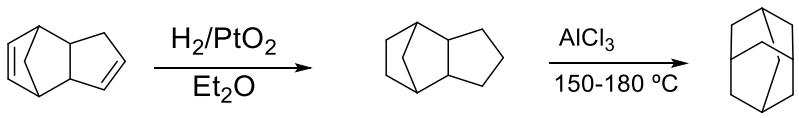
# Chapter 6

# Development of Adamantyl Analogous as NMDA Receptor Antagonist for Treatment of AD

## 6.1 Development of adamantly analogous as NMDA receptor antagonist

Adamantanes considered as potential polymer intermediates have several useful biological activities. Adamantine was successfully synthesized from dicyclopentadiene, which was hydrogenated with of platinum dioxide and finally converted to adamantine in presence of Lewis acid *viz.* aluminium chloride as catalyst (**Figure 6.1**)(411).

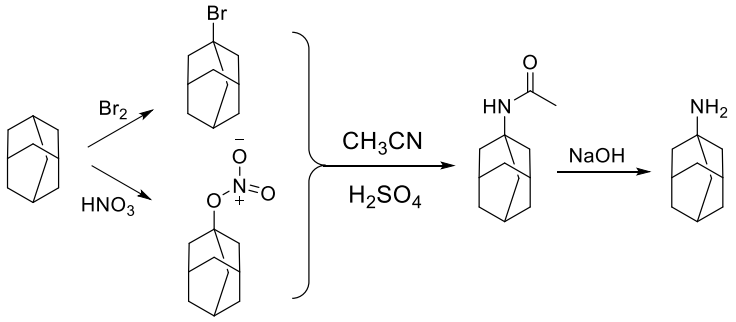
**Figure 6.1.** Paul von Ragué Schleyer method of adamantane synthesis.




Adamantane nucleus easily undergo bromination, chlorination, sulfonation, hydroxymethylation, and nitration type of reactions. The tertiary position of the nucleus is highly selective for bromination and nitration. Adamantane containing marketed drug amantadine was prepared by the bromination and nitration which yielded to bromide or nitroester. The product was further converted to acetamide and finally to amantadine by action of acetonitrile followed by sodium hydroxide (**Figure 6.2**)(412).

Triazoles are another important class of compounds having diverse biological activities. These are mainly considered neuroprotective in neurodegenerative disorders.

**Figure 6.2** Conversion of adamantane to amantadine.




Chemically, triazoles are of two types, *i.e.*, 1,2,3-triazoles or *v*-triazoles (**1**) and 1,2,4-triazoles or *s*-triazoles (**2**) (**Figure 6.3**). 1,2,3-triazoles undergo alkylation reaction in presence of alkyl iodide on silver salt. Alkyl or aryl azides, when added to acetylene yielded l-substituted *v*-triazoles. This reaction is commonly used in the synthesis of l-phenyl-, 2,4-dichlorophenyl-, and 2,5-dichlorophenyl triazoles. 1,4-disubstituted triazoles are prepared by reaction of azides with acetylenic compounds. Propargyl aldehyde on treatment with phenyl azide produce 4-formyl-1-phenyl-*v*-triazole. Further, the reaction leads to the formation of corresponding acid and hydroxymethyl derivatives by Cannizzaro reaction (**Figure 6.4**)(413).

