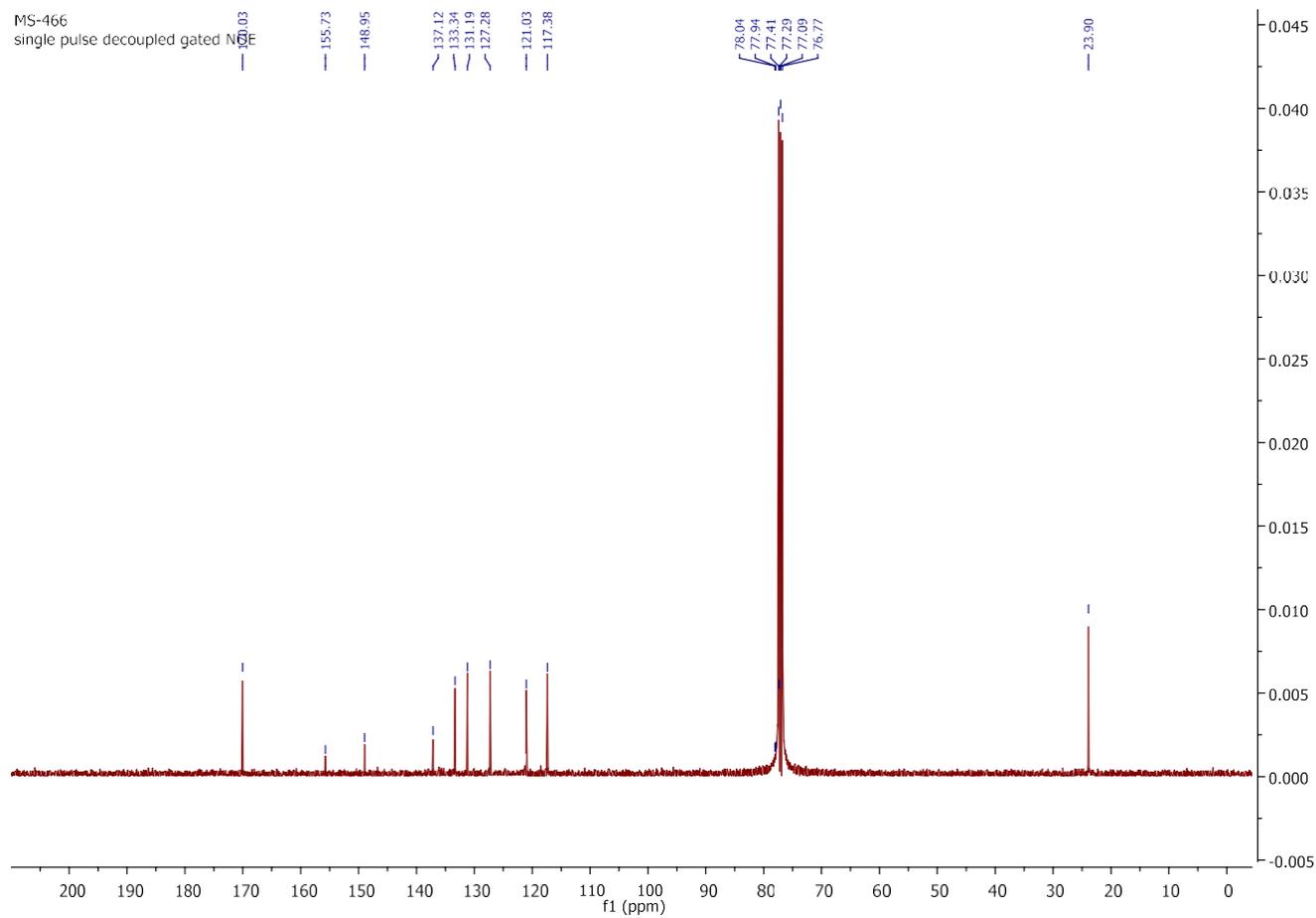
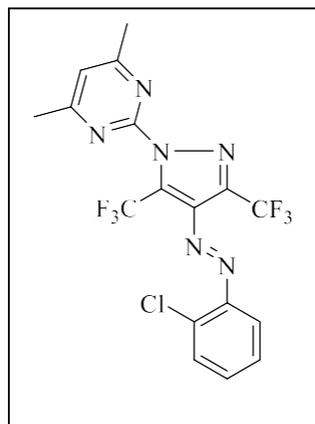
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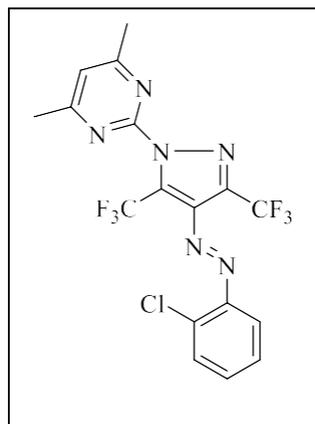
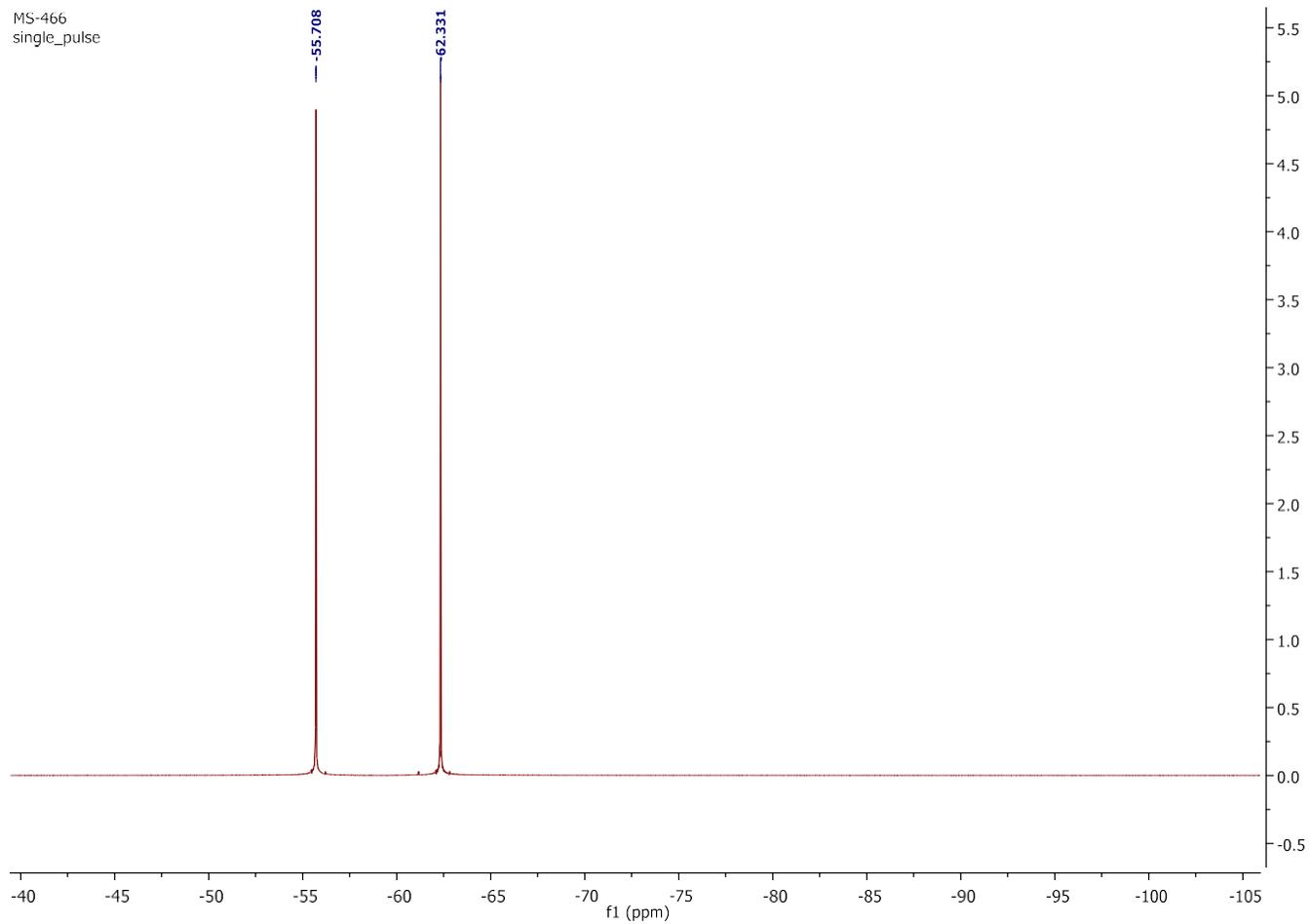
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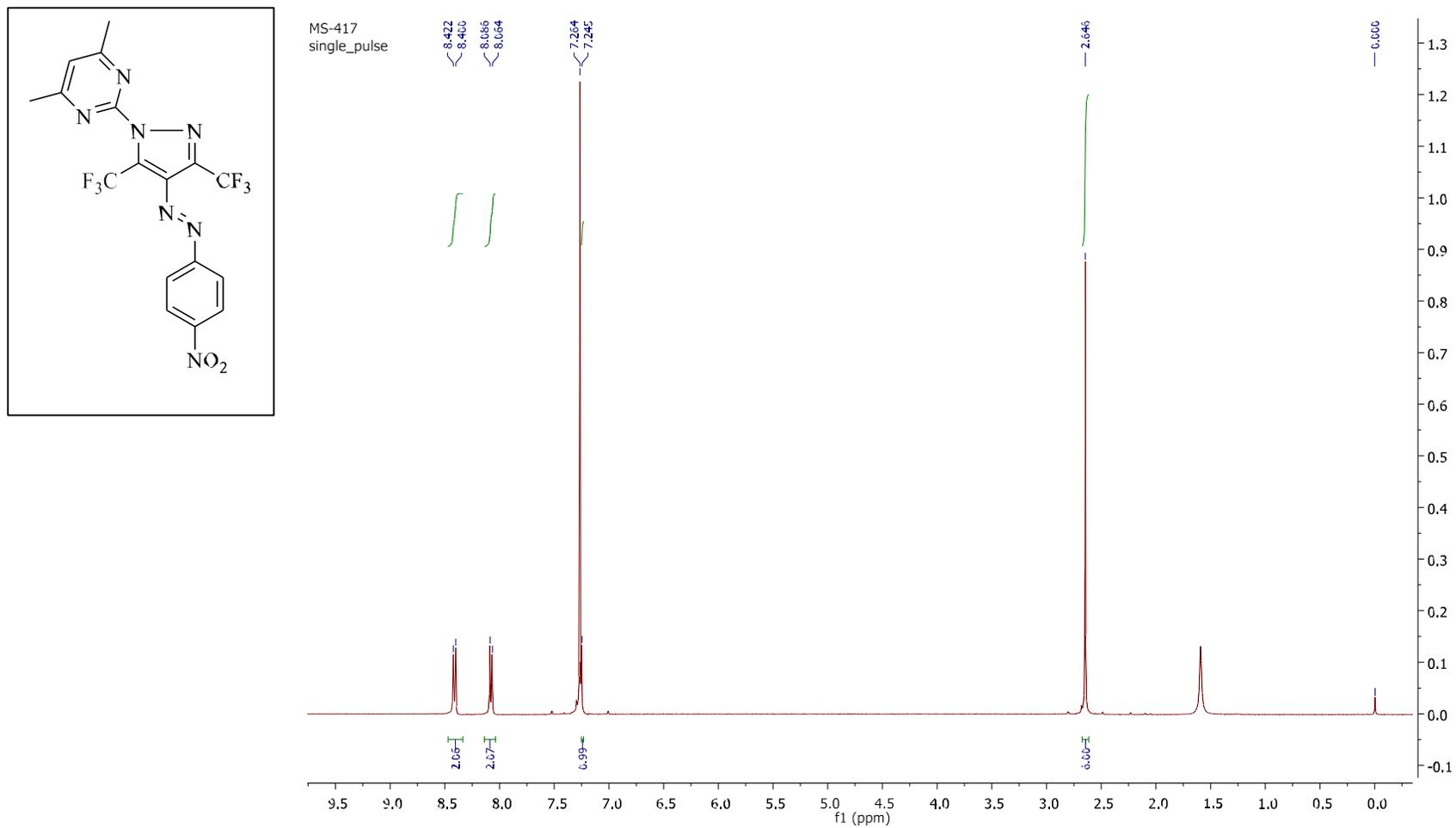


^{19}F -NMR spectra of 1-(4,6-dimethylpyrimidinyl)-4-(3-chlorophenylazo)-3,5-bistrifluoromethylpyrazoleMS-455
single_pulse

¹H-NMR spectra of 1-(4,6-dimethylpyrimidinyl)-4-(2-chlorophenylazo)-3,5-bistrifluoromethylpyrazoleMS-466
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^{13}C -NMR spectra of 1-(4,6-dimethylpyrimidinyl)-4-(2-chlorophenylazo)-3,5-bis(trifluoromethyl)pyrazole

