Electronic Supplementary Information

Design and Development of Sulfonylurea Derivatives as Zinc Metalloenzyme Modulators

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Materials

All the reagents were obtained from Sigma-Aldrich, Alfa-Aesar and Merck Chemicals. Solvents were obtained from Merck Chemicals and Rankem and were used without further purification. All reactions were performed under an inert atmosphere of dry nitrogen. ^{1}H NMR spectra were recorded on a 500 MHz Bruker Instrument. Mass spectra were measured by LC-MS on a Waters SYNAPT-G2S-S using electrospray ionization technique. All compounds were purified by using normal column chromatography technique and were characterized by NMR and LC/MS.

Synthetic Procedure

N-((4-phenylbutyl)carbamoyl)methanesulfonamide (1): Methanesulfonyl chloride (0.2 mL, 2.6 mmol) was treated with pyridine (0.25 mL, 3.4 mmol) and allowed to stir for 5 min at 0 ^{o}C. The resultant solution was transferred to a mixture of sodium cyanate (0.2g, 2.9 mmol) in acetonitrile (5 mL) and allowed to stir for about 5 min at 0 ^{o}C. To the resultant mixture phenylbutyl amine (0.5 mL, 3.3 mmol) was added and reaction mixture was gradually brought to room temperature and then further stirred for 30 min at room temperature. The resulting reaction mixture was poured on crushed ice and acidified with dil. HCl (pH 5-6). Aqueous layer was extracted with ethyl acetate three times and combined extract was washed with brine and dried over anhydrous Na_2SO_4. Solvent was evaporated under vacuum and resulting residue was further purified by column chromatography to afford a white coloured title compound **1** (60 mg, 18%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.42 (brs, 1H), 7.29-7.26 (m, 2H), 7.19-7.15 (m, 3H), 6.35 (brs, 1H), 3.27 (q, 2H, J = 6.2 Hz), 3.15 (s, 3H), 2.64 (t, 2H, J = 7.4 Hz), 1.68-1.62 (m, 2H), 1.59-1.54 (m, 2H).

MS (ESI): 271.10 $[M+H]^+$.

N-((4-phenylbutyl)carbamoyl)ethanesulfonamide (2): The title compound was synthesized as a white solid (87 mg, 14%) by treatment of phenylbutyl amine (0.5 mL, 3.3 mmol) and ethanesulfonyl chloride (0.2 mL, 2.2 mmol) using the detailed procedure of compound **1**.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29-7.28 (m, 2H), 7.20-7.15 (m, 3H), 6.99 (brs, 1H), 6.48 (brs, 1H), 3.29-3.21 (m, 4H), 2.64 (t, 2H, *J* = 7.4 Hz), 1.68-1.64 (m, 2H), 1.59-1.57 (m, 2H), 1.42 (t, 3H, *J* = 7.5 Hz).

MS (ESI): 285.12 $[M+H]^+$, 307.10 $[M+Na]^+$.

N-((4-phenylbutyl)carbamoyl)propane-1-sulfonamide (3): The title compounds was synthesized as a white solid (100 mg, 16%) by treatment of phenylbutyl amine (0.5 mL, 3.3 mmol) and propanesulfonyl chloride (0.25 mL, 2.2 mmol) using the detailed procedure of compound **1**.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57 (brs, 1H), 7.29-7.28 (m, 2H), 7.20-7.15 (m, 3H), 6.45 (brs, 1H), 3.29-3.25 (m, 2H), 3.18 (t, 2H, *J* = 7.8 Hz), 2.63 (t, 2H, *J* = 7.3 Hz), 1.90-1.85 (m, 2H), 1.67- 1.62 (m, 2H), 1.59-1.55 (m, 2H), 1.06 (t, 3H, *J* = 7.5 Hz).

MS (ESI): 299.17 $[M+H]^+$, 321.15 $[M+Na]^+$.

N-((4-phenylbutyl)carbamoyl)propane-2-sulfonamide (4): The title compound was synthesized as a white solid (95 mg, 15%) by treatment of phenylbutyl amine (0.5 mL, 3.3 mmol) and isopropane sulfonyl chloride (0.25 mL, 2.2 mmol) using the detailed procedure of compound **1**.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.09 (brs, 1H), 7.29-7.26 (m, 2H), 7.20-7.15 (m, 3H), 6.61 (brs, 1H), 3.39-3.33 (m, 1H), 3.28-3.24 (m, 2H), 2.62 (t, 2H, *J* = 7.3 Hz), 1.67- 1.61 (m, 2H), 1.58-1.52 (m, 2H), 1.40 (d, 6H, *J* = 6.9 Hz).

MS (ESI): 299.13 $[M+H]^+$, 321.12 $[M+Na]^+$.

N-((4-phenylbutyl)carbamoyl)cyclohexanesulfonamide (5): The title compound was synthesized as a white solid (89 mg, 12 %) by treatment of phenylbutyl amine (0.5 mL, 3.3 mmol) and cyclohexylsulfonyl chloride (0.3 mL, 2.2 mmol) using the detailed procedure of compound **1**.

^{1}H NMR($CDCl_3$, 500 MHz): δ 7.67 (brs, 1H), 7.29-7.27 (m, 2H), 7.20-7.15 (m, 3H), 6.58 (s, 1H), 3.28-3.24 (m, 2H), 2.63 (t, 2H, *J* = 7.4 Hz), 2.20-2.17 (m, 2H), 1.91-1.88 (m, 2H), 1.72-1.62 (m, 7H) 1.59-1.49 (m, 4H).

MS (ESI): 339.20 $[M+H]^+$, 361.19 $[M+Na]^+$.

A typical procedure for the synthesis of aromatic sulfonylurea derivatives.

4-methyl-N-((4-phenylbutyl)carbamoyl)benzenesulfonamide (6): *p*-tosyl chloride (0.5 g, 2.6 mmol) was treated with pyridine (0.4 mL, 5.0 mmol) and allow to stir for 5 min. The resultant solution was transferred to a mixture of sodium cyanate (0.25 g, 3.9 mmol) in acetonitrile (5 mL) and allowed to stir for about 4 hour at room temperature. To the resultant mixture phenylbutylamine (0.6 mL, 3.8 mmol) were added and stir for about 1 hr at room temperature. The resulting reaction mixture was poured on crushed ice and acidified with dil HCl (pH 5-6). Aqueous layer was extracted with ethyl acetate three times and combined extract was washed with brine and dried over anhydrous Na_2SO_4. Solvent was evaporated under vacuum and resulting residue was further purified by column chromatography to afford a white colored title compound **6** (485 mg, 54%).

^{1}H NMR(DMSO-d_6, 500 MHz) : δ 10.45 (brs, 1H), 7.76 (d, 2H, *J* = 8.2 Hz), 7.37 (d, 2H, *J* = 8.0 Hz), 7.25 (t, 2H, *J* = 7.4 Hz), 7.17-7.12 (m, 3H), 6.45 (brs, 1H), 2.96 (q, 2H, *J* = 6.5 Hz), 2.55 – 2.50 (m, 2H), 2.37 (s, 3H), 1.46-1.40 (m, 2H), 1.36-1.31 (m, 2H).

MS (ESI): 347.14 $[M+H]^+$, 369.12 $[M+Na]^+$.

4-chloro-N-((4-phenylbutyl)carbamoyl)benzenesulfonamide (7): The title compound was synthesized as a white solid (600 mg, 57%) by treatment of phenylbutylamine (0.7

mL, 4.4 mmol) and *p*-chlorophenylsulfonyl chloride (0.6 g, 2.9 mmol) using the procedure detailed of compound **6**.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 7.78 (d, 2H, *J* = 8.7 Hz), 7.44 (d, 2H, *J* = 8.7 Hz), 7.29 (t, 2H, *J* = 7.4 Hz), 7.20 (t, 1H, *J* = 7.4 Hz), 7.14 (d, 2H, *J* = 7.2 Hz), 6.49 (brs, 1H), 3.24 (q, 2H, *J* = 6.1 Hz), 2.60 (t, 2H, *J* = 7.2 Hz), 1.59-1.58(m, 2H), 1.53-1.52 (m, 2H).

MS (ESI): 366.97 $[M+H]^+$, 368.97 [M+2], 388.95 $[M+Na]^+$.

4-methoxy-N-((4-phenylbutyl)carbamoyl)benzenesulfonamide (8): The title compound was synthesized as a white solid (535 mg, 55%) by treatment of phenylbutylamine (0.6 mL, 3.8 mmol) and *p*-methoxyphenylsulfonyl chloride (0.55 g, 2.7 mmol) using the procedure detailed of compound **6**.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 7.78 (d, 2H, *J* = 8.7 Hz), 7.28 (t, 2H, *J* = 7.4 Hz), 7.19(t, 1H, *J* = 7.4 Hz), 7.14 (d, 2H, *J* = 7.2 Hz), 6.93 (d, 2H, *J* = 8.7 Hz), 6.53 (brs, 1H), 3.84 (s, 3H), 3.24 (q, 2H, *J* = 6.1 Hz), 2.60 (t, 2H, *J* = 7.2 Hz), 1.62-1.50(m, 4H)

.MS (ESI): 363.02 $[M+H]^+$, 385.00 $[M+Na]^+$.

4-nitro-N-((4-phenylbutyl)carbamoyl)benzenesulfonamide (9): The title compound was synthesized as a white solid (385 mg, 38%) by treatment of phenylbutylamine (0.6 mL, 3.8 mmol) and *p*-nitrophenylsulfonyl chloride (0.6 mL, 2.7 mmol) using the procedure detailed of compound **6**.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 8.30 (d, 2H, *J* = 8.5 Hz), 8.05 (d, 2H, *J* = 8.7 Hz), 7.28 (t, 2H, *J*= 7.4 Hz), 7.20 (t, 1H, *J* = 7.3 Hz), 7.14 (d, 2H, *J* = 7.2 Hz), 6.49 (brs, 1H), 3.25 (q, 2H, *J* = 6.1 Hz), 2.61 (t, 2H, *J* = 7.1 Hz), 1.62-1.52 (m, 4H).

MS (ESI): 378.10 $[M+H]^+$, 400.09 $[M+Na]^+$.

N-((4-phenylbutyl)carbamoyl)benzenesulfonamide (10): The title compound was synthesized as a white solid (535 mg, 52%) by treatment of phenylbutylamine (0.6 mL, 3.8 mmol) and phenylsulfonyl chloride (0.6 mL, 2.7 mmol) using the procedure detailed

of compound **6**.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85 (d, 2H, *J* = 7.5 Hz), 7.59 (t, 1H, *J* = 7.4 Hz), 7.45 (t, 2H, *J* = 7.6 Hz), 7.29-7.26 (m, 2H), 7.19 (t, 1H, *J* = 7.2 Hz), 7.14 (d, 2H, *J* = 7.2 Hz), 6.58 (brs, 1H), 3.25 (q, 2H, *J* = 6.5 Hz), 2.61 (t, 2H, *J* = 7.0 Hz), 1.59-1.53 (m, 4H).

MS (ESI): 332.12 $[M+H]^+$, 355.10 $[M+Na]^+$.

N-(benzo[d]thiazol-2-ylcarbamoyl)-4-methylbenzenesulfonamide (11): The title compound was synthesized as a white solid (370 mg, 41%) by treatment of 2-amino benzothiazole (0.6 g, 4 mmol) and *p*-tosyl chloride (0.5 g, 2.6 mmol) using the procedure detailed of compound **6**.

^{1}H NMR (DMSO-d_6, 500 MHz) : δ 10.30 (brs, 1H), 7.67 (d, 1H, *J* = 7.6 Hz), 7.62 (d, 2H, *J* = 7.3 Hz), 7.42-7.40 (m, 1H), 7.19 (t, 1H, *J* = 7.6 Hz), 7.14 (d, 2H, *J* = 7.6 Hz), 7.02 (t, 1H, *J* = 7.5 Hz), 2.25 (s, 3H).

MS (ESI): 348.16 $[M+H]^+$, 370.14 $[M+Na]^+$.

4-methyl-N-(pyrazin-2-ylcarbamoyl)benzenesulfonamide (12) : The title compound was synthesized as a white solid (340 mg, 45%) by treatment of 2-aminopyrazine (0.38 g, 4 mmol) and *p*-tosyl chloride (0.5 g, 2.6 mmol) using the procedure detailed of compound **6**.

^{1}H NMR (DMSO-d_6, 500 MHz) : δ 11.14 (brs, 1H), 9.46 (s, 1H), 8.90 (s, 1H), 8.32 (d, 2H, *J* = 3.6 Hz), 7.87 (d, 2H, *J* = 8.1 Hz), 7.44 (d, 2H, *J* = 8.0Hz), 2.40 (s, 3H).

MS (ESI): 293.05 $[M+H]^+$, 316.03 $[M+Na]^+$.

4-methyl-N-(phenylcarbamoyl)benzenesulfonamide (13): The title compound was synthesized as a white solid (440 mg, 59%) by treatment of aniline (0.4 mL, 4.4 mmol) and *p*-tosyl chloride (0.5 g, 2.6 mmol) using the procedure detailed of compound **6**.

^{1}H NMR($CDCl_3$, 500 MHz) : δ 8.45 (s, 1H), 8.28 (brs, 1H), 7.82 (d, 2H, *J* = 8.3 Hz), 7.38 (d, 2H, *J* = 7.8 Hz), 7.33-7.30 (m, 4H), 7.13 (t, 1H, *J* = 7.3 Hz), 2.42 (s, 3H).

MS (ESI): 291.12 $[M+H]^+$, 313.11 $[M+Na]^+$

4-methyl-N-(propylcarbamoyl)benzenesulfonamide (14): The title compound was synthesized as a white solid (350 mg, 53%) by treatment of propylamine (0.3 mL, 4 mmol) and *p*-tosyl chloride (0.5 g, 2.6 mmol) using the procedure detailed of compound **6**.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 7.76 (d, 2H, *J* = 8.3 Hz), 7.41 (brs,1H), 7.33 (d, 2H, *J* = 8.0 Hz), 6.57 (brs, 1H), 3.18 (q, 2H, *J* = 6.9 Hz), 2.44 (s, 3H), 1.53-1.49 (m, 2H), 0.88 (t, 3H, *J* = 7.4 Hz).

MS (ESI): 257.09 $[M+H]^+$, 279.07 $[M+Na]^+$.

N-(isobutylcarbamoyl)-4-methylbenzenesulfonamide (15): The title compound was synthesized as a white solid (365 mg, 52%) by treatment of isobutylamine (0.4 mL, 4 mmol) and *p*-tosyl chloride (0.5 g, 2.6 mmol) using the procedure detailed of compound **6**.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 7.88 (brs, 1H), 7.76 (d, 2H, *J* = 8.3 Hz), 7.32 (d, 2H, *J* = 8.1 Hz), 6.61 (brs, 1H), 3.04 (t, 2H, *J* = 6.3 Hz), 2.43 (s, 3H), 1.76-1.71 (m, 1H), 0.86 (d, 6H, *J* = 6.7 Hz).

MS (ESI): 271.15 $[M+H]^+$, 293.14 $[M+Na]^+$.

N-(cyclohexylcarbamoyl)-4-methylbenzenesulfonamide (16): The title compound was synthesized as a white solid (285 mg, 37 %) by treatment of cyclohexylamine (0.45 mL, 4 mmol) and *tosyl* chloride (0.5 g, 2.6 mmol) using the procedure detailed of compound **6**.

^{1}H NMR (DMSO-d_6, 500 MHz) : δ 10.26 (brs, 1H), 7.76 (d, 2H, *J* = 8.2 Hz), 7.38 (d, 2H, *J* = 7.9 Hz), 6.30 (brs, 1H), 2.38 (s, 3H), 1.65-1.56 (m, 4H), 1.49-1.47 (m, 1H), 1.22-1.06 (m, 6H).

MS (ESI): 297.13 $[M+H]^+$, 319.12 $[M+Na]^+$.

4-methyl-N-(phenethylcarbamoyl)benzenesulfonamide (17): The title compound was

synthesized as a white solid (490 mg, 59%) by treatment of phenylethylamine (0.5 mL, 4 mmol) and *tosyl* chloride (0.5 g, 2.6 mmol) using the procedure detailed of compound **6**.

^{1}H NMR (DMSO-d_6, 500 MHz) : δ 10.52 (brs, 1H), 7.74 (d, 2H, *J* = 8.2 Hz), 7.39 (d, 2H, *J* = 8.1 Hz), 7.26 (t, 2H, *J* = 7.3 Hz), 7.19 (t, 1H, *J* = 7.3 Hz), 7.12 (d, 2H, *J* = 7.2 Hz), 6.42 (s, 1H), 3.18 (q, 2H, *J* = 6.7 Hz), 2.64 (t, 2H, *J* = 7.2 Hz), 2.39 (s, 3H).

MS (ESI): 319.09 $[M+H]^+$, 341.07 $[M+Na]^+$.

N-tosylpiperidine-1-carboxamide (18): The title compound was synthesized as a white solid (400 mg, 55%) by treatment of piperidine (0.4 mL, 4 mmol) and *tosyl* chloride (0.5 g, 2.6 mmol) using the procedure detailed of compound **6**.

^{1}H NMR (DMSO-d_6, 500 MHz) : δ 11.17 (brs, 1H), 10.87 (brs, 1H), 7.97 (d, 2H, *J* = 8.3 Hz), 7.33 (d, 2H, *J* = 8.3 Hz), 3.43-3.38 (m, 4H), 2.43 (s, 3H), 1.66-1.65 (m, 2H), 1.60-1.59 (m, 4H).

MS (ESI): 283.12 $[M+H]^+$, 305.10 $[M+Na]^+$.

Biological Assay for HDAC

Assays were carried out in black, low binding NUNC 96-well plates. The ability of sulfonylurea derivatives to inhibit/activate HDAC-1 activity (% inhibition at 10 μM and 100 μM) was determined using an HDAC1 Inhibitor Screening Assay Kit (catalogue no. 10011564, Cayman Chemical) according to the manufacturer's instructions. Stock solutions of 10 mM of all compounds were prepared in DMSO and then diluted to require concentration using supplied assay buffer. Briefly, to a series of supplied reaction buffer solutions (140 μL, 25 mM Tris-HCl, pH 8.0, 137 mM NaCl, 2.7 mM KCl and 1 mM $MgCl_2$) with HDAC-1 enzyme (10 μL) various concentrations of the test compound solutions (final between 10 uM and 100 μM) were added. The reactions were initiated by adding 10 μL of supplied substrate (Acetylated flourometric substrate) and then incubated

for 30 min at 37 ^{o}C. This was followed by addition of HDAC developer (40 µL) to each well and again incubated for 15 min at room temperature. Florescence were then read at an excitation wavelength of 350 nm and an emission wavelength of 450 nm. The intensity of this fluorescence is directly proportional to the amount of product formed after deaceatylation of the fluorescent substrate in presence of HDAC-1. Percentage activation was calculated by comparison of test compounds with 100% initial activity value (no inhibitor or negative control). Blank wells containing no inhibitor or protein were subtracted from all wells. Assay contained each inhibitor in triplicate and values were reported as mean of triplicate.

