Supplementary Material (ESI) for Medicinal Chemistry Communications

Electronic supporting information

Alkynylation of *N*-(3-iodopyridin-2-yl)sulfonamide under Pd/C-Cu catalysis: A direct one pot synthesis of 7-azaindoles and their pharmacological evaluation as potential inhibitors of sirtuins

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Experimental

Chemistry

General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate, dichloromethane. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ solution by using 400 and 50 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT- IR spectrometer. Melting points were determined using melting point apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer. High-resolution mass spectra (HRMS) were recorded using electron ionization (EI) mass spectrometry.

Preparation of methyl 2-(4-ethynylbenzamido)-2-phenylacetate[1] (**2g**): A solution of phenylglycine methyl ester hydrochloride (911 mg, 1.2 equiv.) in water was basified with a saturated solution of $NaHCO_3$ and then extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtrated and concentrated under a reduced pressure. The residue was dissolved in dry CH_2Cl_2 (30 mL) to which was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl, 867 mg, 1.2 equiv.), 1-hydroxybenzotriazole (HOBt, 608 mg, 1.2 equiv.) and 4-ethynylbenzoic acid[31] (550 mg, 1.0 equiv.). The resulting suspension was stirred and monitored by TLC. After completion of the reaction, the mixture was washed with water (30 mL), 1M HCl solution (30 mL), water (30 mL) and a saturated solution of $NaHCO_3$ (15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under a reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) as eluent to give the desired product (980 mg, 89% yield); mp 149-151 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.34-7.45 (m, 5H), 5.75 (d, *J* = 6.9 Hz, 1H), 3.76 (s, 3H), 3.21 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 52.9, 56.8, 79.7, 82.6, 125.7, 127.1 (2C), 127.3 (2C), 128.6, 129.0 (2C), 132.2 (2C), 133.4, 136.3, 165.7, 171.4.

Preparation of methyl 2-(4-ethynylbenzamido)-3-methylbutanoate (2h): This compound was prepared in 65% yield by using Leucine methyl ester hydrochloride and 4-ethynylbenzoic acid

according to a similar procedure described above; mp 60-62 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.98-1.01 (m, 6H), 2.26-2.28 (m, 1H), 3.21 (s, 1H), 3.78 (s, 3H), 4.76-4.78 (m, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H). 7.76 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.9, 18.9, 31.4, 52.1, 57.5, 79.6, 82.6, 125.4, 126.9 (2C), 132.1 (2C), 133.9, 166.4, 172.5.

Preparation of N-(3-iodopyridin-2-yl)benzene sulfonamide[2] (1): To a solution 2-amino-3-iodo pyridine (5.0 g) in pyridine (75 mL), benzenesulfonyl chloride (3.3 mL) was added at 25-35 °C. Reaction mixture was stirred under nitrogen atmosphere at 80 °C for 20 h. The reaction solution was then poured into a saturated aqueous $NaHCO_3$ solution, extracted with dichloromethane, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude bis(benzenesulfonyl) product obtained was dissolved in 1:1 methanol/dioxane (150 mL) and an aqueous solution of 1N KOH (50 mL) was added at 25-35 °C. The mixture was stirred at 60 °C for 1 h. The mixture was then poured into a saturated aqueous $NaHCO_3$ solution, extracted with dichloromethane, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 30% hexane-ethylacetate to afford the desired product as white solid (4 g, 49% yield); mp 151-153 ºC; R_f 0.3 (25% EtOAc / n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.3 (bs, 1H), 8.4-8.13 (m, 4H), 7.79-7.56 (m, 3H), 6.53 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$,, 50 MHz) δ 80.5, 126.8, 129.4 (6C), 132.8, 142.8, 151.8; IR (cm^{-1}, KBr) 3173, 3020, 2924, 1619, 1574, 1381, 1128 Mass (ES) m/z 361.1 (M+1, 100 %)

Preparation of N-(3-iodopyridin-2-yl)methanesulfonamide[2] (**1b**): This compound was prepared from 2-amino-3-iodo pyridine (5.0 g) using methanesulfonyl chloride (2.0 mL) in pyridine (25 mL) according to a similar procedure as described above. This compound was isolated as yellow solid (3.7 g, 55% yield); mp 140-142 ºC; R_f 0.3 (30% EtOAc / n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (d, *J* = 3.6 Hz, 1H), 8.03 (d, *J* = 7.2 Hz, 1H), 6.75 (t, *J* = 6.8 Hz, 1H), 3.5 (s, 3H); ^{13}C NMR ($CDCl_3$,, 200 MHz) δ 42.3, 81.6, 119.4, 128.9, 148.1, 151.0 ; IR (cm^{-1}, KBr) 3237, 3020, 2925, 1573, 1455, 1318, 1150; Mass (ES) m/z 299 (M+1, 100 %).

General method for the preparation of 2-substituted-7-azaindole (**3**): A mixture of compound **1** (300 mg, 0.832 mmol), 10% Pd/C (26.55 mg, 0.025 mmol), PPh_3 (26.18 mg, 0.099 mmol), CuI (9.5 mg, 0.049 mmol) and 2-aminoethanol (152.45 mg, 2.495 mmol) in acetonitrile (6 mL) was stirred at 25 °C for 1 h under nitrogen. The acetylenic compound **2** (1.247 mmol) was added and the mixture was stirred at 80 °C for the time mentioned in Table 2. After completion, the reaction mixture was cooled to room temperature, diluted with EtOAc (12 mL) and filtered through a celite

bed. The filtrate was concentrated and the residue was purified by column chromatography on silica gel using hexane-ethyl acetate to afford the desired product**.**

2-Phenyl-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-b]pyridine (**3a**); Light yellow solid, mp 103-106 ^{0}C; R_f (15% ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.47 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 2H), 7.77 (dd, *J* = 6.8, 1.2 Hz, 1H), 7.56-7.36 (m, 8H), 7.18 (dd, *J* = 4.8, 2.8 Hz, 1H), 6.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) □ 109.2, 119.6, 122.4, 127.6 (4C), 128.6 (4C), 128.7, 128.9, 129.8, 132.5, 133.6, 138.5, 142.2, 144.6; IR (cm^{-1}, KBr) 3060, 2924, 1397, 1376, 1187; Mass (ES) : m/z 335 (M+1, 100%); HRMS (ESI): calcd for $C_{19}H_{15}N_2O_2S$ $(M+H)^+$ 335.0854, found 335.0846.

(1-(Phenylsulfonyl)-1*H*-pyrrolo [2,3-b]pyridin-2-yl) methanol (**3b**): White solid, mp 100-102 °C; R_f (40% ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (dd, *J* =5.2, 1.6 Hz, 1H), 8.16 (t, *J* = 7.2, 1.2 Hz, 2H), 7.77 (dd, *J* = 8, 1.6 Hz, 1H), 7.60 - 7.46 (m, 3H), 7.14 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.59 (s, 1H), 5.00 (d, *J* = 5.6 Hz, 2H), 3.19 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 58.8, 107.0, 119.2, 121.1, 127.7 (2C), 128.9 (2C), 129.2, 134.0, 138.5, 140.7, 144.7, 148.9; IR (cm^{-1}, KBr) 3293, 2922, 1399, 1375, 1178; Mass (ES) m/z 289 (M+1, 100 %); HRMS (ESI): calcd for $C_{14}H_{13}N_2O_3S$ $(M+H)^+$ 289.0647, found 289.0634.

2-(1-(Phenylsulfonyl)-1*H*-pyrrolo[2,3-b]pyridin-2-yl)ethanol (**3c**): Yellow liquid; R_f (50% ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.11 (t, *J* =7.6 Hz, 2H), 7.70 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.56-7.43 (m, 3H), 7.12 (dd, *J* = 8, 4.8 Hz, 1H), 6.46 (s, 1H), 4.08 (t, *J* = 5.6 Hz, 2H), 3.73 (t, *J* = 5.2 Hz, 1H), 3.42 (t, *J* = 5.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.8, 61.5, 106.6, 119.1, 121.6, 127.6 (2C), 128.2, 128.9(2C), 133.8, 139.0, 139.2, 143.9, 149.1; IR (cm^{-1}, KBr) 3426, 2923, 1655, 1375, 1159, 1030; Mass (ES) m/z 303 (M+1, 100 %); HRMS (ESI): calcd for $C_{15}H_{15}N_2O_3S$ $(M+H)^+$ 303.0803, found 303.0797.

1-(1-(Phenylsulfonyl)-1*H*-pyrrolo[2,3-b]pyridin-2-yl)ethanol (**3d**): Yellow solid, mp 120-122 °C; R_f (50% ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.36 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.14 (t, *J* =7.6 Hz, 2H), 7.58-7.44 (m, 4H), 7.16-7.13 (m, 1H), 6.63 (s, 1H), 5.51 (q, *J* = 6.4, 6 Hz, 1H), 3.54 (bs, 1H), 1.72 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.4, 62.6, 104.7, 119.3, 121.0, 127.8 (2C), 128.9, 129.1, 133.9, 138.7, 144.8, 145.4, 146.9, 149.2; IR (cm^{-1}, KBr) 3468, 2963, 2924, 1369, 1176; Mass (ES) m/z 303 (M+1, 100 %); HRMS (ESI): calcd for $C_{15}H_{15}N_2O_3S$ $(M+H)^+$ 303.0803, found 303.0792.

2-(3-Chloropropyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-b]pyridine (**3e**): White solid, mp 150-152 °C; R_f (15% ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35 (dd, *J* = 4.8, 2

Hz, 1H), 8.10 (m, 2H), 7.70 (dd, *J* = 7.6, 1.6, 1H), 7.57-7.43 (m, 3H), 7.11 (m, 1H), 6.39 (s, 1H), 3.64 (t, *J* = 6.4 Hz, 2H), 3.31 (t, *J* = 7.6 Hz, 2H), 2.34-2.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.7, 31.8, 44.1, 105.9, 119.1, 121.5, 127.6 (2C), 128.1, 128.9 (2C), 133.8, 139.0, 141.0, 143.9, 149.2; IR (cm^{-1}, KBr) 2955, 1398, 1370, 1160; Mass (ES) m/z 335 (M+1, 100 %); HRMS (ESI): calcd for $C_{16}H_{16}ClN_2O_2S$ $(M+H)^+$ 335.0621, found 335.0635.

2-((2-Nitrophenoxy)methyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-b]pyridine (**3f**): Yellow solid, mp 110-112 °C; R_f (30 % ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (dd, *J* = 4.8, 1 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 2H), 7.92 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.82 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.63-7.47 (m, 4H), 7.29 (d, *J* = 8.8, 1H), 7.20-7.11 (m, 2H), 6.9 (s, 1H), 5.7 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 65.5, 107.7, 114.9, 119.4, 121.2, 121.3, 125.9, 128.0 (2C), 129.0(2C), 129.4(2C), 134.2(2C), 134.5, 135.1, 138.5, 145, 151.5; IR (cm^{-1}, KBr) 3134, 2925, 1629, 1607, 1525, 1383, 1270, 1138; Mass (ES) m/z 410 (M+1, 100 %); HRMS (ESI): calcd for $C_{20}H_{16}N_3O_5S$ $(M+H)^+$ 410.0811, found 410.0825.

(*S*)-Methyl-2-phenyl-2-(4-(1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-b]pyridin-2-yl)benzamido)acetate (**3g**); Yellow solid, mp 66-68 °C; R_f (40% ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.48 (dd, *J* = 5.2, 2 Hz, 1H), 7.92-7.62 (m, 7H), 7.57-7.35 (m, 11H), 7.25-7.19 (m, 1H), 6.55 (s, 1H), 5.8 (d, *J*= 6.8, 1H), 3.8 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 53.0, 57.0, 110.0, 120.0, 122.0, 126.6 (2C), 127.3 (2C), 127.6 (2C), 128.7 (2C), 128.8 (2C), 129.0 (2C), 130.0 (2C), 133.7, 133.9, 136.0, 136.4, 138.2, 140.9, 145.1, 150.2, 166.0, 171.4; IR (cm^{-1}, KBr) 3245, 3061, 2925, 1765, 1729, 1360, 1244, 1132; Mass (ES) m/z 526 (M+1, 100 %); HRMS (ESI): calcd for $C_{29}H_{24}N_3O_5S$ $(M+H)^+$ 526.1437, found 526.1440.

(S)-Methyl-3-methyl-2-(4-(1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-b]pyridin-2-yl)benzamido)butanoate (**3h**); Low melting solid; R_f (45% ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.49 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.92-7.87 (m, 4H), 7.80 (dd, *J* = 8, 1.6 Hz, 1H), 7.66-7.37 (m, 5H), 7.25-7.20 (m, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 6.56 (s, 1H), 4.83-4.75 (m, 1H), 3.8 (s, 3H), 2.33-2.29 (m, 1H), 1.06-1.02 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.9,18.9, 31.5, 52.1, 57.5, 110.0, 119.0, 122.2, 126.4 (2C), 127.5 (2C), 128.6, 128.8, 129.0, 129.8 (2C), 133.7, 134.0, 135.8, 138.0, 140.8, 144.9, 150.0, 166.0, 172.0; IR (cm^{-1}, KBr) 3240, 3065, 2920, 1760, 1732, 1250, 1370, 1245, 1128; Mass (ES) m/z 492 (M+1, 100 %); HRMS (ESI): calcd for $C_{26}H_{26}N_3O_5S(M+H)^+$ 492.1593, found 492.1600.

2-(t-Butyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-b]pyridine (**3i**); Yellow solid, mp 115-117 °C; R_f (10% ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (dd, *J* = 4.8, 1.6 Hz, 1H),

8.03-8.01 (m, 2H), 7.65 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.49-7.38 (m, 4H), 7.06-7.03 (m, 1H), 6.5 (s, 1H), 1.68 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ29.7, 31.2 (2C), 34.9, 105.4, 118.8, 120.8, 127.9 (3C), 128.3 (2C), 133.1, 140.3, 143.5, 150.4, 153.3; IR (cm^{-1}, KBr) 2924, 1371, 1259, 1132; Mass (ES) m/z 315 (M+1, 100 %); HRMS (ESI): calcd for $C_{17}H_{19}N_2O_2S(M+H)^+$ 315.1177, found 315.1167.

1-(Methylsulfonyl)-2-phenyl-1*H*-pyrrolo[2,3-b]pyridine (**3j**); Yellow solid, mp 140-142 °C; R_f (20% ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.48 (dd, *J* = 5.2, 2 Hz, 1H), 7.90 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.54-7.42 (m, 4H), 7.30-7.27 (m, 2H), 6.55 (s, 1H), 3.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 42.9, 107.9, 119.5, 122.1, 127.7 (2C), 128.8 (2C), 129.1, 129.6 (2C), 132.1, 141.8, 144.5; IR (cm^{-1}, KBr) 3060, 2924, 1387, 1370, 1180; Mass (ES) m/z 273 (M+1, 100 %); HRMS (ESI): calcd for $C_{14}H_{13}N_2O_2S(M+H)^+$ 273.0698, found 273.0682.

2-Pentyl-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-b]pyridine (**3k**); Yellow solid, mp 120-124 °C; R_f (10% ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (d, *J* = 5.2 Hz, 1H), 8.10 (d, *J* = 8 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.55-7.42 (m, 3H), 7.12-7.09 (m, 1H), 6.32 (s, 1H), 3.15 (t, *J* = 7.6 Hz, 2H), 1.84-1.77 (m, 2H) , 1.46-1.25 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 22.5, 28.5, 29.3, 31.5, 104.7, 119.0, 121.8, 127.5 (2C), 127.8, 128.9 (2C), 133.6, 139.4, 143.5, 143.6, 149.3; IR (cm^{-1}, KBr) cm^{-1} 2936, 2857, 1397, 1378, 1254, 1155; Mass (ES) m/z 329 (M+1, 100 %); HRMS (ESI): calcd for $C_{18}H_{21}N_2O_2S(M+H)^+$ 329.1324, found 329.1340.

4-(1-(Phenylsulfonyl)-1*H*-pyrrolo[2,3-b]pyridin-2-yl)butanenitrile (**3l**); Yellow solid, mp 147-150 °C; R_f (30% ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 2H), 7.72 (dd, *J* = 8, 1.6 Hz, 1H), 7.57-7.49 (m, 5H), 7.16-7.13 (m, 1H), 6.42 (s, 1H), 3.3 (t, *J* = 7.2 Hz, 2H), 2.50-2.46 (m, 2H) , 2.2 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.5, 24.9, 28.3, 106.3, 119.1, 119.2, 121.4, 127.6 (2C), 128.3(2C), 128.5 (2C), 128.9 (2C), 133.9, 138.8, 140.0, 144.2, 149.2; IR (cm^{-1}, KBr) 2925, 2230, 1399, 1363, 1258, 1184; Mass (ES) m/z 326 (M+1, 100 %); HRMS (ESI): calcd for $C_{17}H_{16}N_3O_2S(M+H)^+$ 326.0963, found 326.0986.

1-(Phenylsulfonyl)-1*H*-pyrrolo[2,3-b]pyridine-2-carbaldehyde (**6**): To a solution of the **3b** (1.35 g, 4.6 mmol) in anhydrous chloroform was added active MnO_2 (6.1 g, 70.3 mmol). The mixture was stirred at room temperature for 6 h under N_2. After completion, the reaction mixture was cooled to room temperature, diluted with $CHCl_3$ (20 mL) and filtered through a celite bed. The filtrate was concentrated to afford 1.14 g (85% yield) of desired product**;** white solid, mp 140-145

°C; R_f (30% ethyl acetate / n-hexane), 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.6 (s, 1H), 8.61 (d, *J* = 4.0 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.61-7.57 (m, 1H), 7.51-7.47 (m, 2H), 7.40 (s, 1H), 7.29-7.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 114.0, 120.2, 128.0 (2C), 128.7, 129.1, 129.4, 132.0, 134.0, 134.4, 137.4, 137.9, 148.9, 183.2; IR (cm^{-1}, KBr) cm^{-1} 2932, 1682, 1373, 1265, 1176; Mass (ES) m/z 287 (M+1, 100 %); HRMS (ESI): calcd for $C_{14}H_{11}N_2O_3S$ $(M+H)^+$ 287.0490, found 287.1034.

Biology

A yeast cell based assay[3] for identification of potential inhibitors of HDAC Sir2

Reporter silencing assay: In this assay a yeast strain (TEL::URA3 strain (MATα ura3-52 lys2-801 ade2-101 trpΔ63 his3Δ200 leu3Δ200 leu2-Δ1 TEL adh4::URA) was used in which, a reporter gene URA3 was inserted in the silenced telomeric region where it is silenced by yeast Sir2 protein. A compound having the Sir2 protein inhibitory effect will inhibit the Sir2 protein, and thus the URA3 gene will be expressed and this will result in the death of the yeast cell in presence of 5-fluoro orotic acid (5-FOA) through formation of toxic 5-fluorouracil. This assay can also test the toxicity of compounds. The cells when grown in absence of 5-FOA should grow if the compound is not toxic. However in case of a toxic compound yeast cells would die.

