**Electronic Supplementary Information**

# A new three-component reaction: Green synthesis of novel isoindolo[2,1-*a*]quinazoline derivatives as potent inhibitors of TNF-α

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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 $CDCl_3$ or DMSO-$d_6$ solution by using 400 or 500 and 50 or 100 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 4 via camphor sulfonic acid catalyzed MCR:**

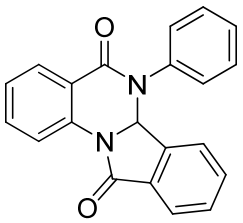
A mixture of isatoic anhydride **1 (**1.0 g, 6.13 mmol), amine **2** (6.7mmol), 2-carboxy benzaldehyde **3** (1.01 g, 6.74 mmol) and catalytic amount of anhydrous camphor sulfonic acid (0.07 g, 0.31mmol) in ethanol (10 mL) was heated to 80-85 °C with stirring for 7-16 h (initially effervescence was observed due to the generation of $CO_2$ gas). After completion of the reaction the mixture was cooled and filtered to give the desired product. The product isolated was found to be pure.

**Preparation of 4 via Montmorillonite K10 catalyzed MCR:**

A mixture of isatoic anhydride **1 (**1.0 g, 6.13 mmol), amine **2** (6.7 mmol), 2-formylbenzoic acid **3** (1.01 g, 6.74 mmol) and catalytic amount of montmorillonite K10 (0.05 g, 5%) in ethanol (10 mL) was stirred at 80-85 °C according to the time mentioned in Table 2 (initially effervescence was observed due to the generation of $CO_2$ gas). After completion of the reaction the mixture was cooled and diluted with ethanol (20 mL). The catalyst was filtered off. The filtrate was

collected and concentrated. The solid separated was filtered and dried to give the desired product.

**6-phenyl-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4a)**



White color solid, Mp = 183-185 °C

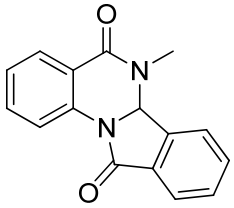
$^1$H NMR (DMSO-$d_6$, 400 MHz): 8.13 (d, J=8.3 Hz, 1H), 8.04 (dd, J=7.8, 1.6 Hz, 1H), 7.89 (d, J=8.3 Hz, 1H), 7.80-7.76 (m, 2H), 7.60-7.36 (m, 6H), 7.02 (s, 1H), 6.8 (br s, 1H), 6.10 (d, J=7.8 Hz, 1H)

$^{13}$C NMR (DMSO-$d_6$, 50 MHz): 164.6, 163.2, 139.0, 138.5, 136.8, 133.6, 132.3, 131.4, 130.2, 129.3 (2C), 128.7 (2C), 128.6 (2C), 125.0 (2C), 123.9, 120.2, 120.0, 71.5

IR (KBr): 3421, 3054, 1723, 1655, 1487, 1464 cm$^{-1}$

HRMS (ESI): calcd for $C_{21}H_{15}N_2O_2$ $(M+H)^+$ 327.1134, found 327.1130

**6-methyl-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4b):**



White color solid, Mp = 187-189 °C

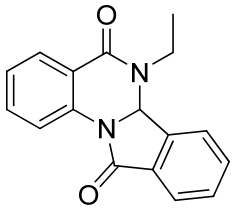
$^1$H NMR ($CDCl_3$, 400 MHz): 8.15 (dd, J=7.8, 1.0 Hz, 1H), 8.11 (dd, J=7.8, 1.0 Hz, 1H), 8.03 (dd, J=7.8, 1.0 Hz, 1H), 7.78-7.61 (m, 4H), 7.35-7.31 (m, 1H), 6.12 (s, 1H), 3.32 (s, 3H, $CH_3$)

$^{13}$C NMR ($CDCl_3$, 50 MHz):164.8, 163.8, 137.9, 136.5, 133.3, 132.6, 132.4, 130.4, 128.9, 125.5, 125.0, 124.9, 120.0 (2C), 71.1, 29.9

IR (KBr): 3417, 1720, 1652, 1605, 1474, 1466 cm$^{-1}$

HRMS (ESI): calcd for $C_{16}H_{13}N_2O_2$ $(M+H)^+$ 265.0977, found 265.0969

**6-ethyl-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4c):**



White color solid, Mp = 155-157 °C

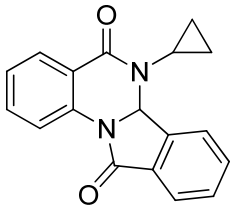
$^{1}$H NMR (DMSO-$d_6$, 400 MHz): 8.01 (d, J=7.4 Hz, 1H), 7.99-7.95 (m, 3H), 7.87-7.84 (m, 1H), 7.77 (d, J=7.4 Hz, 1H), 7.74-7.69 (m, 1H), 7.40-7.36 (m, 1H), 6.60 (s, 1H), 3.90-3.83 (m, 1H), 3.72-3.67 (m, 1H), 1.03 (t, J=7.4 Hz, 3H, $CH_3$)

$^{13}$C NMR (DMSO-$d_6$, 100 MHz): 164.3, 162.6, 138.4. 136.4, 133.2, 133.1, 131.8, 130.6, 128.3, 126.0, 125.0, 124.3, 120.3, 119.9, 69.7, 37.2, 13.4

IR (KBr): 3403, 1711, 1668, 1603, 1490, 1469 cm$^{-1}$

HRMS (ESI): calcd for $C_{17}H_{15}N_2O_2$ $(M+H)^+$ 279.1134, found 279.1135

**6-cyclopropyl-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4d):**



White color solid, Mp = 155-158 °C

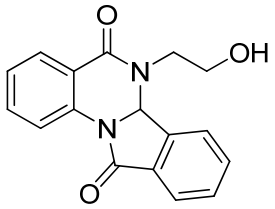
$^{1}$H NMR ($CDCl_3$, 400 MHz): 8.19-8.14 (m, 2H), 8.05 (d, J-6.9Hz, 1H), 7.92 (d, J-6.9Hz, 1H), 7.70-7.60 (m, 3H), 7.32-7.28 (m, 1H), 6.18 (s, 1H), 2.73-2.68 (m, 1H), 1.19-1.11 (m, 1H), 0.90-0.84 (m, 1H), 0.71-0.64 (m, 1H), 0.08-0.02 (m, 1H)

$^{13}$C NMR (DMSO-$d_6$, 100 MHz):164.4, 164.3, 138.8, 136.7, 133.3, 132.3, 131.6, 130.2, 128.4, 127.3, 124.6, 123.7, 120.4, 119.2, 71.2, 25.9, 11.1, 9.1

IR (KBr):3427, 1726, 1663, 1601, 1487, 1466, cm$^{-1}$

HRMS (ESI): calcd for $C_{18}H_{15}N_2O_2$ $(M+H)^+$ 291.1134, found 291.1132

**6-(2-hydroxyethyl)-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4e):**




White color solid, Mp = 215-217 °C

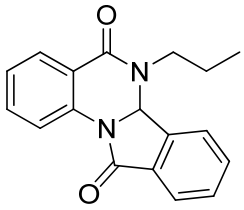
$^{1}$H NMR ($CDCl_3$, 400 MHz): 8.12-8.08 (m, 2H), 8.05-8.01 (m, 2H), 7.73-7.61 (m, 3H), 7.34-7.30 (m, 1H), 6.42 (s, 1H), 4.18-4.03 (m, 2H), 3.94-3.89 (m, 1H), 3.81-3.74 (m, 1H), 2.48 (br s, 1H, OH)

$^{13}$C NMR (DMSO-$d_6$, 100 MHz):164.3, 163.0, 138.5, 136.5, 133.2, 132.9, 132.0, 130.5, 128.3, 127.3, 125.0, 124.1, 120.3, 119.8, 71.0, 58.9, 44.9

IR (KBr): 3423, 3395, 1723, 1660,1601, 1486, 1470, 1108 $cm^{-1}$

HRMS (ESI): calcd for $C_{17}H_{15}N_2O_3$ $(M+H)^+$ 295.1083, found 295.1092

**6-propyl-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4f):**




White color solid, Mp = 127-130 °C

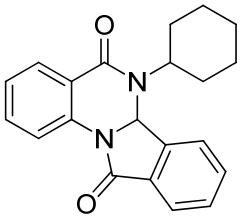
$^{1}$H NMR (DMSO-$d_6$, 500 MHz): 8.01-7.95 (m, 4H), 7.87-7.84 (m, 1H), 7.77-7.69 (m, 2H), 7.39-7.36 (m, 1H), 6.57 (s, 1H), 3.73-3.67 (m, 2H), 1.46-1.29 (m, 1H), 1.27-1.22 (m, 1H), 0.76 (t, J-7.3Hz, 3H, $CH_3$)

$^{13}$C NMR (DMSO-$d_6$, 100 MHz):164.3, 162.7, 138.5, 136.4, 133.1, 133.2, 131.8, 130.7, 128.4, 126.0, 125.0, 124.3, 120.3, 119.9, 70.0, 43.7, 21.3, 10.8

IR (KBr):3423, 2960, 1728, 1653, 1489, 1470 $cm^{-1}$

HRMS (ESI): calcd for $C_{18}H_{17}N_2O_2$ $(M+H)^+$ 293.1290, found 293.1286

**6-cyclohexyl-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4g):**



White color solid, Mp = 148-150 °C

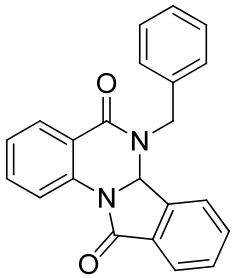
$^{1}$H NMR (DMSO-$d_6$, 500 MHz): 8.01 (d, J=7.9 Hz, 1H), 8.00-7.95 (m, 2H), 7.87-7.86 (m, 2H), 7.80-7.68 (m, 2H), 7.38-7.34 (m, 1H), 6.58 (s, 1H), 3.58-3.53 (m, 1H), 2.51-2.39 (m, 2H), 2.15-2.05 (m, 1H), 1.91-1.01 (m, 7H)

$^{13}$C NMR (DMSO-$d_6$,100 MHz): 164.0, 163.4, 138.5, 136.3, 133.2, 133.0, 132.2, 130.7, 128.2, 126.9, 124.8, 124.4, 121.4, 119.3, 71.1, 57.6, 29.9, 28.1, 26.0, 25.6, 25.0

IR (KBr): 3428, 2965, 1735, 1659, 1495, 1478 cm$^{-1}$

HRMS (ESI): calcd for $C_{21}H_{21}N_2O_2$ $(M+H)^+$ 333.1603, found 333.1602

**6-benzyl-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4h):**



White color solid, Mp = 148-150 °C

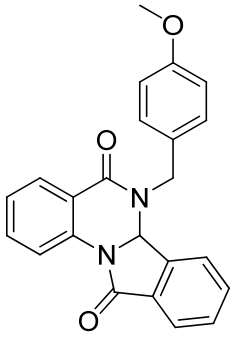
$^{1}$H NMR (DMSO-$d_6$, 400 MHz): 8.06 (d, J-7.9 Hz, 2H), 7.87-7.84 (m, 1H), 7.77-7.72 (m, 2H), 7.65-7.59 (m, 2H), 7.44-7.40 (m, 1H), 7.22-7.05 (m, 5H), 6.72 (s, 1H), 5.11-5.00 (m, 2H)

$^{13}$C NMR (DMSO-$d_6$, 100 MHz):164.3, 163.3, 138.0, 137.3, 136.7, 133.5, 132.9, 131.7, 130.5, 128.6, 128.4 (2C), 126.6, 126.0, 125.9 (2C), 125.1, 124.1, 120.0, 119.9, 70.2, 45.7

IR (KBr):3422, 3055, 1723, 1660, 1486, 1470 cm$^{-1}$

HRMS (ESI): calcd for $C_{22}H_{17}N_2O_2$ $(M+H)^+$ 341.1290, found 341.1282

**6-(4-methoxybenzyl)-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4i):**



White color solid, Mp = 137-139 °C

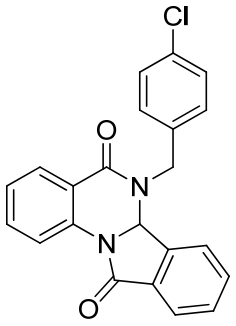
$^{1}$H NMR (DMSO-$d_6$, 400 MHz): 8.06-8.04 (m, 2H), 7.88-7.86 (m, 1H), 7.77-7.62 (m, 4H), 7.43-7.39 (m, 1H), 6.95 (d, J-8.8 Hz, 2H), 6.77 (d, J-8.8 Hz, 2H), 6.68 (s, 1H), 5.04-4.89 (m, 2H), 3.66 (s, 3H, $CH_3$)

$^{13}$C NMR (DMSO-$d_6$, 100 MHz):164.3, 163.2, 157.9, 138.1, 136.6, 133.4, 132.9, 131.7, 130.5, 129.0, 128.6, 127.3 (2C), 126.1, 125.1, 124.1, 120.1, 119.8, 113.8 (2C), 70.2, 54.9, 45.1

IR (KBr):3428, 2833, 1724, 1660, 1488, 1466 cm$^{-1}$

HRMS (ESI): calcd for $C_{23}H_{19}N_2O_3$ $(M+H)^+$ 371.1396, found 371.1398

**6-(4-chlorobenzyl)-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4j):**



White color solid, Mp = 178-181 °C

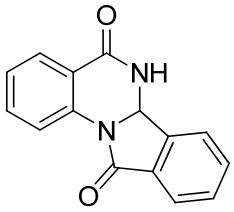
$^{1}$H NMR (DMSO-$d_6$, 400 MHz): 8.06-8.04 (m, 2H), 7.86-7.84 (m, 1H), 7.78-7.73 (m, 2H), 7.65-7.61 (m, 2H), 7.44-7.40 (m, 1H), 7.24 (d, J-8.8 Hz, 2H), 7.07 (d, J-8.8 Hz, 2H), 6.71 (s, 1H), 5.12-4.99 (m, 2H)

$^{13}$C NMR (DMSO-$d_6$, 100 MHz): 164.3, 163.4, 138.0, 136.7, 136.6, 133.6, 133.0, 131.7, 131.1, 130.6, 128.7, 128.3 (2C), 127.9 (2C), 126.1, 125.2, 124.1, 120.0 (2C), 70.2, 45.1

