ELECTRONIC SUPPORTING INFORMATION

Easy one-pot synthesis of multifunctionalized indole-pyrrole hybrids as a new class of antileishmanial agents

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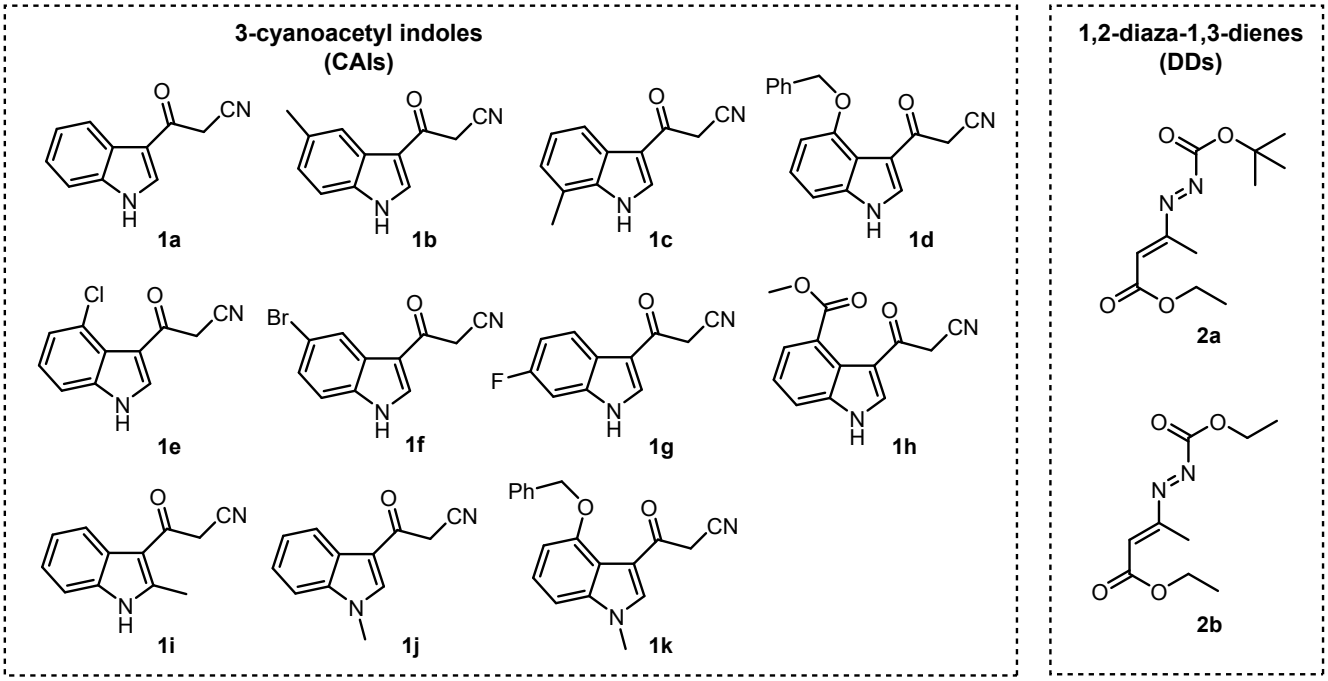
1. General Remarks

All the commercially available reagents and solvents were used without further purification. Indoles (**Ia-k**), cyanoacetic acid (**A**) and acetic anhydride (**B**) were commercial materials; 3-Cyanoacetyl indoles (CAIs) **1a-k**[1] and 1,2-diaza-1,3-dienes (DDs) **2a,b**[2-4] were prepared according to literature procedures. Chromatographic purification of compounds was carried out on silica gel (60-200 μm). TLC analysis was performed on Merck silica gel plates (silica gel 60 F254); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulphuric acid followed by heating on a hot plate. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, using DMSO-d_6 or $CDCl_3$ as solvent on a Bruker Ultrashield 400 spectrometer (Bruker, Billerica, MA, USA) and analyzed using TopSpin 1.3 (2013) software package. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in descending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, sept = septet, m = multiplet and br = broad signal. All coupling constants (J value) are given in Hertz [Hz]. High-resolution mass spectra were performed by slow direct infusion (5 μL/min) of ≈ 0.1 μg/mL solution (acetonitrile/0.1% aqueous formic acid 1:1) of new compounds, using Orbitrap Exploris 240 mass spectrometer (Thermo Scientific, Waltham, MA, USA) equipped with an ESI source; only molecular ions $[M + H]^+$ are given. Melting points were determined by Buchi (Gallen, Switzerland) B-540 in open capillary tubes and are uncorrected.

2. Synthesis of substrates

2.1. List of substrates **1a–k** and **2a,b** prepared according to the general procedures.[1],[2–4]



2.2. Procedure for the synthesis of 3-cyanoacetyl indoles (CAIs) **1a–k**[1]:

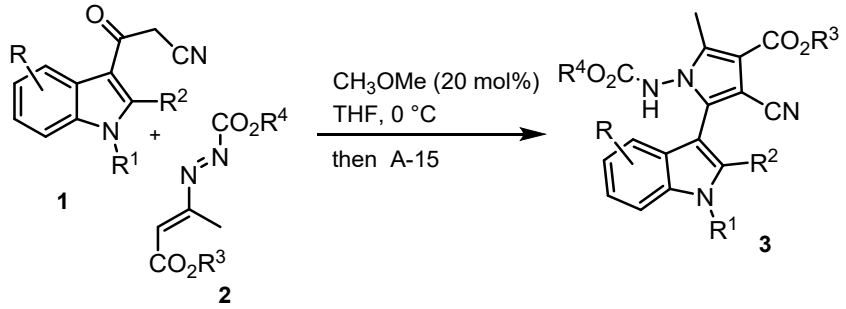
A stirred solution of cyanoacetic acid (4.8 mmol, 1.2 equiv) and acetic anhydride (4 mL) was heated to 65 °C using an oil bath for 10 min. Then, corresponding indole (4 mmol, 1.0 equiv) was added to reaction mixture and heated to 85 °C. After completion of the reaction as monitored by TLC, the mixture was cooled to room temperature, and then in ice bath and the solid formed was collected, washed with methanol (5 mL) and dried to give desired compound **1**.

2.3. Procedure for the synthesis of 1,2-diaza-1,3-dienes (DDs) **2a,b**[2–4]:

Commercially available ethyl 2 chloroacetoacetate (5 mmol) was added to a magnetically stirred of ethyl or *tert*-butyl carbazate (5 mmol) in tetrahydrofuran (50 mL). The reaction was allowed to stand under magnetic stirring at room temperature until the disappearance of the reagents (monitored by TLC chromatography). The reaction solvent was then evaporated under reduced pressure, the crude α-chloro-hydrazone was dissolved in ethyl acetate and treated with aqueous saturated solution of sodium carbonate (50 mL x 2) and then with an aqueous solution of sodium hydroxide (1%, 50 mL x 1). Ethyl acetate was evaporated under reduced pressure and the final 1,2-diaza-1,3-diene **2** were purified by chromatography on silica gel column.

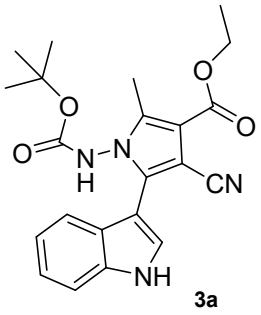
3. Synthesis and characterization of products

3.1 General procedure for the one-pot two-step synthesis of indole-pyrrole hybrids **3a–l**



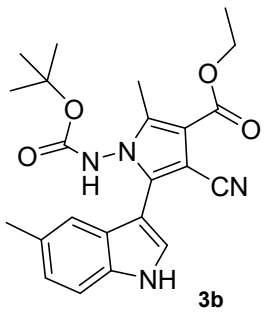
To a stirred solution of the 3-cyanoacetyl indole **1** (0.4 mmol) in THF (2 mL) in the presence of a catalytic amount of sodium methoxide (0.08 mmol) was added dropwise a solution of azoalkene **2** (0.4 mmol) in THF (2 mL) at 0 °C. The mixture was magnetically stirred at 0°C until consumption of the starting material (TLC check). Once the Michael addition was completed (the formation of two isomers of adduct intermediate as major components was revealed by TLC), Amberlyst 15(H) (1.5 equiv.) was added, and the reaction was stirred for an additional 12 hours. After completion of the reaction (monitored by TLC), the resin was filtered off, washed with THF and the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography using cyclohexane and EtOAc as an eluent to obtain the corresponding product **3**.

3.2 Characterization of products



3a

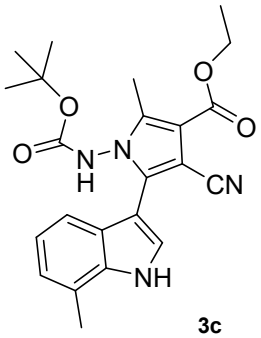
Ethyl 1-((*tert*-butoxycarbonyl)amino)-4-cyano-5-(1*H*-indol-3-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (3a): compound **3a** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 89% yield (145.4 mg); white solid; mp: 188−190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 10.56 (s, 1H), 7.53 (d, *J* = 2.8 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.36 (s, 9H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 154.7, 139.0, 138.4, 136.3, 127.2, 126.0, 122.4, 120.3, 119.9, 116.0, 112.5, 110.2, 101.8, 90.4, 81.9, 60.5, 28.2, 14.5, 10.9; HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{22}H_{25}N_4O_4$ $[M+H]^+$ 409.1870; Found 409.1882.



3b

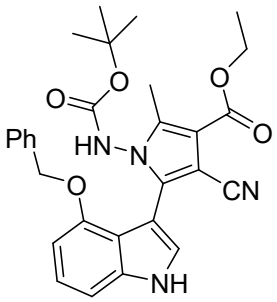
Ethyl 1-((*tert*-butoxycarbonyl)amino)-4-cyano-2-methyl-5-(5-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylate (3b): compound **3b** was isolated by column chromatography (ethyl acetate/cyclohexane 35:65) in 41% yield (69.3 mg); white solid; mp: 182−184 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1H),

10.52 (s, 1H), 7.46 (d, *J* = 2.7 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.27 (s, 1H), 7.02 (dd, *J* = 8.3, 1.6 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 3H), 1.36 (s, 9H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 154.7, 138.9, 138.6, 134.7, 128.9, 127.2, 126.4, 124.0, 119.4, 116.0, 112.1, 110.2, 101.3, 90.5, 81.8, 60.5, 28.2, 21.8, 14.6, 10.9. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{23}H_{27}N_4O_4$ $[M+H]^+$ 423.2027; Found 423.2029.



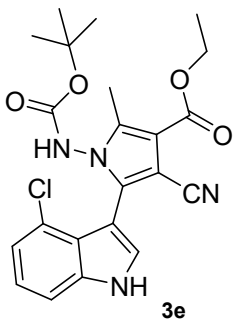
3c

Ethyl 1-((*tert*-butoxycarbonyl)amino)-4-cyano-2-methyl-5-(7-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylate (3c): compound **3c** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 60% yield (101.4 mg); white solid; mp: 148−150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 10.54 (s, 1H), 7.50 (d, *J* = 2.5 Hz, 1H), 7.33 (t, *J* = 4.4 Hz, 1H), 7.00 (d, *J* = 4.6 Hz, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 2.51 (s, 3H), 2.41 (s, 3H), 1.38 (s, 9H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2, 154.9, 139.4, 138.8, 135.7, 126.7, 125.6, 123.1, 121.9, 120.8, 117.3, 116.3, 110.2, 102.1, 90.1, 82.5, 60.9, 28.0, 16.9, 14.4, 10.7. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{23}H_{27}N_4O_4$ $[M+H]^+$ 423.2027; Found 423.2008.