The yeast strain was inoculated in 5.0 mL of YPDA media. The cells growing at the exponential phase were dispensed in the round bottom 96-well plate using cell dispenser. A Stock concentration of 10% 5-FOA was used to make a final concentration of 0.3% 5-FOA in the wells of 96-well plate. The compounds at a concentration of 50 uM were added to each well and the plates were incubated at 30 ^{0}C. Absorbance at 590 was measured using 96 well plate reader after 24 and 48 h. The inhibitory effect of compounds was analyzed after plotting the OD vs concentration of the compound in Excel data sheet. Splitomicin was used as a control (data not shown).

Docking studies

The Docking studies of azaindole derivatives were carried out on the Yeast Sir2 protein (PDB ID : 2HJH) with the help of the Schrodinger software.[4] Thus, the energy minimization and conformational search was performed with the MACROMODEL application in the Schrodinger package. The azaindole molecules were energy minimized for flexibility and conformational search was performed. We used OPLS_2005 force field and water as implicit solvent. We have followed the PRCG (Polak-Ribier conjugate gradient) method of minimization with 500 iterations

with a threshold gradient on 0.05 kJ/mol. The conformational search was performed based on Montecarlo multiple minimum torsional sampling. The docking studies were done by creating the GLIDE GRID in the protein and ligand docking was carried out using the azaindole molecules.

Procedure for molecular docking: The 2HJH (yeast Sir2) protein crystal structure was obtained from protein data bank (PDB) and it was further refined with the protein preparation wizard application in which the hyderogens were added and the missing loops and aminoacid residues were arranged through PRIME application. The water molecules beyond the 5 Å distance from the protein were removed. Finally the protein was optimized and then minimized with IMPREF application using the OPLS_2005 force field. GLIDE GRID was created and ligand docking was done with the molecules previously prepared through the LIGPREP application of the software. Flexible type of docking was done and the glide score was calculated with the simple glide docking with XP mode application in the MASTERO 9.1 Interface.

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4. H. Maruoka, M. O. Barrett, H. Ko, D. K. Tosh, A. Melman, L. E. Burianek, R. Balasubramanian, B. Berk, S. Costanzi, T. K. Harden, K. A. Jacobson, *J. Med. Chem.* 2010, **53**, 4488.

Supplementary Material (ESI) for Medicinal Chemistry Communications

Copies of spectra

Alkynylation of *N*-(3-iodopyridin-2-yl)sulfonamide under Pd/C-Cu catalysis: A direct one pot synthesis of 7-azaindoles and their pharmacological evaluation as potential inhibitors of sirtuins

Mohosin Layek,[a,b] Syam Kumar Y.,[a] Aminul Islam,[a] Ravikumar Karavarapu,[c] Amrita Sengupta,[c] Devyani Halder,[c] K. Mukkanti,[b] Manojit Pal[c,*]

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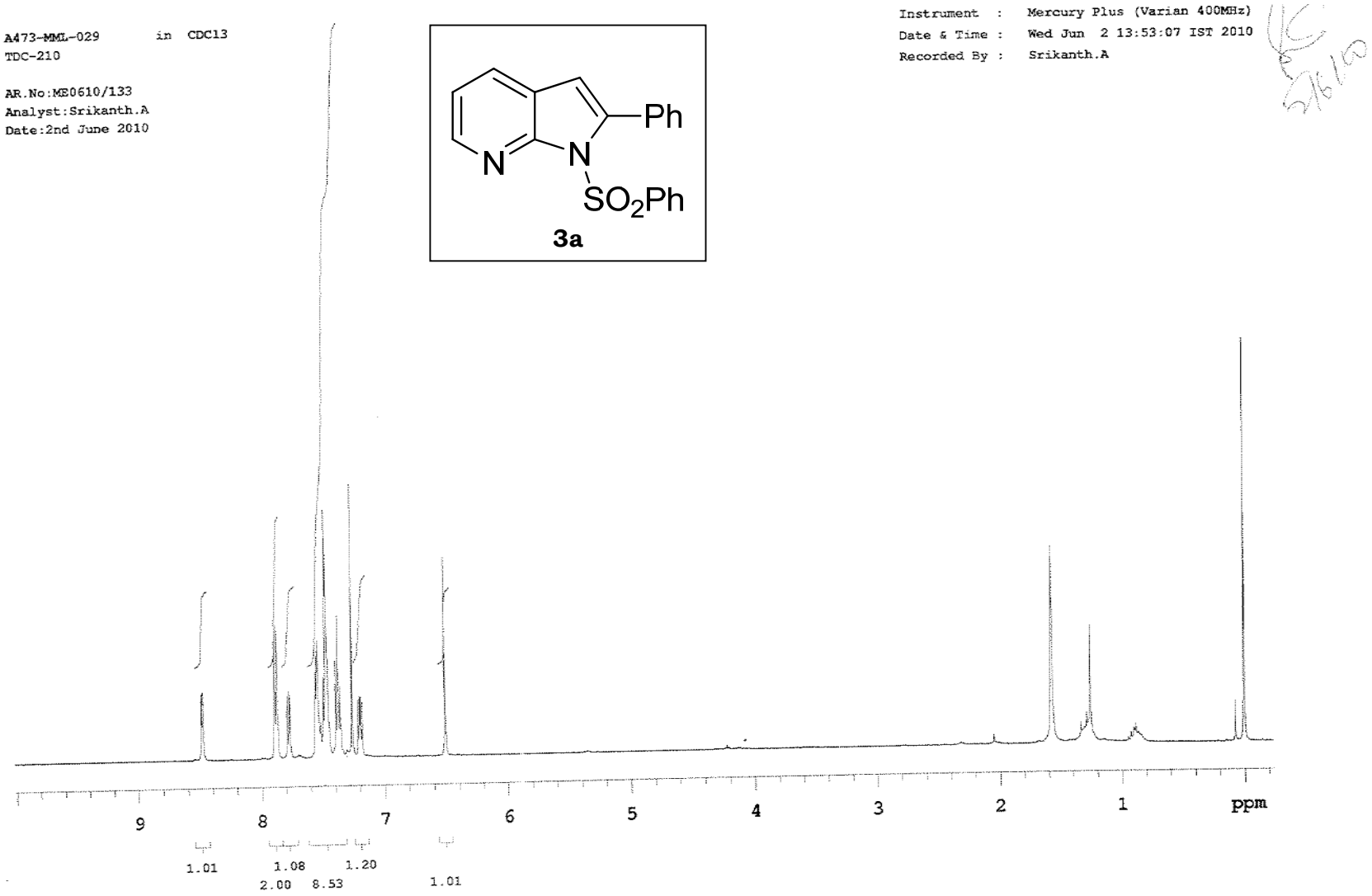
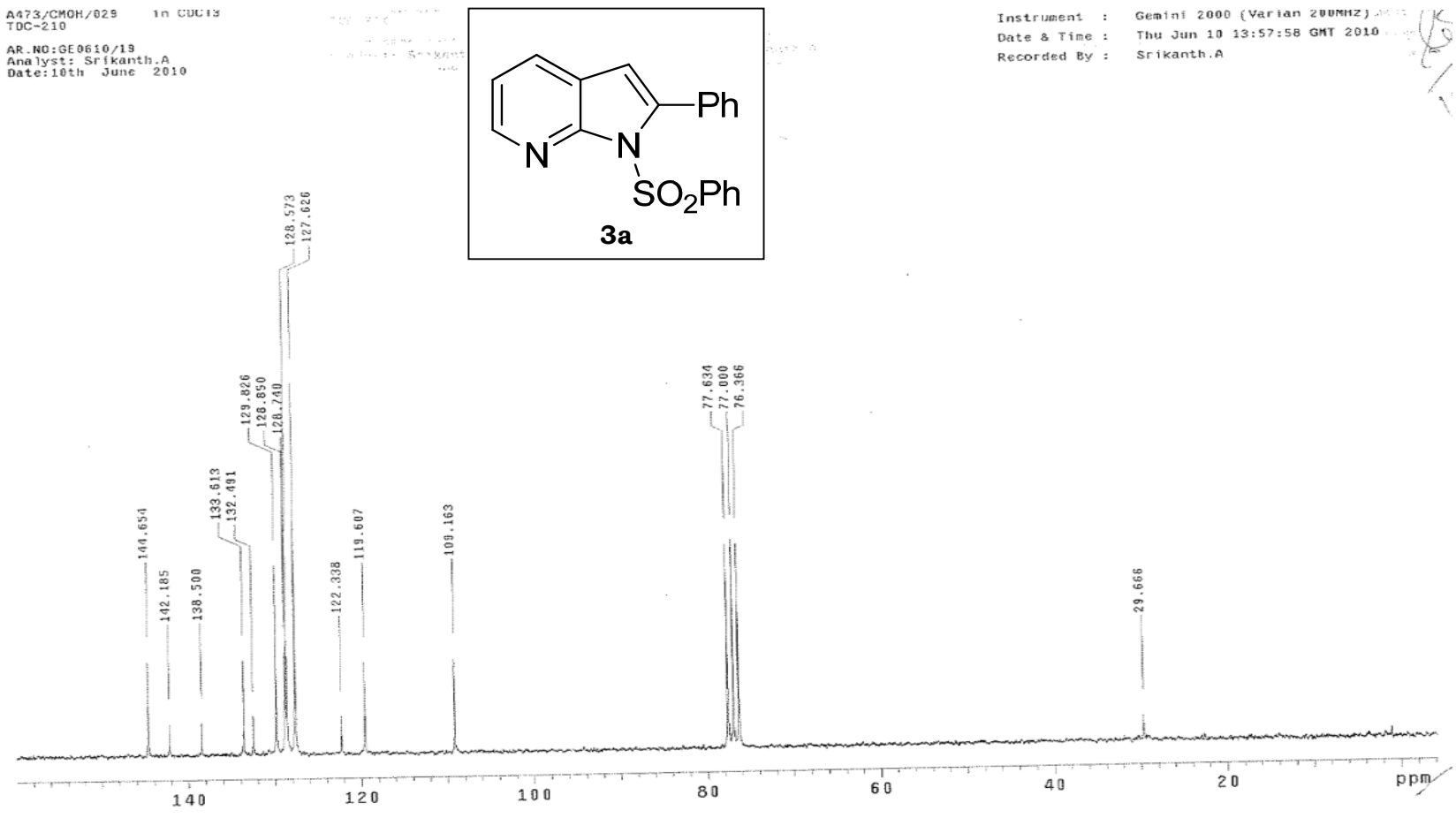
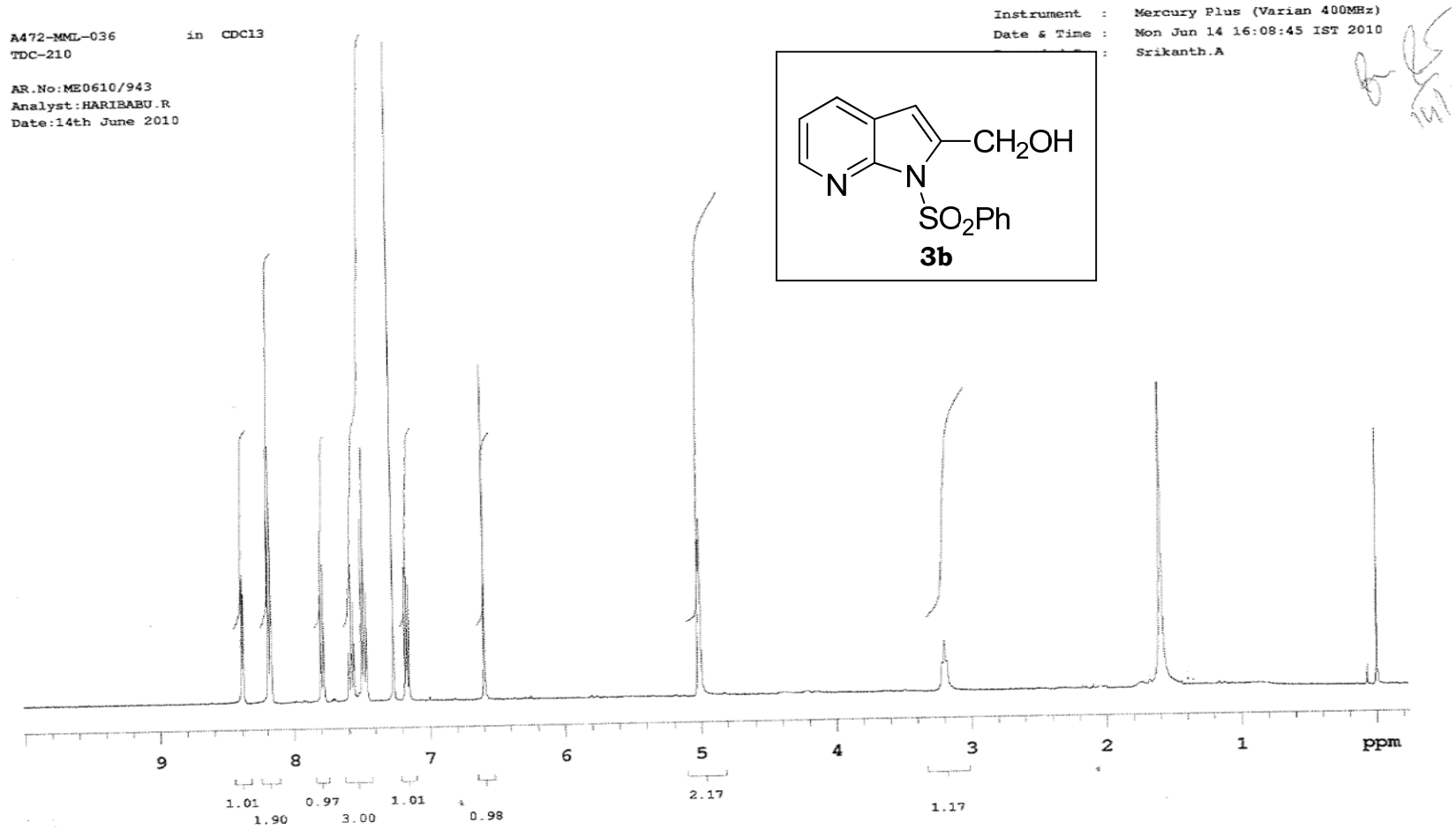
[b]*Chemistry Division, Institute of Science and Technology, JNT University, Kukatpally, Hyderabad 500072;*

[c]*Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, Andhra Pradesh, India*

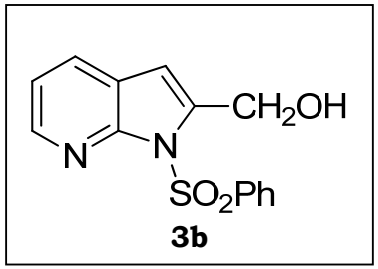

A473-MML-029 in CDCl3
TDC-210
AR.No:ME0610/133
Analyst:Srikanth.A
Date:2nd June 2010
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Wed Jun 2 13:53:07 IST 2010
Recorded By : Srikanth.A
Ph
N
N
SO2Ph
3a
9
8
7
6
5
4
3
2
1
ppm
1.01
1.08
1.20
2.00
8.53
1.01


A473/CMOH/029 In CDCl3
TDC-210
AR.NO:GE0610/13
Analyst: Srikanth.A
Date:10th June 2010
Instrument : Gemini 2000 (Varian 200MHz)
Date & Time : Thu Jun 10 13:57:58 GMT 2010
Recorded By : Srikanth.A
Ph
N
N
SO2Ph
3a
144.654
142.185
138.500
133.613
132.491
129.026
128.850
128.240
128.573
127.626
122.338
119.607
109.163
77.634
77.000
76.366
29.666
140
120
100
80
60
40
20
ppm


A472-MML-036 in CDCl3
TDC-210
AR.No:ME0610/943
Analyst:HARIBABU.R
Date:14th June 2010
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Mon Jun 14 16:08:45 IST 2010
Srikanth.A
CH2OH
N
N
SO2Ph
3b
9
8
7
6
5
4
3
2
1
ppm
1.01
1.90
0.97
3.00
1.01
0.98
2.17
1.17