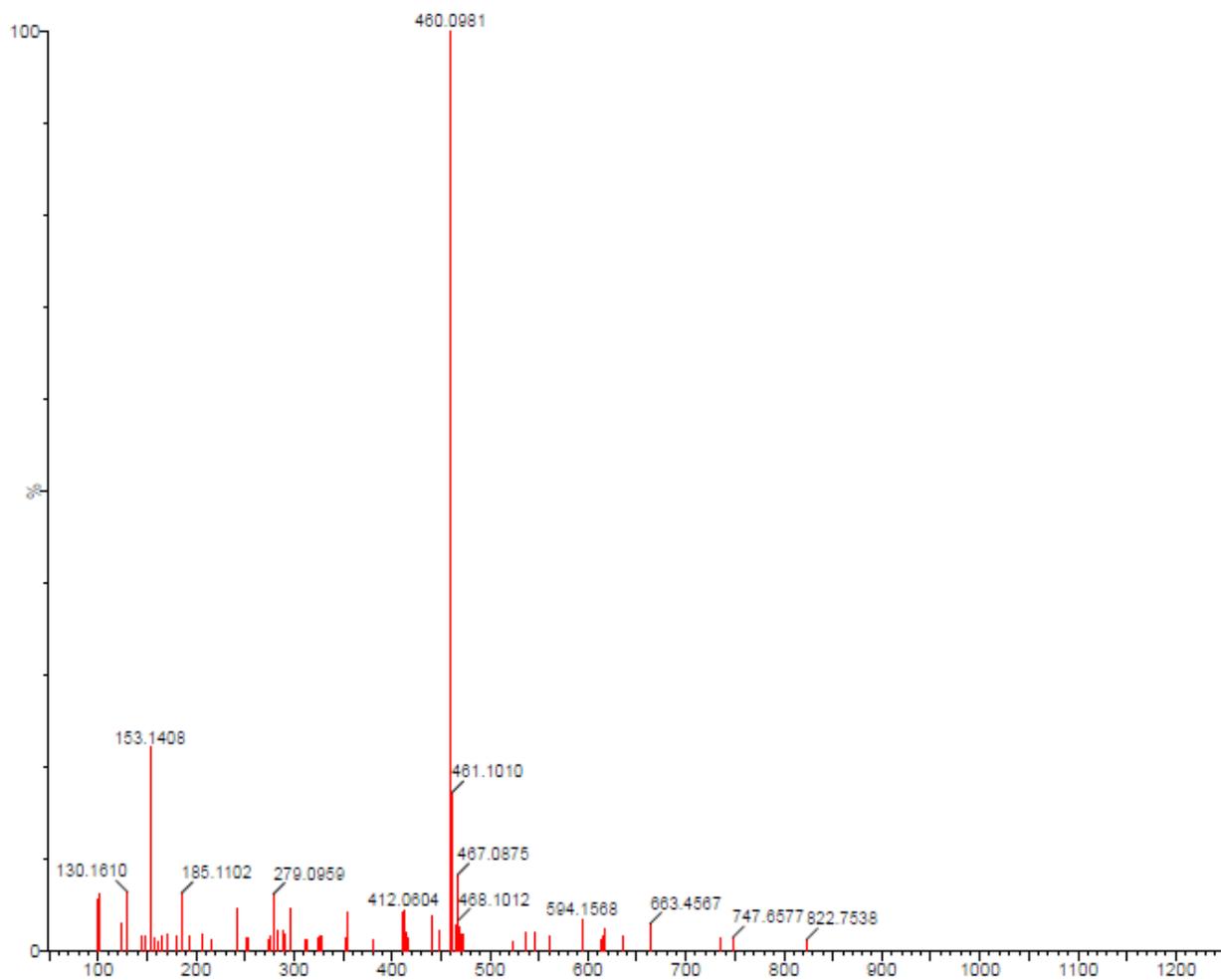
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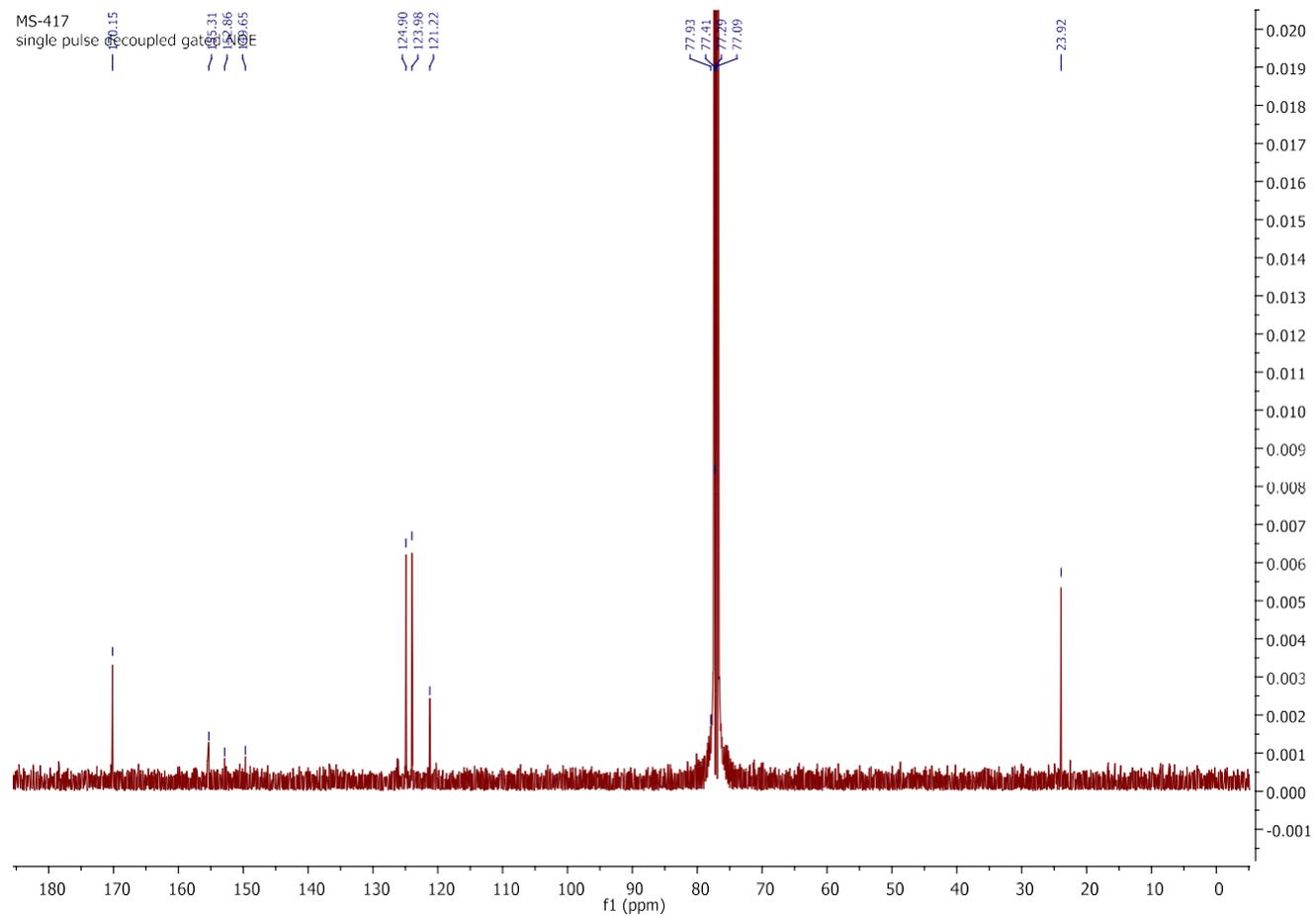
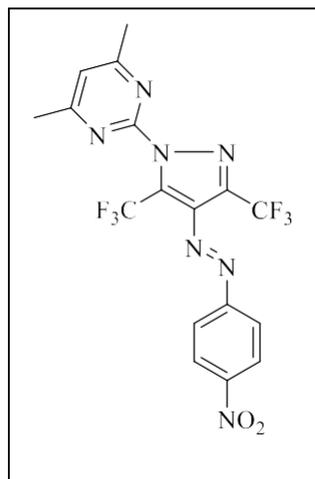
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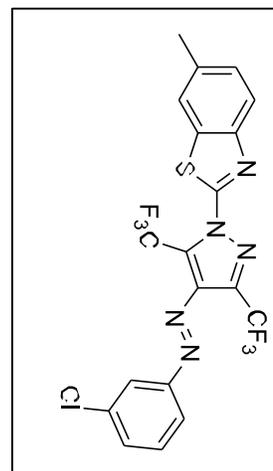
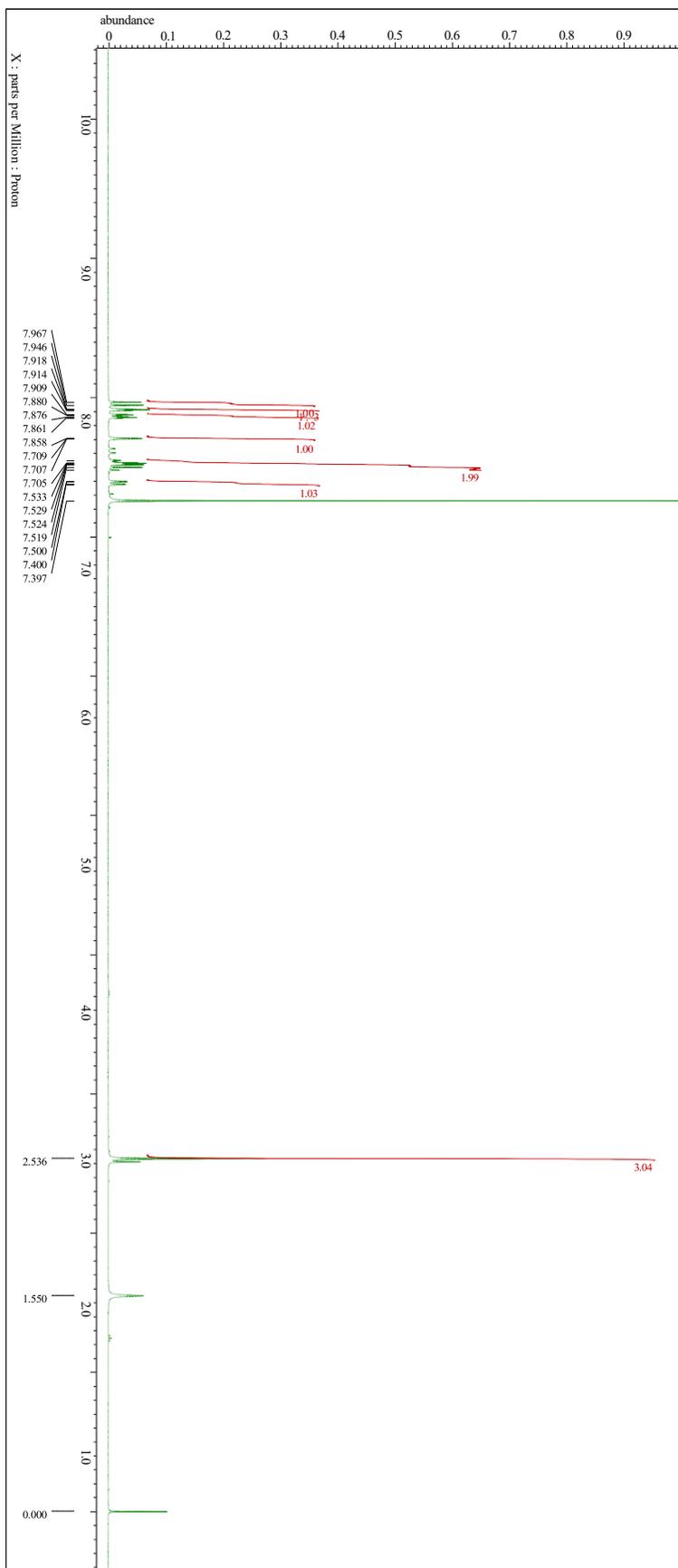
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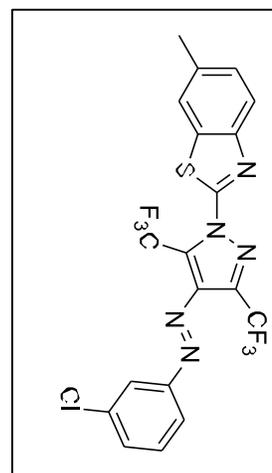
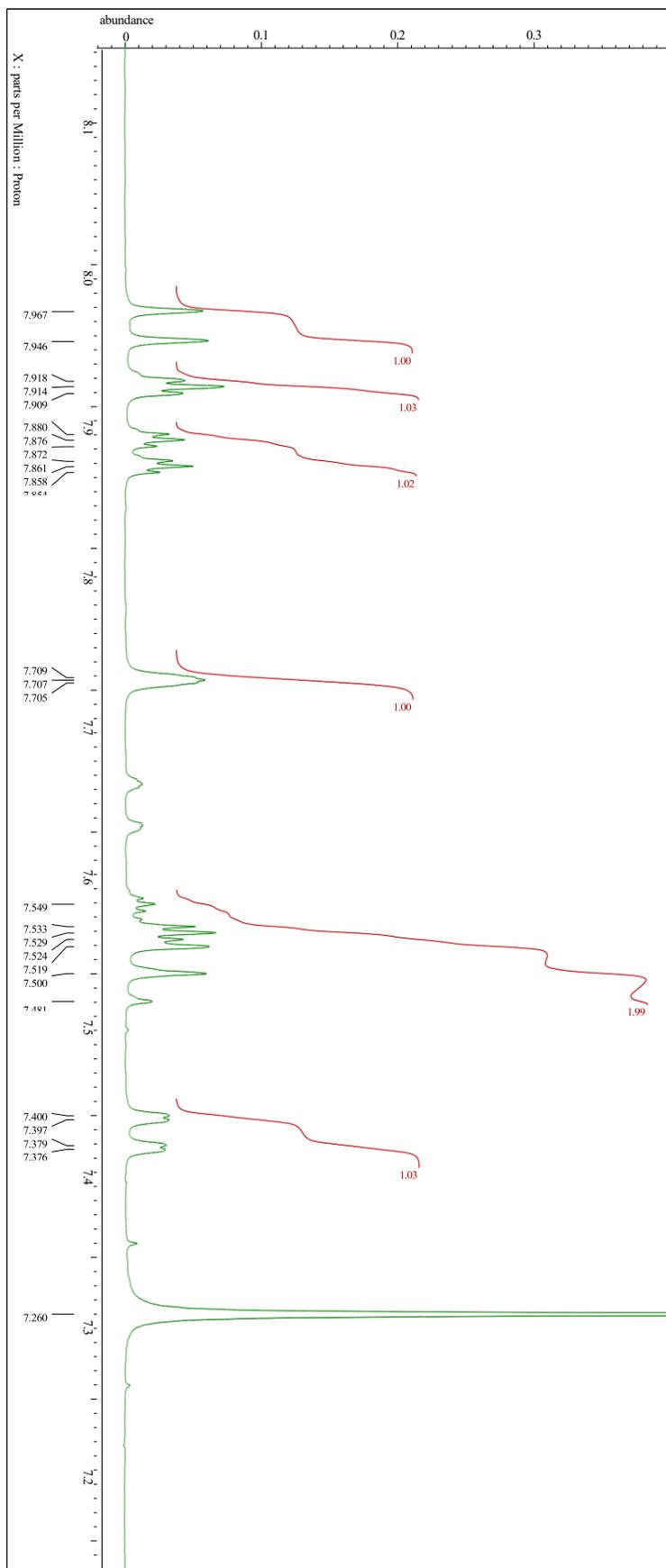
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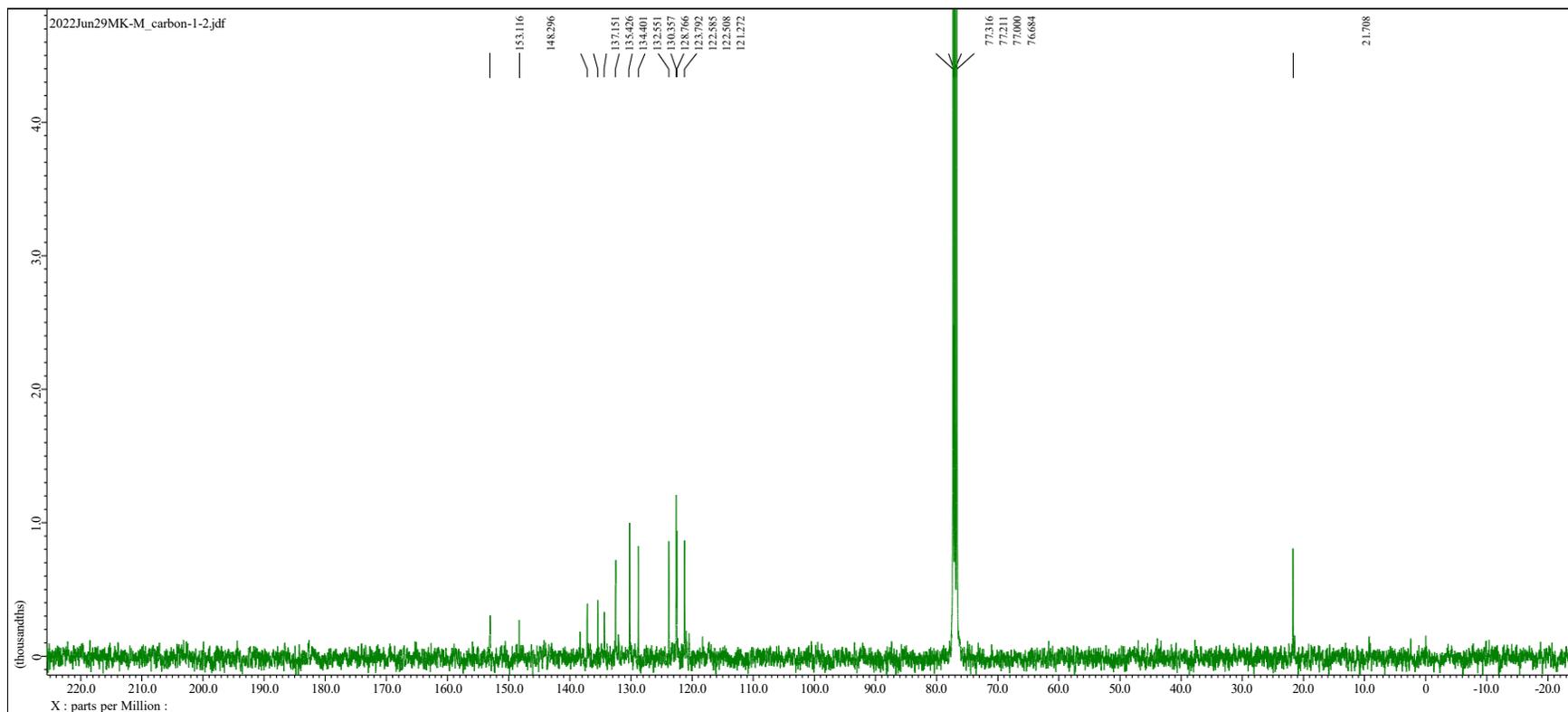
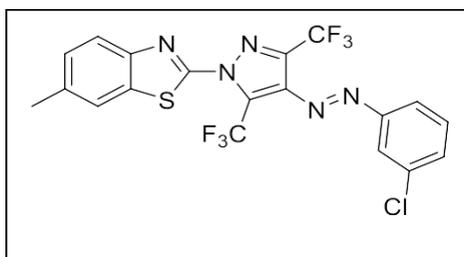
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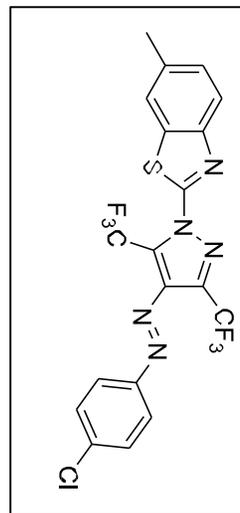
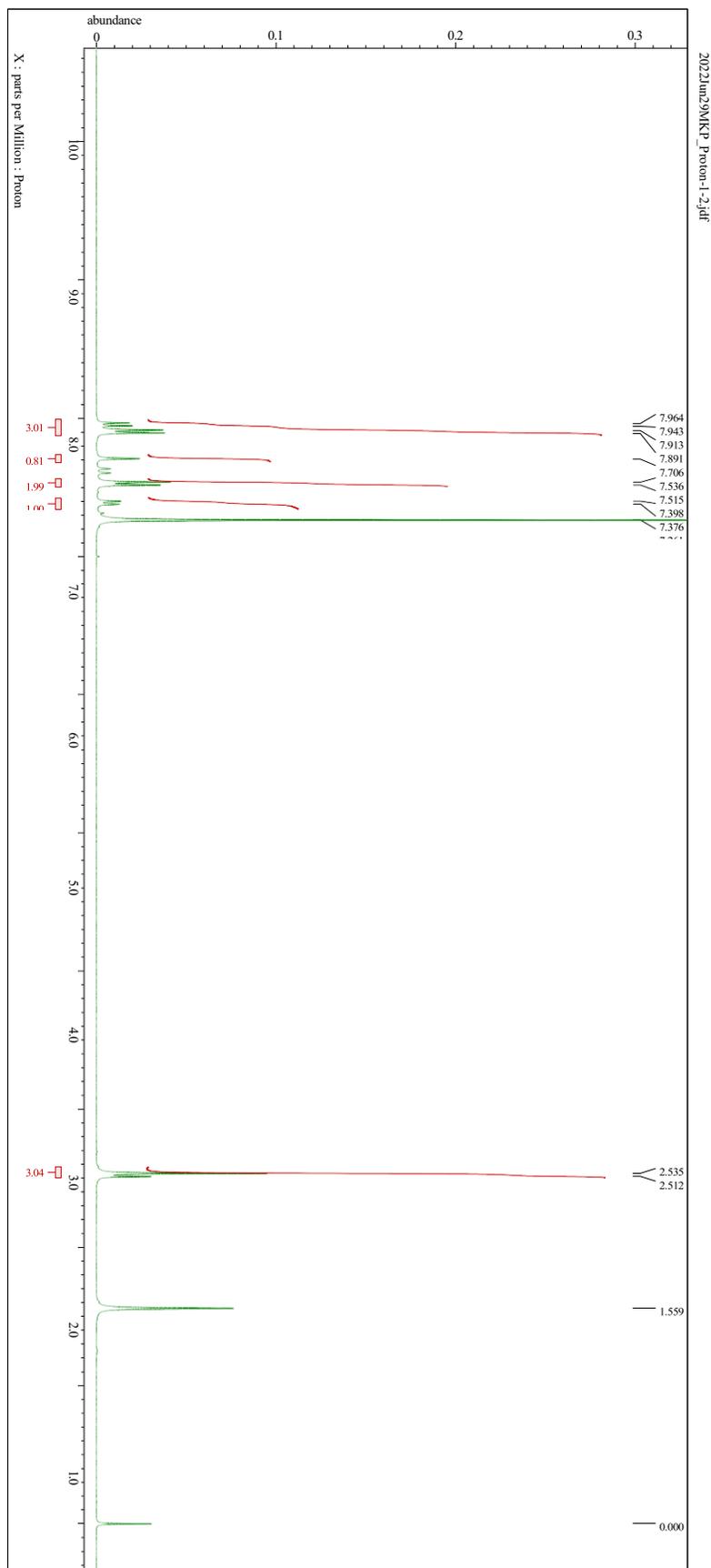


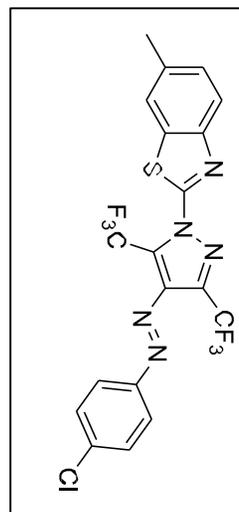
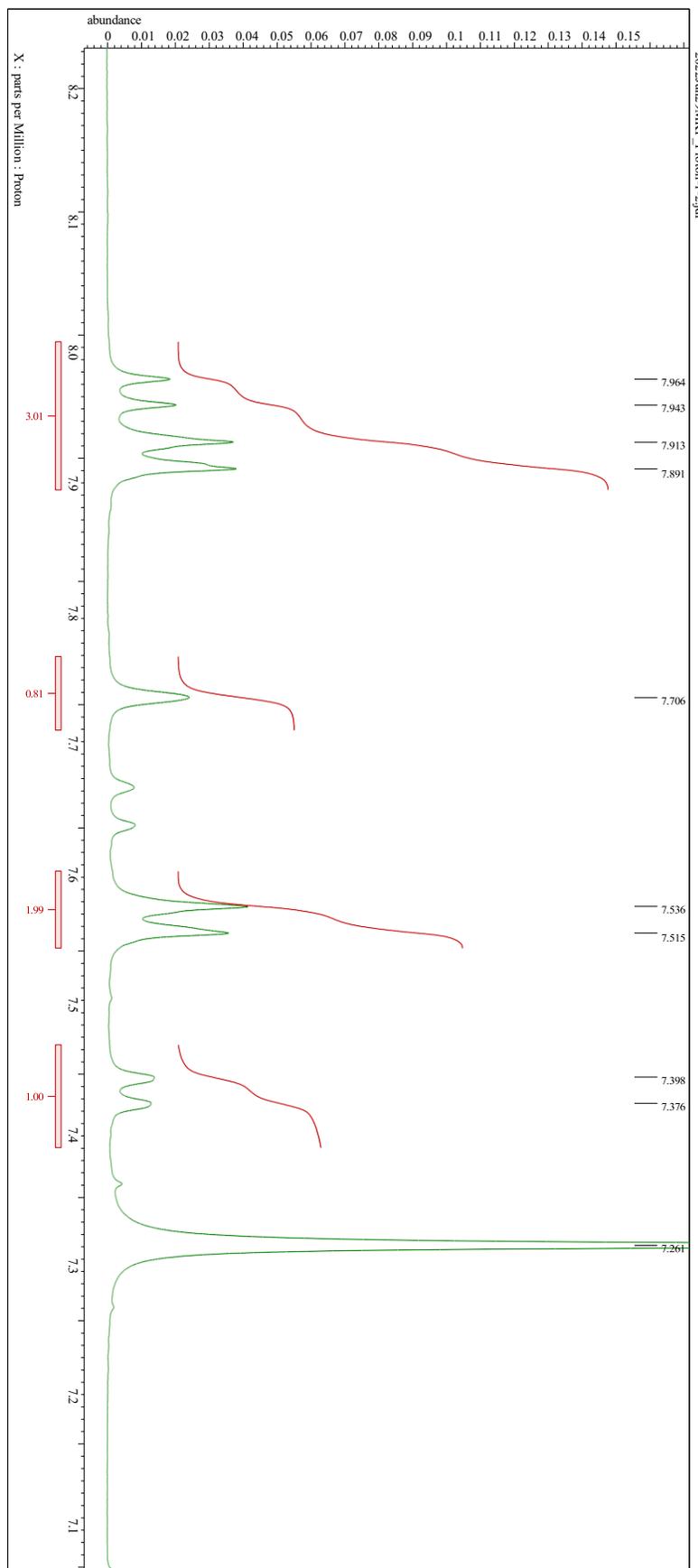
¹³C-NMR spectra of 1-(4,6-dimethylpyrimidinyl)-4-(4-nitroPhenylazo)-3,5-bistrifluoromethylpyrazole 9e

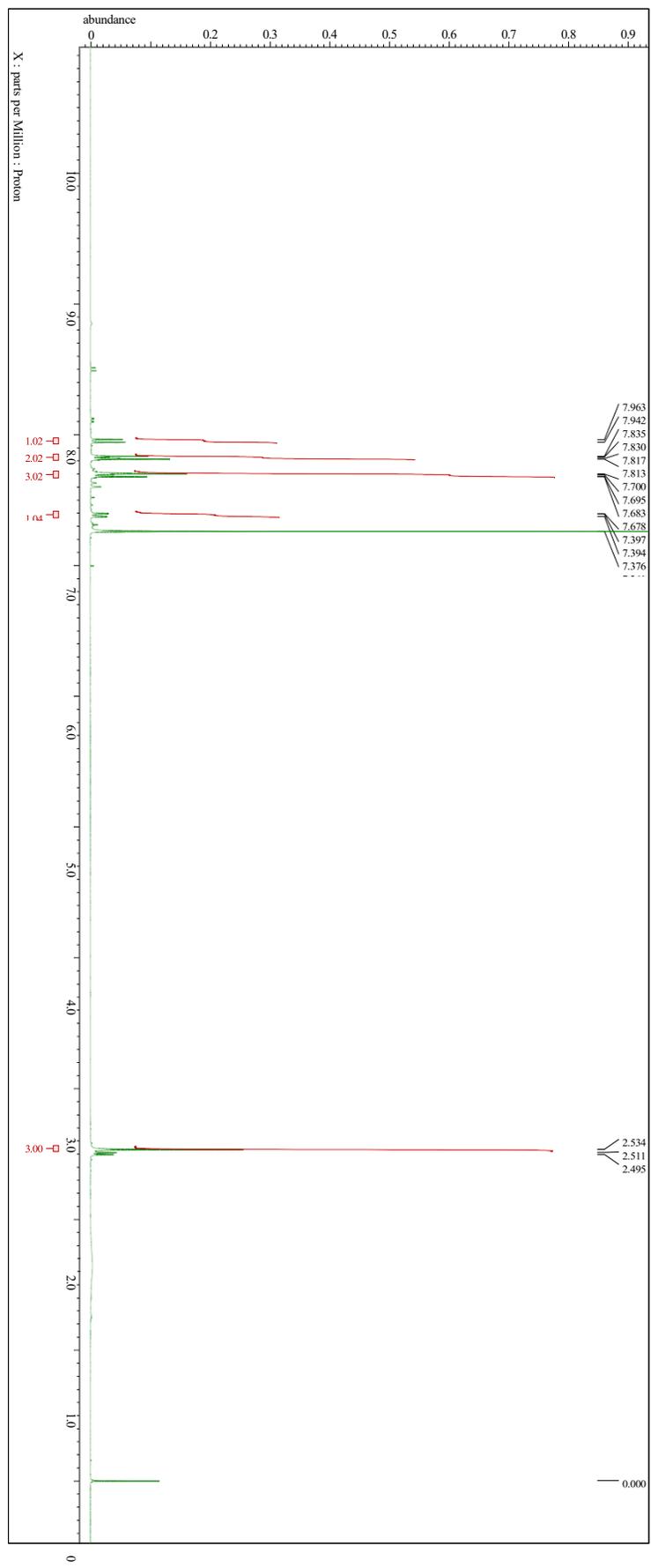




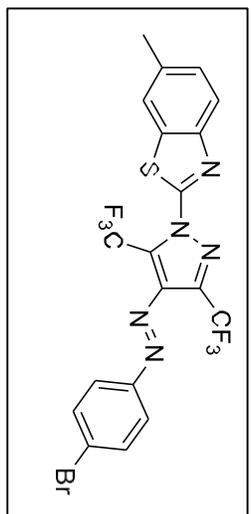




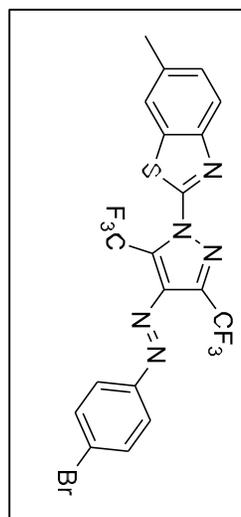
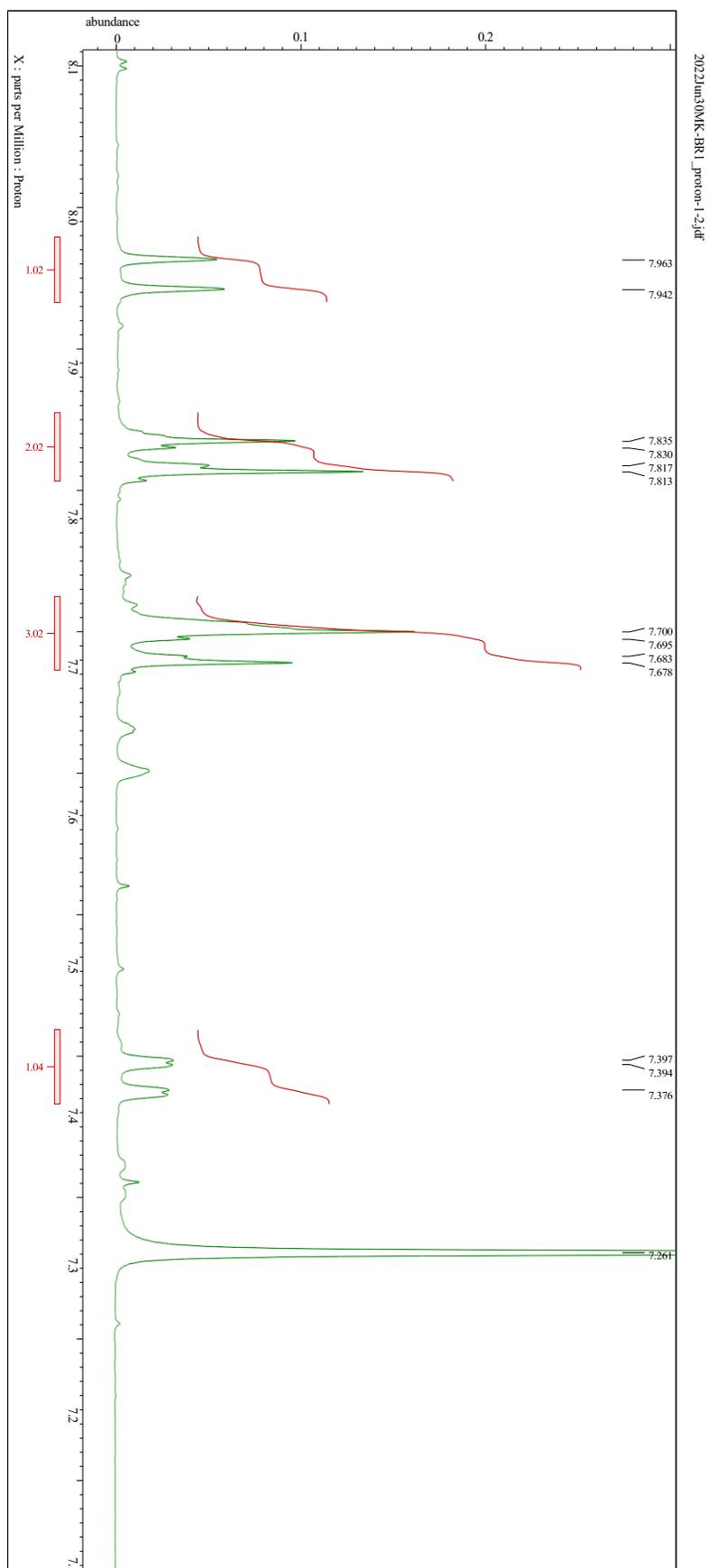