IR (KBr): 3429, 2932, 1726, 1664, 1490, 1470 cm$^{-1}$

HRMS (ESI): calcd for $C_{22}H_{16}ClN_2O_2$ $(M+H)^+$ 375.0900, found 375.0902

**6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4k)**




White color solid, Mp = 240-242 °C

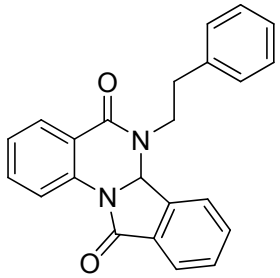
$^1$H NMR (DMSO-$d_6$, 400 MHz): 9.29 (s, 1H, NH), 8.13 (d, J=7.7 Hz, 1H), 8.05 (dd, J=7.9 Hz, 1.2 Hz, 1H), 7.90 (d, J=7.7 Hz, 2H), 7.75-7.61 (m, 3H), 7.33-7.29 (m, 1H), 6.33 (s, 1H)

$^{13}$C NMR (DMSO-$d_6$, 100 MHz): 164.4, 163.6, 140.7, 137.1, 133.5, 133.2, 131.1, 130.1, 128.2, 124.7, 124.1, 123.8, 120.0, 119.5, 67.0

IR (KBr):3058, 2930, 1731, 1676, 1495, 1475 cm$^{-1}$

HRMS (ESI): calcd for $C_{15}H_{11}N_2O_2$ $(M+H)^+$ 251.0821, found 251.0830

**6-phenethyl-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4l):**




White color solid, Mp = 123-125 °C

$^1$H NMR (DMSO-$d_6$, 400 MHz): 8.05 (d, J=7.4 Hz, 1H), 8.02-7.98 (m, 2H), 7.92 (d, J=7.4 Hz, 1H), 7.90-7.86 (m, 1H), 7.77 (d, J=7.4 Hz, 1H), 7.74-7.69 (m, 1H), 7.41-7.37 (m, 1H), 7.24-7.14 (m, 3H), 7.08-7.06 (m, 2H), 6.57 (s, 1H), 4.02-3.88 (m, 2H), 2.80-2.73 (m, 1H), 2.50-2.42 (m, 1H)

$^{13}$C NMR (DMSO-$d_6$, 100 MHz):164.3, 162.8, 138.3, 138.2, 136.5, 133.3, 133.2, 132.0, 130.7, 128.5, 128.4, 128.3, 128.2, 127.4, 126.3, 125.1, 124.9, 124.4, 120.3, 120.0, 70.0, 43.8, 34.1

IR (KBr): 3060, 2932, 1734, 1680, 1497, 1479 cm$^{-1}$

HRMS (ESI): calcd for $C_{23}H_{19}N_2O_2$ $(M+H)^+$ 355.1447, found 355.1438

**Single crystal X-ray data for compound 4j**

Single crystals suitable for X-ray diffraction of **4j** were grown from methanol. The crystals were carefully chosen using a stereo zoom microscope supported by a rotatable polarizing stage. The data was collected at room temperature on Bruker's KAPPA APEX II CCD Duo with graphite monochromated Mo-K$\alpha$ radiation (0.71073 Å). The crystals were glued to a thin glass fibre using FOMBLIN immersion oil and mounted on the diffractometer. The intensity data were processed using Broker's suite of data processing programs (SAINT), and absorption corrections were applied using SADABS.[1] The crystal structure was solved by direct methods using SHELXS-97 and the data was refined by full matrix least-squares refinement on $F^2$ with anisotropic displacement parameters for non-H atoms, using SHELXL-97.[2]

Crystal data of **4j:** Molecular formula = $C_{22}H_{15}ClN_2O_2$, Formula weight = 374.1, Crystal system = Monoclinic, space group = $P2_1/c$, $a$ = 11.6223 (6) Å, $b$ = 7.8255 (4)Å, $c$ = 19.9457 (10)Å, $V$ = 1772.91 (16)Å$^3$, $T$ = 296 K, $Z$ = 4, $D_c$ = 1.404 Mg m$^{-3}$, μ(Mo-Kα) = 0.71073 mm$^{-1}$, 27323 reflections measured, 3833 independent reflections, 3311 observed reflections [I > 2.0 σ (I)], $R_1$_obs = 0.047, Goodness of fit =1.030. Crystallographic data (excluding structure factors) for **4j** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 807140.

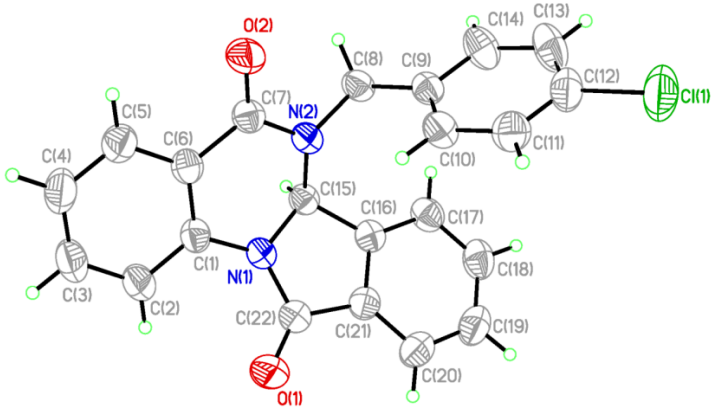



**Figure 1**. X-ray crystal structure of **4j** (ORTEP diagram). Thermal ellipsoids are drawn at 50% probability level.

**Single crystal X-ray data for 6-(3-chlorophenyl)-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione**

Single crystals suitable for X-ray diffraction of 6-(3-chlorophenyl)-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione [prepared by via the reaction of isatoic anhydride (1.0 g, 6.13 mmol), 3-chloroaniline (6.7 mmol), 2-formylbenzoic acid (1.01 g, 6.74 mmol) in the presence of catalytic amount of montmorillonite K10 (0.05 g, 5%) in ethanol (10 mL) at 80-85 °C for 15h] were grown from methanol and the X-ray analysis data were generated following the procedure as described above.

Crystal data of 6-(3-chlorophenyl)-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione**:** Molecular formula = $C_{22}H_{17}ClN_2O_3$, Formula weight =392.83, Crystal system = Orthorhombic, space group = *Pbca*, $a$ = 21.631 (5) Å, $b$ =7.564 (12)Å, $c$ = 22.783 (4)Å, $V$ = 3728.1 (12)Å$^3$, $T$ = 296 K, $Z$ = 8, $D_c$ = 1.389 Mg m$^{-3}$, μ(Mo-Kα) = 0.71073 mm$^{-1}$,8092 reflections measured, 1634 independent reflections, 1098 observed reflections [I > 2.0 σ (I)], $R_1$_obs = 0.079, Goodness of fit =1.124.

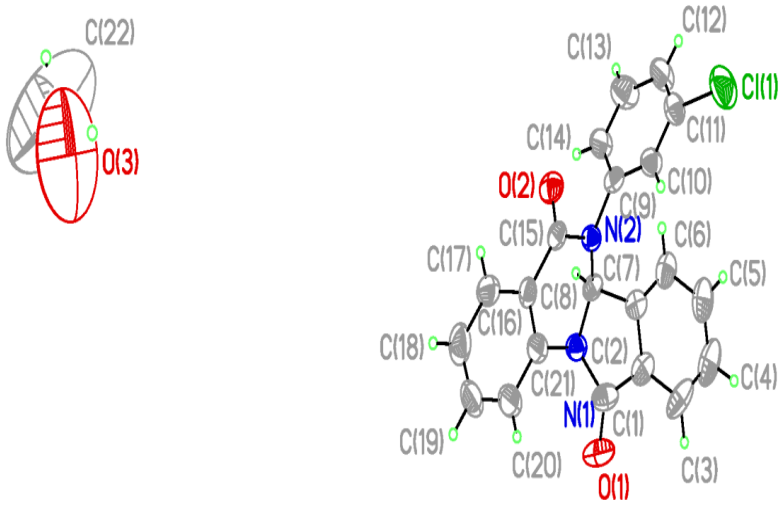



**Figure 2**. X-ray crystal structure of 6-(3-chlorophenyl)-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (ORTEP diagram). Thermal ellipsoids are drawn at 50% probability level.

**Reference**

1. Bruker SADABS V2008-1, Bruker AXS.: Madison, WI, USA, **2008**.

2. Sheldrick, G. M.; SHELX-97, Program for Crystal Structure Determination, University of Göttingen, **1997**.

## Pharmacology

### Materials and Methods

### Cells and reagents

RAW 264.7 cells (murine macrophage cell line) were obtained from ATCC (Washington D.C., USA) and routinely maintained in RPMI 1640 medium with 10% fetal bovine serum (Invitrogen Inc., San Diego, CA, USA). Lipopolysaccharide (LPS) was from *Escherichia coli* strain 0127:B8 obtained from Sigma (St. Louis, MO, USA). Mouse TNF-α ELISA kit was procured from R&D Systems (Minneapolis, MN, USA).

### TNF-α production assay

The production of TNF-α is measured following a procedure described previously after few modifications.[1] Briefly, RAW 264.7 cells were pre-incubated either with DMSO (vehicle control) or compound for 30 minutes and then stimulated with 1 μg/ml of LPS overnight. Preliminary screening of the compounds was performed at 30 μM and dose response studies were carried out at eight different concentrations (30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01 μM). Post-stimulation, cell supernatants were harvested, centrifuged to clear cell debris and the amount of TNF-α in the supernatants was measured using mouse TNF-α DuoSet ELISA kit from R&D Systems according to manufacturer's recommendations. The percentage of inhibition was calculated using the following formula:

$$\% \text{ inhibition} = 100 - \left| \frac{(\text{LPS stimulated}_{\text{compound}} - \text{unstimulated})}{(\text{LPS stimulated}_{\text{DMSO}} - \text{unstimulated})} \text{ X } 100 \right|$$

The $IC_{50}$ values were determined by a nonlinear regression analysis from dose response curve using Graphpad Prism software (San Diego, U.S.A). IC50 values are expressed as mean ± SD.

**Reference:**

1. K. V. Parsa, L. P. Ganesan, M. V. Rajaram, M. A. Gavrilin, A. Balagopal, N. P. Mohapatra, M. D. Wewers, L. S. Schlesinger, J. S. Gunn and S. Tridandapani, *PLoS Pathog.* 2006, 2:e71.

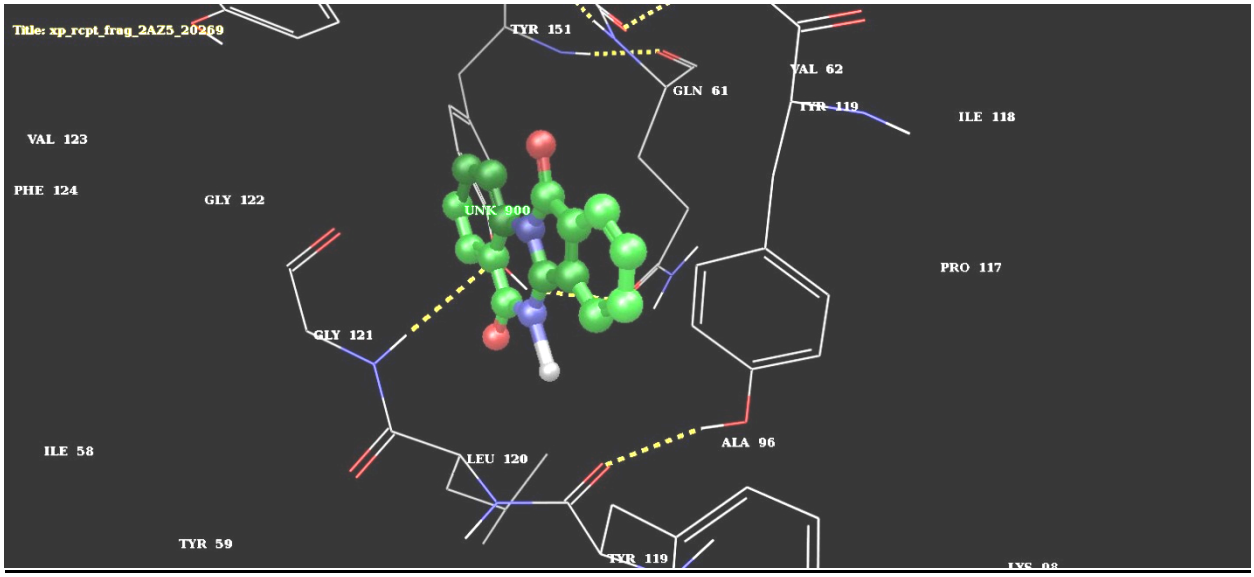
**Docking studies**

**Docking Procedure:** In the present study we have performed the energy minimization and conformational search with the MACROMODEL application in the Schrodinger package with MASTERO 9.1 version interface. The ligand molecules were energy minimized for flexibility followed by the conformational search. 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 0.05kJ/mol. The conformational search was based on Montecarlo multiple minimum torsional sampling. The ligand molecules were then finally prepared with LIGPREP application.

The protein 2AZ5 (TNF-α) crystal structure was retrieved from the protein data bank and was refined with the PROTEIN PREPERATION WIZARD application in which the hydrogen atoms were added and missing side chains and loops were filled with PRIME application. The water molecules were observed within the 5A distance and other water molecules were deleted beyond 5A from the het(hetroatom) groups. Finally the protein was then optimized and minimized with impref using OPLS_2005 force filed.

GRID based Docking was carried out in the present study.

