

Regioselective Cross-Coupling Reactions of Boronic Acids with Dihalo Heterocycles

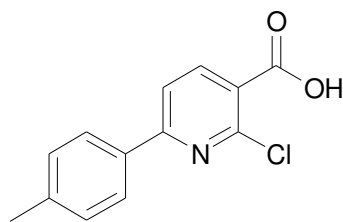
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Ulrike Nettekoven^c,

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28	¹ H NMR, ¹³ C NMR, HRMS Compound 11a :

¹H NMR, ¹³C NMR and HRMS Compound 3b:



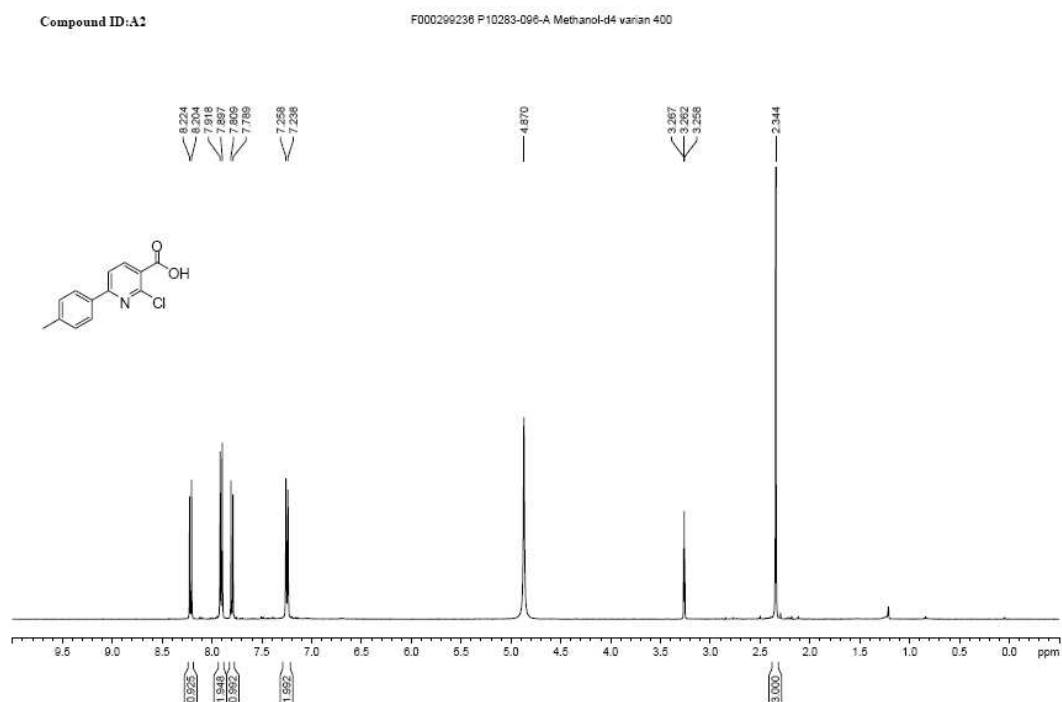
2-Chloro-6-p-tolyl-nicotinic acid

¹H NMR (DMSO, 400MHz) 2.35 (3H, s, CH₃), 7.32 (2H, d, J = 8Hz, Ar), 8.0 (2H, d, J = 8Hz, Ar), 8.03 (1H, d, J = 8Hz, Ar), 8.26 (1H, d, J = 8Hz, Ar)

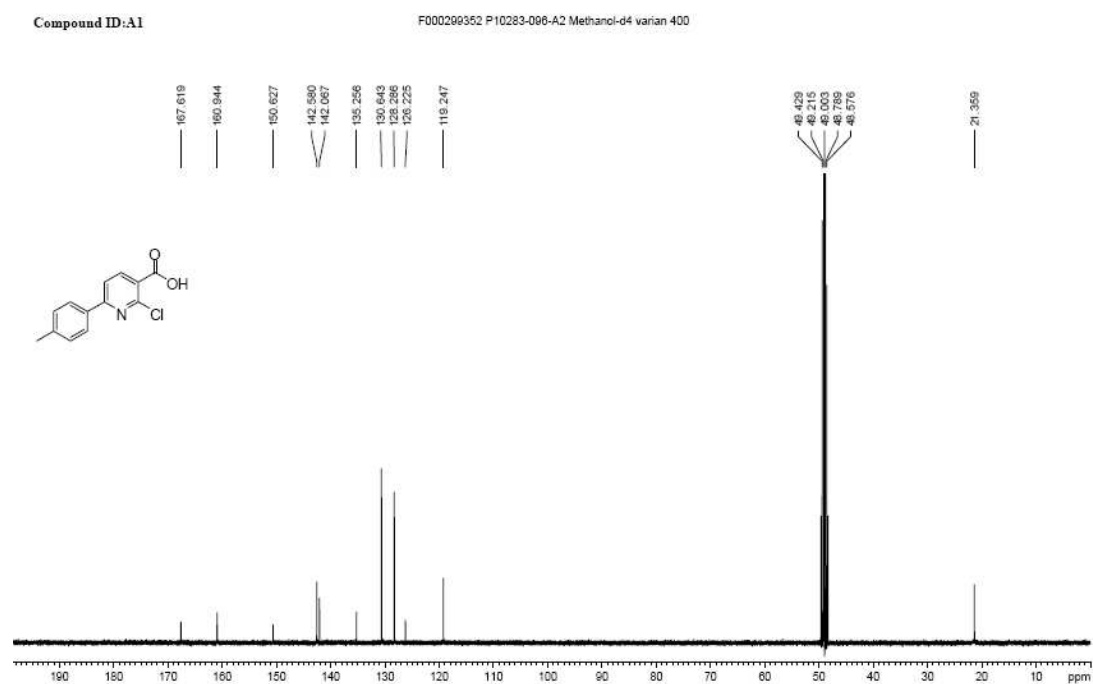
¹³C NMR (DMSO, 400MHz) 21.3, 119.0, 125.9, 130.1, 133.7, 140.9, 141.9, 148.5, 158.7, 166.0

H RMS calcd. for C₁₃H₁₁ClNO₂ [M+H]⁺ 248.0473, found 248.0471.

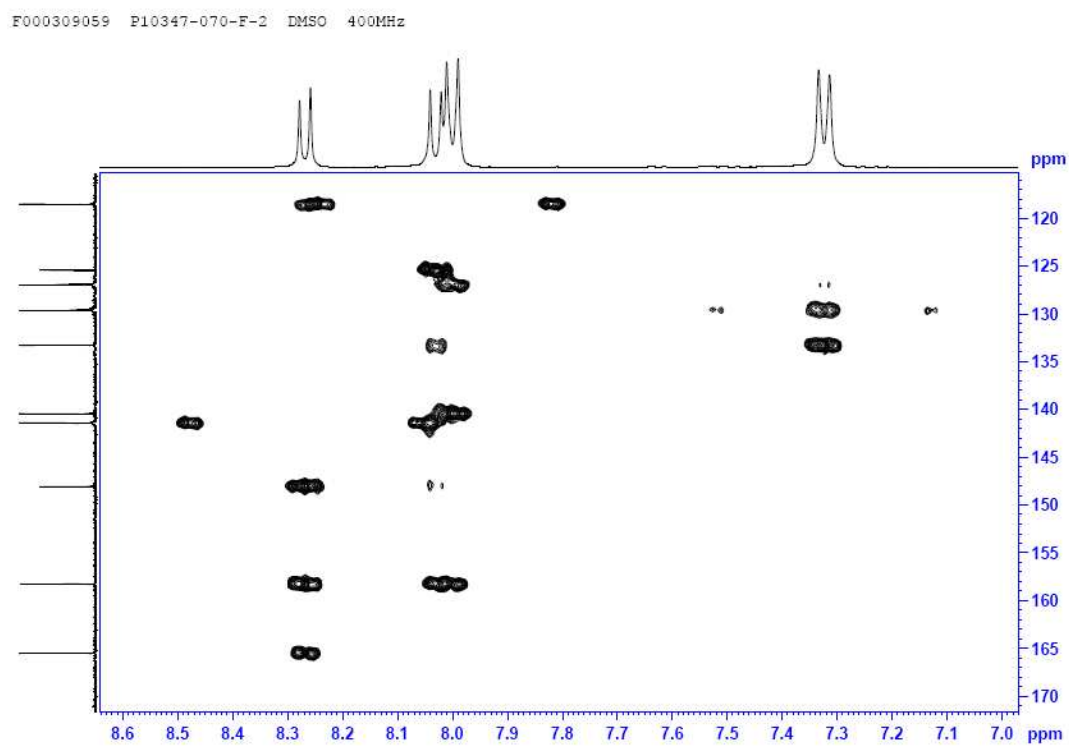
¹H NMR (DMSO, 400MHz):



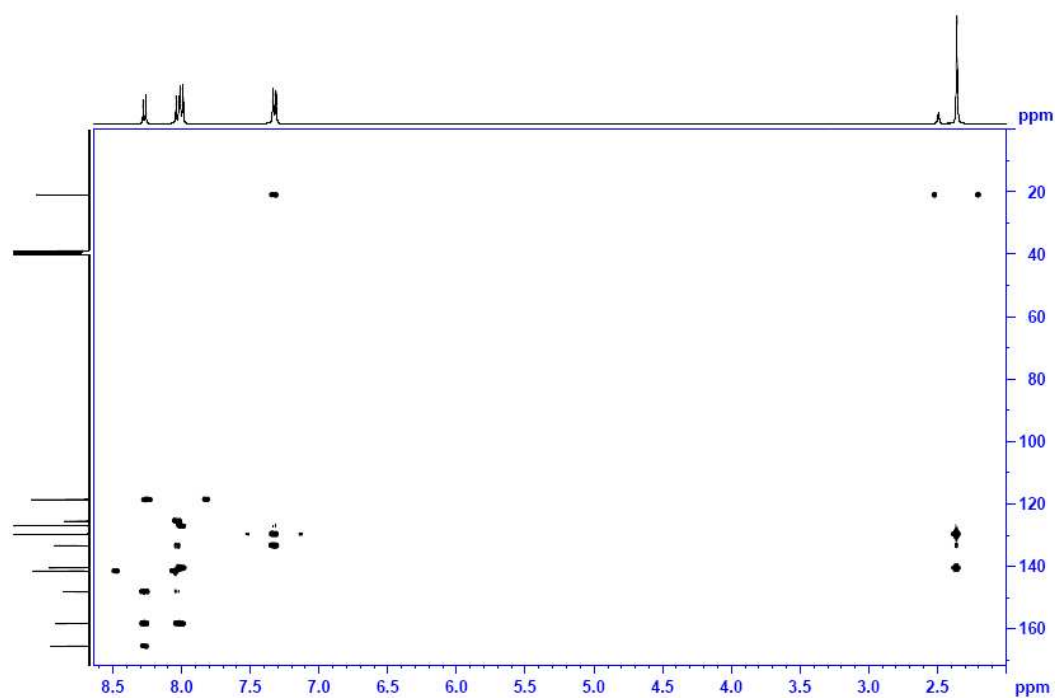
^{13}C NMR (DMSO, 400MHz):



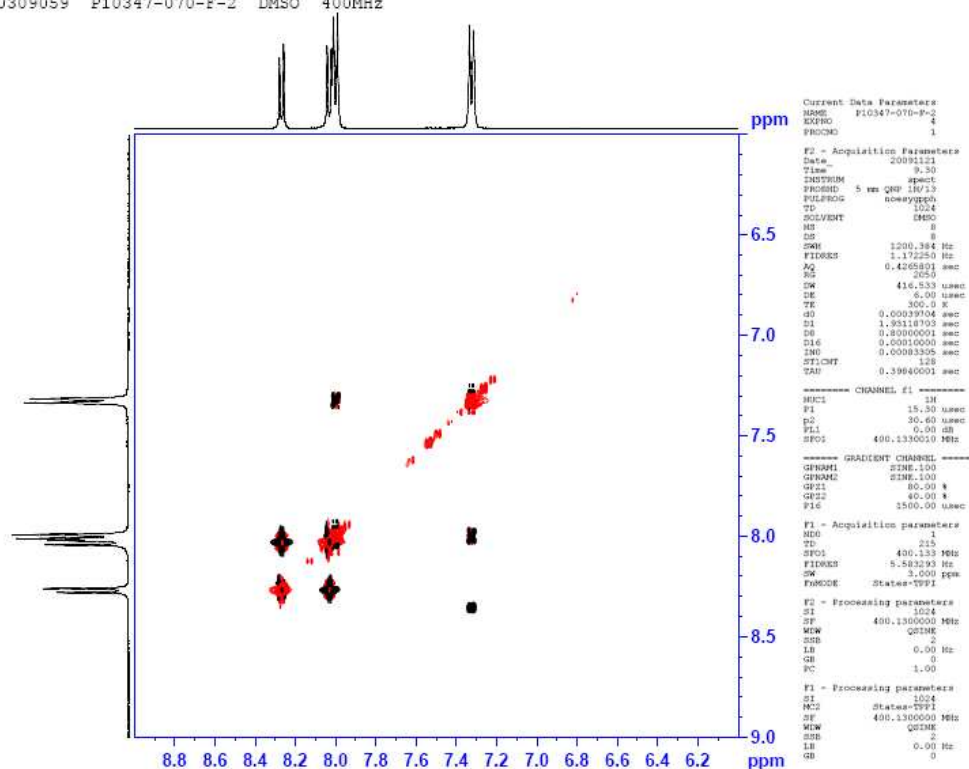
Proof of Regiochemistry



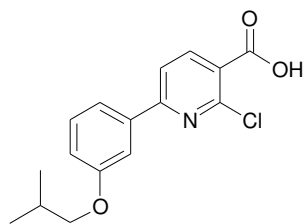
F000309059 P10347-070-F-2 DMSO 400MHz



F000309059 P10347-070-F-2 DMSO 400MHz



¹H NMR, ¹³C NMR and HRMS Compound 5b:



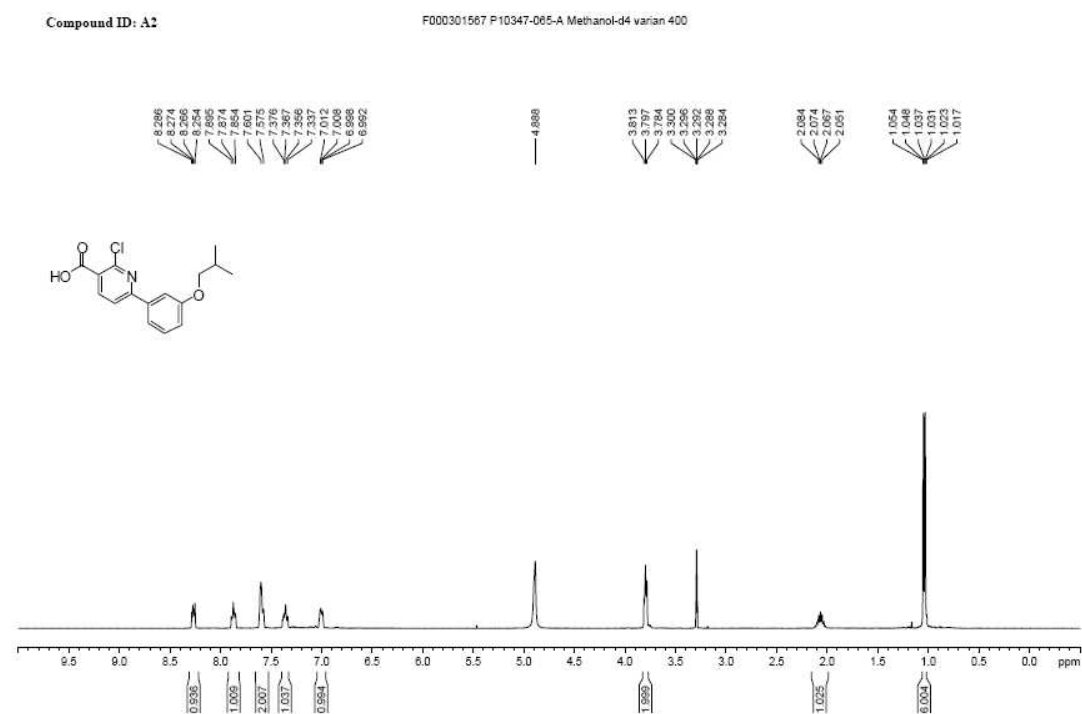
2-Chloro-6-(3-isobutoxy-phenyl)-nicotinic acid

¹H NMR (DMSO, 400MHz) 0.99 (6H, d, J = 6.8Hz, CH₃), 2.04 (1H, m, CH), 3.83 (2H, d, J = 6.8Hz, CH₂), 7.06 (1H, m, Ar), 7.42 (1H, dd, J₁ = 8Hz, J₂ = 8Hz, Ar), 7.61-7.68 (2H, m, Ar), 8.11 (1H, d, J = 8Hz, Ar), 8.28 (2H, d, J = 8Hz, Ar)

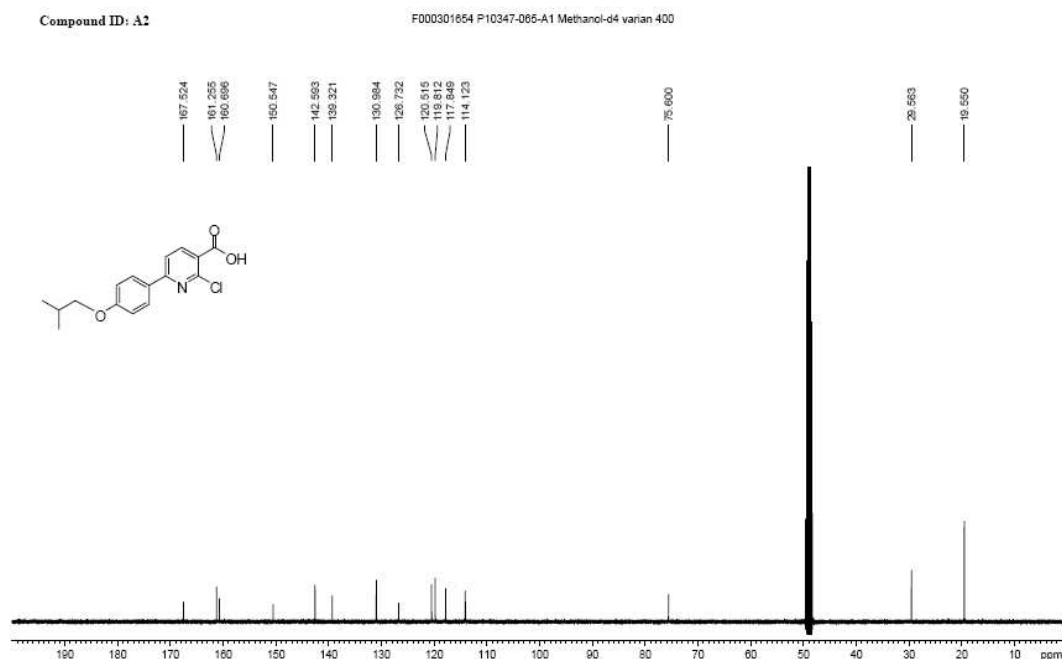
¹³C NMR (DMSO, 400MHz) 19.0, 27.8, 73.9, 112.8, 116.7, 119.2, 126.1, 130.1, 137.4, 141.4, 147.9, 158.0, 159.3, 165.5

H RMS calcd. for C₁₆H₁₇ClNO₃ [M+H]⁺ 306.0891, found 306.0889.

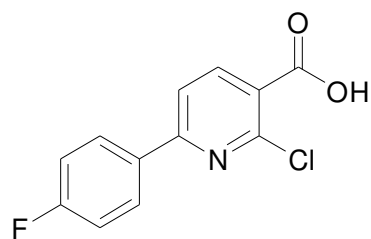
¹H NMR (DMSO, 400MHz):



^{13}C NMR (DMSO, 400MHz):



^1H NMR, ^{13}C NMR and HRMS Compound 6b:



2-Chloro-6-(4-fluorophenyl)-nicotinic acid

^1H NMR (DMSO, 400MHz) 7.34 (2H, dd, $J_1 = 8.8\text{Hz}$, $J_2 = 9.2\text{Hz}$, Ar), 8.05 (1H, d, $J = 8\text{Hz}$, Ar), 8.15 (2H, dd, $J_1 = 9.2\text{Hz}$, $J_2 = 5.2\text{Hz}$, Ar), 8.26 (1H, d, $J = 8\text{Hz}$, Ar)

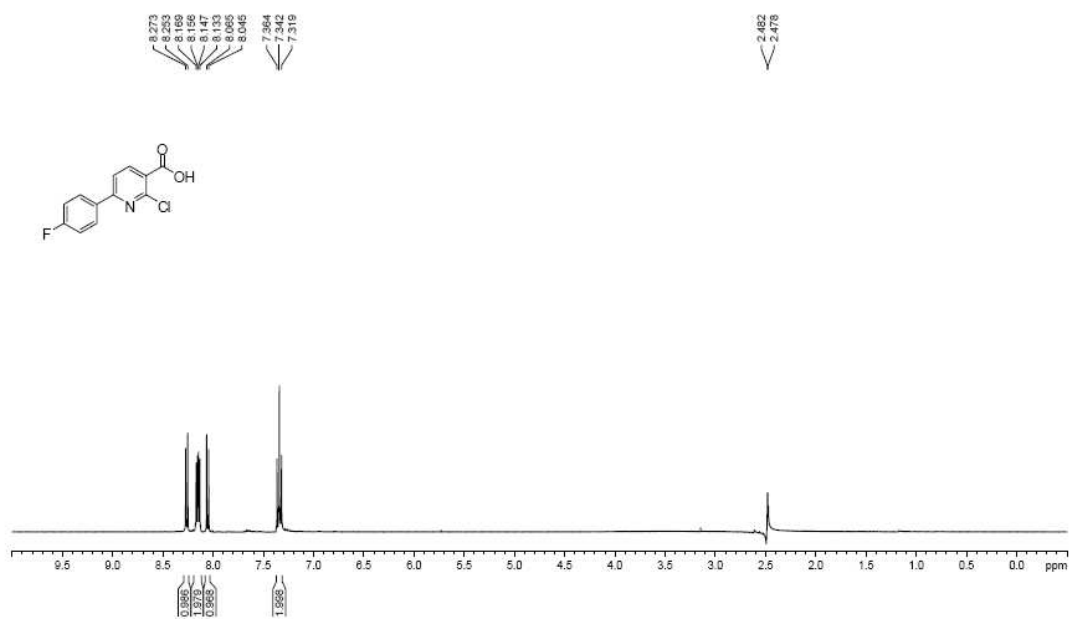
^{13}C NMR (DMSO, 400MHz) 116.0, 118.8, 126.3, 129.4, 132.6, 141.3, 147.9, 156.9, 162.3, 164.8, 165.6.

H RMS calcd. for $\text{C}_{12}\text{H}_8\text{ClFNO}_2$ $[\text{M}+\text{H}]^+$: 252.0222, found 252.0221.

^1H NMR (DMSO, 400MHz):

Compound ID: A2

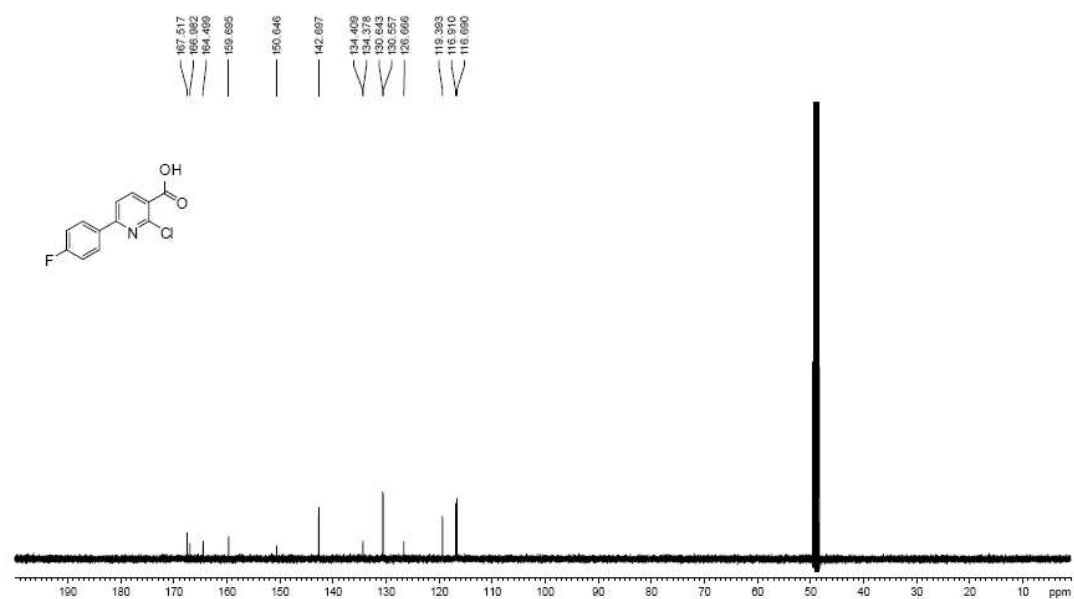
F000303579 P10347-070-C DMSO-d6 varian 400



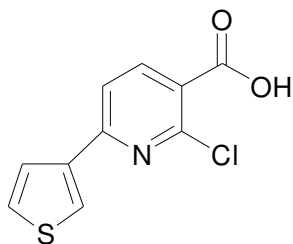
^{13}C NMR (DMSO, 400MHz):

Compound ID: A2

F000301111 P10347-066-C1 Methanol-d4 varian 400



¹H NMR, ¹³C NMR and HRMS Compound 9b:



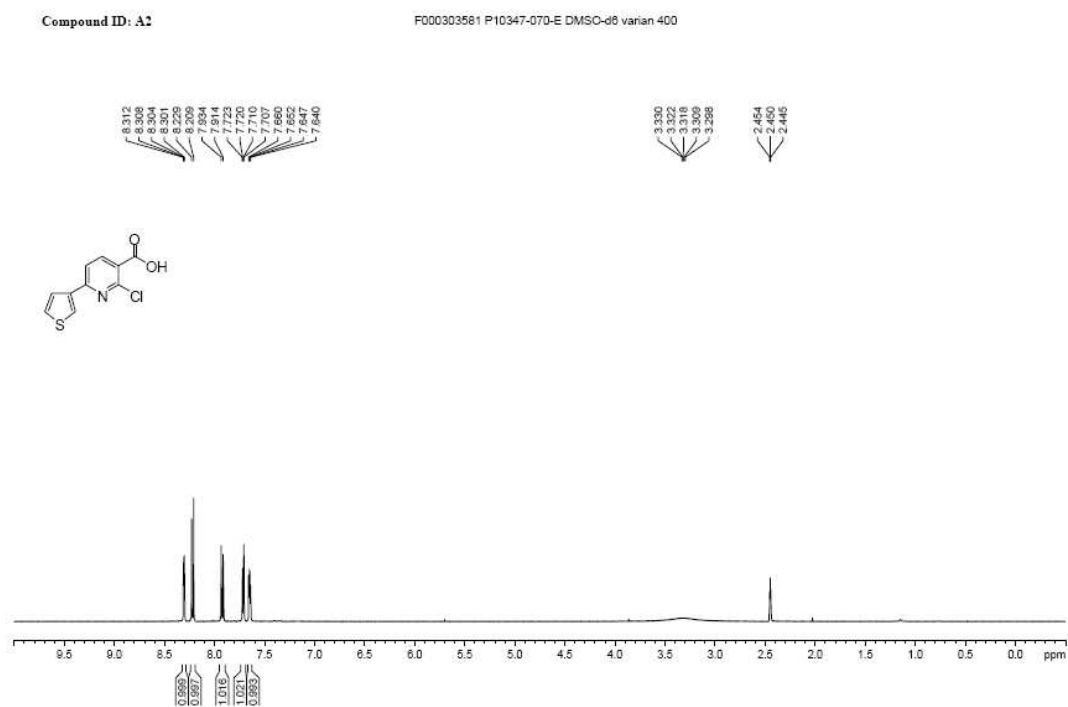
2-Chloro-6-thiophen-3-yl-nicotinic acid

¹H NMR (DMSO, 400MHz) 7.65 (1H, m, Ar), 7.71 (1H, m, Ar), 7.92 (1H, d, J = 8Hz, Ar), 8.21 (1H, d, J = 8Hz, Ar), 8.30 (1H, m, Ar)

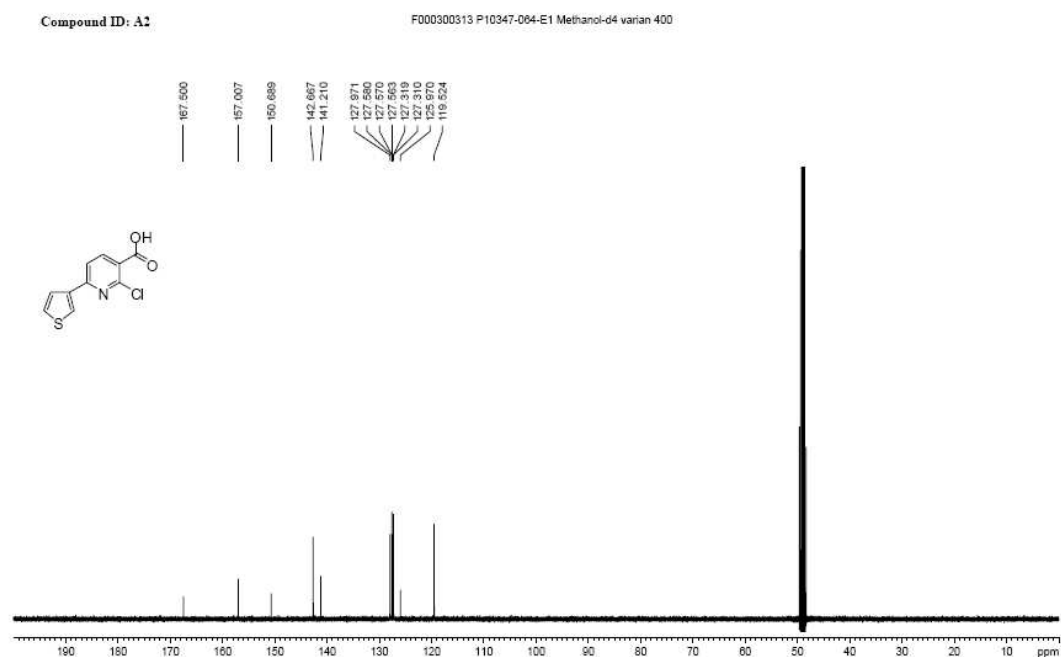
¹³C NMR (DMSO, 400MHz) 118.9, 125.1, 126.2, 127.1, 127.8, 139.4, 141.1, 148.0, 154.7, 165.4

H RMS calcd. for C₁₀H₇ClNO₂S [M+H]⁺ 239.9881, found 239.9877.