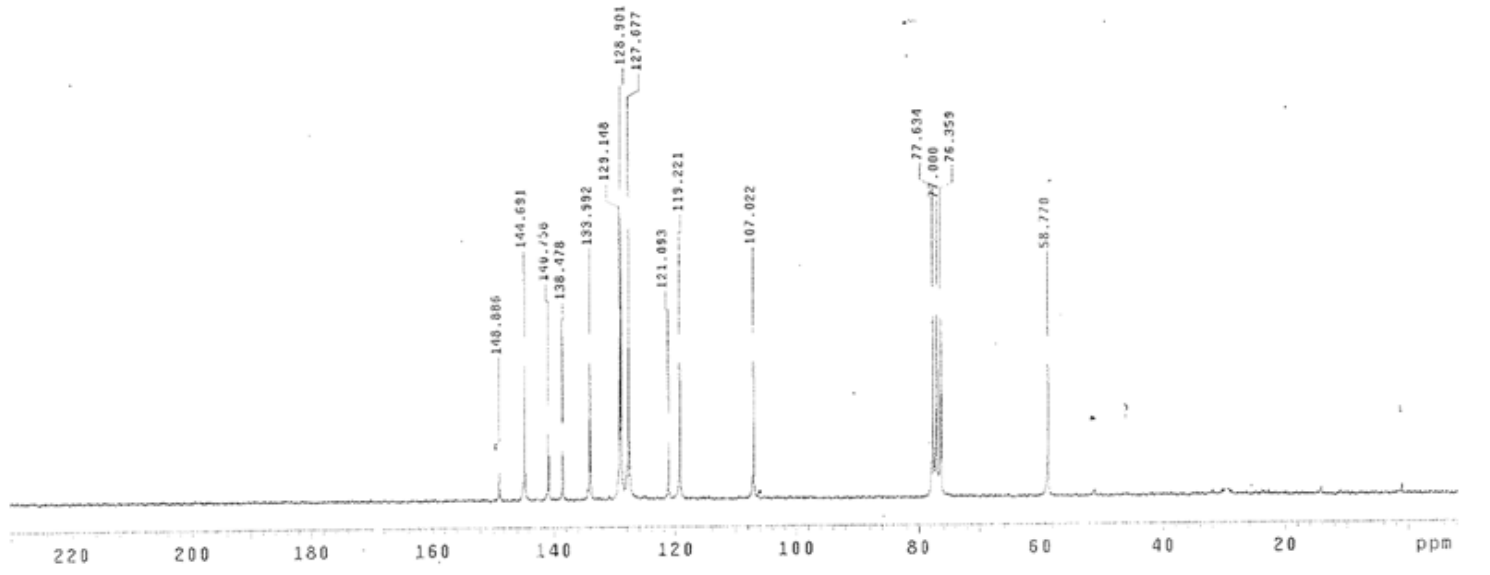
A472-MML/036 in CDCl3
TDC-210

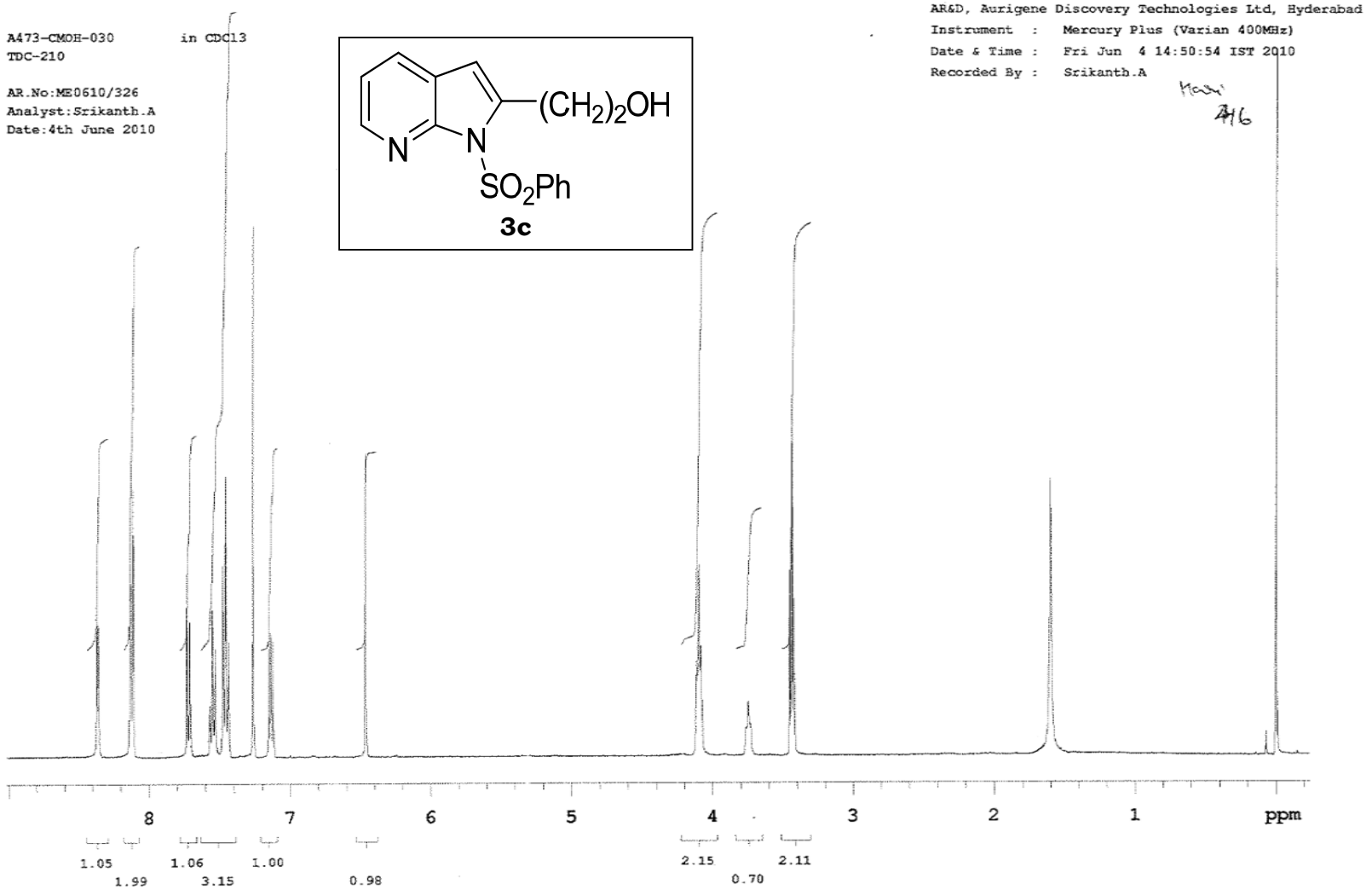
AR NO:GE0810/79
Analyst:Haribabu.R
Date: 30 th Aug.2010



3b

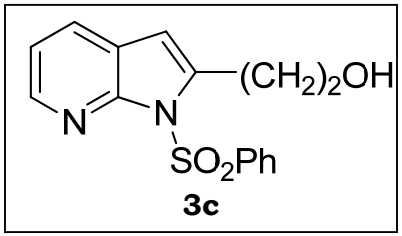
AR&D, Aurigene Discovery Technologies Ltd, Hydera
Instrument : Gemini 2000 (Varian 200MHz)
Date & Time : Tue Aug 31 14:47:18 GMT 2010
Recorded By : Haribabu.R




A473-CMOH-030 in CDCl3
TDC-210
AR.No:ME0610/326
Analyst:Srikanth.A
Date:4th June 2010
AR&D, Aurigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Fri Jun 4 14:50:54 IST 2010
Recorded By : Srikanth.A
(CH2)2OH
N
N
SO2Ph
3c
8
7
6
5
4
3
2
1
ppm
1.05
1.99
1.06
3.15
1.00
0.98
2.15
0.70
2.11

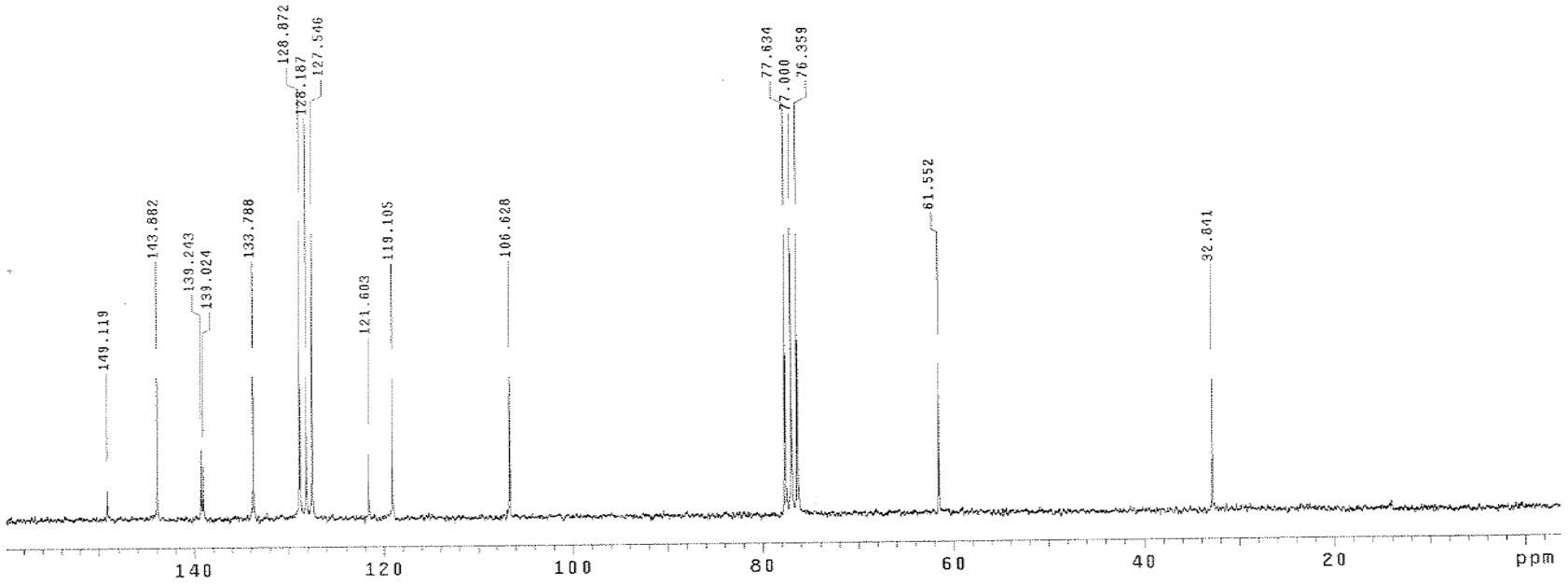
A473/CMOH/030 in CDCl3
TDC-210

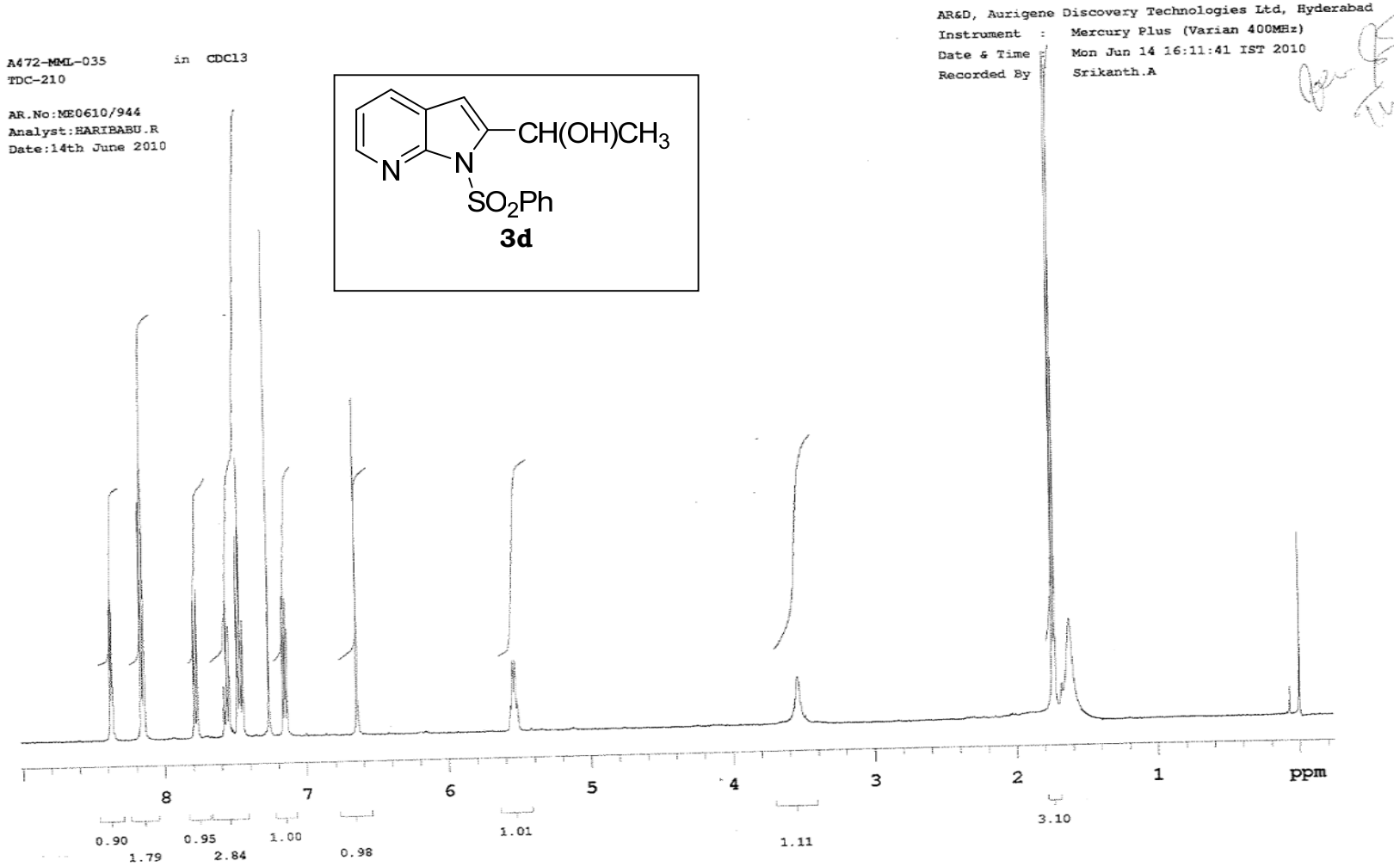
AR.NO:GE0610/18
Analyst: Srikanth.A
Date:10th June 2010