**Figure 6.3** 1,2,3 and 1,2,4-triazoles in different tautomeric forms.

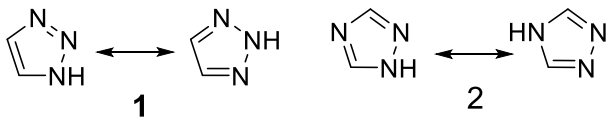
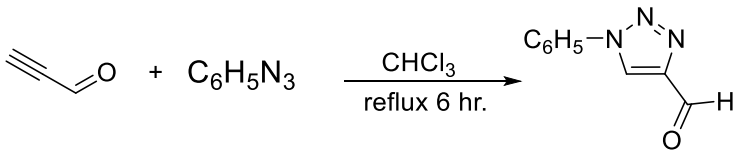
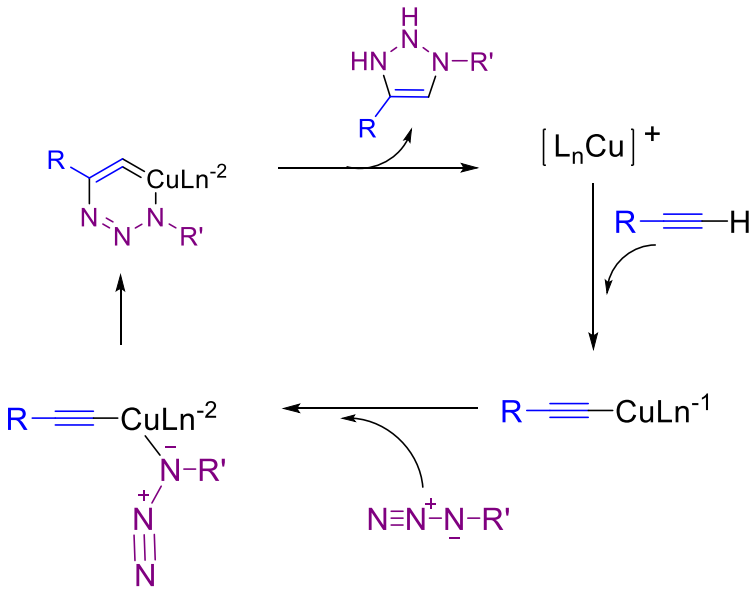



**Figure 6.4** Synthesis of 4-formyl-1-phenyl-*v*-triazole



Synthesis of 1,2,3-triazoles is greatly transformed by the use of copper. Huisgen's 1,3-dipolar cycloadditions converted to nonconcerted on reacting copper(I) acetylides with azides and nitrile oxides. It provides one pot synthesis strategy for 1,4-disubstituted 1,2,3-triazoles. The method is vastly consistent and provides an unusually wide scope with respect to triazole synthesis. Recently, Himo *et.al.*, proposed mechanism based on density functional theory (DFT) study. The reaction was found to be started with an endothermic step in which ligand bonded with sp carbon was replaced by copper. The reaction was found to move forward by ligand exchange and cyclization, which led to 1,2,3-triazoles (**Figure 6.5**).

**Figure 6.5** Mechanism of copper catalyzed selective synthesis of 1,2,3-triazoles.

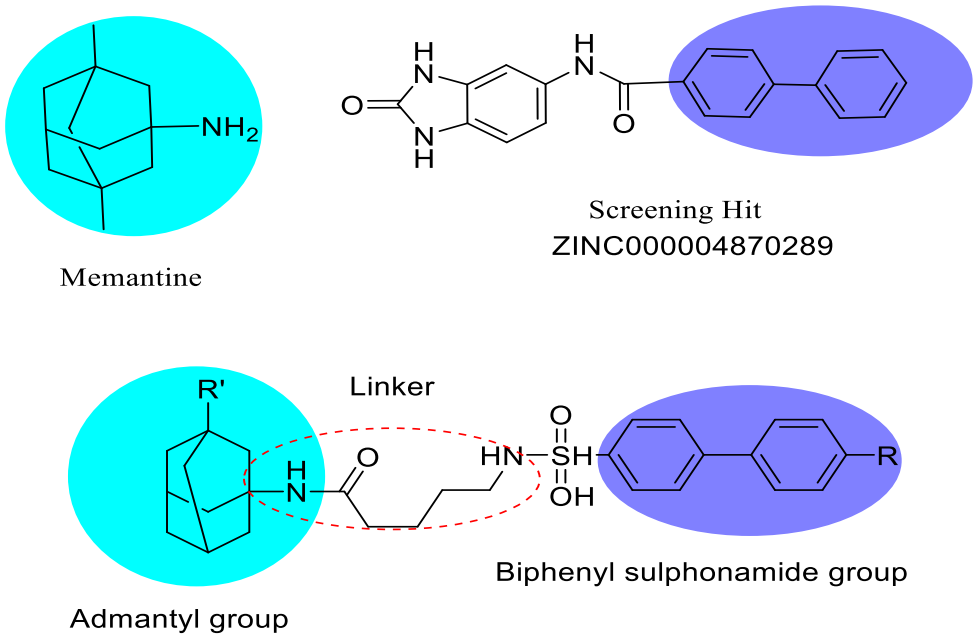



## 6.2 Rationale of drug design & *in-silico* optimization

Memantine is the only NMDA receptor antagonist, that is used in treatment of Alzheimer's disease, therefore it has been retained in the final designed compounds Shape based Pharmacophore virtual screening of Zinc15 ligand database yielded a hit

(compound id-ZINC000004870289). The docking study of this hit with NMDA receptor indicate that biphenyl ring exhibited good interaction with amino terminal domain of GluN2B subunit of NMDA receptor. This observations formed basis of inclusion of biphenyl ring in designed compounds (**Figure 6.6)**

**Figure 6.6** Drug design strategy of NMDA series




## 6.3 Experimental work

### 6.3.1 Pharmacophore development and virtual screening

Protein structure of GluN1A-GluN2B subunit of NMDA receptor was obtained from Protein Data Bank server (PDB ID. 5EWJ). Co-crystallized ligand ifenprodil, a GluN2B selective antagonist, was used for the development of pharmacophore.