Biological Assay for hCA II

Human Carbonic Anhydrase II was purchased from Sigma Aldrich. Assays were carried out in clear Costar 96-well plates using previously described procedure.[5] Each well contained 45 µL buffer (50 mM Tris-SO4, pH = 8.0), 15 µL hCAII (200 nM), 15 µL inhibitor (10 µM), and 75 µL p-nitrophenyl acetate (500 µM) for a total volume of 150 µL. The enzyme and inhibitor were incubated in solution at 30 °C for 10 min followed by addition of the p-nitrophenyl acetate. Absorbance at 405 nm was recorded immediately thereafter for 20 min at regular interval of 10 sec initially for 5 min and then at an interval of 30 sec for remaining 15 minutes. The intensity of this absorbance is directly proportional to the amount of product (p-nitrophenolate ion) formed after hydrolysis of the p-nitrophenyl acetate in presence of hCA II. Percentage inhibition was calculated by comparison of test compounds with 100% initial activity value (no inhibitor or negative control). Blank wells containing no inhibitor or protein were subtracted from all wells. Assay contained each inhibitor in triplicate and values were reported as mean ± standard deviation.

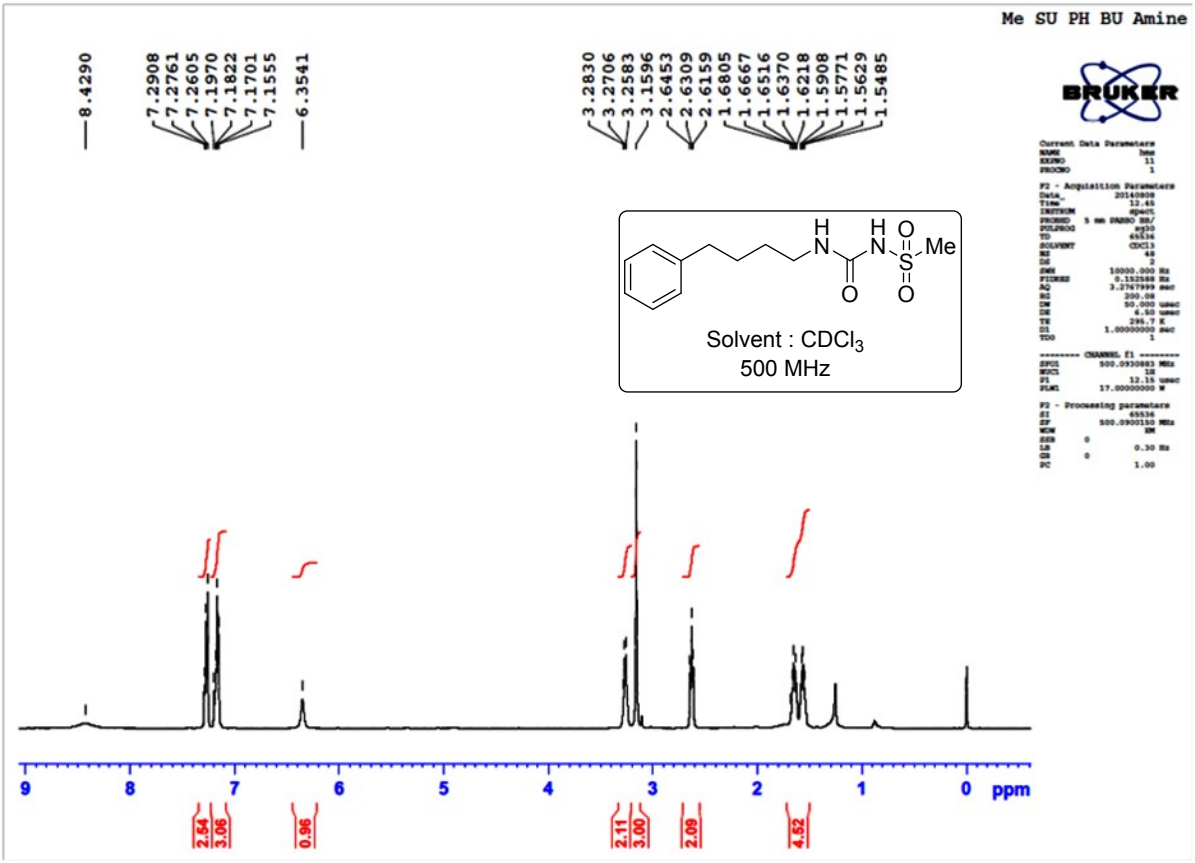
FRET based Assay

Assays were carried out in clear Costar 96-well plates. Each well contained 105 µL buffer (50 mM Tris-SO4, pH = 8.0), 15 µL hCAII (250 nM), 15 µL dansylsulfonamide (25 µM) and 15 µL inhibitor (10 µM) for a total volume of 150 µL. The enzyme and dansylsulfonamide were incubated in solution at 30 °C for 10 min and their fluorescence at 470 nm were recorded using excitation wavelength of 280 nm. Acetazolamide or inhibitors were added and again fluorescence were recorded at 470 nm using excitation wavelength 280 nm for 20 min at regular interval of 2 minutes. Decrease in fluorescence was directly proportional to the displacement of dansylsulfonamide from the active site of hCA II. Percentage FRET observed was calculated by considering 100% FRET for the well without inhibitor (positive control). Blank wells (negative control) containing only buffer and hCA II were subtracted from all wells. Assay contained each inhibitor in triplicate and values were reported as mean from three different experiment.

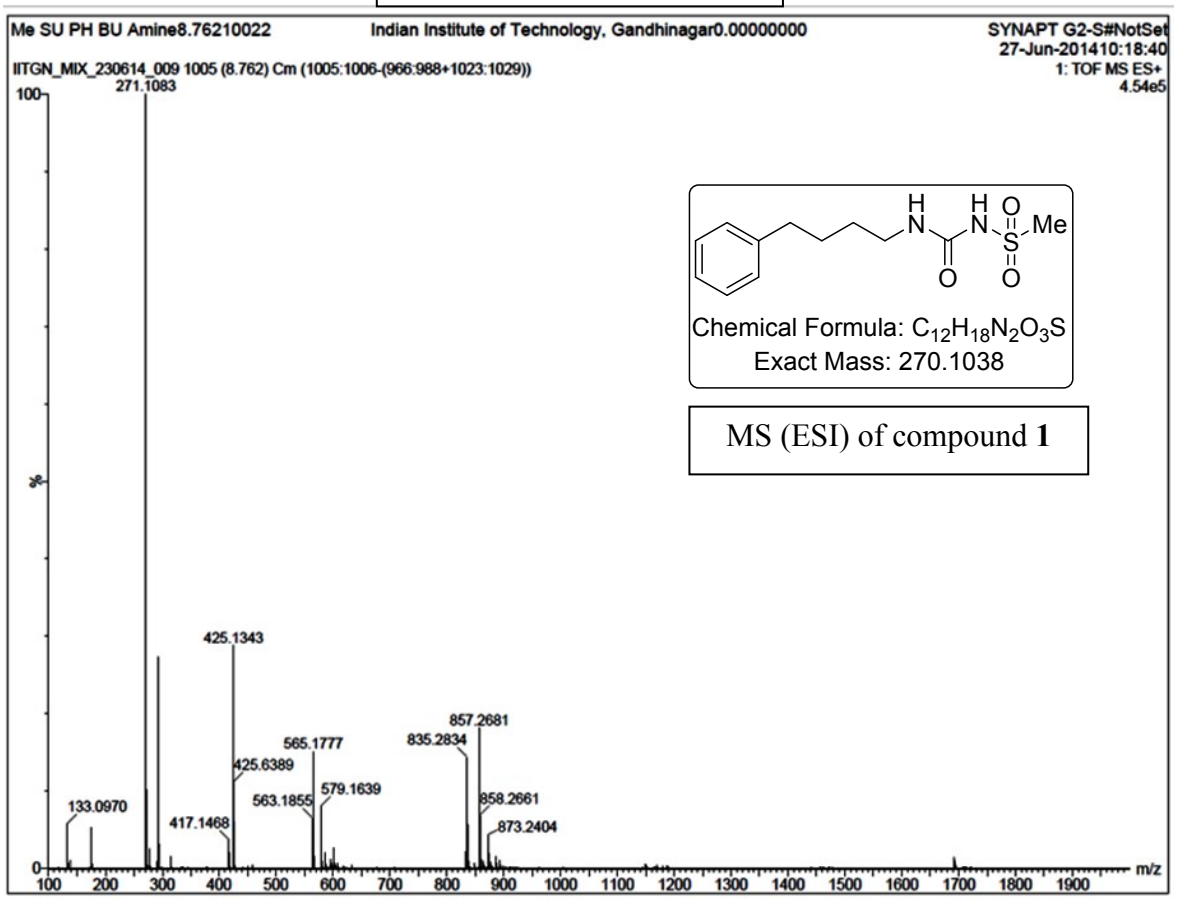
Molecular Docking

Atomic coordinates of histone deacetylase 2 (HDAC-2) and human carbonic anhydrase II (hCA II) were retrieved from Protein Data Bank (PDB) (entry 4LXZ and 4E3D). Initial coordinates of both HDAC-2 and hCA II were further modified using protein preparation wizard of Glide software (Schrodinger, LLC, New York, NY, USA). Proteins were minimized by applying OPLS- 2005 force field using standard parameters as included in the Glide. After refinement and minimization of protein a 10 Å grid was generated around the respective ligands by using receptor grid generation tool of Glide and applying standard parameters of Glide (Schrodinger, LLC, New York, NY, USA). All the compounds were built using Molecule Builder tool of Maestro (Schrodinger, LLC, New York, NY, USA). The built compounds were further prepared using LigPrep tool of Maestro software (Schrodinger,

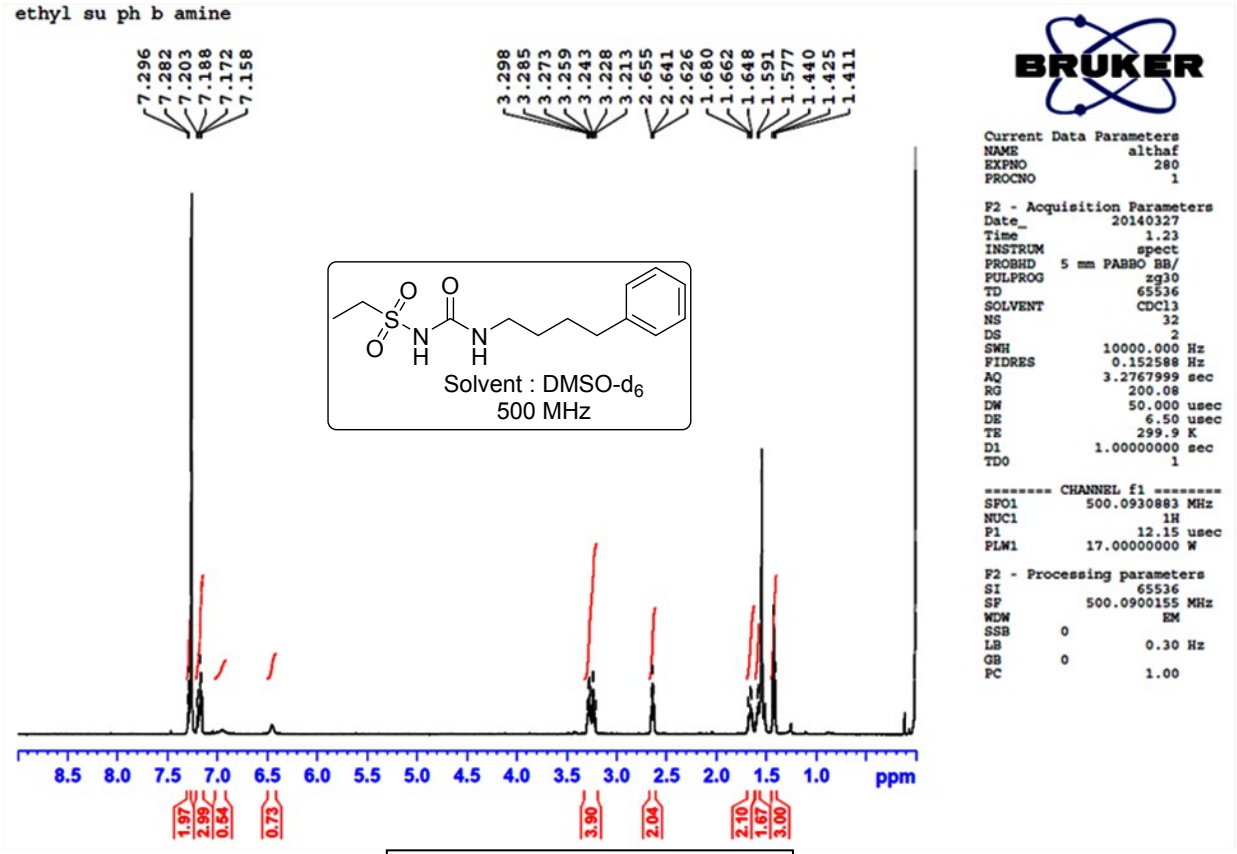
LLC, New York, NY, USA). In LigPrep all the possible ionization states at pH 7.0 +/- 2.0, all possible tautomers, stereoisomer (unless stereochemistry is known or specified) were generated for each compound and finally minimized using OPLS-2005 force field. Energy minimized conformations of compounds were subjected to Glide XP docking using standard protocol of GLIDE (Schrodinger, LLC, New York, NY, USA) and results were analyzed using Glide XP Visualizer tool.