Docking of compound **4k** with TNF-α protein:




GLIDE SCORE = -8.57 Kcal/mol

Hydrophobic ensure reward = - 0.55 Kcal/mol

Total protein-ligand Van der Waals energy = - 4.50 K.cal/mol

## Copies of spectra

# A new three-component reaction: "Green" synthesis of novel isoindolo[2,1-*a*]quinazoline derivatives as potent inhibitors of TNF-α

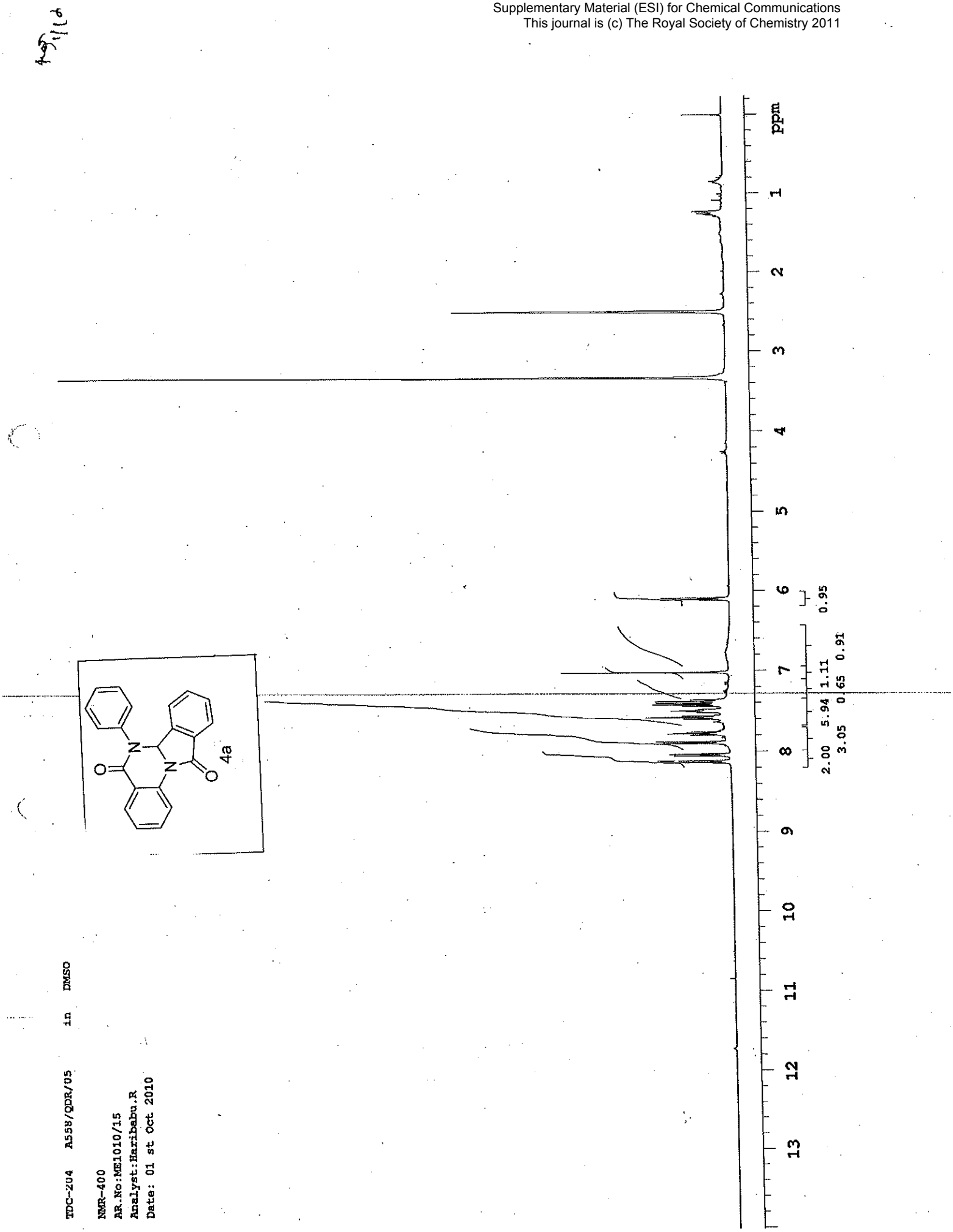
K. Siva Kumar,[a,b] P. Mahesh Kumar,[a] K. Anil Kumar, [a] M. Sreenivasulu,[a] Ahamed A. Jafar,[b] D. Rambabu,[c] G. Rama krishna,[d] C. Malla Reddy,[d] Ravikumar Kapavarapu,[c] K. Shivakumar,[c] K. Krishna Priya,[c] Kishore V. L. Parsa,[c] Manojit Pal[c,]*

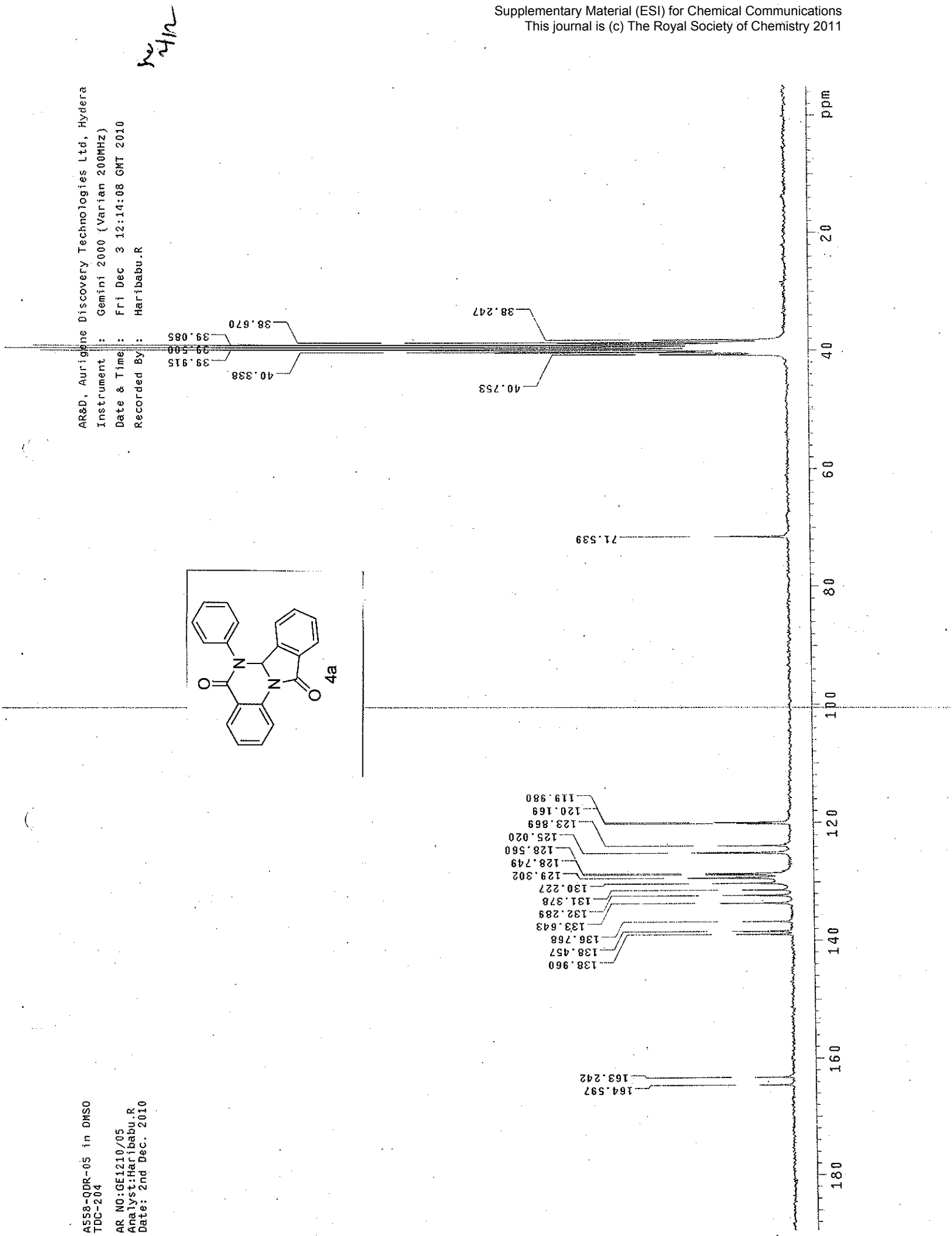
[a]*Custom Pharmaceutical Services, Dr. Reddy's Laboratories Limited, Bollaram Road Miyapur, Hyderabad 500 049, India*

[b]*PG and Research Department of Chemistry, Jamal Mohamed College, Tiruchirappalli 620020, Tamil Nadu, India*

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

[d]*Department of Chemical Sciences, Indian Institute of Science Education and Research, Kolkata, West Bengal, 741252, India.*


TDC-204 A538/QDR/05 in DMSO
NMR-400
AR.No:ME1010/15
Analyst:Haribabu.R
Date: 01 st Oct 2010
4a
ppm
0.95
1.11
0.91
0.65
5.94
2.00
3.05


AR&D, Aurigene Discovery Technologies Ltd, Hydera
Instrument : Gemini 2000 (Varian 200MHz)
Date & Time : Fri Dec 3 12:14:08 GMT 2010
Recorded By : Haribabu.R
A558-QDR-05 in DMSO
TDC-204
AR NO:GE1210/05
Analyst:Haribabu.R
Date: 2nd Dec. 2010
38.670
39.085
39.500
39.915
40.338
38.247
40.753
71.539
119.980
120.169
123.869
125.020
128.560
128.749
129.302
130.227
131.378
132.289
133.643
136.768
138.457
138.960
163.242
164.597
4a
ppm
20
40
60
80
100
120
140
160
180

## Elemental Composition Report

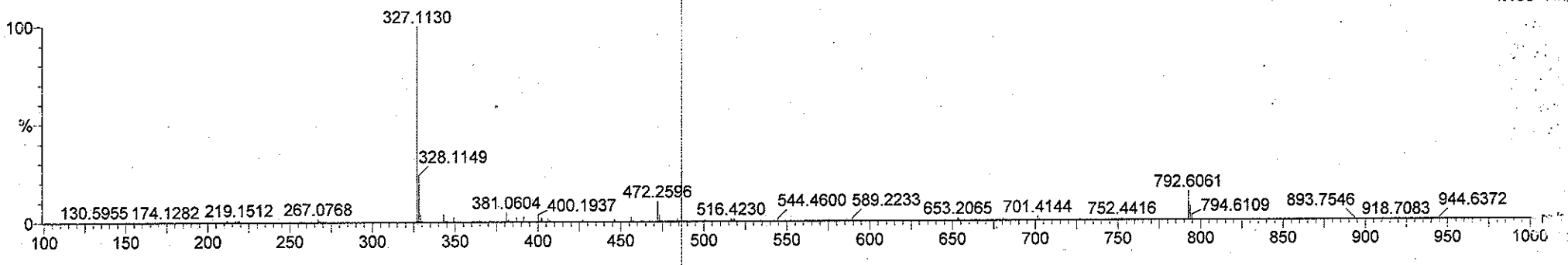
Page

### Single Mass Analysis

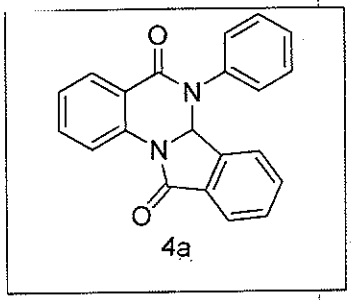
Tolerance = 5.0 PPM / DBE: min = -1.0, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
109 formula(e) evaluated with 1 results within limits (up to 4 best isotopic matches for each mass)
Elements Used:
C: 0-45 H: 0-55 N: 0-2 O: 0-8
A558-QDR-05
UT1110_66 26 (0.487) Cm (26:35-81:93)

1: TOF MS E
4.13e+0




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.0 | | |
| Maximum: | | 5.0 | 5.0 | 80.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 327.1130 | 327.1134 | -0.4 | -1.2 | 15.5 | 1.5 | C21 H15 N2 O2 |




4a

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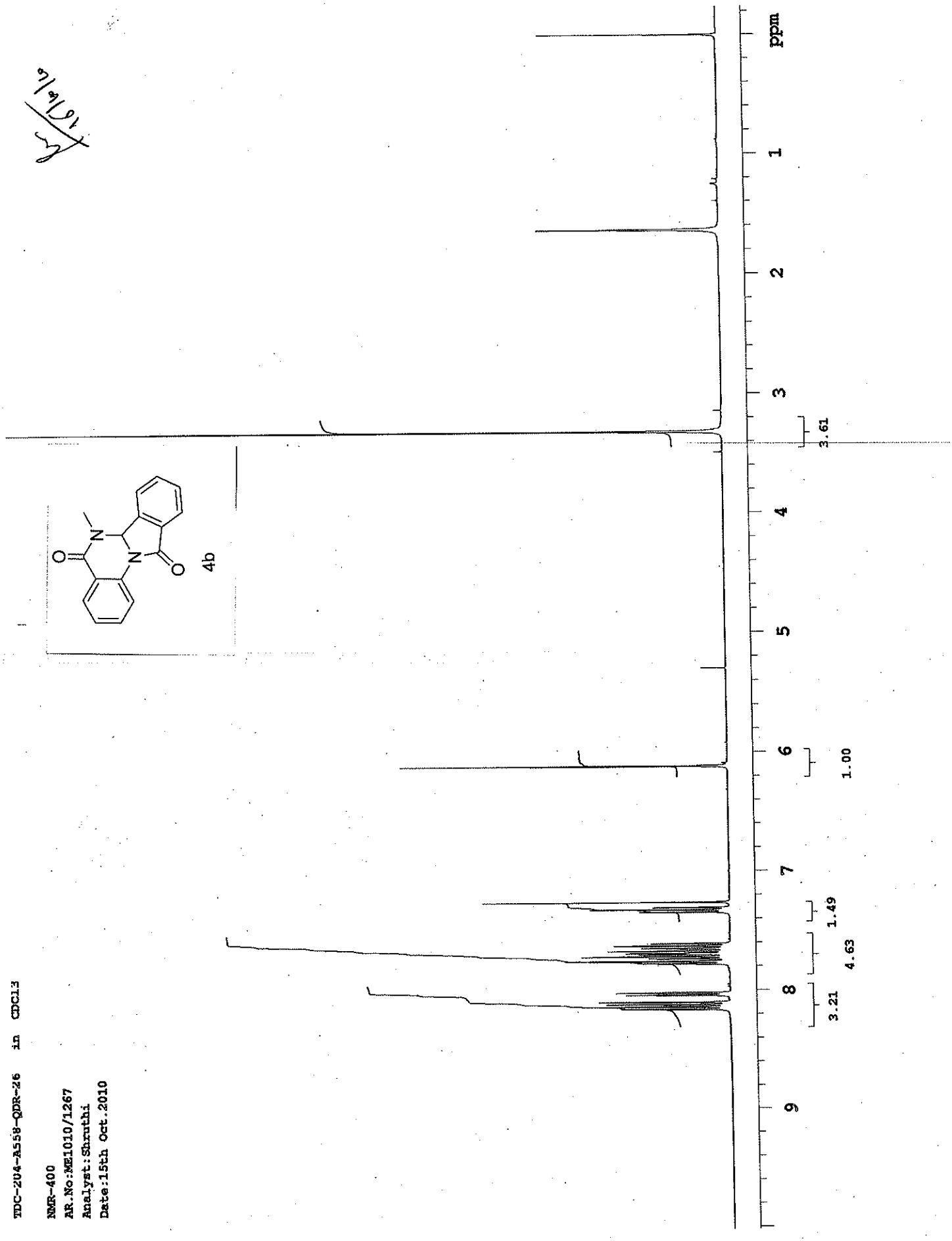
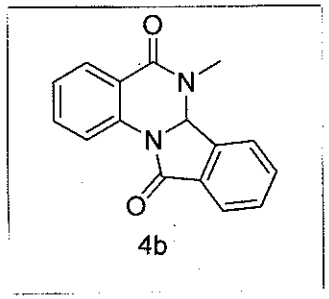

