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 (6.7 mmol), 2-carboxy benzaldehyde 3 (1.01 g, 6.74 mmol) and catalytic amount of anhydrous camphor sulfonic acid (0.07 g, 0.31 mmol) 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)**

![Chemical Structure](image)

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$_2$O$_2$ (M+H)$^+$ 327.1134, found 327.1130

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

![Chemical Structure](image)

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, 136.3, 133.3, 133.1, 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$_2$O$_2$ (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$_2$O$_2$ (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, 1487, 1466, cm$^{-1}$

HRMS (ESI): calcd for C$_{18}$H$_{15}$N$_2$O$_2$ (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 cm$^{-1}$

HRMS (ESI): calcd for C$_{17}$H$_{15}$N$_2$O$_3$ (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$_2$O$_2$ (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$_2$O$_2$ (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, 1495, 1470 cm$^{-1}$

HRMS (ESI): calcd for C$_{22}$H$_{17}$N$_2$O$_2$ (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$_2$O$_3$ (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, 1724, 1660, 1488, 1466 cm$^{-1}$
HRMS (ESI): calcd for C$_{22}$H$_{16}$ClN$_2$O$_2$ (M+H)$^+$ 375.0900, found 375.0902

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

![Structure of 6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4k)](image)

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$_2$O$_2$ (M+H)$^+$ 251.0821, found 251.0830

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

![Structure of 6-phenethyl-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione (4l)](image)

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$_2$O$_2$ (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-Kα 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. The crystal structure was solved by direct methods using SHELXS-97 and the data was refined by full matrix least-squares refinement on $R^2$ with anisotropic displacement parameters for non-H atoms, using SHELXL-97.

Crystal data of 4j: Molecular formula = C$_{22}$H$_{15}$ClN$_2$O$_2$, 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$^{-3}$, $\mu$(Mo-Kα) = 0.71073 mm$^{-1}$, 27323 reflections measured, 3833 independent reflections, 3311 observed reflections [I > 2.0 $\sigma$(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](image_url). 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 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_{2}O_{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\(^{-3}\), \(\mu(\text{Mo-K}\alpha) = 0.71073\) mm\(^{-1}\), 8092 reflections measured, 1634 independent reflections, 1098 observed reflections \([I > 2.0 \sigma (I)]\), \(R_{1_{\text{obs}}} = 0.079\), 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**.

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. 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:

\[
\% \text{ inhibition} = 100 - \left( \frac{(LPS \text{ stimulated}_\text{compound} - \text{unstimulated})}{(LPS \text{ stimulated}_\text{DMSO} - \text{unstimulated})} \right) \times 100
\]

The IC50 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:


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 MASTER 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 Palc,*

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cInstitute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India
dDepartment of Chemical Sciences, Indian Institute of Science Education and Research, Kolkata, West Bengal, 741252, India.
**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

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

A563-QDR-05

UT1110_56 26 (0.487) Cm (26:35:81:93)

Minimum: 5.0  5.0  -1.0
Maximum: 5.0  80.0

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![Chemical Structure](image)
**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**
- 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

**A5616QDR26**
**UT1010_197 22 (0.413) Cm (21:24-85:94)**

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**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

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**Diagram:**
- Chemical structure of compound 4b

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Footer: This journal is (c) The Royal Society of Chemistry 2011
**Supplementary Material**

**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

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**Mass**

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<td>0.1</td>
<td>0.4</td>
<td>11.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>

---

![Chemical Structure](image)
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)

Minimum:
Maximum:
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
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
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
A658QDR28
UT1010_194 16 (0.293) Cm (16:22-77:88)

Minimum:
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
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: 0-46  H: 0-56  N: 0-4  O: 0-4  Br: 0-1

A556-ODR-31
UT1110_73 20 (0.357) Cm (20:27-73:81)

Minimum: 5.0  5.0  -1.0
Maximum: 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
**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
A658/QDR/18
UT1210_148 16 (0.292) Cm (16:18-61:70)

```
<table>
<thead>
<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBE</th>
<th>i-FIT</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>333.1602</td>
<td>333.1603</td>
<td>-0.1</td>
<td>-0.3</td>
<td>12.5</td>
<td>0.4</td>
<td>C21 H21 N2 O2</td>
</tr>
</tbody>
</table>
```