Features from the resultant pharmacophore was used to screen ZINC database of small ligands using Pharmit server. The resulting compounds were further subjected to

various filters *i.e.*, Drug-likeness, and pains. The compounds were further subjected to high-througput virtual screening, standard precision docking and extended precision docking.

### 6.3.2 Drug-likeness, BBB permeability and toxicity filtration

*In-silico* prediction of Drug-likliness, BBB permeability and toxicity of selected compounds was performed by using PreADMET web based server.

### 6.3.3 Molecular docking

#### 6.3.3.1 Protein structure analysis

The structural analysis of amino terminal domain of GluN1-GluN2B NMDA receptor (PDB id 5EWJ) was performed by Chimera 1.13.1rc in order to ascertain missing loops and side chains.

#### 6.3.3.2 Homology modelling and validation

Homology model was developed for human GluN1A-GluN2B subunit of NMDA receptor using SWISS-MODEL accessible via ExPASy web server. Human GluN1-GluN2B NMDA receptor (PDB id 5EWJ) was used as template and sequence of protein was retrieved from UniProtKB (protein id A0A1L8F5J9 and Q13224 for GluN1 and GluN2B respectively) for developing homology model. The developed homology model was evaluated using RAMPAGE, PROCHECK, Verify 3D, GMQE, QMEANDisco and QMEAN.

#### 6.3.3.3 Protein preparation

The model was refined on Dockprep and PDB2PQR utility(414). Ligands complexed with protein were removed, hydrogen atoms were added, charges and pKa were assigned to amino acid residues using PDB2PQR server at physiological pH of 7.3 and energy minimization of the protein was performed. Further, protein was opened in

Autodock tools 1.5.6 to merge non-polar hydrogens and atom types were assigned. The pdb was saved as pdbqt file.

**6.3.3.4 Ligand preparation**

The ligands were sketched in chemdraw and saved in sdf format. The resultant structures were minimized using Open Babel 2.4.0. Generalized Amber Force Field (GAFF) was used by applying steepest descent algorithm for 4000 steps. The resultant minimized structures were imported to Autodock tools 1.5.6 and were converted to PDBQT format.

**6.3.3.5 Grid generation**

Autodock uses autogrid 4.0 to calculate grid maps of interaction energies with various atom types present in the ligands (A, C, HD, NA, N, OA, S, Br, Cl and I). The grid size was set to 60X60X60 xyz points for the developed homology model with a grid spacing of 0.375 Å. The grid center was placed at coordinates (x, y, and z) 21.578, -6.531 & -32.509 respectively.

**6.3.3.6 Docking**

Docking was performed by Autodock 4.0 using Lamarckian Genetic Algorithm (LGA), with 10 runs, 150 population size, 2,500,000 maximum number of energy evaluations and 27,000 maximum number of generations. The free binding energy of ligand-receptor complex for scoring various conformations was estimated and was used 'semiempirical free energy force field' to evaluate conformations obtained by molecular docking. The docked conformers were visualized by using Discovery Studio 2017R2.

### 6.3.4 Molecular dynamics & simulation

MD simulation was performed on protein ligand complex of compound **22**. PDB file was optimized through Protein Preparation Wizard of Maestro Academic Visualizer ver. 11.5.01. The bond order, hydrogens were assigned and incorrect bonds were corrected. The global cell was defined as orthorhombic water box with buffer spacing of 10 Å between protein atoms and box sides. Further, the system was neutralized with $Na^+$ ions and salt concentrations were adjusted to 0.15 M. This system was assigned with default OPLS force field and energy minimization was performed with convergence gradient of 1 Kcal/mole for maximum number of iterations as 2000. The system was subjected to molecular dynamic simulation for 50 ns run in the NPT ensemble (T = 310.15 K) at a constant pressure of 1.01 bar. The trajectory coordinate and energy of the system was recorded at 1.2 ns.

