

SUPPORTING INFORMATION

Novel synthesis of 5-amino-3-bromo-1-(*tert*-butyl)-1*H*-pyrazole-4-carbonitrile: A versatile intermediate for the preparation of 5-amino-3-aryl-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxamides

Mark A. Bobko, Arun C. Kaura, Karen A. Evans*, Dai-Shi Su

GlaxoSmithKline, Cancer Research, Protein Dynamics Discovery Performance Unit, 1250 South Collegeville Road, Collegeville, PA, 19426, U.S.A.

karen.a.evans@gsk.com

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General synthetic experimental procedures

Proton Nuclear Magnetic Resonance (^1H NMR) spectra were recorded on a Bruker UltraShieldTM 400 spectrometer operating at 400.132 MHz using a 5mm QNP probe unless otherwise specified. The 2D NMR spectra were recorded on a Bruker Avance 600 spectrometer operating at 600.13 MHz using a 5mm TXI cryoprobe. Spectra were taken in the indicated solvent at ambient temperature, and the chemical shifts are reported in parts per million (ppm (δ)) relative to the lock of the solvent used. Resonance patterns are recorded with the following notations: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Second order spectra in which coupling cannot be obtained by inspection are reported as multiplets, with the center of the signal indicated by the δ value given.

Starting reagents were purchased from commercial suppliers and were used without further purification unless otherwise specified. Microwave reactions were performed in a BiotageTM Initiator Sixty reactor using the manufacturer supplied vials, stir bars, and caps. Microwave reaction times are for time held at the specified temperature.

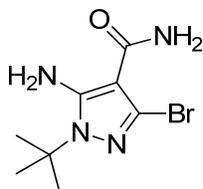
Normal phase column chromatography was carried out in the indicated solvent system (in the percentage of volume) using pre-packed silica gel cartridges (Reveleris[®] or Analogix[®]) on the Analogix Intelliflash280[®] or the Varian Intelliflash 971-FP purification system. Analytical thin layer chromatography (TLC) visualization was performed using 254 nm wavelength ultraviolet light. Preparative HPLC purifications (reversed-phase) were performed using a Gilson 215 Liquid Handler with Trilution software, typically with a SunFire(TM) Prep C18 OBD(TM) 5 μM , 30 mm x 50 mm column. A 7 min gradient followed by a 3 min 100% organic hold time (47 mL/min, 30% gradient of ACN/H₂O, 0.1%TFA) with UV detection at 254 nm was typically used.

All novel compounds were characterized by LCMS, and gave satisfactory results in agreement with the proposed structure. LCMS M+H signals were consistent with expected molecular weight for all reported products. LCMS data were acquired from a Waters Acquity Ultra Performance LC system with UV detector (Waters Acquity PDA) set to 210-350 nm. Samples were injected (0.2 μL) onto a Thermo Hypersil Gold column (C18, 20x2.1 mm, 1.9 μ particle diam.) maintained at 55 $^{\circ}\text{C}$. A linear gradient (1.9 min) from 2% to 95% B (MeCN/H₂O, 0.02% TFA) with a flow rate of 1.6 mL/min was used. The mass spectra (MS) data were acquired in positive ion mode using a Water Acquity SQD (single quadrupole) mass spectrometer with a positive electrospray ionization source.

Detailed synthetic procedures and characterization for compounds 2, 3, 7, 8, 10, 12, 13, 14, 15, 1a-e

Compound 2

5-amino-3-bromo-1-(tert-butyl)-1H-pyrazole-4-carboxamide



In a 250 mL round bottom flask, 5-amino-3-bromo-1-(tert-butyl)-1H-pyrazole-4-carbonitrile (5.1 g, 20.98 mmol) was dissolved in 80 mL of EtOH. DMSO (16 mL) was added, followed by sodium hydroxide (24 mL, 24.0 mmol). The contents were cooled to 0 °C and hydrogen peroxide (7.5 mL, 73.4 mmol) was added dropwise. The contents were then allowed to stir at 0 °C for 30 min. The contents were allowed to warm to room temperature and stir at room temperature for another 2 h (2.5 h total), at which time the LCMS showed complete conversion to the desired product. The contents were then evaporated to remove much of the ethanol (approx. 60 mL), and the same amount of water added. The contents were stirred for about 10 min, and the solid filtered off, washed with water and dried to give 4.35 g (79%) of **2** as a white solid.

$^1\text{H NMR}$ (400MHz, DMSO- d_6) δ 7.24 (br. s., 1 H), 6.55 (s, 3 H), 1.52 (s, 9 H).

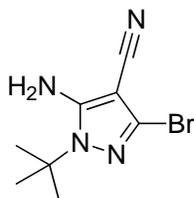
$^{13}\text{C NMR}$ (100 MHz, DMSO- d_6) δ 165.5, 151.0, 121.1, 96.6, 59.7, 28.6.

LCMS: (M+H) $^+$: 261.1/263.1 (100%).

Anal. Calcd for C₈H₁₃BrN₄O: C, 36.80; H, 5.02; N, 21.46. Found: C, 36.79; H, 4.72; N, 21.08.

Compound 3

5-amino-3-bromo-1-(t-butyl)-1H-pyrazole-4-carbonitrile



In a 50 mL round bottom flask, copper(II) bromide (374 mg, 1.67 mmol) and tert-butyl nitrite (0.20 mL, 1.67 mmol) were taken up in 10 mL of acetonitrile. The contents were cooled to 0 °C, and a solution of 3,5-diamino-1-(tert-butyl)-1H-pyrazole-4-carbonitrile (300 mg, 1.67 mmol) in 10 mL of acetonitrile was added dropwise over 5 min. The contents were allowed to stir at 0 °C for 2 hrs, before being allowed to warm to room temperature and stir for 16 hrs. The contents were evaporated to near dryness, and the crude partitioned between 100 mL of water and 100 mL of ethyl acetate. The water layer was further extracted (2 x 50 mL) with ethyl acetate, the organic fractions combined and washed (2 x 100 mL) with brine, dried over sodium sulfate, filtered and evaporated to dryness. The crude material was then purified by automated flash chromatography (Varian) on a 12 g silica gel cartridge and eluted using a 0 -> 20% B gradient over 20 min, where A: DCM and B: 80:20:2 DCM / MeOH / NH₄OH. The desired fractions were pooled and evaporated to dryness to give 250 mg (59%) of **3** as a yellow solid

¹H NMR (400 MHz, DMSO-*d*₆) δ 6.64 (s, 2 H), 1.50 (s, 9 H).

¹³C NMR (151 MHz, DMSO-*d*₆) δ 151.8, 124.1, 113.8, 77.4, 60.0, 28.0.

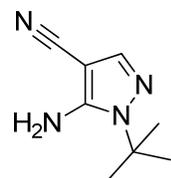
LCMS: (M+H)⁺: 243.1/245.1 (96%).

Anal. Calcd for C₈H₁₁BrN₄: C, 39.52; H, 4.56; N, 23.05. Found: C, 39.63; H, 4.55; N, 22.93.

Regiochemistry of bromination was unambiguously assigned by nOe between the C-5 amino and the *tert*-butyl group.

Compound 7

5-amino-1-(tert-butyl)-1H-pyrazole-4-carbonitrile



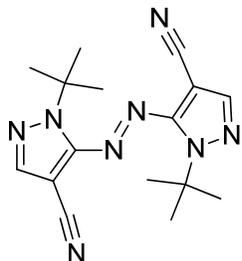
A mixture of tert-butylhydrazine hydrochloride (8.67 g, 69.6 mmol) and triethylamine (9.7 mL, 69.6 mmol) in anhydrous ethanol (460 mL) was stirred at room temperature and 2-(ethoxymethylene)malononitrile (8.50 g, 69.6 mmol) was added in small portions. The mixture was heated at reflux for 3 hours, then cooled and solvent evaporated to give a sticky orange colored solid (12.35 g). This residue was partitioned between EtOAc (0.5 L) and water (0.25 L). After drying (MgSO₄), the separated organic phase was filtered and filtrate evaporated to an orange-yellow gum that rapidly solidified. This solid was layered with 10% EtOAc in hexane (60 mL) and the mixture sonicated. The resulting crystalline solid was filtered, washed with more 10% EtOAc in hexane and suction-dried to afford 9.54 g (83%) of 5-amino-1-(tert-butyl)-1H-pyrazole-4-carbonitrile **7** as light-orange crystals.

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.45 (s, 1H), 6.2 (br s, 2H) and 1.51 (s, 9H).

LCMS (M+H)⁺: 165.1 (96%).

Compound 8

(E)-5,5'-(diazene-1,2-diyl)bis(1-(tert-butyl)-1H-pyrazole-4-carbonitrile)



A solution of 5-amino-1-(tert-butyl)-1H-pyrazole-4-carbonitrile (2.04 g, 12.42 mmol) in N,N-dimethylformamide (DMF) (10 mL) at rt was treated portionwise with solid N-bromosuccinimide (2.66 g, 14.95 mmol). Reagent addition resulted in immediate color change (from orange to reddish-brown) with gradual appearance of a precipitate. The suspension was filtered. The filtrant was washed with water and filter cake suction-dried overnight to afford 1.34 g (66%) of (E)-5,5'-(diazene-1,2-diyl)bis(1-(tert-butyl)-1H-pyrazole-4-carbonitrile) **8** as an orange-colored solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.35 (s, 2H), 1.78 (s, 18H).

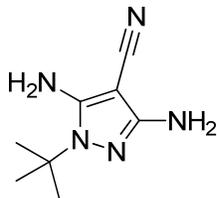
¹³C NMR (100 MHz, DMSO-*d*₆) δ 153.4, 142.8, 114.1, 82.5, 65.1, 30.4.

LCMS: (M+H)⁺: 325.3, (M+Na)⁺: 347.3 (100%).

Anal. Calcd for C₁₆H₂₀N₈: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.14; H, 6.39; N, 34.47.

Compound 10

3,5-diamino-1-(*t*-butyl)-1H-pyrazole-4-carbonitrile



In a 25 mL microwave vial, methanetricarbonitrile potassium salt (5.0 g, 38.4 mmol) and tert-butylhydrazine hydrochloride (4.79 g, 38.4 mmol) were taken up in 20 mL of water and heated to 100 °C for 24 h. The contents were cooled to room temperature and allowed to sit for 16 h, during which time a precipitate had formed. The crude material was then purified by automated flash chromatography on a 60

g Analogix silica gel cartridge, by first preadsorbing onto silica gel, and eluted using a 0 → 20% B gradient over 20 min, where A: DCM and B: 80:20:2 DCM / MeOH / NH₄OH. The desired fractions were pooled and evaporated to dryness to give 2.9 g (41%) of **10** as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 5.85 (s, 2H), 4.93 (s, 2H), 1.43 (s, 8H)

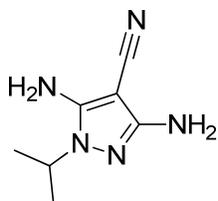
¹³C NMR (100 MHz, DMSO-*d*₆) δ 153.2, 150.7, 116.2, 64.7, 58.1, 29.1.

LCMS: (M+H)⁺: 180.1 (100%).

Anal. Calcd for C₈H₁₃N₅: C, 53.61; H, 7.31; N, 39.08. Found: C, 53.70; H, 7.61; N, 38.84.

Compound 12

3,5-diamino-1-isopropyl-1H-pyrazole-4-carbonitrile



In a 25 mL microwave vial, methanetricarbonitrile potassium salt (2.5 g, 19.2 mmol) and isopropylhydrazine hydrochloride (2.12 g, 19.2 mmol) were taken up in 10 mL of water and heated to 100 °C for 24 h. The contents were cooled to room temperature and allowed to sit for 2 h, during which time a precipitate had formed. The precipitate was filtered, washed with water, and dried to afford 1.76 g (48%) of the product **12**.

¹H NMR (400 MHz, DMSO-*d*₆) δ 6.20 (s, 2H), 5.03 (s, 2H), 4.24 (spt, *J* = 6.48 Hz, 1H), 1.18 (d, *J* = 6.57 Hz, 6H).

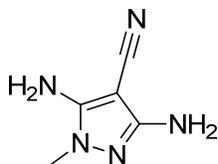
¹³C NMR (100 MHz, DMSO-*d*₆) δ 155.0, 150.3, 116.4, 62.2, 46.8, 21.7.

LCMS: (M+H)⁺: 166.1 (86%).

Anal. Calcd for C₇H₁₁N₅·0.5H₂O: C, 48.26; H, 6.94; N, 40.20. Found: C, 48.74; H, 6.88; N, 40.34.

Compound 13

3,5-diamino-1-methyl-1H-pyrazole-4-carbonitrile



To a solution of methylhydrazine (567 μL, 10.7 mmol) in water (5 mL) was added concentrated HCl (1.08 mL, 13.5 mmol) to give a solution at pH 1. Potassium tricyanomethanide (1.39 g, 10.7 mmol) was added

and the dark orange solution was heated to reflux at 145 °C for 24 h. The contents were cooled to room temperature, and the dark insoluble solids were filtered. After standing for 7 days at rt, a light tan granular solid precipitated out of the filtrate. This was filtered and dried to afford 609.9 mg of the product. The filtrate was saved, and after standing for another 5 days, a light tan solid precipitated out of solution. This was filtered, washed with a minimal amount of water, and dried under suction to afford 120.3 mg of **13** as a flaky pale yellow solid (49% combined total yield).

$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 6.23 (s, 2H), 5.00 (s, 2H), 3.27 (s, 3H).

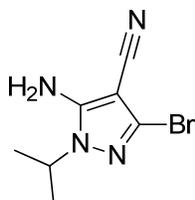
$^{13}\text{C NMR}$ (100 MHz, $\text{DMSO-}d_6$) δ 154.9, 151.5, 116.3, 62.1, 34.1.