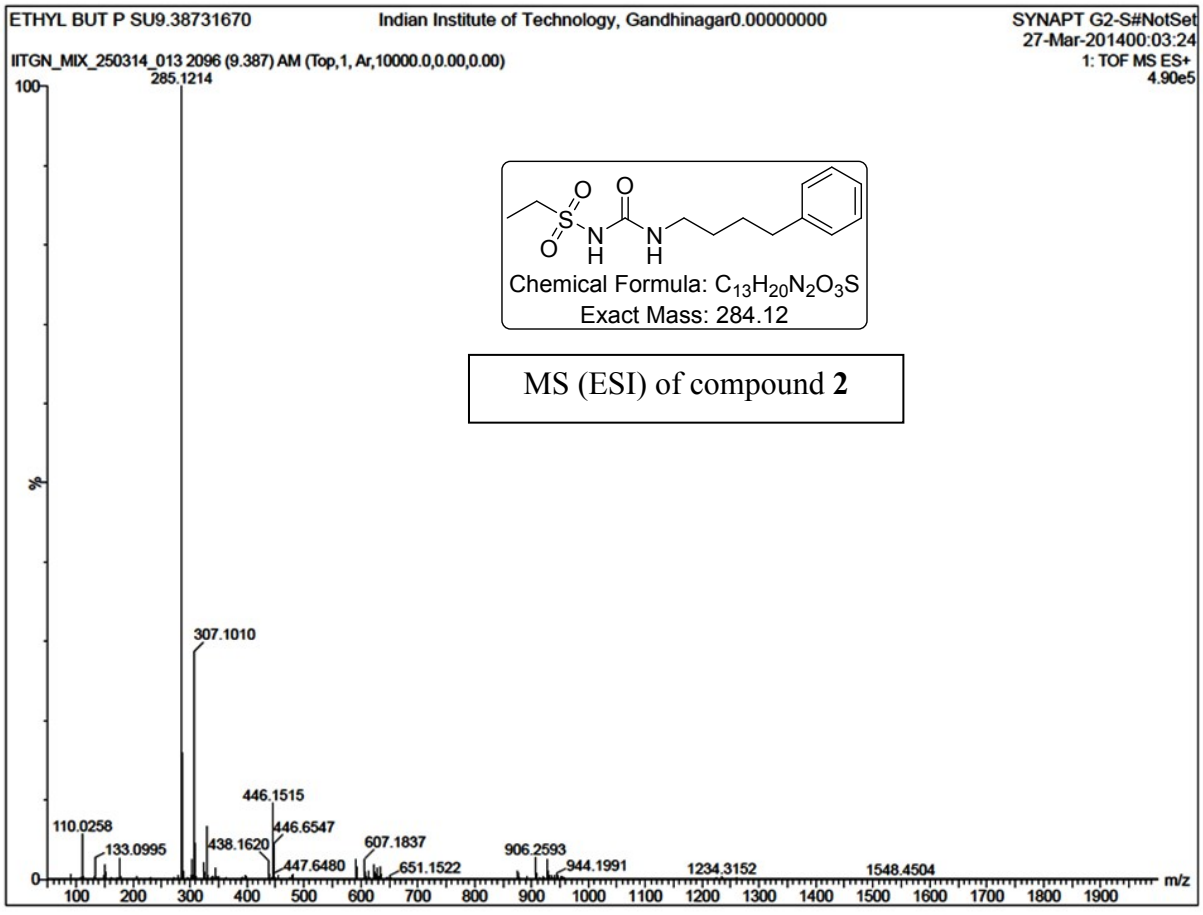
^{1}H NMR of compound **1**



MS (ESI) of compound **1**



^{1}H NMR of compound **2**



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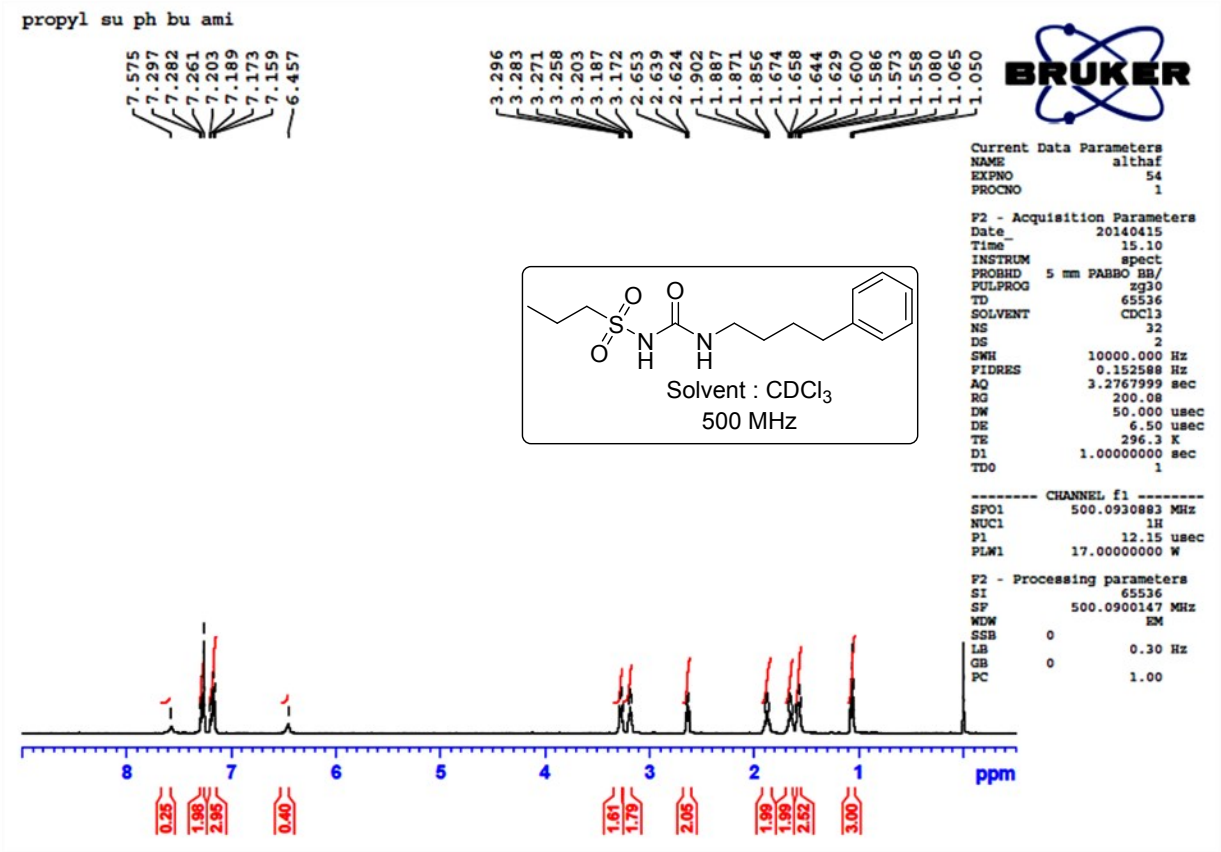
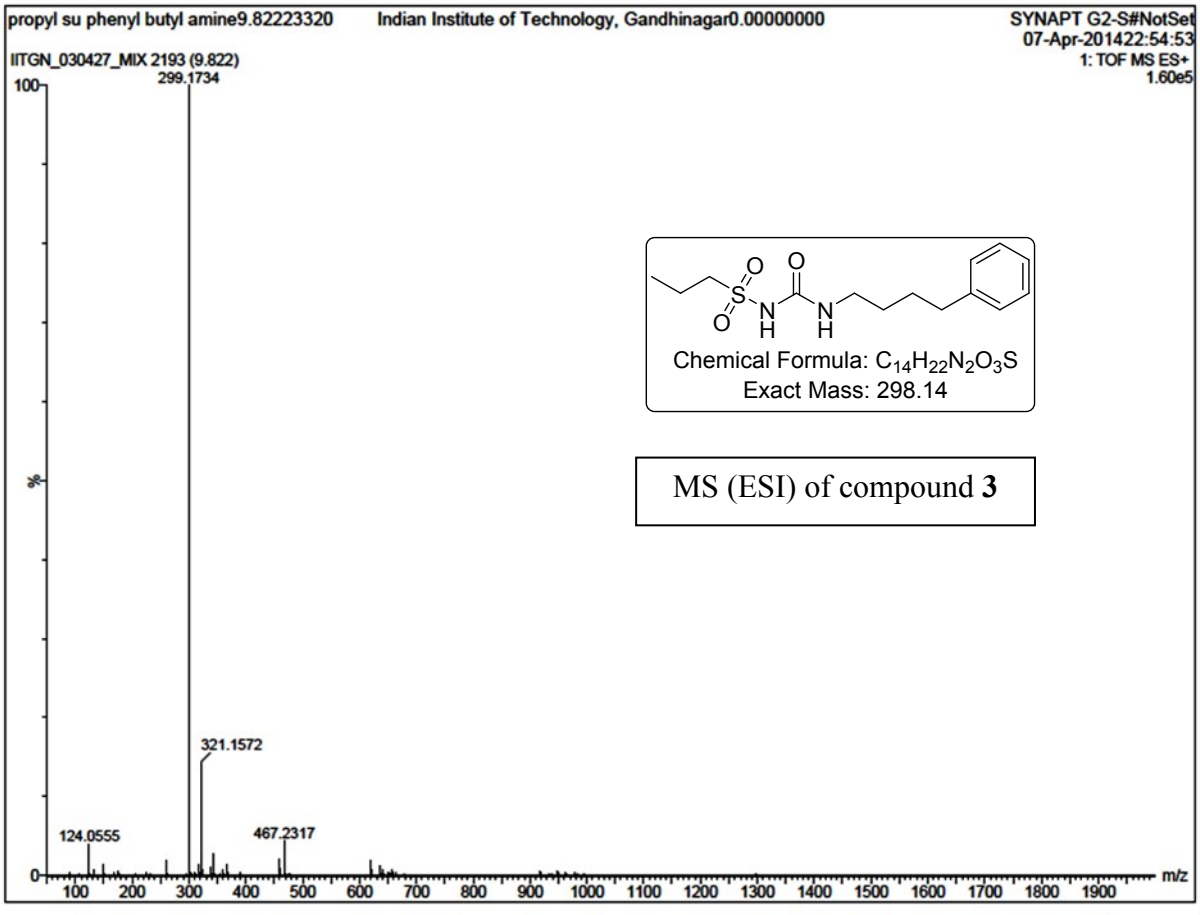
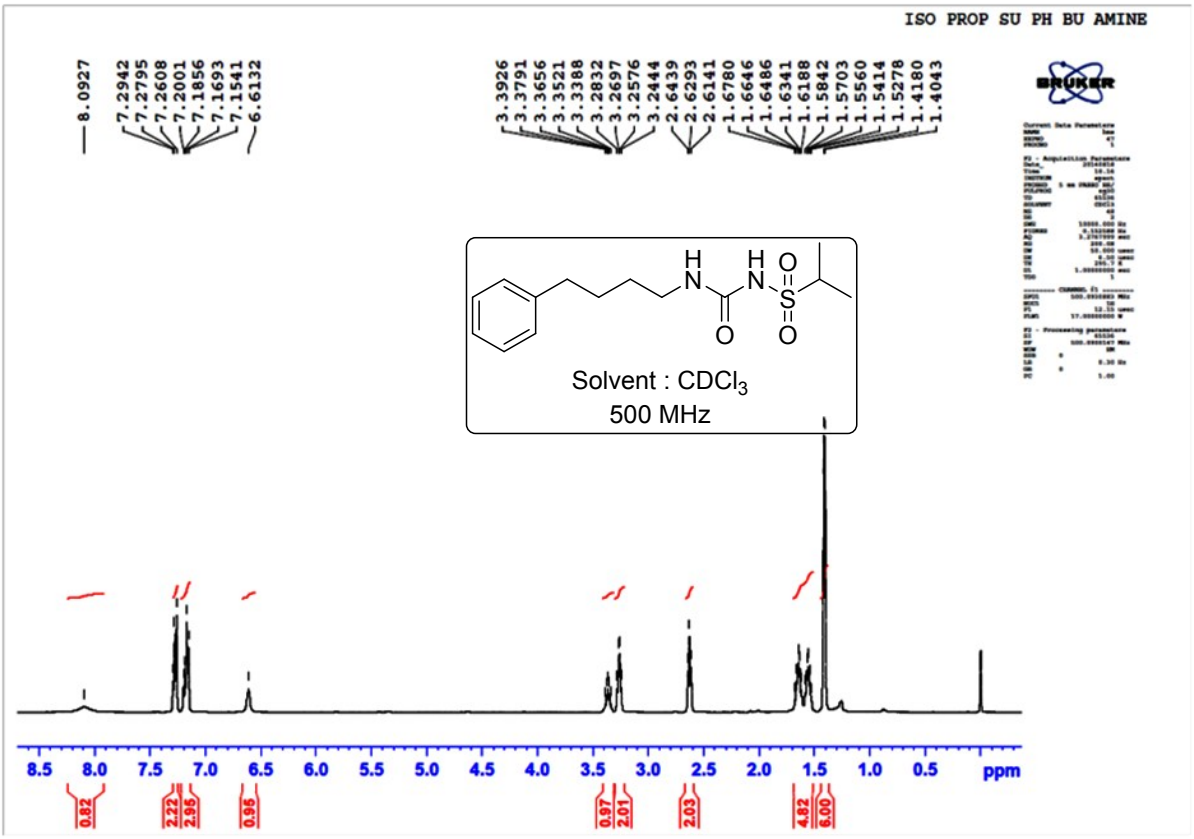