3d

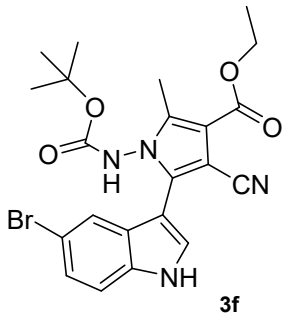
Ethyl 5-(4-(benzyloxy)-1*H*-indol-3-yl)-1-((*tert*-butoxycarbonyl)amino)-4-cyano-2-methyl-1*H*-pyrrole-3-carboxylate (3d): compound **3d** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 39% yield (80.3 mg); white solid; mp: 180−182 °C; Notably, compound **3d** at NMR analysis shows two sets of peaks. This fact is probably ascribable to the presence of bulky substituents around C3-C2' bond that determines the existence of rotamers (ca 95:5 ratio). For clarity only the signals of the main rotamer are reported; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (s, 1H), 10.27 (s, 1H), 7.35–7.11 (m, 8H), 6.72 (dd, *J* = 6.3, 2.0 Hz, 1H), 5.05 (s, 2H), 4.46–3.99 (m, 2H), 2.27 (s, 3H), 1.35 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.9, 155.1, 152.8, 139.3, 137.9, 137.6, 128.3, 128.1, 127.7, 127.3, 126.1, 123.4, 117.4, 116.3, 109.7, 105.9, 102.0, 100.5, 92.8, 81.7, 69.5, 60.3, 28.2, 14.6, 10.8. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{29}H_{31}N_4O_5$ $[M+H]^+$ 515.2289; Found 515.2301.



3e

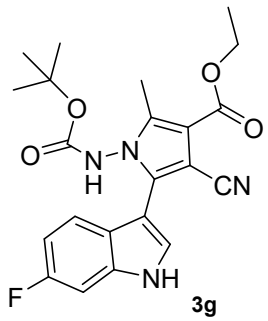
Ethyl 1-((*tert*-butoxycarbonyl)amino)-5-(4-chloro-1*H*-indol-3-yl)-4-cyano-2-methyl-1*H*-pyrrole-3-carboxylate (3e): compound **3e** was isolated by column chromatography (ethyl acetate/cyclohexane 35:65) in 63% yield (111.6 mg); white solid; mp: 202–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 7.38 (s, 1H), 7.36 (d, *J* = 3.1 Hz, 1H), 7.27 (s, 1H), 7.14–7.19 (m, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 2.57 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 155.1, 138.3, 137.5, 129.3, 124.8, 124.4, 123.2, 120.9, 116.0, 115.9, 111.8,

109.9, 100.5, 94.4, 81.8, 60.5, 28.2, 14.5, 11.0. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{22}H_{24}ClN_4O_4$ $[M+H]^+$ 443.1481; Found 443.1495.



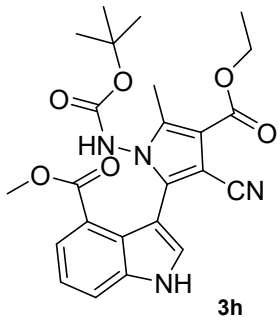
3f

Ethyl 5-(5-bromo-1*H*-indol-3-yl)-1-((*tert*-butoxycarbonyl)amino)-4-cyano-2-methyl-1*H*-pyrrole-3-carboxylate (3f): compound **3f** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 38% yield (74.1 mg); white solid; mp: 188–190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 10.57 (s, 1H), 7.62 (m, 2H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.32 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.34 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 154.7, 139.1, 137.6, 135.1, 129,0, 127.8, 125.1, 121.9, 115.9, 114.6, 113.1, 110.3, 101.5, 90.9, 82.0, 60.6, 28.2, 14.5, 10.9. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{22}H_{24}BrN_4O_4$ $[M+H]^+$ 487.0975; Found 487.0969.



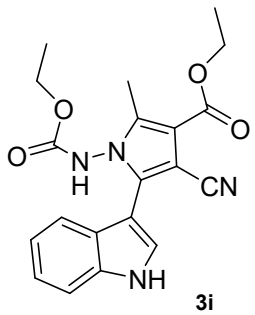
3g

Ethyl 1-((*tert*-butoxycarbonyl)amino)-4-cyano-5-(6-fluoro-1*H*-indol-3-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (3g): compound **3g** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 65% yield (110.9 mg); pale yellow solid; mp: 182–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 10.57 (s, 1H), 7.54 (d, *J* = 2.6 Hz, 1H), 7.48 (dd, *J* = 8.8, 5.3 Hz, 1H), 7.30 (dd, *J* = 9.8, 2.4 Hz, 1H), 6.98 (dt, *J* = 9.2, 2.4 Hz 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.36 (m, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 159.5 (*J* = 234.3 Hz), 154.7, 139.1, 137.9, 136.2 (*J* = 12.7), 127.9, 122.8, 121.0 (*J* = 10.3 Hz), 115.9, 110.3, 108.8 (*J* = 24.5 Hz), 102.0, 98.5 (*J* = 25.5), 90.7, 81.9, 60.5, 28.2, 14.5, 10.9. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{22}H_{24}FN_4O_4$ $[M+H]^+$ 427.1776; Found 427.1759.



3h

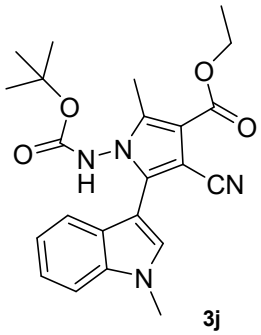
Methyl 3-(1-((*tert*-butoxycarbonyl)amino)-3-cyano-4-(ethoxycarbonyl)-5-methyl-1*H*-pyrrol-2-yl)-1*H*-indole-4-carboxylate (3h): compound **3h** was isolated by column chromatography (ethyl acetate/cyclohexane 35:65) in 90% yield (167.9 mg); white solid; mp: 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.78 (brs, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.22–7.11 (m, 2H), 4.39 (m, 2H), 3.72 (s, 3H), 2.59 (s, 3H), 1.43 (s, 9H), 1.26 (t, *J* = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 163.4, 154.1, 139.2, 139.0, 137.2, 130.9, 124.7, 124.3, 122.0, 121.7, 116.9, 116.5, 109.8, 101.6, 93.2, 82.5, 60.4, 52.3, 26.9, 14.3, 10.8. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{24}H_{27}N_4O_6$ $[M+H]^+$ 467.1925; Found 467.1911.



3i

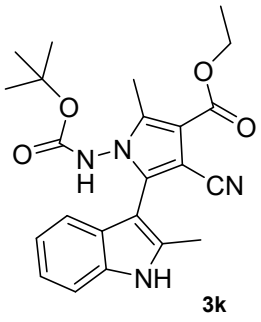
Ethyl 4-cyano-1-((ethoxycarbonyl)amino)-5-(1*H*-indol-3-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (3i): compound **3i** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 67% yield (101.9 mg); white solid; mp: 206–

208 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 10.87 (s, 1H), 7.55 (d, *J* = 2.4 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.08 (q, *J* =6.8 Hz, 2H), 2.41 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 155.7, 139.0, 138.3, 136.3, 127.2, 125.9, 122.5, 120.3, 119.8, 115.9, 112.5, 110.3, 101.9, 90.5, 62.4, 60.6, 14.7, 14.5, 10.9. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{20}H_{21}N_4O_4$ $[M+H]^+$ 381.1557; Found 381.1535.



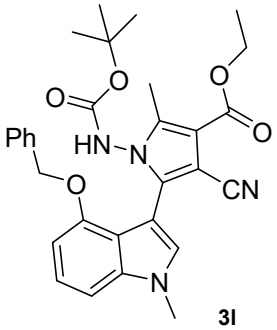
3j

Ethyl 1-((*tert*-butoxycarbonyl)amino)-4-cyano-2-methyl-5-(1-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylate (3j): compound **3j** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 80% yield (135.2 mg); white solid; mp: 182–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.51 (s, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 2.41 (s, 3H), 1.37 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 154.8, 139.0, 137.9, 136.9, 131.0, 126.4, 122.5, 120.5, 120.0, 115.9, 110.9, 110.3, 101.0, 90.6, 81.9, 60.5, 33.3, 28.2, 14.6, 10.9. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{23}H_{27}N_4O_4$ $[M+H]^+$ 423.2027; Found 423.2033.



3k

Ethyl 1-((*tert*-butoxycarbonyl)amino)-4-cyano-2-methyl-5-(2-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylate (3k): compound **3k** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 77% yield (130.1 mg); white solid; mp: 146–148 °C; Notably, compound **3k** at NMR analysis shows two sets of peaks. This fact is probably ascribable to the presence of bulky substituents around C3-C2' bond that determines the existence of rotamers (ca 60:40 ratio). For clarity only the signals of the main rotamer are reported; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 10.47 (s, 1H), 7.37–6.91 (m, 4H), 4.29 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 2.32 (s, 3H), 1.40 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 154.5, 139.3, 138.7, 138.1, 135.5, 127.9, 121.5, 120.0, 118.8, 118.6, 115.9, 111.4, 110.1, 99.1, 92.1, 81.7, 60.5, 28.2, 26.8, 14.5. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{23}H_{27}N_4O_4$ $[M+H]^+$ 423.2027; Found 423.2041.



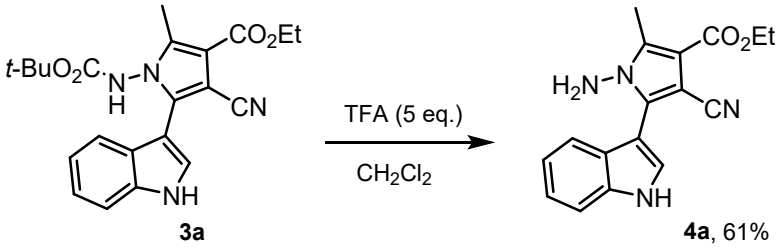
3l

Ethyl 5-(4-(benzyloxy)-1-methyl-1*H*-indol-3-yl)-1-((*tert*-butoxycarbonyl)amino)-4-cyano-2-methyl-1*H*-pyrrole-3-carboxylate (3l): compound **3l** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 45% yield (95.1 mg); white solid; mp: 163–165 °C; Notably, compound **3l** at NMR analysis shows two sets of peaks. This fact is probably ascribable to the presence of bulky substituents around C3-C2' bond that determines the existence of rotamers (ca 95:5 ratio). For clarity only the signals of the main rotamer are reported; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (br, 1H), 7.30–7.10 (m,

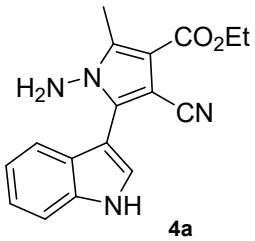
8H), 6.77 (d, *J* = 7.2 Hz, 1H), 5.06 (s, 2H), 4.27 (*J* = 7.2 Hz, 2H), 3.82 (s, 3H), 2.28 (s, 3H), 1.36 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.9, 155.1, 152.8, 138.4, 137.5, 130.0, 128.3, 128.1, 127.7, 127.3, 127.2, 123.5, 117.6, 116.2, 109.7, 104.2, 102.3, 99.6, 92.9, 81.7, 69.6, 60.3, 33.4, 28.1, 14.5, 10.8. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{30}H_{33}N_4O_5$ $[M+H]^+$ 529.2445; Found 529.2432.

4. Synthetic transformations

4.1 Access to compound **4a**



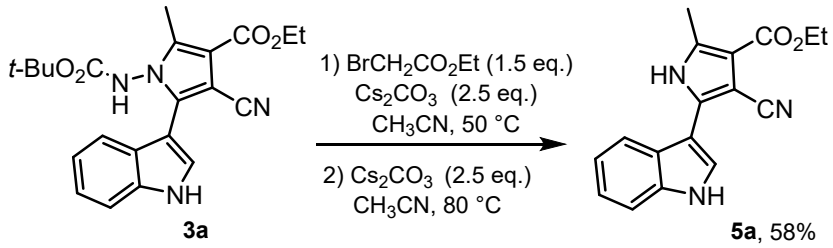
Compound **4a** was prepared according to the literature procedure[5]. To a solution of **3a** (81.7 mg, 0.2 mmol) in dichloromethane (2 mL) was added TFA (96.0 mg, 1.0 mmol) dropwise at 0 °C. The mixture was stirred at rt until TLC showed complete consumption of starting material. Water was added and the mixture was extracted with AcOEt (2 × 10 mL). The combined organic layer was washed with brine, separated, dried over Na_2SO_4 and filtered. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate/cyclohexane 40:60) to afford **4a** as white solid (37.6 mg, 61%).



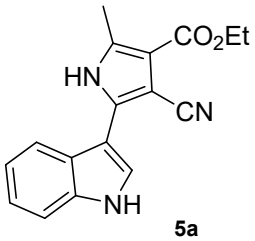
4a

Ethyl 1-amino-4-cyano-5-(1*H*-indol-3-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (4a): compound **4a** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 61% yield (37.6 mg); white solid; mp: 209–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (s, 1H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2, 139.1, 138.0, 136.3, 127.7, 126.2, 122.1, 120.5, 120.0, 116.9, 112.3, 109.9, 102.9, 88.9, 60.1, 14.6, 11.6. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{17}H_{17}N_4O_2$ $[M+H]^+$ 309.1346; Found 309.1341.

