Supplementary Information

Synthesis of Novel Pyrazole Acetals of Andrographolide and Isoandrographolide as Potent Anticancer Agents

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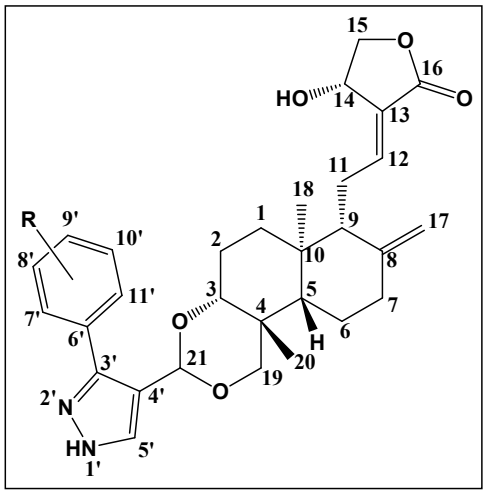
Characterization Data



(1a-1h)

3,19-(NH-3-phenyl-pyrazole) acetal of andrographolide (1a)

White solid, yield 70%, m.p. 170.0-172.3°C; **UV (λ_{max})**: 230 nm; **IR (KBr) cm^{-1}**: 3520 (O-H stretch), 3340 (N-H stretch), 3080 (aromatic C-H stretch), 2943 (sp^3 C-H stretch), 1759 (C=O stretch), 1679 (exocyclic C=C stretch), 1618 & 1464 (conjugated C=C stretch), 1201 and 1103 (C-O stretch), 896 & 775 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.81 (1H, s, H-5'), δ 7.63 (2H, d, J=7.72 Hz, H-7' and H-11'), δ 7.42-7.38 (3H, m, H-8', H-10' and H-9'), δ 6.95 (1H, t, J=6.44 Hz, H-12), δ 5.82 (1H, s, H-21), δ 5.01 (1H, d, J=5.66 Hz, H-14), δ 4.88 (1H, s, H_a-17), δ 4.58 (1H, s, H_b-17), δ 4.44 (1H, dd, J=10.28 Hz, 6.12 Hz, H_a-15), δ 4.24 (2H, dd, J=10.36 Hz, H_b-15), δ 4.16 (2H, d, J=11.36 Hz, H_a-19), δ 3.64 (1H, dd, J=12.48 Hz, 3.56 Hz, H-3), δ 3.55 (1H, d, J=11.44, H_b-19), δ 2.54-2.25 (5H, m), δ 2.03-1.96 (1H, m), δ 1.83-1.75 (4H, m), δ 1.47 (3H, s, H-18), δ 1.26-1.20 (3H, m), δ 0.76 (3H, s, H-20); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.12 (C-16), δ 148.56 (C-8), δ 146.34 (C-12), δ 146.14 (C-3'), δ 133.93 (C-5'), 131.10 (C-6'), δ 128.70 (C-8' and C-10'), δ 128.43 (C-9'), δ 128.11 (C-13), δ 127.96 (C-7' and C-11'), δ 117.74 (C-4'), δ 109.20 (C-17), δ 90.13 (C-21), δ 80.80 (C-3), δ 74.41 (C-15), δ 69.48 (C-19), δ 65.93 (C-14), δ 55.70 (C-9), δ 54.76 (C-5), δ 38.79 (C-4),

δ 37.53 (C-7), δ 36.76 (C-10), δ 35.93 (C-1), δ 26.03 (C-2), δ 24.67 (C-6), δ 22.75 (C-11), δ 21.55 (C-20), δ 15.26 (C-18); **HRMS (*m/z*)**: $[M+H]^+$ = 505.2680.

3,19-(NH-3-(3-chlorophenyl)-pyrazole) acetal of andrographolide (1b)

White solid, yield 82%, m.p. 226.0-227.3°C; **UV (λ_{max})**: 230 nm; **IR (KBr) cm^{-1}:** 3520 (O-H stretch), 3312 (N-H stretch), 3087 (aromatic C-H stretch), 2944 (sp^3 C-H stretch), 1756 (C=O stretch), 1677 (exocyclic C=C stretch), 1605 (conjugated C=C stretch) 1454 (aromatic C=C), 1200 and 1101 (C-O stretch), 1049 (aromatic C-Cl stretch), 900 & 793 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.80 (1H, s, H-5'), δ 7.74 (1H, s, H-7'), δ 7.56 (1H, t, J=4.8 Hz, H-10'), δ 7.34 (2H, d, J=4.8 Hz, H-9', H-11'), δ 6.96 (1H, t, J=6.68 Hz, H-12), δ 5.84 (1H, s, H-21), δ 5.02 (1H, d, J=5.64 Hz, H-14), δ 4.89 (1H, s, H_a-17), δ 4.59 (1H, s, H_b-17), δ 4.45 (1H, dd, J=10.44 Hz, H_a-15), δ 4.25 (1H, dd, J=10.4 Hz, H_b-15), δ 4.19 (1H, d, J=11.44 Hz, H_a-19), δ 3.67 (1H, dd, J=12.28 Hz, 4.48 Hz, H-3), δ 3.57 (1H, d, J=11.28 Hz, H_b-19), δ 2.55-2.33 (5H, m), δ 2.02-1.97 (1H, m, H_a-1), δ 1.85-1.83 (5H, m, H_b-1, H_a-6, H-9, H_b-6), δ 1.46 (3H, s, H-18), δ 1.29-1.25 (3H, m), δ 0.80 (3H, s, H-20); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.02 (C-16), δ 148.72 (C-8), δ 146.37 (C-12), δ 145.78 (C-3'), δ 134.48 (C-5'), δ 133.64 (C-8'), δ 131.90 (C-6'), δ 129.89 (C-7'), δ 128.25 (C-10'), δ 128.22 (C-9'), δ 128.07 (C-13), δ 125.98 (C-11'), δ 118.24 (C-4'), δ 109.26 (C-17), δ 90.05 (C-21), δ 80.95 (C-3), δ 74.37 (C-15), δ 69.52 (C-19), δ 66.11 (C-14), δ 55.71 (C-9), δ 54.73 (C-5), δ 38.82 (C-4), δ 37.54 (C-7), δ 36.78 (C-10), δ 36.02 (C-1), δ 26.03 (C-2), δ 24.72 (C-6), δ 22.76 (C-11), δ 21.54 (C-20), δ 15.30 (C-18); **HRMS (*m/z*):** $[M+H]^+$ = 539.2300, $[M+H+2]^+$ = 541.2300.

3,19-(NH-3-(3-bromophenyl)-pyrazole) acetal of andrographolide (1c)

White solid, yield 84%, m.p. 247.0-249.3°C; **UV (λ_{max})**: 245 nm; **IR (KBr) cm^{-1}**: 3419 (O-H stretch), 3270 (N-H stretch), 3079 (aromatic C-H stretch), 2938 (sp^3 C-H stretch), 1753 (C=O stretch), 1675 (exocyclic C=C stretch), 1601 & 1447 (conjugated C=C stretch), 1198 and 1101 (C-O stretch), 1018 (aromatic C-Br stretch), 895 & 790 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.89 (1H, s, H-7'), δ 7.80 (1H, s, H-5'), δ 7.61 (1H, d, J=7.68 Hz, H-11'), δ 7.49 (1H, d, J=8 Hz, H-9'), δ 7.27 (1H, t, J=7.84 Hz, H-10'), δ 6.95 (1H, t, J=6.44 Hz, H-12), δ 5.83 (1H, s, H-21), δ 5.02 (1H, d, J=5.56 Hz, H-14), δ 4.89 (1H, s, H_a-17), δ 4.59 (1H, s, H_b-17), δ 4.44 (1H, dd, J=10.48 Hz, 6.12 Hz, H_a-15), δ 4.25 (1H, dd, J=10.48 Hz, H_b-15), δ 4.18 (1H, d, J=11.48 Hz, H_a-19), δ 3.67 (1H, dd, J=12.36 Hz, 4.16 Hz, H-3), δ 3.57 (1H, d, J=11.36, H_b-19), δ 2.56-2.32 (5H, m), δ 2.03-1.97 (1H, m, H_a-1), δ 1.91-1.83 (5H, m, H_b-1, H_a-6, H-9, H_b-6), δ 1.46 (3H, s, H-18), δ 1.27-1.25 (3H, m), δ 0.79 (3H, s, H-20); **^{13}C NMR**

(100 MHz, $CDCl_3$): δ 170.04 (C-16), δ 148.68 (C-8), δ 146.38 (C-12), δ 145.71 (C-3'), δ 133.92 (C-5'), δ 131.94 (C-6'), 131.17 (C-10'), 131.09 (C-7'), 130.16 (C-9'), δ 128.10 (C-13), δ 126.46 (C-11'), δ 122.68 (C-8'), δ 118.26 (C-4'), δ 109.26 (C-17), δ 90.05 (C-21), δ 80.96 (C-3), δ 74.38 (C-15), δ 69.52 (C-19), δ 66.10 (C-14), δ 55.72 (C-9), δ 54.75 (C-5), δ 38.83 (C-4), δ 37.55 (C-7), δ 36.79 (C-10), δ 36.01 (C-1), δ 26.05 (C-2), δ 24.72 (C-6), δ 22.77 (C-11), δ 21.62 (C-20), δ 15.30 (C-18); **HRMS (*m/z*):** $[M+H]^+$ = 583.1751, $[M+H+2]^+$ = 585.1751.

3,19-(NH-3-(4-fluorophenyl)-pyrazole) acetal of andrographolide (1d)

White solid, yield 79%, m.p. 241.0-243.0°C; **UV (λ_{max})**: 245 nm; **IR (KBr) cm^{-1}**: 3421 (O-H stretch), 3275 (N-H stretch), 3081 (aromatic C-H stretch), 2942 (sp^3 C-H stretch), 1759 (C=O stretch), 1673 (exocyclic C=C stretch), 1606 & 1455 (conjugated C=C stretch), 1222 (aromatic C-F stretch), 1208 and 1102 (C-O stretch), 896, 842 & 812 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.79 (1H, s, H-5'), δ 7.62 (2H, dd, J=8.4 Hz, H-7' and H-11'), δ 7.09 (2H, dd, J=8.60 Hz, H-8' and H-10'), δ 6.95 (1H, t, J=6.68 Hz, H-12), δ 5.79 (1H, s, H-21), δ 5.02 (1H, d, J=5.48 Hz, H-14), δ 4.89 (1H, s, H_a-17), δ 4.60 (1H, s, H_b-17), δ 4.44 (1H, dd, J=10.44 Hz, 6.12 Hz, H_a-15), δ 4.24 (1H, dd, J=10.32 Hz, H_b-15), δ 4.15 (1H, d, J=11.4 Hz, H_a-19), δ 3.65 (1H, dd, J=12.96 Hz, 4.56 Hz, H-3), δ 3.56 (1H, d, J=11.12 Hz, H_b-19), 2.54-2.39 (5H, m), δ 2.03-1.97 (1H, m), δ 1.83-1.76 (4H, m), δ 1.46 (3H, s, H-18), δ 1.28-1.20 (3H, m), δ 0.79 (3H, s, H-20); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.09 (C-16), δ 162.87 (J_{C-F} = 246.0 Hz, C-9'), δ 148.65 (C-8), δ 146.40 (C-12), δ 145.71 (C-3'), δ 132.57 (C-5'), 130.77 and 130.69 (J_{C-F} = 8.0 Hz, C-6'), 129.88 (J_{C-F} = 8.0 Hz, C-7' and C-11'), δ 128.12 (C-13), δ 117.85 (C-4'), δ 115.60 (J_{C-F} = 21.0 Hz, C-8' and C-10'), δ 109.28 (C-17), δ 90.14 (C-21), δ 80.84 (C-3), δ 74.40 (C-15), δ 69.51 (C-19), δ 66.08 (C-14), δ 55.74 (C-9), δ 54.76 (C-5), δ 38.83 (C-4), δ 37.55 (C-7), δ 36.79 (C-10), δ 36.00 (C-1), δ 26.05 (C-2), δ 24.75 (C-6), δ 22.77 (C-11), δ 21.60 (C-20), δ 15.33 (C-18); **HRMS (*m/z*):** $[M+H]^+$ = 523.2564.

3,19-(NH-3-(4-bromophenyl)-pyrazole) acetal of andrographolide (1e)

White solid, yield 75%, m.p. 225.0-226.5°C; **UV (λ_{max})**: 240 nm; **IR (KBr) cm^{-1}**: 3419 (O-H stretch), 3272 (N-H stretch), 3081 (aromatic C-H stretch), 2939 (sp^3 C-H stretch), 1756 (C=O stretch), 1674 (exocyclic C=C stretch), 1603 & 1447 (conjugated C=C stretch), 1200 and 1101 (C-O stretch), 1010 (aromatic C-Br stretch), 898, 835 & 783 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.79 (1H, s, H-5'), δ 7.53 (4H, br-s, H-7', H-8', H-10' and H-11'), δ 6.95 (1H, t, J=6.52 Hz, H-12), δ 5.79 (1H, s, H-21), δ 5.02 (1H, d, J=5.68

Hz, H-14), δ 4.89 (1H, s, H_a-17), δ 4.60 (1H, s, H_b-17), δ 4.45 (1H, dd, J=10.48 Hz, 6.2 Hz, H_a-15), δ 4.25 (2H, dd, J=10.44 Hz, H_b-15), δ 4.17 (2H, d, J=11.40 Hz, H_a-19), δ 3.65 (1H, dd, J=12.48 Hz, H-3), δ 3.56 (1H, d, J=11.20, H_b-19), δ 2.56-2.28 (5H, m), δ 2.03-1.97 (1H, m), δ 1.84-1.72 (4H, m), δ 1.46 (3H, s, H-18), δ 1.28-1.20 (3H, m), δ 0.79 (3H, s, H-20); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.05 (C-16), δ 148.67 (C-8), δ 146.38 (C-12), δ 145.77 (C-3') δ 132.01 (C-5'), δ 131.75 (C-8' and C-10'), 130.26 (C-6'), 129.63 (C-7' and C-11'), δ 128.08 (C-13), δ 122.59 (C-9'), δ 118.07 (C-4'), δ 109.28 (C-17), δ 90.06 (C-21), δ 80.84 (C-3), δ 74.39 (C-15), δ 69.50 (C-19), δ 66.09 (C-14), δ 55.72 (C-9), δ 54.74 (C-5), δ 38.82 (C-4), δ 37.53 (C-7), δ 36.78 (C-10), δ 35.99 (C-1), δ 26.04 (C-2), δ 24.75 (C-6), δ 22.75 (C-11), δ 21.60 (C-20), δ 15.33 (C-18); **HRMS (*m/z*):** $[M+H]^+$ = 583.1796, $[M+H+2]^+$ = 585.1796, $[M+H+4]^+$ = 587.1796.

3,19-(NH-3-(4-methylphenyl)-pyrazole) acetal of andrographolide (1f)

White solid, yield 88%, m.p. 248.1-250.0°C; **UV (λ_{max})**: 240 nm; **IR (KBr) cm^{-1}**: 3415 (O-H stretch), 3275 (N-H stretch), 3079 (aromatic C-H stretch), 2939 (sp^3 C-H stretch), 1758 (C=O stretch), 1675 (exocyclic C=C stretch), 1601 & 1447 (conjugated C=C stretch), 1203 and 1101 (C-O stretch), 892, 827 & 775 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.81 (1H, s, H-5'), δ 7.50 (2H, d, J=8.04 Hz, H-7' and H-11'), δ 7.23 (2H, d, J=7.96 Hz, H-8' and H-10'), δ 6.97 (1H, dt, J=6.4 Hz, H-12), δ 5.81 (1H, s, H-21), δ 5.02 (1H, d, J=5.54 Hz, H-14), δ 4.89 (1H, s, H_a-17), δ 4.59 (1H, s, H_b-17), δ 4.45 (1H, dd, J=10.44 Hz, 6.12 Hz, H_a-15), δ 4.26 (1H, dd, J=10.40 Hz, H_b-15), δ 4.16 (1H, d, J=11.44 Hz, H_a-19), δ 3.65 (1H, dd, J=12.64 Hz, 4.20 Hz, H-3), δ 3.55 (1H, d, J=11.24, H_b-19), δ 3.45 (2H, m), δ 2.58-2.37 (5H, m), δ 2.41 (3H, s, C$\underline{H}_3$), δ 2.03-1.96 (1H, m), δ 1.84-1.75 (4H, m), δ 1.47 (3H, s, H-18), δ 1.30-1.17 (3H, m), δ 0.76 (3H, s, H-20); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.22 (C-16), δ 148.58 (C-8), δ 146.38 (C-12), δ 145.00 (C-3'), δ 138.38 (C-13), δ 132.91 (C-5'), 130.33 (C-6'), 129.46 (C-8' and C-10'), 129.17 (C-9'), δ 128.09 (C-13), δ 127.83 (C-7' and C-11'), δ 117.46 (C-4'), δ 109.21 (C-17), δ 90.19 (C-21), δ 80.80 (C-3), δ 74.47 (C-15), δ 69.49 (C-19), δ 65.90 (C-14), δ 55.74 (C-9), δ 54.75 (C-5), δ 38.83 (C-4), δ 37.56 (C-7), δ 36.78 (C-10), δ 35.96 (C-1), δ 26.06 (C-2), δ 24.68 (C-6), δ 22.78 (C-11), δ 21.58 (C-20), δ 21.34 ($\underline{C}H_3$), δ 15.27 (C-18); **HRMS (*m/z*):** $[M+H]^+$ = 519.2808.

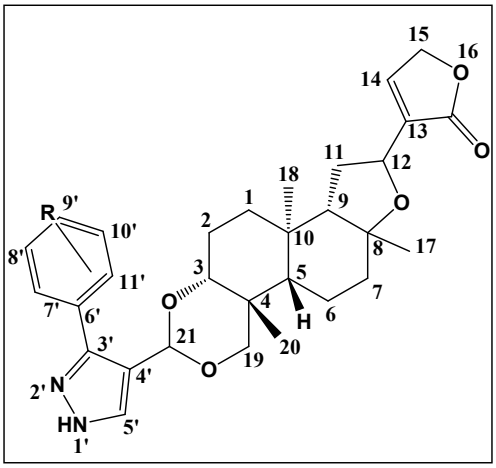
3,19-(NH-3-(4-methoxyphenyl)-pyrazole) acetal of andrographolide (1g)

White solid, yield 89%, m.p. 154.0-156.2°C; **UV (λ_{max})**: 240 nm; **IR (KBr) cm^{-1}**: 3401 (O-H stretch), 3321 (N-H stretch), 3070 (aromatic C-H stretch), 2933 (sp^3 C-H stretch), 1759 (C=O

stretch), 1675 (exocyclic C=C stretch), 1612 & 1455 (conjugated C=C stretch), 1250 and 1101 (C-O stretch), 889, 837 & 779 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.79 (1H, s, H-5'), δ 7.55 (2H, d, J=8.6 Hz, H-7'and H-11'), δ 6.94 (2H, d, J=8.6 Hz, H-12, H-8' and H-10'), δ 5.79 (1H, s, H-21), δ 5.00 (1H, d, J=5.60 Hz, H-14), δ 4.89 (1H, s, H_a-17), δ 4.60 (1H, s, H_b-17), δ 4.44 (1H, dd, J=10.00 Hz, 6.12 Hz, H_a-15), δ 4.24 (1H, d, J=10.32 Hz, H_b-15), δ 4.17 (1H, d, J=11.16 Hz, H_a-19), δ 3.84 (-O$\underline{C}H_3$), δ 3.65 (1H, dd, J=12.44 Hz, H-3), δ 3.60 (1H, d, J=11.16, H_b-19), δ 3.38 (2H, m), δ 2.55-2.30 (5H, m), δ 2.03-1.98 (1H, m), δ 1.83-1.77 (4H, m), δ 1.47 (3H, s, H-18), δ 1.28-1.22 (3H, m), δ 0.77 (3H, s, H-20); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 170.09 (C-16), δ 159.79 (C-9'), δ 148.58 (C-8), δ 146.39 (C-12), δ 145.1 (C-3'), δ 132.91 (C-5'), 130.17 (C-6'), 129.25 (C-7' and C-11'), δ 128.12 (C-13), δ 117.97 (C-4'), δ 114.11 (C-8' and C-10'), δ 109.21 (C-17), δ 90.21 (C-21), δ 80.77 (C-3), δ 74.40 (C-15), δ 69.47 (C-19), δ 65.97 (C-14), δ 55.72 (C-9), δ 55.31 (-O$\underline{C}H_3$), δ 54.73 (C-5), δ 38.81 (C-4), δ 37.54 (C-7), δ 36.77 (C-10), δ 35.97 (C-1), δ 26.04 (C-2), δ 24.69 (C-6), δ 22.76 (C-11), δ 21.58 (C-20), δ 15.29 (C-18); **HRMS (*m/z*):** $[M+H]^+$ = 535.2747.

3,19-(NH-3-(3-fluorophenyl)-pyrazole) acetal of andrographolide (1h)

White solid, yield 79%, m.p. 178.0-180.0°C; **UV (λ_{max})**: 235 nm; **IR (KBr) cm^{-1}**: 3530 (O-H stretch), 3355 (N-H stretch), 3080 (aromatic C-H stretch), 2942 (sp^3 C-H stretch), 1760 (C=O stretch), 1679 (exocyclic C=C stretch), 1618 & 1464 (conjugated C=C stretch), 1234 (aromatic C-F stretch), 1201 and1102 (C-O stretch), 887 & 791 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.81 (1H, m, H-11'), δ 7.57 (1H, s, H-5'), δ 7.48-7.44 (2H, m, H-7', H-10'), δ 7.05 (1H, dd, J=8.84 Hz, H-9'), δ 6.95 (1H, t, J=6.42 Hz, H-12), δ 5.84 (1H, s, H-21), δ 5.01 (1H, d, J=5.58 Hz, H-14), δ 4.86 (1H, s, H_a-17), δ 4.63 (1H, s, H_b-17), δ 4.44 (1H, dd, J=10.44 Hz, 6.08 Hz, H_a-15), δ 4.24 (1H, dd, J=10.44 Hz, H_b-15), δ 4.17 (1H, d, J=11.52 Hz, H_a-19), δ 3.65 (1H, dd, J=12.30 Hz, 4.16 Hz, H-3), δ 3.56 (1H, d, J=11.36, H_b-19), δ 2.55-2.35 (5H, m), δ 2.04-1.97 (1H, m, H_a-1), δ 1.86-1.84 (5H, m, H_b-1, H_a-6, H-9, H_b-6), δ 1.45 (3H, s, H-18), δ 1.27-1.25 (3H, m), δ 0.78 (3H, s, H-20); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 171.20 (C-16), δ 163.00 (C-8'), δ 148.87 (C-8), δ 146.40 (C-12), δ 146.19 (C-3'), δ 132.88 (C-5'), δ 130.20 (C-6'), δ 131.76 (C-6'), δ 129.68 (C-10'), δ 128.04 (C-12), δ 123.64 (C-11'), δ 117.39 (C-12'), δ115.24 (C-7'), δ 115.00 (C-9'), δ 109.32 (C-17), δ 90.04 (C-21), δ 80.96 (C-3), δ 74.43 (C-15), δ 69.52 (C-19), δ 66.25 (C-14), δ 55.73 (C-9), δ 54.78 (C-5), δ 39.14 (C-4), δ 37.55 (C-7), δ 36.81 (C-10), δ 35.79 (C-1), δ 26.09 (C-2), δ 24.69 (C-6), δ 22.78 (C-11), δ 21.51 (C-20), δ 15.40 (C-18); **HRMS (*m/z*):** $[M+H]^+$ = 523.2566.



(2a-2g, 2i)

3,19-(NH-3-phenyl-pyrazole) acetal of isoandrographolide (2a)

White solid, yield 72%, m.p. 110.3-113.5°C; **UV (λ_{max})**: 240 nm; **IR (KBr) cm^{-1}**: 3291 (N-H stretch), 3064 (aromatic C-H stretch), 2926 (sp^3 C-H stretch), 1753 (C=O stretch), 1608 & 1448 (conjugated C=C stretch), 1195 and 1099 (C-O stretch), 891 & 773 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.81 (1H, s, H-5'), δ 7.65 (2H, d, J=7.04 Hz, H-7' and H-11'), δ 7.43 (3H, m, H-8', H-9' and H-10'), δ 7.28 (1H, sd, H-14), δ 5.85 (1H, s, H-21), δ 4.81 (2H, s, H-15), δ 4.69 (1H, dt, J=7.44 Hz, H-12), δ 4.28 (1H, d, J=11.48 Hz, H_a-19), δ 3.65 (1H, dd, J=12.68 Hz, H-3), δ 3.61 (1H, d, J=11.84 Hz, H_b-19), δ 2.46 (1H, m, H_a-11), δ 2.37-2.17 (1H, m, H_b-11), δ 2.05-1.98 (1H, m, H_a-1), δ 1.85-1.69 (3H, m, H_a-7, H-2), δ 1.58-1.51 (4H, m, H_b-1, H_a-6, H-9, H_b-6), δ 1.48 (3H, s, H-18), δ 1.12 (3H, s, H-17), δ 1.10 (3H, s, H-20), δ 1.02 -0.97 (2H, m, H-5, H_b-7); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.63 (C-16), δ 145.75 (C-3'), δ 143.27 (C-14), δ 138.31 (C-13), δ 131.31 (C-5'), δ 130.93 (C-6'), δ 128.68 (C-8' and C-10'), δ 128.35 (C-9'), δ 128.02 (C-7' and C-11'), δ 117.73 (C-4'), δ 90.37 (C-21), δ 82.76 (C-8), δ 81.55 (C-3), δ 73.04 (C-12), δ 70.56 (C-15), δ 69.69 (C-19), δ 57.90 (C-9), δ 51.64 (C-5), δ 38.16 (C-4), δ 36.33 (C-7), δ 35.91 (C-10), δ 35.59 (C-1), δ 32.73 (C-11), δ 31.76 (C-17), δ 25.94 (C-18), δ 20.91 (C-2), δ 17.28 (C-6), δ 16.38 (C-20); **HRMS (*m/z*)**: $[M+H]^+$ = 505.2686.

3,19-(NH-3-(3-chlorophenyl)-pyrazole) acetal of isoandrographolide (2b)

White solid, yield 87%, m.p. 216.1-218.0°C; **UV (λ_{max})**: 245 nm; **IR (KBr) cm^{-1}**: 3302 (N-H stretch), 3069 (aromatic C-H stretch), 2941 (sp^3 C-H stretch), 1757 (C=O stretch), 1603 & 1448

(conjugated C=C stretch), 1204 and 1099 (C-O stretch), 1058 (aromatic C-Cl stretch), 889 & 795 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.80 (1H, s, H-5'), δ 7.75 (1H, s, H-7'), δ 7.57 (1H, t, J=4.32 Hz, H-10'), δ 7.34 (2H, d, J=4.68 Hz, H-9', H-11') , δ 7.29 (1H, d, H-14), δ 5.85 (1H, s, H-21), δ 4.81 (2H, s, H-15), δ 4.70 (1H, dt, J=7.76 Hz, H-12), δ 4.29 (1H, d, J=11.52 Hz, H_a-19), δ 3.67 (1H, dd, J=12.68 Hz, 4.48 Hz, H-3), δ 3.62 (1H, d, J=11.64, H_b-19), δ 2.46 (1H, m, H_a-11), δ 2.40-2.31 (1H, m, H_b-11), δ 2.06-1.98 (1H, m, H_a-1), δ 1.88-1.77 (3H, m, H_a-7, H-2), δ 1.60-1.56 (4H, m, H_b-1, H_a-6, H-9, H_b-6), δ 1.47 (3H, s, H-18), δ 1.13 (3H, s, H-17), δ 1.09 (3H, s, H-20), δ 1.03 -1.00 (2H, m, H-5, H_b-7); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.64 (C-16), δ 145.86 (C-3'), δ 143.27 (C-14), δ 138.33 (C-13), δ 134.51 (C-5'), δ 133.73 (C-8'), δ 131.91 (C-6'), δ 129.87 (C-7'), δ 128.24 (C-10' and C-9'), δ 126.04 (C-11'), δ 118.23 (C-7'), δ 90.28 (C-21), δ 82.77 (C-8), δ 81.69 (C-3), δ 73.07 (C-12), δ 70.57 (C-15), δ 69.76 (C-19), δ 57.94 (C-9), δ 51.65 (C-5), δ 38.19 (C-4), δ 36.35 (C-7), δ 35.92 (C-10), δ 35.61 (C-1), δ 32.76 (C-11), δ 31.78 (C-17), δ 25.98 (C-18), δ 20.89 (C-2), δ 17.31 (C-6), δ 16.39 (C-20); **HRMS (*m/z*):** $[M+H]^+$ = 539.2297, $[M+H+2]^+$ = 541.2297.

3,19-(NH-3-(3-bromophenyl)-pyrazole) acetal of isoandrographolide (2c)

White solid, yield 83%, m.p. 111.0-112.5°C; **UV (λ_{max})**: 245 nm; **IR (KBr) cm^{-1}**: 3284 (N-H stretch), 3067 (aromatic C-H stretch), 2940 (sp^3 C-H stretch), 1755 (C=O stretch), 1600 & 1447 (conjugated C=C stretch), 1209 and 1100 (C-O stretch), 1018 (aromatic C-Br stretch), 892 & 790 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.90 (1H, s, H-7'), δ 7.81 (1H, s, H-5'), δ 7.62 (1H, d, J=7.76 Hz, H-11'), δ 7.50 (1H, d, H-9'), δ 7.29 (2H, t, J=7.72 Hz, H-10' and H-14), δ 5.84 (1H, s, H-21), δ 4.81 (2H, s, H-15), δ 4.70 (1H, dt, J=9.28 Hz, H-12), δ 4.30 (1H, d, J=11.52 Hz, H_a-19), δ 3.67 (1H, dd, J=12.76 Hz, 4.56 Hz, H-3), δ 3.62 (1H, d, J=11.72 Hz, H_b-19), δ 2.47 (1H, m, H_a-11), δ 2.41-2.31 (1H, m, H_b-11), δ 2.06-1.98 (1H, m, H_a-1), δ 1.88-1.79 (3H, m, H_a-7, H-2), δ 1.60-1.56 (4H, m, H_b-1, H_a-6, H-9, H_b-6), δ 1.47 (3H, s, H-18), δ 1.13 (3H, s, H-17), δ 1.09 (3H, s, H-20), δ 1.04 -1.00 (2H, m, H-5, H_b-7); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.62 (C-16), δ 145.60 (C-3'), δ 143.24 (C-14), δ 138.32 (C-13), δ 133.94 (C-5'), δ 131.76 (C-6'), δ 131.17 (C-11'), δ 131.07 (C-7'), δ 130.13 (C-9'), δ 126.48 (C-12'), δ122.69 (C-8'), δ 118.27 (C-7'), δ 90.24 (C-21), δ 82.75 (C-8), δ 81.68 (C-3), δ 73.05 (C-12), δ 70.56 (C-15), δ 69.76 (C-19), δ 57.92 (C-9), δ 51.63 (C-5), δ 38.20 (C-4), δ 36.32 (C-7), δ 35.90 (C-10), δ 35.60 (C-1), δ 32.75 (C-11), δ 31.76 (C-17), δ 25.97 (C-18), δ 20.94 (C-2), δ 17.29 (C-6), δ 16.37 (C-20); **HRMS (*m/z*):** $[M+H]^+$ = 583.1800, $[M+H+2]^+$ = 585.1800, $[M+H+4]^+$ = 587.1800.