LCMS: $(\text{M}+\text{H})^+$: 138.1.

Anal. Calcd for $\text{C}_5\text{H}_7\text{N}_5 \cdot 0.25\text{H}_2\text{O}$: C, 42.40; H, 5.34; N, 49.44. Found: C, 42.71; H, 4.73; N, 49.57 which is within 0.3-0.6% of the expected value.

Compound 14

5-amino-3-bromo-1-isopropyl-1H-pyrazole-4-carbonitrile



Copper(II) bromide (2.028 g, 9.08 mmol) and tert-butyl nitrite (1.080 mL, 9.08 mmol) were taken up in 50 mL of acetonitrile. The contents were cooled to 0 °C, and a solution of 3,5-diamino-1-isopropyl-1H-pyrazole-4-carbonitrile (1.50 g, 9.08 mmol) in 50 mL of acetonitrile was added dropwise over 15 min. The contents were allowed to stir at 0 °C for 2 h, before being allowed to warm to rt and stir for 16 h. The contents were evaporated to near dryness, and the crude partitioned between 250 mL of water and 250 mL of ethyl acetate. The water layer was further extracted (2 x 150 mL) with ethyl acetate. The combined organic fractions were combined and washed (2 x 300 mL) with brine, dried over sodium sulfate, filtered and evaporated to dryness. The crude material was then purified by automated flash chromatography on a 80 g silica gel cartridge and eluted using a 0 -> 20% B gradient over 20 min, where A: DCM and B: 80:20:2 DCM / MeOH / NH_4OH . The desired fractions were pooled and evaporated to dryness to give 2 lots of material. The purest fractions were combined to afford **14** as an off-white solid (350 mg, 98% purity by LCMS).

$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 6.92 (s, 2H), 4.43 (quin, $J = 6.51$ Hz, 1H), 1.26 (d, $J = 6.57$ Hz, 6H).

$^{13}\text{C NMR}$ (100 MHz, $\text{DMSO-}d_6$) δ 151.9, 126.4, 114.3, 75.8, 48.8, 21.7.

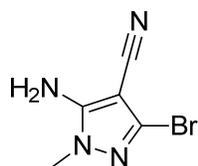
LCMS: $(\text{M}+\text{H})^+$: 229.1, 231.2.

Anal. Calcd for C₇H₉BrN₄: C, 36.70; H, 3.96; N, 24.46. Found: C, 36.88; H, 3.36; N, 24.18.

The remaining fractions were combined to give **14** as an orange solid (1.1 g, 85% by LCMS, 61% total yield).

Compound 15

5-amino-3-bromo-1-methyl-1H-pyrazole-4-carbonitrile



To a solution of copper(II) bromide (98 mg, 0.438 mmol) and 90% tert-butyl nitrite (58 uL, 0.438 mmol) in acetonitrile (2 mL) cooled to 0 °C, was added a suspension of 3,5-diamino-1-methyl-1H-pyrazole-4-carbonitrile (60 mg, 0.438 mmol) in acetonitrile (2 mL) dropwise over 10 min. The contents were allowed to stir at 0 °C for 2 hrs. The dark brown reaction mixture was allowed to warm to rt and then concentrated in vacuo to near dryness. The residue was partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate (3x). The combined organic layers were washed with brine (2x), dried over MgSO₄, filtered, and concentrated in vacuo to afford a pale orange solid. The crude material was purified by automated flash chromatography on a 12 g Reveleris silica column (40 um), using a 0-100% ethyl acetate/hexanes gradient over 10 min at 30 mL/min. The desired fractions were combined and concentrated in vacuo to afford 41.2 mg (45%) of **15** as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 6.92 (s, 2H), 3.51 (s, 3H).

¹³C NMR (100 MHz, DMSO-*d*₆) δ 152.6, 125.7, 113.8, 75.4, 34.9.

LCMS: (M+H)⁺: 201.1, 203.1 (97%).

Anal. Calcd for C₅H₅BrN₄: C, 29.87; H, 2.51; N, 27.87. Found: C, 30.81 %; H, 2.42 %; N, 26.95 %.

Based on ¹H NMR (maximum of 0.067 equiv EtOAc), the expected theory is: C, 30.58; H, 2.70; N, 27.08 which is within 0.3% of the observed value.

General procedure A for the preparation of 5-amino-3-aryl-1-*t*-butyl-pyrazole-4-carboxamides (**1a-e**) from 3,5-diamino-1-(*t*-butyl)-1H-pyrazole-4-carboxamide (**2**)

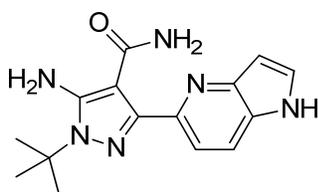
The following compounds were prepared in the following manner, unless otherwise described.

In a 10 mL microwave vial, 5-amino-3-bromo-1-(*t*-butyl)-1H-pyrazole-4-carboxamide (100-150 mg, 1 equiv) and boronic acid or boronate ester (1.1 equiv) were taken up in 4 mL of 3:1 dioxane / water. K₃PO₄ (2 equiv), (tBu)₃PHBF₄ (0.1 equiv) and Pd₂dba₃ (0.05 equiv) were added, the vial capped and

heated to 120 °C in a microwave reactor for 30 min. The reaction contents were allowed to cool to room temperature.

Compound 1a

N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-2-carboxamide



Following general procedure A and subsequent cooling of the reaction, brine (1 mL) was added. The contents stirred for 5 min then the stirring stopped and the layers were allowed to separate. The dioxane layer was drawn off, and the aqueous layer extracted (2 x 5 mL) with ethyl acetate. The extractions were combined with the dioxane layer and preadsorbed onto 1.5 g of silica gel, purified by automated flash chromatography on a 25 g silica gel cartridge using a 0 -> 40% B gradient over 40 min, where A: DCM and B: 80:20:2 DCM / MeOH / NH₄OH. The desired fractions were pooled and evaporated to give 102 mg (87%) of the desired compound **1a** as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 11.37 (br. s., 1H), 8.42 (d, *J* = 1.52 Hz, 1H), 7.83 (s, 1H), 7.69 (t, *J* = 2.78 Hz, 1H), 6.59 (br. s., 1H), 6.25 (s, 2H), 1.59 (s, 9H), 2 amide protons not fully resolved seen as two very broad peaks between 5.0 and 7.0 ppm.

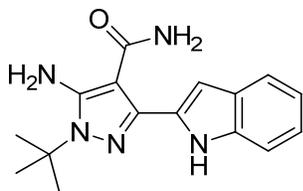
¹³C NMR (100 MHz, DMSO-*d*₆) δ: 166.8, 150.0, 145.8, 144.4, 142.8, 130.0, 127.7, 122.3, 118.4, 101.6, 96.2, 58.2, 28.4.

LCMS: (M+H)⁺: 299.3 (100%).

Anal. Calcd for C₁₅H₁₈N₆O: C, 60.39; H, 6.08; N, 28.17. Found: C, 58.78; H, 5.73; N, 27.02. Based on ¹H NMR (maximum of 0.15 equiv DCM), the expected theory is: C, 58.49; H, 5.93; N, 27.01 which is within 0.3% of the observed value.

Compound 1b

5-amino-1-(tert-butyl)-3-(1H-indol-2-yl)-1H-pyrazole-4-carboxamide



Following general procedure A and subsequent cooling of the reaction, brine (1 mL) was added. The contents stirred for 5 min then the stirring stopped and the layers were allowed to separate. The dioxane layer was drawn off, and the aqueous layer extracted with ethyl acetate (2 x 5 mL). The extractions were combined with the dioxane layer and filtered through a pad of sodium sulfate and evaporated to dryness. The crude material was purified by automated RP-HPLC using a 15 -> 70% B gradient over 7 min, where A: 0.1% TFA / water and B: 0.1% TFA / acetonitrile. The desired fractions were pooled and evaporated to remove much of the acetonitrile and then poured into 100 mL of sat. sodium bicarbonate. The contents were then extracted (3 x 50 mL) with EtOAc. The organic fractions were pooled, washed with brine (1 x 100 mL), dried over sodium sulfate, filtered and evaporated to dryness to give 30 mg (25%) of the desired compound **1b** as a light tan solid.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.36 (s, 1H), 7.56 (d, $J = 8.08$ Hz, 1H), 7.42 (dd, $J = 0.76, 8.08$ Hz, 1H), 7.12 (ddd, $J = 1.26, 7.01, 8.15$ Hz, 1H), 6.99 - 7.06 (m, 1H), 6.65 (dd, $J = 0.76, 2.02$ Hz, 1H), 6.34 (br. s., 2H), 1.57 - 1.66 (m, 9H), 2 NH_2 protons not fully resolved; seen as broad peak between 6.0 and 7.0 ppm.

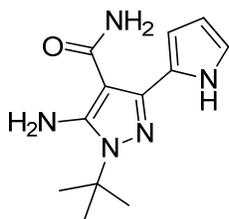
^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 166.5, 150.0, 138.7, 131.3, 127.8, 123.8, 121.7, 120.1, 119.3, 111.5, 101.3, 96.2, 58.5, 28.4.

LCMS: $(\text{M}+\text{H})^+$: 298.3 (95%).

Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{Cl}_2\text{N}_5\text{O}$: C, 64.63; H, 6.44; N, 23.55. Found: C, 64.07; H, 6.45; N, 22.29. Based on ^1H NMR (0.13 equiv EtOAc), the expected theory is: C, 64.25; H, 6.54; N, 22.68 which is within 0.4% of the observed value.

Compound 1c

5-amino-1-(tert-butyl)-3-(1H-pyrrol-2-yl)-1H-pyrazole-4-carboxamide



In a 5 mL microwave vial, 5-amino-3-bromo-1-(tert-butyl)-1H-pyrazole-4-carboxamide (150 mg, 0.57 mmol) and (1-(tert-butoxycarbonyl)-1H-pyrrol-2-yl)boronic acid (121 mg, 0.57 mmol) were taken up in 4 mL of 3:1 dioxane / water. K_3PO_4 (244 mg, 1.15 mmol), $(tBu)_3PHBF_4$ (16.7 mg, 0.057 mmol) and Pd_2dba_3 (26.3 mg, 0.029 mmol) were added, the vial capped and heated to 120 °C in the microwave for 30 min. The reaction contents were allowed to cool. Brine (1 mL) was added and the contents allowed to stir for 2 min. The phases were allowed to separate. The organic layer was drawn off, and the aqueous layer was extracted with ethyl acetate (3 x 2 mL). All of the organic fractions were combined and filtered through a pad of sodium sulfate. The solvent was removed under vacuum, dissolved in 3 mL of methanol and purified by automated RP-HPLC using a 5 → 55% B gradient over 7 min, where A: 0.1% TFA / water and B: 0.1% TFA / acetonitrile. The desired fractions were pooled, basified with sat. sodium bicarbonate to a volume of 100 mL, and extracted with ethyl acetate (3 x 50 mL). The organic fractions were pooled, washed with brine (2 x 100 mL), dried over sodium sulfate, filtered and evaporated to give 47 mg (31%) of compound **1c** as a white solid.

1H NMR (400 MHz, $DMSO-d_6$) δ 11.16 (br. s., 1H), 6.83 (d, $J = 1.52$ Hz, 1H), 6.55 (br. s., 1H), 6.31 (s, 2H), 6.23 (br. s., 1H), 6.09 - 6.16 (m, 1H), 1.56 (s, 9H). One amide NH not fully resolved.

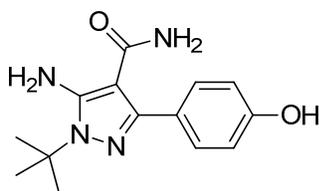
^{13}C NMR (100 MHz, $DMSO-d_6$) δ 167.1, 150.2, 139.9, 124.5, 119.3, 108.7, 108.6, 96.3, 58.6, 28.9.

LCMS: $(M+H)^+$: 248.2 (95%).

Anal. Calcd for $C_{12}H_{17}N_5O \cdot 0.5 H_2O$: C, 56.23; H, 7.08; N, 27.32. Found: C, 56.05; H, 6.69; N, 26.97.

Compound 1d

5-amino-1-(tert-butyl)-3-(4-hydroxyphenyl)-1H-pyrazole-4-carboxamide



Following general procedure A and subsequent cooling of the reaction, brine (1 mL) was added. The contents stirred for 5 min then the stirring stopped and the layers were allowed to separate. The dioxane layer was drawn off, and the aqueous layer extracted (2 x 5 mL) with ethyl acetate. The extractions were combined and filtered through a plug of sodium sulfate and evaporated to dryness. The crude material was purified by automated RP-HPLC using a 5 → 30% B gradient over 7 min., where A: 0.1% TFA / water and B: 0.1% TFA / acetonitrile. The desired fractions were pooled, and made neutral with sat.

sodium bicarbonate solution (100 mL), and extracted with ethyl acetate (3 x 30 mL). The organic fractions were pooled, washed with brine (2 x 50 mL), dried over sodium sulfate, filtered and evaporated to dryness to give 64 mg (48%) of the desired compound **1d** as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.66 (s, 1H), 7.19 - 7.31 (m, 2H), 6.55 - 7.07 (m, 3H), 6.28 (s, 2H), 5.01 - 5.55 (m, 1H), 1.55 (s, 9H).

¹³C NMR (100 MHz, DMSO-*d*₆) δ 166.7, 157.5, 149.9, 146.1, 130.2, 124.6, 115.3, 95.4, 58.0, 28.4.

LCMS: (M+H)⁺: 275.3 (100%).