TDC-2U4-A558-QDR-26 in CDCl3
NMR-400
AR.No:ME1010/1267
Analyst:Shruthi
Date:15th Oct.2010
4b
ppm
1
2
3
4
5
6
7
8
9
3.61
1.00
1.49
4.63
3.21

A558/QDR/26 in CDCl3
TDC-204

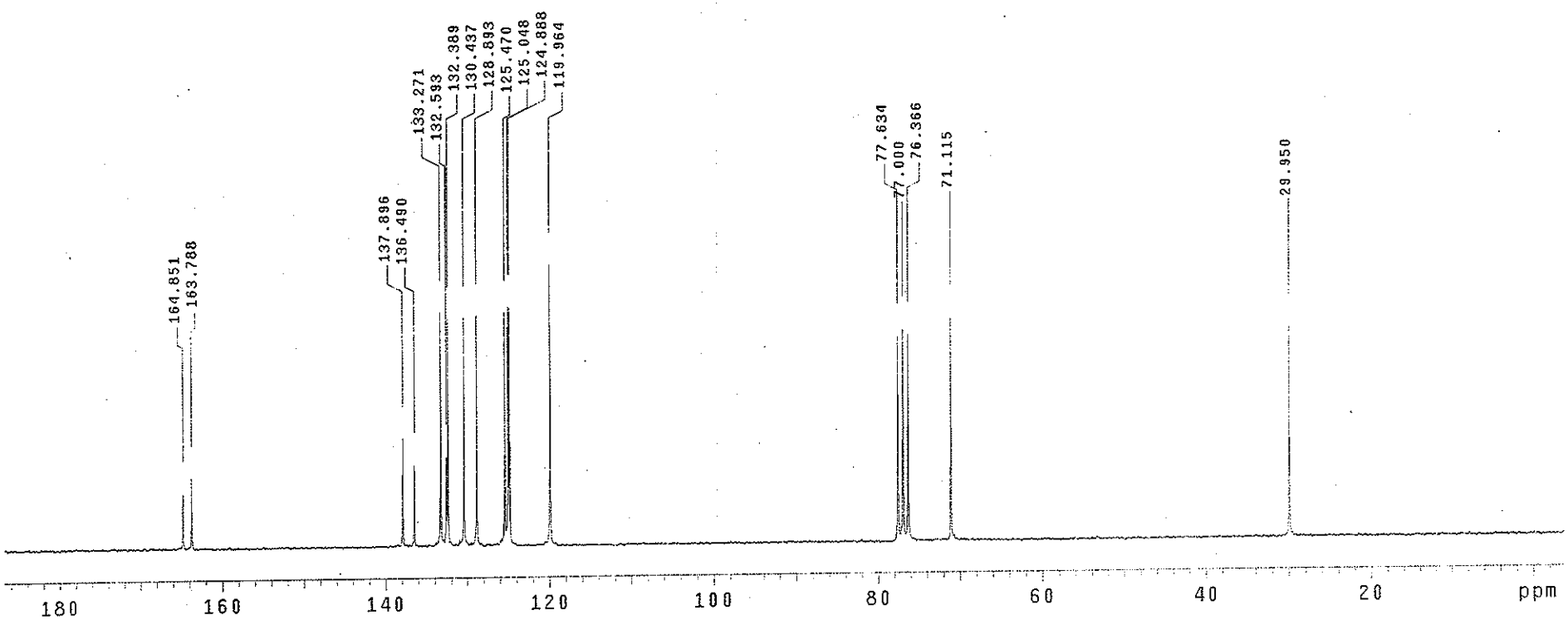
AR NO:GE1010/54
Analyst:Haribabu.R
Date: 20 th Oct 2010

AR&D, Aurigene Discovery Technologies Ltd, Hydera
Instrument : Gemini 2000 (Varian 200MHz)
Date & Time : Wed Oct 20 20:17:15 GMT 2010
Recorded By : Haribabu.R

20/10



4b

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## Elemental Composition Report

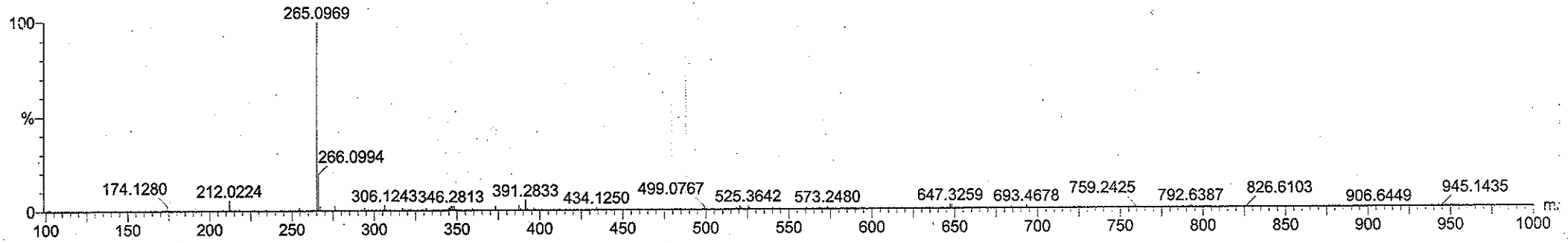
29/10/10

### Single Mass Analysis

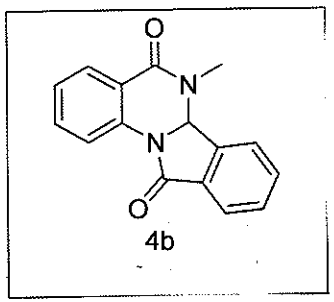
Tolerance = 5.0 PPM / DBE: min = -1.0, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
62 formula(e) evaluated with 1 results within limits (up to 4 closest results for each mass)
Elements Used:
C: 0-45 H: 0-70 N: 0-3 O: 0-3
A558\QDR\26
UT1010_197 22 (0.413) Cm (21:24-85:94)

1: TOF MS ES
1.05e+0




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.0 | | |
| Maximum: | | 5.0 | 5.0 | 80.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 265.0969 | 265.0977 | -0.8 | -3.0 | 11.5 | 0.4 | C16 H13 N2 O2 |




4b

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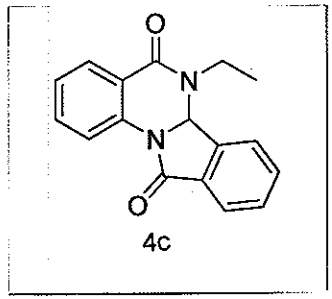
TDC-204 A558/QDR/32 in DMSO

NMR-400
AR.No:ME1110/901
Analyst:Haribabu.R
Date: 15 th Nov 2010

Sample Name:
901-TDC-204_A558_QDR_32
Data Collected on:
mercuryj-mercury400
Archive directory:
/home/sms50/routine/Nov2010/d_15
Sample directory:
901-TDC-204_A558_QDR_32_20101115_01
FidFile: 901-TDC-204_A558_QDR_32_20101115_01

Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Nov 15 2010



4c

VARIAN




Plotname: 901-TDC-204_A558_QDR_32_20101115_01_plot01

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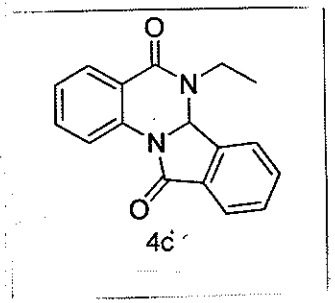
TDC-204 A558-QDR-32 in DMSO

NMR-400
AR.No:ME1110/1252
Analyst:Haribabu.R
Date: 17 th Nov 2010

Sample Name:
1252-TDC-204_A558-QDR-32
Data Collected on:
mercuryj-mercury400
Archive directory:
/home/sms50/routine/Nov2010/d_17
Sample directory:
1252-TDC-204_A558-QDR-32_20101118_01
FidFile: 1252-TDC-204_A558-QDR-32_20101118_01

Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Nov 18 2010



4c

VARIAN




Plotname: 1252-TDC-204_A558-QDR-32_20101118_01_plot01

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## Elemental Composition Report

Page

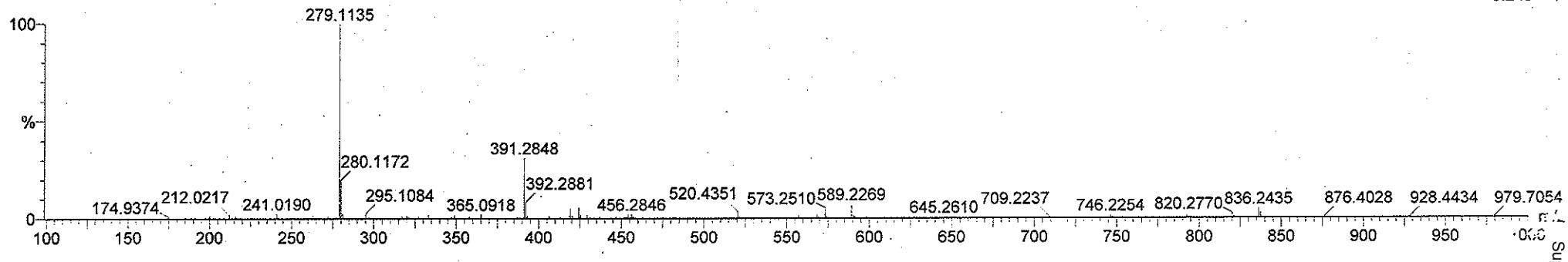
### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.0, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

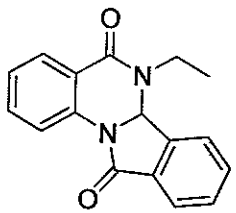
Monoisotopic Mass, Even Electron Ions
159 formula(e) evaluated with 1 results within limits (up to 4 best isotopic matches for each mass)
Elements Used:
C: 0-45 H: 0-55 N: 0-4 O: 0-4 Br: 0-1

A558-QDR-32
UT1110_74 17 (0.326) Cm (17:24-81:90)

1: TOF MS




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.0 | | |
| Maximum: | | 5.0 | 5.0 | 80.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 279.1135 | 279.1134 | 0.1 | 0.4 | 11.5 | 0.1 | C17 H15 N2 O2 |




4c

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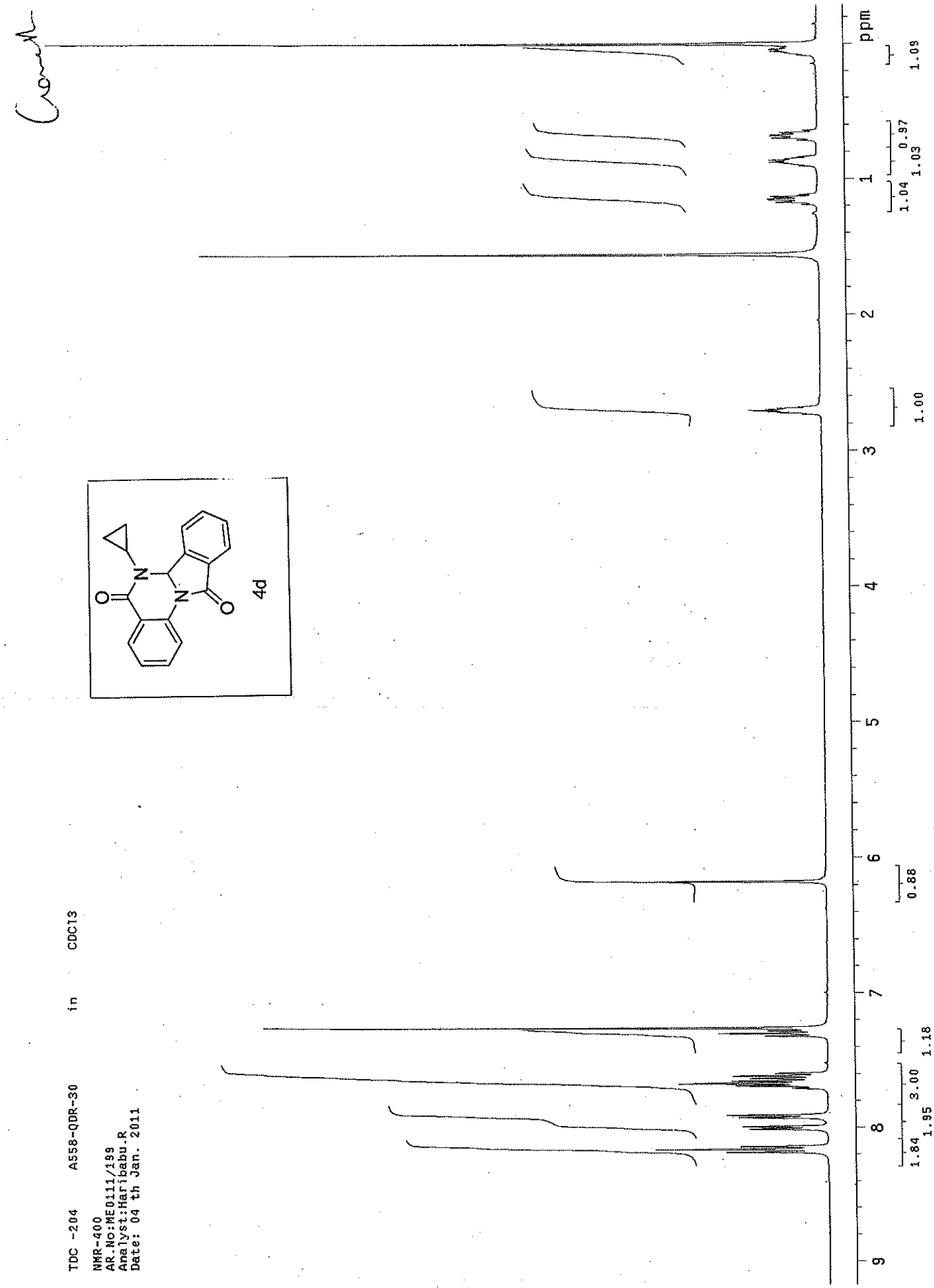
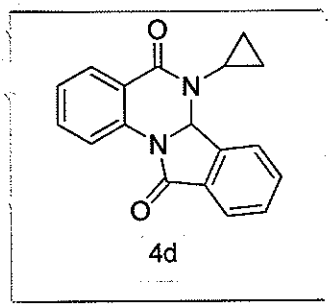

TDC -204 A558-QDR-30 in CDCl3
NMR-400
AR.No:ME0111/189
Analyst:Haribabu.R
Date: 04 th Jan. 2011
4d
ppm
1.09
0.97
1.03
1.04
1.00
0.88
1.18
3.00
1.84
1.95