4.2 Access to compound **5a**



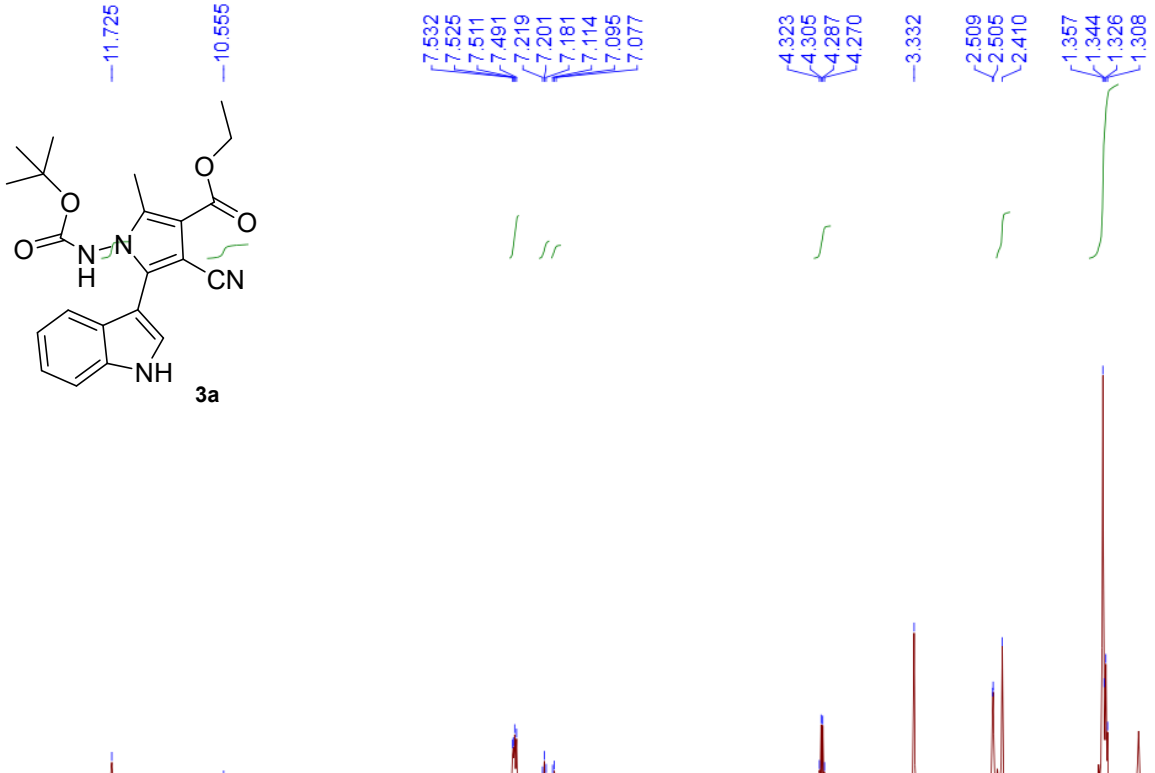
Compound **5a** was prepared according to a modified version of the Magnus method.[6] To a solution of **3a** (81.7 mg, 0.2 mmol) in acetonitrile (5 mL), ethyl bromoacetate (0.033 mL, 0.3 mmol) and Cs_2CO_3 (162.9 mg, 0.5 mmol) were added. The mixture was stirred at 50 °C (oil bath) until the disappearance of the starting material (0.5 h, TLC check). The solvent was removed under vacuum, water (5 mL) was added, and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and filtered. After the solvent was removed under reduced pressure, the residue was dissolved in acetonitrile (5 mL) and Cs_2CO_3 (162.9 mg, 0.5 mmol) was added. The mixture was stirred at 80 °C until TLC showed complete consumption of intermediate. The solvent was removed under vacuum, water (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The collected organic phase was washed with brine, dried over Na_2SO_4 and filtered. After the solvent was removed under vacuum, the residue was purified by column chromatography (ethyl acetate/cyclohexane 30:70) to afford compound **5a** as a white solid (34.1 mg, 58% yield).



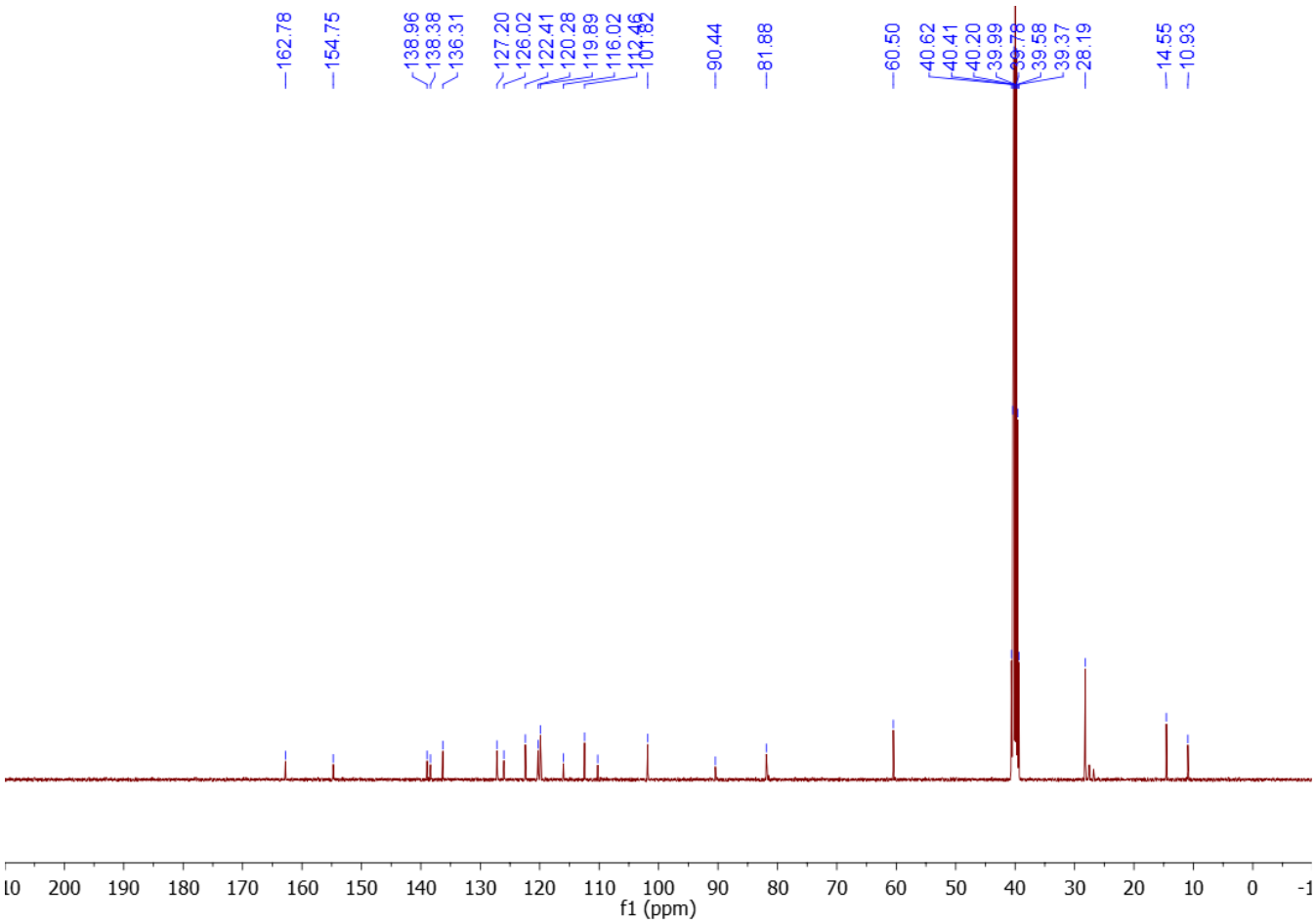
5a

Ethyl 4-cyano-5-(1*H*-indol-3-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (5a): was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 58% yield (34.1 mg); orange solid; mp: 231–233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 11.65 (s, 1H), 7.75–7.71 (m, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.51 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3, 137.9, 136.5, 136.0, 125.9, 125.0, 122.5, 120.2, 120.1, 117.4, 112.5, 112.0, 105.0, 89.1, 60.0, 14.7, 13.1. HRMS (ESI-Orbitrap, *m/z*): Calcd for $C_{17}H_{16}N_3O_2$ $[M+H]^+$ 294.1237; Found 294.1252.