3,19-(NH-3-(4-flurophenyl)-pyrazole) acetal of isoandrographolide (2d)

White solid, yield 82%, m.p. 148.5-150.0°C; **UV (λ_{max})**: 240 nm; **IR(KBr) cm^{-1}**: 3296 (N-H stretch), 3079 (aromatic C-H stretch), 2933 (sp^3 C-H stretch), 1757 (C=O stretch), 1606 & 1453 (conjugated C=C stretch), 1219 (aromatic C-F stretch), 1195 and 1102 (C-O stretch), 889, 834 & 770 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.80 (1H, s, H-5'), δ 7.64 (2H, dd, J=6.36 Hz, H-7' and H-11'), δ 7.29 (1H, s, H-14), δ 7.11 (2H, dd, J=8.60 Hz, H-8' and H-10'), δ 5.81 (1H, s, H-21), δ 4.82 (2H, s, H-15), δ 4.70 (1H, dt, J=7.40 Hz, H-12), δ 4.28 (1H, d, J=11.52 Hz, H_a-19), δ 3.65 (1H, dd, J=12.80 Hz, H-3), δ 3.61 (1H, d, J=11.52 Hz, H_b-19), δ 2.46 (1H, m, H_a-11), δ 2.36-2.20 (1H, m, H_b-11), δ 2.06-1.99 (1H, m, H_a-1), δ 1.86-1.67 (3H, m, H_a-7, H-2), δ 1.57-1.52 (4H, m, H_b-1, H_a-6, H-9, H_b-6), δ 1.47 (3H, s, H-18), 1.12 (3H, s, H-17), δ 1.08 (3H, s, H-20), δ 1.03-0.93 (2H, m, H-5, H_b-7); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.64 (C-16), δ 162.84 (J_{C-F} = 246.0 Hz, C-9'), δ 145.61 (C-3'), δ 143.29 (C-14), δ 138.41 (C-13), δ 132.40 (C-5'), δ 130.98 (J_{C-F} = 8.0 Hz, C-6'), δ 129.87 (J_{C-F} = 8.0 Hz, C-7' and C-11'), δ 117.80 (C-4'), δ 115.59 (J_{C-F} = 21.0 Hz, C-8' and C-10'), δ 90.32 (C-21), δ 82.74 (C-8), δ 81.54 (C-3), δ 73.03 (C-12), δ 70.57 (C-15), δ 69.70 (C-19), δ 57.89 (C-9), δ 51.64 (C-5), δ 38.12 (C-4), δ 36.32 (C-7), δ 35.91 (C-10), δ 35.59 (C-1), δ 32.71 (C-11), δ 31.74 (C-17), δ 25.96 (C-18), δ 20.91 (C-2), δ 17.28 (C-6), δ 16.39 (C-20); **HRMS (*m/z*):** $[M+H]^+$ = 523.2560

3,19-(NH-3-(4-bromophenyl)-pyrazole) acetal of isoandrographolide (2e)

White solid, yield 74%, m.p. 100.1-101.8°C; **UV (λ_{max})**: 250 nm; **IR (KBr) cm^{-1}**: 3299 (N-H stretch), 3077 (aromatic C-H stretch), 2931 (sp^3 C-H stretch), 1756 (C=O stretch), 1602 & 1450 (conjugated C=C stretch), 1206 and 1099 (C-O stretch), 1015 (aromatic C-Br stretch), 888, 835 & 779 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.80 (1H, s, H-5'), δ 7.55 (4H, s, H-7', H-8', H-10' and H-11'), δ 7.29 (1H, s, H-14), δ 5.82 (1H, s, H-21), δ 4.81 (2H, s, H-15), δ 4.70 (1H, dt, J=7.28 Hz, H-12), δ 4.27 (1H, t, J=11.92 Hz, H_a-19), δ 3.65 (1H, dd, J=12.76 Hz, H-3), δ 3.61 (1H, d, J=11.52 Hz, H_b-19), δ 2.46 (1H, m, H_a-11), δ 2.35-2.31 (1H, m, H_b-11), δ 2.24-2.17 (1H, m, H_a-1), δ 1.87-1.68 (3H, m, H_a-7, H-2), δ 1.58-1.51 (4H, m, H_b-1, H_a-6, H-9, H_b-6), δ 1.47 (3H, s, H-18), δ 1.13 (3H, s, H-17), δ 1.09 (3H, s, H-20), δ 1.03-0.97 (2H, m, H-5, H_b-7); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.62 (C-16), δ 145.82

(C-3'), δ 143.29 (C-14), δ 138.31 (C-13), δ 132.06 (C-5'), δ 131.74 (C-8' and C-10'), 130.80 (C-6'), 129.64 (C-7' and C-11'), δ 122.55 (C-9'), δ 118.09 (C-4'), δ 90.26 (C-21), δ 82.74 (C-8), δ 81.57 (C-3), δ 73.04 (C-12), δ 70.56 (C-15), δ 69.70 (C-19), δ 57.92 (C-9), δ 51.65 (C-5), δ 38.14 (C-4), δ 36.34 (C-7), δ 35.91 (C-10), δ 35.60 (C-1), δ 32.72 (C-11), δ 31.75 (C-17), δ 25.96 (C-18), δ 20.93 (C-2), δ 17.29 (C-6), δ 16.40 (C-20); **HRMS (*m/z*):** $[M+H]^+$ = 583.1785, $[M+H+2]^+$ = 585.1785, $[M+H+4]^+$ = 587.1785.

3,19-(NH-3-(4-methylphenyl)-pyrazole) acetal of isoandrographolide (2f)

White solid, yield 84%, m.p. 206.0-208.4°C; **UV (λ_{max})**: 245 nm; **IR (KBr) cm^{-1}**: 3293 (N-H stretch), 3082 (aromatic C-H stretch), 2935 (sp^3 C-H stretch), 1756 (C=O stretch), 1603 & 1447 (conjugated C=C stretch), 1200 and 1106 (C-O stretch), 889, 830 & 775 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.80 (1H, s, H-5'), δ 7.52 (2H, d, J=8.0 Hz, H-7' and H-11'), δ 7.29 (1H, s, H-14), δ 7.24 (2H, d, J=7.92 Hz, H-8' and H-10'), δ 5.83 (1H, s, H-21), δ 4.81 (2H, s, H-15), δ 4.69 (1H, t, J=7.52 Hz, H-12), δ 4.28 (1H, d, J=11.48 Hz, H_a-19), δ 3.65 (1H, dd, J=12.64 Hz, H-3), δ 3.61 (1H, d, J=11.68 Hz, H_b-19), δ 2.45 (1H, m, H_a-11), δ 2.41 (3H, s, C-$\underline{H}_3$), δ 2.37-2.23 (1H, m, H_b-11), δ 2.06-1.98 (1H, m, H_a-1), δ 1.85-1.69 (3H, m, H_a-7, H-2), δ 1.58-1.53 (4H, m, H_b-1, H_a-6, H-9, H_b-6), δ 1.48 (3H, s, H-18), δ 1.12 (3H, s, H-17), δ 1.07 (3H, s, H-20), δ 1.02 -0.99 (2H, m, H-5, H_b-7); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.64 (C-16), δ 145.09 (C-3'), δ 143.27 (C-14), δ 138.31 (C-13), δ 133.99 (C-5'), 129.41 (C-8' and C-10'), 128.20 (C-6'), δ 127.86 (C-7' and C-11'), δ 117.43 (C-4'), δ 90.41 (C-21), δ 82.76 (C-8), δ 81.53 (C-3), δ 73.04 (C-12), δ 70.57 (C-15), δ 69.68 (C-19), δ 57.90 (C-9), δ 51.64 (C-5), δ 38.16 (C-4), δ 36.33 (C-7), δ 35.91 (C-10), δ 35.59 (C-1), δ 32.73 (C-11), δ 31.76 (C-17), δ 25.94 (C-18), 21.30 ($\underline{C}H_3$), δ 20.93 (C-2), δ 17.28 (C-6), δ 16.37 (C-20); **HRMS (*m/z*):** $[M+H]^+$ = 519.2793.

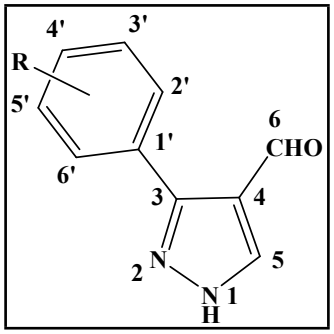
3,19-(NH-3-(4-metoxyphenyl)-pyrazole) acetal of isoandrographolide (2g)

White solid, yield 80%, m.p. 120.0-121.3°C; **UV (λ_{max})**: 250 nm; **IR (KBr) cm^{-1}**: 3299 (N-H stretch), 3081 (aromatic C-H stretch), 2930 (sp^3 C-H stretch), 1755 (C=O stretch), 1605 & 1450 (conjugated C=C stretch), 1284 and 1101 (C-O stretch), 890, 833 & 765 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.81 (1H, s, H-5'), δ 7.56 (2H, d, J=8.56 Hz, H-7' and H-11'), δ 7.29 (1H, s, H-14), δ 6.95 (2H, d, J=8.56 Hz, H-8' and H-10'), δ 5.81 (1H, s, H-21), δ 4.81 (2H, s, H-15), δ 4.69 (1H, dt, J=7.56 Hz, H-12), δ 4.29 (1H, d, J=11.52 Hz, H_a-19), δ 3.85 (-OC$\underline{H}_3$), δ 3.65 (1H, dd, J=12.48 Hz, H-3), δ 3.61 (1H, d, J=11.96 Hz, H_b-19), δ 2.46 (1H, m, H_a-11), δ 2.40-2.19 (1H, m, H_b-11), δ 2.06-1.98 (1H, m, H_a-1), δ 1.86-1.68 (3H,

m, H_a-7, H-2), δ 1.60-1.52 (4H, m, H_b-1, H_a-6, H-9, H_b-6), δ 1.48 (3H, s, H-18), δ 1.12 (3H, s, H-17), δ 1.08 (3H, s, H-20), δ 1.03 -1.00 (2H, m, H-5, H_b-7); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.63 (C-16), δ 159.78 (C-9'), δ 144.91 (C-3'), δ 143.27 (C-14), δ 138.31 (C-13), δ 134.04 (C-5'), δ 129.56 (C-6'), δ 129.28 (C-7' and C-11'), δ 117.26 (C-4'), δ 114.11 (C-8' and C-10'), δ 90.42 (C-21), δ 82.76 (C-8), δ 81.51 (C-3), δ 73.04 (C-12), δ 70.57 (C-15), δ 69.68 (C-19), δ 57.90 (C-9), δ 55.31 (-O<u>C</u>H_3), δ 51.64 (C-5), δ 38.16 (C-4), δ 36.33 (C-7), δ 35.91 (C-10), δ 35.59 (C-1), δ 32.73 (C-11), δ 31.76 (C-17), δ 25.95 (C-18), δ 20.93 (C-2), δ 17.29 (C-6), δ 16.38 (C-20); **HRMS (*m/z*):** $[M+H]^+$ = 535.2811.

3,19-(NH-3-(4-chlorophenyl)-pyrazole) acetal of isoandrographolide (2i)

White solid, yield 78%, m.p. 176-178.1°C; **UV (λ_{max})**: 245 nm; **IR (KBr) cm^{-1}**: 3285 (N-H stretch), 3075 (aromatic C-H stretch), 2931 (sp^3 C-H stretch), 1758 (C=O stretch), 1604 & 1448 (conjugated C=C stretch), 1204 and 1098 (C-O stretch), 1056 (aromatic C-Cl stretch), 889, 839 & 794 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.79 (1H, s, H-5'), δ 7.61 (2H, d, J=8.48 Hz, H-7' and H-11'), δ 7.38 (2H, d, J=8.48 Hz, H-8' and H-10'), δ 7.29 (1H, s, H-14), δ 5.82 (1H, s, H-21), δ 4.81 (2H, s, H-15), δ 4.70 (1H, dt, J=9.12 Hz, H-12), δ 4.30 (1H, d, J=11.52 Hz, H_a-19), δ 3.65 (1H, dd, J=12.8 Hz, H-3), δ 3.61 (1H, d, J=11.52 Hz, H_b-19), δ 2.46 (1H, m, H_a-11), δ 2.38-2.27 (1H, m, H_b-11), δ 2.06-1.99 (1H, m, H_a-1), δ 1.87-1.65 (3H, m, H_a-7, H-2), δ 1.60-1.53 (4H, m, H_b-1, H_a-6, H-9, H_b-6), δ 1.47 (3H, s, H-18), δ 1.12 (3H, s, H-17), δ 1.08 (3H, s, H-20), δ 1.03-0.95 (2H, m, H-5, H_b-7); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.62 (C-16), δ 145.63 (C-3'), δ 143.30 (C-14), δ 138.31 (C-13), δ 134.22 (C-9'), 132.11 (C-5'), δ 130.39 (C-6'), 129.35 (C-8' and C-10'), 128.76 (C-7' and C-11'), δ 117.95 (C-4'), δ 90.32 (C-21), δ 82.75 (C-8), δ 81.56 (C-3), δ 73.03 (C-12), δ 70.56 (C-15), δ 69.70 (C-19), δ 57.93 (C-9), δ 51.65 (C-5), δ 38.15 (C-4), δ 36.34 (C-7), δ 35.91 (C-10), δ 35.61 (C-1), δ 32.72 (C-11), δ 31.75 (C-17), δ 25.96 (C-18), δ 20.93 (C-2), δ 17.29 (C-6), δ 16.39 (C-20); **HRMS (*m/z*):** $[M+H]^+$ = 539.2303, $[M+H+2]^+$ = 541.2303.



(a-i)

3-Phenyl-1H-pyrazole-4-carboxaldehyde (a)

White solid, yield 61%, m.p. 139.1-140.6°C; **UV (λ_{max})**: 255.4 nm; **IR (KBr) cm^{-1}**: 3192 (N-H stretch), 3060 (aromatic C-H stretch), 2850 (aldehyde C-H stretch), 1642 (C=O stretch), 1580 & 1446 (aromatic skeletal bands), 1321 (aromatic C-N stretch), 822 & 772 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, DMSO-d6)**: δ 13.77 (1H, s, H-1), δ 9.90 (1H, s, H-6), δ 8.50 (1H, s, H-5), δ 7.82 (2H, d, J=5.92 Hz, H-2', H-6'), δ 7.50-7.49 (3H, m, H-3', 4' and 5'); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 185.06 (C-6), δ 137.06 (C-5), δ 132.65 (C-1'), δ 130.37 (C-4'), δ 129.47-128.85 (C-2', C-3', C-5'and C-6'), δ 127.84 (C-3), 120.50 (C-4); **HRMS (*m/z*):** $[M-H]^+$ = 171.0539.

3-(3-Chlorophenyl)-1H-pyrazole-4-carboxaldehyde (b)

White solid, yield 72%, m.p. 133.6-135.0°C; **UV (λ_{max})**: 255.8 nm; **IR (KBr) cm^{-1}**: 3181 (N-H stretch), 3064 (aromatic C-H stretch), 2865 (aldehyde C-H stretch), 1641 (C=O stretch), 1575 & 1444 (aromatic skeletal bands), 1330 (aromatic C-N stretch), 1062 (aromatic C-Cl stretch), 825 & 792 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, DMSO-d6)**: δ 13.83 (1H, s, H-1), δ 9.91 (1H, s, H-6), δ 8.65 (1H, s, H-5), δ 7.98 (1H, s, H-2'), δ 7.86 (1H, s, H-6'), δ 7.51 (2H, s, H-4', H-5', overlapped); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 185.10 (C-6), δ 138.50 (C-5), δ 134.74 (C-3'), δ 133.63 (C-1'), δ 130.79 (C-2'), δ 128.93 (C-3), δ 128.45 (C-4', C-5'), δ 127.51 (C-6'), δ 120.49 (C-4); **HRMS (*m/z*):** $[M-H]^+$ = 205.0170, $[M-H+2]^+$ = 207.0170.

3-(3-Bromophenyl)-1H-pyrazole-4-carboxaldehyde (c)

White solid, yield 67%, m.p. 116.5-118.4°C; **UV (λ_{max})**: 256.2 nm; **IR (KBr) cm^{-1}**: 3174 (N-H stretch), 3064 (aromatic C-H stretch), 2870 (aldehyde C-H stretch), 1636 (C=O stretch), 1568 & 1446 (aromatic skeletal bands), 1330 (aromatic C-N stretch), 1024 (aromatic C-Br

stretch), 828 & 791 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, DMSO-d6)**: δ 13.81 (1H, s, H-1), δ 9.91 (1H, s, H-6), δ 8.66 (1H, s, H-5), δ 8.13 (1H, s, H-2'), δ 7.93 (1H, d, J=6.40 Hz, H-6'), δ 7.63 (1H, d, J=6.44 Hz, H-4'), δ 7.43 (1H, t, J=7.0 Hz, H-5'); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 185.03 (C-6), δ 138.45 (C-5), δ 134.97 (C-1'), δ 131.79 (C-2'), δ 131.21 (C-5'), δ 130.99 (C-4'), δ 127.82 (C-3), δ 122.09 (C-3'), δ 120.60 (C-4); **HRMS (*m/z*):** $[M-H]^+$ = 248.9655, $[M-H+2]^+$ = 250.9655

3-(4-Fluorophenyl)-1H-pyrazole-4-carboxaldehyde (d)

White solid, yield 63%, m.p. 165.1-166.8°C; **UV (λ_{max})**: 254.5 nm; **IR (KBr) cm^{-1}**: 3187 (N-H stretch), 3060 (aromatic C-H stretch), 2845 (aldehyde C-H stretch), 1651 (C=O stretch), 1580 & 1442 (aromatic skeletal bands), 1317 (aromatic C-N stretch), 1217 (aromatic C-F stretch), 836 & 781 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, DMSO-d6)**: δ 13.78 (1H, s, H-1), δ 9.89 (1H, s, H-6), δ 8.46 (1H, s, H-5), δ 7.91 (2H, dd, J= 8.4 Hz, H-2' and H-6'), δ 7.33 (2H, dd, J=8.4 Hz, H-3' and H-5'); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 185.18 (C-6), δ 163.06 (C-4', d, J_{C-F}=244.82 Hz), δ 138.50 (C-5), δ 131.23-131.15 (C-1', C-2' and C-6'), δ 128.50 (C-3), 120.10 (C-4), δ 116.00 (C-3' and C-5', d, J_{C-F}=21.23 Hz); **HRMS (*m/z*):** $[M-H]^+$ = 189.0448.

3-(4-Bromophenyl)-1H-pyrazole-4-carboxaldehyde (e)

White solid, yield 58%, m.p. 130.2-132.8°C; **UV (λ_{max})**: 259.4 nm; **IR (KBr) cm^{-1}**: 3186 (N-H stretch), 3050 (aromatic C-H stretch), 2854 (aldehyde C-H stretch), 1635 (C=O stretch), 1568 & 1443 (aromatic skeletal bands), 1320 (aromatic C-N stretch), 1027 (aromatic C-Br stretch), 835 & 790 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, MeOD)**: δ 13.58 (1H, s, H-1), δ 9.92 (1H, s, H-6), δ 8.42 (1H, s, H-5), δ 7.76-7.62 (4H, m, H-2', H-3', H-5' and H-6'); **^{13}C NMR (100 MHz, MeOD)**: δ 185.06 (C-6), δ 138.09 (C-5), δ 132.40 (C-1'), δ 131.78 (C-2' and C-6'), δ 130.85 (C-3' and C-5'), δ 127.08 (C-3), δ 122.48 (C-4'), δ 120.55 (C-4); **HRMS (*m/z*):** $[M-H]^+$ = 248.9637, $[M-H+2]^+$ = 250.9637

3-(4-Methylphenyl)-1H-pyrazole-4-carboxaldehyde (f)

White solid, yield 63%, m.p. 114.5-116.3°C; **UV (λ_{max})**: 257.2 nm; **IR (KBr) cm^{-1}**: 3187 (N-H stretch), 3058 (aromatic C-H stretch), 2855 (aldehyde C-H stretch), 1653 (C=O stretch), 1575 & 1455 (aromatic skeletal bands), 1317 (aromatic C-N stretch), 829 & 768 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, MeOD)**: δ 13.60 (1H, s, H-1), δ 9.88 (1H, s, H-

6), δ 8.37 (1H, s, H-5), δ 7.63 (2H, d, J= 8.24, H-2' and H-6'), δ 7.33 (2H, d, J=8.26, H-3' and H-5'), δ 2.42 (3H, s, C-$\underline{H}_3$); **^{13}C NMR (100 MHz, MeOD)**: δ 185.23 (C-6), δ 138.84 (C-5), δ 134.60 (C-4'), δ 129.42 (C-3' and C-5'), δ 128.82 (C-1'), δ 128.50 (C-2' and C-6'), δ 124.40 (C-3), δ 119.48 (C-4), δ 19.96 ($\underline{C}H_3$); **HRMS (*m/z*):** $[M-H]^+$ = 187.0391.

3-(4-Methoxyphenyl)-1H-pyrazole-4-carboxaldehyde (g)

White solid, yield 65%, m.p. 155.5-156.4°C; **UV (λ_{max})**: 284 nm; **IR (KBr) cm^{-1}**: 3187 (N-H stretch), 3051 (aromatic C-H stretch), 2858 (aldehyde C-H stretch), 1636 (C=O stretch), 1579 & 1453 (aromatic skeletal bands), 1324 (aromatic C-N stretch), 839 & 757 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, MeOD)**: δ 13.47 (1H, s, H-1), δ 9.86 (1H, s, H-6), δ 8.12 (1H, s, H-5), δ 7.67 (2H, d, J=8.28 Hz, H-2' and H-6'), δ 7.05 (2H, d, J=8 Hz, H-3' and H-5'), δ 3.85 (3H, s, -OC$\underline{H}_3$); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 185.23 (C-6), δ 160.08 (C-4'), δ 137.22 (C-5), δ 130.44 (C-1', C-2' and C-6'), δ 125.20 (C-3), δ 120.10 (C-4), δ 114.61 (C-3' and C-5'), δ 55.72 (O-$\underline{C}H_3$); **HRMS (*m/z*):** $[M+H]^+$ = 203.0807.

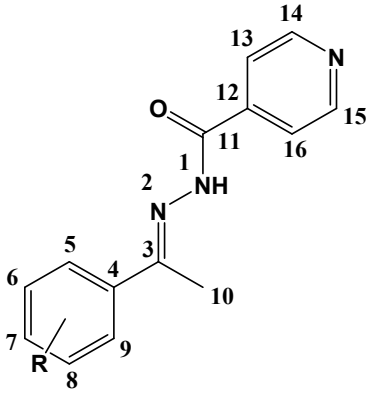
3-(3-Fluorophenyl)-1H-pyrazole-4-carboxaldehyde (h)

White solid, yield 66%, m.p. 131.2-133.5°C; **UV (λ_{max})**: 255.4 nm; **IR (KBr) cm^{-1}**: 3169 (N-H stretch), 3071 (aromatic C-H stretch), 2874 (aldehyde C-H stretch), 1648 (C=O stretch), 1589 & 1464 (aromatic skeletal bands), 1336 (aromatic C-N stretch), 1221 (aromatic C-F stretch), 830 & 781 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, DMSO-d6)**: δ 13.80 (1H, s, H-1), δ 9.92 (1H, s, H-6), δ 8.66 (1H, s, H-5), δ 8.13 (1H, s, H-2'), δ 7.77 (1H, d, J=8.20 Hz, H-6'), δ 7.50 (1H, dd, J=7.48 Hz, H-4'), δ 7.26 (1H, t, J=8.08 Hz, H-5'); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 185.10 (C-6), δ 162.65 (C-3',d, J_{C-F} = 241.23), δ 142.66 (C-5), δ 134.96 (C-1',d, J_{C-F} = 8.33 Hz), δ 130.82 (C-5',d, J_{C-F} = 8.32 Hz), δ 125.36 (C-3), δ 124.87 (C-6'), δ 120.62 (C-4), δ 115.83 (C-2',d, J_{C-F} = 20.88), δ 115.44 (C-4', J_{C-F} = 22.95); **HRMS (*m/z*):** $[M-H]^+$ = 189.0450.

3-(4-Chlorophenyl)-1H-pyrazole-4-carboxaldehyde (i)

White solid, yield 68%, m.p. 132.9-134.5°C; **UV (λ_{max})**: 260.3 nm; **IR (KBr) cm^{-1}**: 3176 (N-H stretch), 3063 (aromatic C-H stretch), 2869 (aldehyde C-H stretch), 1675 (C=O stretch), 1570 & 1445 (aromatic skeletal bands), 1335 (aromatic C-N stretch), 1060 (aromatic C-Cl stretch), 830 & 787 (aromatic C-H out of plane bending); **^{1}H NMR (400 MHz, MeOD)**: δ 13.77 (1H,

s, H-1), δ 9.90 (1H, s, H-6), δ 8.63 (1H, s, H-5), δ 7.91 (2H, br-s, H-2' and H-6'), δ 7.54 (2H, br-s, H-3' and H-5'); **^{13}C NMR (100 MHz, MeOD)**: δ 185.13 (C-6), δ 138.09 (C-5), δ 133.77 (C-4'), δ 131.57 (C-1'), δ 130.64 (C-2' and C-6'), δ 128.91 (C-3' and C-5'), δ 126.73 (C-3), δ 120.52 (C-4); **HRMS (*m/z*):** $[M+H]^+$ = 207.0564, $[M+H+2]^+$ = 209.0564



(A-I)

(*E*)-*N*'-(1-ethylidene)isonicotinohydrazide (A)

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 (1H, s, H-1), δ 8.78 (2H, br-s, H-14 and H-15), δ 7.76 (2H, br-s, H-5 and H-9), δ 7.63 (2H, br-s, H-13 and H-16), δ 7.39 (3H, m, H-6, H-7 and H-8), δ 2.34 (3H, s, H-10); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 168.72 (C-11), δ 150.84 (C-14 and C-15), δ 149.76 (C-3), δ 140.83 (C-12), δ 137.29 (C-4), δ 129.7653 (C-6 and C-8), δ 128.60 (C-7), δ 126.20 (C-5 and C-9), δ 123.74 (C-13); **MS (*m/z*):** $[M]^+$ = 239.15.

(E)-N'-(1-(3-Chlorophenyl) ethylidene) isonicotinohydrazide (B)

^{1}H NMR (400 MHz, DMSO-d6): δ 11.16 (1H, s, H-1), δ 8.78 (2H, d, J=5.0 Hz, H-14, H-15), δ 7.90 (1H, s, H-5), δ 7.82 (3H, br-s, H-9, H-13 and H-16), δ 7.61-7.49 (2H, m, H-7 and H-8), δ 2.39 (3H, s, H-10); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 163.21 (C-11), δ 150.60 (C-14 and C-15), δ 149.98 (C-3), δ 141.46 (C-12), δ 133.78 (C-4), δ 130.81 (C-8), δ 129.91 (C-6), δ 126.55 (C-5), δ 125.75 (C-9), δ 122.40 (C-13 and C-16), δ 15.20 (C-10); **MS (*m/z*):** $[M]^+$ = 273.10, $[M+2]^+$ = 275.10.

(*E*)-*N*'-(1-(3-bromophenyl)ethylidene)isonicotinohydrazide (C)

^{1}H NMR (400 MHz, DMSO-d6): δ 11.11 (1H, s, H-1), δ 8.78 (2H, d, J=5.24 Hz, H-14, H-15), δ 8.04 (1H, s, H-5), δ 7.85 (2H, d, J=7.76 Hz, H-9), δ 7.81 (2H, d, J=5.28 Hz, H-13 and H-16), δ 7.66 (1H, d, J=7.72 Hz, H-7), δ 7.43 (1H, t, J=7.88 Hz, H-8), δ 2.38 (3H, s, H-10); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 163.22 (C-11), δ 150.60 (C-14 and C-15), δ 149.85 (C-3), δ 141.95 (C-12), δ 132.81 (C-4), δ 131.09 (C-8), δ 129.39 (C-6), δ 126.60 (C-7), δ 122.40 (C-9, C-13 and C-16), δ 122.36 (C-5), δ 15.19 (C-10); **MS (*m/z*):** $[M-H]^+$ = 317.00, $[M-H+2]^+$ = 319.00.

(*E*)-*N*'-(1-(4-bromophenyl)ethylidene)isonicotinohydrazide (E)

^{1}H NMR (400 MHz, DMSO-d6): δ 11.07 (1H, s, H-1), δ 8.77 (2H, d, J=4.88 Hz, H-14, H-15), δ 7.82-7.80 (4H, m, H-5, H-9, H-13 and H-16), δ 7.66 (2H, d, J=8.36 Hz, H-6, H-8), δ 2.37 (3H, s, H-10); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 163.09 (C-11), δ 150.59 (C-14 and C-15), δ 149.90 (C-3), δ 141.51 (C-12), δ 133.18 (C-4), δ 131.85 (C-8), δ 129.05 (C-5 and C-9), δ 123.73 (C-7), δ 122.38 (C-13 and C-16), δ 15.08 (C-10); **MS (*m/z*):** $[M-H]^+$ = 317.00, $[M-H+2]^+$ = 319.00.

(E)-N'-(1-(4-fluorophenyl)ethylidene)isonicotinohydrazide (D)

^{1}H NMR (400 MHz, DMSO-d6): δ 11.05 (1H, s, H-1), δ 8.77 (2H, br-s, H-14 and H-15), δ 7.93 (2H, br-s, H-13), δ 7.80 (2H, br-s, H-5 and H-9), δ 7.29 (2H, br-s, H-6, H-8), δ 2.38 (3H, s, H-10); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 163.66 (d, J=242.68, C-7), δ 162.94 (C-11), δ 150.59 (C-14 and C-15), δ 149.90 (C-3), δ 141.56 (C-12), δ 134.80 (C-4), δ 129.32 (d, J=33.68, C-5 and C-9), δ 122.35 (C-13 and C-16), δ 115.80 (d, J=85.88, C-6 and C-8), δ 15.31 (C-10); **MS (*m/z*):** $[M]^+$ = 250.20.

(*E*)-*N*'-(1-(4-methylphenyl)ethylidene)isonicotinohydrazide (F)

^{1}H NMR (400 MHz, DMSO-d6): δ 9.49 (1H, s, H-1), δ 8.76 (2H, d, J=4.80 Hz, H-14 and H-15), δ 7.75 (2H, d, J= 4.36 Hz, H-13 and H-16), δ 7.52 (2H, d, J=7.88 Hz, H-5 and H-9), δ 7.16 (2H, d, J=7.84 Hz, H-6, H-8), δ 2.36 (3H, s, $C\underline{H}_3$), δ 2.33 (3H, s, H-10); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 162.02 (C-11), δ 149.69 (C-14 and C-15), δ 149.32 (C-3), δ 140.99 (C-12), δ 140.54 (C-7), δ 134.59 (C-4), δ 129.29 (C-6 and C-8), δ 126.26 (C-5 and C-9), δ 123.78 (C-13 and C-16), δ 115.80 (C-6 and C-8), δ 21.30 ($\underline{C}H_3$), δ 12.68 (C-10); **MS (*m/z*):** $[M+H]^+$ = 254.25.

(*E*)-*N*'-(1-(4-methoxyphenyl)ethylidene)isonicotinohydrazide (G)

^{1}H NMR (400 MHz, DMSO-d6): δ 10.96 (1H, s, H-1), δ 8.76 (2H, d, J=5.60 Hz, H-14 and H-15), δ 7.83 (2H, d, J=8.72 Hz, H-5 and H-9), δ 7.80 (2H, d, J=5.56 Hz, H-13 and H-16), δ 7.00 (2H, d, J=8.72 Hz, H-6 and H-8), δ 3.81 (3H, s, O$\underline{C}H_3$), δ 2.34 (3H, s, H-10); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 162.63 (C-11), δ 161.10 (C-7), δ 150.59 (C-14 and C-15), δ 149.86 (C-3), δ 141.68 (C-12), δ 130.61 (C-4), δ 128.60 (C-5 and C-9), δ 122.28 (C-13 and C-16), δ 114.21 (C-6 and C-8), δ 55.73 (O$\underline{C}H_3$), δ 15.16 (C-10); **MS (*m/z*):** $[M]^+$ = 269.20.

(E)-N'-(1-(3-Fluorophenyl)ethylidene)isonicotinohydrazide (H)

^{1}H NMR (400 MHz, DMSO-d6): δ 11.10 (1H, s, H-1), δ 8.78 (2H, d, J=4.76 Hz, H-14 and H-15), δ 7.81 (2H, d, J=4.80 Hz, H-13 and H-16), δ 7.71 (1H, d, J=7.68 Hz, H-5), δ 7.66 (1H, d, J=10.76 Hz, H-9), δ 7.50 (1H, dd, J=10.76 Hz, H-7), δ 7.30 (1H, t, J=8.16 Hz, H-8), δ 2.38 (3H, s, H-10); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 163.50 (C-6), δ 161.46 (C-11), δ 150.60 (C-14 and C-15), δ 149.92 (C-3), δ 141.49 (C-12), δ 140.86 (C-4), δ 130.90 (C-8), δ 123.30 (C-9), δ 122.39 (C-13 and C-16), δ 116.97 (C-7), δ 113.50 (C-5), δ 15.20 (C-10); **MS (*m/z*):** $[M+H]^+$ = 258.10.

(*E*)-*N*'-(1-(4-chlorophenyl)ethylidene)isonicotinohydrazide (I)

^{1}H NMR (400 MHz, DMSO-d6): δ 11.08 (1H, s, H-1), δ 8.77 (2H, d, J=4.56 Hz, H-14, H-15), δ 7.89 (2H, d, J=8.40 Hz, H-5, H-9), δ 7.81 (2H, d, J=4.92 Hz, H-13), δ 7.52 (2H, d, J=8.36 Hz, H-6, H-8), δ 2.38 (3H, s, H-10); **^{13}C NMR (100 MHz, DMSO-d6)**: δ 163.08 (C-11), δ 150.59 (C-14 and C-15), δ 149.93 (C-3), δ 141.51 (C-12), δ 137.12 (C-7), δ 134.93 (C-4), δ 128.92 (C-6 and C-8), δ 128.79 (C-5 and C-9), δ 122.38 (C-13 and C-16), δ 15.14 (C-10); **MS (*m/z*):** $[M-H]^+$ = 272.10, $[M+2]^+$ = 274.10.

Characterization

The UV-Vis spectra of all 3-aryl-1H-pyrazole-4-carbaldehydes exhibited bands between 254 to 284 nm. In the IR spectra, peaks at ~ 3180 cm^{-1} and ~3060 cm^{-1} correspond to the NH and aromatic CH stretching bands respectively. While the C=O peak appeared in the range 1675-1635 cm^{-1}. In ^{1}H NMR spectra of the carbaldehydes, the peak at ~ δ 13.70 is due to the presence of N$\underline{H}$. All the aromatic proton signals appeared between ~ δ 9.90 to 7.30. Whereas in ^{13}C NMR spectra, the $\underline{C}$=O peak appeared at ~ δ 185.00 and all the aromatic carbon peaks are discernible within the range ~ δ 163.00 - δ 116.00.