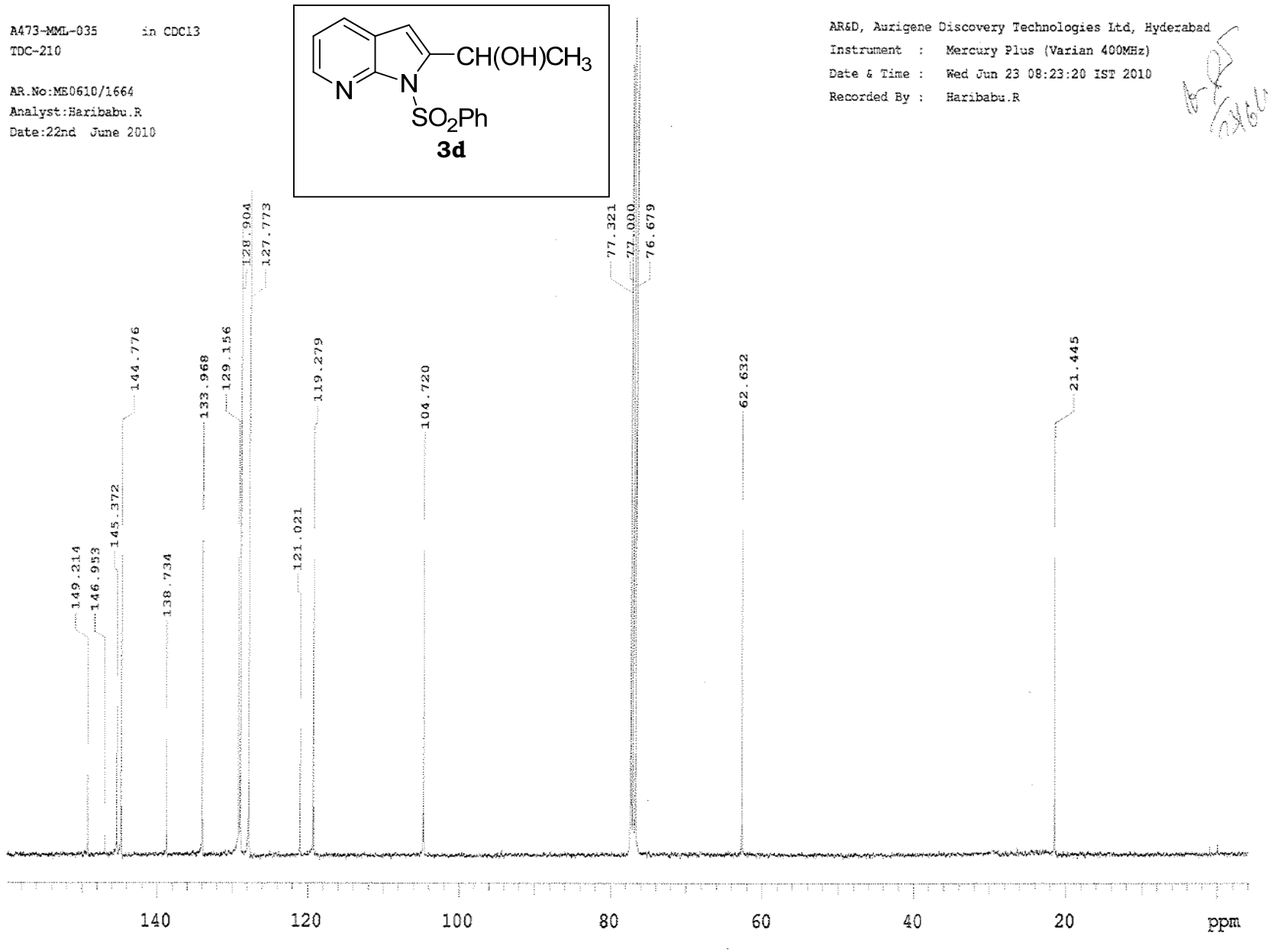


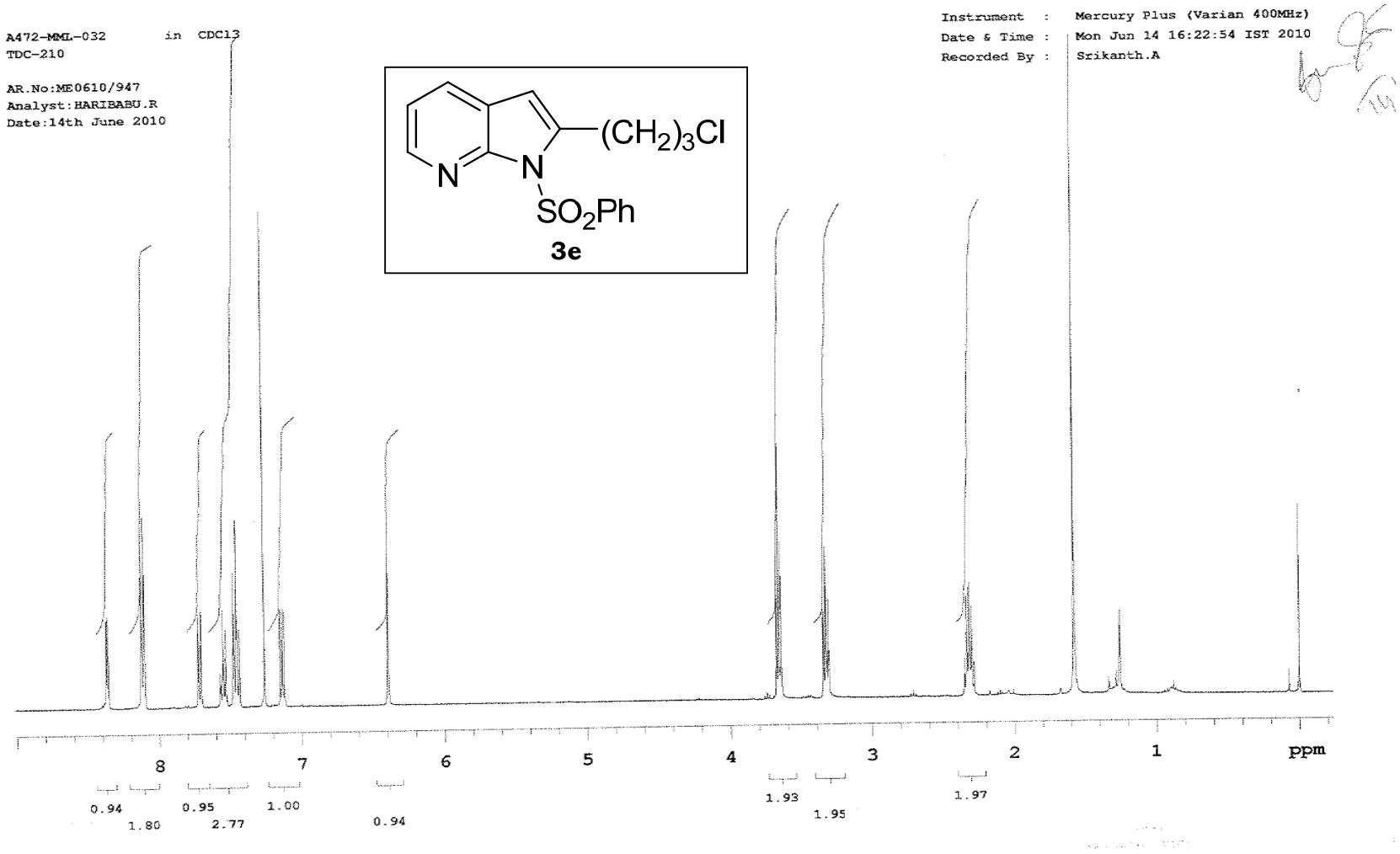
3c

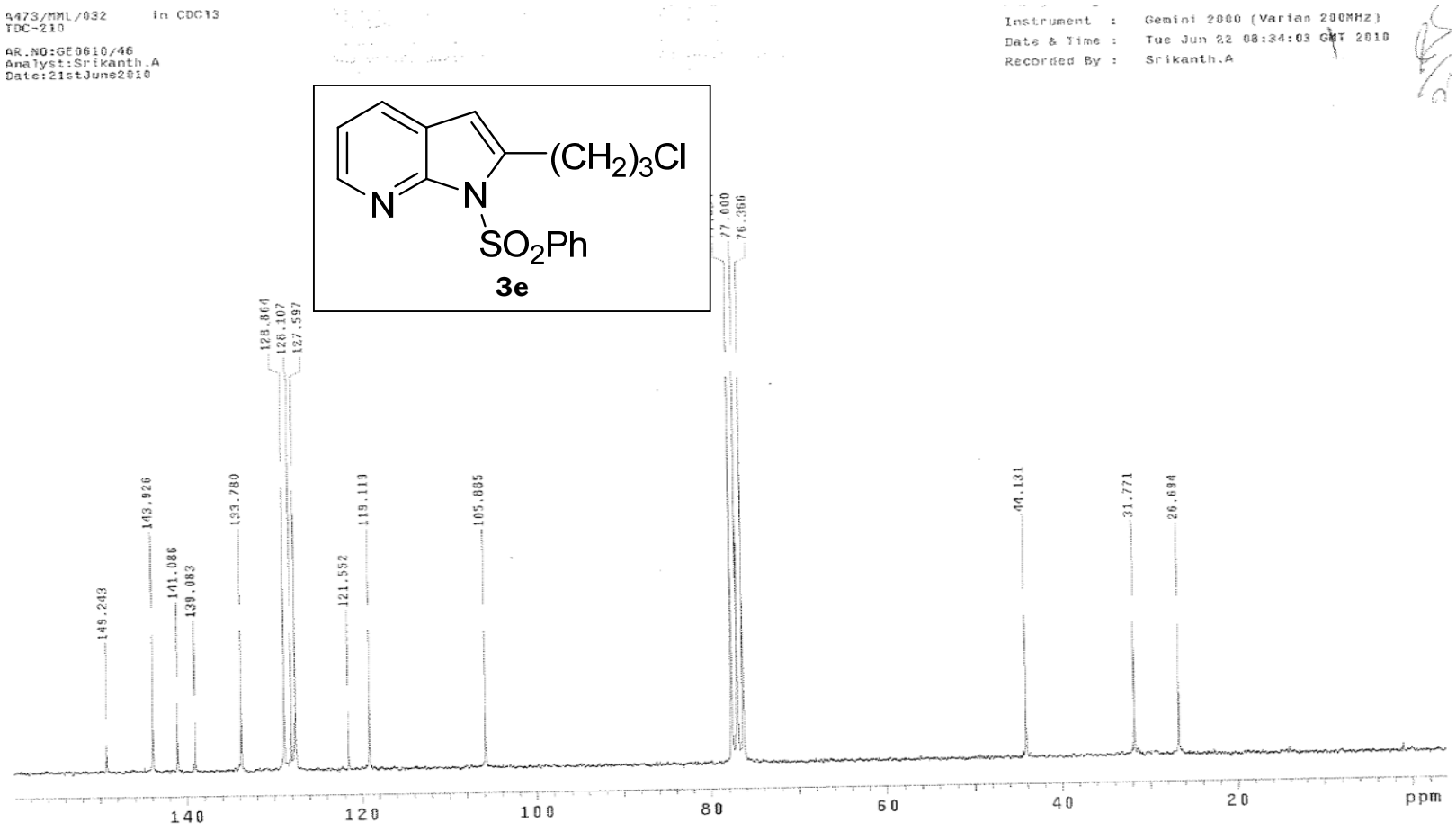
AR&D, Aurigene Discovery Technologies Ltd, Hydera
Instrument : Gemini 2000 (Varian 200MHz)
Date & Time : Thu Jun 10 10:45:59 GMT 2010
Recorded By : Srikanth.A

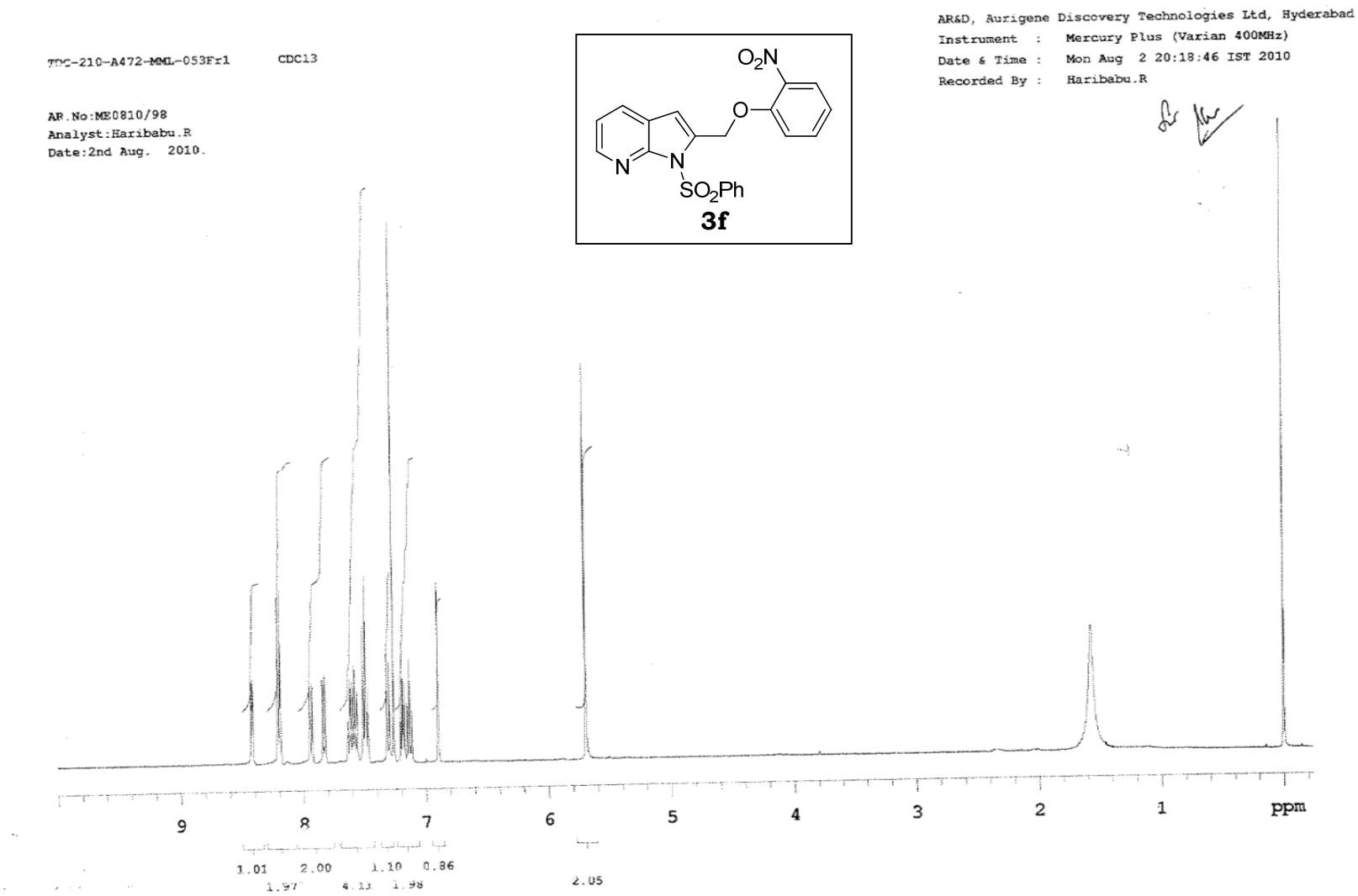


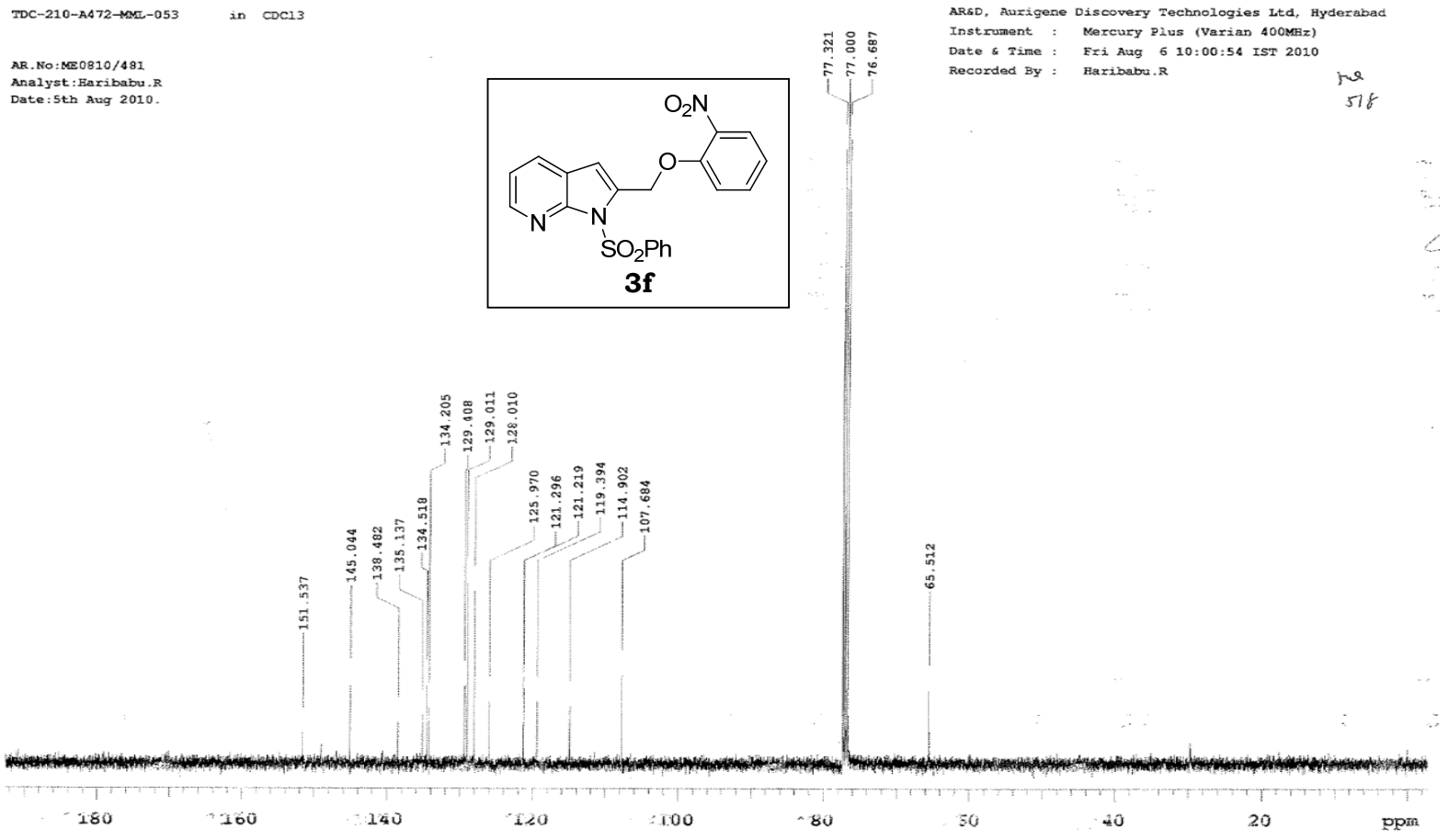

AR&D, Aurigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Mon Jun 14 16:11:41 IST 2010
Recorded By : Srikanth.A
A472-MML-035 in CDCl3
TDC-210
AR.No:ME0610/944
Analyst:HARIBABU.R
Date:14th June 2010
CH(OH)CH3
N
N
SO2Ph
3d
8
7
6
5
4
3
2
1
ppm
0.90
1.79
0.95
2.84
1.00
0.98
1.01
1.11
3.10


A473-MML-035 in CDCl3
TDC-210
AR.No:ME0610/1664
Analyst:Haribabu.R
Date:22nd June 2010
CH(OH)CH3
N
N
SO2Ph
3d
AR&D, Aurigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Wed Jun 23 08:23:20 IST 2010
Recorded By : Haribabu.R
149.214
146.953
145.372
144.776
138.734
133.968
129.156
128.904
127.773
121.021
119.279
104.720
77.321
77.000
76.679
62.632
21.445
140
120
100
80
60
40
20
ppm


A472-MML-032 in CDCl3
TDC-210
AR.No:ME0610/947
Analyst:HARIBABU.R
Date:14th June 2010
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Mon Jun 14 16:22:54 IST 2010
Recorded By : Srikanth.A
(CH2)3Cl
N
N
SO2Ph
3e
8
7
6
5
4
3
2
1
ppm
0.94
1.80
0.95
2.77
1.00
0.94
1.93
1.95
1.97


9473/MML/032 in CDCl3
TDC-210
AR.NO:GE0610/46
Analyst:Srikanth.A
Date:21stJune2010
Instrument : Gemini 2000 (Varian 200MHz)
Date & Time : Tue Jun 22 08:34:03 GMT 2010
Recorded By : Srikanth.A
(CH2)3Cl
N
N
SO2Ph
3e
149.243
143.926
141.086
139.083
133.780
128.864
128.107
127.597
121.552
119.119
105.885
77.000
76.366
44.131
31.771
26.694
140
120
100
80
60
40
20
ppm

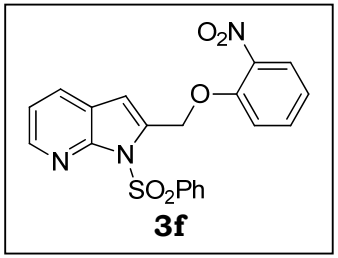

TDC-210-A472-MML-053Fr1
CDCl3
AR.No:ME0810/98
Analyst:Haribabu.R
Date:2nd Aug. 2010.
AR&D, Aurigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Mon Aug 2 20:18:46 IST 2010
Recorded By : Haribabu.R
O2N
O
N
N
SO2Ph
3f
9
8
7
6
5
4
3
2
1
ppm
1.01
2.00
1.10
0.86
1.97
4.13
1.98
2.05


TDC-210-A472-MML-053 in CDCl3
AR.No:ME0810/481
Analyst:Haribabu.R
Date:5th Aug 2010.
AR&D, Aurigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Fri Aug 6 10:00:54 IST 2010
Recorded By : Haribabu.R
O2N
O
N
N
SO2Ph
3f
77.321
77.000
76.687
134.205
129.408
129.011
128.010
125.970
121.296
121.219
119.394
114.902
107.684
151.537
145.044
138.482
135.137
134.518
65.512
180
160
140
120
100
80
60
40
20
ppm

CPS.MIYAPUR

Mass Analysis Report

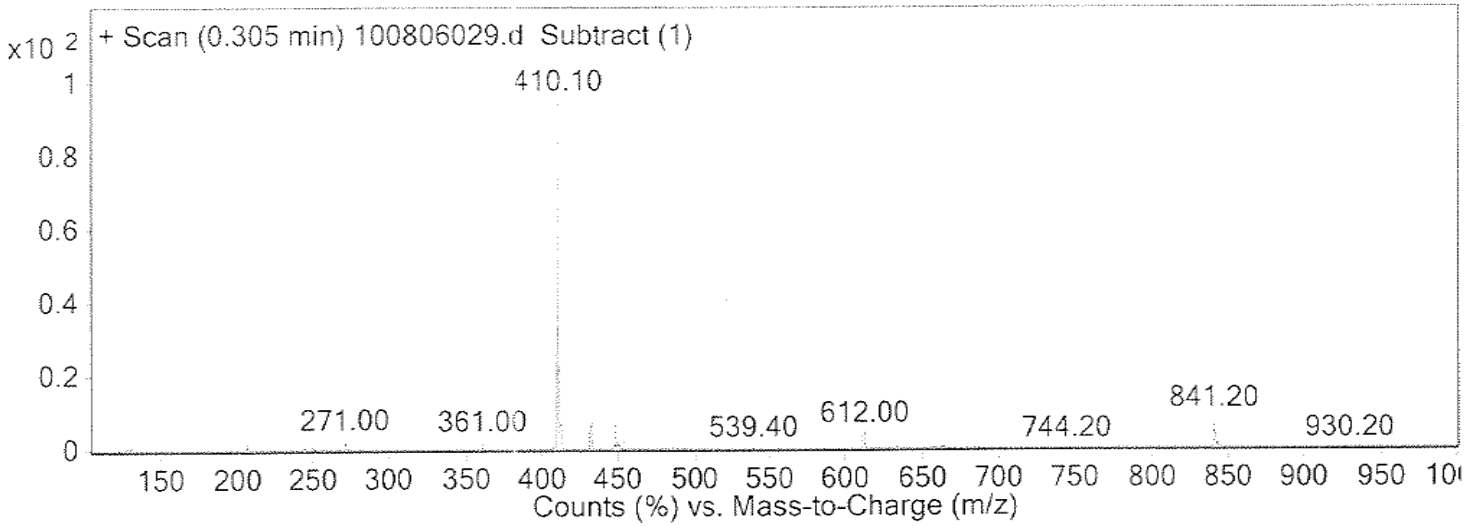
Data Filename	100806029.d	**Sample Name**	A472/MML/053
Sample Type	Sample	**Position**	Vial 42
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI.m	**IRM Calibration Status**	Success
DA Method	default.m	**Comment**	



