Electronic Supplementary Material (ESI) for RSC Advances.
This journal is © The Royal Society of Chemistry 2016

Supplementary Information

Bovine Serum Albumin catalyzed one-pot, three-component synthesis of dihydropyrano[2,3-c]pyrazole derivatives in aqueous ethanol

Kiran S. Dalal[a], Yogesh A. Tayade[b], Yogesh B. Wagh[b], Darshak R. Trivedi[c], Dipak S. Dalal[b] and Bhushan L. Chaudhari[a]*

[a] School of Life Sciences, North Maharashtra University, Jalgaon - 425 001 (MS) India.

[b] School of Chemical Sciences, North Maharashtra University, Jalgaon - 425 001 (MS) India.

[c] Supramolecular Chemistry Laboratory, Department of Chemistry, National Institute of Technology Karnataka (NITK), Srinivasnagar, Surathkal, Mangalore 575025 Karnataka, India.

*Corresponding author. Tel.: +91 2572257424; Fax: +91-2572258403

*E-mail address: blchaudhari@nmu.ac.in, blchaudhari@hotmail.com

---

CONTENT

Experimental

General Information

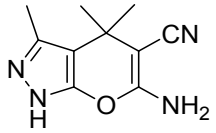
Lipase from porcine pancreas (Type II, 100-400 units/mg protein, PCode: 1001673475, Lot # SLBH6427V), Lipase from *Candida rugosa* type VII, 700 units/mg, PCode: 101476316, Lot # BCBM7677V was purchased from Sigma Aldrich. Trypsin from Porcine (1000-1500 units/mg, Lot# 0000193847), Trypsin from Bovine (0.2 Anson U/g, RM 618, Lot# 0000003913), Diastase α-Amylase from *Aspergillus oryzae* (1300 lu/gm, RM 638, Lot4-1843), Papain from Papaya latex (RM 058) were purchased from Hi media and 3-methyl-1-phenyl-2-pyrazoline-5-one (PCode: M70800-100G, Lot #BCBP1308V) were purchased from Sigma Aldrich. All other chemicals including ketones, isatins, and malononitrile were purchased from Spectrochem, India used without further purification. 3-methyl-1H-pyrazol-5(4H)-one was prepared by reaction of beta-keto ester and hydrazine hydrate. Reactions were monitored by thin-layer chromatography (TLC) using silica gel-coated plates and EtOAc/hexane solutions as the mobile phase. Spots were visualized under UV light. Melting points were recorded in open glass capillary method and are uncorrected. . Infrared (IR) spectra were obtained by Perkin-Elmer Spectrum using KBr pellets. ^{1}H NMR and ^{13}C NMR were recorded on Bruker Avance-II spectrophotometer operating at 400 MHz and 100 MHz. The mass spectra were recorded under ESI mode with Waters micromass equipment (model Q-TOF MICROMASS).

General procedure for synthesis of dihydropyran[2,3-c]pyrazoles (4a-n) and spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives (6a-j):

In a 25 ml round bottom flask, the mixture of ketone (2 mmol) or isatin (2 mmol), malononitrile (2 mmol), 3-methyl-1*H*-pyrazol-5(4*H*)-one (2 mmol) and bovine serum albumin (60 mg) was added in mixture of H_2O: Ethanol (7:3). The resulting suspension was stirred at 40 °C for

appropriate reaction time. For isatins, reactions were carried out at room temperature. The progress of reaction was monitored by TLC (Ethyl acetate: Hexane, 1:1). After completion of the reaction, the reaction mixture was poured into water under constant stirring. Filtered the product and washed with water. The crude product was recrystallized from 20% aqueous ethanol to afford the pure desired product.

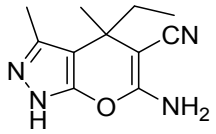
Characterization data



6-amino-3,4,4-trimethyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4a**)

FT-IR (KBr) ν_{max}(cm^{-1}): 1035, 1458, 1488, 1635, 2183, 2962, 3533, 3481 cm^{-1};

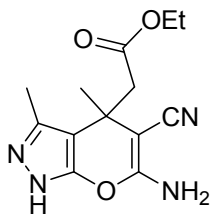
^{1}H-NMR (400 MHz, DMSO-*d_6*) δ: 1.36 (s, 6H), 2.25 (s, 3H), 6.52 (s, 2H), 11.99 (s, 1H); **^{13}C-NMR (100 MHz, DMSO-*d_6*) δ:** 10.7, 30.0, 30.1, 63.6, 102.1, 119.8, 134.5, 153.6; **MS (ESI)** *m/z* = 205[M+1] 100%.



6-amino-4-ethyl-3,4-dimethyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4b**)

FT-IR (KBr) ν_{max}(cm^{-1}): 807, 1390, 1608, 1639, 2190, 2963, 3309, 3450, cm^{-1};

^{1}H-NMR (400 MHz, DMSO-*d_6*) δ: 0.59 (t, *J* = 7.2 Hz, 3H), 1.36 (s, 3H), 1.50-1.59 (m, 1H), 1.61-1.70 (m, 1H), 2.19 (s, 3H), 6.54 (s, 2H), 11.97 (s, 1H); **^{13}C-NMR (100 MHz, DMSO-*d_6*) δ:** 9.5, 10.7, 29.5, 32.8, 34.8, 60.6, 99.2, 119.5, 134.2, 155.1, 161.2; **MS (ESI):** *m/z* = 219[M+1] 100%; **HRMS Analysis (TOF MS ES+)** found 219.1151 $[M+H]^+$; $C_{11}H_{14}N_4O$ requires Mol. Wt.: 218.1168.



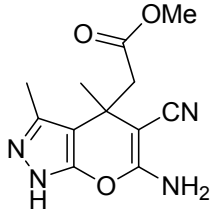
Ethyl 2-(6-amino-5-cyano-3,4-dimethyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)acetate (**4c**)

FT-IR (KBr) ν_{max}(cm^{-1}): 1146, 1483, 1593, 1733, 2198, 2977, 3314, 3434, cm^{-1};

^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ: 0.95 (t, *J* = 7.12 Hz, 3H), 2.23 (s, 3H), 1.41(s, 3H), 2.49 (d, *J* = 13.8 Hz, 1H), 2.64 (d, *J* = 13.8 Hz, 1H), 3.80-3.86 (m, 2H), 6.70 (s, 2H), 12.03 (s, 1H);

^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ: 10.8, 13.6, 29.5, 33.2, 45.0, 59.2, 60.9, 99.1, 119.7, 135.1, 154.4, 160.8, 169.5; **MS (ESI)**: *m/z* = 277[M+1] 100%;

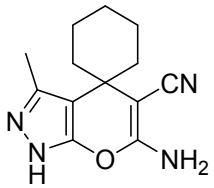
HRMS Analysis (TOF MS ES+) found 299.0899 $[M+ Na]^+$; $C_{13}H_{16}N_4O_3$ requires Mol. Wt.: 276.1222.



Methyl 2-(6-amino-5-cyano-3,4-dimethyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)acetate (**4d**)

FT-IR (KBr) ν_{max}(cm^{-1}): 1403, 1488, 1593, 1691, 1714, 2184, 3143, 3286, 3379; cm^{-1};

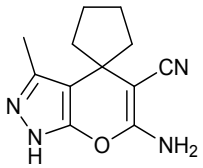
^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ: 1.41 (s, 3H), 2.22 (s, 3H), 2.53 (d, *J* = 14.3 Hz, 1H), 2.67 (d, *J* = 14.3 Hz, 1H), 3.39 (d, *J* = 2.4Hz, 3H), 6.71 (s, 2H), 12.02 (s, 1H); **^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ:** 10.7, 29.2, 32.9, 45.1, 50.9, 60.7, 99.3, 119.7, 134.9, 154.4, 160.9, 170.1; **MS(ESI)** *m/z*= 285[M+Na] 100%; **HRMS Analysis (TOF MS ES+)** found 263.1063 $[M+ H]^+$; $C_{12}H_{14}N_4O_3$ requires Mol. Wt.: 262.1066.



6'-amino-3'-methyl-1'H-spiro[cyclohexane-1,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (**4e**)

FT-IR (KBr) ν_{max}(cm^{-1}): 1393, 1487, 1583, 1636, 3160, 3206, 3328 cm^{-1};

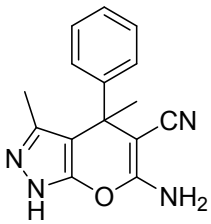
^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.26-1.33 (m, 1H), 1.53-1.57 (m, 2H), 1.70-1.85 (m, 5H), 2.04-2.14 (m, 2H), 2.26 (s, 3H), 6.58 (s, 2H), 12.04 (s, 1H); **^{13}C-NMR (100 MHz, DMSO- d_6) δ:** 11.6, 21.5, 24.8, 32.8, 60.4, 103.6, 124.0, 134.1, 154.1, 161.5; **MS(ESI)** *m/z*= 240[M-3] 100%.



6'-amino-3'-methyl-1'H-spiro[cyclopentane-1,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (**4f**)

FT-IR (KBr) ν_{max}(cm^{-1}): cm^{-1}; 653, 817, 1035, 1170, 1390, 1469, 1633, 2187, 3113, 3348, 3452;

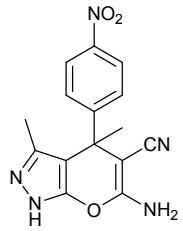
^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.75-1.79 (m, 2H), 1.82-1.94 (m, 6H), 2.22 (s, 3H), 6.36 (s, 2H), 11.94 (s, 1H); **^{13}C-NMR (100 MHz, DMSO- d_6) δ:** 10.9, 26.6, 43.4, 64.5, 103.4, 121.2, 133.5, 154.0, 159.4; **MS(ESI)** *m/z*= 231[M+1] 100%.



6-amino-3,4-dimethyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4g**)

FT-IR (KBr) ν_{max}(cm^{-1}): 747.31, 1363, 1422, 1478, 1565, 1667, 2180, 3208, 3397 cm^{-1};

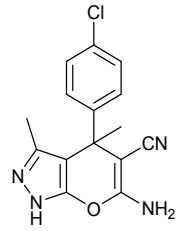
^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.76 (s, 3H), 1.79 (s, 3H), 6.78 (s, 2H), 7.17-7.21 (m, 1H), 7.24-7.26 (m, 2H), 7.29-7.33 (m, 2H), 12.12 (s, 1H); **^{13}C-NMR (100 MHz, DMSO-d_6) δ:** 10.2, 27.1, 37.4, 64.5, 102.5, 119.9, 126.0, 126.3, 128.0, 134.9, 147.2, 153.9, 159.9; **MS(ESI)** *m/z*= 266 [M+1] 100%.



6-amino-1,4-dihydro-3,4-dimethyl-4-(4-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (**4h**)

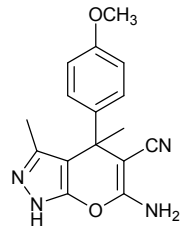
FT-IR (KBr) ν_{max}(cm^{-1}): cm^{-1}; 611, 702, 833, 1004, 1068, 1170, 1340, 1402, 1591, 2193, 3250, 3471;

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.81 (s, 3H), 1.83 (s, 3H), 6.86 (s, 2H), 7.52 (dd, *J*= 1.96 & 1.91 Hz, 2H), 8.17 (dd, *J* =1.92 & 1.87 Hz, 2H,), 12.17 (s, 1H); **^{13}C-NMR (100 MHz, DMSO-d_6) δ:** 10.1, 26.9, 37.8, 63.4, 101.3, 119.4, 123.1, 127.7, 135.0, 145.7, 153.8, 154.7, 160.1; **MS(ESI)** *m/z*= 312 [M+1] 100%.



6-amino-4-(4-chlorophenyl)-1,4-dihydro-3,4-dimethylpyrano[2,3-c]pyrazole-5-carbonitrile (**4i**)

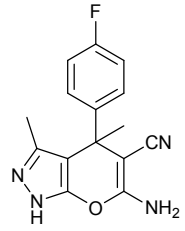
FT-IR (KBr) ν_{max}(cm^{-1}): 537, 695, 961, 1063, 1115, 1399, 1373, 1457, 1594, 2186, 3144, 3289 cm^{-1}; **^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ**: 1.76 (s, 3H), 1.81 (s, 3H), 6.76 (s, 2H), 7.25-7.28 (m, 2H), 7.31-7.34 (m, 2H), 12.12 (s, 1H); **^{13}C-NMR (100 MHz, DMSO- *d*$_6$) δ:** 10.1, 27.1, 37.2, 64.2, 102.0, 119.7, 127.8, 128.3, 130.8, 134.9, 146.2, 153.9, 159.9; **MS(ESI)** *m/z*= 301 [M+1] 100%.



6-amino-4-(4-methoxyphenyl)-3,4-dimethyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4j**)

FT-IR (KBr) ν_{max}(cm^{-1}): 1507, 1084, 1400, 1651, 2189, 3170, 3318, cm^{-1}

^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ: 1.72 (s, 3H,), 1.79 (s, 3H), 3.72 (s, 3H), 6.73 (s, 2H), 6.85 (d, *J* = 6.8 Hz, 2H), 7.15(d, *J* = 6.8 Hz, 2H), 12.10 (s, 1H); **^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ:** 10.2, 27.4, 36.8, 54.9, 64.9, 102.7, 113.2, 119.9, 127.5, 134.9, 139.3, 153.9, 157.3, 159.7; **MS(ESI)** *m/z*= 298 [M+2] 80%.



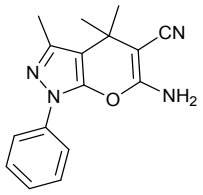
6-amino-4-(4-fluorophenyl)-3,4-dimethyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4k**)

FT-IR (KBr) ν_{max}(cm^{-1}): 3450, 3295, 3160, 2187, 1641, 1611, 1509, 1485 cm^{-1}

^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ: 1.77 (s, 3H), 1.80 (s, 3H), 6.70 (s, 2H), 7.04-7.09 (m, 2H),

---

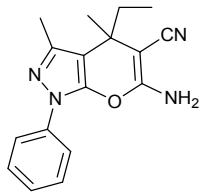
7.26-7.29 (m, 2H), 12.09 (s, 1H); **^{13}C-NMR (100 MHz, DMSO- d_6) δ:** 10.1, 27.4, 37.0, 64.5, 102.2, 114.4 (d, J_{FCC} = 21), 119.7, 128.3 (d, J_{FCCC} = 8), 134.8, 143.3 (d, J_{FCCCC} = 3), 153.9, 159.8, 160.4 (d, J_{FC} = 242.4); **MS (ESI):** *m/z* = 285 [M+1] 100%; **HRMS Analysis (TOF MS ES+)** found 285.1098 $[M+1]^+$; $C_{15}H_{13}FN_4O$ requires Mol. Wt.: 284.1073.



6-amino-3,4,4-trimethyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4m**)

FT-IR (KBr) ν_{max}(cm^{-1}): 657, 694, 1150, 1258, 1529, 1651, 2191, 2931, 2968, 3197, 3315 cm^{-1}

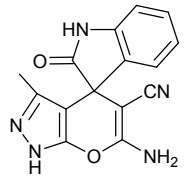
^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.65 (t, *J* = 7.1 Hz, 3H), 1.42 (s, 3H), 1.58 (q, *J* = 7.2 Hz, 1H), 1.74 (q, *J*= 7.2 Hz, 1H), 2.23 (s, 3H), 6.92 (s, 2H), 7.25-7.29 (m, 1H), 7.47-7.43 (m, 2H), 7.75-7.77 (m, 2H); **^{13}C-NMR (100 MHz, DMSO-d_6) δ:** 9.6, 13.9, 29.4, 32.3, 35.7, 61.4, 100.0, 118.7, 119.7, 125.7, 129.0, 137.5, 143.9, 144.3, 159.9; **HRMS Analysis (TOF MS ES+)** found 281.1239 $[M+1]^+$; $C_{16}H_{16}N_4O$ requires Mol. Wt.: 280.1324.



6-amino-4-ethyl-3,4-dimethyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4n**)

FT-IR (KBr) ν_{max}(cm^{-1}): 583, 696, 764, 2930, 2188, 1650, 1596, 1456, 1596, 1650, 2188, 2930, 2962, 3384 cm^{-1}; **^{1}H-NMR (400 MHz, DMSO-d_6) δ**: 1.43 (s, 6H), 2.13 (s, 1H), 2.28 (s, 3H), 2.29 (s, 1H), 6.85 (s, 2H), 7.27-7.29 (m, 1H), 7.44 (t, J = 7.98 Hz, 2H), 7.74-7.76 (m, 2H); **^{13}C-NMR**

(100 MHz, DMSO- d_6) δ: 13.9, 29.8, 30.9, 64.3, 102.9, 119.1, 120.0, 126.1, 129.2, 137.4, 142.6, 144.5, 158.6; **HRMS Analysis (TOF MS ES+)** found 295.1547 $[M+1]^+$; $C_{17}H_{18}N_4O$ requires Mol. Wt.: 294.1481

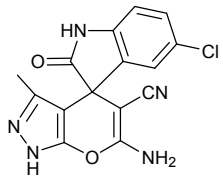


6'-amino-3'-methyl-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (**6a**)

FT-IR (KBr) ν_{max}(cm^{-1}):1470, 1518, 1641, 1712, 2183, 3135, 3371, cm^{-1};

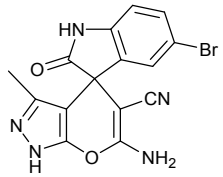
^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.56 (s, 3H), 6.91 (d, *J* = 7.72 Hz, 1H), 6.96-7.04 (m, 2H), 7.12 (s, 2H), 7.20-7.24 (m, 1H), 10.54 (s, 1H), 12.20 (s, 1H); **^{13}C-NMR (100 MHz, DMSO-d_6) δ:** 8.9, 47.2, 55.2, 95.3, 109.6, 118.6, 122.3, 124.3, 128.67, 132.6, 134.6, 141.4, 155.2, 162.4, 178.0;

MS (ESI): *m/z* = 292[M-1] 100%.



6'-amino-3'-methyl-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (**6b**)

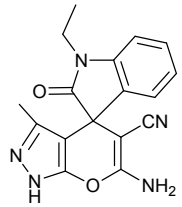
FT-IR (KBr) ν_{max}(cm^{-1}): 605, 626, 692, 1053, 1159, 1209, 1301, 1415, 1581, 1608, 1712, 2181, 3062, 3348 cm^{-1}; **^{1}H-NMR (400 MHz, DMSO-d_6) δ**: 1.59 (s, 3H), 6.94 (d, *J* = 8.28 Hz, 1H), 7.13 (d, *J* = 2.16 Hz, 1H), 7.29-7.31 (m, 3H), 10.76 (s, 1H), 12.35 (s, 1H);**^{13}C-NMR (100 MHz, DMSO-d_6) δ:** 8.9, 47.5, 54.5, 94.6, 111.2, 118.6, 124.5, 126.5, 128.9, 134.7, 134.8, 140.3, 155.1, 162.5, 177.7; **MS (ESI)**: *m/z* = 328[M+1] 100%.



6'-amino-5-bromo-3'-methyl-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile

(**6c**)

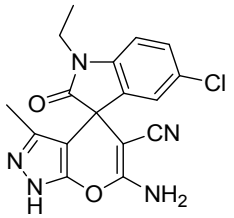
FT-IR (KBr) ν_{max}(cm^{-1}): 694, 812, 937, 1064, 1153, 1296, 1408, 1492, 1591, 1708, 2179, 3140, 3356 cm^{-1}; **^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ**: 1.62 (s, 3H), 6.88 (d, *J* = 8.24 Hz, 1H), 7.16-7.22 (m, 3H), 7.38 (dd, *J* = 1.96 & 1.99 Hz, 1H), 10.69 (s,1H), 12.26 (s,1H), **^{13}C-NMR (100 MHz, DMSO- *d*$_6$) δ:** 9.0, 47.4, 54.6, 94.6, 111.5, 114.1, 118.5, 127.1, 131.4, 134.7, 135.0, 140.6, 155.1, 162.5, 177.5; **MS (ESI)**: *m/z* = 372[M+1] 100%.



6'-amino-1-ethyl-3'-methyl-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile

(**6d**)

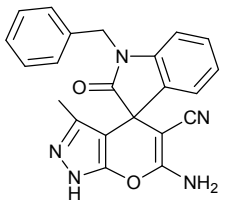
FT-IR (KBr) ν_{max}(cm^{-1}): 1346, 1495, 1698, 2189, 3139, 3384, cm^{-1}; **^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ**: 1.17 (t, *J* = 7.04 Hz, 3H), 1.48 (s, 3H), 3.77 (m, 2H), 7.04-7.11 (m, 2H), 7.15 (d, *J* = 7.84 Hz, 1H), 7.27 (s, 2H), 7.36-7.32 (m, 1H), 12.32 (s, 1H); **^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ:** 8.9, 12.5, 34.4, 46.8, 54.9, 95.1, 108.7, 118.4, 123.0, 124.3, 129.0, 132.1, 134.7, 141.8, 155.2, 162.4, 175.8, **MS (ESI)**: *m/z* = 322 [M+1] 100%.



6'-amino-5-chloro-1-ethyl-3'-methyl-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (**6e**)

FT-IR (KBr) ν_{max}(cm^{-1}): 1338, 1586, 1637, 1405, 1637, 1708, 2190, 3337, 3396, cm^{-1};

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.18 (t, *J* = 7.12 Hz, 3H), 1.55 (s, 3H), 3.73-3.81 (m, 2H), 7.17-7.20 (m, 2H), 7.31 (s, 2H), 7.39 (dd, *J* = 2.1 & 6.1 Hz, 1H), 12.35 (s, 1H); **^{13}C NMR (100 MHz, DMSO-d_6) δ:** 9.0, 12.4, 34.6, 47.0, 54.3, 94.4, 110.2, 118.3, 124.5, 127.2, 128.9, 134.1, 134.7, 140.6, 155.1, 162.5, 175.5; **ESI-MS** *m/z* = 378 [M+Na] 100%; **HRMS Analysis (TOF MS ES+)** found 356.0916 $[M+1]^+$; $C_{17}H_{14}ClN_5O_2$ requires Mol. Wt.: 355.0836.



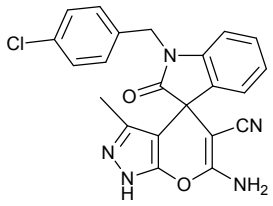
6'-amino-1-benzyl-3'-methyl-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (**6f**)

FT-IR (KBr) ν_{max}(cm^{-1}): 1338, 1469, 1968, 2200, 3235, 3394, cm^{-1};

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.37 (s, 3H), 4.91 (d, *J* = 15.6 Hz, 1H), 5.01 (d, *J* = 15.6 Hz, 1H), 7.00-7.12 (m, 3H), 7.24-7.28 (m, 2H), 7.30 (s, 2H), 7.31 (d, *J* = 7.04 Hz, 2H), 7.41 (d, *J* = 7.28 Hz, 2H), 12.29 (s, 1H); **^{13}C-NMR (100 MHz, DMSO-d_6) δ:** 8.9, 43.1, 47.0, 54.9, 95.1, 109.2, 118.7, 123.2, 124.4, 127.4, 128.4, 128.8, 131.8, 134.7, 136.0, 141.9, 155.2, 162.6, 176.6; **MS (ESI)**:

---

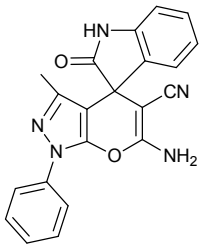
m/z = 384 [M+1] 100%.



6'-amino-1-(4-chlorobenzyl)-3'-methyl-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (**6g**)

FT-IR (KBr) ν_{max}(cm^{-1}): 1493, 1408, 1593, 1511, 1643, 1708, 2197, 3157, 3230;cm^{-1};

^{1}H-NMR (400 MHz, DMSO-*d_6*) δ: 1.37 (s, 3H), 4.89 (d, *J* = 15.52, 1H), 5.0 (d, *J* = 15.5, 1H), 7.02-7.07 (m, 2H), 7.08-7.13 (m, 3H), 7.24-7.28 (m, 3H); **^{13}C-NMR (100 MHz, DMSO- *d_6*) δ:** 8.9, 42.4, 46.9, 54.9, 95.0, 109.1, 115.3, 118.6, 123.2, 124.3, 128.8, 129.5, 132.1, 134.7, 141.7, 155.2, 160.3, 162.6, 176.6; **ESI-MS** (*m/z*) = 400[M-H_2O] 100%; **HRMS Analysis (TOF MS ES-)** found 400.1387 [M- H_2O]$^+$; $C_{22}H_{16}ClN_5O_2$ requires Mol. Wt.: 417.0993.

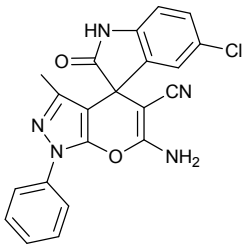


6'-amino-3'-methyl-2-oxo-1'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (**6h**)

FT-IR (KBr) ν_{max}(cm^{-1}): 931, 1026, 1071, 1216, 1334, 1647, 1908, 1953, 2197, 3295, 3461 cm^{-1};

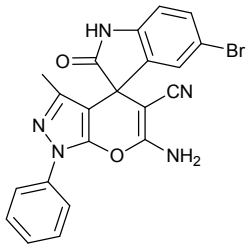
^{1}H-NMR (400 MHz, DMSO-*d_6*) δ: 1.56 (s, 3H), 6.96 (d, *J* =7.7 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.12 Hz, 1H), 7.29 (dt, *J* =1.08, 1.04, & 1.12 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.50-7.54

(m, 2H), 7.58 (s, 2H), 7.80 (d, *J* = 7.8 Hz, 2H), 10.76 (s, 1H); **^{13}C-NMR (100 MHz, DMSO-d_6) δ:** 11.6, 47.7, 56.1, 96.3, 109.8, 117.9, 120.1, 122.6, 124.8, 126.5, 129.2, 132.0, 137.2, 141.5, 143.9, 144.9, 161.0, 177.5; **MS (ESI)**: *m/z* = 370.3[M+1] 100%.



6'-amino-5-chloro-3'-methyl-2-oxo-1'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (**6i**)

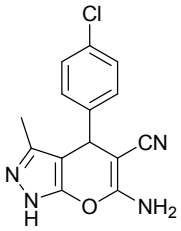
FT-IR (KBr) ν_{max}(cm^{-1}): 641, 692, 752, 817, 872, 1131, 1307, 1524, 1709, 1876, 2208, 3188, 3364 cm^{-1} ; **^{1}H-NMR (400 MHz, DMSO-d_6) δ**: 1.60 (3H, s), 6.97 (d, *J* = 8.08 Hz, 1H), 7.33-7.37 (m, 3H), 7.50-7.54 (m, 2H), 7.64 (s, 2H), 7.80 (d, *J* = 8.68 Hz, 2H) 10.90 (s,1H); **^{13}C-NMR (100 MHz, DMSO-d_6) δ:** 11.7, 18.5, 48.0, 55.5, 56.0, 95.6, 111.3, 117.8, 120.2, 125.1, 126.5, 126.6, 129.2, 129.3, 134.2, 137.1, 140.3, 143.7, 145.0, 161.0, 177.2; **MS (ESI)**: *m/z* = 404.2[M+1] 100%.



6'-amino-5-bromo-3'-methyl-2-oxo-1'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile (**6j**)

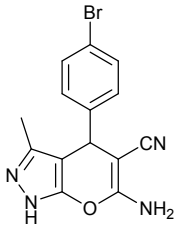
FT-IR (KBr) ν_{max}(cm^{-1}): 637, 750, 1031, 1076, 1225, 1397, 1519, 1659, 1705, 2207, 3188, 3346 cm^{-1} ; **^{1}H-NMR (400 MHz, DMSO-d_6) δ**: 1.61 (s, 3H) 6.94 (s, 1H), 7.36 (s, 1H), 7.48-7.52 (m, 4H), 7.64 (s, 2H), 7.79 (s, 2H), 10.91 (s, 1H); **^{13}C-NMR (100 MHz, DMSO-d_6) δ:** 11.7, 47.9, 55.5, 95.6, 111.8, 114.3, 117.8, 120.2, 126.6, 127.8, 129.3, 132.0, 134.6, 137.1, 143.7, 145.0, 161.0, 177.1;

MS (ESI): *m/z* = 450.2[M+2] 100%



6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**8b**)

FT-IR (KBr) ν_{max}(cm^{-1}): 3483, 3234, 3205, 2190, 1651, 1610, 830, 798 cm^{-1} ; **^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ**: 1.81 (s, 3H), 4.58 (s, 1H), 6.80 (s, 2H), 7.13 (d, *J* = 8.28 Hz, 2H), 7.46 (d, *J*=8.36 Hz, 2H), 12.07 (s, 1H).; **^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ:** 9.7, 35.6, 56.8, 97.0, 120.5, 128.3, 129.2, 131.3, 135.5, 143.2, 154.6, 160.8; **MS (ESI)**: *m/z* = 285 [M-1] 100%



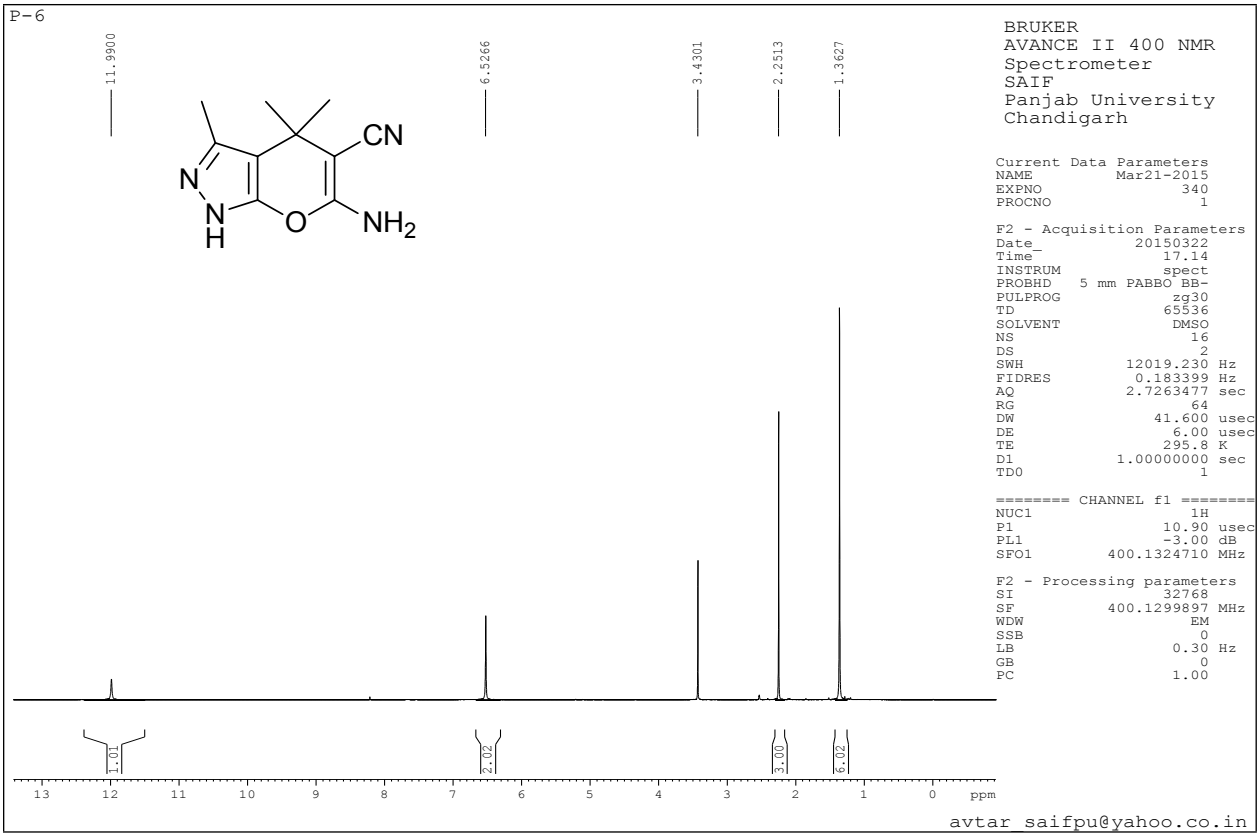
6-amino-4-(4-bromophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**8d**)

FT-IR (KBr) ν_{max}(cm^{-1}): cm^{-1} ; 3478, 3369, 3244, 3140, 2976, 2193, 1633, 748, 619 cm^{-1}; **^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ**: 1.80 (s, 3H), 4.61 (s, 1H), 6.86 (s, 2H), 7.19 (d, *J* = 8.44 Hz, 2H), 7.34 (d, *J* = 8.40 Hz, 2H), 12.09 (s, 1H).; **^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ:** 9.7, 35.8, 56.8, 96.94, 119.8, 120.6, 129.5, 131.2, 132.0, 132.5, 143.6, 154.7, 160.8.