The UV-Vis spectra exhibited bands between 230 and 250 nm for all the acetals. In the IR spectra of 3,19-(NH-3-aryl-pyrazole) acetals of andrographolide, a peak in the range 3520-3401 cm^{-1} observed for –OH whereas a peak at ~1675 cm^{-1} corresponds to exocyclic C=C groups. These peaks were absent for 3,19-(NH-3-aryl-pyrazole) acetals of isoandrographolide. -NH stretching peak in all the acetals appeared in the range 3321-3270 cm^{-1}. The presence of the C-H stretching band within the 3087-3064 cm^{-1} range and the aromatic skeletal bands spanning from 1600 to 1447 cm^{-1}, confirm the existence of the aromatic group. The band situated at 2944-2930 cm^{-1} corresponds to the sp^3 C-H stretch originating from the diterpene moiety. The peak at ~1755 cm^{-1} corresponds to the carbonyl group (C=O) of the lactone moiety. Distinct absorptions at approximately 1200 and 1100 cm^{-1} can be attributed to the C-O stretching bands. Compounds with aryl chloride have bands at ~1150 cm^{-1} (Ar-Cl stretch). Compounds with aryl fluorides showed a band around 1234 and 1219 cm^{-1} (Ar-F stretch), and compounds with aryl bromides have a band between 1018-1010 cm^{-1} (Ar-Br stretch). Furthermore, the C-H out-of-plane bending vibrations of the aromatic ring were observed within the 890 to 773 cm^{-1} range.

In the ^1H NMR spectra of all the acetals, the signal around δ 7.80 is attributed to the presence of H-5', while peaks within the range of δ 7.90 to 6.95 correspond to the aromatic protons linked to the pyrazole ring (H-7' to H-11'). The proton signal for the unsaturated lactone (H-14) in 3,19-(NH-3-aryl-pyrazole) acetals of isoandrographolide is observable at ~ δ 7.29. Additionally, the peak at around δ 6.95 corresponds to H-12 in 3,19-(NH-3-aryl-pyrazole) acetals of andrographolide. Across all compounds, a singlet peak at ~ δ 5.82 is for H-21. H-19, H-15 and H-12 protons in the case of 3,19-(NH-3-aryl-pyrazole) acetals of isoandrographolide and H-19, H-17, H-15, H-14 and H-12 protons in the case of 3,19-(NH-3-aryl-pyrazole) acetals of andrographolide were deshielded and appeared around δ 5.00-3.61. For 3,19-(NH-3-aryl-pyrazole) acetals of isoandrographolide, protons (H-17, H-18 and H-20) of the $-CH_3$ groups were identified by three singlets in the range of ~ δ 1.50-1.11. In 3,19-(NH-3-aryl-pyrazole) acetals of andrographolide, the protons (H-18 and H-20) of the $-CH_3$ group were identified by two singlets at ~ δ 1.50 and ~ δ 0.85. The $-OCH_3$ (H-18') and $-CH_3$ (H-18') substituted derivatives showed singlets at ~ δ 3.85 and δ 2.41.

In the ^{13}C NMR spectra, signals approximately within the range of δ 173-170, confirm the presence of a carbonyl group (C=O). The carbons in the pyrazole ring, and aromatic ring, and olefin carbons were identified in the ~ δ 163 to 110 range. Notably, in the case of 3,19-(NH-3-

aryl-pyrazole) acetals of isoandrographolide, the olefin carbons such as C-8 and C-17 are absent, leading to the absence of a signal around δ 110. A distinct signal around δ 90, associated with C-21 bonded to two oxygen atoms, strongly supports the formation of acetals. Carbon signals related to oxygen atoms (-O-C) were observed within the range of δ 82 to 66. Peaks corresponding to the $–OCH_3$ group were clearly discernible at approximately δ 55. Furthermore, as anticipated, signals corresponding to –C, –CH, $–CH_2$, and $–CH_3$ groups were evident in the range of δ 59 to 16. The complete characterization and spectral data of the compounds (**a-i**, **1a-1h**, **2a-2g** and **2i**) is provided in the supplementary information.

Spectra of all the synthesized compounds

NH-Pyr-ADG Acetal (1a)

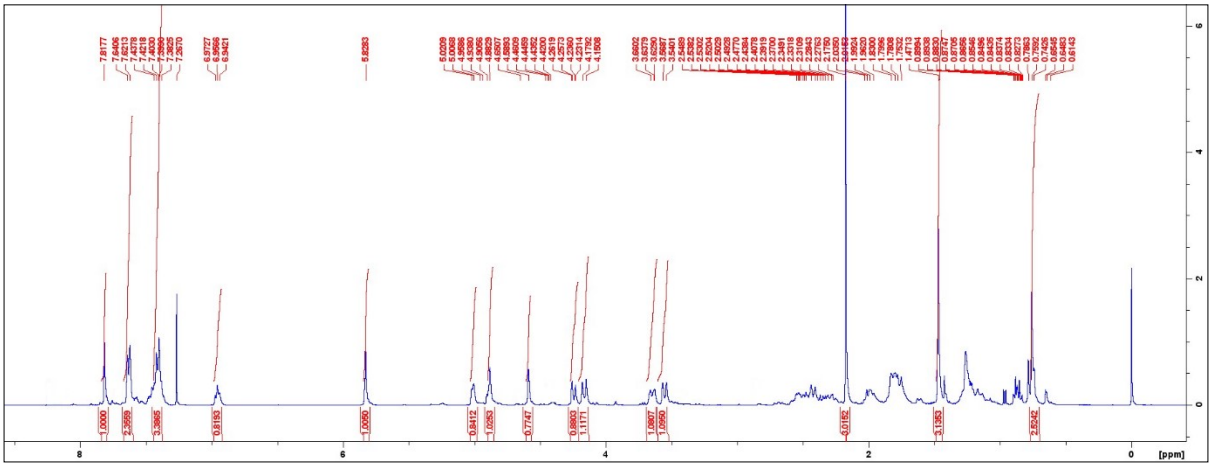


Figure S1: ^{1}H NMR spectrum of NH-Pyr-ADG Acetal (**1a**)

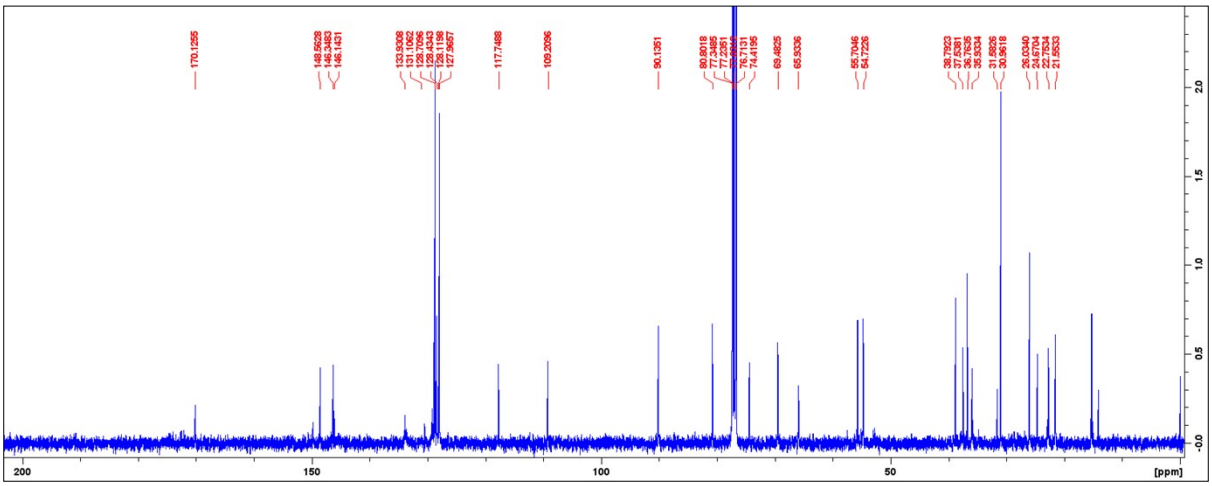


Figure S2: ^{13}C NMR spectrum of NH-Pyr-ADG Acetal (**1a**)

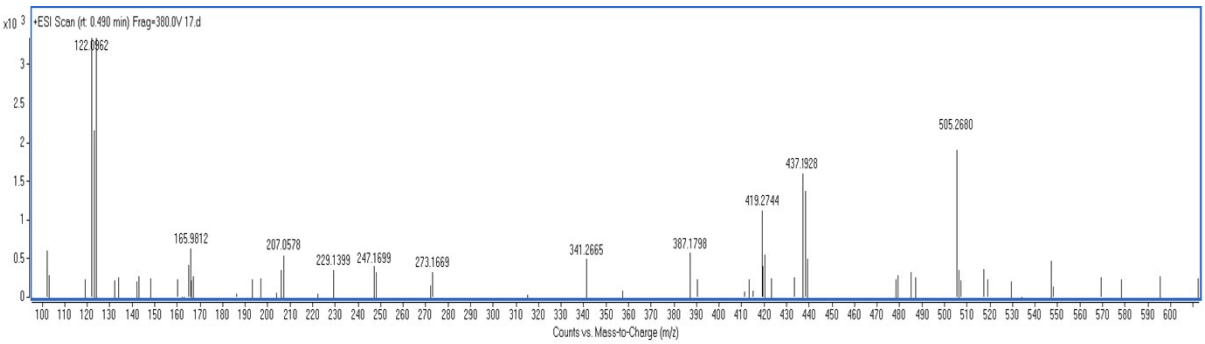


Figure S3: HRMS of NH-Pyr-ADG Acetal (**1a**)

3-Cl- NH-Pyr-ADG Acetal (1b)

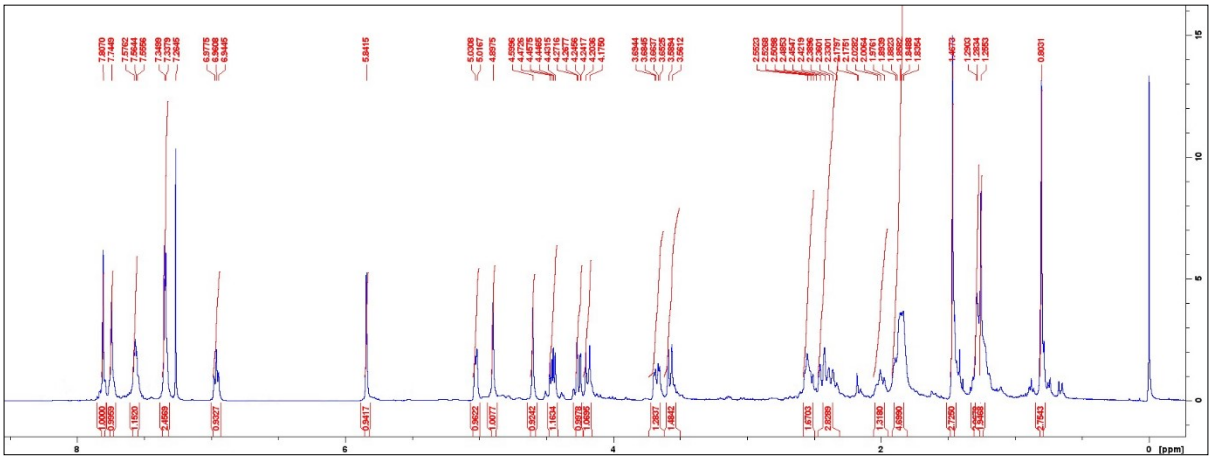


Figure S4: ^{1}H NMR spectrum of 3-Cl- NH-Pyr-ADG Acetal (**1b**)

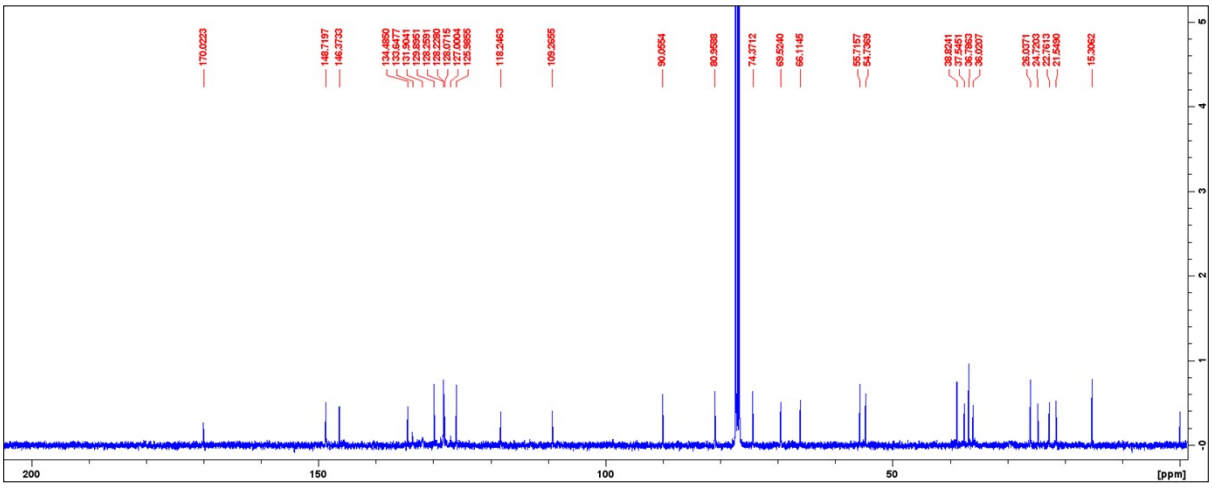


Figure S5: ^{13}C NMR spectrum of 3-Cl- NH-Pyr-ADG Acetal (**1b**)

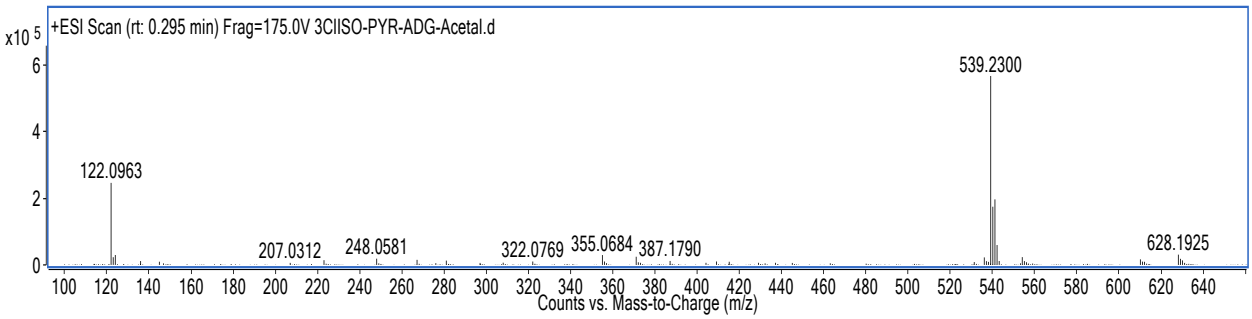


Figure S6: HRMS of 3-Cl-NH-Pyr-ADG Acetal (**1b**)

3-Br-NH-Pyr-ADG Acetal (1c)

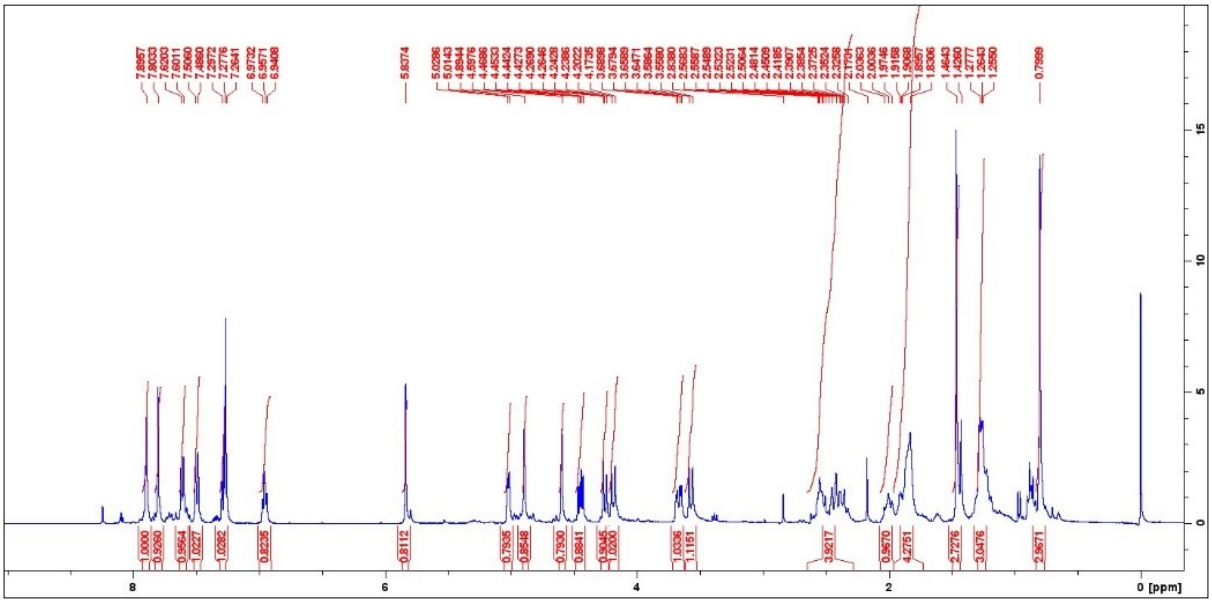


Figure S7: ^{1}H NMR spectrum of 3-Br-NH-Pyr-ADG Acetal (**1c**)

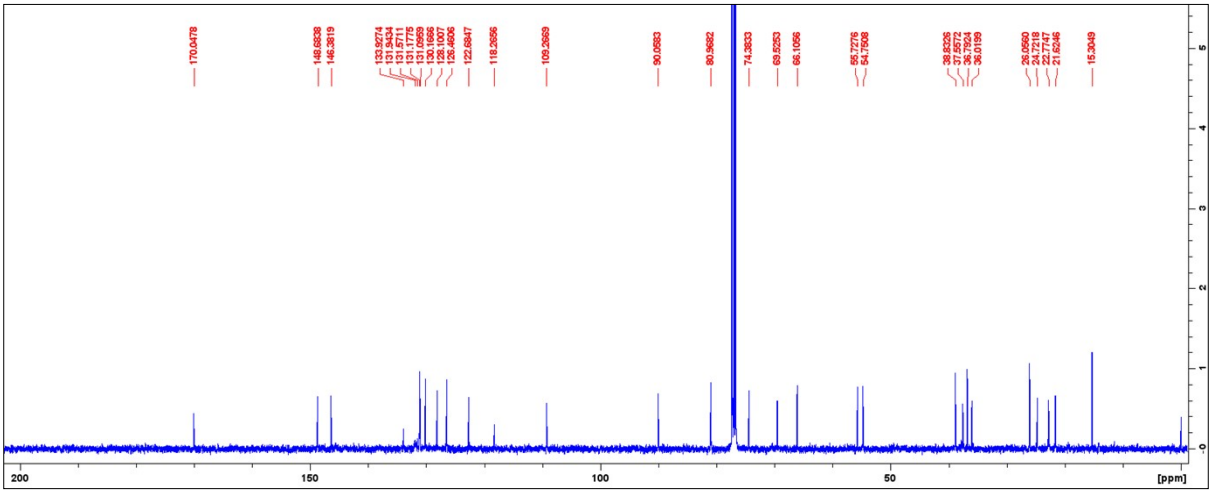


Figure S8: ^{13}C NMR spectrum of 3-Br-NH-Pyr-ADG Acetal (**1c**)

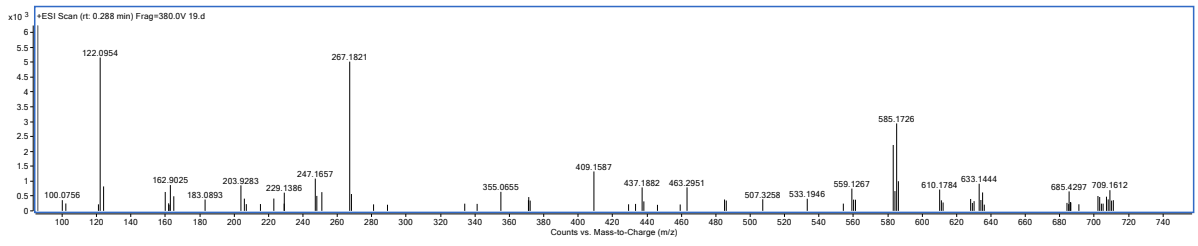


Figure S9: HRMS of 3-Br-NH-Pyr-ADG Acetal (**1c**)

4-F-NH-Pyr-ADG Acetal (1d)

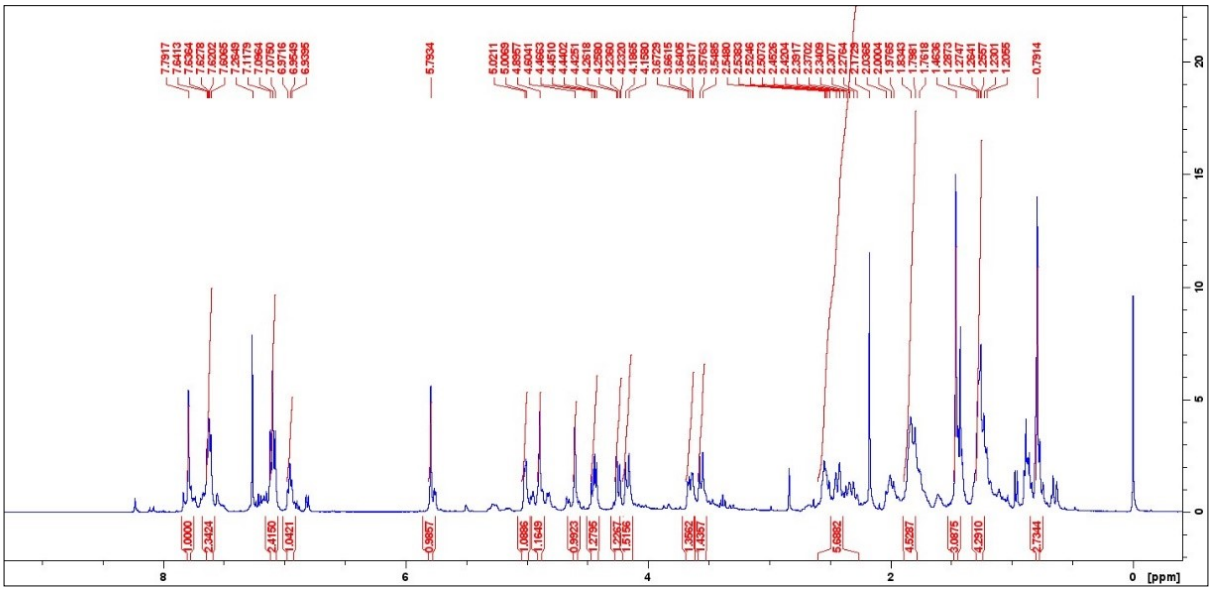


Figure S10: ^{1}H NMR spectrum of 4-F-NH-Pyr-ADG Acetal (**1d**)

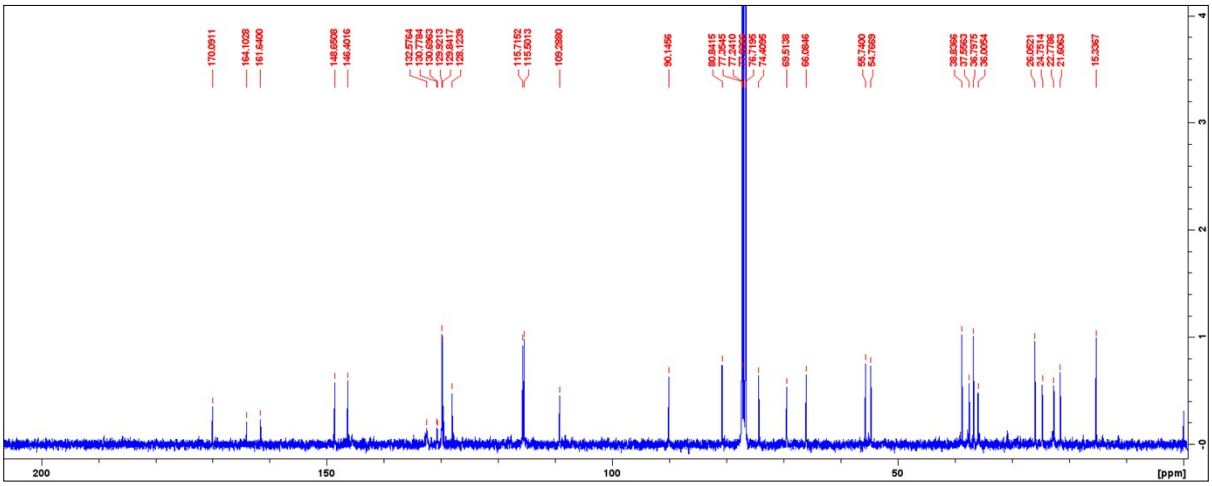


Figure S11: ^{13}C NMR spectrum of 4-F-NH-Pyr-ADG Acetal (**1d**)

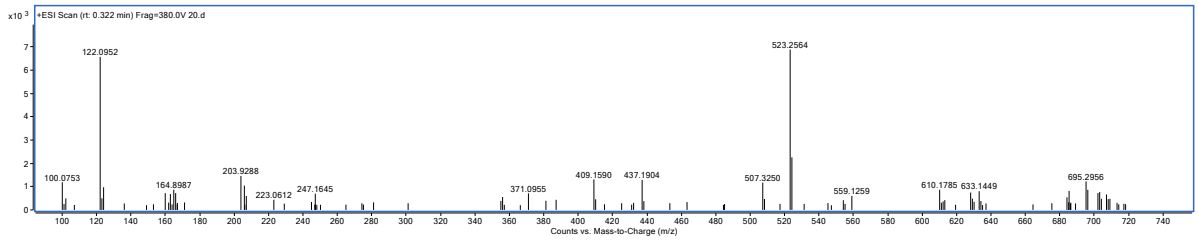


Figure S12: HRMS of 4-F-NH-Pyr-ADG Acetal (**1d**)

4-Br-NH-Pyr-ADG Acetal (1e)

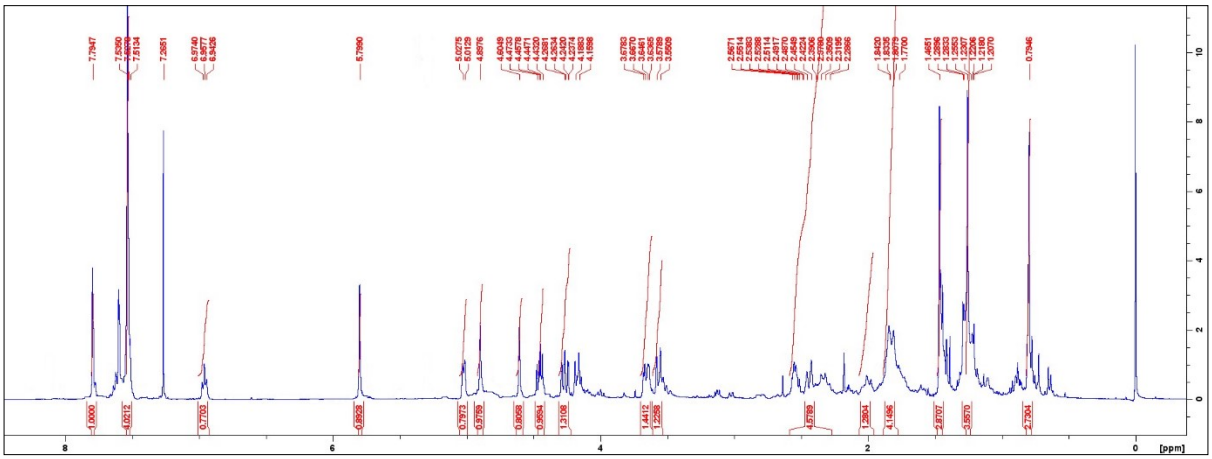


Figure S13: ^{1}H NMR spectrum of 4-Br-NH-Pyr-ADG Acetal (**1e**)

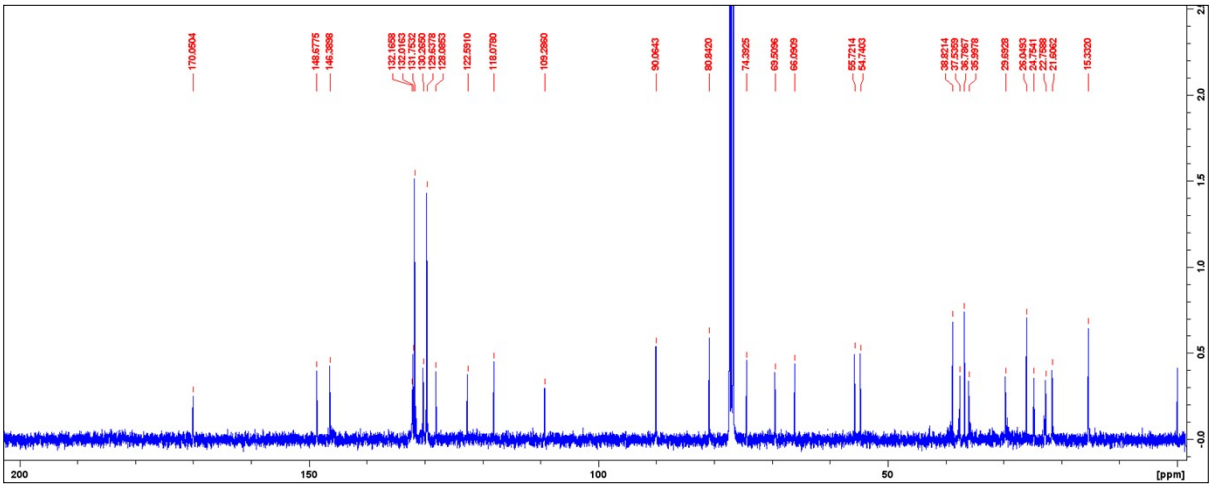


Figure S14: ^{13}C NMR spectrum of 4-Br-NH-Pyr-ADG Acetal (**1e**)

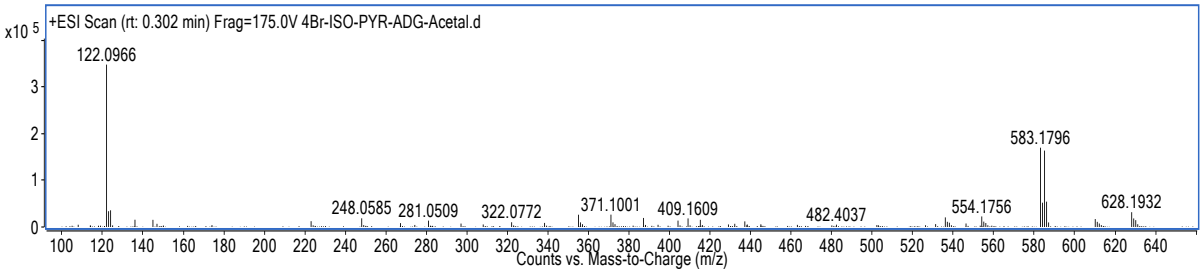


Figure S15: HRMS of 4-Br-NH-Pyr-ADG Acetal (**1e**)

4-CH_3-NH-Pyr-ADG Acetal (1f)

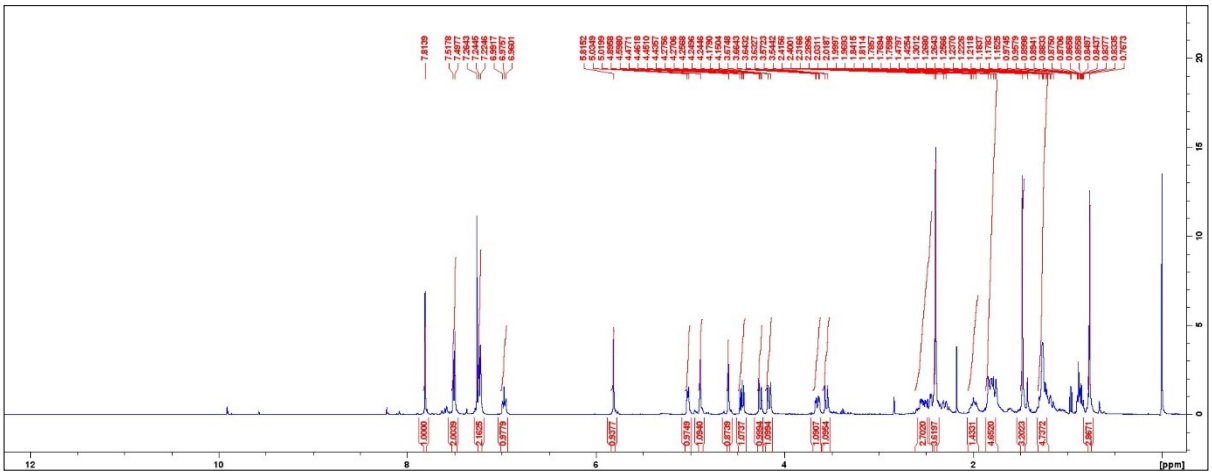


Figure S16: ^{1}H NMR spectrum of 4-CH_3-NH-Pyr-ADG Acetal (**1f**)