5. ^{1}H and ^{13}C NMR spectra



3a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127.20
126.02
122.41
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116.02
90.44
81.88
60.50
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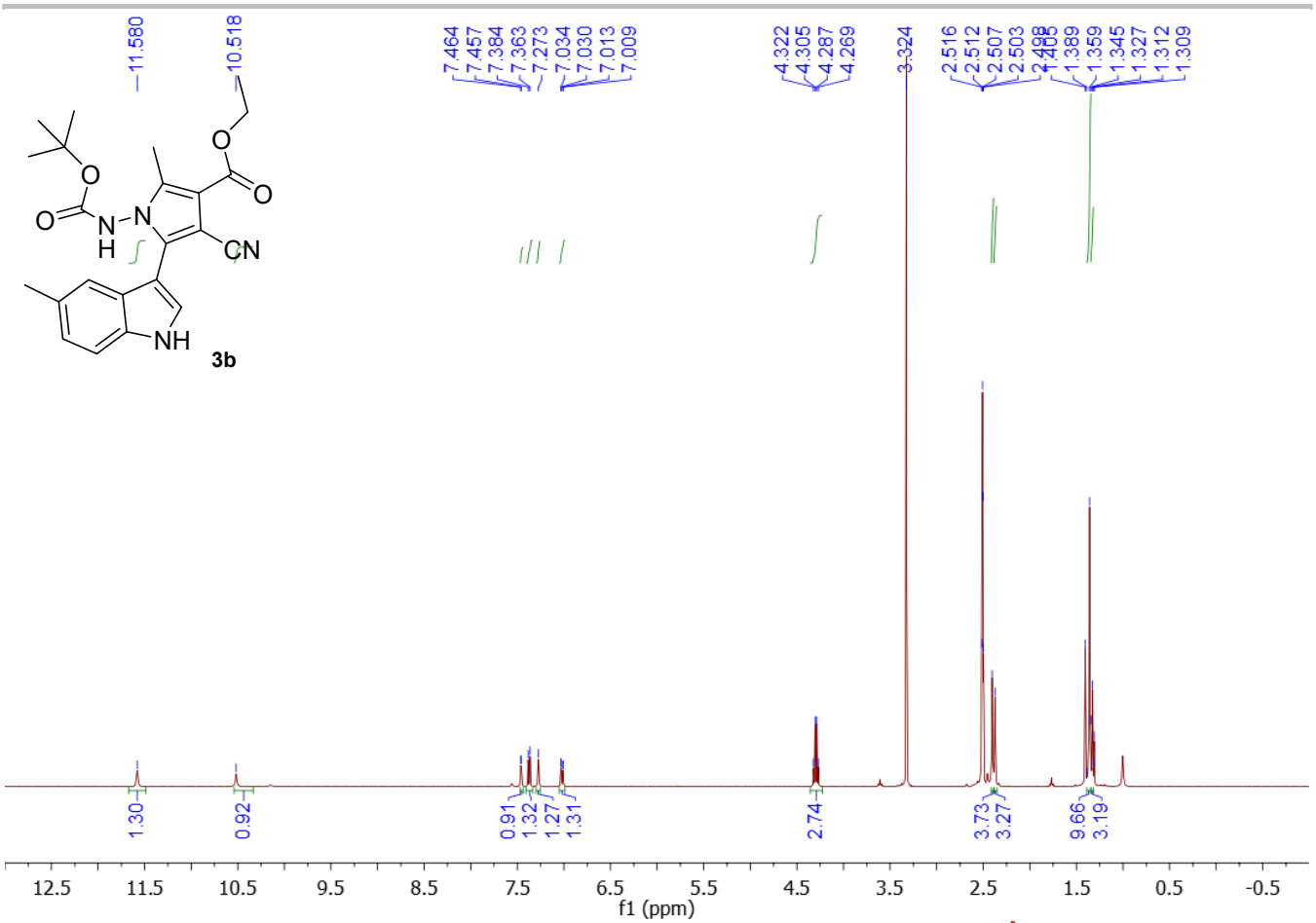
40.20
39.99
39.78
39.58
39.37
28.19
14.55
10.93
f1 (ppm)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7.363
7.273
7.034
7.030
7.013
7.009
4.322
4.305
4.287
4.269
3.324
2.516
2.512
2.507
2.503
1.389
1.359
1.345
1.327
1.312
1.309
1.30
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1.27
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2.74
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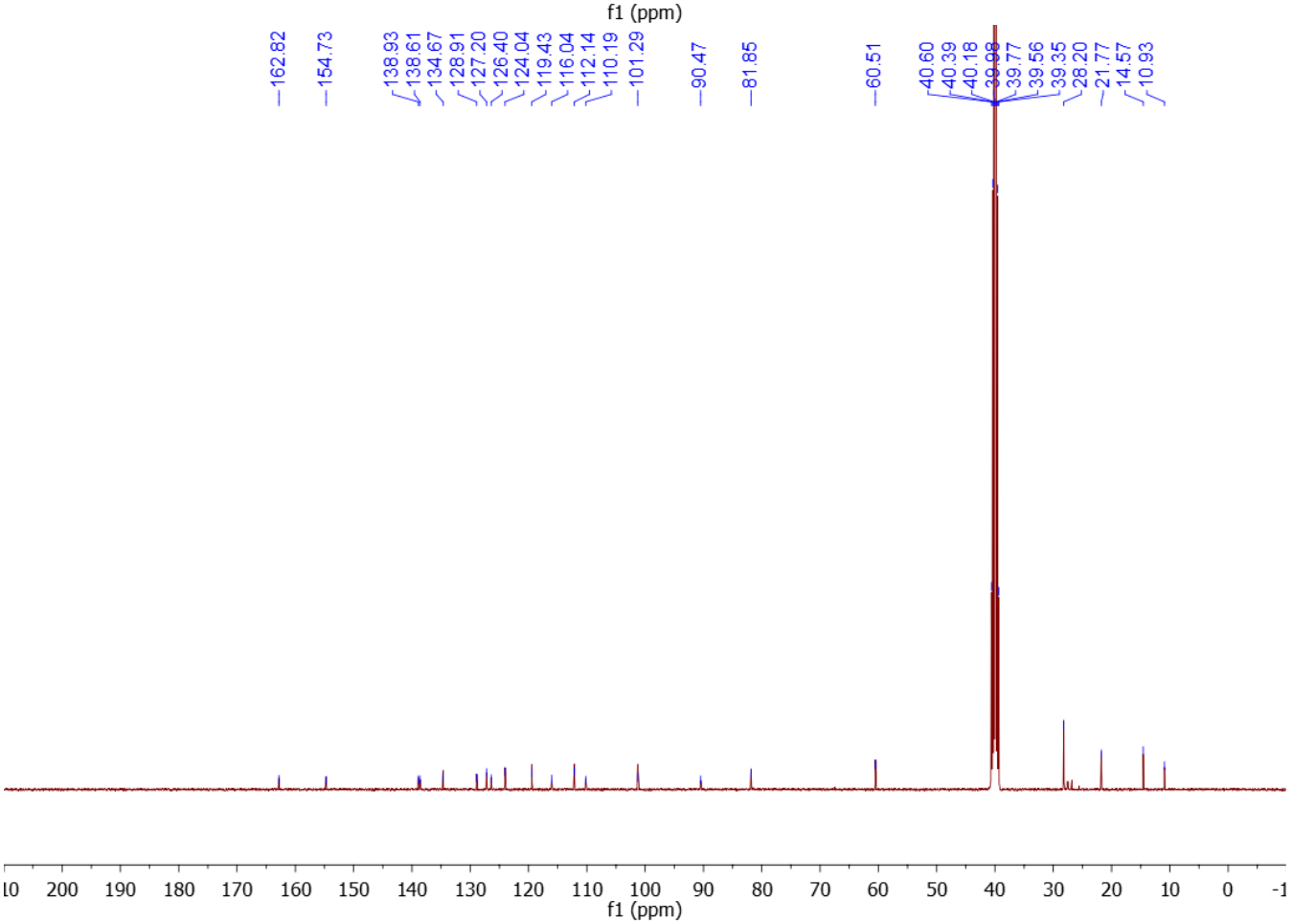
3.19
f1 (ppm)

3b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119.43
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112.14
110.19
101.29
90.47
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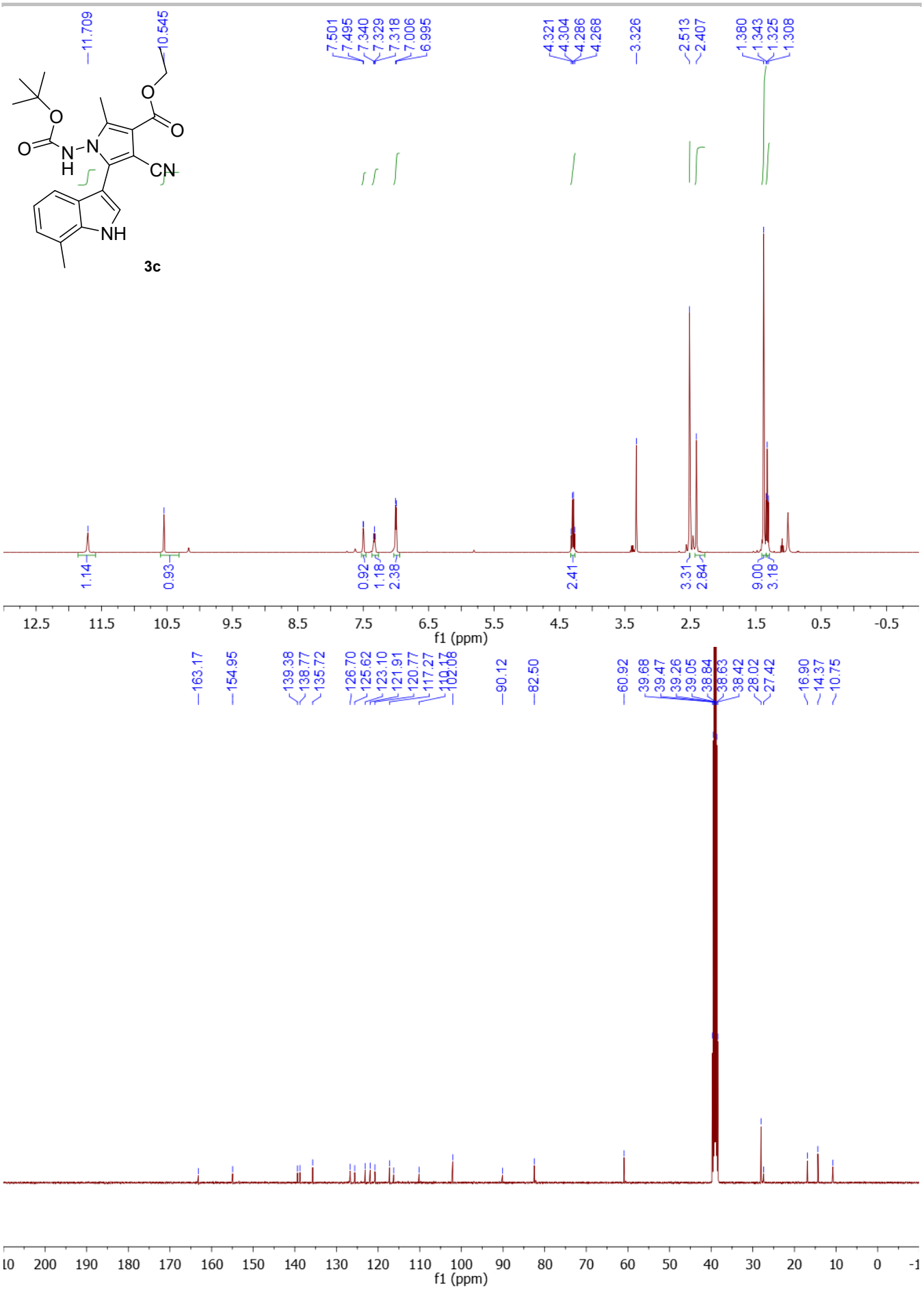
f1 (ppm)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4.304
4.286
4.268
3.326
2.513
2.407
1.380
1.343
1.325
1.308
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O
N
H
N
O
O
CN
NH
3c
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0.92
1.18
2.38
2.41
3.31
2.84
9.00
3.18
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
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0.5
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f1 (ppm)
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154.95
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138.77
135.72
126.70
125.62
123.10
121.91
120.77
117.27
110.17
102.08
90.12
82.50
60.92
39.68
39.47
39.26
39.05
38.84
38.63
38.42
28.02
27.42
16.90
14.37
10.75
200
190
180
170
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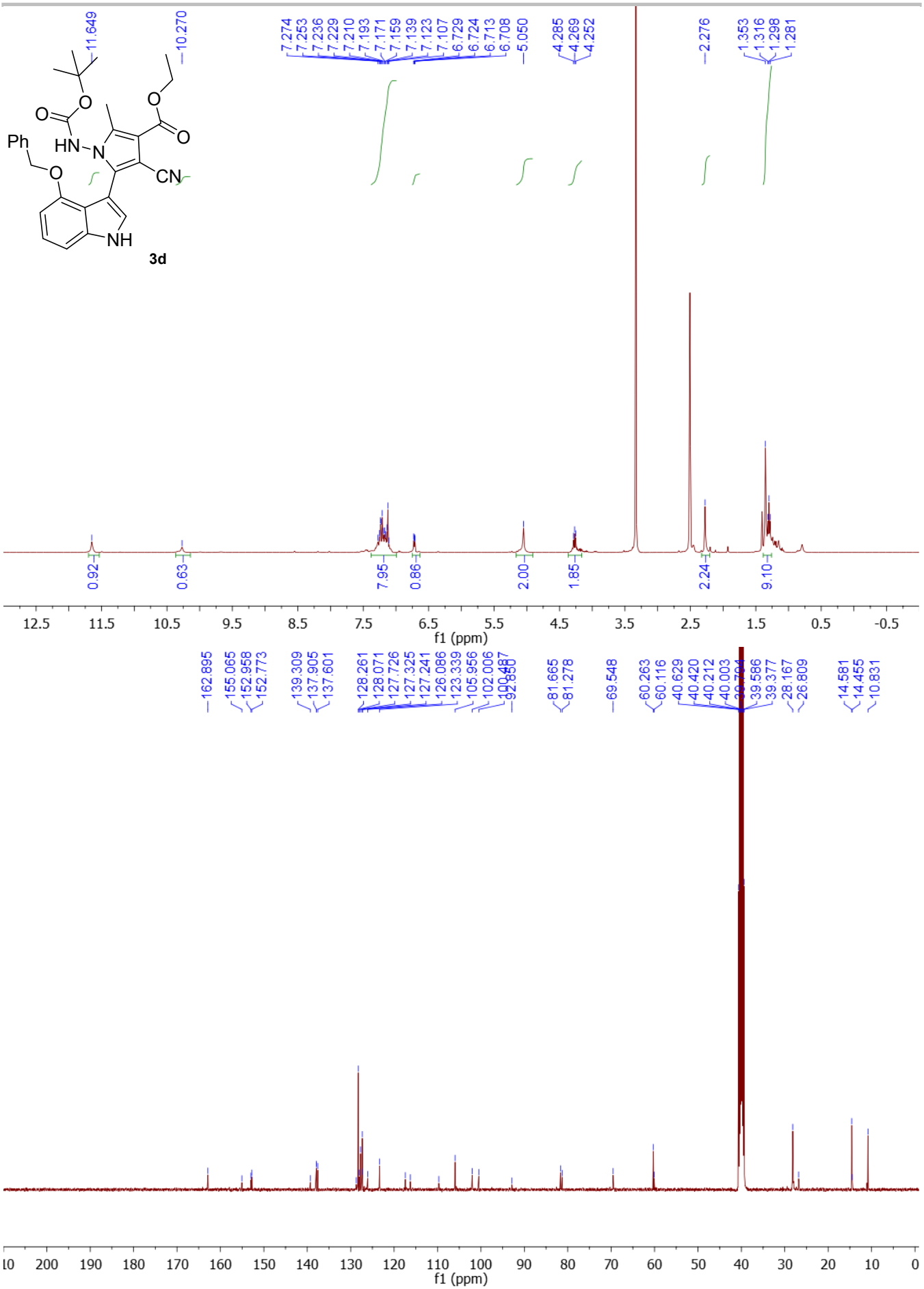
f1 (ppm)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7.107
6.729
6.724
6.713
6.708
5.050
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4.269
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2.276
1.353
1.316
1.298
1.281
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O
O
O
O
CN
NH
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0.86
2.00
1.85
2.24
9.10
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)
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152.958
152.773
139.309
137.905
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128.071
127.726
127.325
127.241
126.086
123.339
105.956
102.006
81.665
81.278
69.548
60.263
60.116
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40.420
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40.003
39.586
39.377
28.167
26.809
14.581
14.455
10.831
200
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120
110
100
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50
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30
20
10
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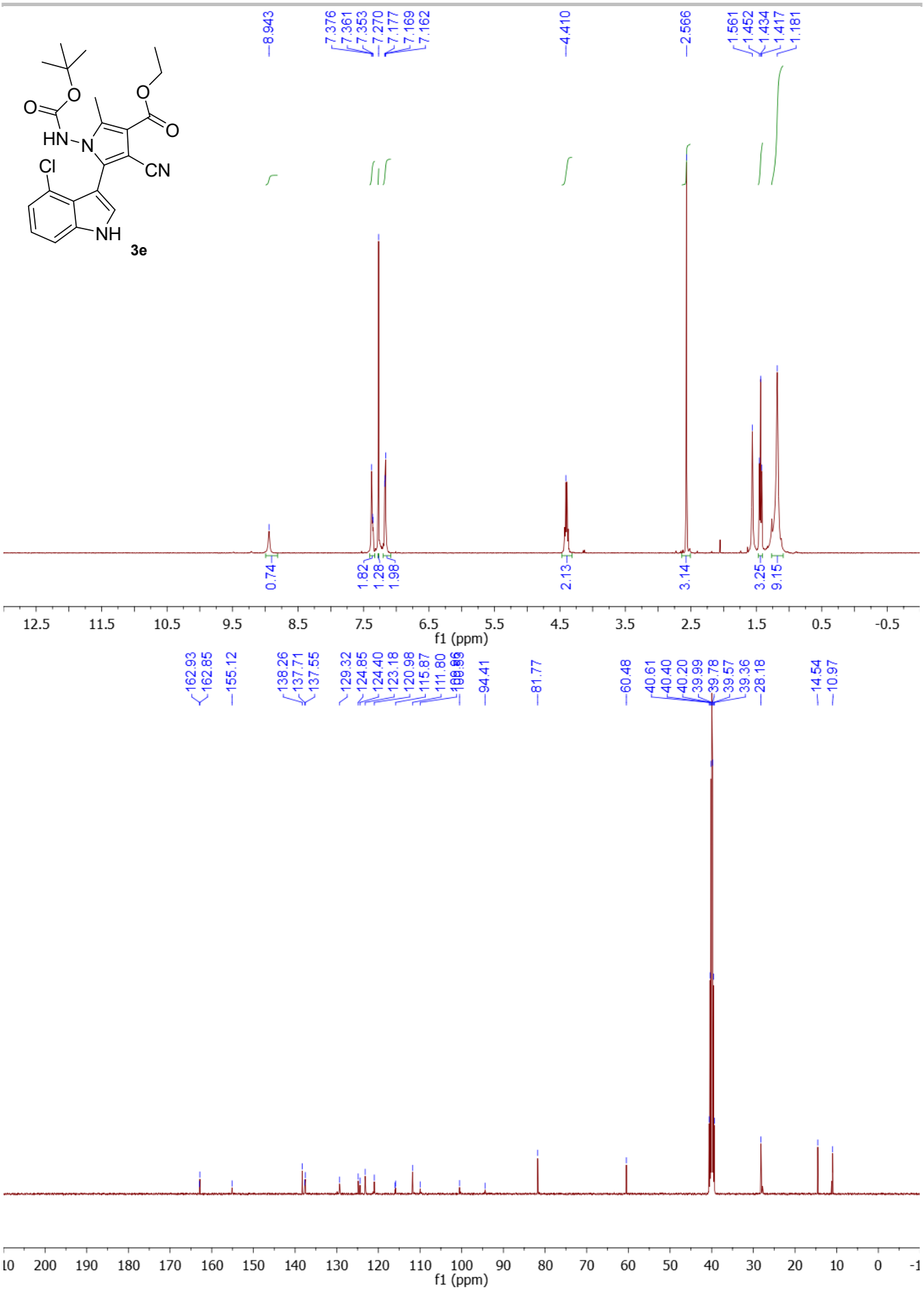
f1 (ppm)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3.14
3.25
9.15
f1 (ppm)
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162.85
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129.32
124.85
124.40
123.18
120.98
115.87
111.80
94.41
81.77
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40.40
40.20
39.99
39.78
39.57
39.36
28.18
14.54
10.97
f1 (ppm)