TDC-204 A558-QDR-30 in DMSO

NMR-400
AR.No:ME1110/1251
Analyst:Haribabu.R
Date: 17 th Nov 2010

Sample Name:
1251-TDC-204_A558-QDR-30
Data Collected on:
mercuryj-mercury400
Archive directory:
/home/sms50/routine/Nov2010/d_17
Sample directory:
1251-TDC-204_A558-QDR-30_20101117_01
FidFile: 1251-TDC-204_A558-QDR-30_20101118_01

Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Nov 17 2010



4d

VARIAN




Plotname: 1251-TDC-204_A558-QDR-30_20101118_01_plot01

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## Elemental Composition Report



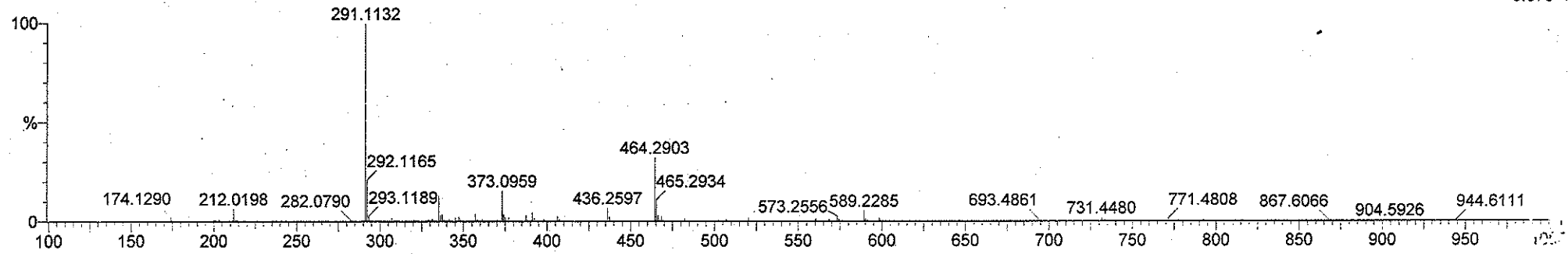
### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.0, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

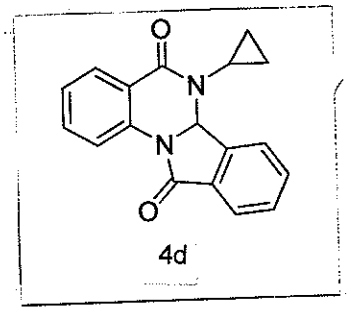
Monoisotopic Mass, Even Electron Ions
168 formula(e) evaluated with 1 results within limits (up to 4 best isotopic matches for each mass)
Elements Used:
C: 0-45 H: 0-55 N: 0-4 O: 0-4 Br: 0-1

A558-QDR-30
UT1110_72 20 (0.367) Cm (20:26-80:99)

1: TOF MS E
6.67e+003




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.0 | | |
| Maximum: | | 5.0 | 5.0 | 80.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 291.1132 | 291.1134 | -0.2 | -0.7 | 12.5 | 0.1 | C18 H15 N2 O2 |




4d

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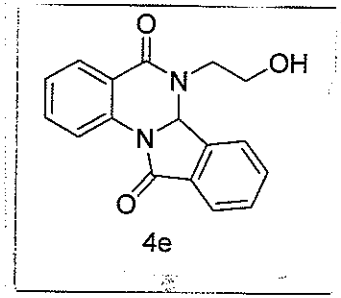
TDC-204 A558/QDR/28 in CDCl3

NMR-400
AR.No:ME1010/1409
Analyst:Haribabu.R
Data: 18 th Oct 2010

18/10




4e

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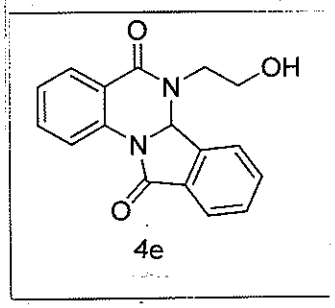
TDC-204 A558/QDR/28 in DMSO

NMR-400
AR.No:ME1010/1709
Analyst:Shruthi
Date: 20 th Oct 2010



4e

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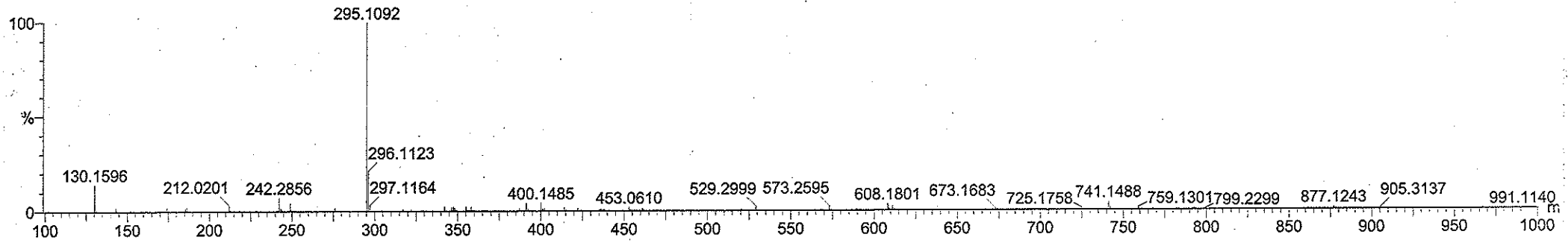
29/10/10

## Single Mass Analysis

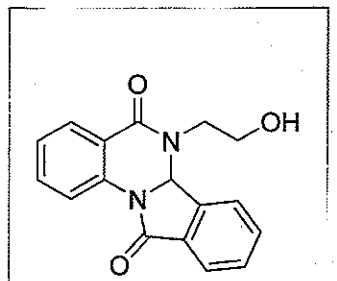
Tolerance = 5.0 PPM / DBE: min = -1.0, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
66 formula(e) evaluated with 1 results within limits (up to 4 closest results for each mass)
Elements Used:
C: 0-45 H: 0-70 N: 0-3 O: 0-3
A558\QDR\28
UT1010_194 16 (0.293) Cm (16:22-77:88)

1: TOF MS ES
6.06e+0




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.0 | | |
| Maximum: | | 5.0 | 5.0 | 80.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 295.1092 | 295.1083 | 0.9 | 3.0 | 11.5 | 2.1 | C17 H15 N2 O3 |




4e

Supplementary Material (ESI) for Chemical Communications
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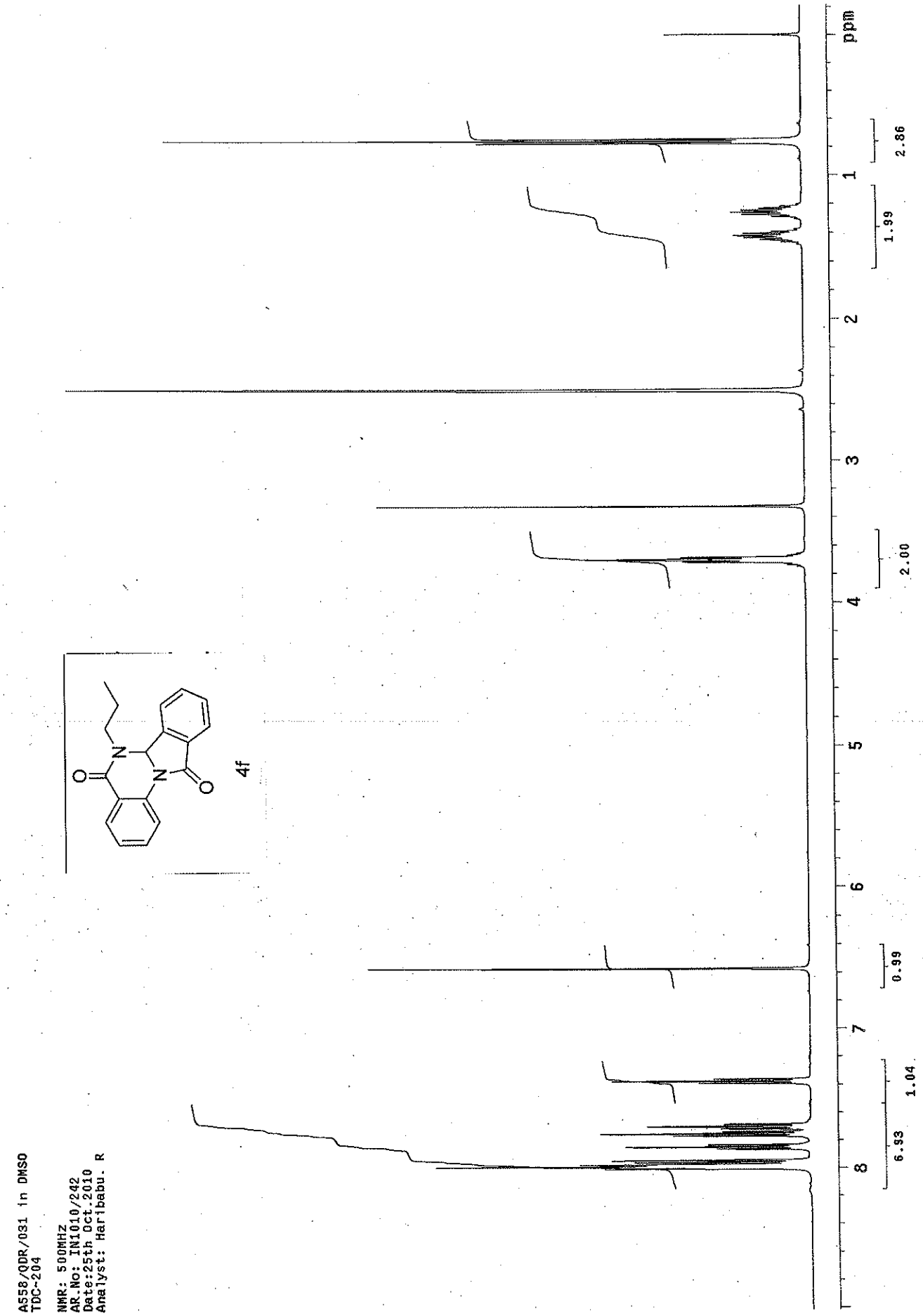
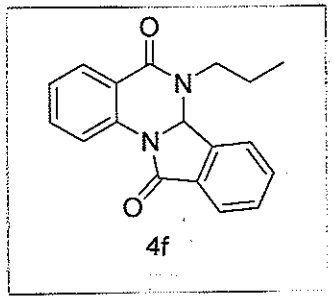

A558/QDR/031 in DMSO
TDC-204
NMR: 500MHz
AR.No: IN1010/242
Date:25th Oct.2010
Analyst: Haribabu. R
4f
ppm
2.86
1.99
2.00
0.99
1.04
6.93

TDC-204 A558-QDR-31 in DMSO

NMR-400
AR.No:ME1110/1656
Analyst:Haribabu.R
Date: 22 th Nov 2010

Sample Name:
1656-TDC-204_A558-QDR-31
Data Collected on:
mercuryj-mercury400
Archive directory:
/home/sms50/routine/Nov2010/d_22
Sample directory:
1656-TDC-204_A558-QDR-31_20101122_01
FidFile: 1656-TDC-204_A558-QDR-31_20101123_01

Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Nov 22 2010



4f

VARIAN




Plotname: 1656-TDC-204_A558-QDR-31_20101123_01_plot01

Supplementary Material (ESI) for Chemical Communications
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## Elemental Composition Report



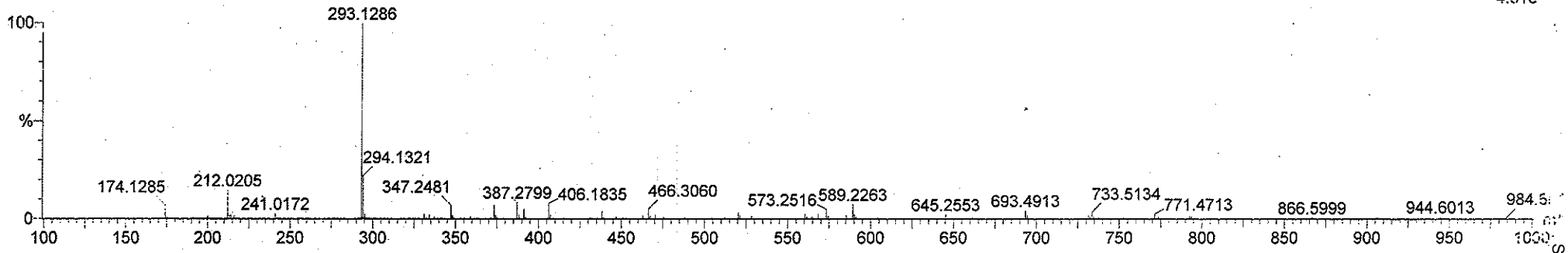
### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.0, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

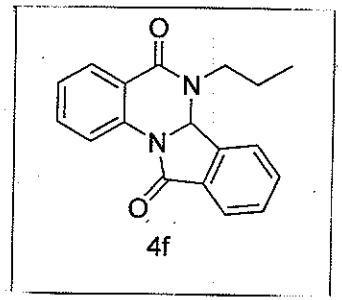
Monoisotopic Mass, Even Electron Ions
166 formula(e) evaluated with 1 results within limits (up to 4 best isotopic matches for each mass)
Elements Used:
C: 0-45 H: 0-55 N: 0-4 O: 0-4 Br: 0-1

A558-QDR-31
UT1110_73 20 (0.367) Cm (20:27-73:81)

1: TOF MS ES+
4.51e




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.0 | | |
| Maximum: | | 5.0 | 5.0 | 80.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 293.1286 | 293.1290 | -0.4 | -1.4 | 11.5 | 0.8 | C18 H17 N2 O2 |




4f

Supplementary Material (ESI) for Chemical Communications
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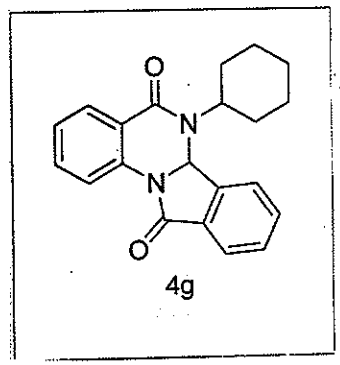
A558/QDR/18 in DMSO