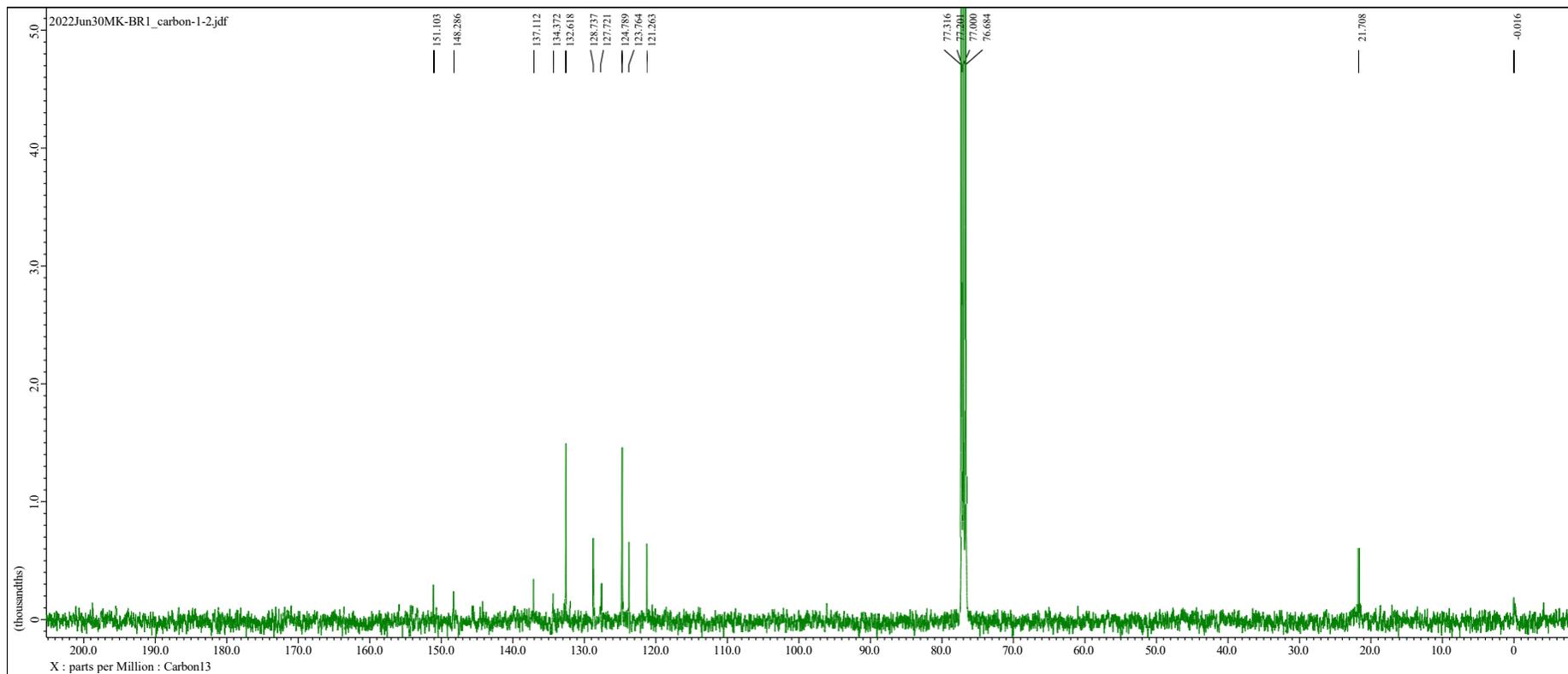
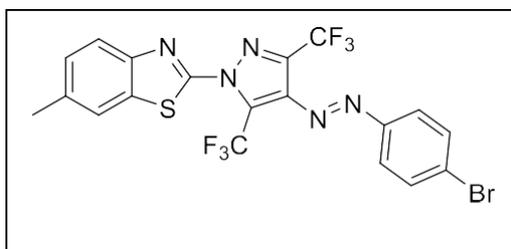


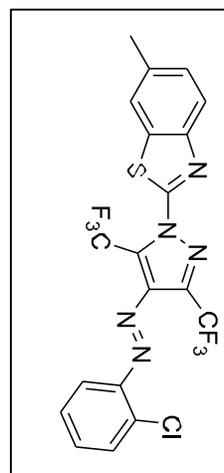
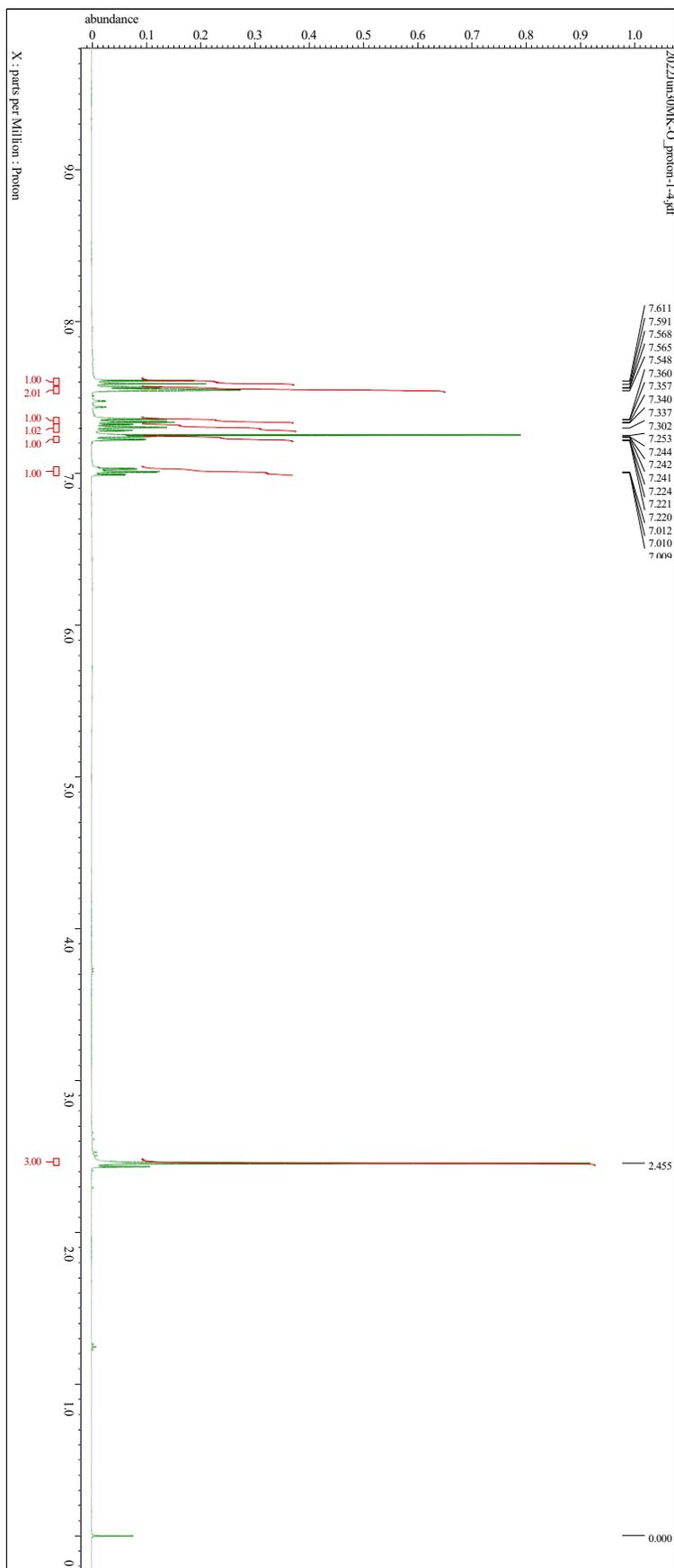
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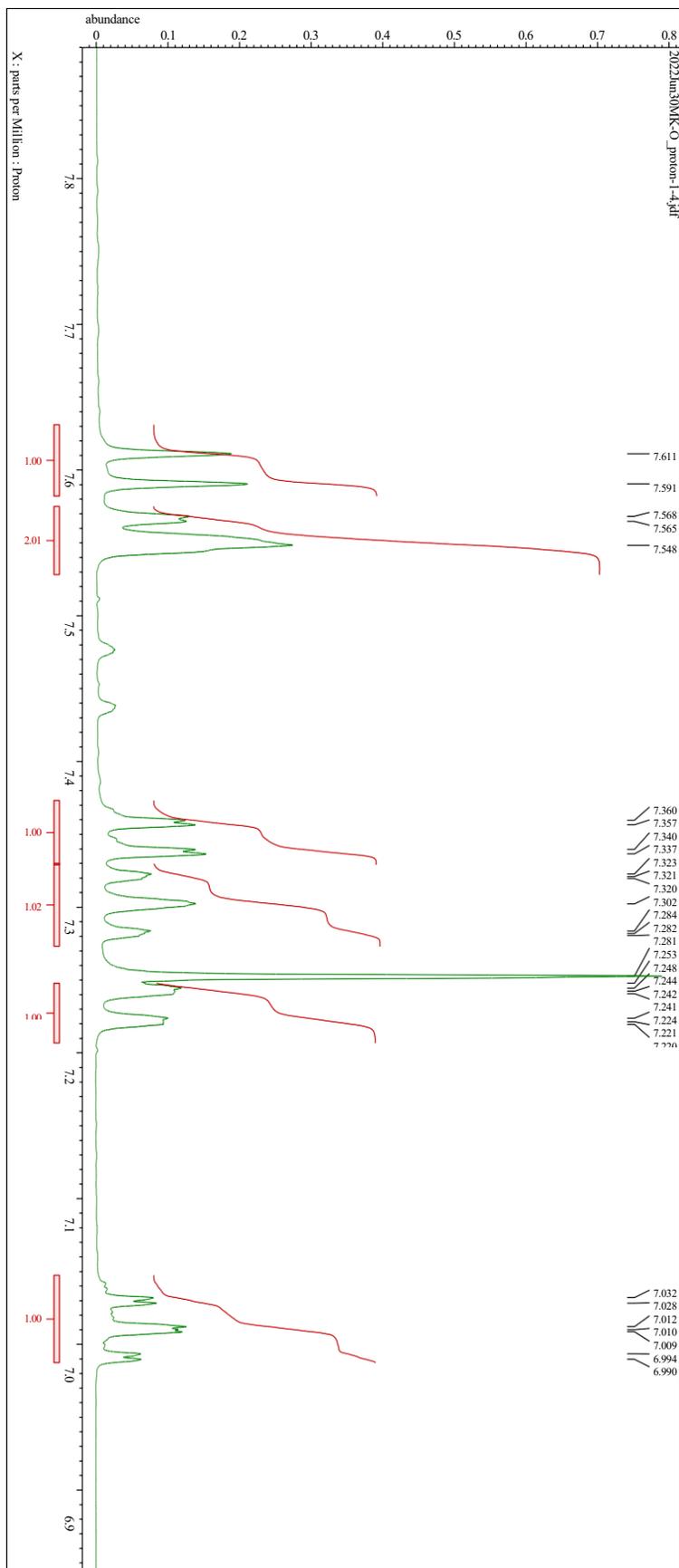


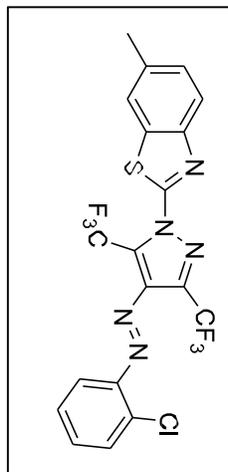
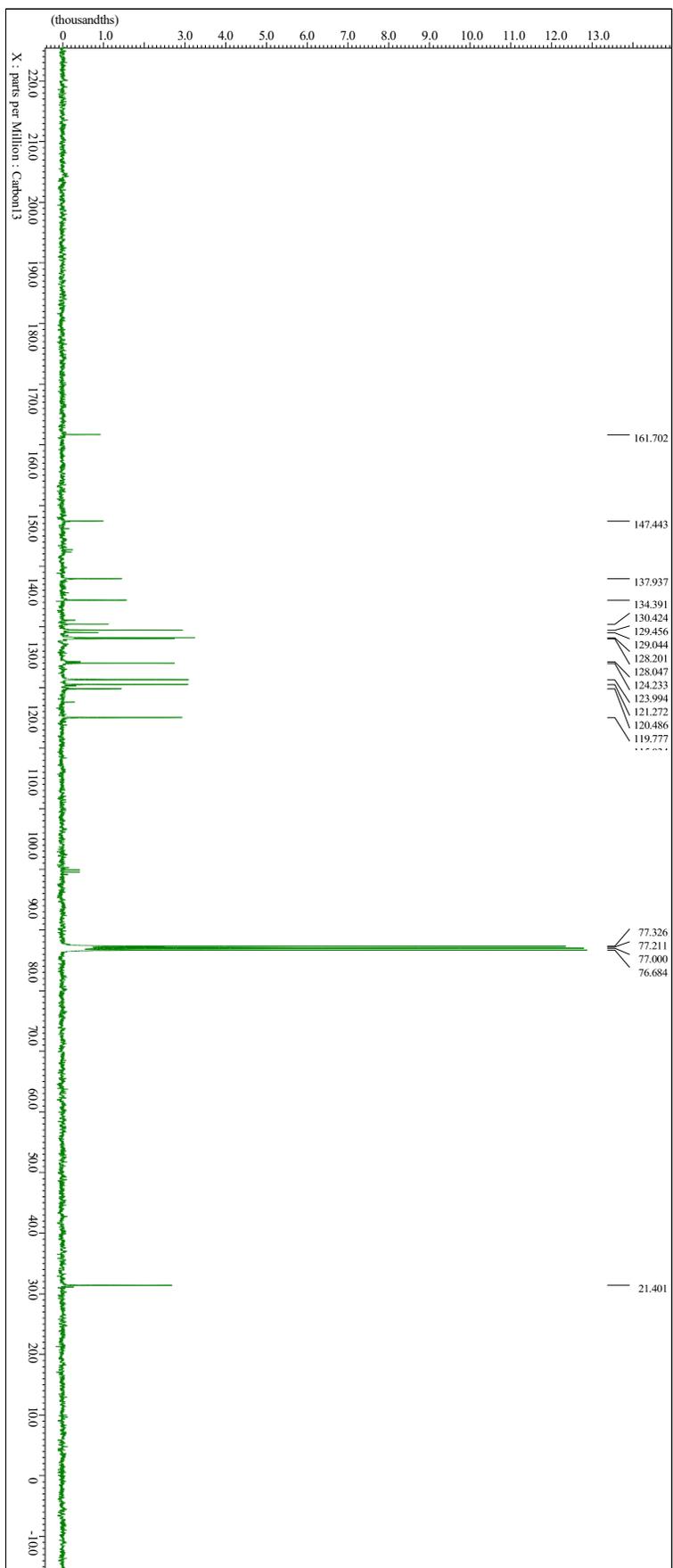
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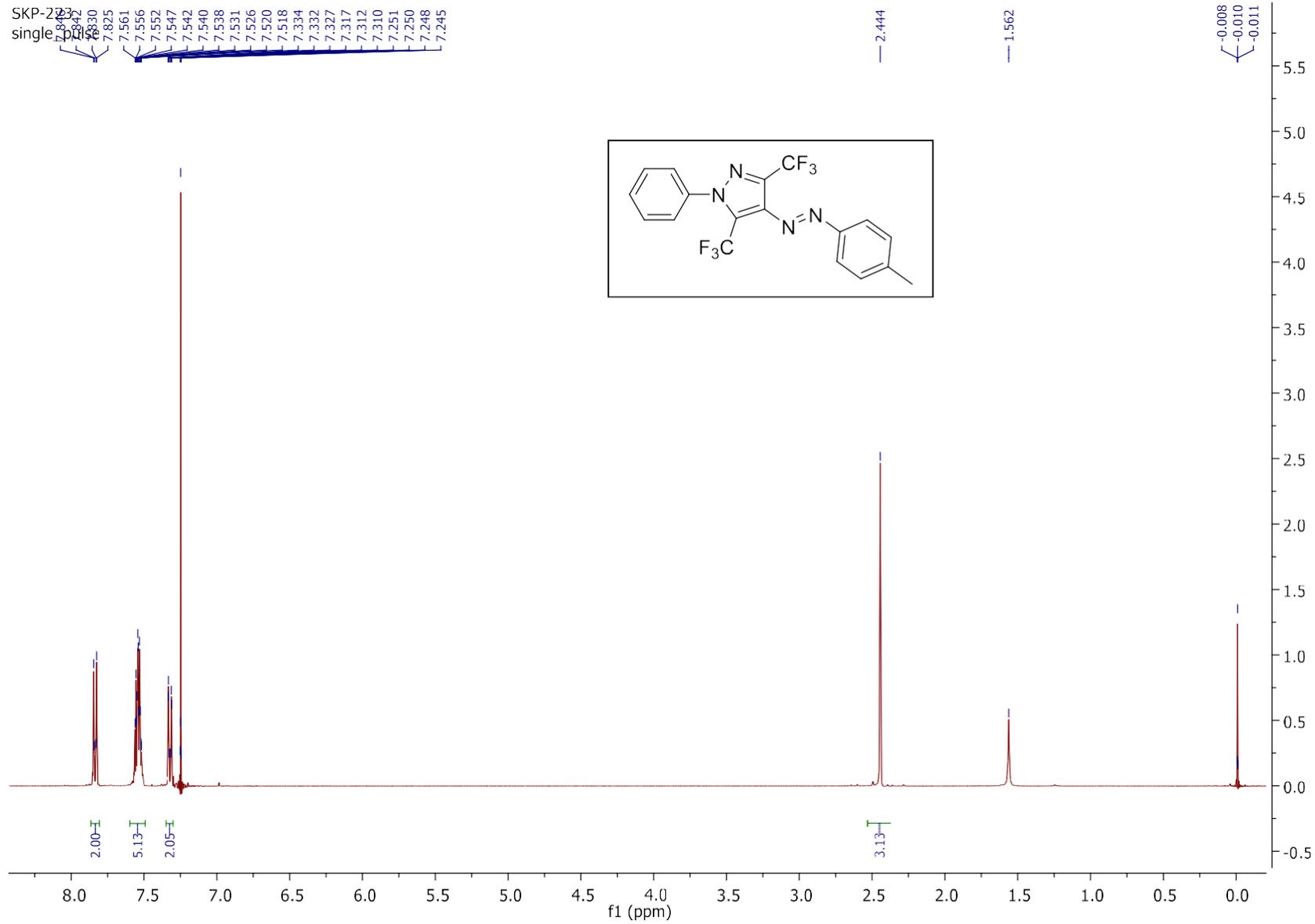


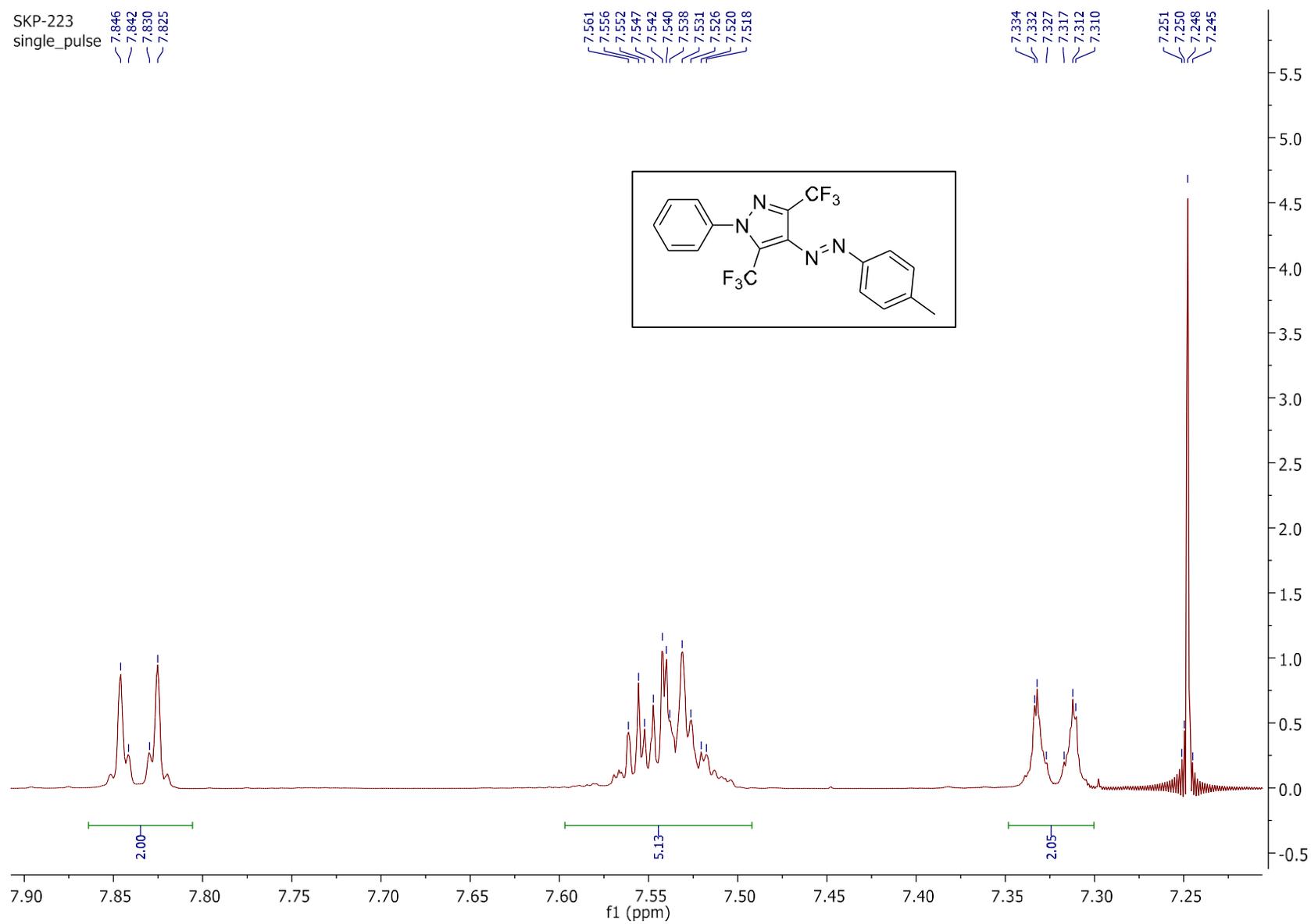
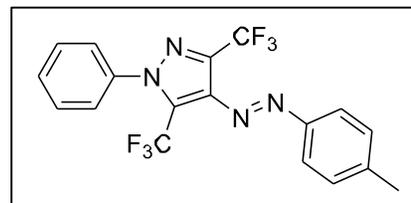