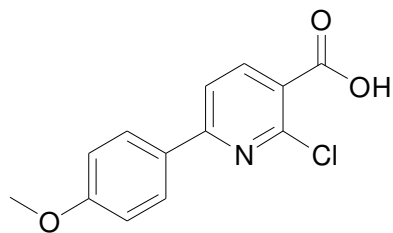
¹H NMR (DMSO, 400MHz):



^{13}C NMR (DMSO, 400MHz):



^1H NMR, ^{13}C NMR and HRMS Compound 8b:



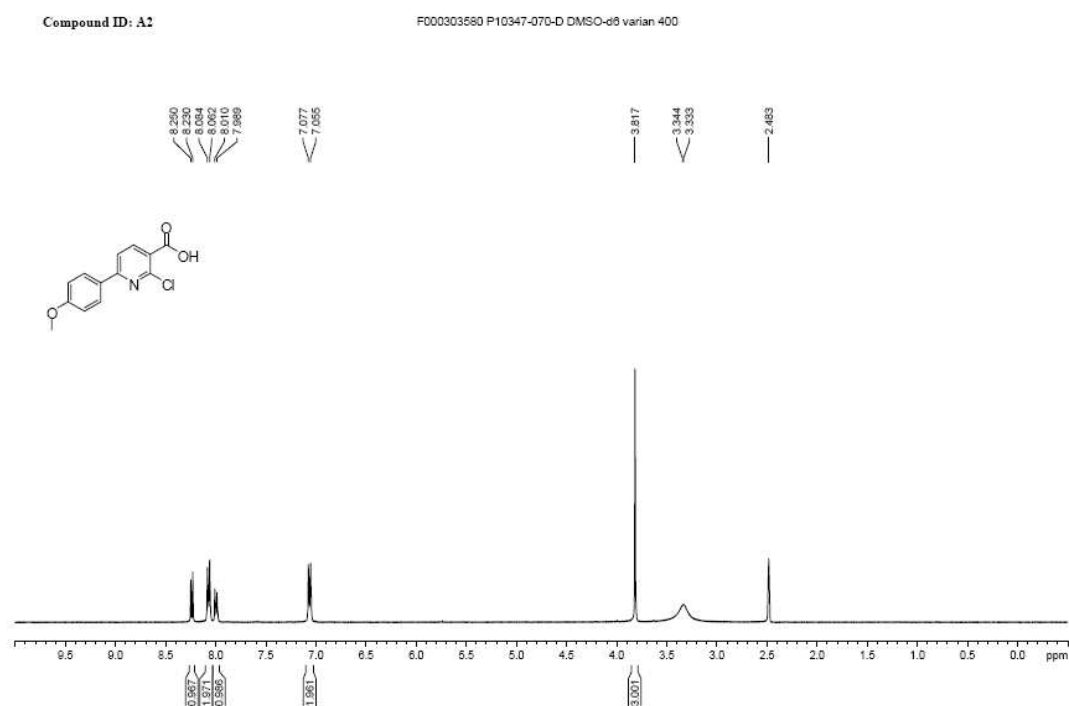
2-Chloro-6-(4-methoxy-phenyl)-nicotinic acid

^1H NMR (DMSO, 400MHz) 3.82 (3H, s, CH_3), 7.06 (2H, d, $J = 8.8\text{Hz}$, Ar), 7.99 (1H, d, $J = 8\text{Hz}$, Ar), 8.07 (2H, d, $J = 8.8\text{Hz}$, Ar), 8.24 (1H, d, $J = 8\text{Hz}$, Ar)

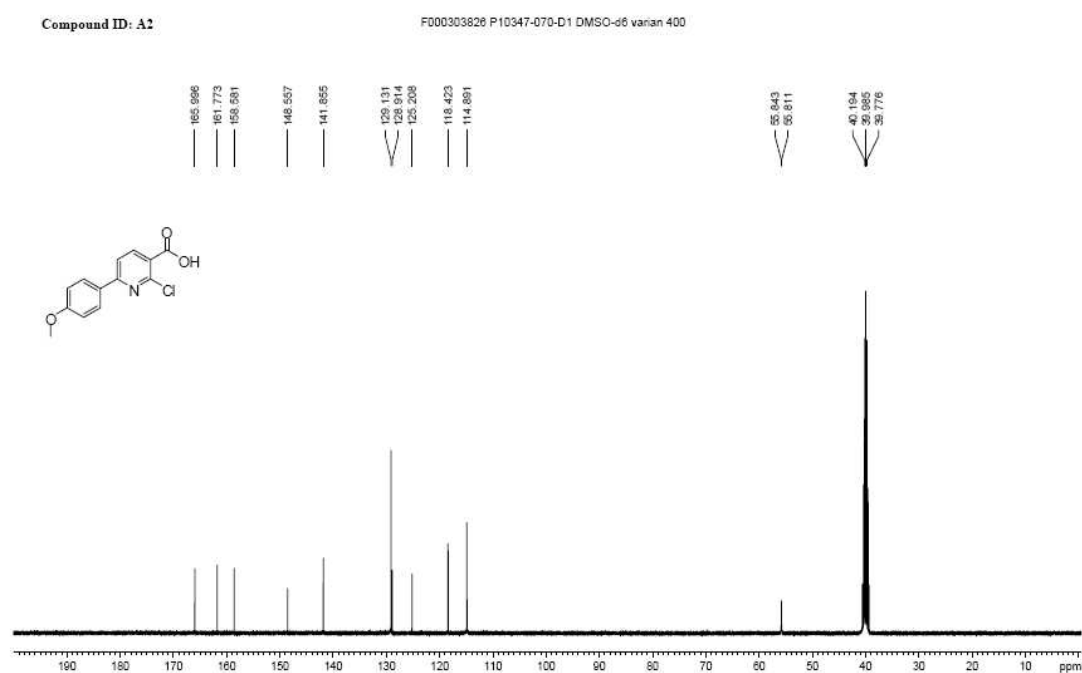
^{13}C NMR (DMSO, 400MHz) 55.8, 114.9, 118.4, 115.2, 128.9, 129.1, 141.8, 148.5, 158.6, 161.7, 165.9

H RMS calcd. for $\text{C}_{13}\text{H}_{11}\text{ClNO}_3$ $[\text{M}+\text{H}]^+$ 264.0422, found 264.0419

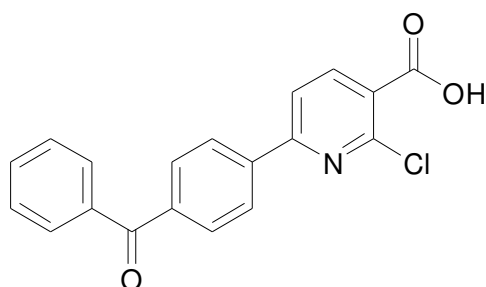
^1H NMR (DMSO, 400MHz):



^{13}C NMR (DMSO, 400MHz):



^1H NMR, ^{13}C NMR and HRMS Compound 7b:



6-(4-Benzoyl-phenyl)-2-chloro-nicotinic acid

^1H NMR (DMSO, 400MHz) 7.58 (2H, dd, $J_1 = 7.2\text{Hz}$, $J_2 = 7.2\text{Hz}$, Ar), 7.70 (1H, dd, $J_1 = 7.2\text{Hz}$, $J_2 = 7.2\text{Hz}$, Ar), 7.77 (2H, d, $J = 7.2\text{Hz}$, Ar), 7.87 (2H, d, $J = 8\text{Hz}$, Ar), 8.20 (1H, d, $J = 8\text{Hz}$, Ar), 8.28 (2H, d, $J = 8\text{Hz}$, Ar), 8.36 (1H, d, $J = 8\text{Hz}$, Ar)

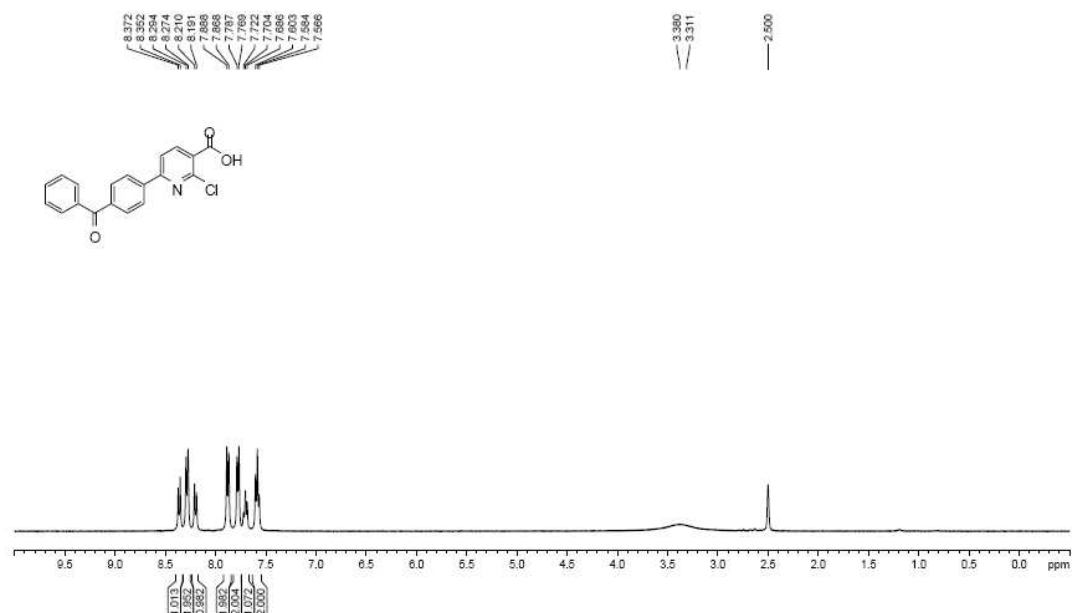
^{13}C NMR (DMSO, 400MHz) 119.8, 126.8, 127.1, 128.6, 129.6, 130.2, 132.8, 136.7, 138.2, 139.5, 141.5, 148.1, 165.4, 195.2

H RMS calcd. for $\text{C}_{19}\text{H}_{13}\text{ClNO}_3$ $[\text{M}+\text{H}]^+$ 338.0578, found 338.0572.

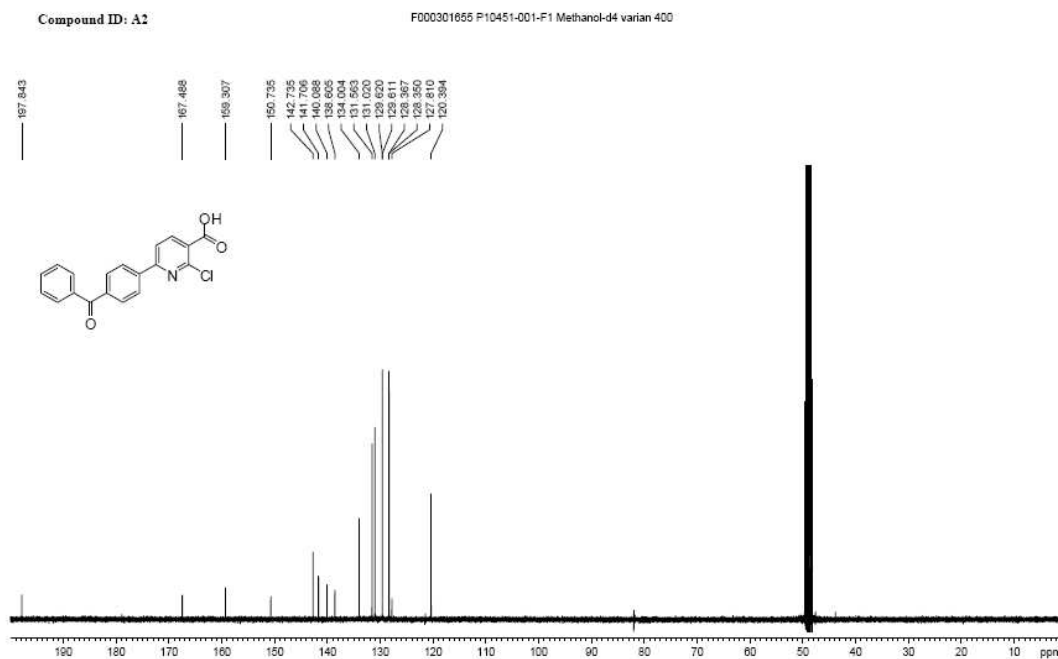
^1H NMR (DMSO, 400MHz):

Compound ID: A2

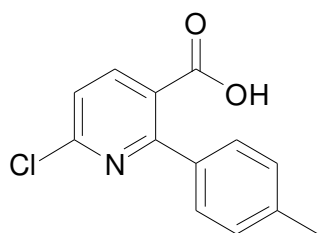
F000303578 P10347-070-B DMSO-d6 varian 400



^{13}C NMR (DMSO, 400MHz):



^1H NMR, ^{13}C NMR and HRMS Compound 3a:



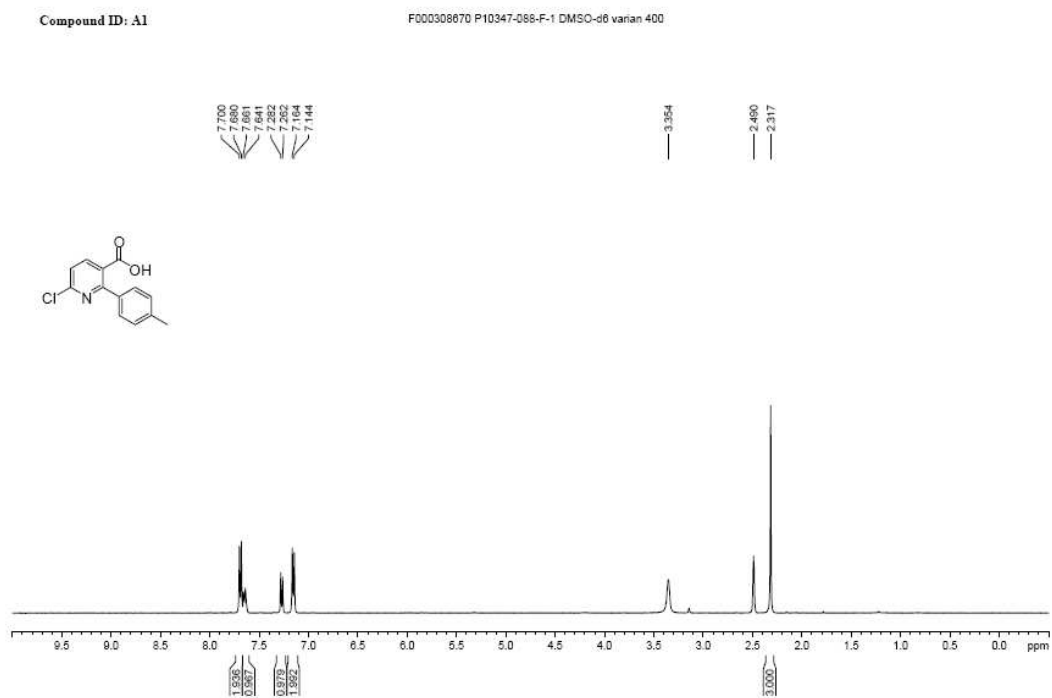
6-Chloro-2-p-tolyl-nicotinic acid

^1H NMR (DMSO, 400MHz) 2.32 (3H, s, CH_3), 7.15 (2H, d, $J = 8\text{Hz}$, Ar), 7.27 (1H, d, $J = 8\text{Hz}$, Ar), 7.65 (1H, d, $J = 8\text{Hz}$, Ar), 7.69 (2H, d, $J = 8\text{Hz}$, Ar)

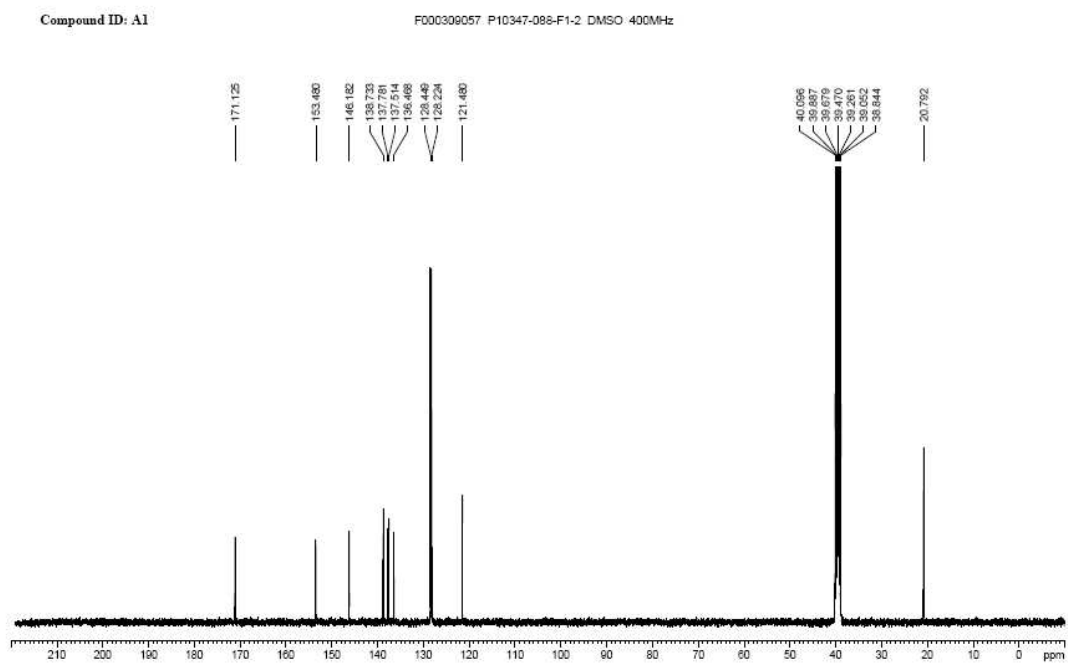
^{13}C NMR (DMSO, 400MHz) 20.8, 121.9, 128.4, 136.5, 137.5, 137.8, 138.7, 146.1, 153.5, 171.1

H RMS calcd. for $\text{C}_{13}\text{H}_{11}\text{ClNO}_2$ $[\text{M}+\text{H}]^+$ 248.0473, found 248.0467.

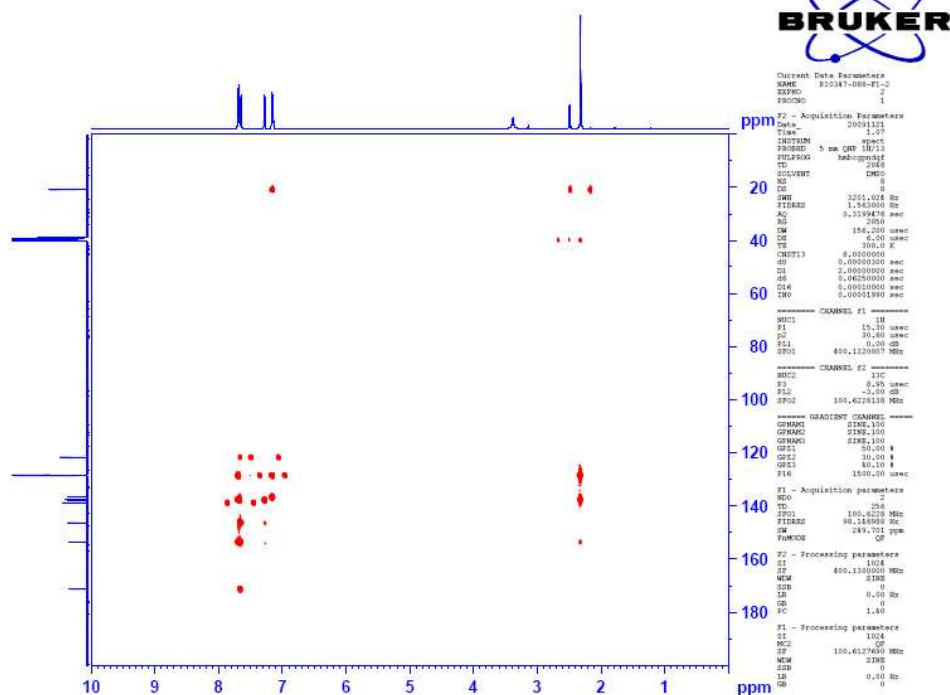
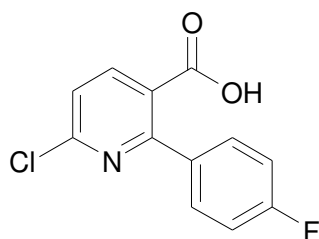
^1H NMR (DMSO, 400MHz):



^{13}C NMR (DMSO, 400MHz):



F000309057 P10347-088-F1-2 DMSO 400MHz

**¹H NMR, ¹³C NMR and HRMS Compound 6a:****6-Chloro-2-(4-fluorophenyl)-nicotinic acid**

¹H NMR (DMSO, 400MHz) 7.16 (2H, dd, J1 = 8.8Hz, J2 = 9.2Hz, Ar), 7.30 (1H, d, J = 8Hz, Ar), 7.68 (1H, d, J = 8Hz, Ar), 7.79 (2H, m, Ar)

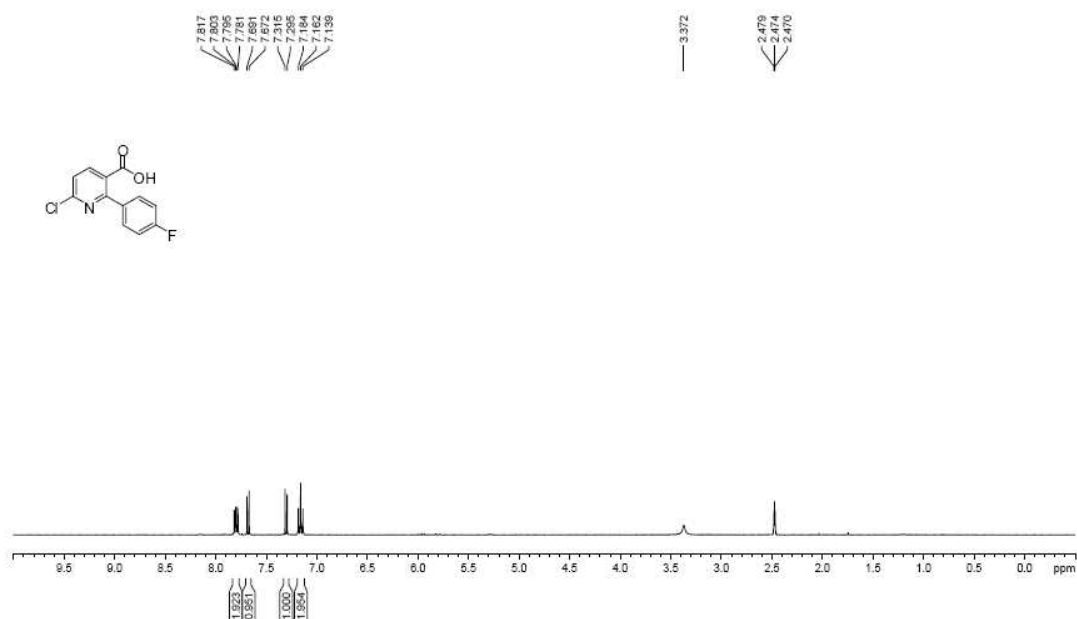
¹³C NMR (DMSO, 400MHz) 115.1, 122.6, 131.4, 136.5, 138.6, 139.7, 147.0, 153.2, 161.9, 163.9, 171.3.

H RMS calcd. for C₁₂H₈ClFNO₂ [M+H]⁺ 252.0222, found 252.0218.

^1H NMR (DMSO, 400MHz):

Compound ID: A1

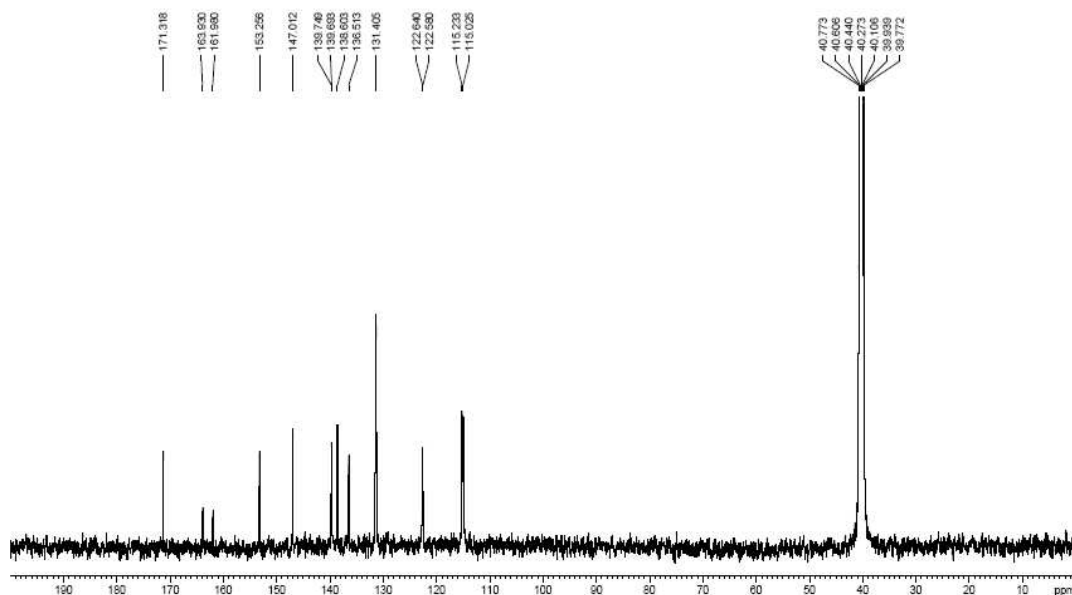
F000308666 P10347-088-C-1 DMSO-d6 varian 400



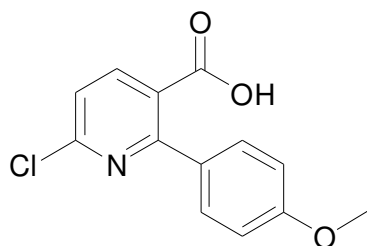
^{13}C NMR (DMSO, 400MHz):

Compound ID:A1

P10347-088-C-2 DMSO VARIAN 500



^1H NMR, ^{13}C NMR and HRMS Compound 8a:



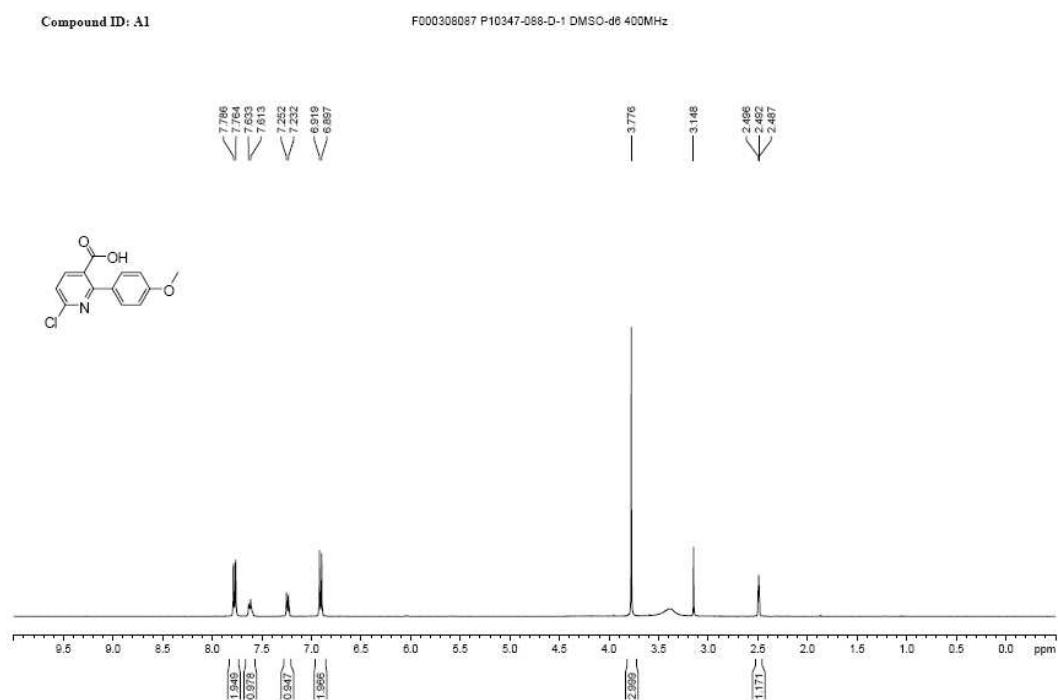
6-Chloro-2-(4-methoxyphenyl)-nicotinic acid

^1H NMR (DMSO, 400MHz) 3.77 (3H, s, CH_3), 6.90 (2H, d, $J = 8.8\text{Hz}$, Ar), 7.24 (1H, d, $J = 8\text{Hz}$, Ar), 7.62 (1H, d, $J = 8\text{Hz}$, Ar), 7.77 (2H, d, $J = 8.8\text{Hz}$, Ar)

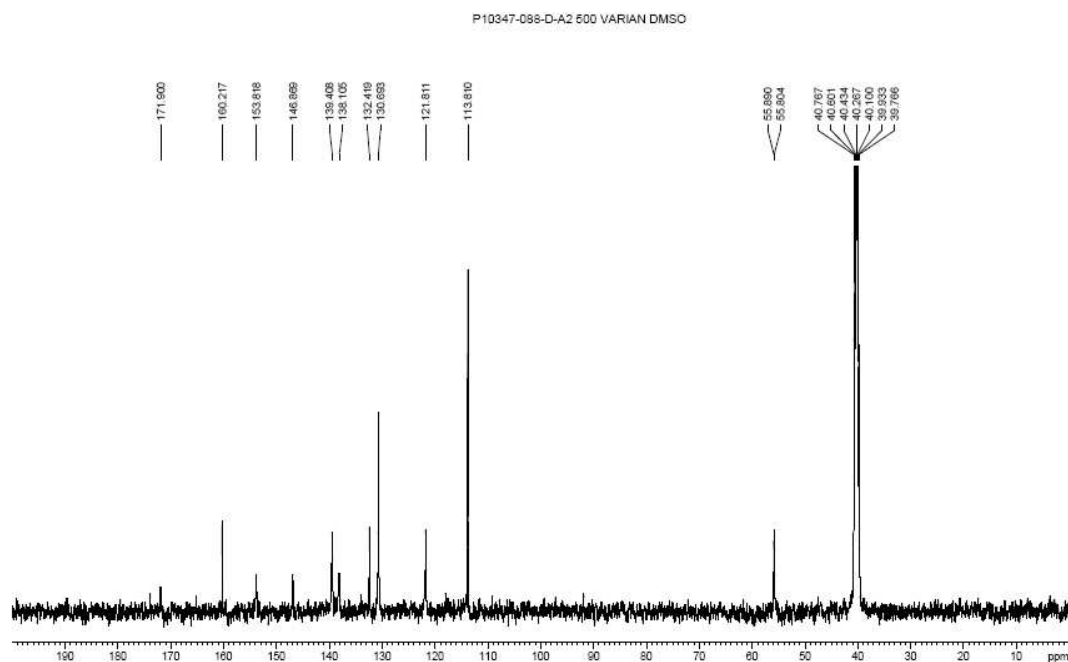
^{13}C NMR (DMSO, 400MHz) 55.8, 113.8, 121.8, 130.7, 132.4, 138.1, 139.4, 146.8, 153.8, 160.2, 171.9

H RMS calcd. for $\text{C}_{13}\text{H}_{11}\text{ClNO}_3$ $[\text{M}+\text{H}]^+$ 264.0422, found 264.0417.

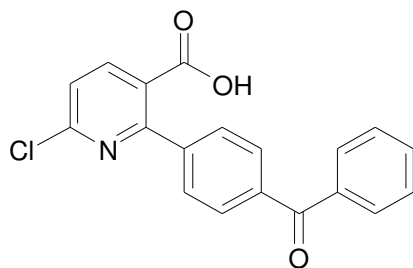
^1H NMR (DMSO, 400MHz):



^{13}C NMR (DMSO, 400MHz):



^1H NMR, ^{13}C NMR and HRMS Compound 7a:



2-(4-Benzoyl-phenyl)-6-chloro-nicotinic acid

^1H NMR (DMSO, 400MHz) 7.58-7.60 (2H, dd, Ar), 7.65-7.82 (8H, m, Ar), 8.24 (2H, dd, Ar)

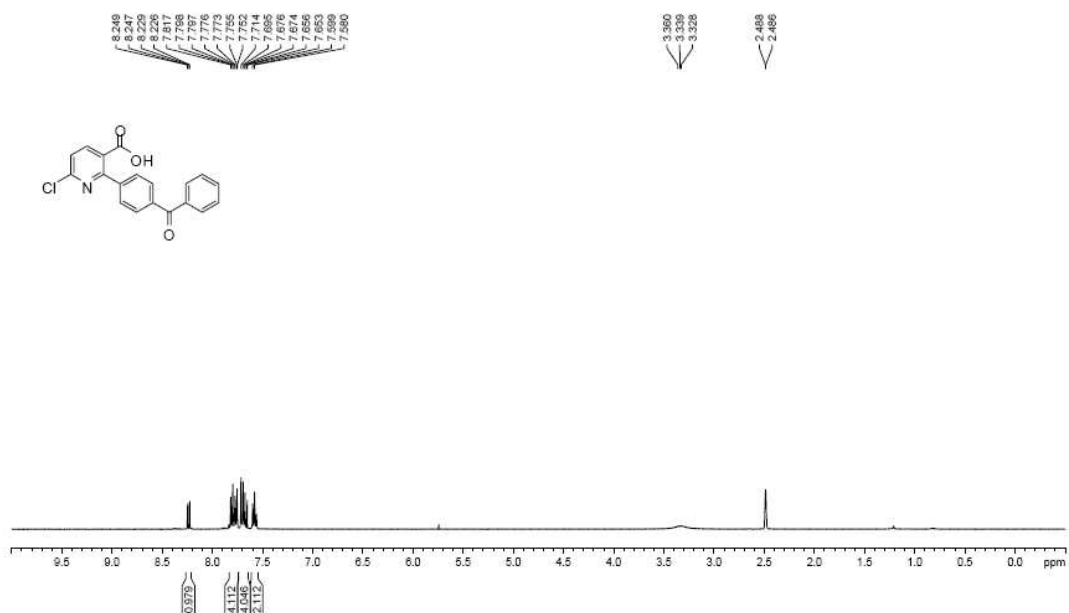
^{13}C NMR (DMSO, 400MHz) 123.8, 129.1, 129.3, 129.8, 130.1, 133.3, 137.3, 137.6, 141.8, 142.7, 151.6, 157.6, 168.1, 195.9

H RMS calcd. for $\text{C}_{19}\text{H}_{13}\text{ClNO}_3$ $[\text{M}+\text{H}]^+$ 338.0578, found 338.0564.

^1H NMR (DMSO, 400MHz):

Compound ID: A1

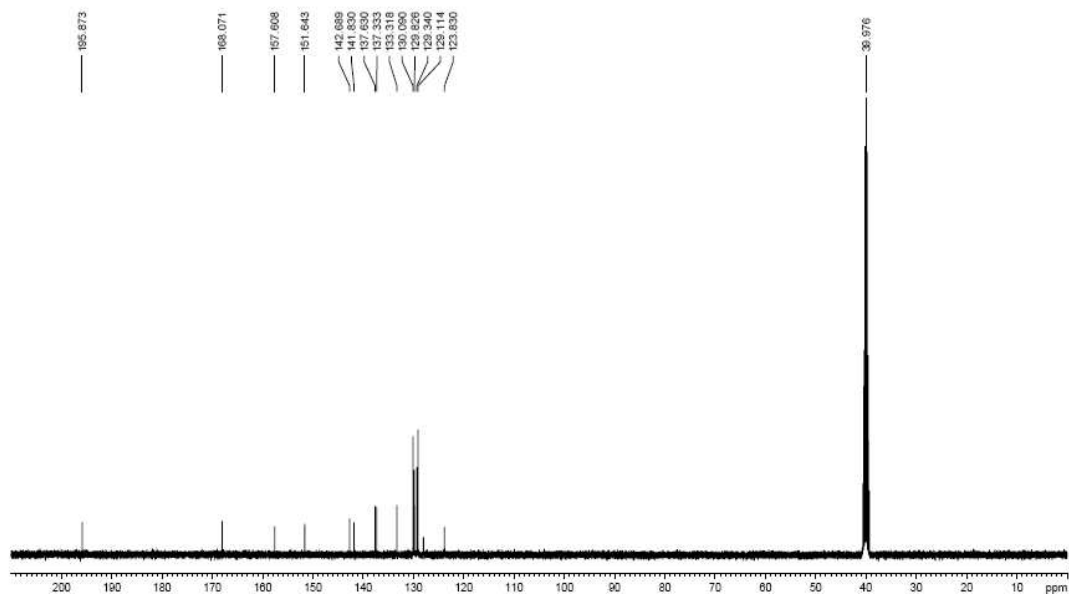
F000307161 P10347-088-B DMSO-d6 varian 400



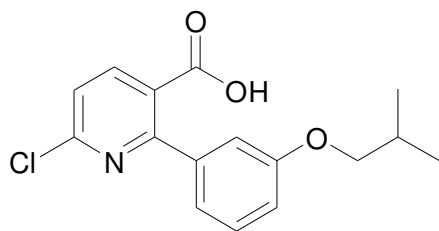
^{13}C NMR (DMSO, 400MHz):

Compound ID: A1

F000307495 P10347-088-B1 DMSO-d6 varian 400



^1H NMR, ^{13}C NMR and HRMS Compound 5a:



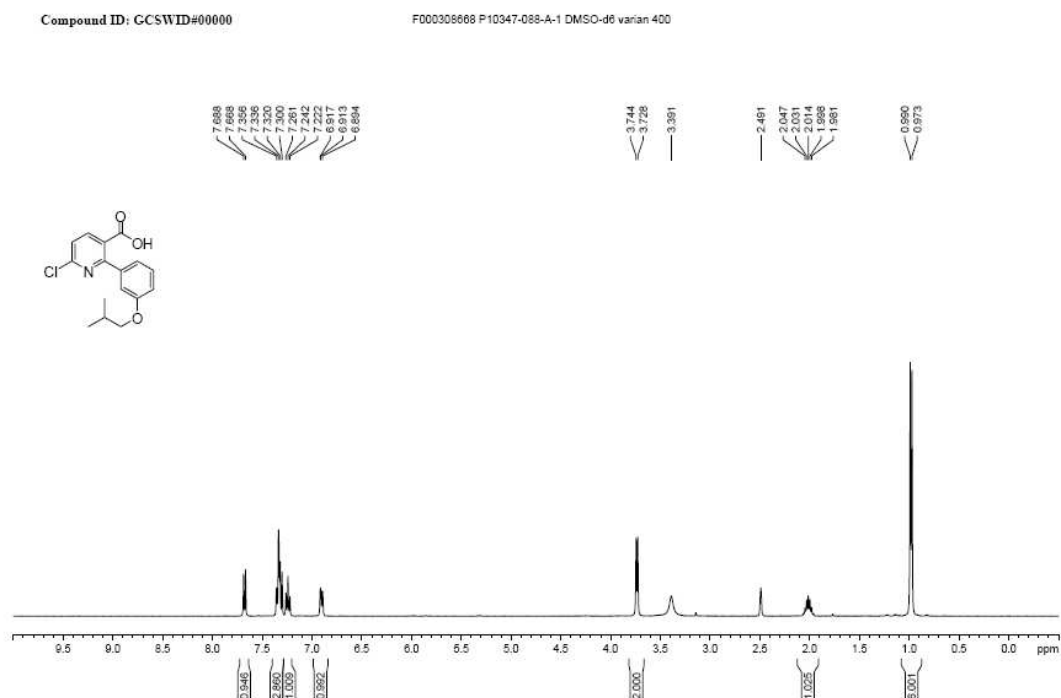
6-Chloro-2-(4-isobutoxy-phenyl)-nicotinic acid

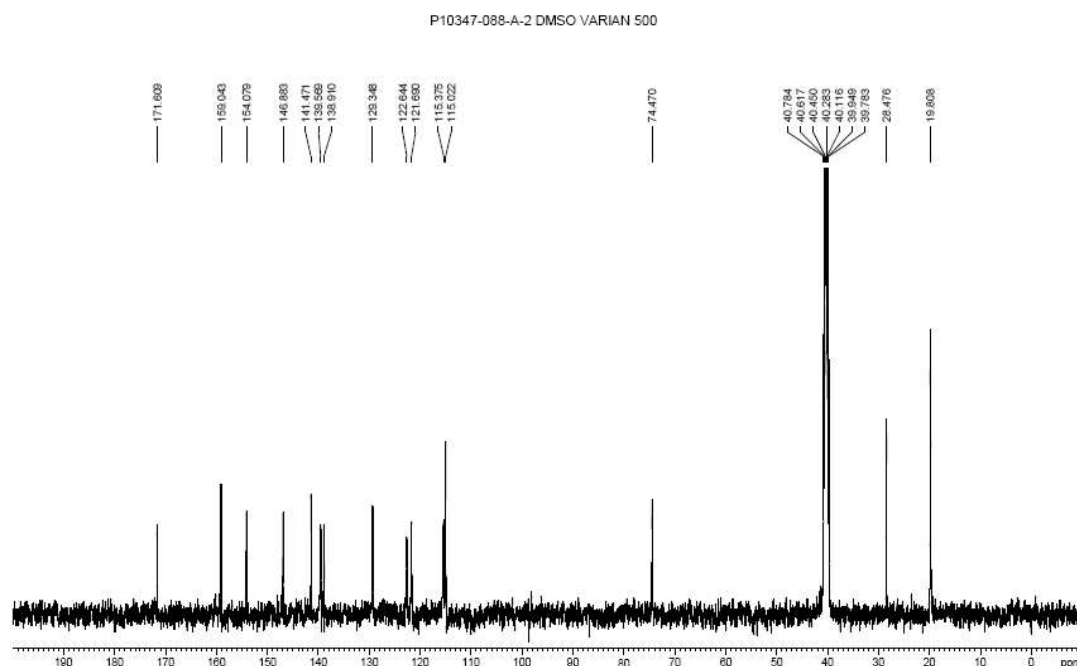
^1H NMR (DMSO, 400MHz) 0.98 (6H, d, $J = 6.8\text{Hz}$, CH_3), 2.01 (1H, m, CH), 3.73 (2H, d, $J = 6.4\text{Hz}$, CH_2), 6.91 (1H, d, $J = 8\text{Hz}$, Ar), 7.24 (1H, dd, $J_1 = 8\text{Hz}$, $J_2 = 8\text{Hz}$, Ar), 7.34 (3H, m, Ar), 7.67 (1H, d, $J = 8\text{Hz}$, Ar).