TDC-204
NMR: 500MHz
AR.No: IN1210/103
Date:6 th Dec.2010
Analyst:Haribabu.R




4g




Supplementary Material (ESI) for Chemical Communications
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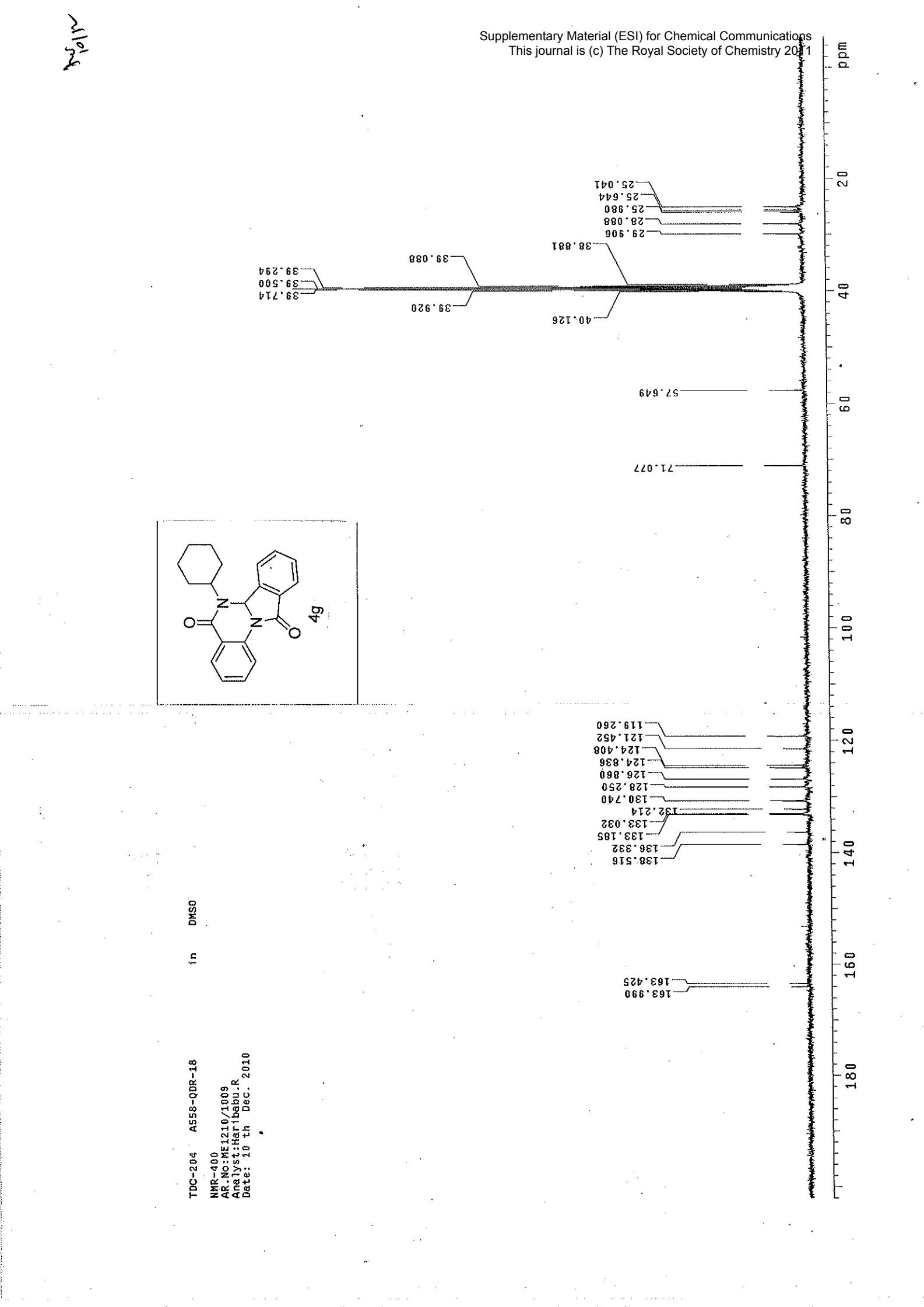

TDC-204 A558-QDR-18
NMR-400
AR.No:ME1210/1009
Analyst:Haribabu.R
Date: 10 th Dec. 2010
in DMSO
4g
ppm
20
40
60
80
100
120
140
160
180
25.041
25.644
25.980
28.088
29.906
38.881
39.088
39.294
39.500
39.714
39.920
40.126
57.649
71.077
119.260
121.452
124.408
124.836
126.860
128.250
130.740
132.214
133.032
133.185
136.332
138.516
163.990
163.425

13/12/10

## Elemental Composition Report

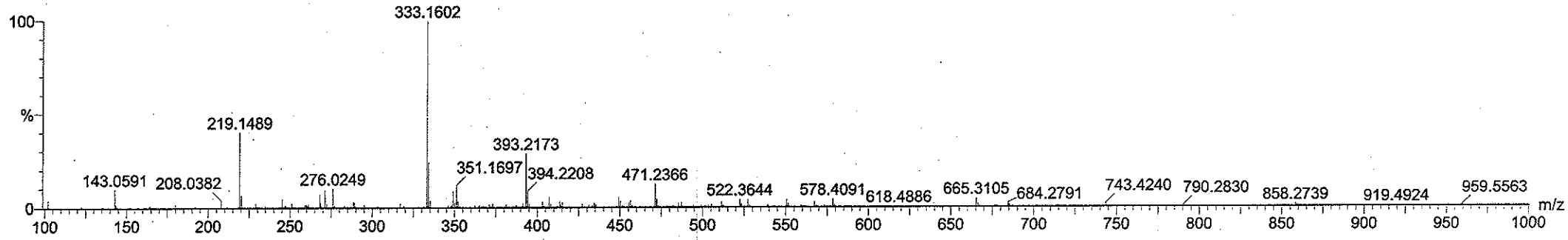
### Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.0, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

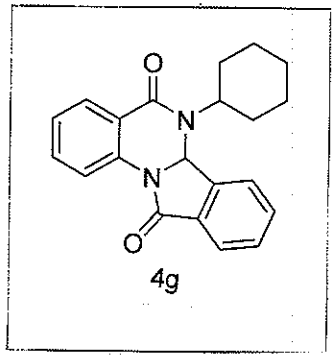
Monoisotopic Mass, Even Electron Ions
181 formula(e) evaluated with 1 results within limits (up to 4 best isotopic matches for each mass)
Elements Used:
C: 0-40 H: 0-55 N: 0-4 O: 0-8

A558/QDR/18
UT1210_148 16 (0.292) Cm (16:18-61:70)

1: TOF MS ES+
5.42e+003




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.0 | | |
| Maximum: | | 5.0 | 10.0 | 80.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 333.1602 | 333.1603 | -0.1 | -0.3 | 12.5 | 0.4 | C21 H21 N2 O2 |




4g

Supplementary Material (ESI) for Chemical Communications
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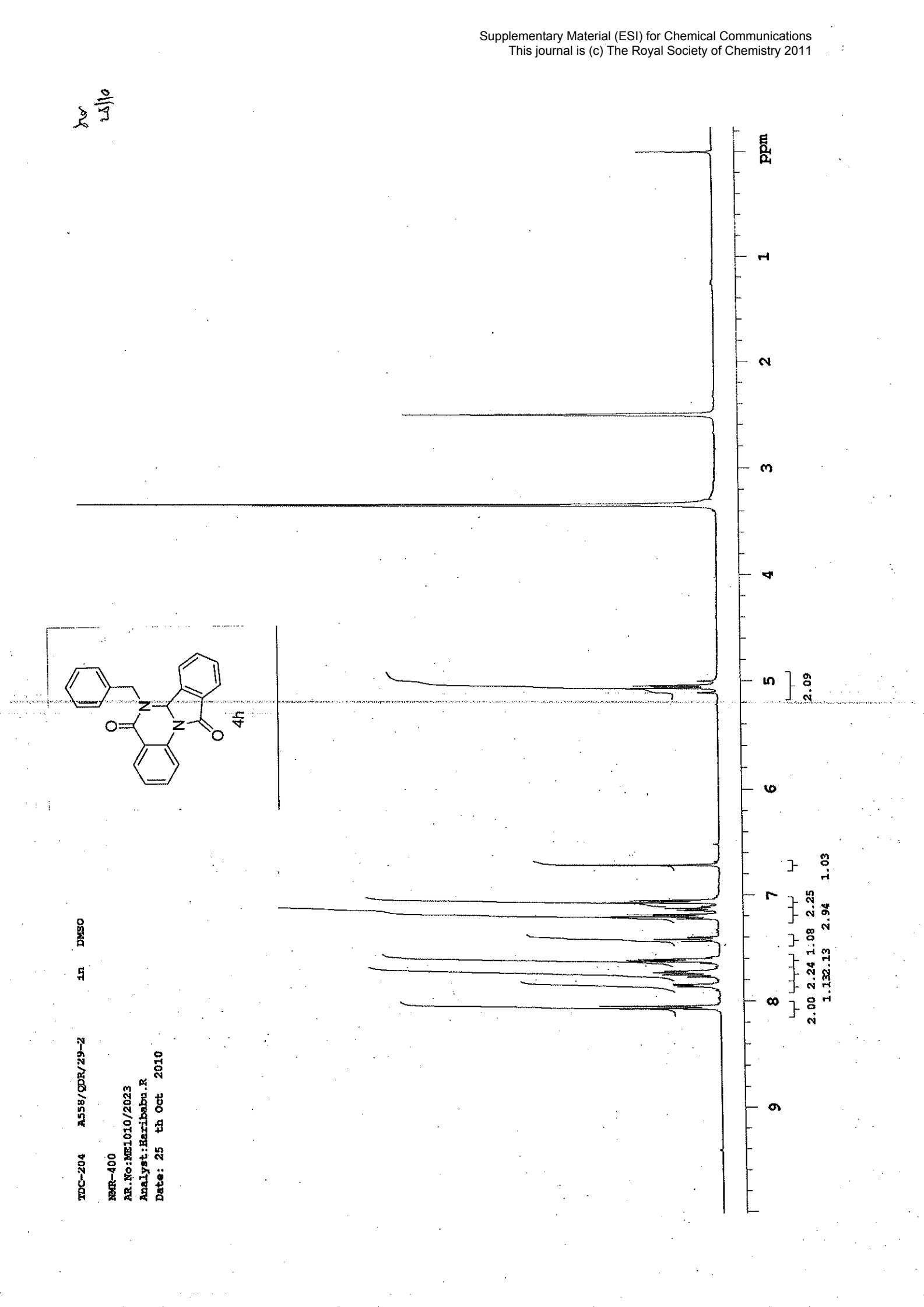
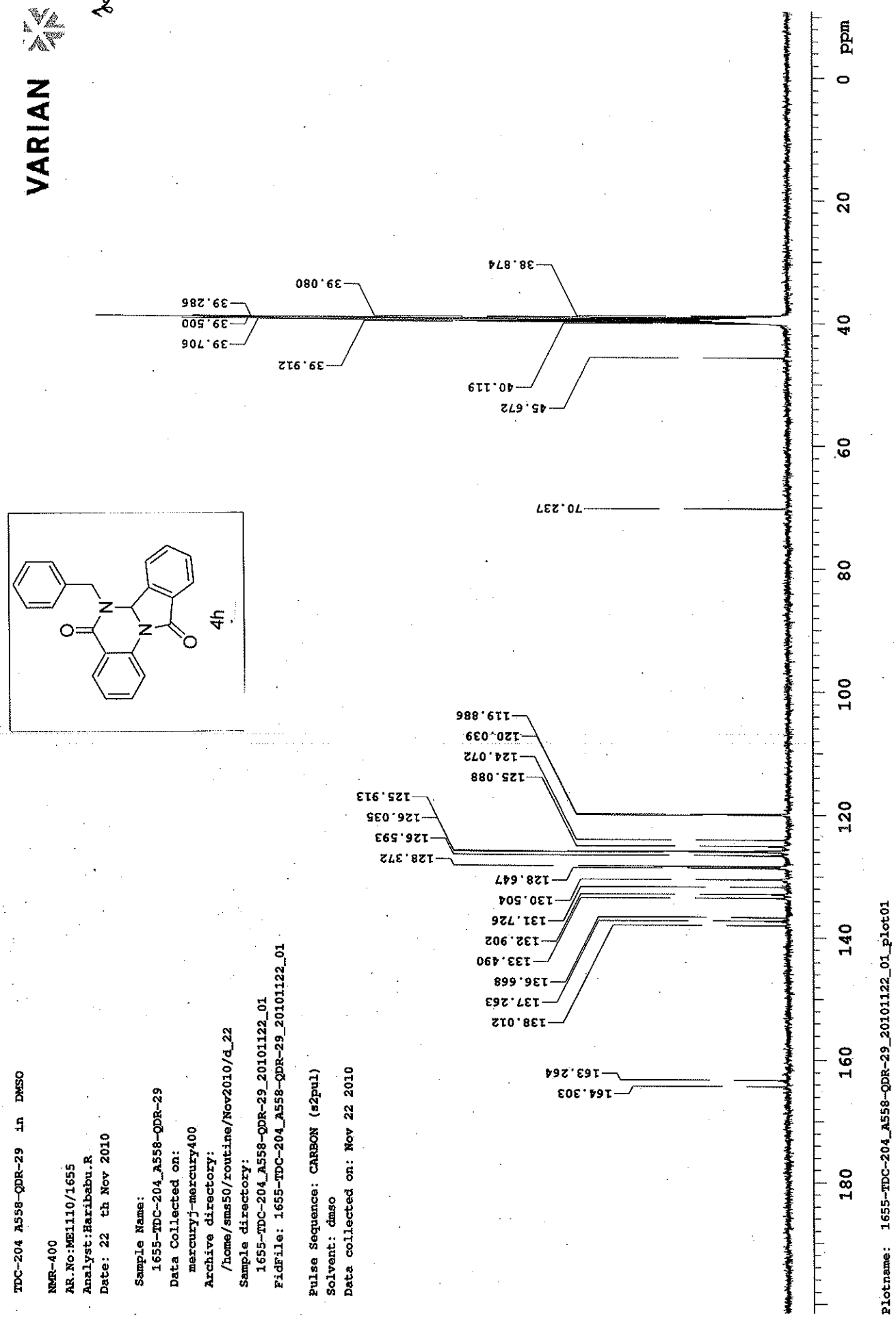

TDC-204 A558/QDR/29-2 in DMSO
NMR-400
AR.No:ME1010/2023
Analyst:Haribabu.R
Date: 25 th Oct 2010
4h
ppm
2.09
2.00 2.24 1.08 2.25
1.13 2.13 2.94 1.03