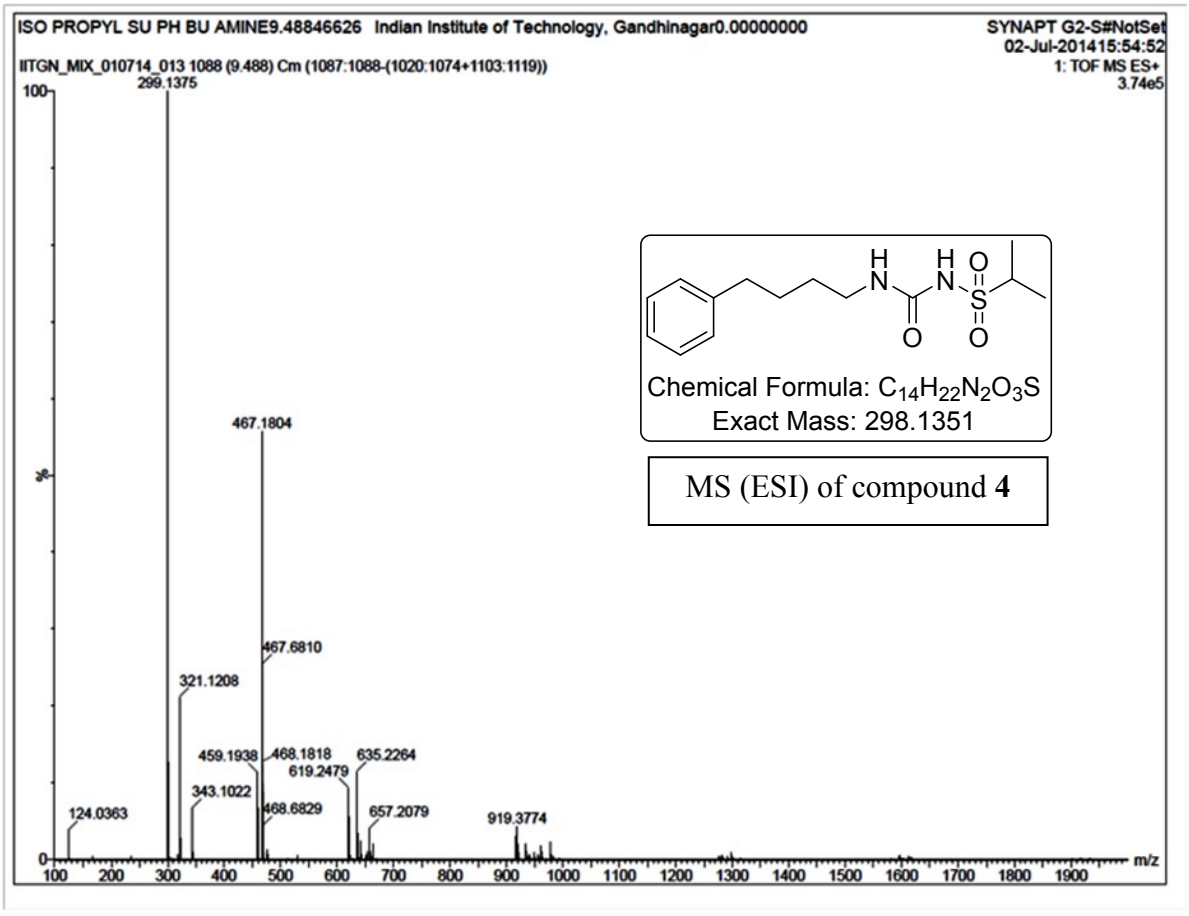
^{1}H NMR of compound **3**



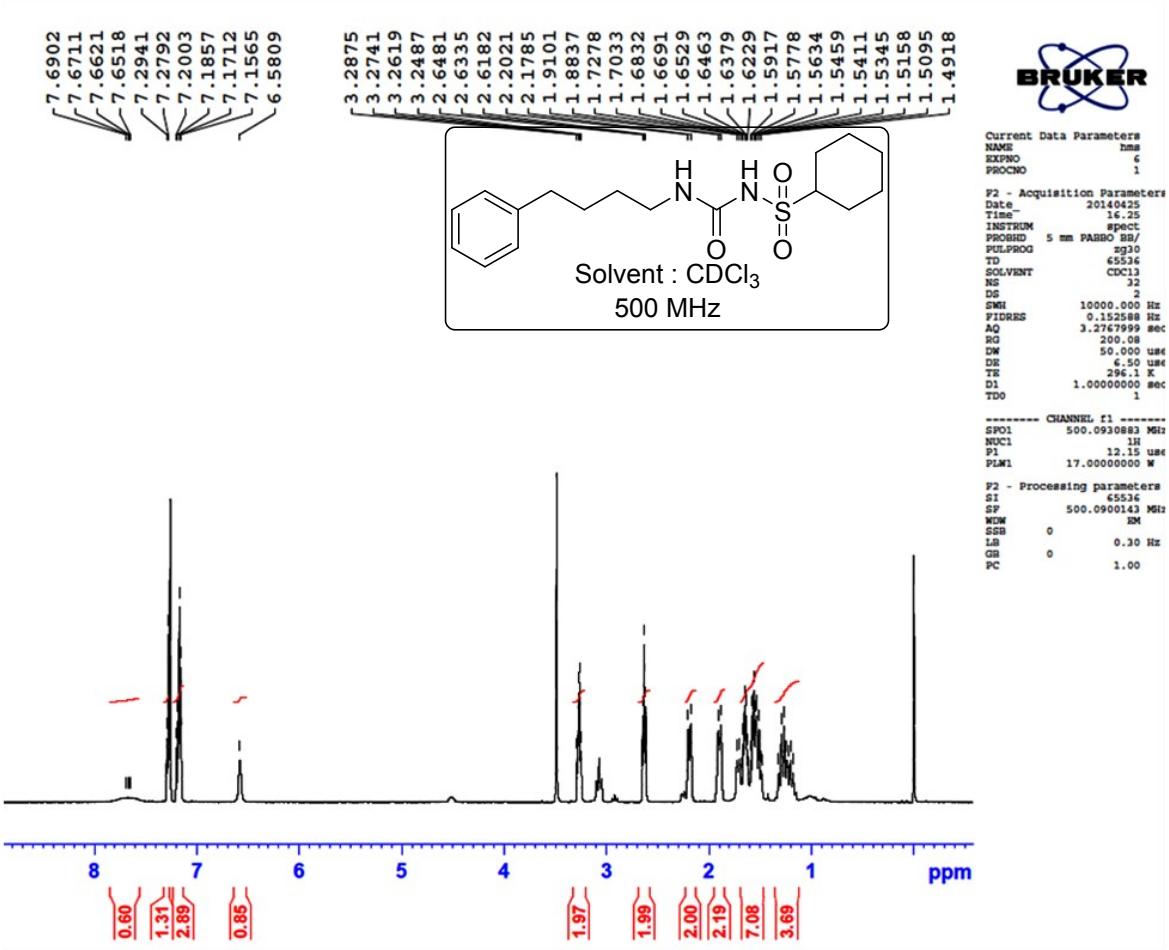
MS (ESI) of compound **3**



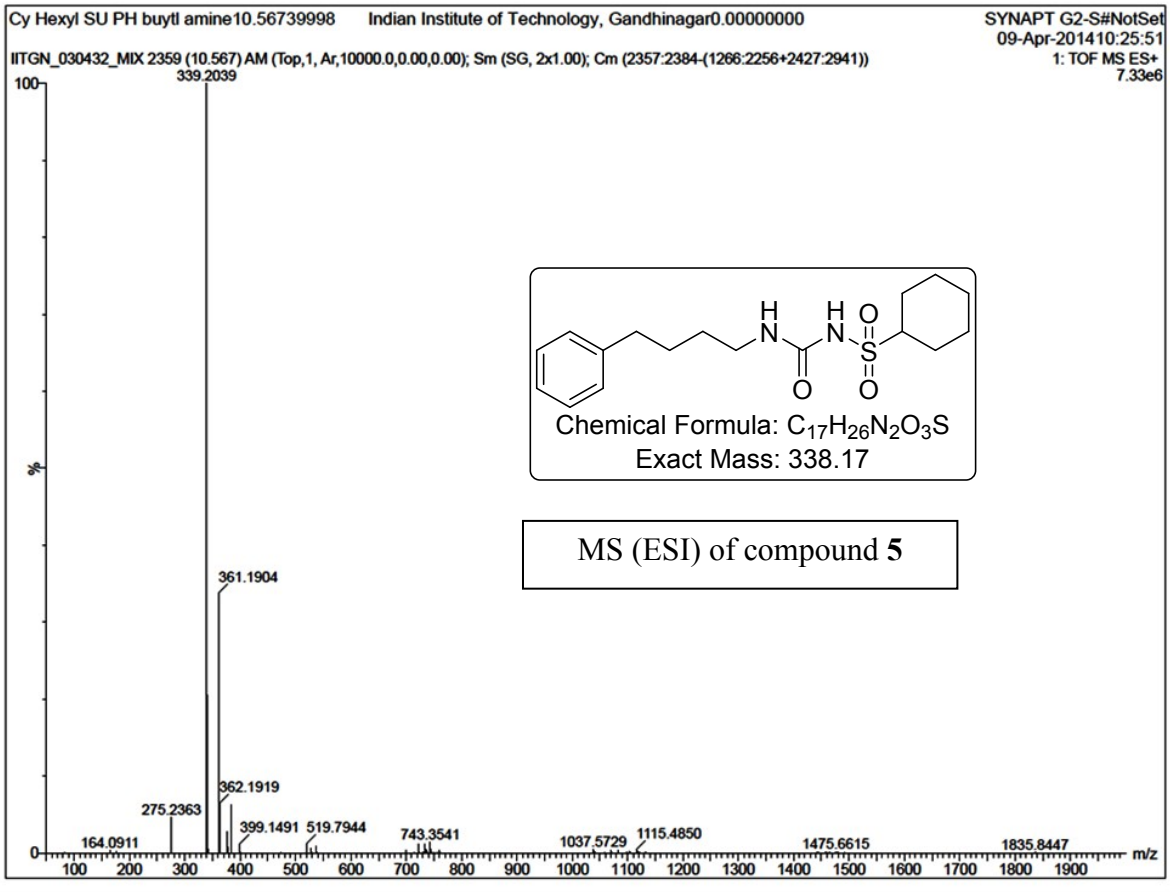
^{1}H NMR of compound **4**



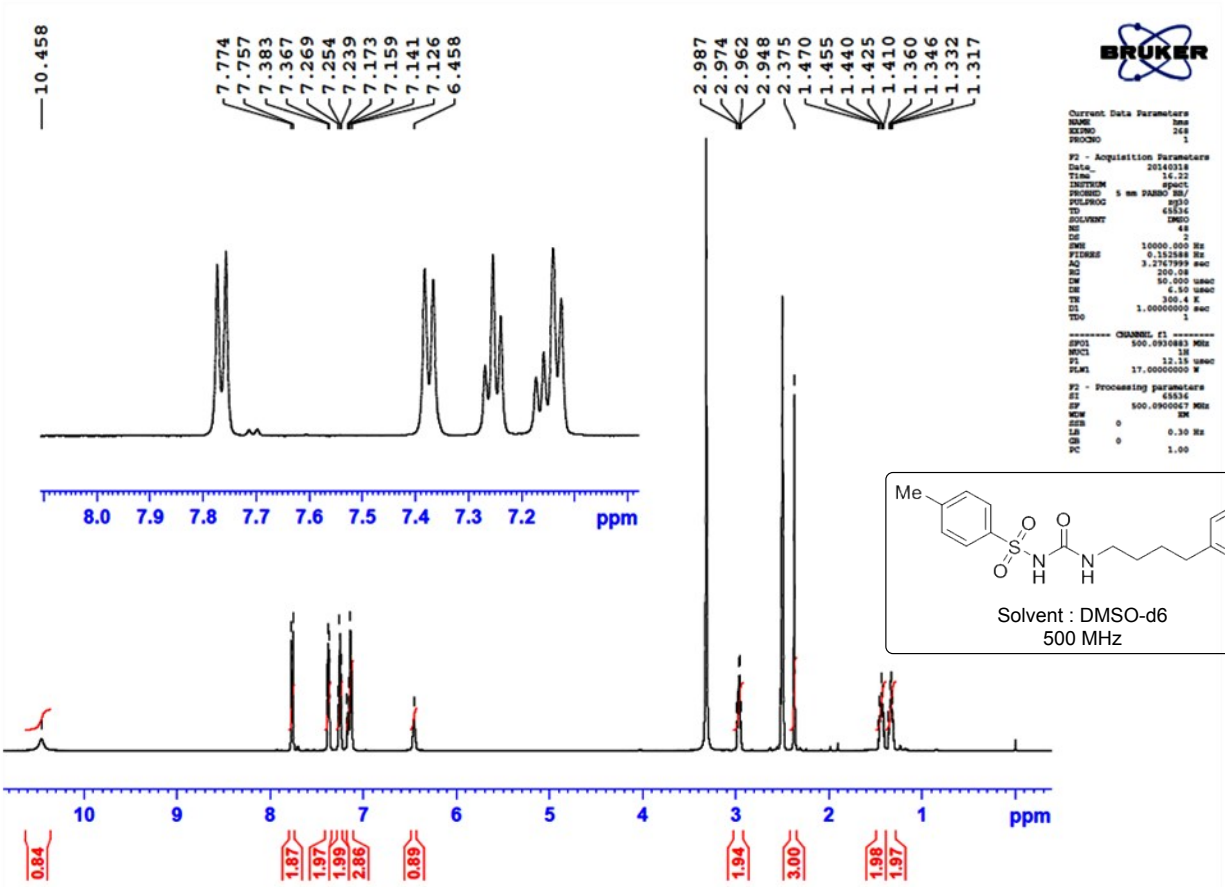
MS (ESI) of compound **4**



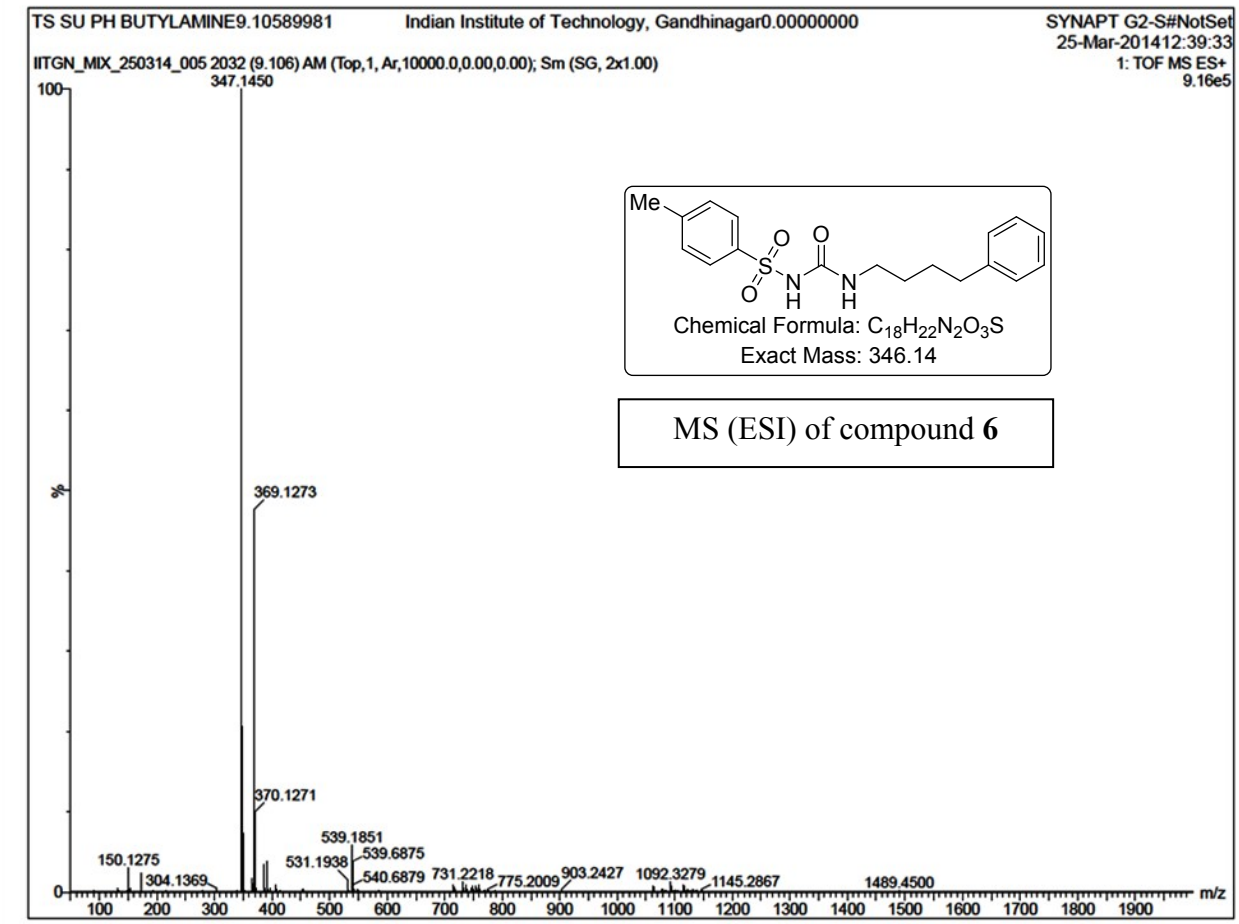
^{1}H NMR of compound **5**



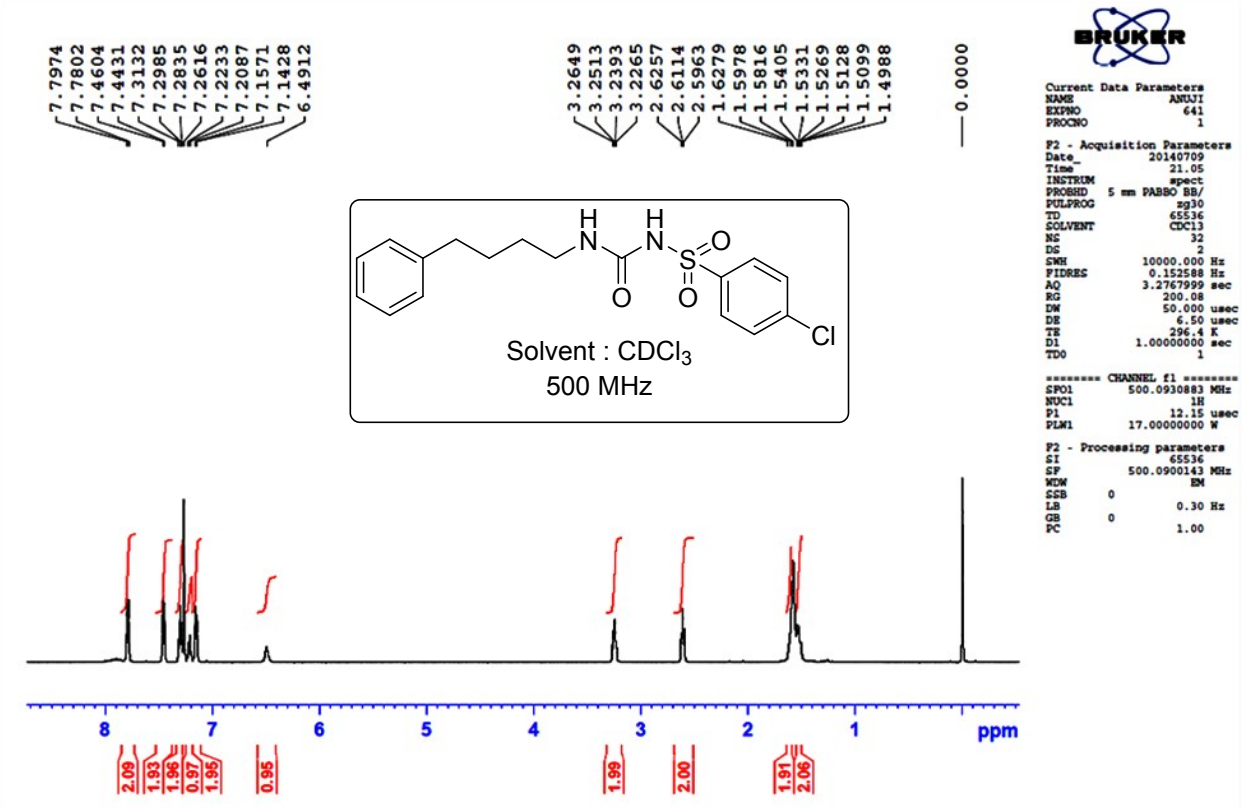
MS (ESI) of compound **5**



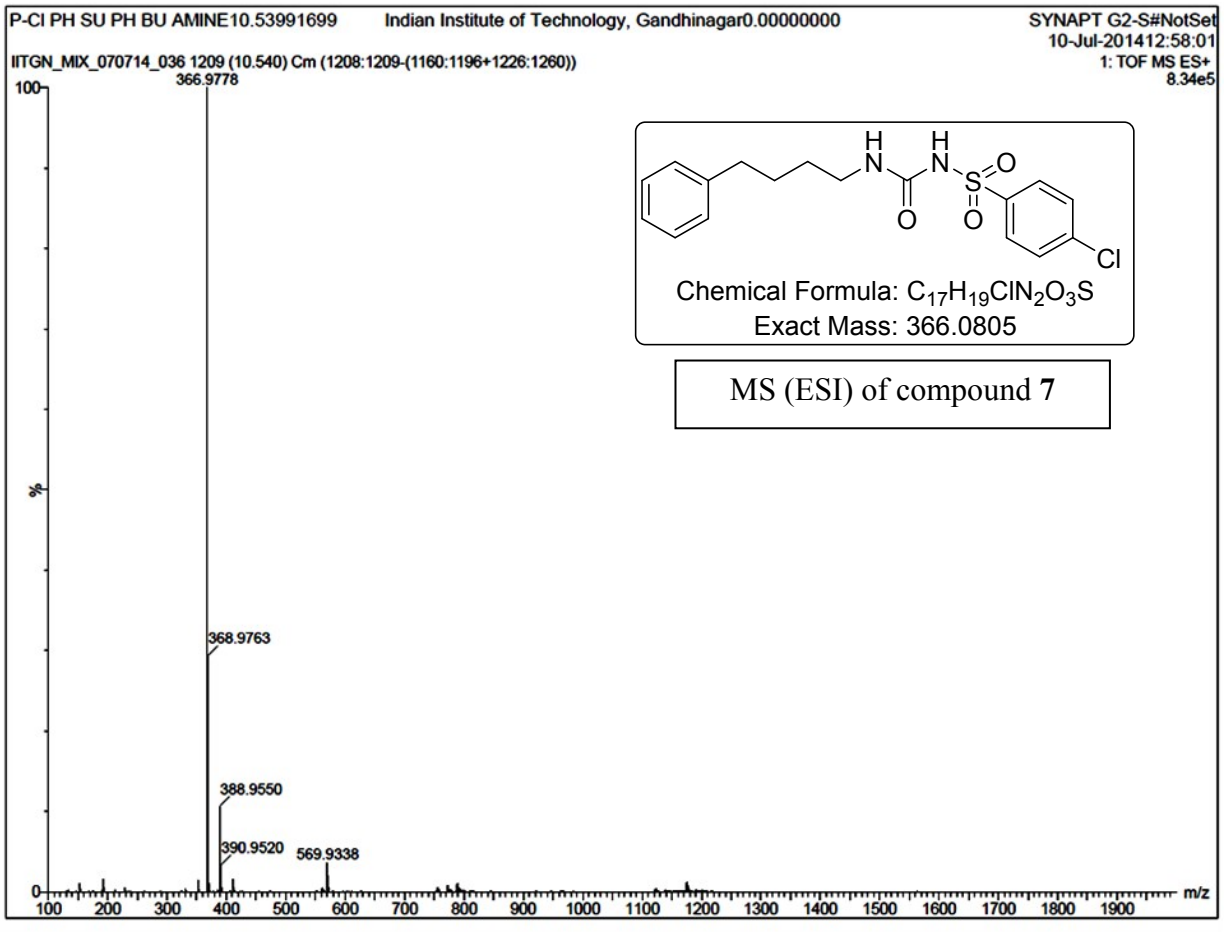
^{1}H NMR of compound **6**



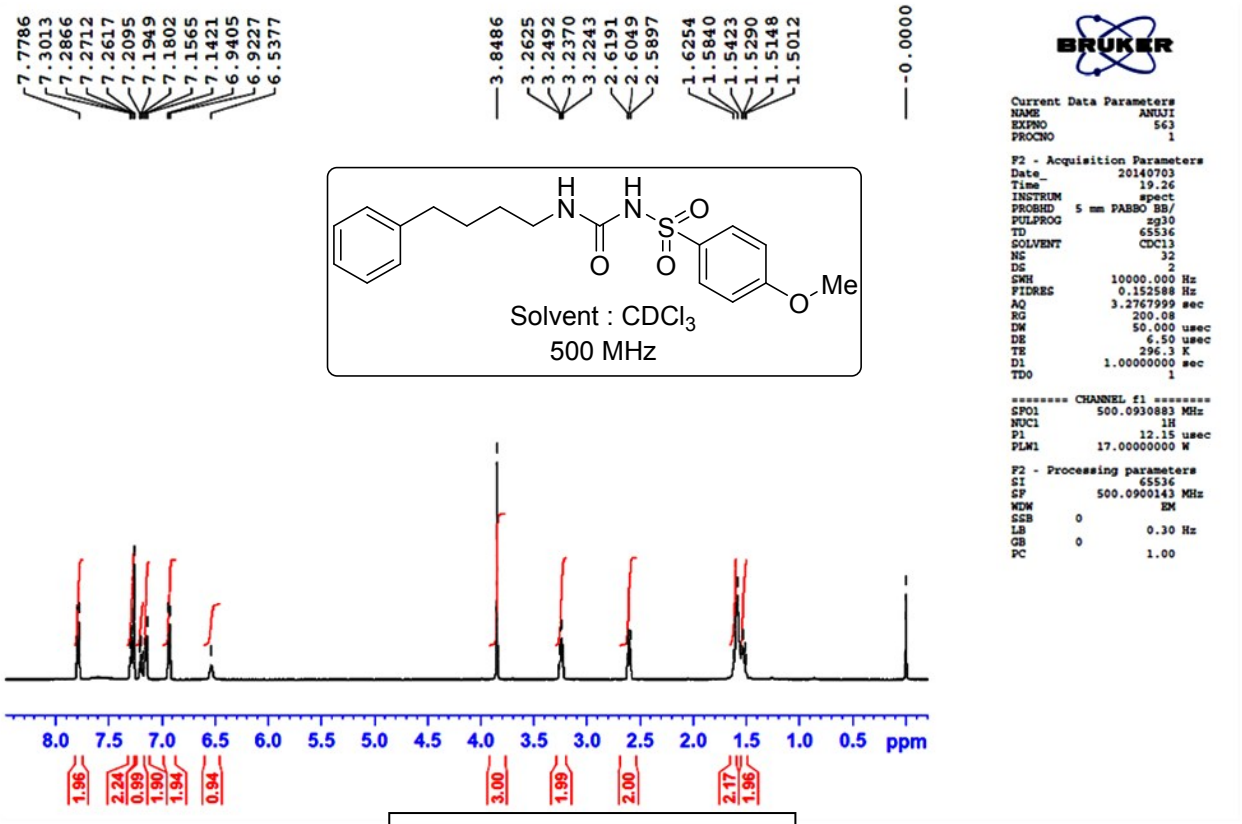
MS (ESI) of compound **6**



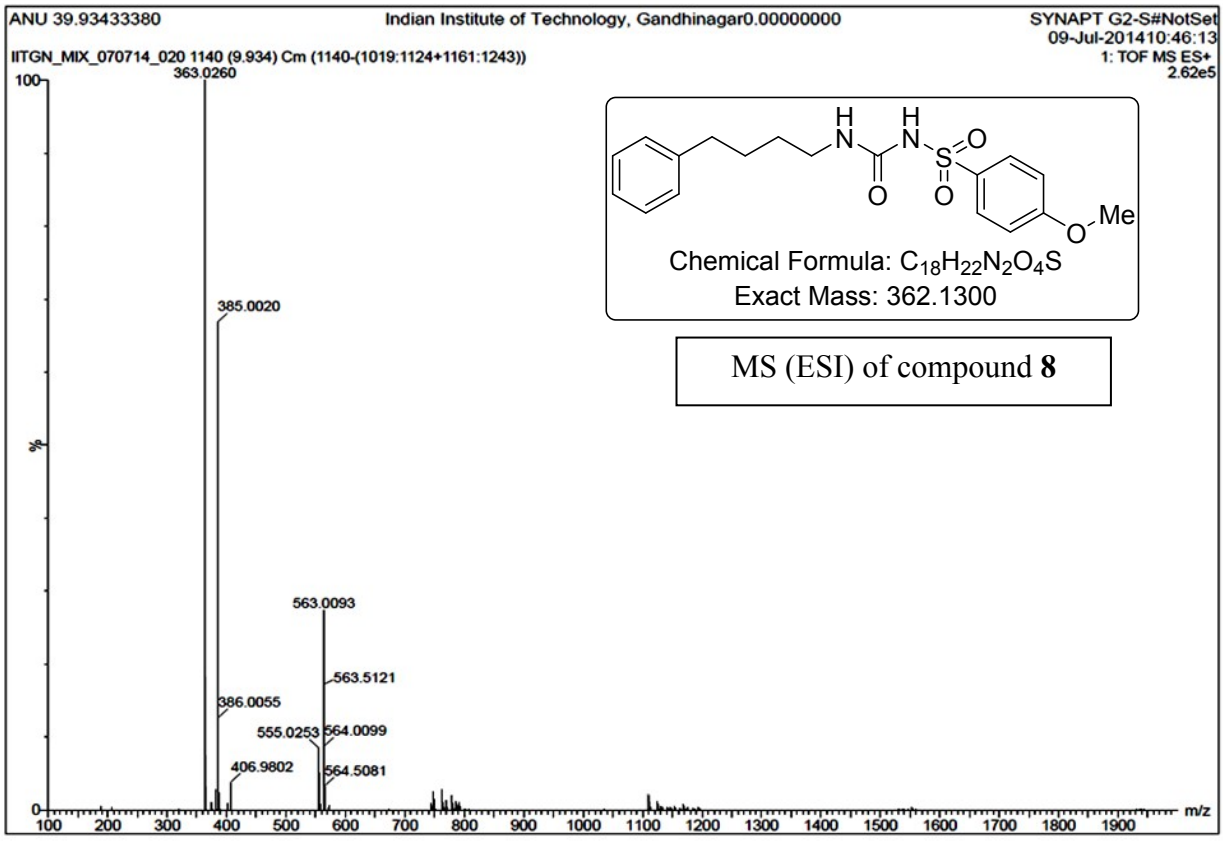
^{1}H NMR of compound **7**



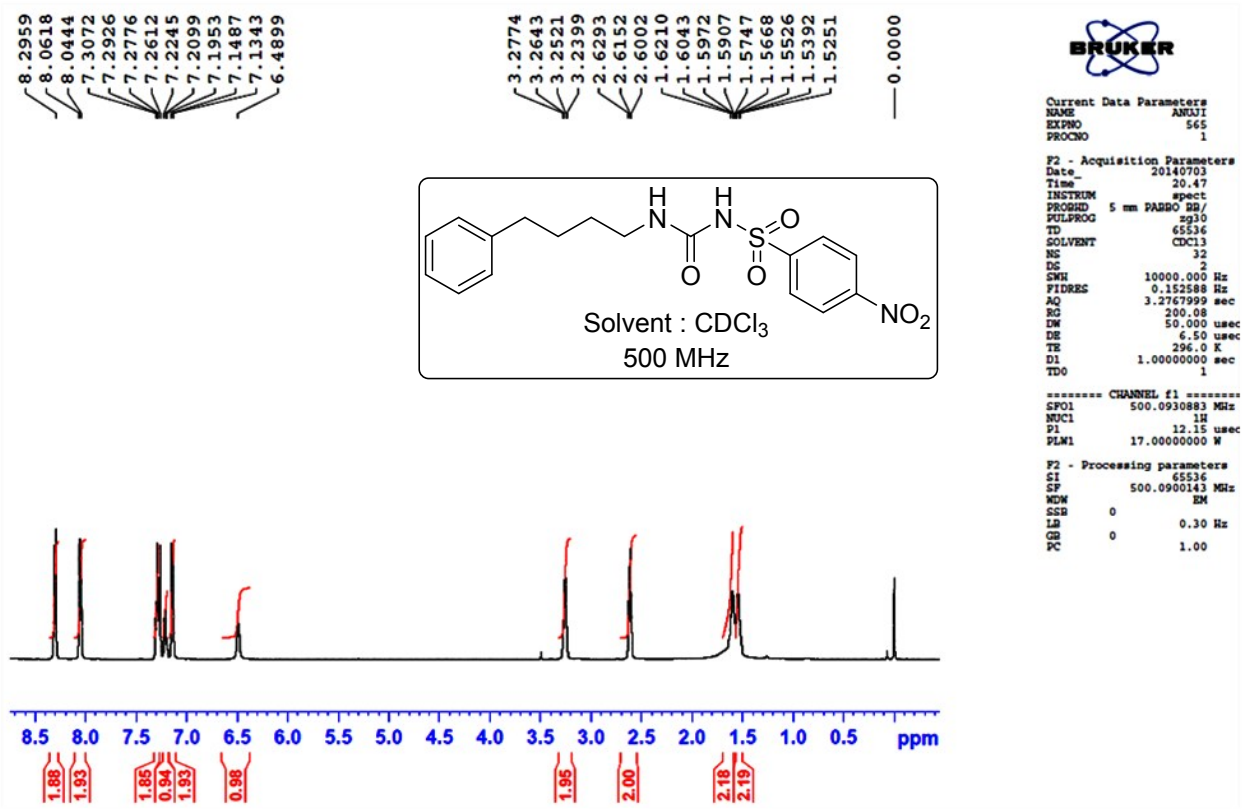