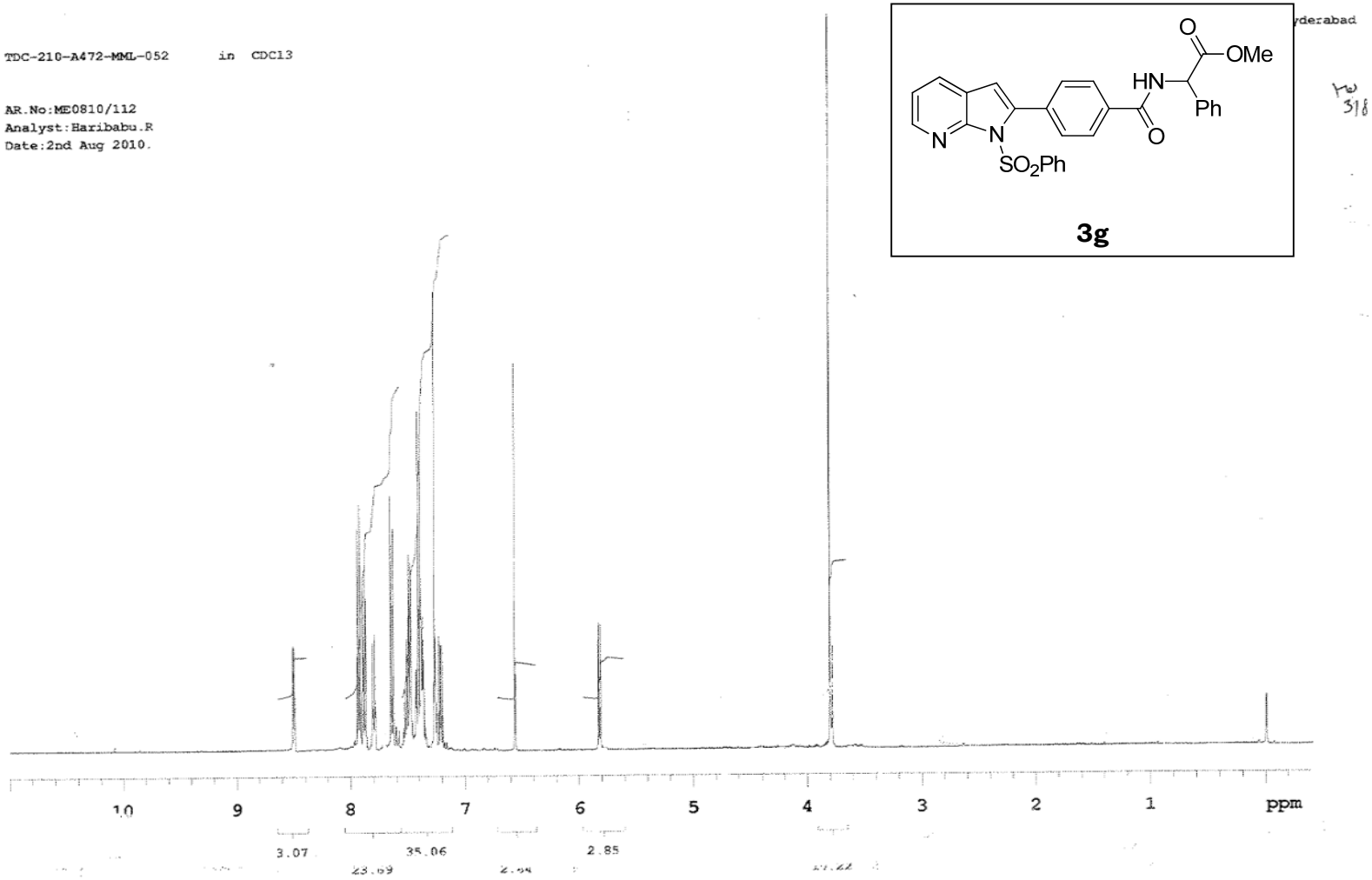
3f

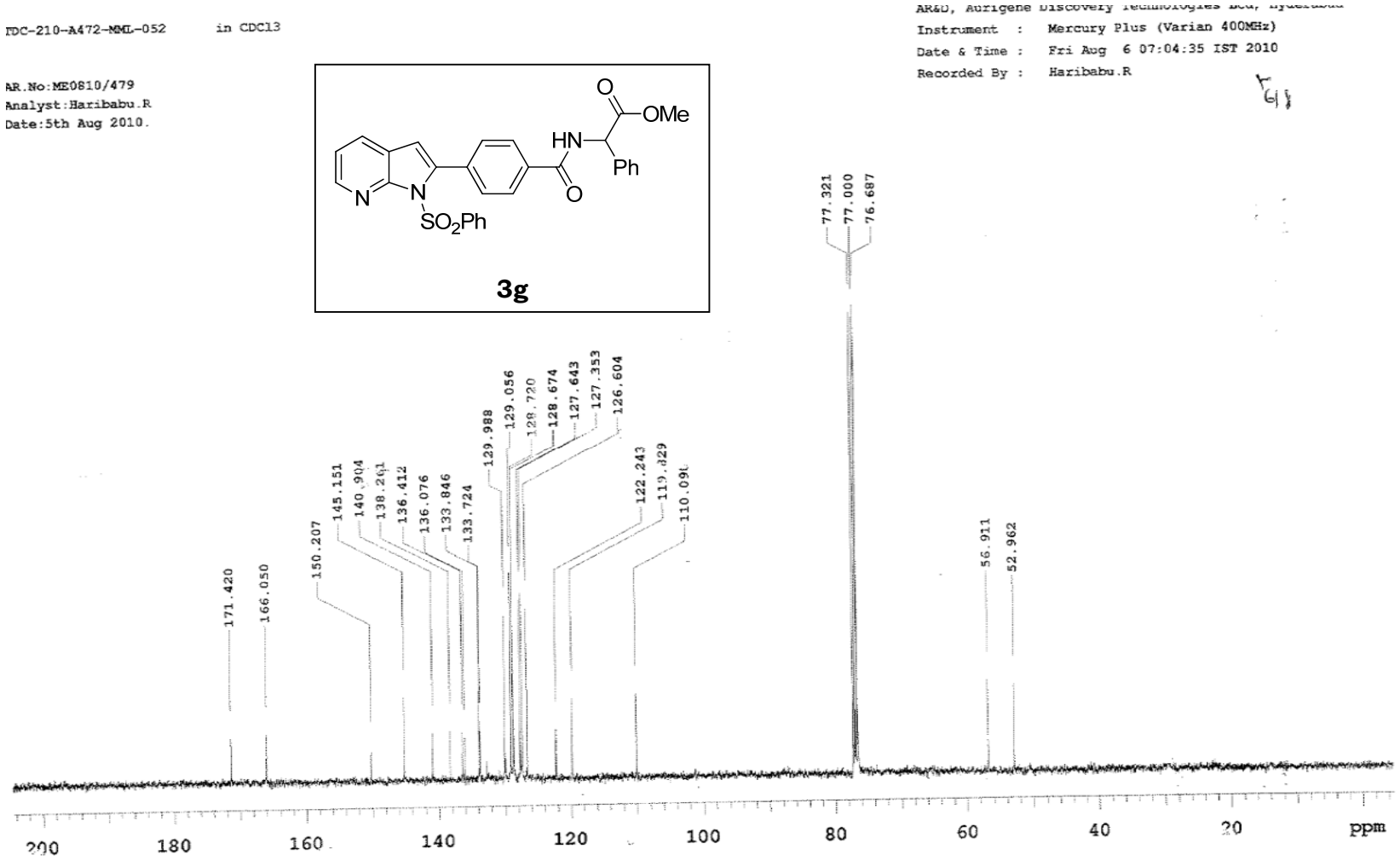
User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
135	0	Es



--- End Of Report ---

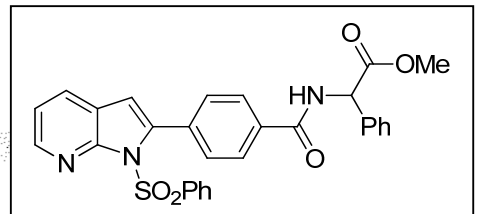

TDC-210-A472-MML-052 in CDCl3
AR.No:ME0810/112
Analyst:Haribabu.R
Date:2nd Aug 2010.
yderabad
O
OMe
HN
Ph
N
N
O
SO2Ph
3g
10
9
8
7
6
5
4
3
2
1
ppm
3.07
35.06
2.85


IDC-210-A472-MML-052 in CDCl3
AR.No:ME0810/479
Analyst:Haribabu.R
Date:5th Aug 2010.
AR&D, Aurigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Fri Aug 6 07:04:35 IST 2010
Recorded By : Haribabu.R
3g
77.321
77.000
76.687
171.420
166.050
150.207
145.151
140.904
138.261
136.412
136.076
133.846
133.724
129.988
129.056
128.720
128.674
127.643
127.353
126.604
122.243
119.829
110.098
56.911
52.962
200
180
160
140
120
100
80
60
40
20
ppm

CPS,MIYAPUR

Mass Analysis Report

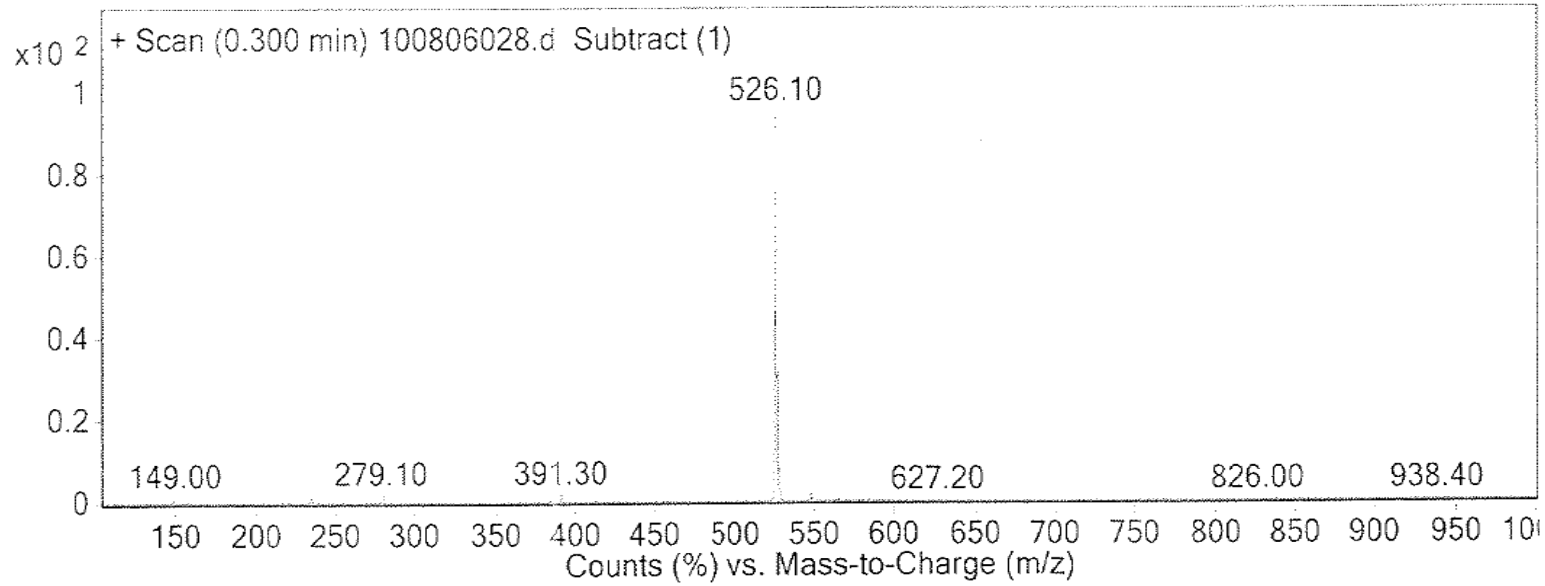
Data Filename	100806028.d	Sample Name	A472/MML/052
Sample Type	Sample	Position	Vial 41
Instrument Name	Instrument 1	User Name	
Acq Method	ESI.m	IRM Calibration Status	Success
DA Method	default.m	Comment	



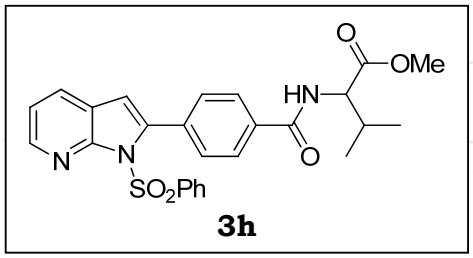
3g

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
135	0	Esi

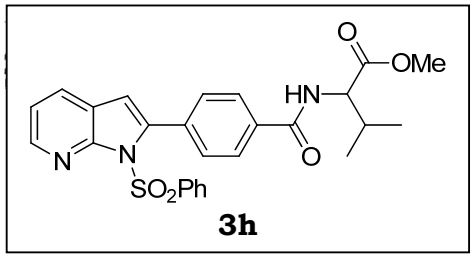


--- End Of Report ---


O
OMe
HN
O
N
N
SO2Ph

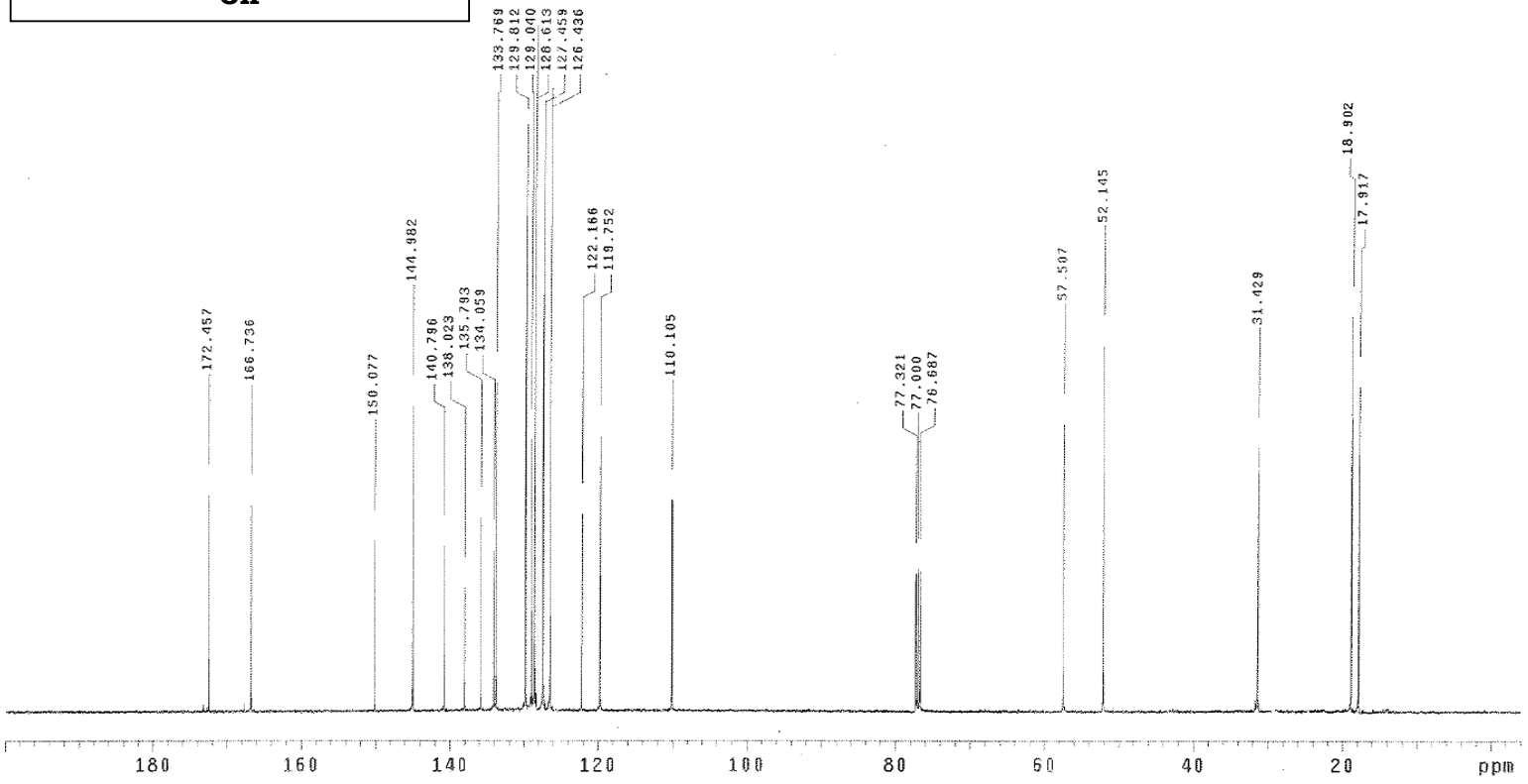
3h

A&D, Aurigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Tue Aug 10 06:59:08 IST 2010
Recorded By : Shruthi. D
10
9
8
7
6
5
4
3
2
1
ppm
3.00
16.57
17.51
5.86
3.35
3.40
3.38
10.82
4.07
9.16
22.89



3h

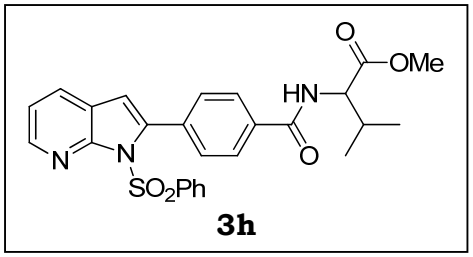
AR&D, Aurigene Discovery Technologies Ltd.
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Tue Aug 31 08:50:20 GMT 2010
Recorded By : HariBabu.R



CPS,MIYAPUR

Mass Analysis Report

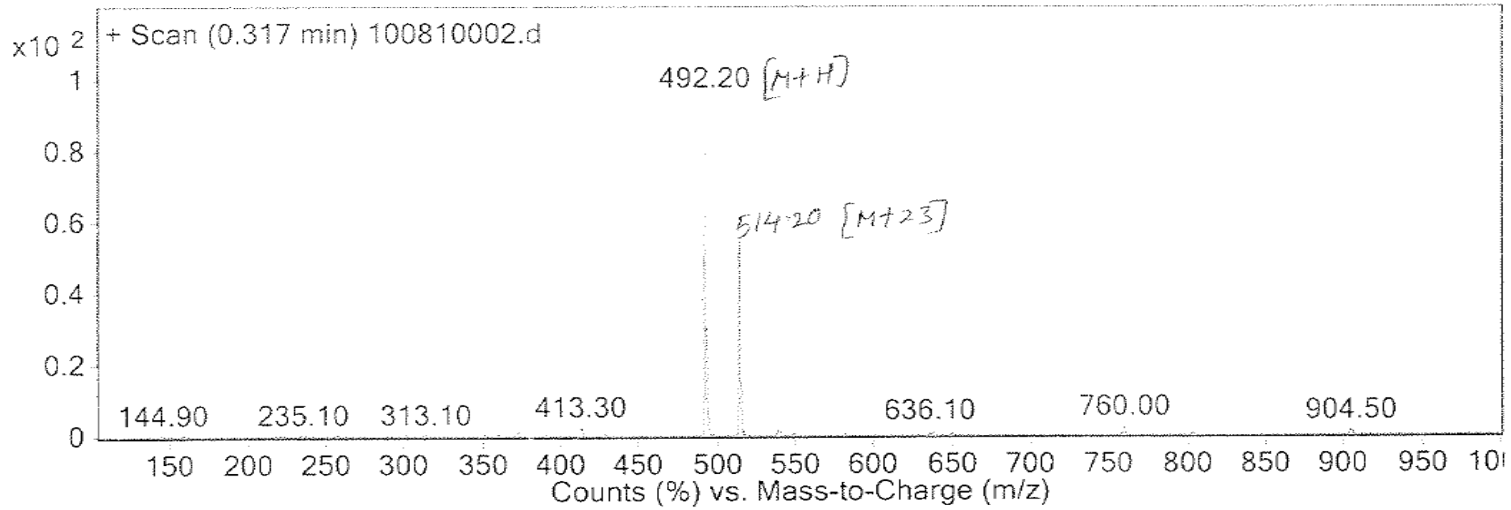
Data Filename	100810002.d	**Sample Name**	A472/MML/054
Sample Type	Sample	**Position**	Vial 52
Instrument Name	Instrument 1	**User Name**	
Acq Method	ESI.m	**IRM Calibration Status**	Success
DA Method	default.m	**Comment**	