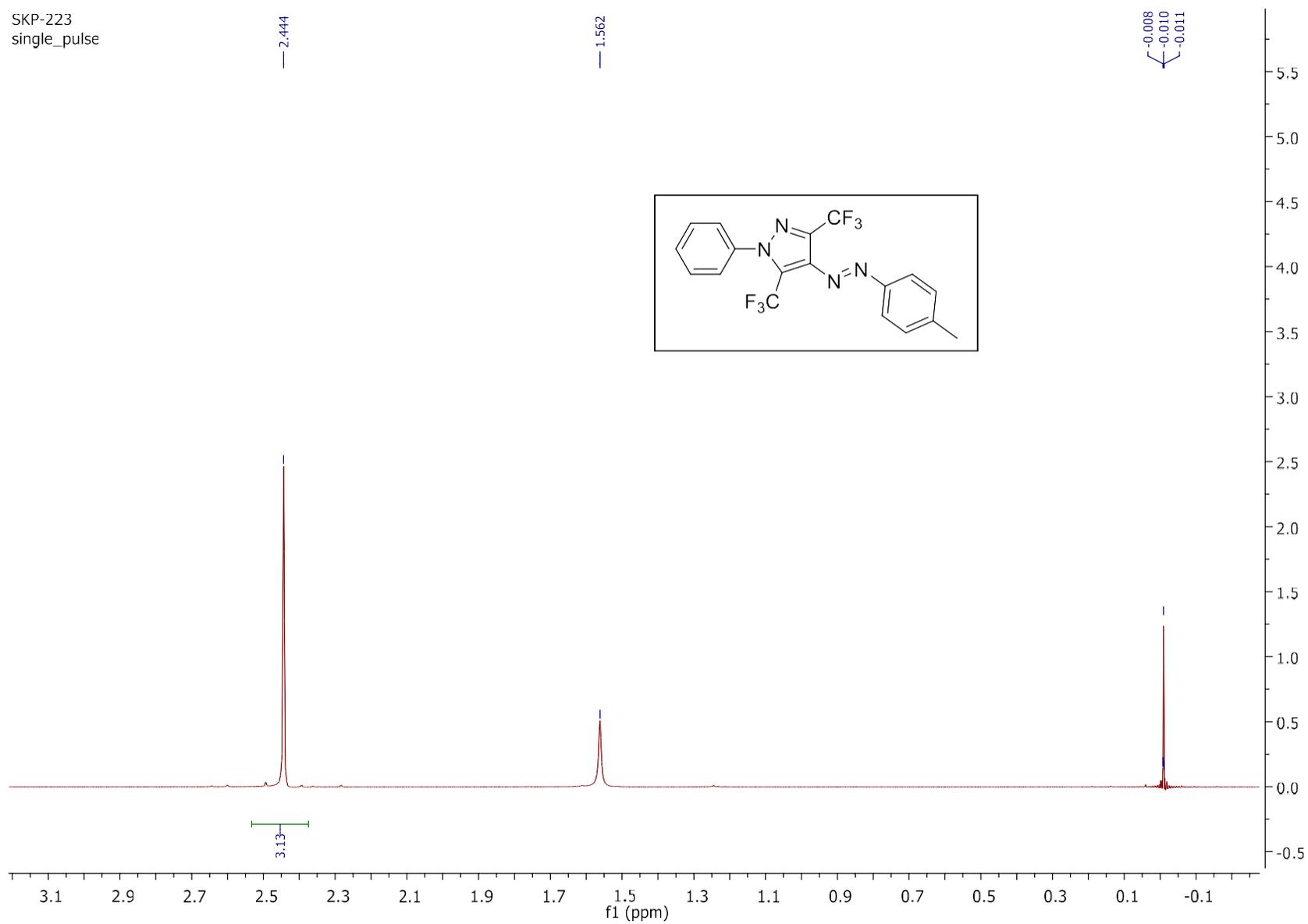
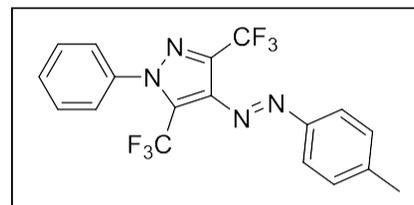
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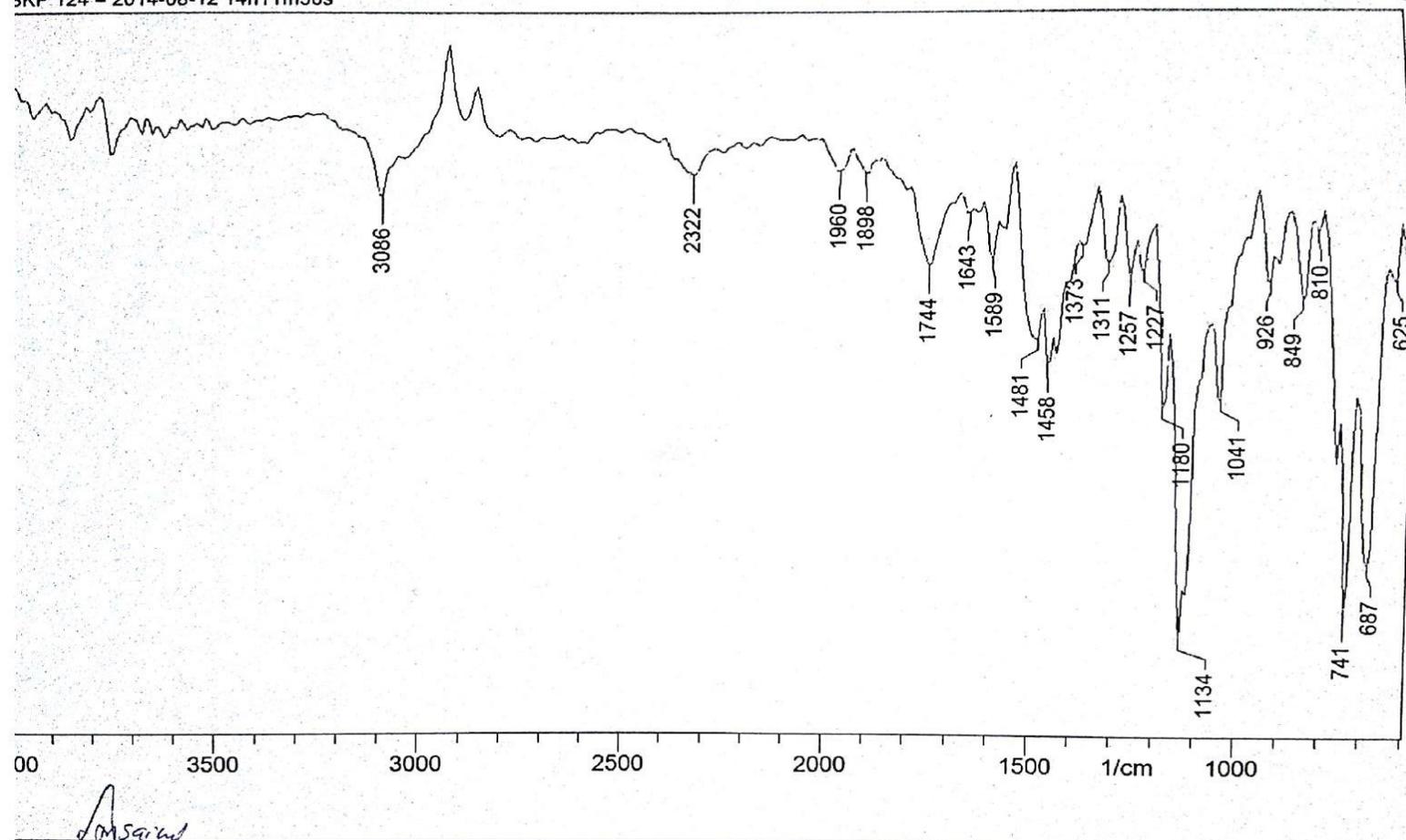
1-Phenyl-4-(4-methylphenylazo)-3,5-bistrifluoromethyl-1H-pyrazole 11b

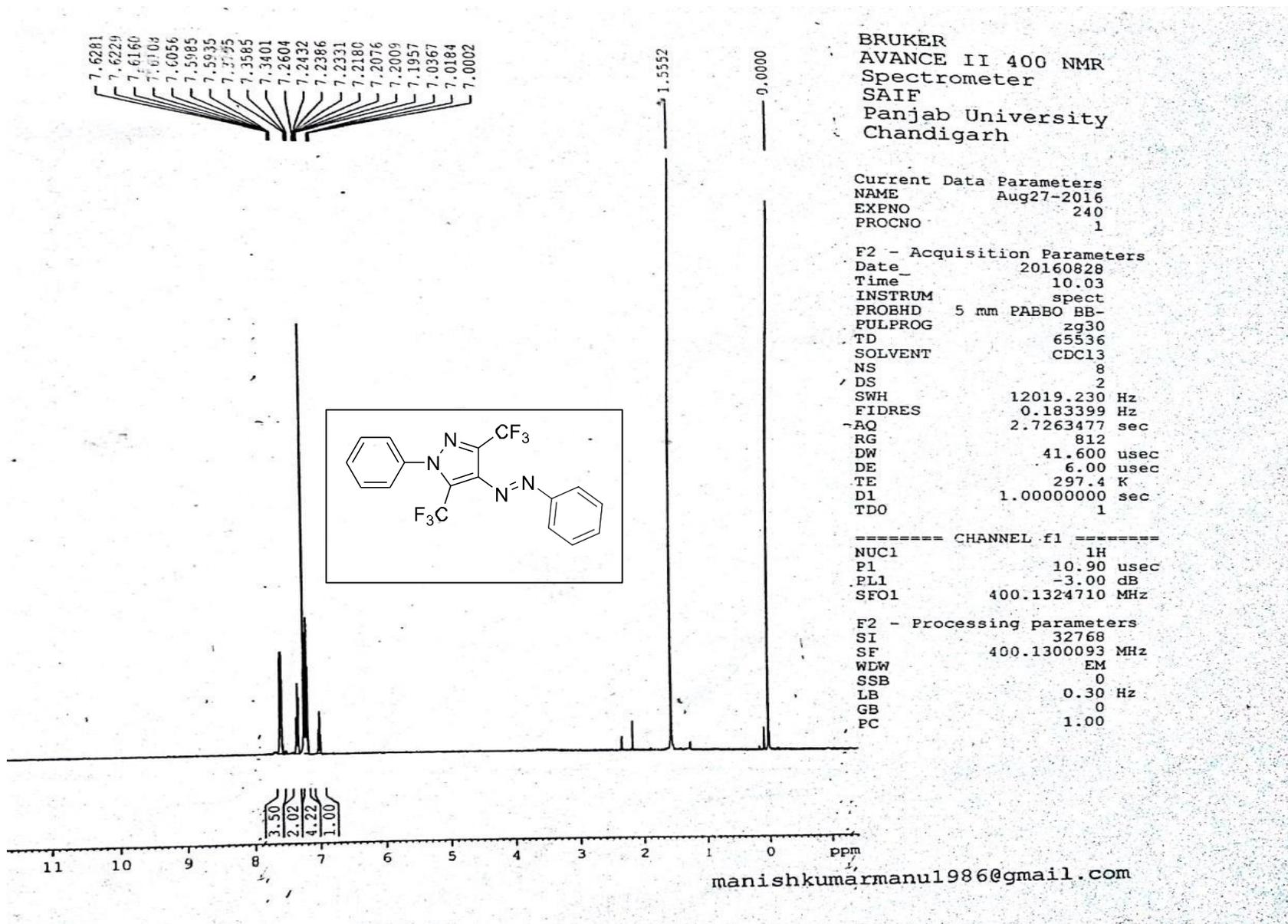
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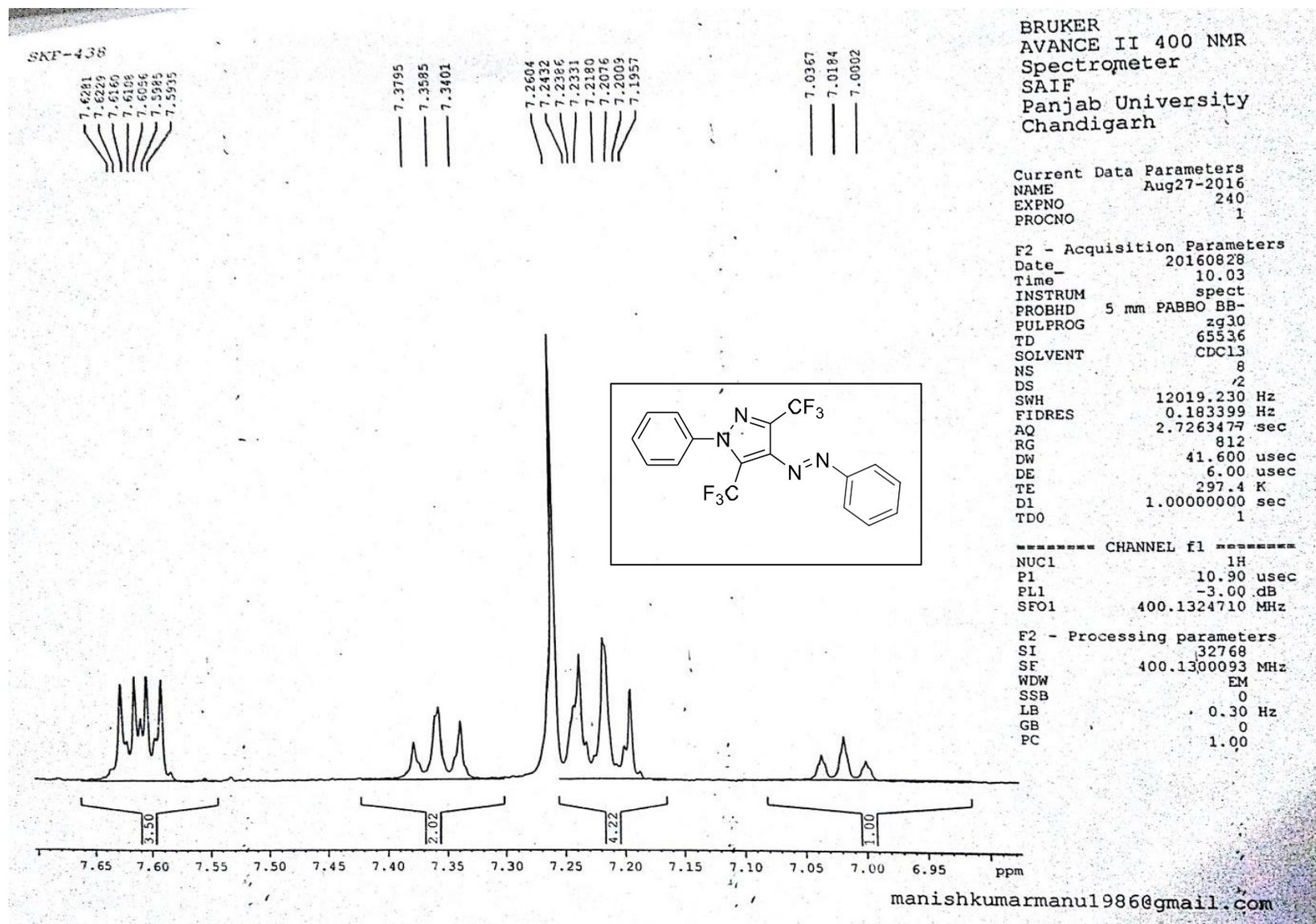
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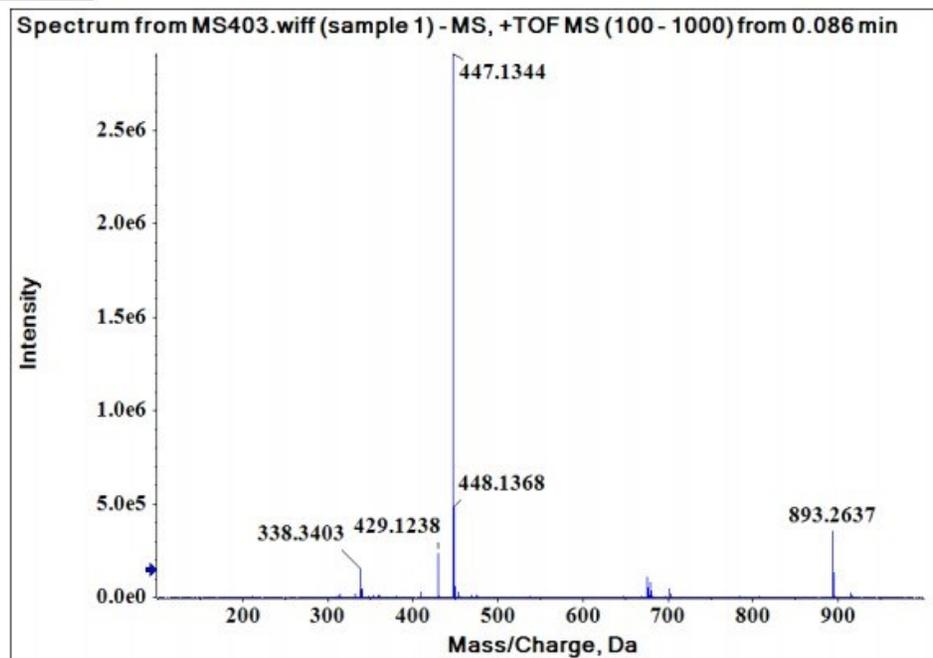
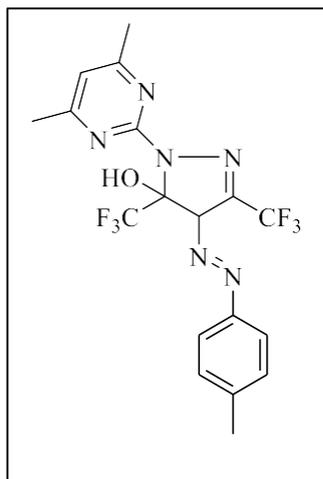
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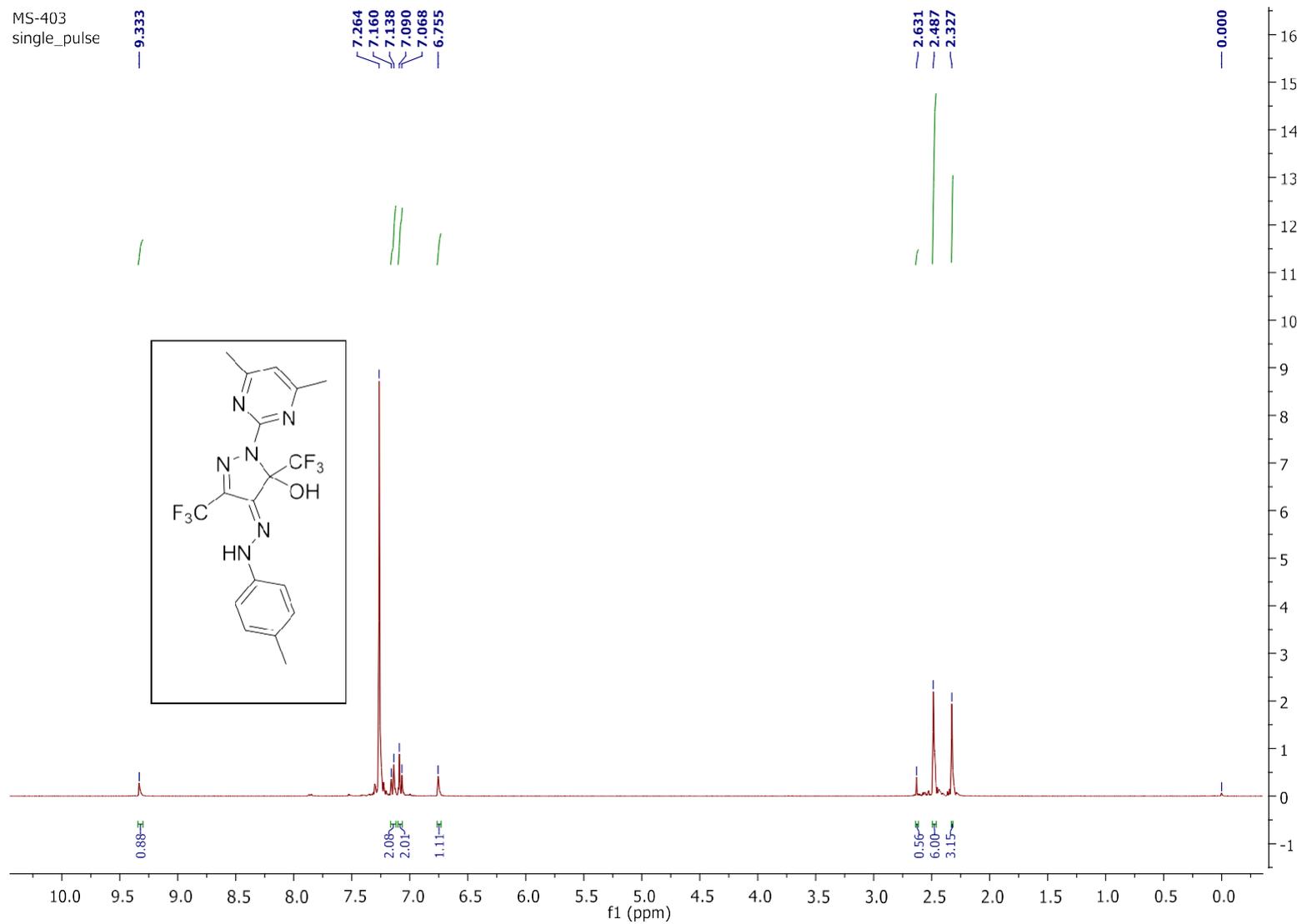


Mass spectra of 1-(4,6-dimethylpyrimidin-2-yl)-4-(4-methylphenylazo)-3,5-bis(trifluoromethyl)-4,5-dihydro-1H-pyrazol-5-ol