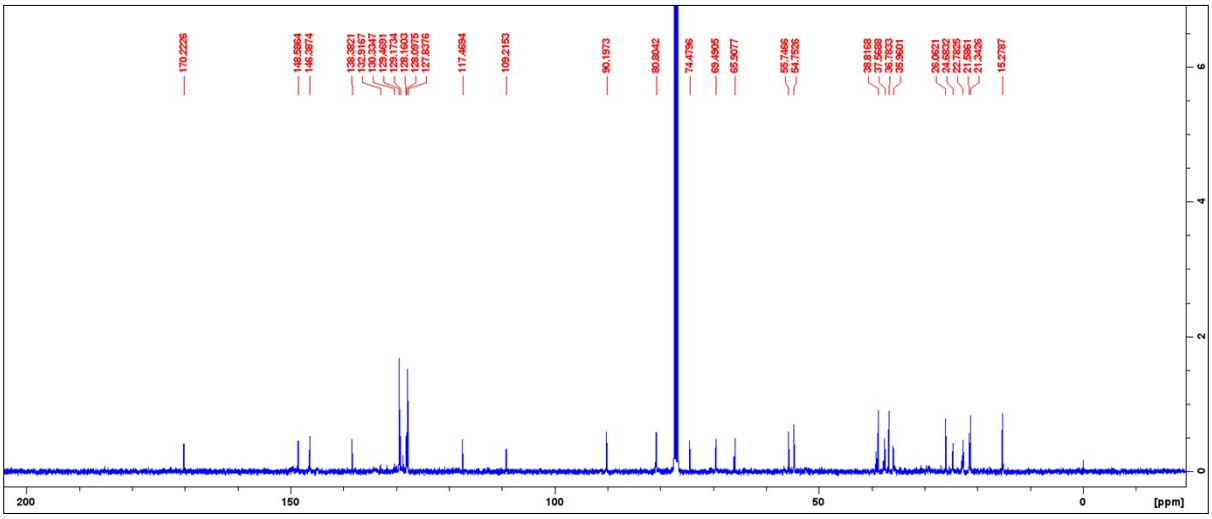


Figure S17: ^{13}C NMR spectrum of 4-CH_3-NH-Pyr-ADG Acetal (**1f**)

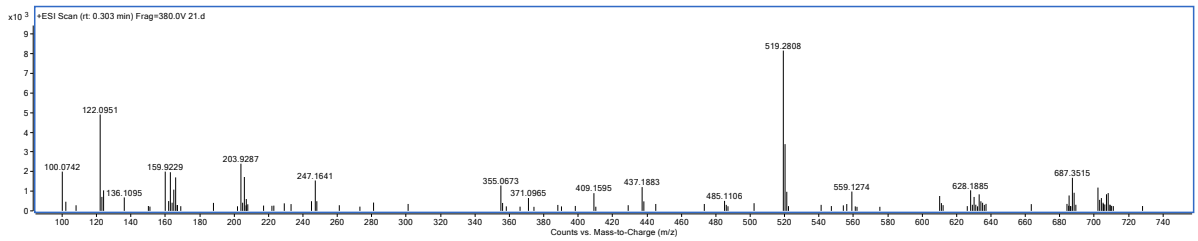


Figure S18: HRMS of 4-CH_3-NH-Pyr-ADG Acetal (**1f**)

4-OCH$_3$-NH-Pyr-ADG Acetal (1g)

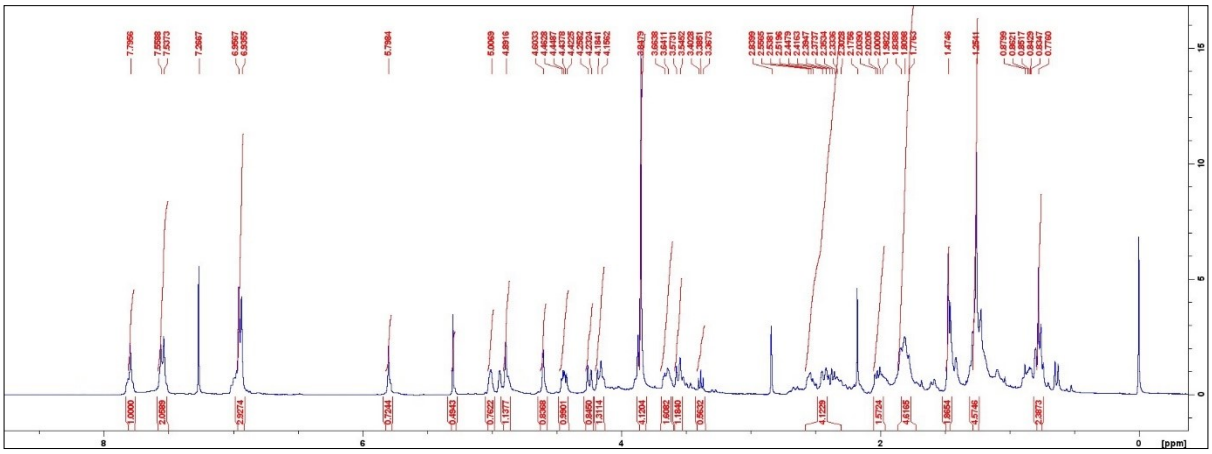


Figure S19: ^{1}H NMR spectrum of 4-OCH$_3$-NH-Pyr-ADG Acetal (**1g**)

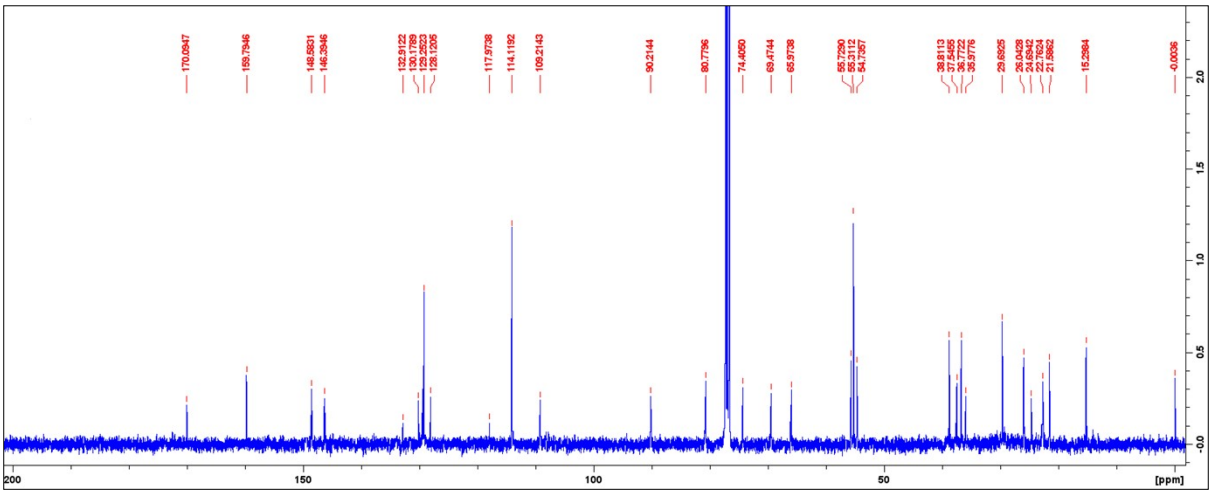


Figure S20: ^{13}C NMR spectrum of 4-OCH$_3$-NH-Pyr-ADG Acetal (**1g**)

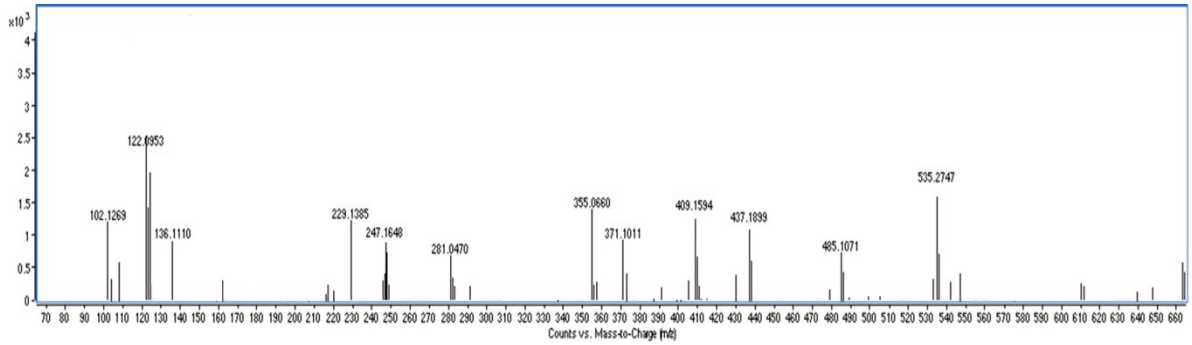


Figure S21: HRMS of 4-OCH$_3$-NH-Pyr-ADG Acetal (**1g**)

3-F-NH-Pyr-ADG Acetal (1h)

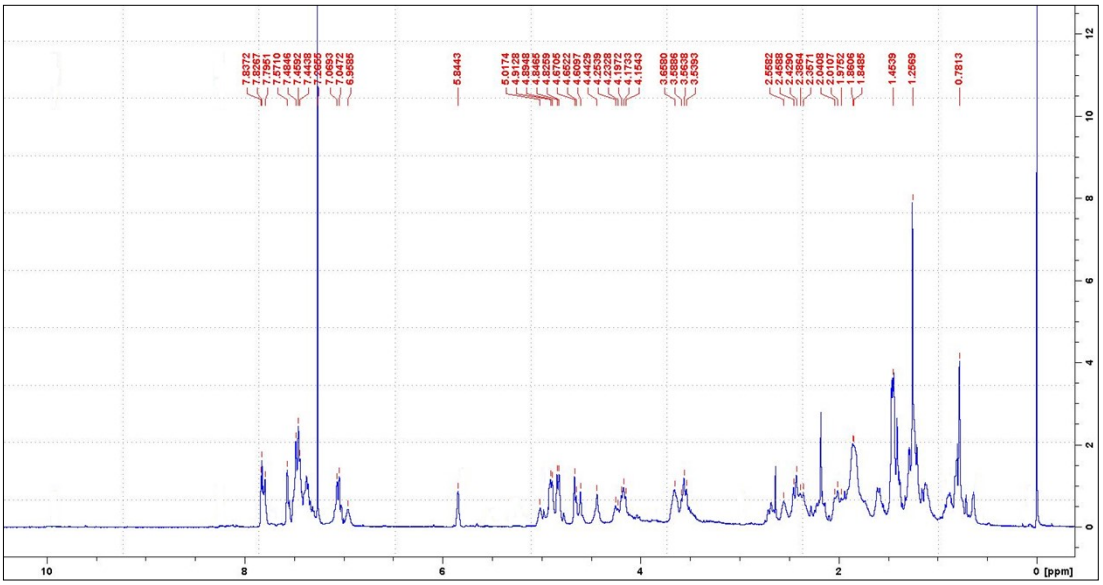


Figure S22: ^{1}H NMR spectrum of 3-F-NH-Pyr-ADG Acetal (**1h**)

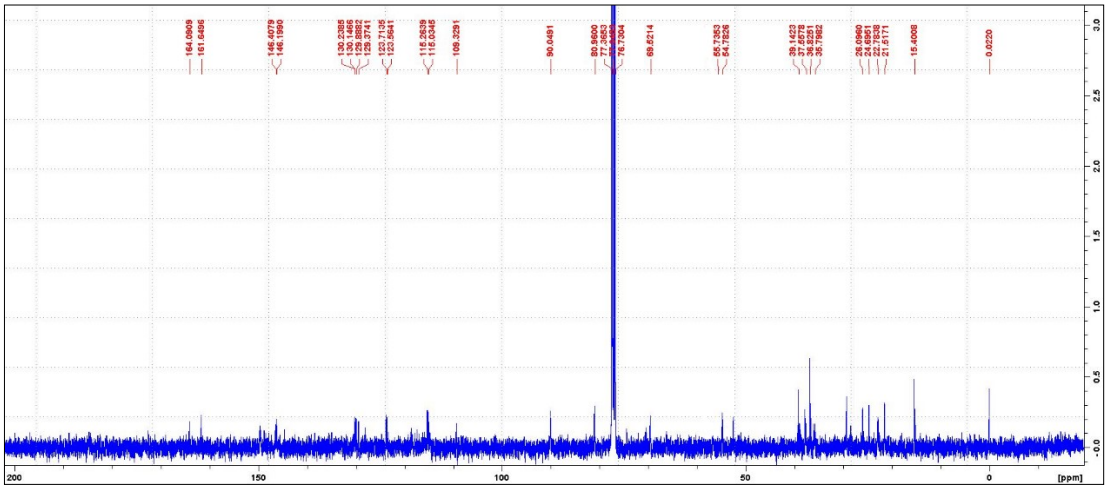


Figure S23: ^{13}C NMR spectrum of 3-F-NH-Pyr-ADG Acetal (**1h**)

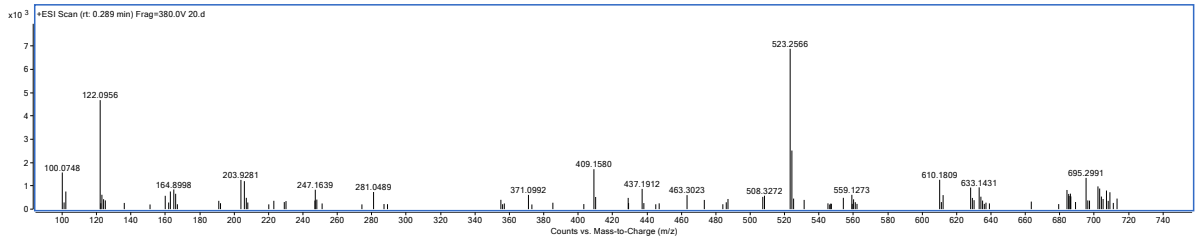


Figure S24: HRMS of 3-F-NH-Pyr-ADG Acetal (**1h**)

NH-Pyr-ISOADG Acetal (2a)

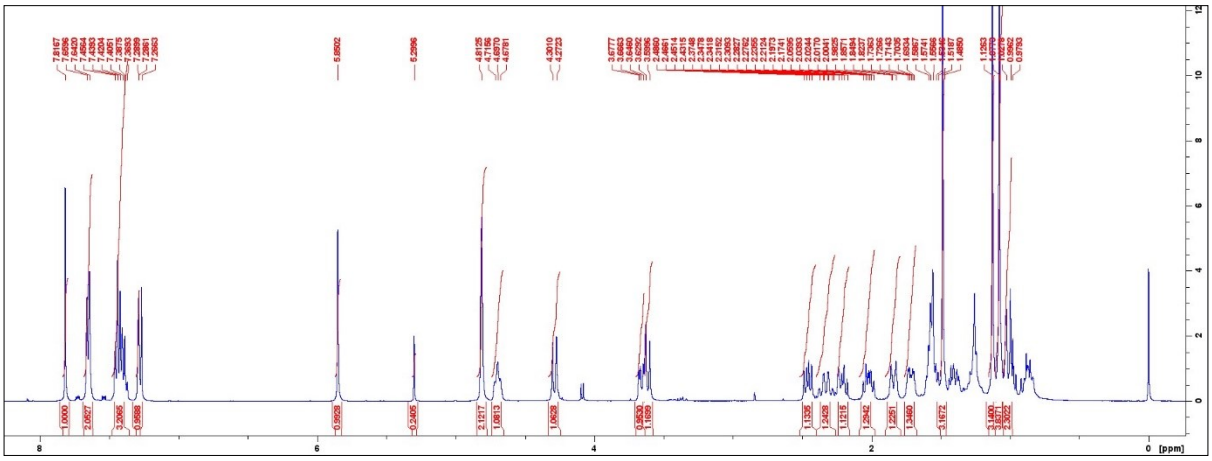


Figure S25: ^{1}H NMR spectrum of NH-Pyr-ISOADG Acetal (**2a**)

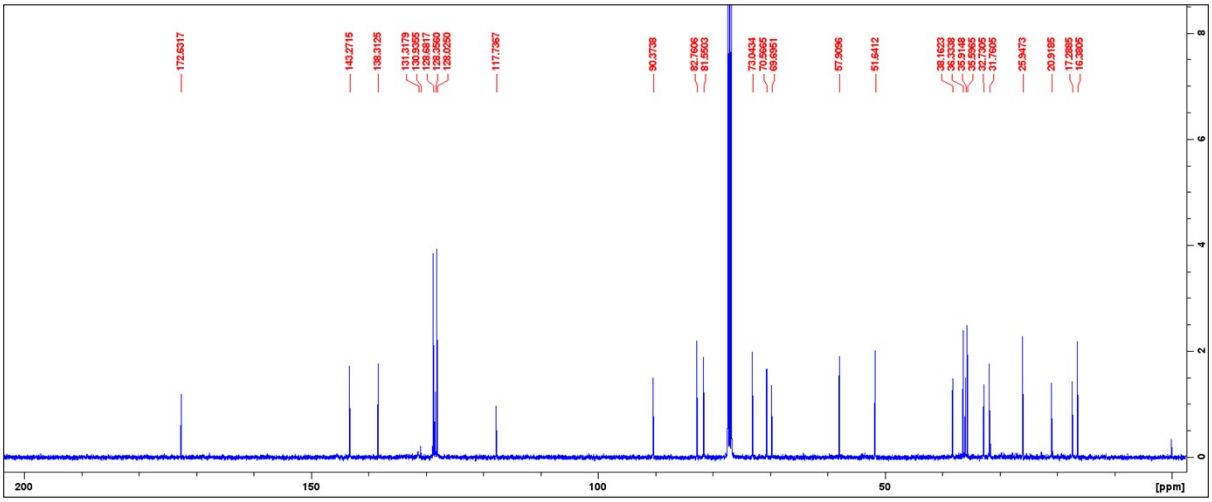


Figure S26: ^{13}C NMR spectrum of NH-Pyr-ISOADG Acetal (**2a**)

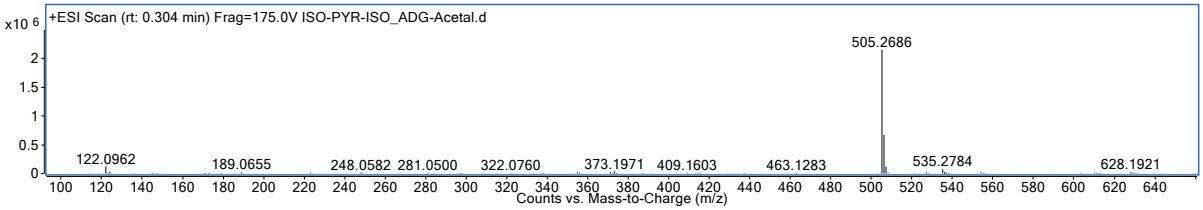


Figure S27: HRMS of NH-Pyr-ISOADG Acetal (**2a**)

3-Cl-NH-Pyr-ISOADG Acetal (2b)

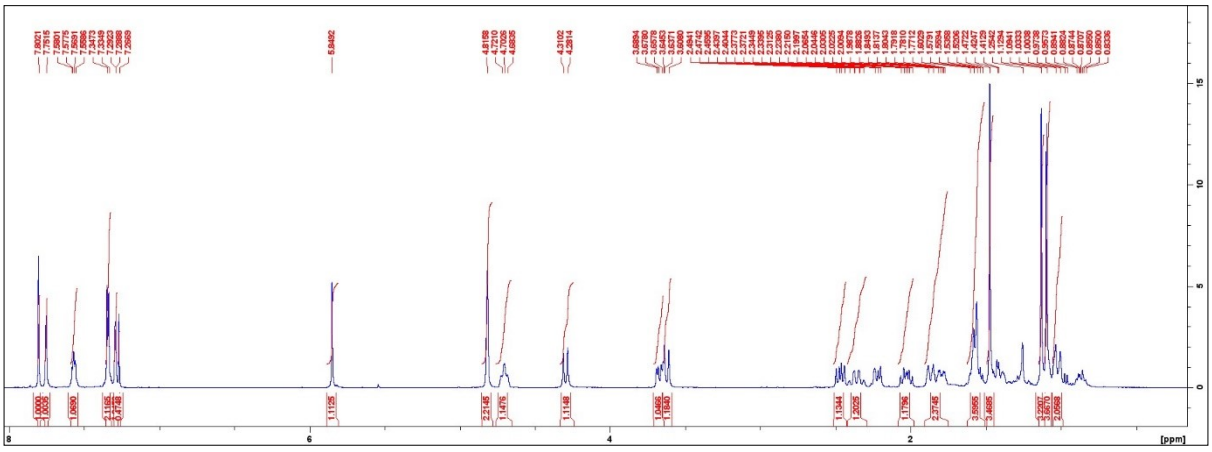


Figure S28: ^{1}H NMR spectrum of 3-Cl-NH-Pyr-ISOADG Acetal (**2b**)

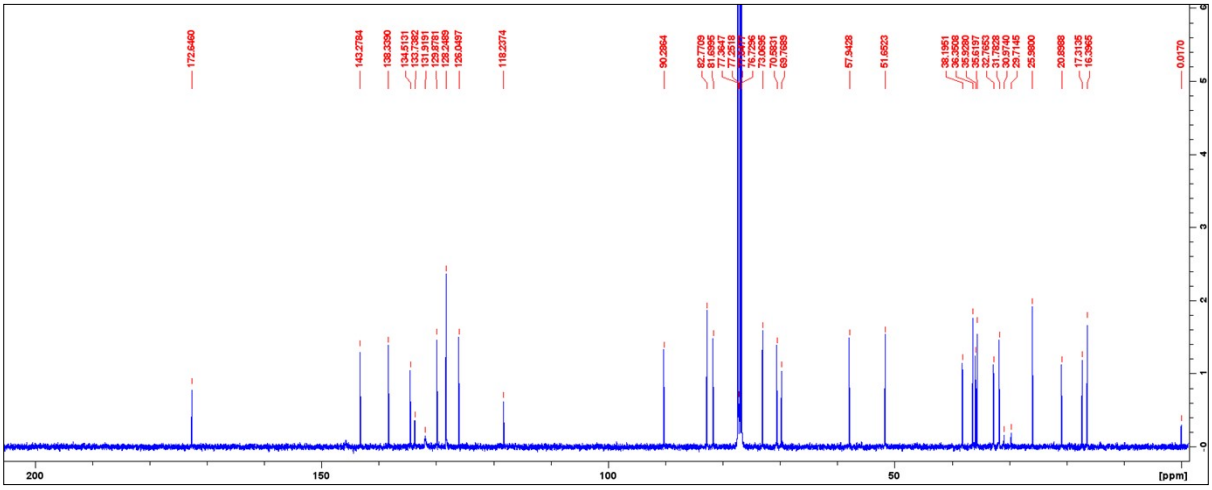


Figure S29: ^{13}C NMR spectrum of 3-Cl-NH-Pyr-ISOADG Acetal (**2b**)

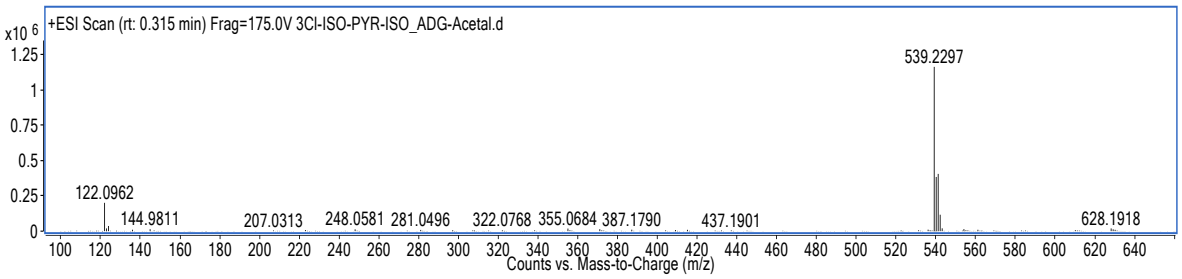


Figure S30: HRMS of 3-Cl-NH-Pyr-ISOADG Acetal (**2b**)

3-Br-NH-Pyr-ISOADG Acetal (2c)

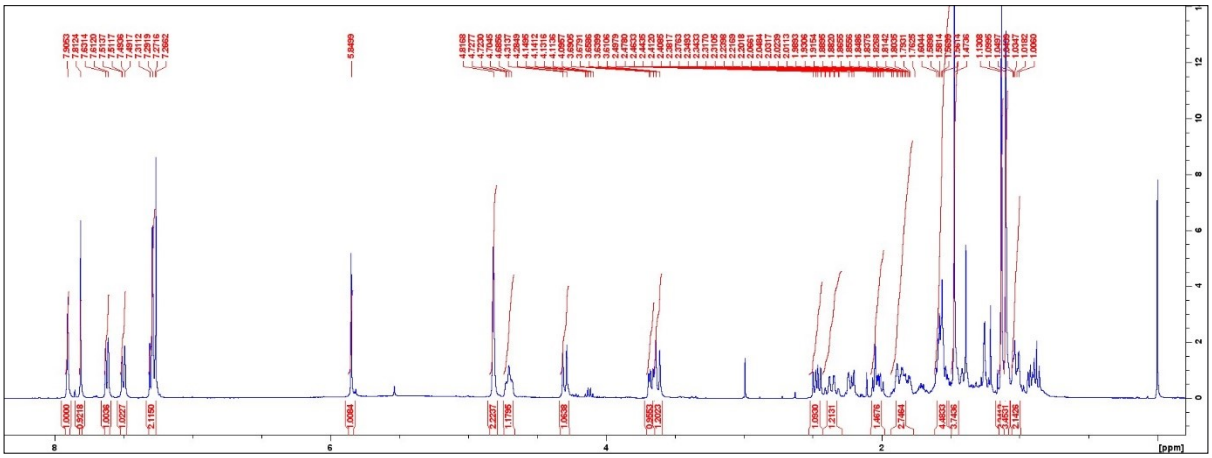


Figure S31: ^{1}H NMR spectrum of 3-Br-NH-Pyr-ISOADG Acetal (**2c**)

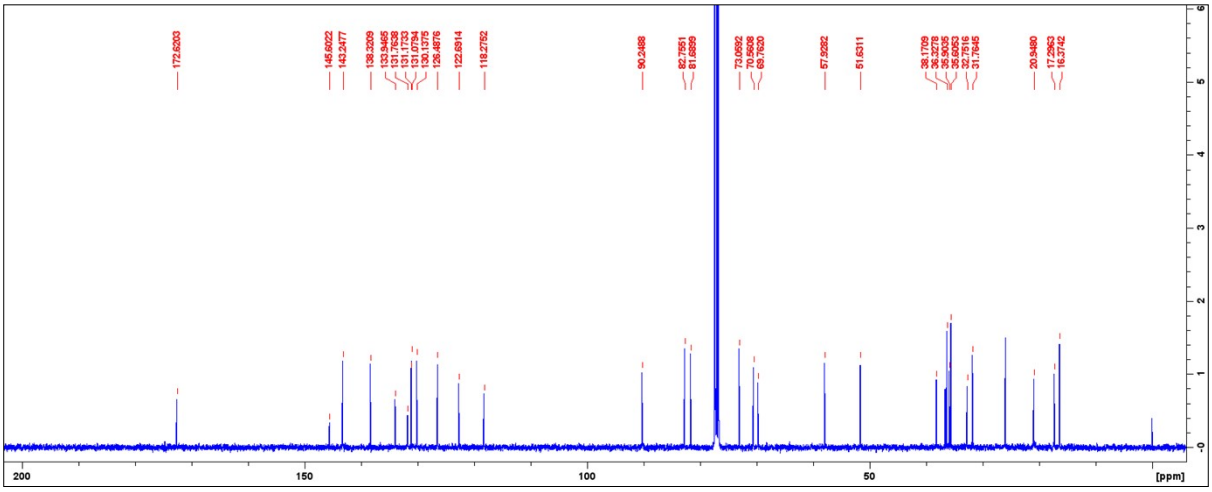


Figure S32: ^{13}C NMR spectrum of 3-Br-NH-Pyr-ISOADG Acetal (**2c**)

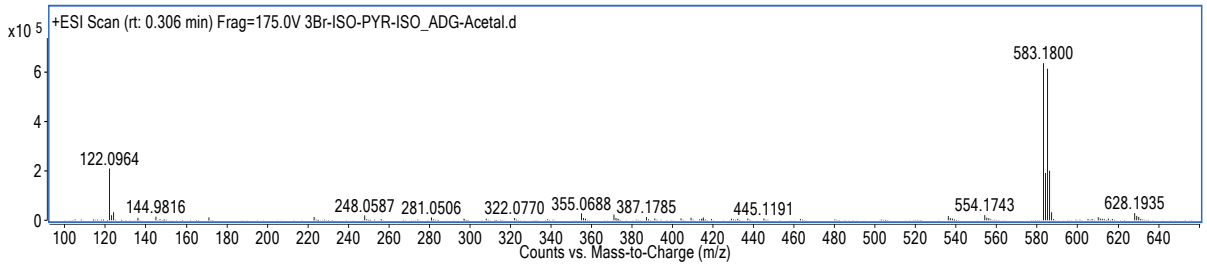


Figure S33: HRMS of 3-Br-NH-Pyr-ISOADG Acetal (**2c**)

4-F-NH-Pyr-ISOADG Acetal (2d)

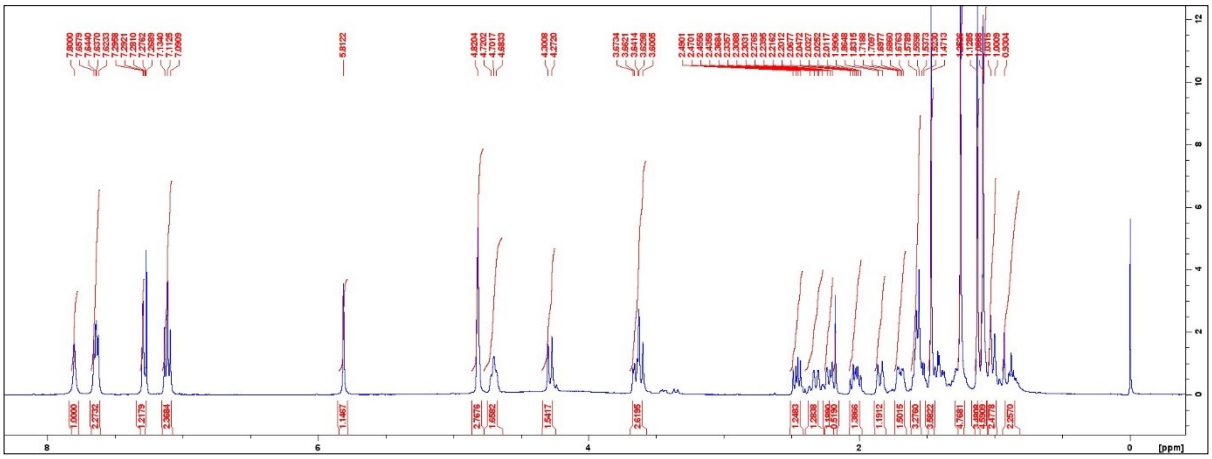


Figure S34: ^{1}H NMR spectrum of 4-F-NH-Pyr-ISOADG Acetal (**2d**)

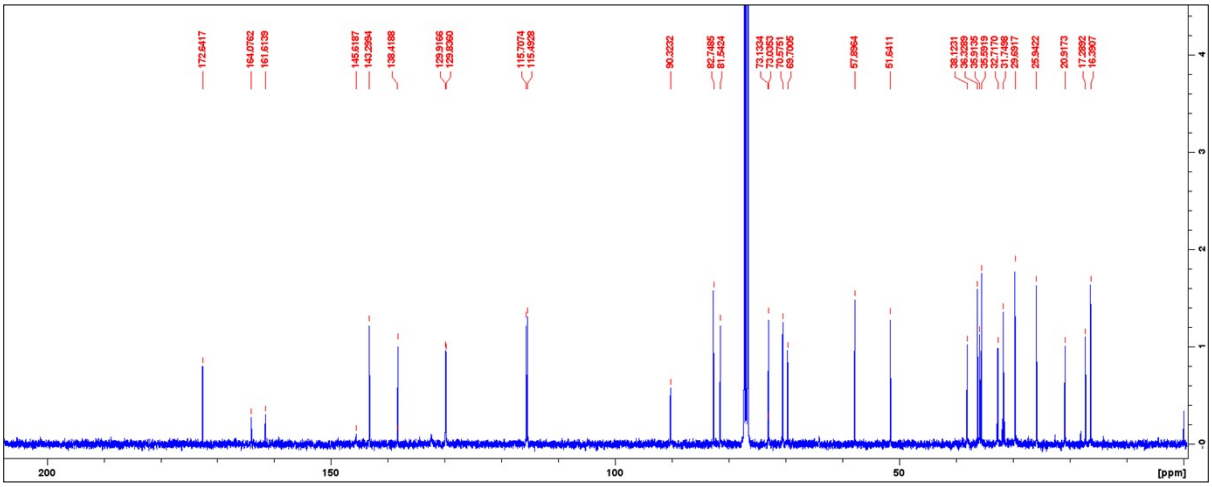


Figure S35: ^{13}C NMR spectrum of 4-F-NH-Pyr-ISOADG Acetal (**2d**)