3e


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7.615
7.490
7.468
7.333
7.328
7.311
7.307
4.325
4.307
4.289
4.271
3.322
2.516
2.511
2.507
2.502
2.498
2.406
1.341
1.327
1.309
Br
NH
CN
3f
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0.68
1.74
0.94
0.94
2.00
3.14
12.12
f1 (ppm)
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139.14
137.57
135.10
129.00
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125.08
121.95
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114.58
113.10
110.34
101.47
90.88
82.01
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28.19
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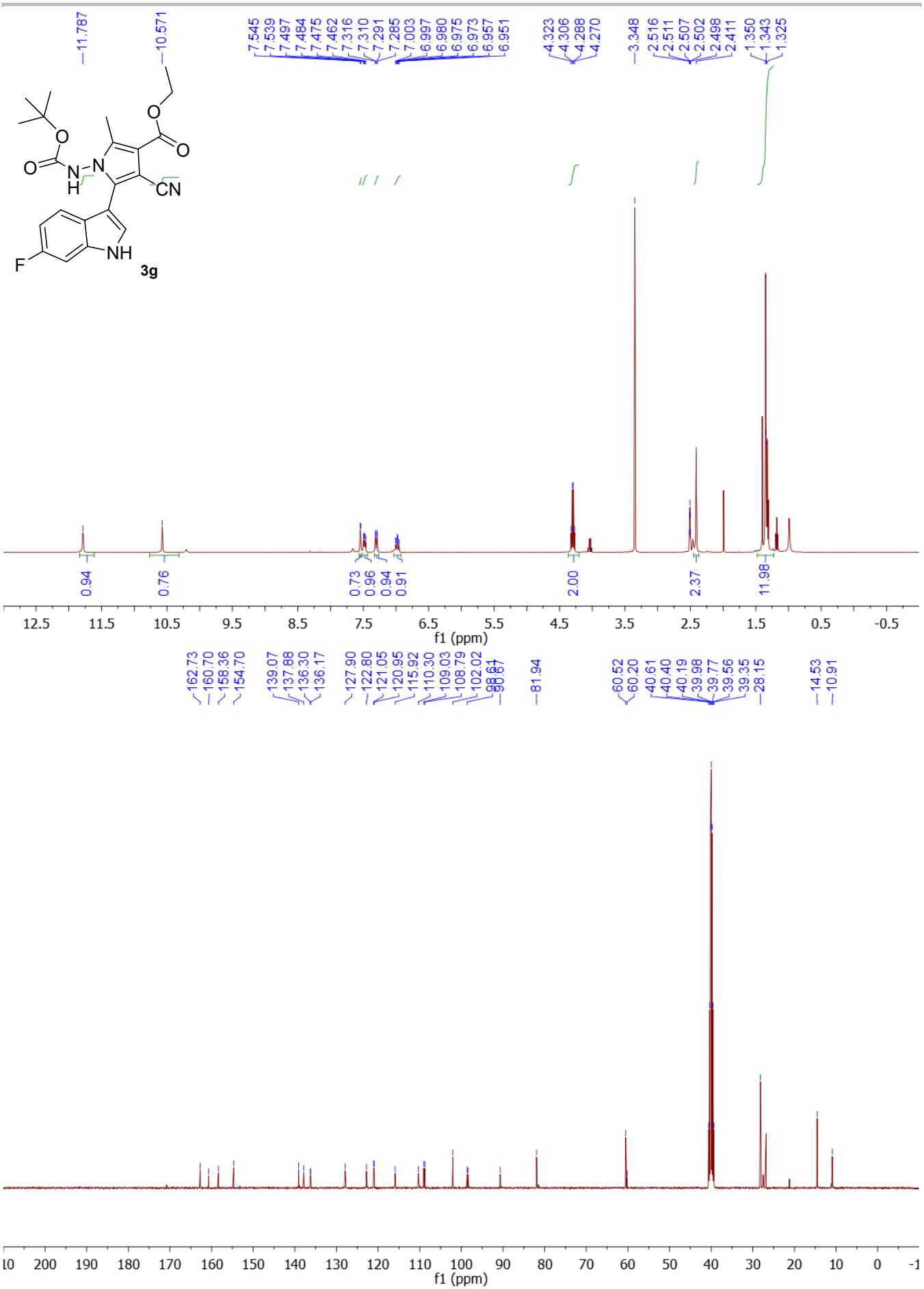
10.90
f1 (ppm)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6.973
6.957
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H
N
O
CN
NH
F
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0.94
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8.5
7.5
6.5
5.5
4.5
3.5
2.5
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154.70
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137.88
136.30
136.17
127.90
122.80
121.05
120.95
115.92
110.30
109.03
108.79
102.02
98.61
90.67
81.94
60.52
60.20
40.61
40.40
40.19
39.98
39.77
39.56
39.35
28.15
14.53
10.91
200
190
180
170
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110
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80
70
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50
40
30
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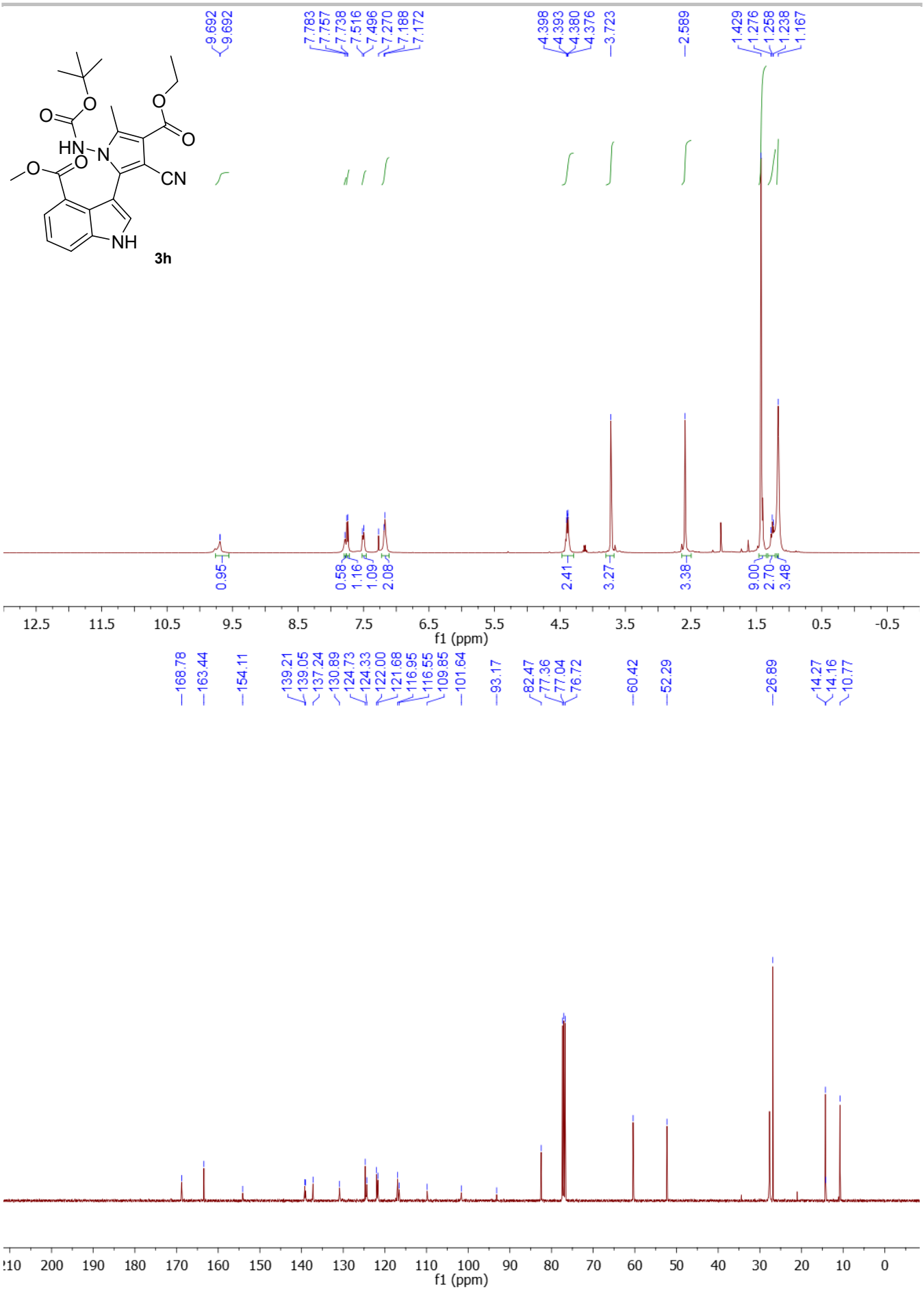
f1 (ppm)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4.380
4.376
3.723
2.589
1.429
1.276
1.258
1.238
1.167
3h
0.95
0.58
1.16
1.09
2.08
2.41
3.27
3.38
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f1 (ppm)
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139.21
139.05
137.24
130.89
124.73
124.33
122.00
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101.64
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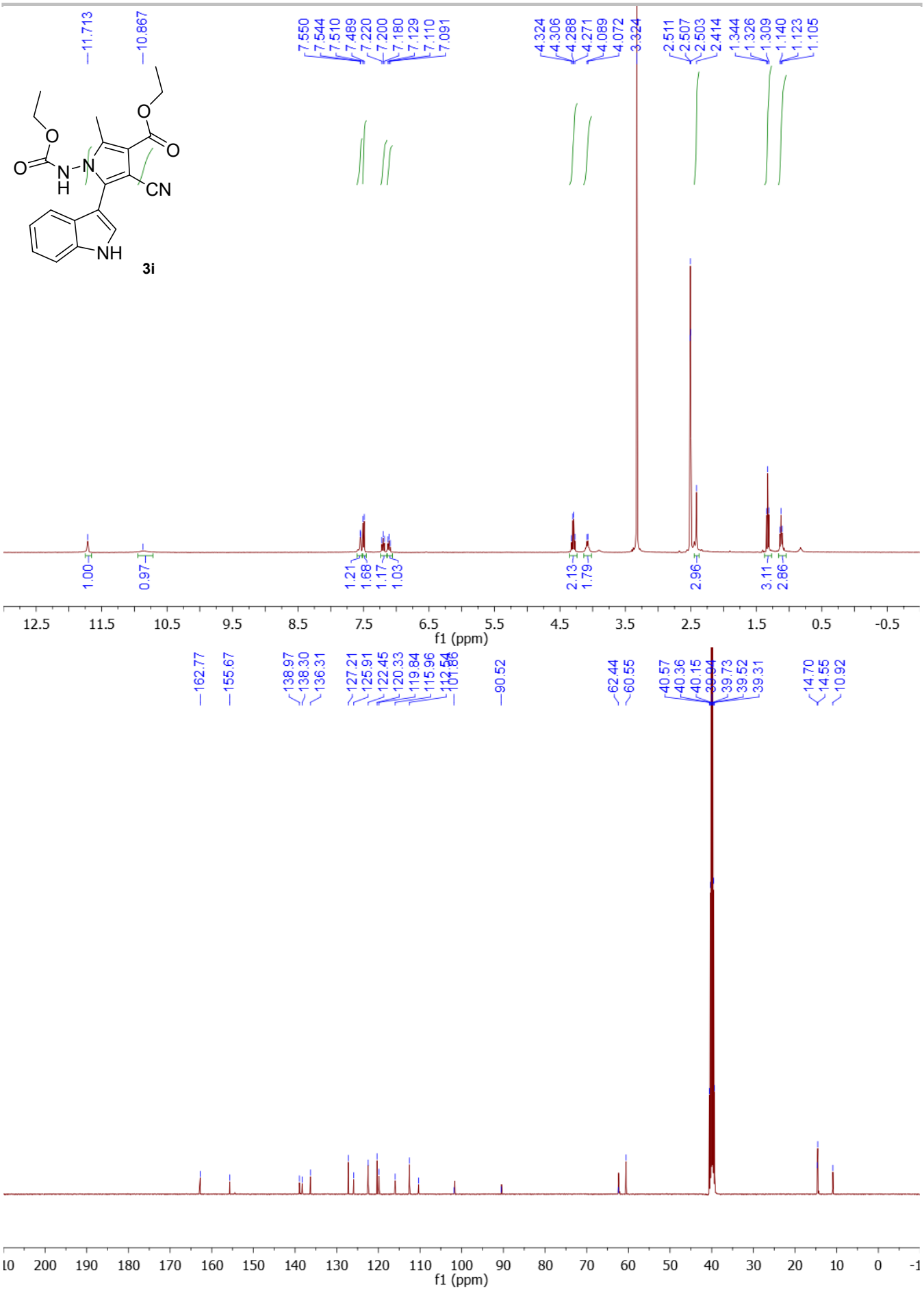
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H
N
CN
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3i
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1.17
1.03
2.13
1.79
2.96
3.11
2.86
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11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