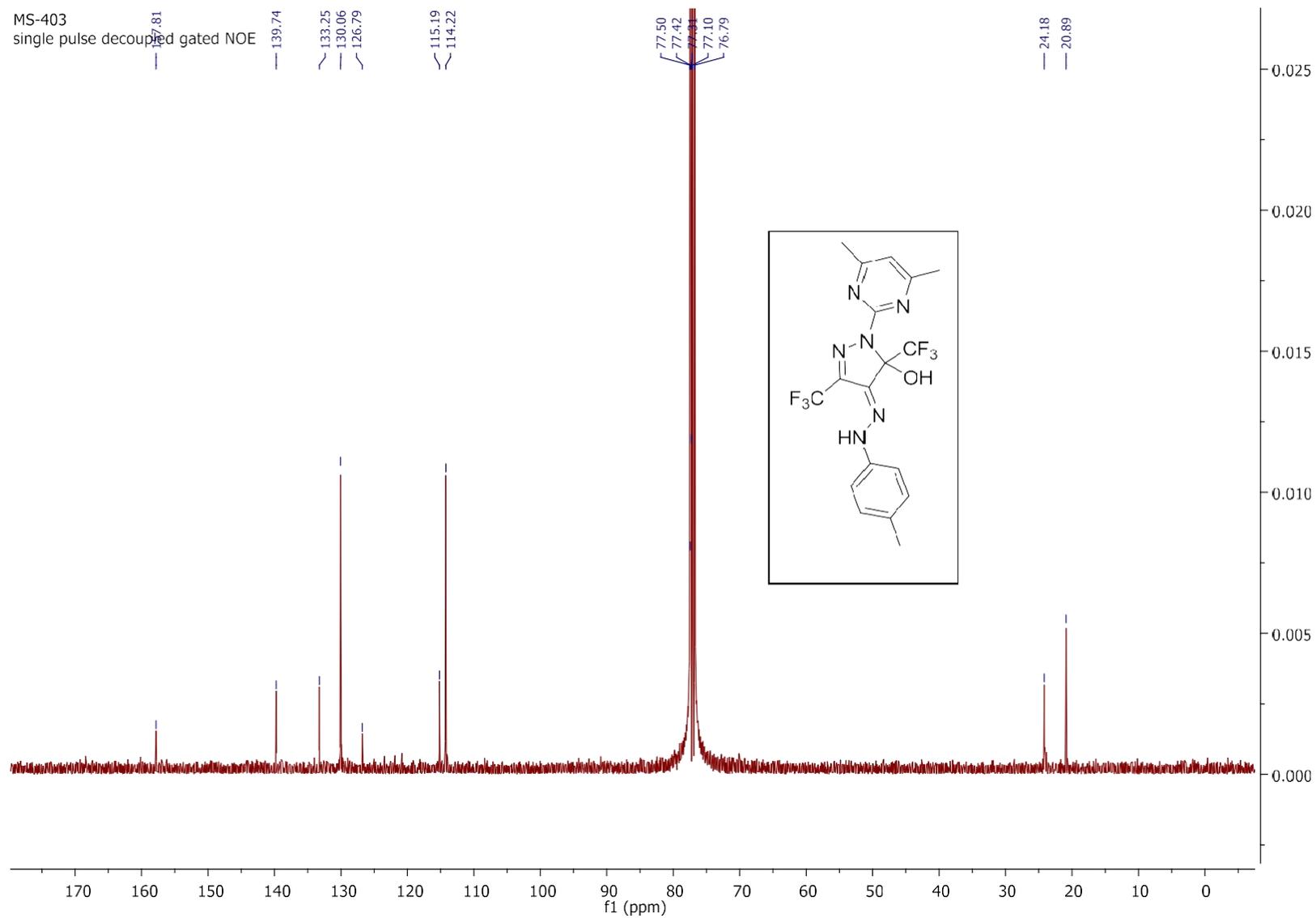


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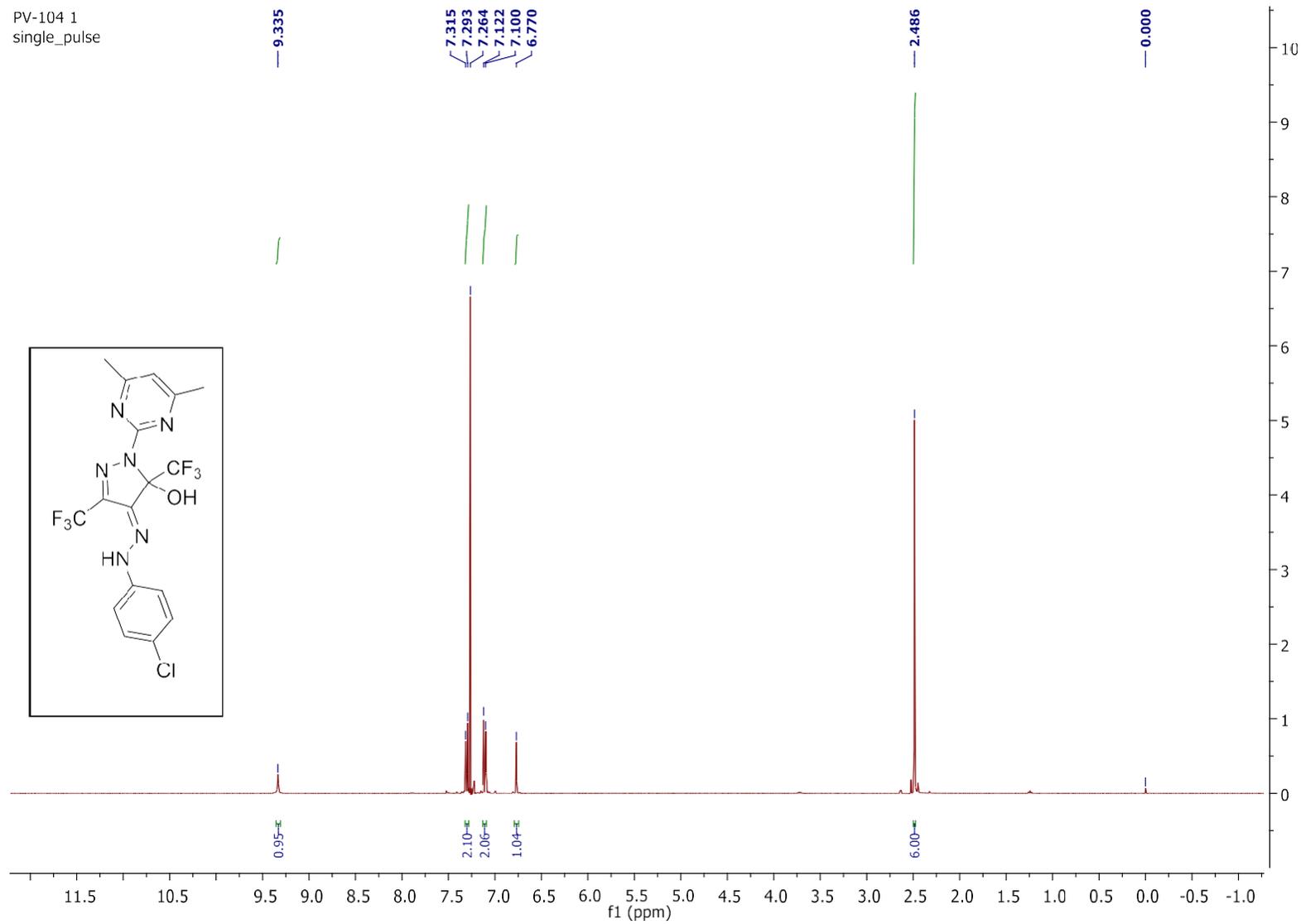
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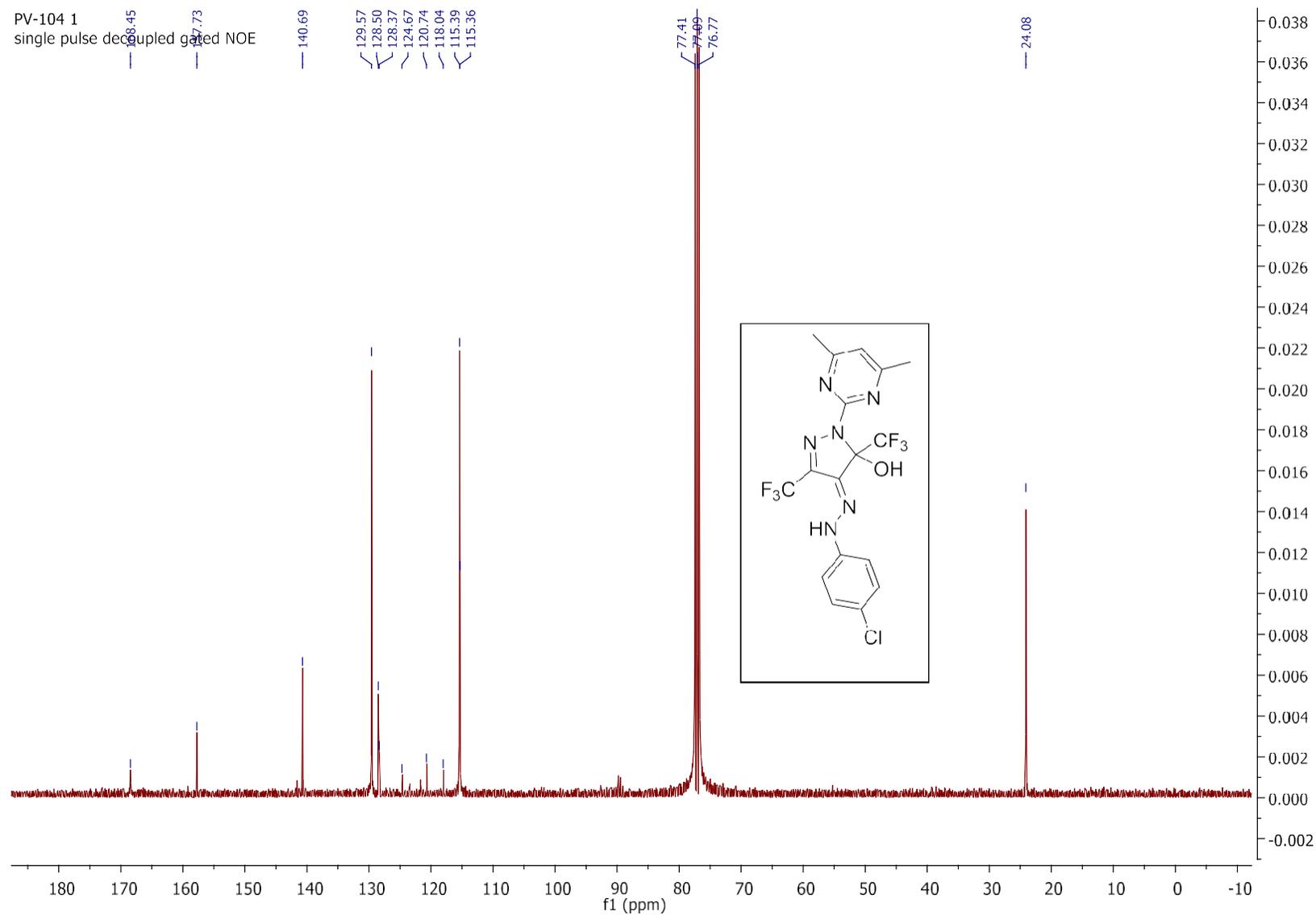
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4-(2-(4-chlorophenyl)hydrazono)-1-(4,6-dimethylpyrimidin-2-yl)-5-hydroxy-3,5-bistrifluoromethylpyrazoline 15b



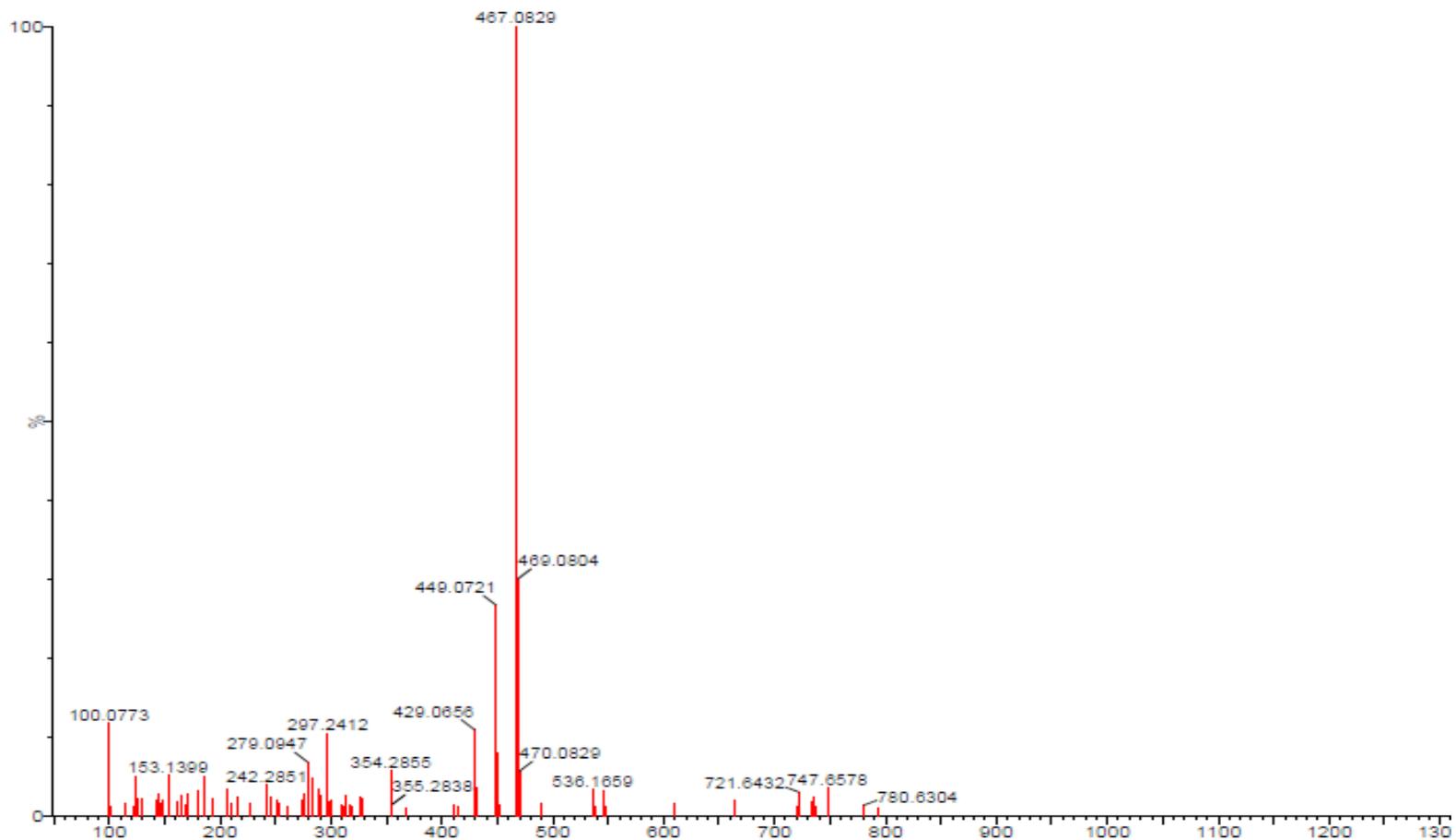
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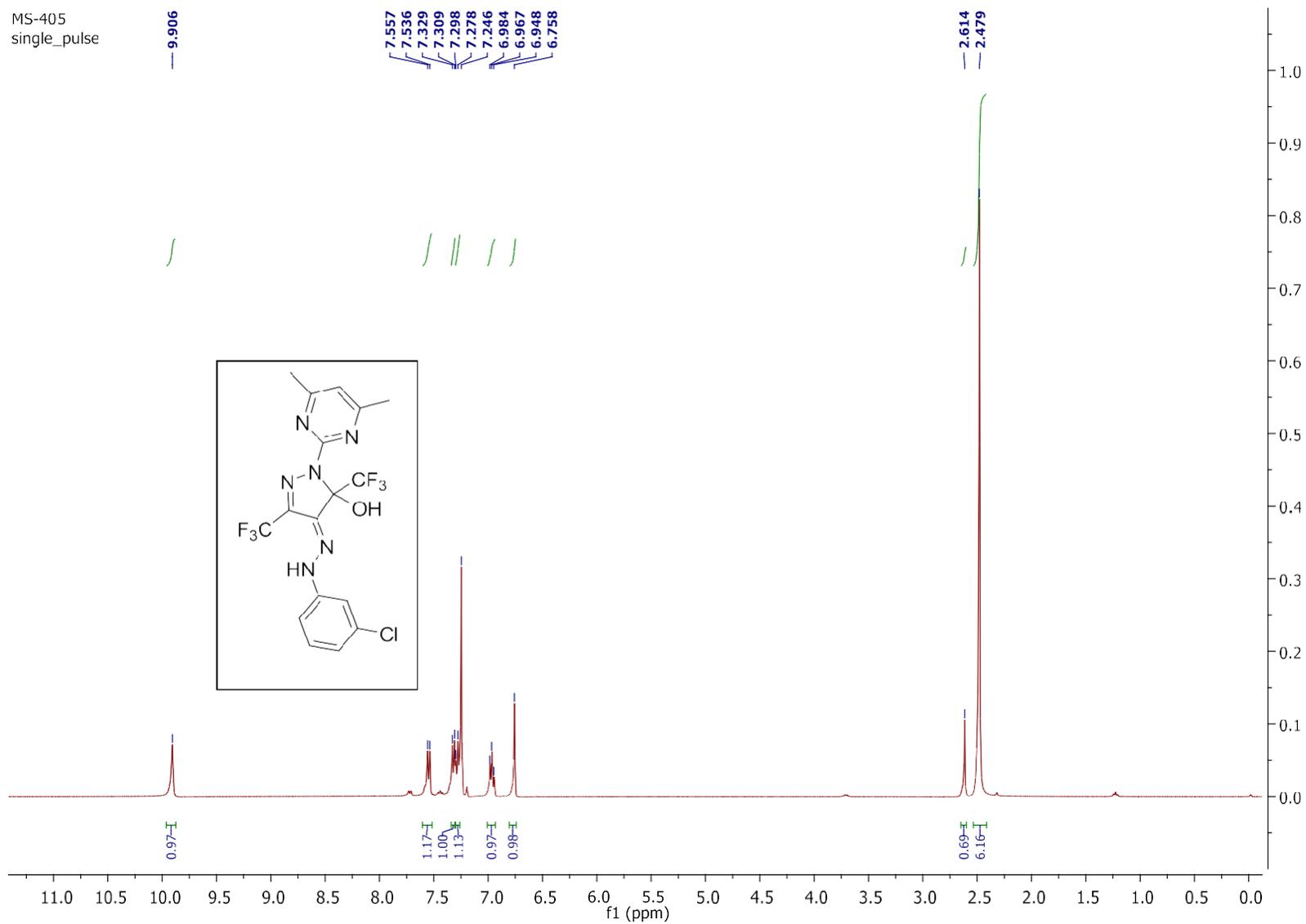
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2

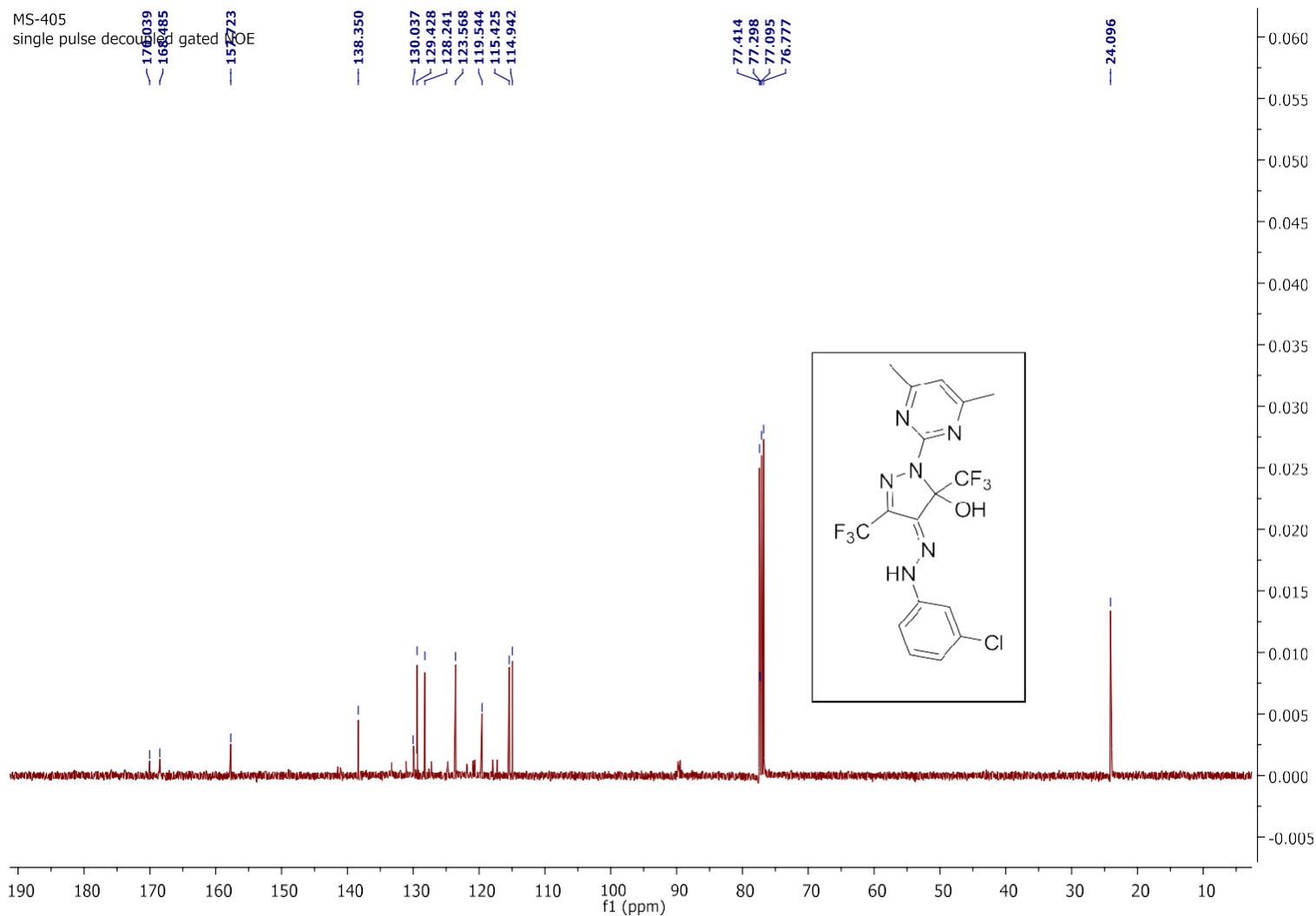
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4-(2-(3-chlorophenyl)hydrazono)-1-(4,6-dimethylpyrimidin-2-yl)-5-hydroxy-3,5-bistrifluoromethylpyrazoline 15c