MS (ESI) of compound **7**



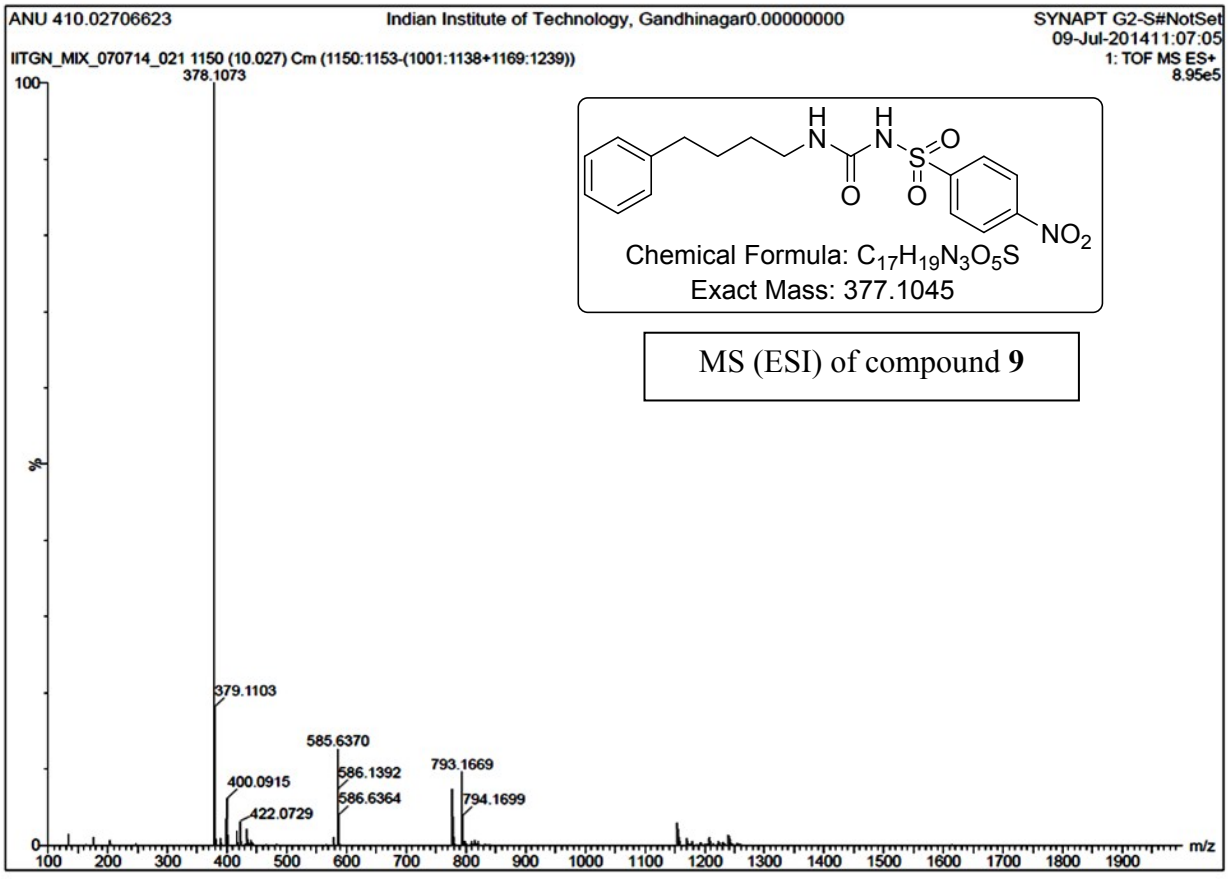
^{1}H NMR of compound **8**



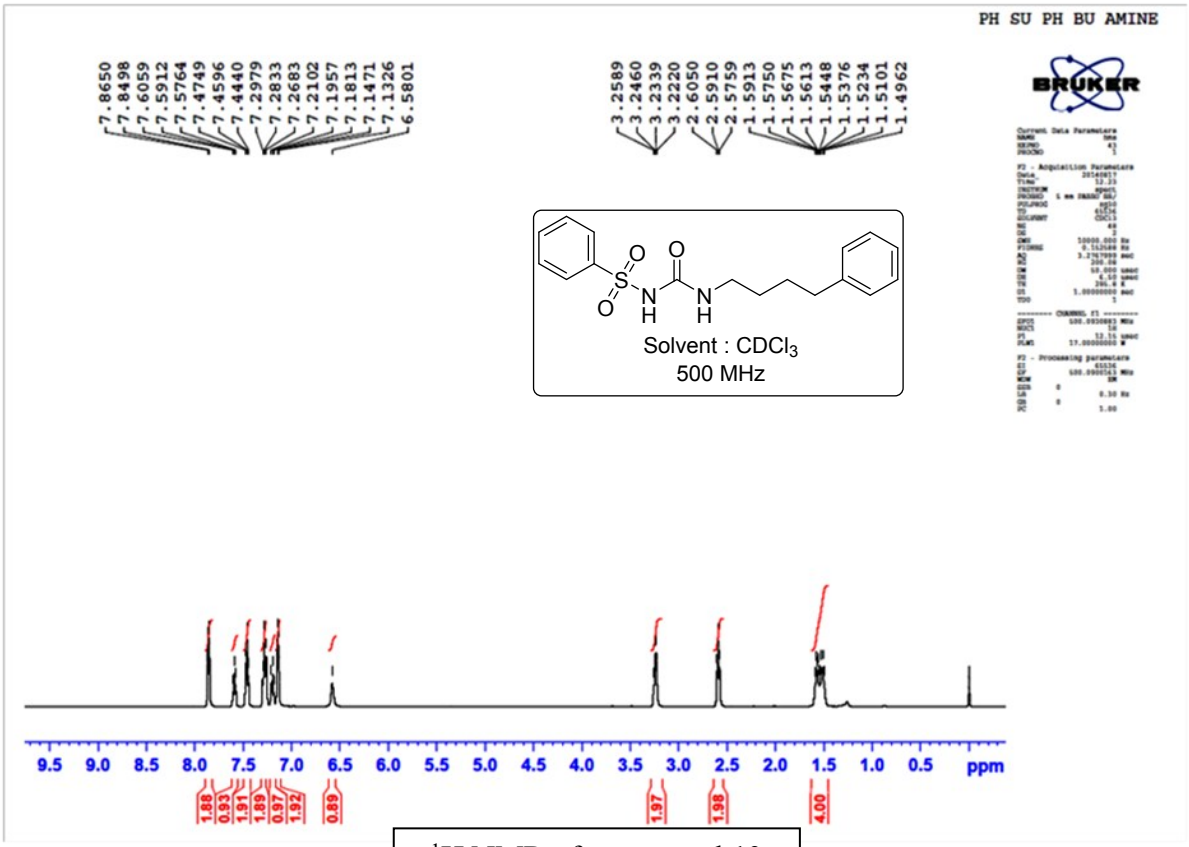
MS (ESI) of compound **8**



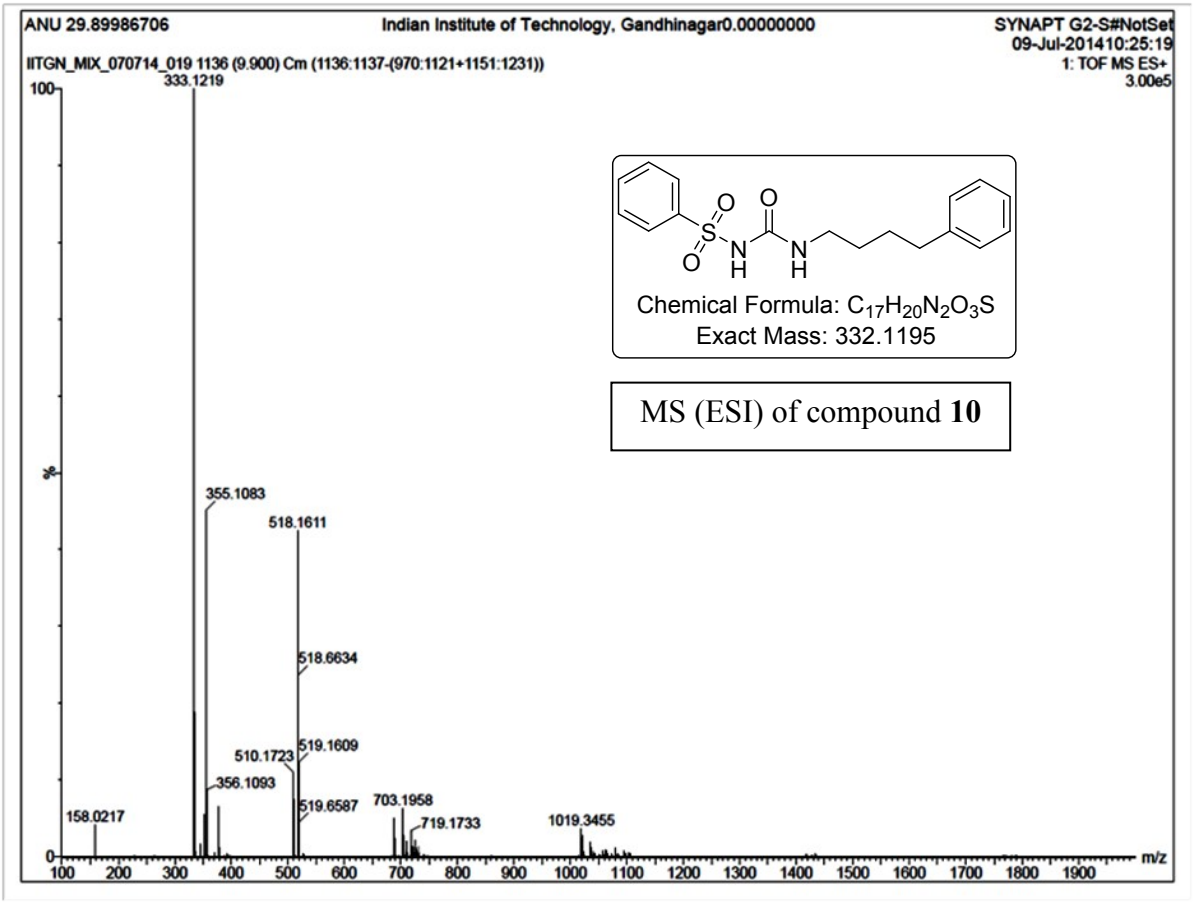
^{1}H NMR of compound **9**



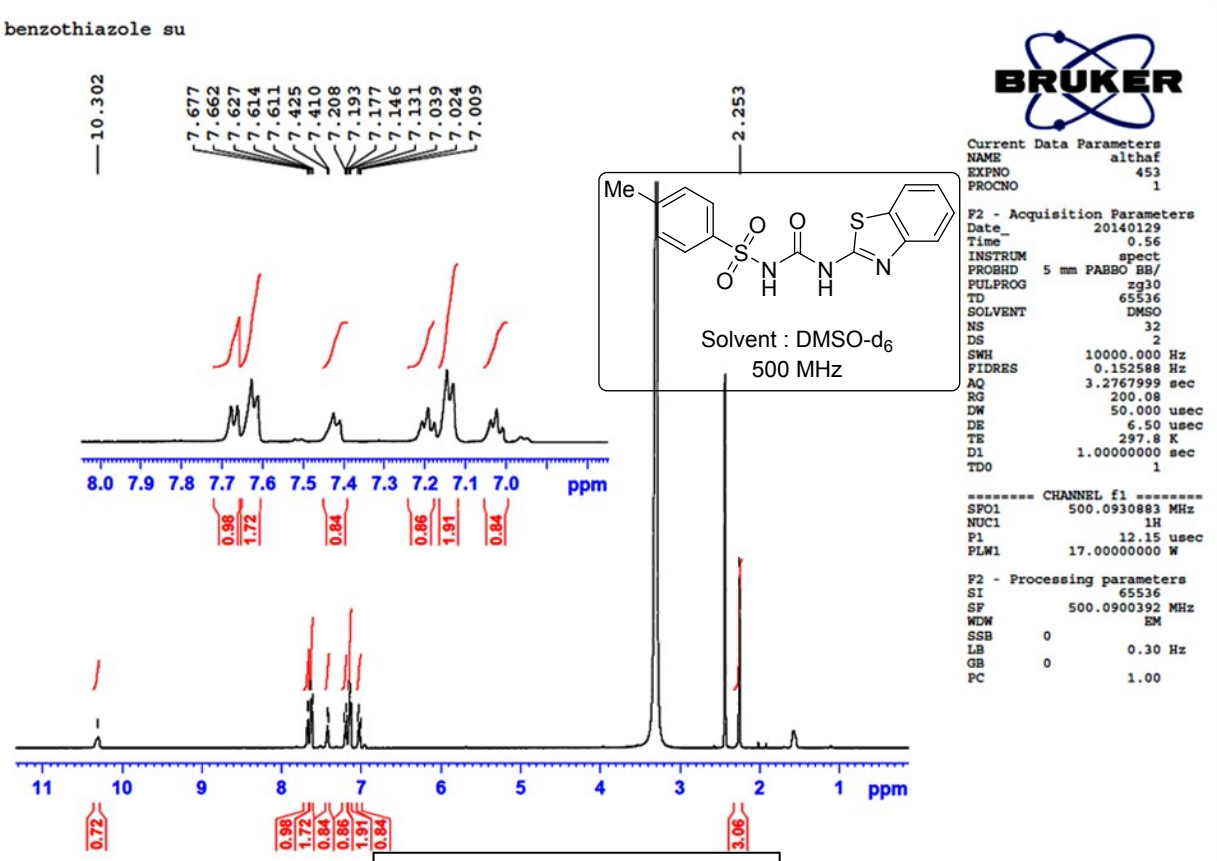
MS (ESI) of compound **9**



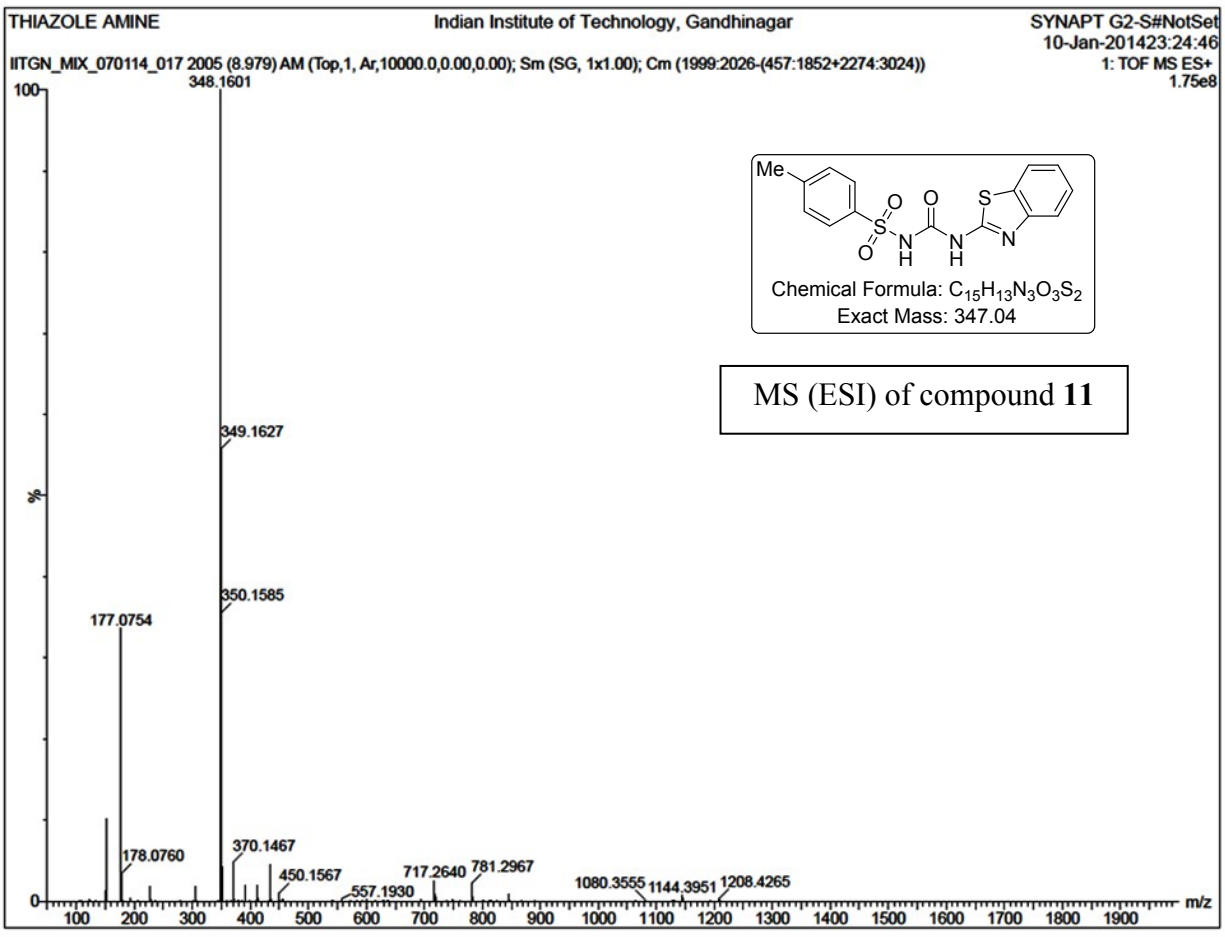
^{1}H NMR of compound **10**



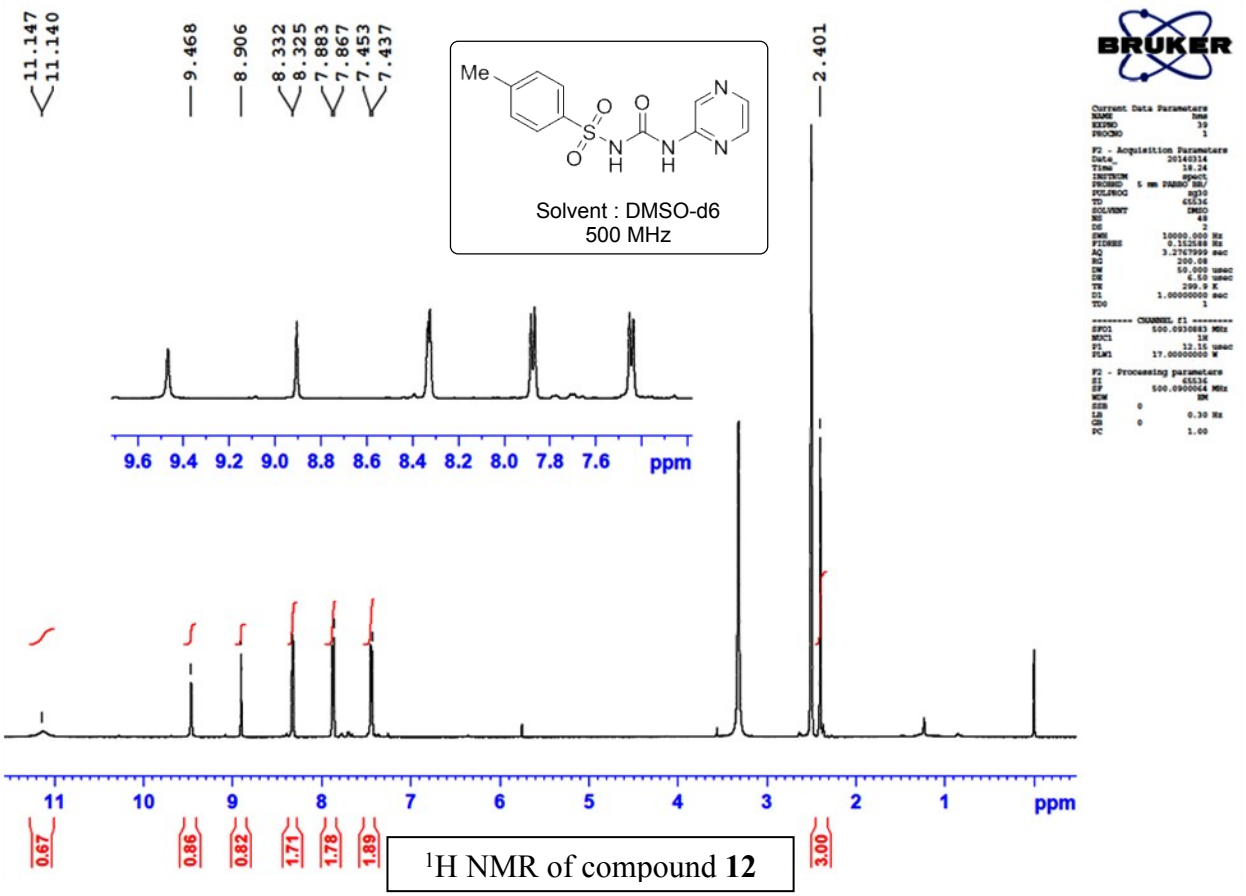
MS (ESI) of compound **10**



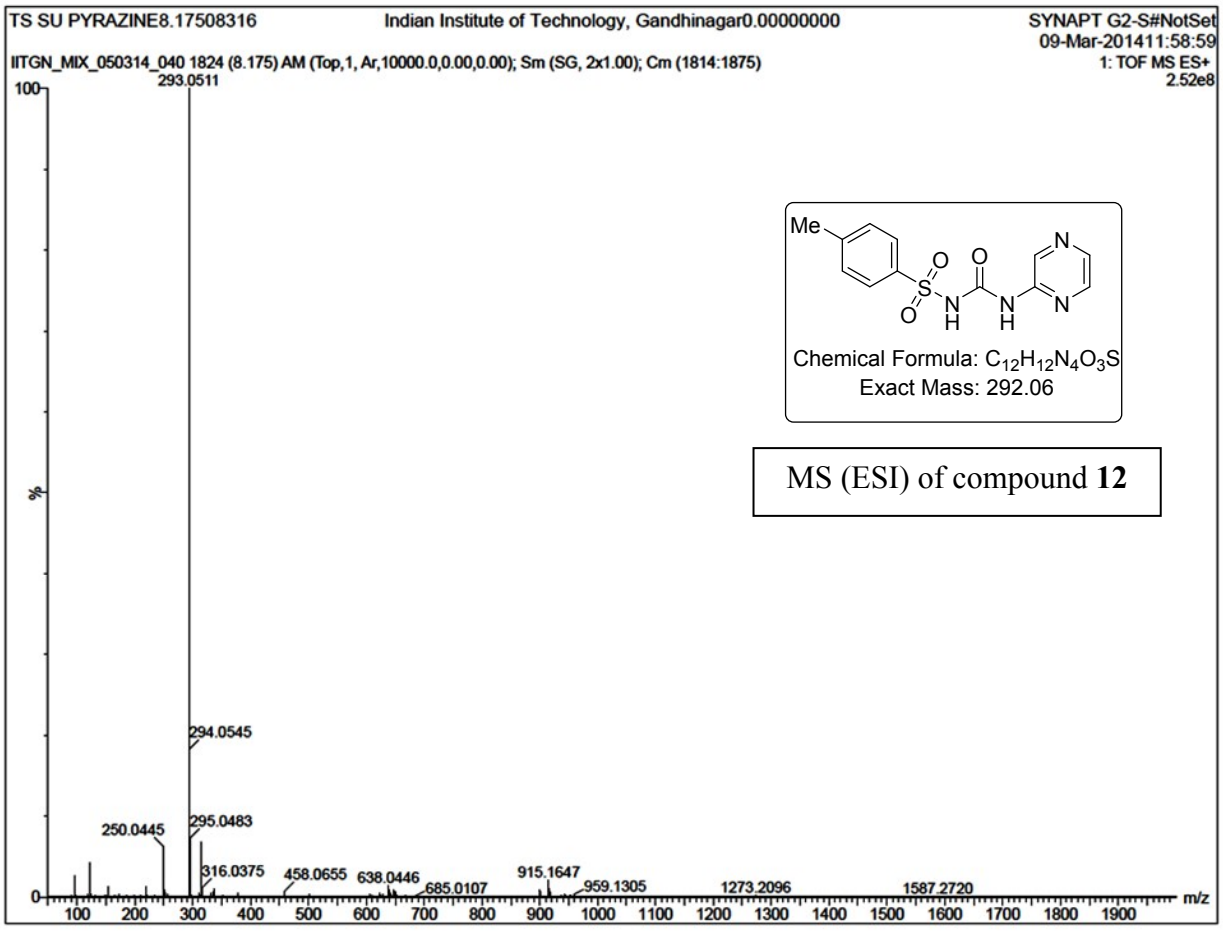
^{1}H NMR of compound **11**



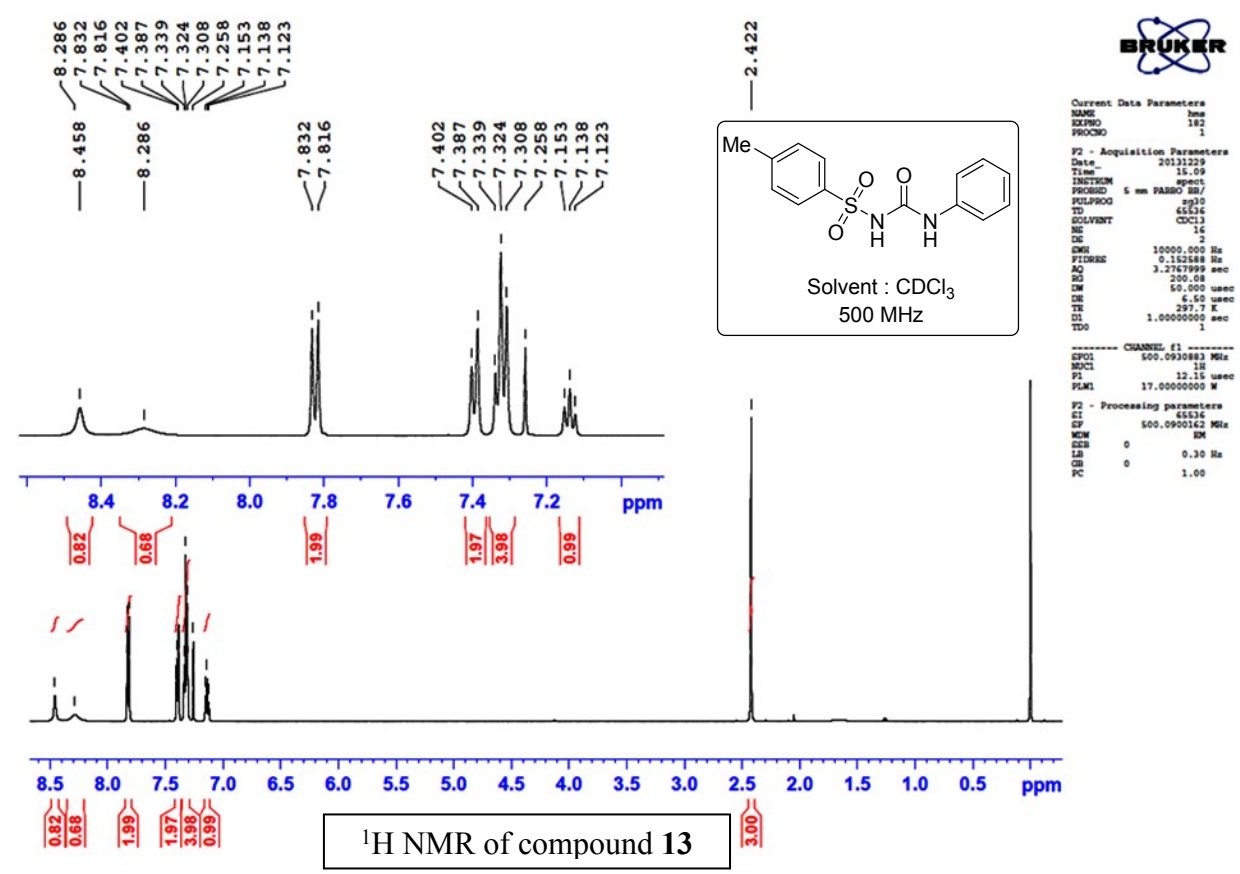
MS (ESI) of compound **11**



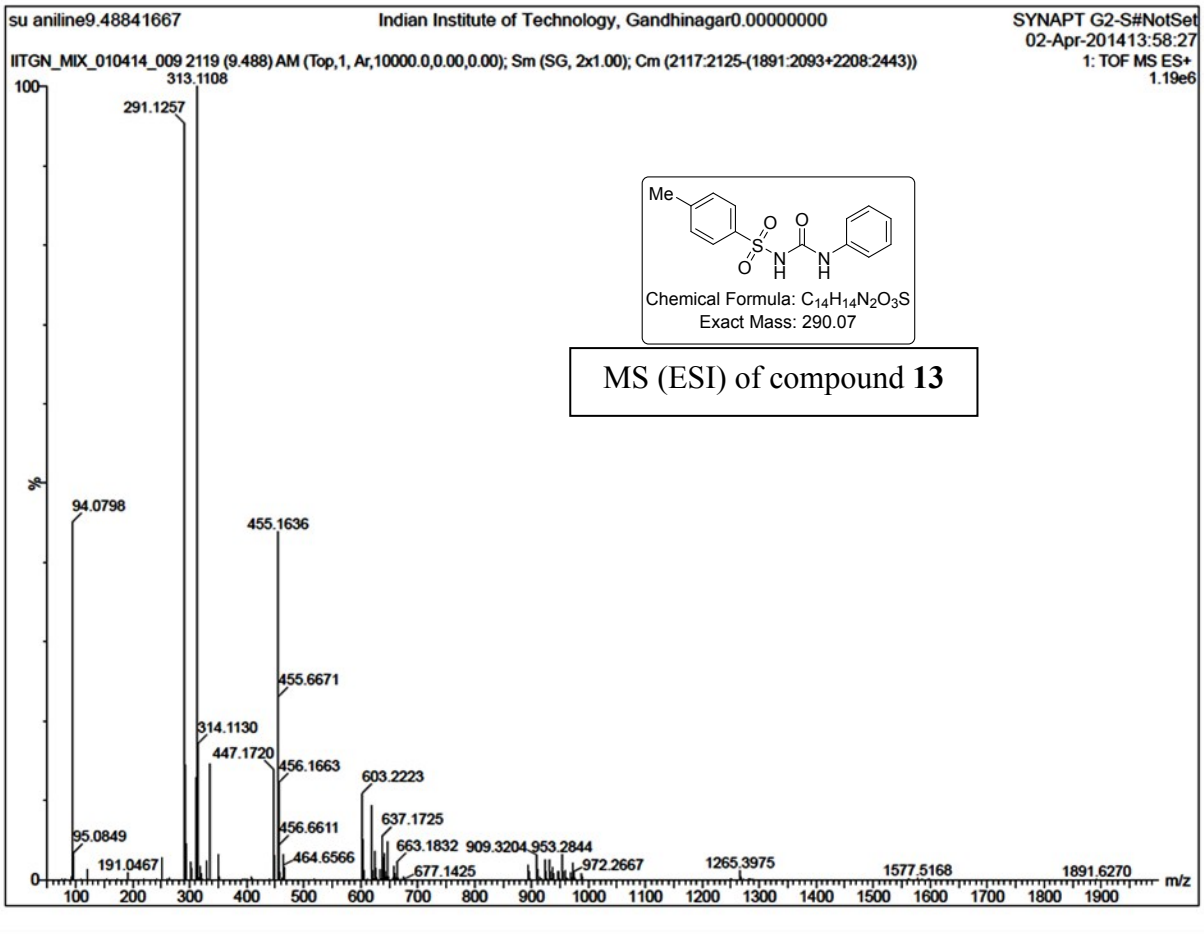
^{1}H NMR of compound **12**



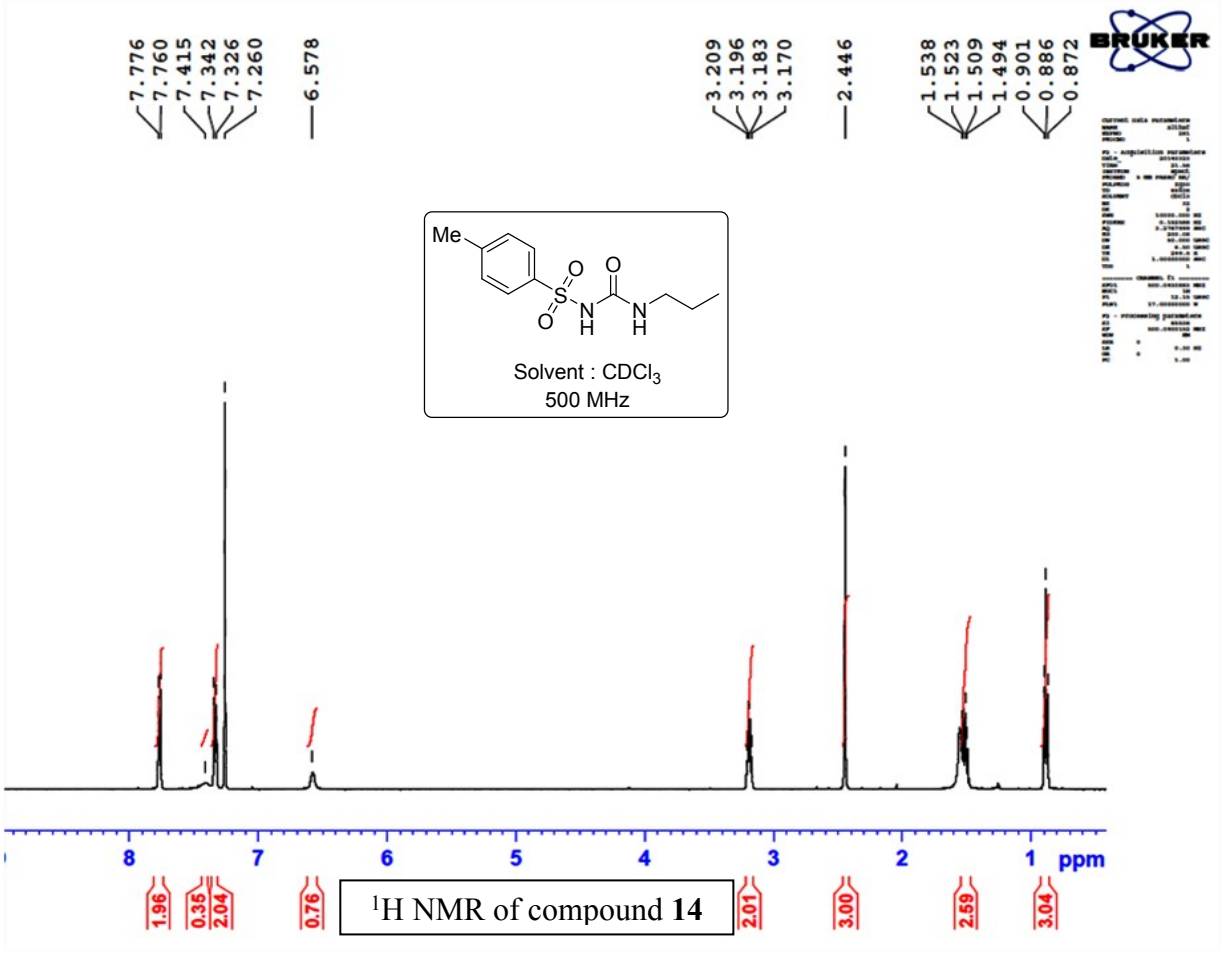