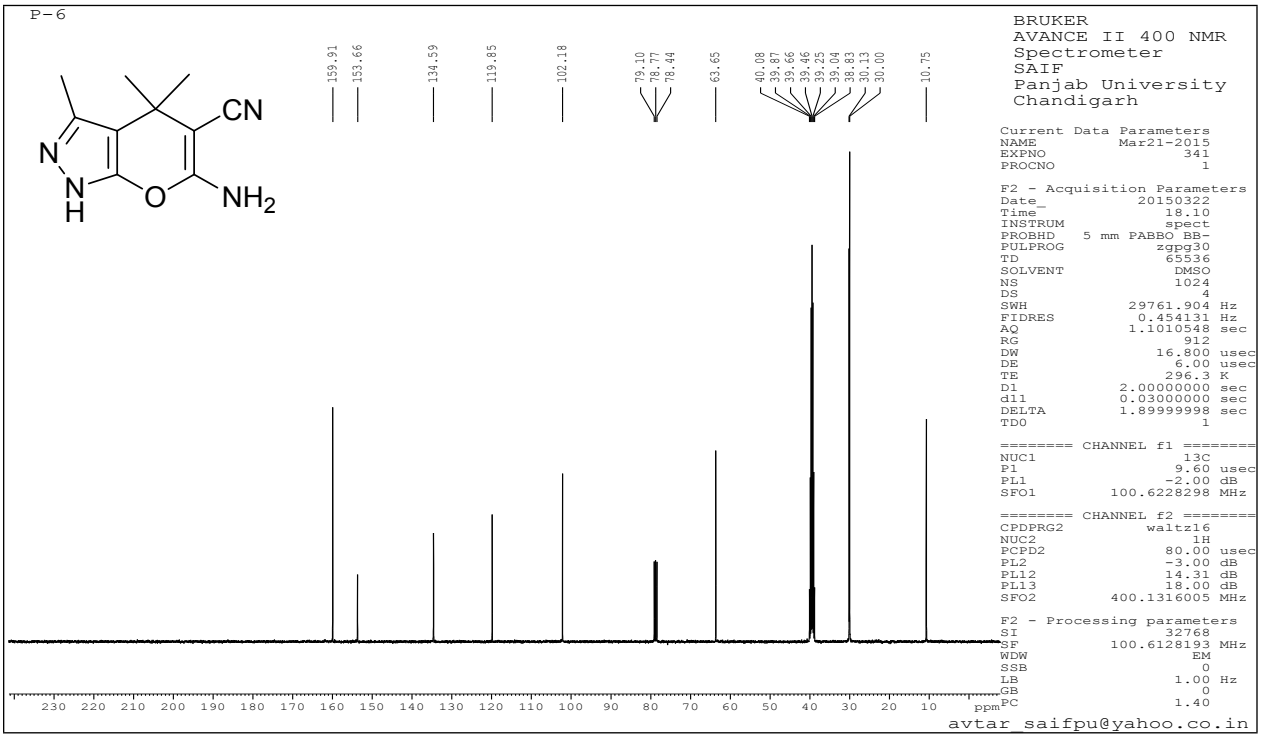
MS (ESI): *m/z* = 331 [M+1] 100%

---

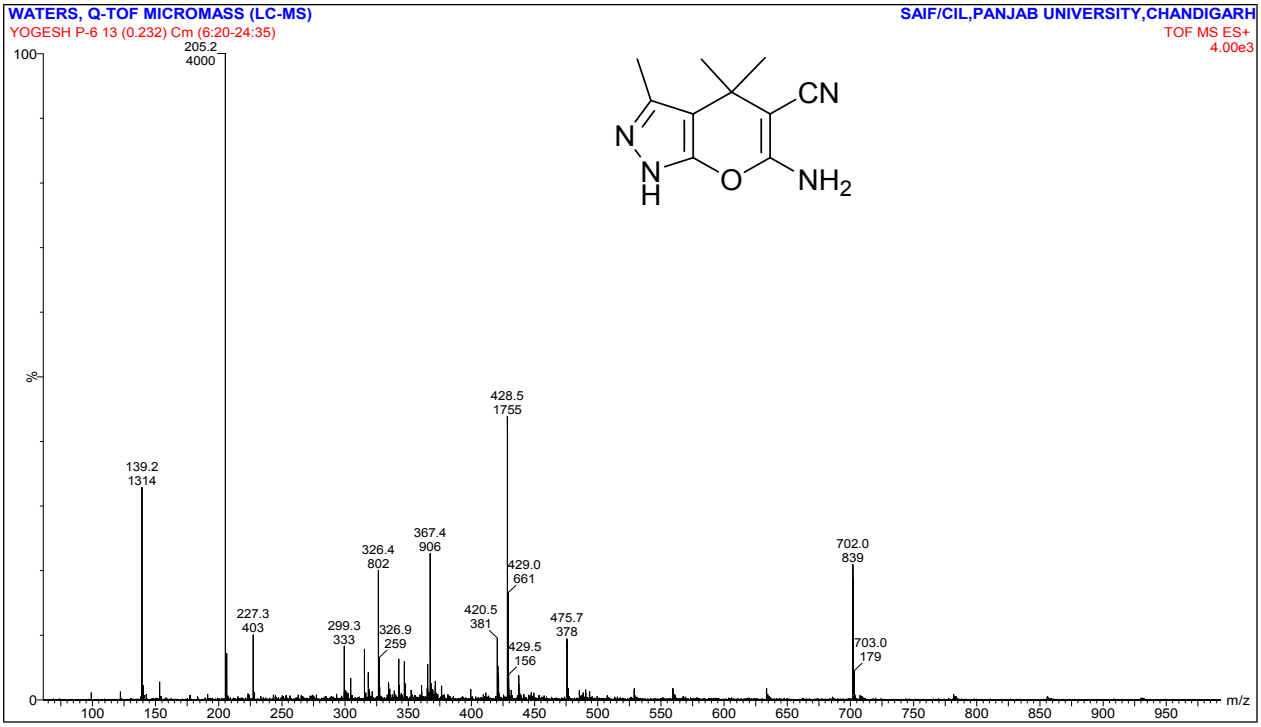
^{1}H NMR for **4a** (400 MHz, DMSO)



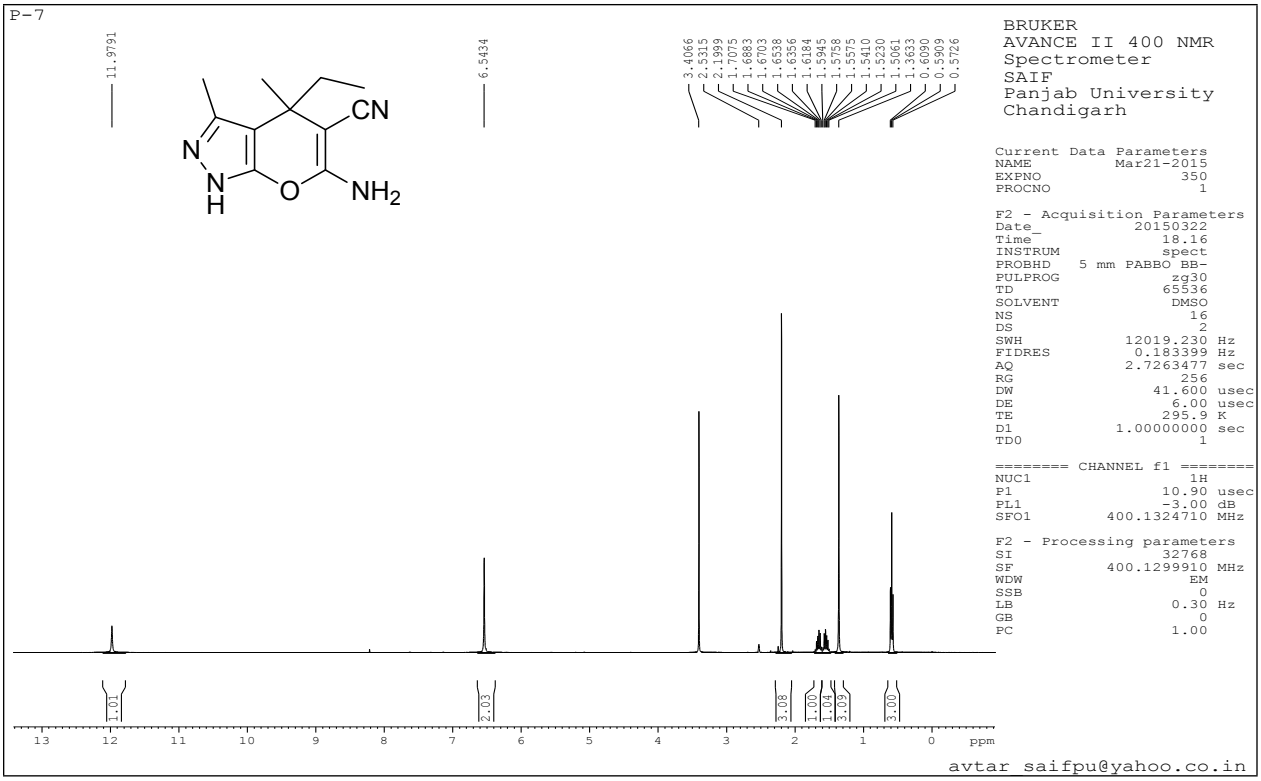
^{13}C NMR for **4a** (100 MHz, DMSO)



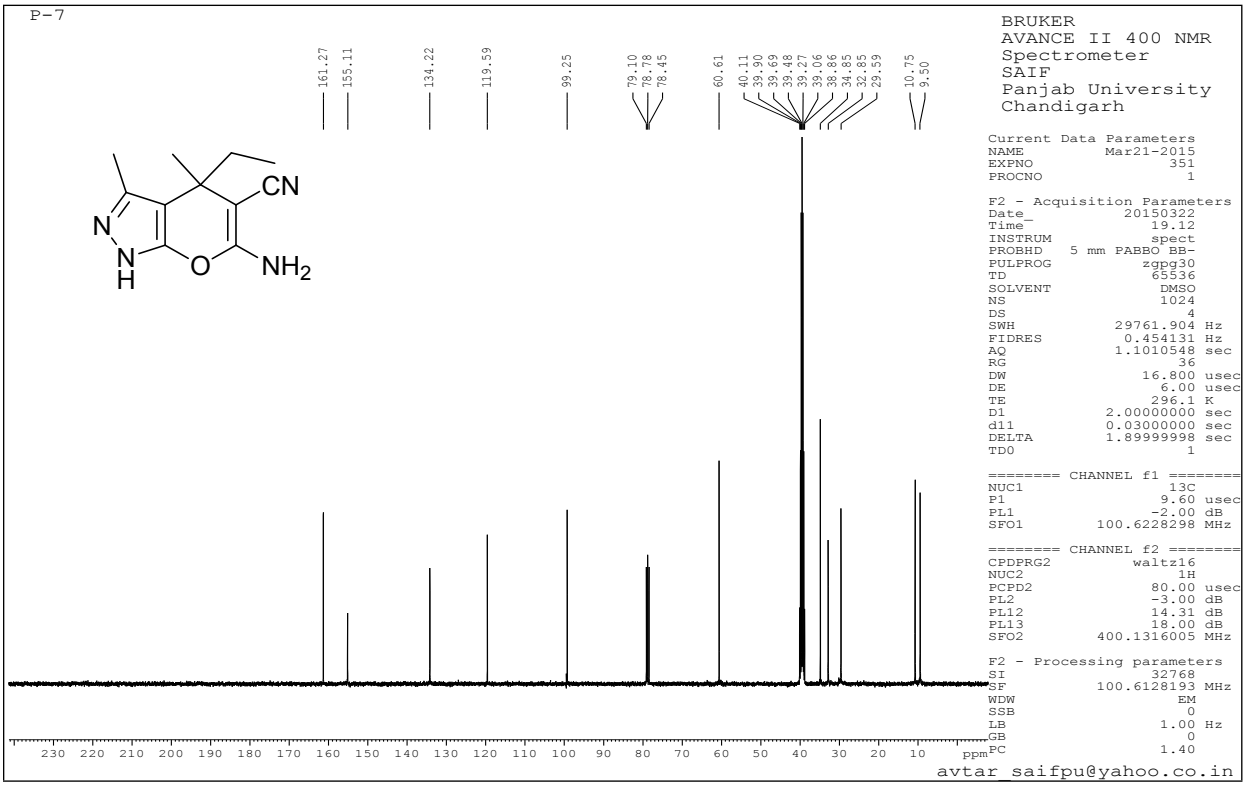
MS (ESI) for **4a**


WATERS, Q-TOF MICROMASS (LC-MS)
YOGESH P-6 13 (0.232) Cm (6:20-24:35)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
4.00e3
205.2
4000
139.2
1314
227.3
403
299.3
333
326.4
802
326.9
259
367.4
906
428.5
1755
429.0
661
420.5
381
429.5
156
475.7
378
702.0
839
703.0
179
CN
N
N
H
O
NH2
%
m/z

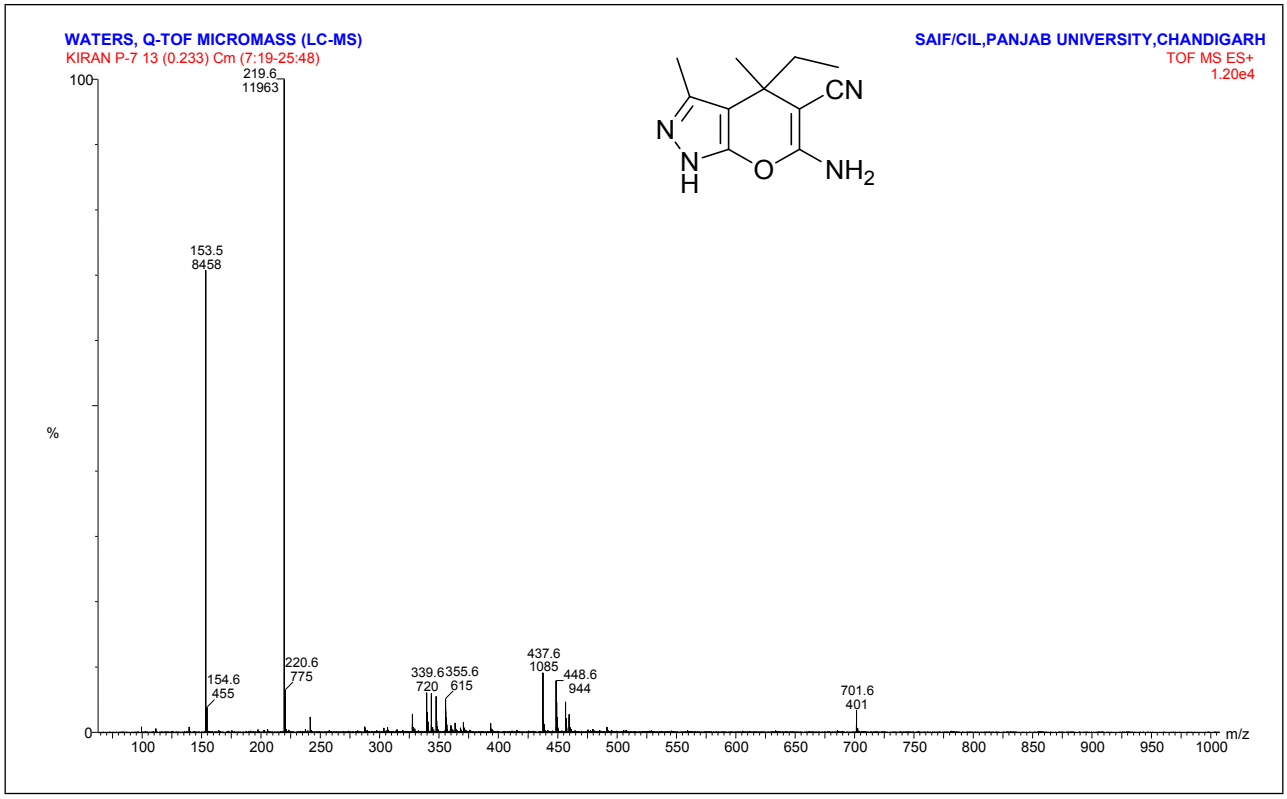
[1]H NMR for **4b** (400 MHz, DMSO)



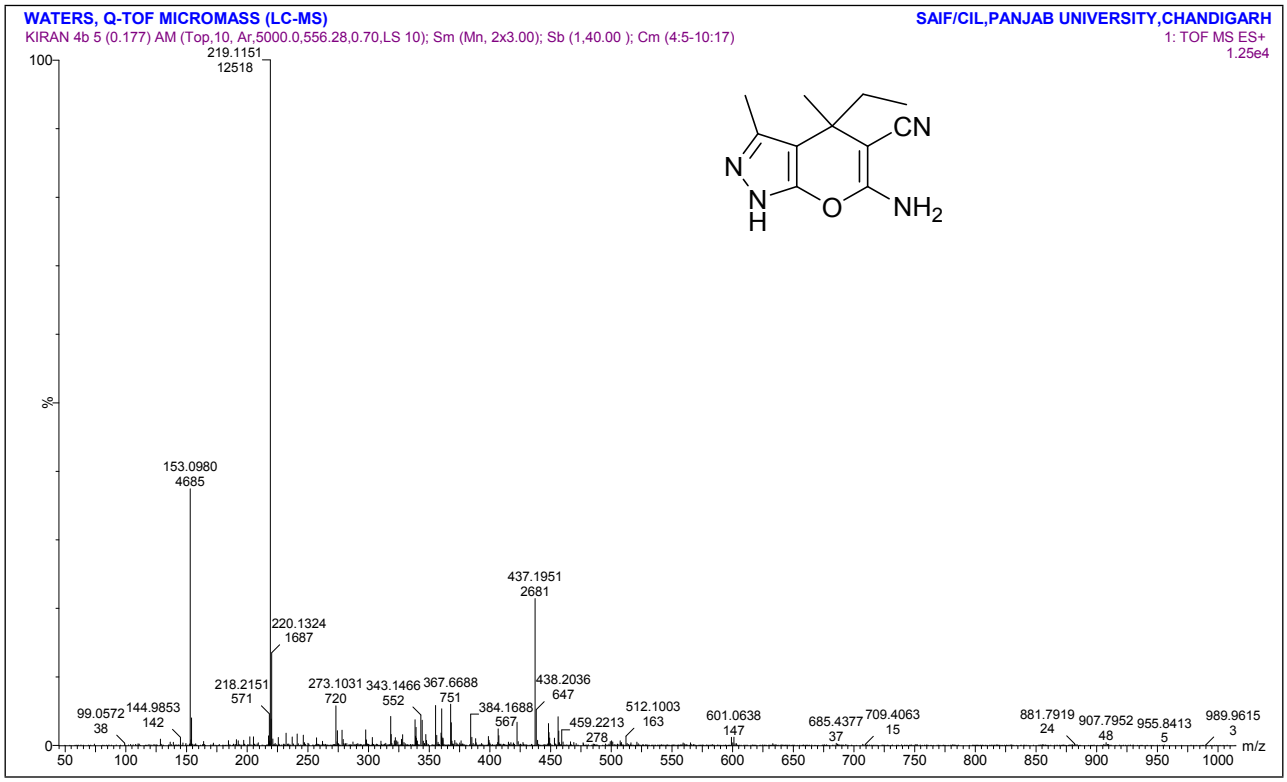
[13]C NMR for **4b** (100 MHz, DMSO)



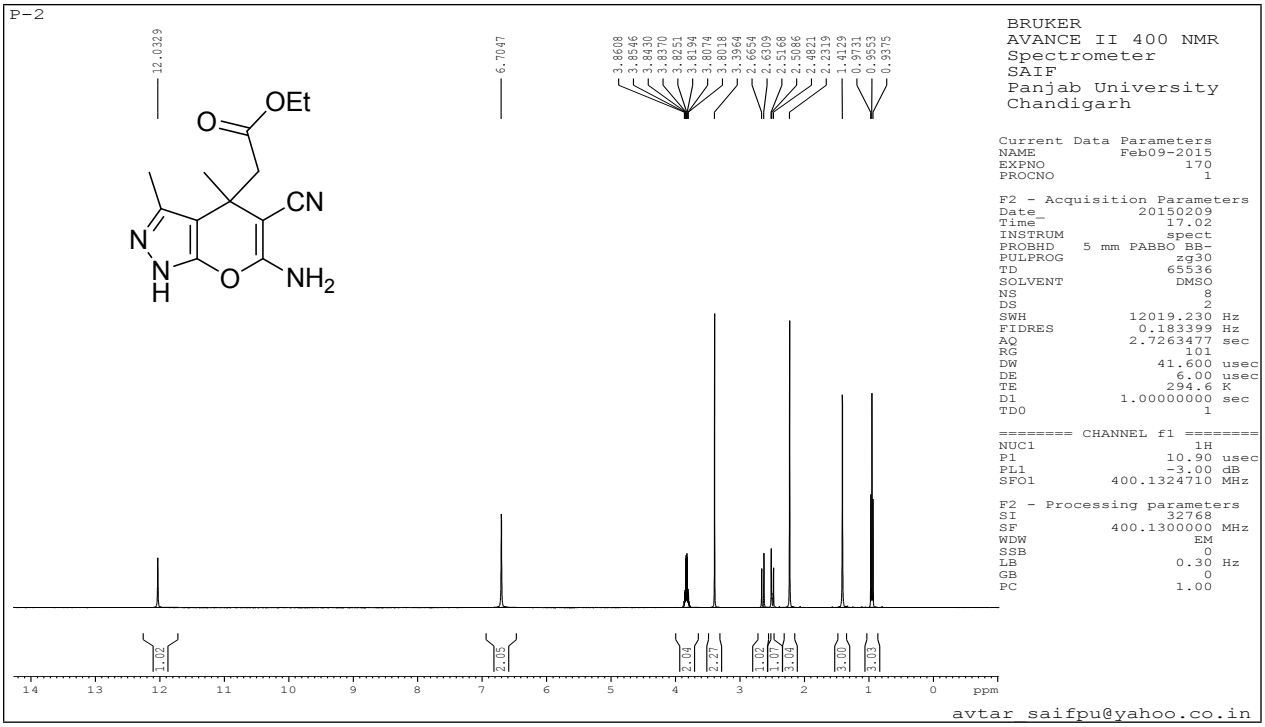
MS (ESI) for **4b**



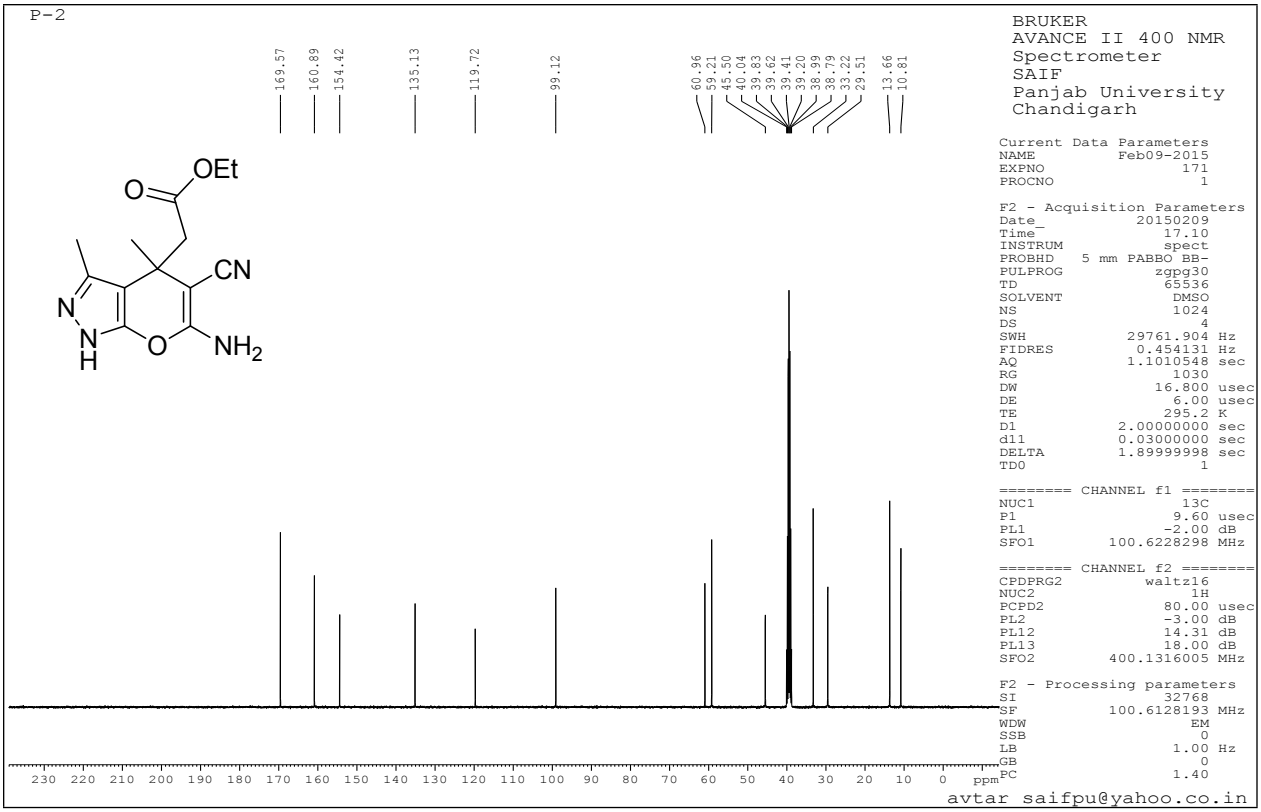
HRMS (ESI) For **4b**



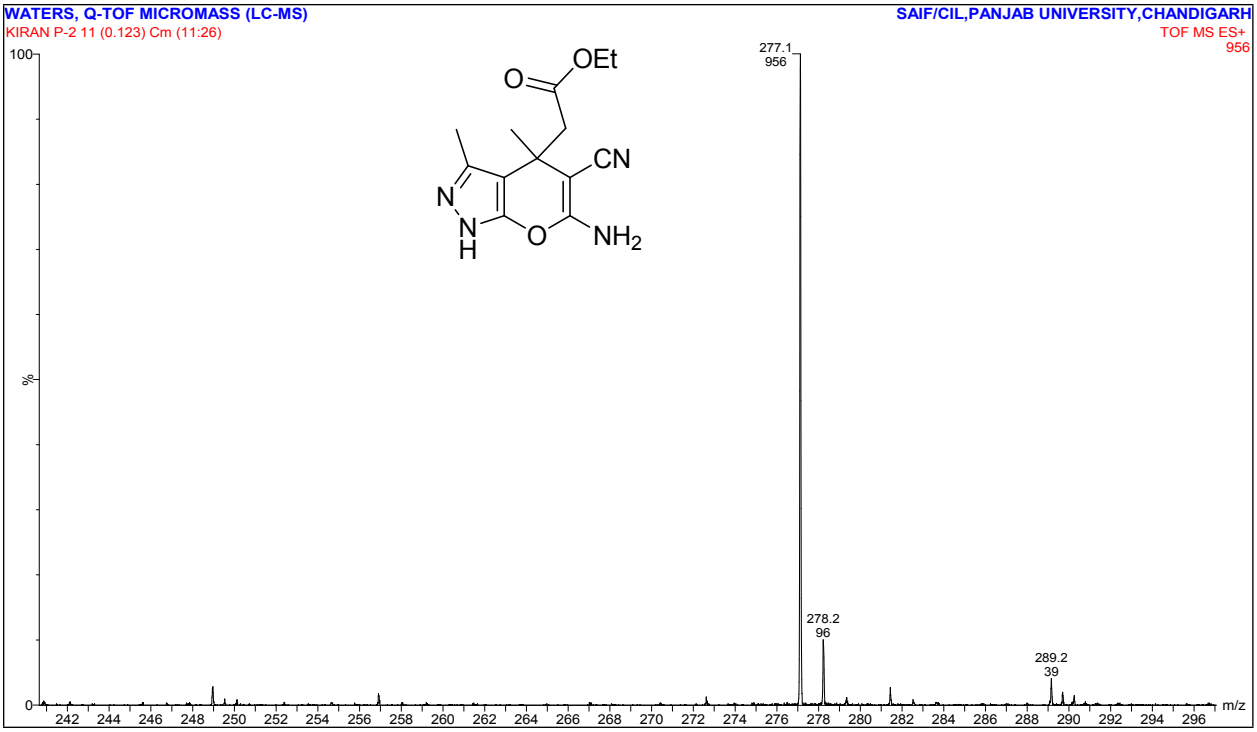
^{1}H NMR for **4c** (400 MHz, DMSO)



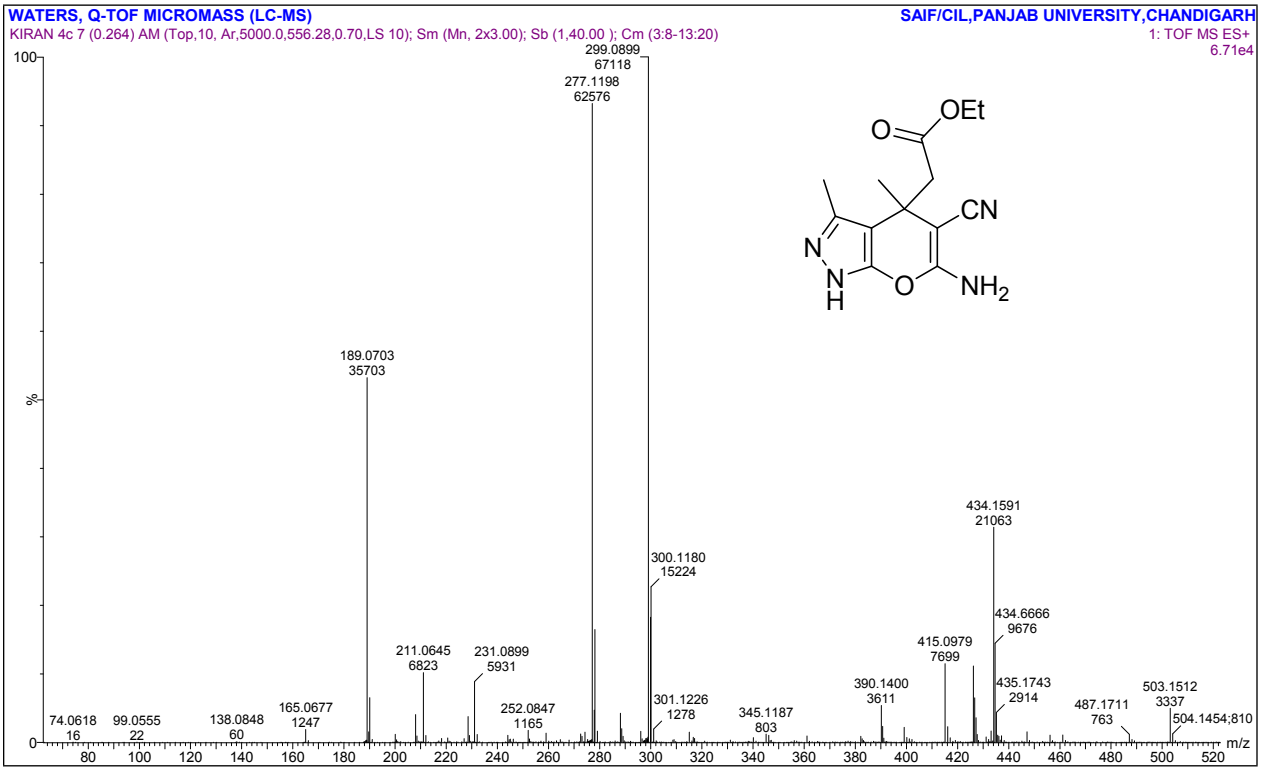
^{13}C NMR for **4c** (100 MHz, DMSO)



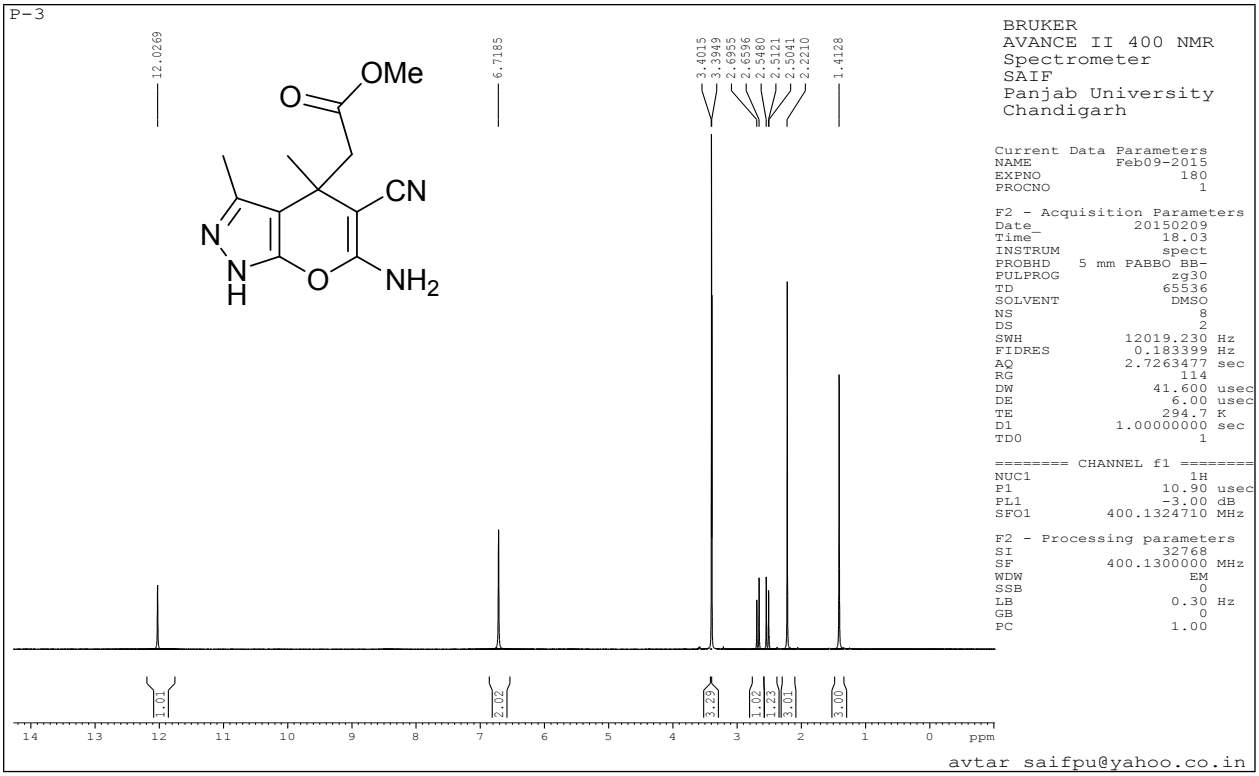
MS (ESI) for **4c**



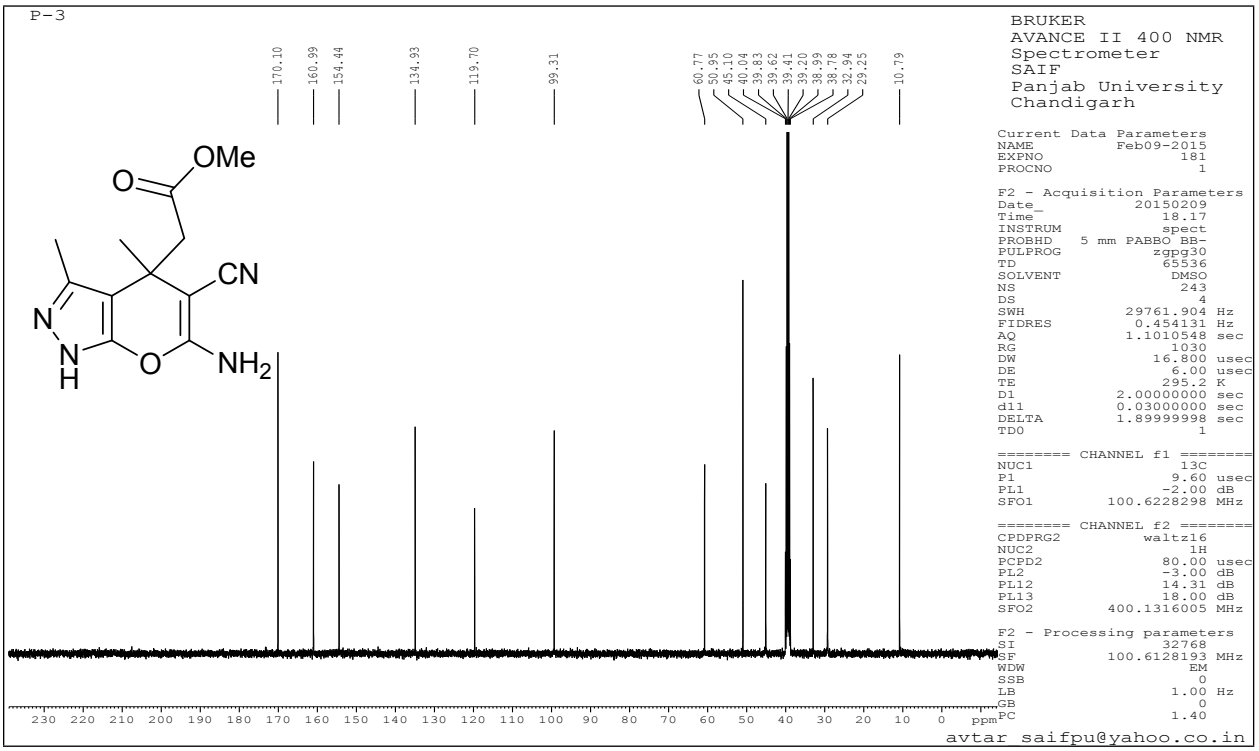
HRMS (ESI) For **4c**



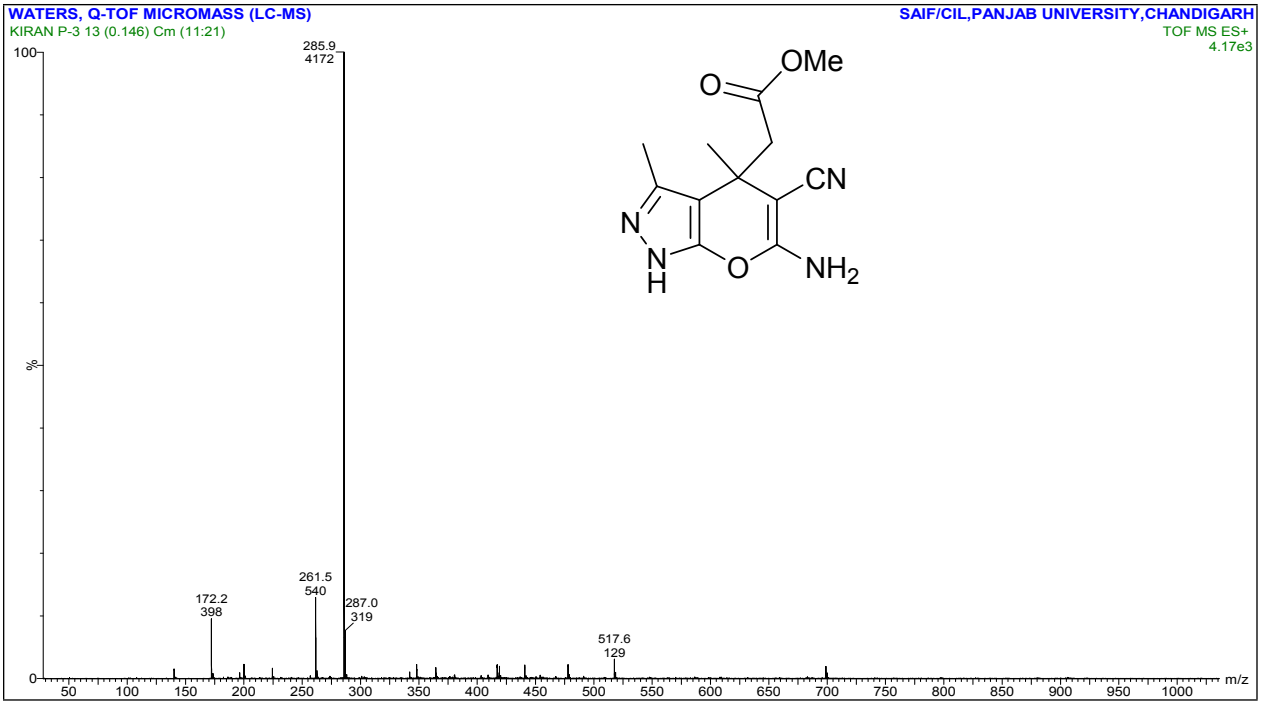
^{1}H NMR for **4d** (400 MHz, DMSO)



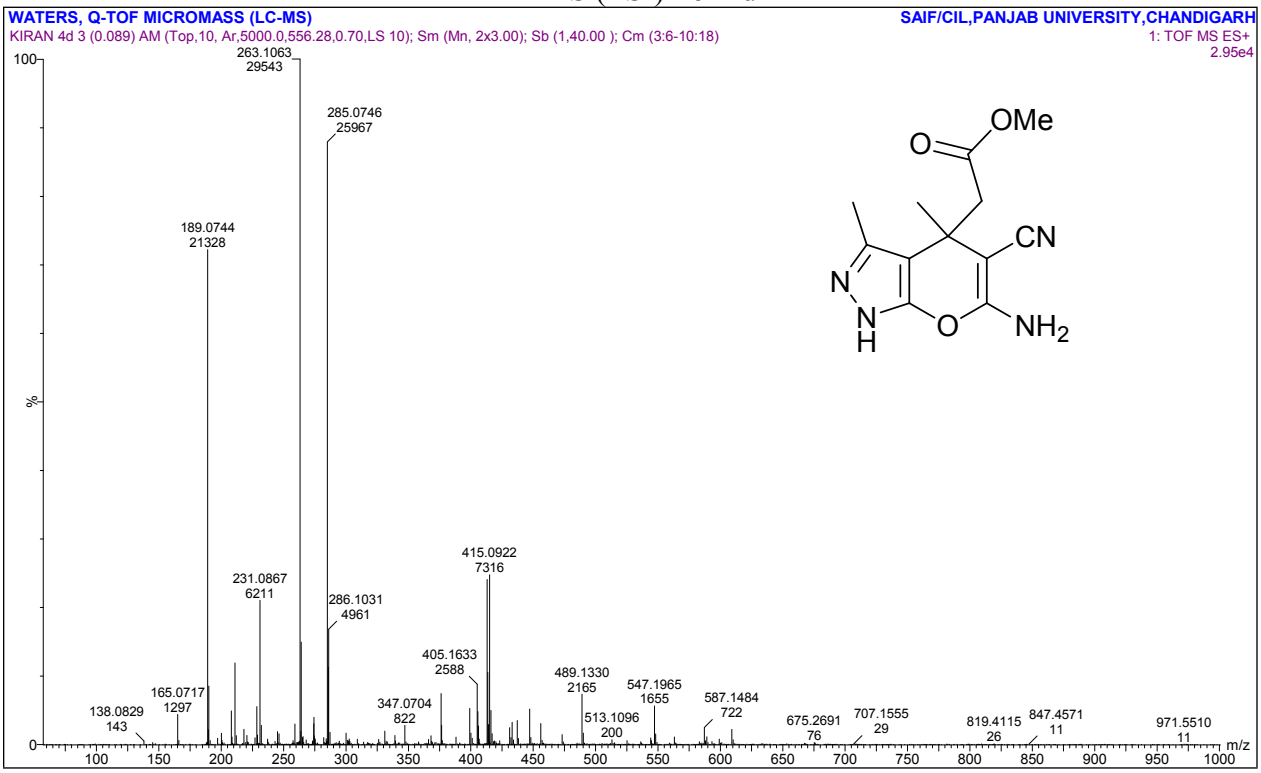
^{13}C NMR for **4d** (100 MHz, DMSO)