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f1 (ppm)
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138.30
136.31
127.21
125.91
122.45
120.33
119.84
115.96
112.54
101.86
90.52
62.44
60.55
40.57
40.36
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39.73
39.52
39.31
14.70
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10.92
200
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180
170
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120
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100
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30
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0
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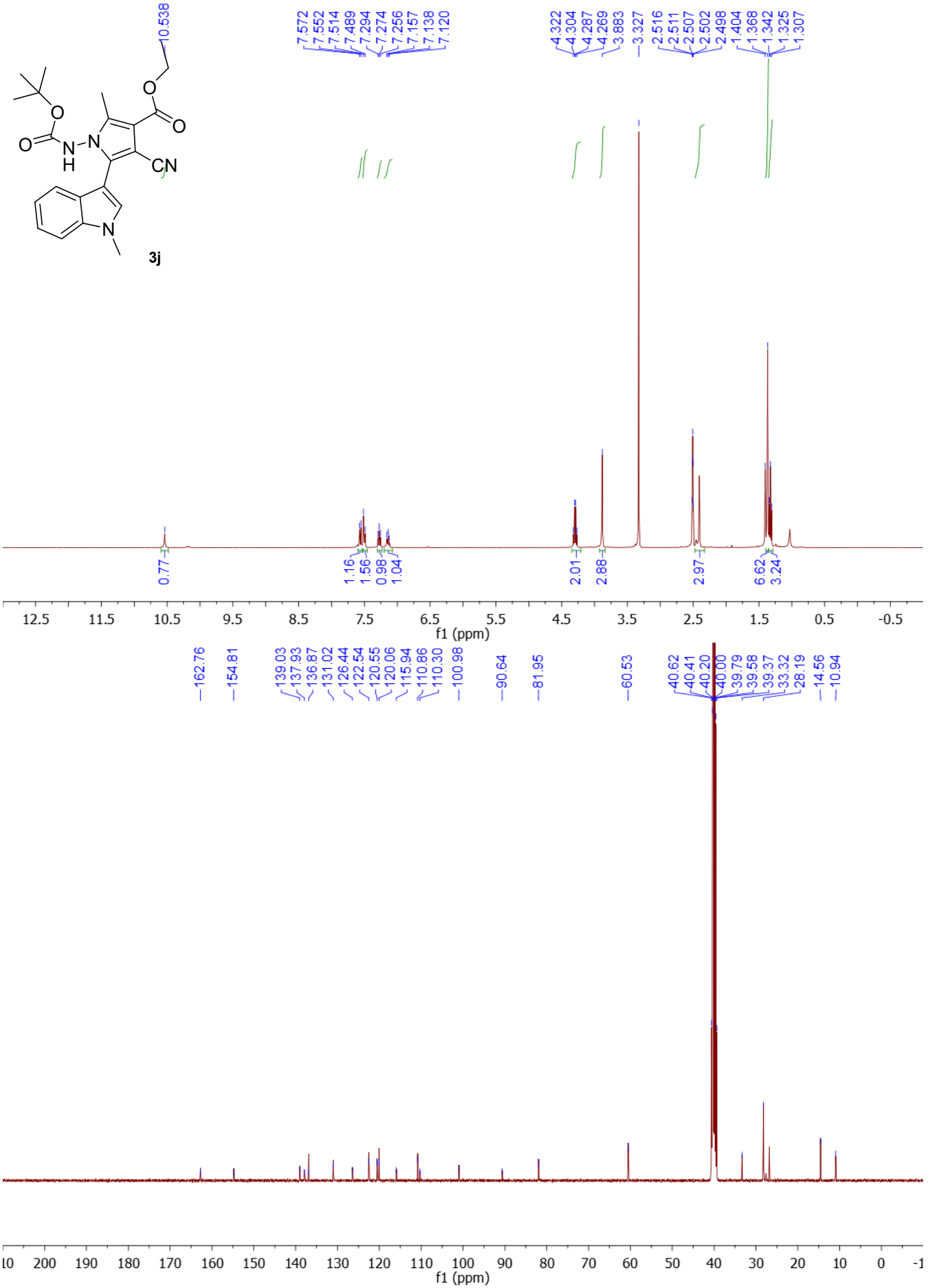
f1 (ppm)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4.287
4.269
3.883
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2.511
2.507
2.502
2.498
1.404
1.368
1.342
1.325
1.307
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O
N
H
N
O
O
CN
N
3j
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1.56
0.98
1.04
2.01
2.88
2.97
6.62
3.24
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
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f1 (ppm)
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154.81
139.03
137.93
136.87
131.02
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122.54
120.55
120.06
115.94
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110.30
100.98
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60.53
40.62
40.41
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40.00
39.79
39.58
39.37
33.32
28.19
14.56
10.94
200
190
180
170
160
150
140
130
120
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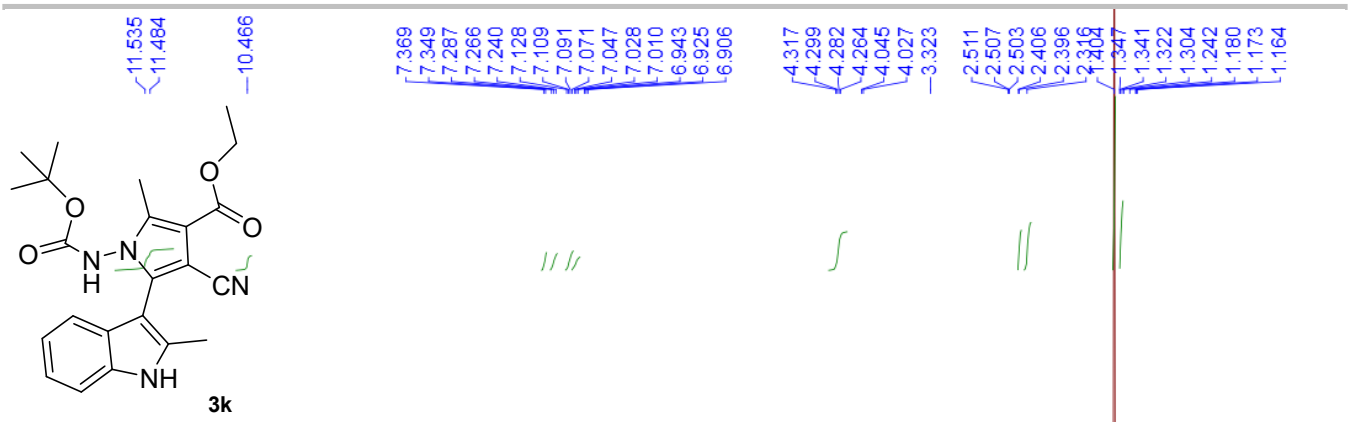
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)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2.503
2.406
2.396
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1.322
1.304
1.242
1.180
1.173
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1.00
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1.08
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2.13
2.23
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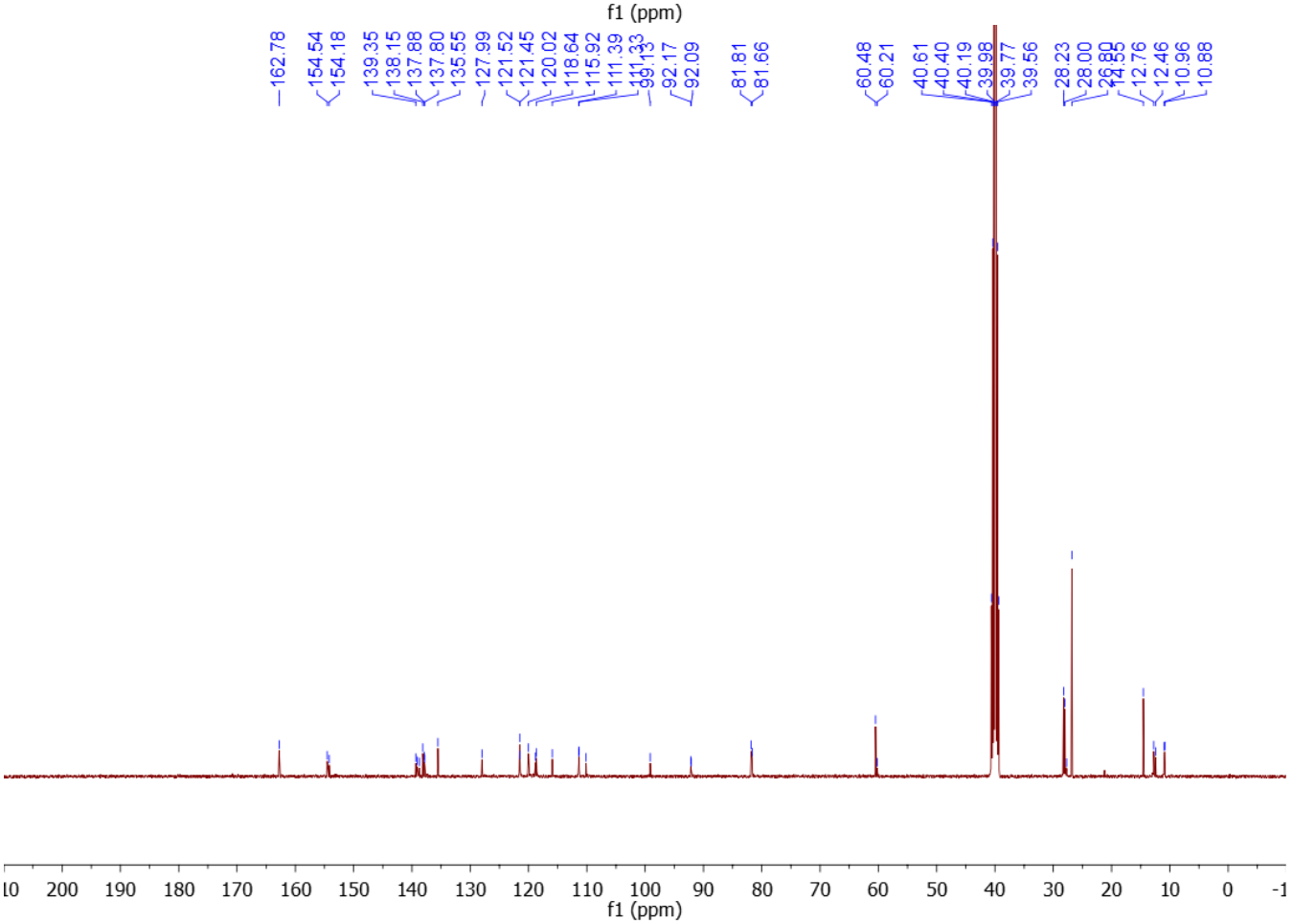
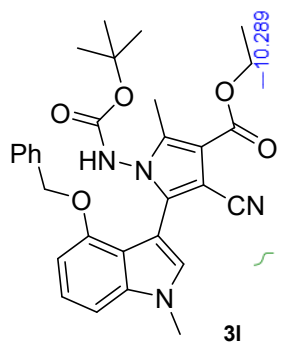
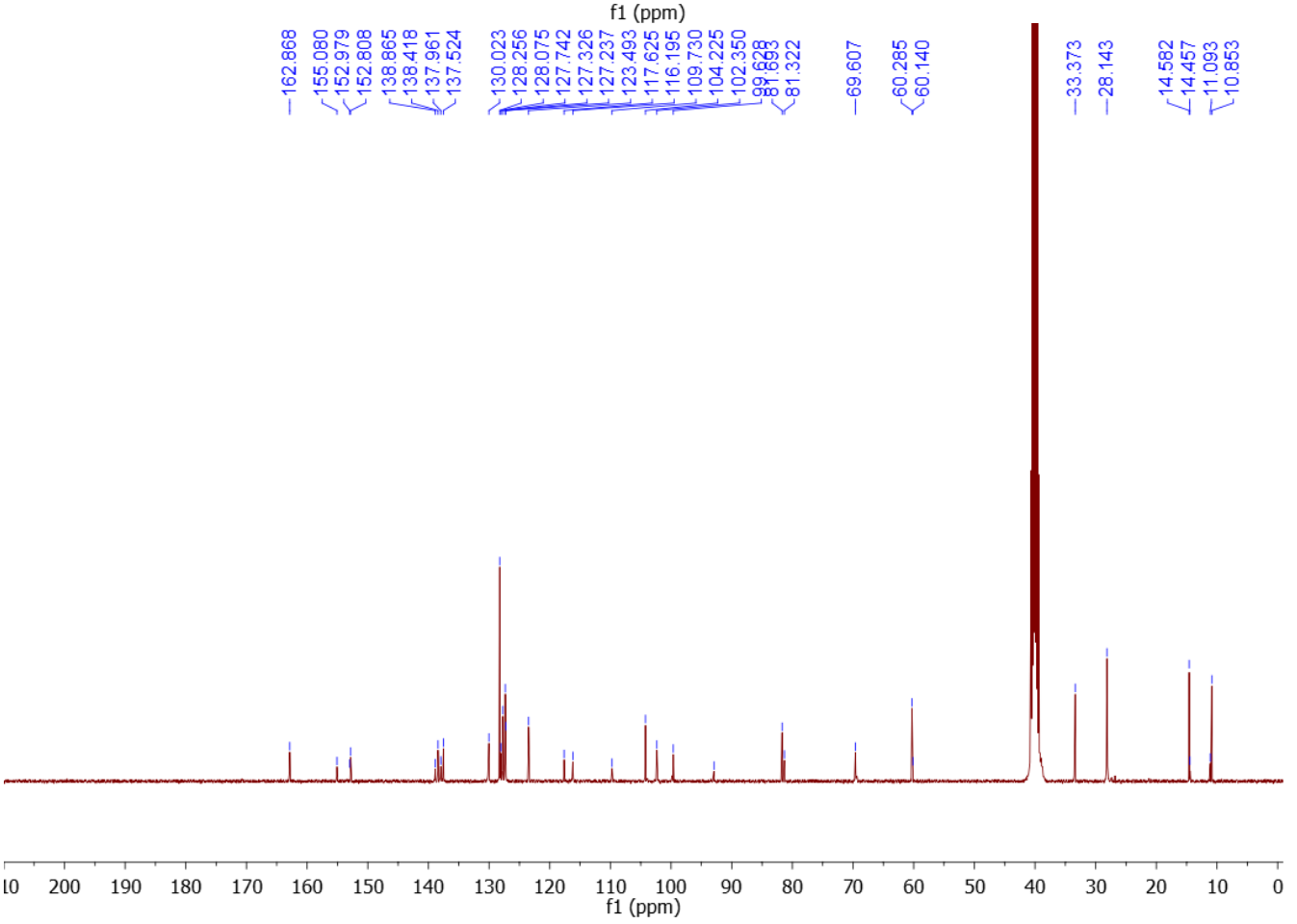
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

