Design, synthesis, anticancer activity and docking studies of theophylline containing 1,2,3-triazoles with variant amide derivatives

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Supplementary material

Figures:

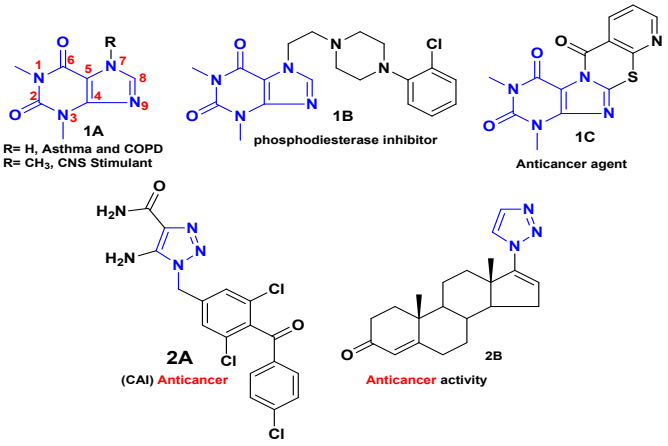


Fig 1. Bioactive theophylline and 1,2,3-triazole moieties.

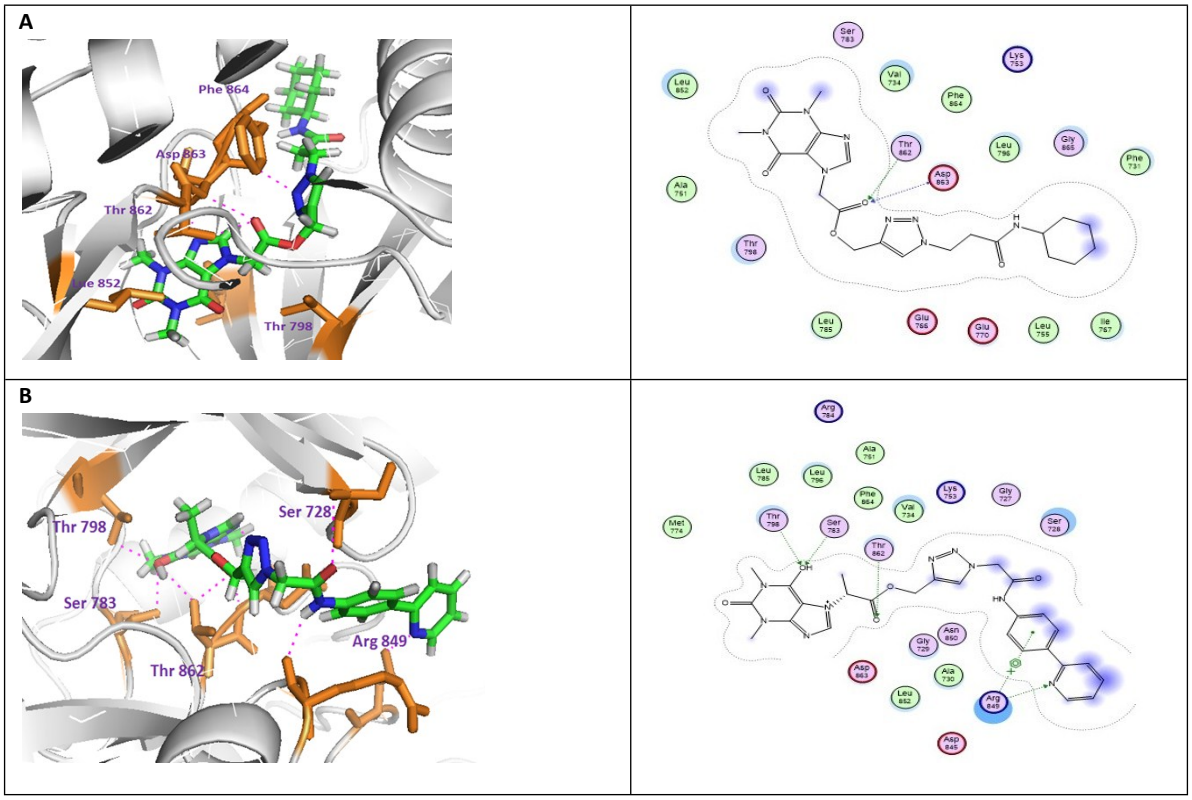
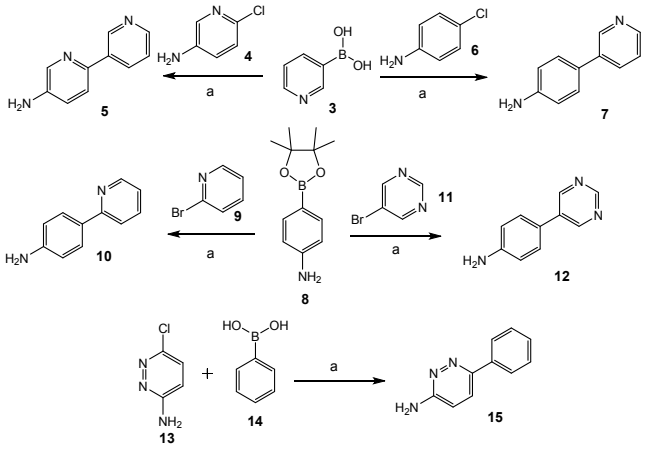
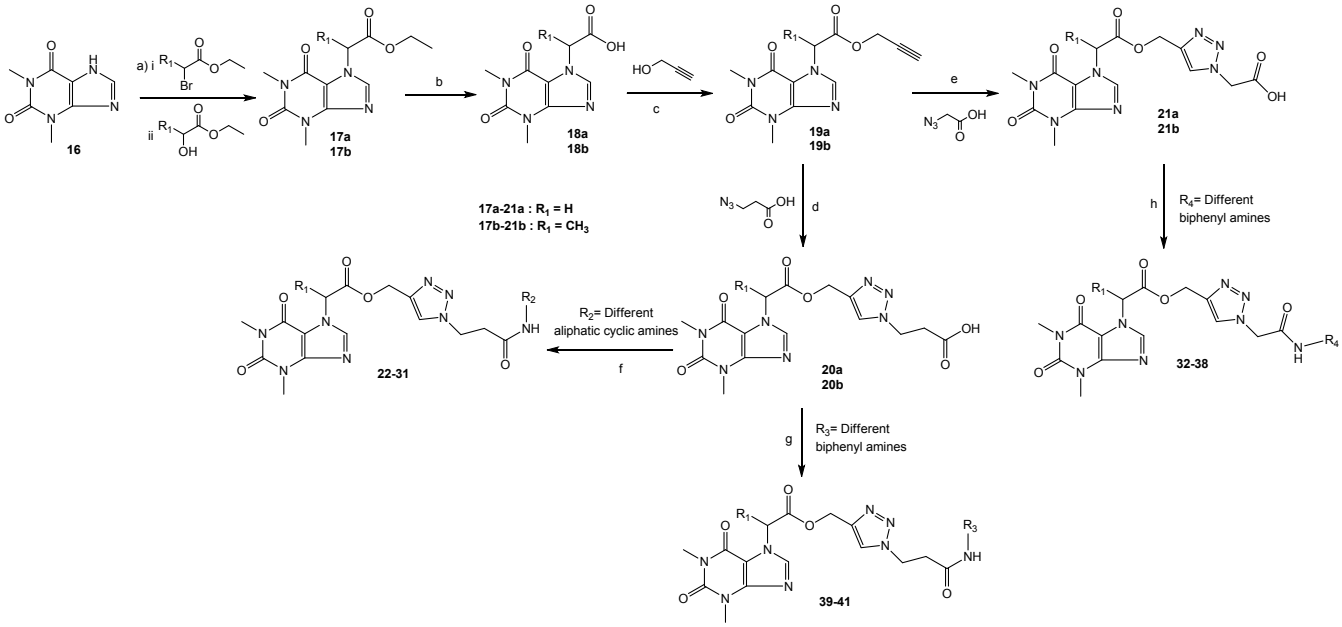


Fig. 2 Molecular and Lig plot interactions of compound **22** (A) and **41** (B) with tyrosine kinase domain of Human epidermal growth factor receptor 2 (HER2).

Schemes:



Scheme 1 Synthesis of biphenyl amine compounds **5**,**7**,**12** and **15**. Reagents and conditions: (a) K_3PO_4, $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, 1,4-dioxane:$H_2O$, 100°C, 10-16 h.



Scheme 2 Synthesis of aliphatic cyclic amide and biphenyl amide compounds **22**–**31** and **32**–**41**. Reagents and conditions: (a) (i) K_2CO_3, DMF, 85°C, 12 h (ii) TPP, DIAD, THF, rt, 5 h; (b) $LiOH{\cdot}H_2O$, THF:H_2O, rt, 2h; (c) DCC, DMAP, DCM, rt, 16 h; (d & e) $CuSO_4{\cdot}5H_2O$, sodium ascorbate, *t*-BuOH:H_2O, rt, 16 h; (f, g & h) HATU, DIPEA, DCM, rt, 16 h.

Experimental Section

Materials and methods

Starting materials were obtained from commercial suppliers and used without further purification. Melting points were determined in open glass capillaries on a Fisher–Johns melting point apparatus and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were taken on a VNMRS 400 MHz spectrometer using the solvent ($CDCl_3$ 7.26 ppm and 77.0 ppm, DMSO-d_6 2.49 ppm and 39.7 ppm) and TMS used as an internal standard. Chemical shifts are given in δ ppm and coupling constant (J) is given in Hz. IR spectra were recorded on a Perkine Elmer FTIR 1600 spectrometer for samples in KBr discs. Low-resolution MS data were obtained using ESI, and high-resolution spectra were recorded on QSTARXL hybrid MS/MS system (Applied Biosystems, USA) under ESI. Elemental analysis (CHN) was performed on a elementar analysensysteme GmbH - vario MICRO element analyzer. All compounds were purified by flash chromatography (FC) was performed using on silica gel (100-200 mesh). All the reactions were monitored by Thin-layer chromatography (TLC) on Silica Gel 60 F254 plates (VWR, Darmstadt); visualization by UV detection at 254 nm.

General procedure for the synthesis of compounds 5, 7, 10, 12 and **15**.

To a stirred solution of aryl halide compounds **4**,**6**,**9**,**11** and **13** (1.0 equiv), corresponding boronic acids or boronate esters **3**,**8** and **14** (1.2 equiv) and potassium phosphate (2.0 equiv) in 1,4-dioxane and water (10:2). The suspension was deoxygenated with argon for 10 min and were added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.05 equiv) and again deoxygenated with argon for 5 min. The reaction mixture was stirred at 100°C for 10-16 h. The reaction mixture was cooled to room temperature, concentrated and added to water and extracted with ethyl acetate twice. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude compounds was purified by flash chromatography over silica gel (100-200 mesh) eluting with 2 to 6% MeOH in dichloromethane to afford desired compounds **5**,**7**,**10**,**12** and **15.**

[2,3'-bipyridin]-5-amine (5). 6-chloropyridin-3-amine **4** (1 g, 7.811 mmol), pyridin-3-ylboronic acid **3** (1.15 g, 9.374 mmol), K_3PO_4 (3.31 g, 15.62 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (318.9 mg, 0.390 mmol) in 1,4-dioxane and H_2O to afford pale brown solid 400 mg (30%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.10 (d, *J* = 2.0 Hz, 1H), 8.46 (dd, *J* = 1.2 Hz, 4.4 Hz, 1H), 8.25 (dd, *J* = 2.0 Hz, 4.0 Hz, 1H), 8.05 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.41–7.38 (m, 1H), 7.01 (dd, *J* = 2.8 Hz, 8.8 Hz, 1H), 5.58 (brs, 2H); *m/z* (MM–ES+APCI)$^+$: 172.0 $[C_{10}H_9N_3+H]^+$.

4-(pyridin-3-yl) aniline (7). 4-chloroaniline **6** (1 g, 5.848 mmol), pyridin-3-ylboronic acid **3** (863 mg, 7.018 mmol), K_3PO_4 (2.48 g, 11.697 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (238 mg, 0.292 mmol) in 1,4-dioxane and H_2O to afford off-white solid 250 mg (25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.50 (d, *J* = 4.4 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.31–7.28 (m, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 3.78 (brs, 2H); *m/z* (ES)$^+$: 170.91 $[C_{11}H_{10}N_2+H]^+$.

4-(pyridin-2-yl)aniline (10). 2-bromopyridine **9** (1 g, 6.371 mmol), 4-aminophenyl boronic acid pinacol ester **8** (1.67 g, 7.645 mmol), K_3PO_4 (2.70 g, 12.742 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (260 mg, 0.318 mmol) in 1,4-dioxane and H_2O to afford pale brown solid 650 mg (60%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.51 (dd, *J* = 1.2 Hz, 3.6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 4.8 Hz, 2H), 7.15–7.12 (m, 1H), 6.62 (d, *J* = 8.4 Hz, 2H), 5.38 (brs, 2H); *m/z* (ES)$^+$: 171.10 $[C_{11}H_{10}N_2+H]^+$.

4-(pyrimidin-5-yl)aniline (12). 5-bromopyrimidine **11** (1 g, 6.331 mmol), 4-aminophenyl boronic acid pinacol ester **8** (2.08 g, 9.496 mmol), K_3PO_4 (2.68 g, 12.662 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (258 mg, 0.316 mmol) in 1,4-dioxane and H_2O to afford brown solid 680 mg (63%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.01 (s, 1H), 8.99 (s, 2H), 7.49 (d, *J* = 9.2 Hz, 2H), 6.67 (d, *J* = 9.2 Hz, 2H), 5.46 (brs, 2H); *m/z* (ES)$^+$: 172.13 $[C_{10}H_9N_3+H]^+$.

6-phenylpyridazin-3-amine (15). 6-chloropyridazin-3-amine **13** (1 g, 7.751 mmol), phenylboronic acid **14** (1.13 g, 9.301 mmol), K_3PO_4 (3.29 g, 15.502 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (316 mg, 0.387 mmol) in 1,4-dioxane and H_2O to afford pale brown solid 350 mg (26%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, *J* = 7.2 Hz, 2H), 7.80 (d, *J* = 9.2 Hz, 1H), 7.48–7.37 (m, 3H), 6.86 (d, *J* = 9.2 Hz, 1H), 6.48 (brs, 2H); *m/z* (ES)$^+$: 172.10 $[C_{10}H_9N_3+H]^+$.

Ethyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate (17a). To a stirred solution of theophylline **16** (6 g, 33.33 mmol) in 60 mL of DMF was added K_2CO_3 (5.97 g, 43.33 mmol) at room temperature. After 20 min, ethyl 2-bromoacetate (5.89 mL, 53.33 mmol) was added to the reaction mixture at room temperature, and was heated to stirred at 85°C for 12 h. As monitored by TLC, the reaction mass was added to water (100 mL) and extracted with ethyl acetate (2 x 50 mL), dried with Na_2SO_4, filtered and concentrated. The crude compound was purified by column chromatography (100-200 mesh) eluted in 2% MeOH in dichloromethane to afford **17a** (7.5 g, 84%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 5.08 (s, 2H), 4.28 (q, *J* = 7.6 Hz, 2H), 3.60 (s, 3H), 3.39 (s, 3H), 1.31 (t, *J* = 7.6 Hz, 3H); *m/z* (ES)$^+$: 267.25 $[C_{11}H_{14}N_4O_4+H]^+$.

Ethyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7 (6H)-yl)propanoate (17b). To a stirred solution of theophylline **16** (1 g, 5.555 mmol) and ethyl 2-hydroxypropanoate (0.318 mL, 2.776 mmol) in THF (20 mL) were added triphenyl phosphine (1.45 g, 5.553 mmol) at room temperature. After 10 min, DIAD (1.09 mL, 5.553 mmol) added drop wise to the reaction mixture and stirring was continued at room temperature for 5 h. As monitored by TLC, the reaction mixture diluted with water (50 mL), extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were washed with brine (1 x 50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (100-200 mesh) eluting with a gradient of 20-60% ethyl acetate in hexane to gave semi solid which was triturated with diethyl ether to afford **17b** (0.78 g, 50%) as an off-white solid. ^{1}H NMR (400 MHz,

DMSO-*d*6): δ 8.21 (s, 1H), 5.55 (q, *J* = 7.6 Hz, 1H), 4.14 (q, *J* = 4.0 Hz, 2H), 3.44 (s, 3H), 3.33 (s, 3H), 1.75 (d, *J* = 7.6 Hz, 3H), 1.18 (t, *J* = 6.4 Hz, 3H); *m/z* (ES)$^+$: 281.16 $[C_{12}H_{16}N_4O_4+H]^+$.

General procedure for the synthesis of compounds (18a and **18b)**

$LiOH{\cdot}H_2O$ (1.5 equiv) was added portionwise to a stirred solution of ester compounds **17a-17b** (1.0 equiv) in THF (10 vol), and H_2O (10 vol) at room temperature and the reaction mixture was stirred for 2 h. As monitored by TLC, from the reaction mixture THF was concentrated and acidified with aqueous $KHSO_4$ solution and extracted with 5% methanol and dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford the desired solid products **18a-18b**.

2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl) acetic acid (18a). Compound **17a** (5 g, 18.78 mmol), $LiOH{\cdot}H_2O$ (1.18 g, 28.18 mmol) in 100 mL of THF:H_2O (1:1) to afford **18a** (4.1 g, 91%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.27 (brs, 1H), 8.04 (s, 1H), 5.07 (s, 2H), 3.44 (s, 3H), 3.20 (s, 3H); *m/z* (ES)$^+$: 239.04 $[C_9H_{10}N_4O_4+H]^+$.

2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl) propanoic acid (18b). Compound **17b** (1 g, 3.569 mmol), $LiOH{\cdot}H_2O$ (224 mg, 5.354 mmol) in 20 mL of THF:H_2O (1:1) to afford **18b** (880 mg, 98%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.24 (brs, 1H), 8.20 (s, 1H), 5.47 (q, *J* = 7.6 Hz, 1H), 3.44 (s, 3H), 3.21 (s, 3H), 1.75 (d, *J* = 7.2 Hz, 3H); *m/z* (ES)$^+$: 253.08 $[C_{10}H_{12}N_4O_4+H]^+$.

General procedure for the synthesis of compounds (19a and 19b). DCC (1.0 equiv) was added to a stirred and cooled (0 °C) solution of acid compounds **18a-18b** (1.0 equiv) and propargyl alcohol (2.0 equiv) in dichloromethane (30 vol). After 5 min, DMAP (0.2 equiv) was added to the reaction mixture and the solution was allowed to stirred at room temperature for 16 h. As monitored by TLC, the reaction mixture was filtered and the filtrate was washed with water, dried with anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was triturated diethyl ether to afford the desired products **19a-19b**.

Prop-2-yn-1-yl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate (19a). Compound **18a** (2 g, 8.396 mmol), propargyl alcohol (0.96 mL, 16.792 mmol), DCC (1.73 g, 8.396 mmol) and DMAP (205 mg, 1.679 mmol) in 60 mL of DCM to afford **19a** (1.8 g, 78%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 1H), 5.15 (s, 2H), 4.82 (d, *J* = 2.8 Hz, 2H), 3.60 (s, 3H), 3.38 (s, 3H), 2.54 (t, *J* = 2.4 Hz, 1H); *m/z* (ES)$^+$: 277.21 $[C_{12}H_{12}N_4O_4+H]^+$.

Prop-2-yn-1-yl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate (19b). Compound **18b** (2 g, 7.933 mmol), propargyl alcohol (0.91 mL, 15.867 mmol), DCC (1.63 g, 7.933 mmol) and DMAP (193 mg, 1.586 mmol) in 60 mL of DCM to afford **19b** (1.92 g, 83%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (s, 1H), 5.61 (q, *J* = 7.6 Hz, 1H), 4.76 (s, 2H), 3.60 (t, *J* = 2.4 Hz, 1H), 3.44 (s, 3H), 3.20 (s, 3H), 1.76 (d, *J* = 7.2 Hz, 3H); *m/z* (ES)$^+$: 291.3 $[C_{13}H_{14}N_4O_4+H]^+$.

General procedure for the synthesis of compounds (20a, 20b and 21a, 21b)

Sodium ascorbate (0.2 equiv) and $CuSO_4{\cdot}5H_2O$ (0.2 equiv) was added in that ordered to a stirred a solution of propynyl compounds **19a-19b** (1.0 equiv) and 3-azidopropanoic acid (1.8 equiv) or 2-azido acetic acid (1.8 equiv) in ter-butyl alcohol (20 vol) and water (7 vol) at room temperature and reaction mixture was stirred at room temperature for 16 h. As monitored by TLC, reaction mixture was filtered, and washed with ethanol and concentrated. The residue was diluted in 10% methanol in dichloromethane, filtered and evaporated under reduced pressure. The crude compound was recrystallized with acetone to afford the desired solid products **20a-20b** and **21a-21b**.

3-(4-((2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7 (6H)-yl)acetoxy)methyl)-1H-1,2,3-triazol-1-yl)propanoic acid (20a). Compound **19a** (1 g, 3.622 mmol), 3-azidopropanoic acid (0.75 g, 6.519 mmol), sodium ascorbate (143 mg, 0.724 mmol) and $CuSO_4{\cdot}5H_2O$ (180 mg, 0.724 mmol) in *t*-BuOH (20 mL) and water (7 mL) to afford **20a** (1.2 g, 85%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.28 (s, 1H), 8.15 (s, 1H), 8.05 (s, 1H), 5.24 (s, 2H), 5.21 (s, 2H), 4.56 (t, *J* = 6.4 Hz, 2H), 3.44 (s, 3H), 3.20 (s, 3H), 2.89 (t, *J* = 6.8 Hz, 2H); *m/z* (ES)$^+$: 392.06 $[C_{15}H_{17}N_7O_6+H]^+$.

3-(4-(((2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl) propanoyl)oxy) methyl) -1H-1,2,3- triazol-1-yl) propanoic acid (20b). Compound **19b** (1 g, 3.447 mmol), 3-azidopropanoic acid (0.71 g, 6.204 mmol), sodium ascorbate (136 mg, 0.689 mmol) and $CuSO_4{\cdot}5H_2O$ (172 mg, 0.689 mmol) in *t*-BuOH (20 mL) and water (7 mL) to afford **20b** (1.09 g, 78%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.18 (brs, 1H), 8.19 (s, 1H), 8.10 (s, 1H), 5.59 (q, *J* = 7.2 Hz, 1H),

5.20 (s, 2H), 4.54 (t, *J* = 6.4 Hz, 2H), 3.44 (s, 3H), 3.20 (s, 3H), 2.88 (t, *J* = 6.8 Hz, 2H), 1.73 (d, *J* = 7.6 Hz, 3H); *m/z* $(ES)^+$: 406.02 $[C_{16}H_{19}N_7O_6+H]^+$.

2-(4-((2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7 (6H)-yl)acetoxy)methyl)-1H-1,2,3-triazol-1-yl)acetic acid (21a). Compound **19a** (0.8 g, 2.897 mmol), 2-azido acetic acid (526 mg, 5.215 mmol), sodium ascorbate (114 mg, 0.579 mmol) and $CuSO_4 \cdot 5H_2O$ (144 mg, 0.579 mmol) in *t*-BuOH (16 mL) and water (6 mL) to afford **21a** (0.9 g, 82%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 8.06 (s, 1H), 5.26–5.22 (m, 4H), 5.05 (s, 2H), 3.44 (s, 3H), 3.20 (s, 3H); *m/z* $(ES)^+$: 378.09 $[C_{14}H_{15}N_7O_6+H]^+$.

2-(4-(((2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)acetic acid (21b). Compound **19b** (0.8 g, 2.757 mmol), 2-azido acetic acid (501 mg, 4.963 mmol), sodium ascorbate (109 mg, 0.551 mmol) and $CuSO_4 \cdot 5H_2O$ (137 mg, 0.551 mmol) in *t*-BuOH (16 mL) and water (6 mL) to afford **21b** (0.96 g, 77%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.22 (brs, 1H), 8.20 (s, 1H), 8.10 (s, 1H), 5.60 (q, *J* = 7.2 Hz, 1H), 5.25–5.22 (m, 4H), 3.44 (s, 3H), 3.20 (s, 3H), 1.74 (d, *J* = 7.2 Hz, 3H); *m/z* $(ES)^+$: 392.06 $[C_{15}H_{17}N_7O_6+H]^+$.

General procedure for the synthesis of compounds 22-41

To a stirred solution of acid compounds **20a-20b** or **21a-21b** (1.0 equiv) and their corresponding aliphatic cyclic amines (2.0 equiv) or biphenyl amines (1.5 equiv) in dichloromethane (20 vol) was added HATU (1.5 equiv) and DIPEA (3.0 equiv) at room temperature. The reaction mixture was stirred for 16 h. On completion of the reaction as monitored by TLC, the reaction mixture was poured into water and extracted with 5% methanol in dichloromethane and washed with brine solution. The organic extracts was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude products were purified by silica-gel (100-200 mesh) short column chromatography using a gradient of 2 to 10 % methanol in dichloromethane to afford desired compounds **22-41**. 13C-NMR of some of new compounds could not be reported because they were synthesized in mg scale and tested for the screening of anticancer activity. HRMS and elemental analysis were reported instead of 13C-NMR, which are technically sufficient for characterization of new compounds.

(1-(3-(cyclohexylamino)-3-oxopropyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate (22). Yield: 66%; white solid; mp: 218–220^{o}C; R_f = 0.78, mobile phase: MeOH/CH_2Cl_2–1:9; IR (KBr cm^{-1}): 3445, 3287, 3123, 3091, 2928, 2850, 1746, 1709, 1682, 1645, 1557, 1472, 1456, 1375, 1223, 1028, 976, 955, 751; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (s, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 5.22 (s, 2H), 5.20 (s, 2H), 4.55 (t, *J* = 6.8 Hz, 2H), 3.50–3.47 (m, 1H), 3.44 (s, 3H), 3.21 (s, 3H), 2.67 (t, *J* = 6.8 Hz, 2H), 1.68–1.61 (m, 4H), 1.53–1.50 (m, 1H), 1.24–1.18 (m, 2H), 1.13–1.03 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.89, 166.91, 155.31, 151.61, 148.63, 141.81, 125.16, 107.11, 59.13, 48.51, 47.30, 46.36, 36.69, 32.95, 29.86, 27.96, 25.37, 24.76; *m/z* $(ES)^+$: 473.30 $[C_{21}H_{28}N_8O_5+H]^+$; HRMS (ESI): calcd for $C_{21}H_{29}N_8O_5$ $[M+H]^+$: 473.2260, found: 473.2256; Anal. calcd for $C_{21}H_{28}N_8O_5$: C, 53.38; H, 5.97; N, 23.72%; Found: C, 53.40; H, 5.99; N, 23.70%.

(1-(3-(cyclopentylamino)-3-oxopropyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate (23). Yield: 58%; white solid; mp: compound melting starts at 192^{o}C and completely melts at 198^{o}C; R_f = 0.75, mobile phase: MeOH/CH_2Cl_2–1:9; IR (KBr cm^{-1}): 3444, 3290, 3131, 3094, 2956, 2871, 1742, 1705, 1653, 1636, 1553, 1472, 1455, 1407, 1376, 1292, 1222, 1056, 1031, 977, 953, 761, 751; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.58 (s, 1H), 5.52 (d, *J* = 6.4 Hz, 1H), 5.34 (s, 2H), 5.07 (s, 2H), 4.68 (t, *J* = 6.4 Hz, 2H), 4.17–4.12 (m, 1H), 3.60 (s, 3H), 3.38 (s, 3H), 2.77 (t, *J* = 6.4 Hz, 2H), 1.95–1.90 (m, 2H), 1.61–1.58 (m, 4H), 1.30–1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 164.7, 156.5, 156.2, 155.3, 150.5, 142.9, 142.3, 118.3, 106.8, 55.5, 54.6, 50.7, 46.4, 34.5, 31.3, 29.4, 26.1; *m/z* $(ES)^+$: 459.25 $[C_{21}H_{26}N_8O_5+H]^+$; HRMS (ESI): calcd for $C_{20}H_{27}N_8O_5$ $[M+H]^+$: 459.2098, found: 459.210; Anal. calcd for $C_{20}H_{26}N_8O_5$: C, 52.38; H, 5.72; N, 24.44%; Found: C, 52.36; H, 5.77; N, 24.42%.

(1-(3-(cyclobutylamino)-3-oxopropyl)-1H-1,2,3-triazol-4-yl) methyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7 (6H)-yl)acetate (24). Yield: 44%; white solid; mp: 102–104^{o}C; R_f = 0.74, mobile phase: MeOH/CH_2Cl_2–1:9; IR (KBr cm^{-1}): 3445, 3288, 3131, 3097, 2958, 1740, 1705, 1651, 1638, 1553, 1471, 1456, 1383, 1376, 1237, 1223, 1058, 1032, 977, 954, 761, 751; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.59 (s, 1H), 5.84 (d, *J* = 7.2 Hz, 1H), 5.34 (s, 2H), 5.08 (s, 2H), 4.67 (t, *J* = 6.4 Hz, 2H), 4.35–4.30 (m, 1H), 3.60 (s, 3H), 3.38 (s, 3H), 2.77 (t, *J* = 6.0 Hz, 2H), 2.29–2.28 (m, 2H), 1.80–1.70 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.92, 166.89, 155.36, 151.59, 148.67, 141.82, 125.19, 59.11, 47.31, 46.21, 44.80, 36.36, 30.99, 29.87, 27.97, 15.07; *m/z* $(ES)^+$: 445 $[C_{19}H_{24}N_8O_5+H]^+$; HRMS (ESI): calcd for $C_{19}H_{25}N_8O_5$ $[M+H]^+$: 445.1942, found: 445.1945; Anal. calcd for $C_{19}H_{24}N_8O_5$: C, 51.35; H, 5.44; N, 25.21%; Found: C, 51.38; H, 5.46; N, 25.20%.

(1-(3-morpholino-3-oxopropyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate (25). Yield: 68%; yellow solid; mp: 122–124°C; R_f = 0.70, mobile phase: MeOH/CH_2Cl_2–1:9; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.60 (s, 1H), 5.34 (s, 2H), 5.10 (s, 2H), 4.72 (t, *J* = 6.0 Hz, 2H), 3.65–3.63 (m, 4H), 3.62–3.59 (m, 5H), 3.42–3.40 (m, 2H), 3.38 (s, 3H), 2.98 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.81, 166.93, 155.34, 151.65, 148.60, 141.79, 125.59, 107.14, 66.67, 66.33, 59.12, 47.26, 45.91, 45.61, 42.04, 33.11, 29.84, 27.91; *m/z* (ES-API)$^+$: 461.0 [$C_{19}H_{24}N_8O_6$+H]$^+$; HRMS (ESI): calcd for $C_{19}H_{25}N_8O_6$ [M+H]$^+$: 461.1897, found: 461.1897; Anal. calcd for $C_{19}H_{24}N_8O_6$: C, 49.56; H, 5.25; N, 24.34%; Found: C, 49.54; H, 5.27; N, 24.36%.

(1-(3-(cyclohexylamino)-3-oxopropyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate (26). Yield: 73%; off-white solid; R_f = 0.79, mobile phase: MeOH/CH_2Cl_2–1:9; mp: 162–164°C; IR (KBr cm^{-1}): 3307, 3141, 3129, 2931, 2854, 1740, 1705, 1660, 1633, 1547, 1471, 1454, 1431, 1381, 1296, 1229, 1202, 1097, 1055, 1036, 998, 976, 763, 751; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 2H), 5.56 (q, *J* = 7.6 Hz, 1H), 5.43 (d, *J* = 7.6 Hz, 1H), 5.31 (s, 2H), 4.67 (t, *J* = 6.0 Hz, 2H), 3.74–3.67 (m, 1H), 3.60 (s, 3H), 3.37 (s, 3H), 2.76 (t, *J* = 6.4 Hz, 2H), 1.86–1.80 (m, 5H), 1.69–1.57 (m, 4H), 1.38–1.25 (m, 2H), 1.17–0.99 (m, 2H); *m/z* (ES)$^+$: 487 [$C_{22}H_{30}N_8O_5$+H]$^+$; HRMS (ESI): calcd for $C_{12}H_{31}N_8O_5$ [M+H]$^+$: 487.2387, found: 487.2416; Anal. calcd for $C_{22}H_{30}N_8O_5$: C, 54.31; H, 6.22; N, 23.03%; Found: C, 54.35; H, 6.24; N, 23.09%.

(1-(3-(cyclopentylamino)-3-oxopropyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate (27). Yield: 62%; white solid; mp: 160–162°C; R_f = 0.76, mobile phase: MeOH/CH_2Cl_2–1:9; IR (KBr cm^{-1}): 3303, 3141, 3101, 2955, 2873, 1741, 1705, 1654, 1549, 1470, 1454, 1430, 1383, 1299, 1227, 1211, 1058, 1036, 1000, 973, 957, 762, 751; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 2H), 5.59–5.51 (m, 2H), 5.31 (s, 2H), 4.67 (t, *J* = 6.0 Hz, 2H), 4.16–4.11 (m, 1H), 3.60 (s, 3H), 3.37 (s, 3H), 2.76 (t, *J* = 6.4 Hz, 2H), 1.94–1.90 (m, 2H), 1.83 (d, *J* = 7.6 Hz, 3H), 1.63–1.55 (m, 4H), 1.30–1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 170.1, 156.8, 155.3, 152.3, 150.2, 143.6, 143.1, 118.0, 105.3, 55.7, 54.5, 50.6, 47.1, 34.7, 31.3, 30.1, 28.4, 26.2, 18.3; *m/z* (ES)$^+$: 473 [$C_{21}H_{28}N_8O_5$+H]$^+$; HRMS (ESI): calcd for $C_{21}H_{29}N_8O_5$ [M+H]$^+$: 473.2260, found: 473.2255; Anal. calcd for $C_{21}H_{28}N_8O_5$: C, 53.38; H, 5.97; N, 23.72%; Found: C, 53.41; H, 5.93; N, 23.70%.

(1-(3-(cyclobutylamino)-3-oxopropyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl) propanoate (28). Yield: 66%; white solid; mp: 60–62°C; R_f = 0.75, mobile phase: MeOH/CH_2Cl_2–1:9; IR (KBr cm^{-1}): 3301, 3140, 3116, 2967, 2949, 1738, 1702, 1665, 1645, 1546, 1471, 1455, 1427, 1295, 1244, 1232, 1198, 1000, 945, 930, 763, 749; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.70 (s, 1H), 5.73 (brs, 1H), 5.56 (q, *J* = 7.2 Hz, 1H), 5.30 (s, 2H), 4.66 (t, *J* = 6.4 Hz, 2H), 4.35–4.29 (m, 1H), 3.60 (s, 3H), 3.37 (s, 3H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.32–2.25 (m, 2H), 1.83 (d, *J* = 7.6 Hz, 3H), 1.80–1.64 (m, 4H); *m/z* (ES)$^+$: 459.25 [$C_{20}H_{26}N_8O_5$+H]$^+$; HRMS (ESI): calcd for $C_{20}H_{27}N_8O_5$ [M+H]$^+$: 459.2104, found: 459.2103; Anal. calcd for $C_{20}H_{26}N_8O_5$: C, 52.39; H, 5.72; N, 24.44%; Found: C, 52.42; H, 5.76; N, 24.48%.

(1-(3-(cyclopropylamino)-3-oxopropyl)-1H-1,2,3-triazol-4-yl) methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl) propanoate (29). Yield: 52%; off-white solid; mp: 118–120°C; R_f = 0.74, mobile phase: MeOH/CH_2Cl_2–1:9; IR (KBr cm^{-1}): 3444, 3263, 3146, 3116, 2955, 1753, 1701, 1666, 1652, 1547, 1470, 1456, 1430, 1384, 1298, 1230, 1192, 1031, 998, 953, 751; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.74 (s, 1H), 6.06 (brs, 1H), 5.54 (q, *J* = 7.6 Hz, 1H), 5.30 (s, 2H), 4.68 (t, *J* = 6.0 Hz, 2H), 3.60 (s, 3H), 3.36 (m, 3H), 2.76 (t, *J* = Hz, 2H), 2.65–2.64 (m, 1H), 1.84 (d, *J* = 7.6 Hz, 3H), 0.73 (q, *J* = 5.6 Hz, 2H), 0.42 (q, *J* = 1.6 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 170.48, 169.55, 155.16, 151.49, 148.81, 141.63, 139.87, 125.21, 106.80, 59.04, 54.84, 46.19, 36.24, 29.82, 28.0, 22.61, 17.85, 6.46, 6.44; *m/z* (ES)$^+$: 445.15 [$C_{19}H_{24}N_8O_5$+H]$^+$; HRMS (ESI): calcd for $C_{19}H_{25}N_8O_5$ [M+H]$^+$: 445.1942, found: 445.1945; Anal. calcd for $C_{19}H_{24}N_8O_5$: C, 51.35; H, 5.44; N, 25.21%; Found: C, 51.32; H, 5.44; N, 25.24%.

(1-(3-morpholino-3-oxopropyl)-1H-1,2,3-triazol-4-yl) methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate (30). Yield: 85%; off-white solid; R_f = 0.71, mobile phase: MeOH/CH_2Cl_2–1:9; mp: 68–70°C; IR (KBr cm^{-1}): 3445, 3132, 2960, 2927, 2855, 1748, 1703, 1660, 1652, 1541, 1472, 1456, 1299, 1272, 1234, 1197, 1113, 1037, 1027, 997, 763, 749; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.72 (s, 1H), 5.59 (q, *J* = 7.6 Hz, 1H), 5.31 (s, 2H), 4.71 (t, *J* = 6.4 Hz, 2H), 3.65–3.58 (m, 9H), 3.41–3.37 (m, 5H), 2.97 (t, *J* = 6.4 Hz, 2H), 1.84 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.59, 167.77, 155.07, 151.45, 148.65, 141.41, 139.83, 125.46, 106.72, 66.58, 66.26, 59.07, 54.72, 45.84, 45.54, 41.96, 33.03, 29.75, 27.90, 17.86; *m/z* (MM-ES+APCI)$^+$: 475.1 [$C_{20}H_{26}N_8O_6$+H]$^+$; HRMS (ESI): calcd for $C_{20}H_{27}N_8O_6$ [M+H]$^+$: 475.2053, found: 475.2064; Anal. calcd for $C_{20}H_{26}N_8O_6$: C, 50.63; H, 5.52; N, 23.62%; Found: C, 50.66; H, 5.50; N, 23.64%.