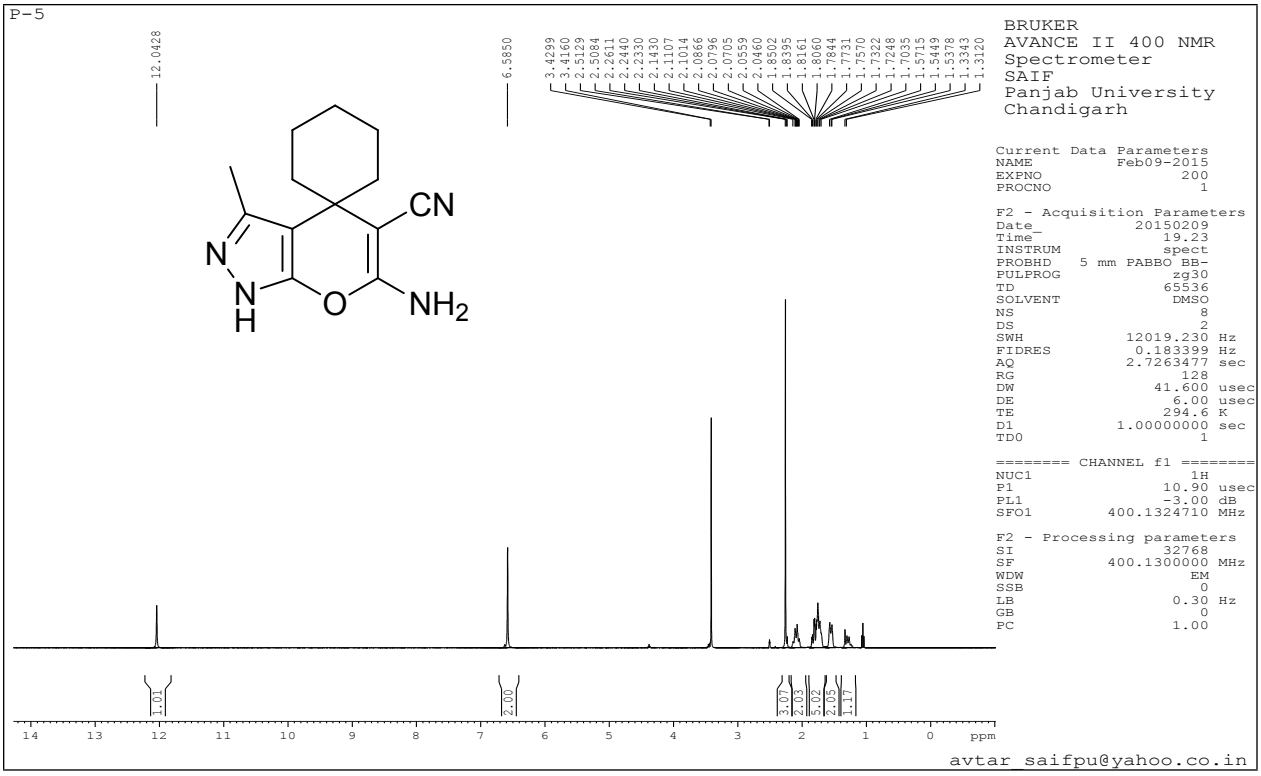
MS (ESI) for **4d**



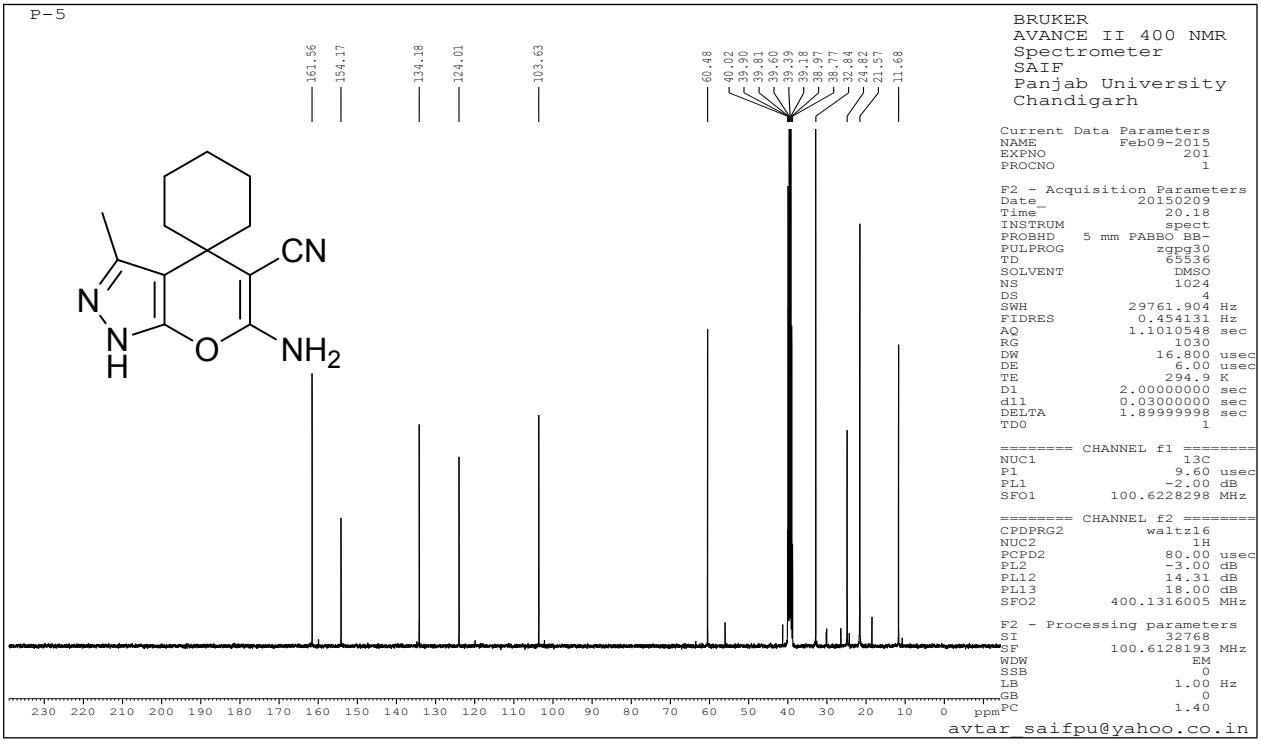
HRMS (ESI) For 4d



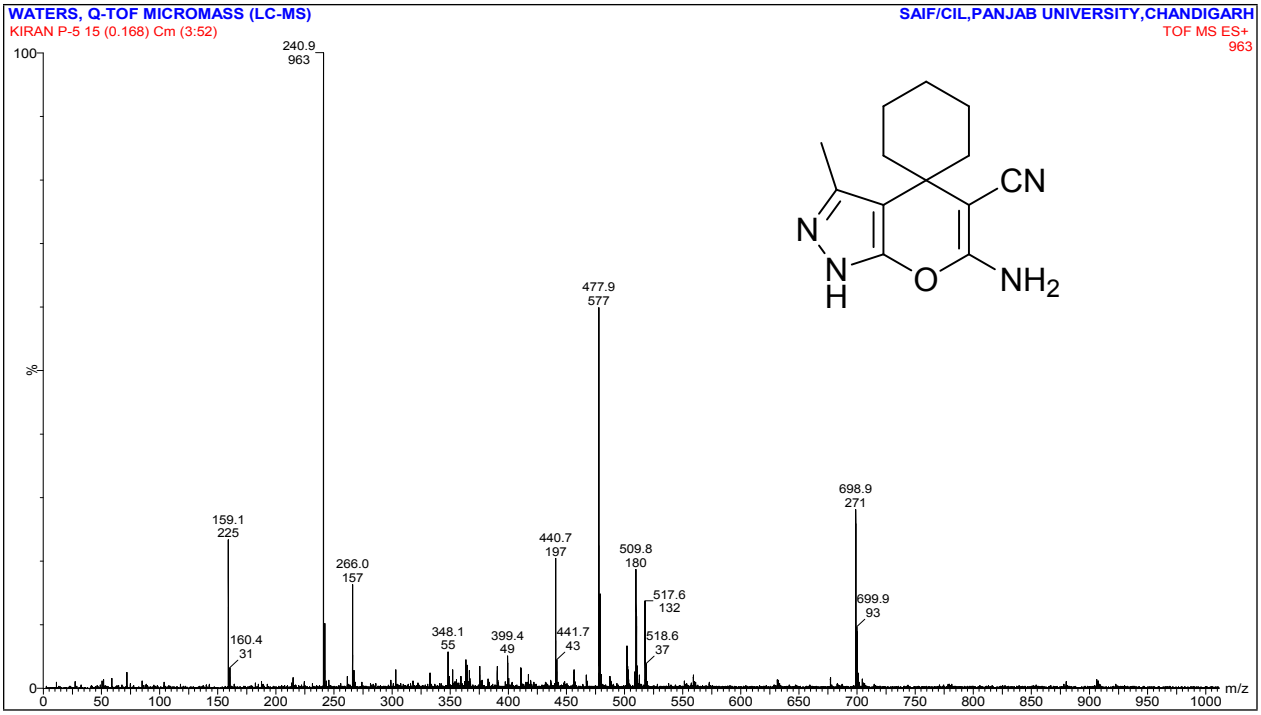
^{1}H NMR for **4e** (400 MHz, DMSO)



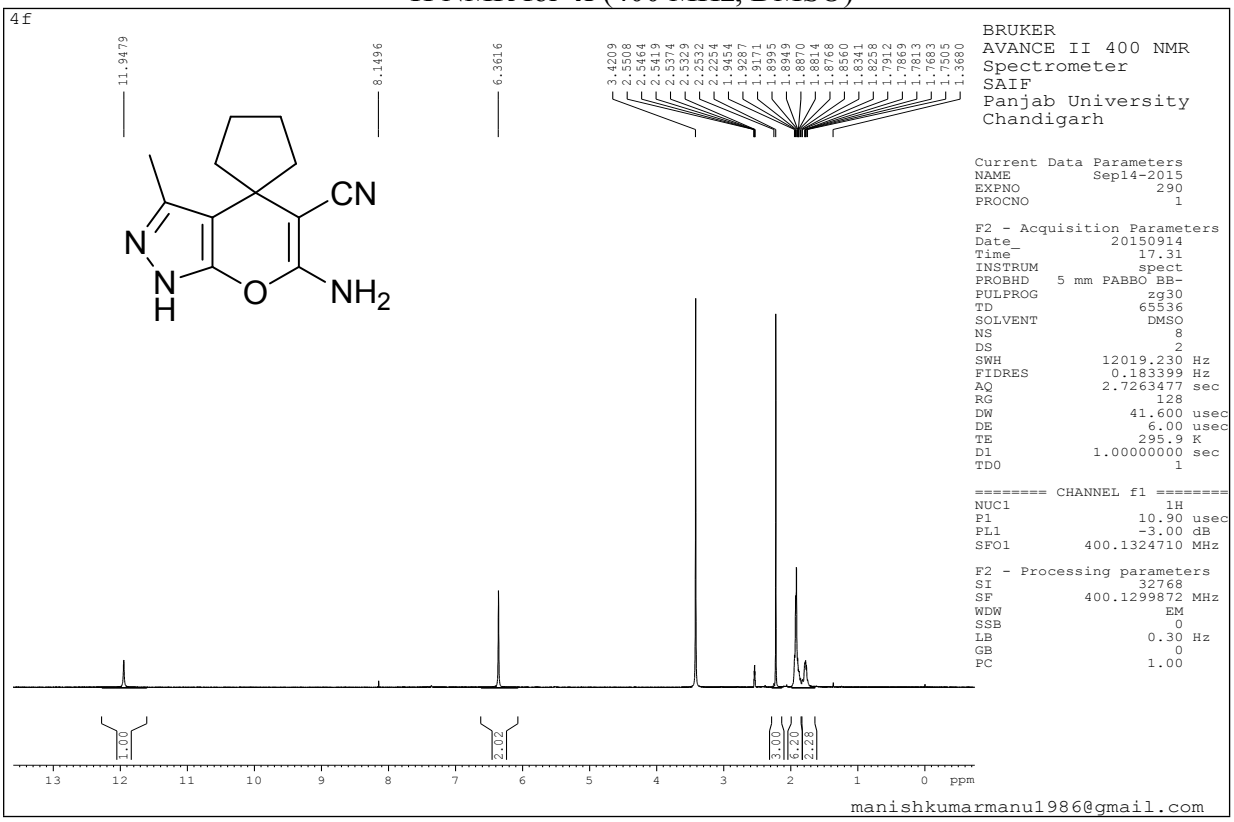
^{13}C NMR for **4e** (100 MHz, DMSO)



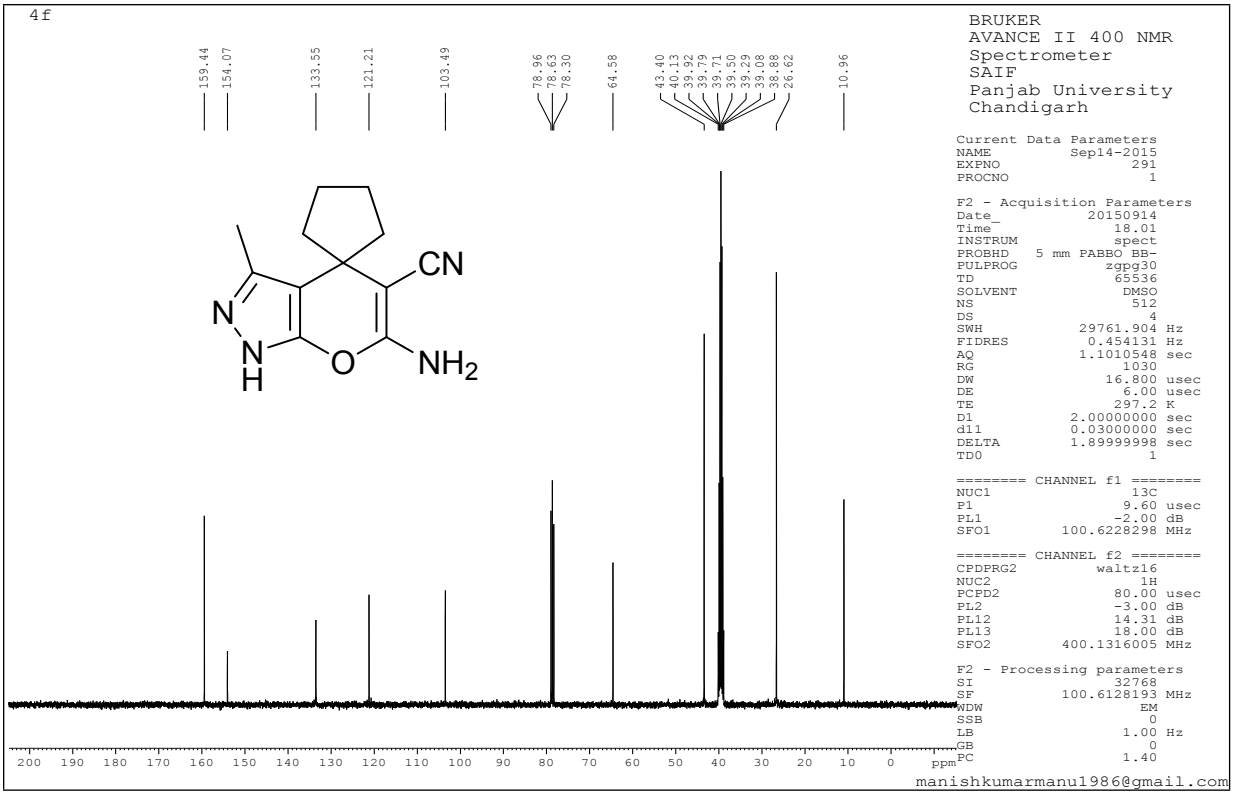
MS (ESI) for **4e**


WATERS, Q-TOF MICROMASS (LC-MS)
KIRAN P-5 15 (0.168) Cm (3:52)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
963
240.9
963
477.9
577
698.9
271
159.1
225
440.7
197
509.8
180
266.0
157
517.6
132
699.9
93
160.4
31
348.1
55
399.4
49
441.7
43
518.6
37
CN
N
N
H
O
NH2
%
m/z

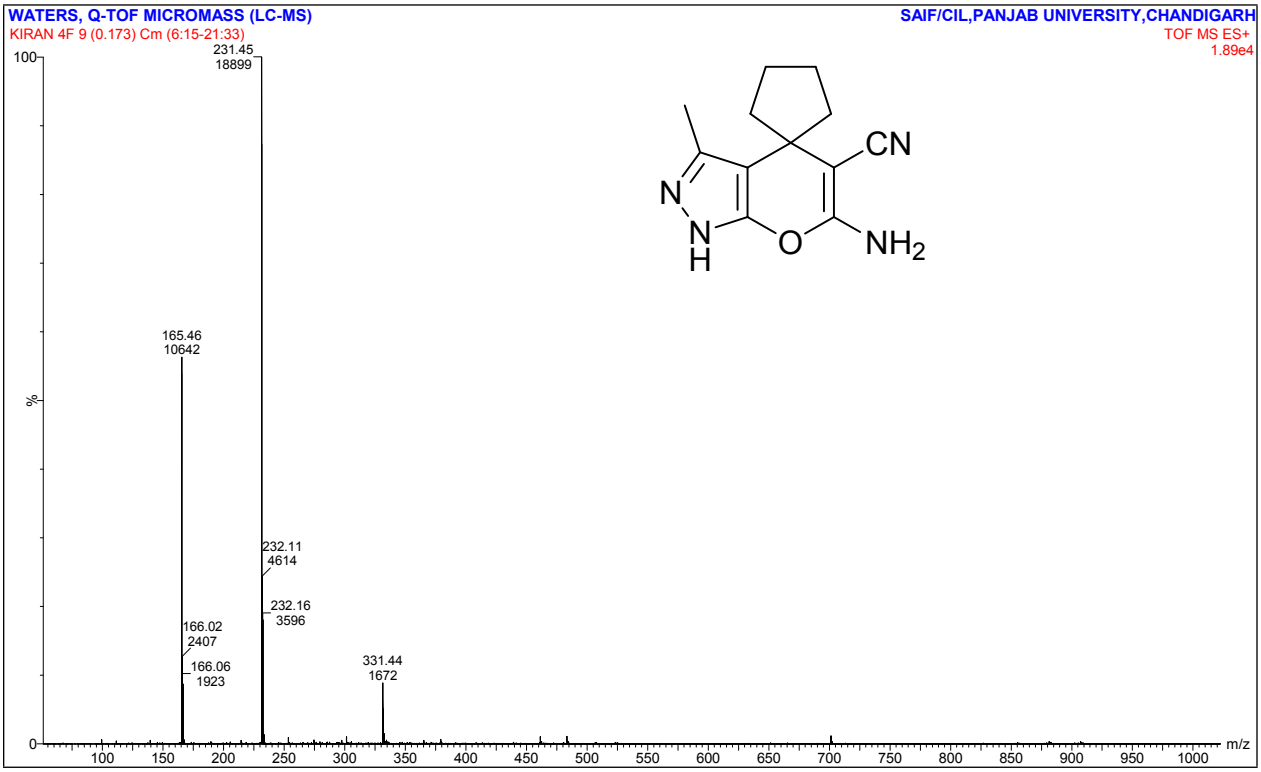
^{1}H NMR for **4f** (400 MHz, DMSO)



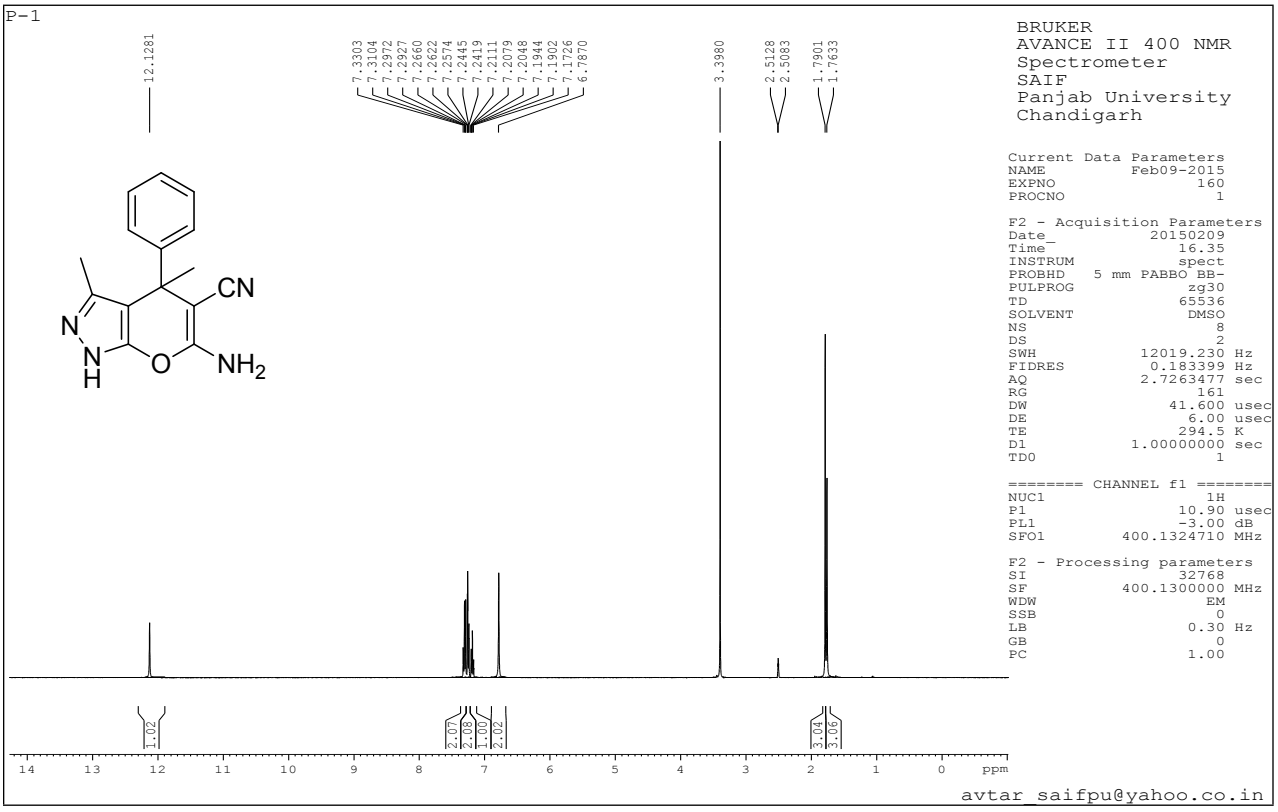
^{13}C NMR for **4f** (100 MHz, DMSO)



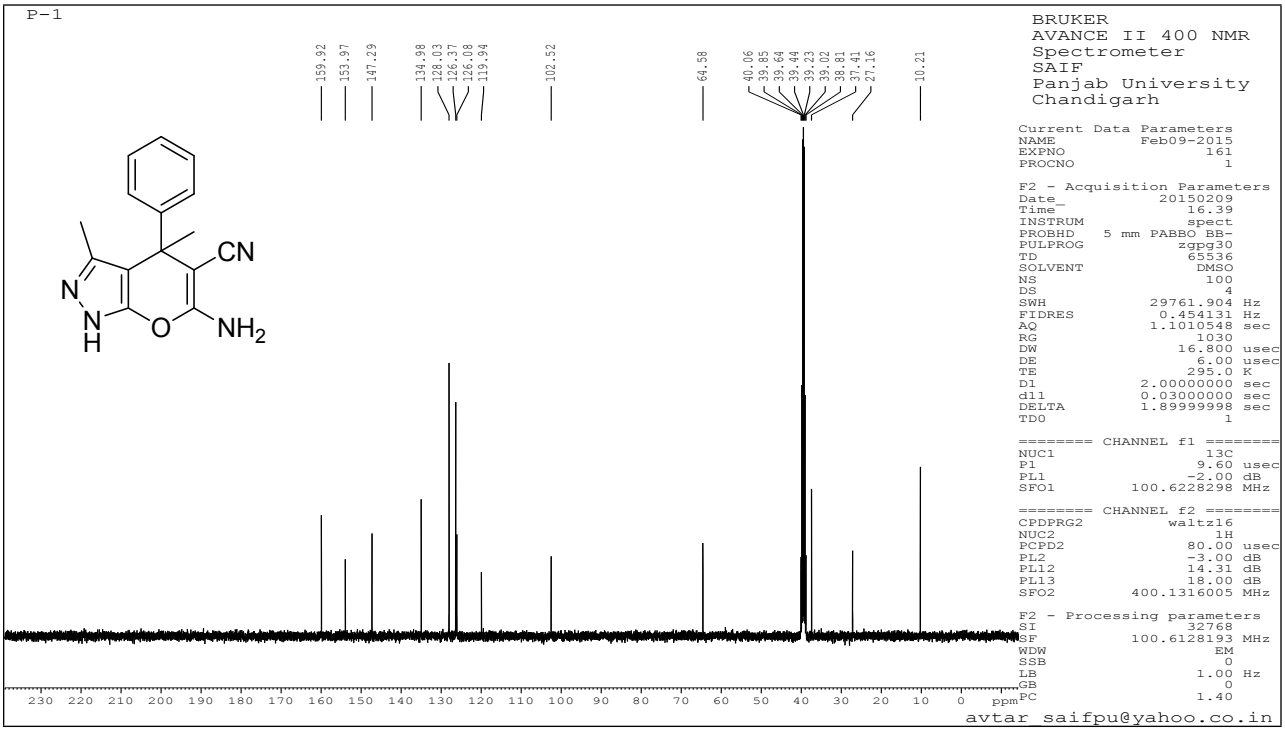
MS (ESI) for **4f**


WATERS, Q-TOF MICROMASS (LC-MS)
KIRAN 4F 9 (0.173) Cm (6:15-21:33)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
1.89e4
231.45
18899
165.46
10642
232.11
4614
232.16
3596
166.02
2407
166.06
1923
331.44
1672
CN
N
N
H
O
NH2
%
m/z

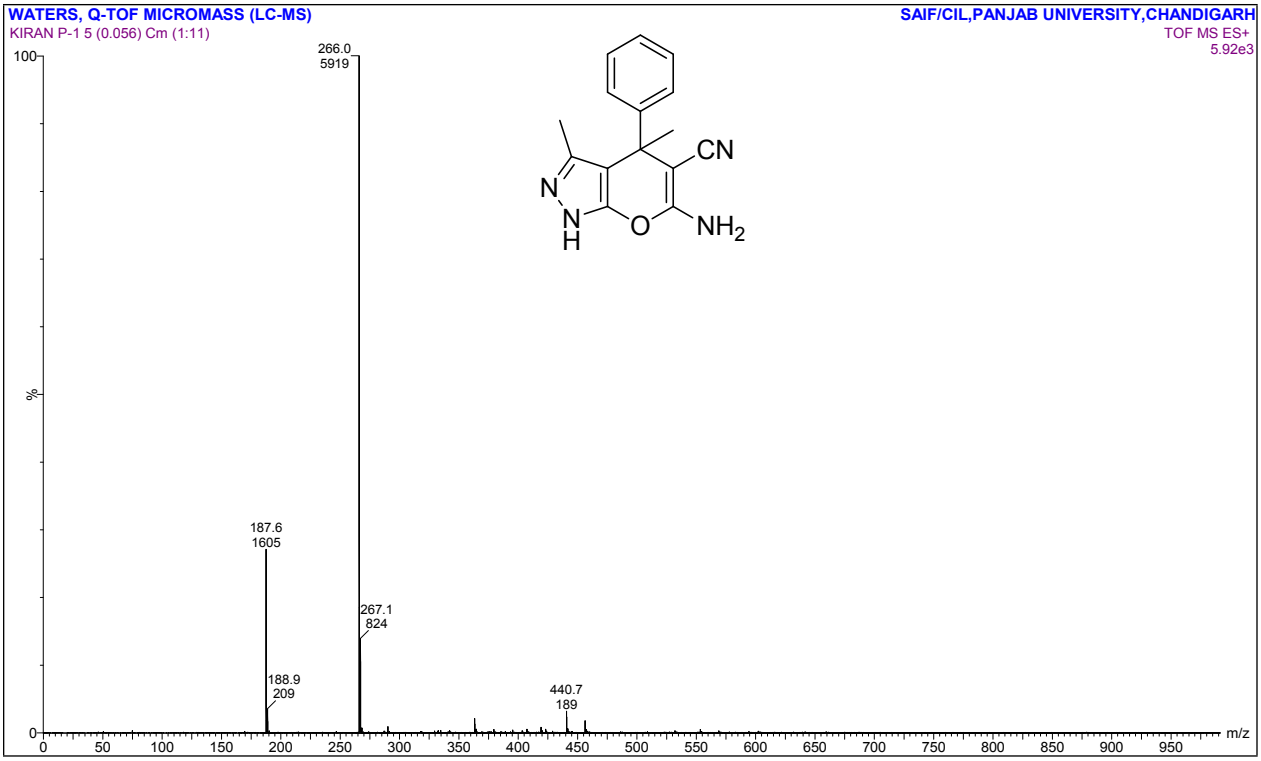
^{1}H NMR for **4g** (400 MHz, DMSO)



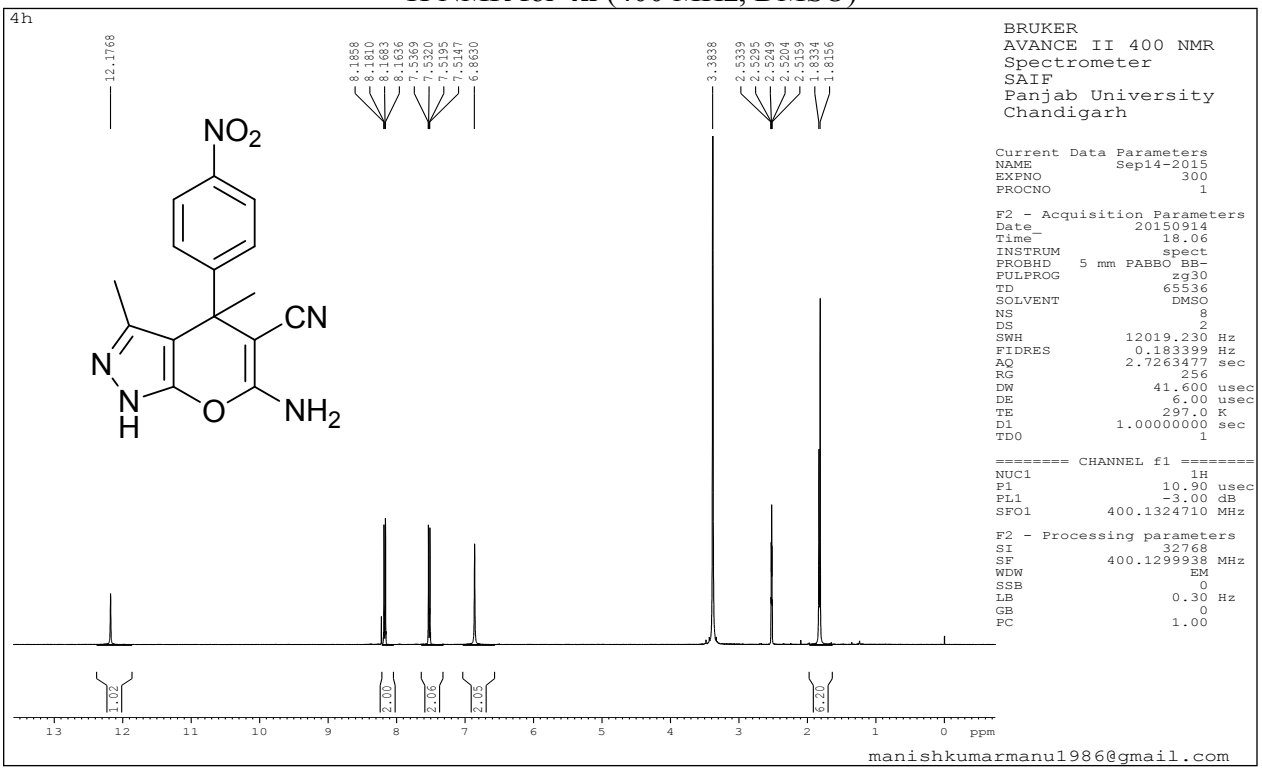
^{13}C NMR for **4g** (100 MHz, DMSO)



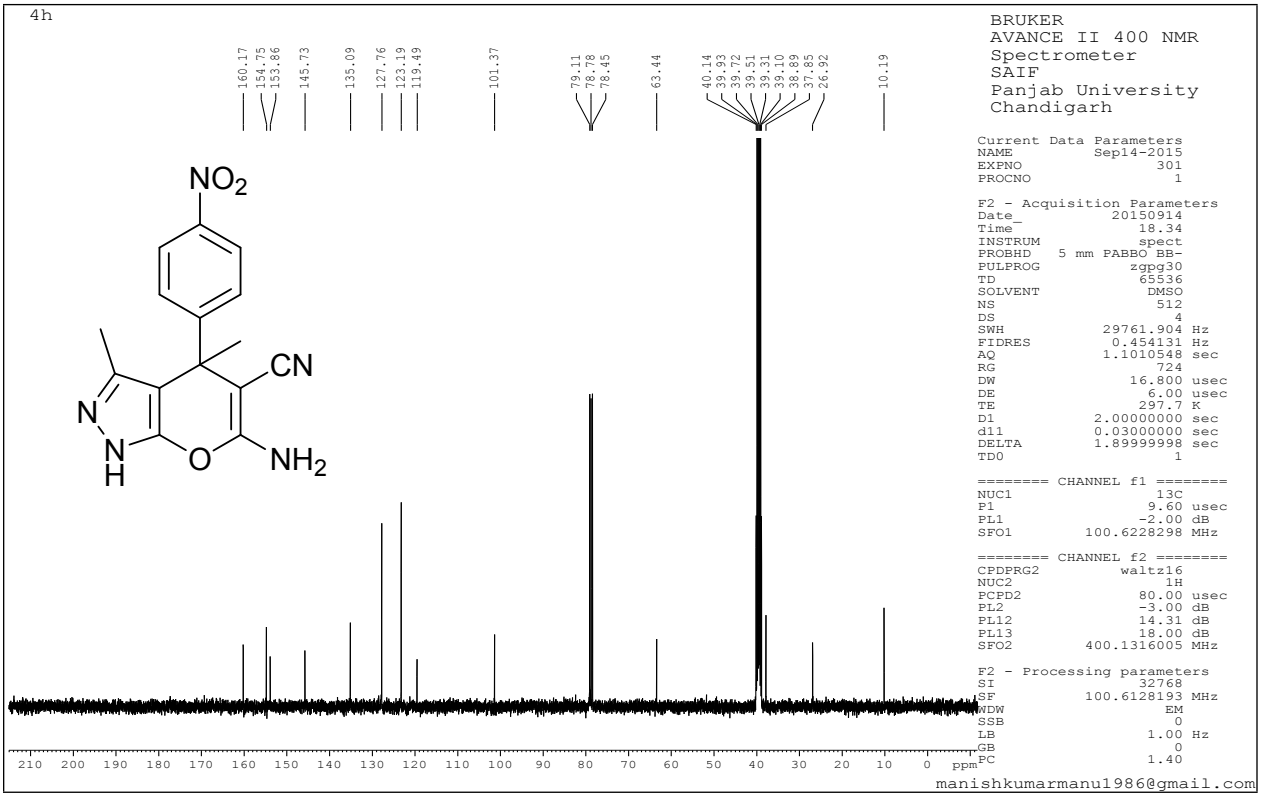
MS (ESI) for **4g**


WATERS, Q-TOF MICROMASS (LC-MS)
KIRAN P-1 5 (0.056) Cm (1:11)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
5.92e3
266.0
5919
187.6
1605
267.1
824
188.9
209
440.7
189
CN
NH2
N
N
H
O
%
m/z