![Chemical Structure](image)
NMR-400
AR.No:ME1110/1655
Analyst:Rajibabu.R
Date: 22 Nov 2010

Sample Name:
1655-TDC-204_A559-QDR-29
Data Collected on:
mercuryj-mercury400
Archive directory:
/home/msk50/routine/Nov2010/4_22
Sample directory:
1655-TDC-204_A559-QDR-29_20101123_01
FidFile: 1655-TDC-204_A559-QDR-29_20101123_01

Pulse Sequence: CARBON (a2pul)
Solvent: dmoa
Data collected on: Nov 22 2010

Plotname: 1655-TDC-204_A559-QDR-29_20101122_01_plot01
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

196 formula(e) evaluated 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

A658-QDR-29
UT1110_76 25 (0.472) Cm (25:33-78:89)

<table>
<thead>
<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBE</th>
<th>i-FIT</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>341.1282</td>
<td>341.1290</td>
<td>-0.8</td>
<td>-2.3</td>
<td>15.5</td>
<td>0.9</td>
<td>C22 H17 N2 O2</td>
</tr>
</tbody>
</table>

![Chemical Structure Image]
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: 0-65  N: 0-4  O: 0-4  Br: 0-1

A568-ODR-33
UT1110_75 17 (0.325) Cm (17:23-77:88)

<table>
<thead>
<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBE</th>
<th>i-FIT</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>371.1398</td>
<td>371.1396</td>
<td>0.2</td>
<td>0.5</td>
<td>15.5</td>
<td>1.4</td>
<td>C23H19N2O3</td>
</tr>
</tbody>
</table>

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Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2011

NMR-400
AR.No: ME1110/1197
Analyst: Haribabu R
Date: 17th Nov 2010

Sample Name:
1197-TDC-204_A558-QDR-35
Data Collected on:
mercury400

Archive directory:
/home/asa50/routine/Nov2010/4_17
Sample directory:
1197-TDC-204_A558-QDR-35_20101117_01
FidFile: 1197-TDC-204_A558-QDR-35_20101117_01

Pulse Sequence: PROTON (a2pul)
Solvent: dmso
Data collected on: Nov 17 2010

Plotname: 1197-TDC-204_A558-QDR-35_20101117_01_plot01
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

A658/QDA/35
UT121_15017 (0.325) Cm (17:20-64:70)

Minimum:
-1.0

Maximum:
5.0 10.0 80.0

<table>
<thead>
<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBE</th>
<th>i-FIT</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>375.0902</td>
<td>375.0900</td>
<td>0.2</td>
<td>0.5</td>
<td>15.5</td>
<td>1.4</td>
<td>C22 H16 N2 O2 Cl</td>
</tr>
<tr>
<td>375.0869</td>
<td>3.3</td>
<td>8.8</td>
<td></td>
<td>15.5</td>
<td>1268.7</td>
<td>C22 H15 O6</td>
</tr>
<tr>
<td>375.0892</td>
<td>2.0</td>
<td>5.3</td>
<td></td>
<td>30.5</td>
<td>1301.7</td>
<td>C23 H14 N4 O2</td>
</tr>
<tr>
<td>375.0922</td>
<td>-2.0</td>
<td>-5.3</td>
<td></td>
<td>24.5</td>
<td>1309.2</td>
<td>C28 H11 N2</td>
</tr>
</tbody>
</table>
Sample Name: 1509-TDC-204_A558_QDR_34
Data Collected on: mercuryj-mercury400
Archive directory: /home/sms50/routine/Nov2010/4_19
Sample directory: 1509-TDC-204_A558_QDR_34_20101120_01
Fidfile: 1509-TDC-204_A558_QDR_34_20101120_01
Pulse Sequence: PROTON (e2pul)
Solvent: dmso
Data collected on: Nov 20 2010
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
A658/GDR/34
UT1210_149 17 (0.325) Cm (17:20-88:72)

Minimum:  5.0  10.0  -1.0  80.0
Maximum:  355.1438  355.1406
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

[Chemical structure image]