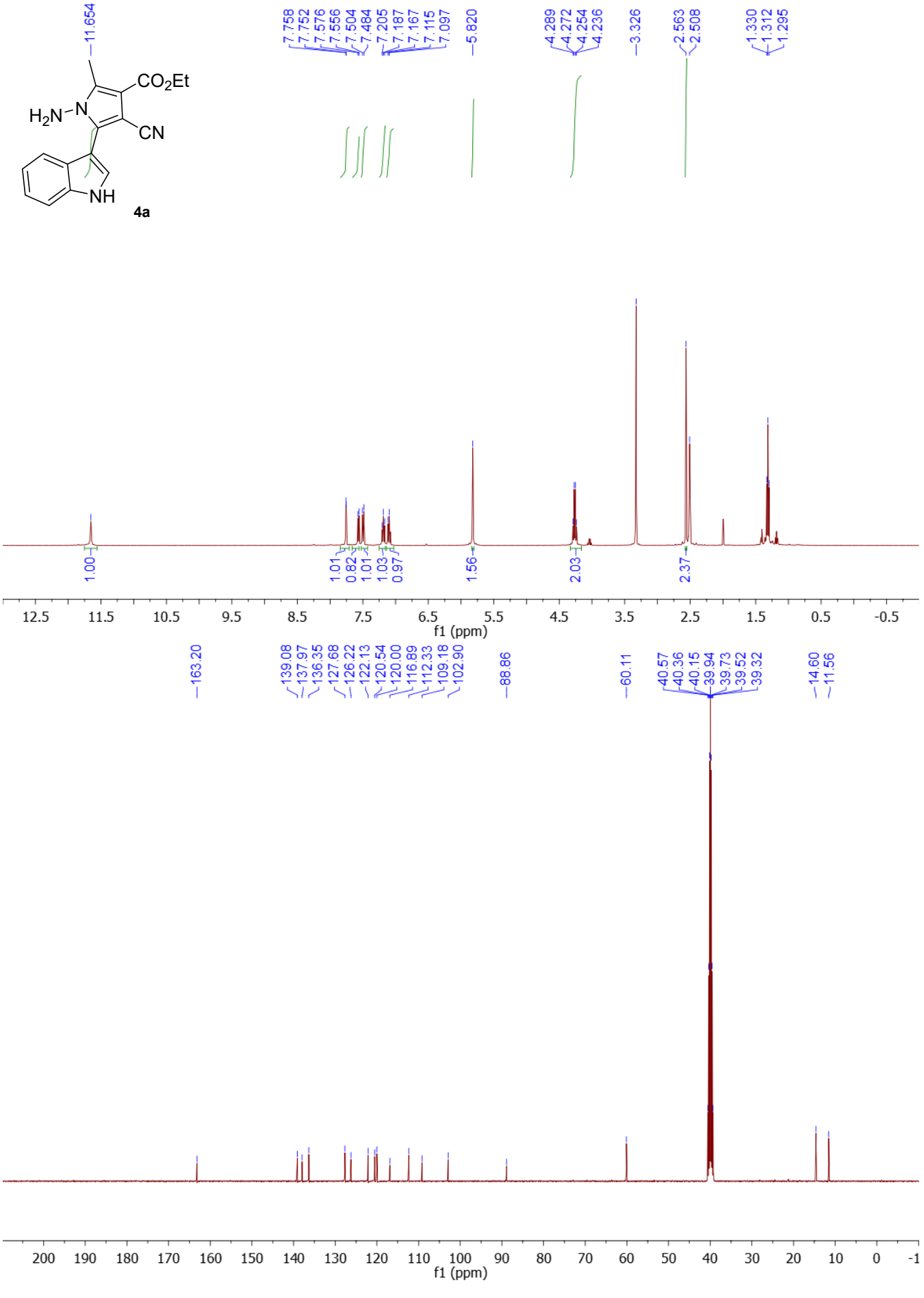

162.78
154.54
154.18
139.35
138.15
137.88
137.80
135.55
127.99
121.52
121.45
120.02
118.64
115.92
111.39
111.33
99.13
92.17
92.09
81.81
81.66
60.48
60.21
40.61
40.40
40.19
39.98
39.77
39.56
28.23
28.00
26.80
14.55
12.76
12.46
10.96
10.88
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