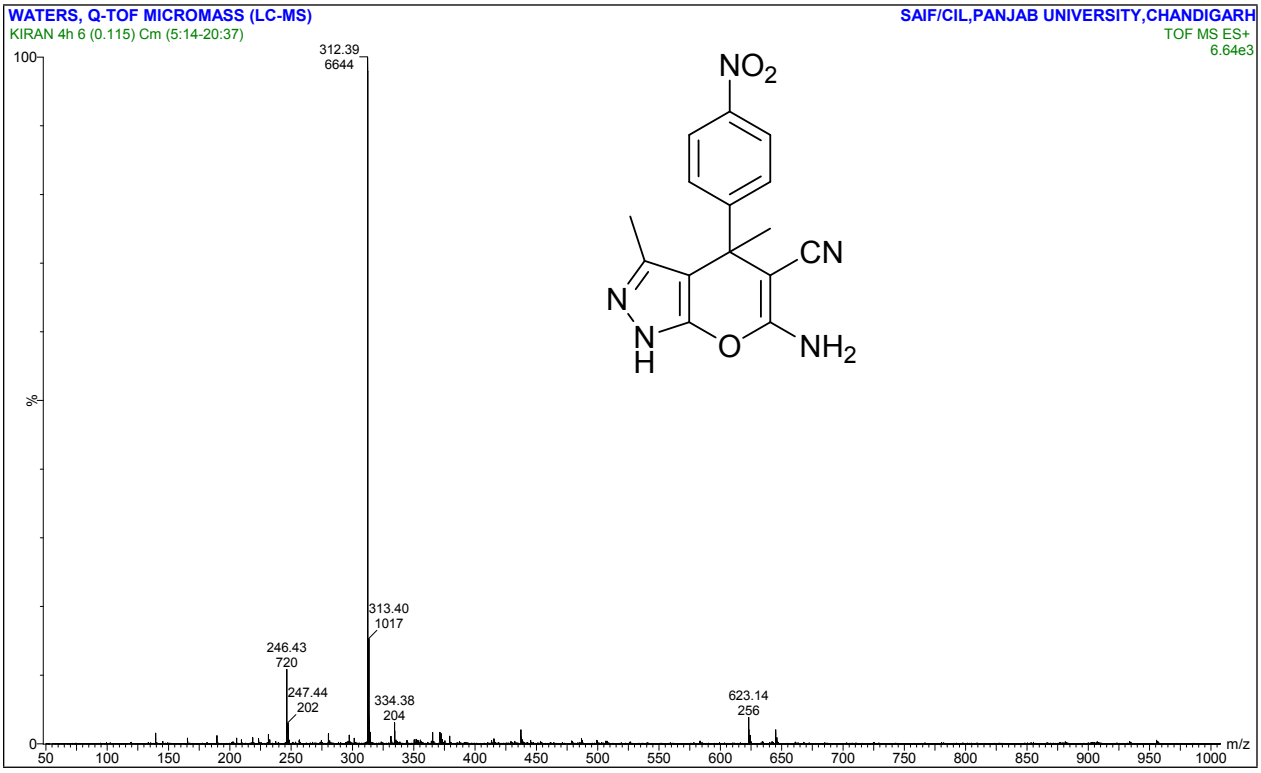
^{1}H NMR for **4h** (400 MHz, DMSO)



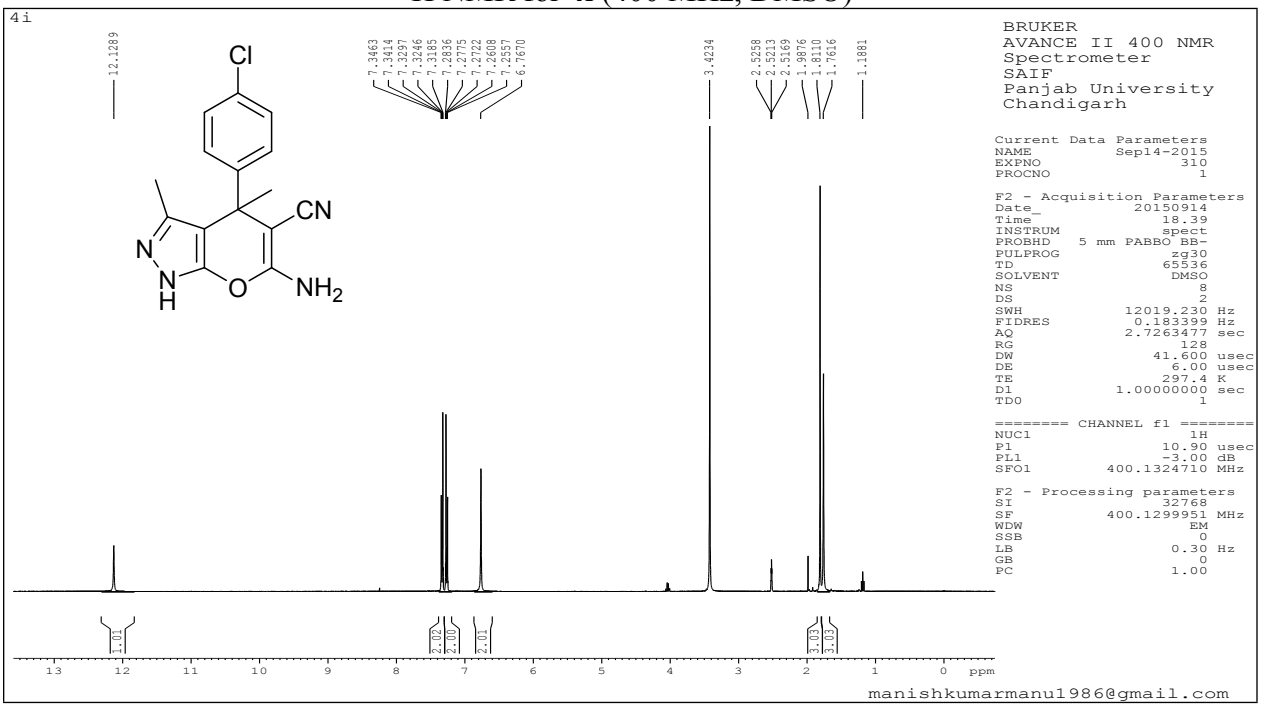
^{13}C NMR for **4h** (100 MHz, DMSO)



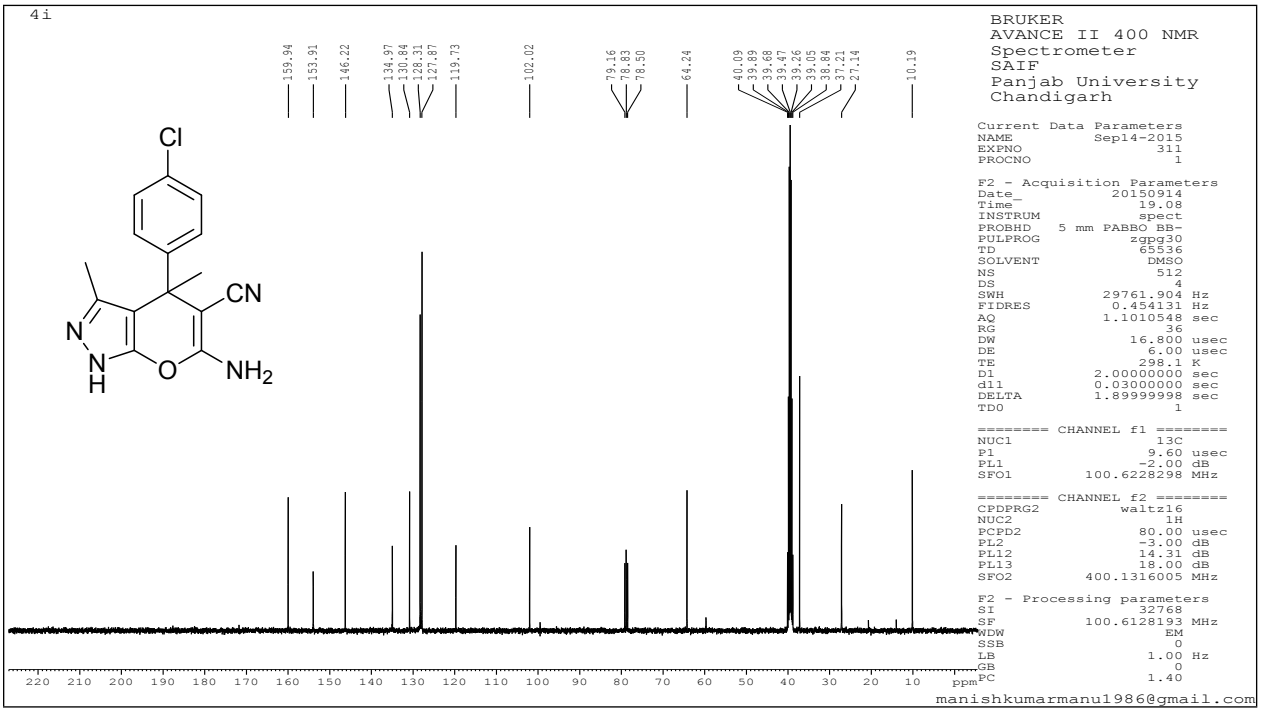
MS (ESI) for **4h**


WATERS, Q-TOF MICROMASS (LC-MS)
KIRAN 4h 6 (0.115) Cm (5:14-20:37)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
6.64e3
312.39
6644
313.40
1017
246.43
720
247.44
202
334.38
204
623.14
256
NO2
CN
NH2
N
N
H
O
%
m/z

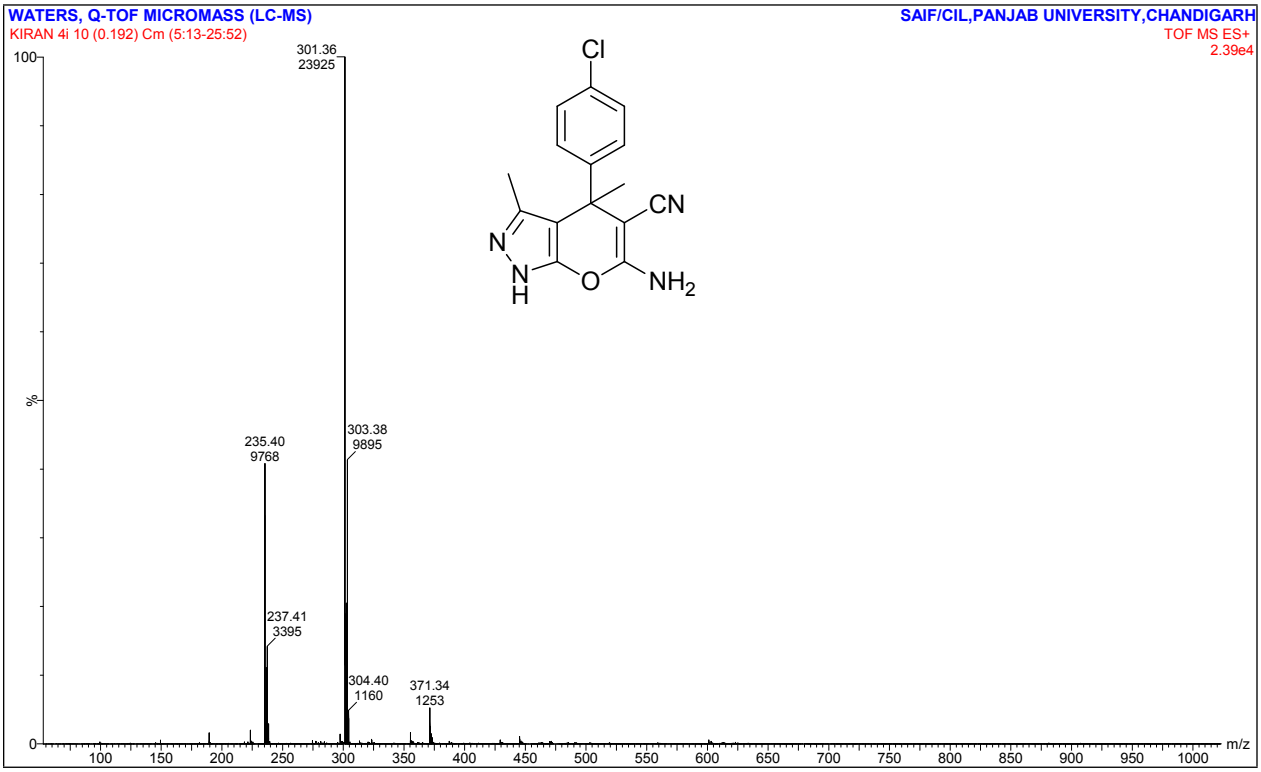
^{1}H NMR for **4i** (400 MHz, DMSO)



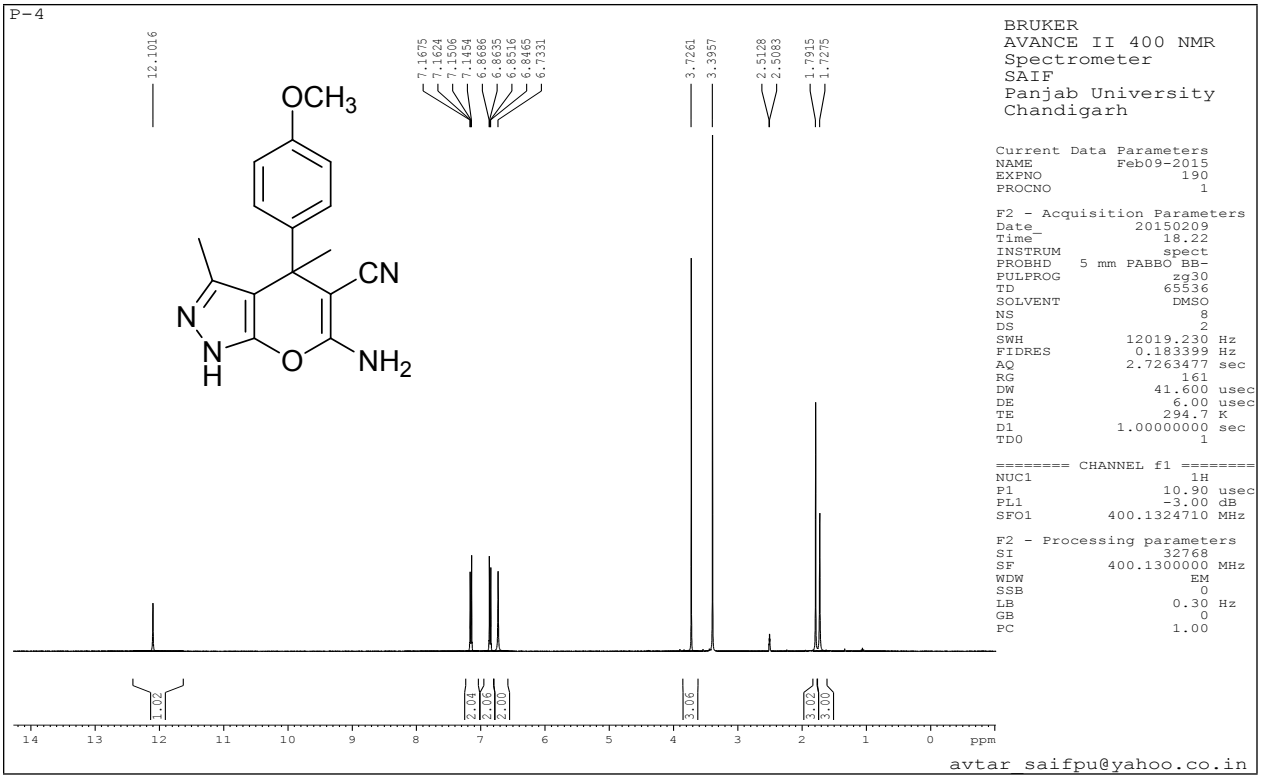
^{13}C NMR for **4i** (100 MHz, DMSO)



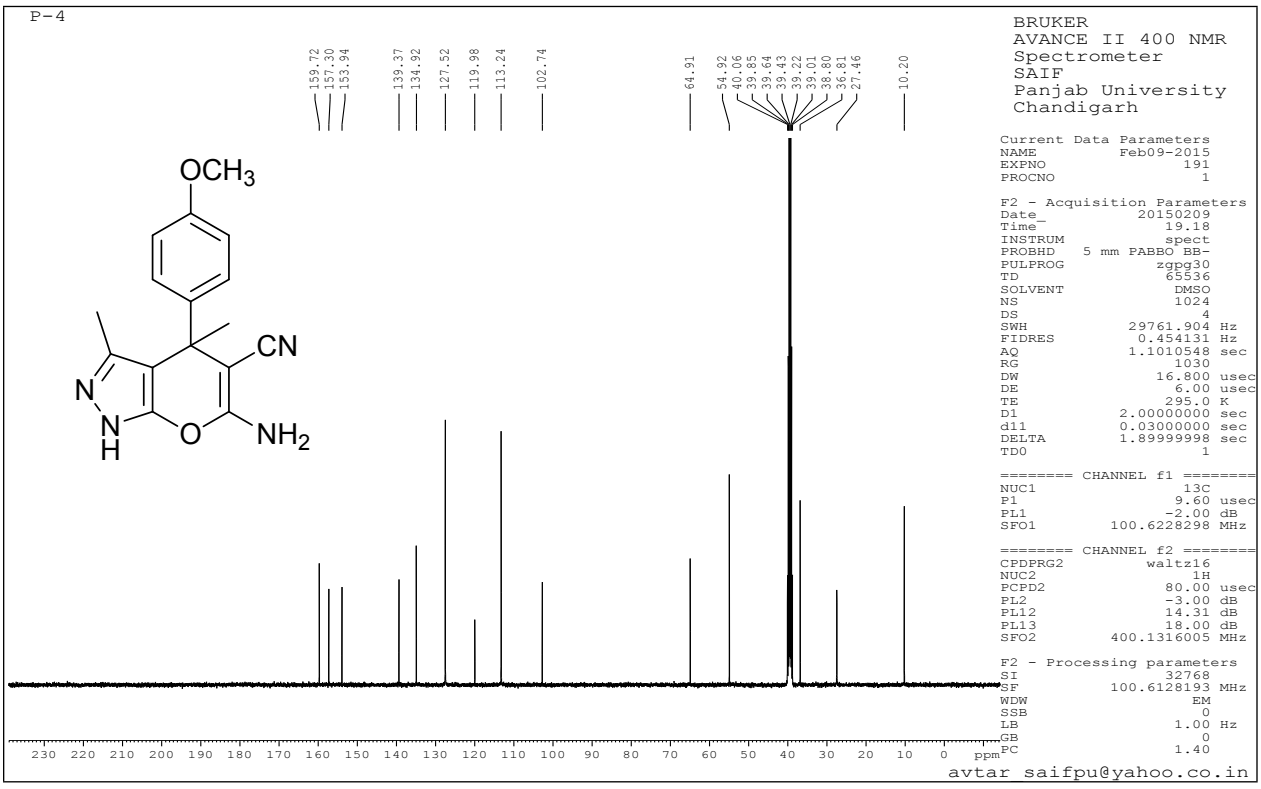
MS (ESI) for **4i**


WATERS, Q-TOF MICROMASS (LC-MS)
KIRAN 4i 10 (0.192) Cm (5:13-25:52)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
2.39e4
301.36
23925
303.38
9895
235.40
9768
237.41
3395
304.40
1160
371.34
1253
Cl
CN
N
N
H
O
NH2
%
m/z

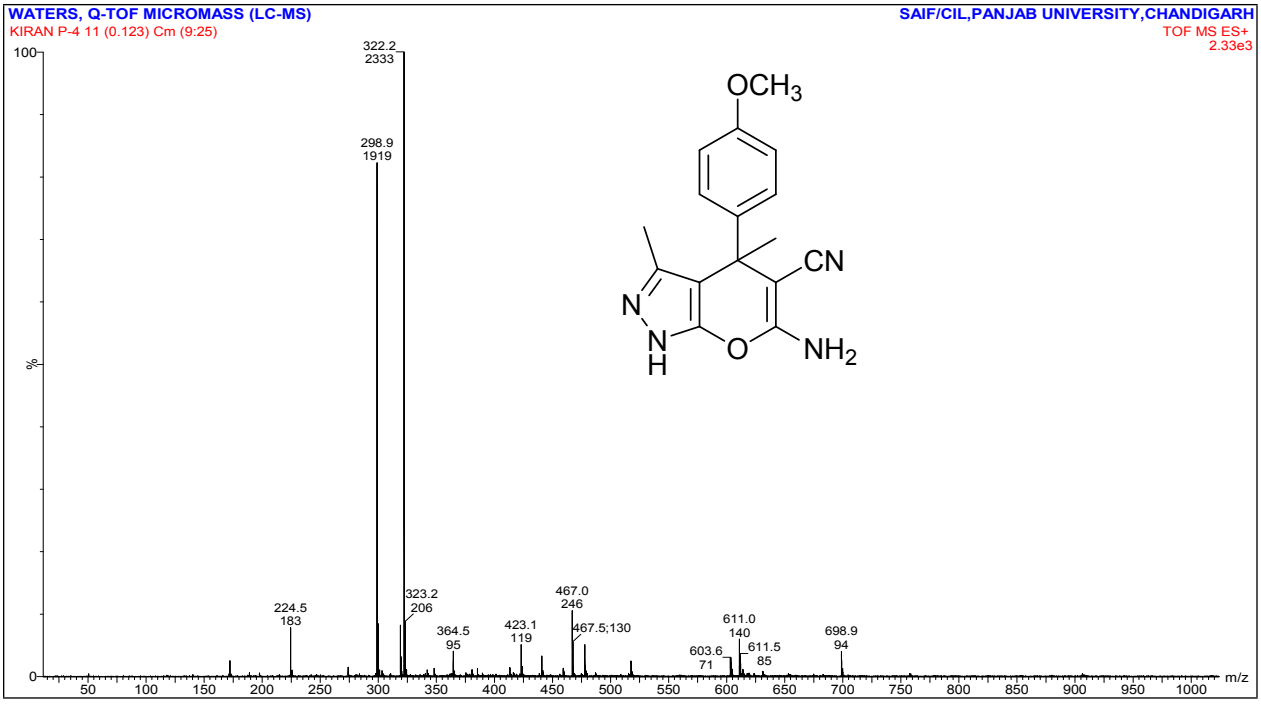
^{1}H NMR for **4j** (400 MHz, DMSO)



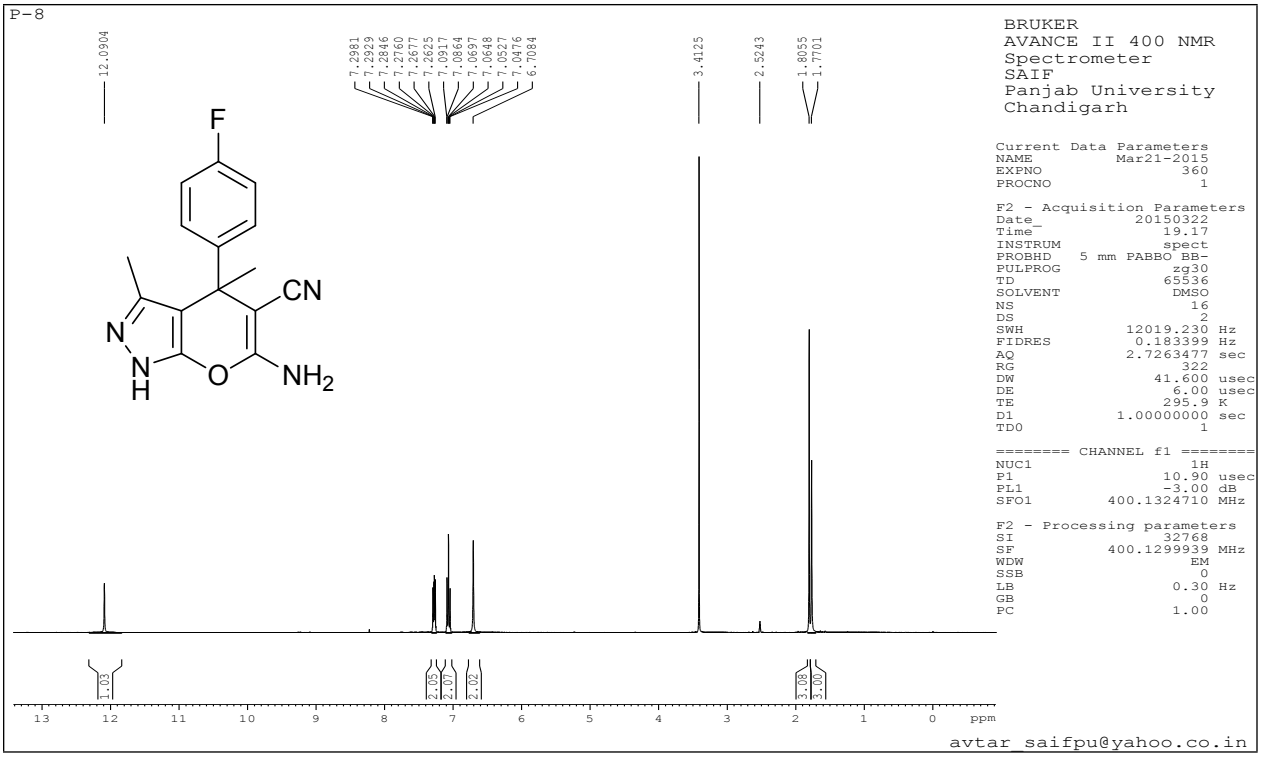
^{13}C NMR for **4j** (100 MHz, DMSO)



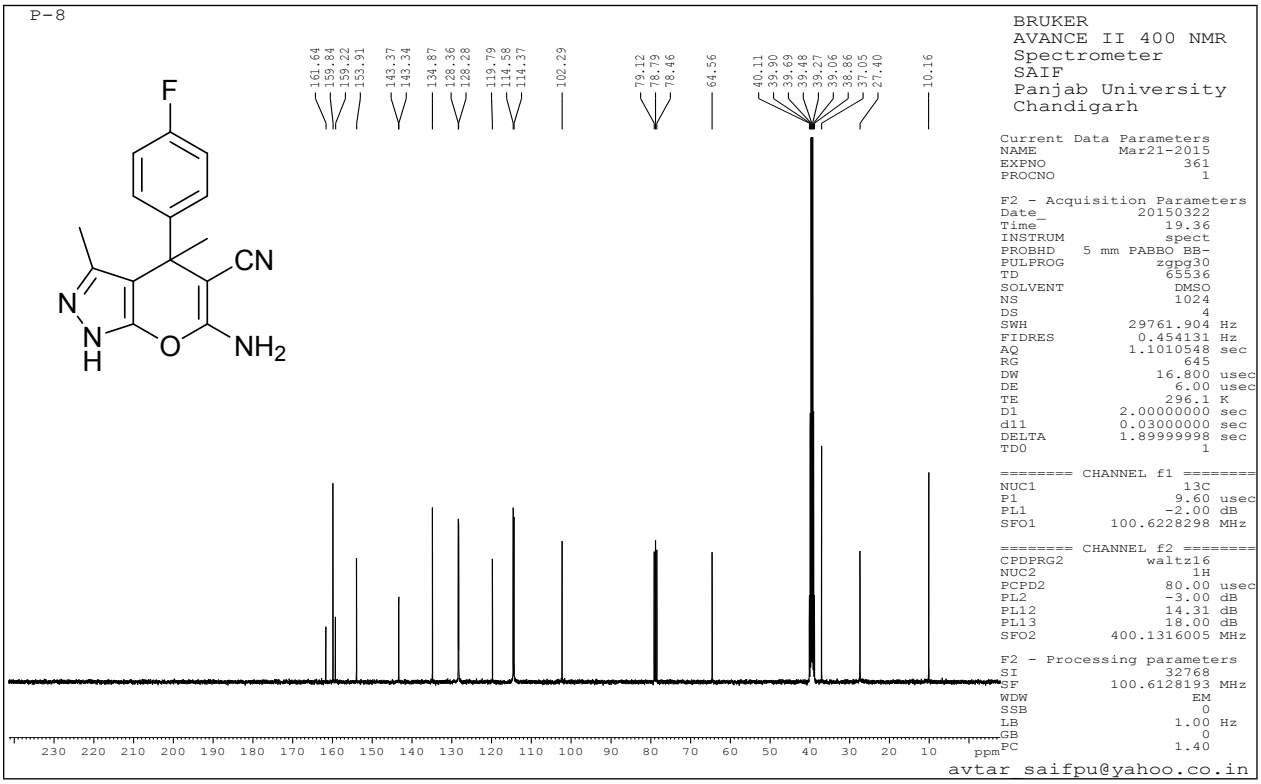
MS (ESI) for **4j**


WATERS, Q-TOF MICROMASS (LC-MS)
KIRAN P-4 11 (0.123) Cm (9:25)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
2.33e3
100
%
0
322.2
2333
298.9
1919
323.2
206
224.5
183
364.5
95
423.1
119
467.0
246
467.5;130
603.6
71
611.0
140
611.5
85
698.9
94
m/z
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
OCH3
CN
N
N
H
O
NH2

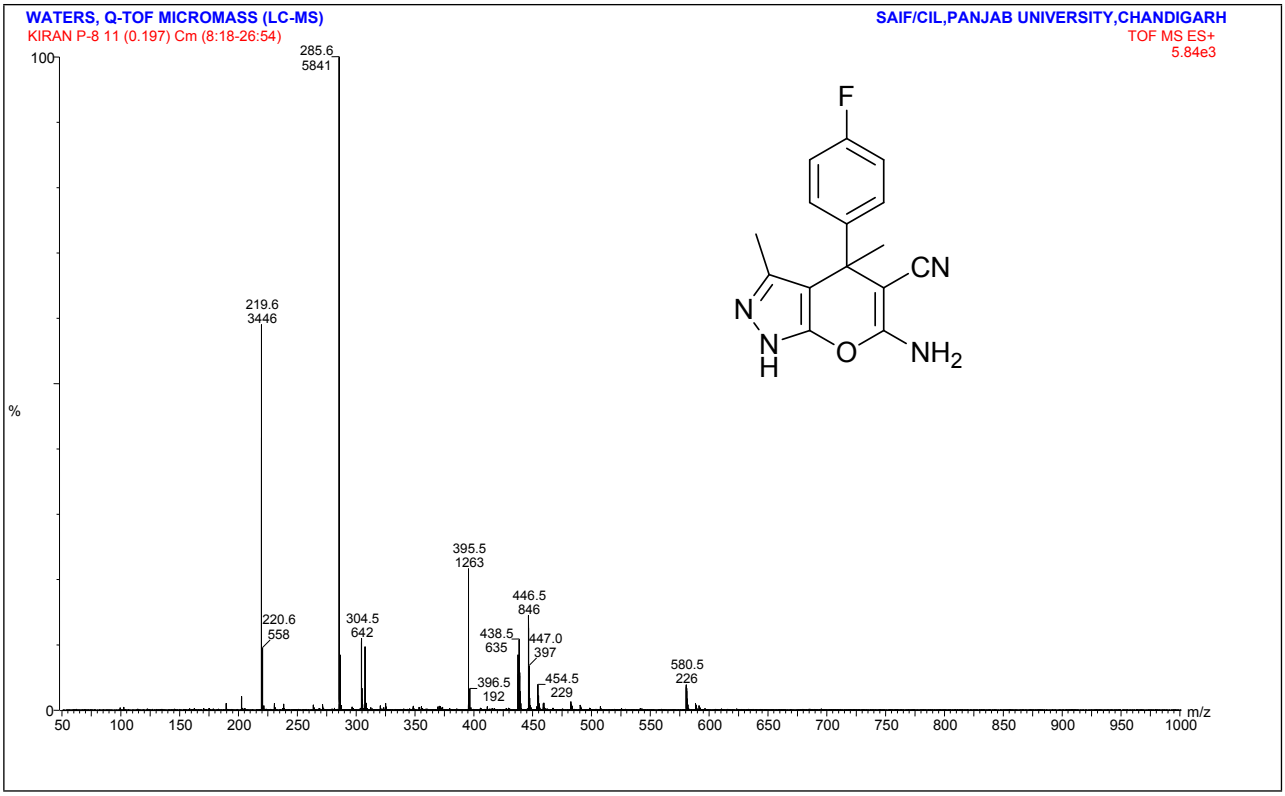
^{1}H NMR for **4k** (400 MHz, DMSO)



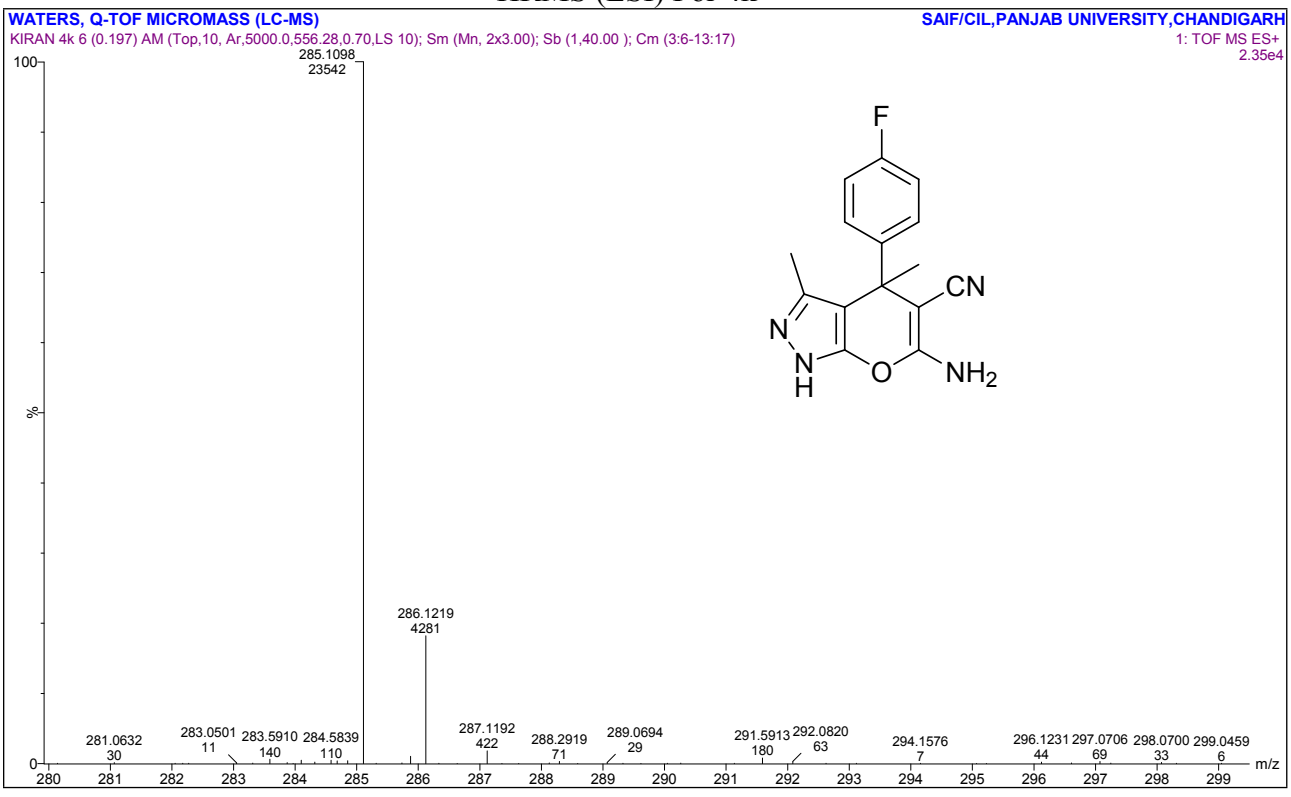
^{13}C NMR for **4k** (100 MHz, DMSO)