(1-(3-(4-ethylpiperazin-1-yl)-3-oxopropyl)-1H-1,2,3-triazol-4-yl) methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl) propanoate (31). Yield: 66%; off-white solid; mp: 68–70°C; R_f = 0.67, mobile phase: MeOH/CH_2Cl_2–1:9; IR (KBr cm^{-1}): 3422, 2952, 1700, 1654, 1547, 1473, 1456, 1407, 1365, 1276, 1237, 1129, 1028, 1006, 930, 879, 825, 953, 764, 748; ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.75–7.67 (m, 2H), 5.35 (q, *J* = 7.2 Hz, 1H), 5.30 (s, 2H), 4.67 (t, *J* = 5.6 Hz, 2H), 3.78–3.72 (m, 2H), 3.59–3.55 (m, 5H), 3.37–3.0 (m, 3H), 2.98–2.94 (m, 2H), 2.73–2.63 (m, 6H), 1.80 (d, *J* = 7.6 Hz, 3H), 1.19–1.15 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.64, 167.87, 155.15, 151.63, 148.56, 141.50, 139.87, 125.47, 107.18, 59.11, 56.66, 56.08, 54.77, 45.91, 45.86, 43.48, 39.91, 32.98, 29.72, 27.84, 18.21, 10.13; *m/z* (ES)$^+$: 502.23 [$C_{22}H_{31}N_9O_5$+H]$^+$; HRMS (ESI): calcd for $C_{22}H_{32}N_9O_5$ [M+H]$^+$: 502.2526, found: 502.2526; Anal. calcd for $C_{22}H_{31}N_9O_5$: C, 52.68; H, 6.23; N, 25.13%; Found: C, 52.62; H, 6.28; N, 25.17%.

(1-(2-([2,3'-bipyridin]-5-ylamino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate (32). Yield: 73%; off-white solid; mp: compound melting starts at 200^{o}C and completely melts at 218^{o}C; R_f = 0.44, mobile phase: MeOH/CH_2Cl_2–1:9; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 9.23 (s, 1H), 8.87 (s, 1H), 8.60 (d, *J* = 4.0 Hz, 1H), 8.39 (d, *J* = 8.0 Hz, 1H), 8.24 (s, 1H), 8.17–8.15 (m, 1H), 8.07–8.05 (m, 2H), 7.51–7.50 (m, 1H), 5.43 (s, 2H), 5.30 (s, 2H), 5.24 (s, 2H), 3.45 (s, 3H), 3.21 (s, 3H); *m/z* (ES)$^+$: 531 [$C_{24}H_{22}N_{10}O_5$+H]$^+$; HRMS (ESI): calcd for $C_{24}H_{23}N_{10}O_5$ [M+H]$^+$: 531.1852, found: 531.1857; Anal. calcd for $C_{24}H_{22}N_{10}O_5$: C, 54.34; H, 4.18; N, 26.40%; Found: C, 54.40; H, 4.25; N, 26.34%.

(1-(2-oxo-2-((4-(pyridin-2-yl)phenyl)amino)ethyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate (33). Yield: 76%; off-white solid; mp: 198–200^{o}C; R_f = 0.48, mobile phase: MeOH/CH_2Cl_2–1:9; IR (KBr cm^{-1}): 3326, 3115, 2928, 2850, 1743, 1705, 1661, 1626, 1572, 1540, 1469, 1434, 1405, 1376, 1312, 1290, 1244, 1227, 1210, 1088, 1053, 1030, 977, 955, 783, 761, 748; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 8.63 (d, *J* = 4.4 Hz, 1H), 8.23 (s, 1H), 8.09–8.07 (m, 3H), 7.93–7.91 (m, 1H), 7.87–7.83 (m, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.32–7.29 (m, 1H), 5.39 (s, 2H), 5.29 (s, 2H), 5.24 (s, 2H), 3.45 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 168.0, 164.72, 154.88, 151.45, 149.90, 148.45, 143.64, 141.39, 139.66, 137.62, 134.41, 127.59, 127.29, 120.12, 119.66, 106.77, 58.85, 52.72, 47.53, 29.95, 27.92; *m/z* (ES)$^+$: 530 [$C_{25}H_{23}N_9O_5$+H]$^+$; HRMS (ESI): calcd for $C_{25}H_{24}N_9O_5$ [M+H]$^+$: 530.190, found: 530.1901; Anal. calcd for $C_{25}H_{23}N_9O_5$: C, 56.71; H, 4.38; N, 23.81%; Found: C, 56.78; H, 4.42; N, 23.79%.

(1-(2-oxo-2-((4-(pyridin-3-yl)phenyl)amino)ethyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate (34). Yield: 63%; off-white solid; mp: compound melting starts at 240^{o}C and completely melts at 250^{o}C; R_f = 0.47 mobile phase: MeOH/CH_2Cl_2–1:9; IR (KBr cm^{-1}): 3434, 3327, 3115, 2927, 2850, 1742, 1705, 1697, 1671, 1626, 1573, 1545, 1475, 1455, 1433, 1382, 1320, 1290, 1243, 1230, 1209, 1088, 1062, 1030, 977, 951, 783, 761, 747, 712; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.89 (brs, 1H), 8.54 (brs, 1H), 8.23 (s, 1H), 8.07–8.04 (m, 2H), 7.75–7.70 (m, 4H), 7.48–7.45 (m, 1H), 5.39 (s, 2H), 5.29 (s, 2H), 5.24 (s, 2H), 3.45 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 164.5, 157.4, 153.3, 150.3, 148.1, 146.9, 146.3, 144.3, 142.9, 142.4, 140.1, 133.1, 127.3, 123.3, 120.1, 114.7, 105.3, 50.5, 50.3, 29.9, 28.1; *m/z* (ES)$^+$: 530 [$C_{25}H_{23}N_9O_5$+H]$^+$; HRMS (ESI): calcd for $C_{25}H_{24}N_9O_5$ [M+H]$^+$: 530.1894, found: 530.1921; Anal. calcd for $C_{25}H_{23}N_9O_5$: C, 56.72; H, 4.38; N, 23.80%; Found: C, 56.62; H, 4.33; N, 23.89%.

(1-(2-([2,3'-bipyridin]-5-ylamino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate (35). Yield: 72%; gray colour solid; mp: compound melting starts at 90^{o}C and completely melts at 102^{o}C; R_f = 0.46, mobile phase: MeOH/CH_2Cl_2–1:9; IR (KBr cm^{-1}): 3430, 2952, 1748, 1701, 1656, 1613, 1546, 1470, 1455, 1420, 1384, 1295, 1283, 1232, 1199, 1057, 1034, 998, 953, 848, 762, 749, 709; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (s, 1H), 8.67–8.61 (m, 2H), 8.28–8.24 (m, 2H), 7.96 (s, 1H), 7.79–7.68 (m, 3H), 7.41–7.38 (m, 1H), 5.57 (q, *J* = 7.6 Hz, 1H), 5.41–5.25 (m, 4H), 3.58 (s, 3H), 3.22 (s, 3H), 1.87 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 168.2, 157.3, 154.5, 153.1, 150.3, 148.1, 147.4, 143.3, 141.4, 135.8, 134.6, 128.7, 128.0, 124.1, 120.3, 119.7, 104.9, 56.1, 49.3, 30.3, 26.9, 18.1; *m/z* (ES)$^+$: 545 [$C_{25}H_{24}N_{10}O_5$+H]$^+$; HRMS (ESI): calcd for $C_{25}H_{25}N_{10}O_5$ [M+H]$^+$: 545.20, found: 545.2034; Anal. calcd for $C_{25}H_{24}N_{10}O_5$: C, 55.14; H, 4.43; N, 25.72%; Found: C, 55.17; H, 4.40; N, 25.78%.

(1-(2-oxo-2-((4-(pyridin-2-yl)phenyl)amino)ethyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate (36). Yield: 65%; off-white solid; mp: 120–122^{o}C; R_f = 0.46, mobile phase: MeOH/CH_2Cl_2–1:9; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (s, 1H), 8.85 (brs, 1H), 8.51 (d, *J* = 3.2 Hz, 1H), 8.18 (s, 1H), 8.14 (s, 1H), 8.04–8.02 (m, 1H), 7.72–7.67 (m, 4H), 7.45–7.42 (m, 1H), 5.62 (q, *J* = 6.8 Hz, 1H) 5.37 (s, 2H), 5.25 (s, 2H), 3.44 (s, 3H), 3.20 (s, 3H), 1.75 (d, *J* = 7.2 Hz, 3H); *m/z* (ES)$^+$: 544 [$C_{26}H_{25}N_9O_5$+H]$^+$; HRMS (ESI): calcd for $C_{26}H_{26}N_9O_5$ [M+H]$^+$: 544.2051, found: 544.2085; Anal. calcd for $C_{26}H_{25}N_9O_5$: C, 57.45; H, 4.64; N, 23.18%; Found: C, 57.54; H, 4.66; N, 23.27%.

(1-(2-oxo-2-((4-(pyridin-3-yl)phenyl)amino)ethyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1*H*-purin-7(6H)-yl)propanoate (37). Yield: 77%; off-white solid; mp: 132–134^{o}C; R_f = 0.47, mobile phase: MeOH/CH_2Cl_2–1:9; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.60 (s, 1H), 8.88 (brs, 1H), 8.53 (d, *J* = 8.8 Hz, 1H), 8.21 (s, 1H), 8.17 (s, 1H), 8.06–8.04 (m, 1H), 7.74–7.69 (m, 4H), 7.47–7.44 (m, 1H), 5.62 (q, *J* = 7.2 Hz, 1H) 5.37 (s, 2H), 5.25 (s, 2H), 3.44 (s, 3H), 3.20 (s, 3H),

1.75 (d, *J* = 7.2 Hz, 3H); *m/z* (ES)$^+$: 544 [$C_{26}H_{25}N_9O_5$+H]$^+$; HRMS (ESI): calcd for $C_{26}H_{26}N_9O_5$ [M+H]$^+$: 544.2051, found: 544.2076; Anal. calcd for $C_{26}H_{25}N_9O_5$: C, 57.44; H, 4.64; N, 23.19%; Found: C, 57.49; H, 4.74; N, 23.20%.

(1-(2-oxo-2-((4-(pyrimidin-5-yl)phenyl)amino)ethyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro -1H-purin-7(6H)-yl)propanoate (38). Yield: 72%; yellow solid; mp: 118–120^{o}C; R_f = 0.43, mobile phase: MeOH/CH_2Cl_2–1:9; IR (KBr cm^{-1}): 3436, 3114, 2951, 1748, 1701, 1655, 1604, 1545, 1471, 1454, 1416, 1384, 1295, 1234, 1197, 1055, 1035, 1000, 951, 839, 762, 748, 724; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.91 (s, 1H), 8.35 (s, 1H), 7.94 (s, 1H), 7.68–7.65 (m, 3H), 7.52 (d, *J* = 4.0 Hz, 2H), 5.43–5.19 (m, 5H), 3.58 (s, 3H), 3.25 (s, 3H), 1.86 (d, *J* = 7.2 Hz, 3H); *m/z* (ES)$^+$: 545 [$C_{25}H_{24}N_{10}O_5$+H]$^+$; HRMS (ESI): calcd for $C_{25}H_{25}N_{10}O_5$ [M+H]$^+$: 545.20, found: 545.2015; Anal. calcd for $C_{25}H_{24}N_{10}O_5$ C, 55.15; H, 4.44; N, 25.72%; Found: C, 55.28; H, 4.41; N, 25.85%.

(1-(3-oxo-3-((4-(pyridin-2-yl)phenyl)amino)propyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro -1H-purin-7(6H)-yl)acetate (39). Yield: 55%; off-white solid; mp: compound melting starts at 210^{o}C and completely melts at 220^{o}C; R_f = 0.45, mobile phase: MeOH/CH_2Cl_2–1:9; IR (KBr cm^{-1}): 3443, 2956, 1748, 1699, 1659, 1551, 1531, 1478, 1455, 1408, 1383, 1291, 1230, 1205, 1058, 1031, 978, 958, 762, 748; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (brs, 2H), 8.73 (brs, 1H), 8.58–8.53 (m, 1H), 8.35 (d, *J* = 6.8 Hz, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.81 (s, 1H), 7.56 (s, 1H), 7.51 (s, 1H), 7.48–7.45 (m, 1H), 5.33 (s, 2H), 5.11 (s, 2H), 4.84 (t, *J* = 5.6 Hz, 2H), 3.60 (s, 3H), 3.39 (s, 3H), 3.26–3.23 (m, 2H); *m/z* (ES)$^+$: 544 [$C_{26}H_{25}N_9O_5$+H]$^+$; HRMS (ESI): calcd for $C_{26}H_{26}N_9O_5$ [M+H]$^+$: 544.2056, found: 544.2085; Anal. calcd for $C_{26}H_{25}N_9O_5$: C, 57.45; H, 4.64; N, 23.19%; Found: C, 57.38; H, 4.70; N, 23.20%.

(1-(3-oxo-3-((6-phenylpyridazin-3-yl)amino)propyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro -1H-purin-7(6H)-yl)acetate (40). Yield: 56%; off-white solid; R_f = 0.40, mobile phase: MeOH/CH_2Cl_2–1:9; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.33 (brs, 1H), 8.32–8.34 (m, 1H), 8.23 (d, *J* = 9.6 Hz, 1H), 8.18 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 8.04 (s, 1H), 7.53–7.50 (m, 3H), 5.24 (s, 2H), 5.20 (s, 2H), 4.70 (t, *J* = 6.0 Hz, 2H), 3.43 (s, 3H), 3.20 (s, 3H), 3.17 (t, *J* = 6.8 Hz, 2H); *m/z* (ES)$^+$: 545 [$C_{25}H_{24}N_{10}O_5$+H]$^+$; HRMS (ESI): calcd for $C_{25}H_{25}N_{10}O_5$ [M+H]$^+$: 545.2003, found: 545.2034; Anal. calcd for $C_{25}H_{24}N_{10}O_5$: C, 55.14; H, 4.44; N, 25.72%; Found: C, 55.20; H, 4.47; N, 25.64%.

(1-(3-oxo-3-((4-(pyridin-3-yl)phenyl)amino)propyl)-1H-1,2,3-triazol-4-yl)methyl-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro -1H-purin-7(6H)-yl)propanoate (41). Yield: 76%; off-white solid; mp: compound melting starts at 92^{o}C and completely melts at 100^{o}C; R_f = 0.43, mobile phase: MeOH/CH_2Cl_2–1:9; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (brs, 1H), 8.59 (brs, 1H), 8.02–7.99 (m, 2H), 7.77 (s, 1H), 7.69 (s, 1H), 7.64–7.62 (m, 2H), 7.54–7.48 (m, 3H), 5.50 (q, *J* = 7.6 Hz, 1H), 5.30 (s, 2H), 4.78 (t, *J* = 6.0 Hz, 2H), 3.58 (s, 3H), 3.36 (s, 3H), 3.08 (t, *J* = 6.0 Hz, 2H), 1.79 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 169.3, 156.7, 154.2, 150.2, 148.3, 146.2, 142.6, 142.3, 140.1, 133.2, 129.3, 124.1, 117.0, 105.3, 56.1, 49.2, 47.3, 33.7, 30.1, 27.6, 18.1; *m/z* (ES)$^+$: 558 [$C_{27}H_{27}N_9O_5$+H]$^+$; HRMS (ESI): calcd for $C_{27}H_{28}N_9O_5$ [M + H]$^+$: 558.2207, found: 558.2228; Anal. calcd for $C_{27}H_{27}N_9O_5$: C, 58.16; H, 4.88; N, 22.61%; Found: C, 58.22; H, 4.89; N, 22.76%.

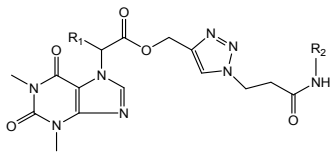
Biological evolution

Anticancer assay

The anticancer activity of the compounds was determined using MTT assay,[1] 1× 10^4 cells/well were seeded in 200 µL DMEM, supplemented with 10% FBS in each well of 96-well microculture plates and incubated for 24 hours at 37 ^{o}C in a CO_2 incubator. Compounds, diluted to the desired concentrations in culture medium, were added to the wells with respective vehicle control. After 48 hours of incubation, 10 µL MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (5 mg/mL) was added to each well and the plates were further incubated for 4 hours. Then the supernatant from each well was carefully removed, formazan crystals were dissolved in 100 µL of DMSO and absorbance at 540 nm wavelength was recorded. The results were represented, from the percentage of cytotoxicity the IC_{50} values are performed in triplicate and presented in the Table 1 & 2.

Table 1 Anticancer activity (IC_{50}) of aliphatic cyclic amide analogues (**22**–**31**)

Compound

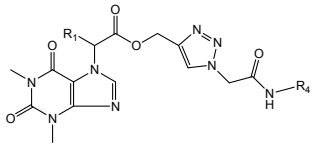


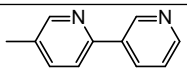
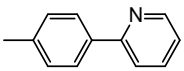
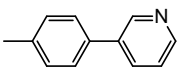
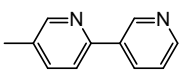
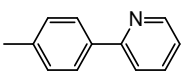
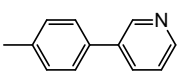
R_1	R_2	No.	A549 (Lung)	HT-29 (Colon)	MCF-7 (Breast)	A375 (Melanoma)
H	Cyclohexyl	**22**	**1.40 ± 0.09**	52.3±1.20	**2.20±0.32**	**2.51±0.58**
H	Cyclopentyl	**23**	4.70±0.14	15.4±1.29	12.8±0.33	60.8±4.61
H	Cyclobutyl	**24**	5.24±0.49	19.2±2.81	9.18±0.99	61.2±3.51
H	Morpholine	**25**	7.24±1.02	38.2±3.22	18.2±1.81	58.2±1.90
CH_3	Cyclohexyl	**26**	34.6±2.49	21.4±0.60	7.54±1.36	3.92±0.59
CH_3	Cyclopentyl	**27**	**1.21±0.16**	**2.30±0.16**	**2.31±0.41**	63.2±2.30
CH_3	Cyclobutyl	**28**	3.54±0.44	55.2±2.76	6.33±1.06	8.52±0.34
CH_3	Cyclopropyl	**29**	10.2±0.68	14.8±0.34	16.8±0.85	68.2±2.71
CH_3	Morpholine	**30**	5.82±0.39	6.2±0.59	5.92±0.30	24.8±1.83
CH_3	N-Ethylpiperazine	**31**	6.82±0.41	24.2±1.94	38.2±2.62	62.3±4.30
Combretastatin-A4			0.11±0.19	0.93±0.82	0.18±0.5	0.21±0.62

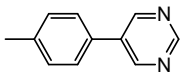
All the assays were performed in triplicate, IC_{50} values were reported as mean± SD

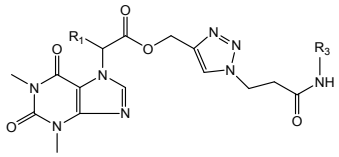
Table 2 Anticancer activity (IC_{50}) of biphenyl amide analogues (**32**–**41**)

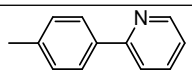
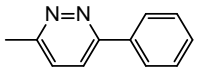
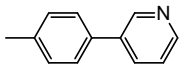
Compound



R_1	R_4	No.	A549 (Lung)	HT-29 (Colon)	MCF-7 (Breast)	A375 (Melanoma)
H		**32**	**2.12 ± 0.26**	54.3±2.10	53.8±3.5	3.80±0.31
H		**33**	4.70±0.35	56.8±2.36	8.41±0.63	9.34±0.55
H		**34**	53.4±2.02	17.3±0.43	**2.40±0.17**	3.62±0.34
CH_3		**35**	6.33±0.18	50.2±0.90	62.8±3.27	**2.80±0.29**
CH_3		**36**	4.90±0.09	**2.90±0.73**	**2.71±0.44**	58.2±1.58
CH_3		**37**	48.2±0.26	27.5±2.06	5.91±0.28	10.31±0.25

CH_3		**38**	6.82±0.12	5.82±0.46	18.4±0.51	50.4±3.41



R_1	R_3	**No.**				
H		**39**	4.20±0.18	**2.96±0.10**	5.72±0.54	61.4±2.56
H		**40**	**1.34±0.14**	11.7±0.19	13.5±0.49	48.2±2.86
CH_3		**41**	8.24±0.05	7.23±0.5	10.2±0.31	63.4±2.8
Combretastatin-A4			0.11±0.19	0.93±0.82	0.18±0.5	0.21±0.62

All the assays were performed in triplicate, IC_{50} values were reported as mean± SD

Docking studies

Protein-ligand docking studies are one of the main challenging aspects in the computer aided drug design. Docking studies was performed to the scheme of compounds (**22**–**41)** with the selective pharmacologically important drug targets for lung, breast, colon and melanoma cancers using docking module implemented in MOE 2010.12 (Molecular Operating Environment).[2] The drug targets namely epidermal growth factor receptor (EGFR) (PDB id: 4HJO), Human epidermal growth factor receptor 2 (HER2) (PDB id: 3PP0), Vascular endothelial growth factor receptor 2 (VEGFR2) (PDB id: 4AG8), Human placental Aromatase Cytochrome P 450 (PDB id: 4EQM), were retrieved from the protein databank (www.rcsb.org). Initially all the structures were protonated with addition of polar hydrogens followed by energy minimization with MMFF94x force field in order to get stabilized conformer of the protein. As per the literature the inhibitor binding sites were identified and highlighted with site finder module implemented in MOE software and docking was carried out with default parameters *i.e*., placement: triangle matcher, Recoring 1: London dG, Refinement: Force field, and maximum of 10 conformations of each compound were allowed to save in a separate database file in .mdb format.

Binding energy and Binding affinity calculations

The binding energy and binding affinity of docked complexes were calculated using molecular mechanics generalized Born interactions/volume integral (MM-GB/VI) implicit solvent method in MOE (Labute, 2008).[3] Non-bonded interaction energies between the receptor proteins and ligand molecule include van der Waals, coulomb and generalized born implicit solvent interactions energies are categorized as Born interaction energy. The binding affinity was calculated for each compound against various target proteins and reported in unit of Kcal/Mol.

References:

1 A. Kamal, A. Mallareddy, P. Suresh, V. L. Nayak, R. V. Shetti, N. S. Rao, J. R. Tamboli, T. B. Shaik, M. V. Vishnuvardhan, S. Ramakrishna, *Eur. J. Med. Chem.,* 2012, **47**, 530–545.

2 MOE (2011) (Molecular Operating Environment 2011.10) Chemical Computing Group Inc., Montreal, QC, Canada

3 P. Labute, The generalized born/volume integral (GB/VI) implicit solvent model: estimation of free energy of hydration using London dispersion instead of atomic surface area. *J. Comput. Chem.,* 2008, 29, 1693–1698.

Toxicity risk assessment screening

Table 3. Toxicity risk assessment screening of compounds (**22-41)** computed with MOLINSPERATION and OSIRIS server.

Compound	cLogP	Solubilitiy	Druglikeness	Drugscore	Mutagenic	Tumorigenic	Irritant	Reproductive effect
22	-0.65	-2.17	-5.27	0.39	No	No	No	No
23	-1.24	-2.26	-3.08	0.42	No	No	No	No
24	-1.33	-1.66	-1.28	0.5	No	No	No	No
25	-1.97	-0.3	-1.39	0.48	No	No	No	No
26	-0.47	-5.39	-7.59	0.27	No	No	No	No
27	-0.81	-5.12	-5.3	0.29	No	No	No	No
28	-1.15	-4.85	-3.58	0.32	No	No	No	No
29	-1.49	-4.58	-2.53	0.36	No	No	No	No
30	-1.79	-3.52	-3.18	0.37	No	No	No	No
31	-1.27	-3.32	1.27	0.61	No	No	No	No
32	-1.2	-2.02	-0.61	0.47	No	No	No	No
33	-0.2	-2.82	-0.61	0.45	No	No	No	No
34	-0.29	-3.12	-0.25	0.47	No	No	No	No
35	-1.02	-5.24	-2.91	0.26	No	No	No	No
36	-0.02	-6.03	-2.94	0.23	No	No	No	No
37	-0.11	-6.34	-2.56	0.56	No	No	No	No
38	-0.67	-6.13	-3.09	0.22	No	No	No	No
39	0.25	-3.09	-0.5	0.44	No	No	No	No
40	-0.22	-3.16	-0.74	0.42	No	No	No	No
41	0.34	-6.61	-2.47	0.21	No	No	No	No

ADME properties

Table 4. ADME properties of compounds (**22-41)** computed through MOE QSAR descriptor module.

Comp No Rule	logP(o/w) <5	MW <500	TPSA <140	HBA <10	HBD <5	nRotB <10	Molar Refractivity
22	-0.57	472.0	144.5	7	1	10.00	12.07
23	-1.21	444.1	153.3	7	2	10.00	11.13
24	-1.45	444.4	144.5	7	1	10.00	11.12
25	-2.78	460.0	144.9	8	0	9.00	11.31
26	0.13	486.2	147.7	7	2	10.00	12.51
27	-0.30	472.2	147.7	7	2	10.00	12.03
28	-0.74	459.0	147.7	7	2	10.00	11.56
29	-1.89	444.19	147.7	7	2	10.00	11.08
30	-2.07	474.2	148.2	8	1	9.00	11.75
31	-1.77	501.24	142.2	7	1	10.00	12.84
32	-1.53	530.18	170.3	9	1	10.00	13.63
33	-0.29	529.18	157.4	8	1	10.00	13.82
34	-0.25	529.18	157.4	8	1	10.00	13.82
35	-0.82	544.52	173.5	9	2	10.00	14.08
36	0.41	543.2	160.6	8	2	10.00	14.27
37	0.45	543.2	160.6	8	2	10.00	14.27
38	-1.69	544.19	173.5	9	2	10.00	14.08
39	-0.20	543.0	157.4	8	1	11.00	14.30
40	0.435	544.0	170	9	1	11.00	14.11
41	0.29	557.2	160.6	8	1	11.00	14.76

logP(o/w): Octanol-water partition coefficient.

TPSA: Topological polar surface area.

MW: Molecular weight.

HBA: Number of hydrogen-bond acceptors (O and N atoms).

HBD: Number of hydrogen-bond donors (HO and NH groups).
nRotB: Number of rotatable bonds.

Docking studies supporting data

Table 5
Bonding Characterization, dock score and binding affinities of compounds (**22-41)** with various pharmacological targets involved in cell proliferation

S. No	Compound	Dock Score (S)	Binding energy (kcal/mol)	Binding affinity	Bonding interaction	Bond length (Å)	Bond type
	Epidermal growth factor receptor (EGFR) (PDB id: 4HJO)						
1	22	-12.85	-28.15	9.90	Lys721NZ----------O	2.64	H-acc
2	23	-13.49	-23.43	9.70	Thr727OG----------H Tyr845OH----------O Ala847N----------O	1.99 2.18 3.00	H-don H-acc H-acc
3	24	-13.40	-33.60	9.94	Lys721NZ----------O	2.43	H-acc
4	25	-11.66	-27.72	8.50	Lys721NZ----------O	2.44	H-acc
5	26	-13.30	-28.27	11.17	Gly850O----------H Arg817NE---------O	1.57 2.50	H-don H-acc
6	27	-15.04	-26.07	11.11			
7	28	-12.69	-20.91	9.69	Asp831OD--------H Lys721NZ---------O	1.40 2.82	H-don H-acc
8	29	-13.06	-21.97	10.20	Gly850O----------H	2.14	H-acc
9	30	-15.33	-26.33	10.16	Tyr845O----------H Lys721NZ----------O	1.89 2.53	H-don H-acc
10	31	-14.01	-28.72	12.30	Arg817NE---------N	2.72	H-acc
11	32	-12.71	-38.93	10.67	Tyr867OH----------N	2.83	H-acc
12	33	-13.04	-26.53	10.48	Tyr867OH---------N	2.83	H-acc
13	34	-13.12	-33.31	8.75	Arg817NH----------O Arg817NE----------O	2.55 2.68	H-acc H-acc
14	35	-16.8	-36.81	12.64	Asp813OD---------H Lys721NZ---------O Arg817NE---------O	1.30 2.69 2.96	H-don H-acc H-acc
15	36	-13.5	-28.64	11.48	Arg817NE---------N	2.73	H-acc
16	37	-14.8	-34.83	11.41	Asn818OD---------H Asp831OD---------H Arg817NH---------O	1.59 2.12 2.79	H-don H-don H-acc
17	38	-14.4	-30.02	10.89	Arg817NE---------O	2.53	H-acc
18	39	-15.85	-29.55	9.84	Tyr845OH----------O	2.21	H-acc
19	40	-14.26	-41.39	11.49	Ala847N----------O	2.72	H-acc
20	41	-12.89	-36.17	10.05	Asp831OD---------H Lys721NZ----------O	1.42 2.64	H-don H-acc
	Human epidermal growth factor receptor (HER2) (PDB id: 3PP0)						
21	22	-15.42	-25.43	10.29	Thr862OG---------O Asp863N----------N	2.49 2.82	H-acc H-acc
22	23	-14.11	-20.35	10.57	Ser783OG---------N	2.95	H-acc
23	24	-13.56	-20.82	9.44	Ser783OG---------O Thr862OG--------O	3.00 2.84	H-acc H-acc
24	25	-13.16	-19.56	8.88			
25	26	-14.54	-33.3	10.61			
26	27	-15.23	-9.673	10.95	Asp863O---------H Ser783OG--------N	1.55 2.71	H-don H-acc
27	28	-13.25	-19.10	9.28			
28	29	-13.56	-17.26	9.74	Asp863O---------H Ser595OG-------N	1.48 2.90	H-don H-acc

S. No	Compound	Dock Score (S)	Binding energy (kcal/mol)	Binding affinity	Bonding interaction	Bond length (Å)	Bond type
29	30	-15.08	-12.08	10.88	Ser783OG---------O Thr798OG---------O Lys724NZ---------O Cys805N----------O	2.72 2.72 2.94 2.52	H-don H-don H-acc H-acc
30	31	-15.81	-13.90	12.21	Thr862OG--------O Asp863N---------O	2.73 2.93	H-acc H-acc
31	32	-16.27	-16.86	10.68	Ser783OG----------O Met801N----------N Thr862OG----------O	2.55 2.76 2.39	H-acc H-acc H-acc
32	33	-15.36	-25.73	9.86	Met801N----------O Cys805N----------O	2.77 2.90	H-acc H-acc
33	34	-14.68	-24.30	10.14	Lys724NZ----------N Ser783OG----------O Thr862OG----------O Thr798OG----------O	2.59 2.63 2.86 2.87	H-acc H-acc H-acc H-acc
34	35	-16.70	-20.10	13.18	Ser783OG----------O Thr798OG----------O Thr862OG----------O Lys736NZ----------N	2.59 2.90 2.79 2.68	H-don H-don H-don H-acc
35	36	-16.71	-25.52	14.10	Ser783OG----------O Thr798OG----------O Arg849NE----------N Thr862OG----------O	2.66 2.76 2.89 2.86	H-don H-don H-acc H-acc
36	37	-16.56	-22.96	11.94	Lys724NZ----------N	2.69	
37	38	-15.89	-30.71	12.79	Glu770OE----------H Asp863OD----------H Lys753NZ----------O Thr862OG----------O	1.31 1.78 2.72 2.49	H-don H-don H-acc H-acc
38	39	-13.78	-21.93	9.82			
39	40	-14.87	-28.17	10.12			
40	41	-16.52	-32.77	11.94	Lys753NZ----------N Met801N----------N Arg868NH----------O	2.81 2.89 2.77	H-acc H-acc H-acc
	Vascular endothelial growth factor receptor 2 (VEGFR2) (PDB id: 4AG8)						
41	22	-13.16	-23.08	10.08	Arg1027NH---------O	2.46	H-acc
41	23	-12.29	-22.36	9.59	Asp1046OD---------H Lys868NZ----------O Asp1046N----------O	1.39 2.81 2.63	H-don H-acc H-acc
43	24	-11.59	-14.05	8.63			
44	25	-13.92	-20.16	10.24	Ile1025N----------O Asp1046N----------O	2.65 2.77	H-acc H-acc
45	26	-14.82	-19.19	10.48	Asp1046N----------O	2.72	H-acc
46	27	-15.04	-20.28	10.35	Asp1046N----------O	2.30	H-acc
47	28	-15.12	-15.98	10.54	Asp1046N----------O	2.38	H-acc
48	29	-13.92	-26.48	10.12	Asp1046OD---------- H Arg1027NH---------O Asp1046N----------N	1.49 2.62 2.68	H-don H-acc H-acc
49	30	-16.11	-18.25	11.56	Cys919N----------O Asp1046N----------O	3.38 2.72	H-acc H-acc
50	31	-14.29	-19.79	11.03	Lys868NZ----------N	2.95	H-acc
51	32	-14.47	-33.73	10.36	Asp1027NH---------O	2.81	H-acc
52	33	-14.24	-24.97	10.44			
53	34	-14.04	-27.98	10.67	Glu855OE----------H	1.89	H-don

S. No	Compound	Dock Score (S)	Binding energy (kcal/mol)	Binding affinity	Bonding interaction	Bond length (Å)	Bond type
					Asn923N----------N Asp1046N----------O	2.59 3.03	H-acc H-acc
54	35	-16.32	-29.80	11.79	Asp1046OD----------H Asp1046N----------N	1.31 2.66	H-don H-acc
55	36	-15.38	-26.88	11.73	Lys868NZ----------N Lys868NZ----------O	2.99 2.97	H-acc H-acc
56	37	-15.66	-25.32	12.68	Asp1046N----------N	2.68	H-acc
57	38	-14.33	-32.87	10.99	Asp1046OD----------H Asp1046N----------O	1.39 2.42	H-don H-acc
58	39	-14.50	-33.70	10.55	Asp1046O----------H	1.83	H-don
59	40	-15.53	-29.27	10.63	Arg1027NH---------O	2.74	H-acc
60	41	-14.93	-35.95	12.01	Glu885OE----------H Asp1046N----------O	1.62 3.02	H-don H-acc
	Human placental Aromatase, Cytochrome P 450 (PDB id: 4EQM)						
61	22	-11.81	-24.32	8.76	Arg115NH----------N	2.57	H-acc
62	23	-13.68	-24.24	9.44	Arg115NH----------N Arg115NH----------O Gly439N----------O	2.86 2.53 2.71	H-acc H-acc H-acc
63	24	-11.49	-23.28	8.85			
64	25	-13.17	-16.69	9.58	Ala438N----------N	2.81	H-acc
65	26	-13.64	-22.60	9.79	Arg115NH----------O	2.50	H-acc
66	27	-13.42	-33.65	9.40	Thr310OG----------O Met374N----------O	2.46 2.90	H-don H-acc
67	28	-12.61	-24.31	8.82	Phe430O----------H	1.79	H-don
68	29	-12.92	-25.27	9.19	Thr310OG----------H	2.24	H-don
69	30	-14.13	-24.01	9.77	Arg115NH----------O Met374N----------O	2.85 2.69	H-acc H-acc
70	31	-13.48	-15.54	10.50	Arg115NH----------O	2.75	H-acc
71	32	-14.34	-32.99	10.89			
72	33	-14.14	-34.61	11.32	Ser314OG----------O	2.48	H-acc
73	34	-15.81	-21.81	11.44	Arg115NE----------N Ser199OG----------N Ala438N----------O	2.99 2.73 2.91	H-acc H-acc H-acc
74	35	-16.49	-29.64	11.97	Thr310OG----------O	2.55	H-don
75	36	-15.13	-26.80	11.72	Thr310OG----------O	2.62	H-acc
76	37	-15.79	-9.17	10.77	Pro429O----------H	2.63	H-don
77	38	-15.24	-21.81	11.66	Arg115NH----------O Gly439N----------O	2.56 2.95	H-acc H-acc
78	39	-16.58	-29.23	11.18	Thr310OG----------H Arg115NH----------O	1.78 2.29	H-don H-acc
79	40	-14.09	-25.20	10.58	Thr310OG----------H	2.24	H-don
80	41	-15.07	-35.54	10.85	Arg115NH----------O	2.57	H-acc