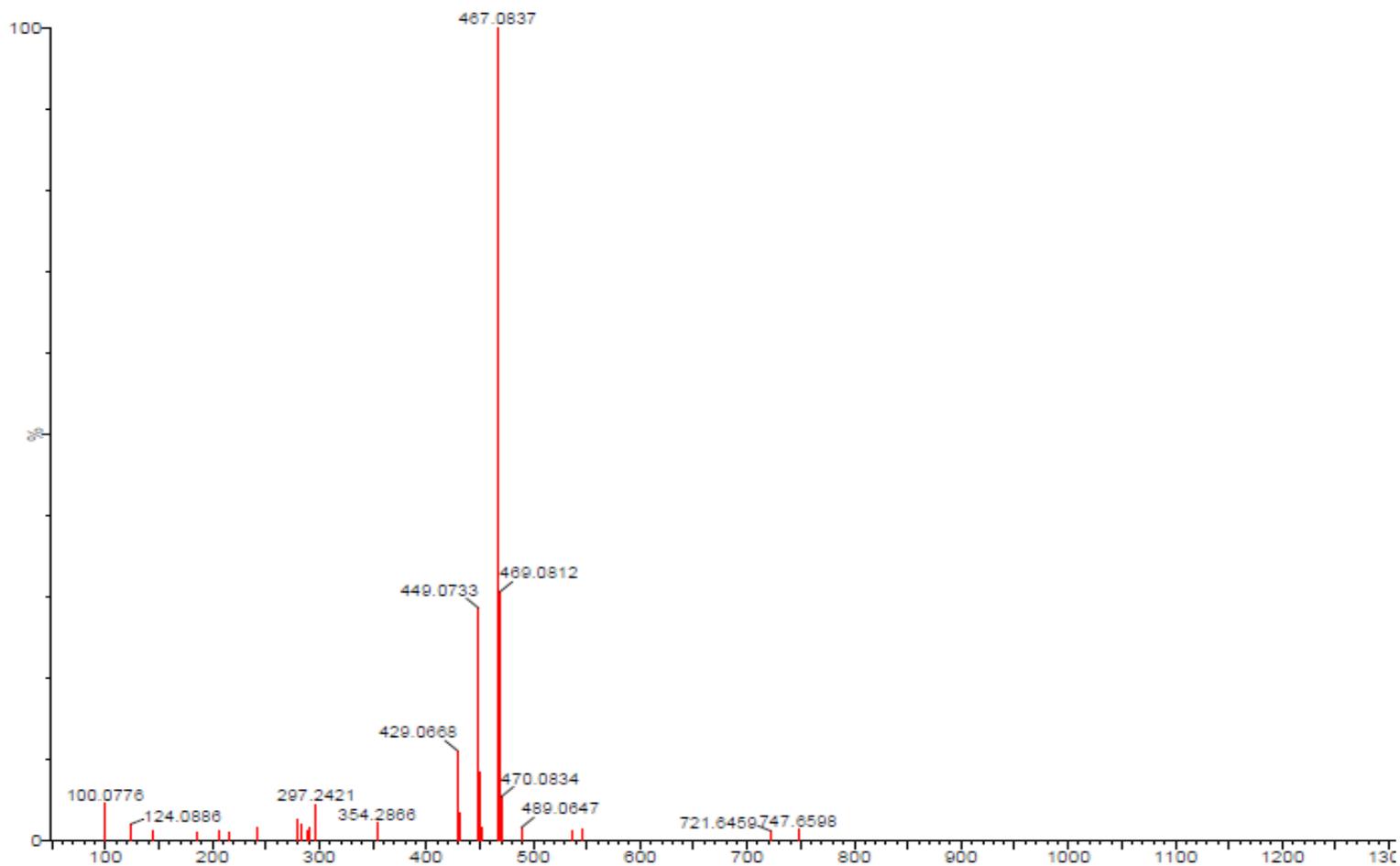
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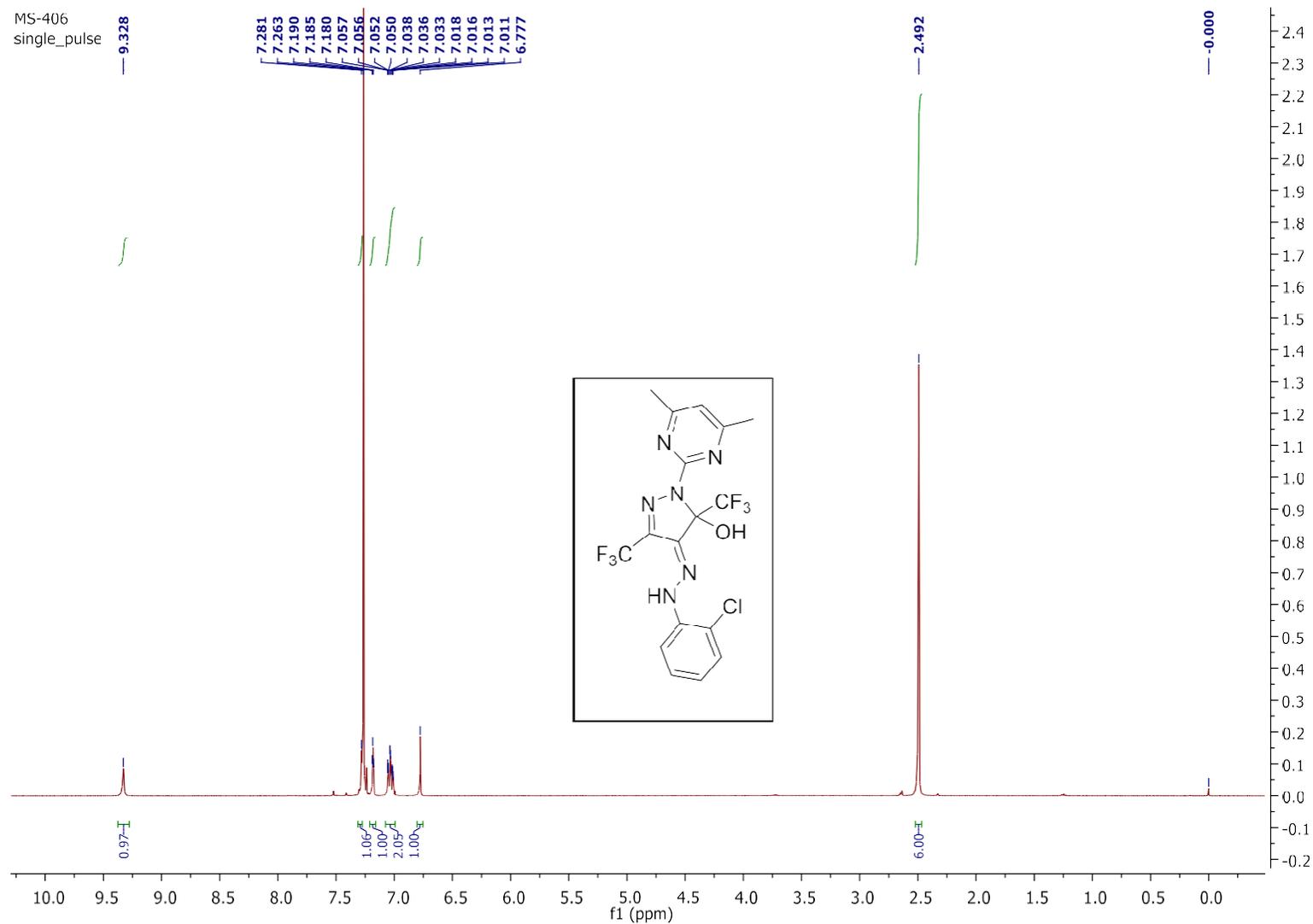
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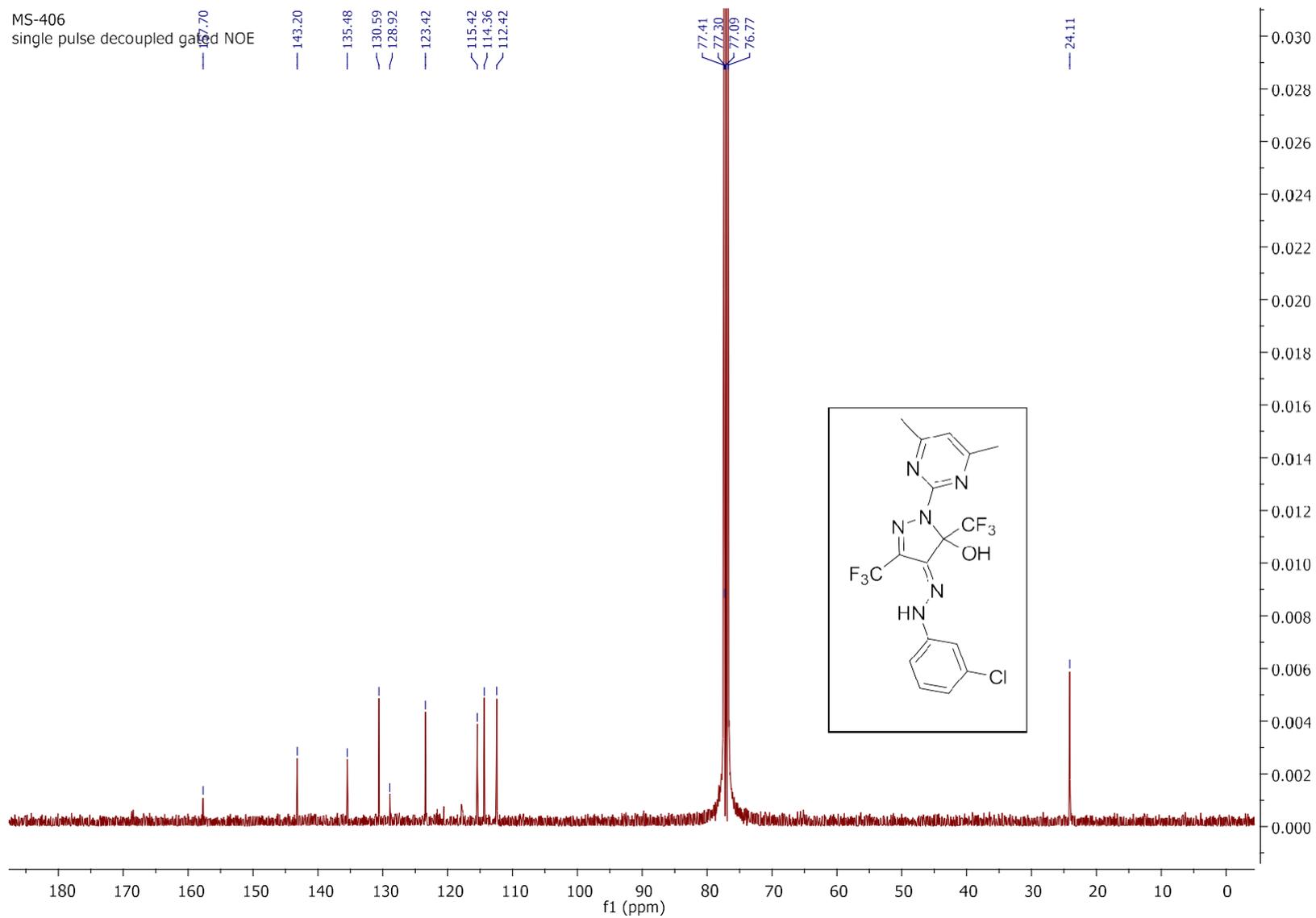
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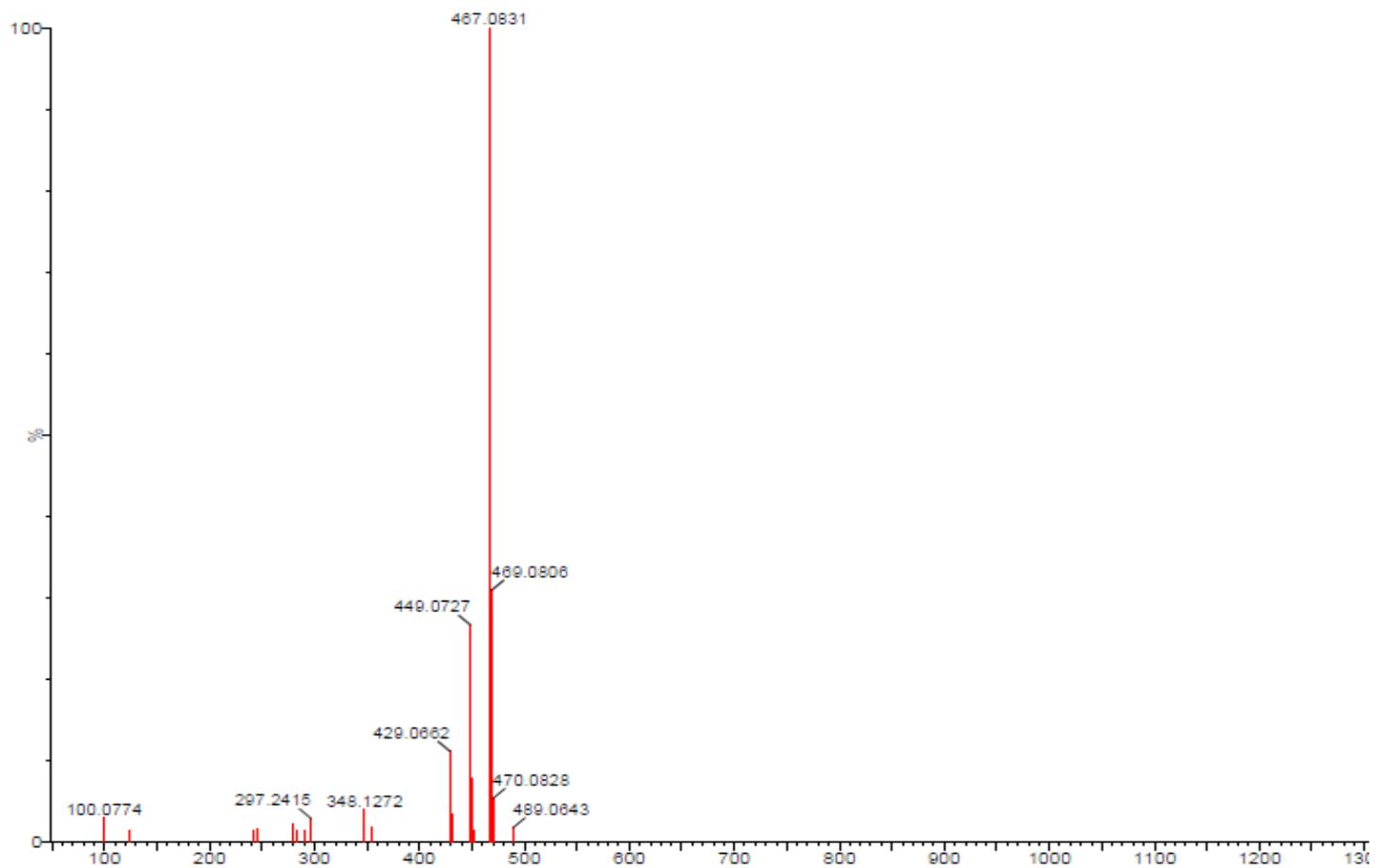
4-(2-(2-chlorophenyl)hydrazono)-1-(4,6-dimethylpyrimidin-2-yl)-5-hydroxy-3,5-bistrifluoromethylpyrazoline 15d



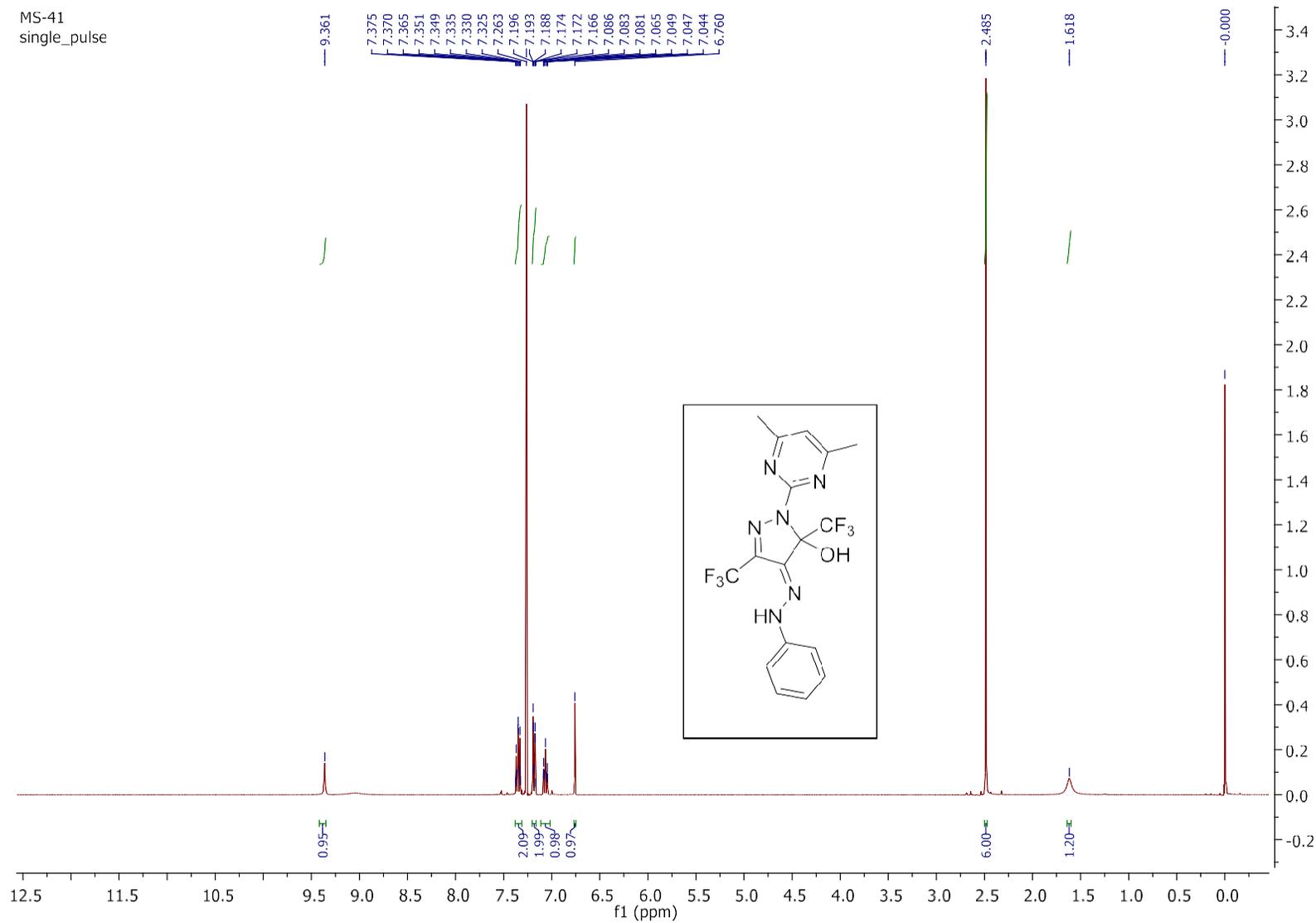
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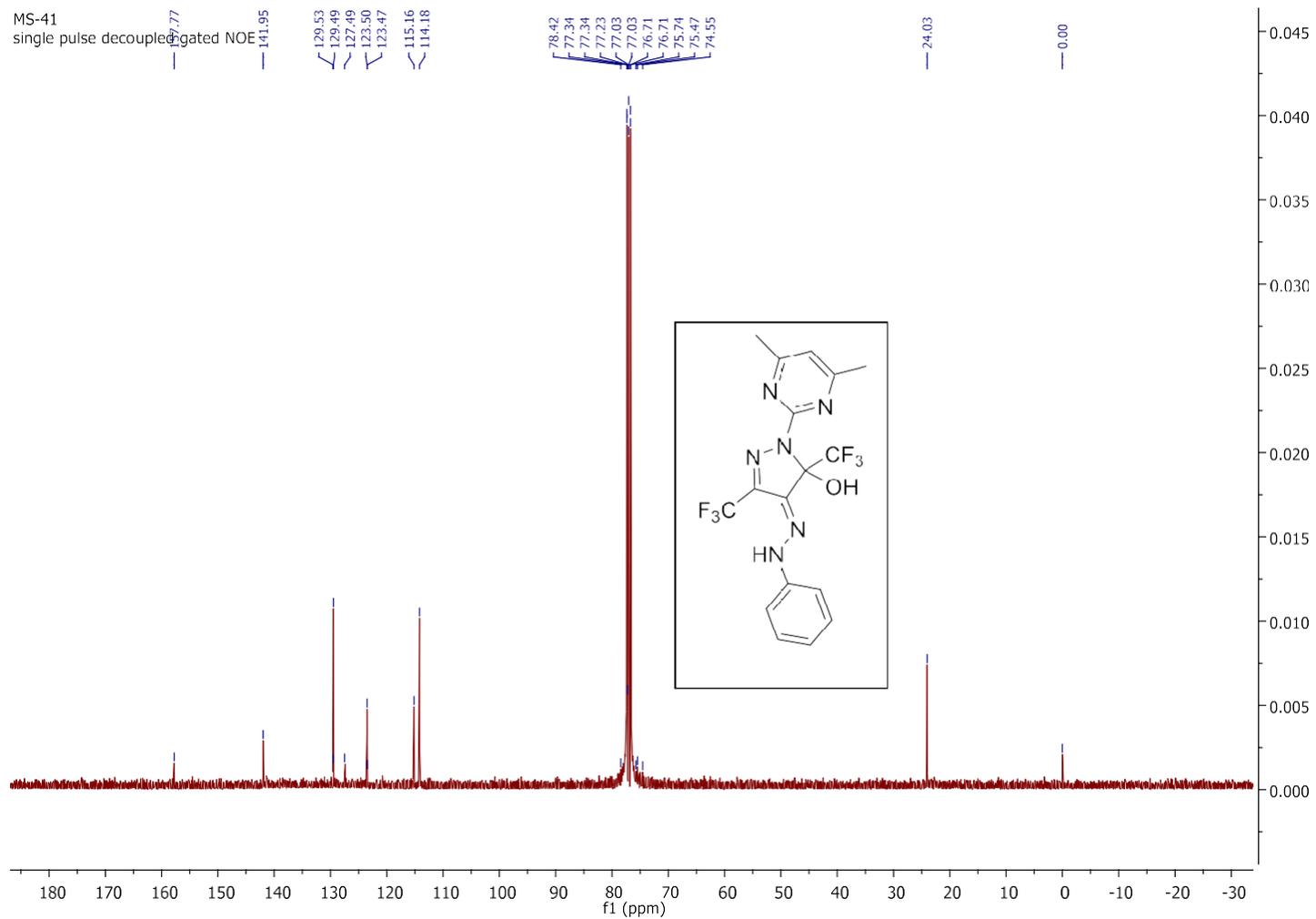
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1-(4,6-dimethylpyrimidin-2-yl)-4-(2-phenylhydrazono)-5-hydroxy-3,5-bistrifluoromethylpyrazoline 15e

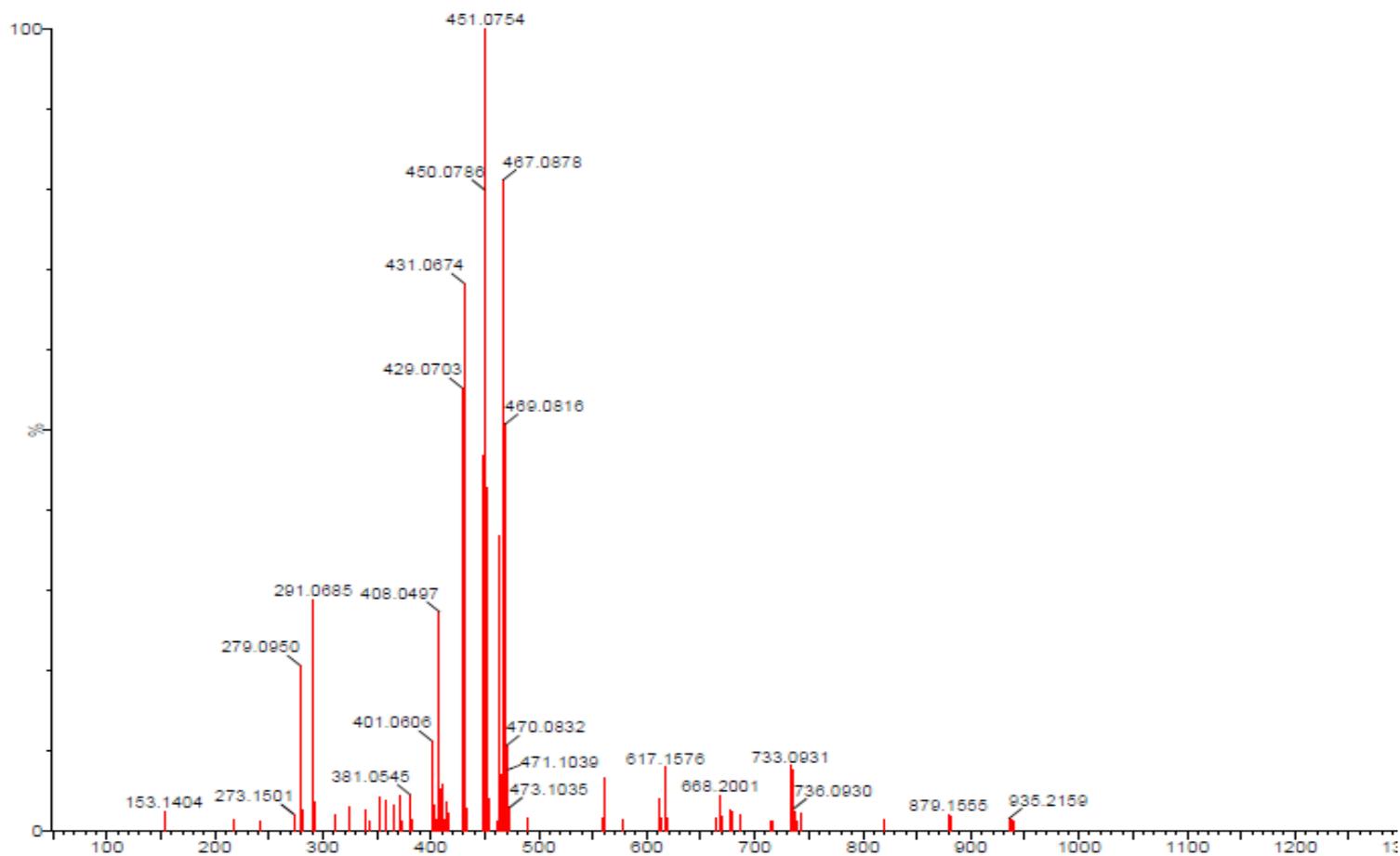


^{13}C 1-(4,6-dimethylpyrimidin-2-yl)-4-(2-phenylhydrazono)-5-hydroxy-3,5-bistrifluoromethylpyrazoline 15e