VARIAN
TDC-204 A558-QDR-29 in DMSO
NMR-400
AR.No:ME1110/1655
Analyst:Baribabu.R
Date: 22 th Nov 2010
Sample Name:
1655-TDC-204_A558-QDR-29
Data Collected on:
mercuryj-mercury400
Archive directory:
/home/sms50/routine/Nov2010/d_22
Sample directory:
1655-TDC-204_A558-QDR-29_20101122_01
FidFile: 1655-TDC-204_A558-QDR-29_20101122_01
Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Nov 22 2010
4h
38.874
39.080
39.286
39.500
39.706
39.912
40.119
45.672
70.237
119.886
120.039
124.072
125.088
125.913
126.035
126.593
128.372
128.647
130.504
131.726
132.902
133.490
136.668
137.263
138.012
163.264
164.303
0 ppm
20
40
60
80
100
120
140
160
180
Plotname: 1655-TDC-204_A558-QDR-29_20101122_01_plot01

## Elemental Composition Report

16/11/10



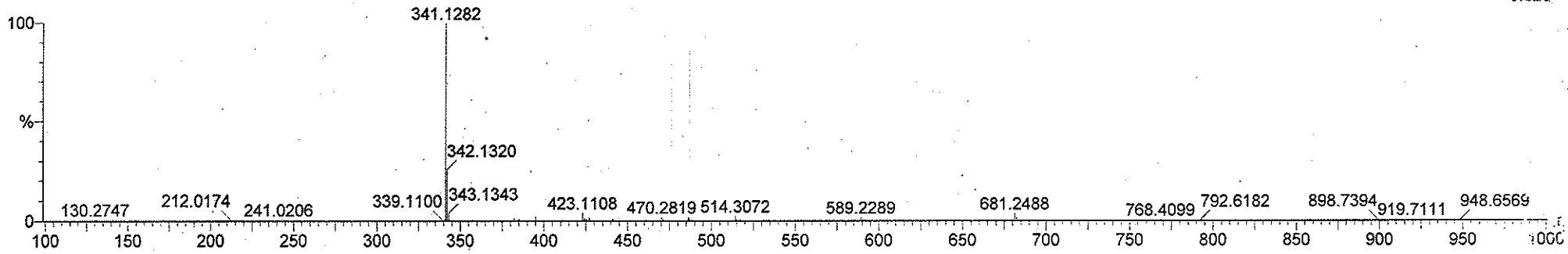
### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.0, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

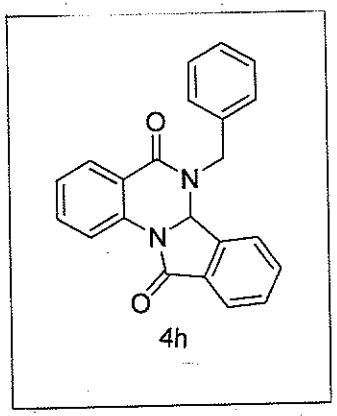
Monoisotopic Mass, Even Electron Ions
196 formula(e) evaluated with 1 results within limits (up to 4 best isotopic matches for each mass)
Elements Used:
C: 0-45 H: 0-55 N: 0-4 O: 0-4 Br: 0-1

A558-QDR-29
UT1110_76 25 (0.472) Cm (25:33-78:89)

1: TOF MS ES+
8.32e+




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.0 | | |
| Maximum: | | 5.0 | 5.0 | 80.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 341.1282 | 341.1290 | -0.8 | -2.3 | 15.5 | 0.9 | C22 H17 N2 O2 |




4h

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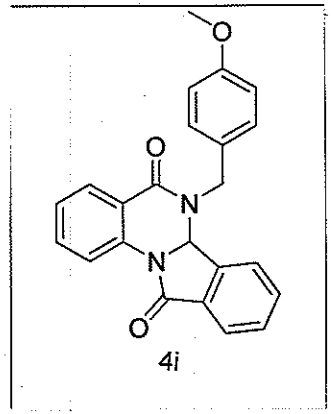
TDC-204 A558/QDR/33 in DMSO

NMR-400
AR.No:ME1110/900
Analyst:Haribabu.R
Date: 15 th Nov 2010

Sample Name:
900-TDC-204_A558_QDR_33
Data Collected on:
mercuryj-mercury400
Archive directory:
/home/sms50/routine/Nov2010/d_15
Sample directory:
900-TDC-204_A558_QDR_33_20101115_01
FidFile: 900-TDC-204_A558_QDR_33_20101115_01

Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Nov 15 2010



4i

VARIAN




Plotname: 900-TDC-204_A558_QDR_33_20101115_01_plot01

Supplementary Material (ESI) for Chemical Communications
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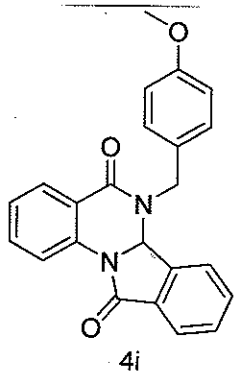
TDC-204 A558-QDR-33 in DMSO

NMR-400
AR.No:ME1110/1657
Analyst:Haribabu.R
Date: 22 th Nov 2010

Sample Name:
1657-TDC-204_A558-QDR-33
Data Collected on:
mercuryj-mercury400
Archive directory:
/home/sms50/routine/Nov2010/d_22
Sample directory:
1657-TDC-204_A558-QDR-33_20101123_01
FidFile: 1657-TDC-204_A558-QDR-33_20101123_01

Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Nov 23 2010



4i

VARIAN

23/11




Plotname: 1657-TDC-204_A558-QDR-33_20101123_01_plot01

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## Elemental Composition Report

16/11/10



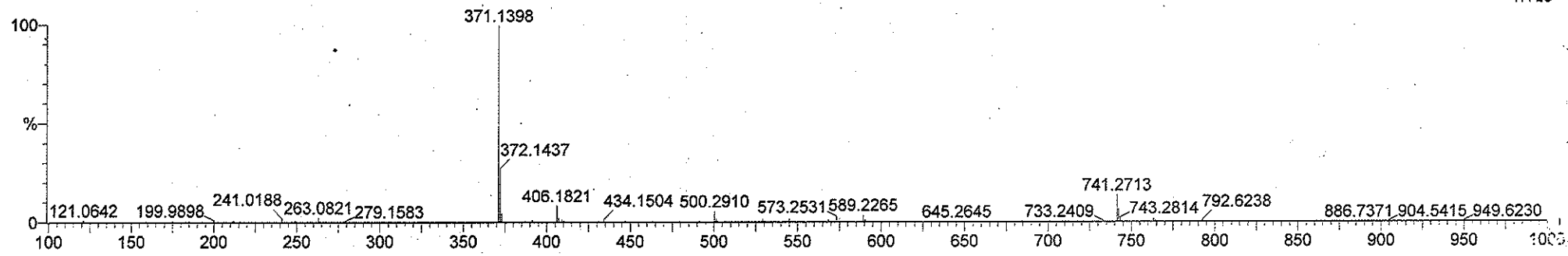
### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.0, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

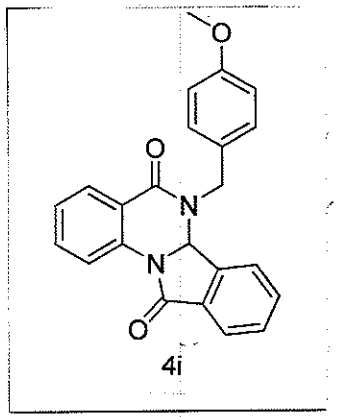
Monoisotopic Mass, Even Electron Ions
213 formula(e) evaluated with 1 results within limits (up to 4 best isotopic matches for each mass)
Elements Used:
C: 0-45 H: 0-55 N: 0-4 O: 0-4 Br: 0-1

A558-QDR-33
UT1110_75 17 (0.325) Cm (17:23-77:88)

1: TOF MS E
1.12e




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.0 | | |
| Maximum: | | 5.0 | 5.0 | 80.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 371.1398 | 371.1396 | 0.2 | 0.5 | 15.5 | 1.4 | C23 H19 N2 O3 |




4i

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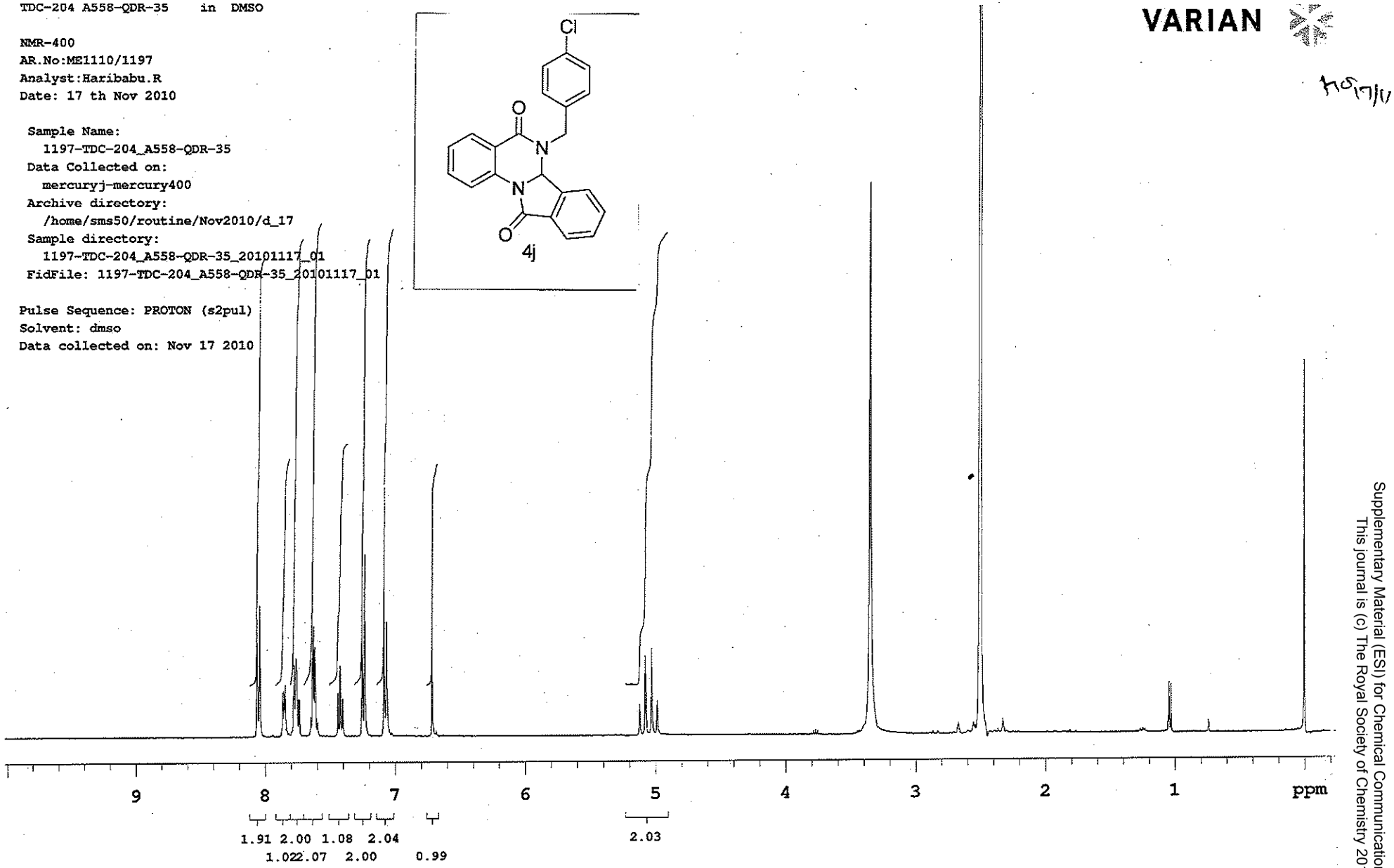


Supplementary Material (ESI) for Chemical Communications
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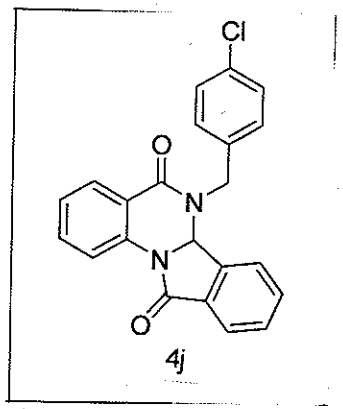
TDC-204 A558-QDR-35 in DMSO

NMR-400
AR.No:ME1210/1011
Analyst:Haribabu.R
Date: 10 th Dec. 2010




4j

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13/12/10

# Elemental Composition Report

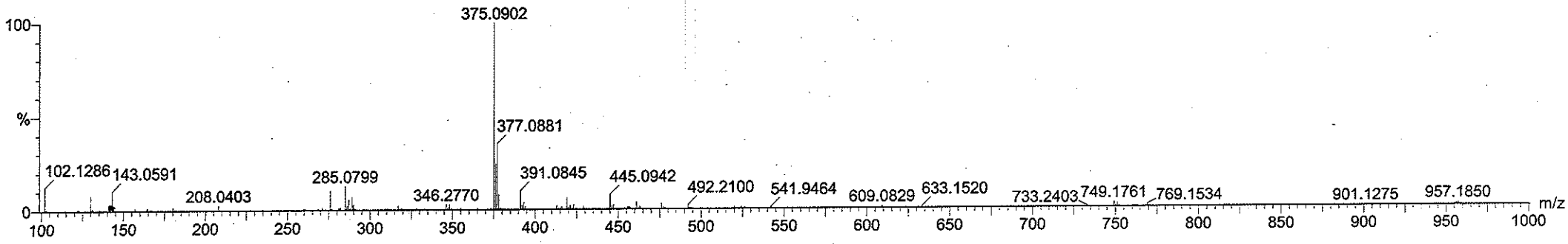
## Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.0, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

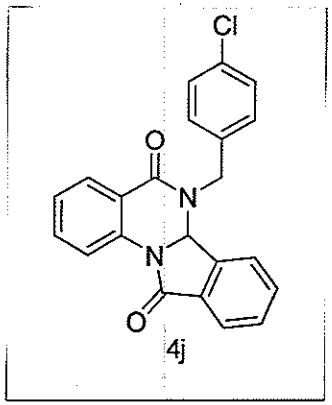
Monoisotopic Mass, Even Electron Ions
376 formula(e) evaluated with 4 results within limits (up to 4 best isotopic matches for each mass)
Elements Used:
C: 0-40 H: 0-55 N: 0-4 O: 0-8 Cl: 0-1

A558/QDR/35
UT1210_150 17 (0.325) Cm (17:20-64:70)