Experimental Supporting Data

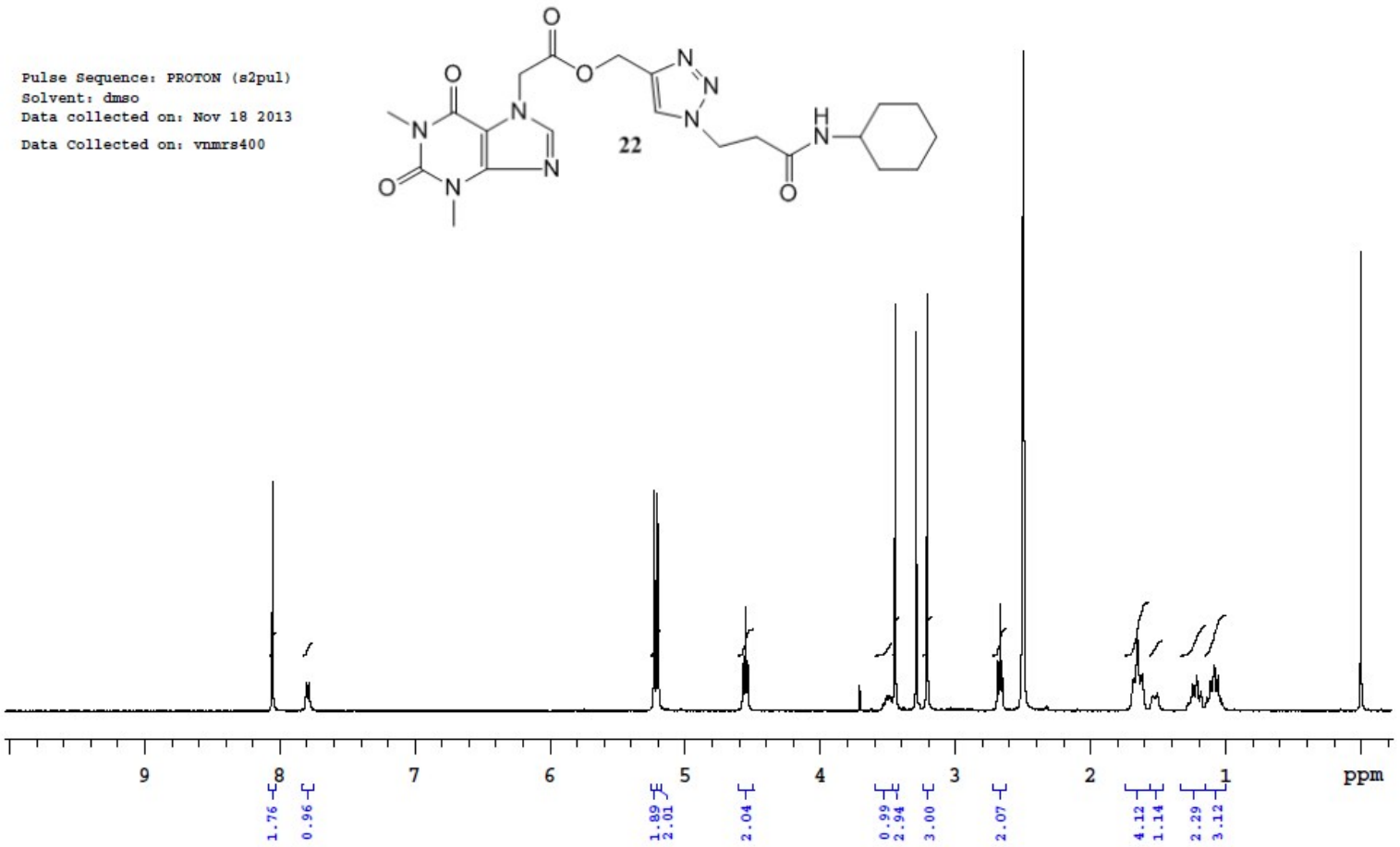


Fig-1: ^{1}H NMR spectrum of compound-**22**

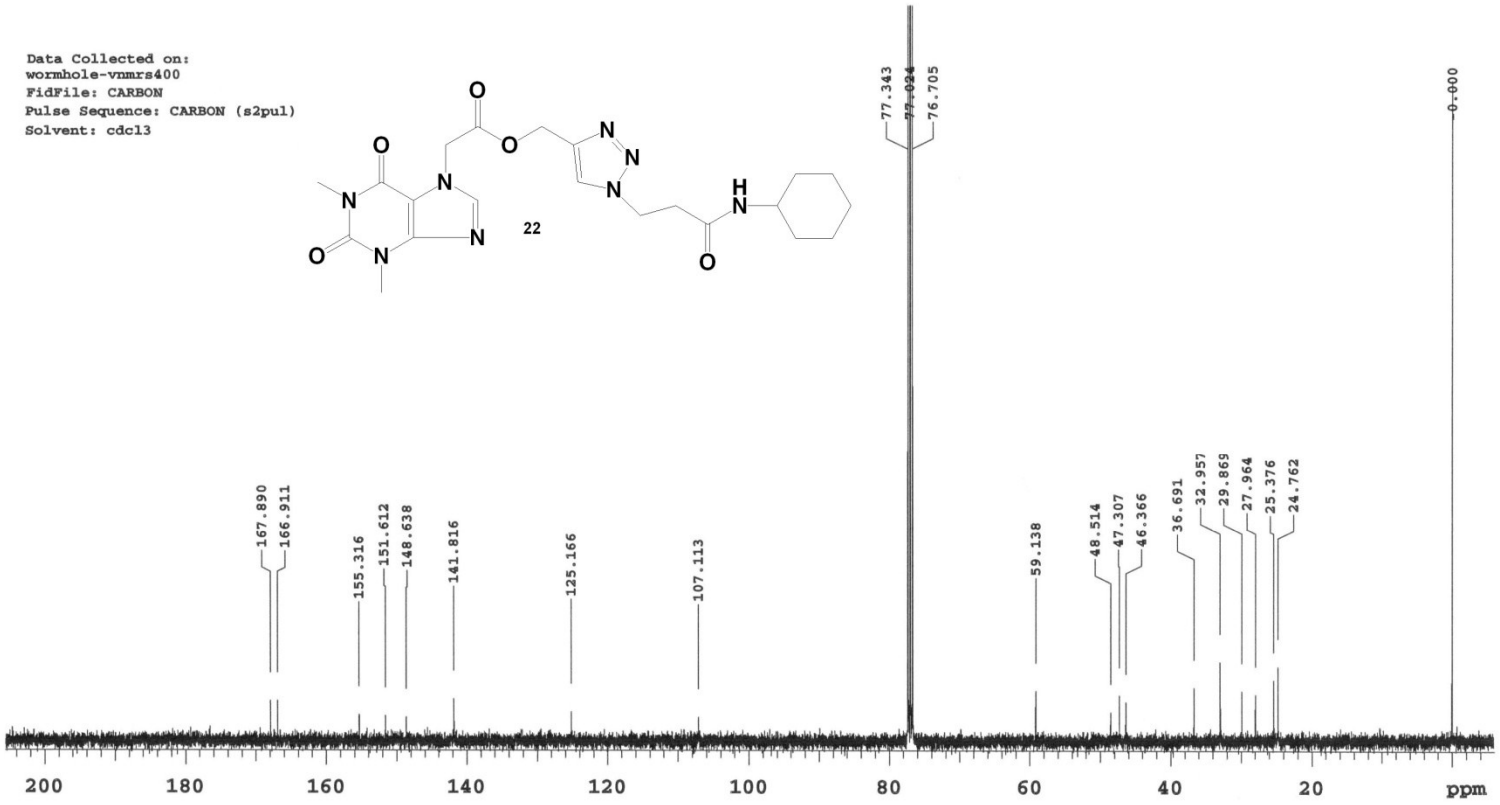
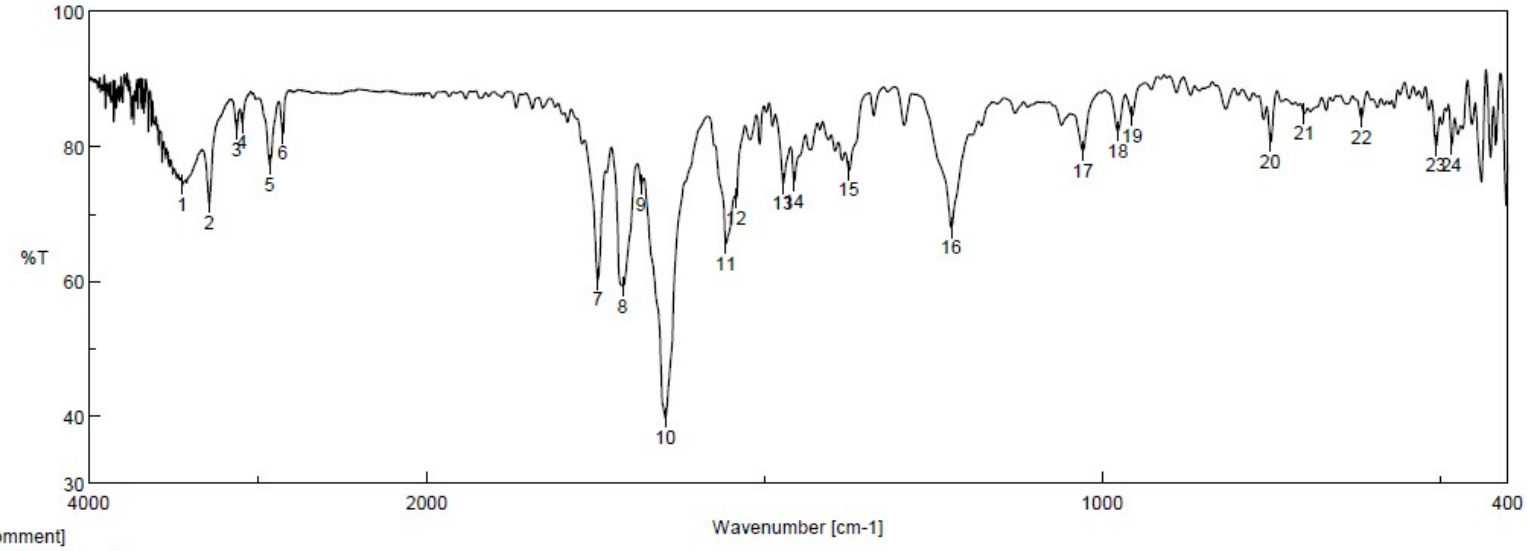


Fig-2: ^{13}C NMR spectrum of compound-**22**



[Comment]

Sample Name	1
Comment	KBr Pellet
User	BSN
Division	QC
Company	SAPALA ORGANICS PVT LTD

[Data Information]

Creation Date	4/6/2015 12:29 PM
Data array type	Linear data array
Horizontal	Wavenumber [cm-1]
Vertical	%T
Start	349.053 cm-1
End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3445.2	74.272	2	3287.1	71.545	3	3123.2	82.497	4	3091.3	83.470	5	2928.4	77.197
6	2850.3	81.901	7	1746.2	60.212	8	1709.6	59.284	9	1682.6	74.272	10	1645.9	39.738
11	1557.2	65.571	12	1541.8	72.242	13	1472.4	74.459	14	1456.0	74.752	15	1375.0	76.486
16	1223.6	67.941	17	1028.8	79.348	18	976.8	82.278	19	955.6	84.493	20	751.1	80.594
21	701.0	84.875	22	616.1	84.253	23	506.2	80.141	24	483.1	80.197			

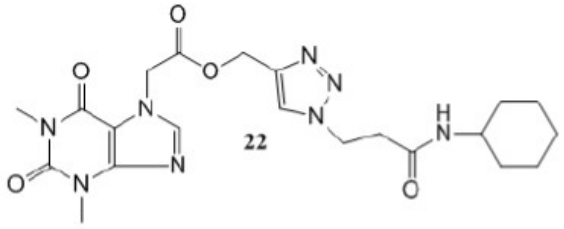
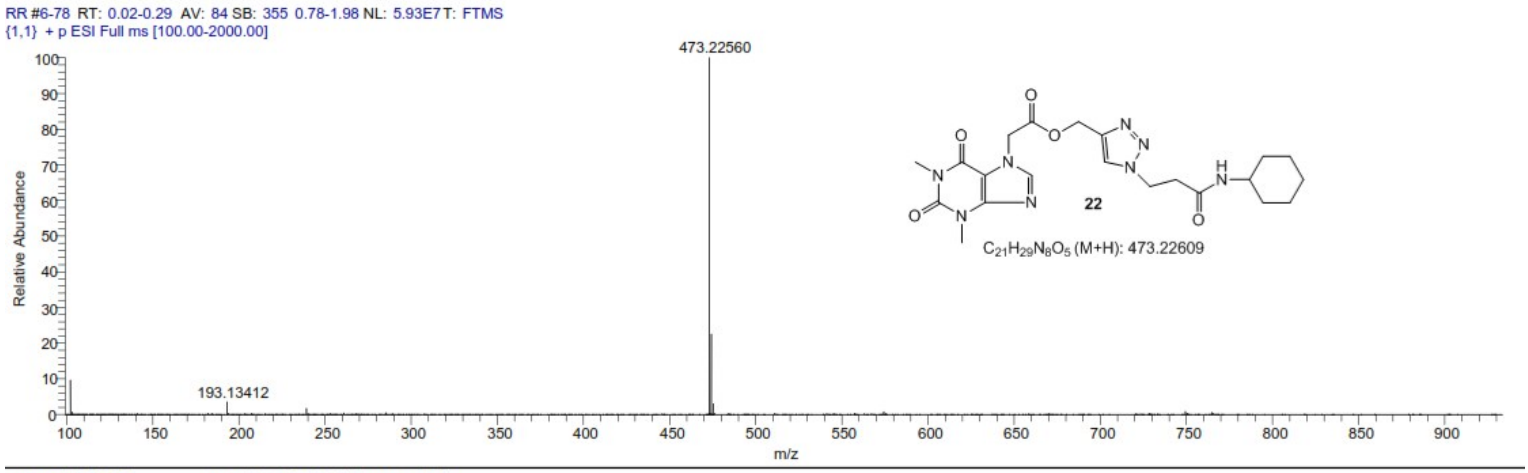


Fig-3: IR spectrum of compound-**22**

National Centre for Mass Spectrometry



RR-S9#8-30 RT: 0.03-0.10 AV: 24
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
473.22556	80853112.0	100.00				

Fig-4: HRMS spectrum of compound-**22**

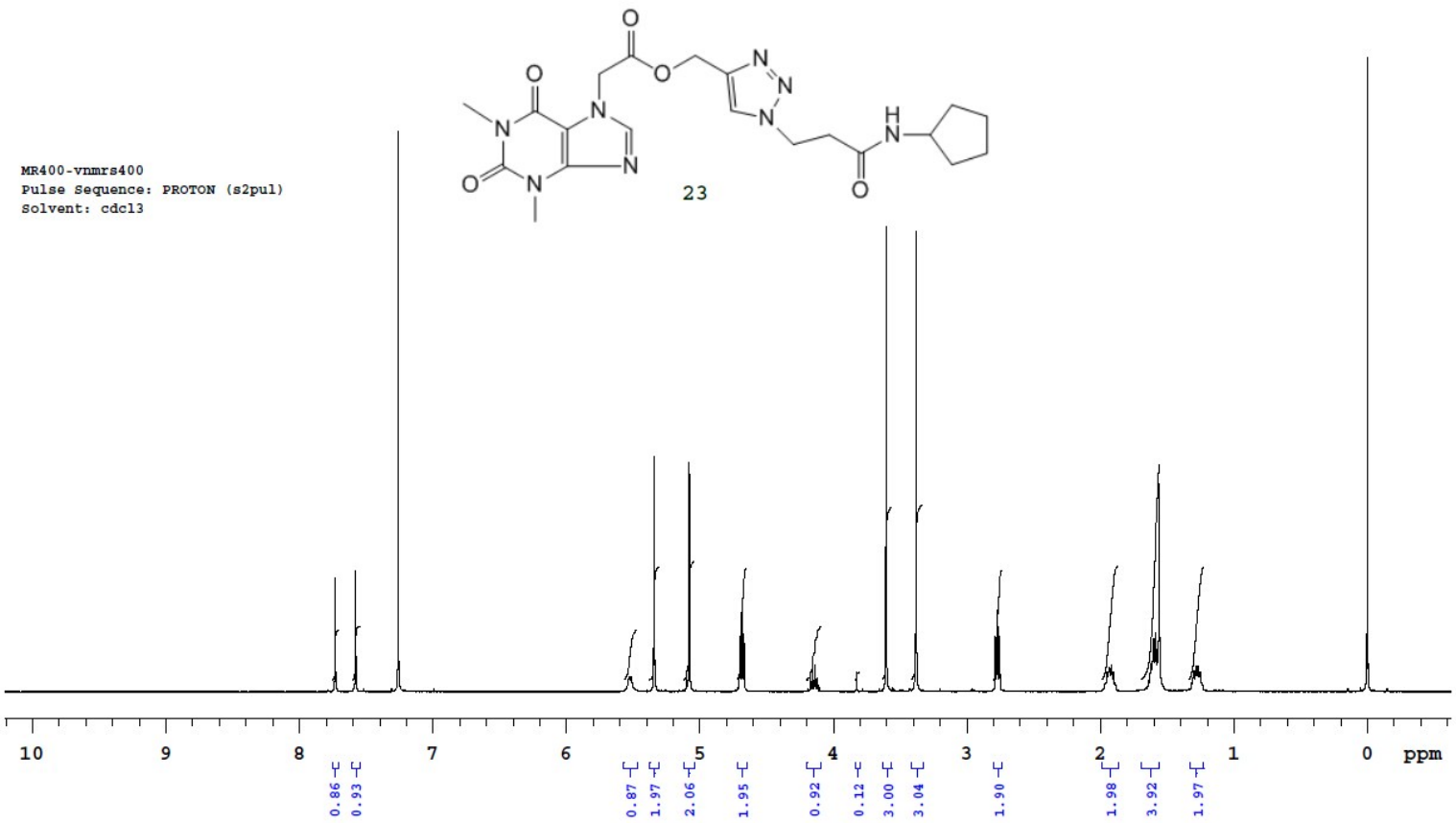


Fig-5: ^{1}H NMR spectrum of compound-**23**

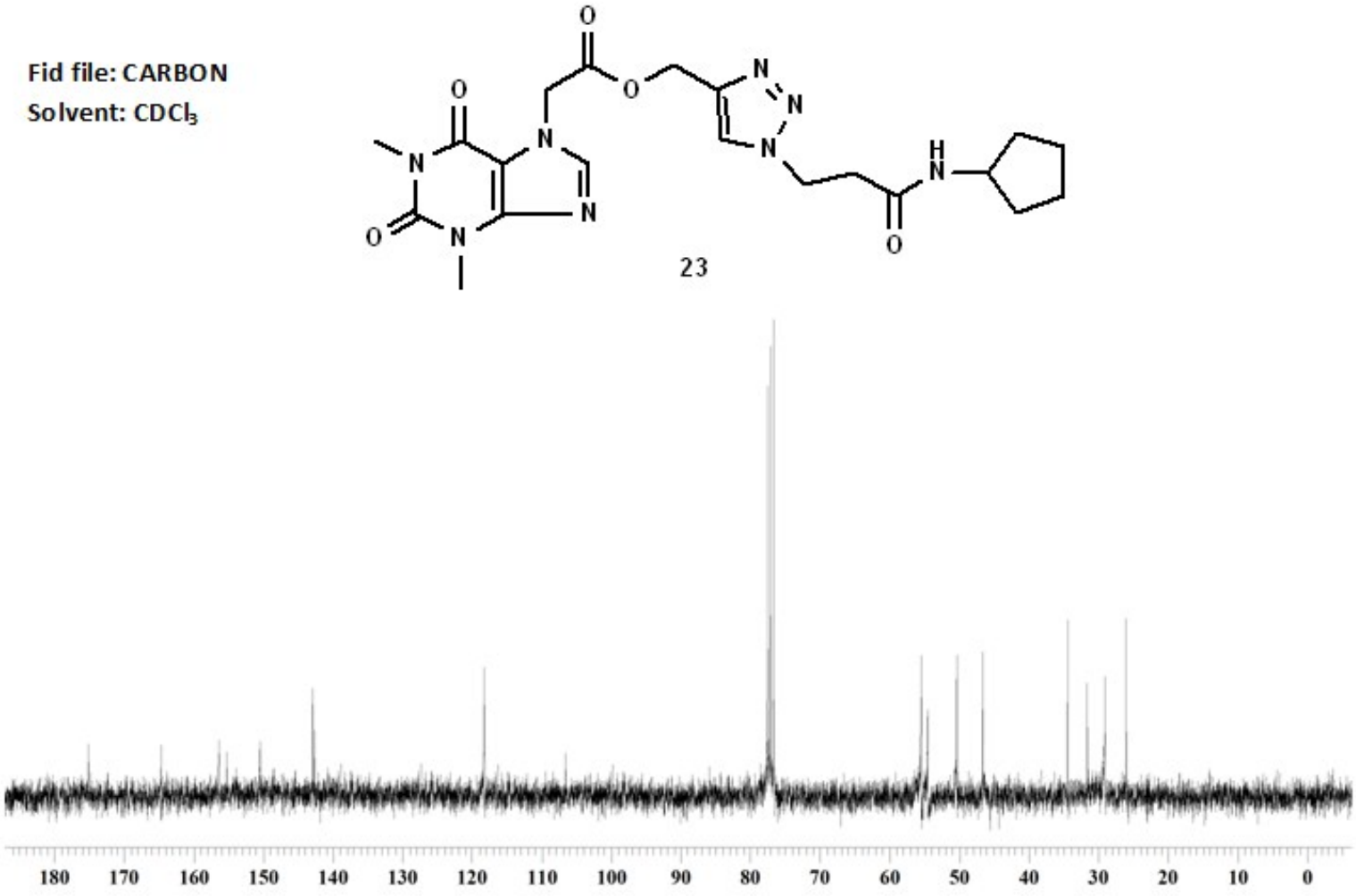
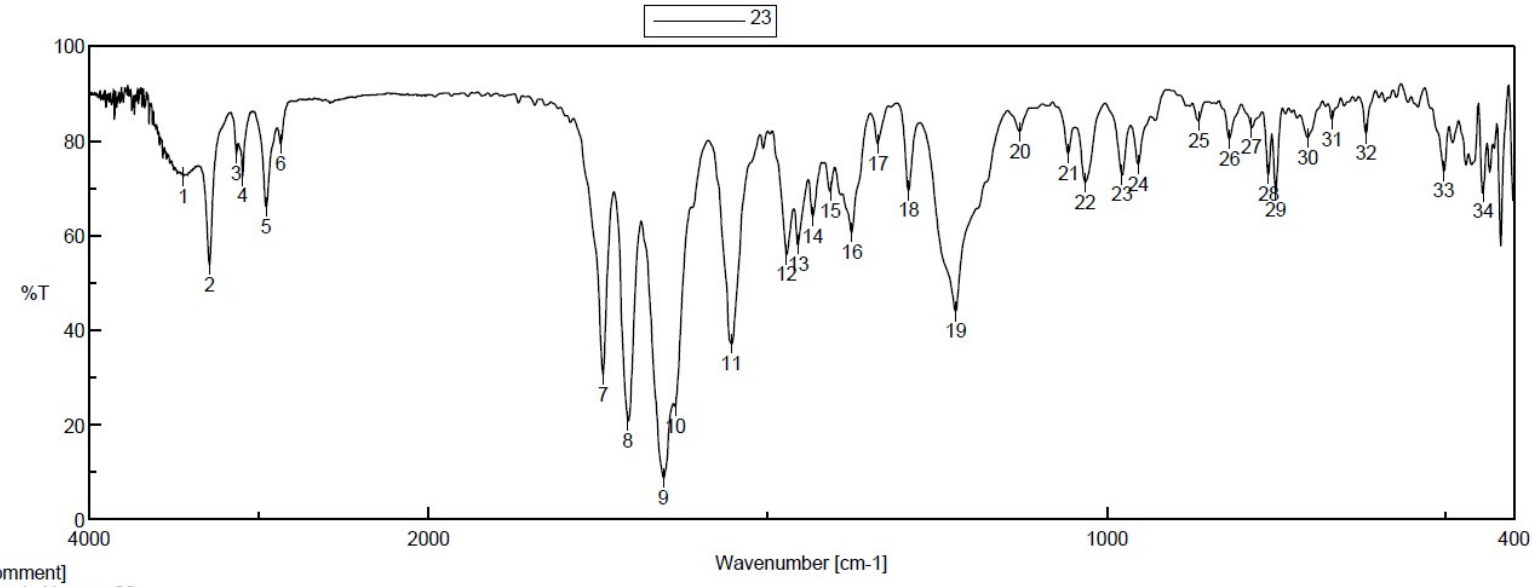


Fig-6: ^{13}C NMR spectrum of compound-**23**



[Comment]

Sample Name	23
Comment	KBr Pellet
User	BSN
Division	QC
Company	SAPALA ORGANICS PVT LTD

[Data Information]

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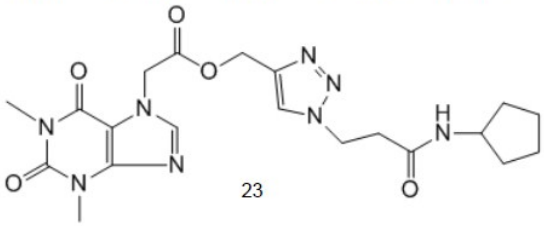
Vertical	%T
Start	349.053 cm-1
End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7729

Result of Peak Picking

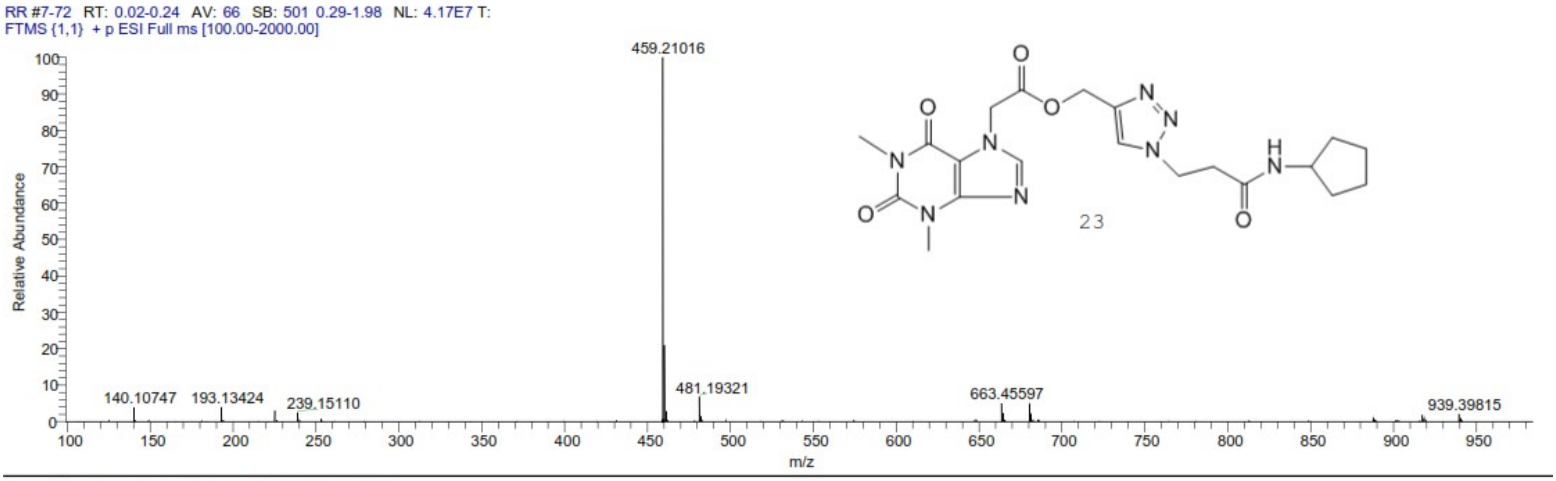
No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3444.2	72.467	2	3290.0	53.762	3	3131.8	77.178	4	3094.2	72.579	5	2956.3	66.031
6	2871.5	79.385	7	1742.4	30.464	8	1705.7	20.728	9	1653.7	8.705	10	1636.3	23.768
11	1553.4	37.058	12	1472.4	55.965	13	1455.0	58.018	14	1433.8	64.009	15	1407.8	69.333
16	1376.0	60.576	17	1337.4	79.325	18	1292.1	69.447	19	1222.6	43.882	20	1128.2	81.877
21	1056.8	77.263	22	1031.7	71.229	23	977.7	72.742	24	953.6	75.017	25	864.9	84.210
26	819.6	80.381	27	786.8	82.774	28	761.7	72.824	29	751.1	69.430	30	703.9	80.676
31	668.2	84.474	32	618.1	81.499	33	503.3	73.572	34	445.5	69.255			



23

Fig-7: IR spectrum of compound-**23**

National Centre for Mass Spectrometry



RR-8#8-30 RT: 0.03-0.10 AV: 23
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
459.21004	68032168.0	100.00	459.20989	0.32	11.5	$C_{20}H_{27}O_5N_8$

Fig-8: HRMS spectrum of compound-**23**

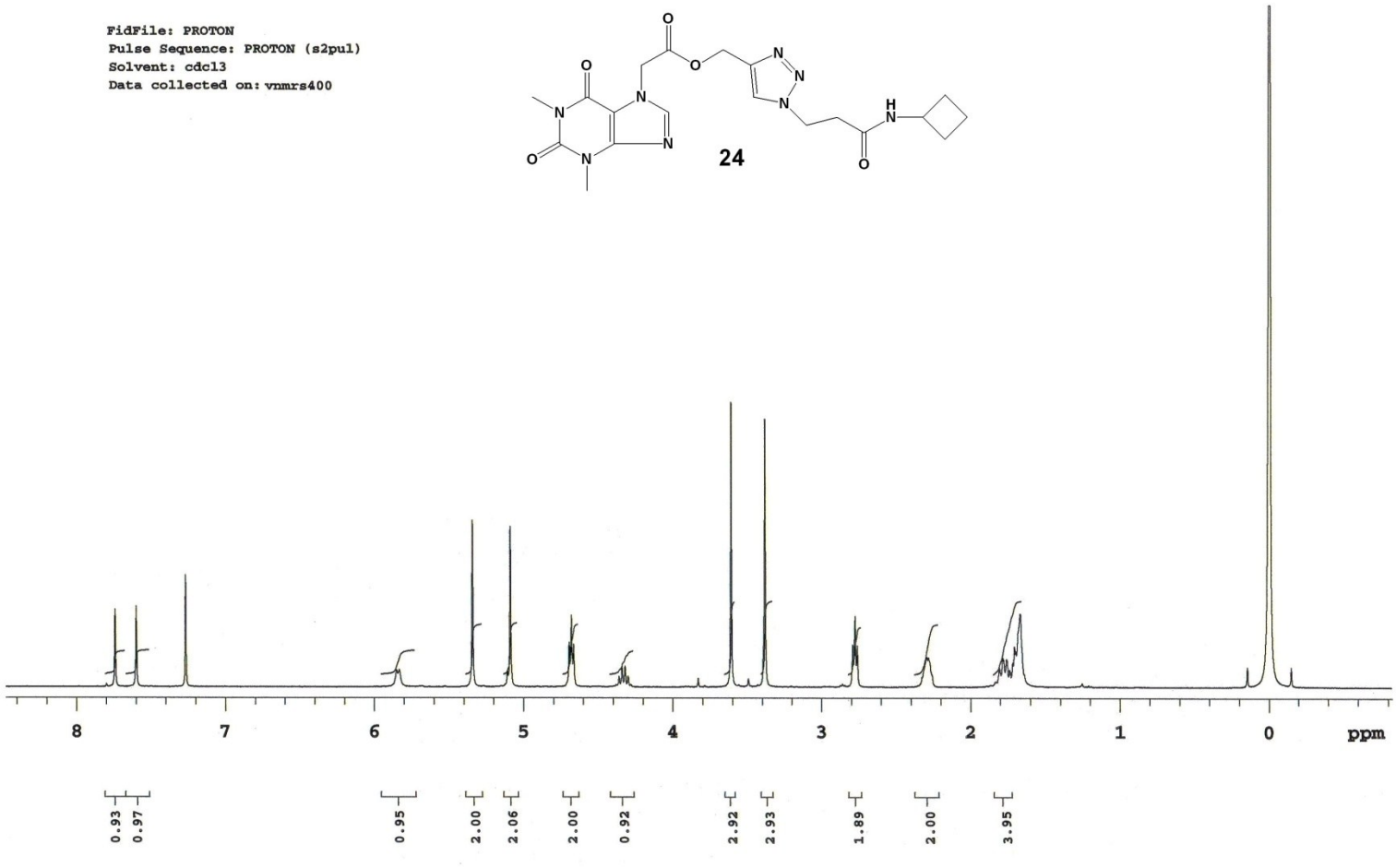


Fig-9: ^{1}H NMR spectrum of compound-**24**

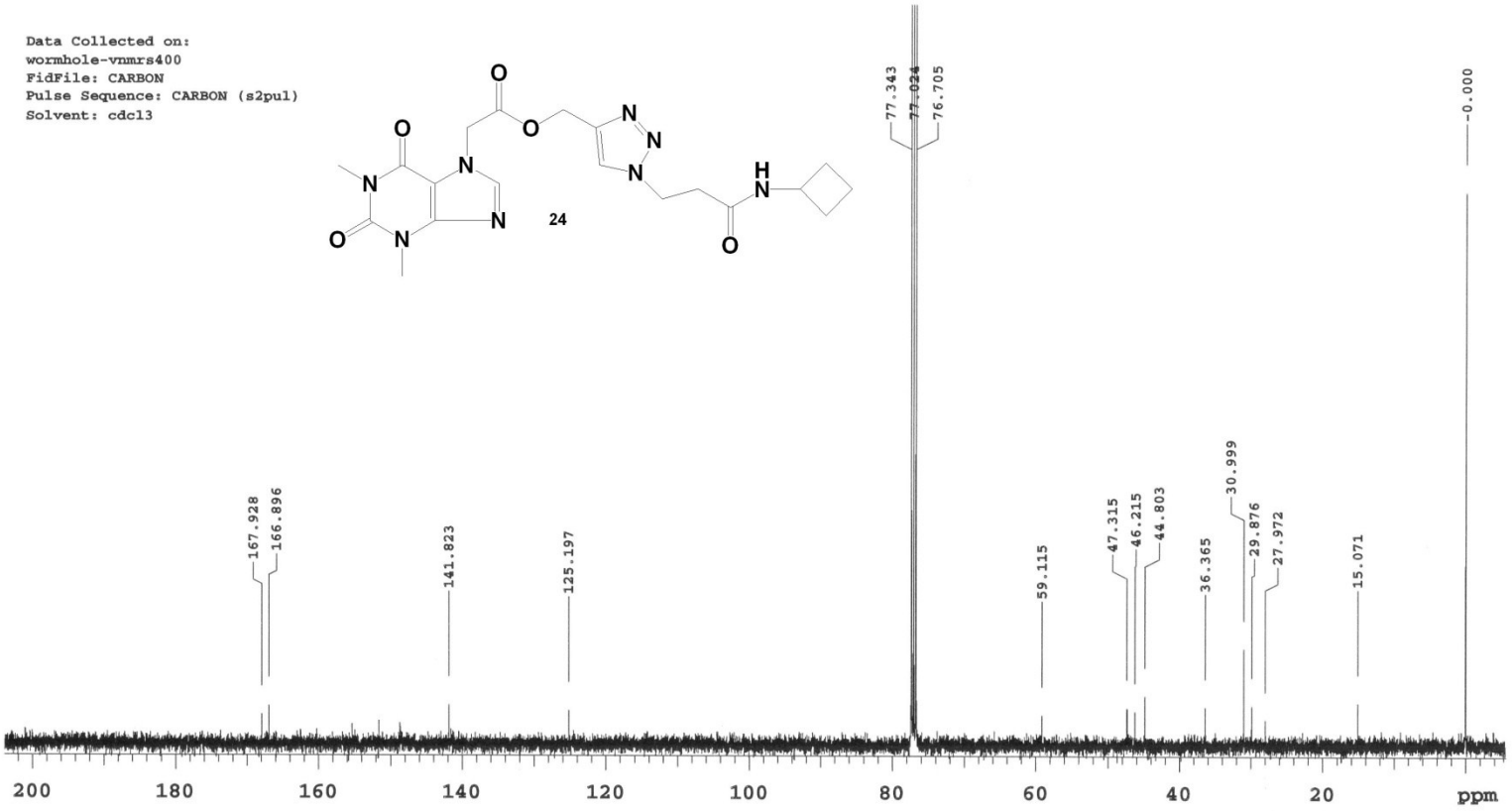
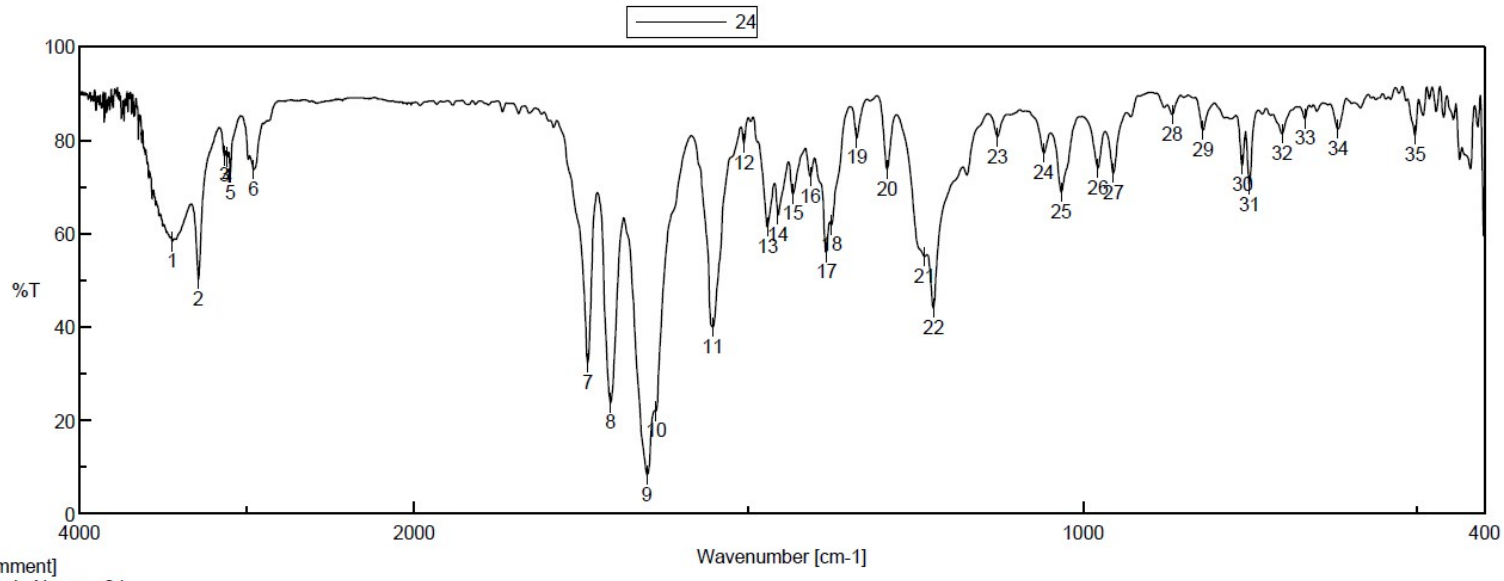


Fig-10: ^{13}C NMR spectrum of compound-**24**



[Comment]

Sample Name	24
Comment	KBr Pellet
User	BSN
Division	QC
Company	SAPALA ORGANICS PVT LTD

[Data Information]

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Vertical	%T
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End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3445.2	58.255	2	3288.0	50.187	3	3131.8	76.627	4	3116.4	76.377	5	3097.1	72.868
6	2958.3	73.626	7	1740.4	32.241	8	1705.7	23.734	9	1651.7	8.277	10	1638.2	21.886
11	1553.4	39.912	12	1507.1	79.222	13	1471.4	61.454	14	1456.0	63.930	15	1433.8	68.423
16	1407.8	72.202	17	1383.7	55.970	18	1376.0	61.798	19	1338.4	80.456	20	1293.0	73.766
21	1237.1	55.051	22	1223.6	43.997	23	1128.2	80.669	24	1058.7	77.226	25	1032.7	68.829
26	977.7	73.980	27	954.6	72.867	28	866.8	85.451	29	820.6	82.078	30	761.7	74.640
31	751.1	70.434	32	702.9	81.278	33	668.2	84.562	34	619.0	82.336	35	503.3	80.993

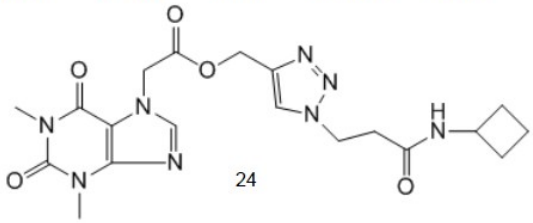
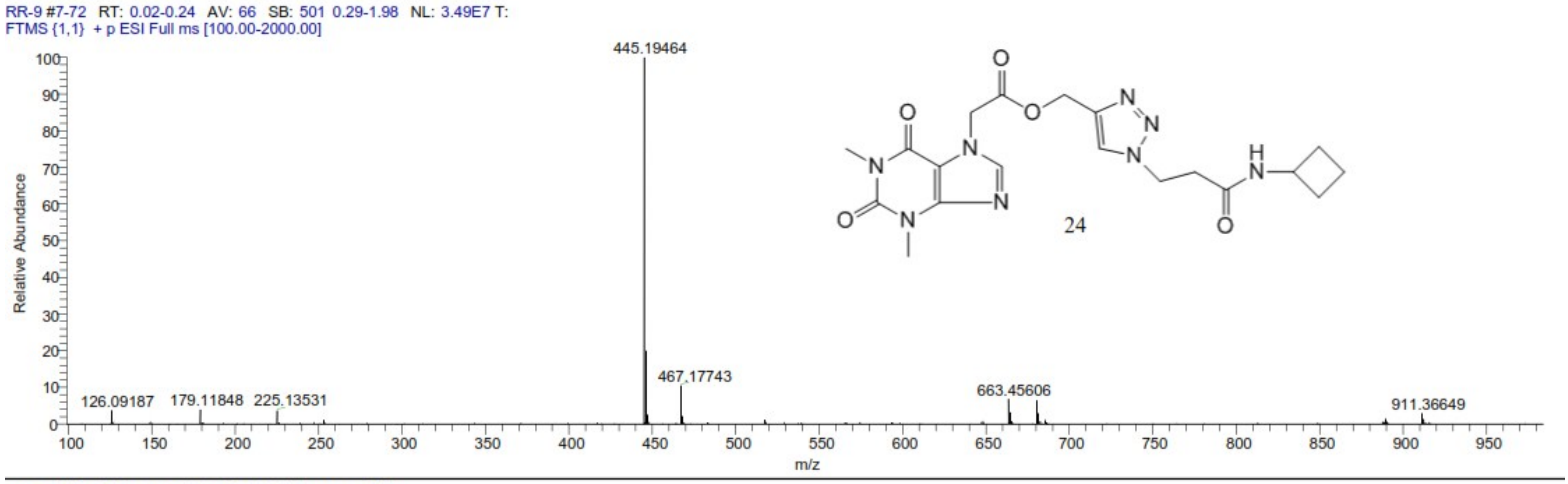