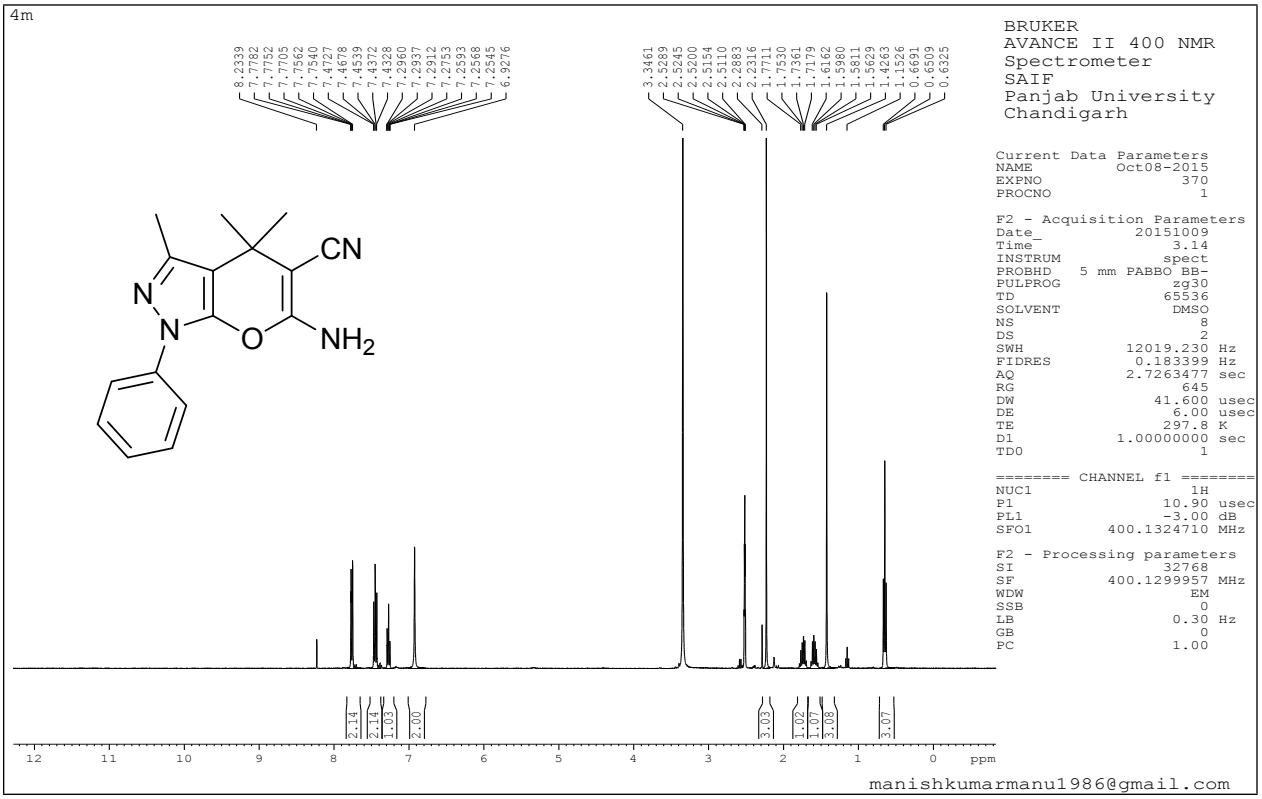
MS (ESI) for **4k**



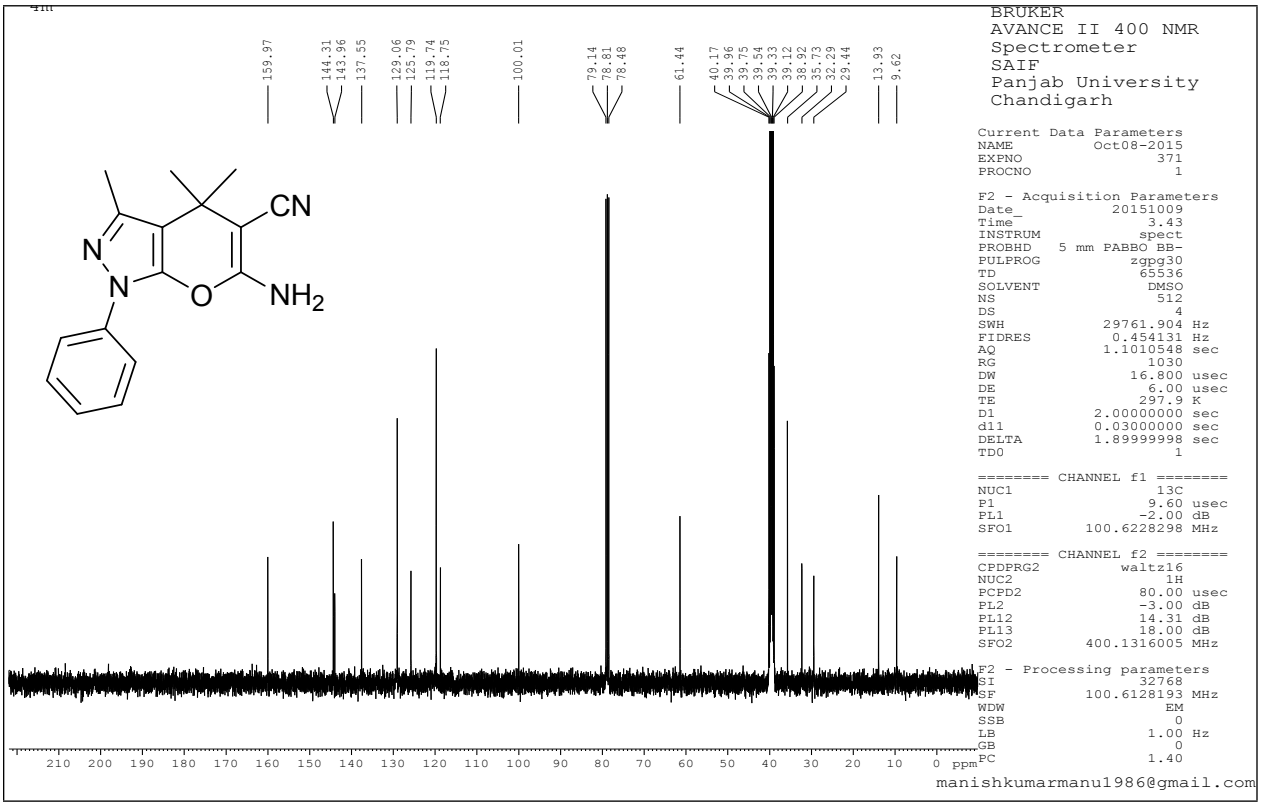
HRMS (ESI) For 4k



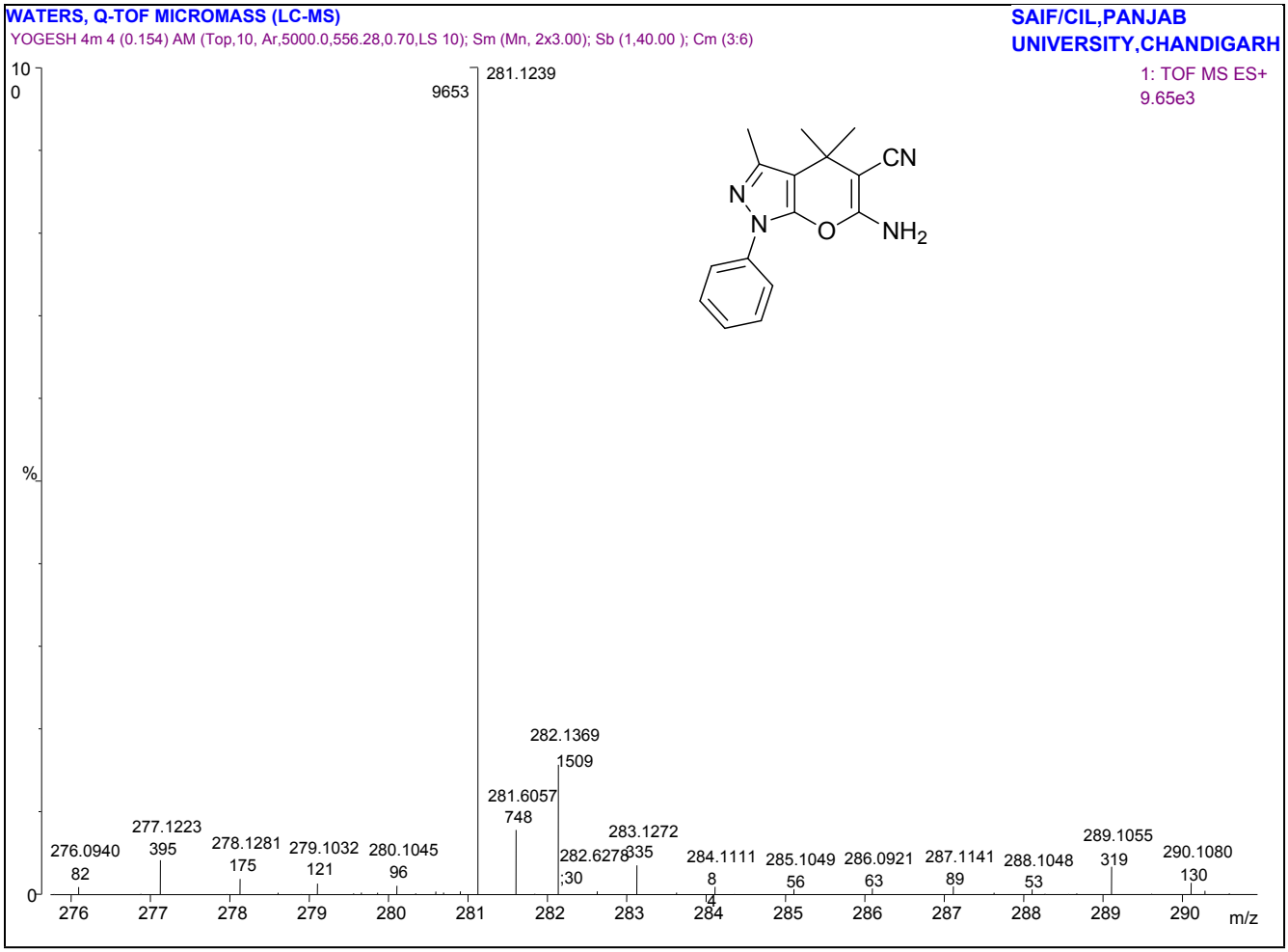
^{1}H NMR for **4m** (400 MHz, DMSO)



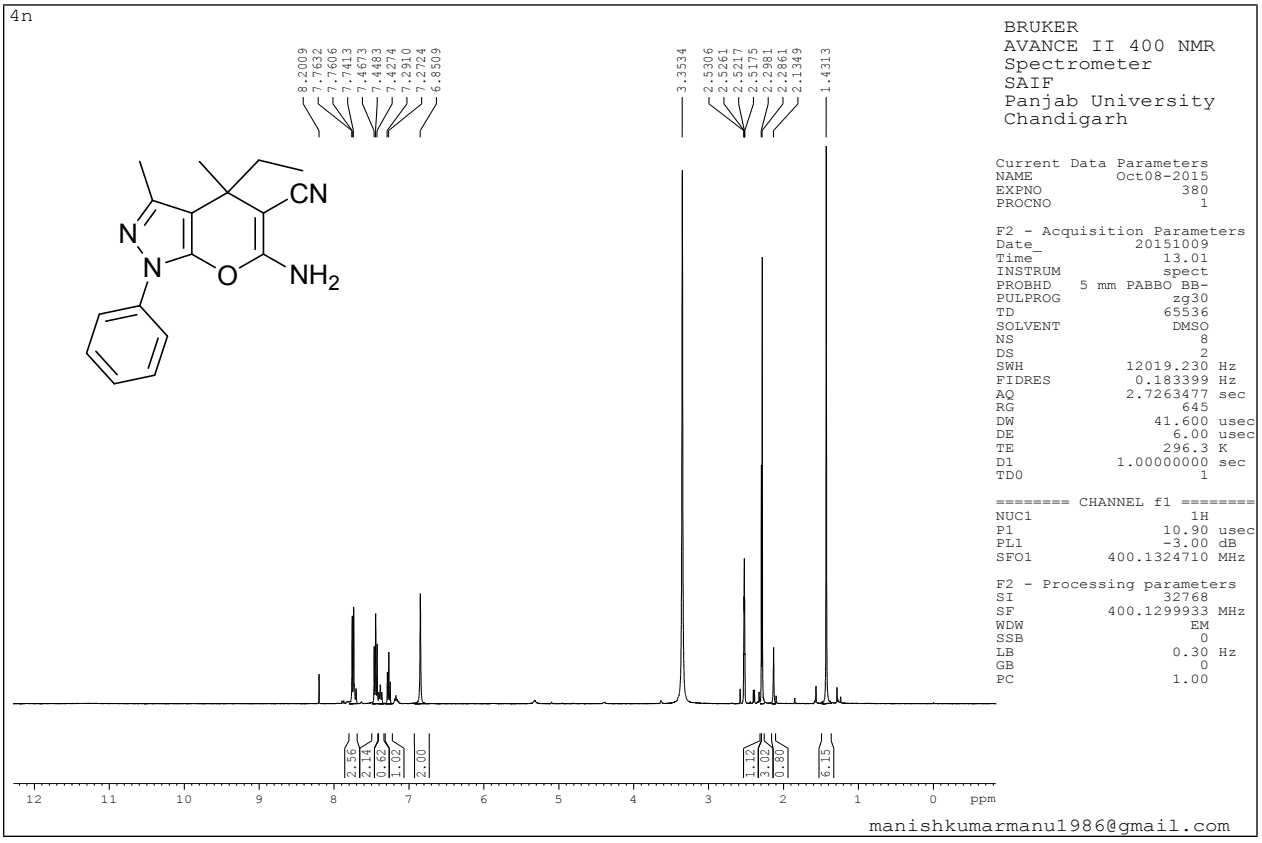
^{13}C NMR for **4m** (100 MHz, DMSO)



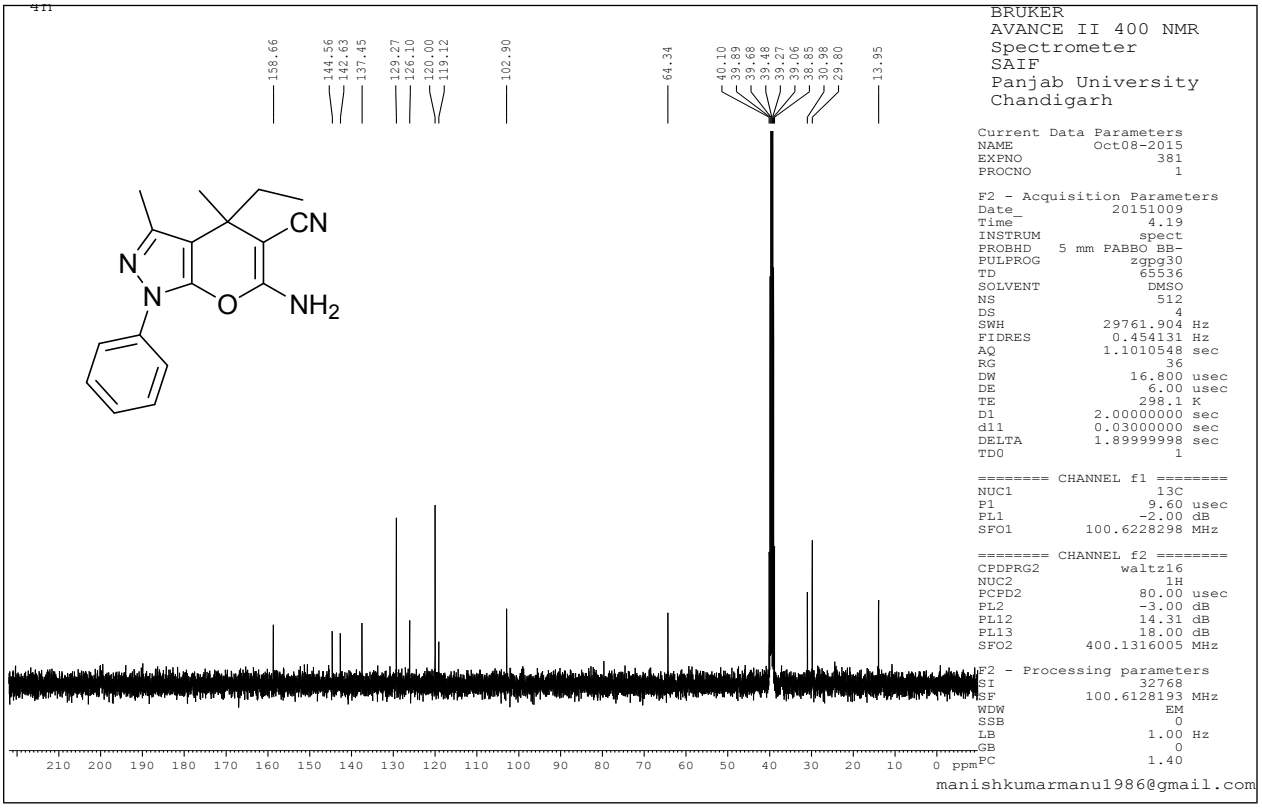
HRMS (ESI) for **4m**



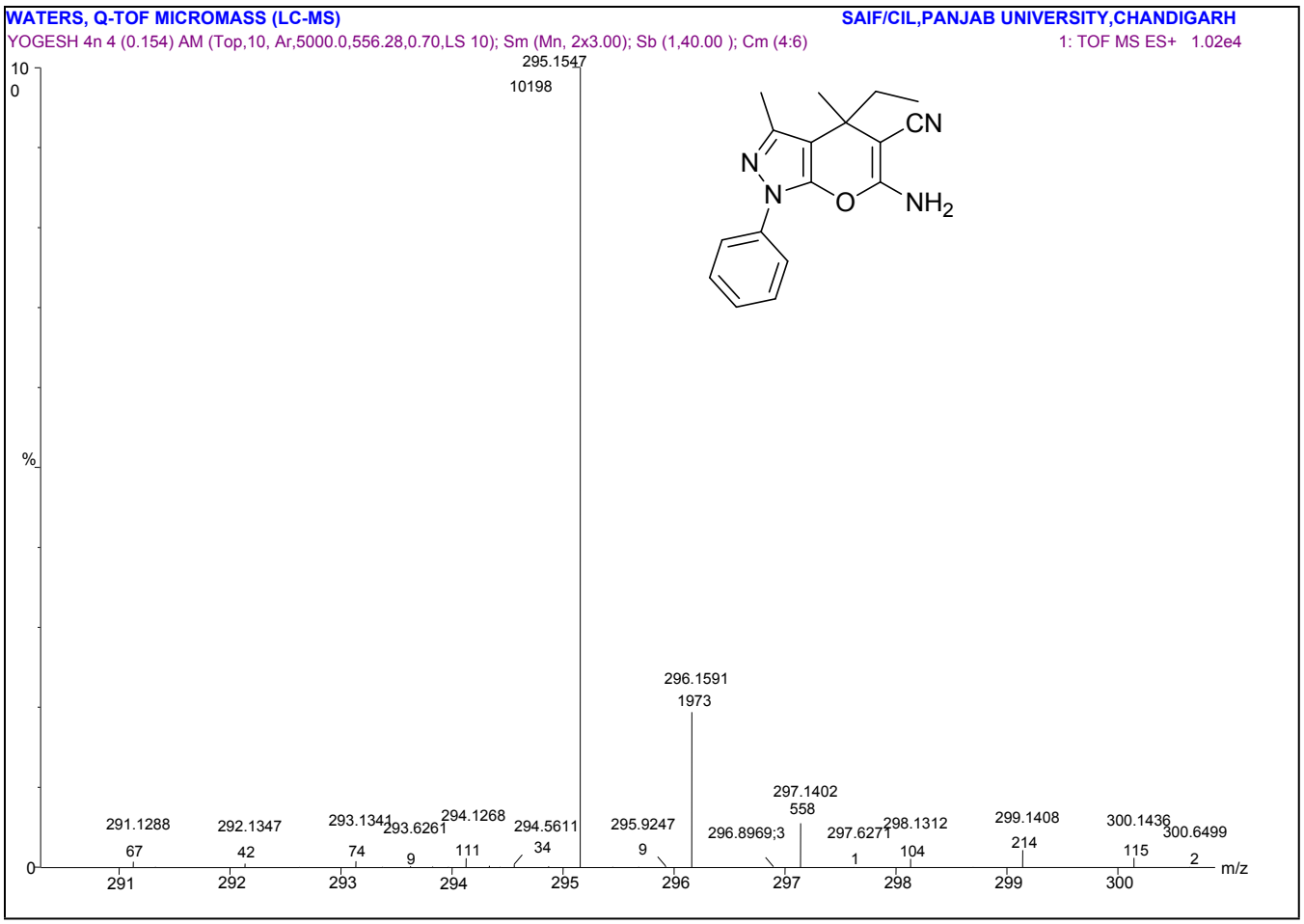
^{1}H NMR for **4n** (400 MHz, DMSO)



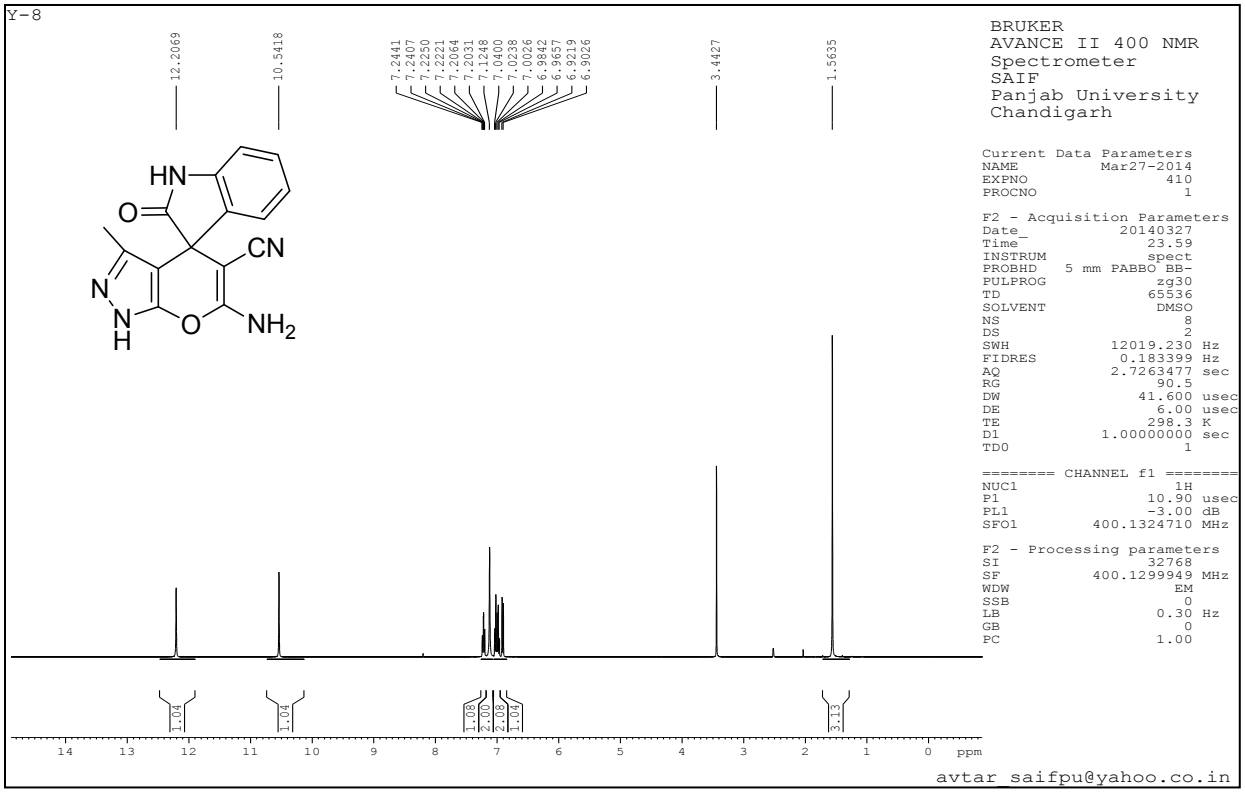
^{13}C NMR for **4n** (100 MHz, DMSO)



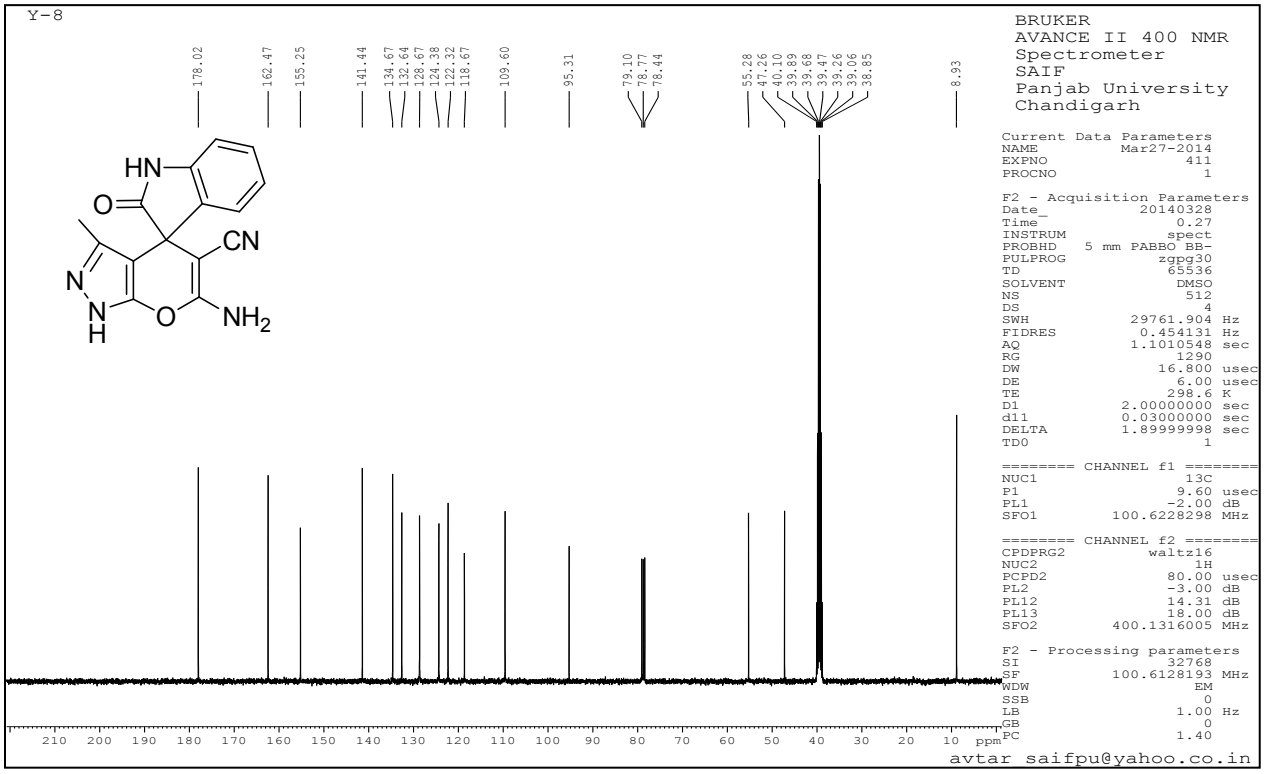
HRMS (ESI) for **4n**



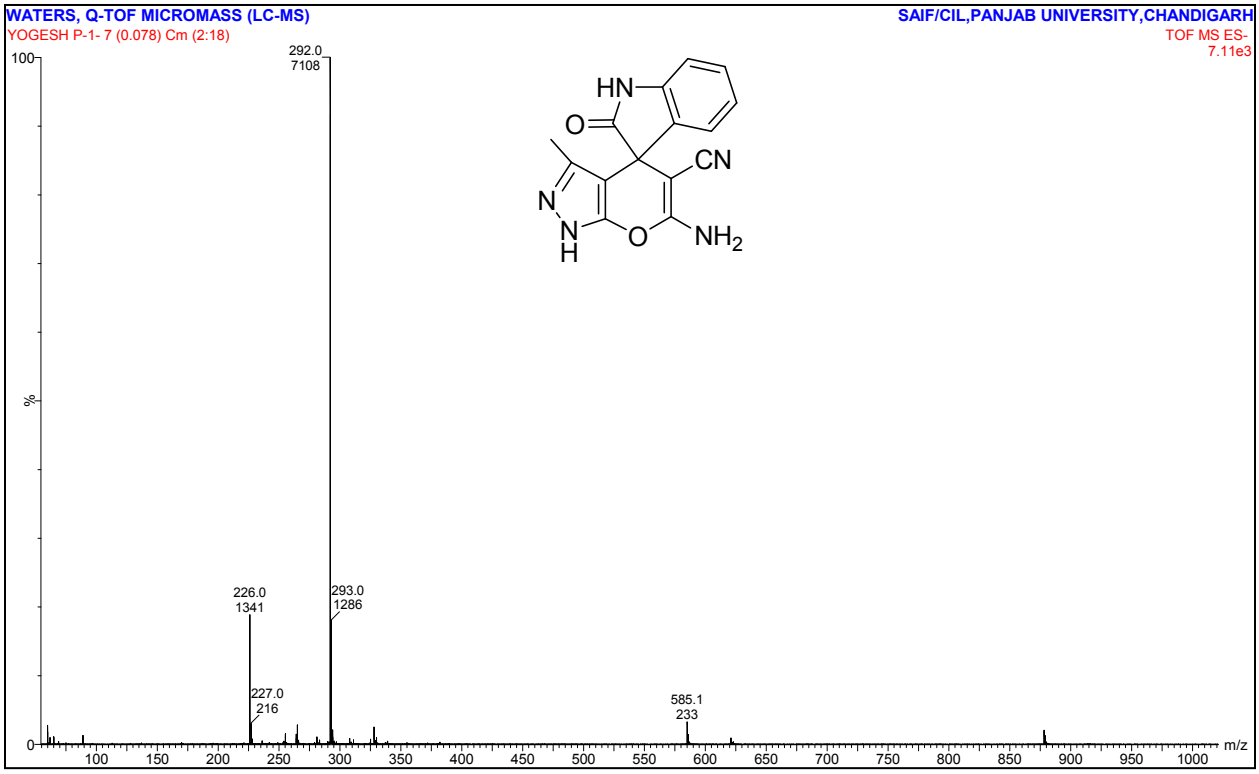
^{1}H NMR for **6a** (400 MHz, DMSO)



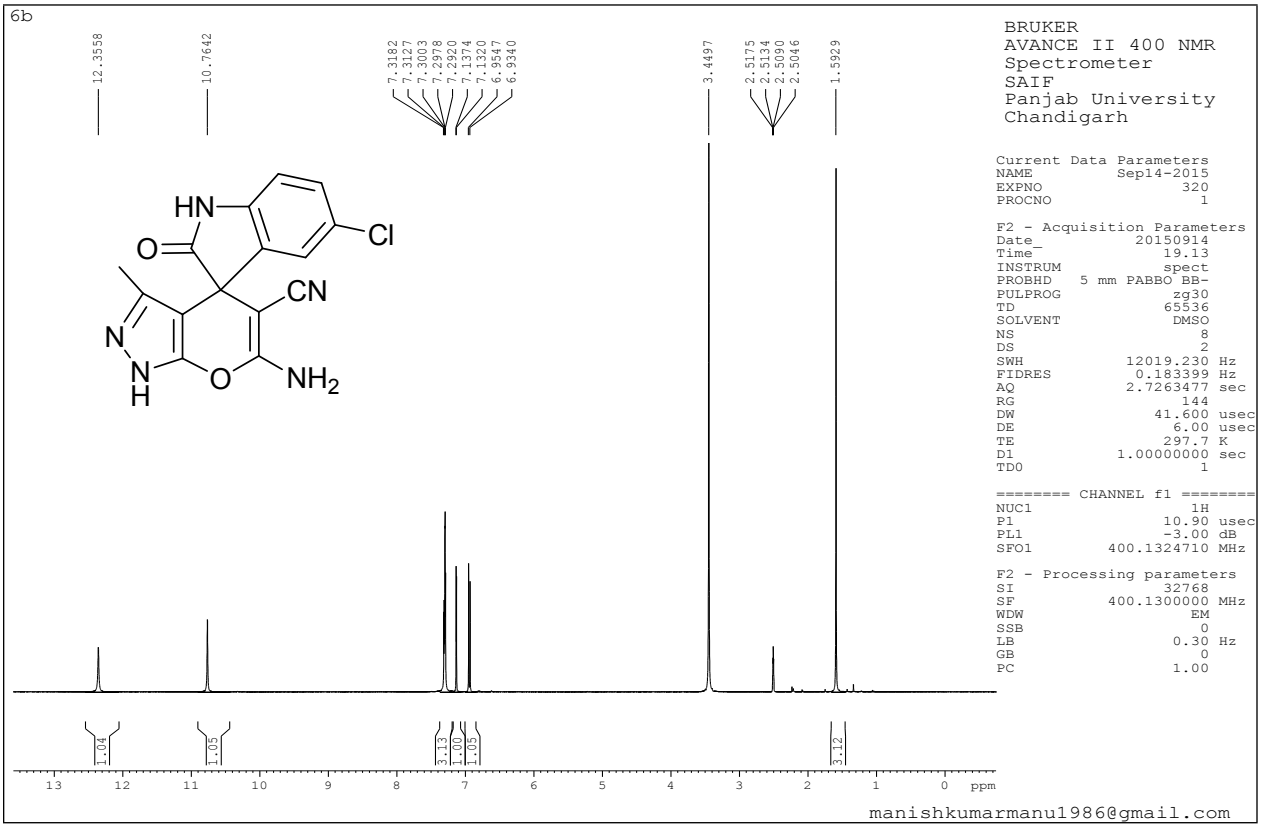
^{13}C NMR for **6a** (100 MHz, DMSO)



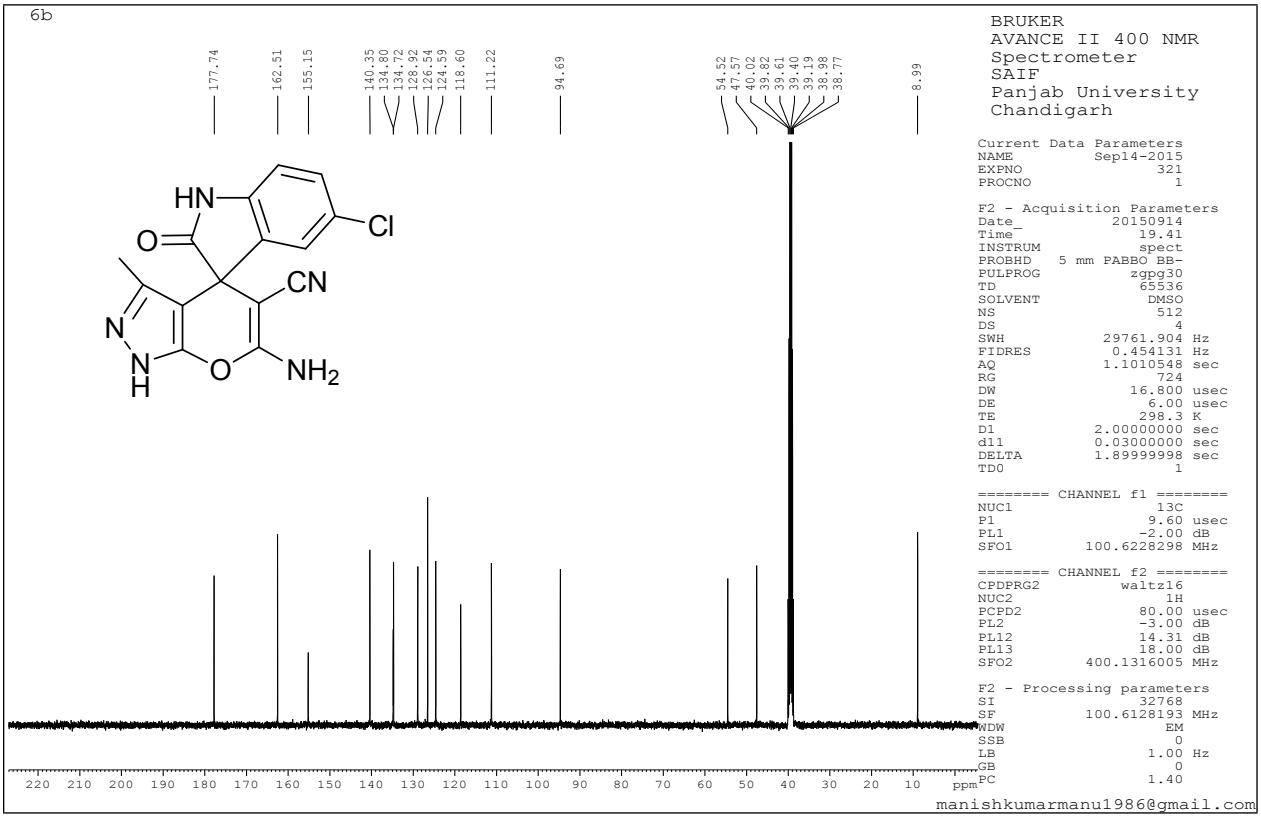
MS (ESI) for **6a**


WATERS, Q-TOF MICROMASS (LC-MS)
YOGESH P-1- 7 (0.078) Cm (2:18)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES-
7.11e3
292.0
7108
226.0
1341
293.0
1286
227.0
216
585.1
233
HN
O
CN
N
N
H
O
NH2
%
m/z

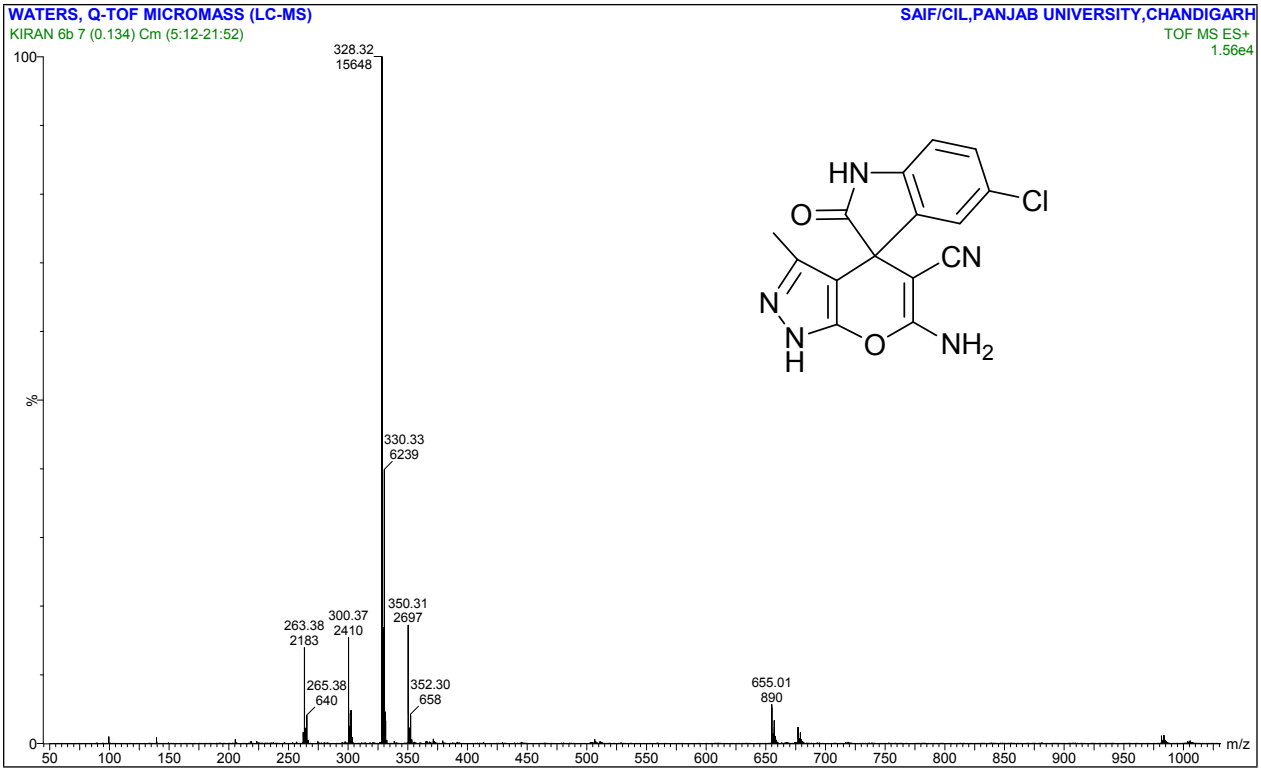
^{1}H NMR for **6b** (400 MHz, DMSO)