Anal. Calcd for C₁₄H₁₈N₄O₂: C, 61.30; H, 6.61; N, 20.42. Found: C, 60.51; H, 6.25; N, 19.93. Based on ¹H NMR (0.06 equiv EtOAc), the expected theory is: C, 61.17; H, 6.66; N, 20.04 which is within 0.4% of the observed value.

Compound 1e

5-amino-1-(tert-butyl)-3-(3,4-dichlorophenyl)-1H-pyrazole-4-carboxamide



Following general procedure A and subsequent cooling of the reaction, brine (1 mL) was added. The contents stirred for 5 min then the stirring stopped and the layers were allowed to separate. The dioxane layer was drawn off, and the aqueous layer extracted (2 x 5 mL) with ethyl acetate. The extractions were combined with the dioxane layer and preadsorbed onto 2.5 g of silica gel, purified by automated flash chromatography on a 24 g silica gel cartridge using a 0 -> 50% EtOAc / hexanes gradient over 50 min. The desired fractions were pooled and evaporated to give 100 mg of the desired compound as an off-white impure solid. The material was then repurified by automated RP-HPLC using a 30 -> 75% B gradient over 7 min., where A: 0.1% TFA / water and B: 0.1% TFA / acetonitrile. The desired fractions were pooled, evaporated to remove much of the acetonitrile, poured into 50 mL of sat. sodium bicarbonate, and extracted with EtOAc (3 x 30 mL). The organic fractions were pooled, washed with brine (2 x 50 mL), dried over sodium sulfate, filtered and evaporated to dryness to give 54 mg (34%) of the desired compound **1e** as a white solid.

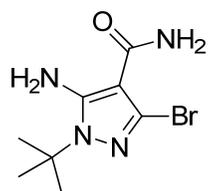
¹H NMR (400 MHz, DMSO-*d*₆) δ 7.62 - 7.77 (m, 2H), 7.48 (dd, *J* = 1.64, 8.21 Hz, 1H), 6.45 (br. s., 2H), 6.16 (s, 2H), 1.57 (s, 9H).

^{13}C NMR (100 MHz, DMSO- d_6) δ 166.6, 149.9, 143.4, 130.8, 130.4, 130.1, 128.7, 123.8, 99.5, 96.4, 58.5, 28.3.

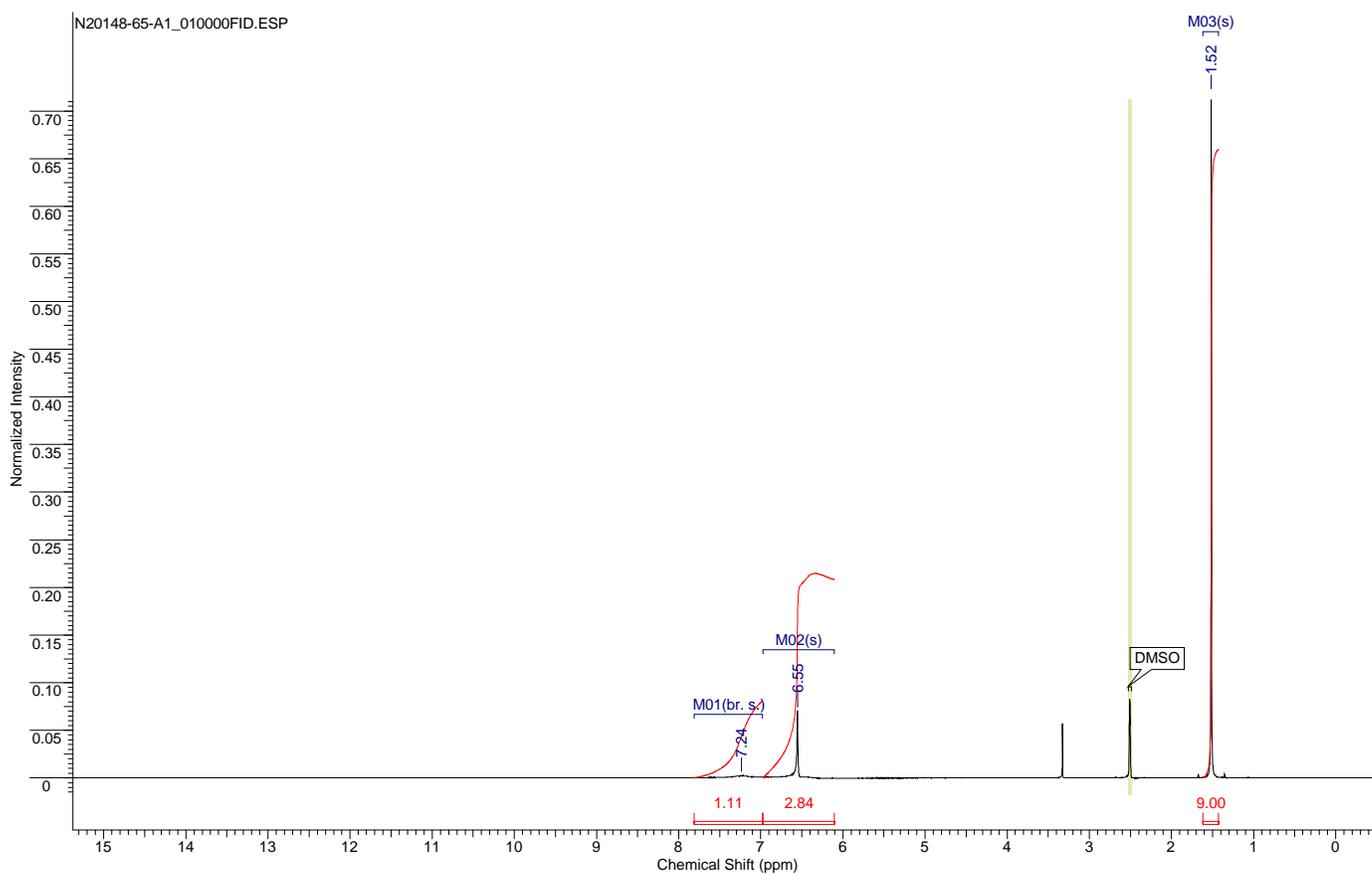
LCMS: (M+H) $^+$: 327.3/329.3 in a 3:2 ratio (100%).

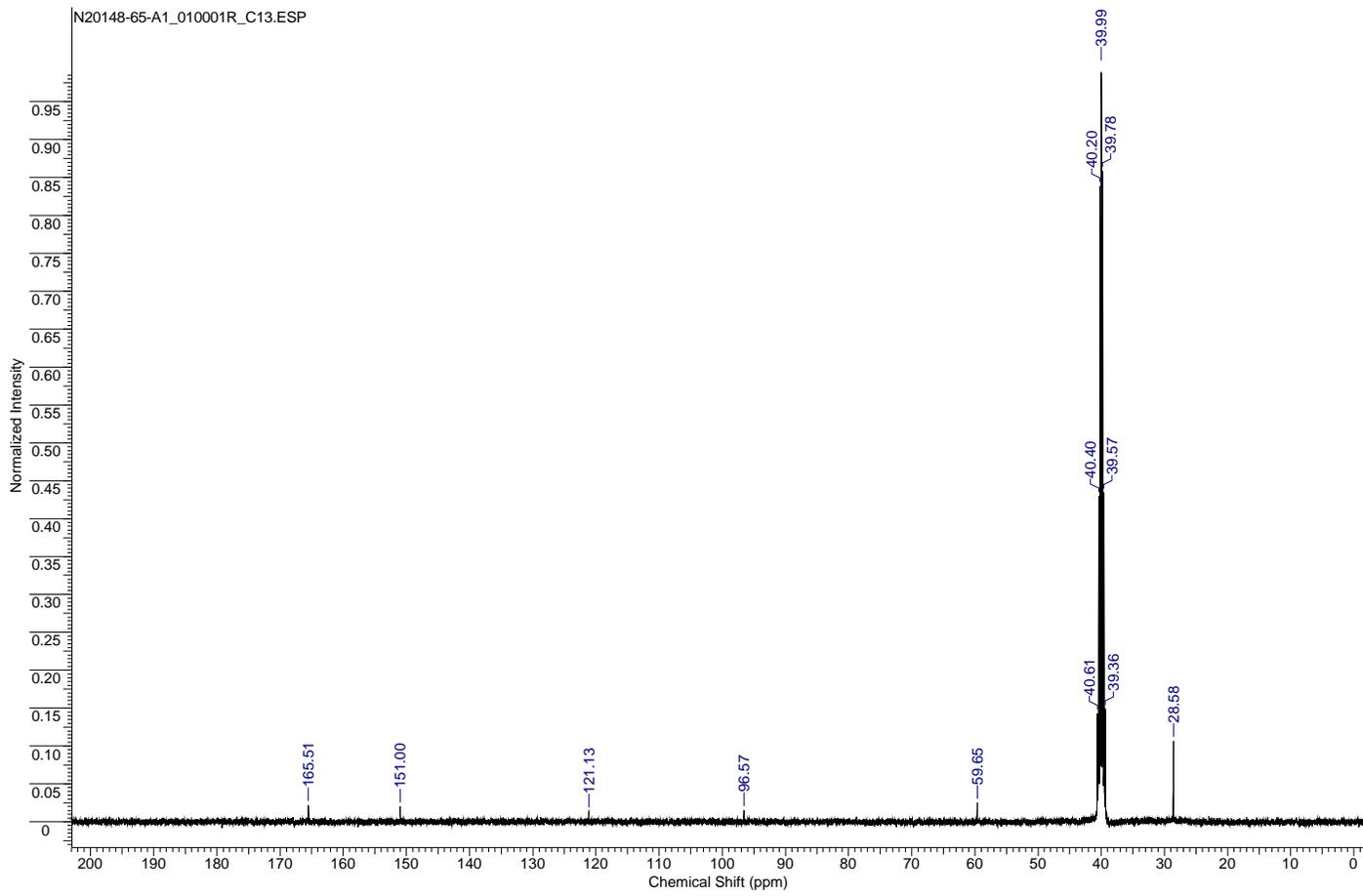
Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}$: C, 51.39; H, 4.93; N, 17.12. Found: C, 50.60; H, 4.55; N, 16.58.

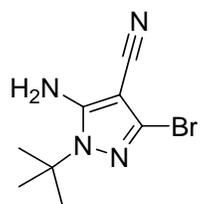
NMR spectra for compounds 2, 3, 7, 8, 10, 12, 13, 14, 15, 1a-e