MS (ESI) of compound **12**



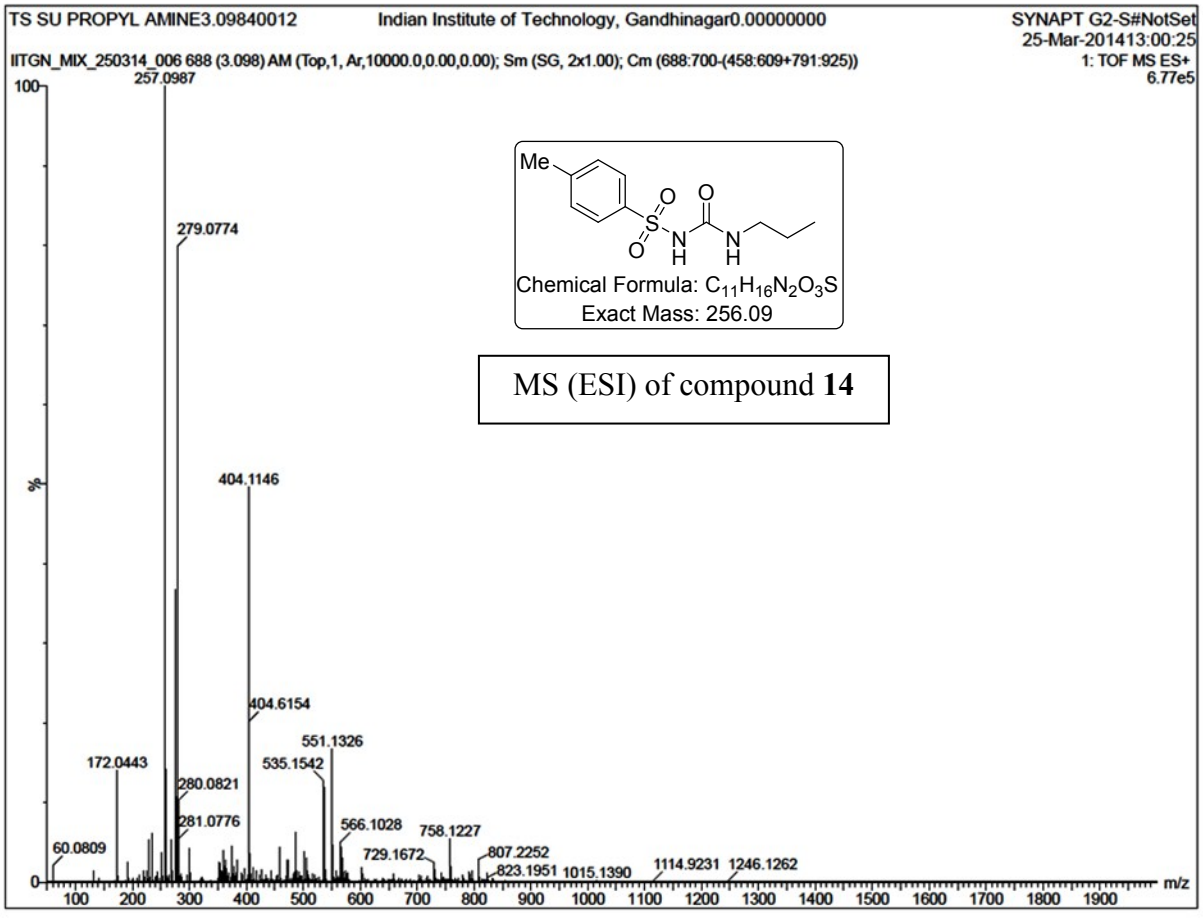
^{1}H NMR of compound **13**



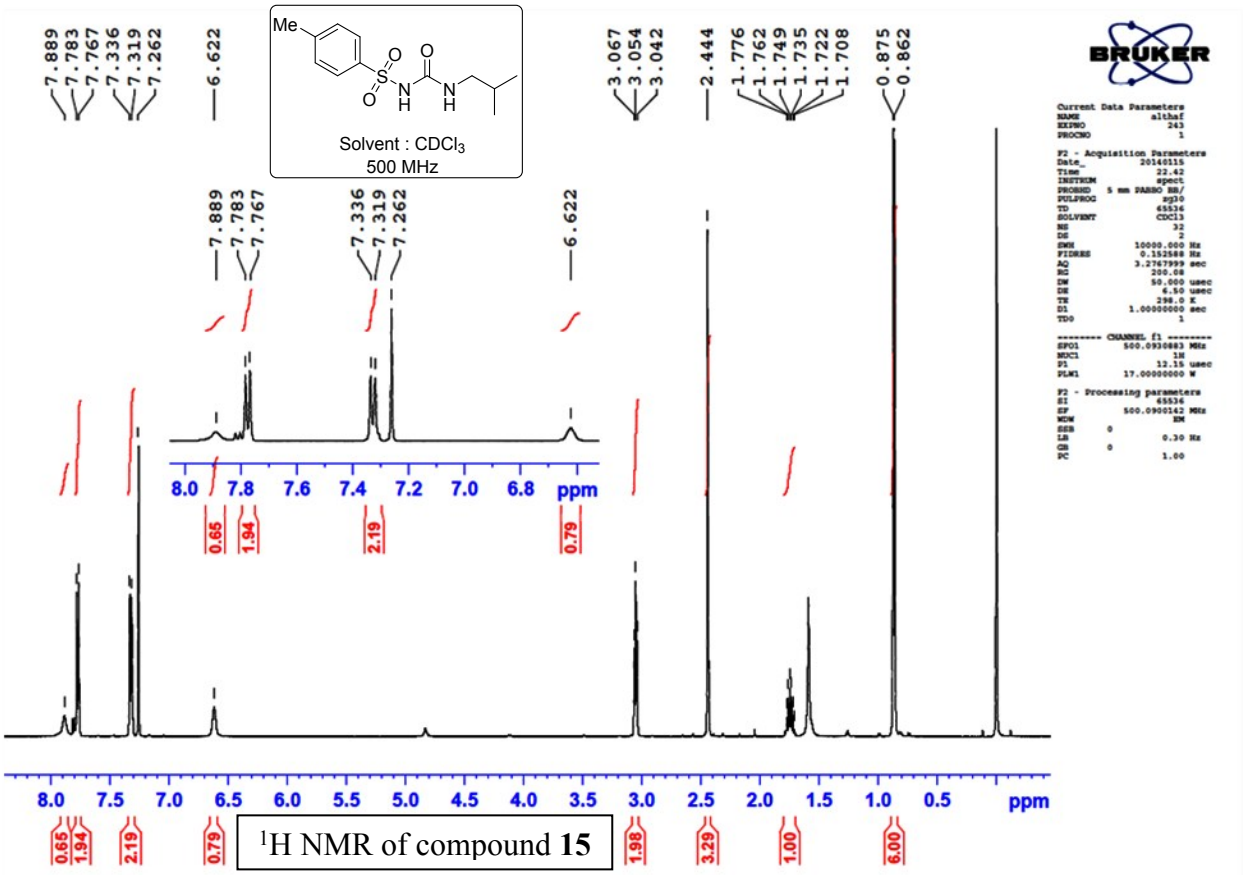
MS (ESI) of compound **13**



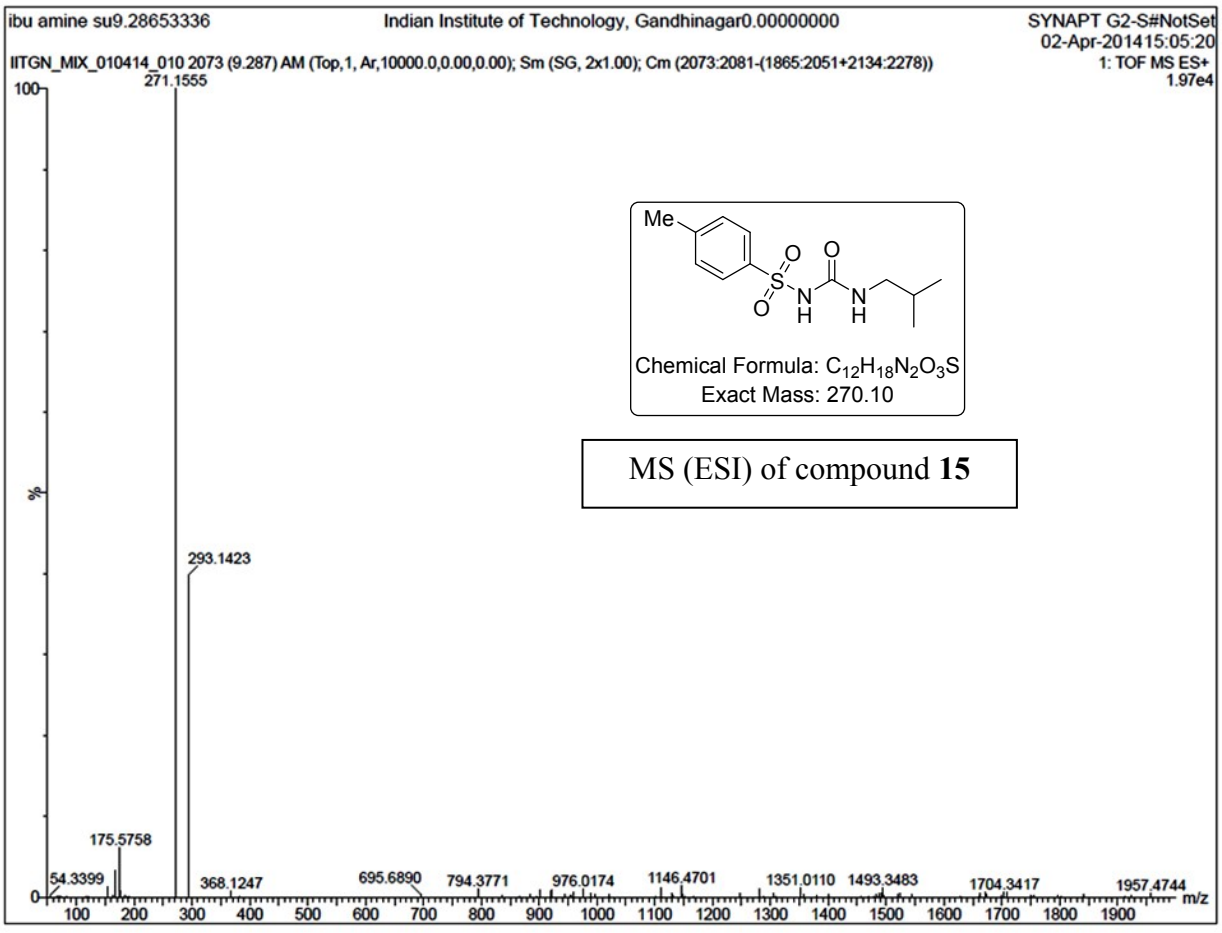
^{1}H NMR of compound **14**



MS (ESI) of compound **14**

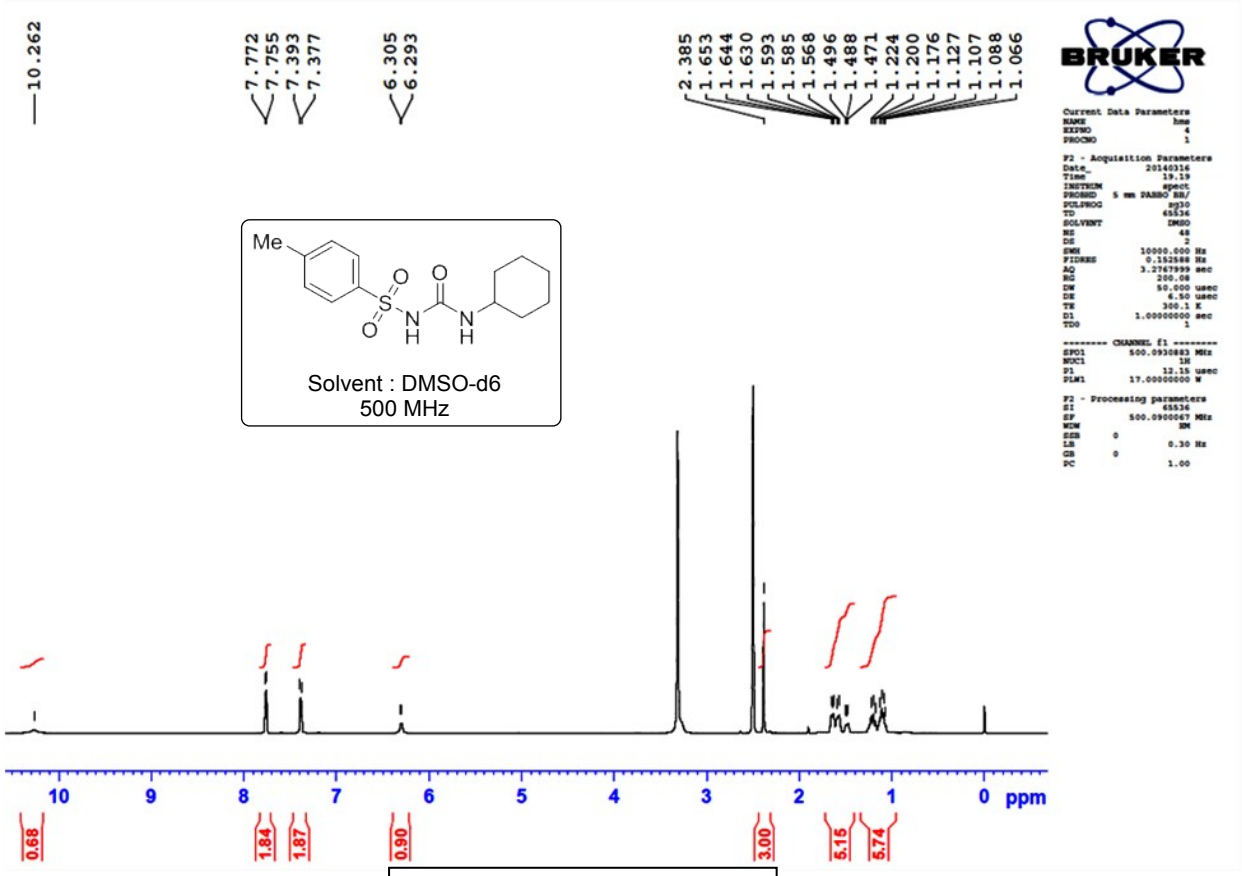


^{1}H NMR of compound **15**

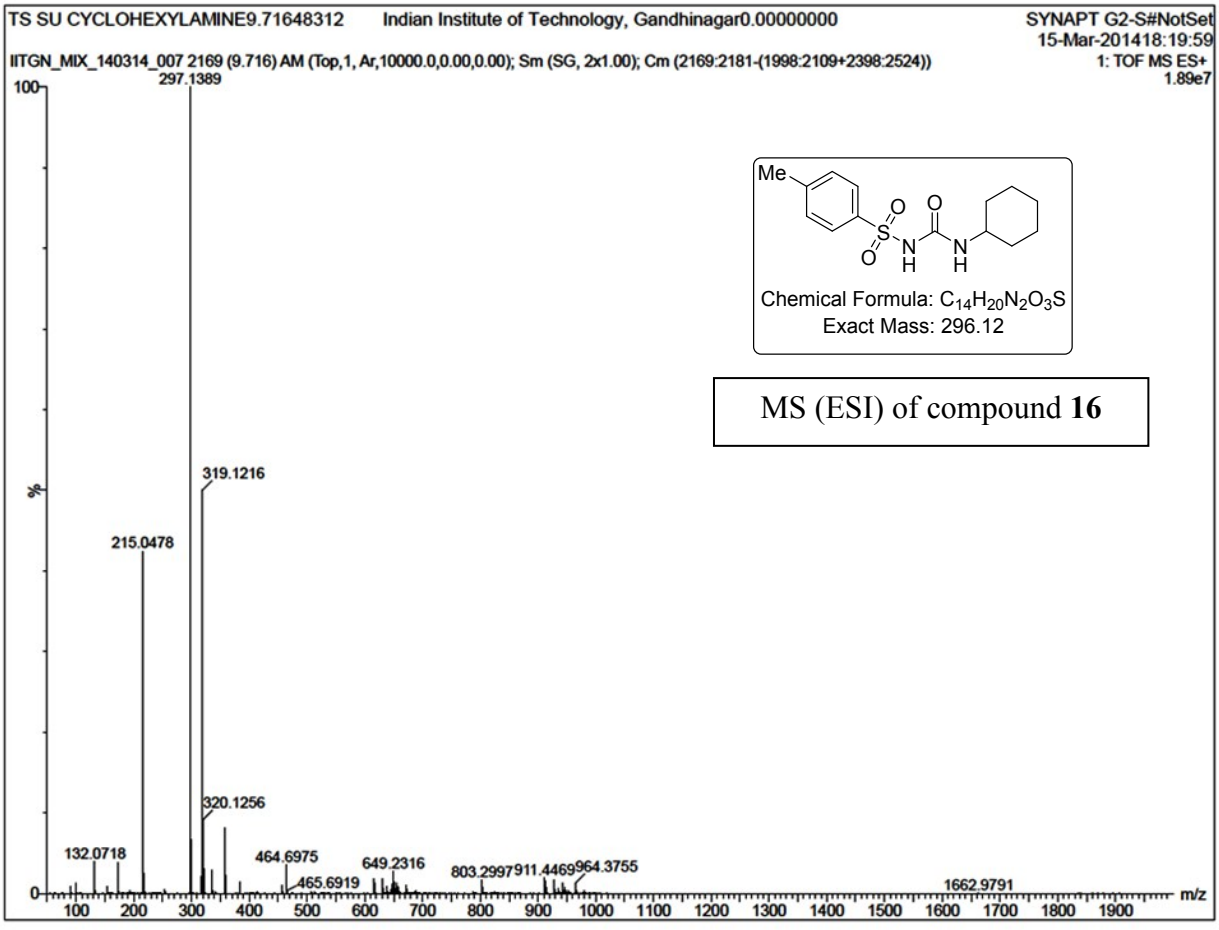


Chemical Formula: $C_{12}H_{18}N_2O_3S$
Exact Mass: 270.10

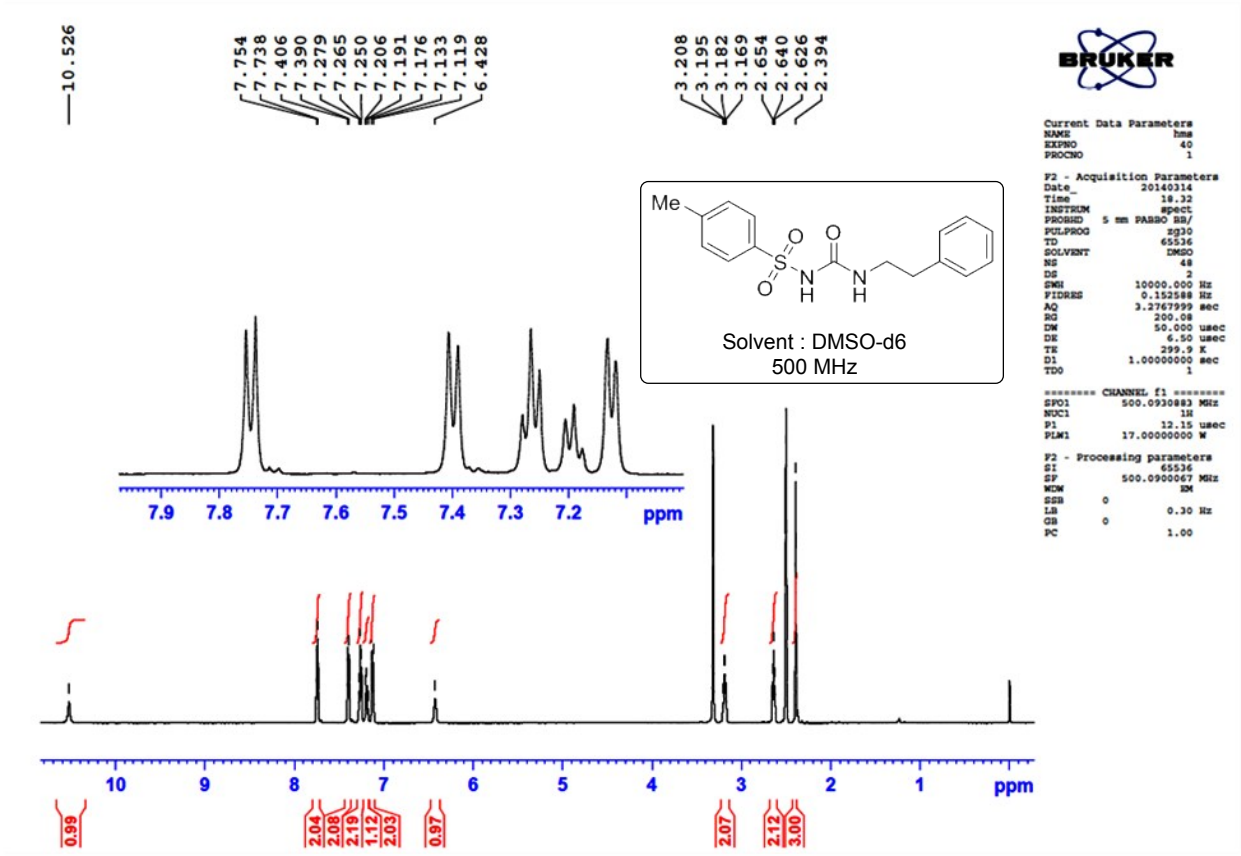
MS (ESI) of compound **15**



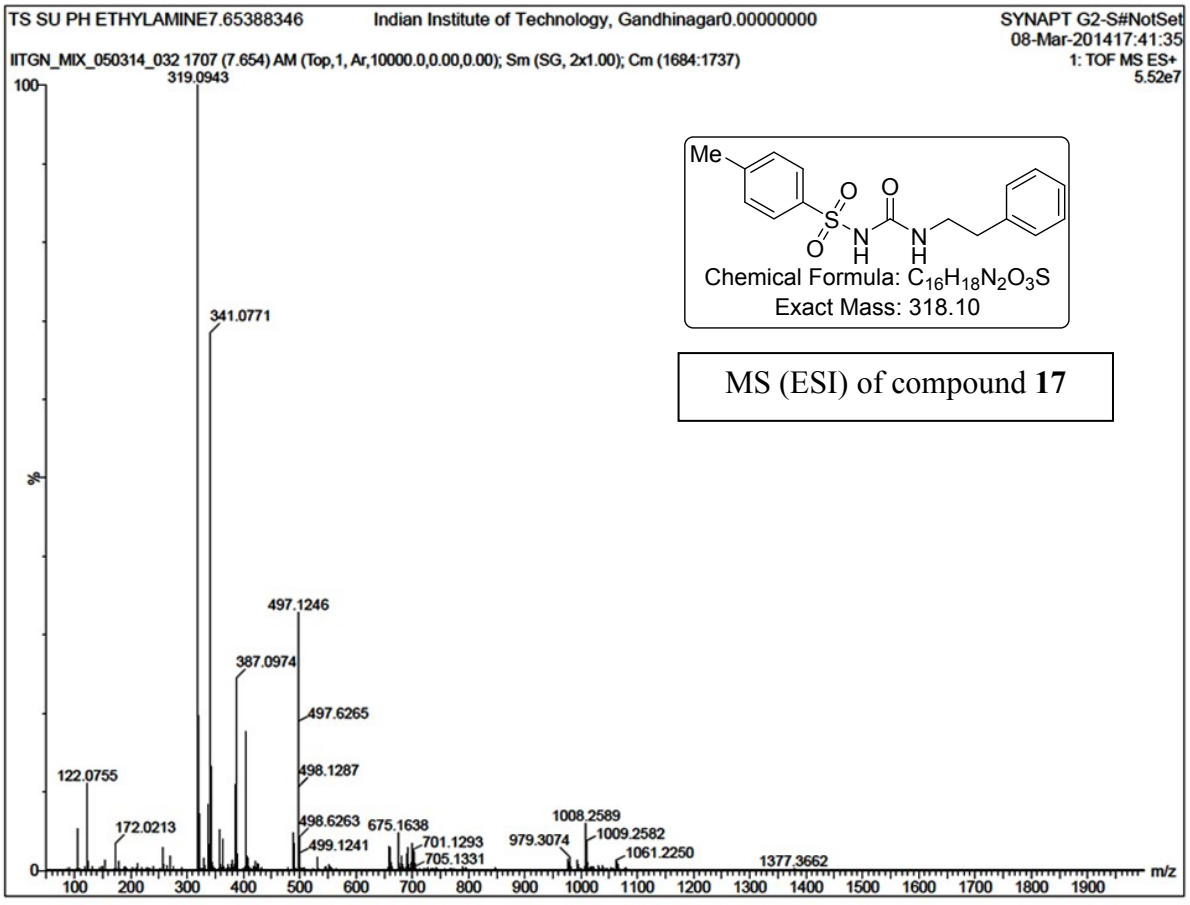
^{1}H NMR of compound **16**



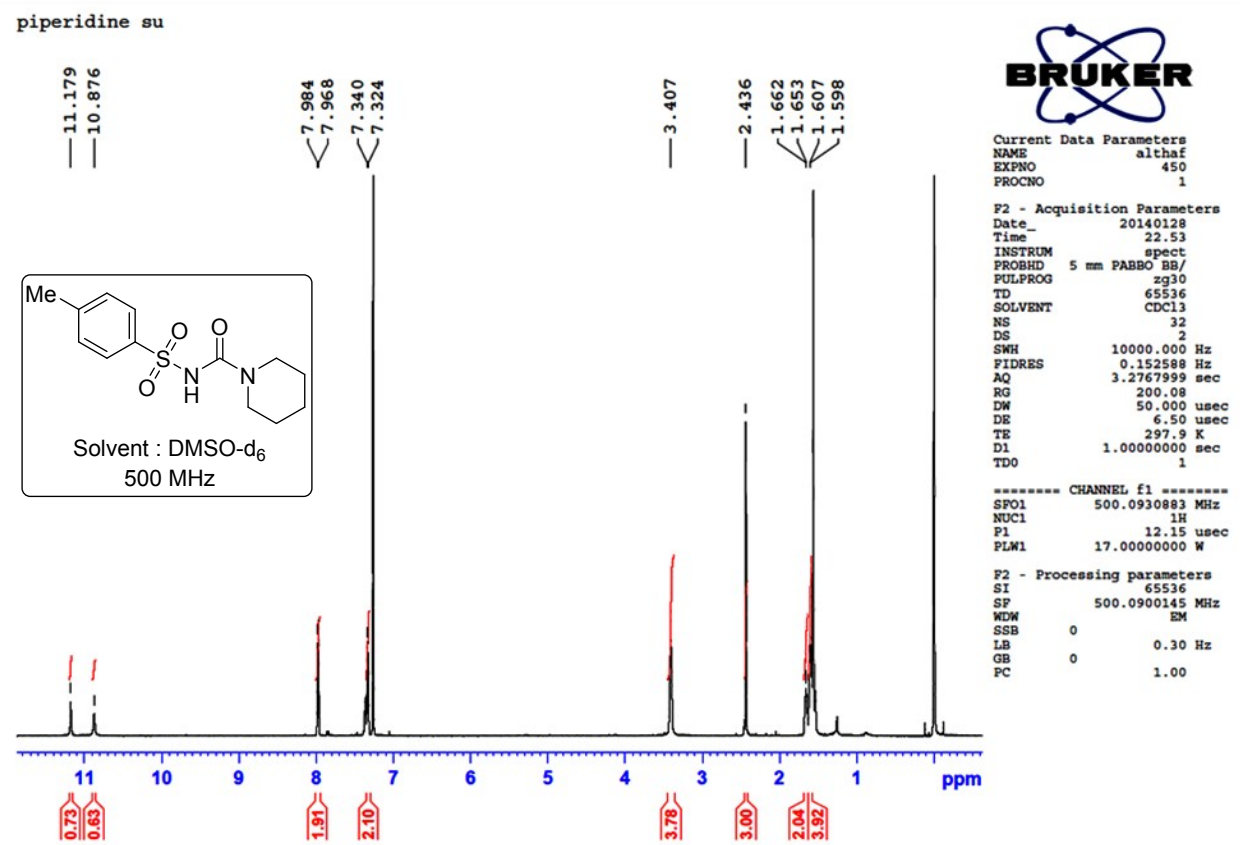
MS (ESI) of compound **16**