3h

User Spectra

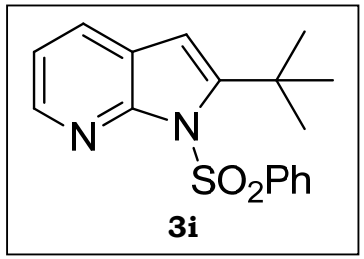
Fragmentor Voltage	Collision Energy	Ionization Mode
135	0	Esi



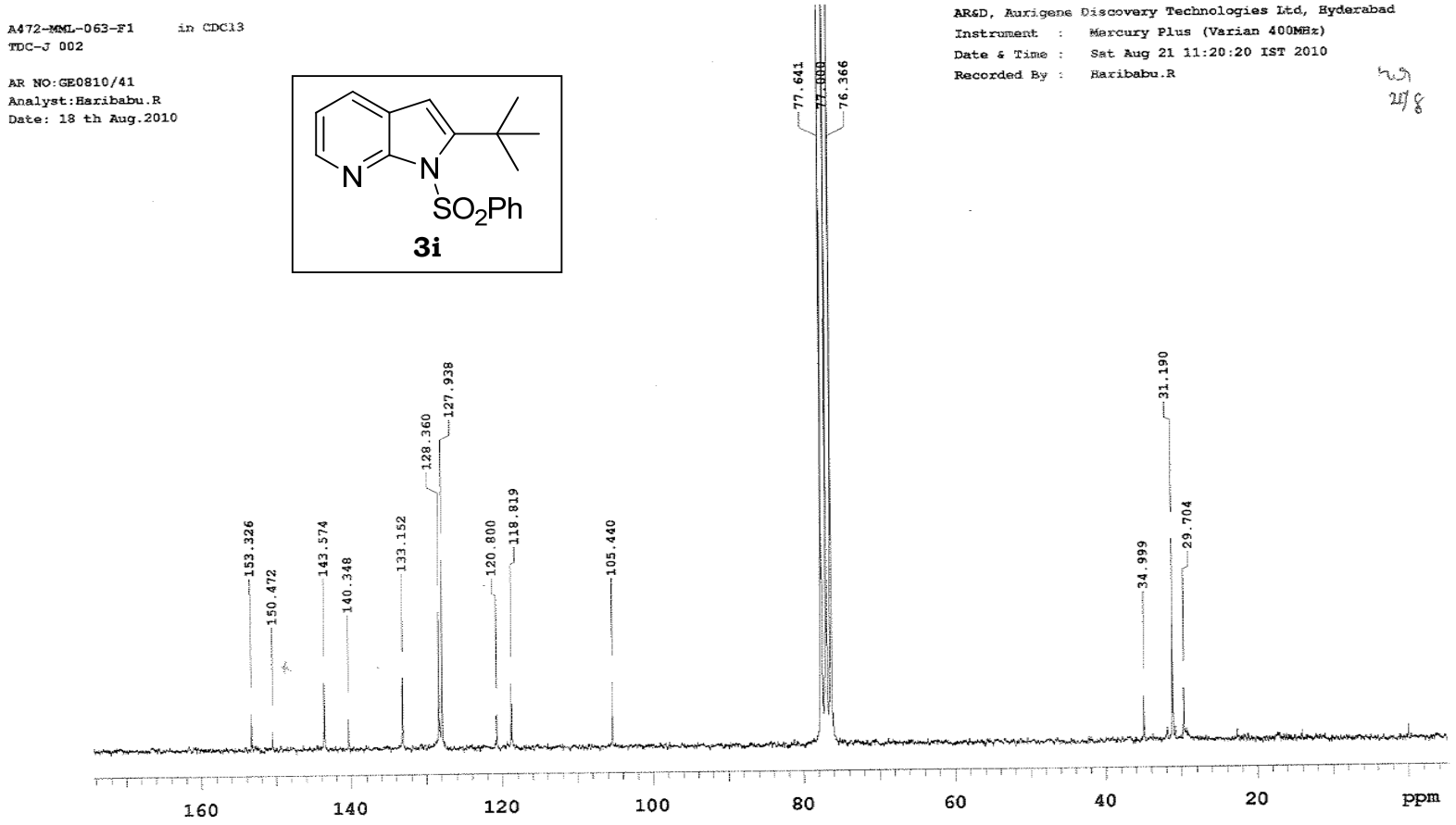
--- End Of Report ---

TDC-210 A472-MML-063F1 in CDCL3

AR.No:ME0810/1385
Analyst:Haribabu.R
Date:17 th Aug 2010



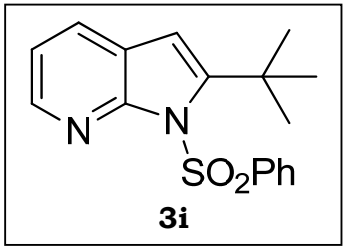
3i


A472-MML-063-F1 in CDCl3
TDC-J 002
AR NO:GE0810/41
Analyst:Haribabu.R
Date: 18 th Aug.2010
AR&D, Auxigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Sat Aug 21 11:20:20 IST 2010
Recorded By : Haribabu.R
N
N
SO2Ph
3i
153.326
150.472
143.574
140.348
133.152
128.360
127.938
120.800
118.819
105.440
77.641
77.000
76.366
34.999
31.190
29.704
160
140
120
100
80
60
40
20
ppm

CPS,MIYAPUR

Mass Analysis Report

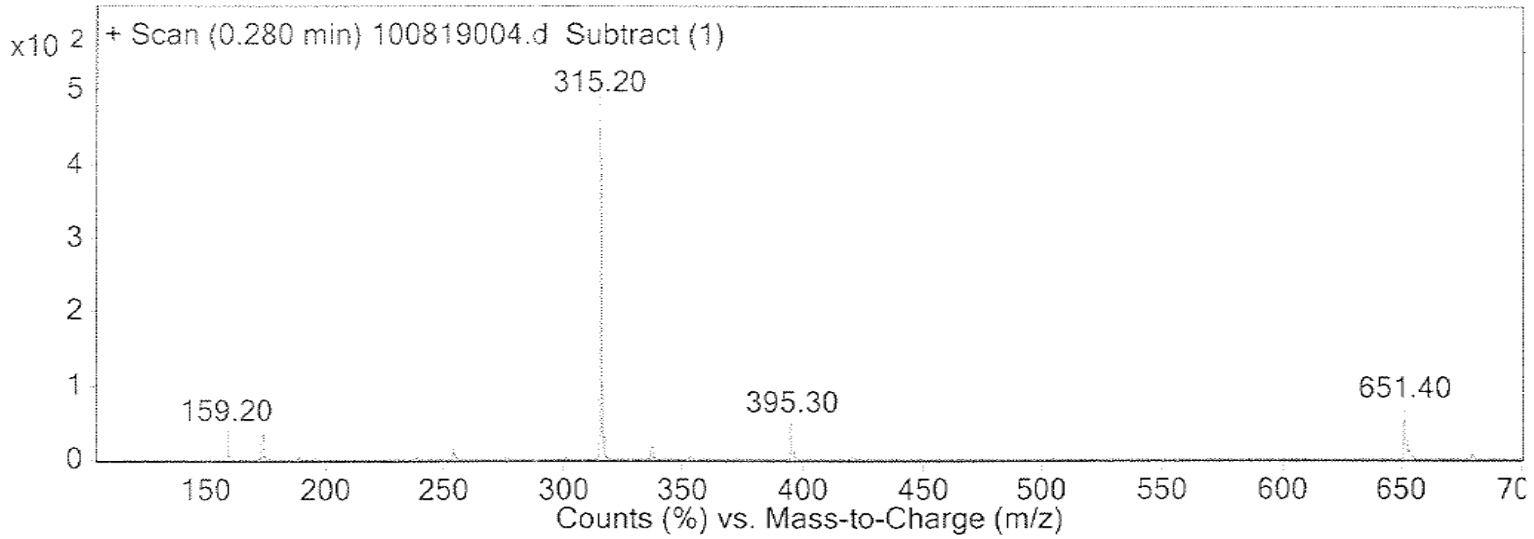
Data Filename	100819004.d	Sample Name	A472/MML/063-F1
Sample Type	Sample	Position	Vial 34
Instrument Name	Instrument 1	User Name	
Acq Method	ESI.m	IRM Calibration Status	Success
DA Method	default.m	Comment	



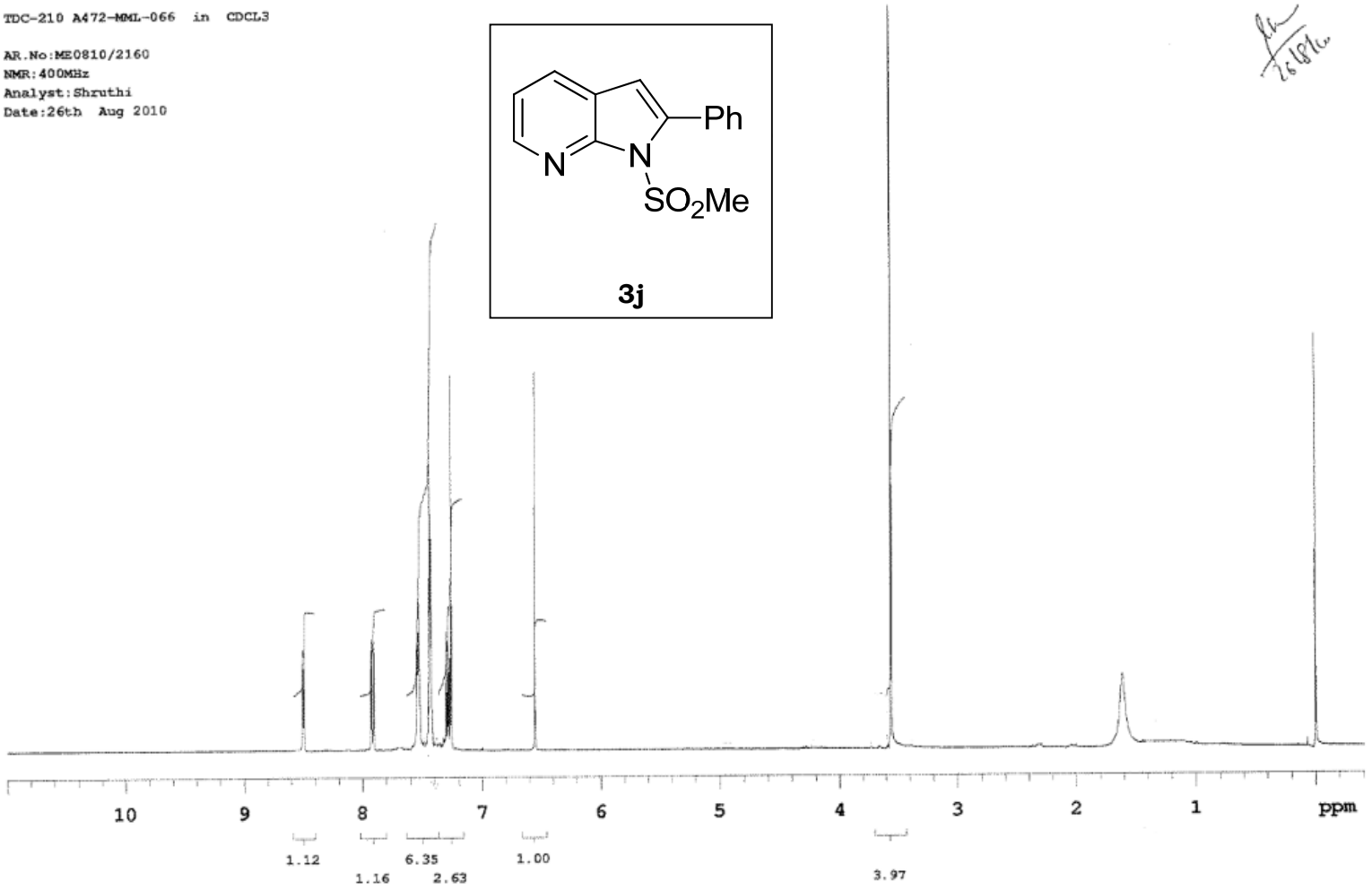
3i

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
135	0	Es



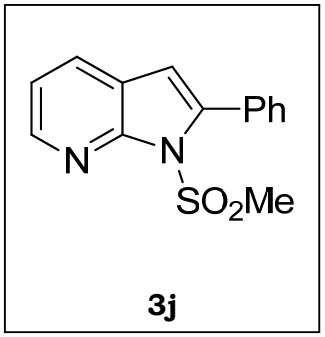
--- End Of Report ---


TDC-210 A472-MML-066 in CDCL3
AR.No:ME0810/2160
NMR:400MHz
Analyst:Shruthi
Date:26th Aug 2010
Ph
N
N
SO2Me
3j
10
9
8
7
6
5
4
3
2
1
ppm
1.12
1.16
6.35
2.63
1.00
3.97

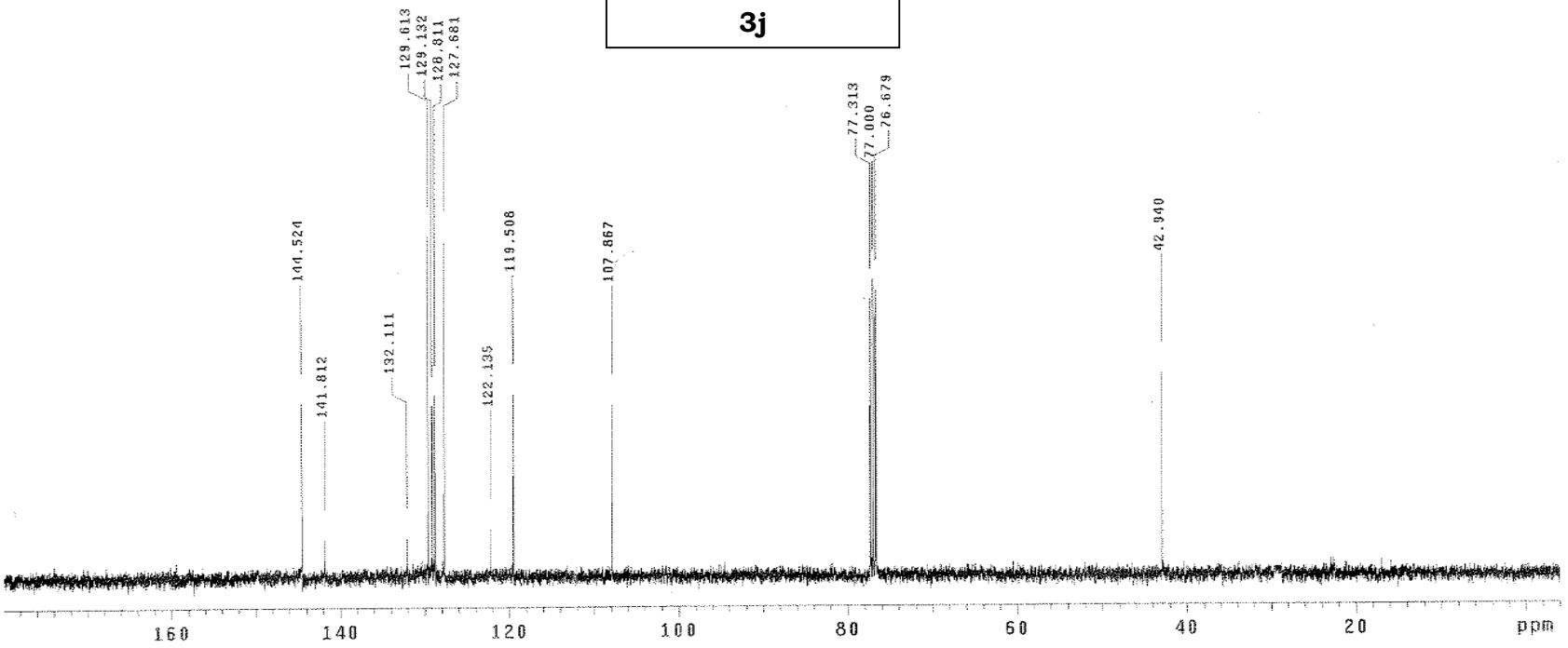
TDC-210 A472-MML-066 in CDCL3

AR.No:ME0810/2374
Date: 31st Aug. 2010
Analyst:Shruthi

Analytical Research, Discovery Research, DRL
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Tue Aug 31 13:22:48 GMT 2010
Recorded By : Shruthi. D



3j



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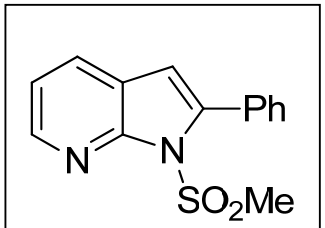
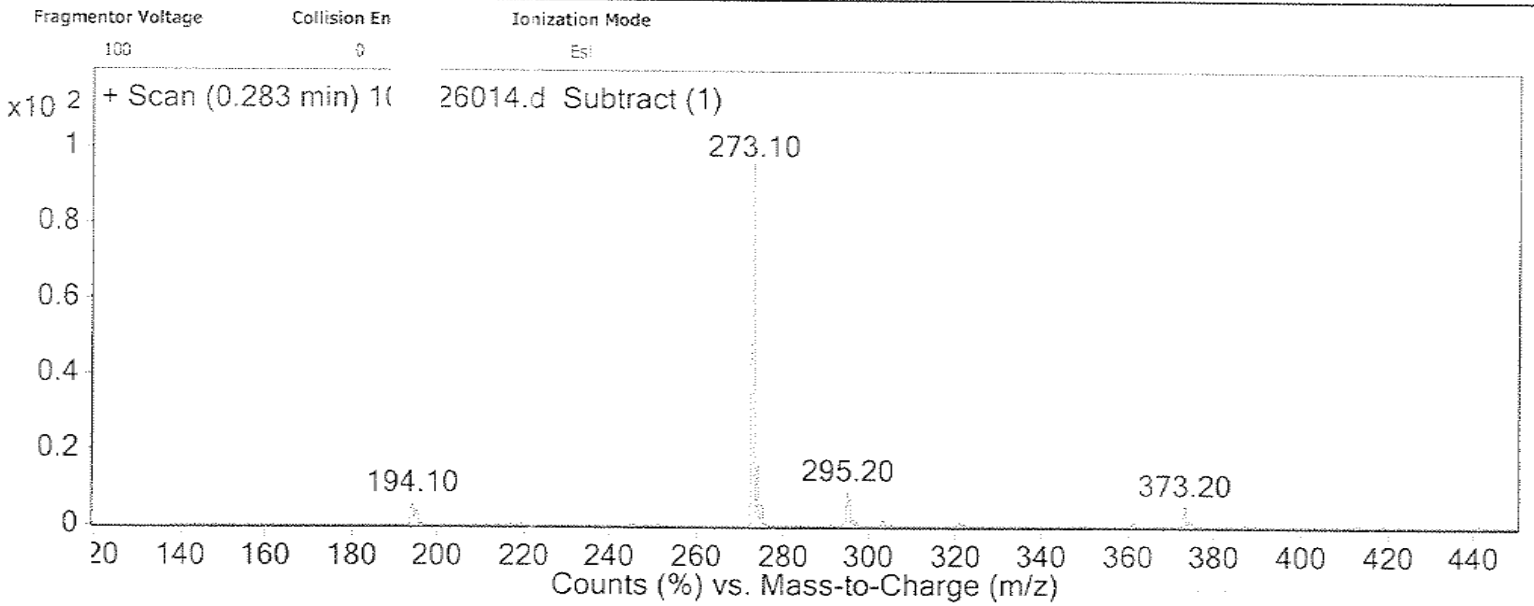
Mass Analysis Report