1: TOF MS ES+
9.30e+003




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.0 | | | | | | |
| Maximum: | | 5.0 | 10.0 | 80.0 | | | | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula | | | | |
| 375.0902 | 375.0900 | 0.2 | 0.5 | 15.5 | 1.4 | C22 | H16 | N2 | O2 | Cl |
| | 375.0869 | 3.3 | 8.8 | 15.5 | 1268.7 | C22 | H15 | O6 | | |
| | 375.0882 | 2.0 | 5.3 | 20.5 | 1301.7 | C23 | H11 | N4 | O2 | |
| | 375.0922 | -2.0 | -5.3 | 24.5 | 1309.2 | C28 | H11 | N2 | | |




4j

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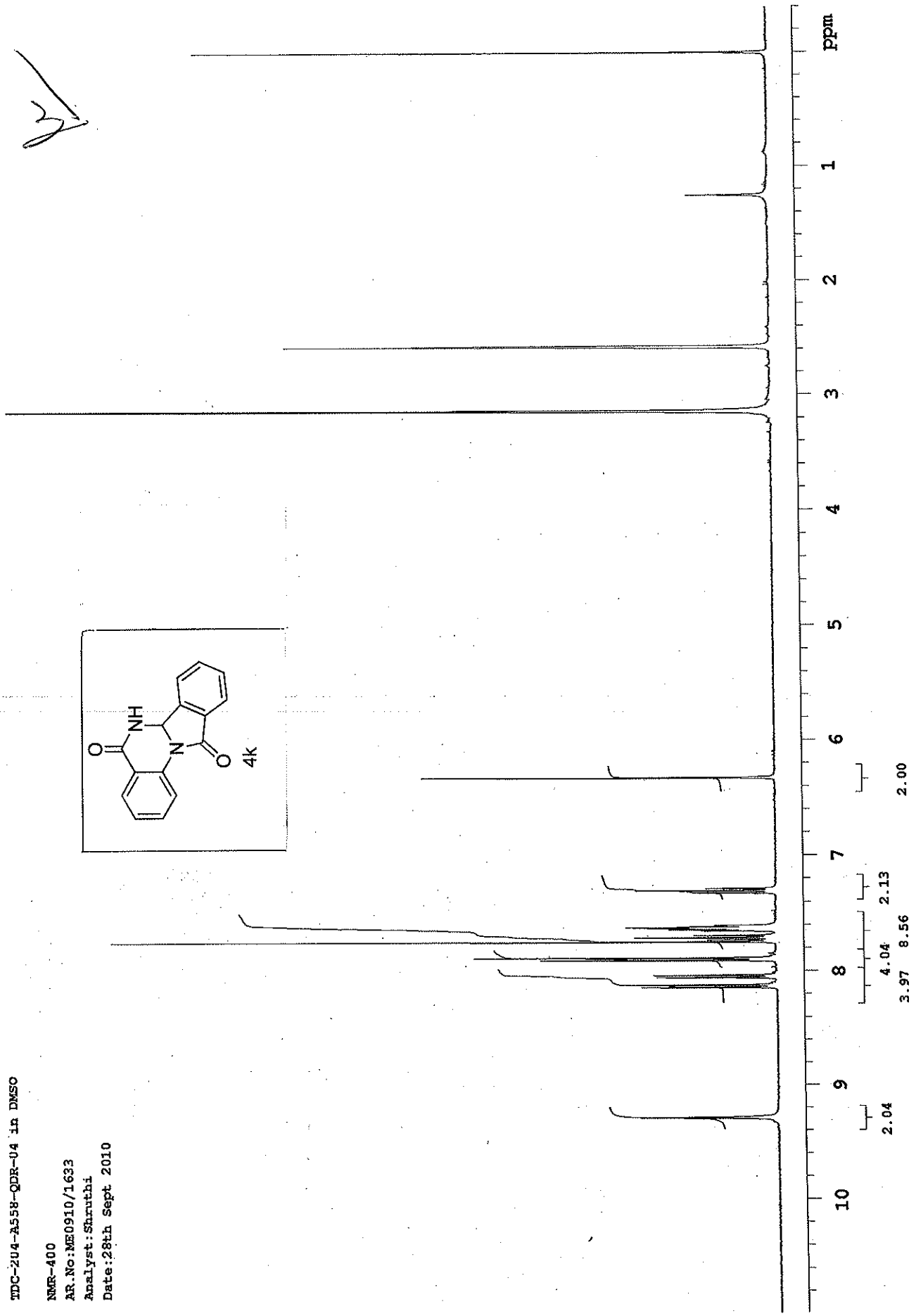

TDC-2U4-A558-QDR-U4 in DMSO
NMR-400
AR.No:ME0910/1633
Analyst:Shruthi
Date:28th Sept 2010
NH
O
N
O
4k
ppm
1
2
3
4
5
6
7
8
9
10
2.04
3.97
4.04
8.56
2.13
2.00

ppm
20
40
60
80
100
120
140
160
180
200
38.881
39.088
39.294
39.500
39.714
39.920
40.126
67.044
119.535
119.955
123.805
124.118
124.737
128.159
130.137
131.137
133.207
133.498
137.072
140.716
163.616
164.441
NH
N
O
O
4k
TDC-204 A558/QDR/04 in DMSO
NMR-400
AR.No:ME1010/1708
Analyst:Shruthi
Date: 20 th Oct 2010

28/10/10

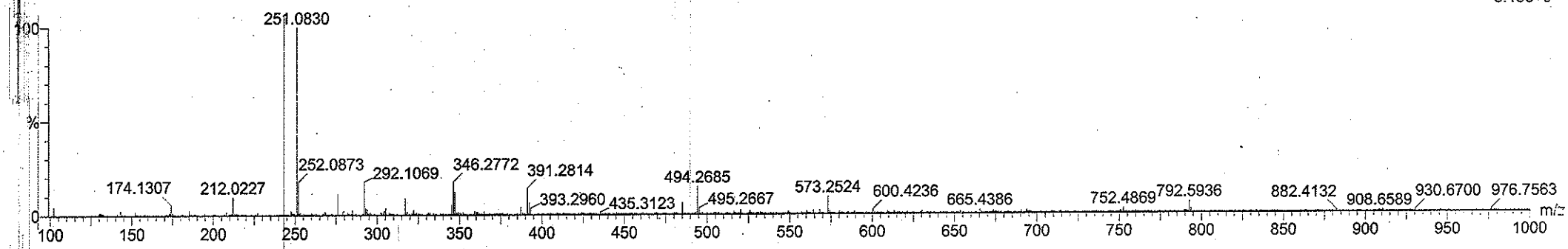
## Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.0, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

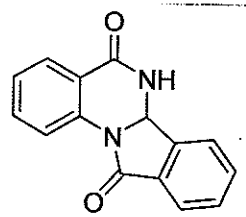
Monoisotopic Mass, Even Electron Ions
405 formula(e) evaluated with 1 results within limits (up to 4 closest results for each mass)
Elements Used:
C: 0-45 H: 0-70 N: 0-6 O: 0-6 S: 0-2

A358\QDR\04
UT1010_191 22 (0.412) Cm (21:24-73:80)

1: TOF MS ES
3.15e+0




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.0 | | |
| Maximum: | | 5.0 | 5.0 | 80.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 251.0830 | 251.0821 | 0.9 | 3.6 | 11.5 | 3.5 | C15 H11 N2 O2 |




4k

Supplementary Material (ESI) for Chemical Communications
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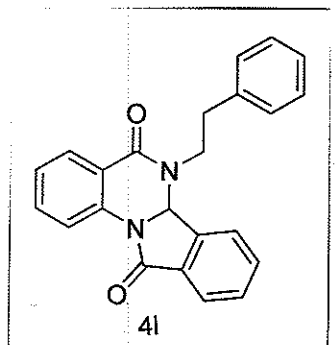
TDC-204 A558/QDR/34 in DMSO

NMR-400
AR.No:ME1110/1509
Analyst:Haribabu.R
Date: 19 th Nov 2010

Sample Name:
1509-TDC-204_A558_QDR_34
Data Collected on:
mercuryj-mercury400
Archive directory:
/home/sms50/routine/Nov2010/d_19
Sample directory:
1509-TDC-204_A558_QDR_34_20101120_01
FidFile: 1509-TDC-204_A558_QDR_34_20101120_01

Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Nov 20 2010




4l

VARIAN




Plotname: 1509-TDC-204_A558_QDR_34_20101120_01_plot01

Supplementary Material (ESI) for Chemical Communications
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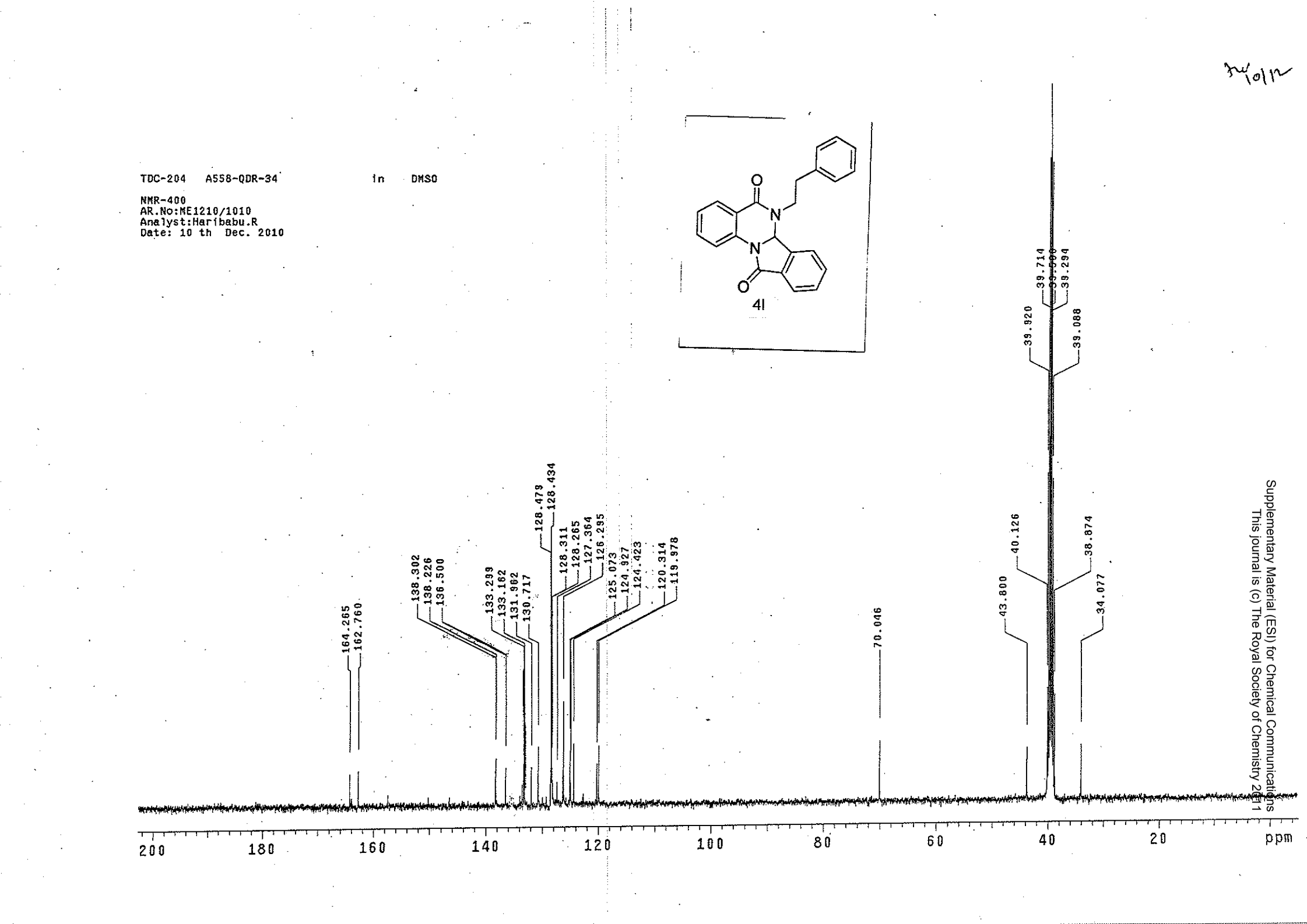


Supplementary Material (ESI) for Chemical Communications
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13/12/10

## Elemental Composition Report

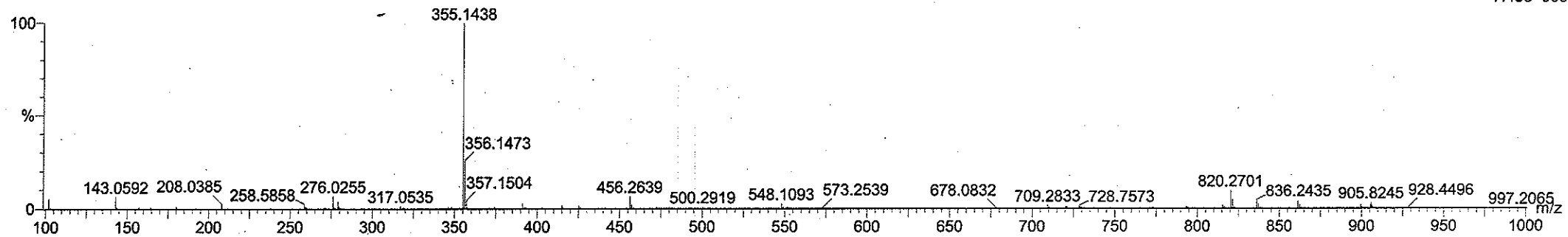
### Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.0, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

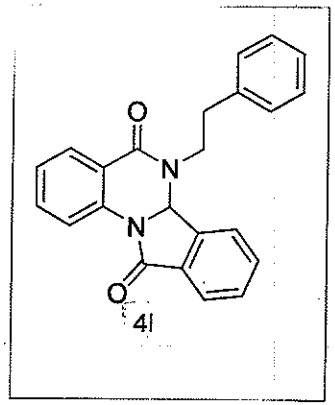
Monoisotopic Mass, Even Electron Ions
191 formula(e) evaluated with 2 results within limits (up to 4 best isotopic matches for each mass)
Elements Used:
C: 0-40 H: 0-55 N: 0-4 O: 0-8

A558/QDR/34
UT1210_149 17 (0.325) Cm (17:20-66:72)

1: TOF MS ES+
7.45e+003




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.0 | | |
| Maximum: | | 5.0 | 10.0 | 80.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 355.1438 | 355.1447 | -0.9 | -2.5 | 15.5 | 3.6 | C23 H19 N2 O2 |
| | 355.1406 | 3.2 | 9.0 | 11.5 | 29.4 | C18 H19 N4 O4 |




Supplementary Material (ESI) for Chemical Communications
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