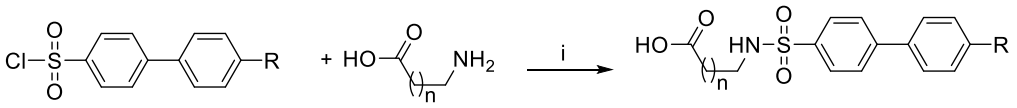
### 6.3.5 Synthesis and characterization

All the reagents were purchased from the Sigma-Aldrich, Avera, Spectrochem and Alfa Aesar. Compounds **42-45** were purchased from Sigma-Aldrich. The progress of the reactions was monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 plates (Merck KGaA) and ultraviolet light (254 nm) or iodine vapors were used for visualization of spots. Silica gel (60-120 mesh size) was used as adsorbent in column chromatography for the purification of compounds. Melting points were determined on automated melting point apparatus (Bamstead Electrothermal, UK). The $_1H$ NMR and $^{13}C$ NMR spectra were recorded on Bruker Advance, 500 MHz spectrometer in DMSO-$d_6$ and $CDCl_3$. Chemical shift was measured in the ppm (δ) and coupling constant (J) was measured in Hz. Mass analysis was performed on LC-MS

Spectrometer Model Q-ToF Micro Waters Mass spectra with EI ion source and FTIR spectra was recorded on Bruker ALPHA-T (Germany) ATR /FT-IR instrument.

### 6.3.5.1 Scheme I. Synthesis of biphenyl analogues of adamantylamine

**Step I**: Synthesis of sulphonamide intermediates

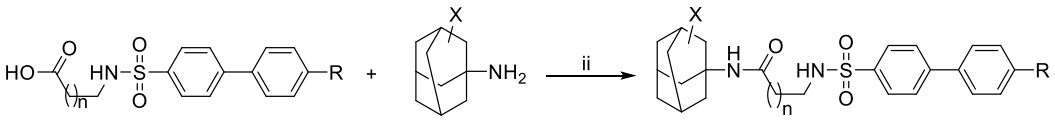



**1-4** **5-12**

| Comp. | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|
| R | -H | -Cl | -F | 4-$CH_3$ | -H | -Cl | -F | 4-$CH_3$ |
| n | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 |

Reagents and conditions: (i) $K_2CO_3$, Acetone, $H_2O$, stirring 24 h at rt.

**Step II**: Synthesis of adamantyl analogues



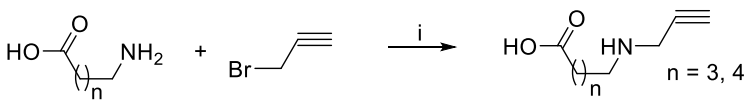

**5-12** **13-15** **16-27**

| Comp. | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R | -- | -- | -- | -H | -Cl | -F | -H | -F | -H | -Cl | -H | -H | -Cl | -Cl | 4-$CH_3$ |
| n | -- | -- | -- | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 3 | 4 | 3 | 4 | 3 |
| X | -H | 3-OH | 3,5-$CH_3$ | 3-OH | 3-OH | 3-OH | 3-OH | 3-OH | 3-H | 3-H | 3,5-$CH_3$ | 3,5-$CH_3$ | 3,5-$CH_3$ | 3,5-$CH_3$ | 3-H |

Reagents and conditions: (ii) DIPEA, EDC.HCl, HOBt, DMF, heat at 120 ºC, 8 h.

### 6.3.5.2 Scheme II. Synthesis of biphenyl analogues of adamantylamine

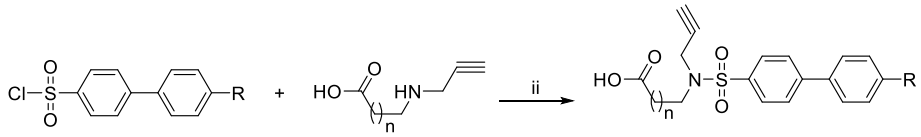
**Step I**: **Synthesis of propargyl derivatives of amino acids**




**28**, **29**

Reagents and conditions: (i) $K_2CO_3$, DMF, 100 ºC, 4-6 h.