Data Filename	100826014.d	Sample Name	A472/MML/066
Sample Type	Sample	Position	Vial 43
Instrument Name	Instrument 1	User Name	
Acq Method	ESI.m	IRM Calibration Status	Success
DA Method	default.m	Comment	

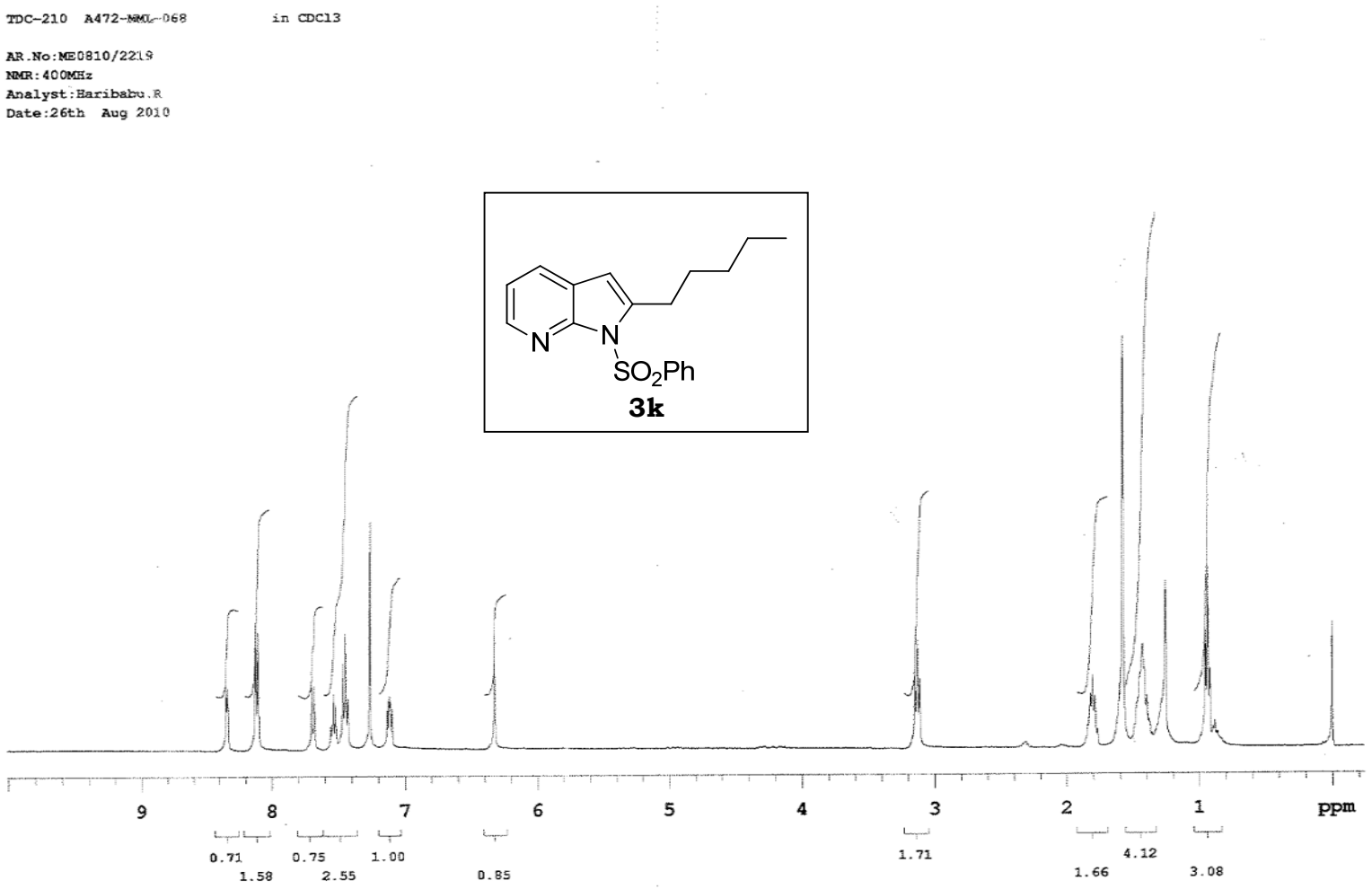


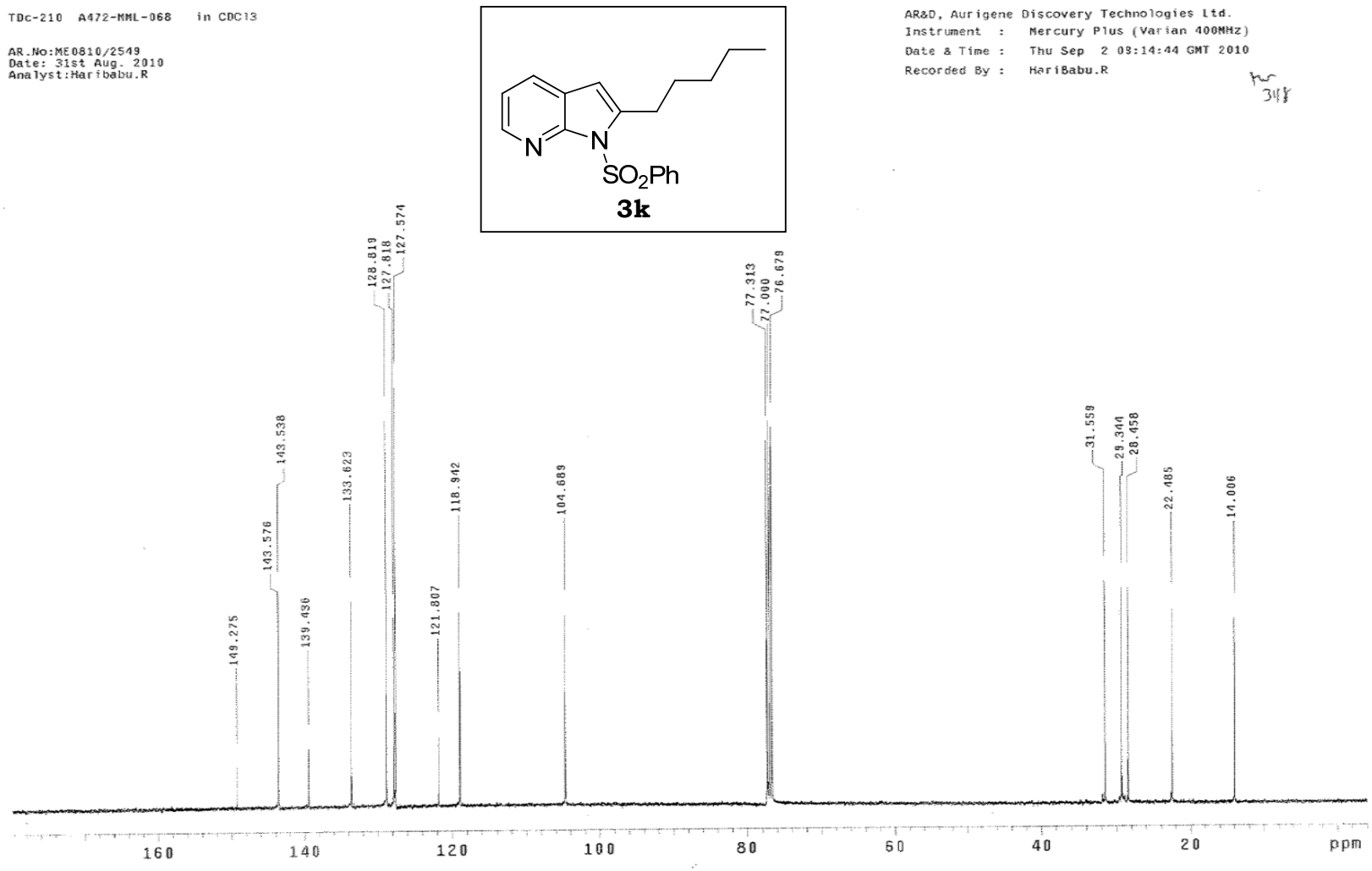
3j

User Spectra



--- End Of Report ---


TDC-210 A472-MML-068 in CDCl3
AR.No:ME0810/2219
NMR:400MHz
Analyst:Haribabu.R
Date:26th Aug 2010
N
N
SO2Ph
3k
9
8
7
6
5
4
3
2
1
ppm
0.71
1.58
0.75
2.55
1.00
0.85
1.71
1.66
4.12
3.08


TDc-210 A472-MML-068 in CDCl3
AR.No:ME0810/2549
Date: 31st Aug. 2010
Analyst:Haribabu.R
AR&D, Aurigene Discovery Technologies Ltd.
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Thu Sep 2 08:14:44 GMT 2010
Recorded By : HariBabu.R
N
N
SO2Ph
3k
149.275
143.576
143.538
139.436
133.623
128.819
127.818
127.574
121.807
118.942
104.689
77.313
77.090
76.679
31.559
29.344
28.458
22.485
14.006
160
140
120
100
80
60
40
20
ppm

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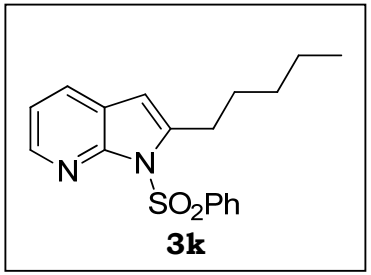
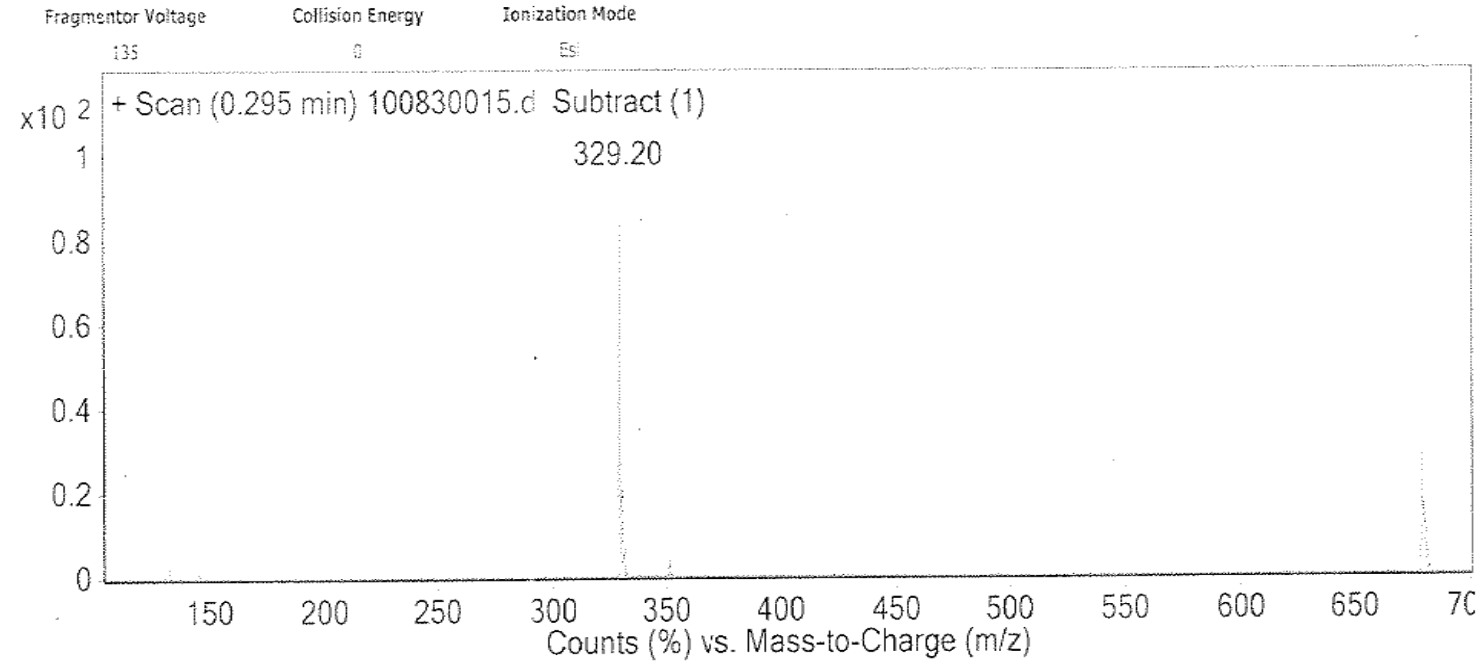
Mass Analysis Report

Data Filename	100830015.d	Sample Name	A472/MML/068
Sample Type	Sample	Position	Vial 15
Instrument Name	Instrument 1	User Name	
Acq Method	ESI.m	IRM Calibration Status	Success
DA Method	default.m	Comment	