1-(4,6-dimethylpyrimidin-2-yl)-4-(2-phenylhydrazono)-5-hydroxy-3,5-bistrifluoromethylpyrazoline 15e

7

XEVO-G2XSQTOF#NotSet



1-(4,6-dimethylpyrimidin-2-yl)-4-(2-phenylhydrazono)-5-hydroxy-3,5-bistrifluoromethylpyrazoline 15e

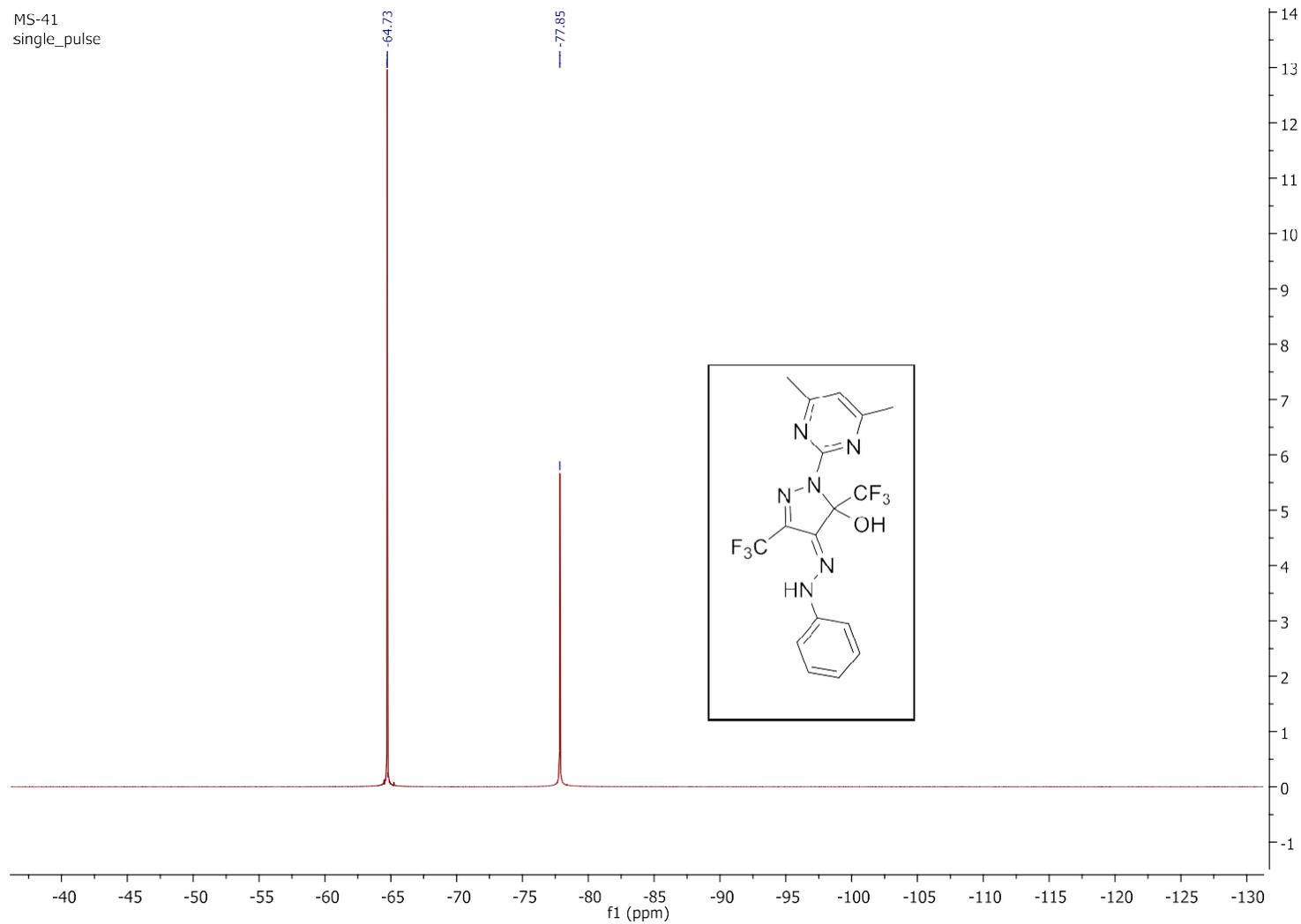
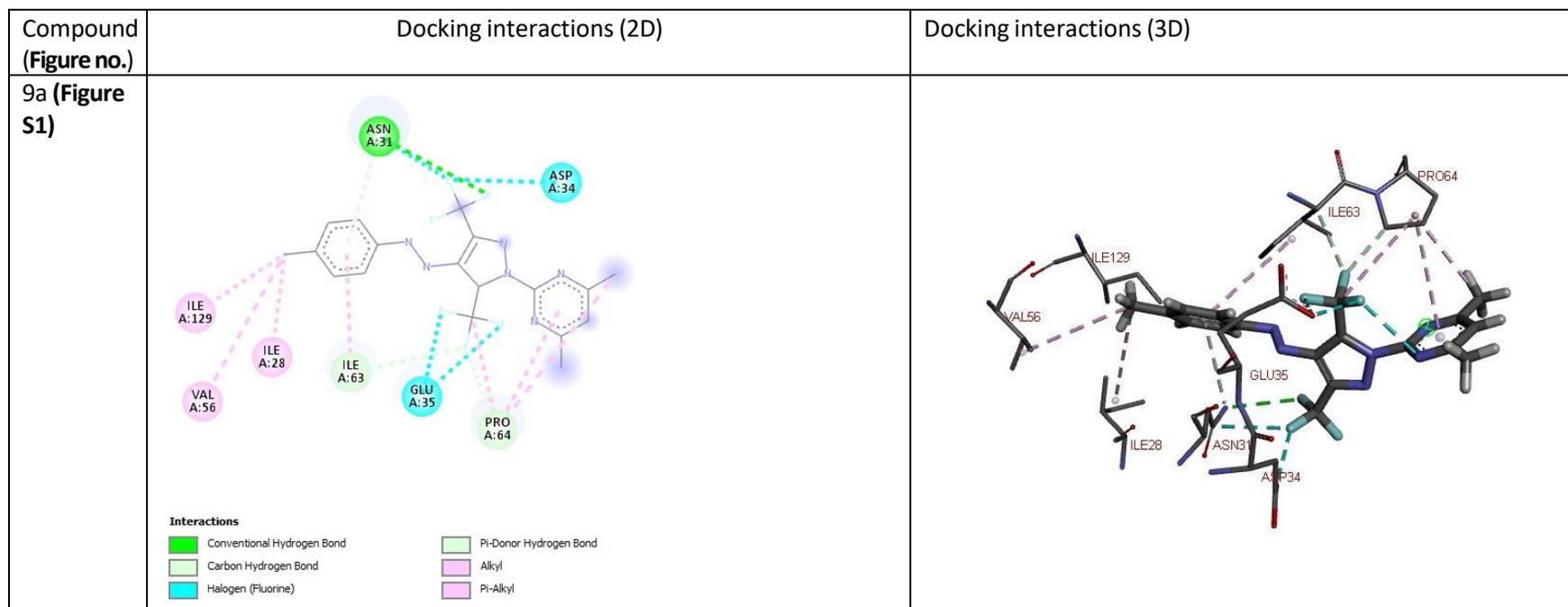
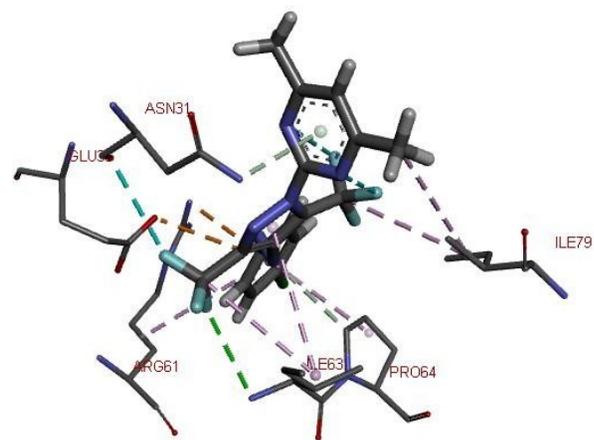
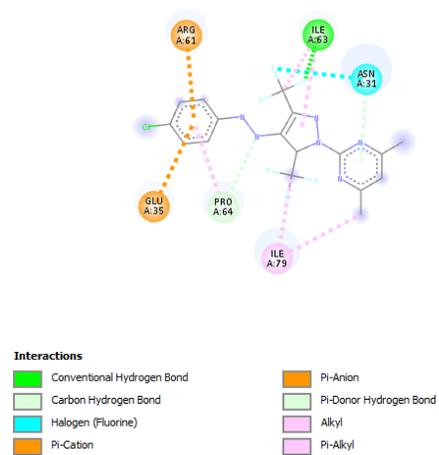


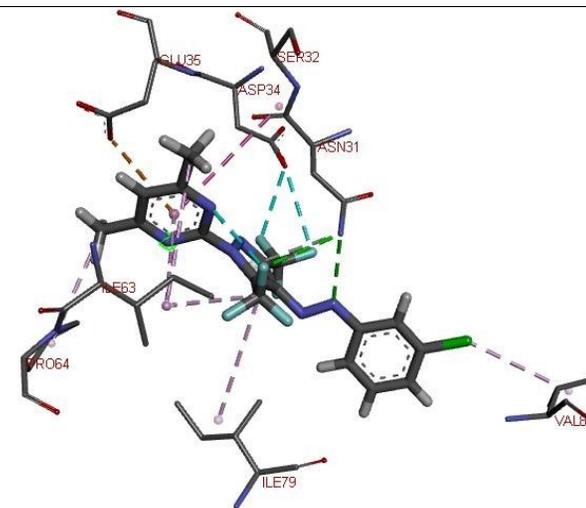
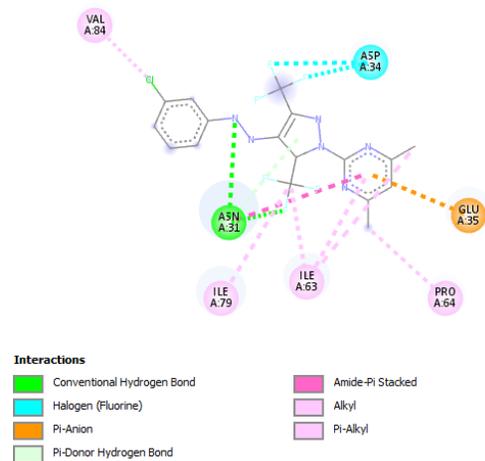
Figure S1-S17: Binding interactions of 9a-f, 10a-d, 11a-b and 15a-e with DNA gyrase.



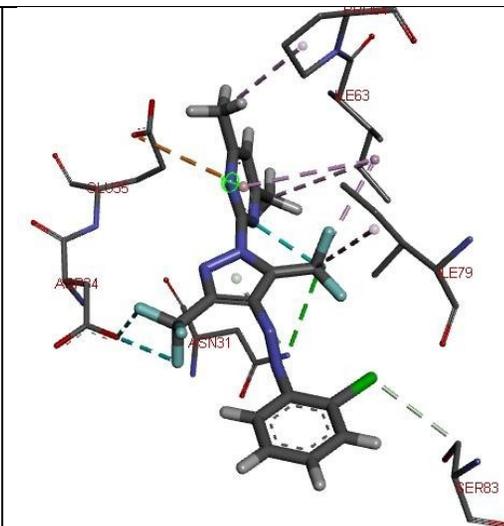
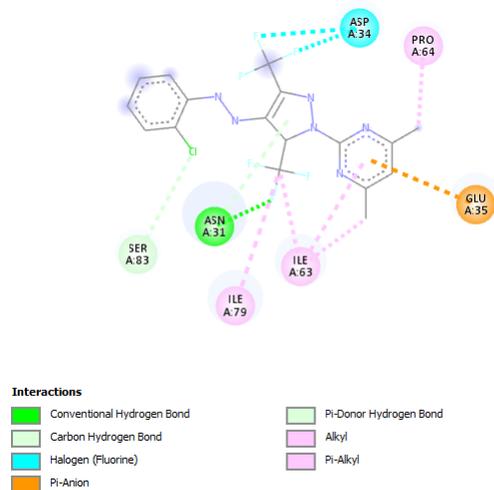
9b (Figure S2)



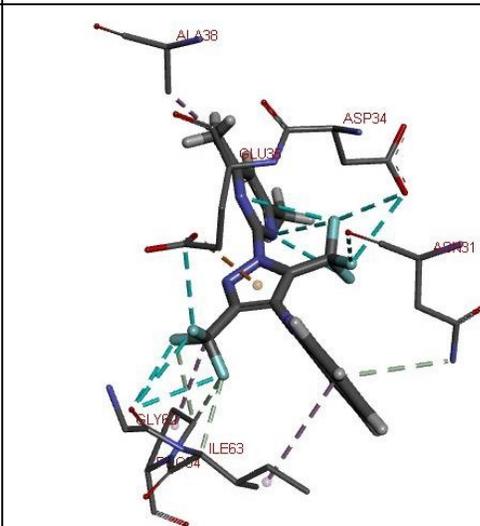
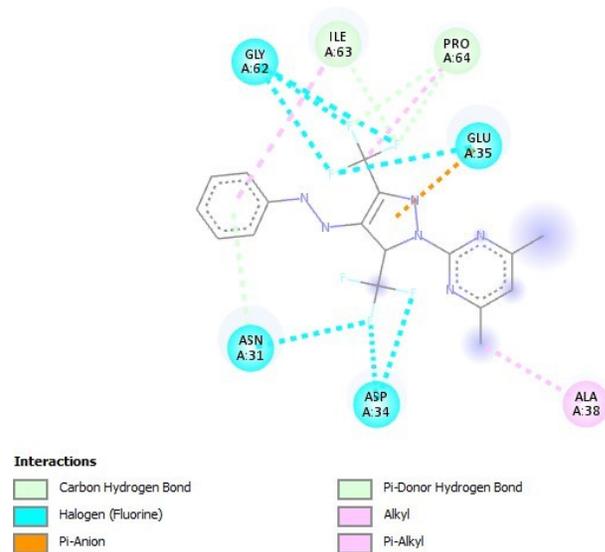
9c (Figure S3)



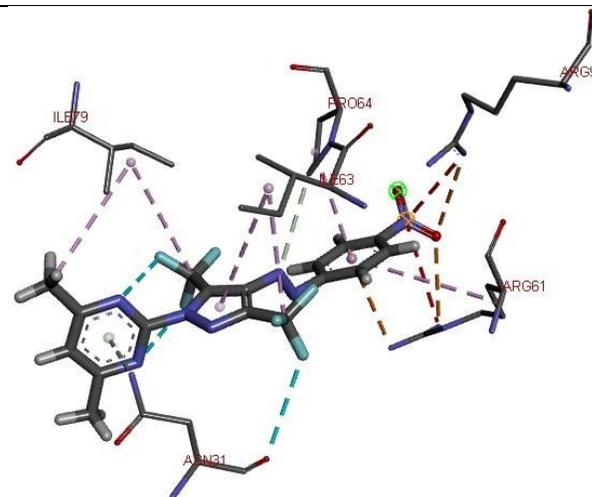
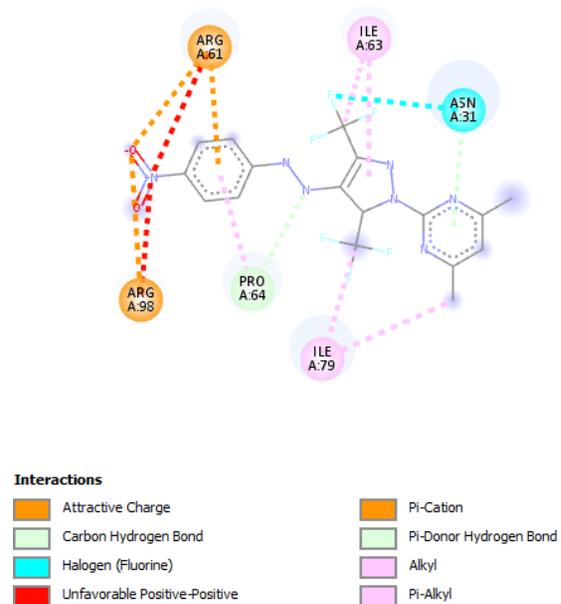
9d (Figure S4)



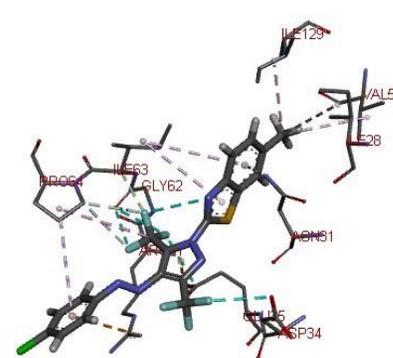
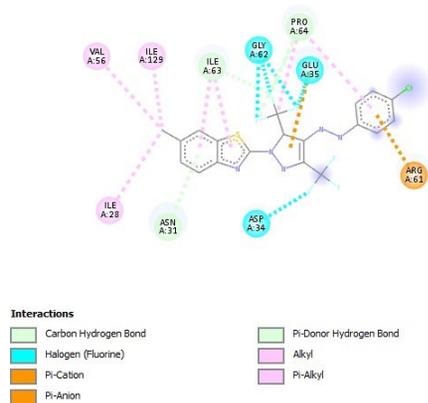
9e (Figure S5)



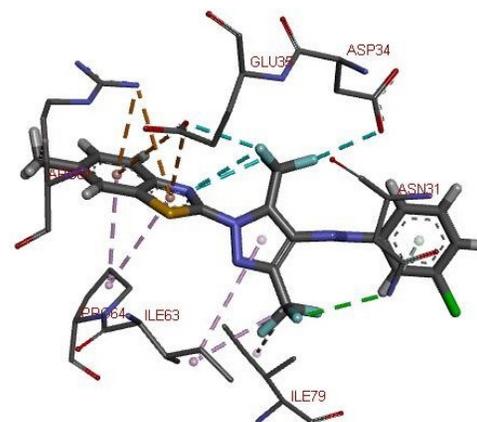
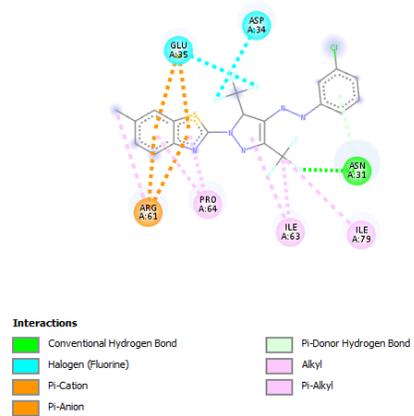
9f (Figure S6)



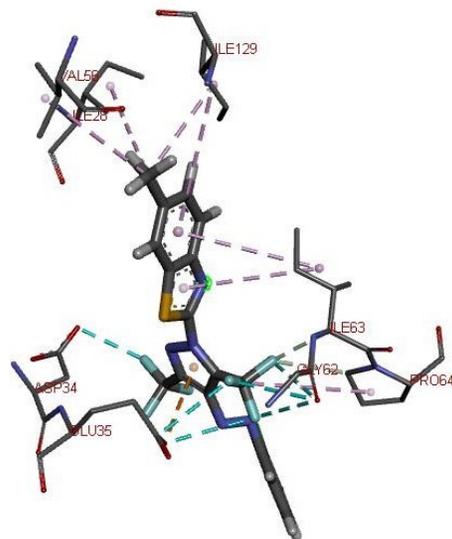
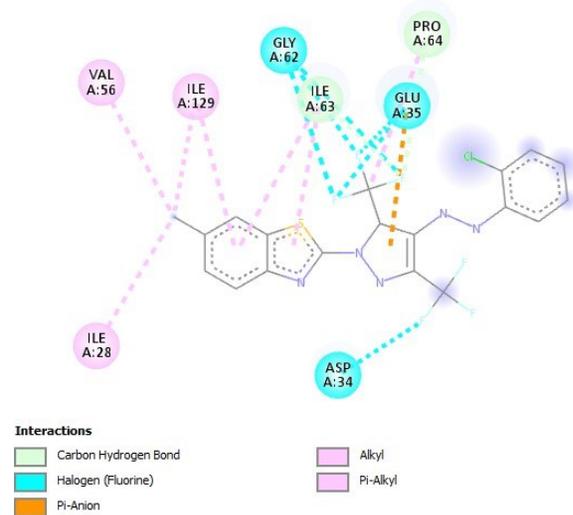
10a (Figure S7)



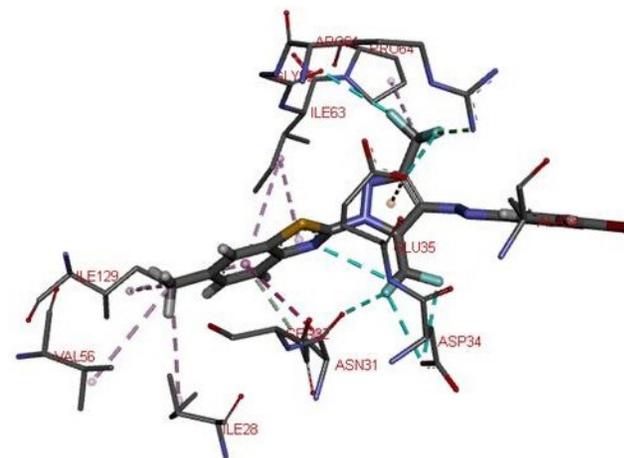
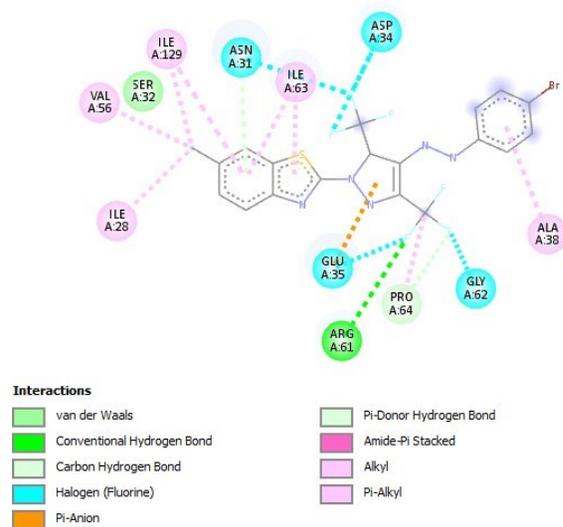
10b (Figure S8)