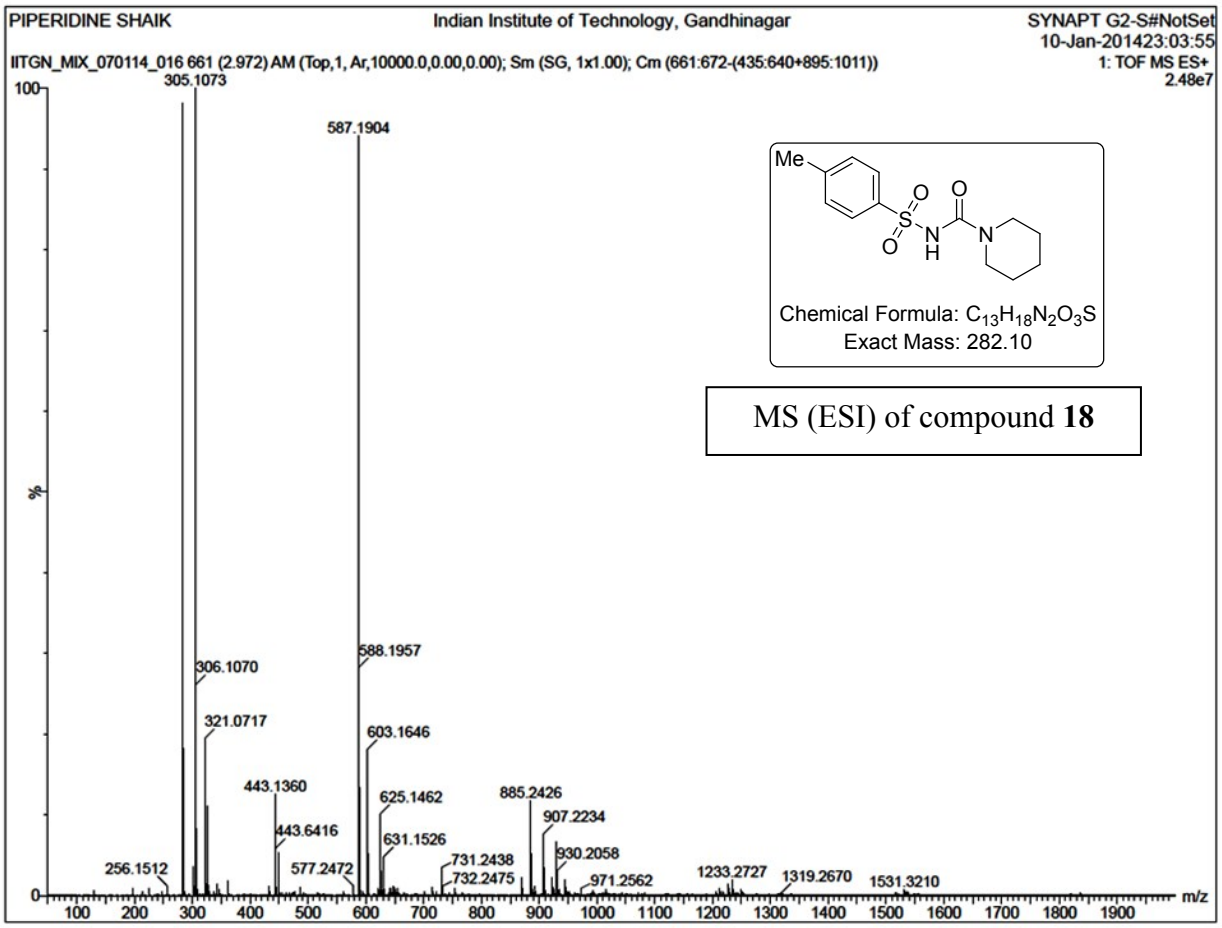
^{1}H NMR of compound **17**



MS (ESI) of compound **17**



^{1}H NMR of compound **18**



MS (ESI) of compound **18**

Table S1

Docking score and predicted binding energy for compound **1** and design 1-3.

Molecule	Docking Score	Predicted binding energy
Compound **1**	-8.8	-55.47
Design 1	-7.5	12.25
Design 2	-7.7	9.14
Design 3	-4.0	0.30

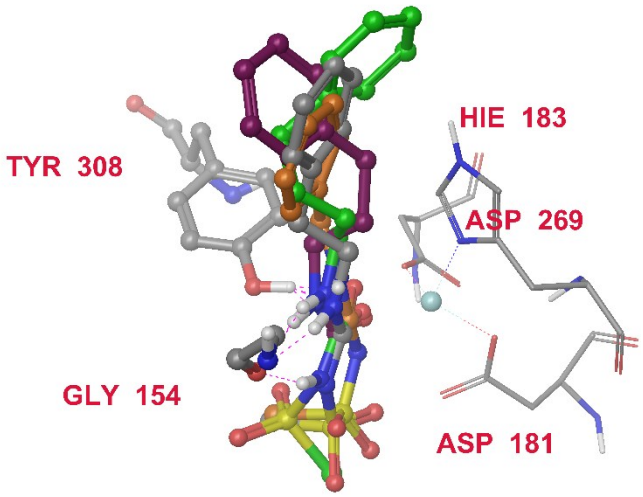


Fig. S1 Binding mode of compound **1** and design 1,2 and 3 in active site of HDAC2

Table S2

Percentage Inhibition of hCA II by compound **1-10** at 10 uM concentration.

Compound	**% Inhibition of hCA II (10 uM)**	**IC_{50} (uM)**
1	23	ND
2	25	ND
3	26	ND

4*	-	ND
5*	-	ND
6	31	ND