Fig-11: IR spectrum of compound-**24**

National Centre for Mass Spectrometry



RR-9#8-30 RT: 0.03-0.10 AV: 23
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
445.19455	59490636.0	100.00	445.19424	0.70	11.5	$C_{19}H_{25}O_5N_8$

Fig-12: HRMS spectrum of compound-**24**

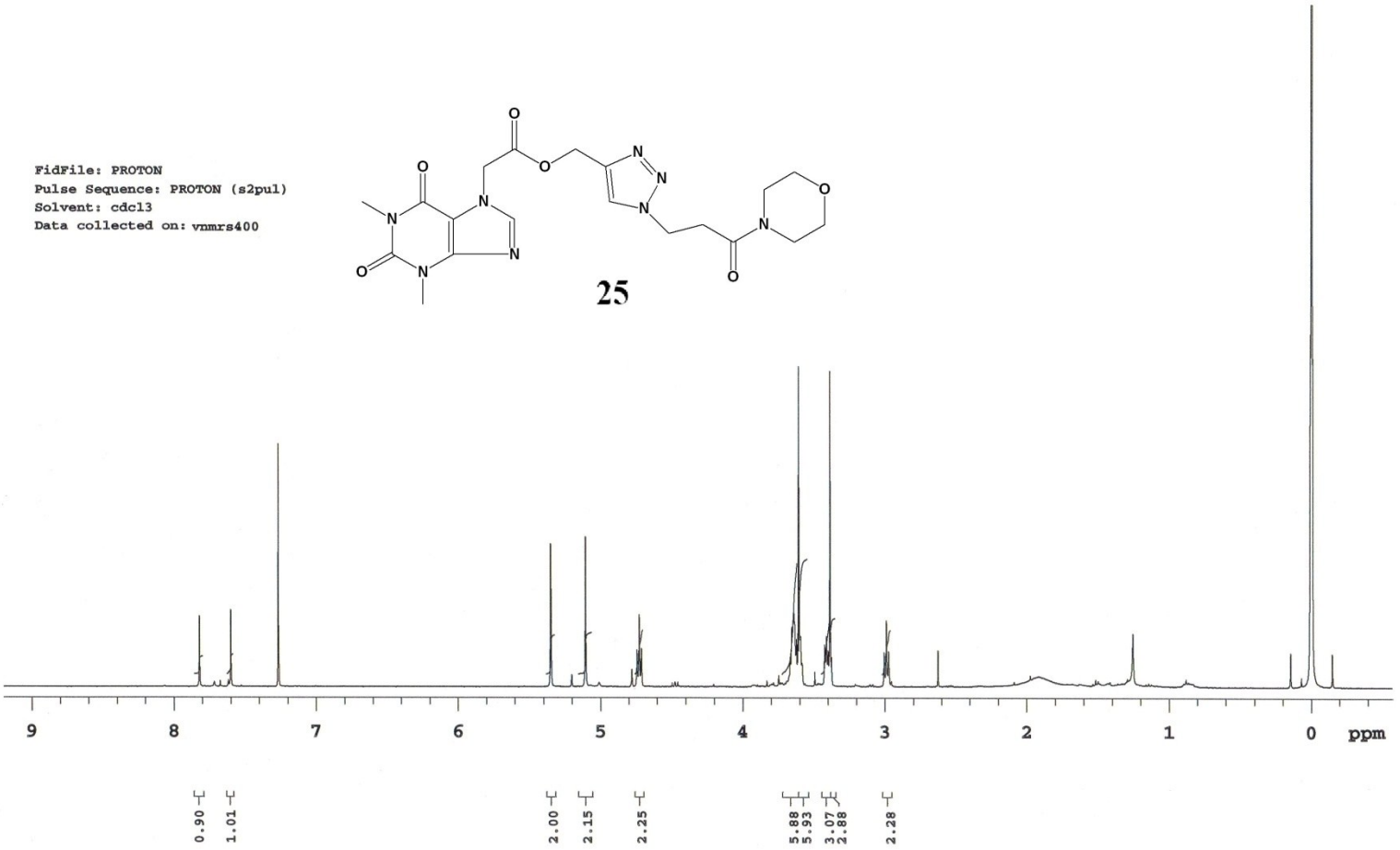


Fig-13: ^{1}H NMR spectrum of compound-**25**

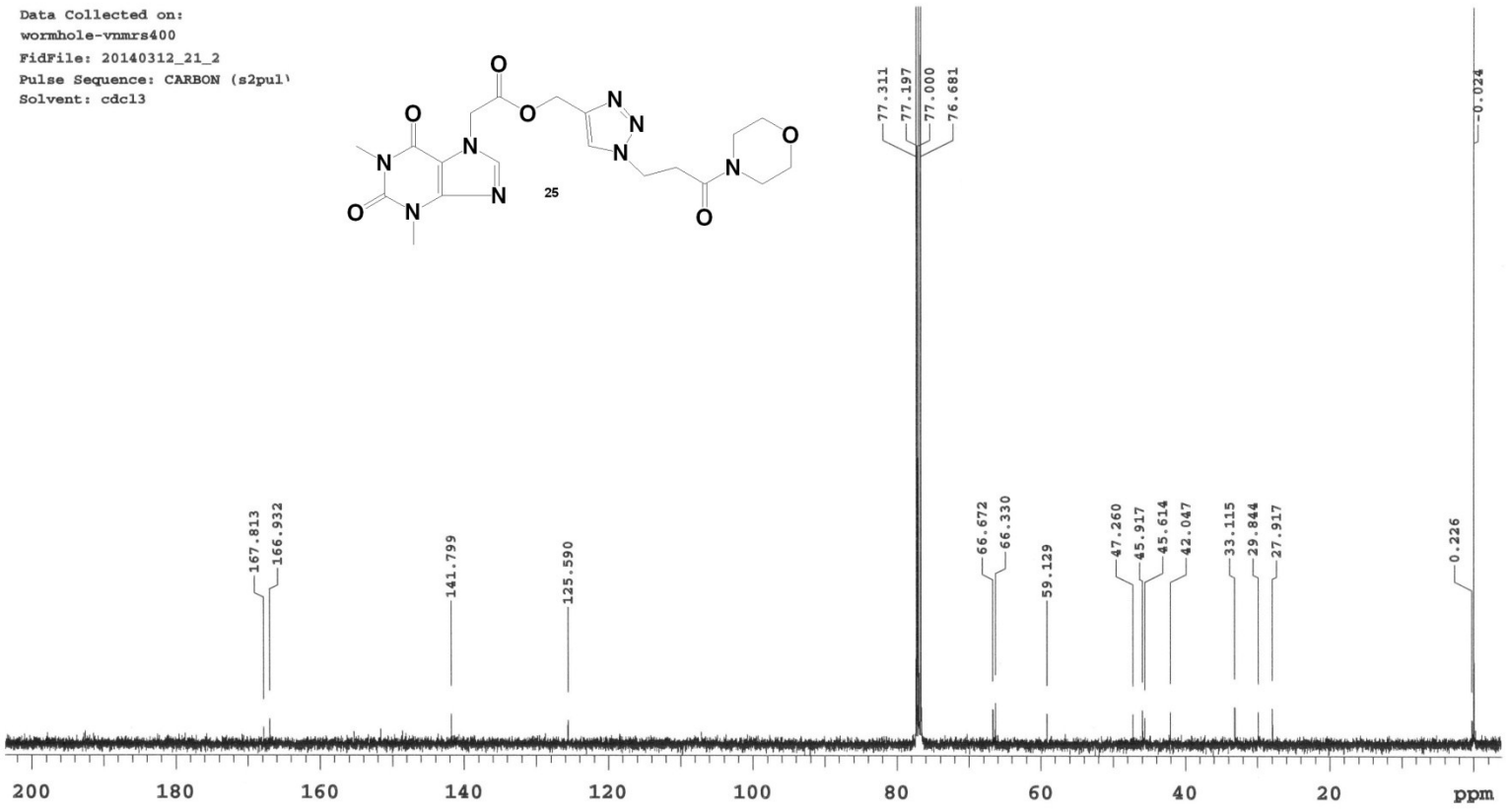
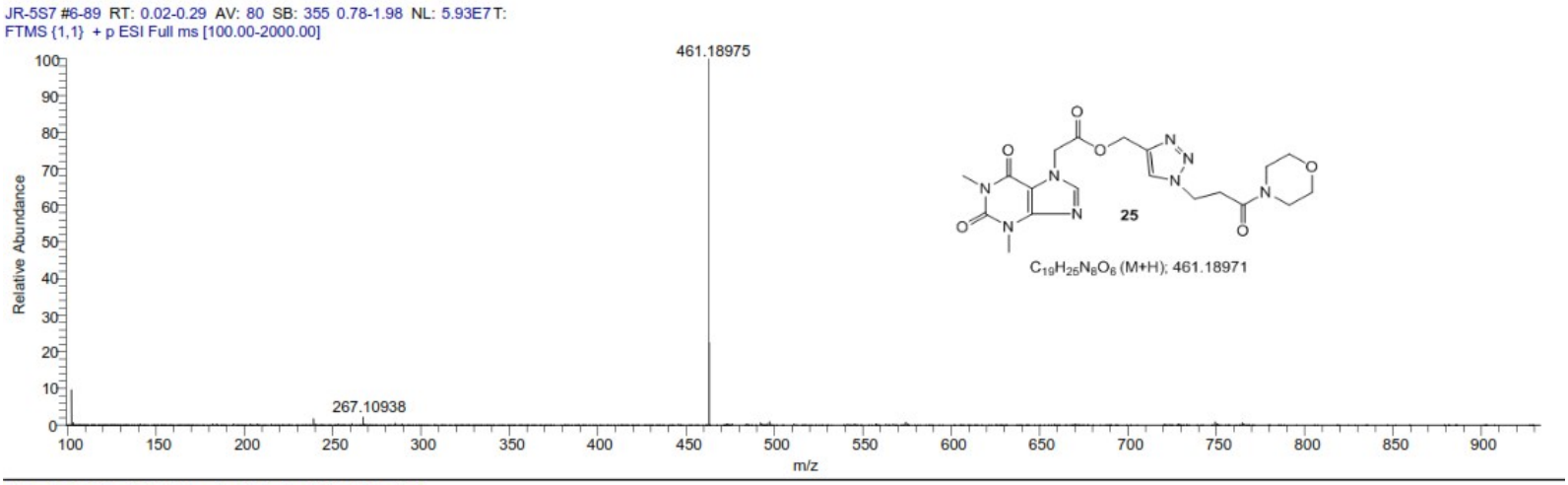


Fig-14: ^{13}C NMR spectrum of compound-**25**

National Centre for Mass Spectrometry



JR-5S7#8-30 RT: 0.03-0.10 AV: 27
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
461.18970	80853112.0	100.00				

Fig-15: HRMS spectrum of compound-**25**

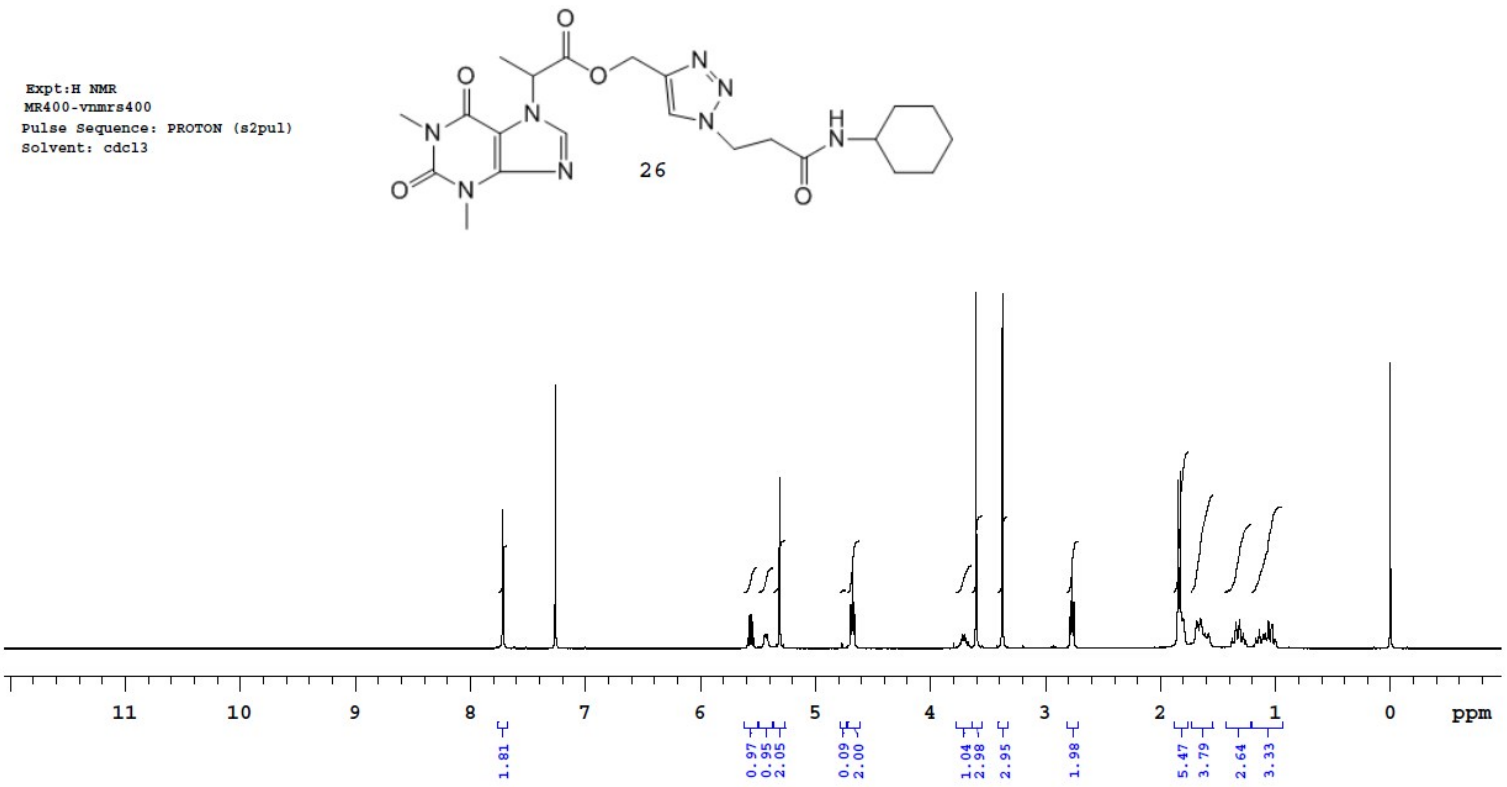
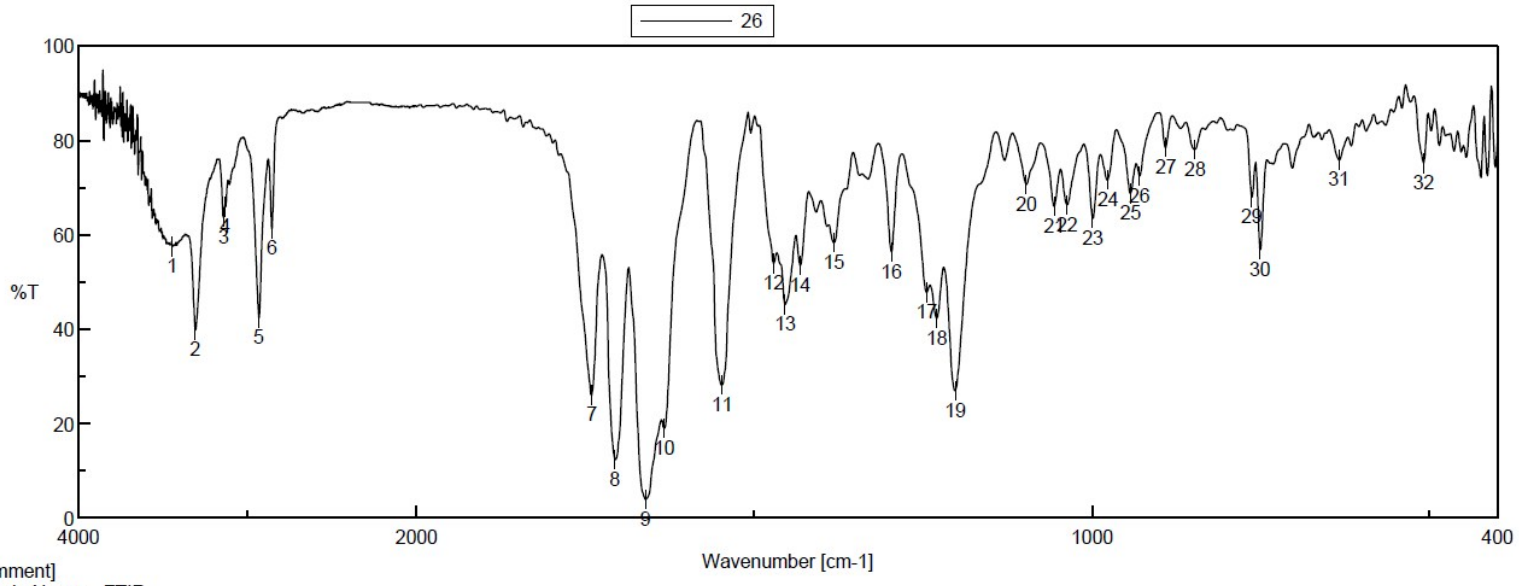


Fig-16: ^{1}H NMR spectrum of compound-**26**



[Comment]

Sample Name	FTIR
Comment	KBr Pellet
User	BSN
Division	QC
Company	SAPALA ORGANICS PVT LTD

[Data Information]

Creation Date	4/6/2015 12:44 PM
Data array type	Linear data array
Horizontal	Wavenumber [cm-1]
Vertical	%T
Start	349.053 cm-1
End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3444.2	57.380	2	3307.3	39.776	3	3141.5	63.710	4	3129.9	65.895	5	2931.3	42.394
6	2854.1	61.217	7	1740.4	25.985	8	1705.7	12.322	9	1660.4	3.852	10	1633.4	18.918
11	1547.6	28.076	12	1471.4	53.859	13	1454.1	45.143	14	1431.9	53.478	15	1381.7	58.283
16	1296.9	56.376	17	1244.8	47.673	18	1229.4	42.228	19	1202.4	26.980	20	1097.3	70.603
21	1055.8	65.969	22	1036.6	66.290	23	998.9	63.469	24	976.8	71.537	25	943.0	68.780
26	929.5	72.411	27	891.0	78.461	28	847.6	78.069	29	763.7	67.939	30	751.1	56.692
31	634.5	75.830	32	509.1	75.089									

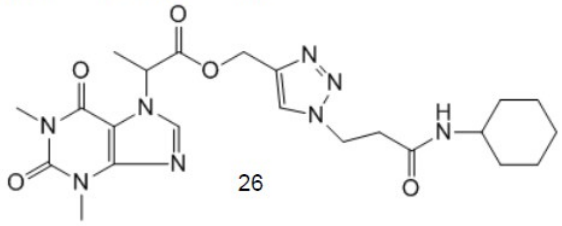
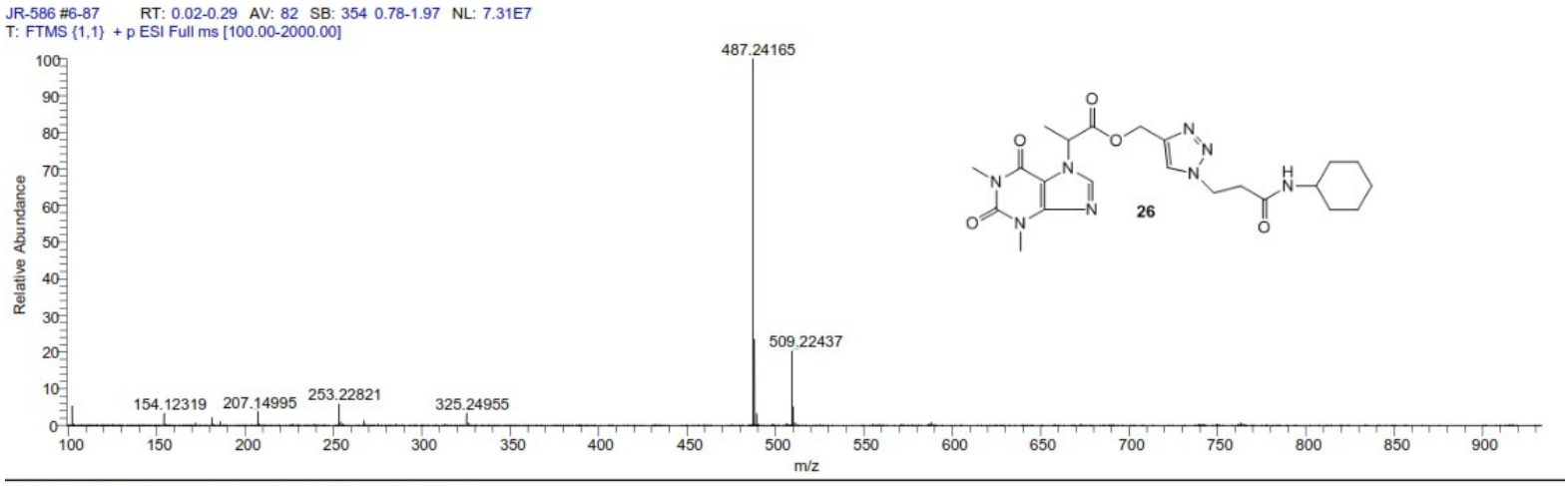


Fig-17: IR spectrum of compound-**26**

National Centre for Mass Spectrometry



JR-586#8-30 RT: 0.03-0.10 AV: 23
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
487.24162	90579128.0	100.00	487.23879	5.82	8.5	$C_{22}H_{31}O_5N_8$

Fig-18: HRMS spectrum of compound-**26**

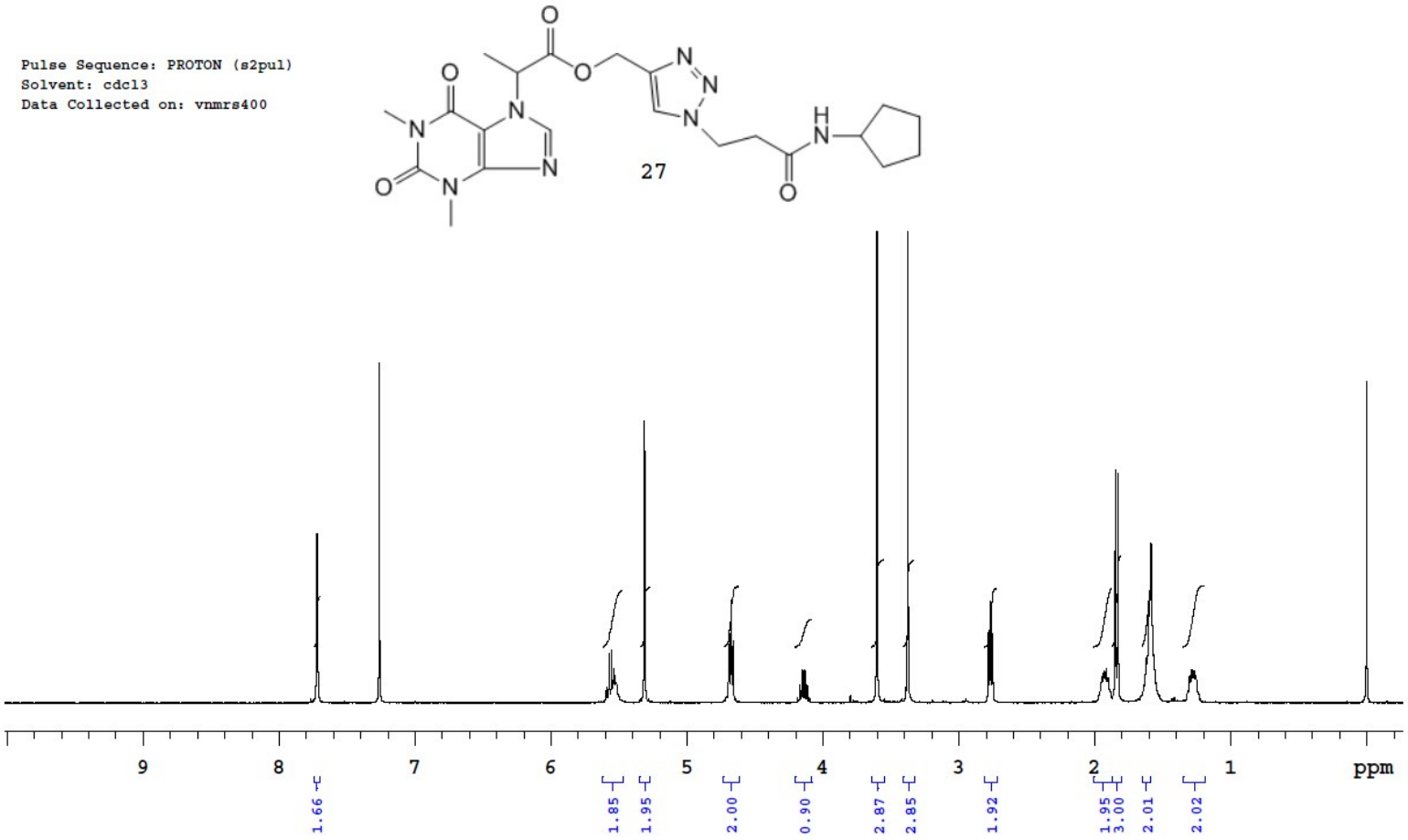


Fig-19: ^{1}H NMR spectrum of compound-**27**

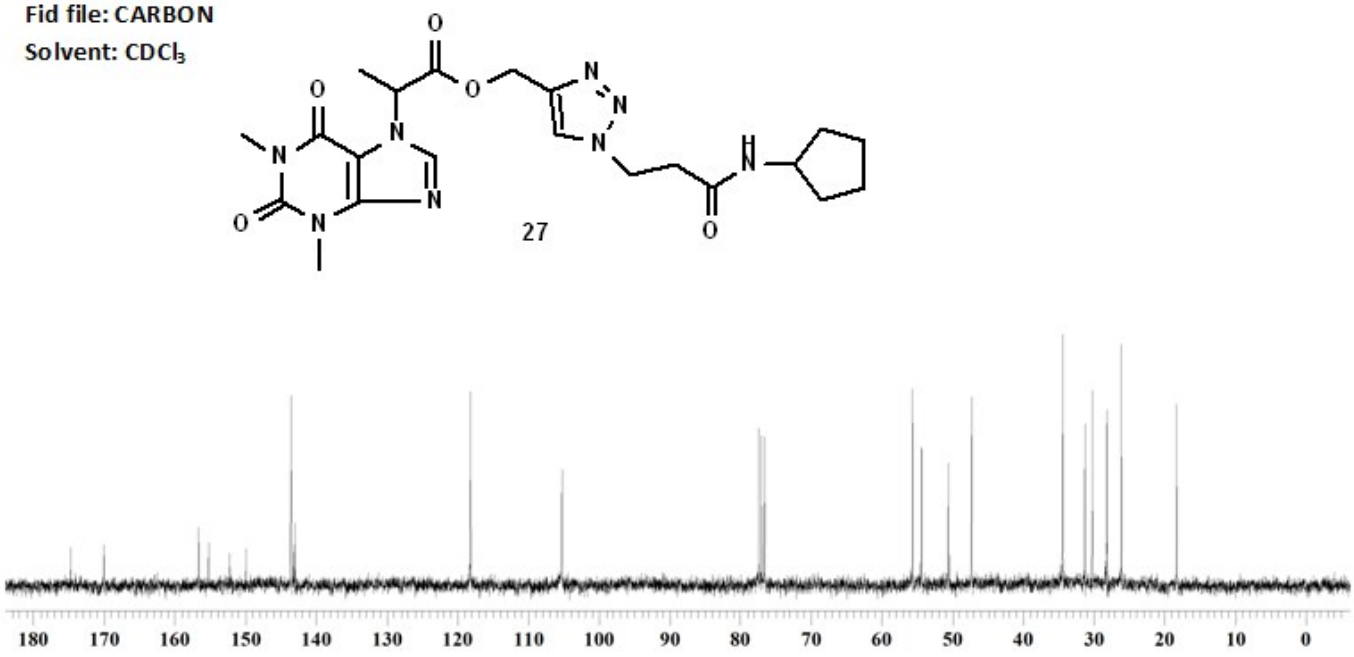
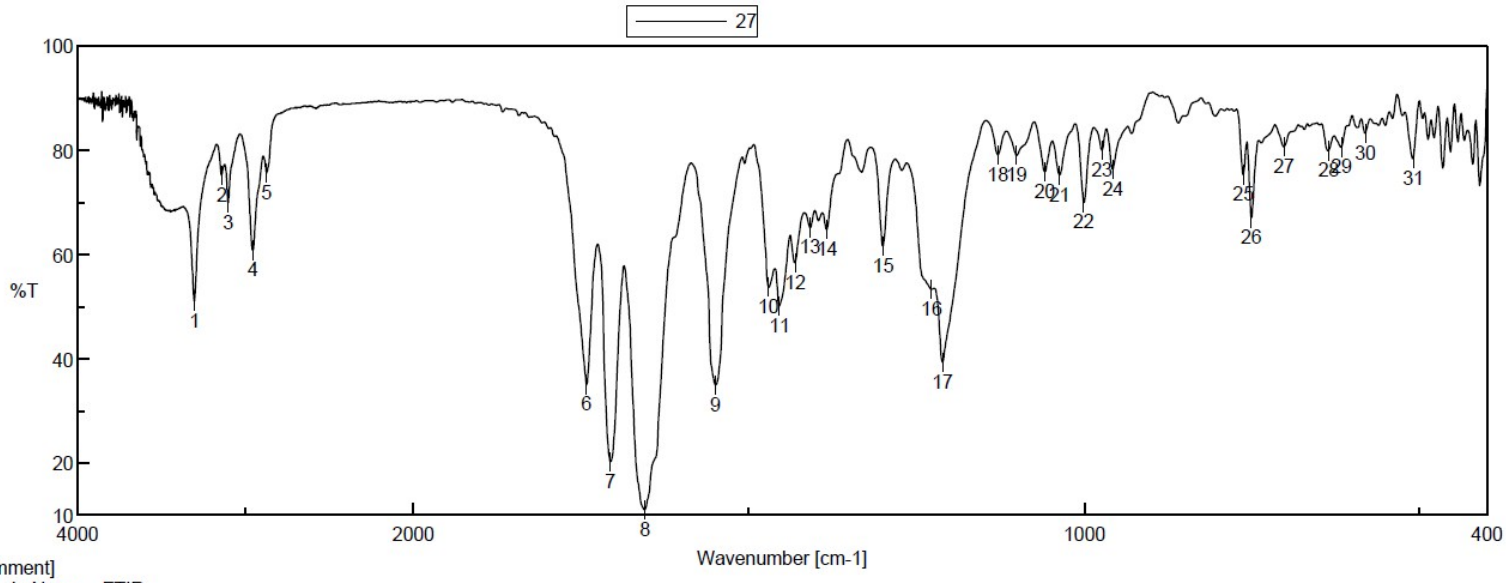


Fig-20: ^{13}C NMR spectrum of compound-**27**



[Comment]

Sample Name	FTIR
Comment	KBr Pellet
User	BSN
Division	QC
Company	SAPALA ORGANICS PVT LTD

[Data Information]

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Horizontal	Wavenumber [cm-1]
Vertical	%T
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End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3303.5	51.043	2	3141.5	75.209	3	3101.9	69.917	4	2955.4	60.776	5	2873.4	75.636
6	1741.4	34.931	7	1705.7	20.133	8	1654.6	10.935	9	1549.5	34.870	10	1470.5	53.696
11	1454.1	50.126	12	1430.9	58.380	13	1408.7	65.171	14	1383.7	64.752	15	1299.8	61.556
16	1227.5	53.305	17	1211.1	39.309	18	1129.1	79.133	19	1101.2	79.012	20	1058.7	75.831
21	1036.6	75.177	22	1000.9	69.974	23	973.9	79.974	24	957.5	76.355	25	762.7	75.331
26	751.1	67.004	27	702.9	80.654	28	636.4	79.903	29	617.1	80.543	30	581.4	83.284
31	510.1	78.365												

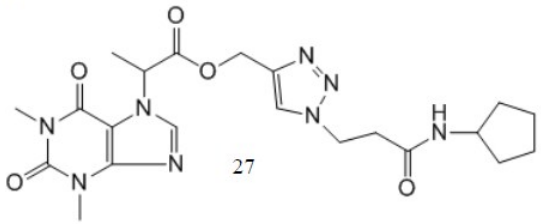

Fig-21: IR spectrum of compound-**27**

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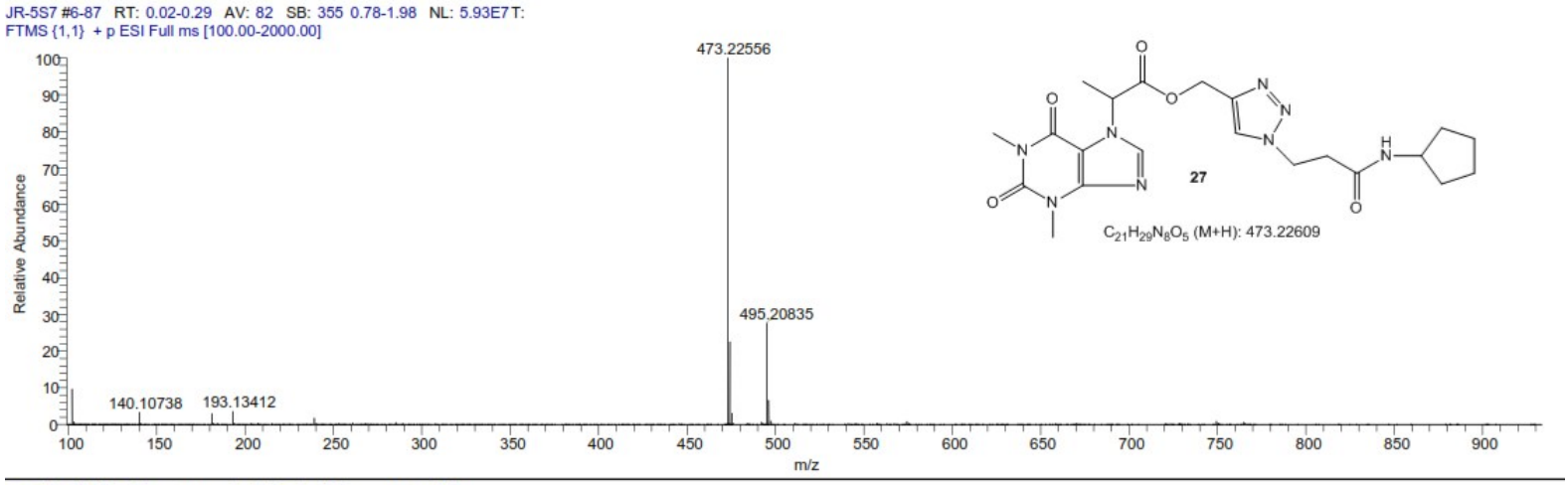


JR-5S7#8-30 RT: 0.03-0.10 AV: 23
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
473.22550	80853112.0	100.00				
495.20827	21342050.0	26.40				

Fig-22: HRMS spectrum of compound-**27**

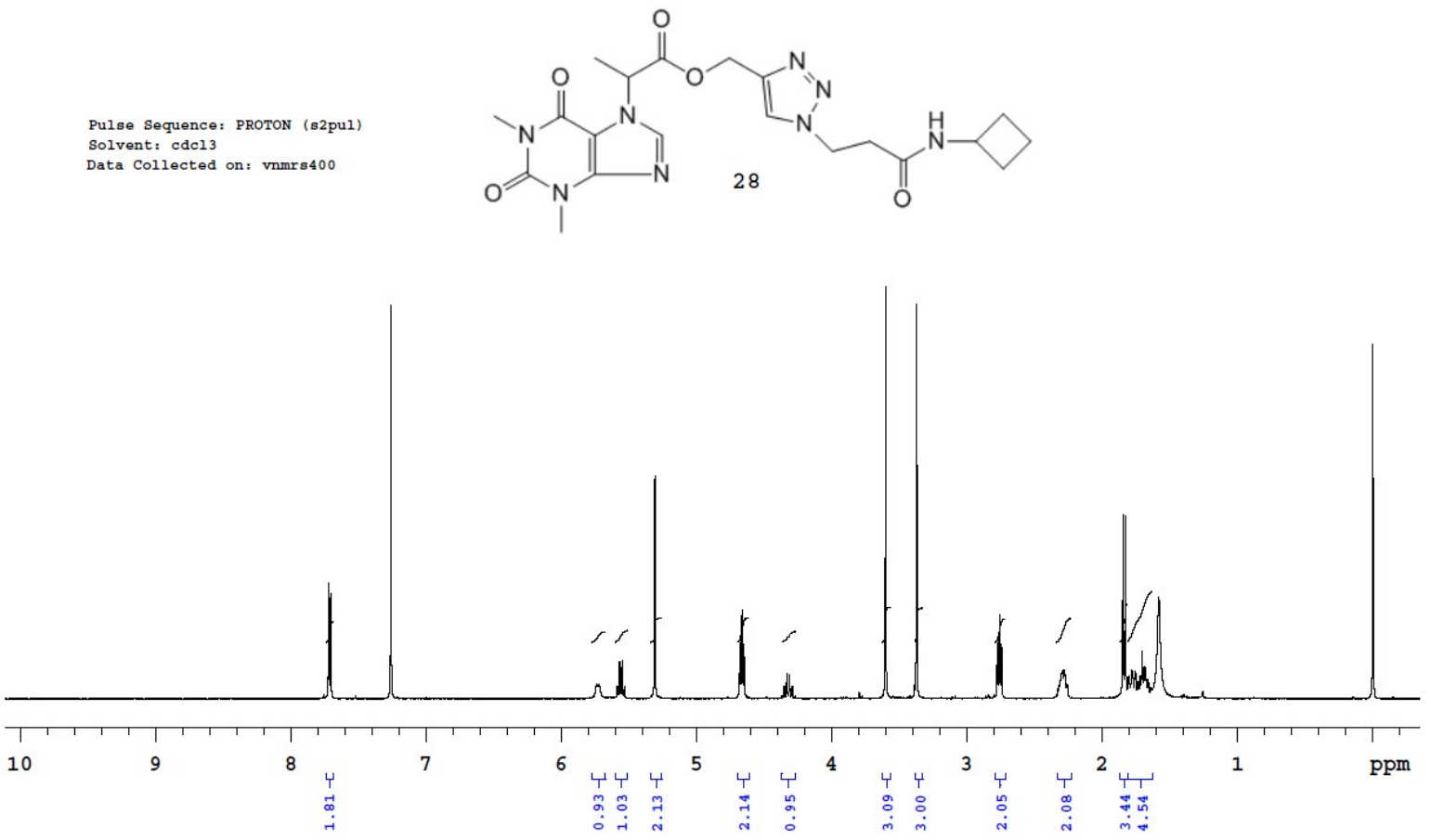
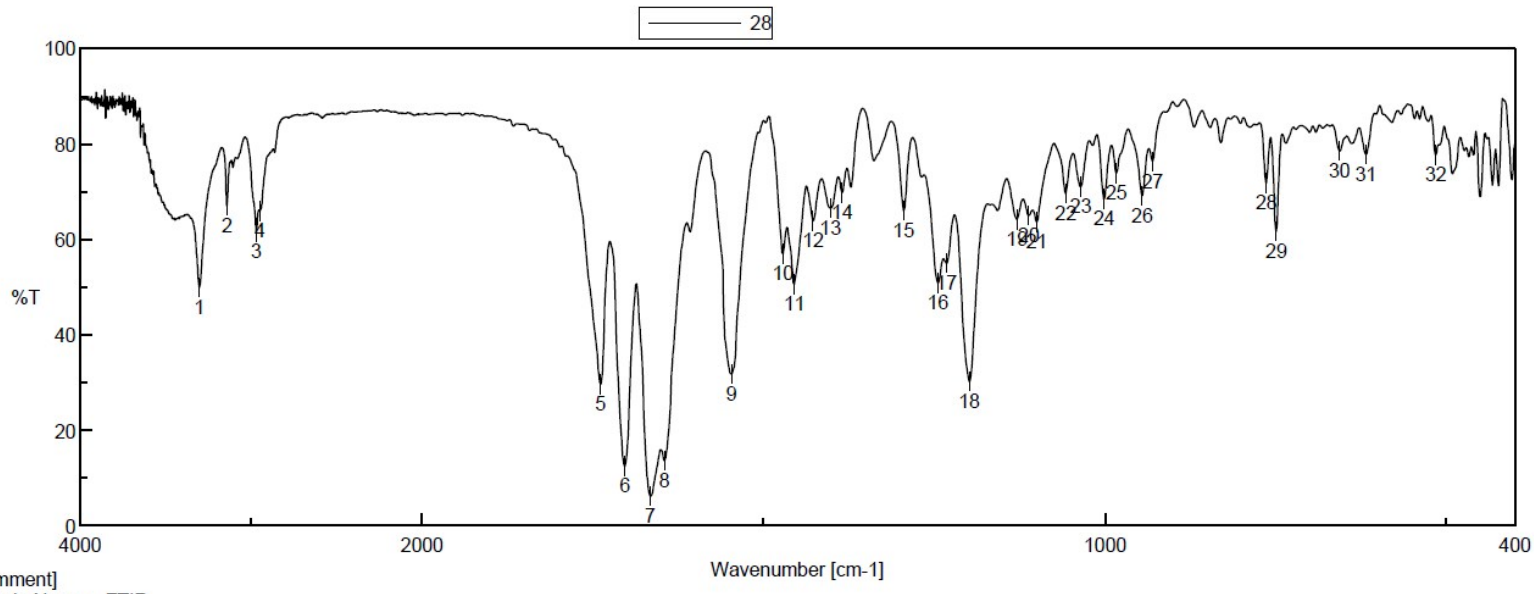