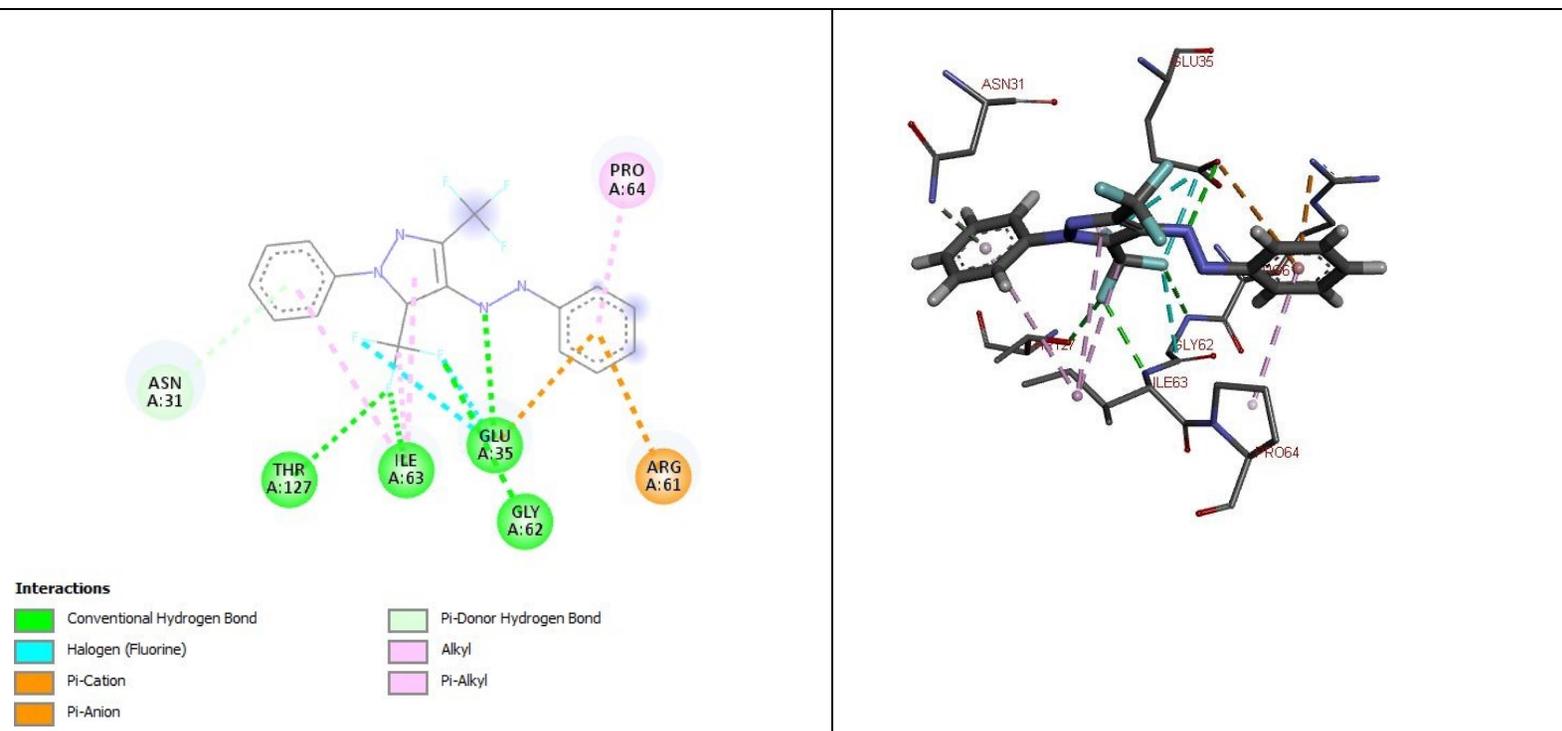
10c (Figure S9)



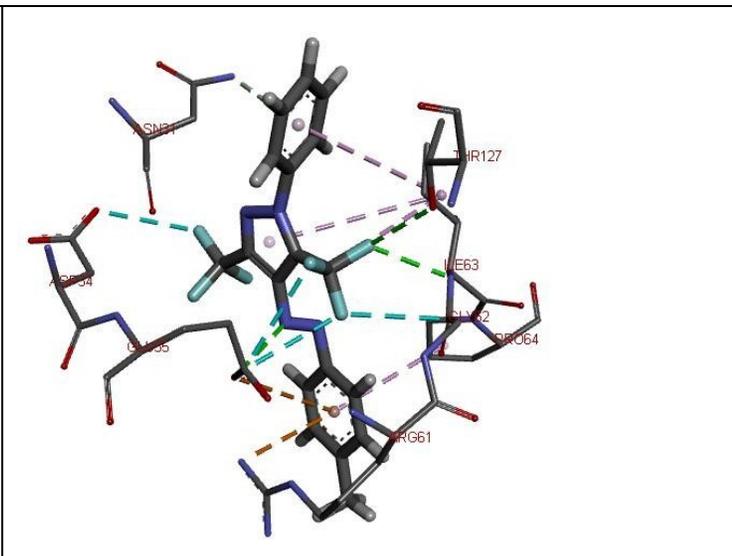
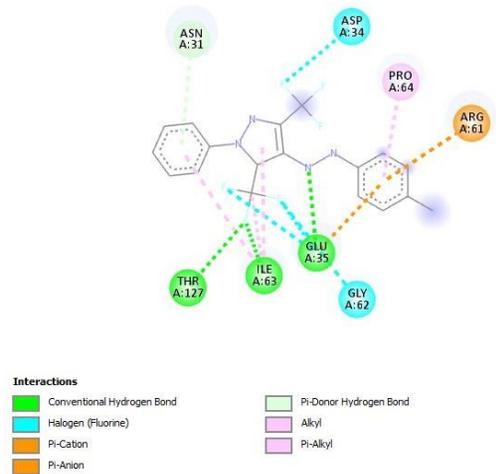
10d (Figure S10)



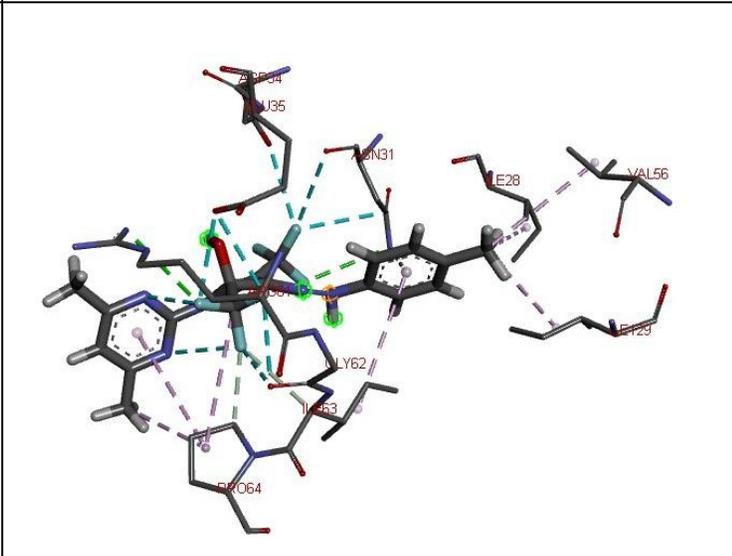
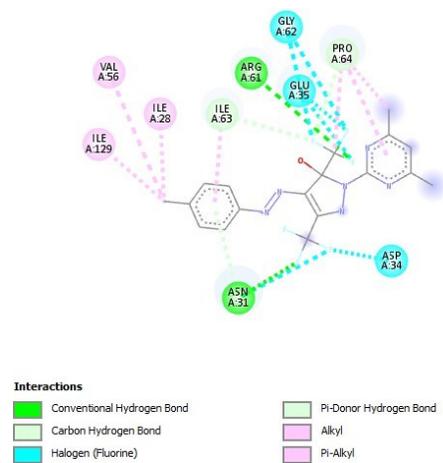
11a (Figure S11)



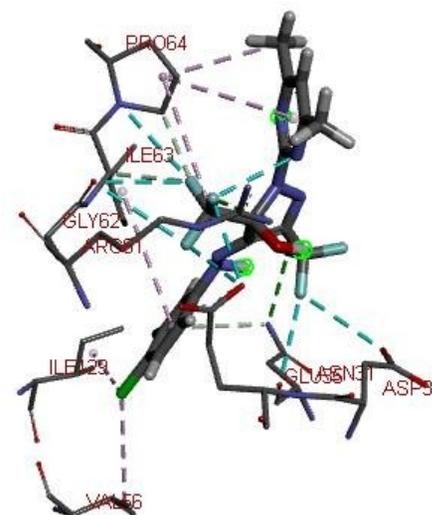
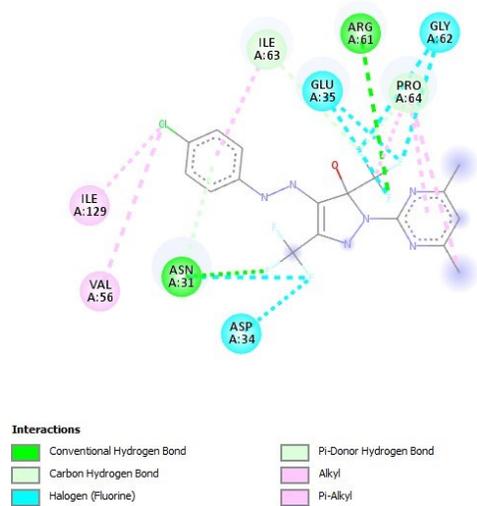
11b (Figure S12)



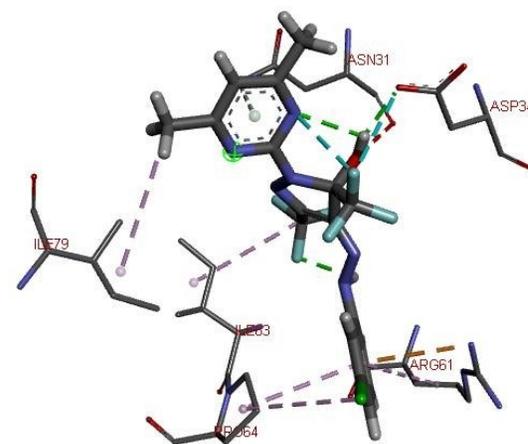
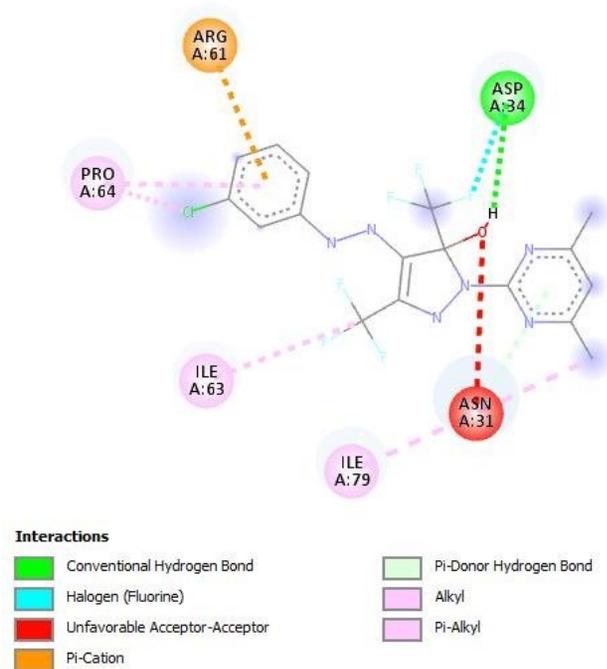
15a (Figure S13)



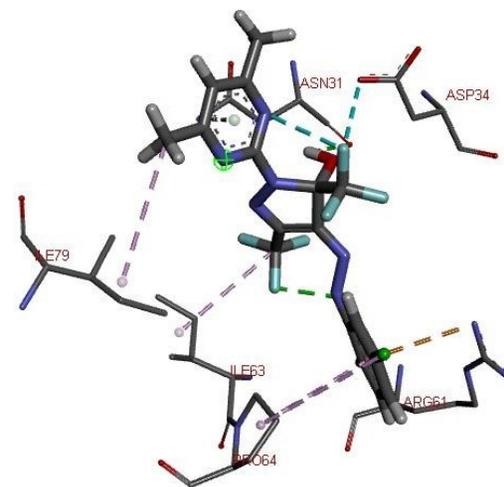
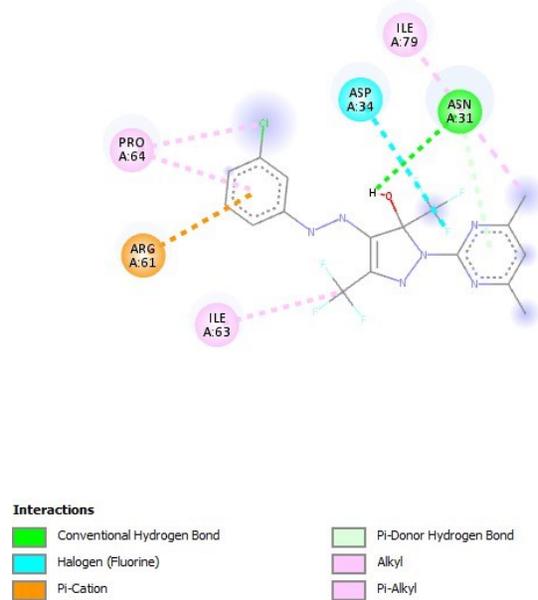
15b (Figure S14)



15c (Figure S15)



15d (Figure S16)



15e (Figure S17)

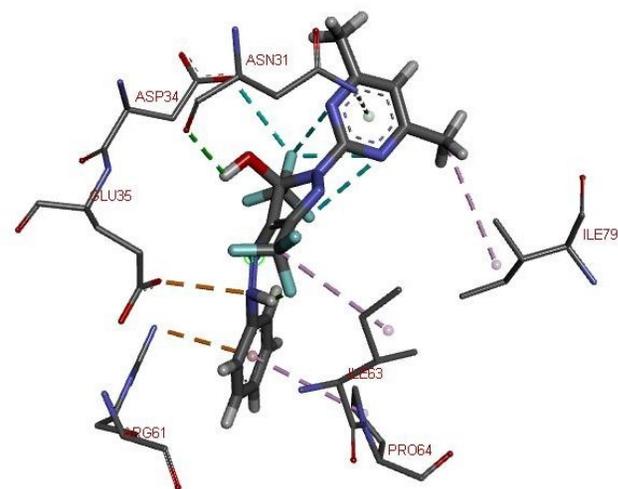
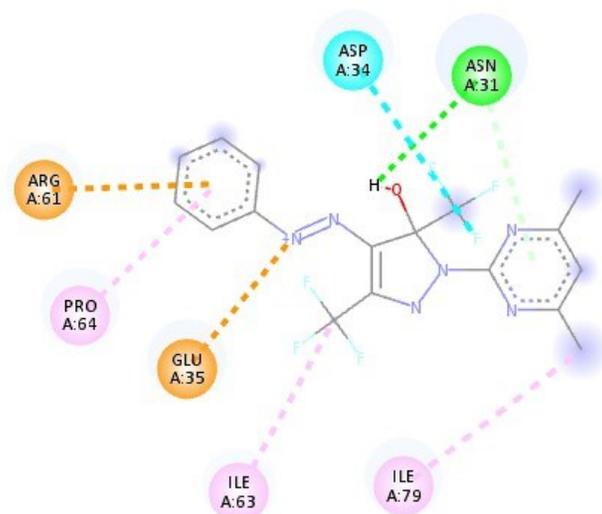


Table S2. Receptor-ligand interactions between binding pocket of DNA gyrase enzyme (PDB code 3G75) and 4-aminopyrazolo[3,4-*b*]pyridines

Compounds	Binding Energy (kcal/mol)	Interacting Residues
15a	-7.7	Asn35 ^a , Ile67 ^b , Arg65 ^c , Glu39 ^c , Ile78 ^b , Pro68 ^b
15b	-6.8	Asn31 ^a , Arg61 ^a , Ile63 ^b , Ile129 ^b , Asp31 ^e , Val56 ^b , Glu35 ^e , Gly62 ^e , Ile78 ^b , Pro64 ^b
15c	-6.8	Asn31 ^k , Arg61 ^g , Asp34 ^{a,e} , Ile63 ^b , Ile79 ^b , Pro64 ^b
15d	-6.6	Asn31 ^a , Arg61 ^g , Ile63 ^b , Asp34 ^e , Ile79 ^b , Pro64 ^b
15e	-6.3	Asn31 ^a , Arg61 ^a , Ile63 ^b , Ile79 ^b , Asp34 ^e , Glu35 ^j
9a	-7.2	Asn31 ^{a,e,f} , Asp34 ^e , Pro64 ^{b,d} , Glu35 ^e , Ile63 ^b , Ile28 ^b , Ile128 ^b , Val56 ^b
9b	-7.4	Arg61 ^{g,h} , Glu35 ^{g,h} , Pro64 ^{f,b} , Ile63 ^{a,b} , Asn31 ^h , Ile79 ^b
9c	-7.7	Val84 ^b , Asp34 ^e , Glu35 ^h , Pro64 ^b , Ile63 ^b , Ile79 ^b , Asn31 ^{a,d,i} , Ser32
9d	-7.5	Ser83 ^d , Asn31 ^{a,d} , Ile79 ^b , Ile63 ^b , Glu35 ^h , Pro64 ^b , Asp34 ^e , Ser32
9e	-8.3	Arg61 ^{j,k,g} , Arg98 ^{i,k} , Pro64 ^{b,d} , Ile79 ^b , Asn31 ^{e,d} , Ile63 ^b
9f	-7.2	Thr127 (2.74) ^a , Glu35 ^c , Ile28 ^e , Val56 ^e , Ile129 ^e , Arg61 (3.51) ^f , Ile63 ^f , Pro64 ^f , Ile79 ^g , Asn31 ^h
10a	-8.3	Thr127 (2.87) ^a , Glu35 (3.47) ^c , Asp34 ^c , Arg61 (3.58) ^d , Ile63 ^f , Pro64 ^f , Asn31 ^h
10b	-8.1	Thr127 ^a , Glu35 ^c , Arg61 ^{d,f} , Asp34 ^c , Asn31 ^h , Pro64 ^f , Ile63 ^f
10c	-8.3	Val56 ^b , Ile129 ^b , Gly62 ^e , Ile63 ^b , Pro64 ^b , Glu35 ^{h,e} , Asp34 ^e , Ile28 ^b
10d	-7.9	Val56 ^b , Ser32, Ile129 ^b , Asn31 ^{d,e} , Ile63 ^b , Asp34 ^e , Ala38 ^b , Gly62 ^e , Pro64 ^{b,d} , Arg61 ^a , Glu35 ^{e,h} , Ile28 ^b
11a	-7.9	Asn31 ^e , Thr127 ^a , Ile63 ^{a,b} , Glu35 ^{a,e,g,h} , Gly ^a , Arg61 ^{g,h} , Pro64 ^b
11b	-7.4	Asn31 ^h , Asp34 ^e , Pro64 ^b , Arg61 ^{g,h} , Gly62 ^e , Glu35 ^{e,a,g,h} , Ile63 ^{a,b} , Thr127 ^a
Amox	-6.4	Thr127 ^a , Arg61 ^a , Glu35 ^c , Ile63 ^f , Pro64 ^f

^ahydrogen bonding, ^balkyl or *n*-alkyl, ^c*n*-carbon, ^d*n*-donor hydrogen bond, ^ehalogen, ^fcarbon hydrogen bond, ^g*n*-cation, ^h*n*-anion, ⁱamide *n*-stacking, ^jattractive charge, ^kunfavourable (++)

Table S3. Solubility, total polar surface area, and calculated Lipinski's rule of five for tested compounds **9a-f**, **10a-d**, **11a-b** and **15a-e**

Comp. No.	Log S ^a	TPSA ^b	MW ^c	cLog P ^d	nHBA ^e	nHBD ^f	RB ^g	nvio ^h
9a	-5.92	68.32	428	5.38	11	0	5	0
9b	-6.21	68.32	448	5.55	11	0	5	0
9c	-6.21	68.32	448	5.54	11	0	5	0
9d	-6.2	68.32	448	5.54	11	0	5	0
9e	-5.68	114.14	459	4.28	13	0	6	0
9f	-5.61	68.32	414	5.04	11	0	5	0
10a	-7.60	83.67	490	6.88	10	0	5	0
10b	-7.60	83.67	490	6.88	10	0	5	0
10c	-7.60	83.67	490	6.84	10	0	5	0
10d	-7.92	83.67	534	6.96	10	0	5	0
11a	-5.83	42.54	384	5.42	9	0	5	0
11b	-6.13	42.54	398	5.80	9	0	5	0
15a	-5.66	86.00	446	3.94	11	0	5	0
15b	-5.95	86.00	466	4.18	11	2	5	0
15c	-5.95	86.00	466	4.19	11	2	5	0
15d	-5.95	86.00	466	4.05	11	2	5	0
15e	-5.36	86.00	432	3.61	11	2	5	0

^aSolubility parameter, ^bTotal polar surface area (Å²), ^cMolecular weight, ^dCalculated lipophilicity, ^eNumber of hydrogen bond acceptors, ^fNumber of hydrogen bond donors, ^gRotatable bonds, ^hNumber of violations to Lipinski's rule of five.

Table S4. Toxicity risks, Druglikeness, and Bioavailability score for tested compounds **9a-f**, **10a-d**, **11a-b** and **15a-e**

Comp. No.	Toxicity risks (Mutagenicity, Tumorigenicity, Irritancy, Reproductive effects)	Druglikeness	Bioavailability score
9a	Nil	Yes	0.55
9b	Nil	Yes	0.55
9c	Nil	Yes	0.55
9d	Nil	Yes	0.55
9e	Nil	Yes	0.55
9f	Nil	Yes	0.55
10a	Nil	Yes	0.55
10b	Nil	Yes	0.55
10c	Nil	Yes	0.55
10d	Nil	Yes	0.55
11a	Nil	Yes	0.55
11b	Nil	Yes	0.55
15a	Nil	Yes	0.55
15b	Nil	Yes	0.55
15c	Nil	Yes	0.55
15d	Nil	Yes	0.55
15e	Nil	Yes	0.55

Table S4 summarizes the *in silico* data as additional information about the toxicity risks, druglikenes

Table S5. MIC values of compounds **9a-f**, **10a-d**, **11a,b** and **15a-e** against tested bacterial and fungal strains

Pathogen → Compounds	Minimum inhibitory concentration (MIC) value ^a (µg/ml)							
	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>S. typhi</i>	<i>S. aureus</i>	<i>L. monocytogenes</i>	<i>B. cereus</i>	<i>S. flexneri</i>	<i>C. albicans</i>
9a	6.25	3.12	6.25	6.25	3.12	3.12	3.12	12.5
9b	3.12	3.12	6.25	6.25	3.12	3.12	3.12	12.5
9c	6.25	3.12	6.25	6.25	3.12	3.12	3.12	12.5
9d	6.25	3.12	3.12	3.12	3.12	3.12	3.12	12.5
9e	6.25	3.12	3.12	3.12	3.12	6.25	3.12	12.5
9f	6.25	3.12	6.25	3.12	3.12	3.12	3.12	12.5
10a	31.25	6.25	31.25	6.25	3.12	3.12	31.25	12.5
10b	31.25	6.25	6.25	6.25	6.25	6.25	12.5	12.5
10c	3.12	6.25	3.12	6.25	6.25	12.5	6.25	12.5
10d	6.25	12.5	6.25	6.25	12.5	12.5	12.5	6.25
11a	25.0	12.5	6.25	6.25	6.25	6.25	6.25	1.56
11b	6.25	6.25	3.12	6.25	3.12	3.12	3.12	12.5
15a	25.0	12.5	12.5	6.25	12.5	6.25	31.25	12.5
15b	12.5	6.25	12.5	6.25	31.25	6.25	25.0	12.5
15c	25.0	12.5	25.0	6.25	6.25	6.25	6.25	12.5
15d	25.0	12.5	6.25	12.5	12.5	6.25	12.5	12.5
15e	12.5	12.5	25.0	6.25	12.5	6.25	31.25	12.5
Amox ^b	3.12	3.12	3.12	3.12	3.12	3.12	3.12	-
Fluc ^c	-	-	-	-	-	-	-	6.25
Broth Control	No growth observed							
Inoculum Control	Growth observed							

^aMean of three replicates. ^bAmox-(Amoxicillin) was used as standard drug for antibacterial activity. ^cFluc-(Fluconazole) was used as standard drug for antifungal activity.

Table S6. Acute toxicity results of compounds **9a-f**, **10a-d**, **11a,b** and **15a-e** against normal cells at 1mg/ml concentration

Pathogen Compounds	Mouse Fibroblast cell Cell Viability %	Plant seed germination Cell Viability %
9a	89.6	98.0
9b	91.4	100
9c	95.2	100
9d	88.3	96
9e	97.8	100
9f	94.2	100
10a	90.2	98
10b	90.5	100
10c	91.8	97
10d	96.6	96
11a	94.5	98
11b	96.6	98
15a	92.5	96
15b	95.6	98
15c	97.2	98
15d	91.2	100
15e	93.5	100