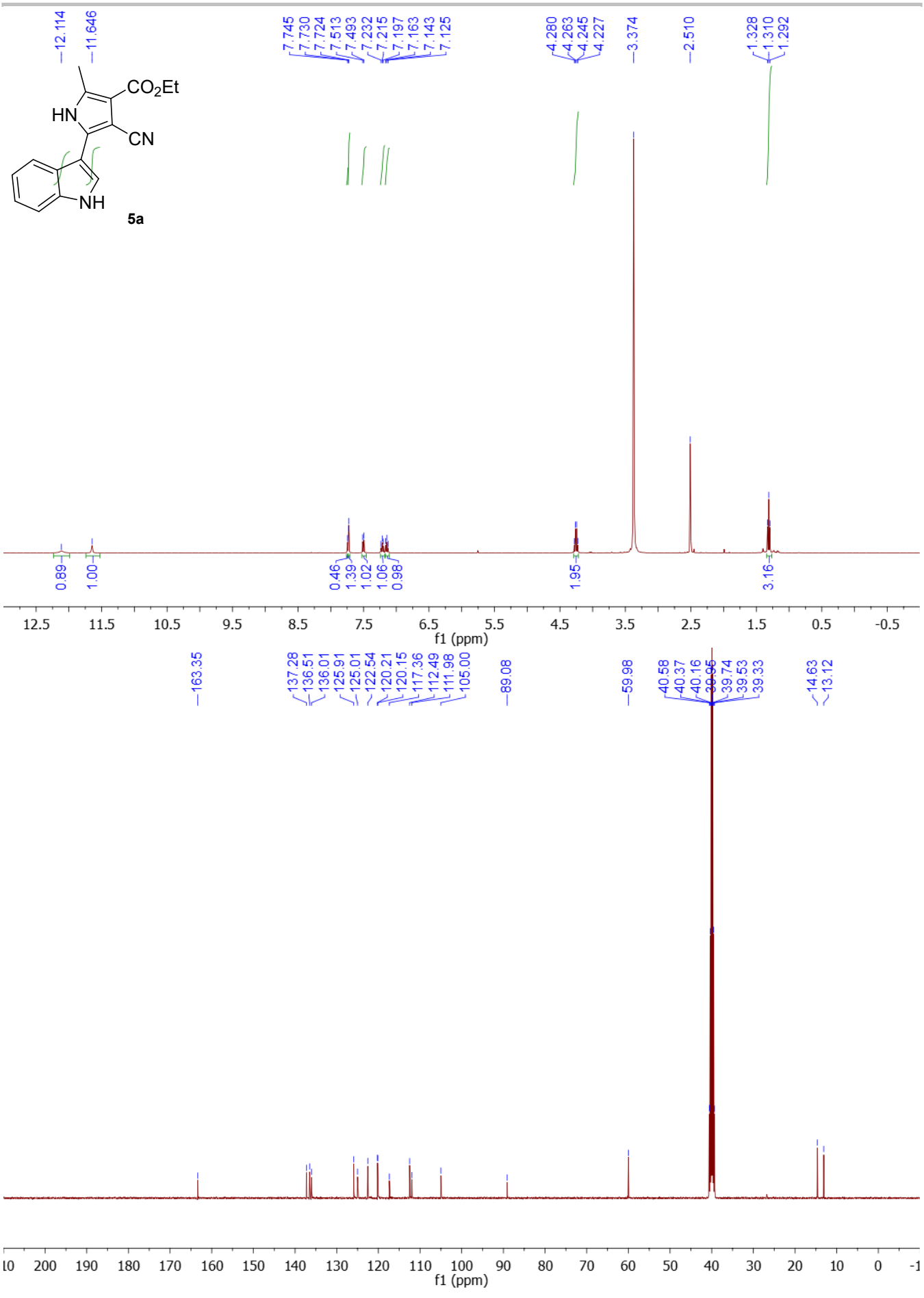

10.289
O
O
O
O
Ph
HN
N
CN
O
N

3l

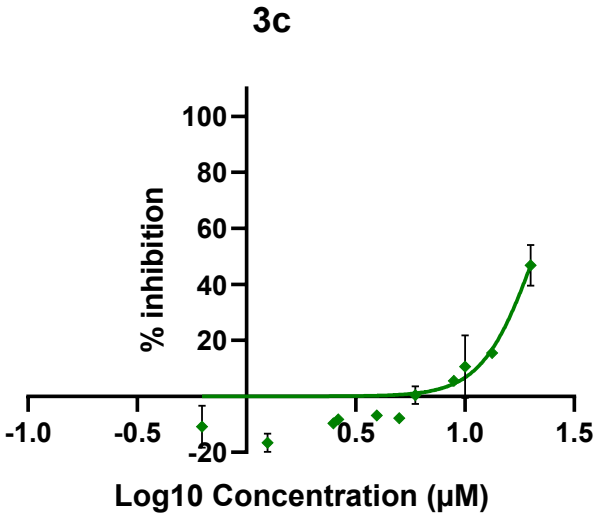
7.252
7.244
7.234
7.231
7.225
7.211
7.206
7.193
7.186
7.183
7.165
7.150
6.780
6.762
5.055
4.283
4.272
4.265
4.255
3.825
3.317
2.516
2.511
2.507
2.502
1.317
1.299
1.281
0.88
9.61
1.21
2.55
2.21
3.00
3.12
12.90
f1 (ppm)

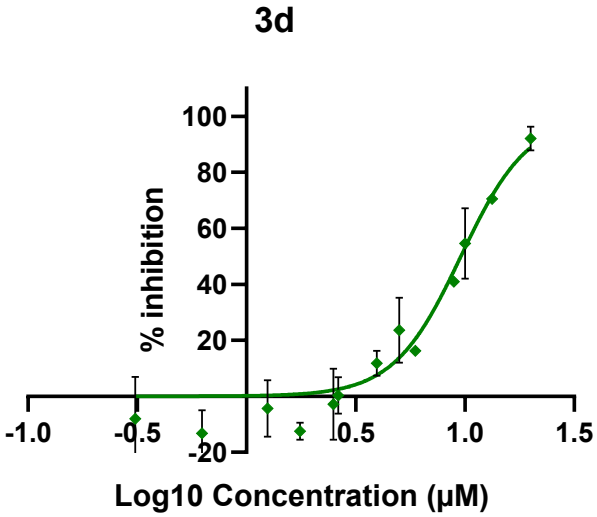

162.868
155.080
152.979
152.808
138.865
138.418
137.961
137.524
130.023
128.256
128.075
127.742
127.326
127.237
123.493
117.625
116.195
109.730
104.225
102.350
81.322
69.607
60.285
60.140
33.373
28.143
14.582
14.457
11.093
10.853
f1 (ppm)

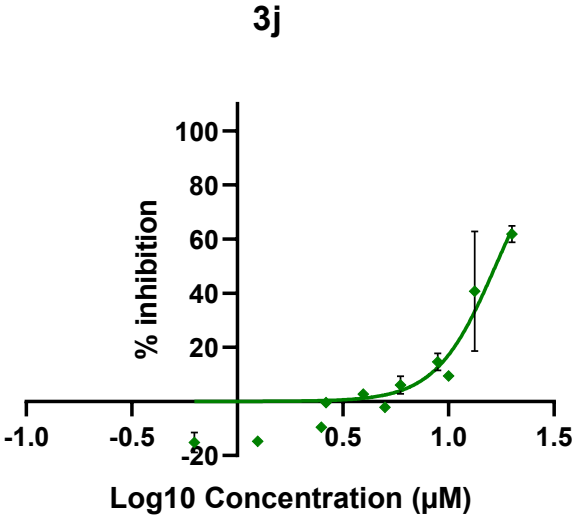

11.654
7.758
7.752
7.576
7.556
7.504
7.484
7.205
7.187
7.167
7.115
7.097
5.820
4.289
4.272
4.254
4.236
3.326
2.563
2.508
1.330
1.312
1.295
CO2Et
H2N
N
CN
NH
4a
1.00
1.01
0.82
1.01
1.03
0.97
1.56
2.03
2.37
f1 (ppm)
163.20
139.08
137.97
136.35
127.68
126.22
122.13
120.54
120.00
116.89
112.33
109.18
102.90
88.86
60.11
40.57
40.36
40.15
39.94
39.73
39.52
39.32
14.60
11.56
f1 (ppm)


12.114
11.646
7.745
7.730
7.724
7.513
7.493
7.232
7.215
7.197
7.163
7.143
7.125
4.280
4.263
4.245
4.227
3.374
2.510
1.328
1.310
1.292
CO2Et
HN
CN
NH
5a
0.89
1.00
0.46
1.39
1.02
1.06
0.98
1.95
3.16
f1 (ppm)
163.35
137.28
136.51
136.01
125.91
125.01
122.54
120.21
120.15
117.36
112.49
111.98
105.00
89.08
59.98
40.58
40.37
40.16
39.95
39.74
39.53
39.33
14.63
13.12
f1 (ppm)

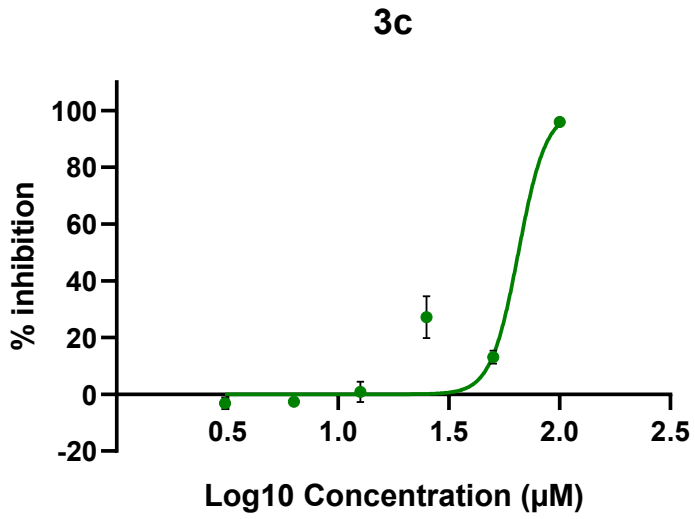
6. Viability evaluation of compounds **3c**, **3d** and **3j** on L. infantum promastigotes

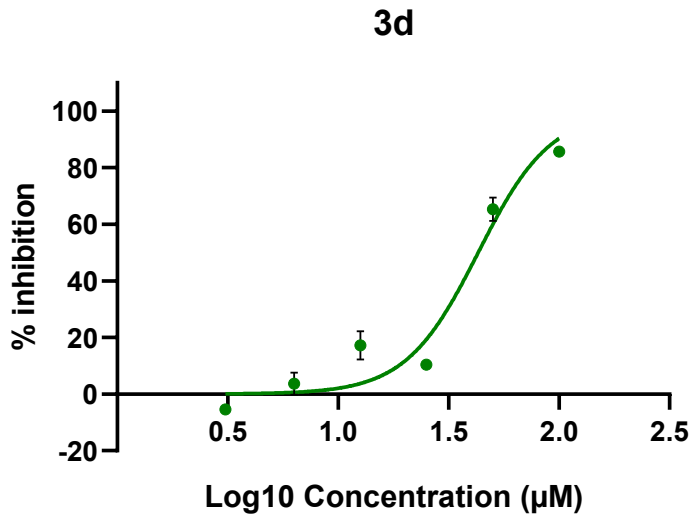


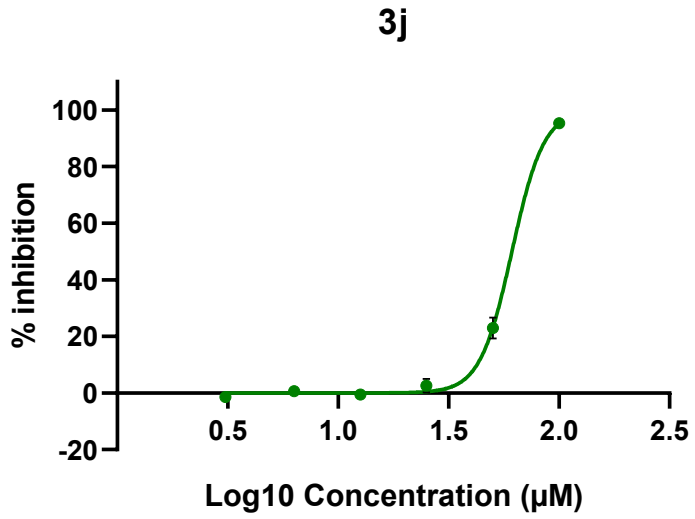




7. Toxicity evaluation of compounds **3c**, **3d** and **3j** on THP-1 cells







8. References

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