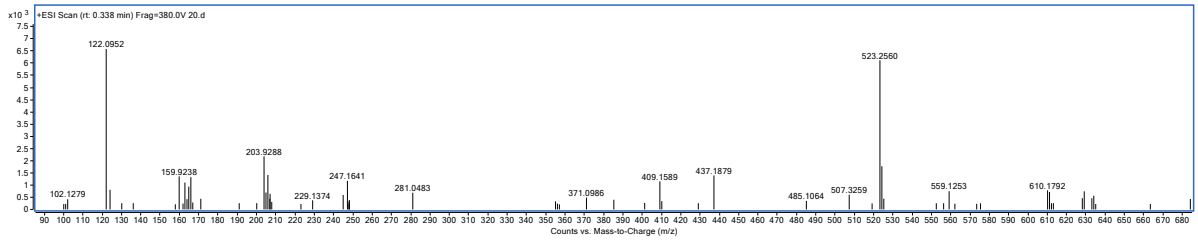


Figure S36: HRMS of 4-F-NH-Pyr-ISOADG Acetal (**2d**)

4-Br-NH-Pyr-ISOADG Acetal (2e)

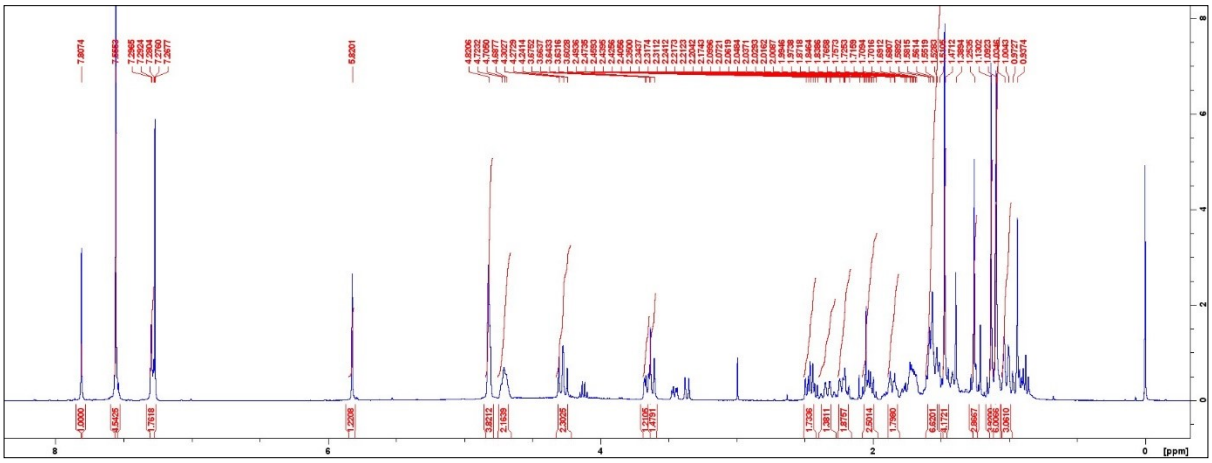


Figure S37: ^{1}H NMR spectrum of 4-Br-NH-Pyr-ISOADG Acetal (**2e**)

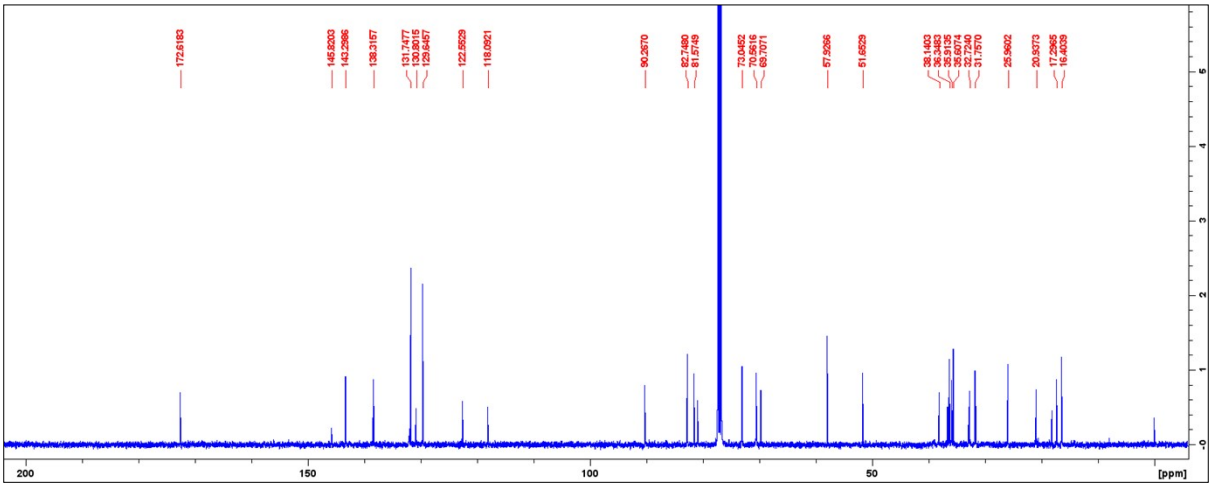


Figure S38: ^{13}C NMR spectrum of 4-Br-NH-Pyr-ISOADG Acetal (**2e**)

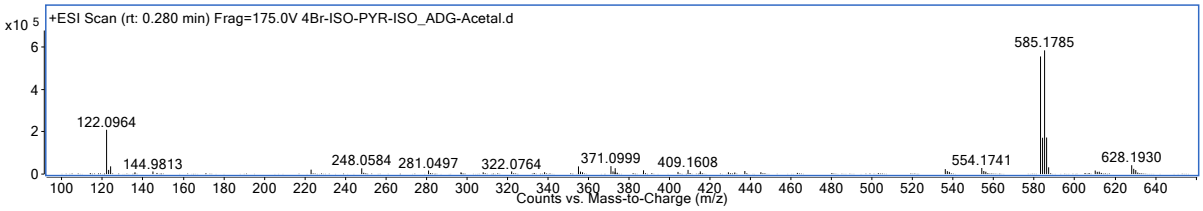


Figure S39: HRMS of 4-Br-NH-Pyr-ISOADG Acetal (**2e**)

4-CH_3-NH-Pyr-ISOADG Acetal (2f)

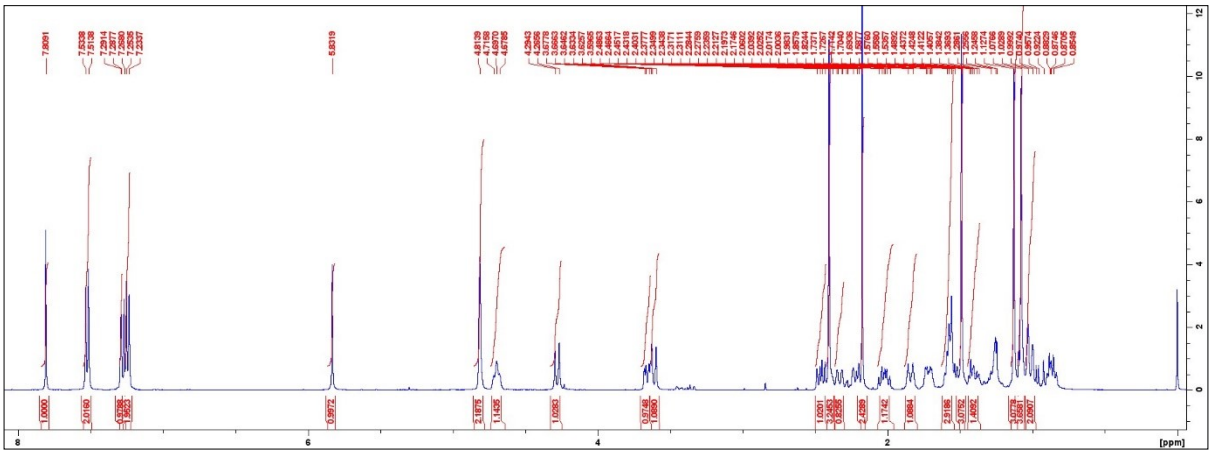


Figure S40: ^{1}H NMR spectrum of 4-CH_3-NH-Pyr-ISOADG Acetal (**2f**)

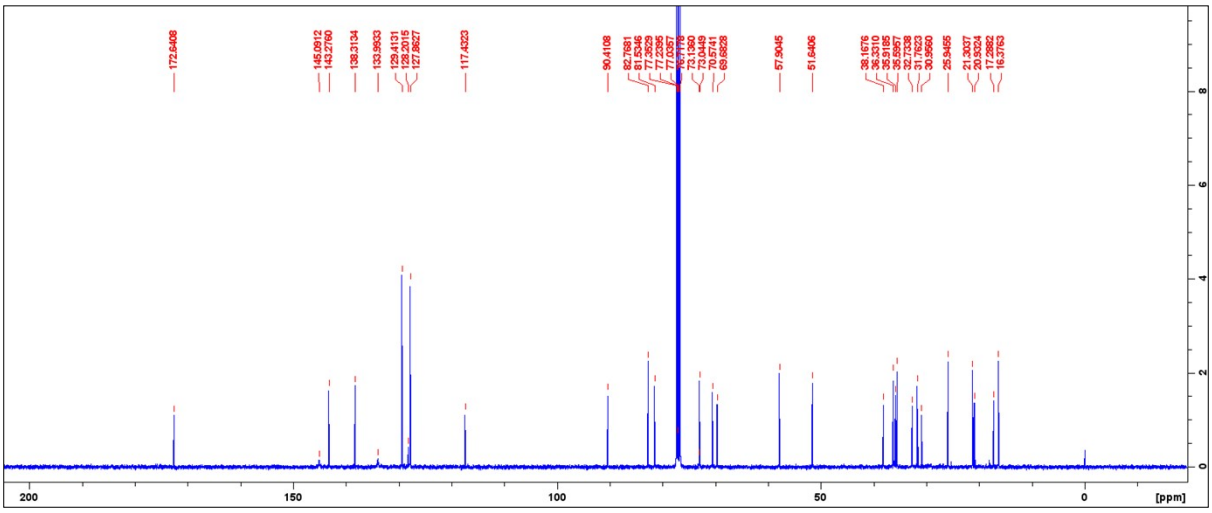


Figure S41: ^{13}C NMR spectrum of 4-CH_3-NH-Pyr-ISOADG Acetal (**2f**)

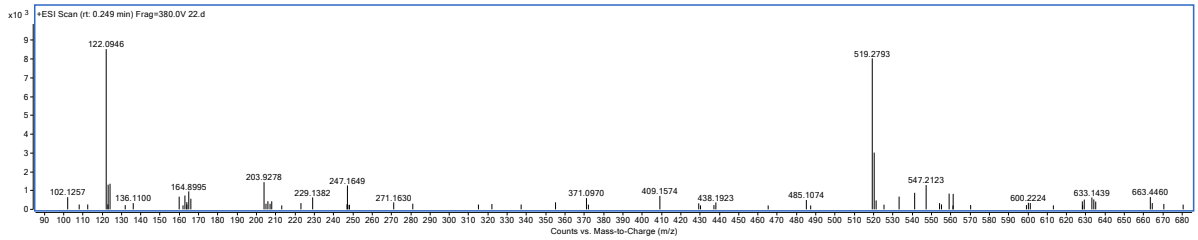


Figure S42: HRMS of 4-CH_3-NH-Pyr-ISOADG Acetal (**2f**)

4-OCH$_3$-NH-Pyr-ISOADG Acetal (2g)

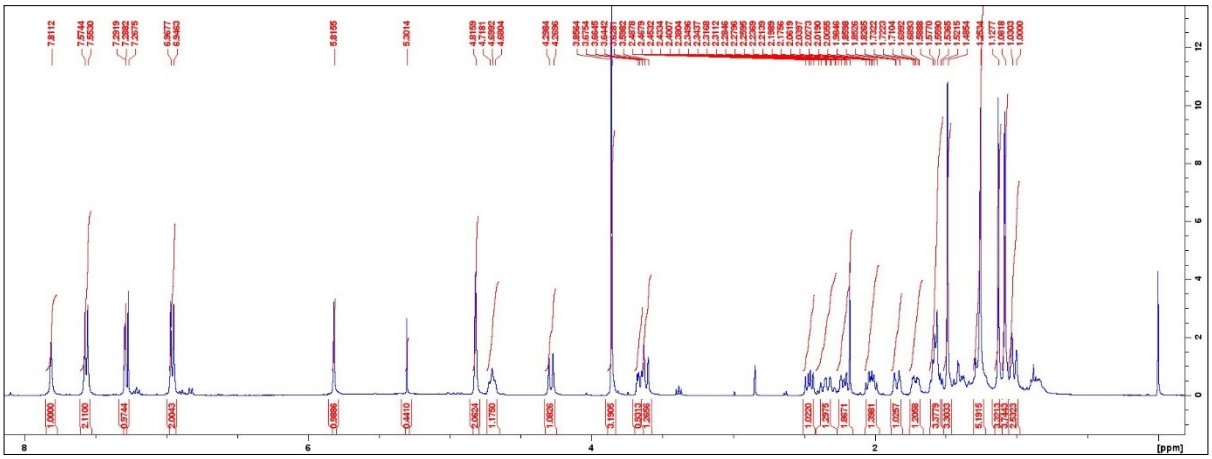


Figure S43: ^{1}H NMR spectrum of 4-OCH$_3$-NH-Pyr-ISOADG Acetal (**2g**)

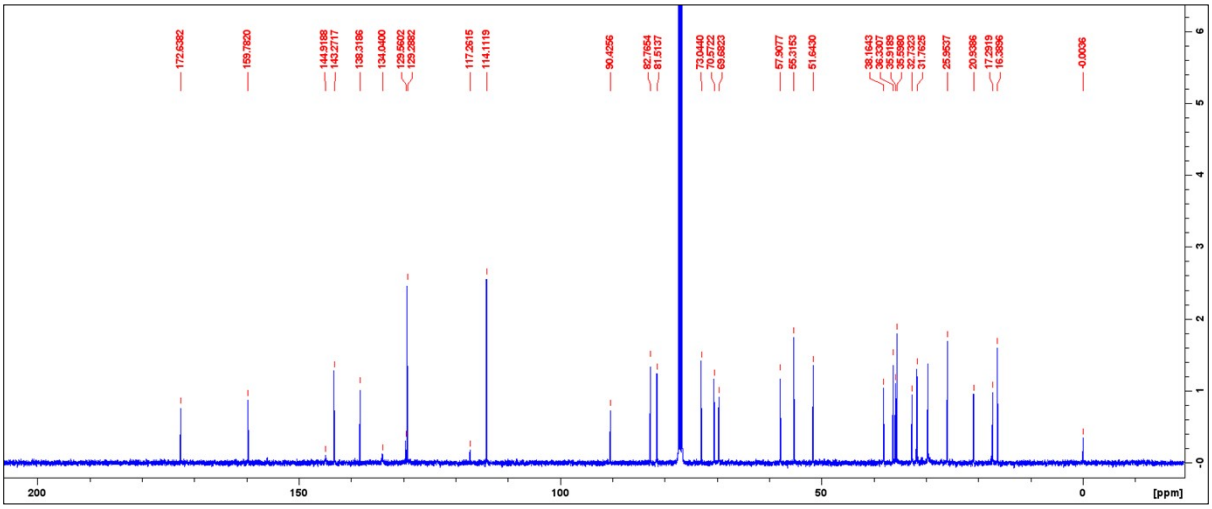


Figure S44: ^{13}C NMR spectrum of 4-OCH$_3$-NH-Pyr-ISOADG Acetal (**2g**)

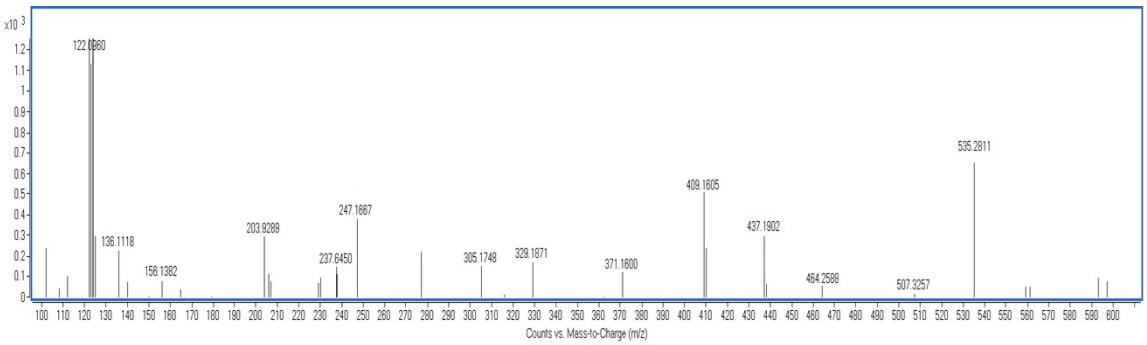


Figure S45: HRMS of 4-OCH$_3$-NH-Pyr-ISOADG Acetal (**2g**)

4-Cl-NH-Pyr-ISOADG Acetal (2i)

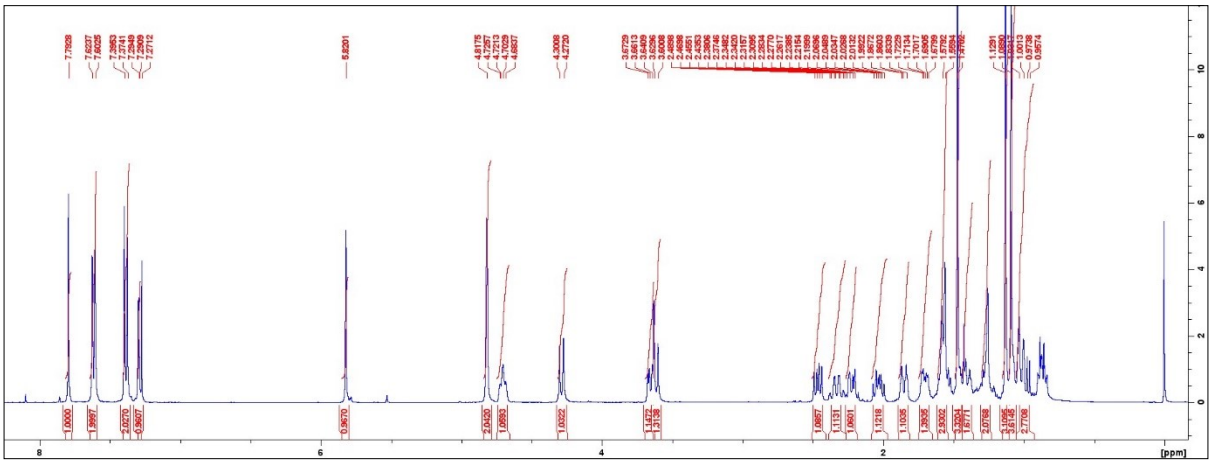


Figure S46: ^{1}H NMR spectrum of 4-Cl-NH-Pyr-ISOADG Acetal (**2i**)

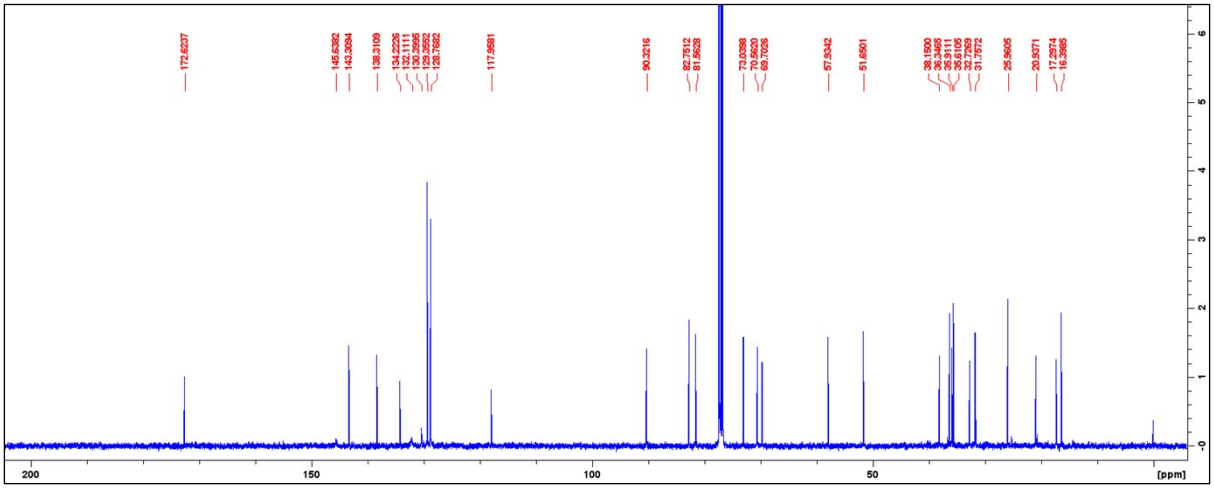


Figure S47: ^{13}C NMR spectrum of 4-Cl-NH-Pyr-ISOADG Acetal (**2i**)

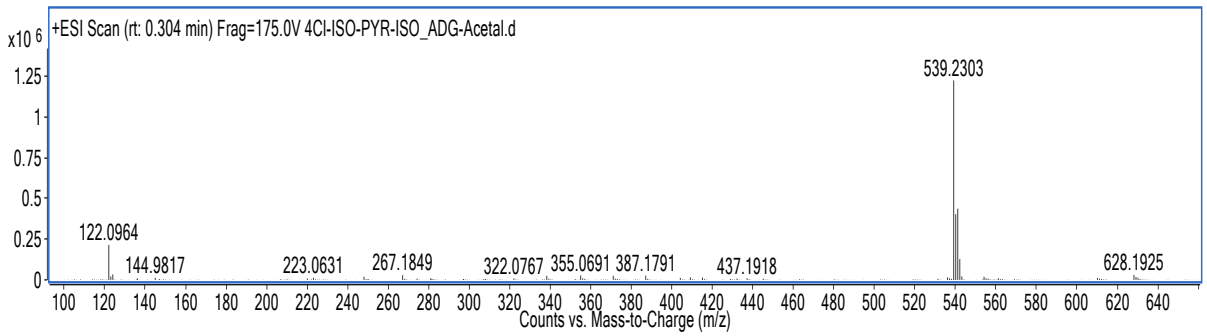


Figure S48: HRMS of 4-Cl-NH-Pyr-ISOADG Acetal (**2i**)

3-phenyl-1H-pyrazole-4-carboxaldehyde (a)

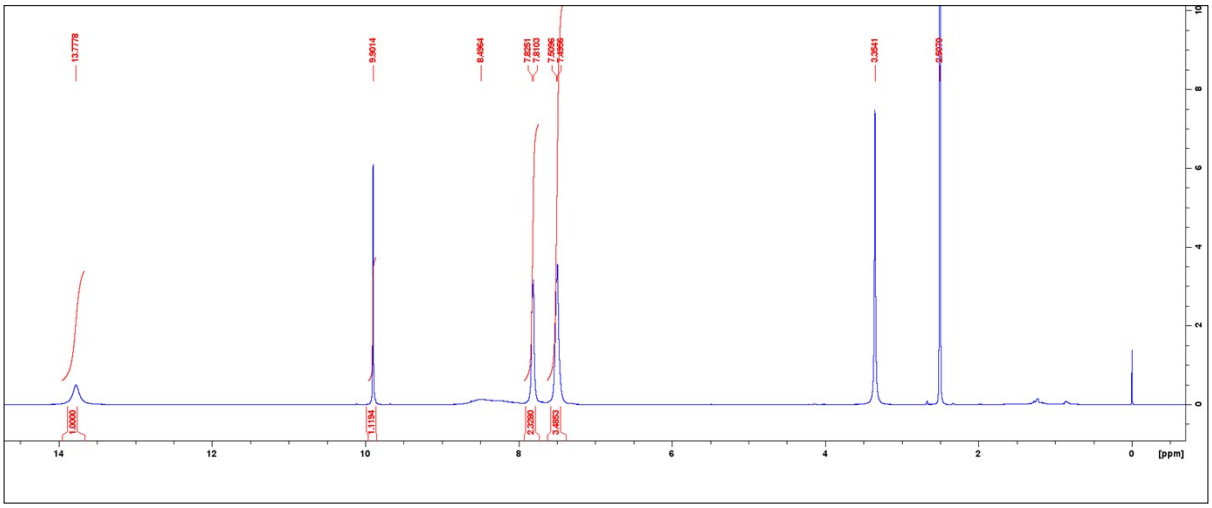


Figure S49: ^{1}H NMR spectrum of 3-phenyl-1H-pyrazole-4-carboxaldehyde (**a**)

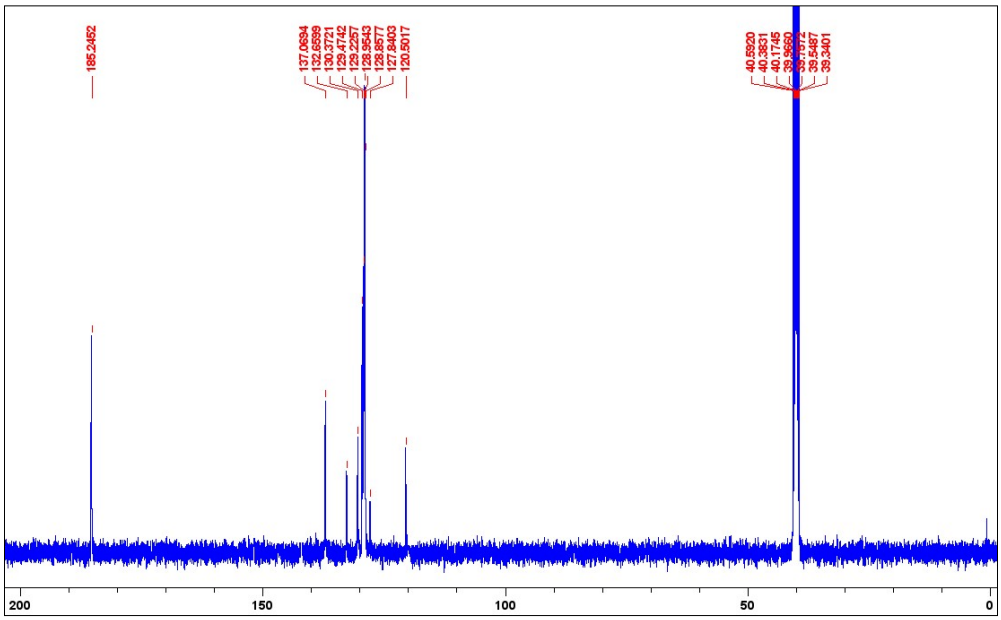


Figure S50: ^{13}C NMR spectrum of 3-phenyl-1H-pyrazole-4-carboxaldehyde (**a**)

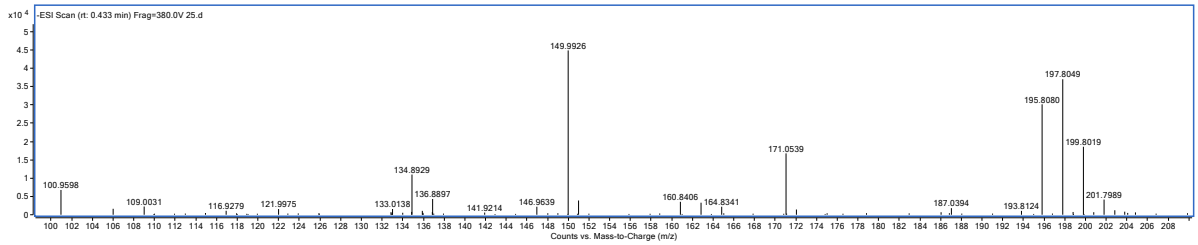


Figure S51: HRMS of 3-phenyl-1H-pyrazole-4-carboxaldehyde (**a**)

3-(3-chlorophenyl)-1H-pyrazole-4-carboxaldehyde (b)

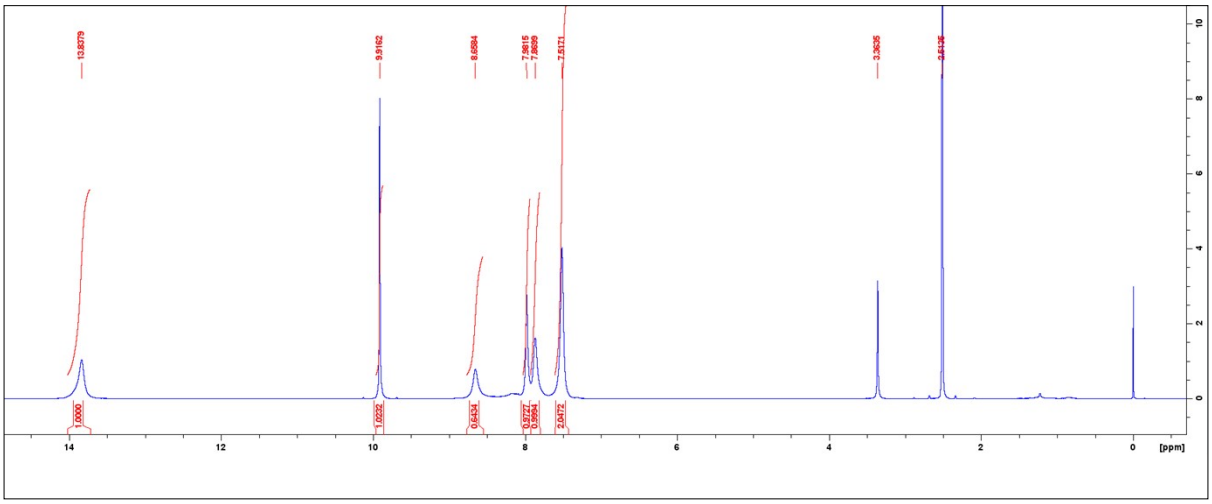


Figure S52: ^{1}H NMR spectrum of 3-(3-chlorophenyl)-1H-pyrazole-4-carboxaldehyde (**b**)

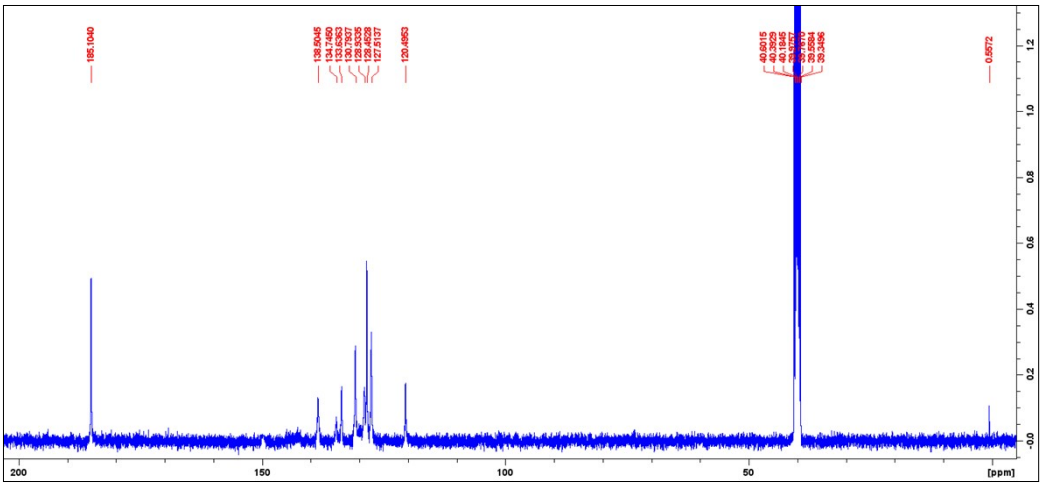


Figure S53: ^{13}C NMR spectrum of 3-(3-chlorophenyl)-1H-pyrazole-4-carboxaldehyde (**b**)

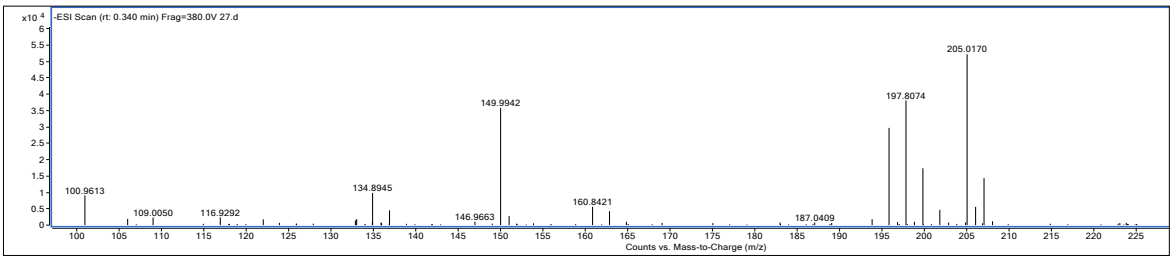


Figure S54: HRMS of 3-(3-chlorophenyl)-1H-pyrazole-4-carboxaldehyde (**b**)

3-(3-bromophenyl)-1H-pyrazole-4-carboxaldehyde (c)