Fig-23: ^{1}H NMR spectrum of compound-**28**



[Comment]

Sample Name	FTIR
Comment	KBr Pellet
User	BSN
Division	QC
Company	SAPALA ORGANICS PVT LTD

[Data Information]

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Horizontal	Wavenumber [cm-1]
Vertical	%T
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End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3301.5	49.953	2	3140.5	66.970	3	2967.9	61.508	4	2949.6	65.920	5	1738.5	29.598
6	1702.8	12.411	7	1665.2	6.136	8	1645.0	13.602	9	1546.6	31.774	10	1471.4	56.938
11	1455.0	50.585	12	1427.1	63.857	13	1402.0	66.487	14	1384.6	69.758	15	1295.0	65.942
16	1244.8	50.866	17	1232.3	54.946	18	1198.5	30.209	19	1129.1	64.146	20	1111.8	64.987
21	1100.2	63.575	22	1057.8	69.555	23	1035.6	70.988	24	1000.9	68.392	25	983.5	73.814
26	945.9	69.152	27	930.5	76.300	28	763.7	71.747	29	749.2	61.616	30	656.6	78.431
31	618.1	77.773	32	515.9	77.653									

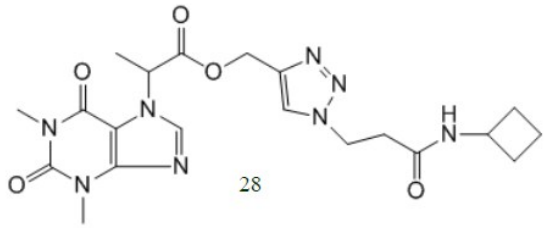

Fig-24: IR spectrum of compound-**28**

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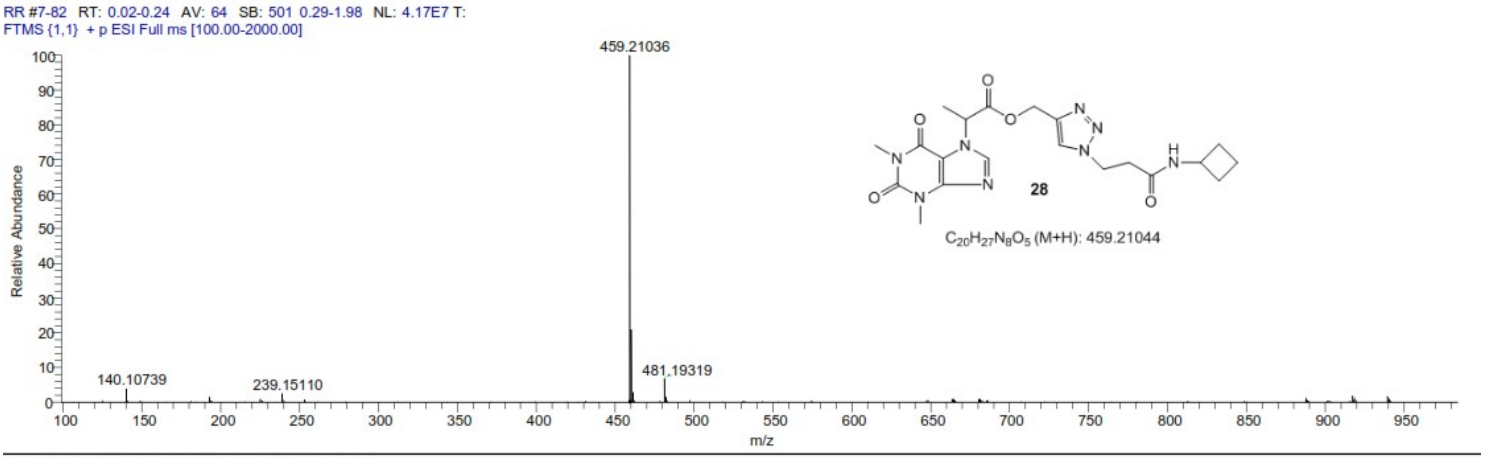


RR-9#8-30 RT: 0.03-0.10 AV: 22
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
459.21032	68032168.0	100.00				

Fig-25: HRMS spectrum of compound-**28**

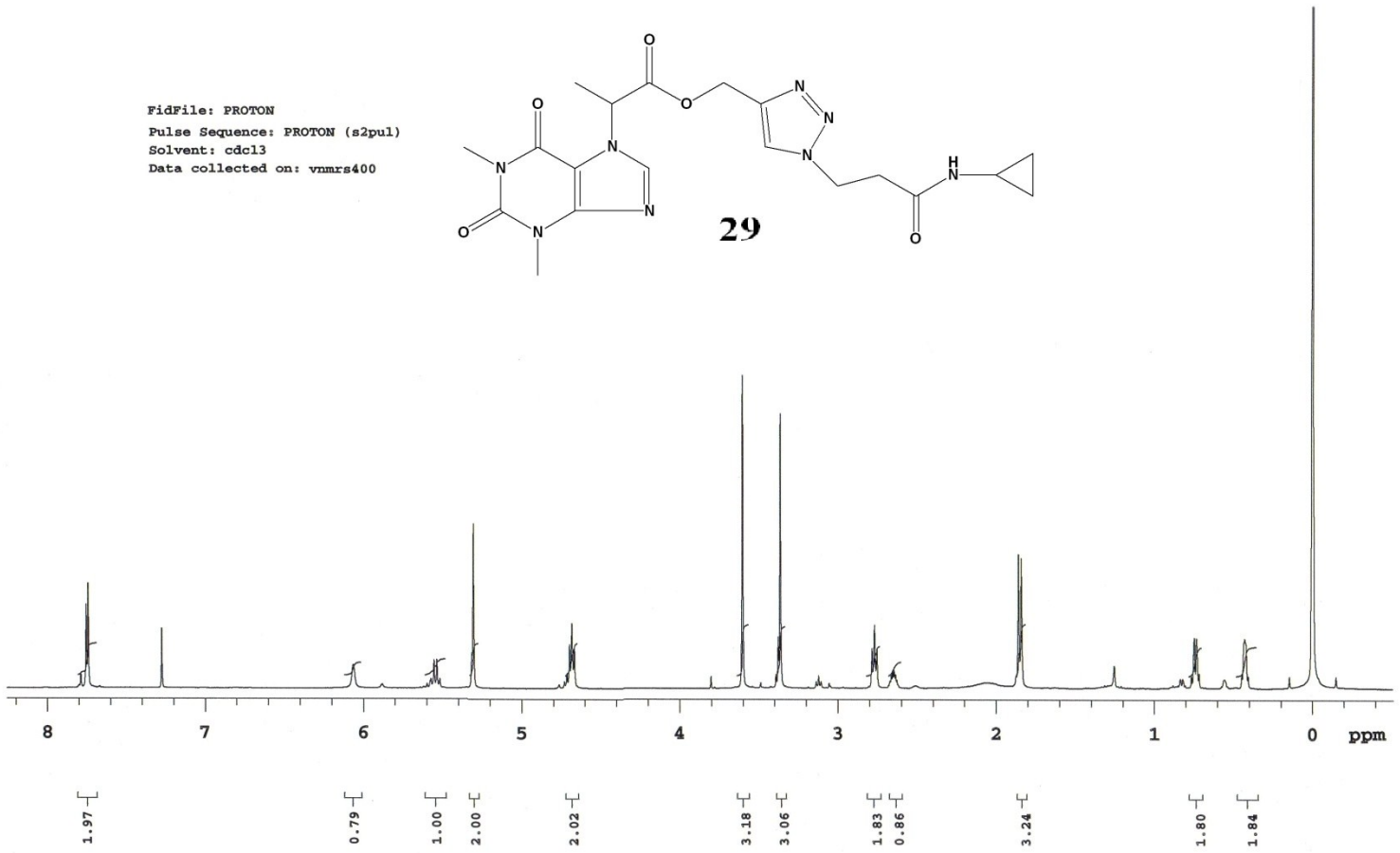


Fig-26: ^{1}H NMR spectrum of compound-**29**

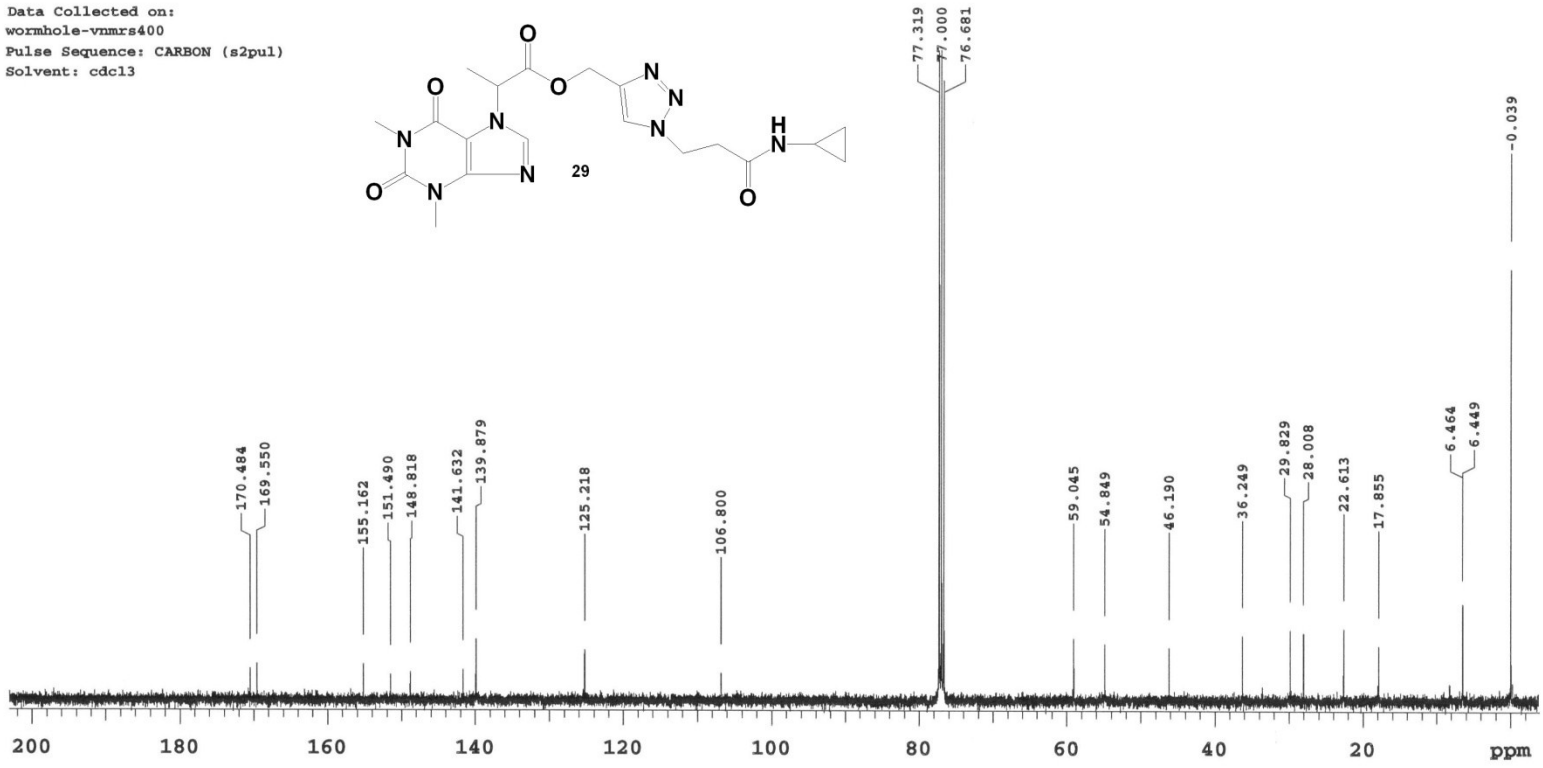
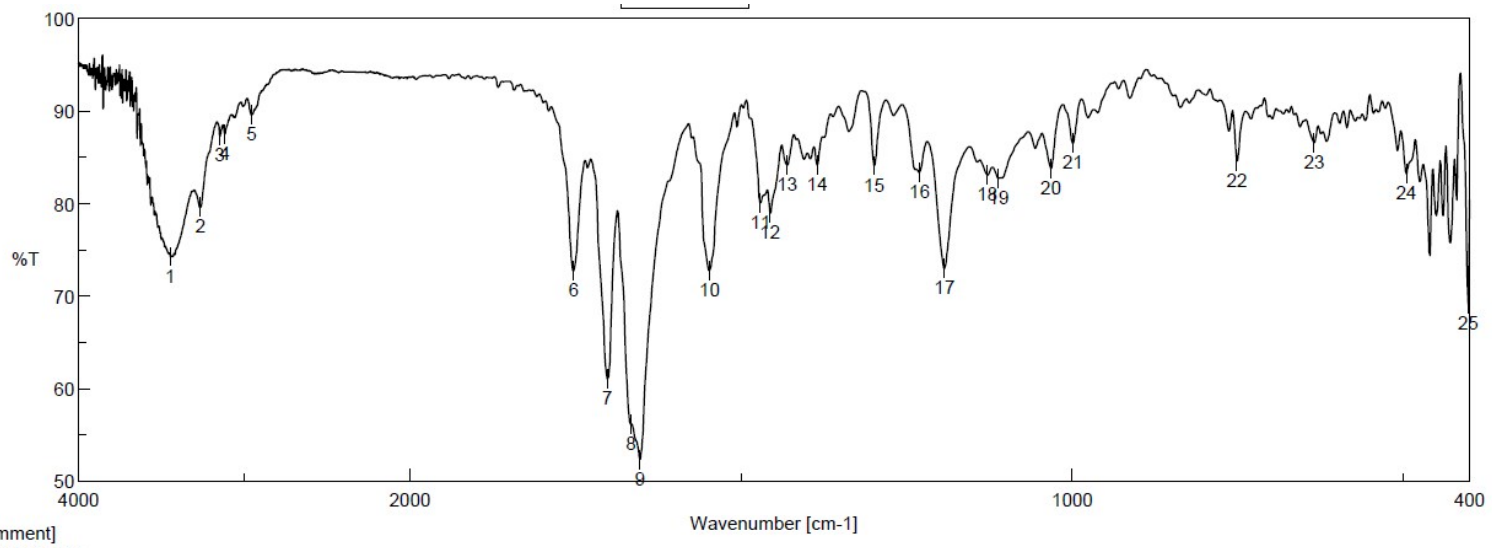


Fig-27: ^{13}C NMR spectrum of compound-**29**

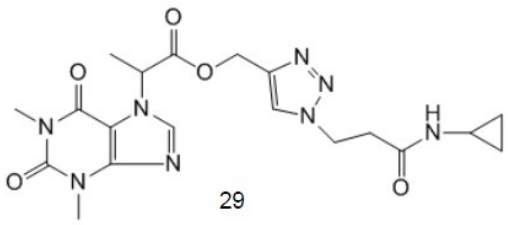


[Comment]
Sample Name
Comment KBr Pellet
User BSN
Division QC
Company SAPALA ORGANICS PVT LTD

[Data Information]
Creation Date 4/6/2015 1:03 PM
Data array type Linear data array
Horizontal Wavenumber [cm-1]
Vertical %T
Start 349.053 cm-1
End 7800.65 cm-1
Data pitch 0.964233 cm-1
Data points 7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3444.2	74.228	2	3263.9	79.575	3	3146.3	87.263	4	3116.4	87.461	5	2955.4	89.553
6	1753.0	72.684	7	1701.9	61.023	8	1666.2	56.122	9	1652.7	52.289	10	1547.6	72.743
11	1470.5	80.030	12	1456.0	78.945	13	1430.0	84.138	14	1384.6	84.129	15	1298.8	84.070
16	1230.4	83.320	17	1192.8	72.964	18	1128.2	83.054	19	1110.8	82.705	20	1031.7	83.732
21	998.9	86.466	22	751.1	84.573	23	634.5	86.531	24	495.6	83.193	25	402.1	69.076



29

Fig-28: IR spectrum of compound-**29**

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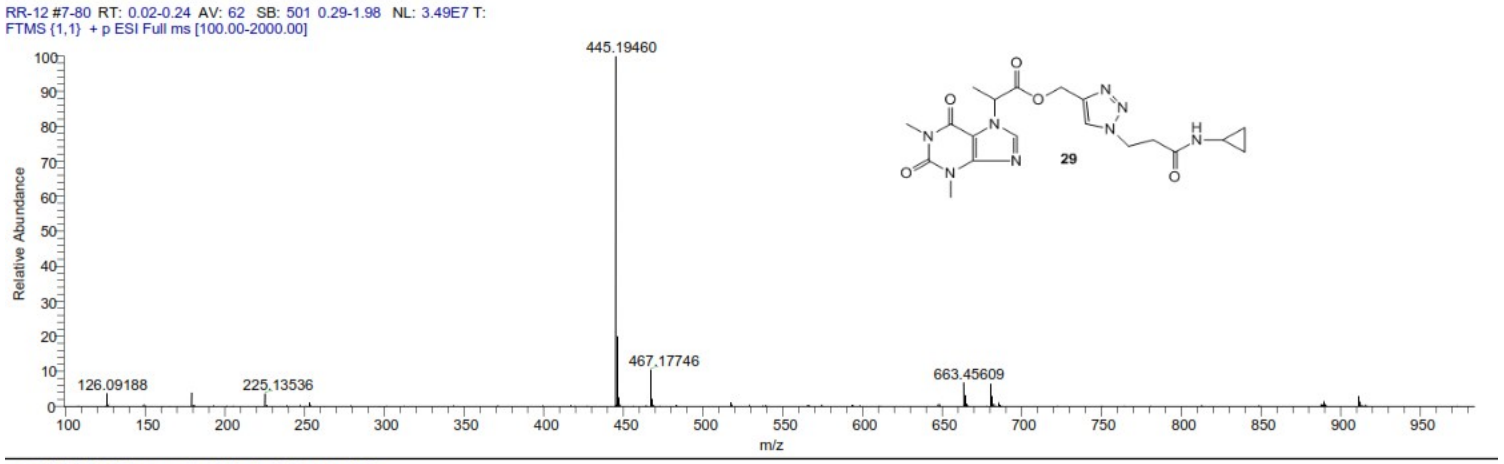


RR-10#8-30 RT: 0.03-0.10 AV: 25
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
445.19456	59490638.0	100.00	445.19429	0.71	11.4	$C_{19}H_{25}O_5N_8$

Fig-29: HRMS spectrum of compound-**29**

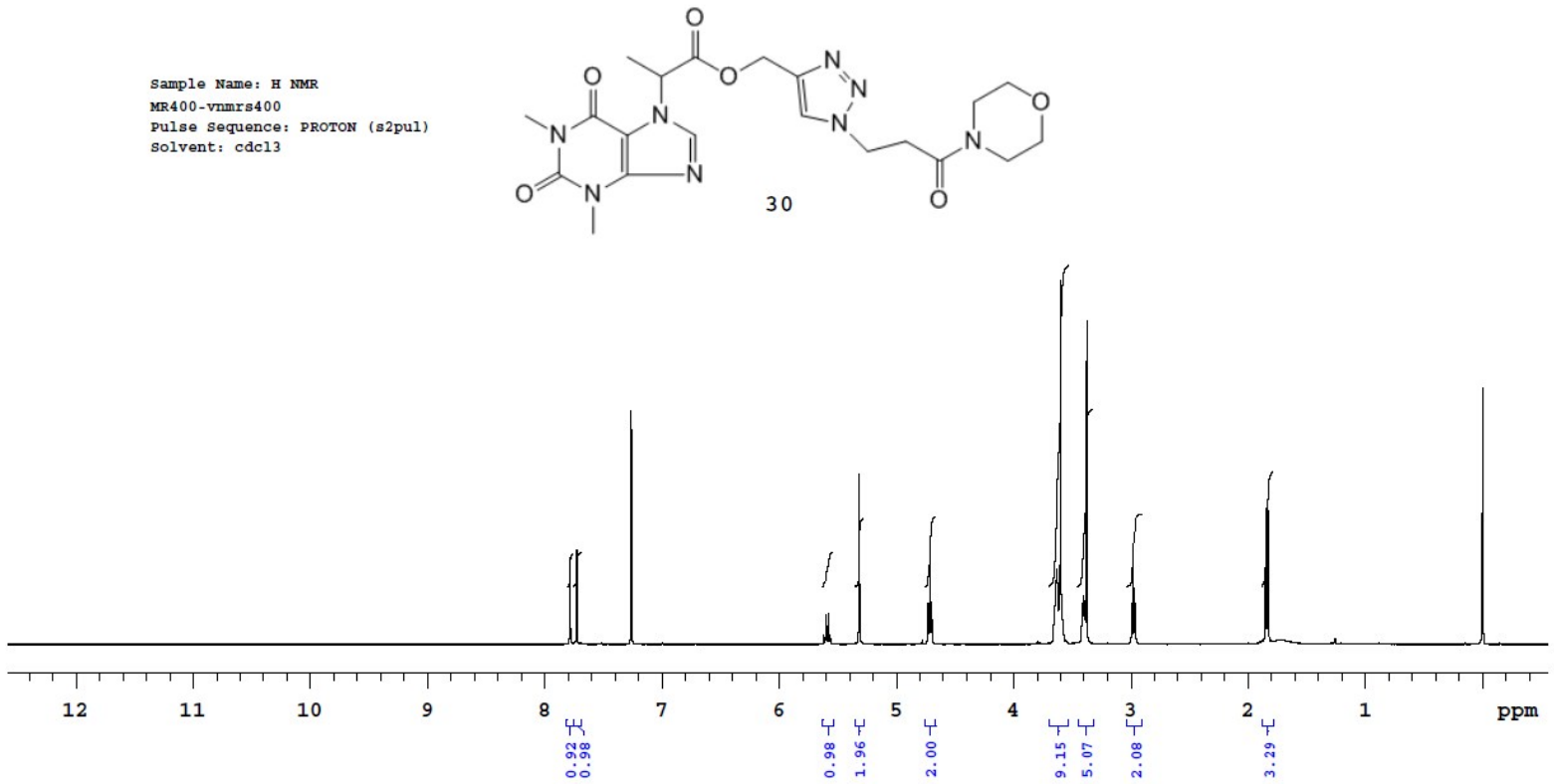


Fig-30: ^{1}H NMR spectrum of compound-**30**

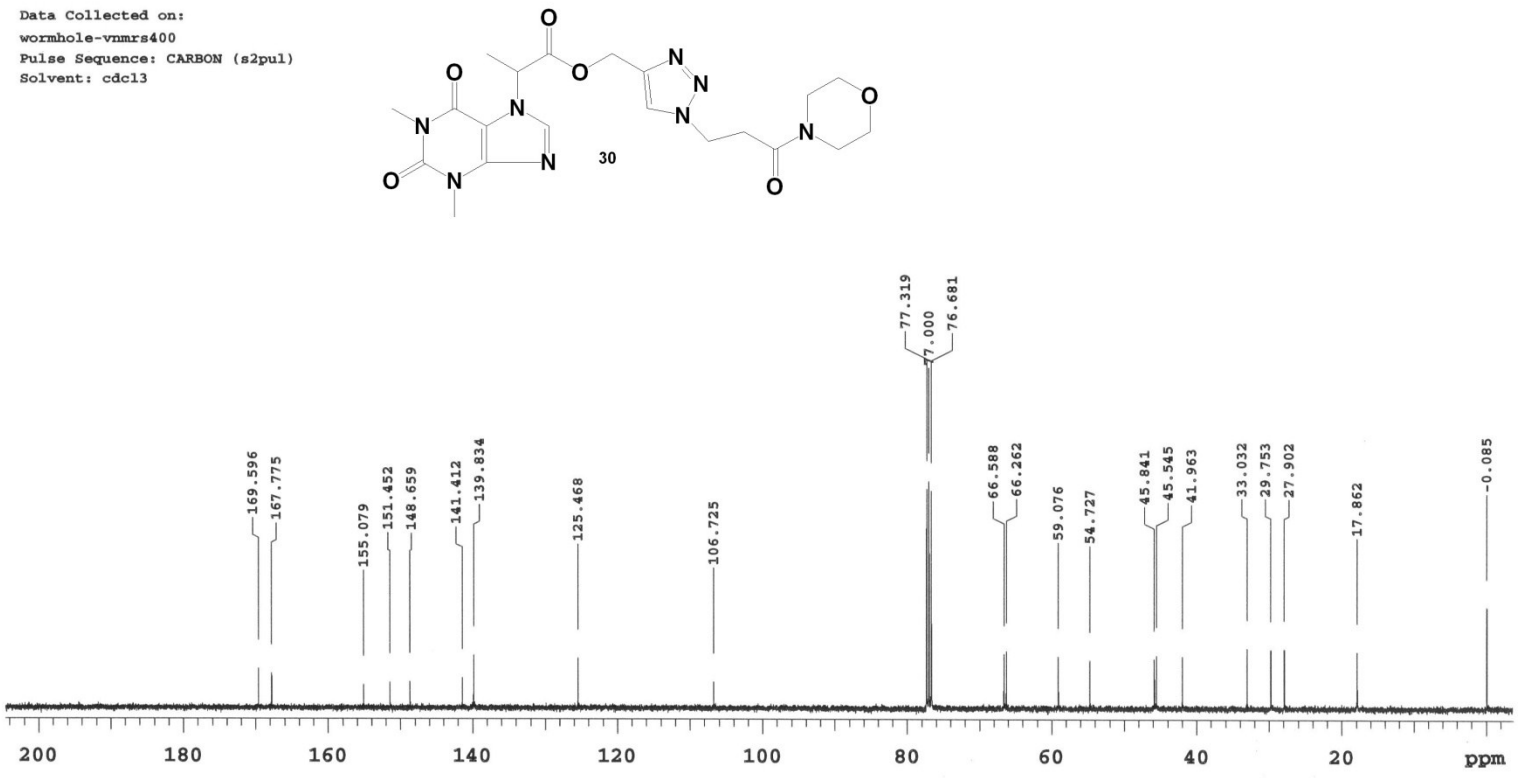
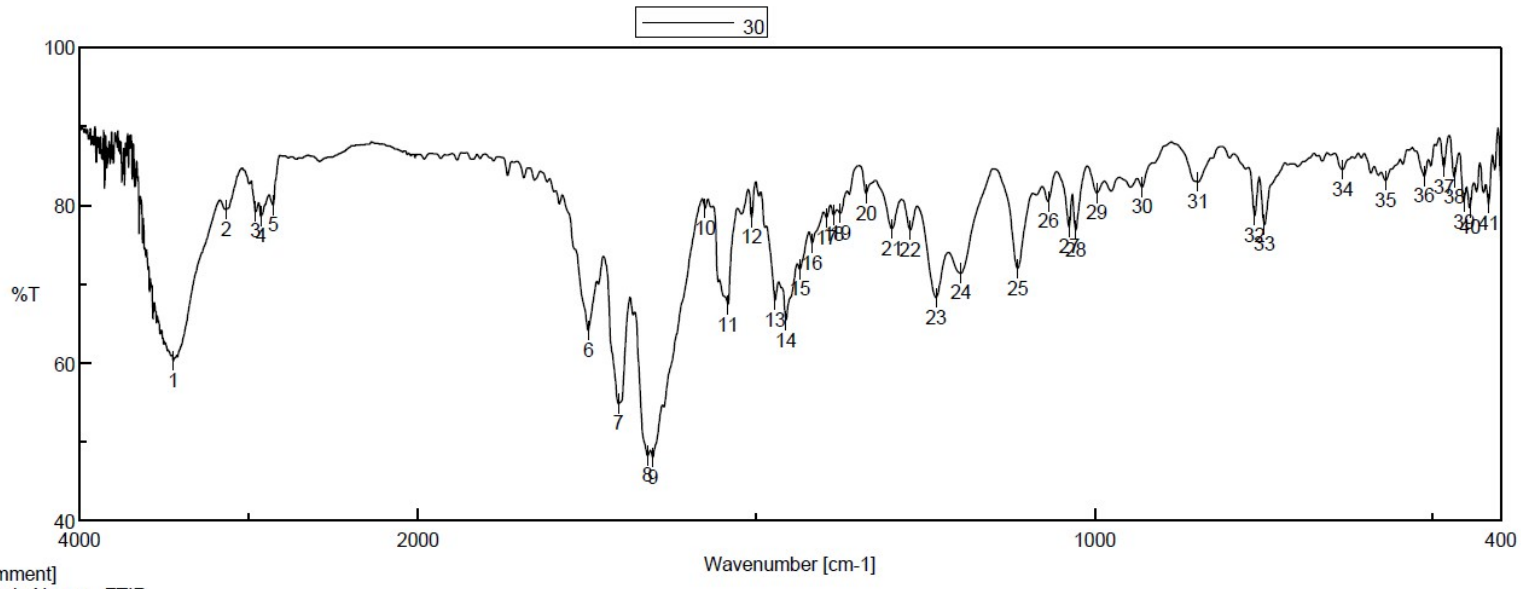


Fig-31: ^{13}C NMR spectrum of compound-**30**



[Comment]

Sample Name	FTIR
Comment	KBr Pellet
User	GBR
Division	QC
Company	SAPALA ORGANICS PVT LTD

[Data Information]

Creation Date	10/19/2015 10:40 AM
Data array type	Linear data array
Horizontal	Wavenumber [cm-1]
Vertical	%T
Start	349.053 cm-1
End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3445.2	60.247	2	3132.8	79.438	3	2960.2	79.209	4	2927.4	78.555	5	2855.1	80.004
6	1748.2	64.073	7	1703.8	54.799	8	1660.4	48.209	9	1652.7	48.003	10	1575.6	79.567
11	1541.8	67.398	12	1507.1	78.468	13	1472.4	67.933	14	1456.0	65.378	15	1435.7	71.839
16	1417.4	75.183	17	1396.2	78.435	18	1385.6	78.746	19	1376.0	79.001	20	1337.4	81.474
21	1299.8	77.009	22	1272.8	76.872	23	1234.2	68.269	24	1197.6	71.371	25	1113.7	71.959
26	1068.4	80.466	27	1037.5	77.214	28	1027.9	76.811	29	997.0	81.563	30	929.5	82.311
31	847.6	82.944	32	763.7	78.621	33	749.2	77.539	34	633.5	84.542	35	569.9	83.136
36	513.0	83.686	37	484.0	84.821	38	468.6	83.531	39	454.2	80.400	40	445.5	79.688
41	417.5	80.180												

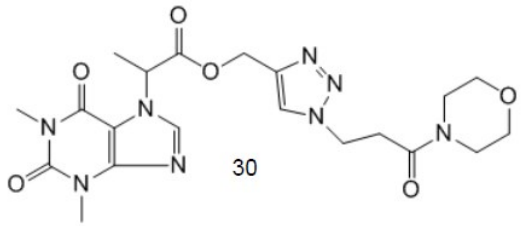
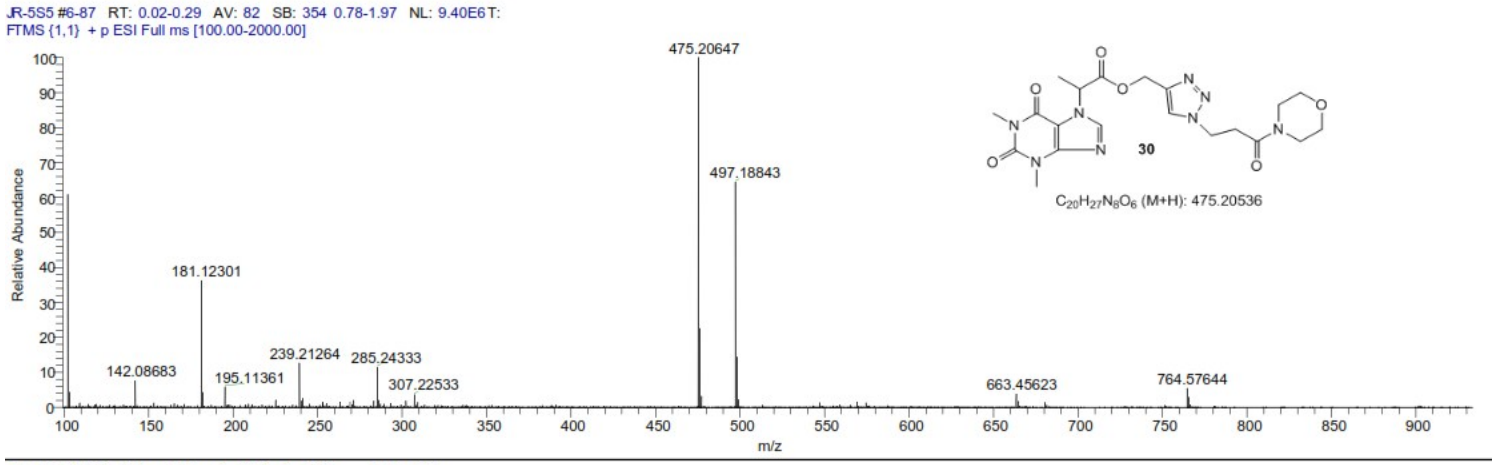


Fig-32: IR spectrum of compound-**30**

National Centre for Mass Spectrometry



JR-5S5#8-30 RT: 0.03-0.10 AV: 23
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
475.20652	14534151.0	100.00				