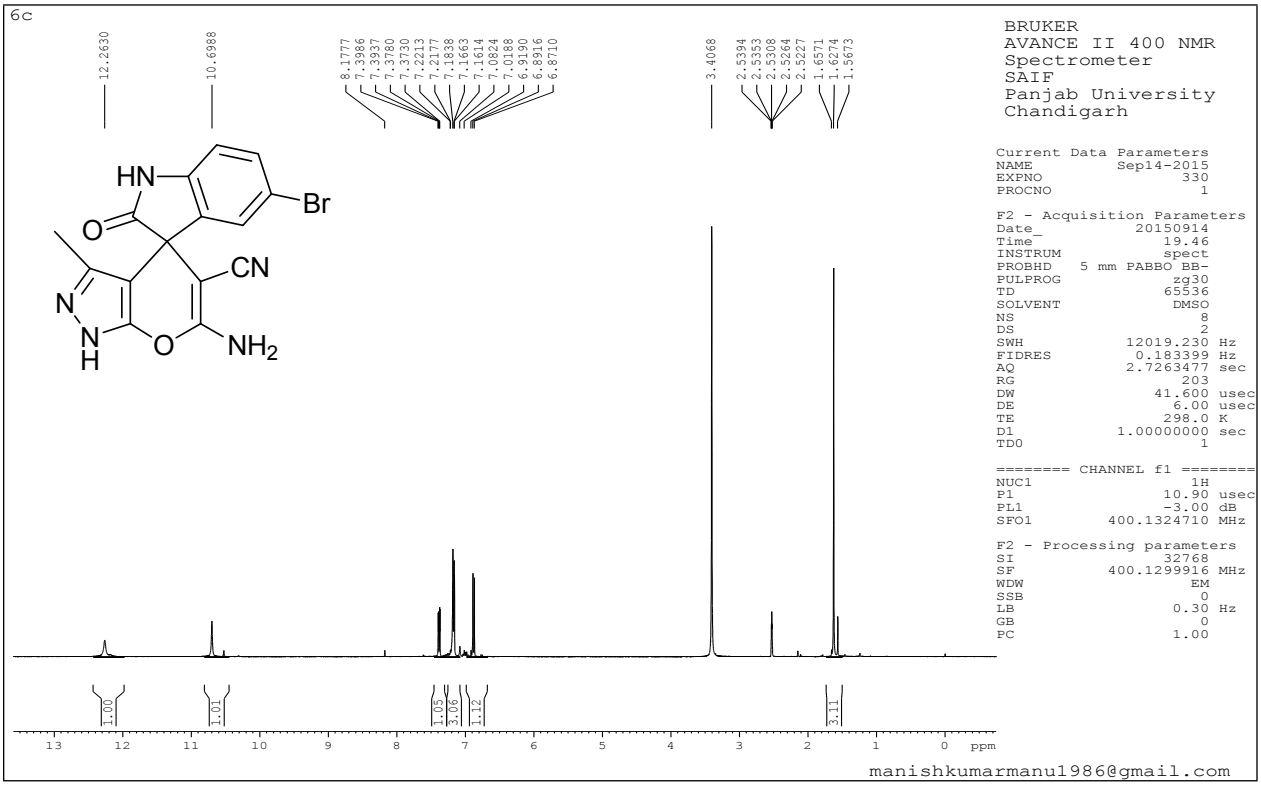
^{13}C NMR for **6b** (100 MHz, DMSO)



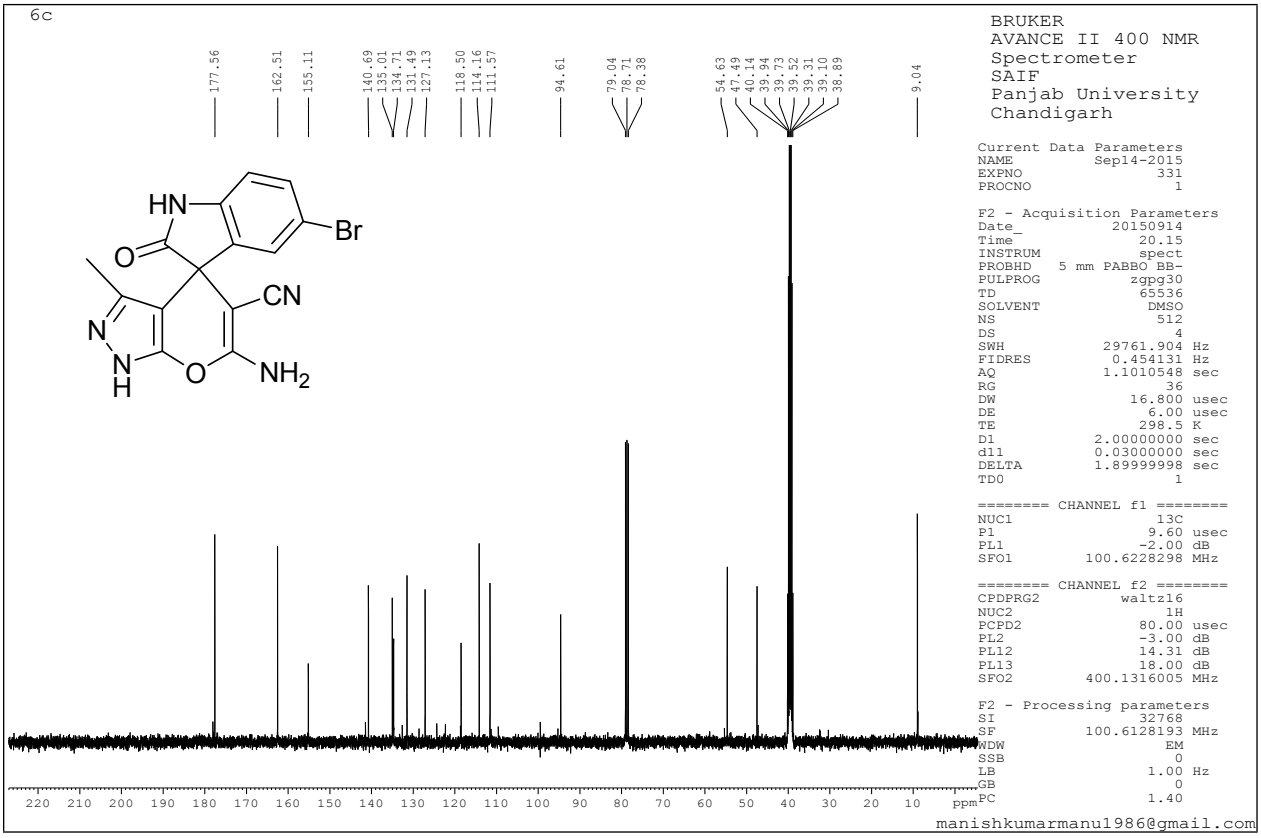
MS (ESI) for **6b**


WATERS, Q-TOF MICROMASS (LC-MS)
KIRAN 6b 7 (0.134) Cm (5:12-21:52)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
1.56e4
328.32
15648
330.33
6239
350.31
2697
300.37
2410
263.38
2183
265.38
640
352.30
658
655.01
890
HN
O
Cl
CN
N
N
H
O
NH2
%
m/z

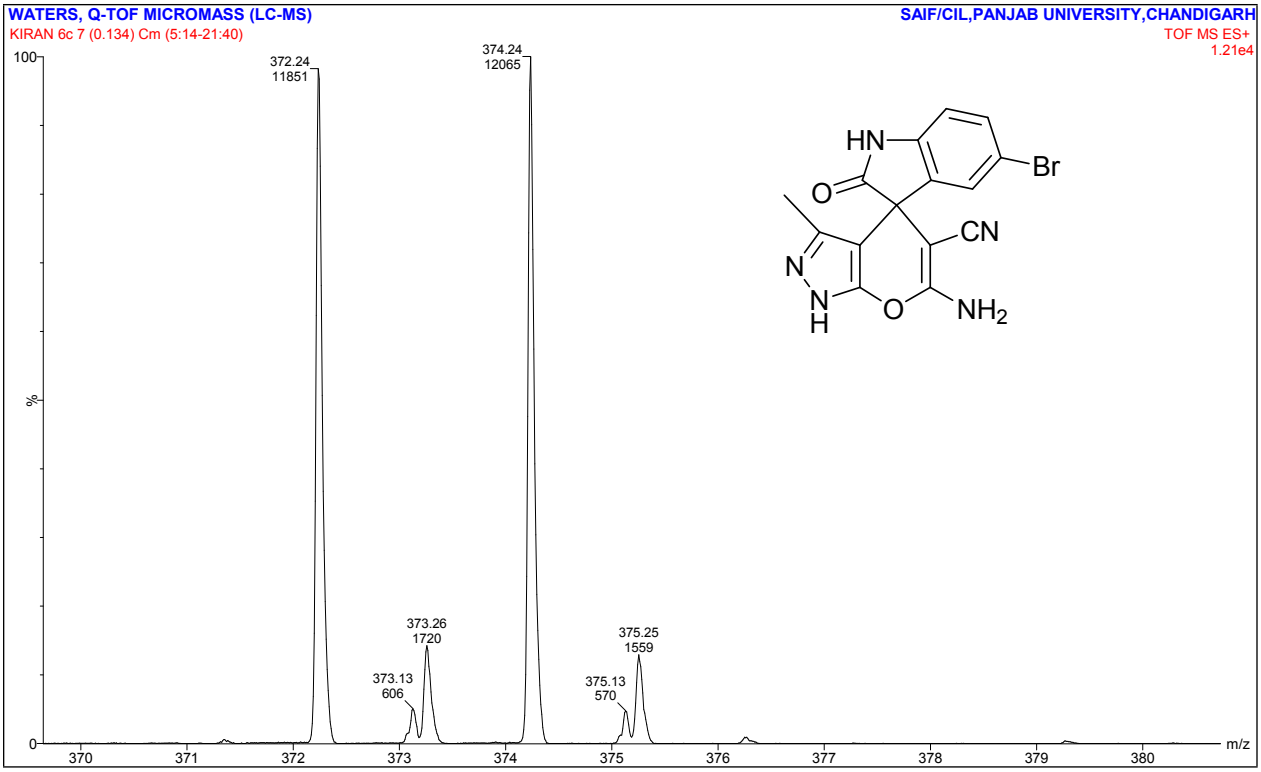
^{1}H NMR for **6c** (400 MHz, DMSO)



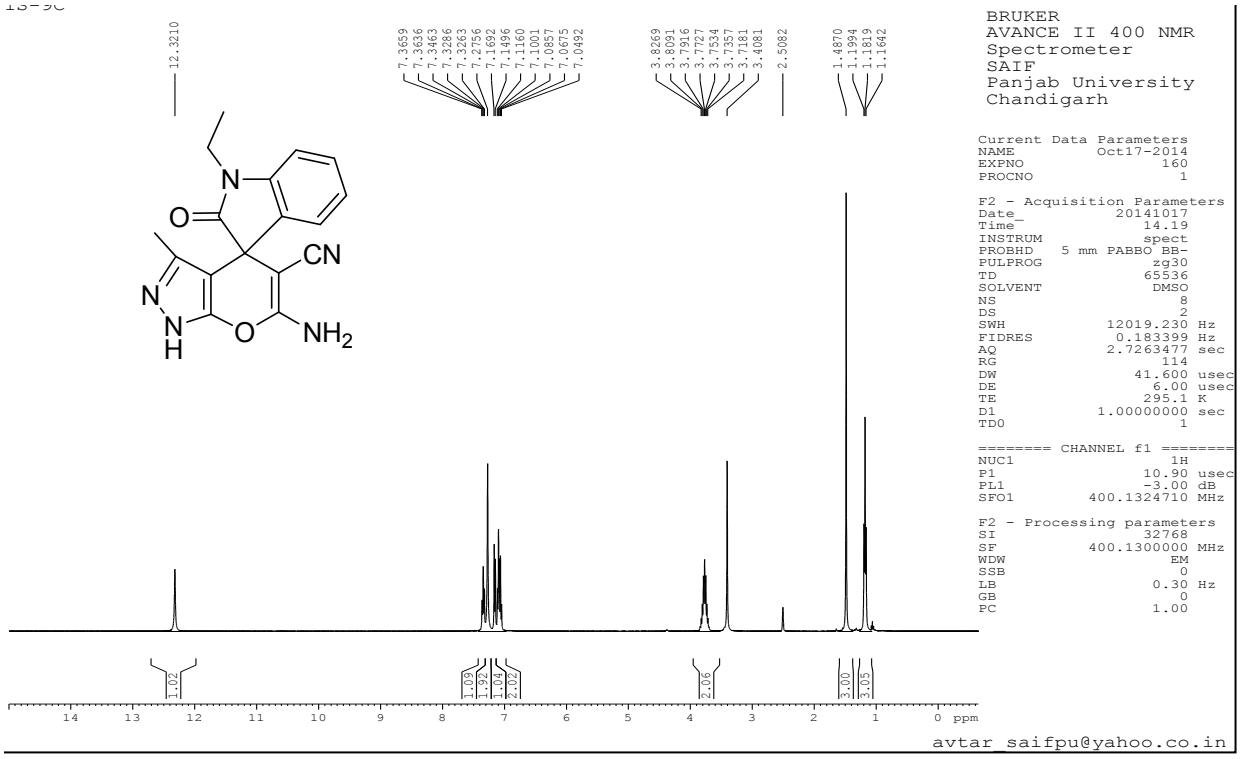
^{13}C NMR for **6c** (100 MHz, DMSO)



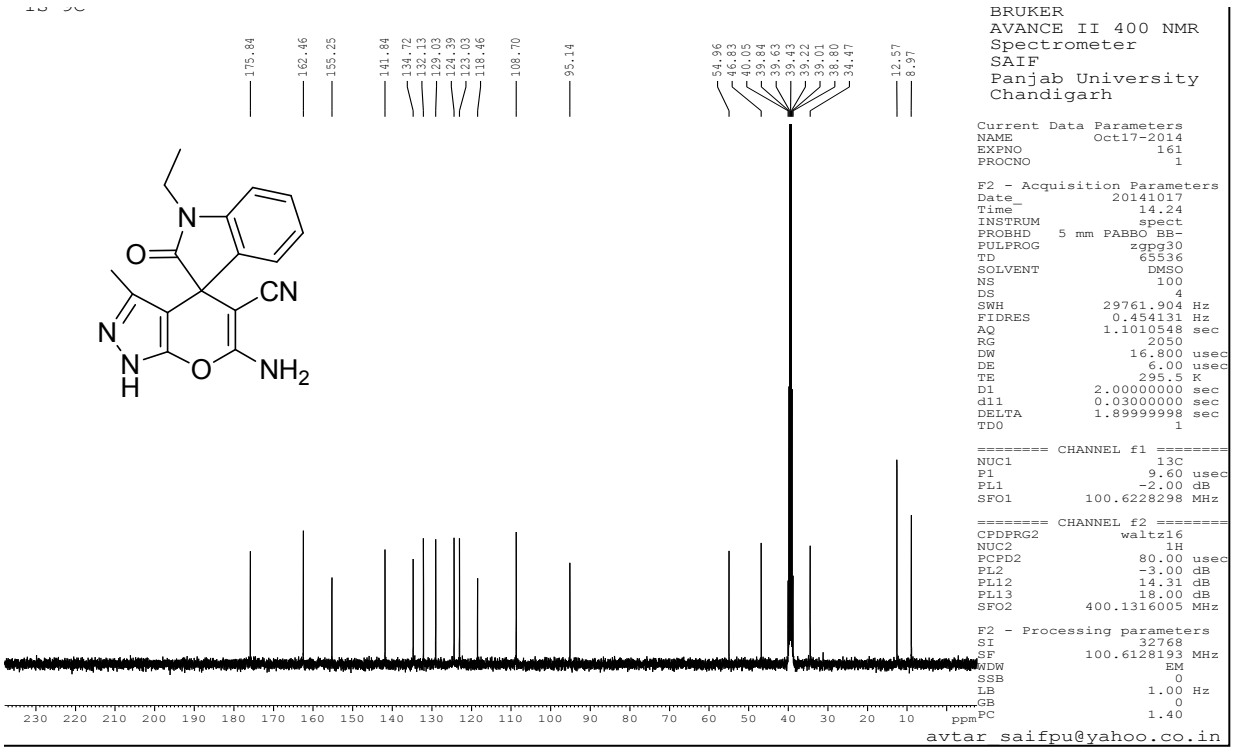
MS (ESI) for **6c**


WATERS, Q-TOF MICROMASS (LC-MS)
KIRAN 6c 7 (0.134) Cm (5:14-21:40)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
1.21e4
100
%
0
372.24
11851
374.24
12065
373.26
1720
373.13
606
375.25
1559
375.13
570
370
371
372
373
374
375
376
377
378
379
380
m/z
HN
O
Br
CN
N
N
H
O
NH2

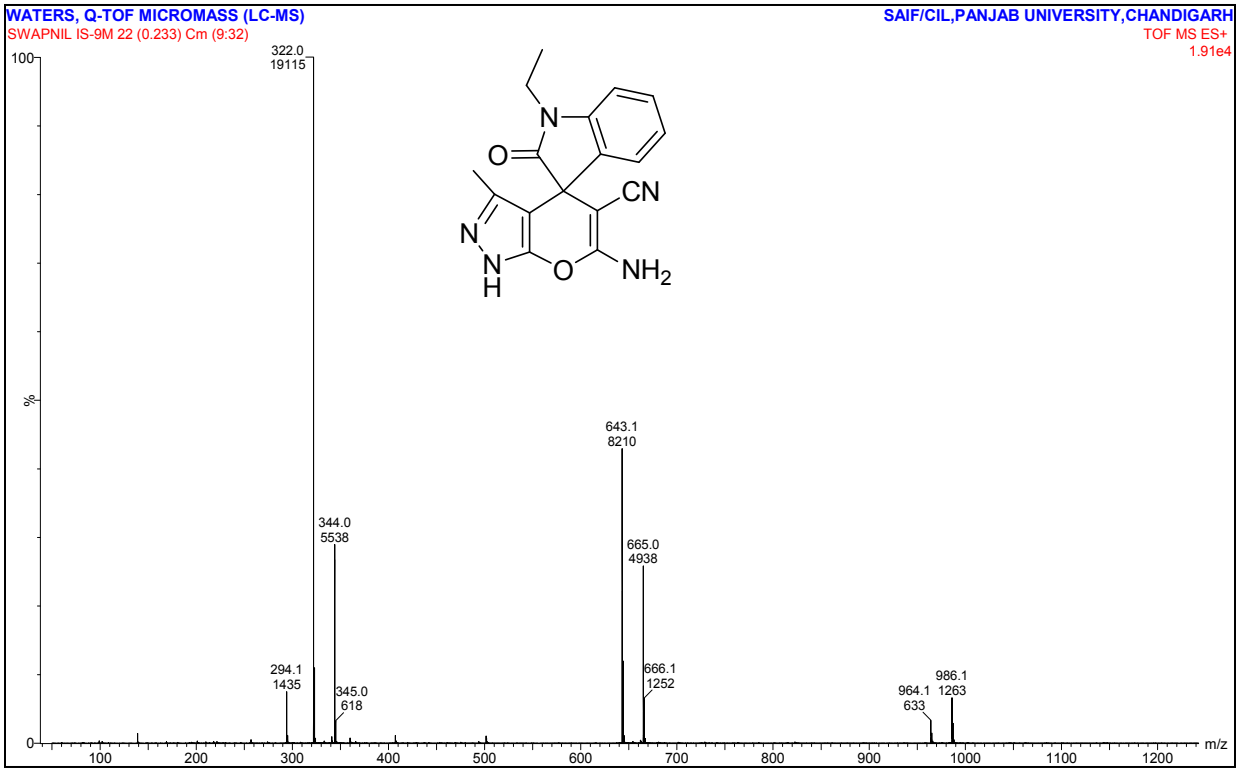
^{1}H NMR for **6d** (400 MHz, DMSO)



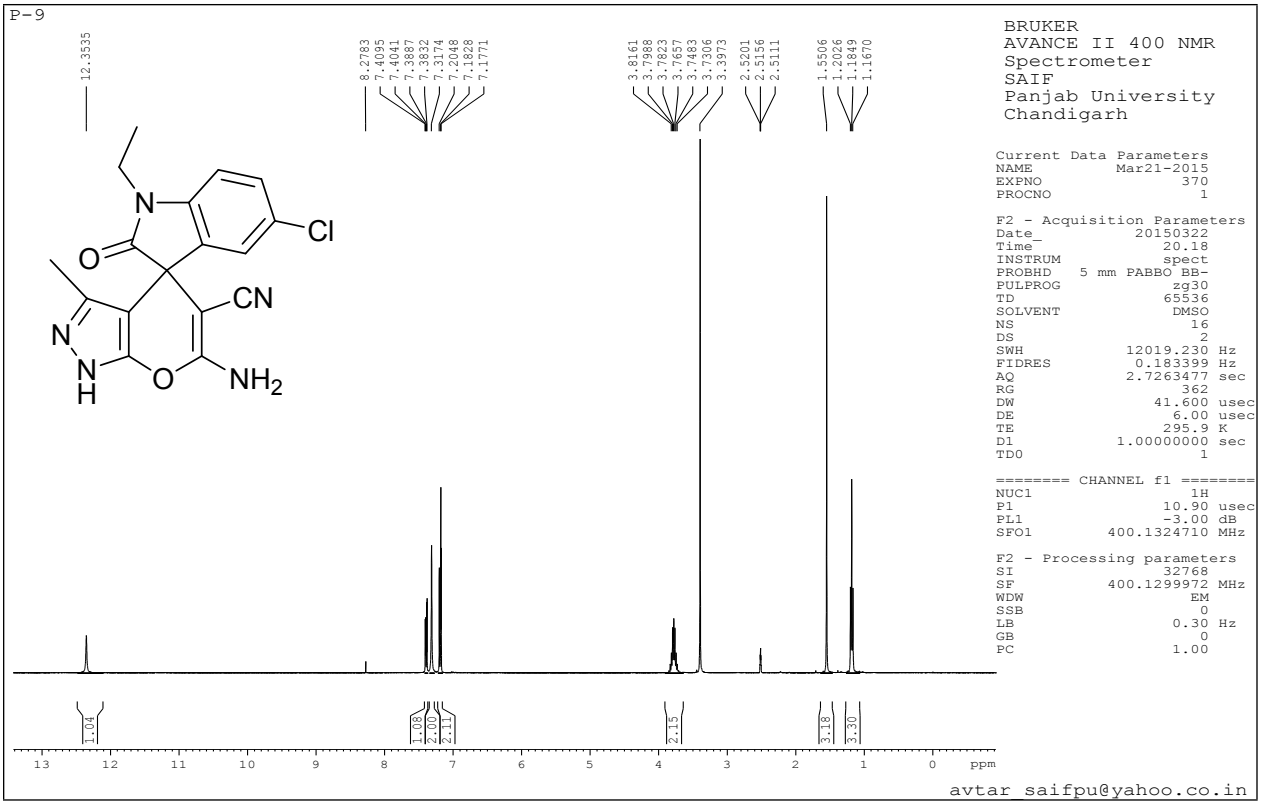
^{13}C NMR for **6d** (100 MHz, DMSO)



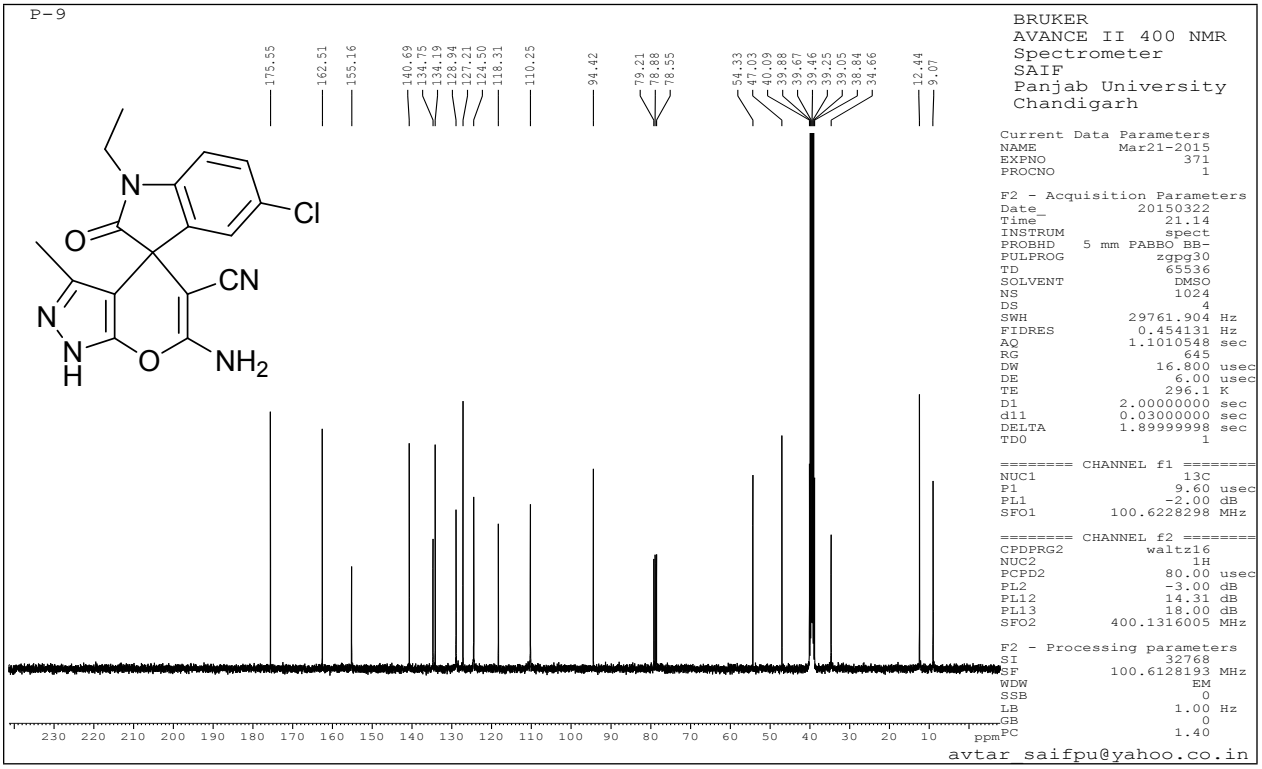
MS (ESI) for **6d**


WATERS, Q-TOF MICROMASS (LC-MS)
SWAPNIL IS-9M 22 (0.233) Cm (9:32)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
1.91e4
100
%
0
322.0
19115
344.0
5538
294.1
1435
345.0
618
643.1
8210
665.0
4938
666.1
1252
964.1
633
986.1
1263
m/z
100
200
300
400
500
600
700
800
900
1000
1100
1200
N
O
CN
N
N
H
O
NH2

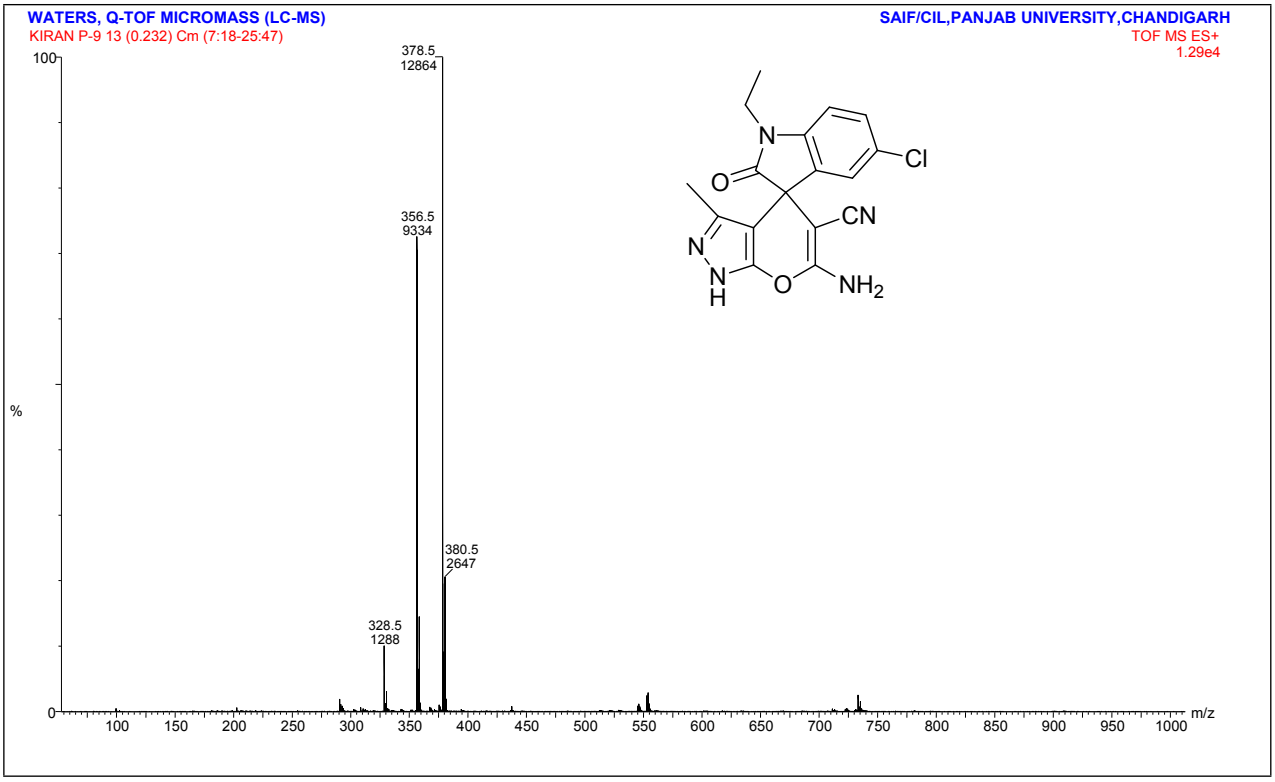
^{1}H NMR for **6e** (400 MHz, DMSO)



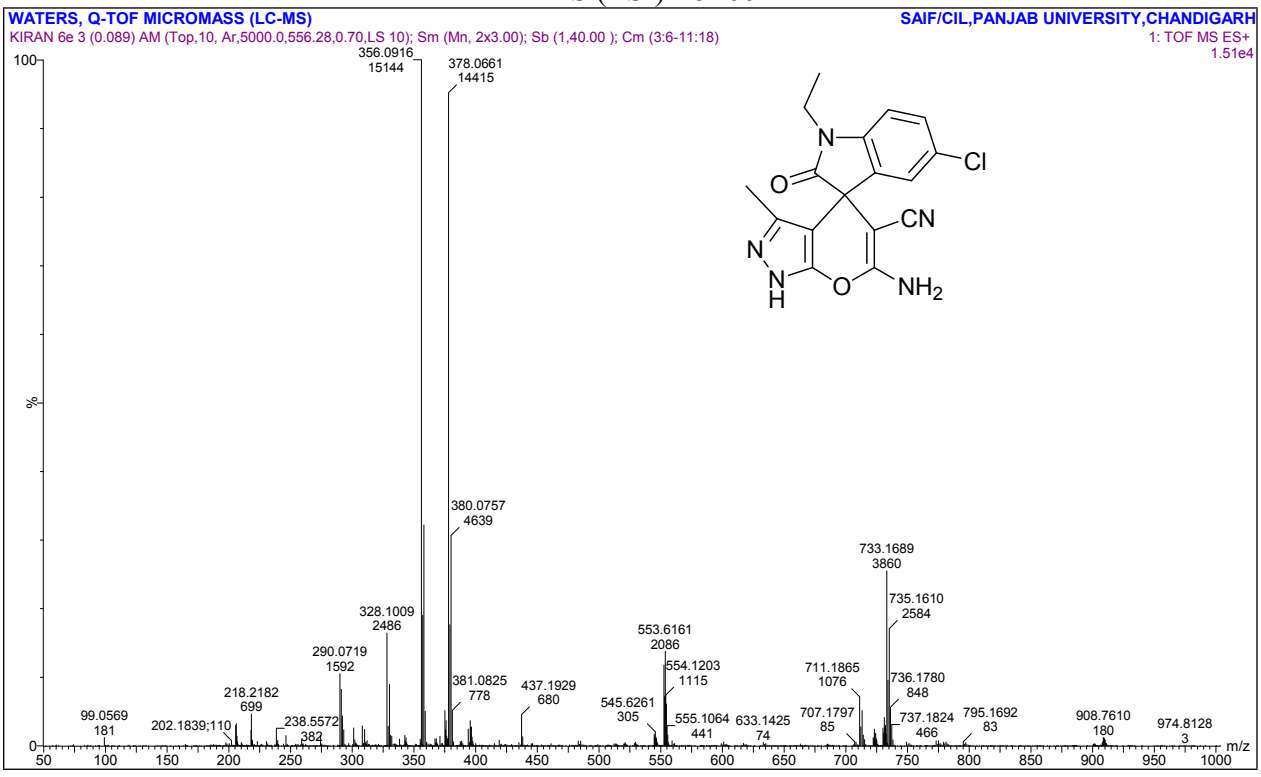
^{13}C NMR for **6e** (100 MHz, DMSO)