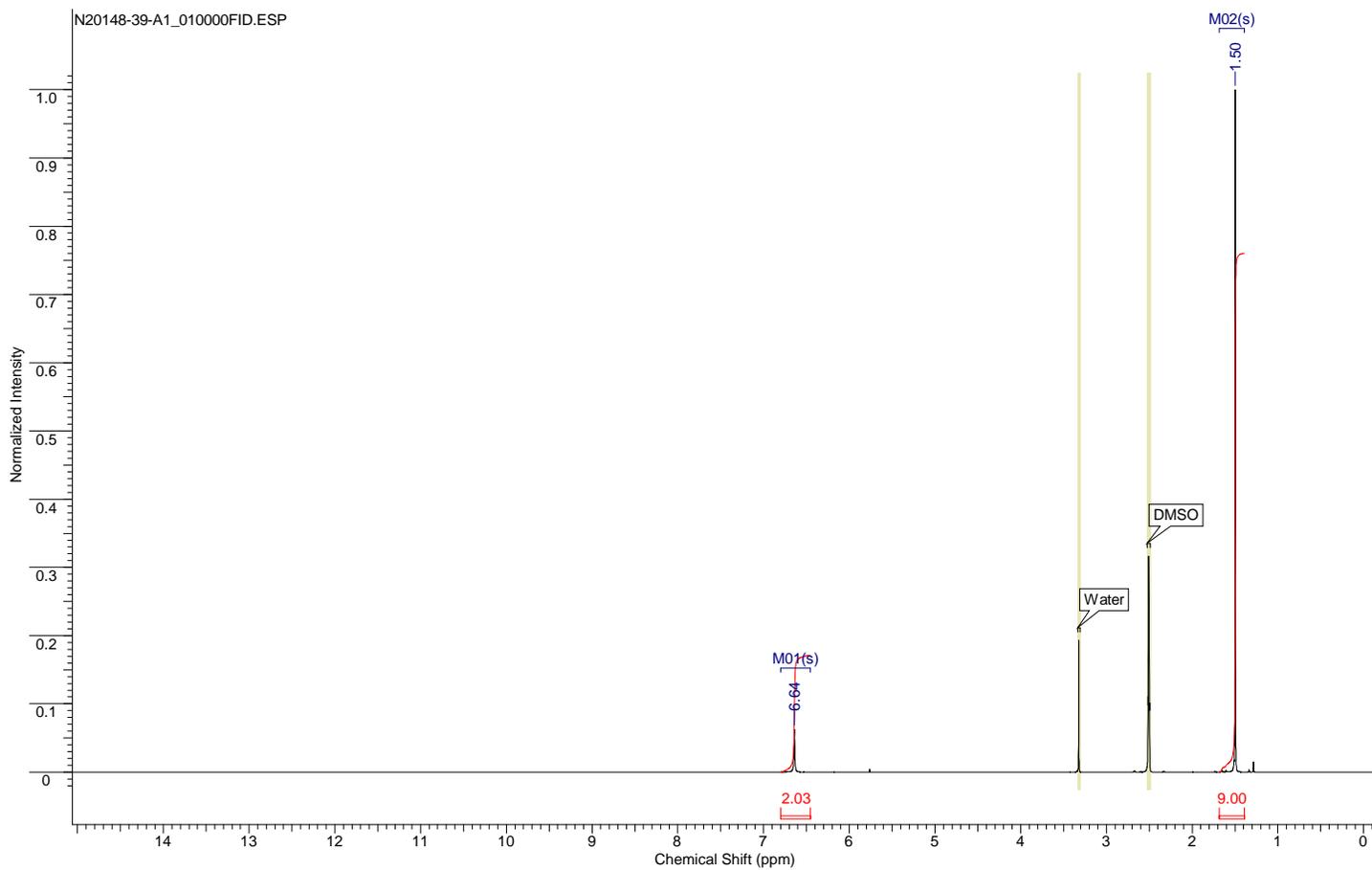
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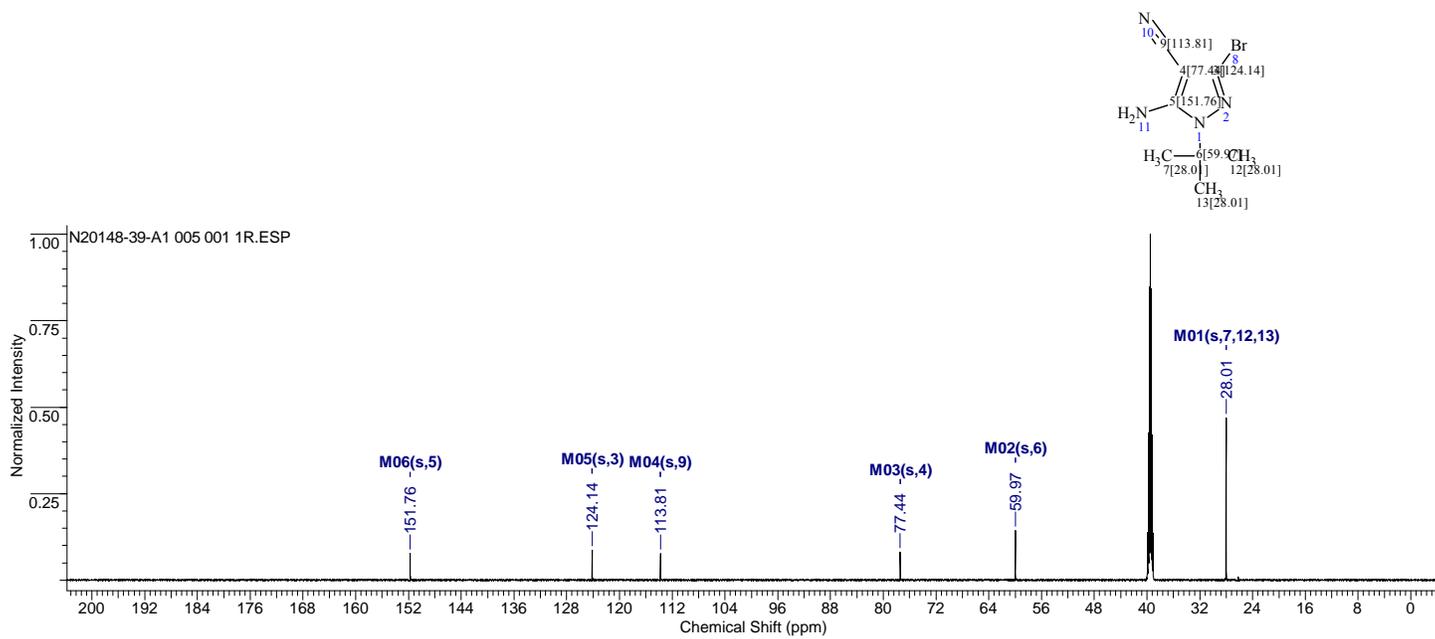




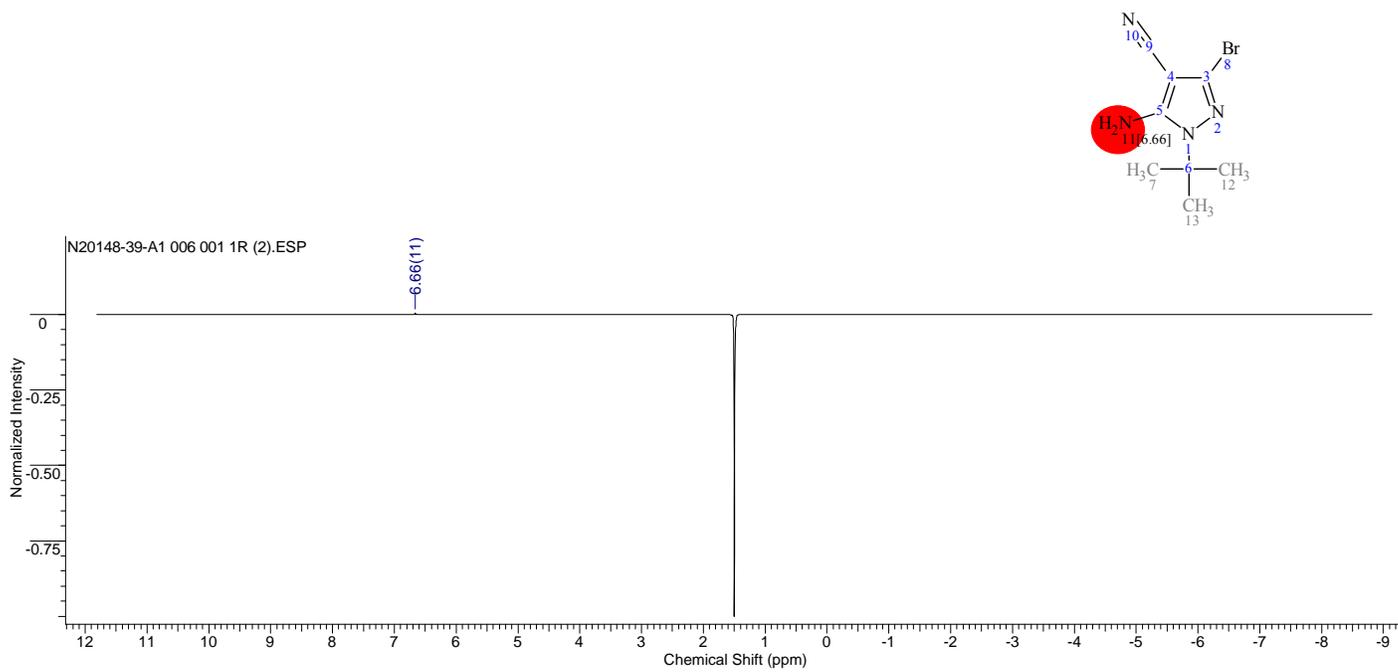


3





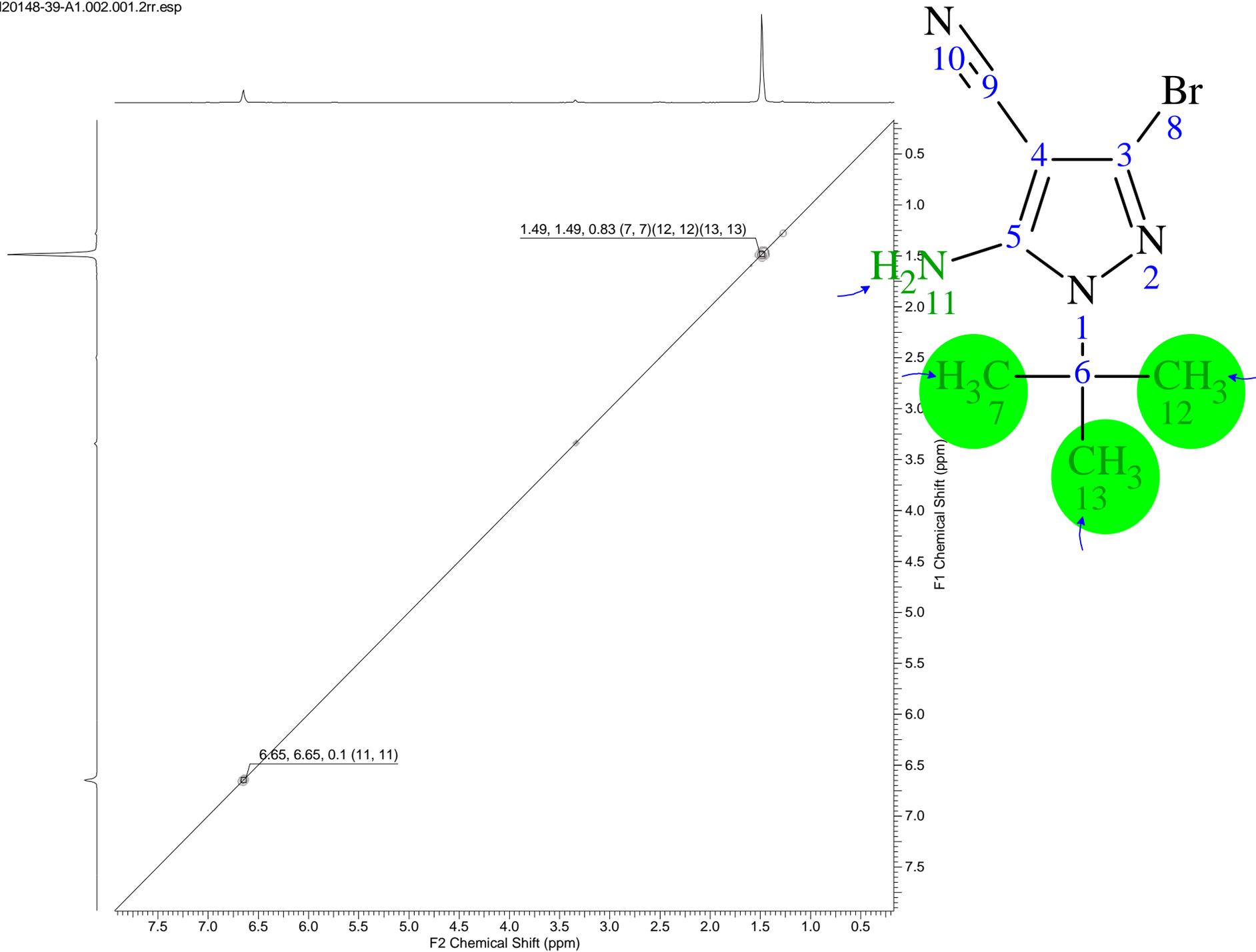
nOe:

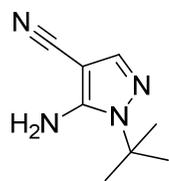


2D Experiment H,H COSY, 2J-3J

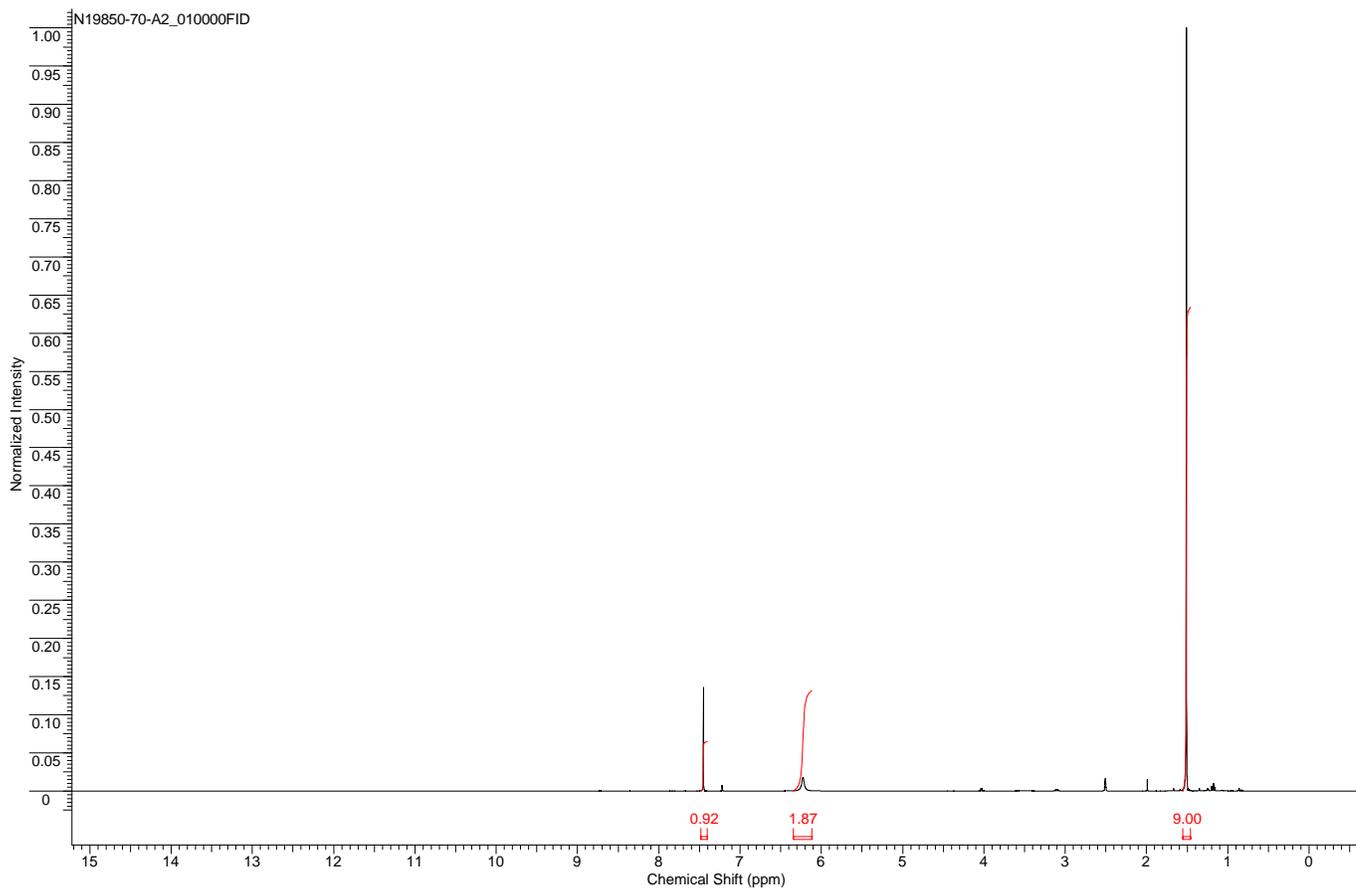
Formula C₈H₁₁BrN₄ | **FW** 243.1037

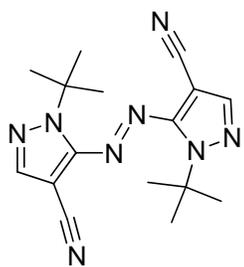
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3	12	12	1.49	1.49
4	13	13	1.49	1.49