^{13}C NMR (DMSO, 400MHz) 19.8, 28.5, 74.5, 115.0, 115.3, 121.7, 122.6, 129.3, 138.9, 139.5, 141.5, 146.8, 154.1, 159.0, 171.6

H RMS calcd. for $\text{C}_{16}\text{H}_{17}\text{ClNO}_3$ $[\text{M}+\text{H}]^+$ 306.0891, found 306.0885.

^1H NMR (DMSO, 400MHz):

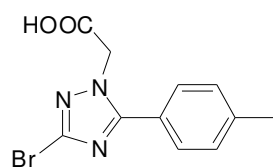


¹³C NMR (DMSO, 400MHz):

Representative experimental procedures for the preparation of compounds **10a-15a**:

PPh₃ (0.11g, 0.42 mmol) was dissolved in NMP (20 mL) and stirred under nitrogen. Pd(acac)₂ (0.064 g, 0.21 mmol) was added and the mixture was stirred at 30°C for 1 h. Addition of 3,5-dibromo-1H-1,2,4 triazole-4-acetic acid (2.0 g, 7.0 mmol), toluene boronic acid (1.90 g, 14.0 mmol), Na₂CO₃ (2.23 g, 21.0 mmol) and water (20 mL), under nitrogen, afforded the reaction mixture was stirred at 30°C for 3~7 days until HPLC indicated complete consumption of the triazole acid (conversion > 80%). Another water portion (20 mL) was added to the reaction mixture. The solution was extracted with Me-THF (2 x 20mL). The aqueous layer was acidified with 2N HCl (20 mL), stirred at room temperature overnight and then it was filtered and dried. The solid was slurried with MeOH (5mL) to afford generally a white solid product.

¹H NMR, ¹³C NMR and HRMS of Compound 10a:



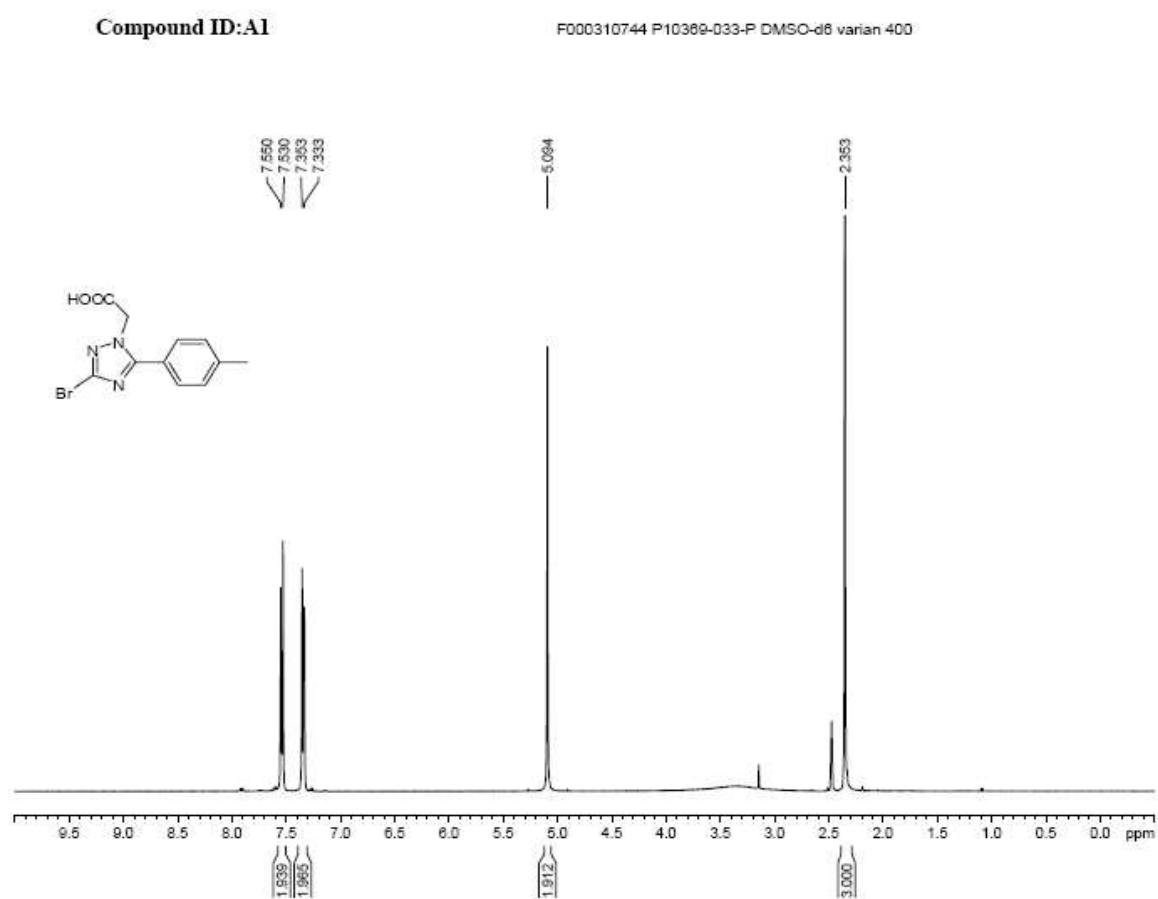
(3-Bromo-5-p-tolyl-[1,2,4]triazol-1-yl)-acetic acid

¹H NMR (DMSO, 400MHz) 2.35 (3H, s, CH₃), 5.09 (2H, s, CH₂), 7.33 (2H, d, J = 8Hz, Ar), 7.53 (2H, d, J = 8Hz, Ar)

¹³C NMR (DMSO, 400MHz) 21.4, 51.5, 123.9(2C), 128.6(2C), 130.1, 138.8, 141.2, 157.4, 168.8

H RMS calcd. for C₁₁H₁₀BrN₃O₂ [M-H]⁻ 293.9956, found 293.9836.

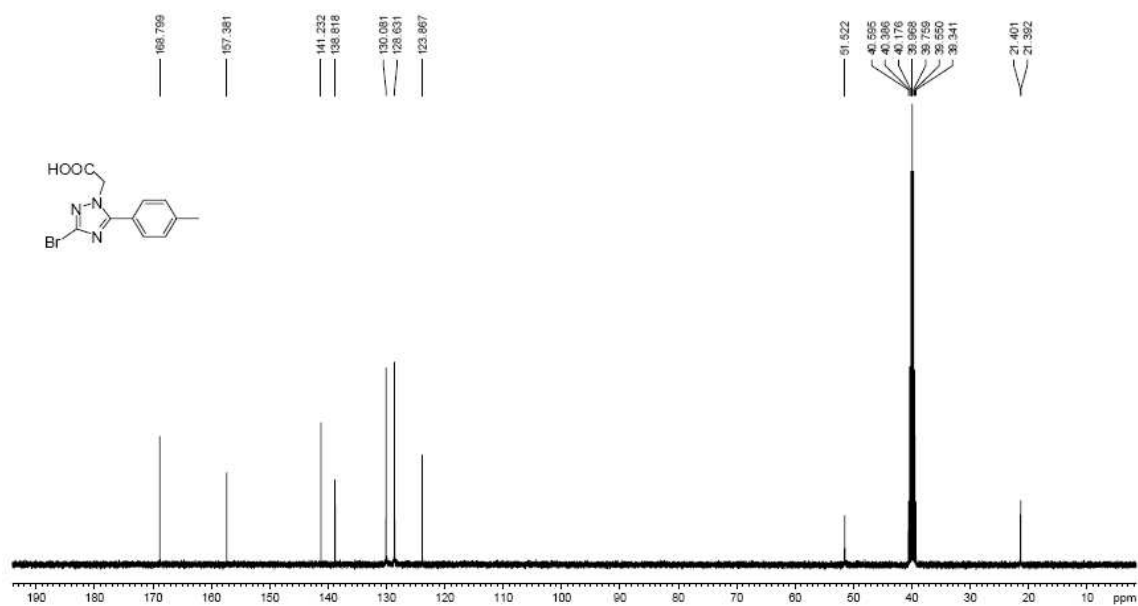
^1H NMR (DMSO, 400MHz):



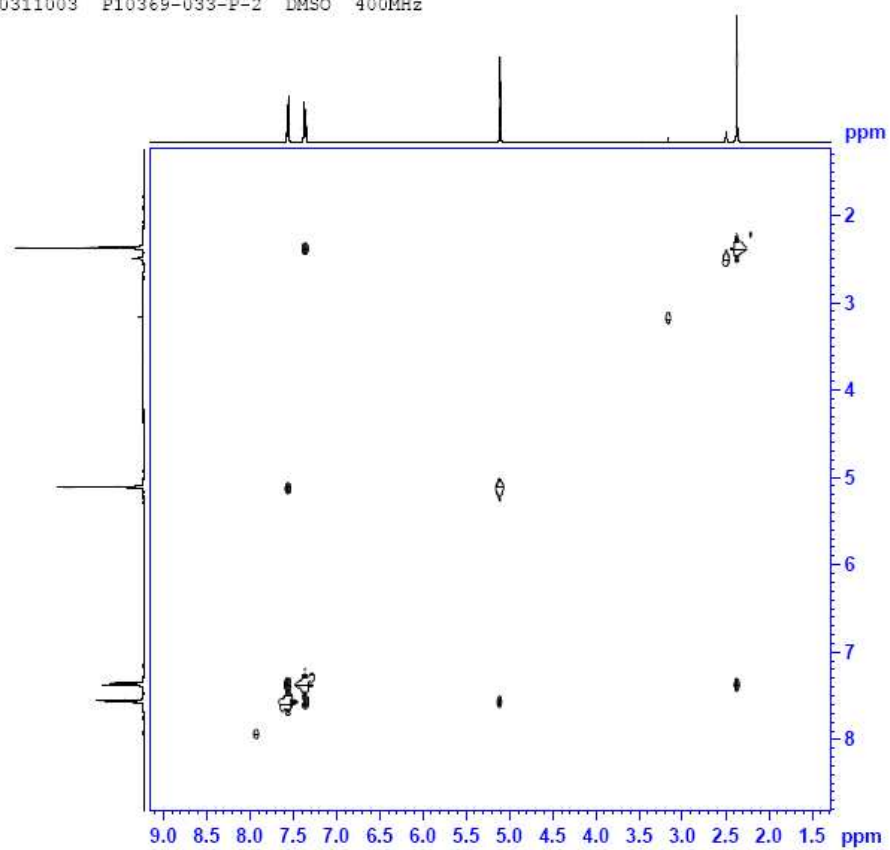
^{13}C NMR (DMSO, 400MHz):

Compound ID: TMC660282-JNJ42751748-AAA

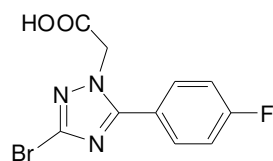
F000311002 P10369-033-P-1 DMSO-d6 varian 400



F000311003 P10369-033-P-2 DMSO 400MHz



^1H NMR, ^{13}C NMR and HRMS of Compound 12a:



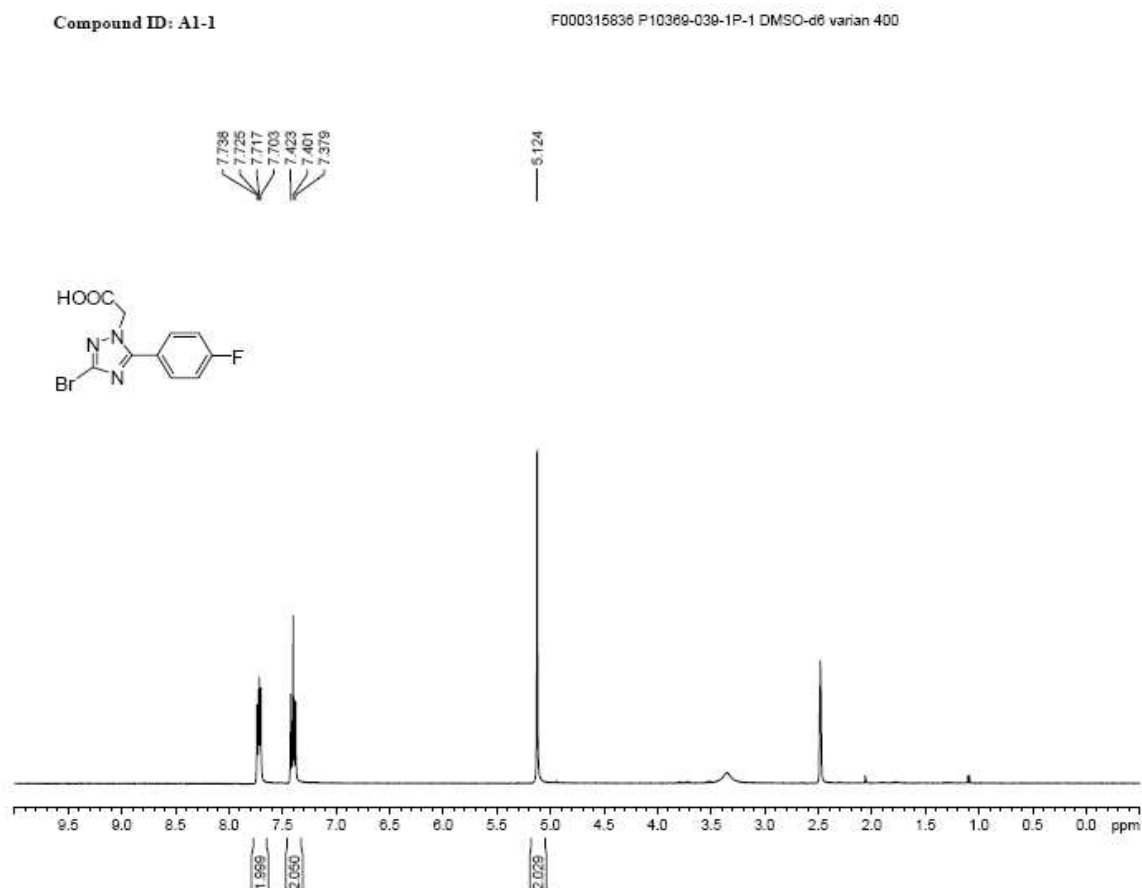
[3-Bromo-5-(4-fluoro-phenyl)-[1,2,4]triazol-1-yl]-acetic acid