Fig-33: HRMS spectrum of compound-**30**

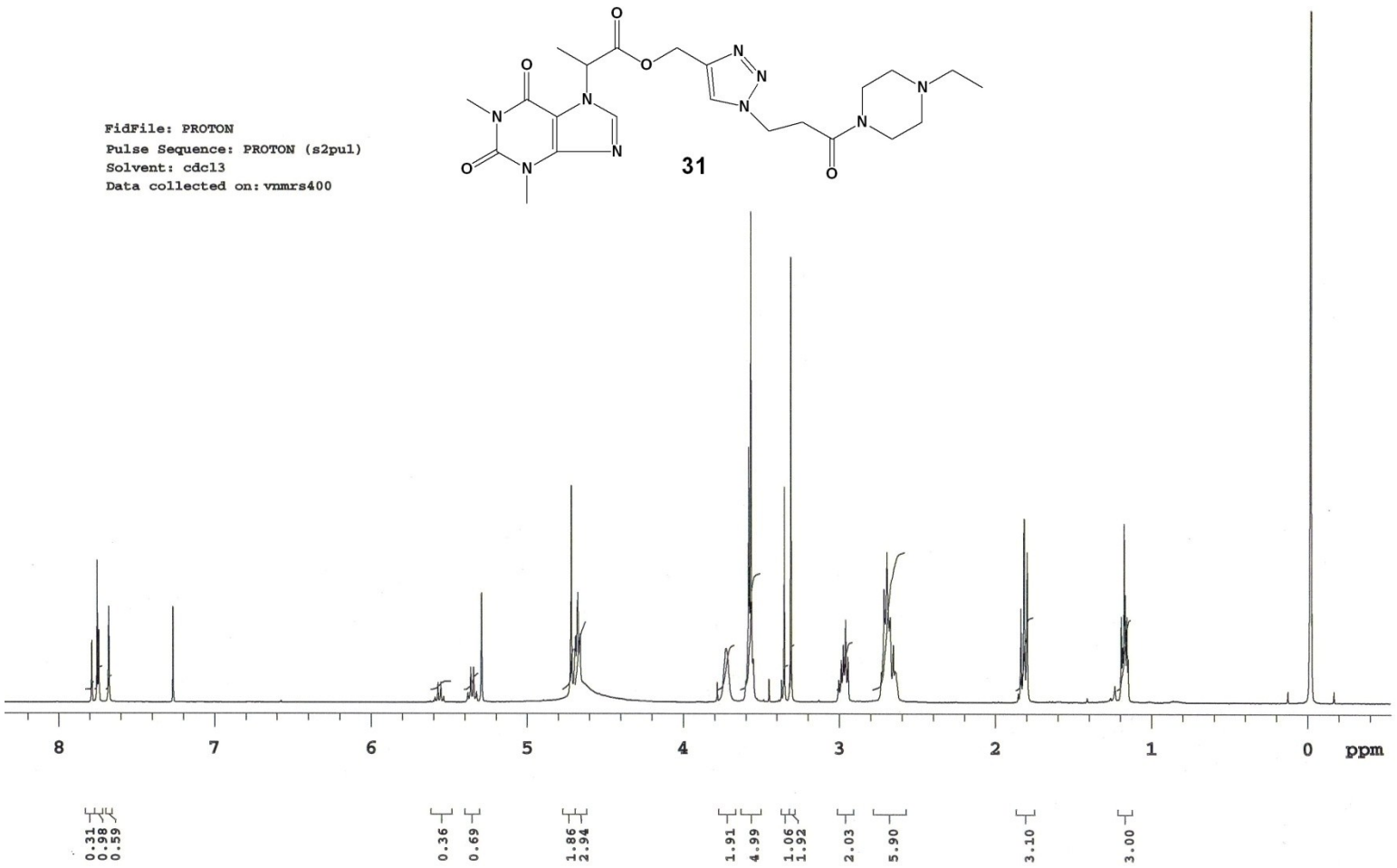


Fig-34: ^{1}H NMR spectrum of compound-**31**

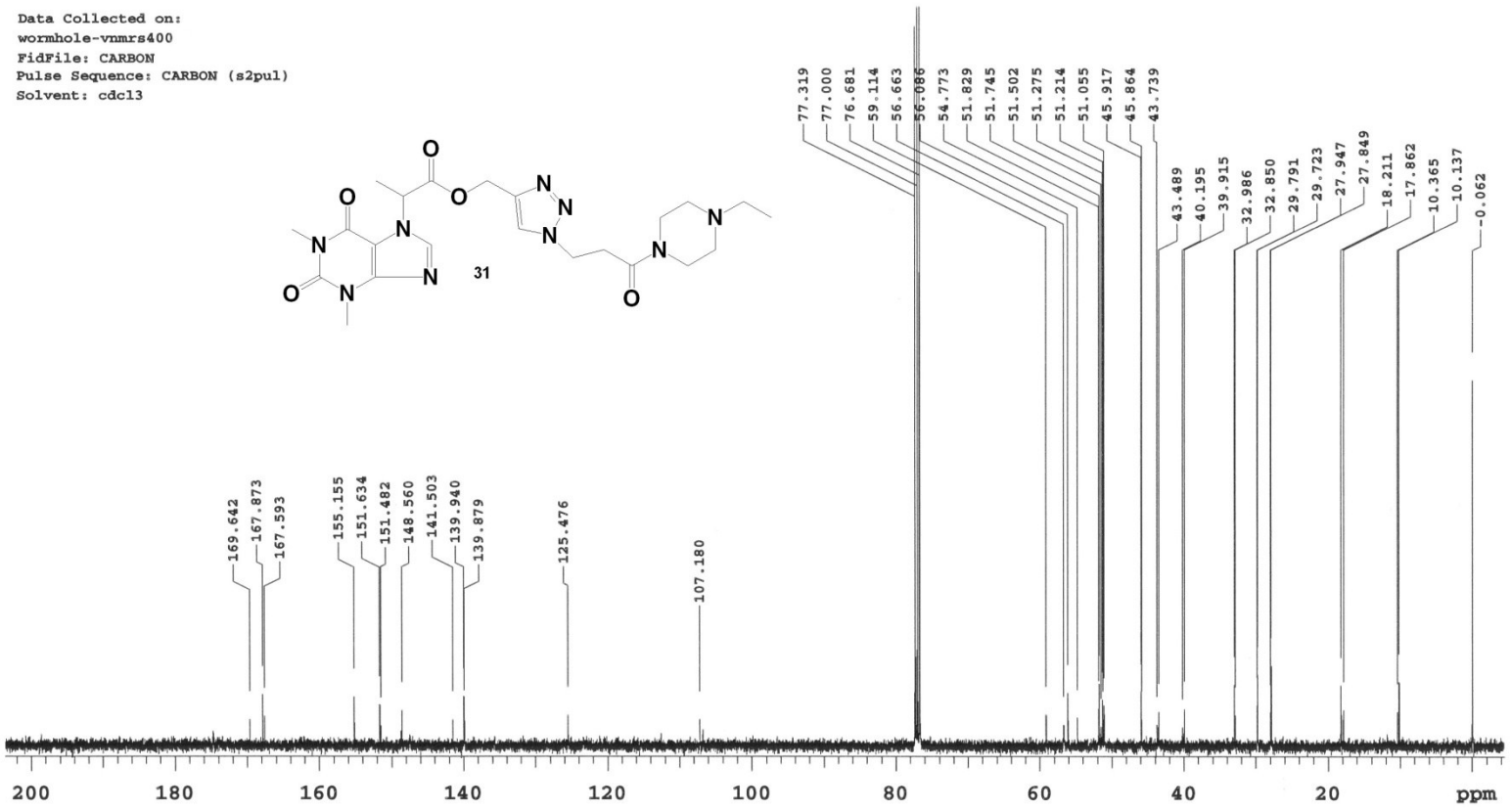
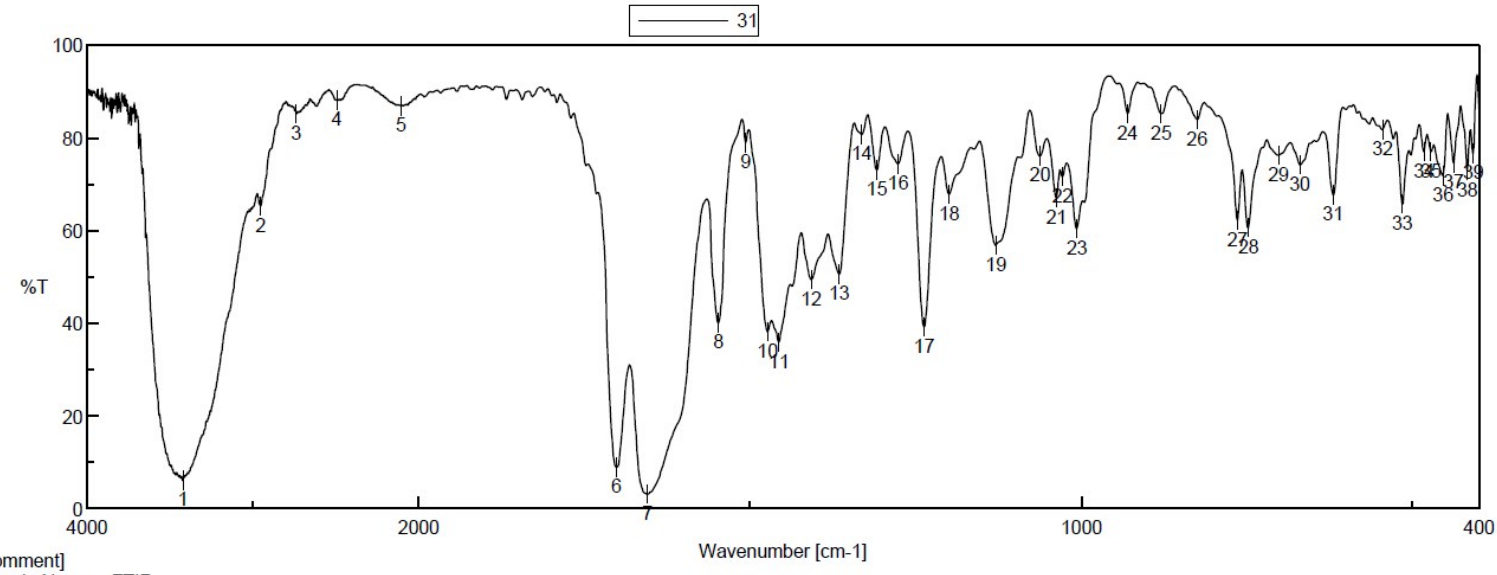


Fig-35: ^{13}C NMR spectrum of compound-**31**



[Comment]

Sample Name	FTIR
Comment	KBr Pellet
User	GBR
Division	QC
Company	SAPALA ORGANICS PVT LTD

[Data Information]

Creation Date	10/19/2015 10:30 AM
Data array type	Linear data array
Horizontal	Wavenumber [cm-1]
Vertical	%T
Start	349.053 cm-1
End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3422.1	5.992	2	2952.5	65.241	3	2736.5	85.112	4	2491.6	88.089	5	2104.9	86.850
6	1700.9	8.850	7	1654.6	3.026	8	1547.6	40.059	9	1506.1	78.967	10	1473.3	38.073
11	1456.0	35.858	12	1407.8	49.402	13	1365.4	50.514	14	1331.6	80.718	15	1308.5	73.043
16	1276.6	74.369	17	1237.1	39.146	18	1199.5	67.733	19	1129.1	56.783	20	1062.6	76.063
21	1037.5	66.997	22	1028.8	71.565	23	1006.7	60.362	24	930.5	85.268	25	879.4	85.220
26	825.4	83.966	27	764.6	62.185	28	748.2	60.581	29	702.9	76.220	30	670.1	74.093
31	620.0	67.651	32	545.8	81.744	33	515.9	65.639	34	483.1	77.031	35	472.5	76.963
36	454.2	71.817	37	438.7	74.507	38	417.5	72.980	39	408.8	76.590			

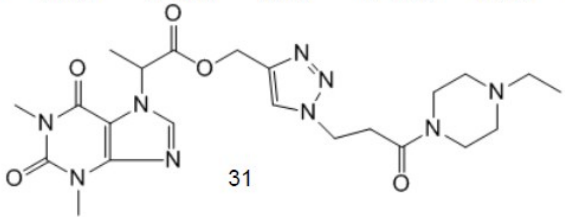
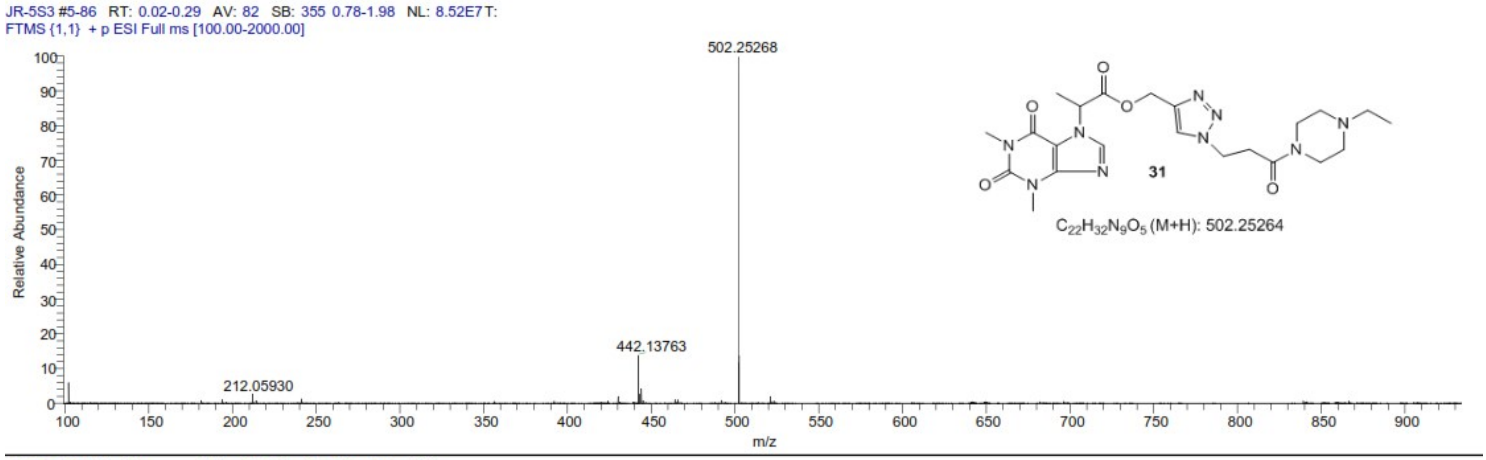


Fig-36: IR spectrum of compound-**31**

National Centre for Mass Spectrometry



JR-5S3#8-30 RT: 0.03-0.10 AV: 23
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
502.25262	12689913.0	100.00				

Fig-37: HRMS spectrum of compound-**31**

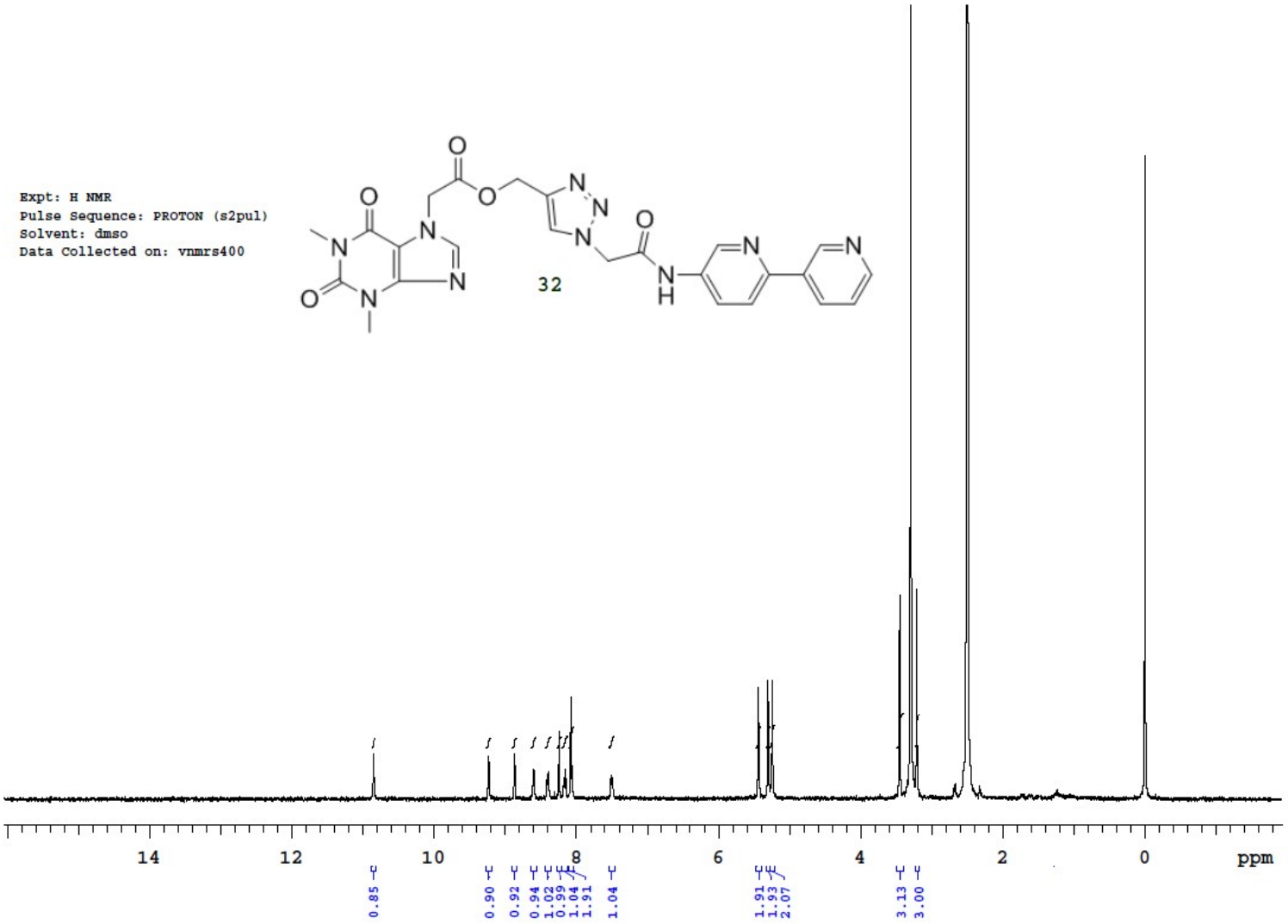
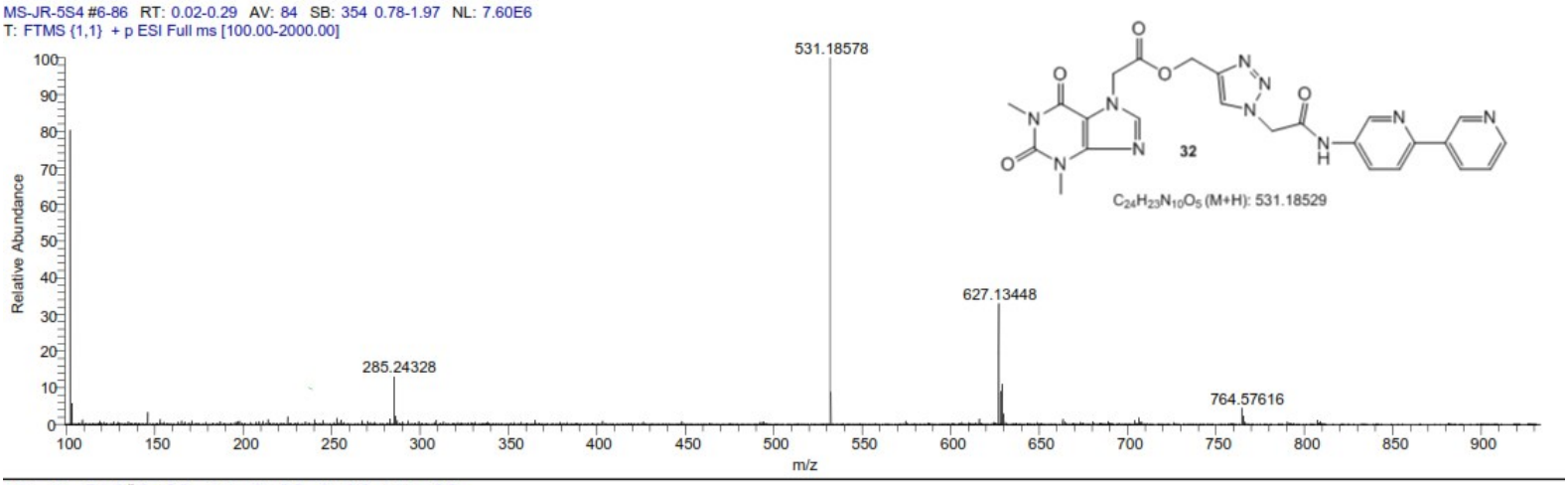


Fig-38: ^{1}H NMR spectrum of compound-**32**

National Centre for Mass Spectrometry



MS-JR-5S4#8-30 RT: 0.03-0.10 AV: 22
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
531.18540	2564460.3	100.00				

Fig-39: HRMS spectrum of compound-**32**

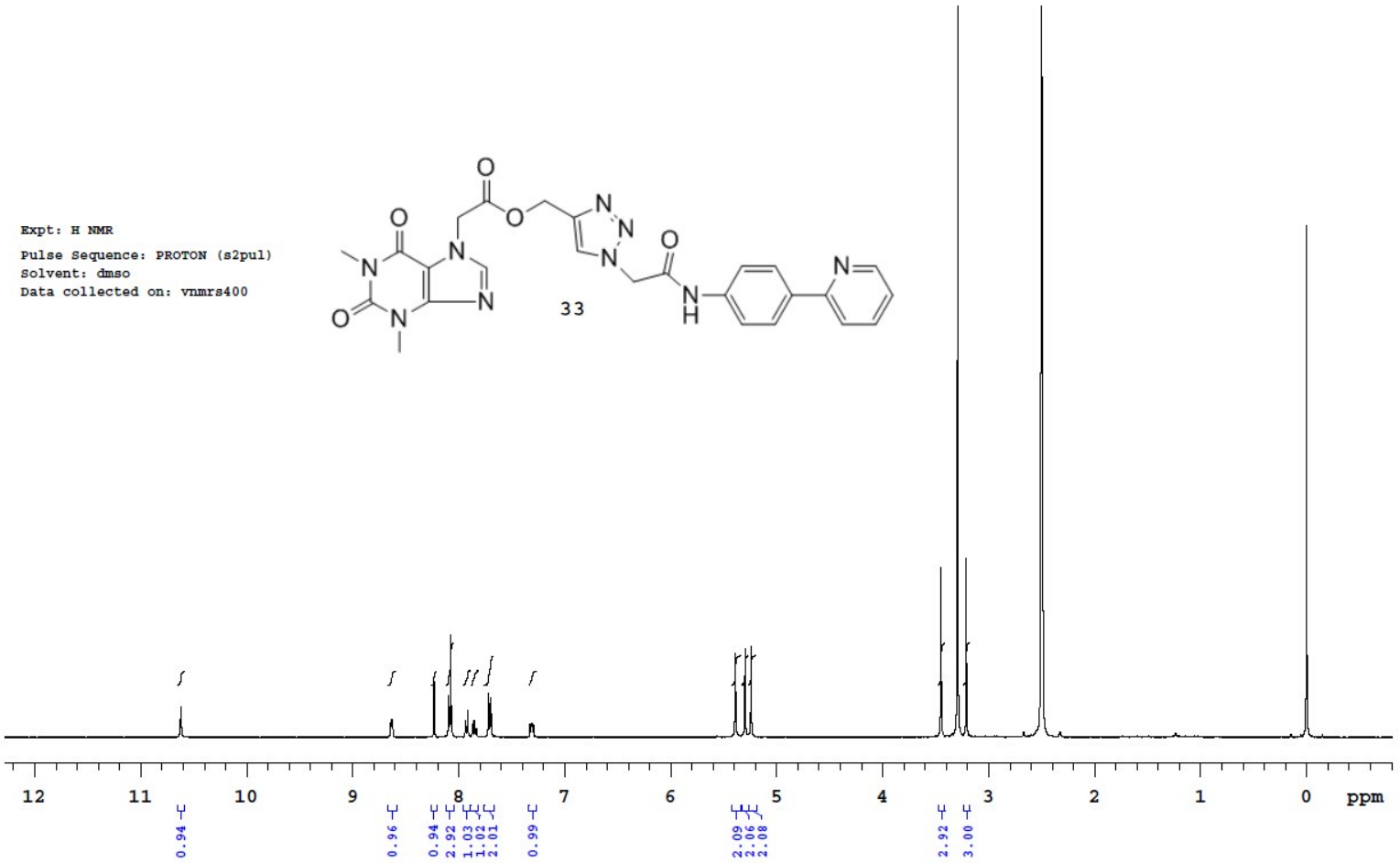


Fig-40: ^{1}H NMR spectrum of compound-**33**

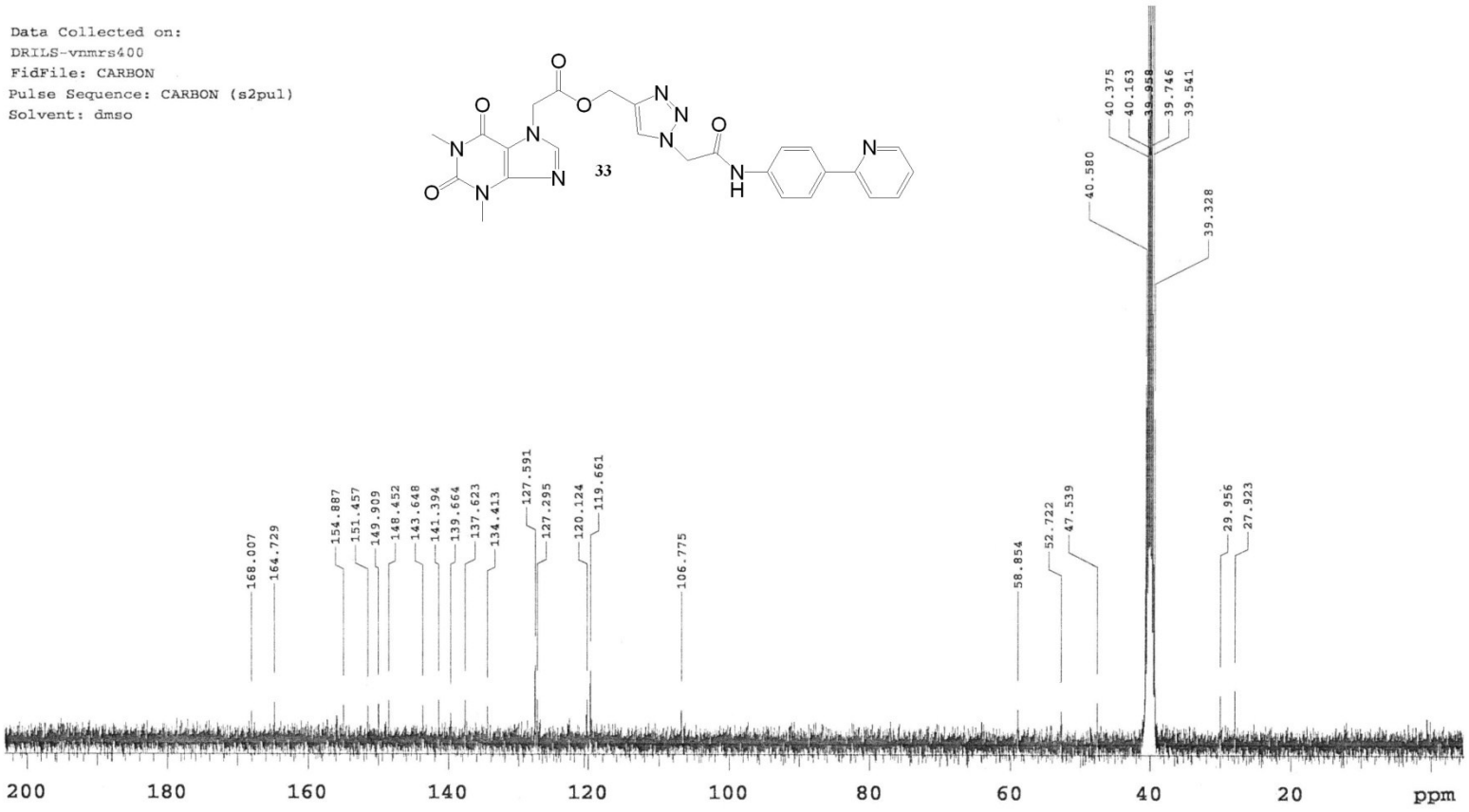
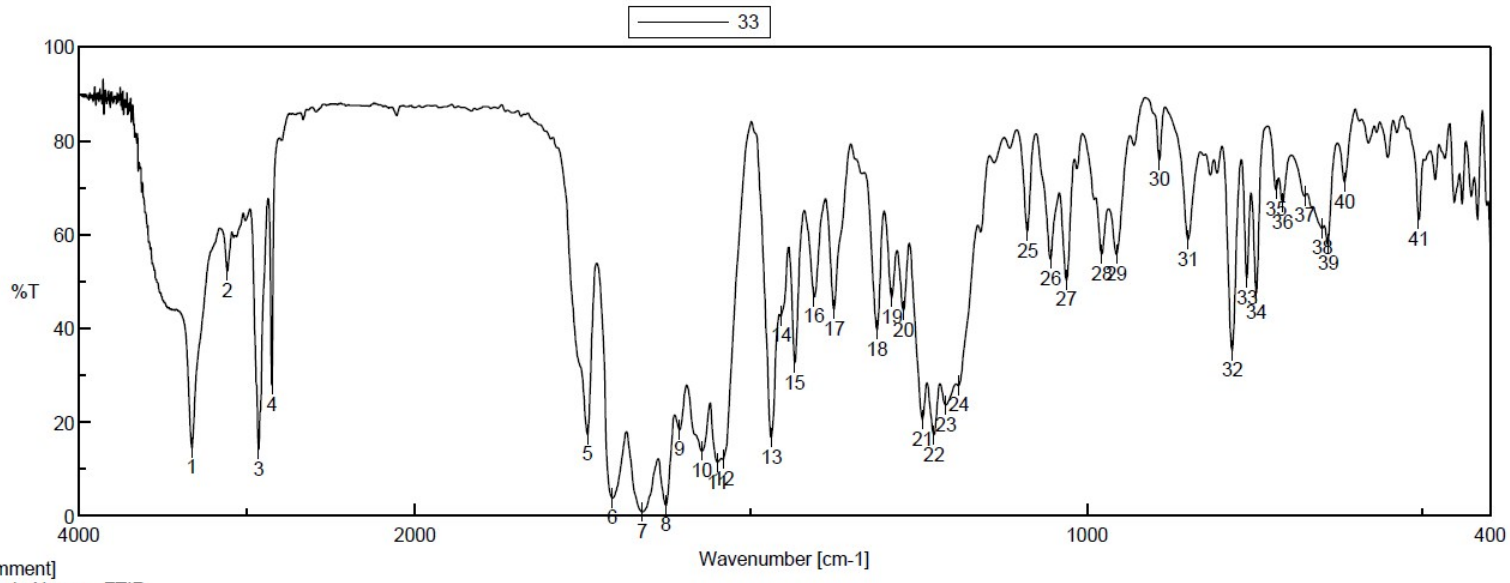


Fig-41: ^{13}C NMR spectrum of compound-**33**



[Comment]

Sample Name	FTIR
Comment	KBr Pellet
User	BSN
Division	QC
Company	SAPALA ORGANICS PVT LTD

[Data Information]

Creation Date	4/6/2015 4:12 PM
Data array type	Linear data array
Horizontal	Wavenumber [cm-1]
Vertical	%T
Start	349.053 cm-1
End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3326.6	14.462	2	3115.4	52.199	3	2928.4	14.206	4	2850.3	27.795	5	1743.3	17.301
6	1705.7	3.782	7	1661.4	0.763	8	1626.7	2.136	9	1606.4	18.308	10	1572.7	13.755
11	1549.5	11.351	12	1540.8	12.004	13	1469.5	16.745	14	1455.0	42.597	15	1434.8	32.588
16	1405.9	46.659	17	1376.0	44.091	18	1312.3	39.591	19	1290.1	46.491	20	1272.8	43.709
21	1244.8	20.404	22	1227.5	17.243	23	1210.1	23.554	24	1190.8	27.706	25	1088.6	60.634
26	1053.9	54.725	27	1030.8	50.259	28	977.7	55.709	29	955.6	55.783	30	891.9	75.838
31	849.5	58.803	32	783.9	35.213	33	761.7	50.689	34	748.2	47.467	35	718.4	69.516
36	708.7	66.780	37	675.9	68.185	38	649.9	61.238	39	641.2	57.871	40	616.1	71.163
41	506.2	63.100												

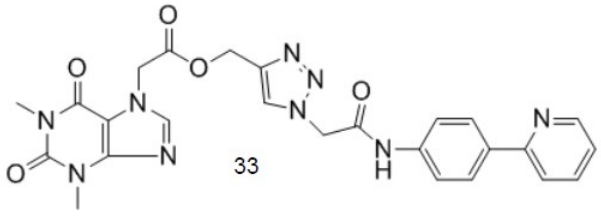


Fig-42: IR spectrum of compound-**33**

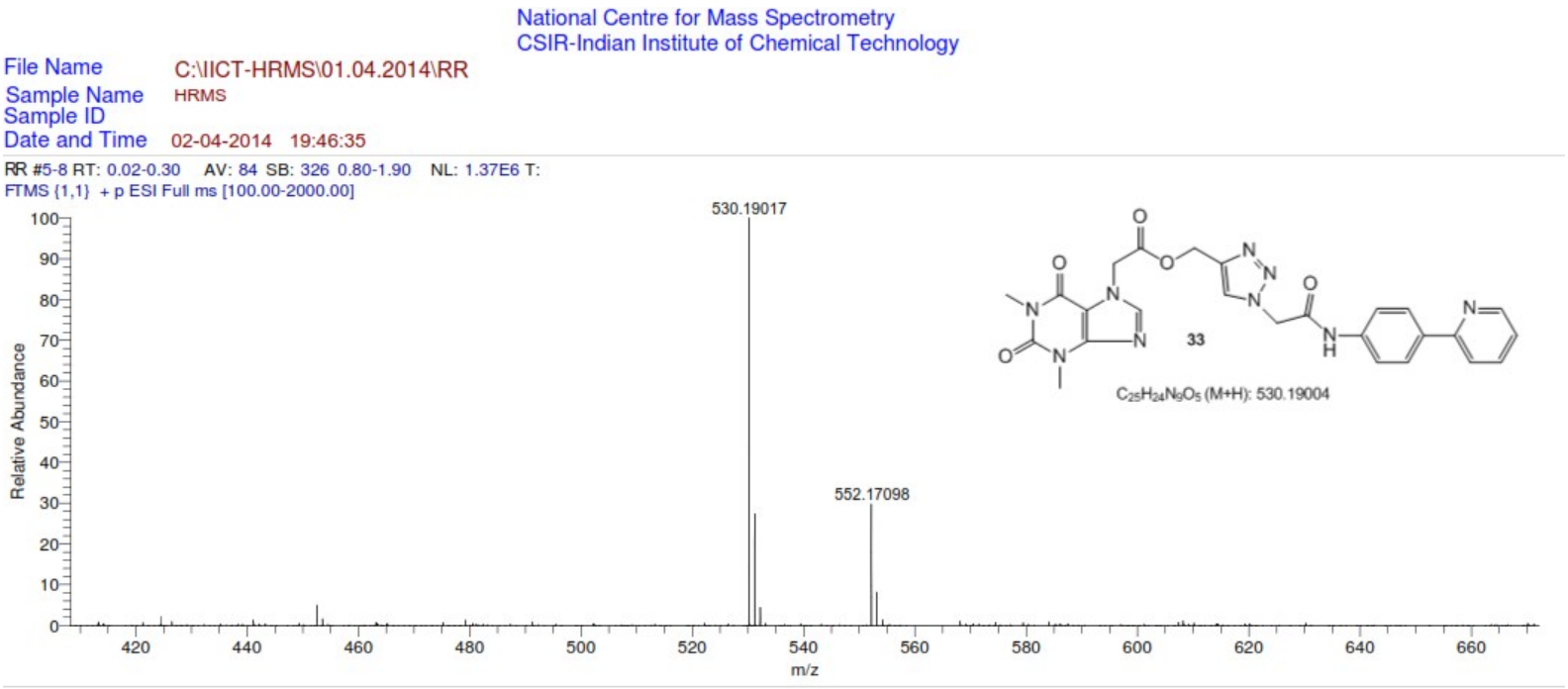


Fig-43: HRMS spectrum of compound-**33**

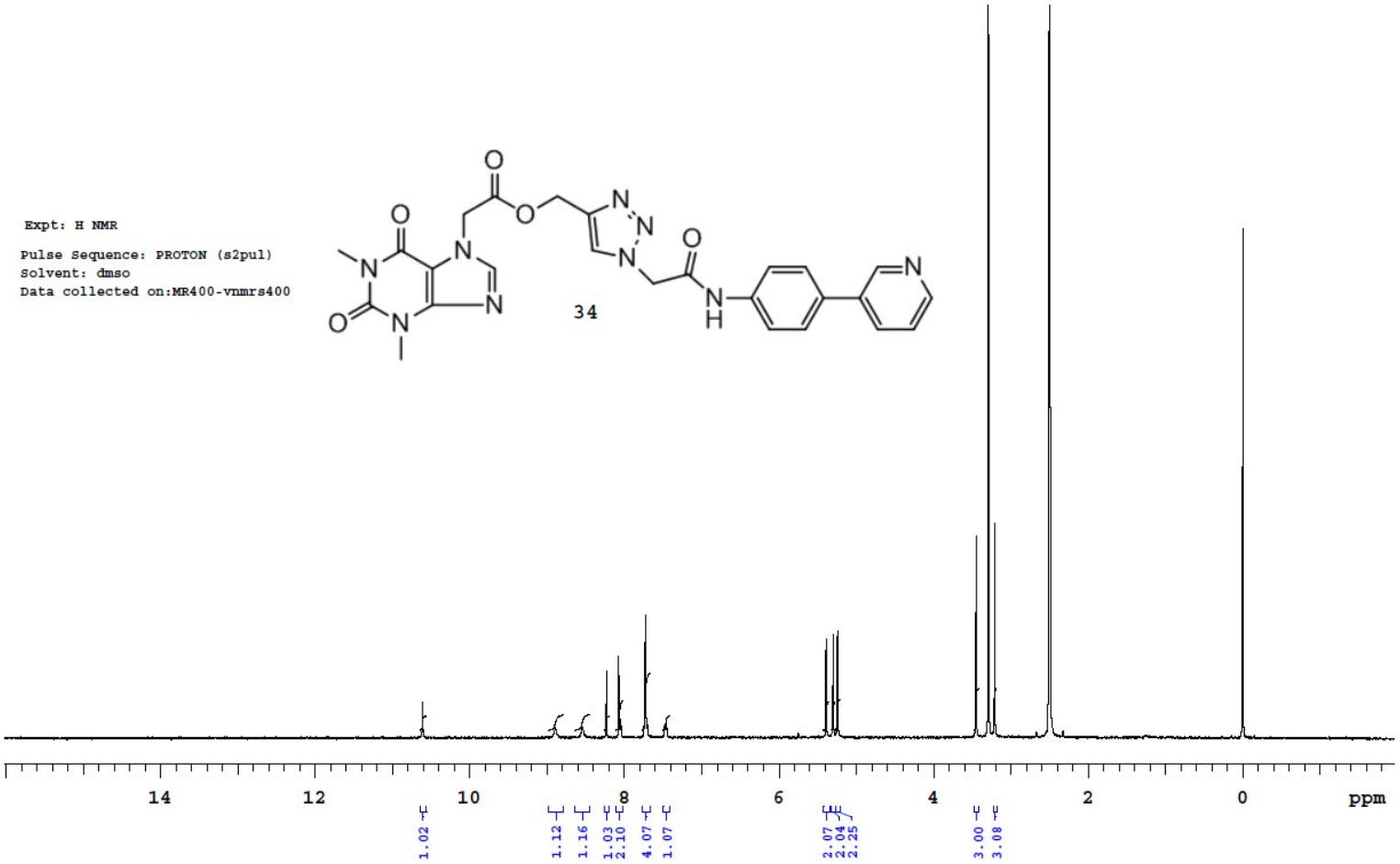


Fig-44: ^{1}H NMR spectrum of compound-**34**

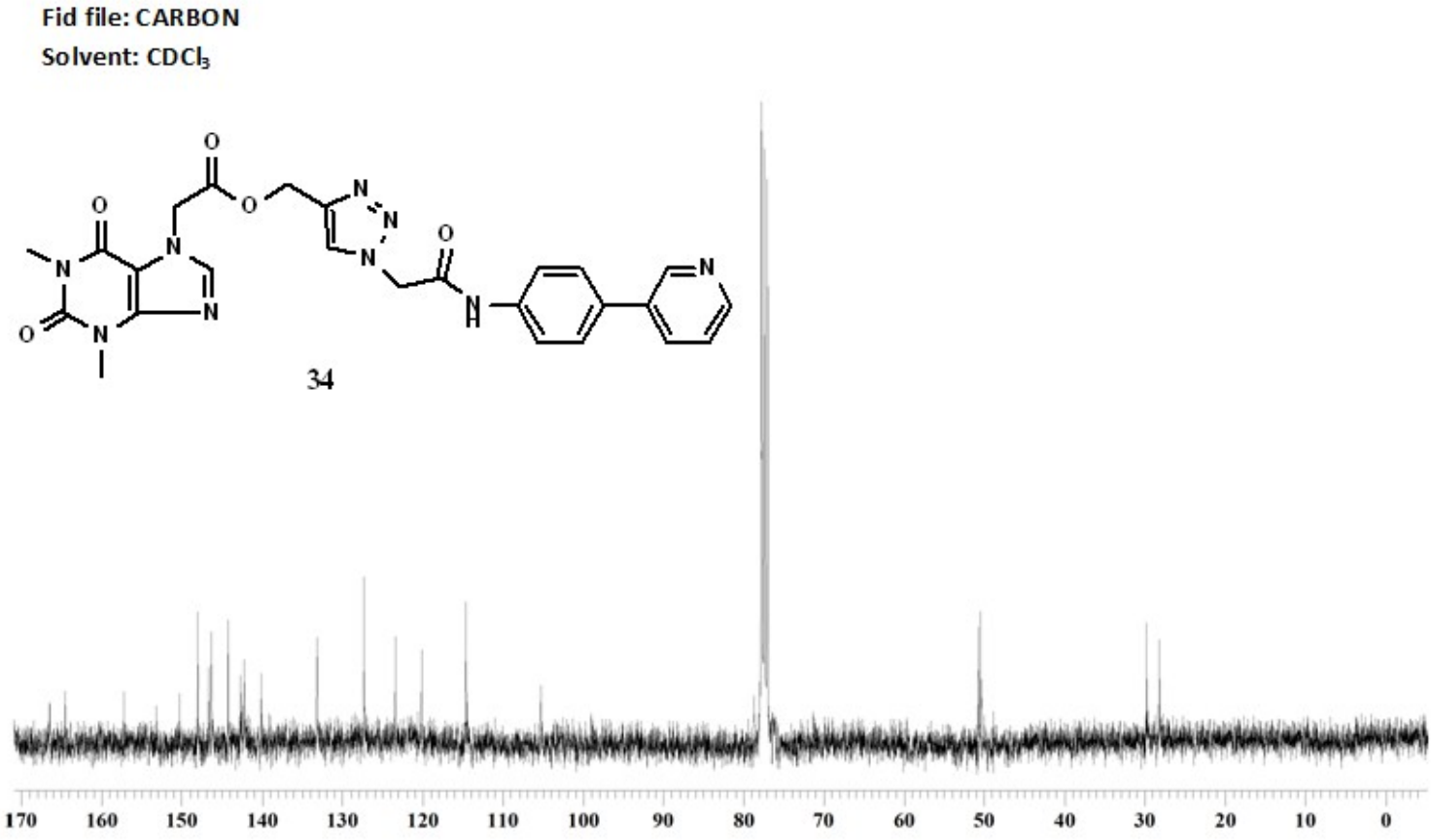
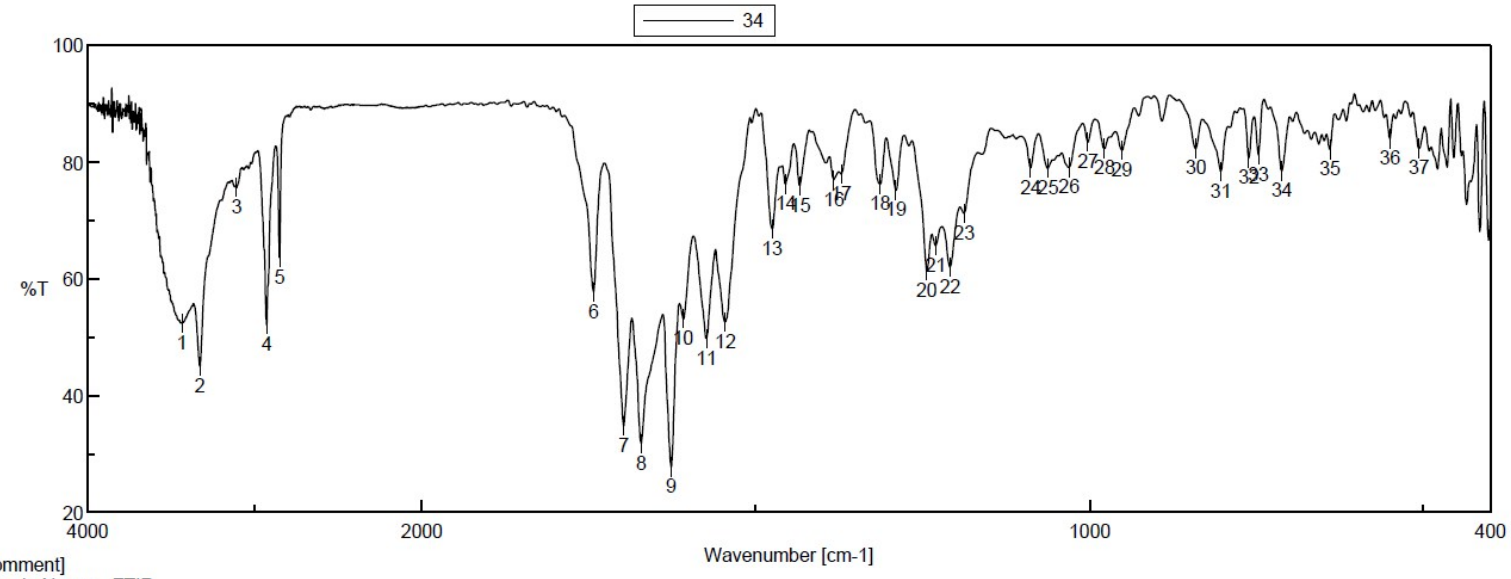