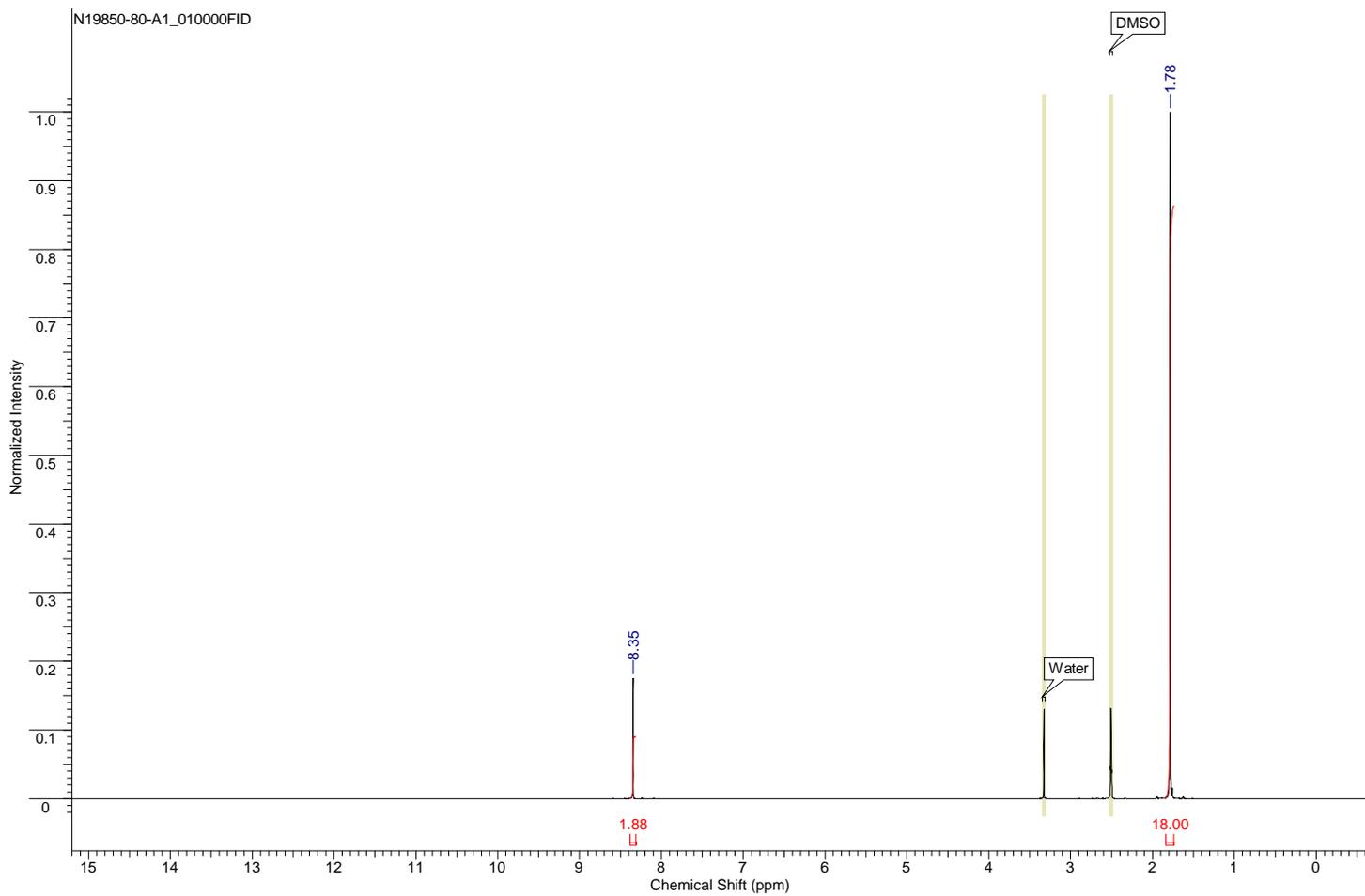


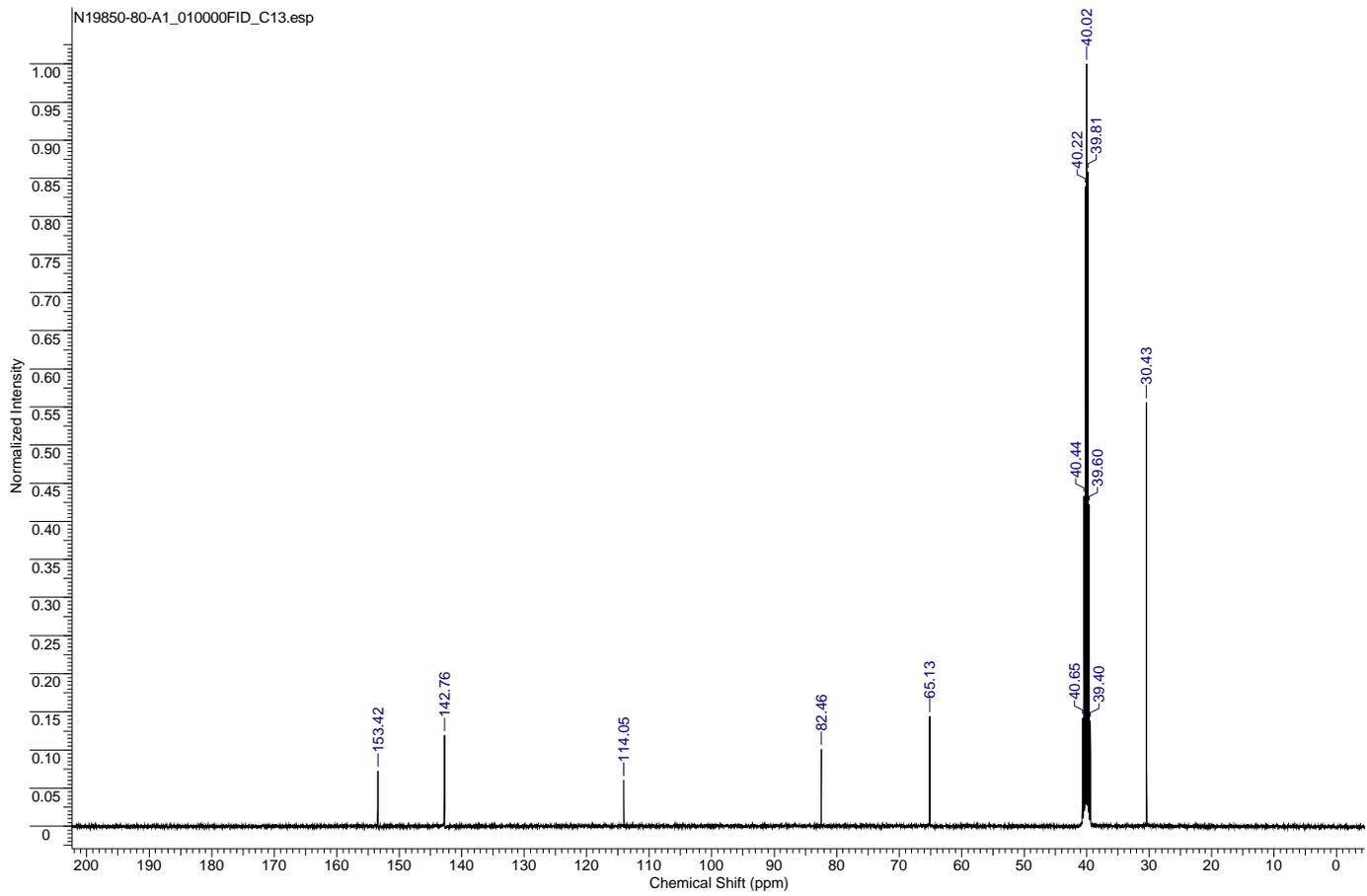
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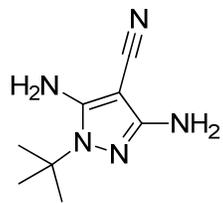




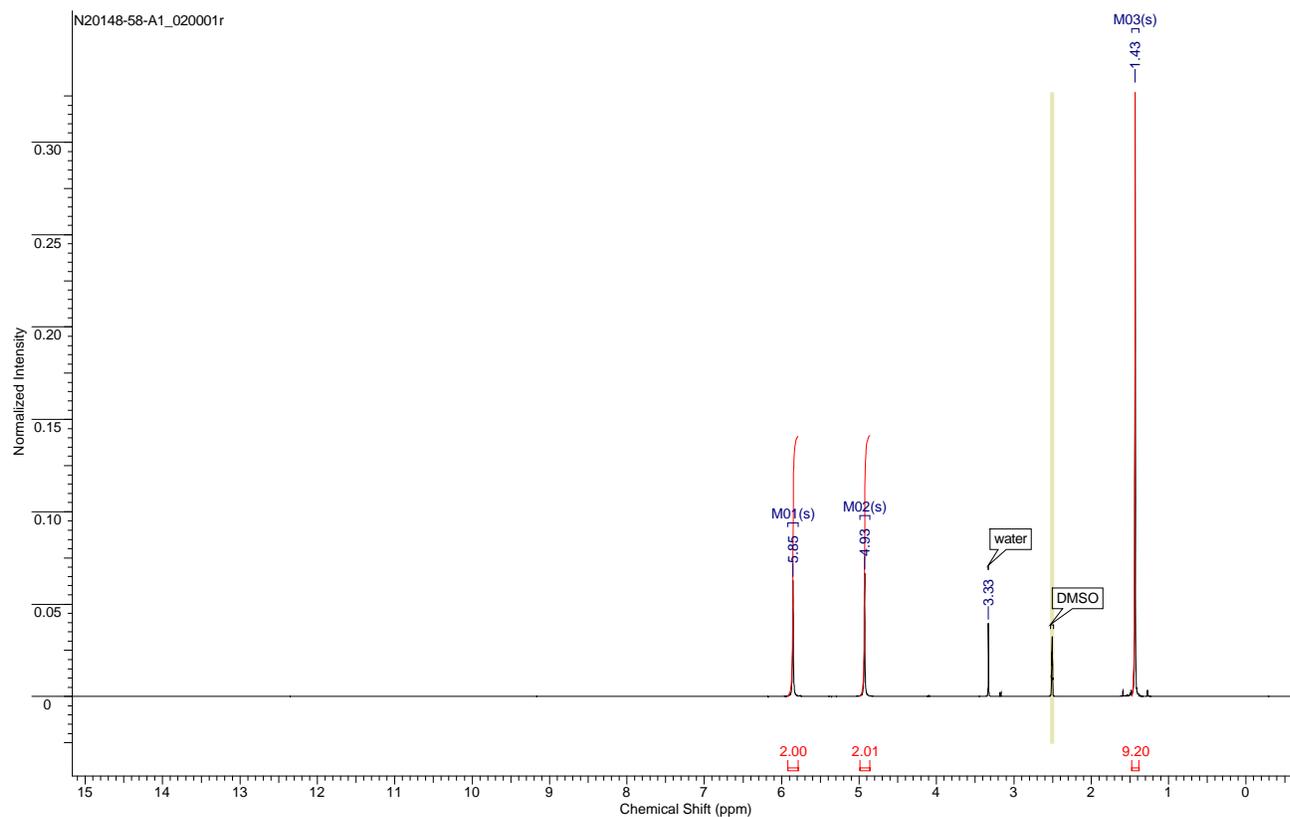
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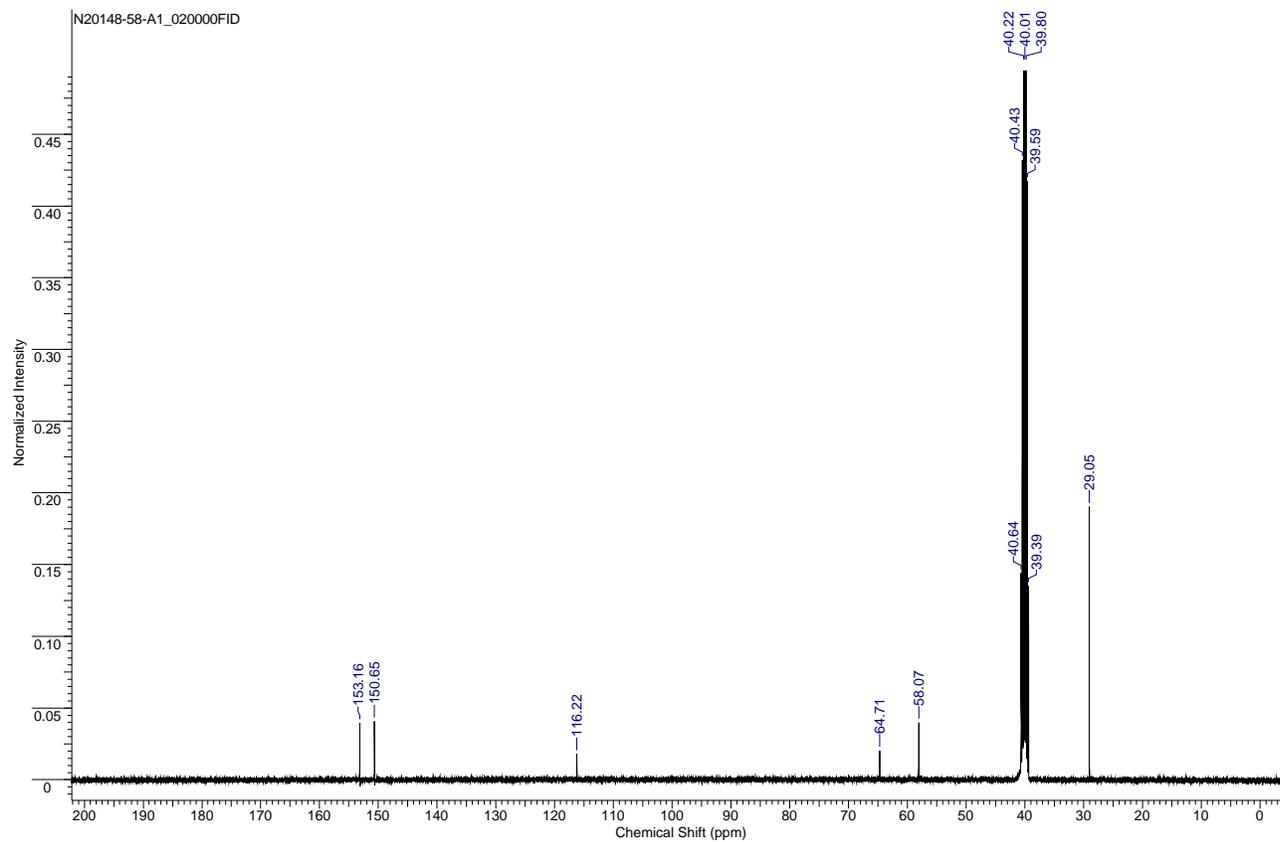