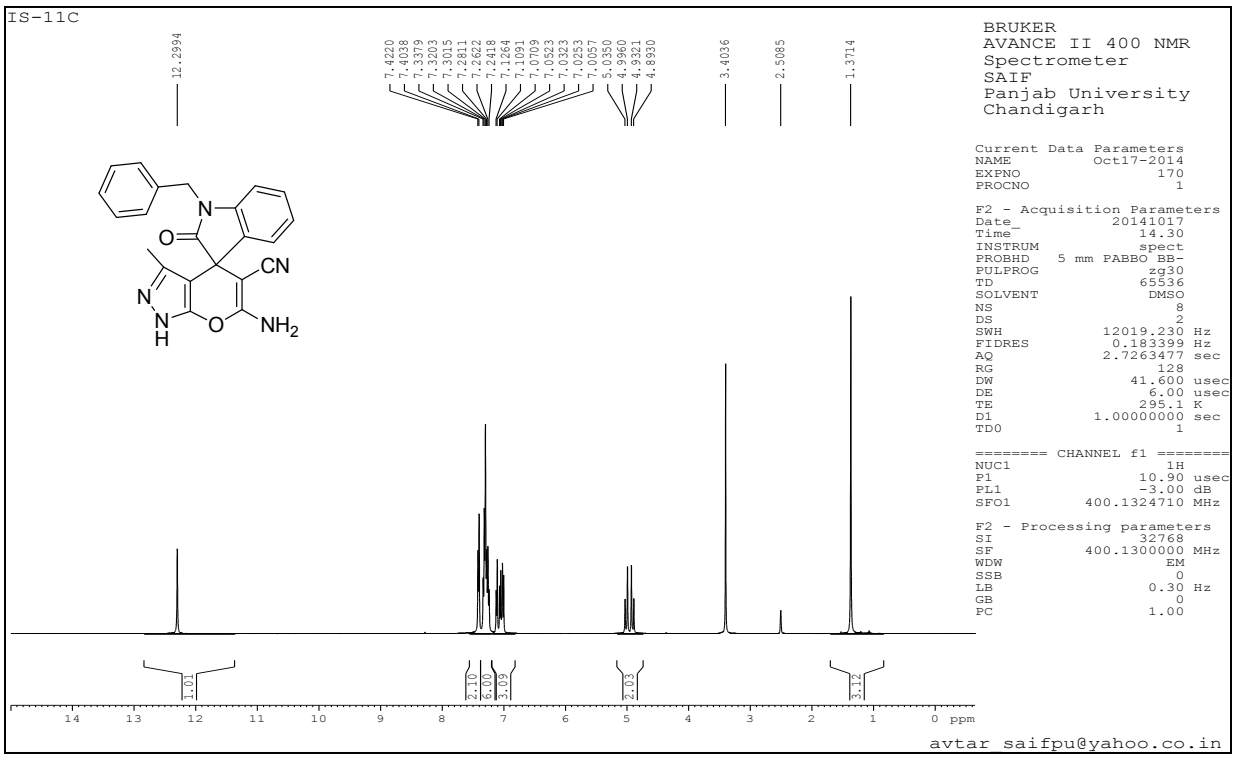
MS (ESI) for **6e**



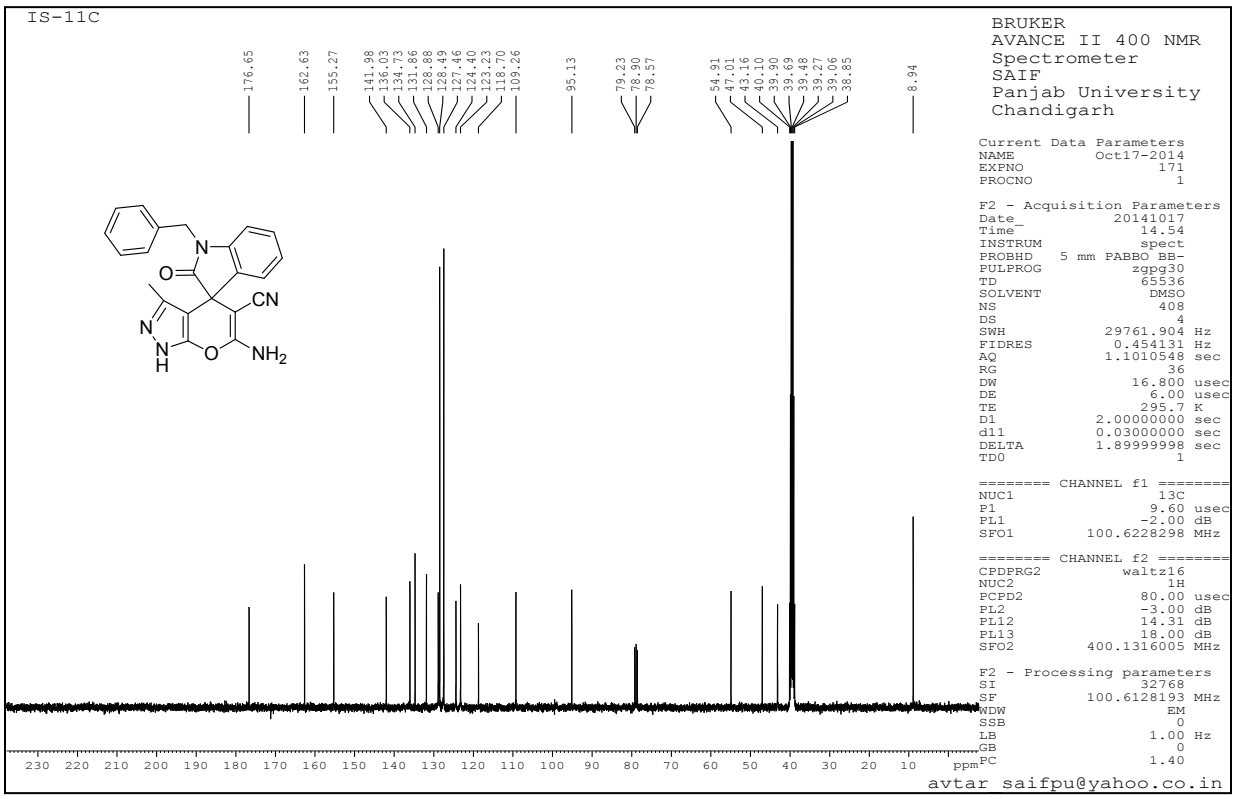
HRMS (ESI) For 6e



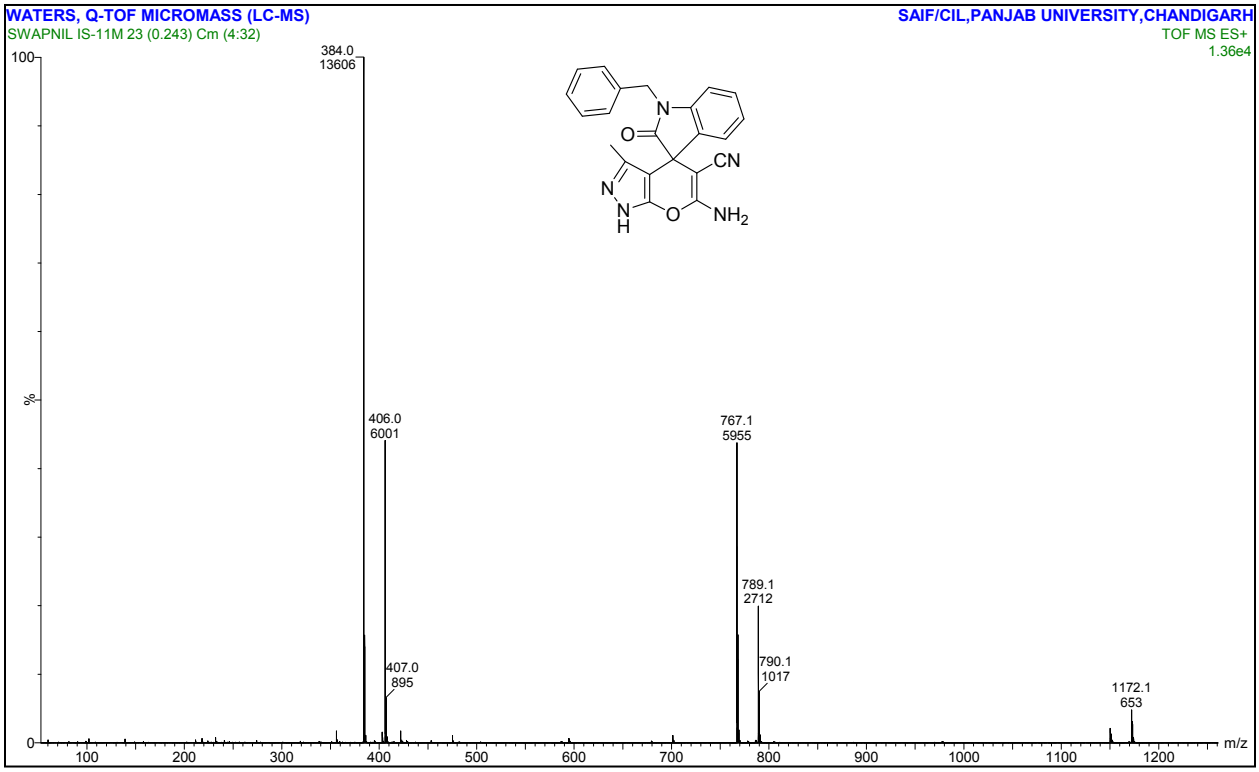
^{1}H NMR for **6f** (400 MHz, DMSO)



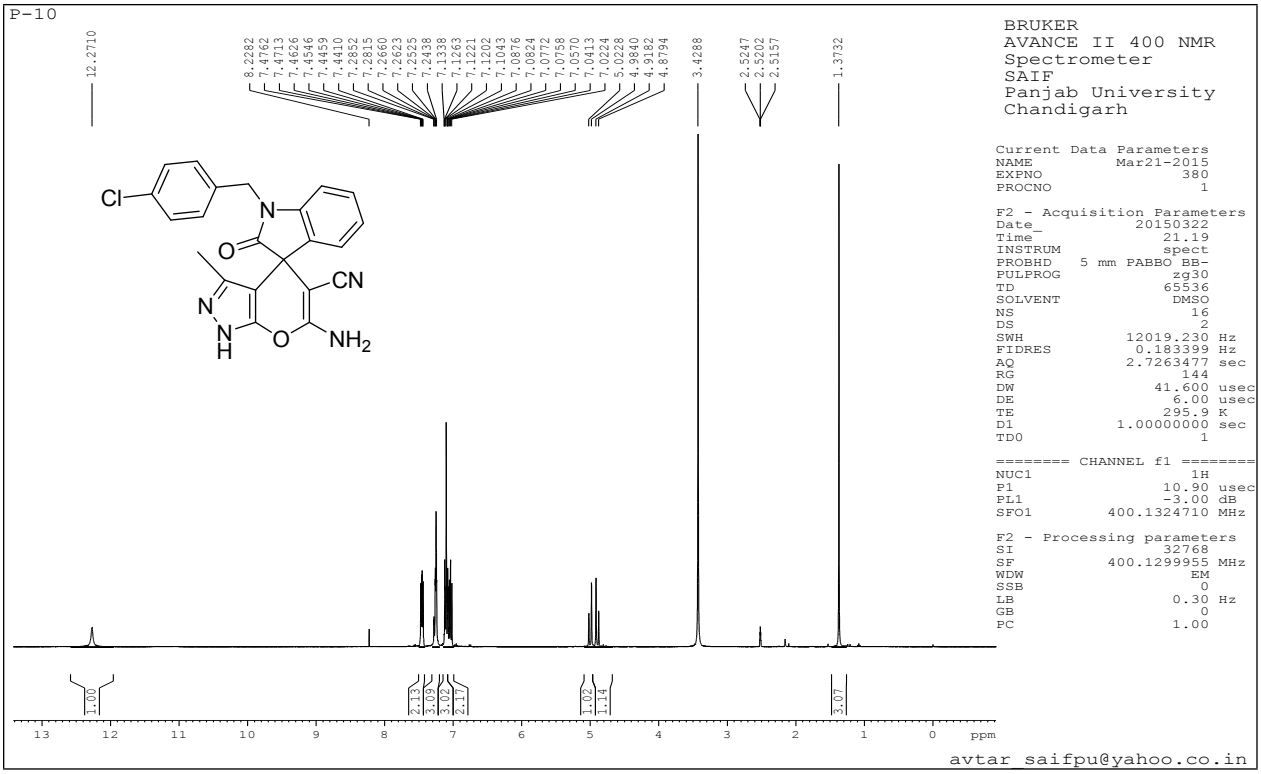
^{13}C NMR for **6f** (100 MHz, DMSO)



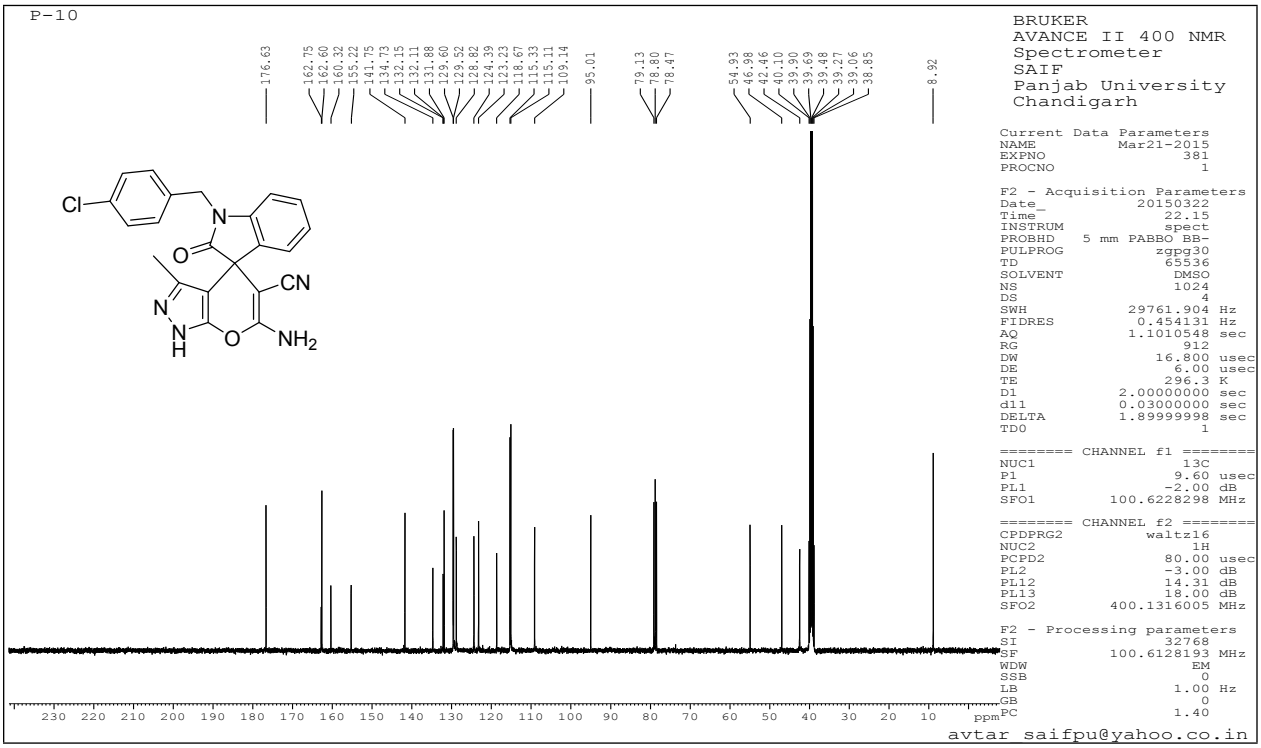
MS (ESI) for **6f**


WATERS, Q-TOF MICROMASS (LC-MS)
SWAPNIL IS-11M 23 (0.243) Cm (4:32)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
1.36e4
384.0
13606
406.0
6001
407.0
895
767.1
5955
789.1
2712
790.1
1017
1172.1
653
%
m/z
O
N
CN
NH2
H

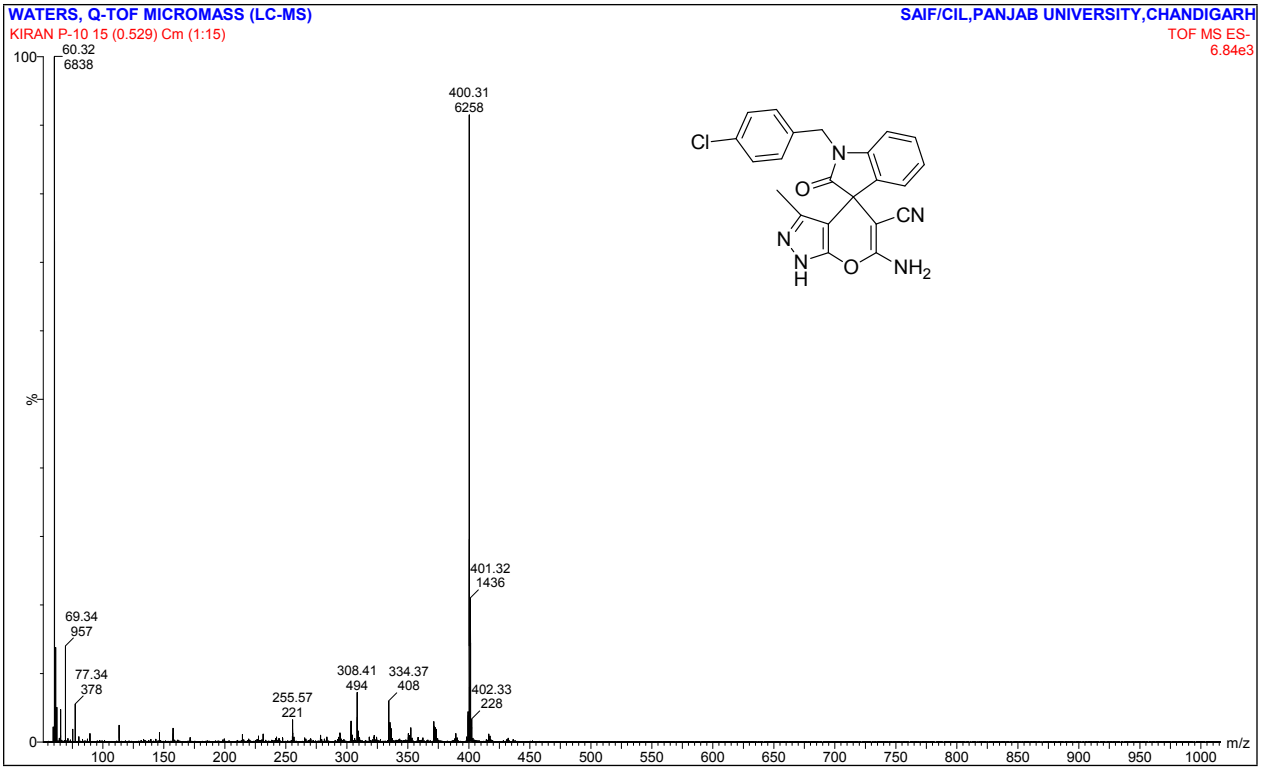
^{1}H NMR for **6g** (400 MHz, DMSO)



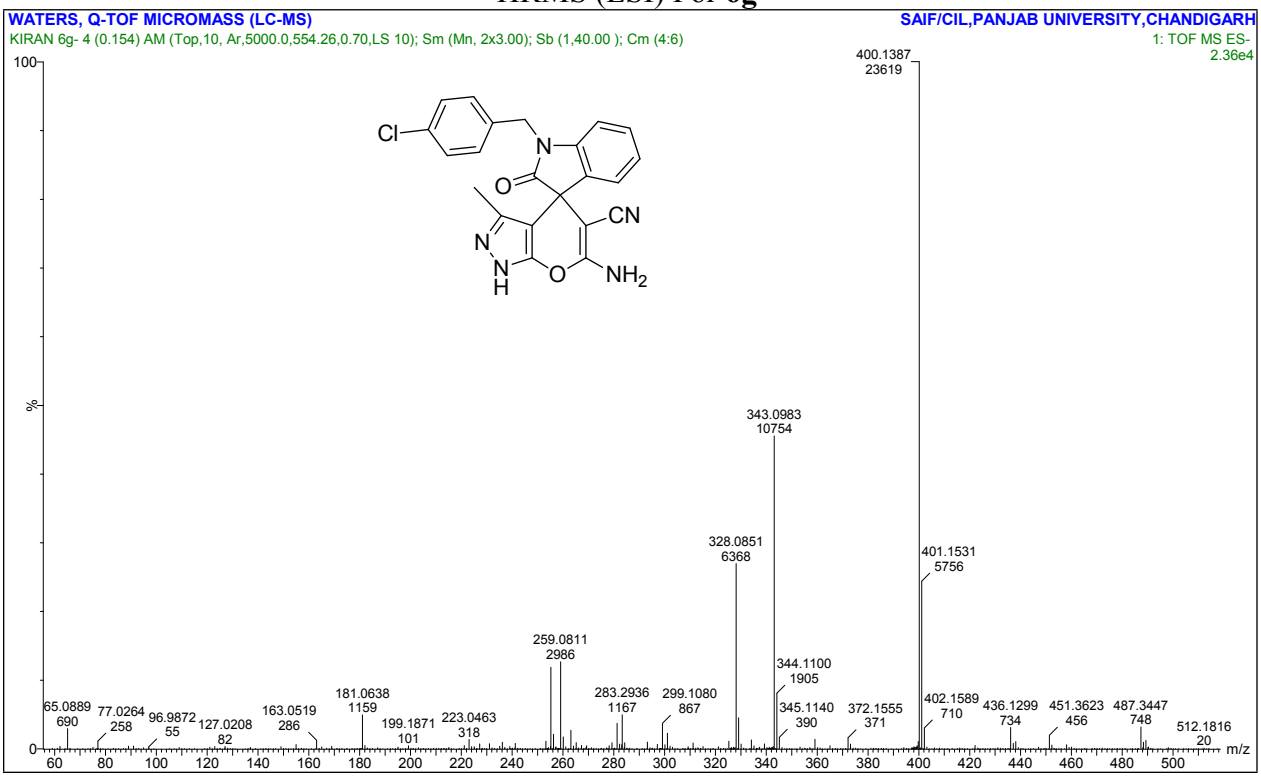
^{13}C NMR for **6g** (100 MHz, DMSO)



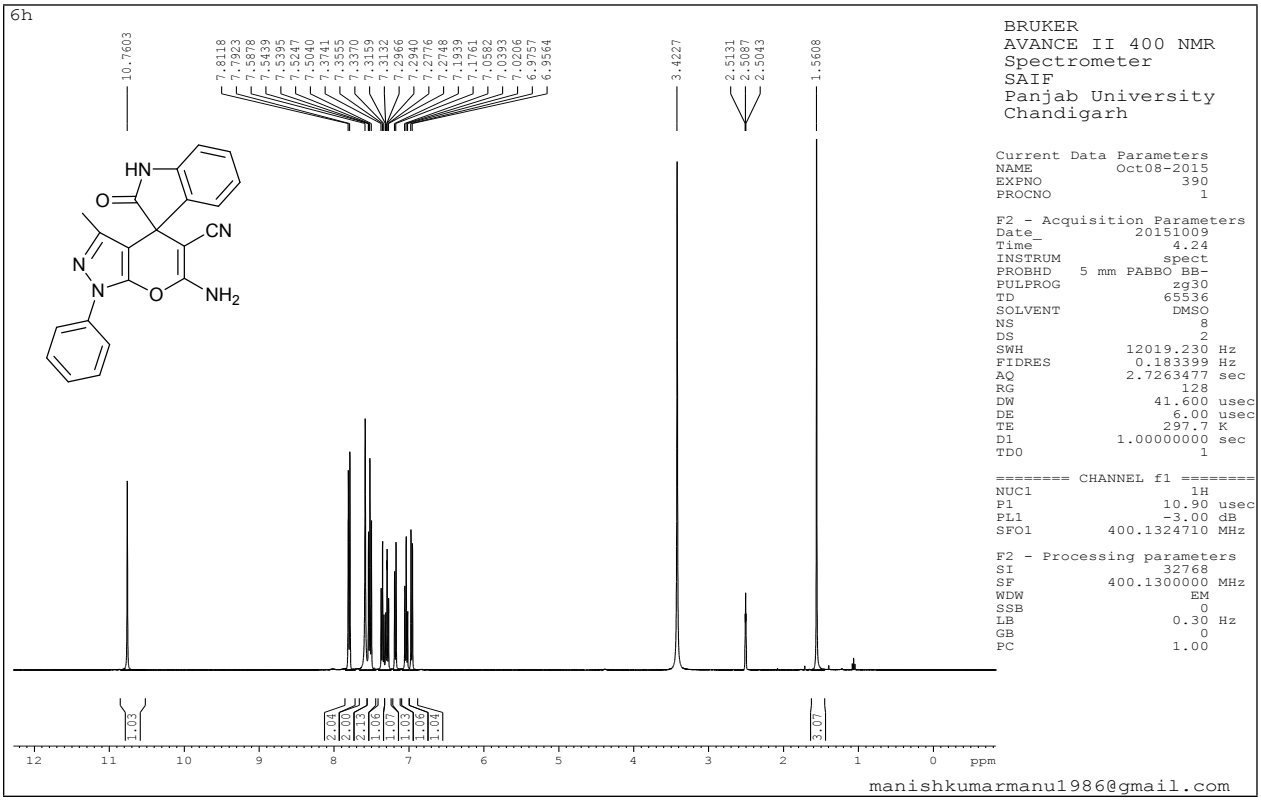
MS (ESI) for **6g**



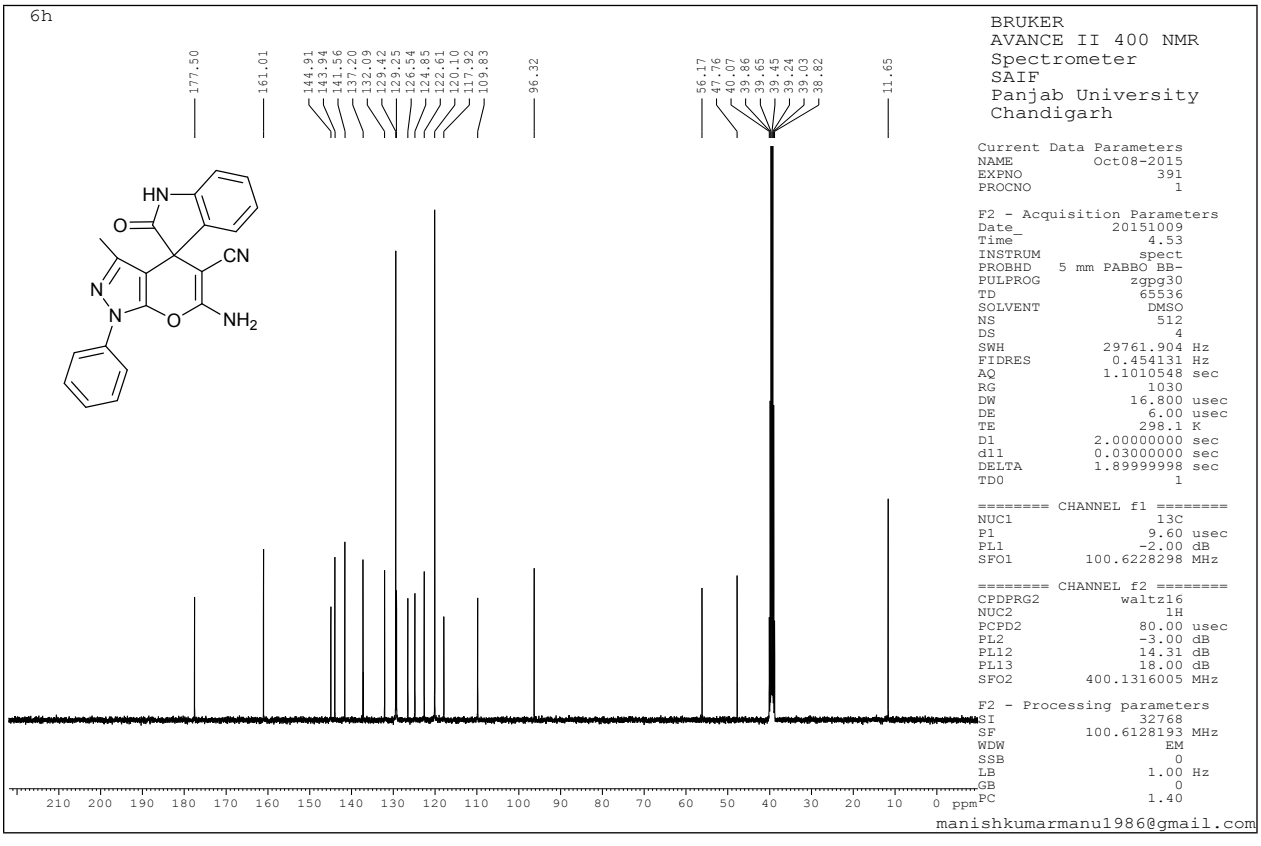
HRMS (ESI) For **6g**



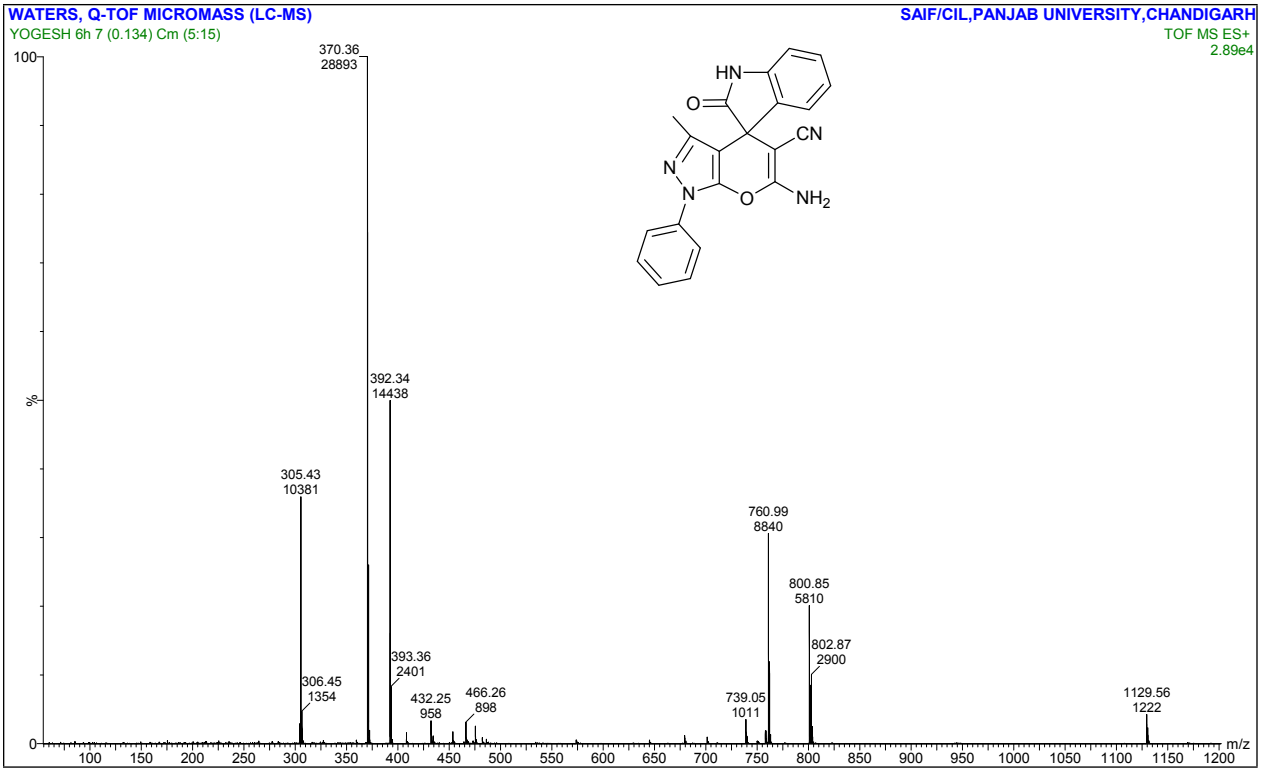
^{1}H NMR for **6h** (400 MHz, DMSO)



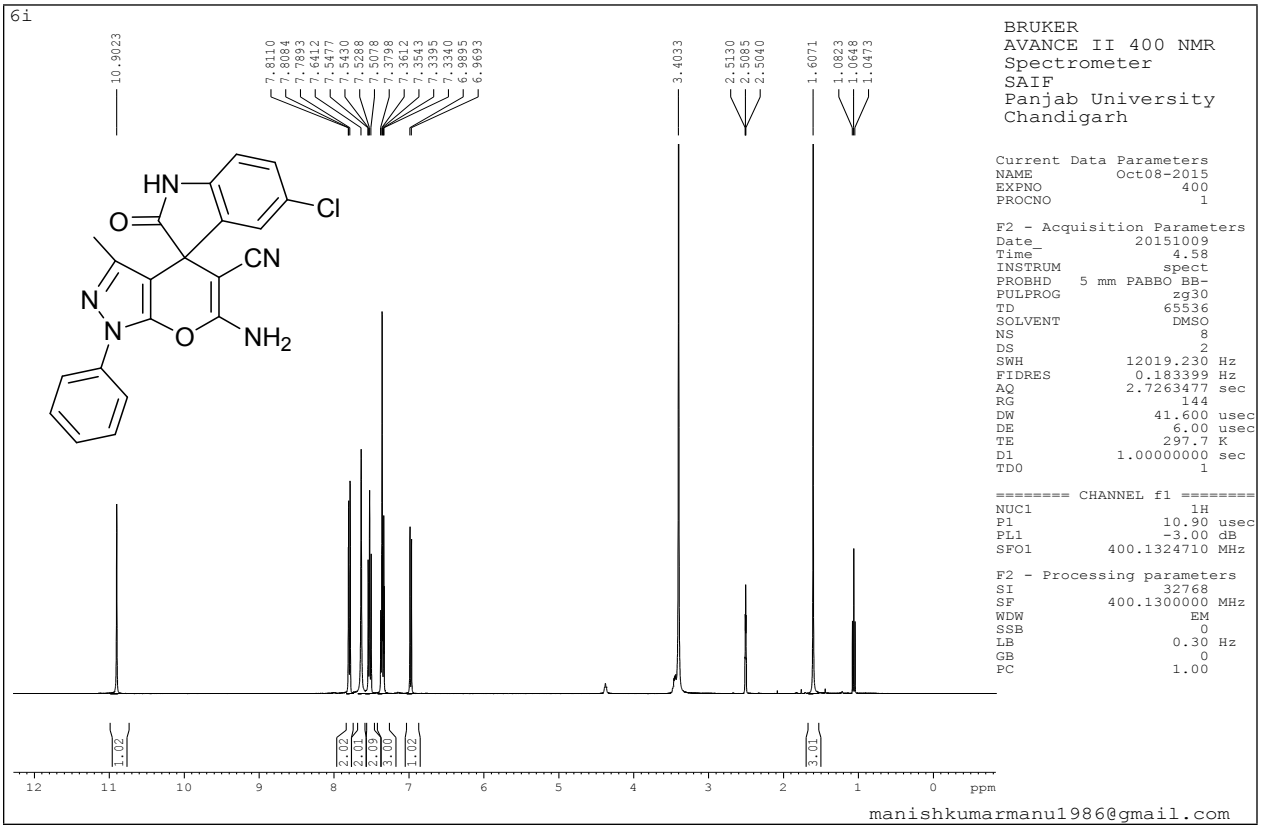
^{13}C NMR for **6h** (100 MHz, DMSO)



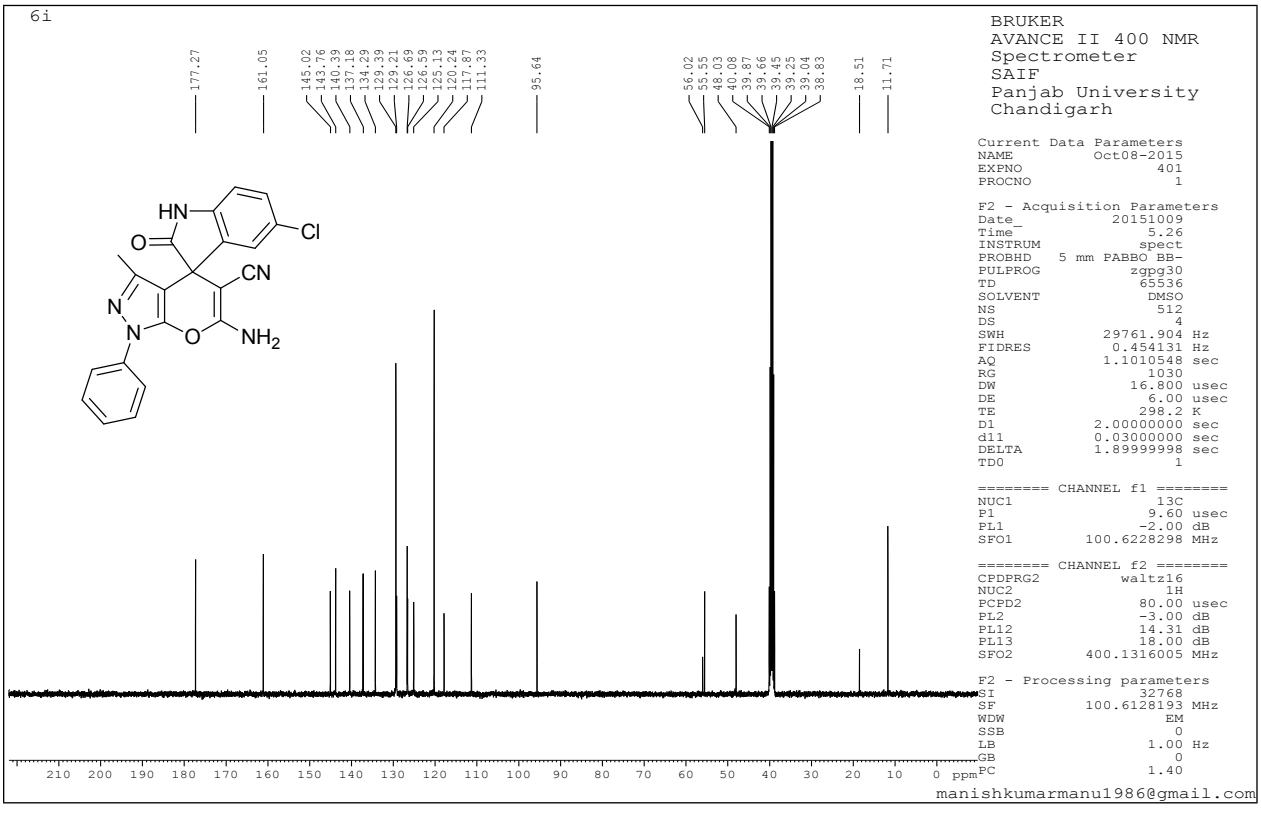
MS (ESI) for **6h**


WATERS, Q-TOF MICROMASS (LC-MS)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
YOGESH 6h 7 (0.134) Cm (5:15)
TOF MS ES+
2.89e4
370.36
28893
392.34
14438
305.43
10381
760.99
8840
800.85
5810
802.87
2900
393.36
2401
306.45
1354
432.25
958
466.26
898
739.05
1011
1129.56
1222
HN
O
CN
N
N
O
NH2
%
m/z

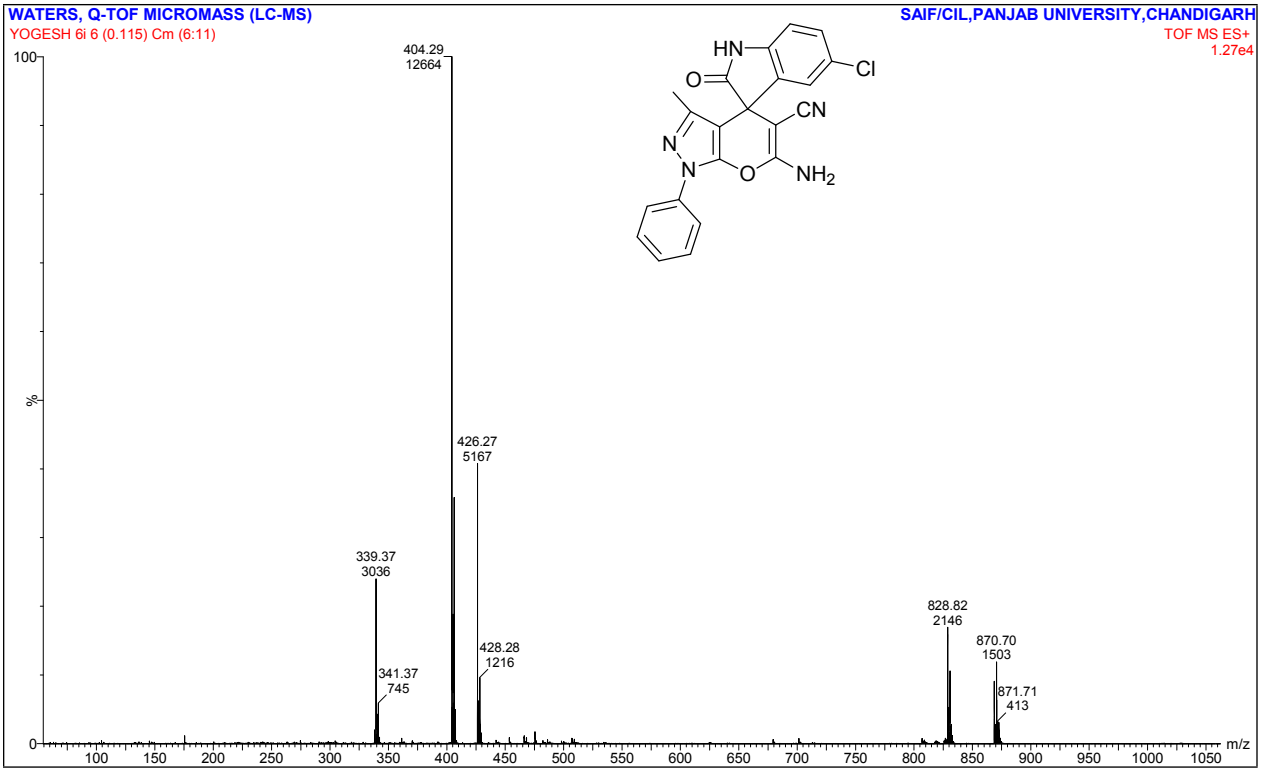
^{1}H NMR for **6i** (400 MHz, DMSO)