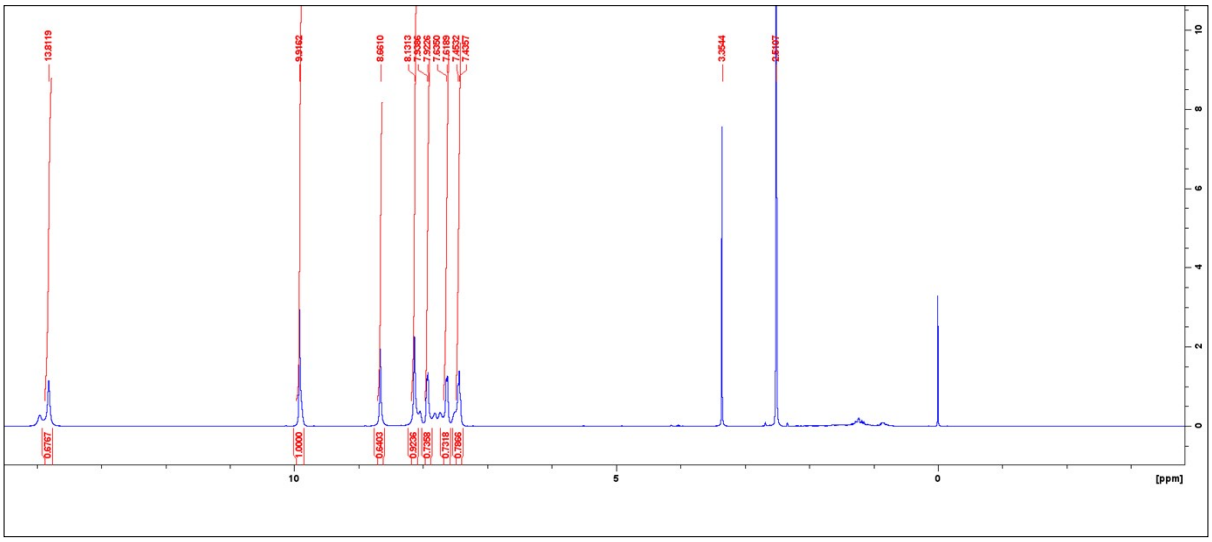


Figure S55: ^{1}H NMR spectrum of 3-(3-bromophenyl)-1H-pyrazole-4-carboxaldehyde (**c**)

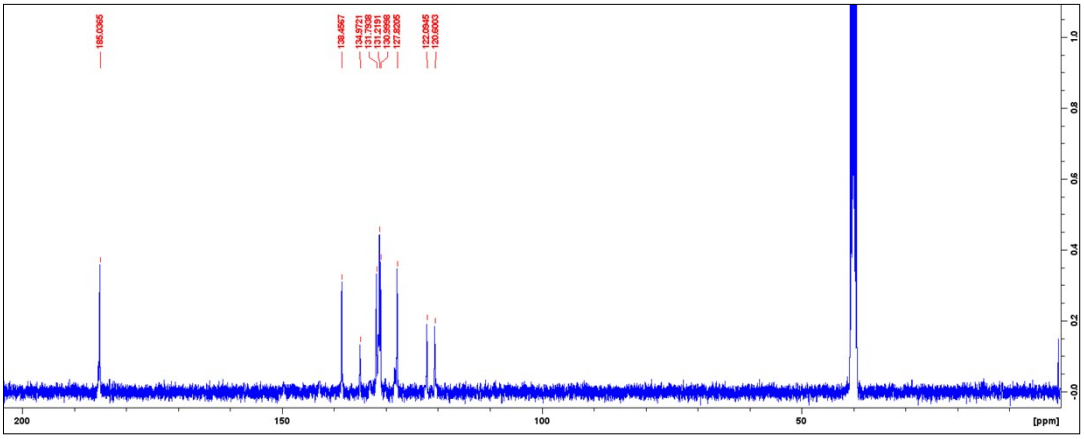


Figure S56: ^{13}C NMR spectrum of 3-(3-bromophenyl)-1H-pyrazole-4-carboxaldehyde (**c**)

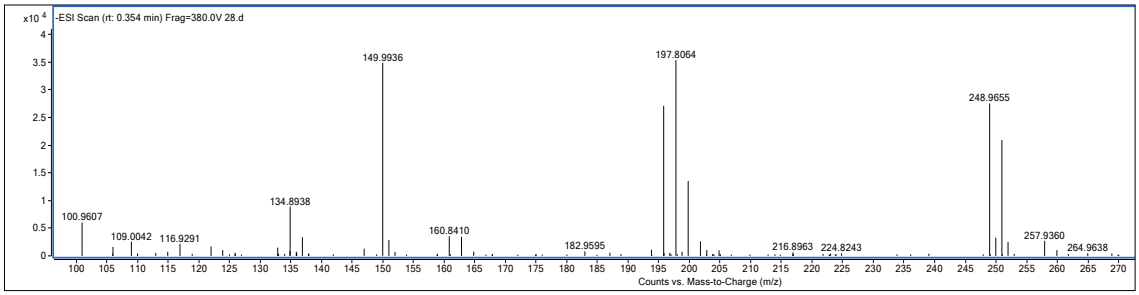


Figure S57: HRMS of 3-(3-bromophenyl)-1H-pyrazole-4-carboxaldehyde (**c**)

3-(4-fluorophenyl)-1H-pyrazole-4-carboxaldehyde (d)

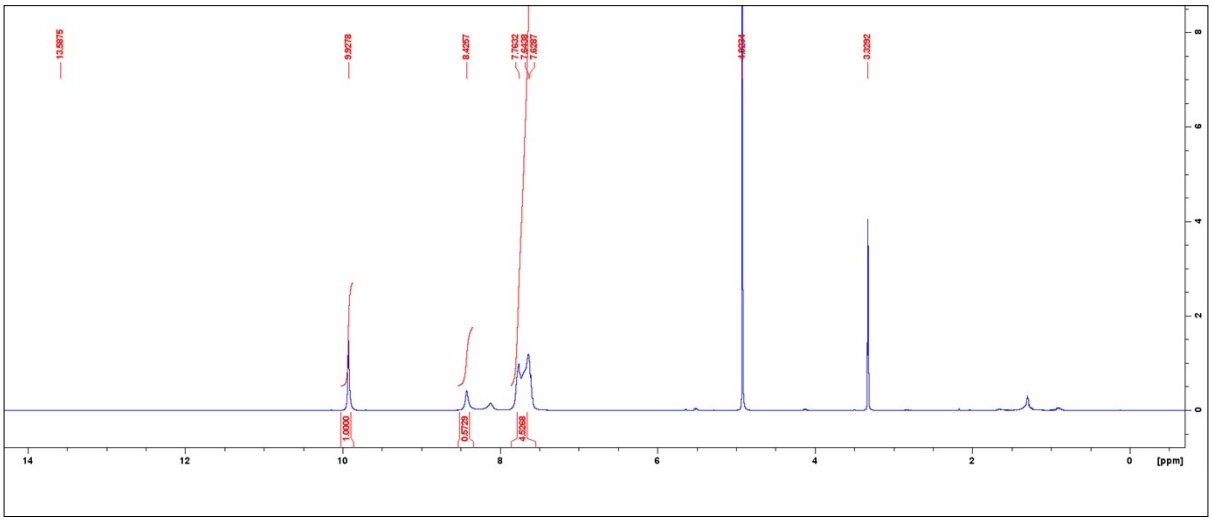


Figure S58: ^{1}H NMR spectrum of 3-(4-fluorophenyl)-1H-pyrazole-4-carboxaldehyde (**d**)

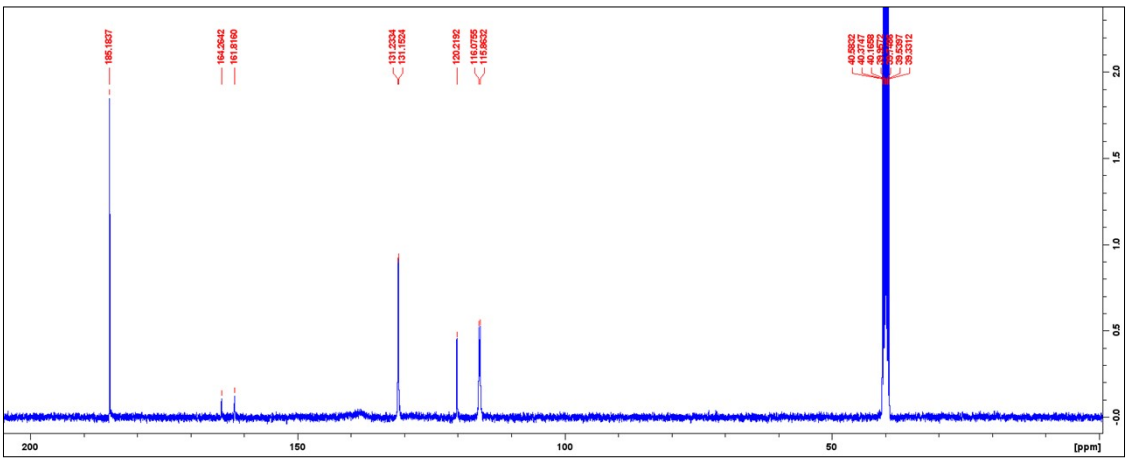


Figure S59: ^{13}C NMR spectrum of 3-(4-flurophenyl)-1H-pyrazole-4-carboxaldehyde (**d**)

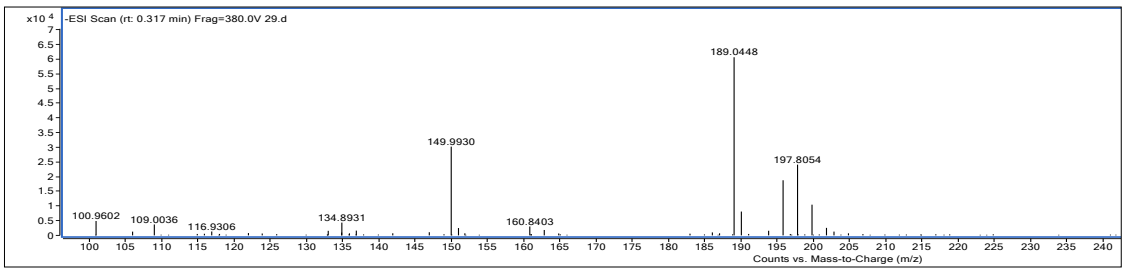


Figure S60: HRMS of 3-(4-flurophenyl)-1H-pyrazole-4-carboxaldehyde (**d**)

3-(4-bromophenyl)-1H-pyrazole-4-carboxaldehyde (e)

Figure S61: ^{1}H NMR spectrum of 3-(4-bromophenyl)-1H-pyrazole-4-carboxaldehyde (**e**)

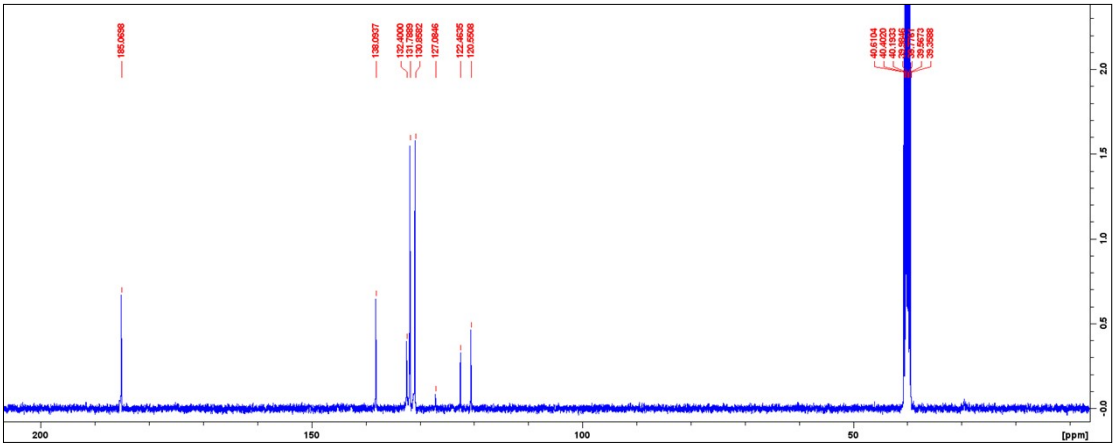


Figure S62: ^{13}C NMR spectrum of 3-(4-bromophenyl)-1H-pyrazole-4-carboxaldehyde (**e**)

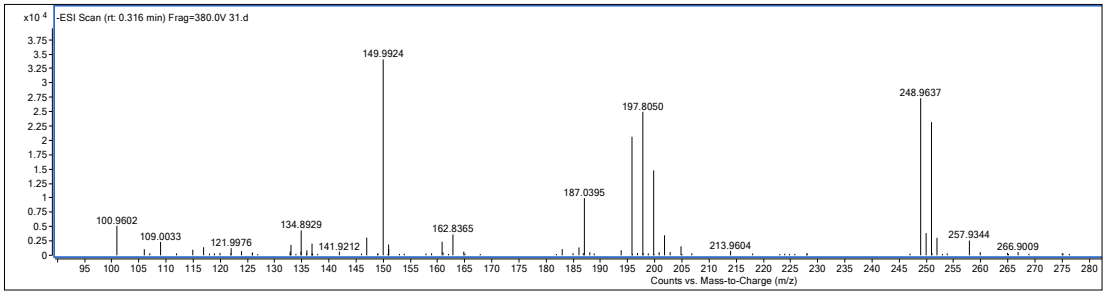


Figure S63: HRMS of 3-(4-bromophenyl)-1H-pyrazole-4-carboxaldehyde (**e**)

3-(4-methylphenyl)-1H-pyrazole-4-carboxaldehyde (f)

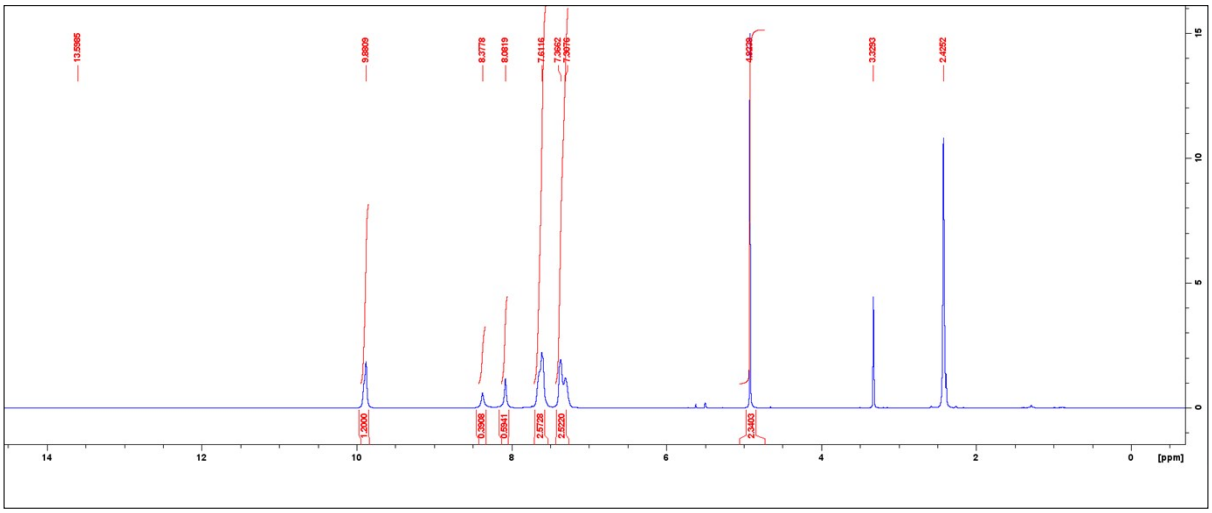


Figure S64: ^{1}H NMR spectrum of 3-(4-methylphenyl)-1H-pyrazole-4-carboxaldehyde (**f**)

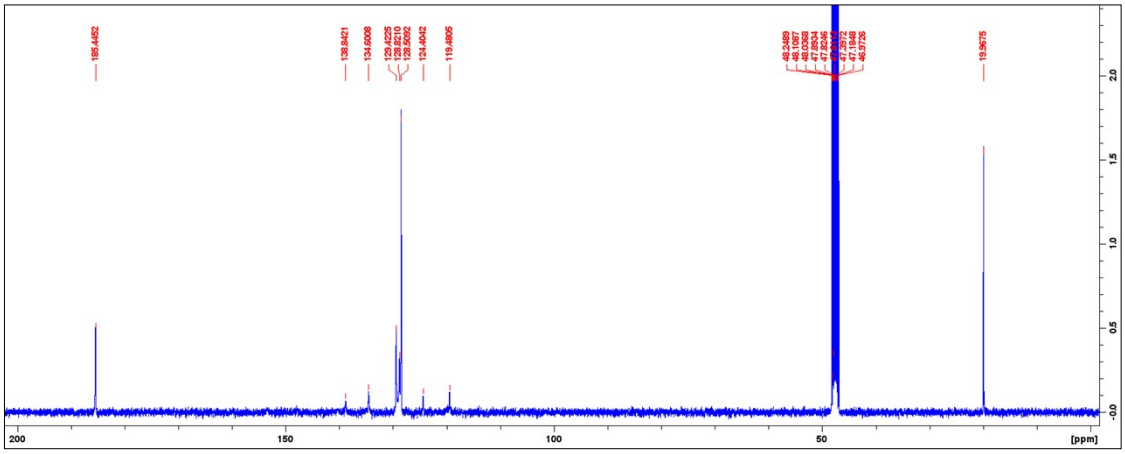


Figure S65: ^{13}C NMR spectrum of 3-(4-methylphenyl)-1H-pyrazole-4-carboxaldehyde (**f**)

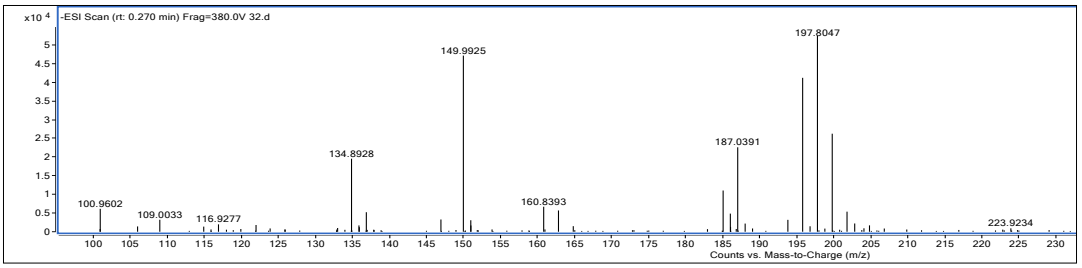


Figure S66: HRMS of 3-(4-methylphenyl)-1H-pyrazole-4-carboxaldehyde (**f**)

3-(4-methoxyphenyl)-1H-pyrazole-4-carboxaldehyde (g)

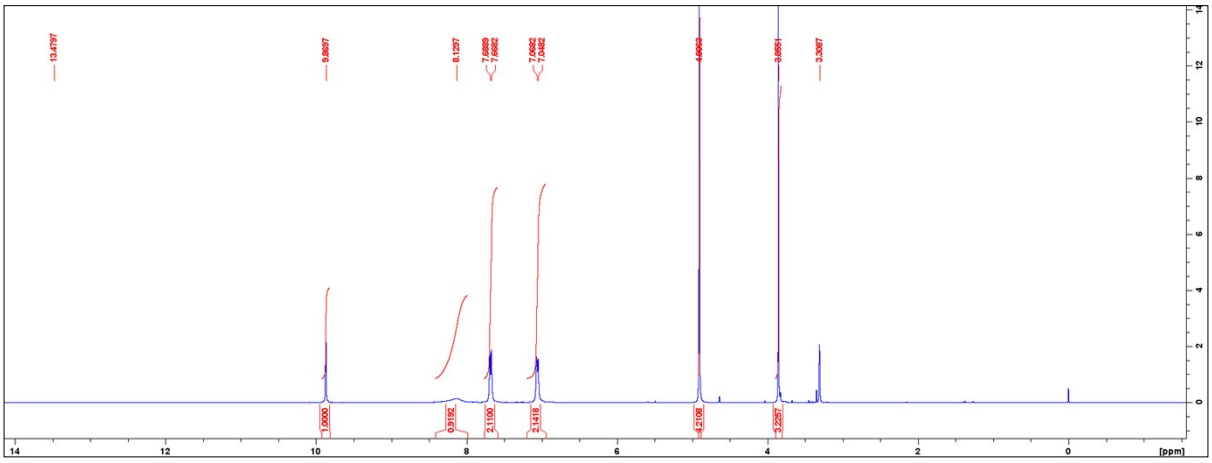


Figure S67: ^{1}H NMR spectrum of 3-(4-methoxyphenyl)-1H-pyrazole-4-carboxaldehyde (**g**)

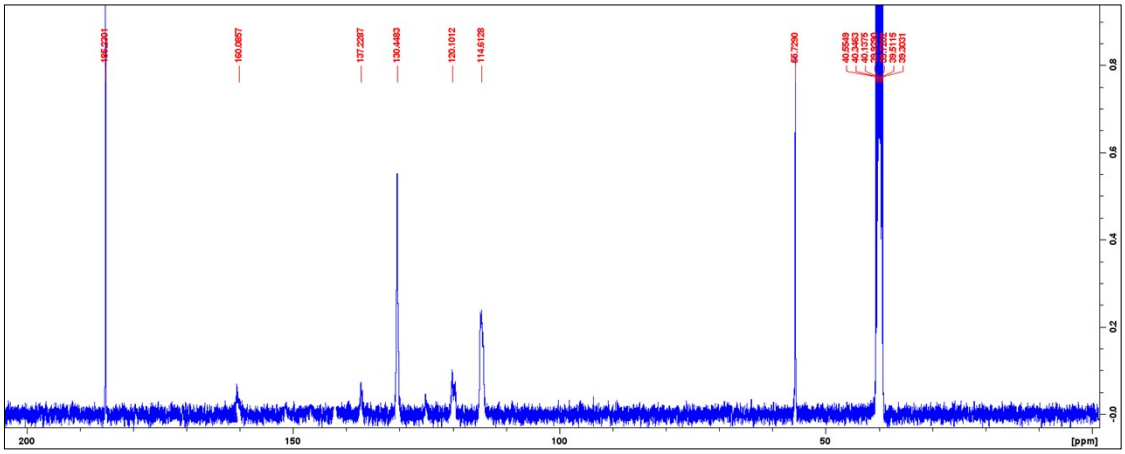


Figure S68: ^{13}C NMR spectrum of 3-(4-methoxyphenyl)-1H-pyrazole-4-carboxaldehyde (**g**)

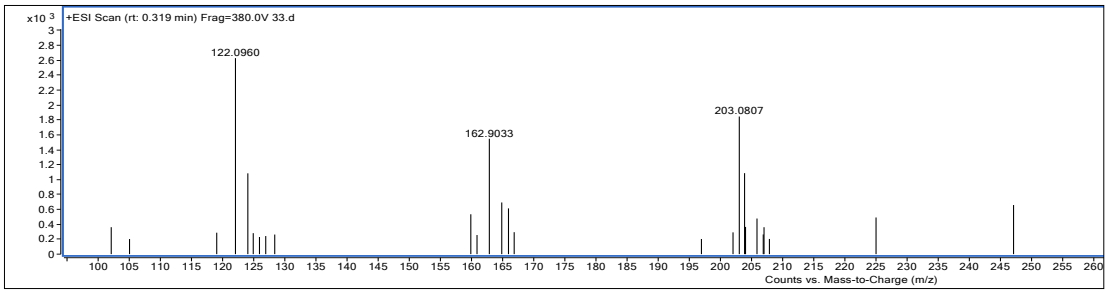


Figure S69: HRMS of 3-(4-methoxyphenyl)-1H-pyrazole-4-carboxaldehyde (**g**)

3-(3-flourophenyl)-1H-pyrazole-4-carboxaldehyde (h)

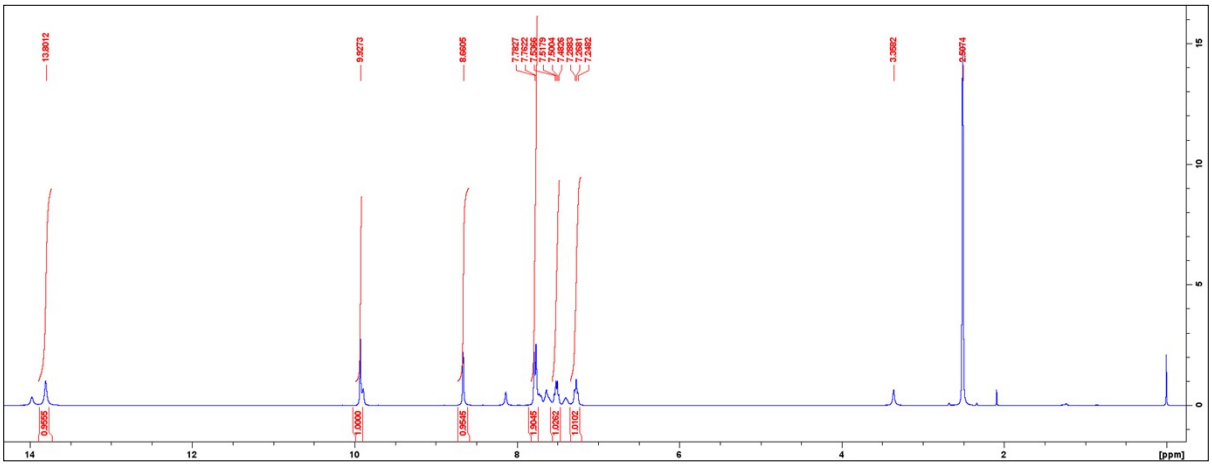


Figure S70: ^{1}H NMR spectrum of 3-(3-flourophenyl)-1H-pyrazole-4-carboxaldehyde (**h**)

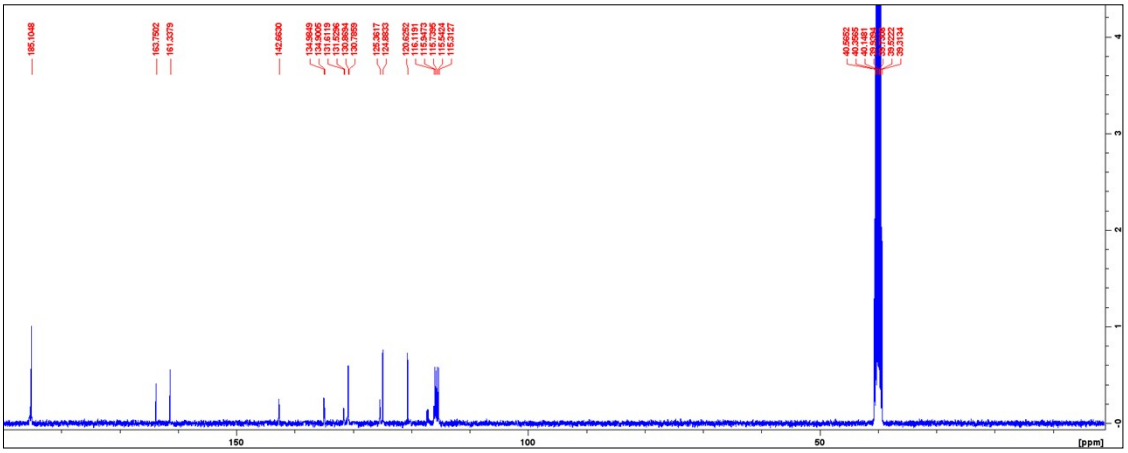


Figure S71: ^{13}C NMR spectrum of 3-(3-flourophenyl)-1H-pyrazole-4-carboxaldehyde (**h**)

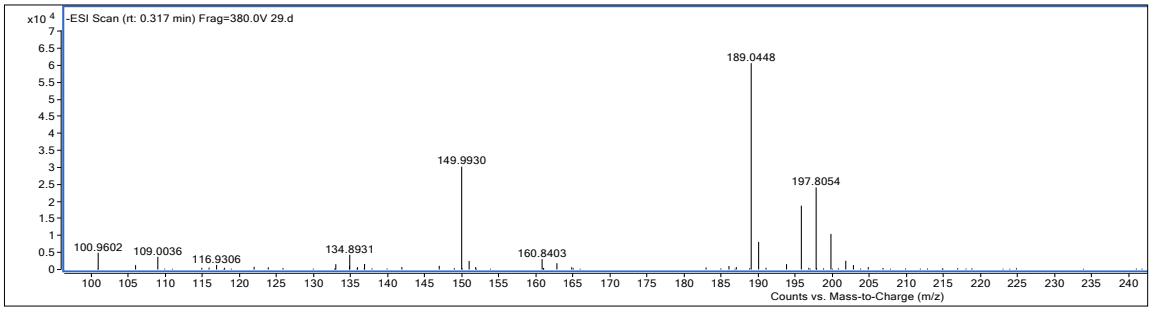


Figure S72: HRMS of 3-(3-flourophenyl)-1H-pyrazole-4-carboxaldehyde (**h**)

3-(4-Chlorophenyl)-1H-pyrazole-4-carboxaldehyde (i)

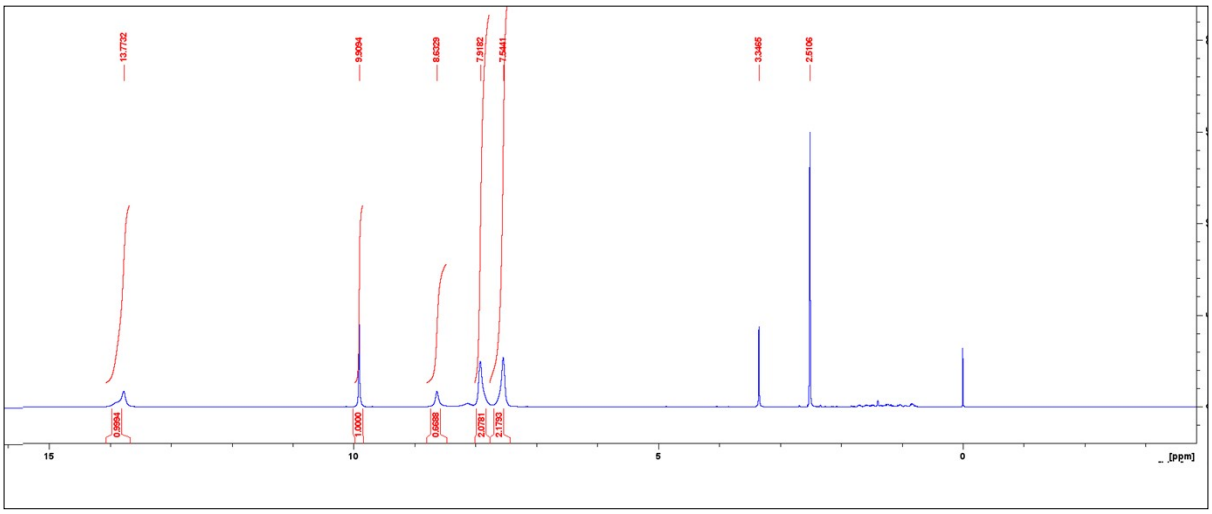


Figure S73: ^{1}H NMR spectrum of 3-(4-chlorophenyl)-1H-pyrazole-4-carboxaldehyde (**i**)

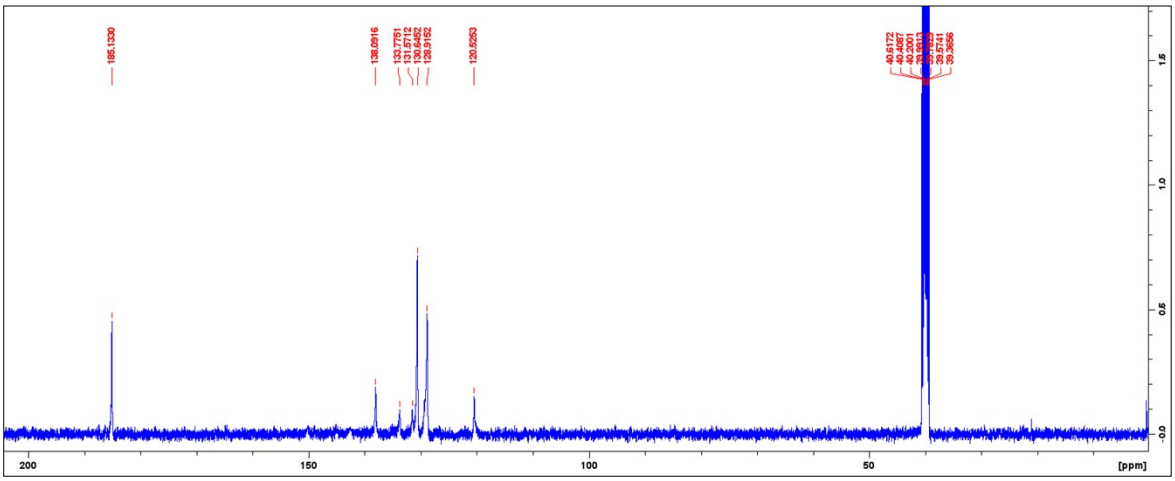


Figure S74: ^{13}C NMR spectrum of 3-(4-chlorophenyl)-1H-pyrazole-4-carboxaldehyde (**i**)