^1H NMR (DMSO, 400MHz) 5.12 (2H, s, CH_2), 7.40(2H, t, $J_1 = 8.8\text{Hz}$, $J_2 = 8.8\text{Hz}$ Ar), 7.72 (2H, dd, $J_1 = 8.4\text{Hz}$, J_2 (H-F) = 5.2Hz, Ar)

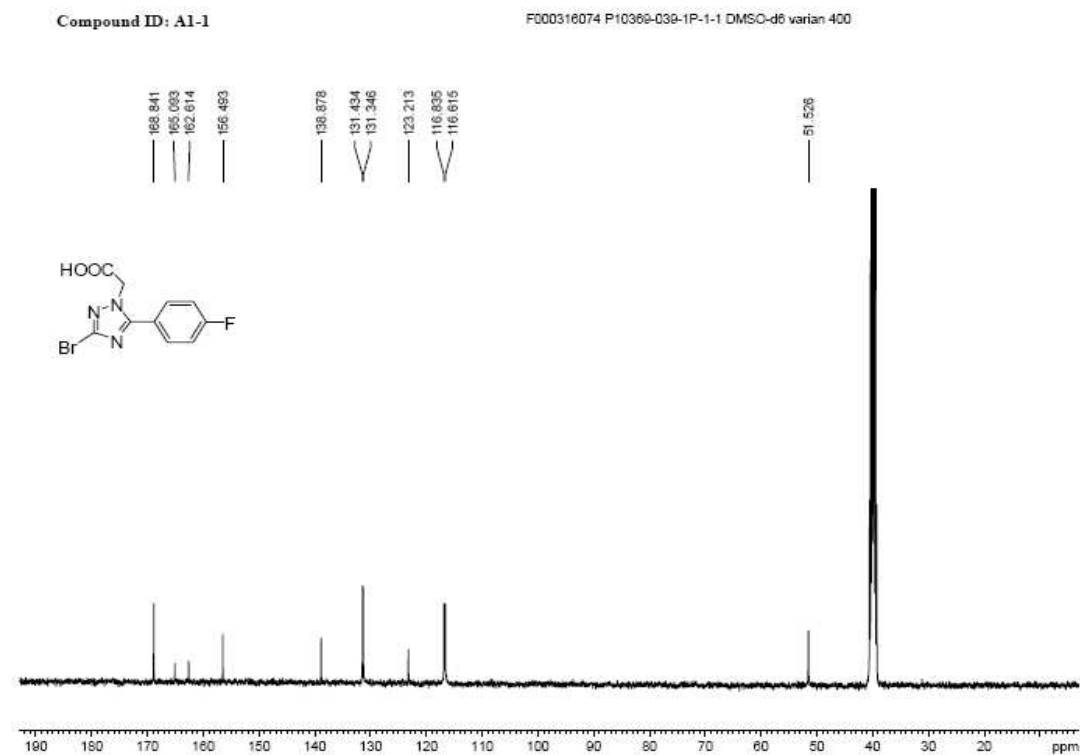
^{13}C NMR (DMSO, 400MHz) 51.5, 116.7(2C), 123.2, 131.3(2C), 138.9, 156.5, 162.6, 165.1, 168.8

H RMS calcd. for $\text{C}_{10}\text{H}_7\text{BrFN}_3\text{O}_2$ $[\text{M}-\text{H}]^-$ 297.9706, found 297.9583.

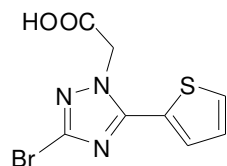
^1H NMR (DMSO, 400MHz):



^{13}C NMR (DMSO, 400MHz):



¹H NMR, ¹³C NMR and HRMS of Compound 15a:



(3-Bromo-5-thiophen-2-yl-[1,2,4]triazol-1-yl)-acetic acid

¹H NMR (DMSO, 400MHz) 5.21 (2H,s,CH₂), 7.44(1H, m, Ar), 7.76 (1H, m, Ar), 8.08(1H, m, Ar),

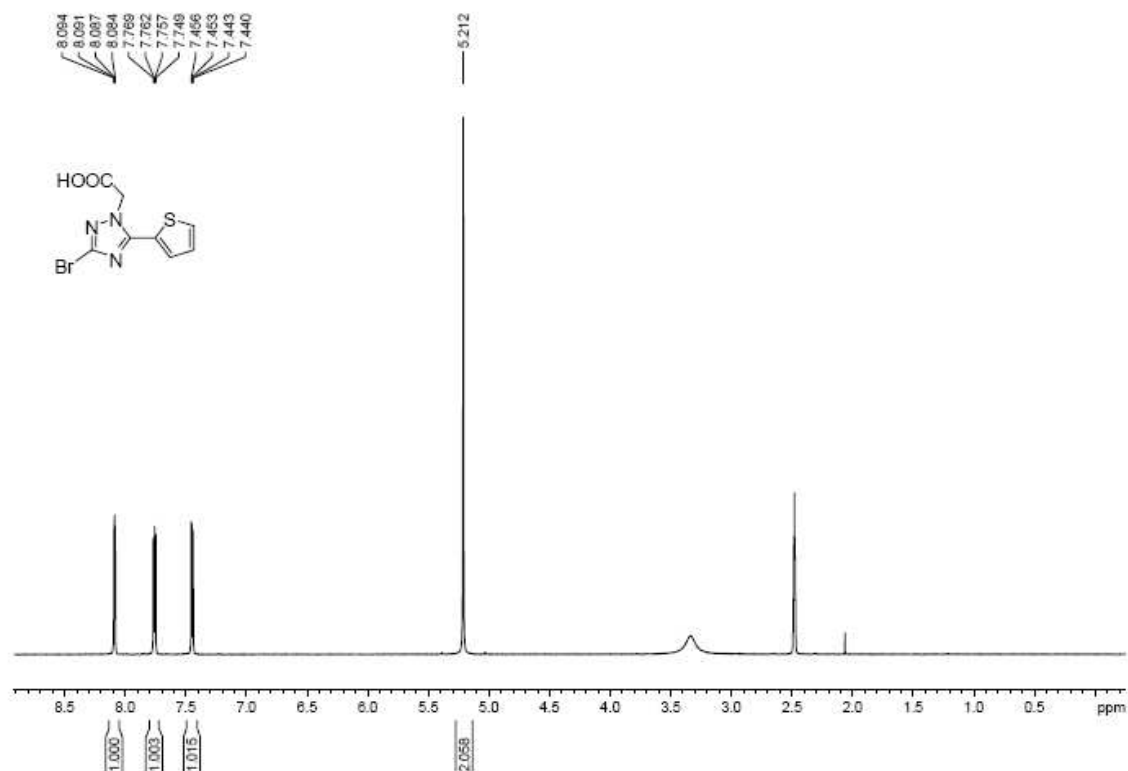
¹³C NMR (DMSO, 400MHz) 51.6, 127.1, 127.6, 128.6(2C), 138.7, 153.2, 168.8

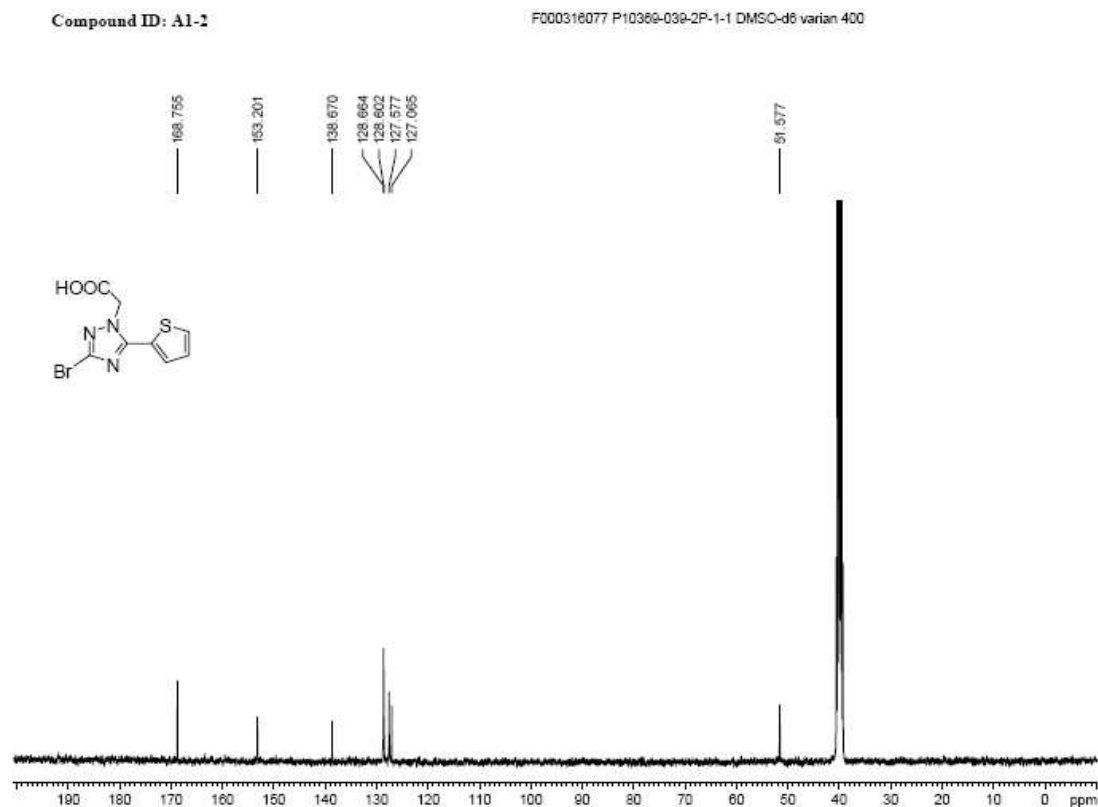
H RMS calcd. for C₈H₆BrN₃O₂S [M-H]⁻ 285.9364, found 285.9244.

¹H NMR (DMSO, 400MHz):

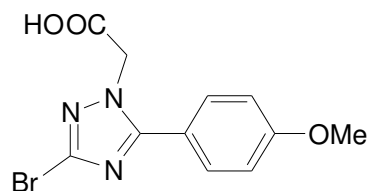
Compound ID: A1-2

F000315977 P10369-039-2P-1 DMSO-d6 varian 400

¹³C NMR (DMSO, 400MHz):



¹H NMR, ¹³C NMR and HRMS of Compound 14a:



[3-Bromo-5-(4-methoxy-phenyl)-[1,2,4]triazol-1-yl]-acetic acid

¹H NMR (DMSO, 400MHz) 3.86 (3H, s, OCH₃), 5.02 (2H, s, CH₂), 7.09 (2H, d, J = 8.8Hz, Ar), 7.58 (2H, d, J = 8.8Hz, Ar)

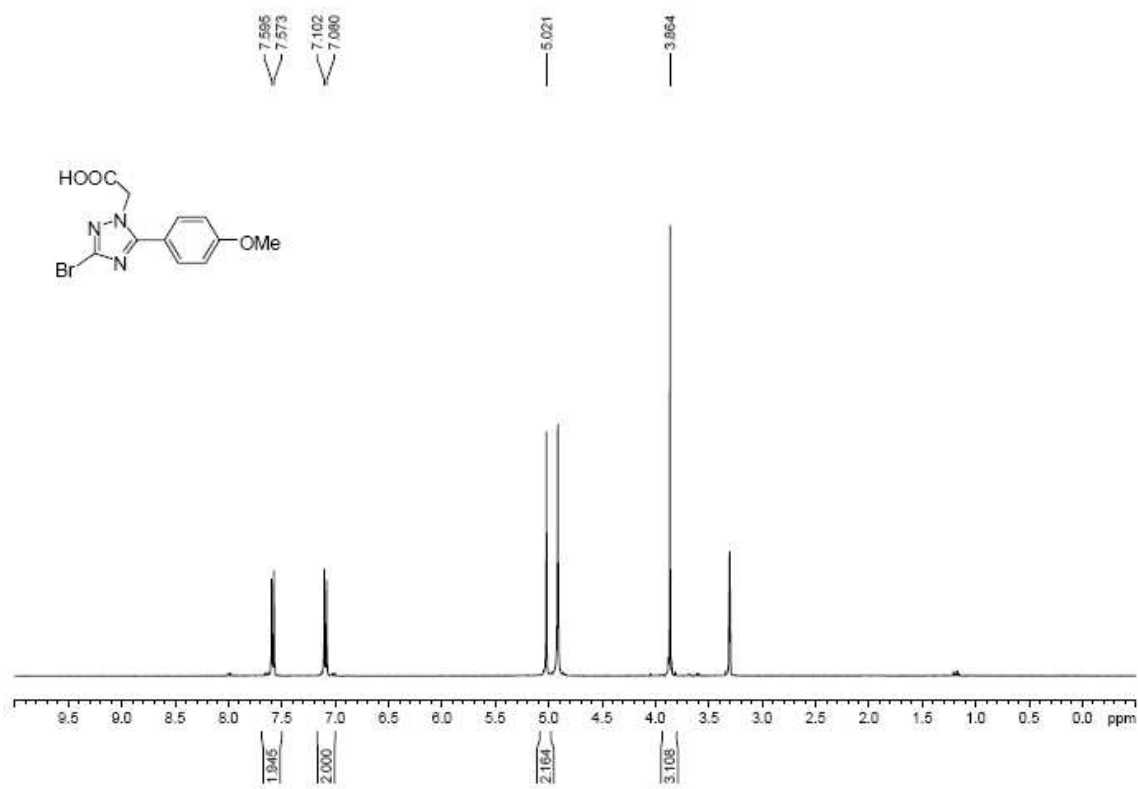
¹³C NMR (DMSO, 400MHz) 50.3, 54.6, 114.2(2C), 117.9, 129.9(2C), 138.3, 157.7, 162.0, 168.5

H RMS calcd. for C₁₁H₁₀BrN₃O₃ [M-H]⁻ 309.9906, found 309.9779.