7	30	ND
8	24	ND
9	33	ND
10	27	ND

* Compound not involved in Biological assay
ND = Not Determine

Table S3

Percentage activation of HDAC1 by compound **11-18** at 10 uM and 100 uM concentration.

Compound	% Activation of HDAC 1 (10 uM)	% Activation of HDAC 1 (100 uM)
11	NA	ND
12	5	13
13	11	18

14	NA	ND
15	NA	ND
16	NA	ND
17	NA	ND
18	NA	ND

NA= Not Active
ND= Not Determine

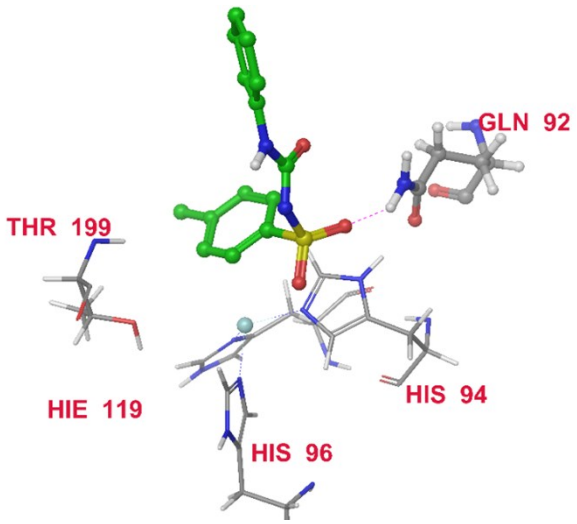


Fig. S2 Binding mode of compound **13** in active site of hCAII

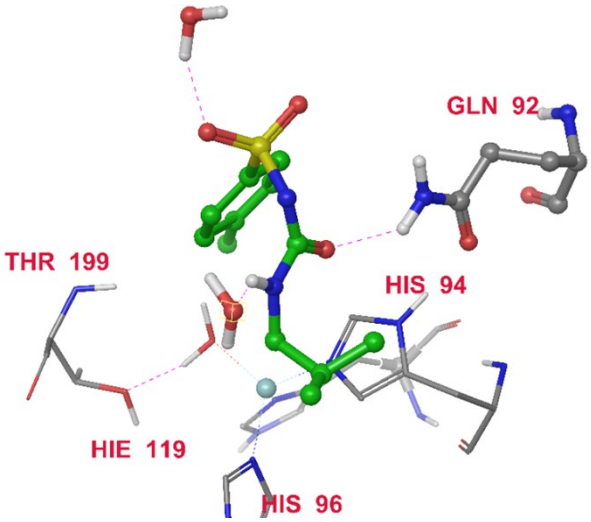


Fig. S3 Binding mode of compound **15** in active site of hCAII

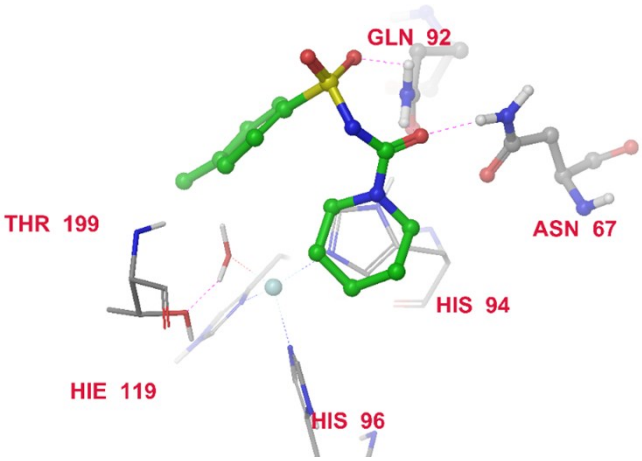


Fig. S4 Binding mode of compound **18** in active site of hCAII