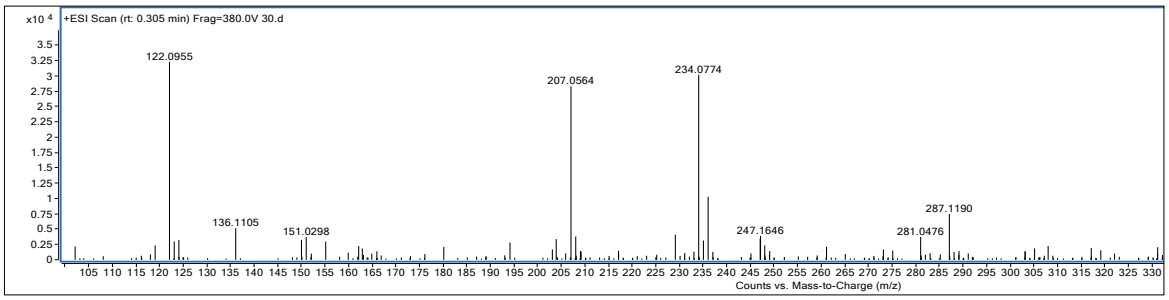


Figure S75: HRMS of 3-(4-chlorophenyl)-1H-pyrazole-4-carboxaldehyde (**i**)

(*E*)-*N*'-(1-ethylidene)isonicotinohydrazide (A)

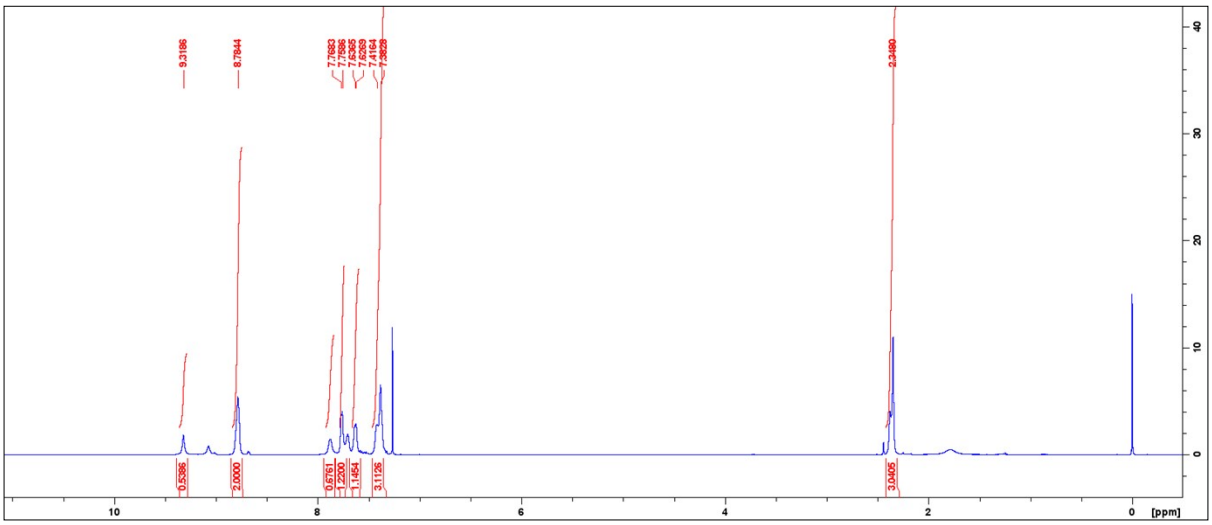


Figure S76: ^{1}H NMR spectrum of (E)-N'-(1-ethylidene)isonicotinohydrazide

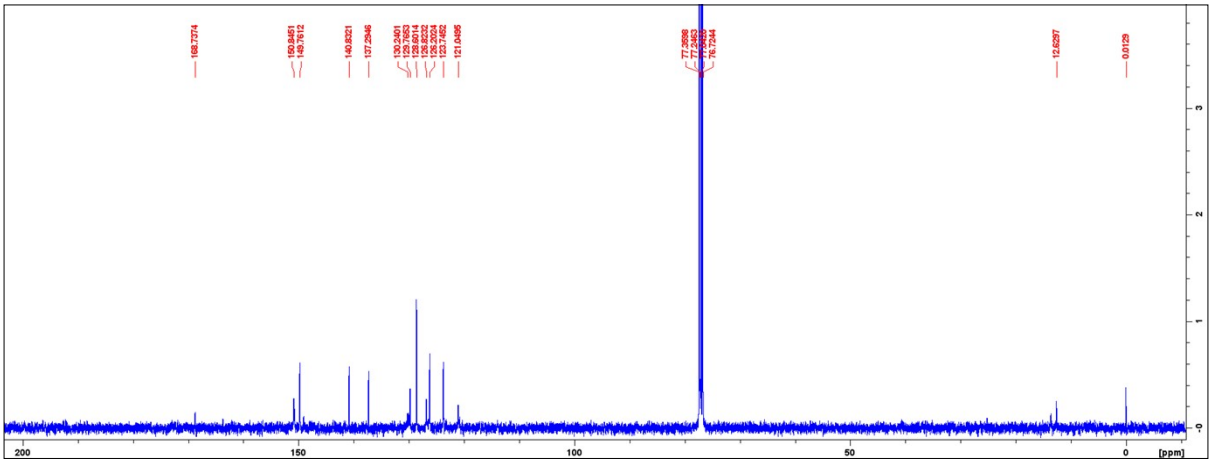


Figure S77: ^{13}C NMR spectrum of (E)-N'-(1-ethylidene)isonicotinohydrazide

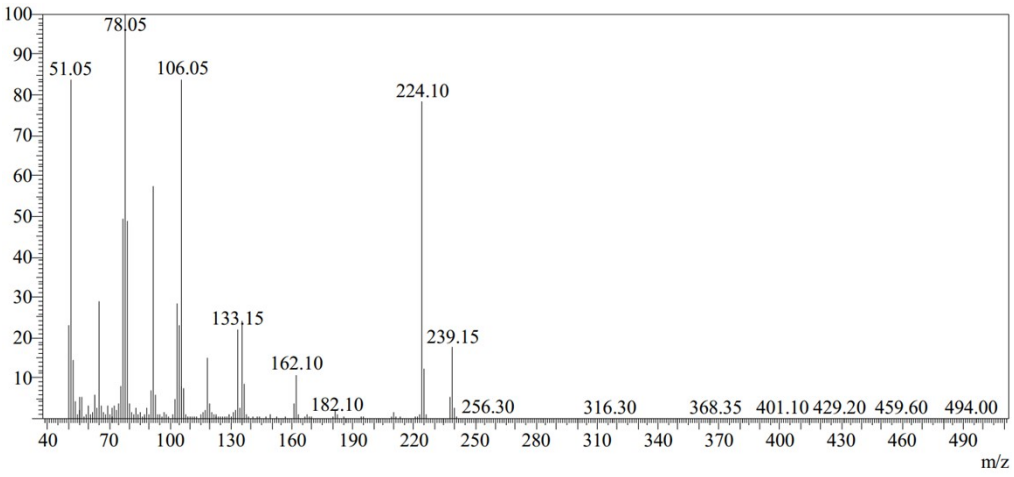


Figure S78: Mass spectrum of (E)-N'-(1-ethylidene)isonicotinohydrazide

(E)-N'-(1-(3-chlorophenyl)ethylidene)isonicotinohydrazide (B)

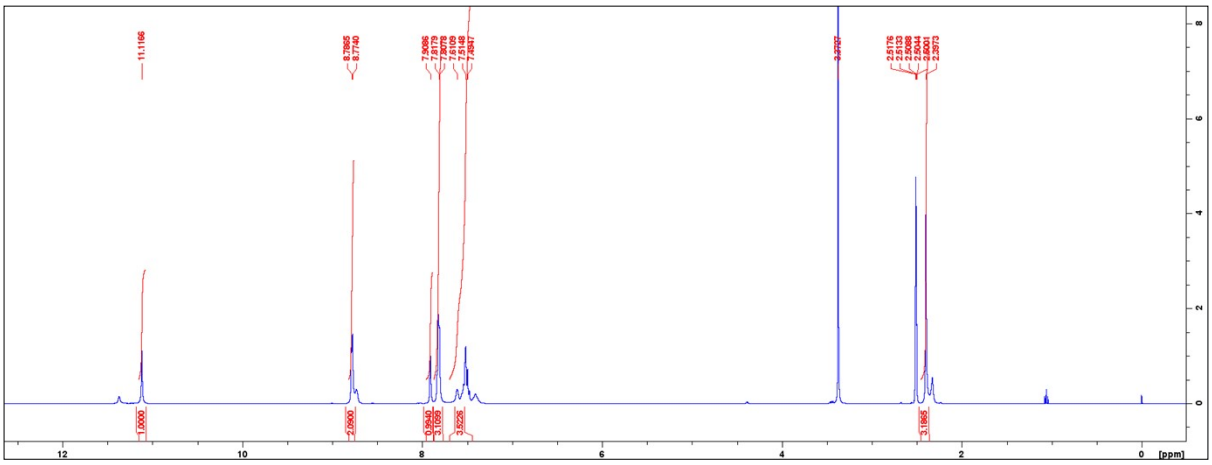


Figure S79: ^{1}H NMR spectrum of (E)-N'-(1-(3-chlorophenyl)-ethylidene)isonicotinohydrazide

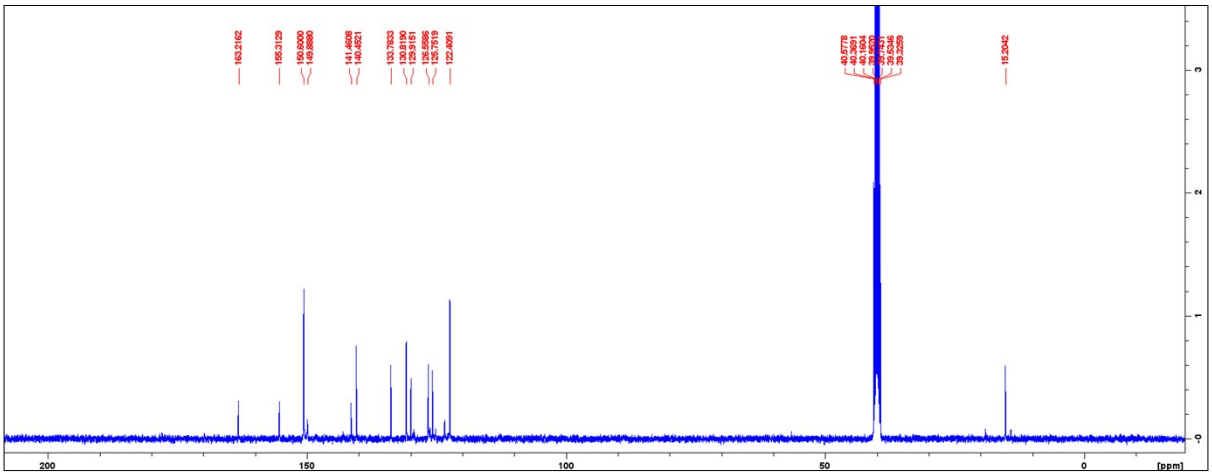


Figure S80: ^{13}C NMR spectrum of (E)-N'-(1-(3-chlorophenyl)-ethylidene)isonicotinohydrazide

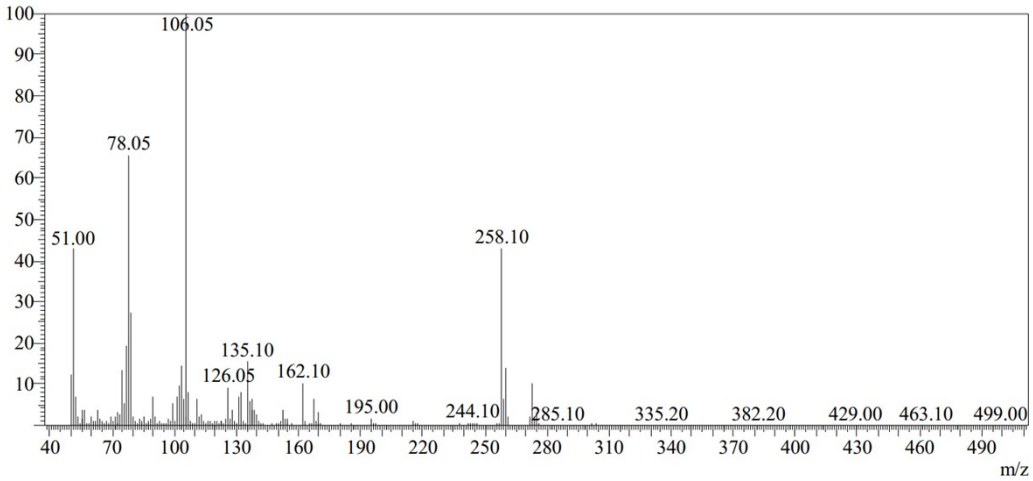


Figure S81: Mass spectrum of (E)-N'-(1-(3-chlorophenyl)-ethylidene)isonicotinohydrazide

(*E*)-*N*'-(1-(3-bromophenyl)ethylidene)isonicotinohydrazide (C)

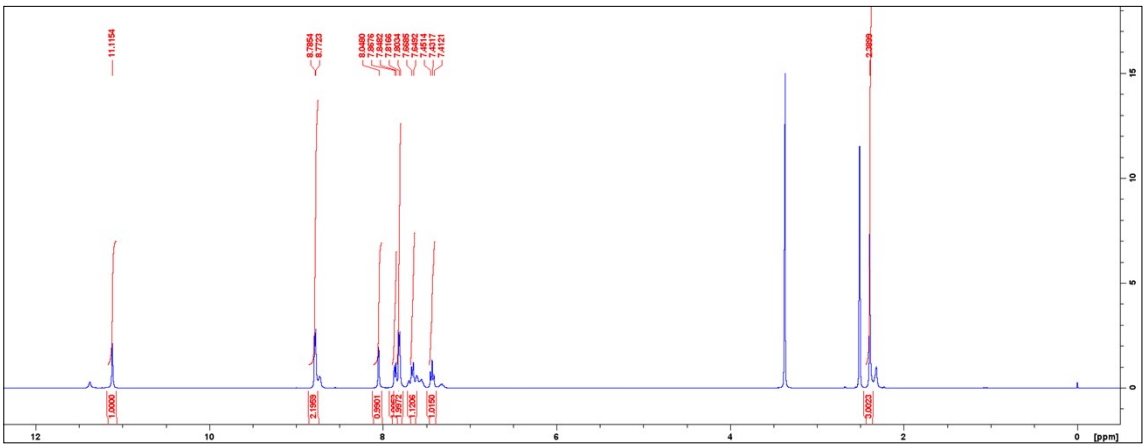


Figure S82: ^{1}H NMR spectrum of (E)-N'-(1-(3-bromophenyl)-ethylidene)isonicotinohydrazide

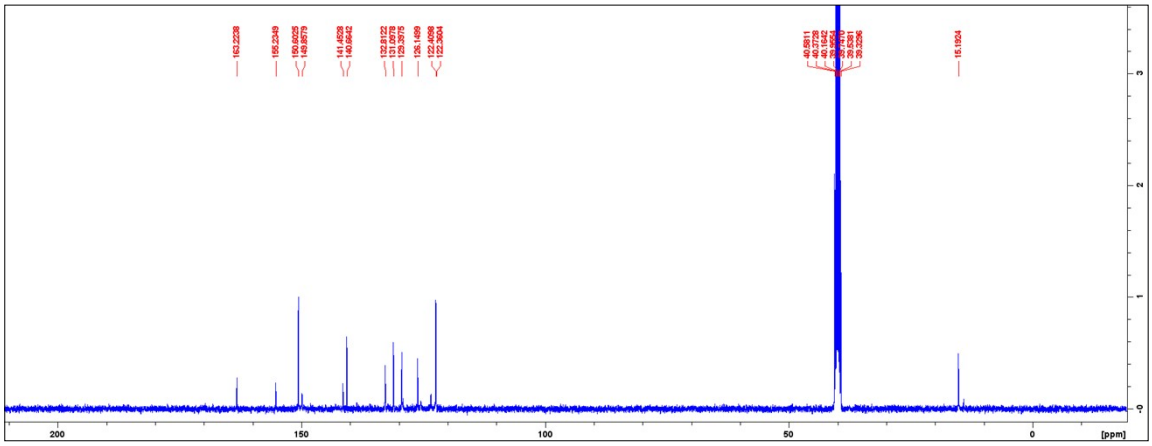


Figure S83: ^{13}C NMR spectrum of (E)-N'-(1-(3-bromophenyl)-ethylidene)isonicotinohydrazide

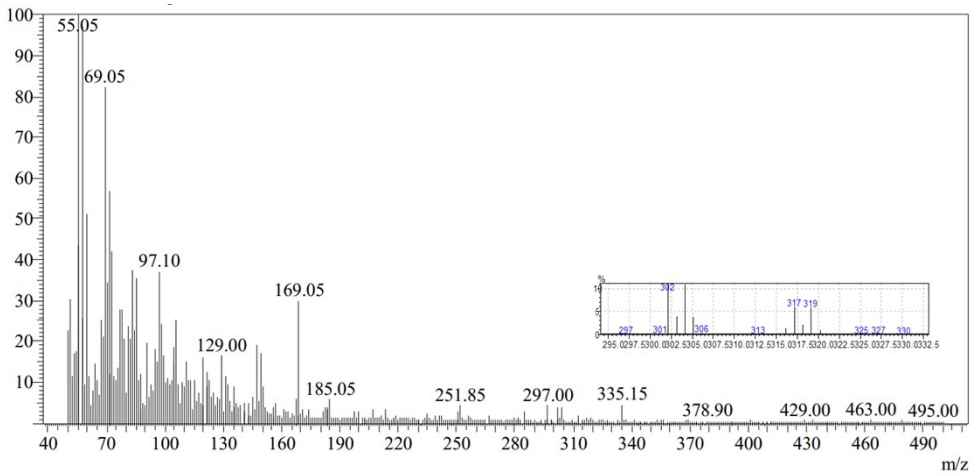


Figure S84: Mass spectrum of (E)-N'-(1-(3-bromophenyl)-ethylidene)isonicotinohydrazide

(E)-N'-(1-(4-fluorophenyl)ethylidene)isonicotinohydrazide (D)

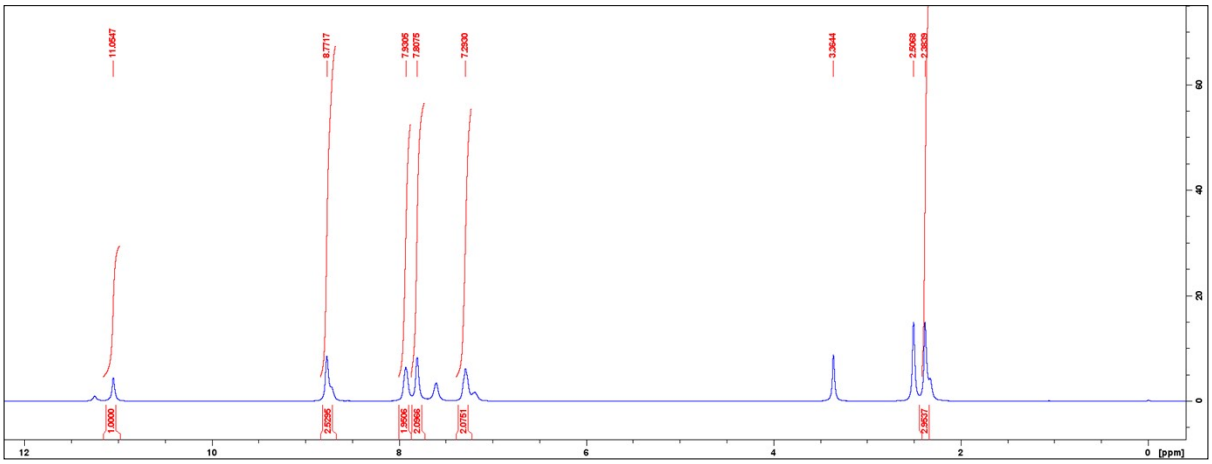


Figure S85: ^{1}H NMR spectrum of (E)-N'-(1-(4-fluorophenyl)-ethylidene)isonicotinohydrazide

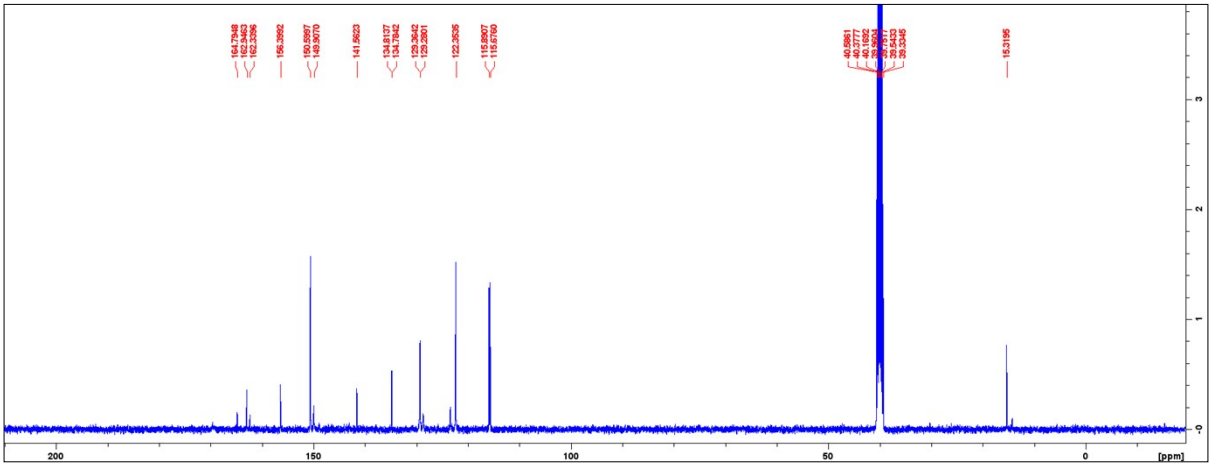


Figure S86: ^{13}C NMR spectrum of (E)-N'-(1-(4-fluorophenyl)-ethylidene)isonicotinohydrazide

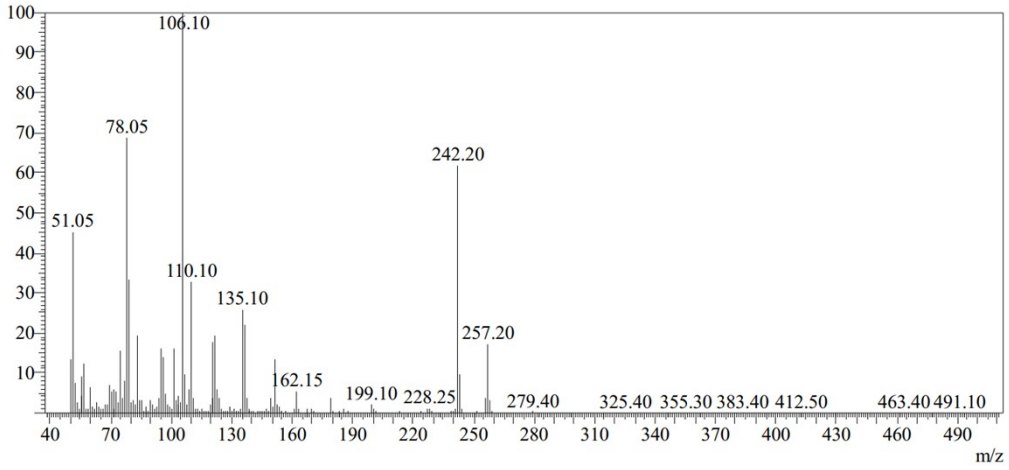


Figure S87: Mass spectrum of (E)-N'-(1-(4-fluorophenyl)-ethylidene)isonicotinohydrazide

(*E*)-*N*'-(1-(4-bromophenyl)ethylidene)isonicotinohydrazide (E)

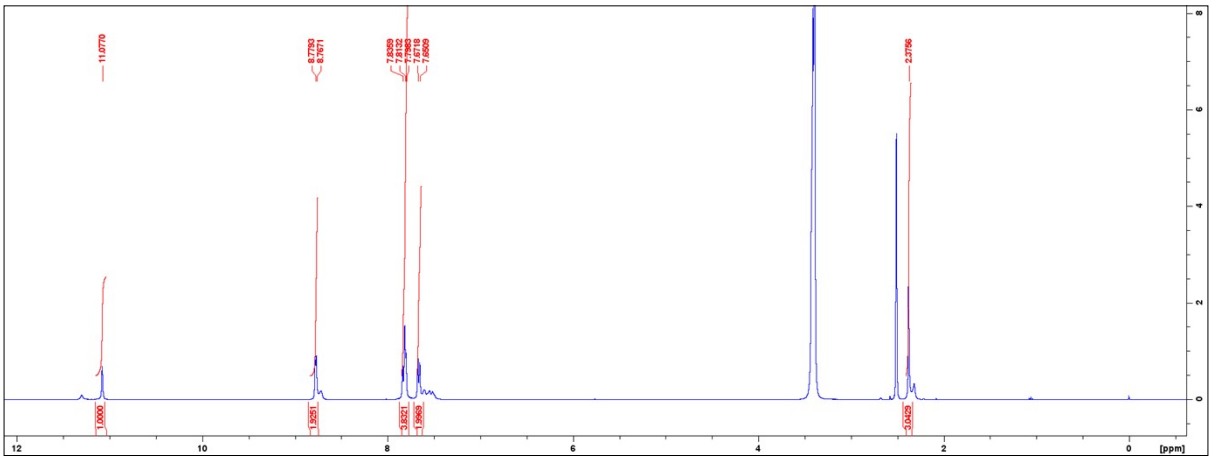


Figure S88: ^{1}H NMR spectrum of (E)-N'-(1-(4-bromophenyl)-ethylidene)isonicotinohydrazide

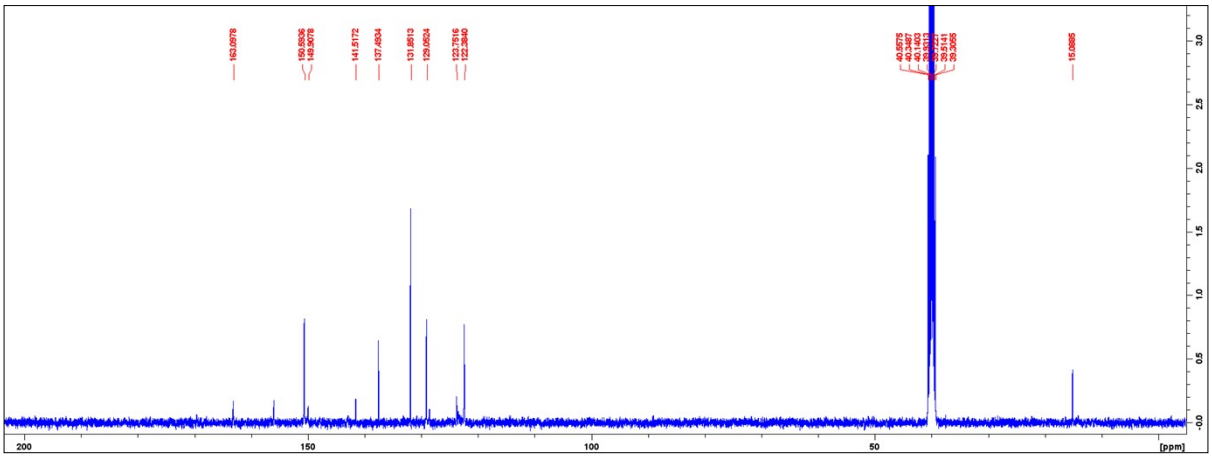


Figure S89: ^{13}C NMR spectrum of (E)-N'-(1-(4-bromophenyl)-ethylidene)isonicotinohydrazide

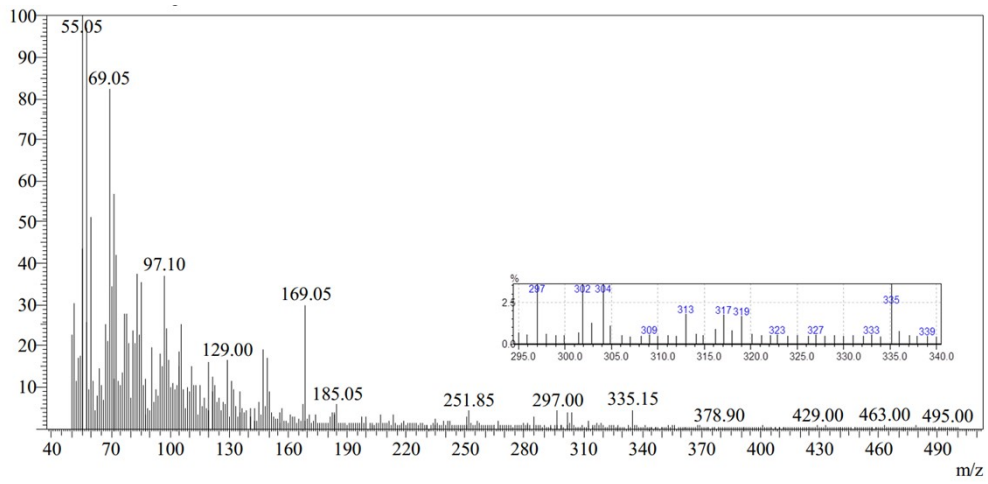


Figure S90: Mass spectrum of (E)-N'-(1-(4-bromophenyl)-ethylidene)isonicotinohydrazide

(*E*)-*N*'-(1-(4-methylphenyl)ethylidene)isonicotinohydrazide (F)

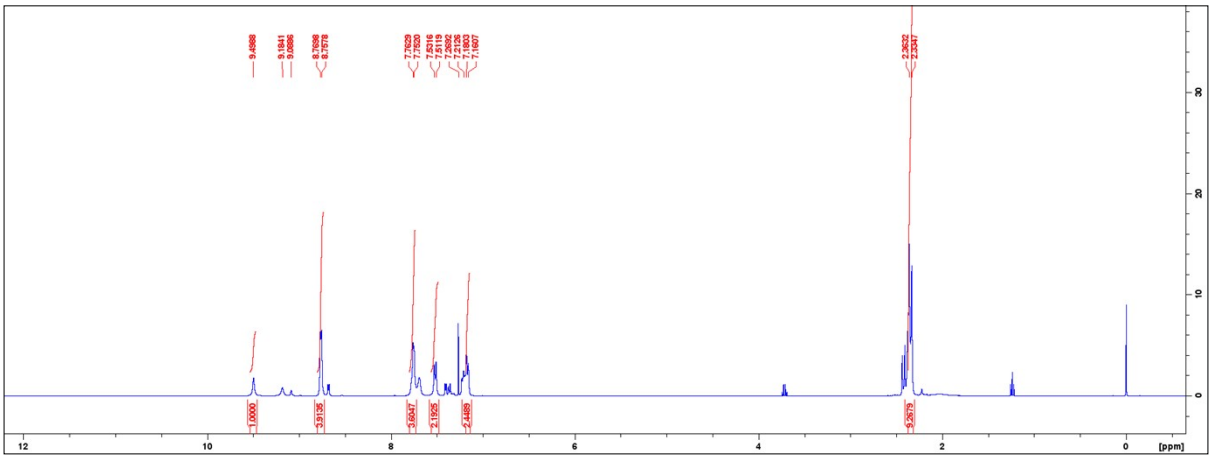


Figure S91: ^{1}H NMR spectrum of (E)-N'-(1-(4-methylphenyl)-ethylidene)isonicotinohydrazide

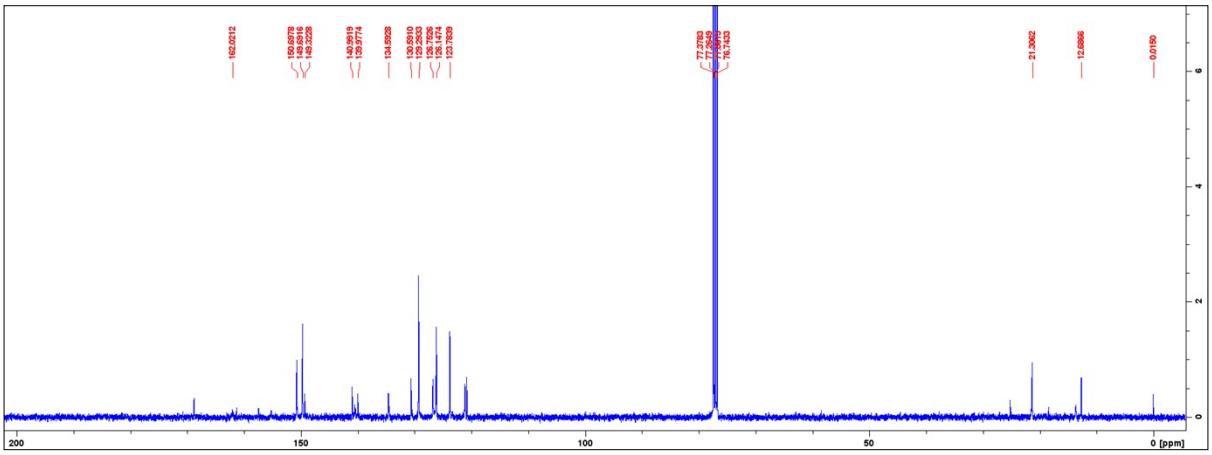


Figure S92: ^{13}C NMR spectrum of (E)-N'-(1-(4-methylphenyl)-ethylidene)isonicotinohydrazide