Fig-45: ^{13}C NMR spectrum of compound-**34**



[Comment]

Sample Name	FTIR
Comment	KBr Pellet
User	BSN
Division	QC
Company	SAPALA ORGANICS PVT LTD

[Data Information]

Creation Date	4/6/2015 4:06 PM
Data array type	Linear data array
Horizontal	Wavenumber [cm-1]
Vertical	%T
Start	349.053 cm-1
End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3434.6	52.352	2	3327.6	44.929	3	3107.7	75.577	4	2927.4	52.126	5	2850.3	63.606			
6	1742.4	57.667	7	1697.1	34.755	8	1671.0	31.703	9	1626.7	27.709	10	1608.3	53.108			
11	1573.6	49.714	12	1545.7	52.543	13	1475.3	68.573	14	1455.0	76.161	15	1433.8	75.936			
16	1382.7	76.989	17	1372.1	77.906	18	1313.3	76.174	19	1290.1	75.115	20	1243.9	61.355			
21	1230.4	65.623	22	1209.1	61.939	23	1187.9	71.233	24	1088.6	78.967	25	1062.6	78.879			
26	1030.8	79.054	27	1002.8	83.397	28	977.7	82.274	29	951.7	82.000	30	840.8	82.304			
31	803.2	78.384	32	761.7	80.679	33	747.3	81.167	34	712.6	78.408	35	640.3	82.138			
36	550.6	83.948	37	507.2	82.331												

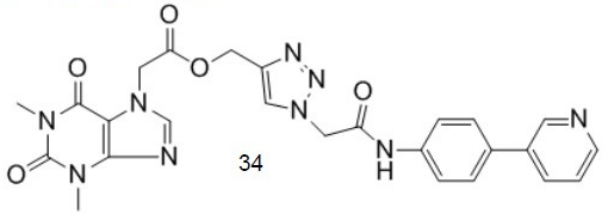
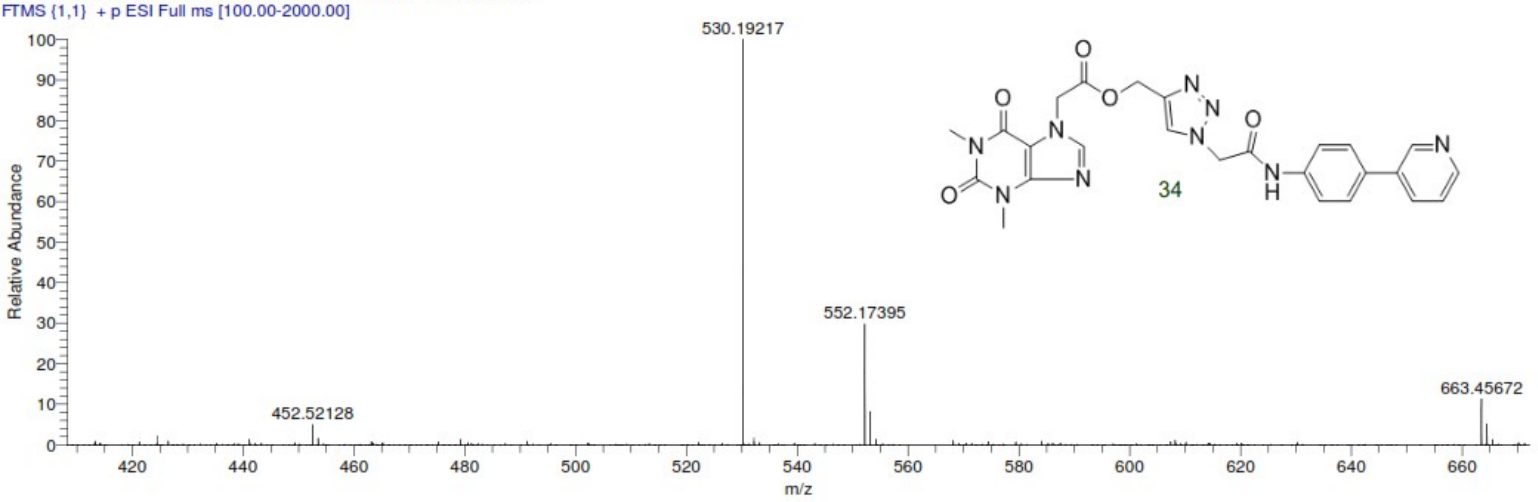


Fig-46: IR spectrum of compound-**34**

National Centre for Mass Spectrometry
CSIR-Indian Institute of Chemical Technology

File Name C:\IICT-HRMS\01.04.2014\RR
Sample Name HRMS
Sample ID 1
Date and Time 02-04-14 18:43:29

RR #5-88 RT: 0.02-0.30 AV: 84 SB: 326 0.80-1.90 NL: 1.37E6 T:
FTMS {1,1} + p ESI Full ms [100.00-2000.00]



RR #8-30 RT: 0.03-0.10 AV: 23
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
530.19213	2929195.3	100.00	530.18949	4.97	18.5	$C_{25}H_{24}O_5N_9$

Fig-47: HRMS spectrum of compound-**34**

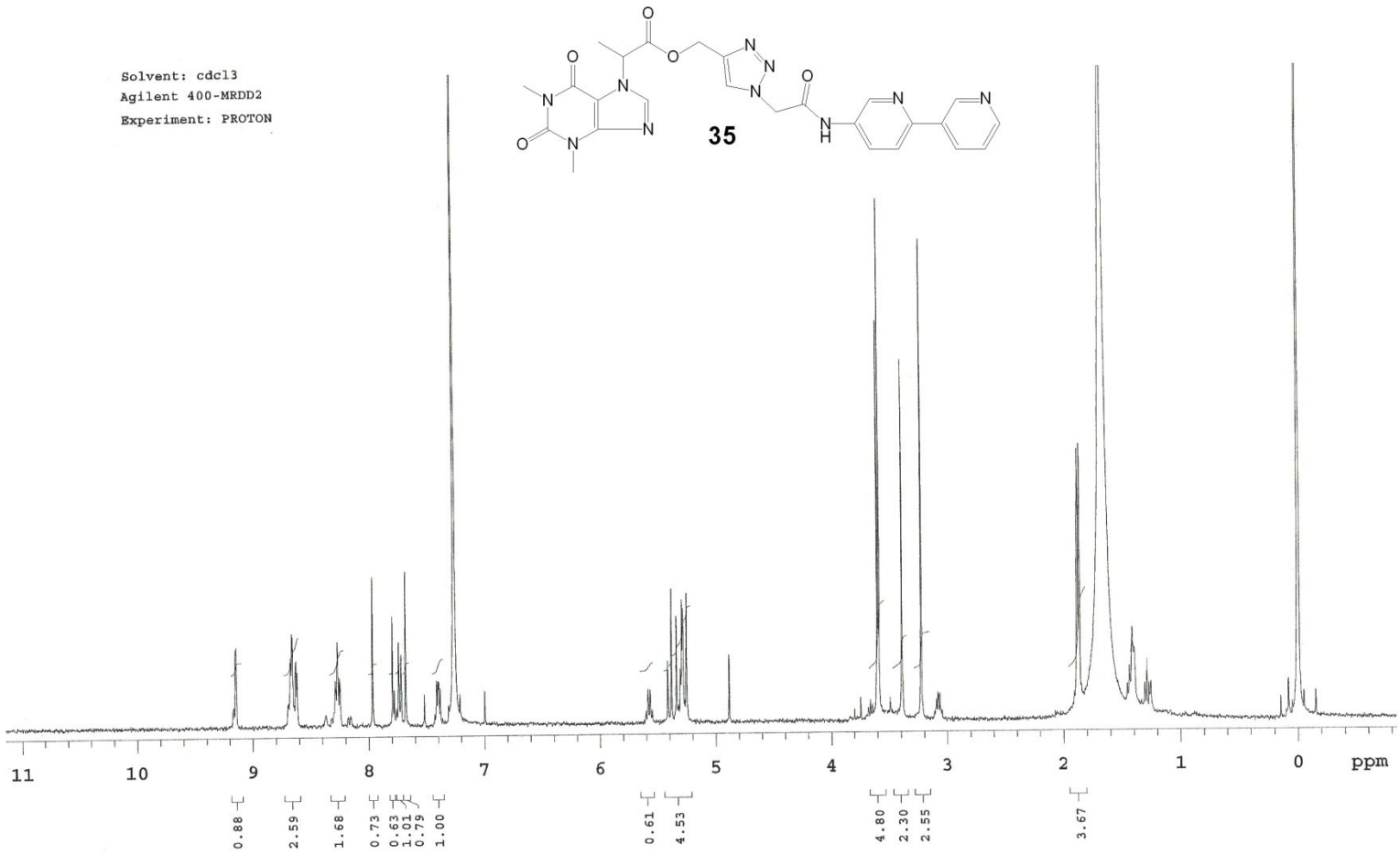


Fig-48: ^{1}H NMR spectrum of compound-**35**

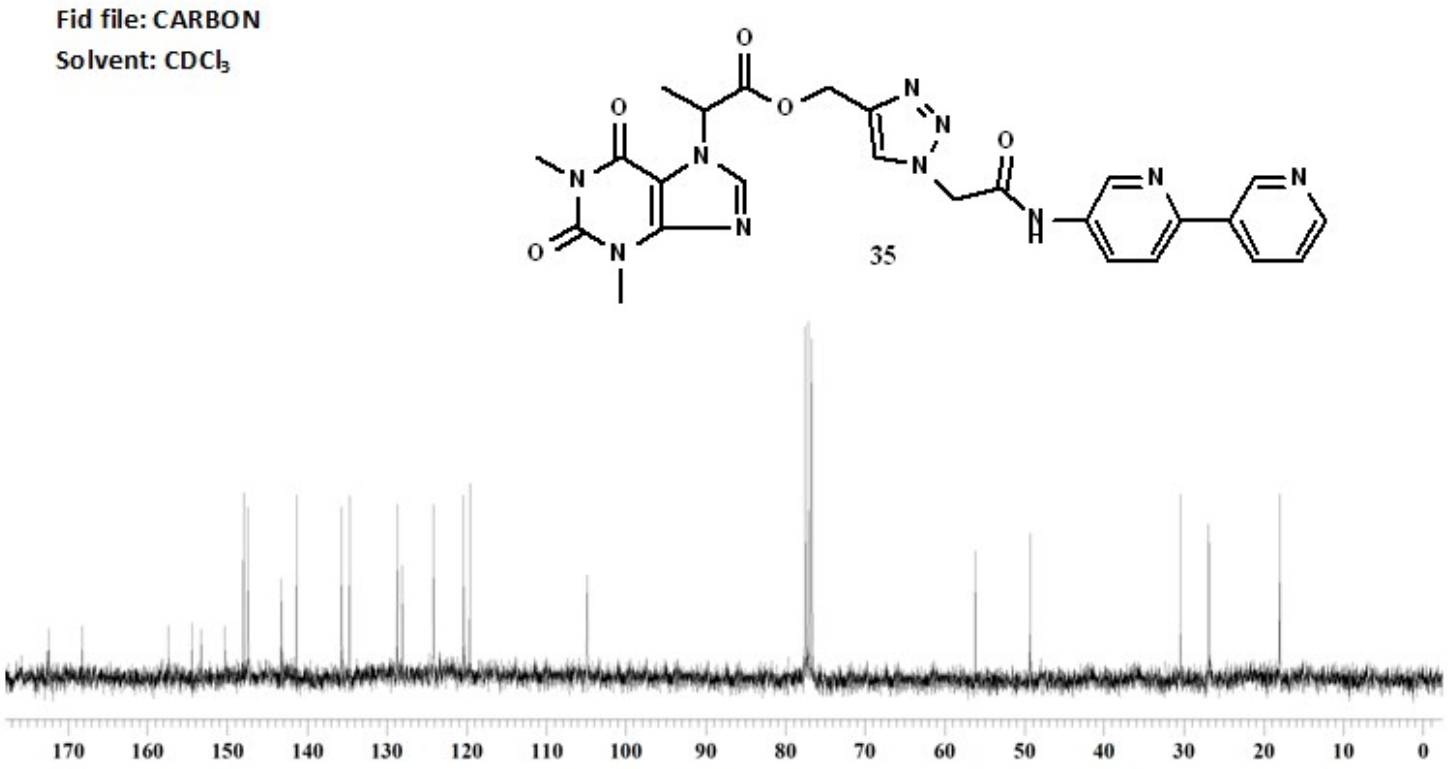
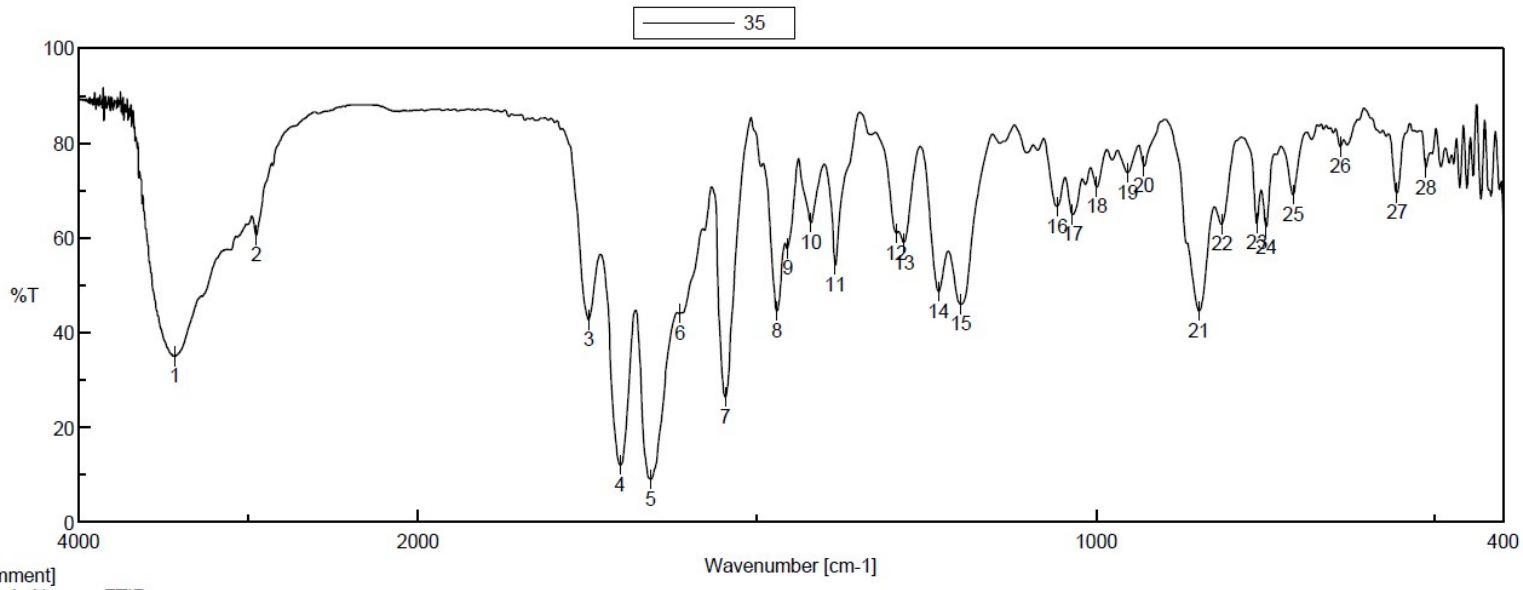


Fig-49: ^{13}C NMR spectrum of compound-**35**



[Comment]

Sample Name	FTIR
Comment	KBr Pellet
User	BSN
Division	QC
Company	SAPALA ORGANICS PVT LTD

[Data Information]

Creation Date	4/6/2015 3:09 PM
Data array type	Linear data array
Horizontal	Wavenumber [cm-1]
Vertical	%T
Start	349.053 cm-1
End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3430.7	34.864	2	2952.5	60.429	3	1748.2	42.563	4	1701.9	11.956	5	1656.6	9.069
6	1613.2	44.007	7	1546.6	26.333	8	1470.5	44.434	9	1455.0	57.672	10	1420.3	63.100
11	1384.6	54.168	12	1295.0	60.998	13	1283.4	58.945	14	1232.3	48.600	15	1199.5	45.898
16	1057.8	66.604	17	1034.6	64.849	18	998.9	70.674	19	953.6	73.724	20	929.5	75.150
21	848.5	44.483	22	814.8	62.801	23	762.7	62.987	24	749.2	62.212	25	709.7	69.017
26	640.3	79.135	27	556.4	69.436	28	513.9	74.763						

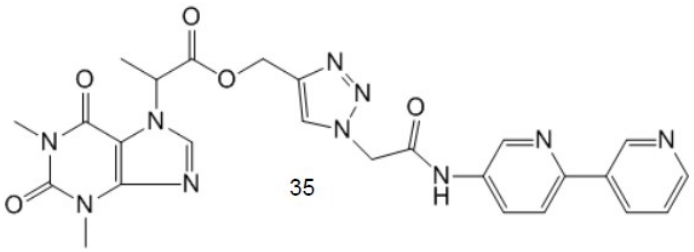
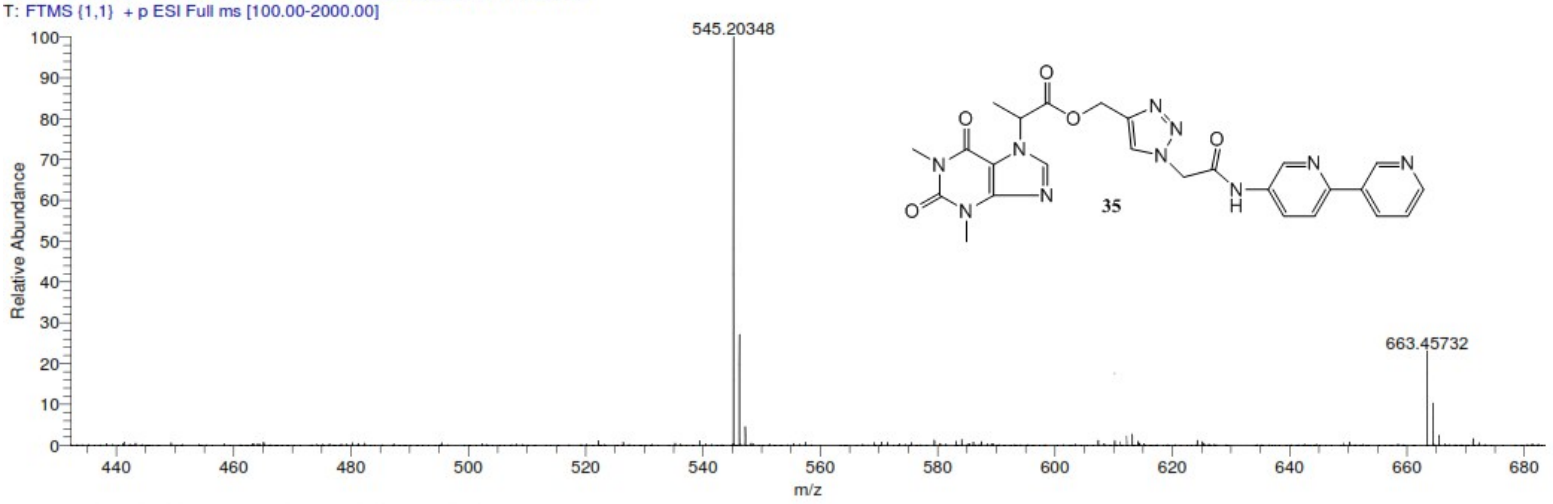


Fig-50: IR spectrum of compound-**35**

National Centre for Mass Spectrometry
CSIR-Indian Institute of Chemical Technology

File Name C:\IICT-HRMS\01.06.2014\BN-N-K2H
Sample Name HRMS
Sample ID 35
Date and Time 02-06-14 13:23:36

BN-N-K2H #5-97 RT: 0.02-0.30 AV: 86 SB: 326 0.80-1.90 NL: 7.35E5
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]



BN-N-K2H#8-30 RT: 0.03-0.11 AV: 24
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
545.20346	1800364.2	100.00	545.20032	5.56	18.4	$C_{25}H_{25}O_5N_{10}$

Fig-51: HRMS spectrum of compound-**35**

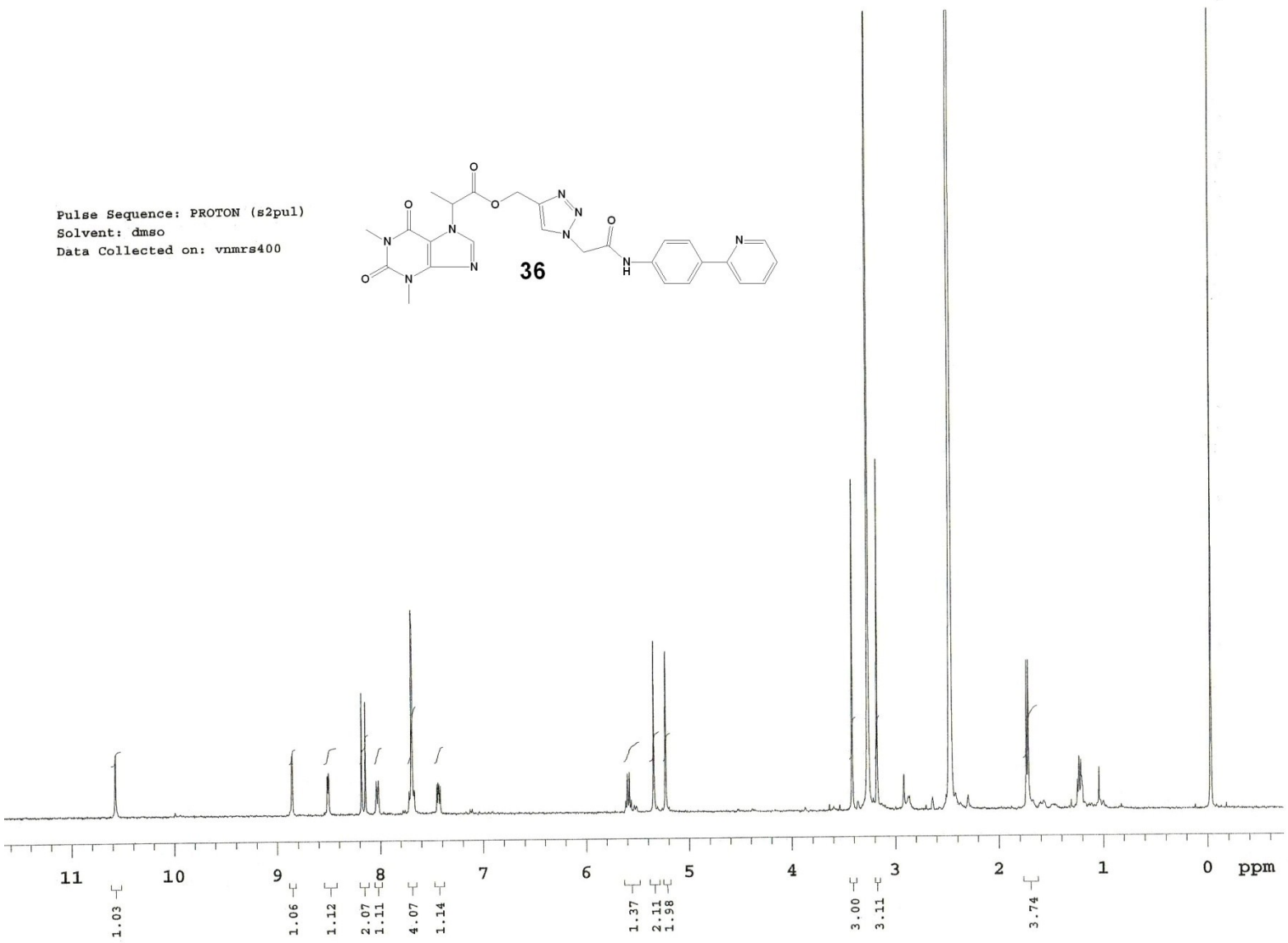
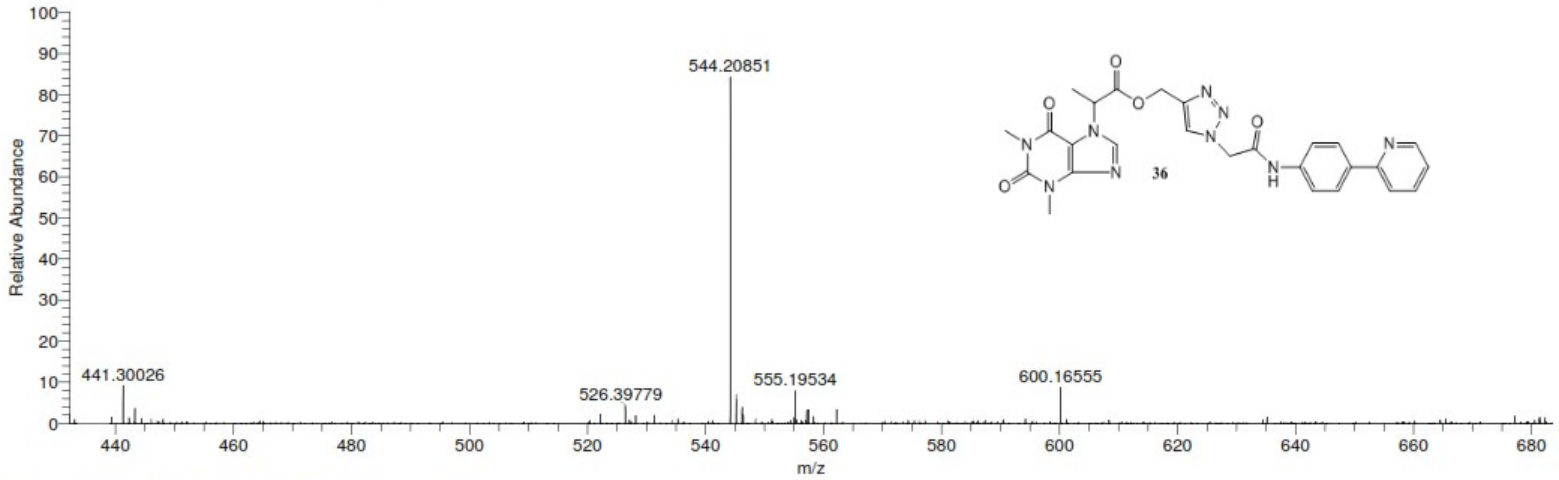


Fig-52: ^{1}H NMR spectrum of compound-**36**

National Centre for Mass Spectrometry
CSIR-Indian Institute of Chemical Technology

File Name C:\IICT-HRMS\01.04.2014\BN-N-K2C
Sample Name HRMS
Sample ID 36
Date and Time 02-04-14 18:51:12

BN-N-K2C #5-87 RT: 0.02-0.30 AV: 83 SB: 326 0.80-1.90 NL: 1.54E5
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]



BN-N-K2C#8-30 RT: 0.03-0.11 AV: 23
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
544.20854	279631.9	100.00	544.20514	6.25	18.5	$C_{26}H_{26}O_5N_9$

Fig-53: HRMS spectrum of compound-**36**

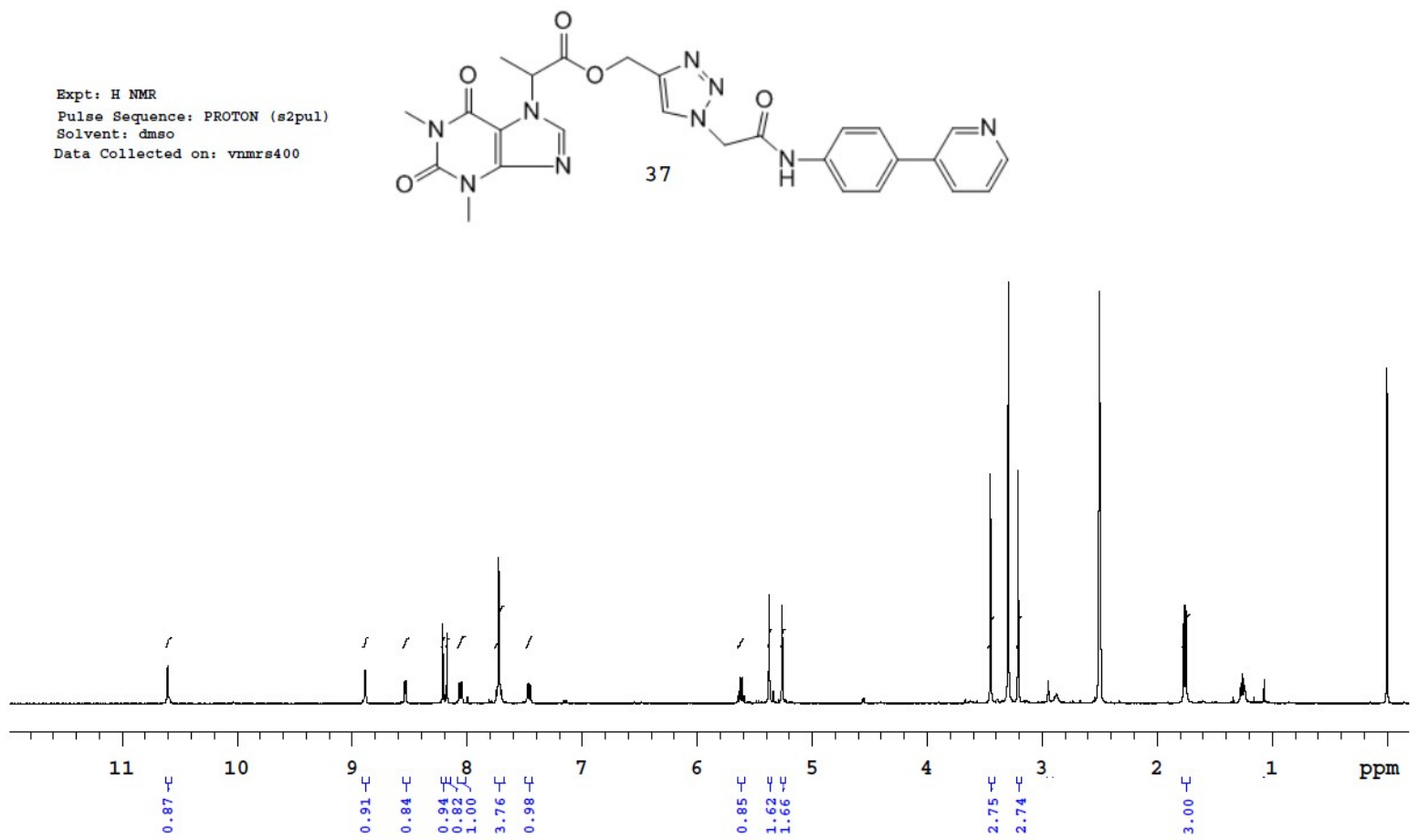
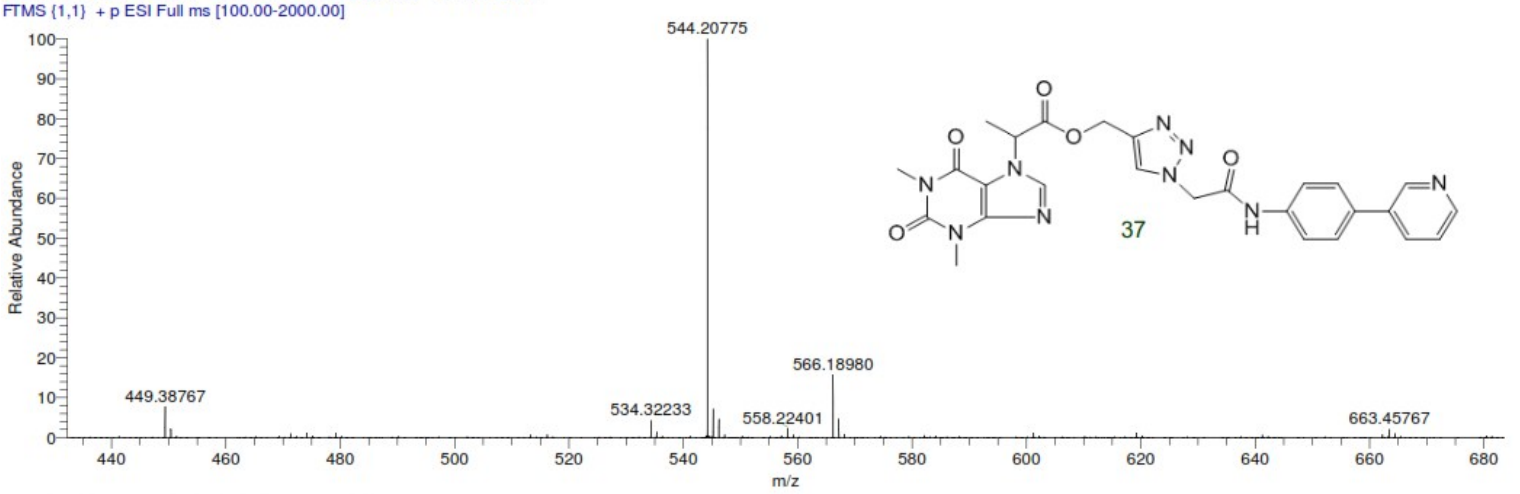


Fig-54: ^{1}H NMR spectrum of compound-**37**

National Centre for Mass Spectrometry
CSIR-Indian Institute of Chemical Technology

File Name C:\IICT-HRMS\01.04.2014
Sample Name HRMS
Sample ID
Date and Time 02-04-14 19:01:26

RR #4-87 RT: 0.02-0.30 AV: 84 SB: 326 0.80-1.90 NL: 6.71E6 T:
FTMS {1,1} + p ESI Full ms [100.00-2000.00]



RR#8-30 RT: 0.03-0.11 AV: 23
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
544.20769	12692146.0	100.00	544.20514	4.68	18.5	$C_{26}H_{26}O_5N_9$