3k

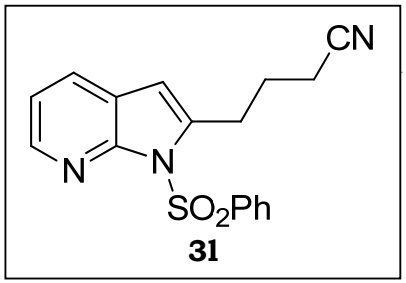
User Spectra



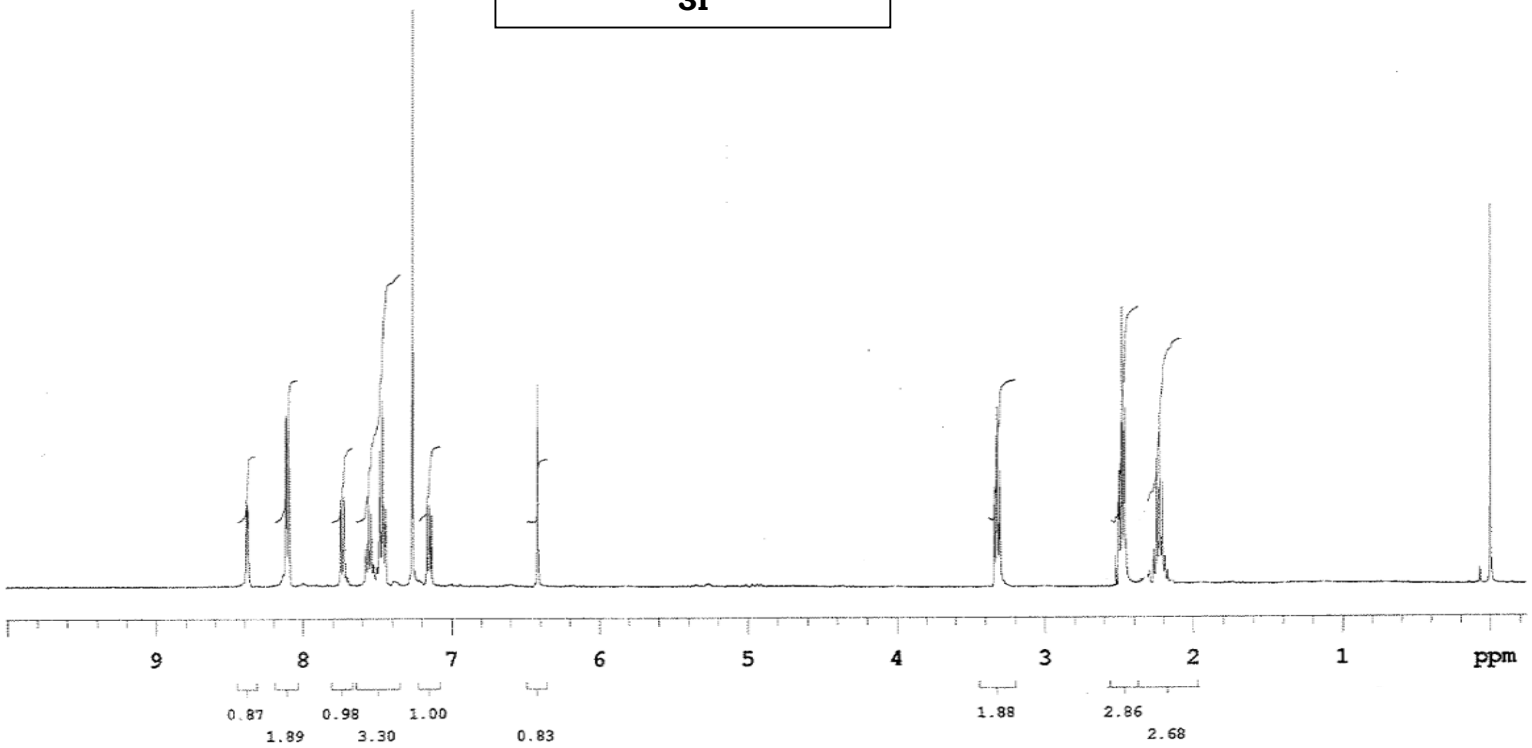
--- End Of Report ---

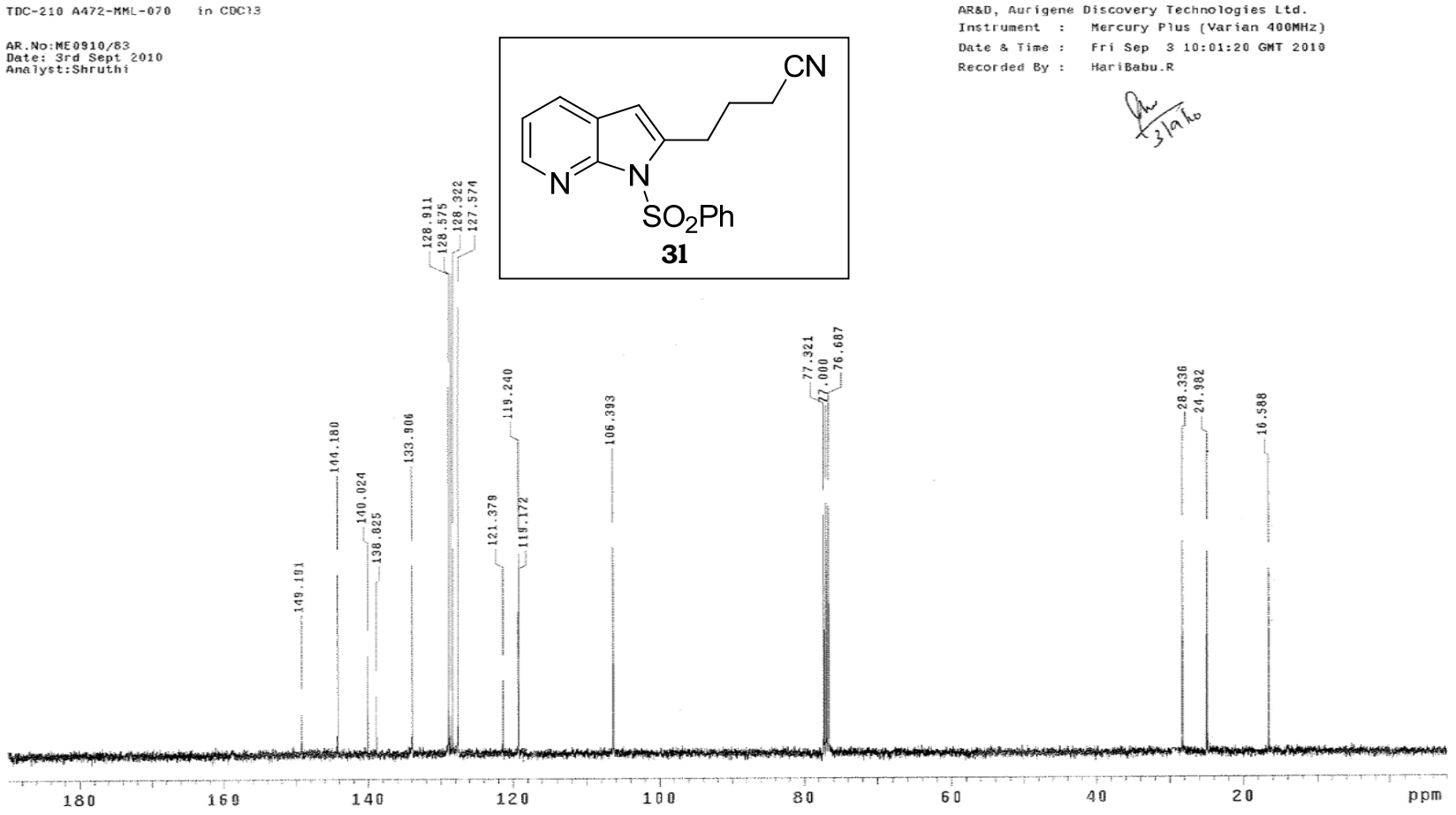
TDC-210 A472-MML-070 in CDCl3

AR.No:ME0810/2218
NMR:400MHz
Analyst:Haribabu.R
Date:26th Aug 2010



31




TDC-210 A472-MML-070 in CDCl3
AR.No:ME0910/83
Date: 3rd Sept 2010
Analyst:Shruthi
AR&D, Aurigene Discovery Technologies Ltd.
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Fri Sep 3 10:01:20 GMT 2010
Recorded By : HariBabu.R
CN
N
N
SO2Ph
31
128.911
128.575
128.322
127.574
149.191
144.180
140.024
138.025
133.906
121.379
119.240
119.172
106.393
77.321
77.000
76.687
28.336
24.982
16.588
180
160
140
120
100
80
60
40
20
ppm

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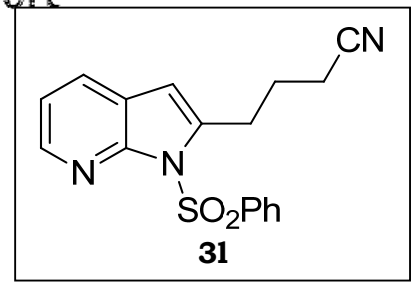
Mass Analysis Report

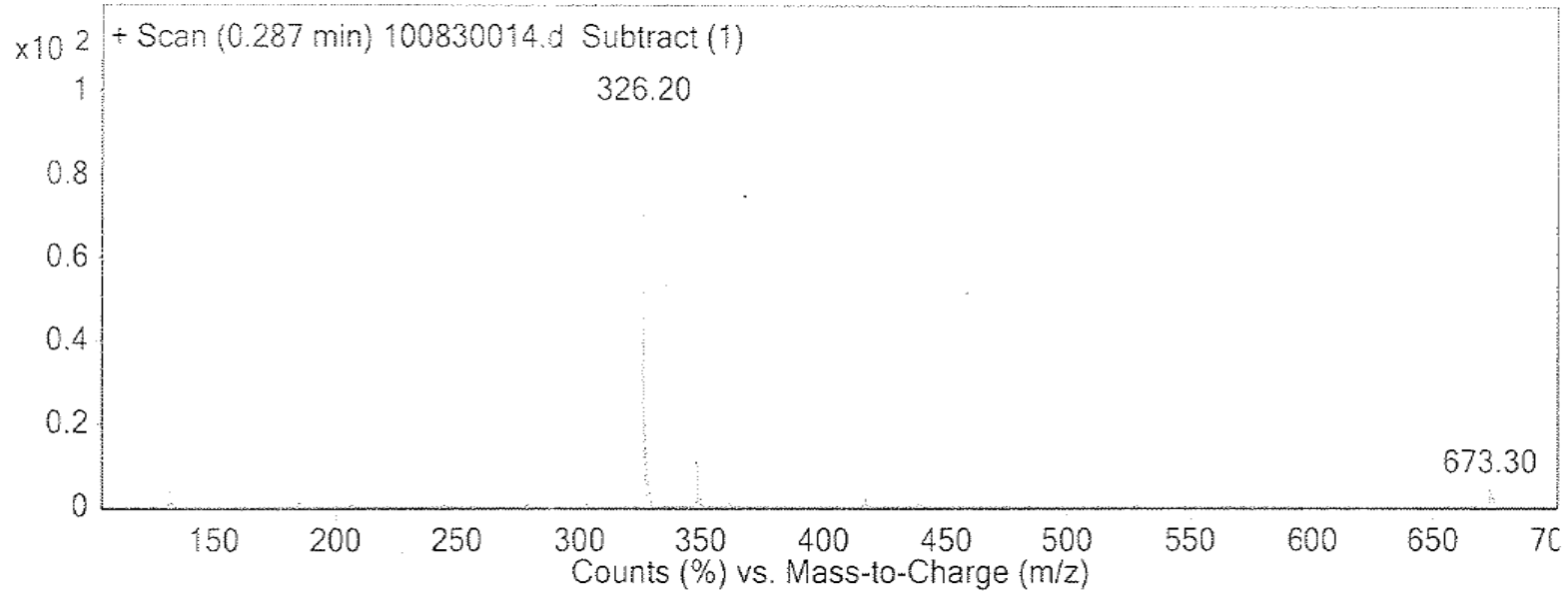
Data Filename	100830014.d	Sample Name	A472/MML/070
Sample Type	Sample	Position	Vial 14
Instrument Name	Instrument 1	User Name	
Acq Method	ESI.m	IRM Calibration Status	Success
DA Method	default.m	Comment	



31

User Spectra

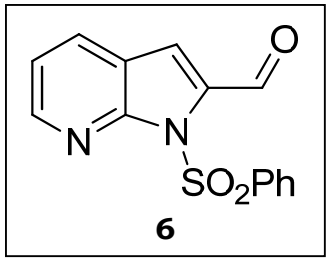
Fragmentor Voltage 135 | Collision Energy 0 | Ionization Mode Es-



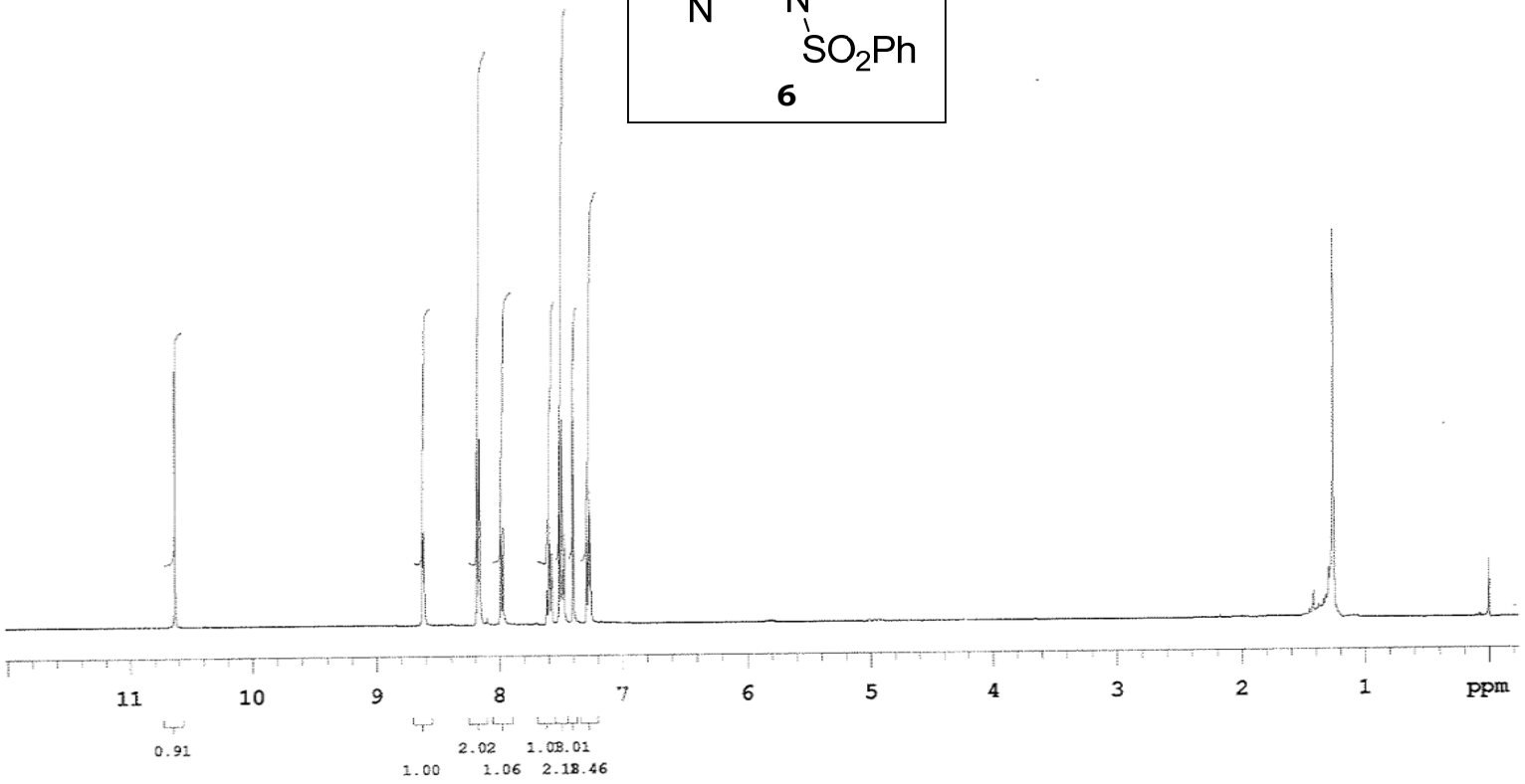
--- End Of Report ---

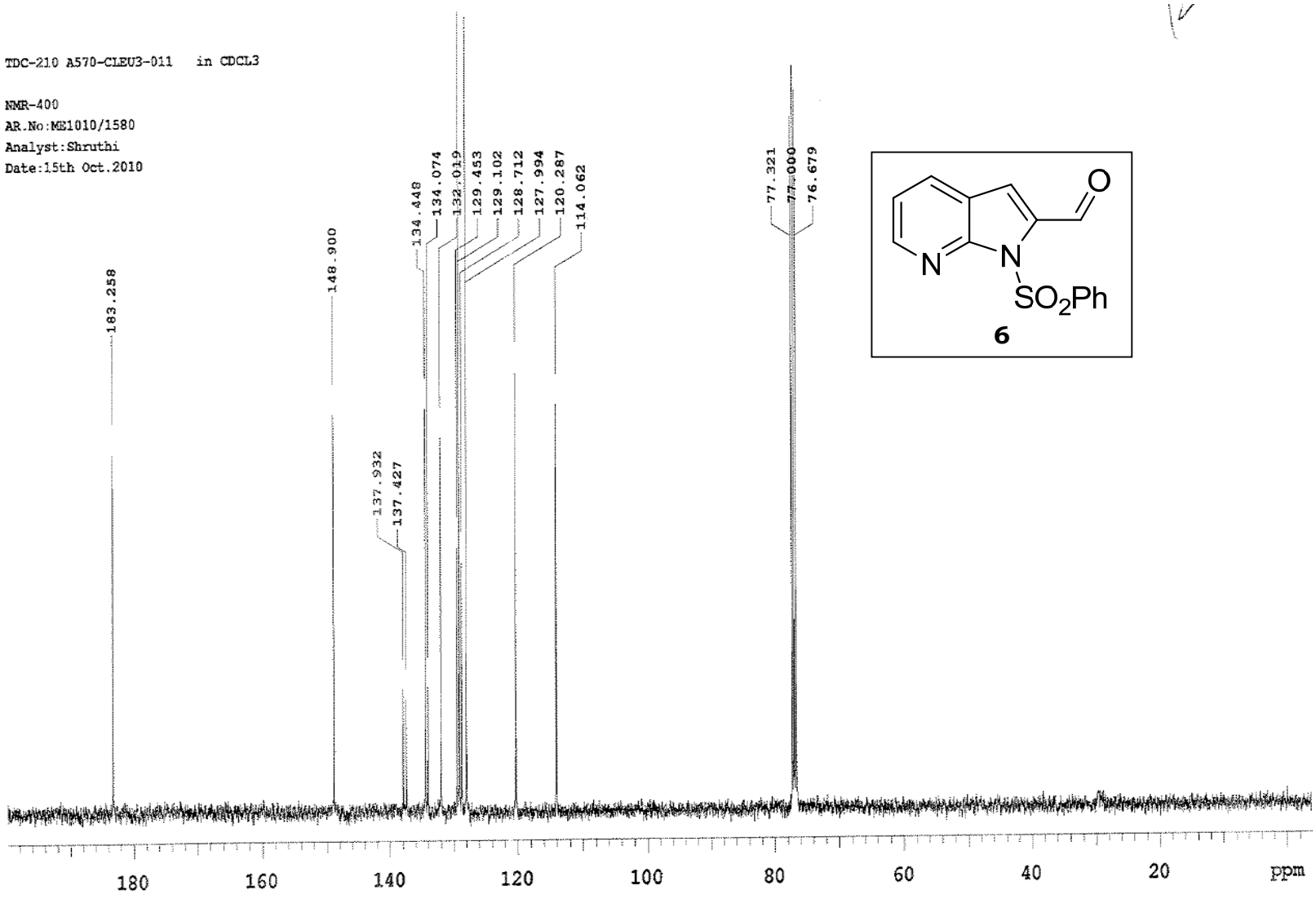
TDC-210-A570-CLEU3-011 in CDCl3

NMR-400
AR.No:ME0910/1768
Analyst:Shruthi
Date:29th Sept 2010



6

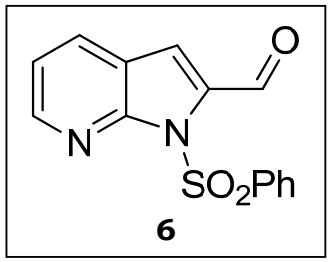



TDC-210 A570-CLEU3-011 in CDCL3
NMR-400
AR.No:ME1010/1580
Analyst:Shruthi
Date:15th Oct.2010
183.258
148.900
137.932
137.427
134.448
134.074
132.019
129.453
129.102
128.712
127.994
120.287
114.062
77.321
77.000
76.679
O
N
N
SO2Ph
6
180
160
140
120
100
80
60
40
20
ppm

CPS.MIYAPUR

Mass Analysis Report

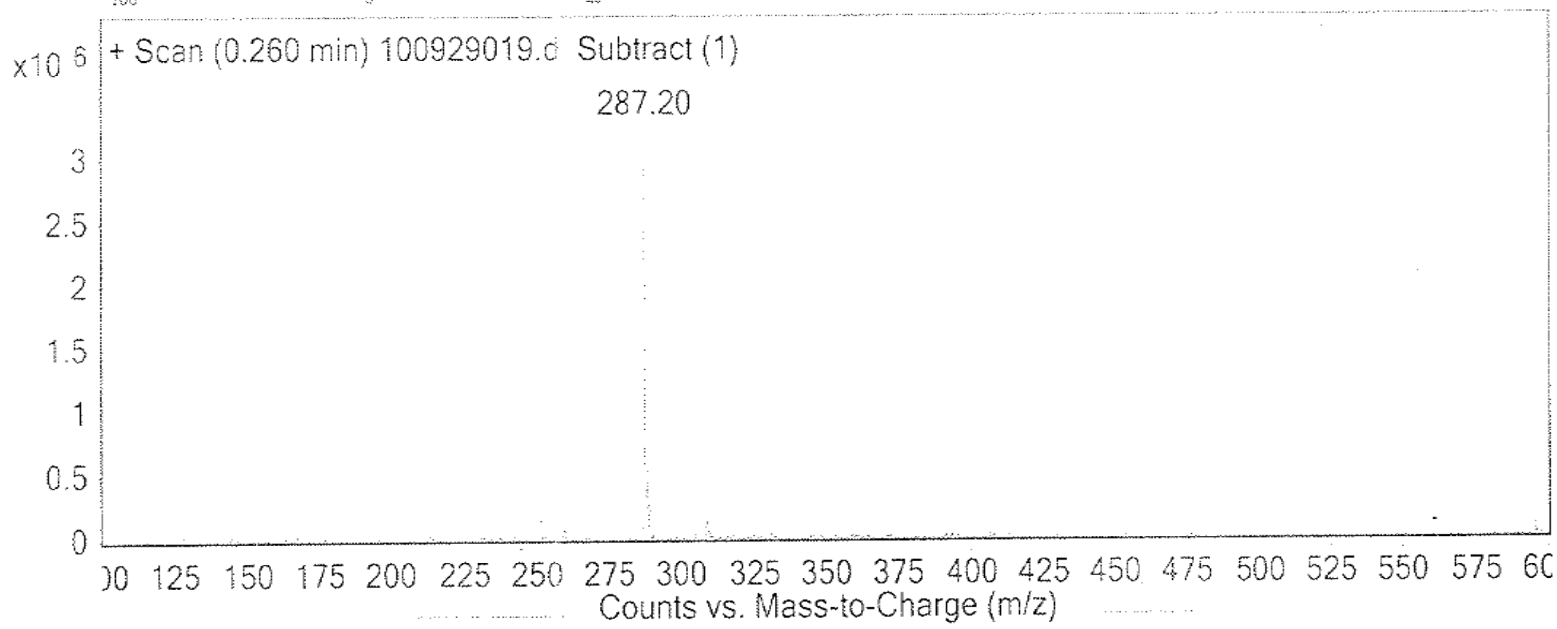
Data Filename	100929019.d	Sample Name	AS70/CLEU3/011
Sample Type	Sample	Position	Vial 19
Instrument Name	Instrument 1	User Name	
Acq Method	ESI.m	IRM Calibration Status	Success
DA Method	CDD-MRM.m	Comment	



6

User Spectra

Fragmentor Voltage 100 | Collision Energy 0 | Ionization Mode ESI



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