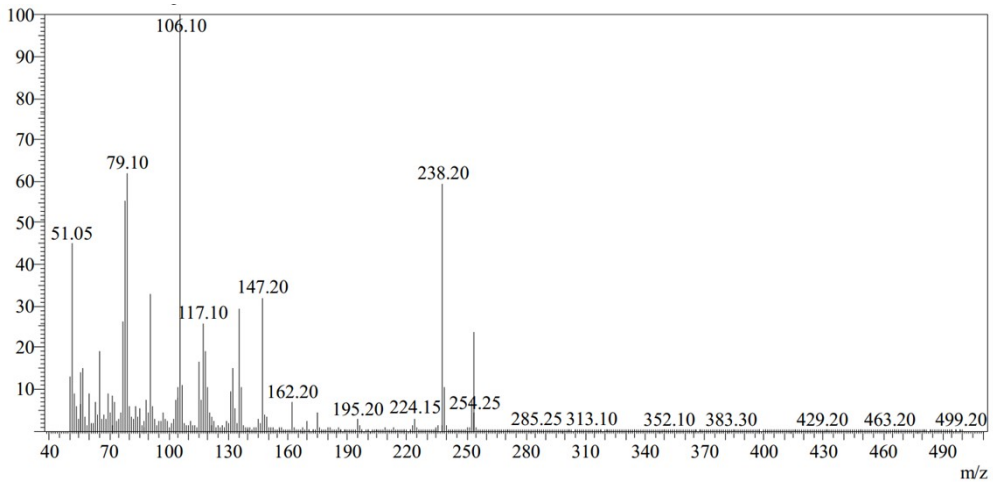


Figure S93: Mass spectrum of (E)-N'-(1-(4-methylphenyl)-ethylidene)isonicotinohydrazide

(*E*)-*N*'-(1-(4-methoxyphenyl)ethylidene)isonicotinohydrazide (G)

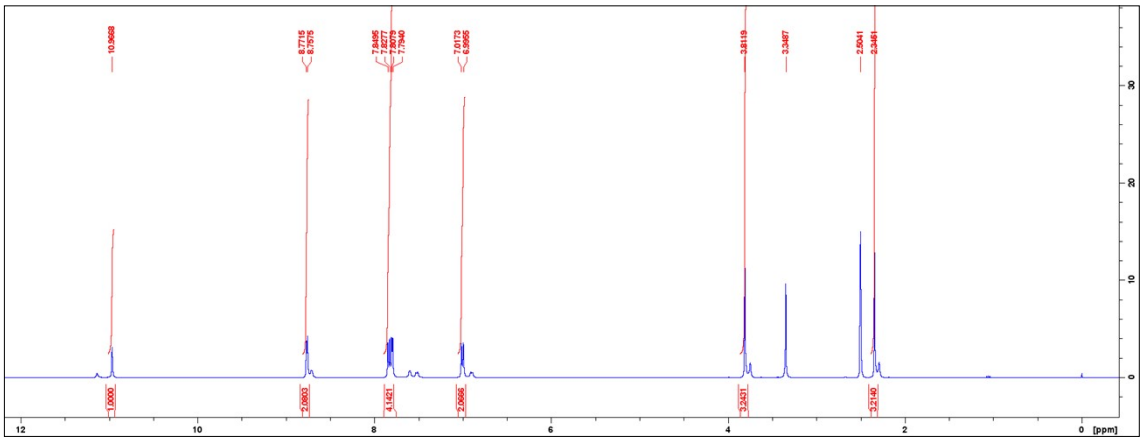


Figure S94: ^{1}H NMR spectrum of (E)-N'-(1-(4-methoxyphenyl) ethylidene)isonicotinohydrazide

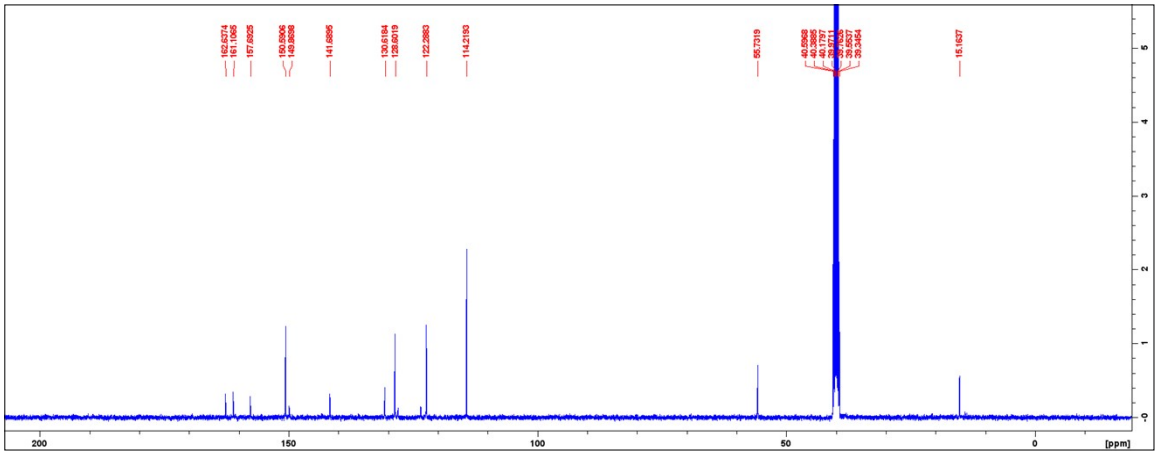


Figure S95: ^{13}C NMR spectrum of (E)-N'-(1-(4-methoxyphenyl) ethylidene)isonicotinohydrazide

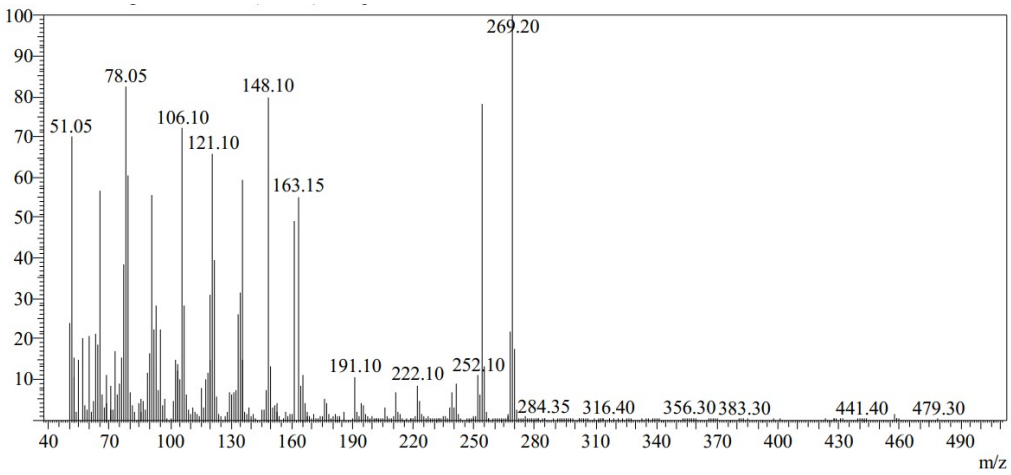


Figure S96: Mass spectrum of (E)-N'-(1-(4-methoxyphenyl) ethylidene)isonicotinohydrazide

(E)-N'-(1-(3-fluorophenyl)ethylidene)isonicotinohydrazide (H)

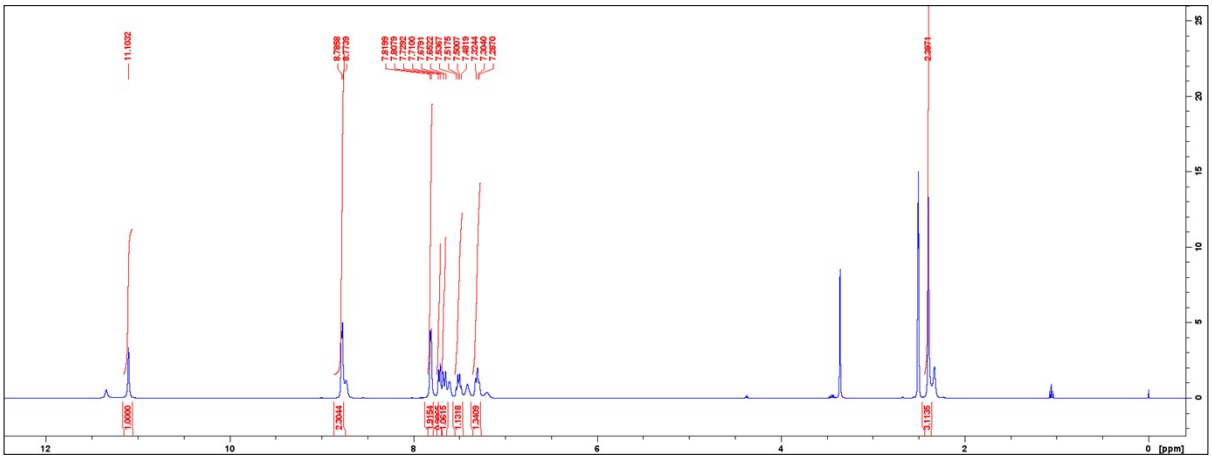


Figure S97: ^{1}H NMR spectrum of (E)-N'-(1-(3-fluorophenyl) ethylidene)isonicotinohydrazide

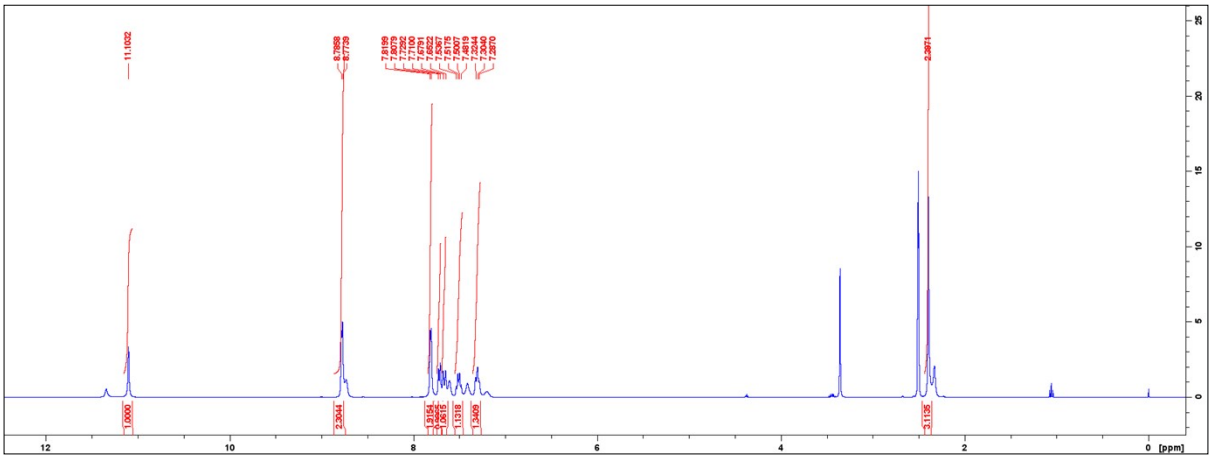


Figure S98: ^{13}C NMR spectrum of (E)-N'-(1-(3-fluorophenyl) ethylidene)isonicotinohydrazide

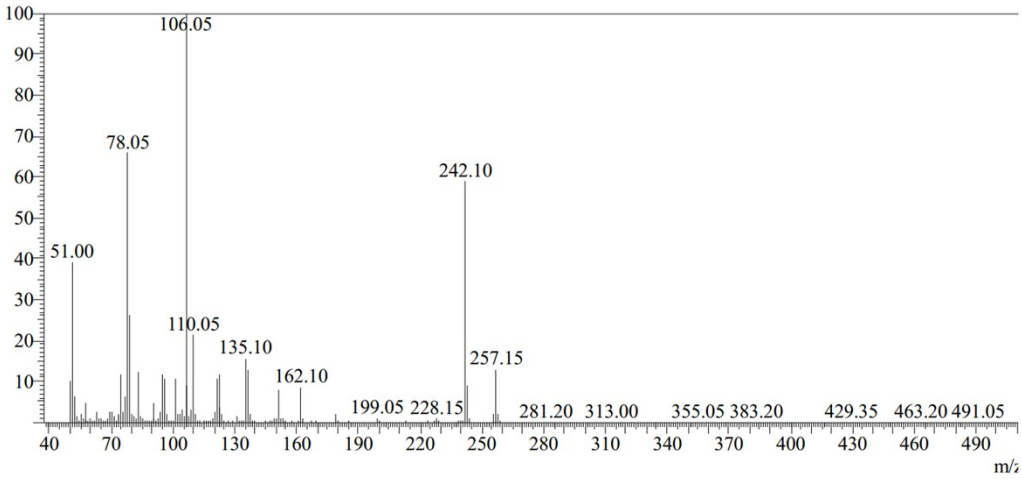


Figure S99: Mass Spectrum of (E)-N'-(1-(3-fluorophenyl) ethylidene)isonicotinohydrazide

(*E*)-*N*'-(1-(4-chlorophenyl)ethylidene)isonicotinohydrazide (I)

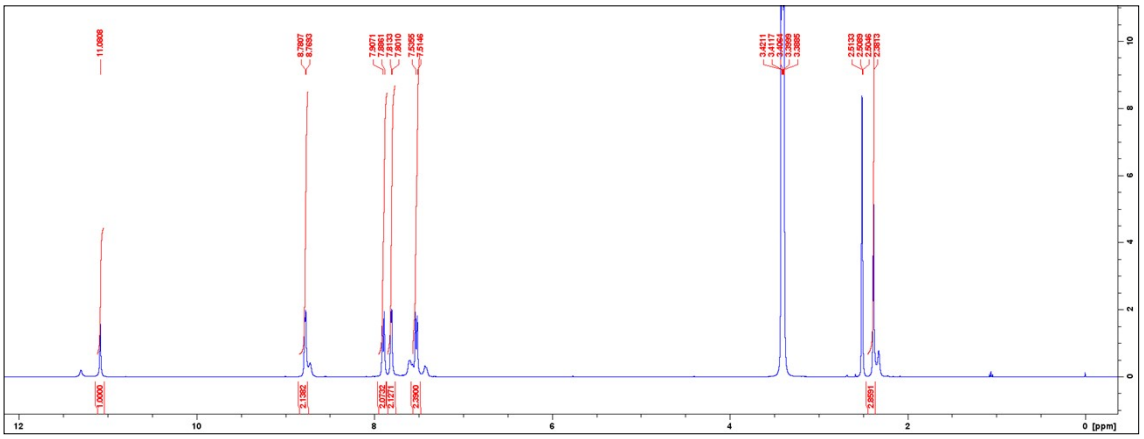


Figure S100: ^{1}H NMR spectrum of (E)-N'-(1-(4-chlorophenyl) ethylidene)isonicotinohydrazide

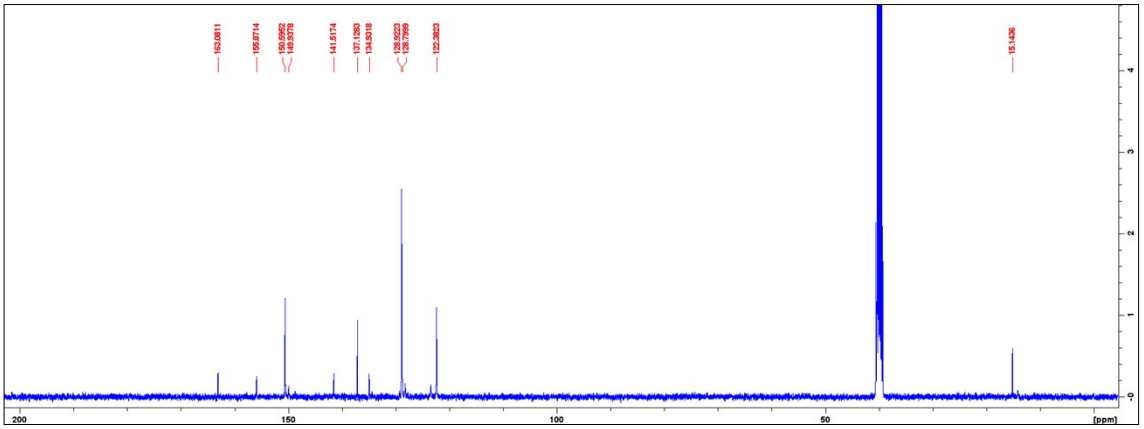


Figure S101: ^{13}C NMR spectrum of (E)-N'-(1-(4-chlorophenyl) ethylidene)isonicotinohydrazide

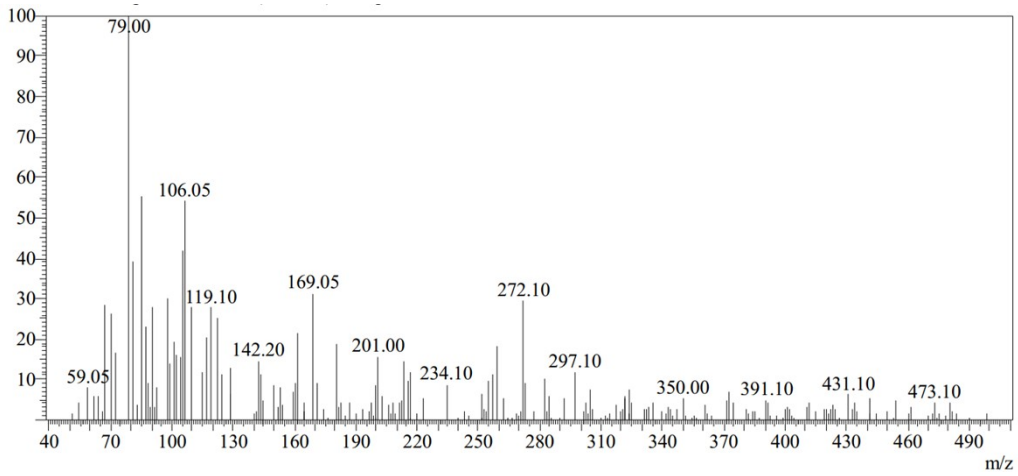


Figure S102: Mass spectrum of (E)-N'-(1-(4-chlorophenyl) ethylidene)isonicotinohydrazide

NCI protocol for *in vitro* anticancer testing

Concisely, in RPMI 1640 medium containing 5% foetal bovine serum and 2 mM L-glutamine, the human tumour cell lines used in the cancer screening panel were cultured. Depending on the doubling time of specific cell lines, 100 µL of each type of cells were plated at densities ranging from 5,000 to 40,000 cells/well in 96-well microtiter plate. Prior to the addition of the test compounds the microtiter plates were incubated for 24 hours at 37° C, 5% CO_2, 95% air, and 100% relative humidity. To reflect a measurement of the cell population for each cell line at the moment of drug administration (Tz), two plates of each cell line were fixed *in situ* with TCA after 24 hours. The test compounds were dissolved in DMSO and added to microplate wells with 100 µL of complete medium and 50 mg/mL gentamicin. The microplates were then incubated at 37 °C, 5% CO_2, 95% air, and 100% relative humidity for 48 hours. The assay was terminated for adherent cells, and cells were fixed by adding 50 µL of cold, 50% (w/v) TCA and allowing them to remain at 4°C for 60 min. The plates were rinsed with tap water five times after the removal of supernatant, and allowed to air dry. All wells were then filled with 100 µL of a 0.4% (w/v) sulforhodamine B (SRB) solution in 1% acetic acid, and the plates were incubated for 10 min at room temperature. Following five rounds of washing with 1% acetic acid to remove unbound colour, the plates were air dried. After the dissolution of bound dye in 10 mM trizma base, the absorbance was measured employing an automated microplate reader at 515 nm. The same protocol was followed for suspension cells, with the exception that the assay was terminated by fixing settling cells at the bottom of the wells by adding 50 µL of 80% TCA. Following equation was used to calculate % growth inhibition:

$$[(Ti-Tz)/(C-Tz)] \times 100 \text{ for concentrations for which } Ti \geq Tz$$

$$[(Ti-Tz)/Tz] \times 100 \text{ for concentrations for which } Ti < Tz.$$

Where, Tz = absorbance at time zero, C = absorbance of control growth, and Ti = absorbance of test after the addition of the test compound.

Table S1: NCI One dose study (10 μM) result of the most active compounds **1a-1g** (compounds selected for five-dose study)

Cancer	Sub Panel	% growth inhibition						
		1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**
Leukemia	CCRF-CEM	2.72	-14.87	-15.57	-3.97	-6.18	-17.82	0.60
	HL-60(TB)	8.64	-15.08	-16.26	-21.73	-8.14	7.26	1.59
	K-562	-10.24	5.00	-2.18	-24.21	7.76	2.59	-31.21
	MOLT-4	4.60	12.72	12.17	1.15	2.63	13.93	8.30
	RPMI-8226	-28.60	-11.69	-6.49	0.90	3.94	-25.20	-27.00
	SR	-18.90	14.71	12.68	9.73	3.62	-25.00	-29.91
Non-Small Cell Lung	A549/ATCC	56.13	-19.19	-17.44	-14.25	-30.55	41.55	7.46
	EKVX	-45.23	8.03	-62.33	-6.56	-50.98	12.93	-59.84
	HOP-62	63.81	0.17	-58.30	-10.71	-46.08	27.39	-59.84
	HOP-92	-12.38	-91.11	-88.44	NT	NT	-9.12	-56.89
	NCI-H226	-30.57	-79.79	-94.47	-83.45	-83.33	-65.34	-34.55
	NCI-H23	-27.15	37.85	-0.56	-67.26	-86.15	-8.25	-44.98
	NCI-H322M	83.73	-3.88	-68.90	44.01	32.00	79.92	-12.60
	NCI-H460	17.96	-59.98	-55.96	-63.46	-82.26	67.01	32.62
	NCI-H522	1.15	-19.19	-17.44	-59.68	-57.50	-58.41	-49.64
Colon	COLO 205	-10.82	-34.95	-58.29	-39.37	-54.57	12.80	-83.10
	HCC-2998	16.92	-91.25	-100.00	-95.31	-98.00	2.89	-24.20
	HCT-116	-20.26	-91.58	-95.92	-88.86	-93.55	-68.50	-19.04
	HCT-15	-80.97	-59.20	-67.53	-56.84	-62.58	-72.86	-35.29
	HT29	-78.95	0.31	1.52	-2.38	0.50	-6.69	-26.28
	KM12	-11.30	-25.18	-67.05	-44.28	-64.29	39.34	-5.21
	SW-620	-10.82	-57.57	-81.14	-60.66	-70.48	NT	3.80
CNS	SF-268	36.50	34.28	-22.72	16.93	-13.30	54.20	-41.88
	SF-295	50.18	-32.78	-78.59	-26.76	-65.61	49.51	-87.21
	SF-539	-74.77	-89.83	-97.78	-83.19	-94.43	-88.13	18.52
	SNB-19	45.28	5.54	-87.86	21.62	-36.55	37.67	-16.53
	SNB-75	105.27	-85.82	NT	-83.19	NT	87.82	-76.05
	U251	-18.59	34.28	-90.85	16.93	-86.74	-63.31	3.80
Melanoma	LOX IMVI	NT	-100.00	-100.00	-100.00	-100.00	NT	NT
	MALME-3M	-81.19	-50.66	-74.48	-44.71	-70.73	-52.61	-62.10
	M14	-17.48	-73.43	-75.72	-63.38	-69.47	-42.21	-50.88
	MDA-MB-435	1.50	-32.51	-50.23	-62.18	-64.39	-16.59	-52.16
	SK-MEL-2	73.81	-23.75	-69.80	-39.02	-68.41	51.39	-42.22
	SK-MEL-28	-55.21	-76.63	-76.74	-75.59	-77.96	6.80	-52.17
	SK-MEL-5	-77.24	-79.55	-99.60	-79.01	-97.04	-63.94	-94.29
	UACC-257	13.47	-33.09	-71.99	-44.57	-71.38	-0.18	-24.59
	UACC-62	-12.68	-86.94	-83.17	-73.69	-79.09	-31.27	-75.22
Ovarian	IGROV1	30.61	-44.11	-60.16	-31.07	-44.91	24.03	17.06
	OVCAR-3	34.66	-61.95	-97.64	-68.60	-78.90	-23.14	5.62
	OVCAR-4	11.49	35.17	10.80	32.89	8.76	31.90	3.78
	OVCAR-5	22.65	-62.03	-76.24	-42.22	-75.90	20.44	-27.14
	OVCAR-8	32.98	-23.31	-42.49	1.20	-9.48	-21.75	-3.29
	NCI/ADR-RES	37.82	-56.43	-50.15	-45.62	-40.00	-41.80	16.67
	SK-OV-3	107.27	49.55	-33.05	46.57	-31.82	79.93	6.09
Renal	786-0	-72.81	-92.75	-95.54	-89.18	-95.48	-64.00	-89.71
	A498	137.36	150.96	-93.72	146.42	97.78	133.28	50.21

	ACHN	11.05	-87.44	-100.00	-80.29	-100.00	-53.54	3.82
	CAKI-1	11.38	32.58	-39.33	1.51	-40.88	50.26	-23.45
	RXF 393	-59.37	-91.01	-90.80	-86.03	-89.12	-31.68	-58.51
	SN12C	21.86	-69.57	-77.70	-51.45	-64.89	7.06	-14.31
	TK-10	-8.55	3.28	-59.65	-19.07	-65.00	49.02	5.62
	UO-31	-0.82	-94.37	-99.98	-80.39	-92.05	4.54	-44.25
Prostate	PC-3	33.34	-0.11	-47.87	8.84	-44.09	37.60	39.27
	DU-145	5.40	25.53	-85.50	-23.04	-78.55	37.16	-27.21
Breast	MCF7	-28.32	NT	NT	NT	NT	8.74	2.05
	MDA-MB-231/ATCC	8.20	-52.69	-47.31	-40.50	-65.78	-49.82	-28.86
	HS 578T	NT	26.80	5.37	44.78	19.12	NT	NT
	BT-549	52.20	-92.39	-94.24	-93.40	-96.59	-30.53	-32.90
	T-47D	19.27	-2.68	-6.99	11.56	12.20	39.44	6.85
	MDA-MB-468	-37.04	-84.32	-95.39	-82.44	-85.86	-49.34	-7.84

*NT- Not Tested

Table S2: Total growth inhibition (TGI) of the most active compounds from NCI five-dose study

Cancer	**Sub Panel**	**TGI (μM)**			
		1b	**1c**	**1g**	**1e**
Leukemia	CCRF-CEM	11.40	>100	6.90	44.20
	HL-60(TB)	16.30	7.43	14.70	17.60
	K-562	10.50	8.65	>100	13.60
	MOLT-4	18.20	18.70	>100	15.40
	RPMI-8226	7.02	10.00	>100	>100
	SR	NT	NT	>100	NT
Non-Small Cell Lung	A549/ATCC	30.40	14.10	19.50	26.40
	EKVX	13.90	4.81	10.50	17.70
	HOP-62	32.00	13.70	14.20	37.30
	HOP-92	22.30	5.10	5.00	22.70
	NCI-H226	3.21	3.90	18.40	4.32
	NCI-H23	15.90	3.62	7.96	23.10
	NCI-H322M	22.10	18.0	27.40	25.60
	NCI-H460	25.60	6.29	3.90	29.70
	NCI-H522	3.59	3.77	7.81	5.75
Colon	COLO 205	19.50	4.48	3.73	18.10
	HCC-2998	11.50	3.53	8.28	21.40
	HCT-116	3.93	3.65	3.57	5.19
	HCT-15	3.81	3.78	8.37	5.30
	HT29	6.80	4.81	7.91	10.50
	KM12	13.10	6.13	5.43	29.20
	SW-620	5.95	5.05	5.56	6.36
CNS	SF-268	41.40	40.30	>100	42.30
	SF-295	16.10	3.99	4.77	25.40
	SF-539	3.36	3.22	4.36	5.67
	SNB-19	12.30	7.86	19.4	25.70
	SNB-75	NT	NT	5.86	NT
	U251	5.29	3.36	10.70	19.90
Melanoma	LOX IMVI	2.83	2.70	3.42	2.72

	MALME-3M	4.26	4.24	3.64	17.70
	M14	5.88	7.22	13.20	16.70
	MDA-MB-435	7.62	14.10	6.42	15.30
	SK-MEL-2	8.53	5.90	17.80	20.80
	SK-MEL-28	4.05	3.83	5.91	4.95
	SK-MEL-5	5.37	3.19	2.95	23.40
	UACC-257	27.00	9.70	8.92	27.50
	UACC-62	3.62	3.15	4.06	15.80
Ovarian	IGROV1	15.80	6.46	30.25	30.90
	OVCAR-3	3.77	3.99	20.00	4.49
	OVCAR-4	45.70	30.10	5.87	32.80
	OVCAR-5	14.00	4.72	>100	23.10
	OVCAR-8	7.70	6.17	13.40	61.90
	NCI/ADR-RES	42.10	3.65	>100	6.91
	SK-OV-3	35.10	21.40	67.40	32.20
Renal	786-0	11.70	3.60	3.60	18.80
	A498	32.60	3.54	50.50	3.60
	ACHN	6.95	3.97	14.10	6.16
	CAKI-1	14.60	7.05	12.10	22.00
	RXF 393	3.24	3.23	3.40	4.42
	SN12C	10.50	4.78	16.50	21.50
	TK-10	25.70	18.9	16.70	33.40
	UO-31	NT	NT	3.91	NT
Prostate	PC-3	30.70	11.6	>100	30.30
	DU-145	19.50	9.43	10.10	23.60
Breast	MCF7	9.16	3.95	11.80	10.40
	MDA-MB-231/ATCC	NT	NT	5.48	NT
	HS 578T	62.70	59.40	>100	>100
	BT-549	6.03	3.00	7.22	12.30
	T-47D	NT	NT	>100	NT
	MDA-MB-468	4.97	3.22	5.60	9.41

*NT- Not Tested

Table S3: 50% lethal concentration (LC_{50}) of the most active compounds from NCI five-dose study

Cancer	**Sub Panel**	**LC_{50} (µM)**			
		1c	**1b**	**1g**	**1e**
Leukemia	CCRF-CEM	>100	>100	>100	>100
	HL-60(TB)	>100	>100	>100	>100
	K-562	>100	>100	>100	>100
	MOLT-4	>100	>100	>100	>100
	RPMI-8226	>100	>100	>100	>100
	SR	>100	>100	>100	>100
Non-Small Cell Lung	A549/ATCC	>100	93.50	62.20	62.40
	EKVX	13.20	38.20	>100	45.30
	HOP-62	56.60	67.10	86.30	73.80
	HOP-92	47.20	90.50	6.20	79.40

	NCI-H226	59.10	6.20	6.55	9.69
	NCI-H23	71.30	42.70	8.20	50.60
	NCI-H322M	43.00	47.30	>100	52.60
	NCI-H460	40.30	69.00	7.01	70.00
	NCI-H522	74.80	7.38	6.06	23.30
Colon	COLO 205	92.40	65.10	NT	69.00
	HCC-2998	6.68	34.70	5.98	47.40
	HCT-116	. >100	8.37	NT	29.20
	HCT-15	8.63	8.13	7.20	39.30
	HT29	21.50	37.10	6.73	43.10
	KM12	>100	59.20	6.63	NT
	SW-620	20.00	29.80	8.55	33.80
CNS	SF-268	NT	99.30	7.77	53.30
	SF-295	8.68	41.70	5.39	19.80
	SF-539	5.94	6.38	5.70	76.30
	SNB-19	NT	65.80	34.60	45.70
	SNB-75	>100	18.30	24.40	53.30
	U251	6.24	99.30	5.78	19.80
Melanoma	LOX IMVI	5.25	5.57	5.47	5.39
	MALME-3M	9.33	9.87	5.59	47.20
	M14	57.90	31.60	7.27	56.80
	MDA-MB-435	>100	90.50	6.51	85.10
	SK-MEL-2	25.60	35.40	6.02	54.60
	SK-MEL-28	7.58	8.29	7.01	15.00
	SK-MEL-5	5.81	17.50	5.41	52.70
	UACC-257	66.50	65.20	6.56	64.10
	UACC-62	6.41	7.75	9.48	41.20
Ovarian	IGROV1	49.30	57.10	6.52	68.90
	OVCAR-3	7.88	7.33	5.84	9.71
	OVCAR-4	>100	>100	>100	>100
	OVCAR-5	11.70	43.40	9.52	53.40
	OVCAR-8	>100	>100	5.97	>100
	NCI/ADR-RES	>100	>100	>100	>100
	SK-OV-3	66.30	76.60	>100	61.90
Renal	786-0	6.75	41.40	>100	48.40
	A498	60.20	57.60	39.20	55.60
	ACHN	8.09	31.30	5.41	24.00
	CAKI-1	27.60	40.50	5.54	52.10
	RXF 393	5.88	6.06	4.98	10.80
	SN12C	14.50	36.20	65.10	51.60
	TK-10	54.70	53.40	8.77	60.50
	UO-31	>100	>100	5.25	48.40
Prostate	PC-3	>100	>100	>100	>100
	DU-145	69.40	63.50	16.40	60.10
Breast	MCF7	>100	>100	>100	44.20
	MDA-MB-231	25.00	>100	6.01	>100
	HS 578T	>100	49.90	>100	>100
	BT-549	6.26	27.40	>100	44.60
	T-47D	>100	>100	>100	>100
	MDA-MB-468	6.44	18.10	6.16	36.10

*NT- Not Tested