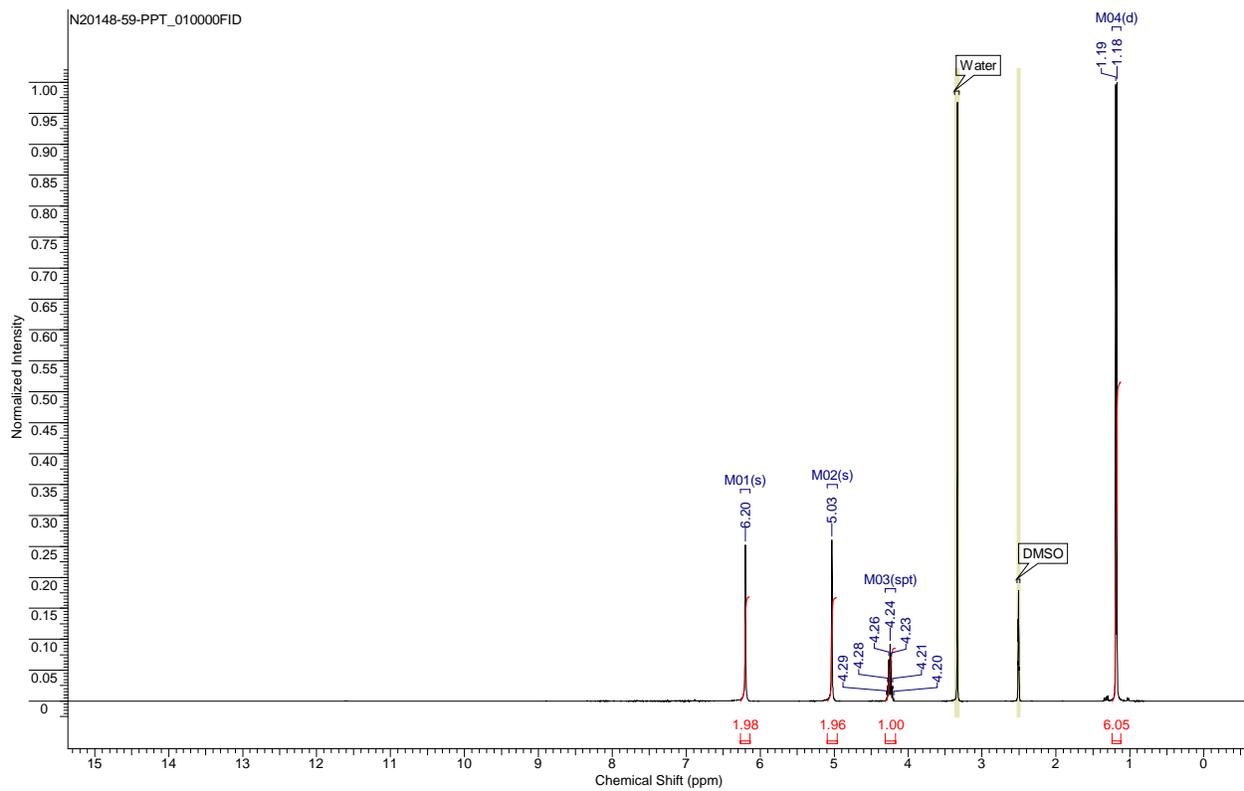
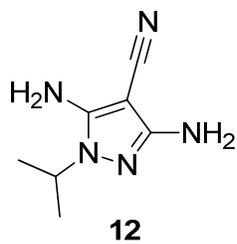


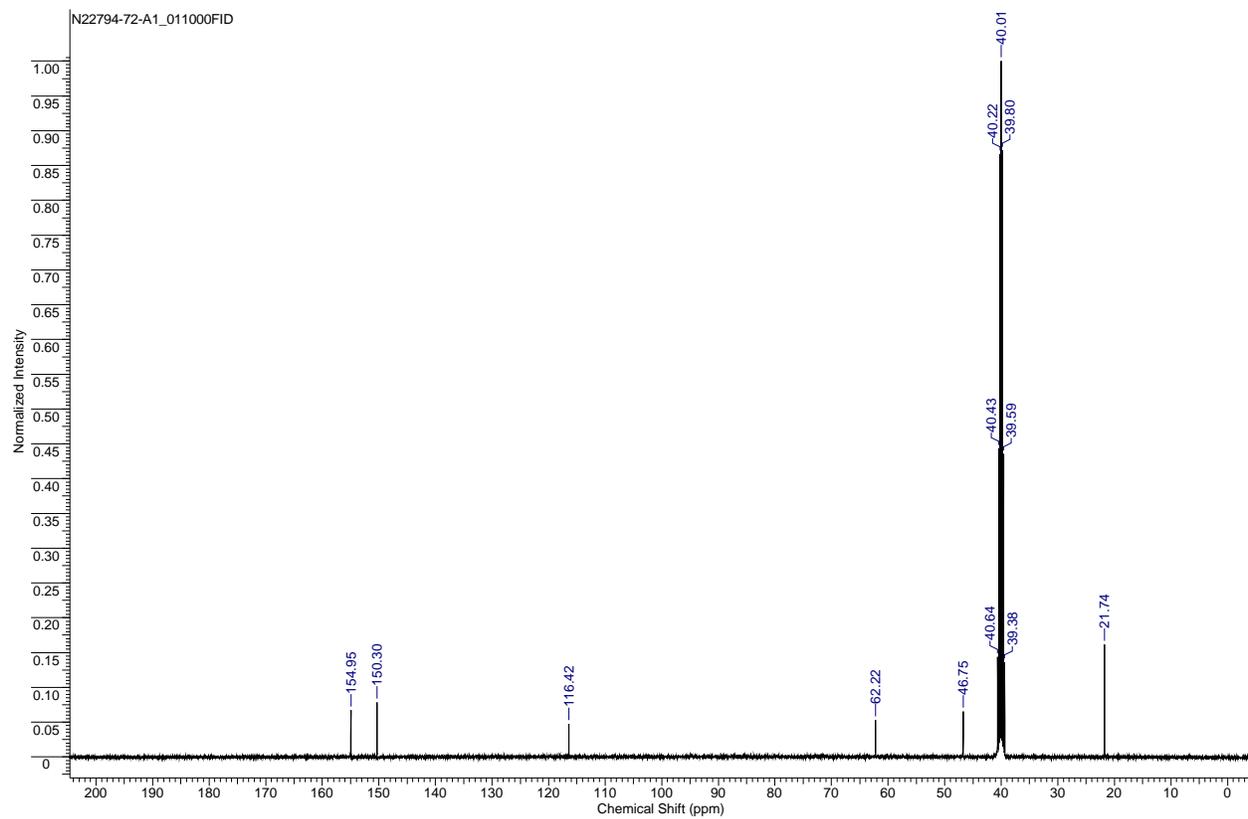


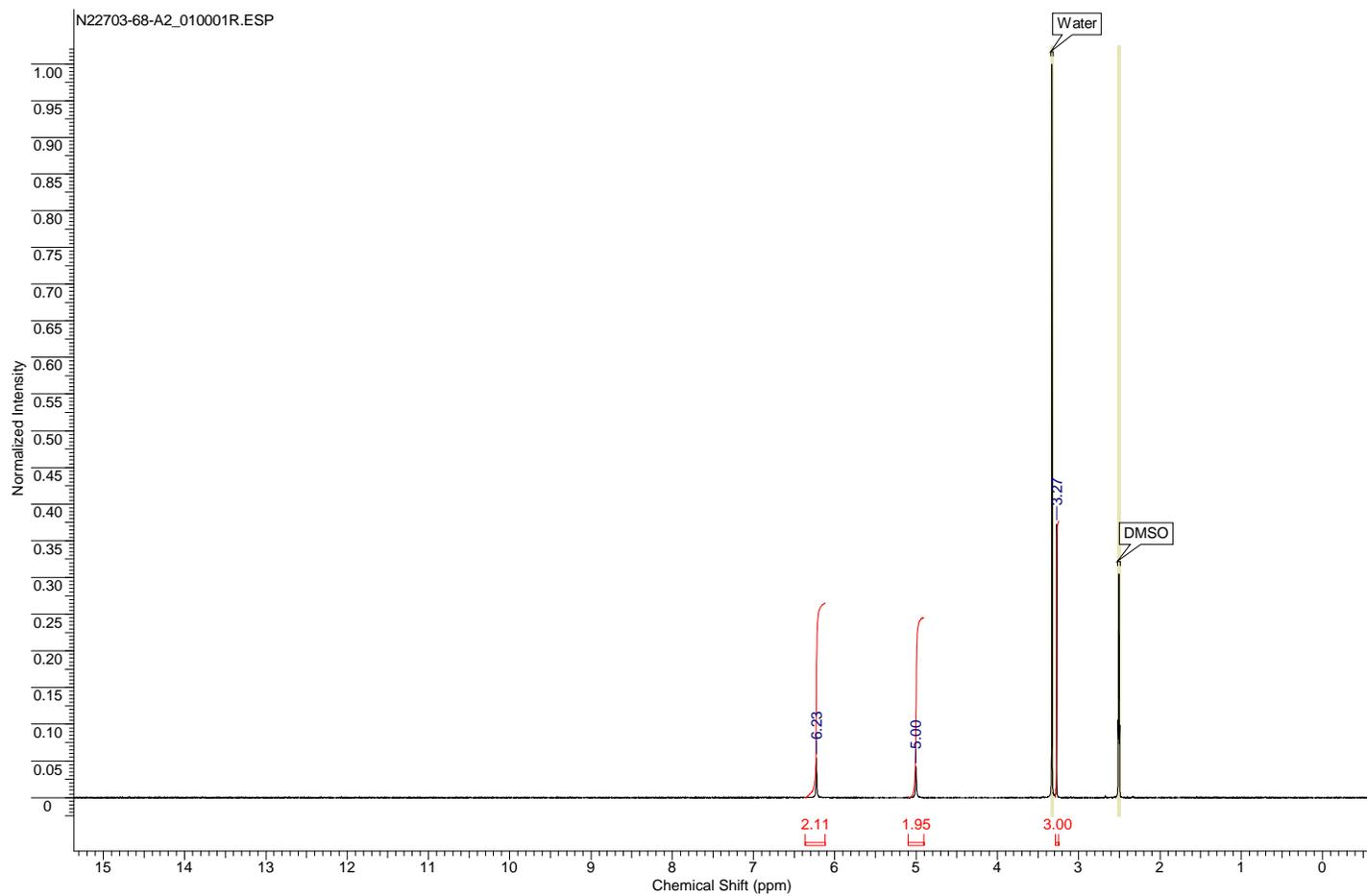
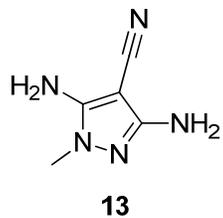
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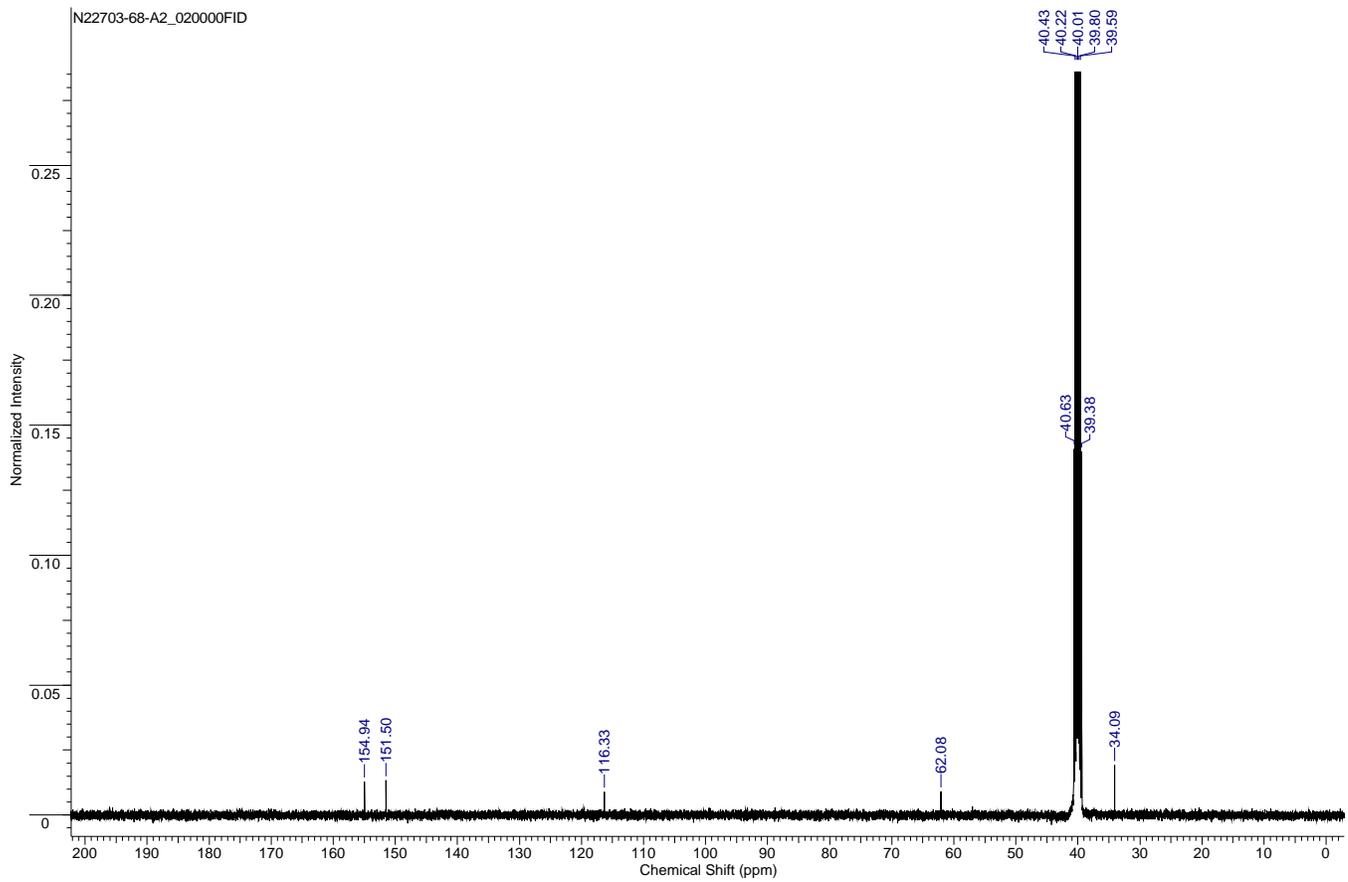