Fig-55: HRMS spectrum of compound-**37**

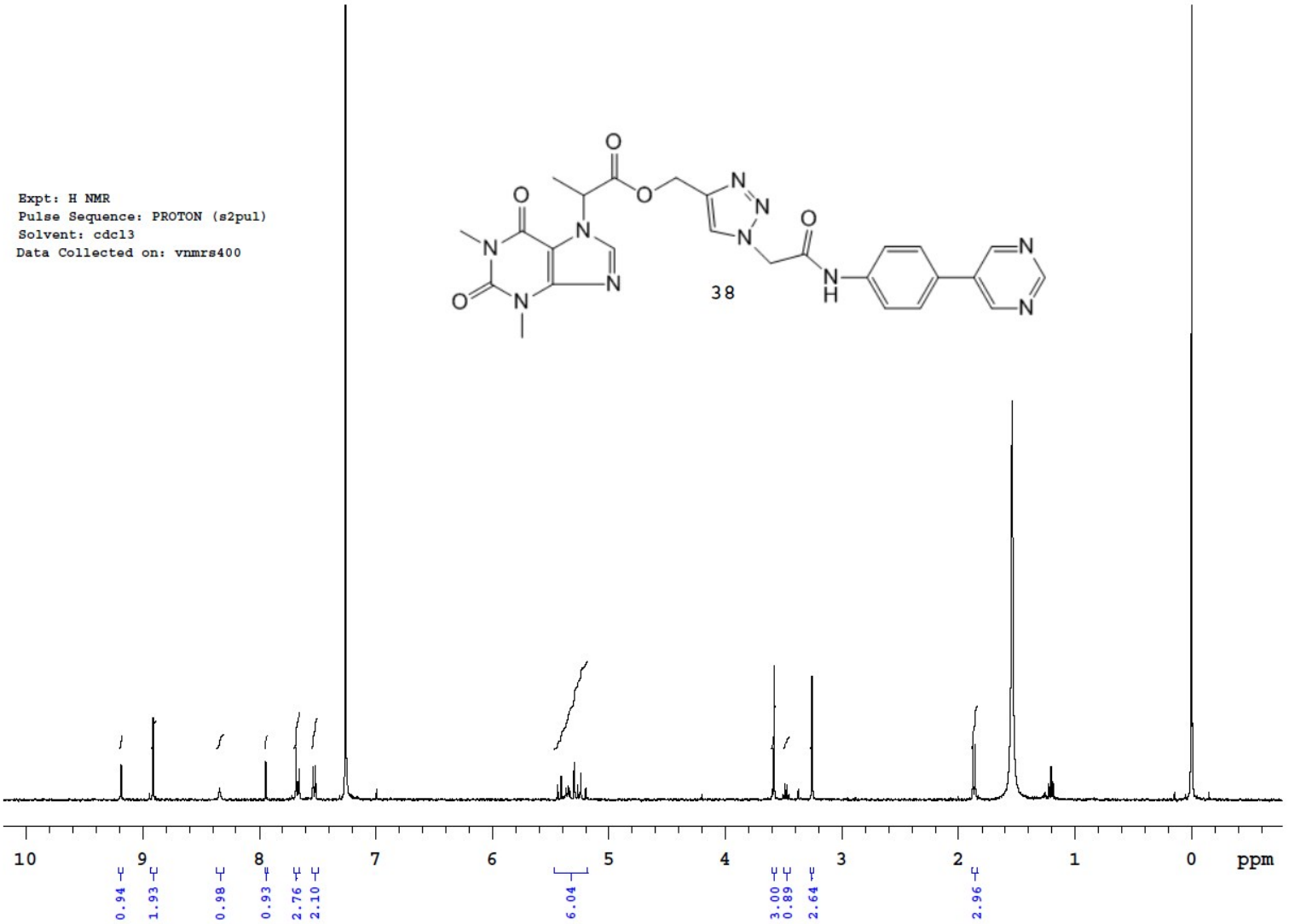
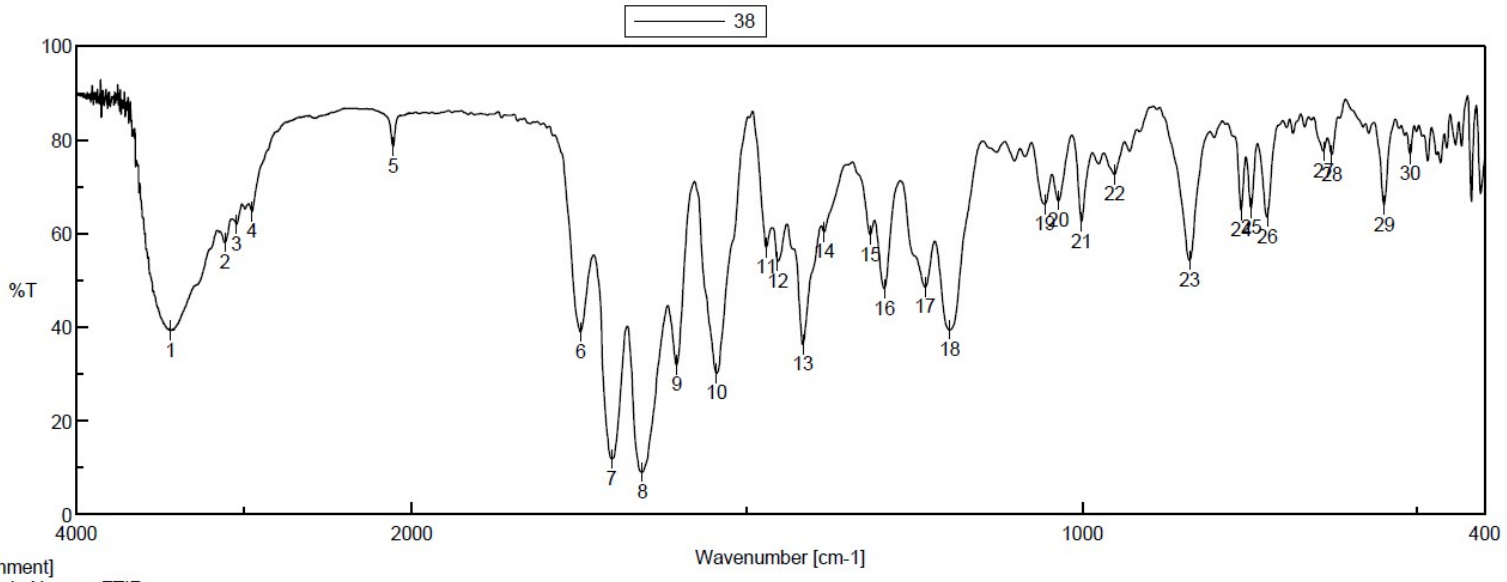


Fig-56: ^{1}H NMR spectrum of compound-**38**



[Comment]

Sample Name	FTIR
Comment	KBr Pellet
User	BSN
Division	QC
Company	SAPALA ORGANICS PVT LTD

[Data Information]

Creation Date	4/6/2015 3:51 PM
Data array type	Linear data array
Horizontal	Wavenumber [cm-1]
Vertical	%T
Start	349.053 cm-1
End	7800.65 cm-1
Data pitch	0.964233 cm-1
Data points	7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3436.5	39.257	2	3114.5	58.004	3	3044.1	61.884	4	2951.5	64.612	5	2109.7	78.575
6	1748.2	38.823	7	1701.9	11.825	8	1655.6	8.911	9	1604.5	31.899	10	1545.7	30.103
11	1471.4	56.943	12	1454.1	53.953	13	1416.5	36.220	14	1384.6	60.281	15	1316.2	59.643
16	1295.0	48.139	17	1234.2	48.475	18	1197.6	39.285	19	1055.8	66.218	20	1035.6	66.918
21	1000.9	62.486	22	951.7	72.578	23	839.8	54.193	24	762.7	64.928	25	748.2	65.366
26	724.1	63.392	27	640.3	77.530	28	627.7	76.809	29	549.6	66.126	30	511.0	76.905

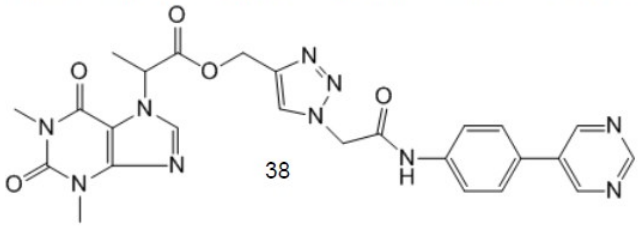
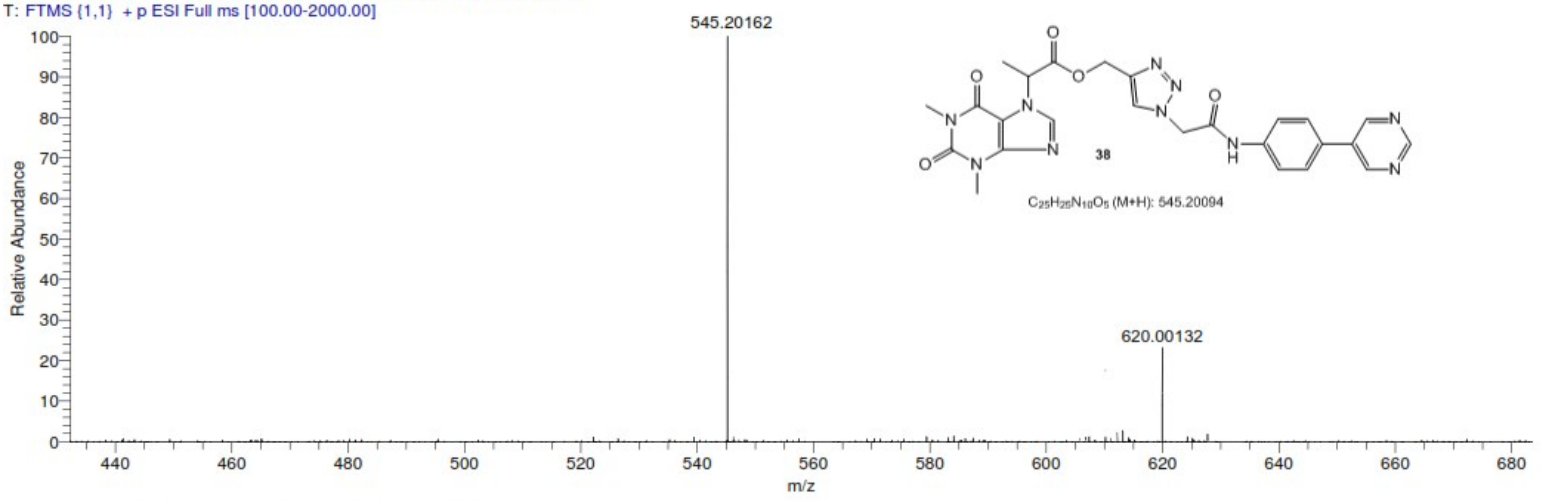


Fig-57: IR spectrum of compound-**38**

National Centre for Mass Spectrometry
CSIR-Indian Institute of Chemical Technology

File Name C:\IICT-HRMS\01.07.2014\BN-N-K2
Sample Name HRMS
Sample ID 38
Date and Time 02-08-14 12:33:16

BN-N-K2H #5-90 RT: 0.02-0.30 AV: 82 SB: 326 0.80-1.90 NL: 7.35E5
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]



BN-N-K2H#8-30 RT: 0.03-0.11 AV: 25
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
545.20158	1800365.1	100.00				

Fig-58: HRMS spectrum of compound-**38**

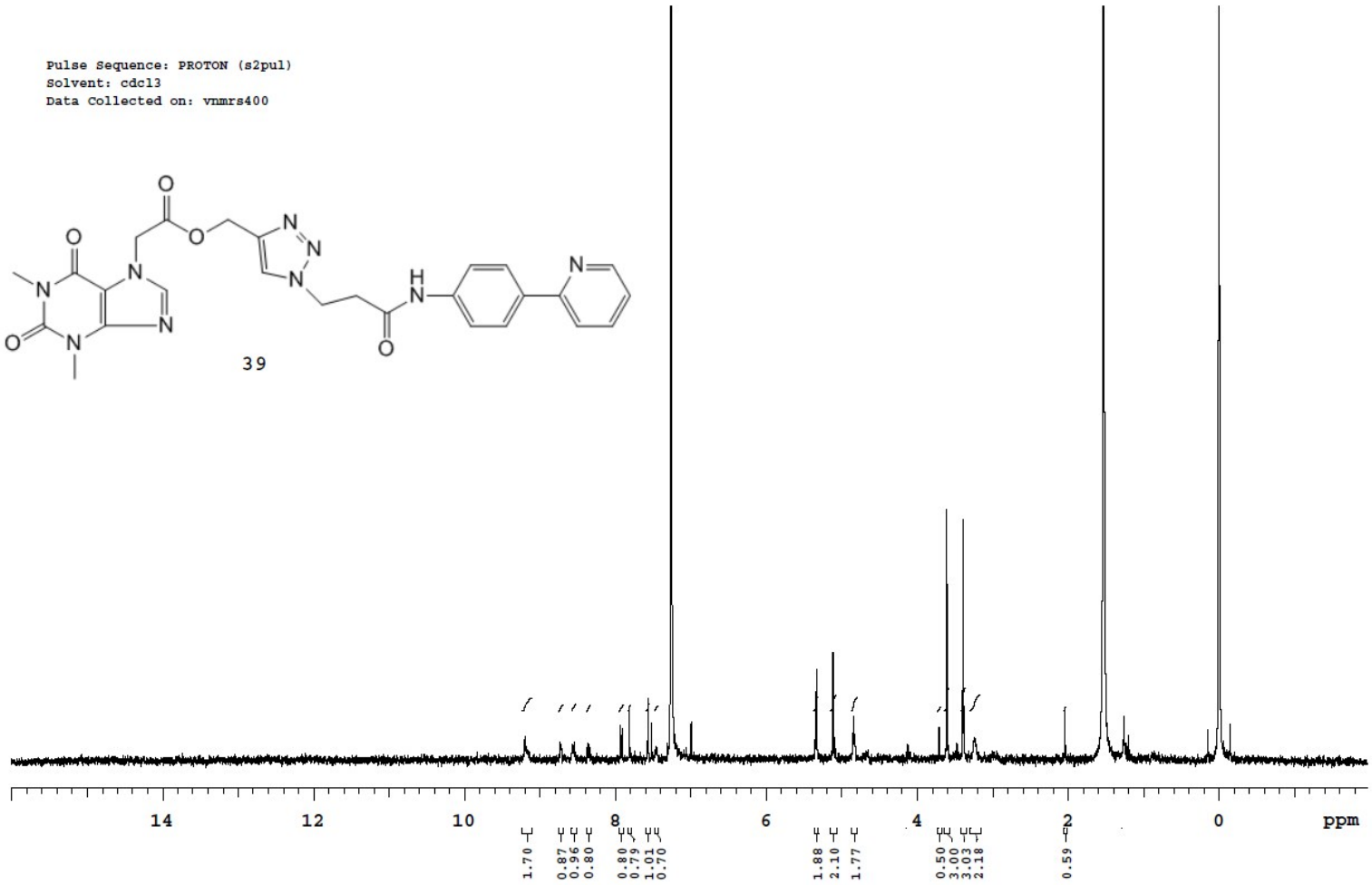
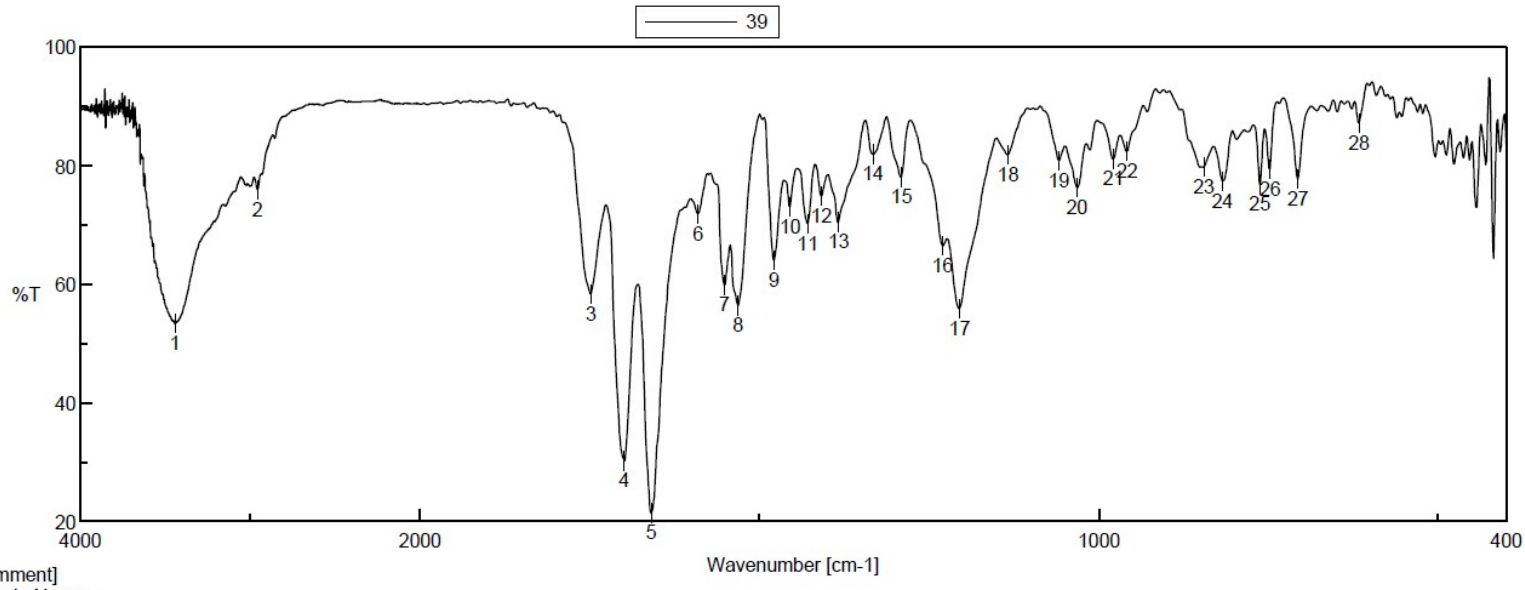


Fig-59: ^{1}H NMR spectrum of compound-**39**



[Comment]
Sample Name
Comment KBr Pellet
User BSN
Division QC
Company SAPALA ORGANICS PVT LTD

[Data Information]
Creation Date 4/6/2015 3:36 PM
Data array type Linear data array
Horizontal Wavenumber [cm-1]
Vertical %T
Start 349.053 cm-1
End 7800.65 cm-1
Data pitch 0.964233 cm-1
Data points 7729

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3443.3	53.322	2	2956.3	75.966	3	1748.2	58.323	4	1699.0	30.180	5	1659.4	21.359
6	1590.0	71.839	7	1551.5	59.815	8	1531.2	56.375	9	1478.2	63.984	10	1455.0	73.045
11	1429.0	70.184	12	1408.7	74.822	13	1383.7	70.392	14	1332.6	81.907	15	1291.1	78.029
16	1230.4	66.476	17	1205.3	55.840	18	1133.9	81.819	19	1058.7	80.841	20	1031.7	76.280
21	978.7	81.087	22	958.4	82.350	23	845.6	79.724	24	817.7	77.370	25	762.7	76.786
26	748.2	79.424	27	706.8	77.683	28	617.1	87.152						

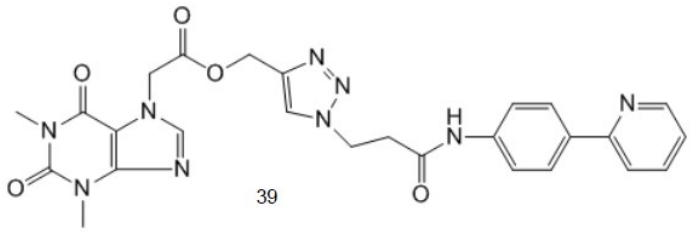


Fig-60: IR spectrum of compound-**39**

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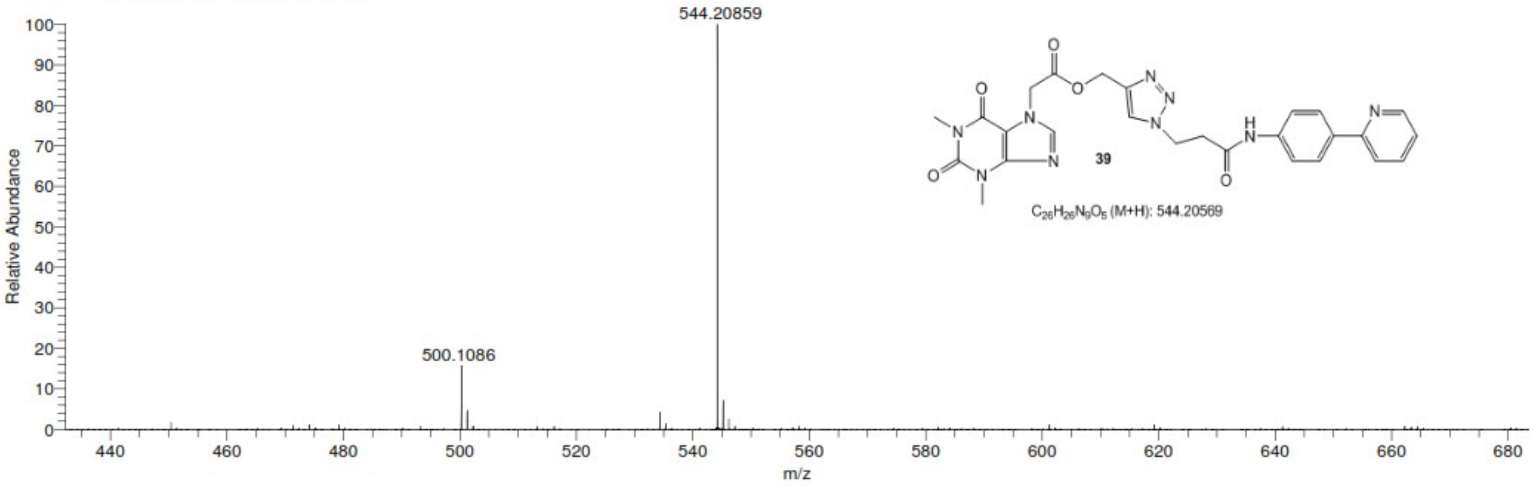
File Name C:\IICT-HRMS\03.05.2014\BN-N-K2B
Sample Name HRMS
Sample ID 39
Date and Time 04-05-14 16:18:36

BN-N-K2B #4-77 RT: 0.02-0.30 AV: 74 SB: 326 0.80-1.90 NL: 6.71E6
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]



BN-N-K2B#8-31 RT: 0.03-0.11 AV: 20
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
544.20848	12692145.0	100.00				

Fig-61: HRMS spectrum of compound-**39**

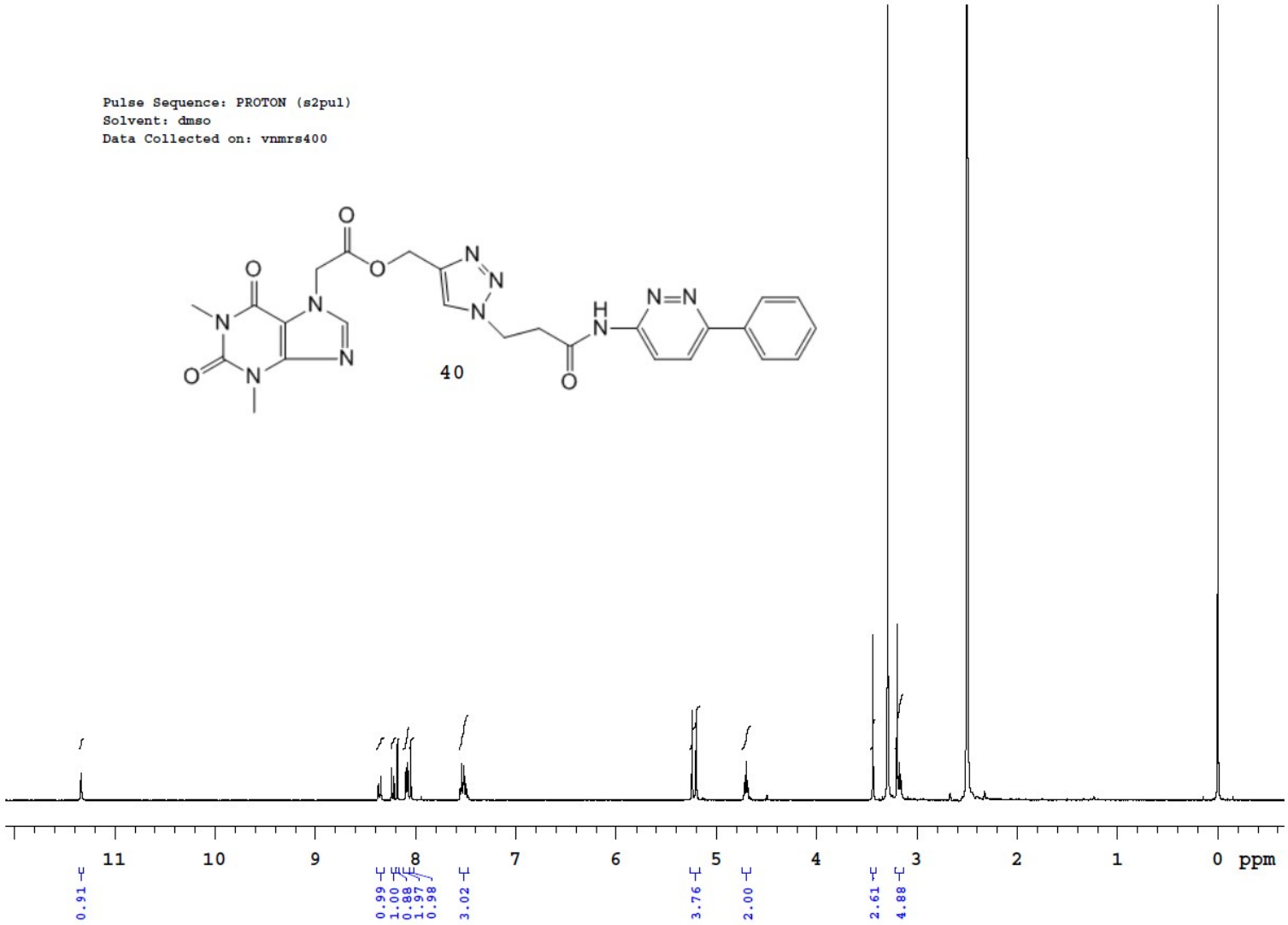
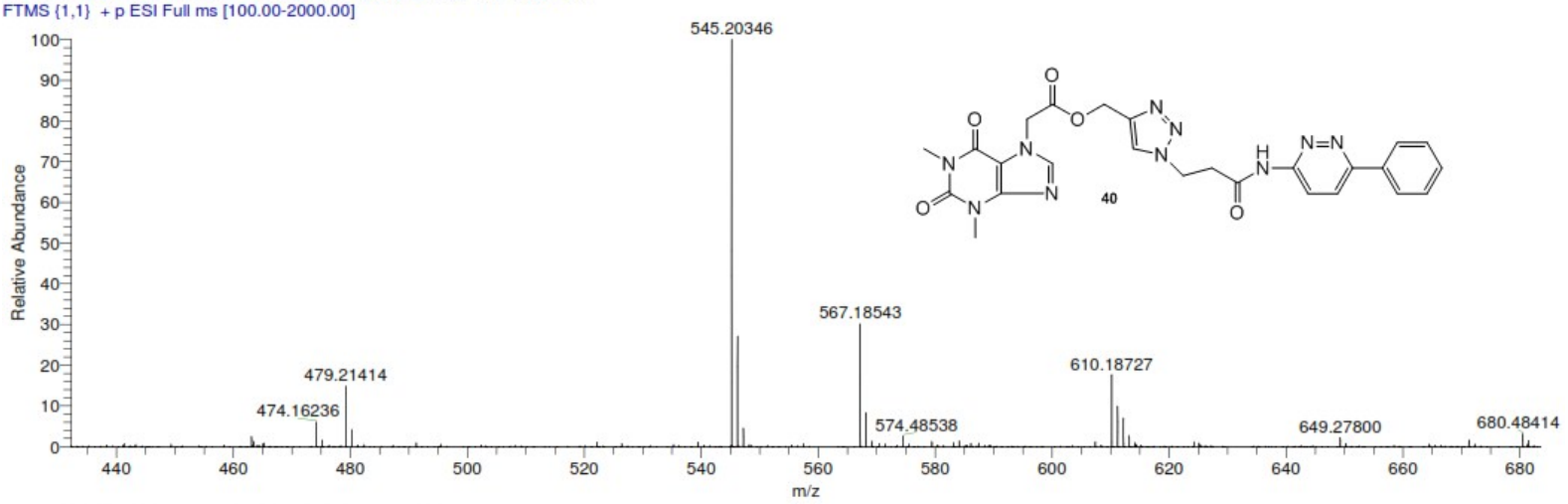


Fig-62: ^{1}H NMR spectrum of compound-**40**

National Centre for Mass Spectrometry
CSIR-Indian Institute of Chemical Technology

File Name C:\IICT-HRMS\01.04.2014\ RK
Sample Name
Sample ID
Date and Time 02-04-14 18:58:53

RR-K2H #5-87 RT: 0.02-0.30 AV: 83 SB: 326 0.80-1.90 NL: 7.35E5 T:
FTMS {1,1} + p ESI Full ms [100.00-2000.00]



RR-K2H#8-30 RT: 0.03-0.11 AV: 23
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
545.20343	1800362.6	100.00	545.20039	5.57	18.5	$C_{25}H_{25}O_5N_{10}$

Fig-63: HRMS spectrum of compound-**40**

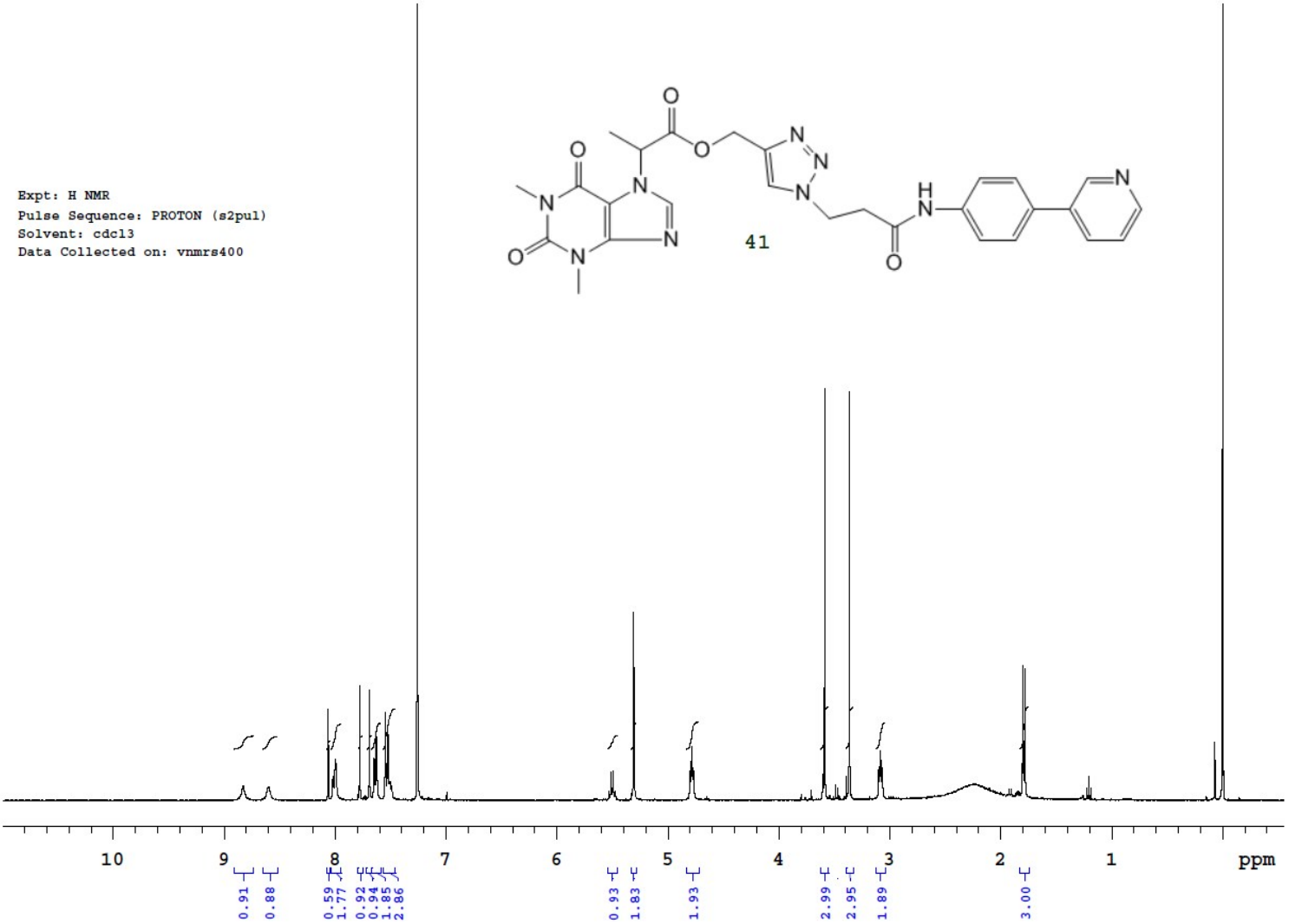


Fig-64:[1]H NMR spectrum of compound-**41**

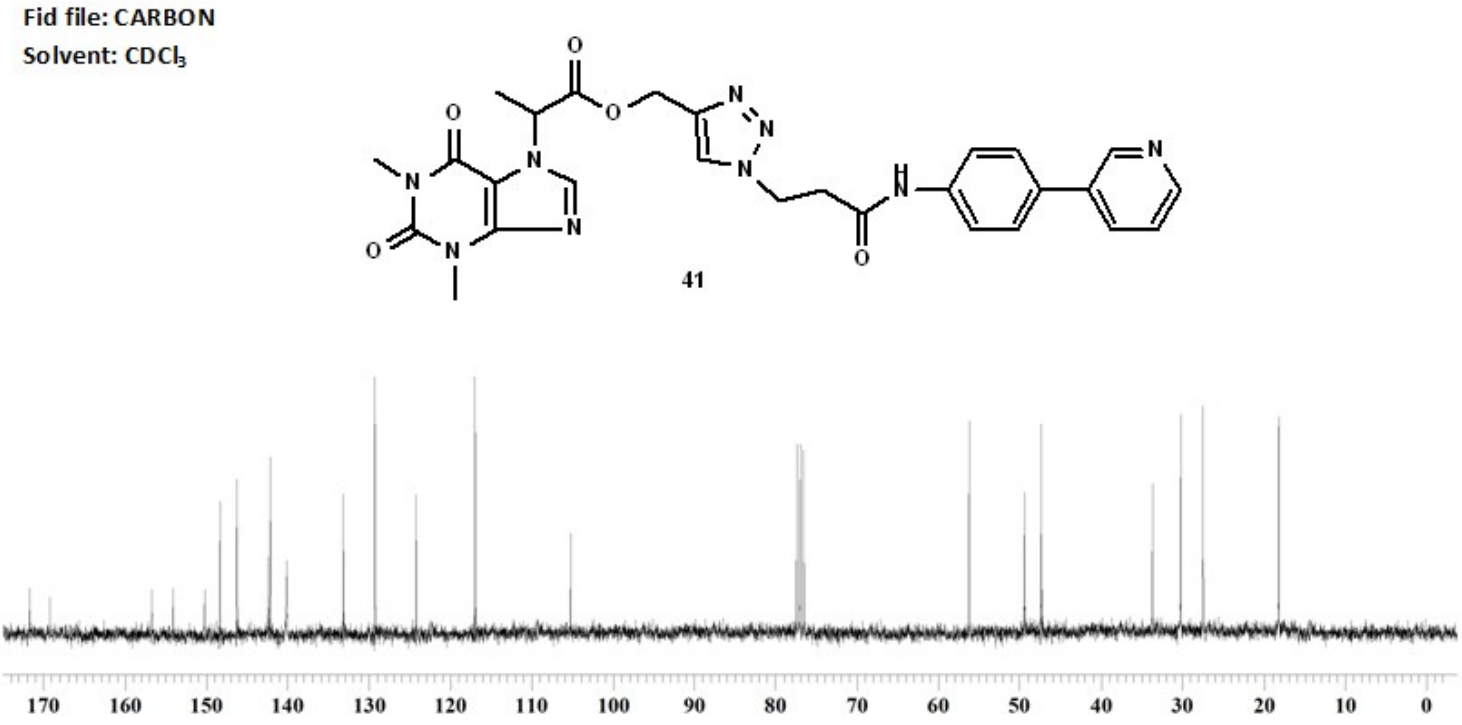


Fig-65: ^{13}C NMR spectrum of compound-**41**

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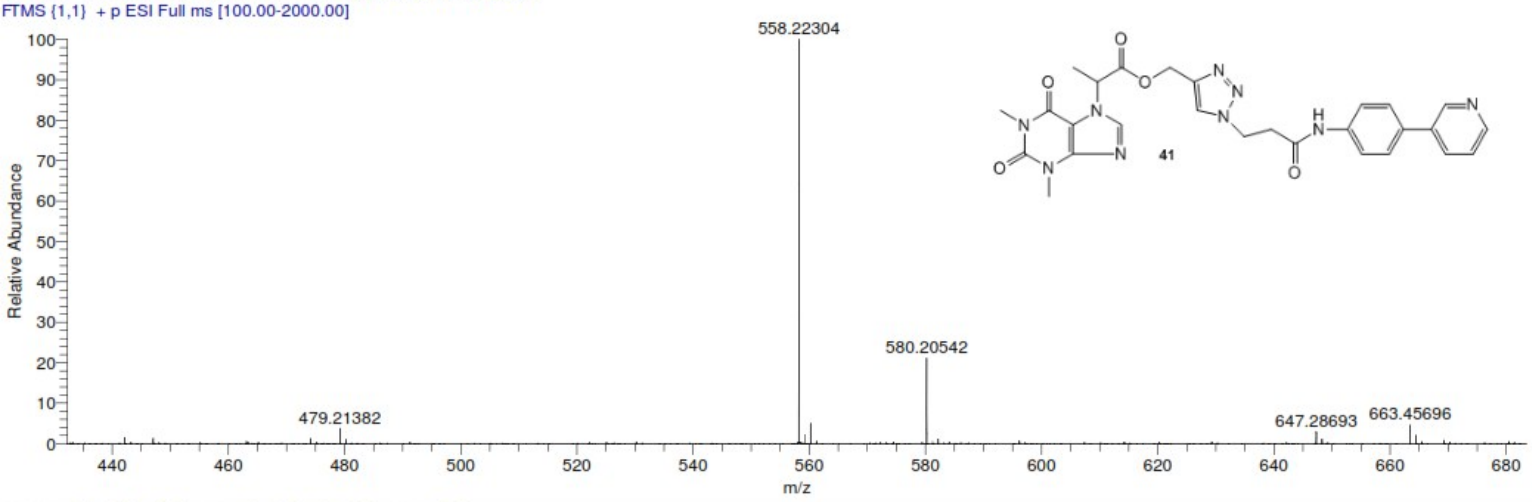
CSIR-Indian Institute of Chemical Technology

File Name C:\IICT-HRMS\01.04.2014\RR
Sample Name HRMS
Sample ID 1
Date and Time 02-04-14 18:53:45

RR #4-87 RT: 0.02-0.30 AV: 84 SB: 326 0.80-1.90 NL: 3.34E6 T:
FTMS {1,1} + p ESI Full ms [100.00-2000.00]



BN-N-K2G#8-30 RT: 0.03-0.11 AV: 23
T: FTMS {1,1} + p ESI Full ms [100.00-2000.00]

m/z	Intensity	Relative	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
558.22281	8032459.5	100.00	558.22079	3.62	18.5	$C_{27}H_{28}O_5N_9$

Fig-66: HRMS spectrum of compound-**41**