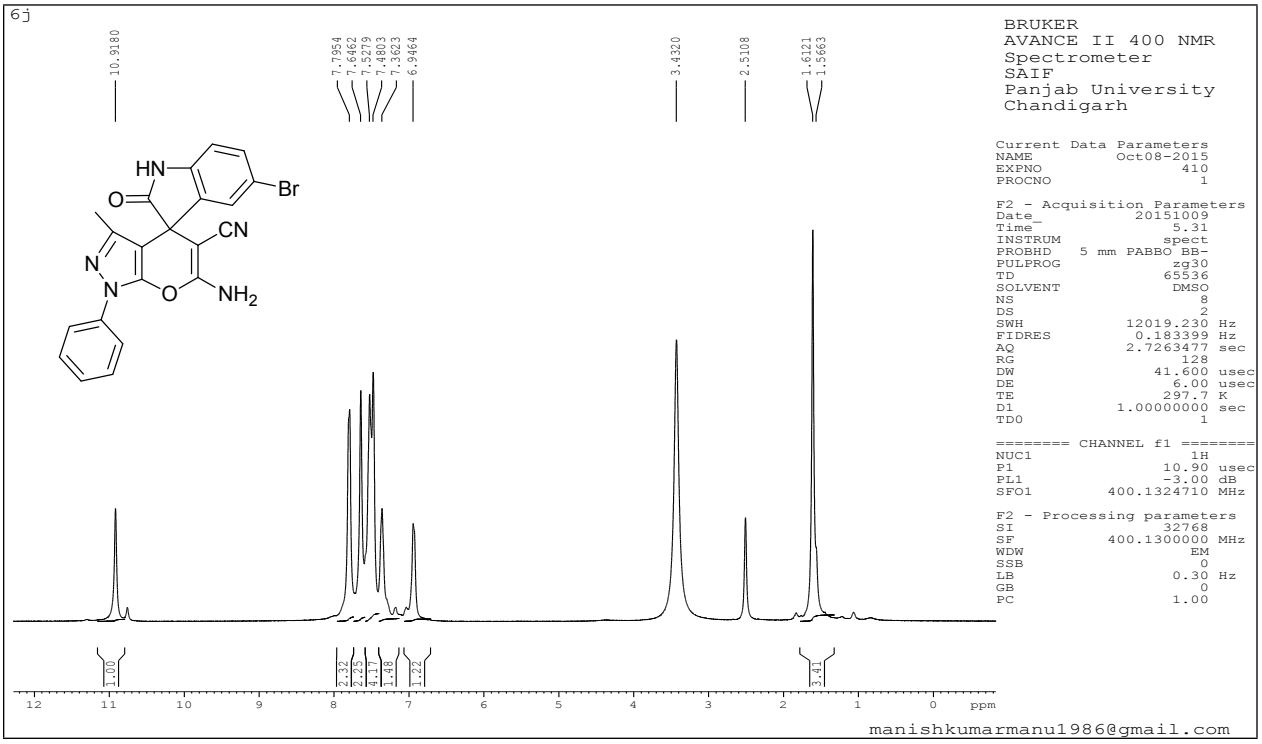
^{13}C NMR for **6i** (100 MHz, DMSO)



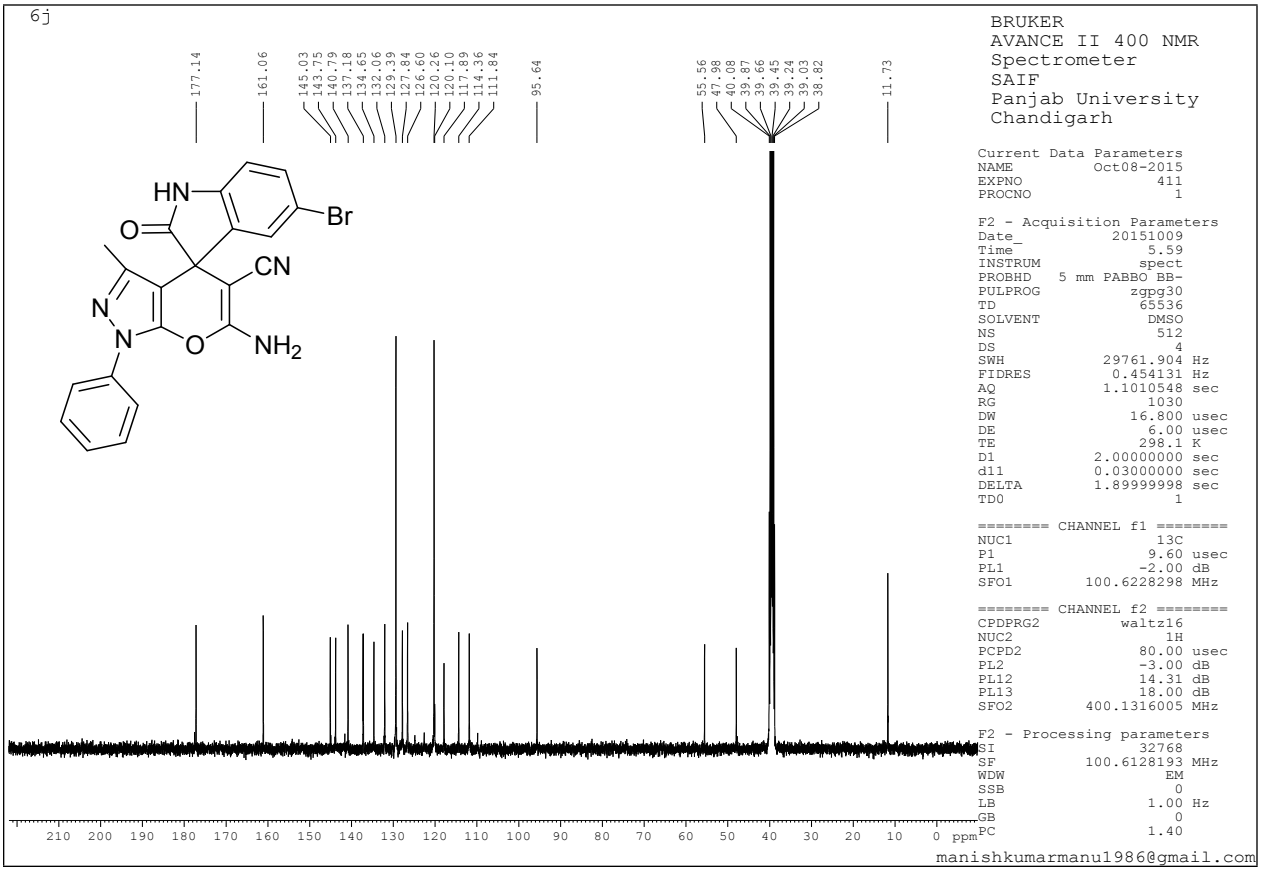
MS (ESI) for **6i**


WATERS, Q-TOF MICROMASS (LC-MS)
YOGESH 6i 6 (0.115) Cm (6:11)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
1.27e4
404.29
12664
426.27
5167
339.37
3036
341.37
745
428.28
1216
828.82
2146
870.70
1503
871.71
413
HN
O
Cl
CN
N
N
O
NH2
%
m/z

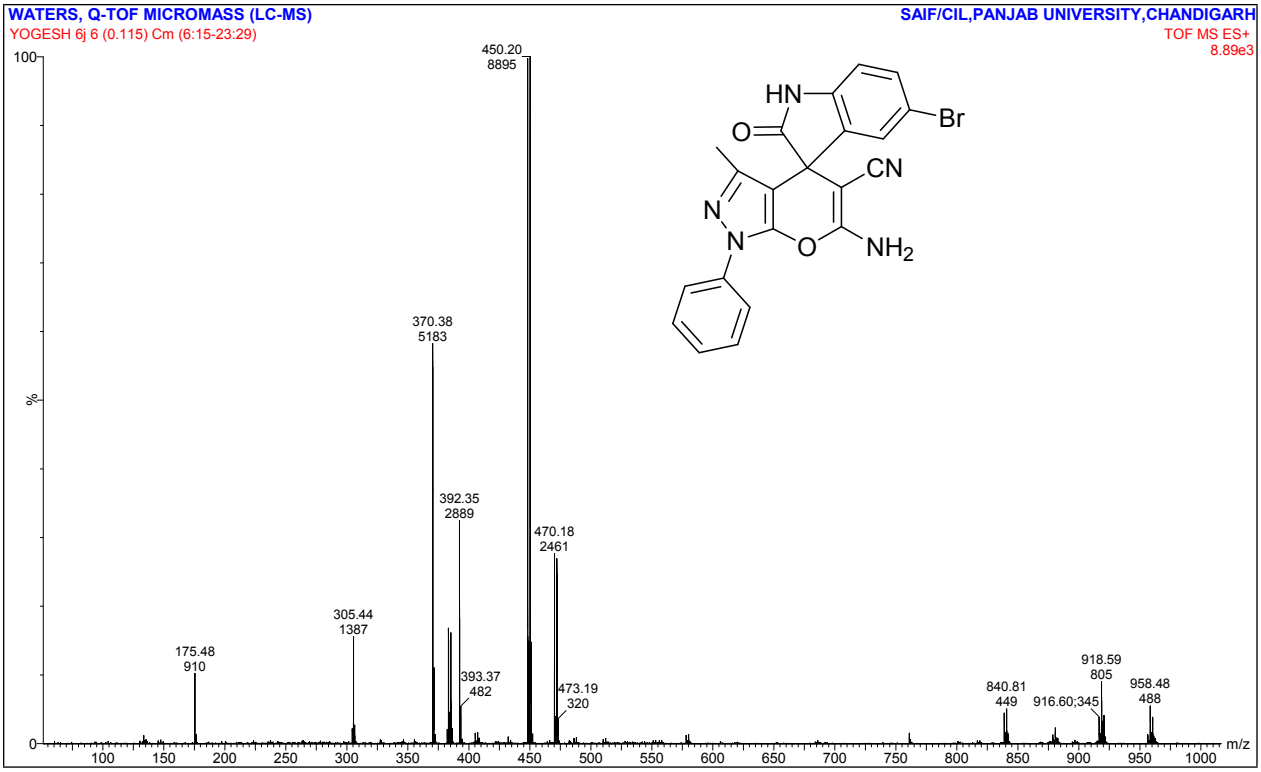
^{1}H NMR for **6j** (400 MHz, DMSO)



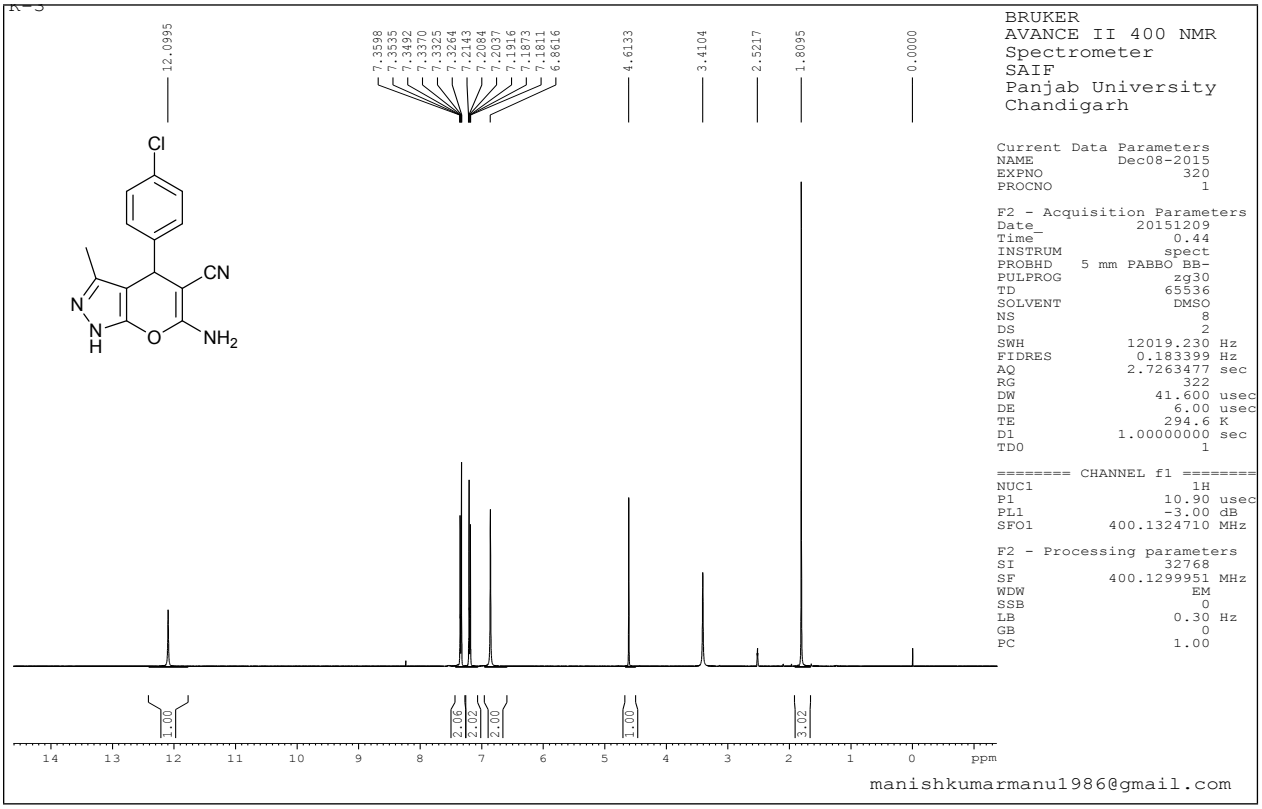
^{13}C NMR for **6j** (100 MHz, DMSO)



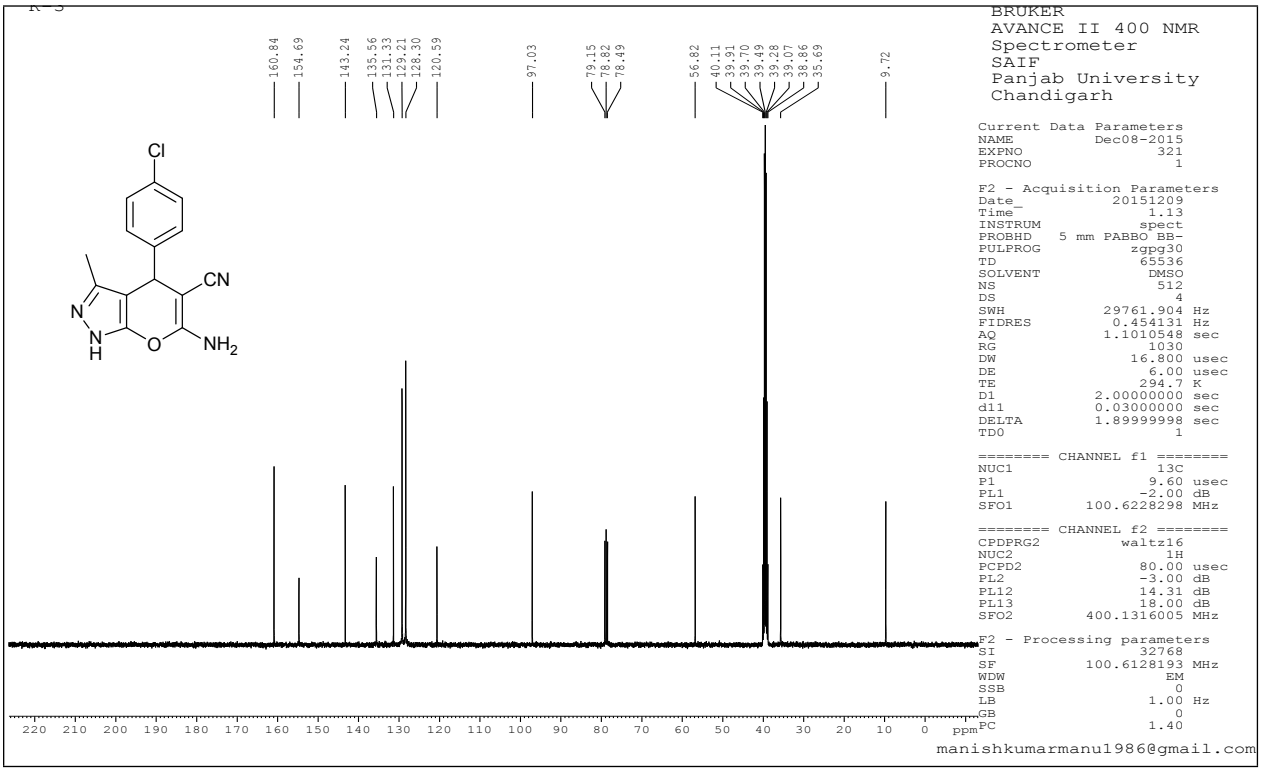
MS (ESI) for **6j**


WATERS, Q-TOF MICROMASS (LC-MS)
YOGESH 6j 6 (0.115) Cm (6:15-23:29)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
8.89e3
100
%
0
450.20
8895
370.38
5183
392.35
2889
470.18
2461
305.44
1387
175.48
910
393.37
482
473.19
320
840.81
449
916.60;345
918.59
805
958.48
488
HN
O
Br
CN
N
N
O
NH2
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
1000
m/z

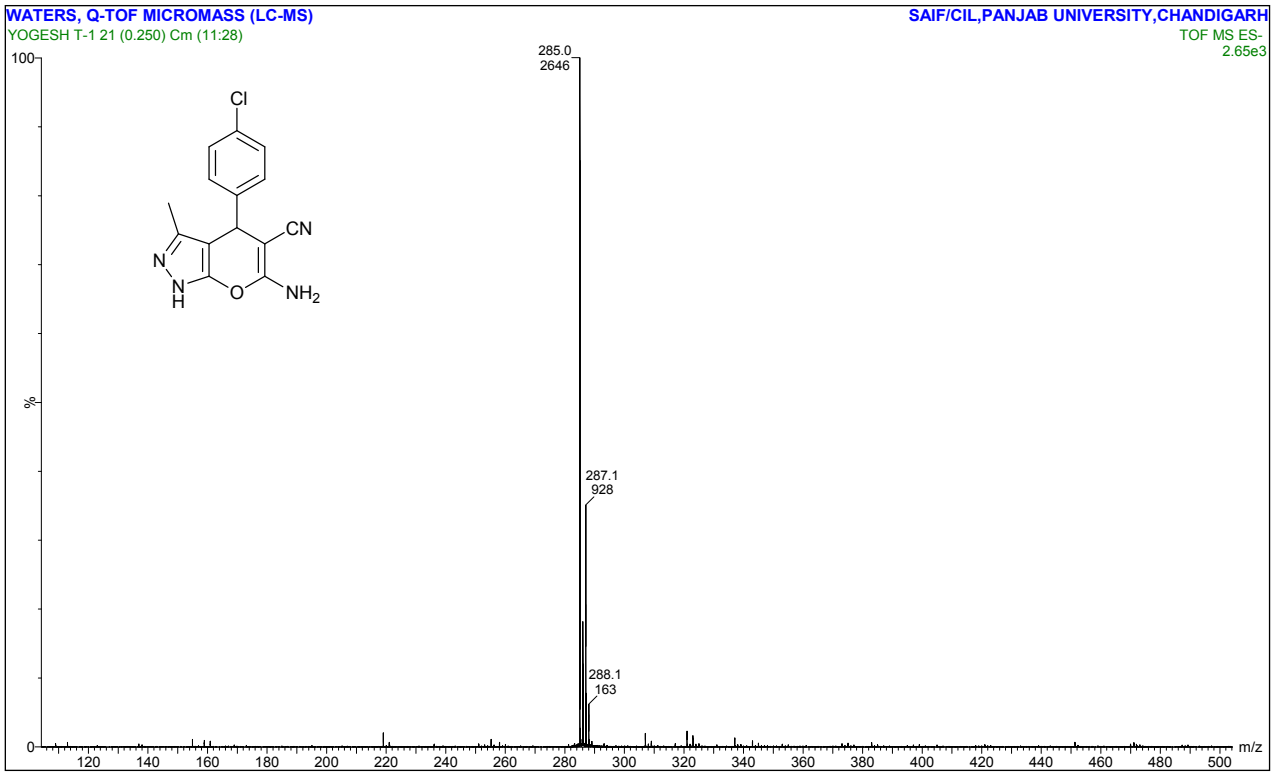
1H NMR for **8b** (400 MHz, DMSO)



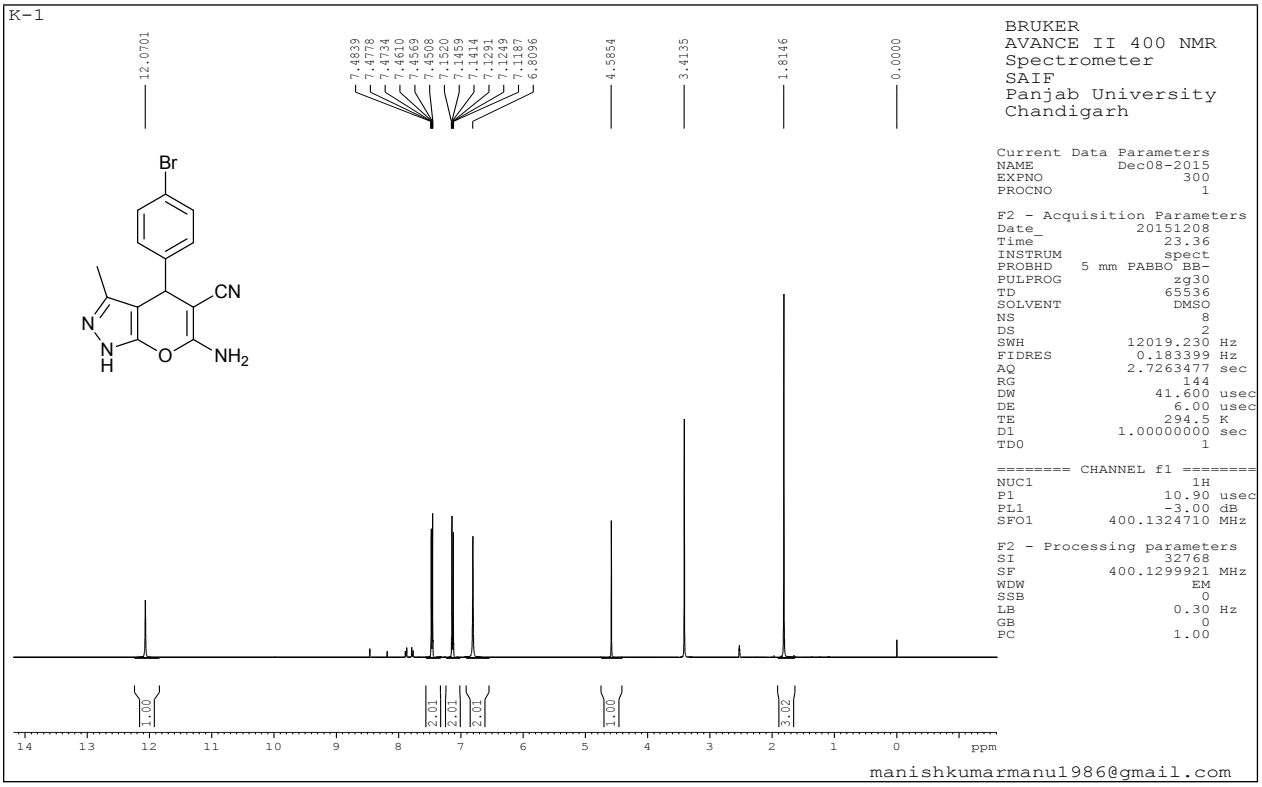
13C NMR for **8b** (100 MHz, DMSO)



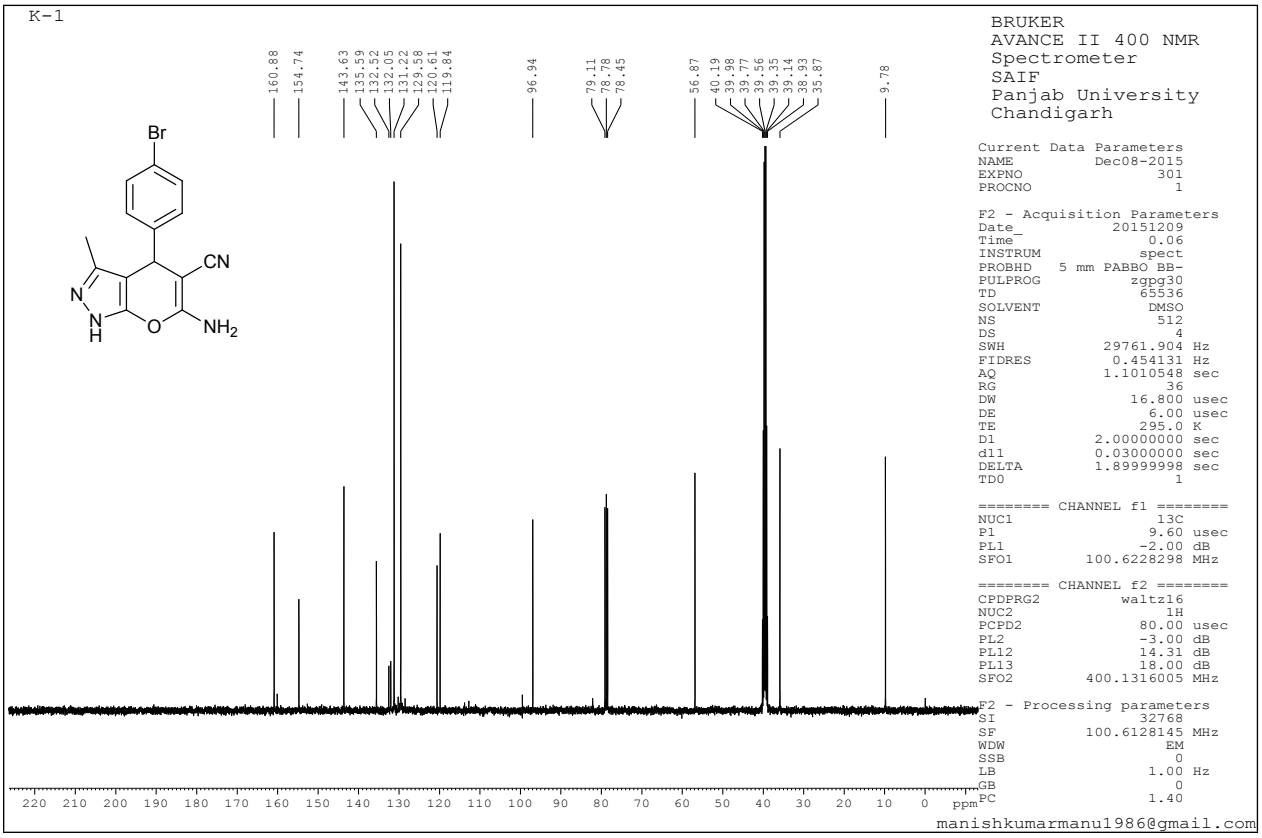
MS (ESI) for 8b


WATERS, Q-TOF MICROMASS (LC-MS)
YOGESH T-1 21 (0.250) Cm (11:28)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES-
2.65e3
100
%
0
285.0
2646
287.1
928
288.1
163
Cl
CN
N
N
H
O
NH2
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500
m/z

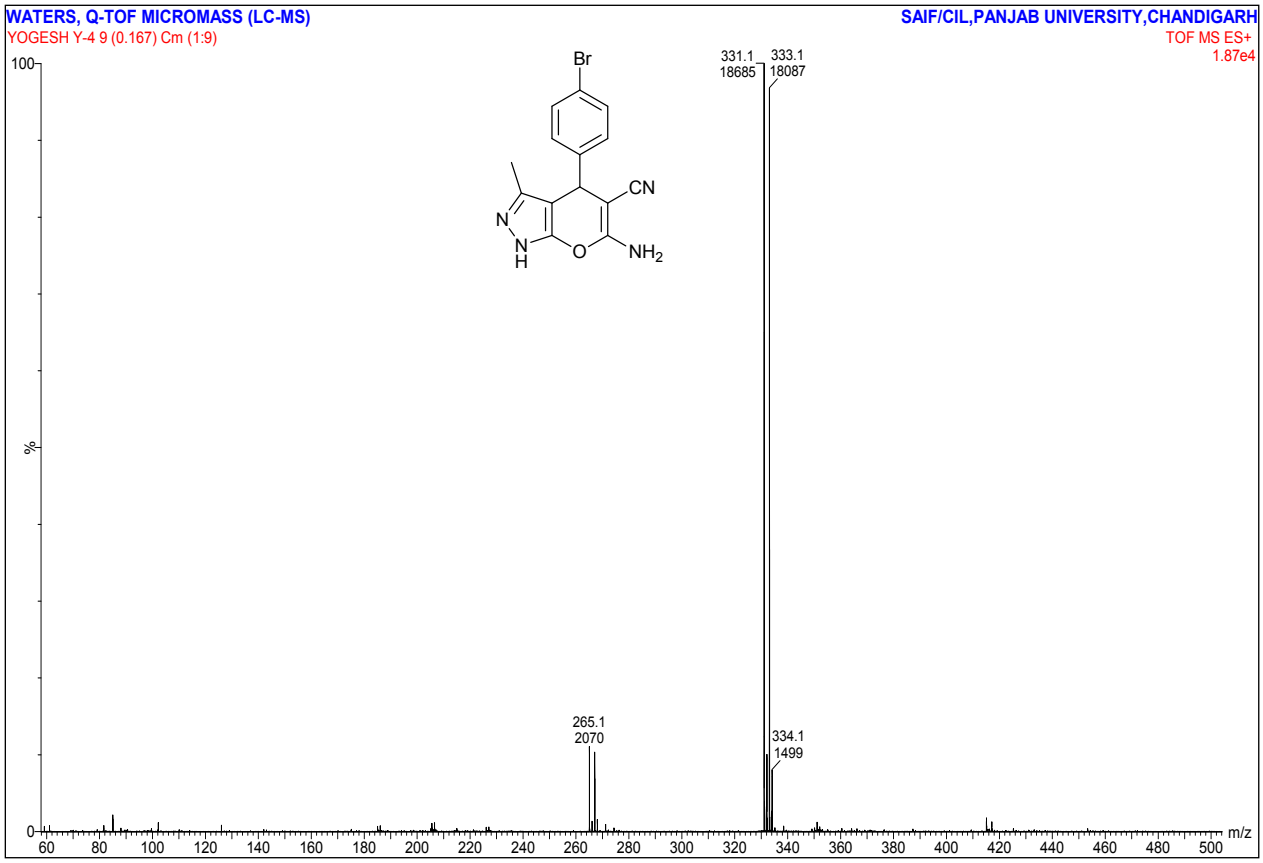
^{1}H NMR for **8d** (400 MHz, DMSO)

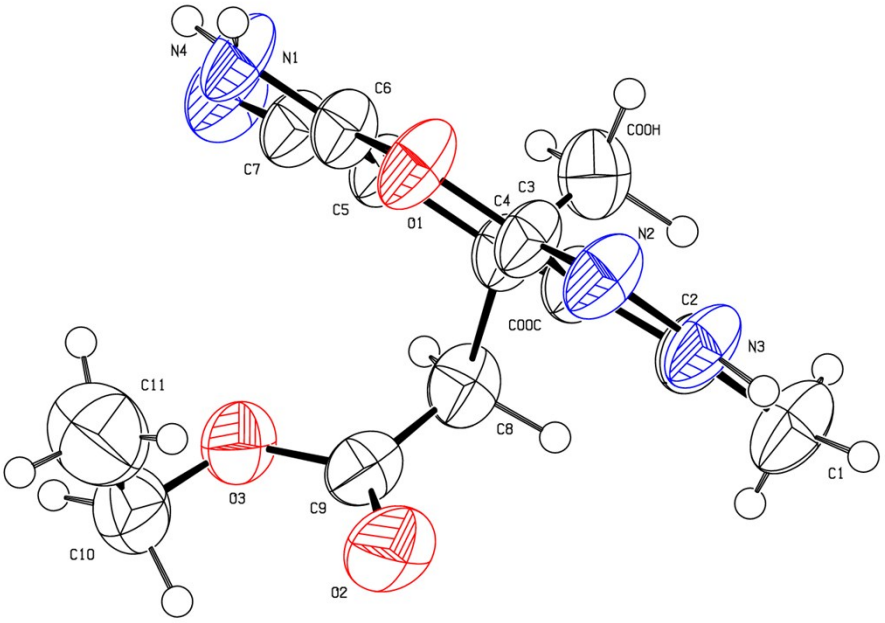


^{13}C NMR for 8d (100 MHz, DMSO)

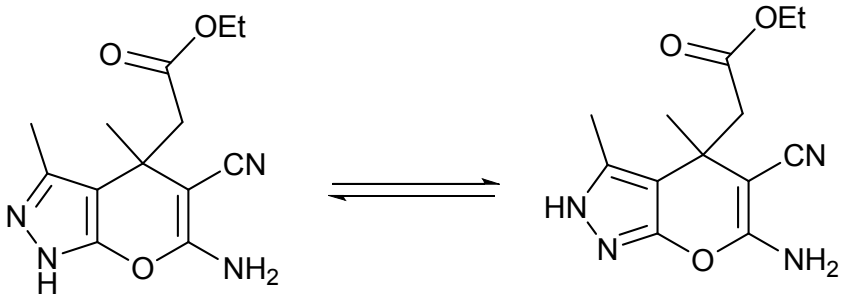


MS (ESI) for **8d**


WATERS, Q-TOF MICROMASS (LC-MS)
YOGESH Y-4 9 (0.167) Cm (1:9)
SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
1.87e4
Br
CN
NH2
N
N
H
O
331.1
18685
333.1
18087
265.1
2070
334.1
1499
100
%
0
m/z
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500

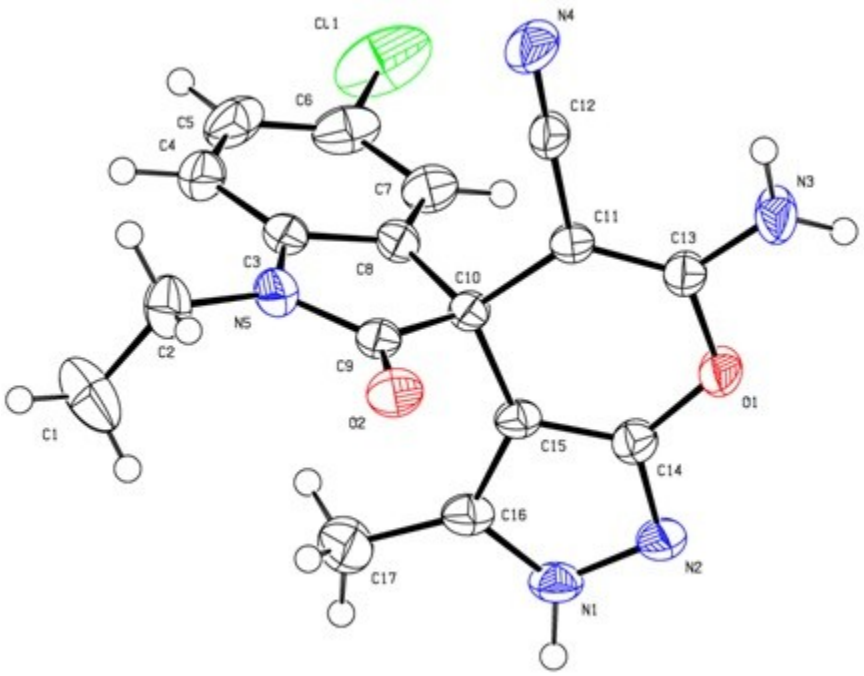


(a)

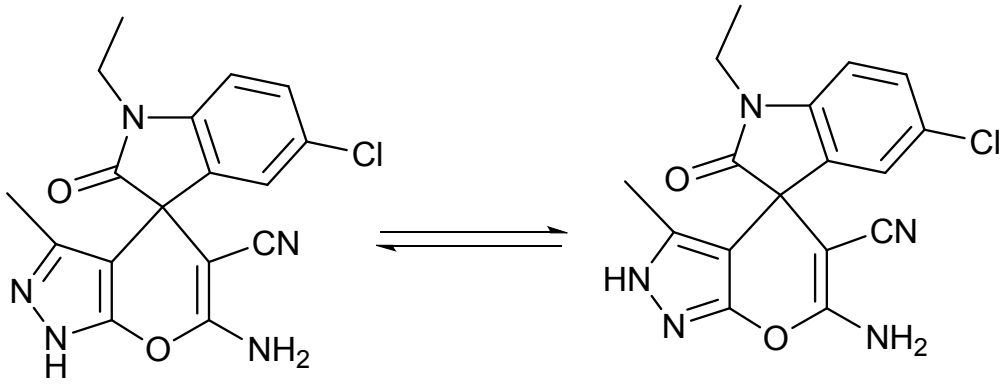


(b)

Figure S1 (a) ORTEP molecular diagram of **4c** (CCDC No- 1432094) with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radius. (b) 1H, 2H-tautomers of **4c**.



(a)



(b)

Figure S2 (a) ORTEP molecular diagram of **6e** (CCDC No- 1432095) with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radius. (b) 1H, 2H-tautomers of **6e**.