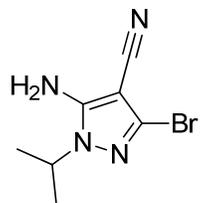




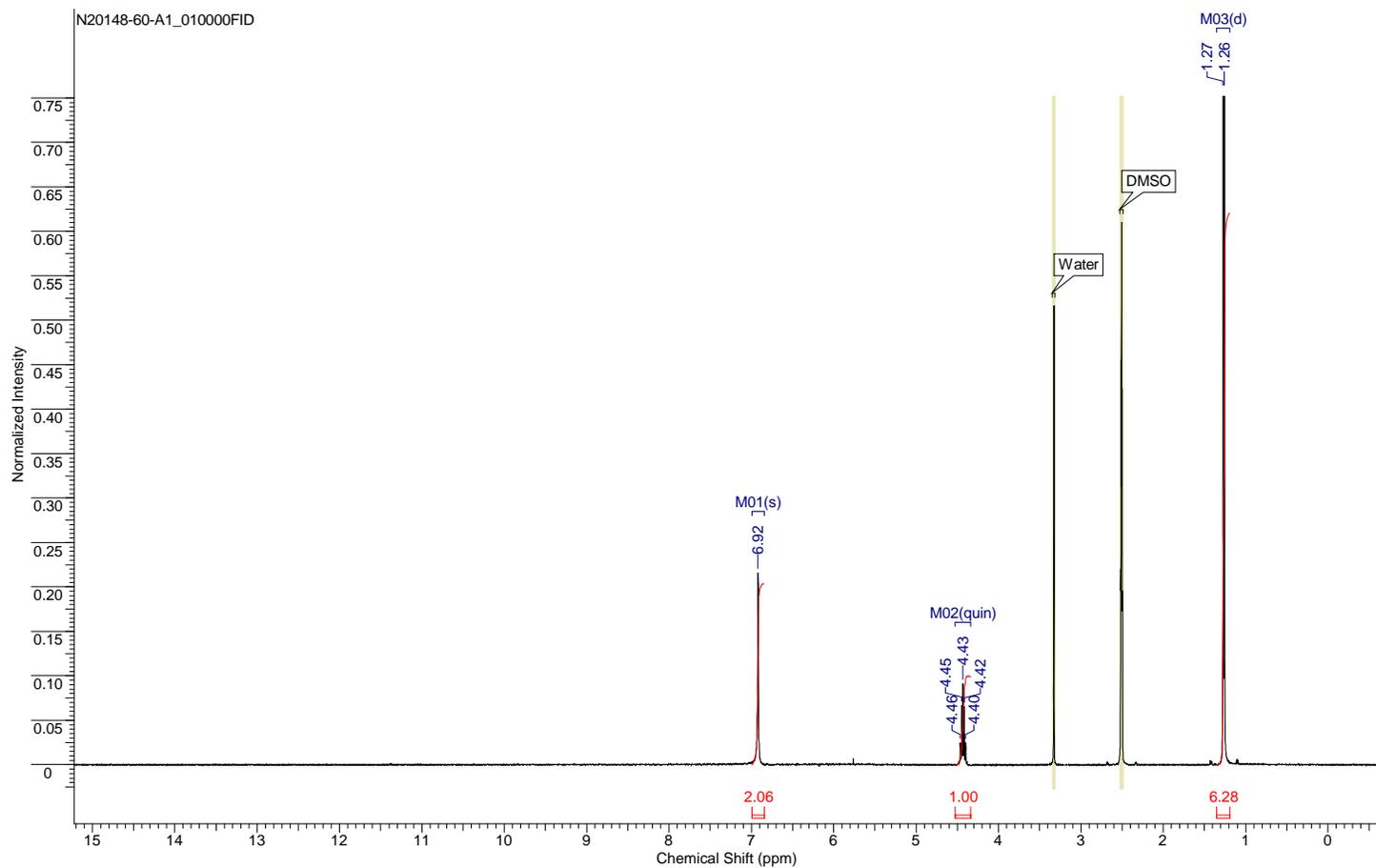


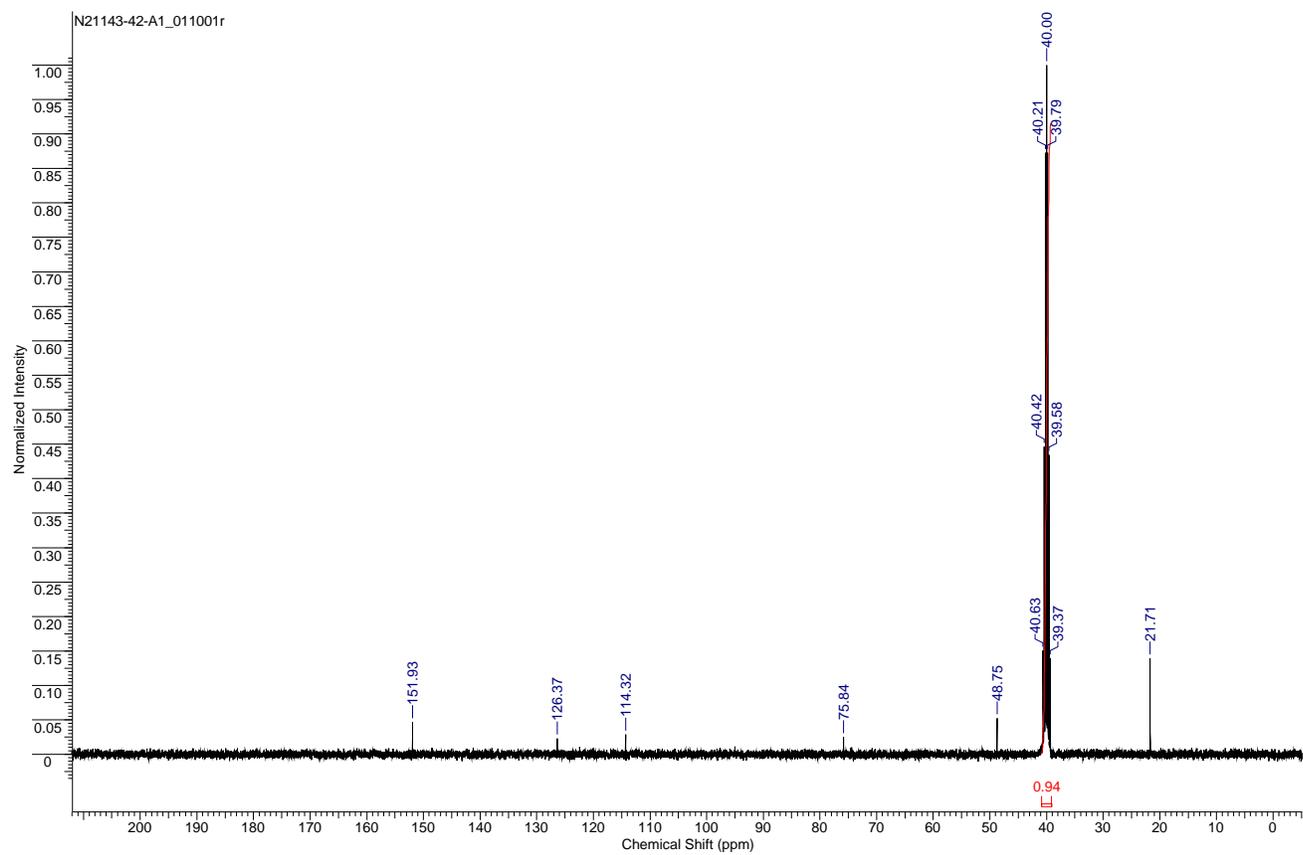






14



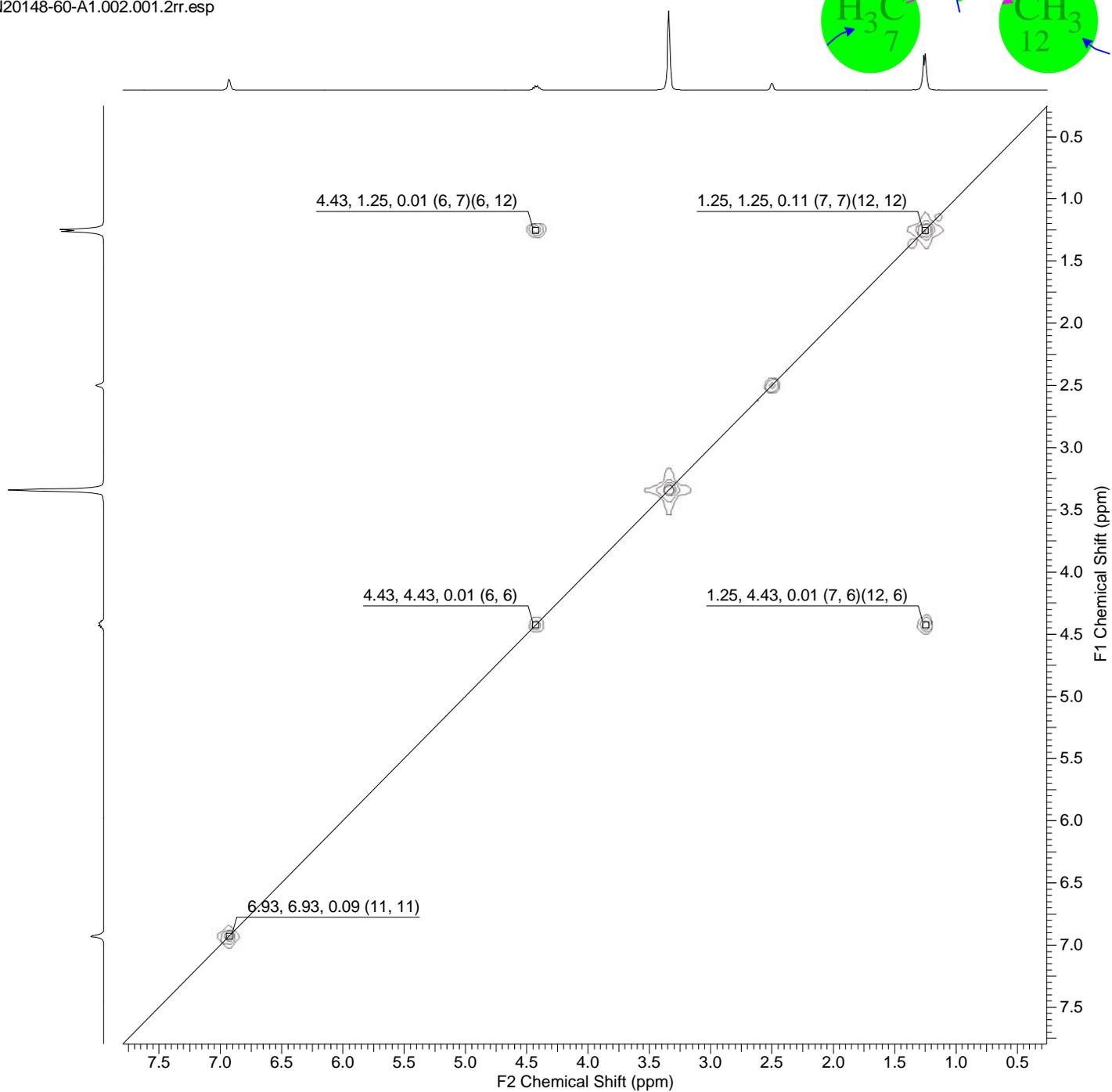
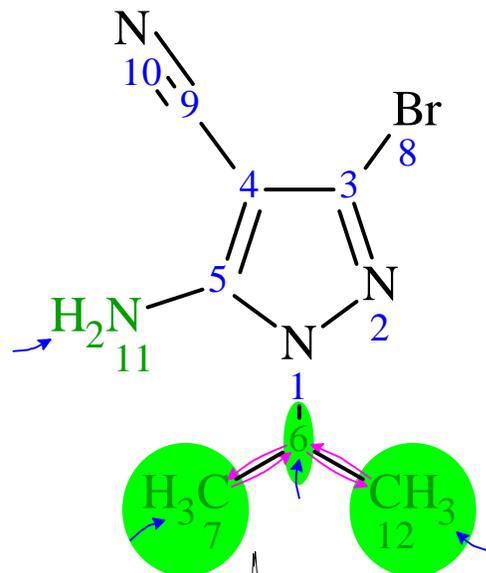