¹H NMR (DMSO, 400MHz):

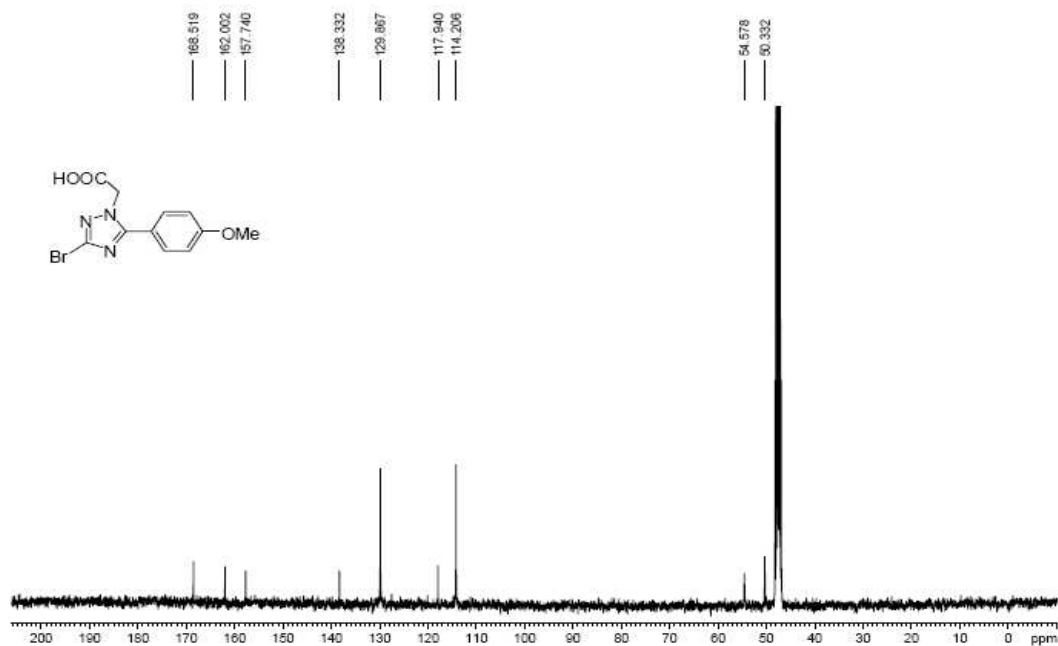
Compound ID: A1-3

F000315075 P10369-039-3P-1 Methanol-d4 varian 400

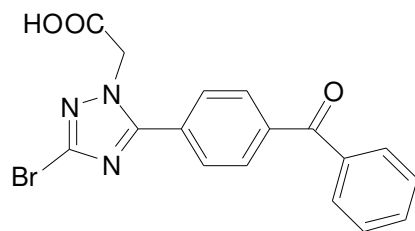
¹³C NMR (DMSO, 400MHz):

Compound ID: A1-3

F000315076 P10369-039-3P-1-1 Methanol-d4 varian 400



¹H NMR, ¹³C NMR and HRMS of Compound 13a:



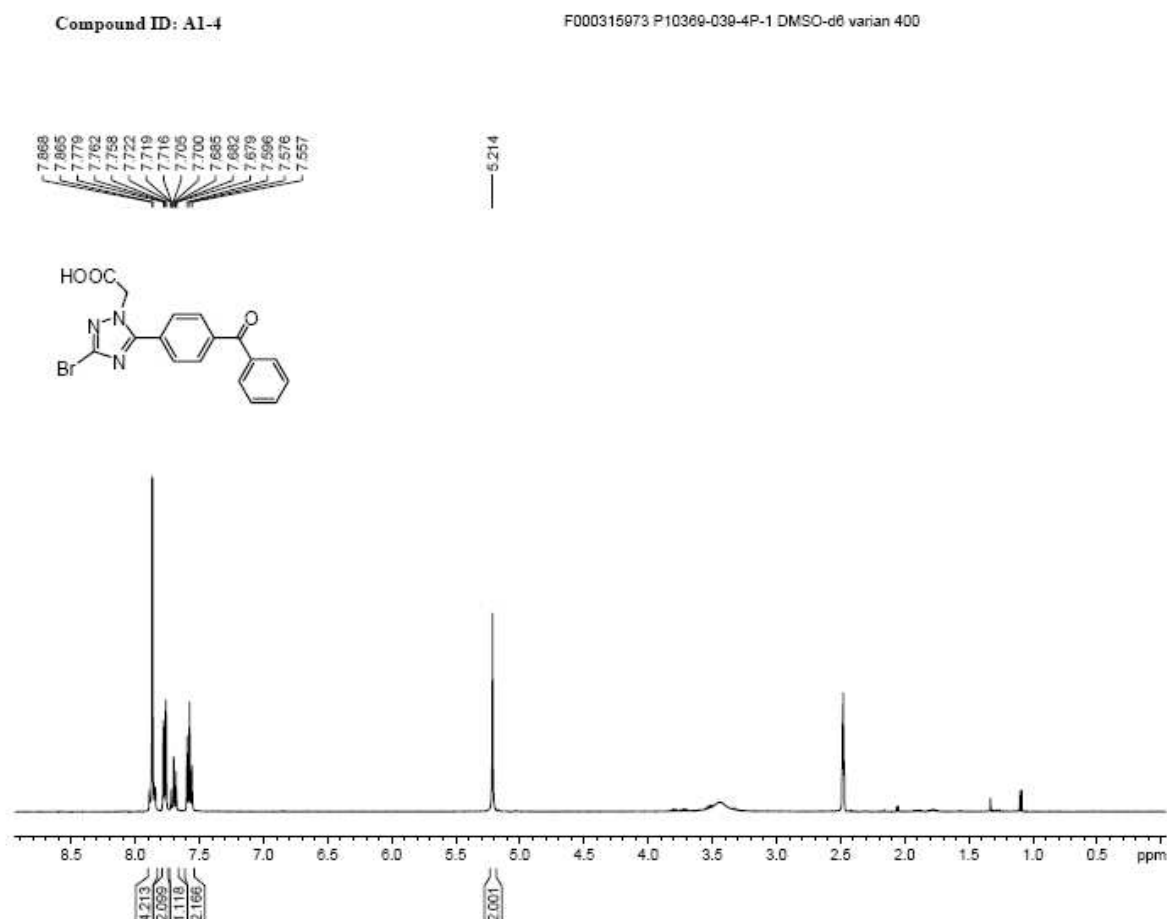
[5-(4-Benzoyl-phenyl)-3-bromo-[1,2,4]triazol-1-yl]-acetic acid

¹H NMR (DMSO, 400MHz) 5.21 (2H, s, CH₂), 7.57(2H, t, J1 = 7.6Hz, J2 = 8.0Hz Ar), 7.70(1H, m, Ar), 7.76(2H, m, Ar), 7.70(4H, m, Ar),

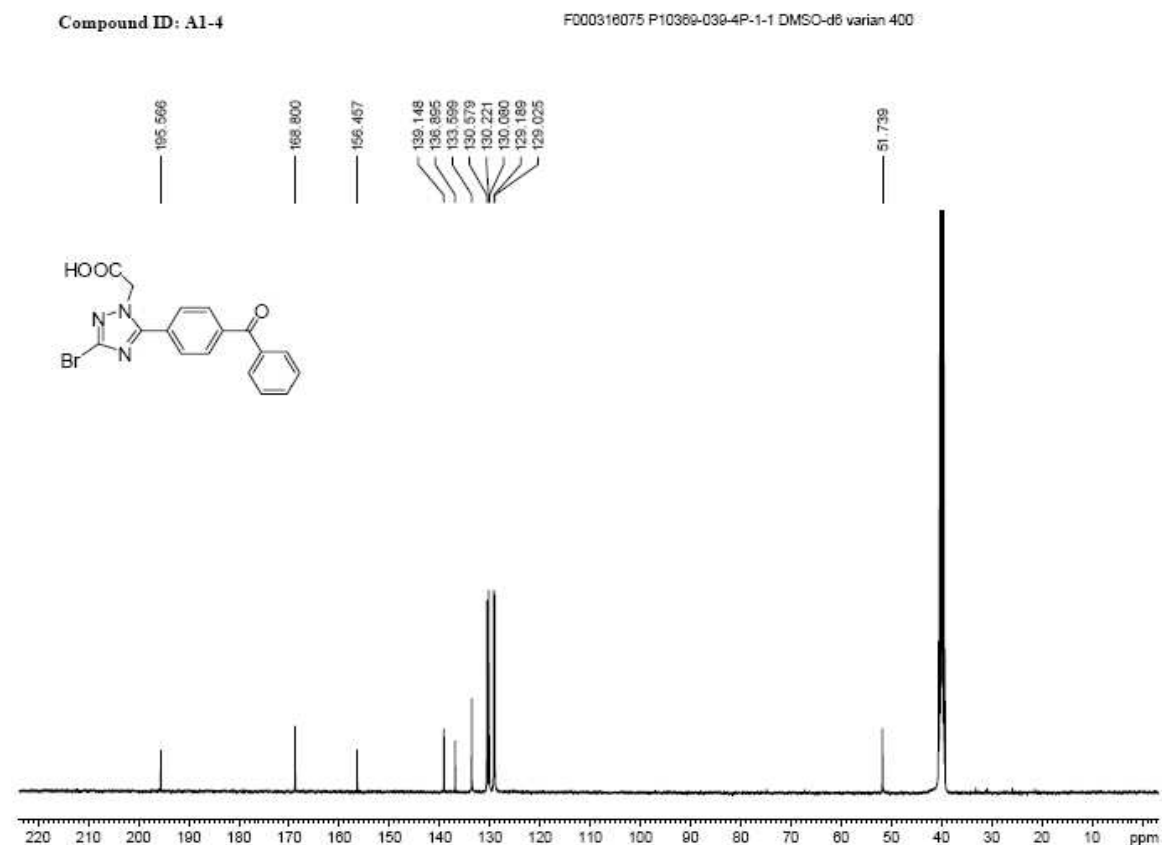
¹³C NMR (DMSO, 400MHz) 51.7, 129.0(2C), 129.2(2C), 130.1(2C), 130.2(2C), 130.6(2C), 133.6, 136.9, 139.1, 156.4, 168.8, 195.6

H RMS calcd. for C₁₇H₁₂BrN₃O₃ [M-H]⁻ 384.0062, found 383.9933.

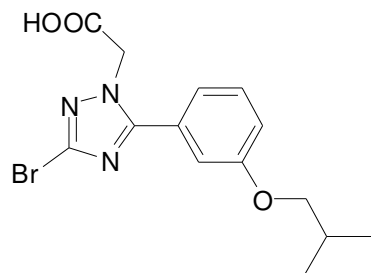
¹H NMR (DMSO, 400MHz):



¹³C NMR (DMSO, 400MHz):



¹H NMR, ¹³C NMR and HRMS of Compound 11a:



[3-Bromo-5-(3-isobutoxy-phenyl)-[1,2,4]triazol-1-yl]-acetic acid

¹H NMR (DMSO, 400MHz) 1.03 (6H,d, CH₃), 2.05 (1H, m, CH), 3.78 (2H, d, J1 = 7.6Hz, CH₂), 5.04 (2H, s, CH₂), 7.16(3H, m, Ar), 7.44 (1H, t, J1 = 8.0Hz, J2 = 8.4Hz, Ar)

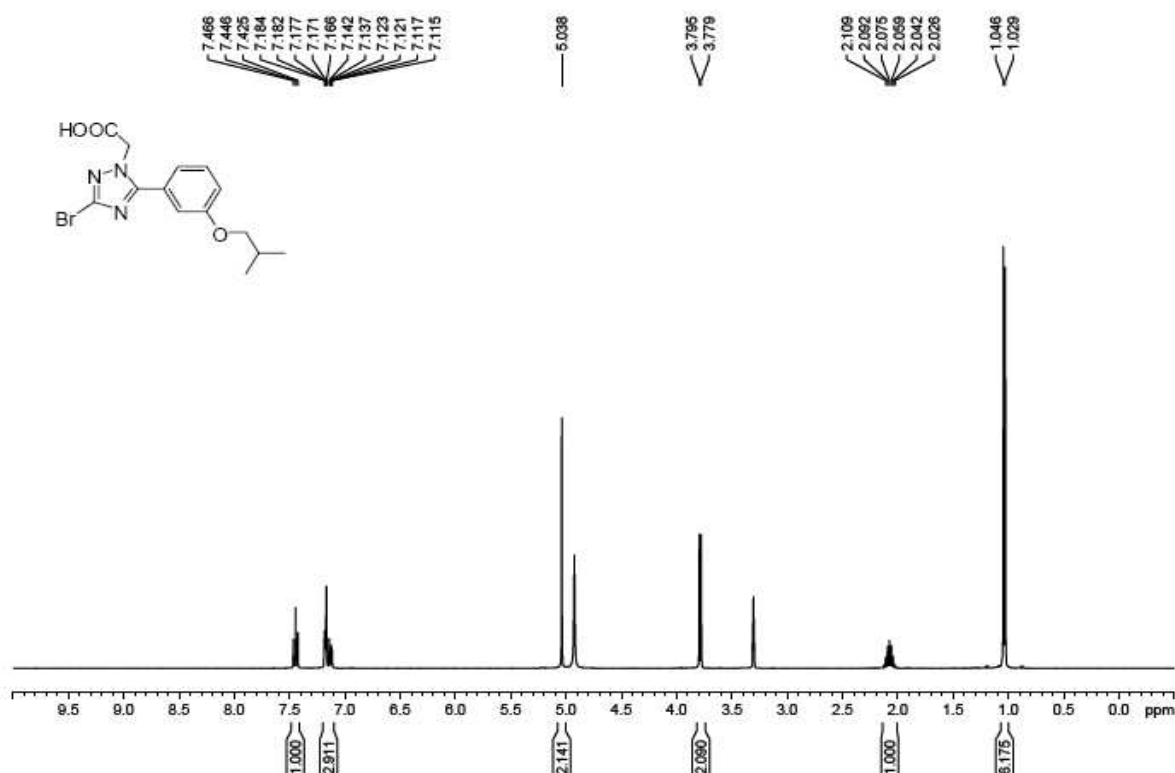
¹³C NMR (DMSO, 400MHz) 18.1(2C), 28.0, 50.4, 74.2, 113.9, 117.4, 120.2, 127.0, 130.0, 138.5, 157.6, 159.6, 168.5

H RMS calcd. for C₁₄H₁₆BrN₃O₃ [M-H]⁻ 352.0375, found 352.0281.

¹H NMR (DMSO, 400MHz):

Compound ID: A1-5

F000315078 P10369-039-5P-1 Methanol-d4 varian 400

¹³C NMR (DMSO, 400MHz):

Compound ID: A1-5

F000315079 P10369-039-5P-1-1 Methanol-d4 varian 400