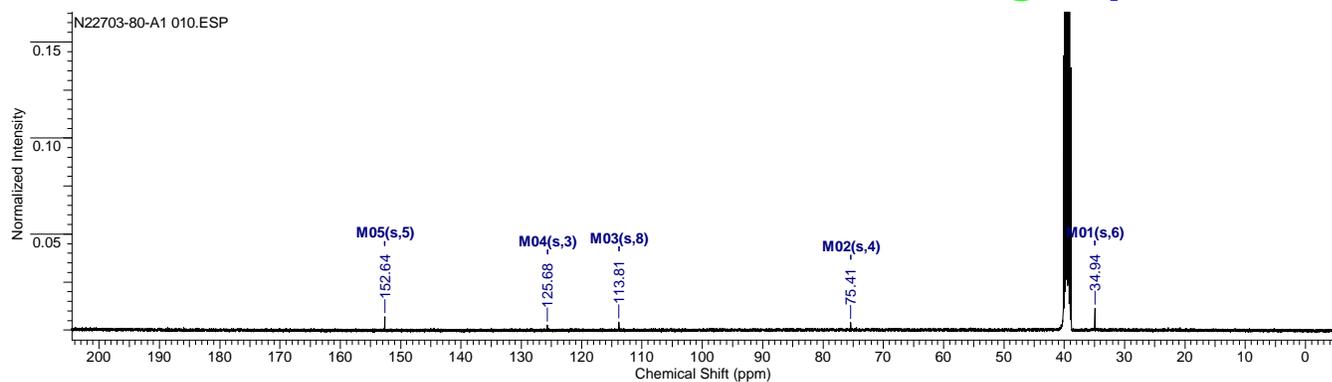
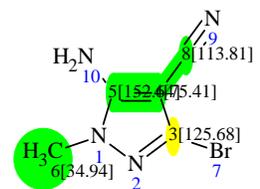
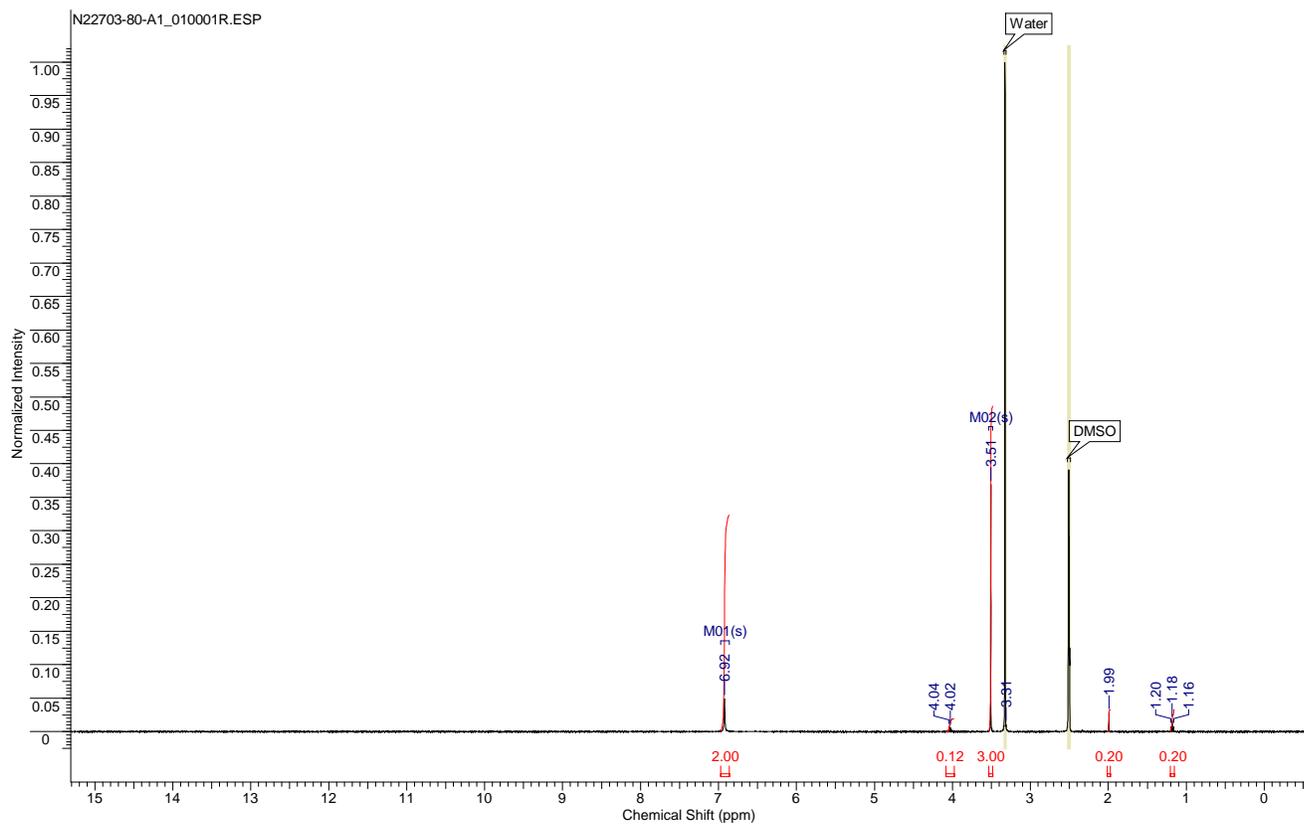
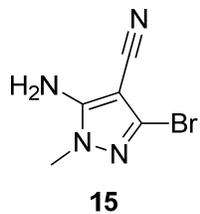
2D Experiment H,H COSY, 2J-3J

Formula C₇H₉BrN₄ | **FW** 229.0772

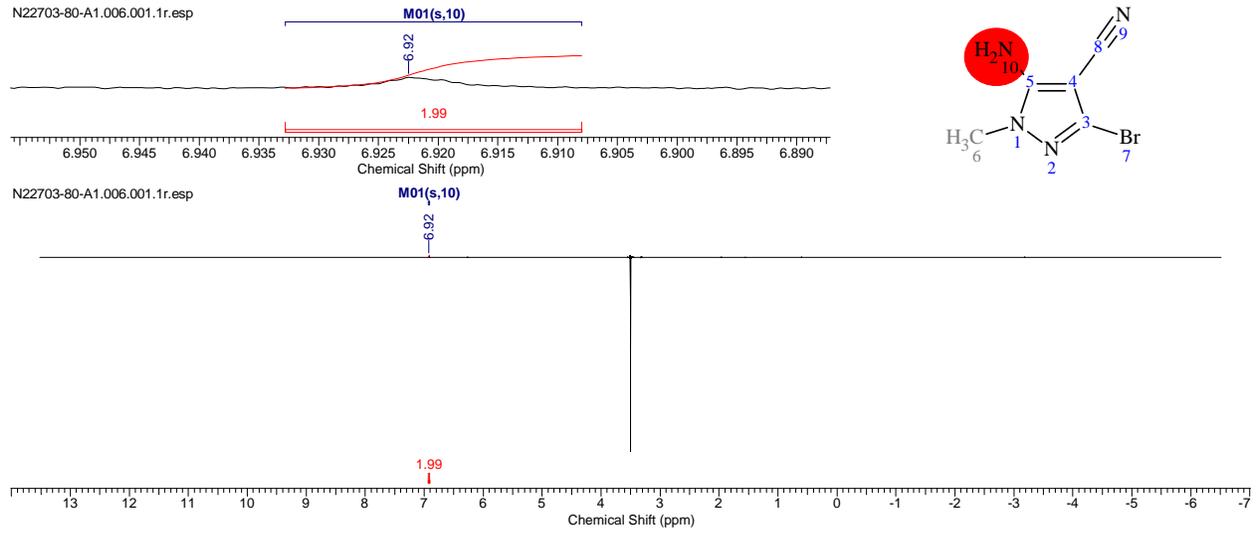
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4	6	7	4.43	1.25
5	7	7	1.25	1.25
6	11	11	6.93	6.93
7	6	12	4.43	1.25
8	12	12	1.25	1.25

N20148-60-A1.002.001.2rr.esp

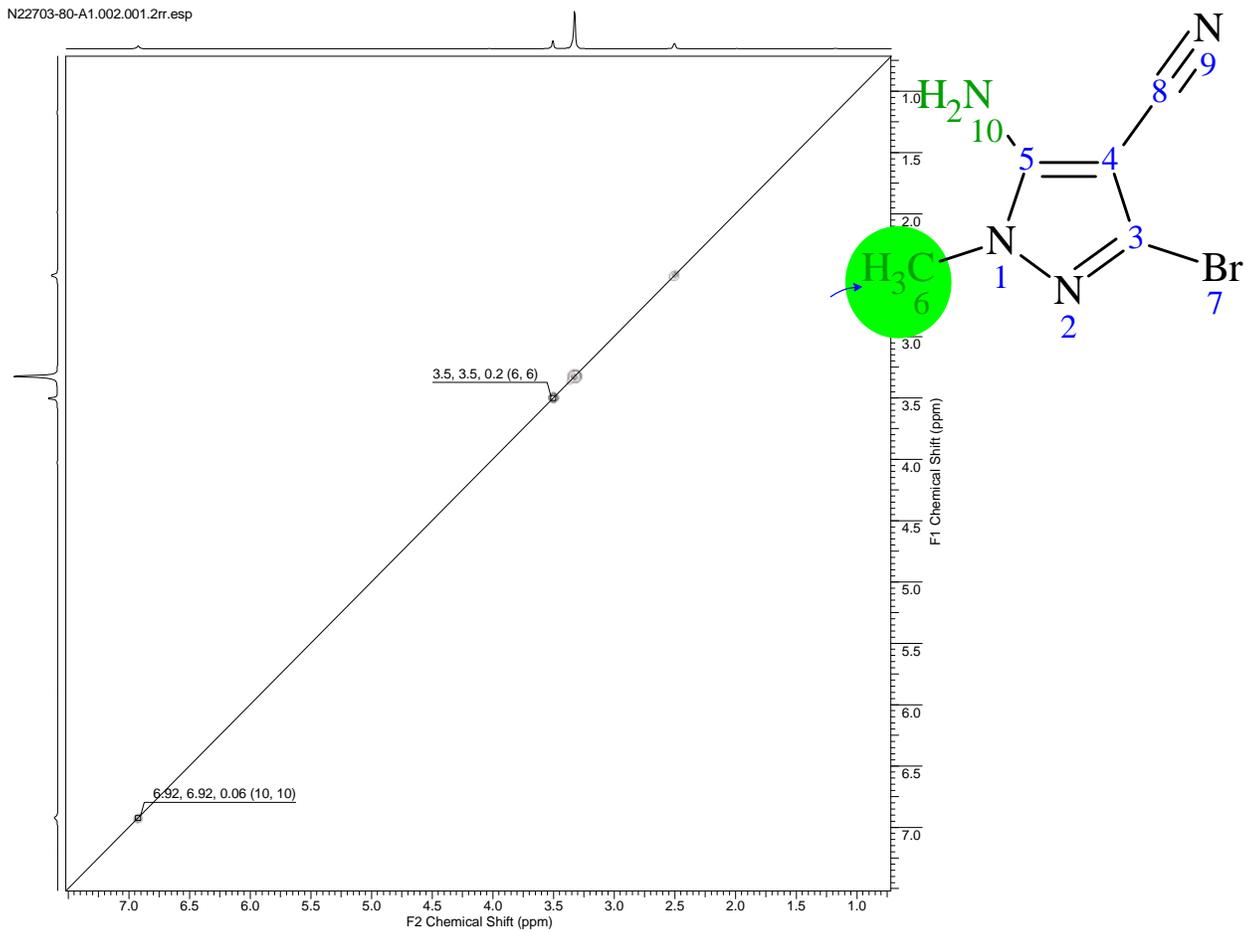




nOe:



2D NMR Experiment: H,H COSY, 2J-3J



2D Experiment: HMBC

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