**Step II**: **Synthesis of propargyl derivatives of biphenyl sulfonamides**

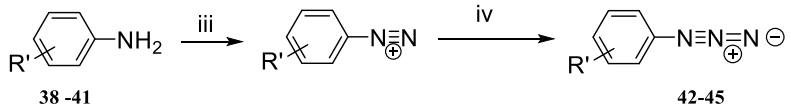


**1-4** **28, 29** **30-37**

| **Comp.** | **30** | **31** | **32** | **33** | **34** | **35** | **36** | **37** |
|---|---|---|---|---|---|---|---|---|
| **R** | -H | -Cl | -F | 4-$CH_3$ | -H | -Cl | -F | 4-$CH_3$ |
| **n** | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 |

Reagents and conditions: (ii) $K_2CO_3$, Acetone, stirring 24 h at rt

**Step III**: **Diazonium reaction with sodium azide**

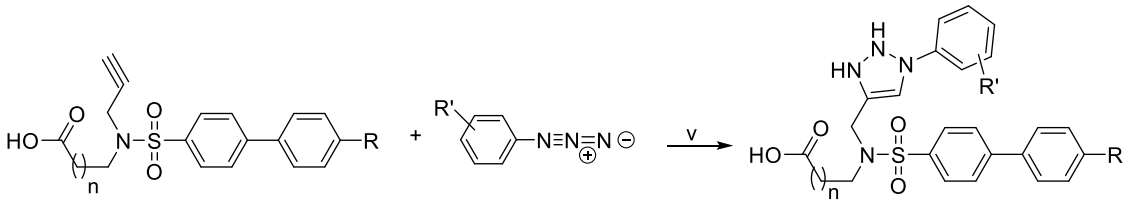


**38 -41** **42-45**

| **Comp.** | **42** | **43** | **44** | **45** |
|---|---|---|---|---|
| **R'** | -Cl | -H | -F | 4-$CH_3$ |

Reagents and conditions: (iii) $NaNO_2$, HCl, 0-5 ºC, 30 min. (iv) Sodium azide ($NaN_3$)

**Step IV**: **Synthesis of 1,4-disubstituted 1,2,3-triazoles**

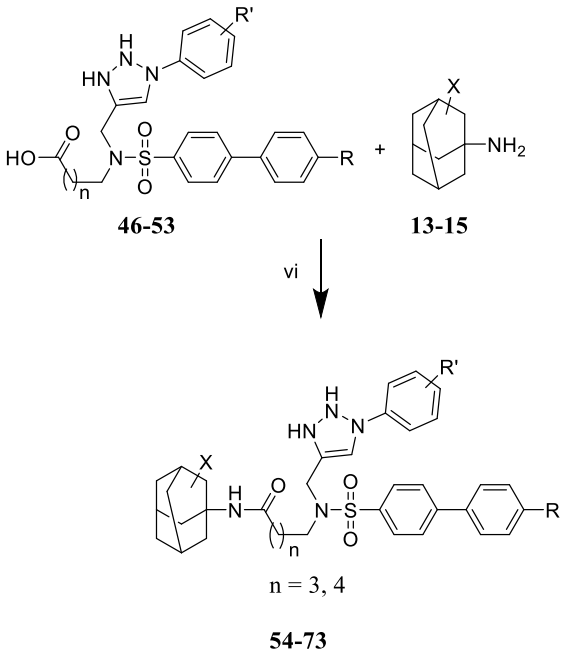


**30-37** **42-45** **46-53**

| **Comp.** | **46** | **47** | **48** | **49** | **50** | **51** | **52** | **53** |
|---|---|---|---|---|---|---|---|---|
| **R** | -H | -Cl | -F | 4-$CH_3$ | -H | -Cl | -F | 4-$CH_3$ |
| **R'** | -Cl | -H | -$CH_3$ | F | -Cl | -H | -$CH_3$ | F |
| **n** | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 |

Reagents and conditions: Copper metal, $H_2O$:BuOH (2:1) at r.t 6-8 h.

**Step V**: **Synthesis of 1,4-disubstituted 1,2,3-triazoles analogues of adamantyl**




| Comp. | R | R' | X | n |
|---|---|---|---|---|
| **54** | -H | -Cl | -H | 3 |
| **55** | -Cl | -H | -H | 3 |
| **56** | -F | $-CH_3$ | -H | 3 |
| **57** | 4-$CH_3$ | -F | -H | 3 |
| **58** | -H | -Cl | -H | 4 |
| **59** | -Cl | -H | -H | 4 |
| **60** | -F | $-CH_3$ | -H | 4 |
| **61** | 4-$CH_3$ | -F | -H | 4 |
| **62** | -H | -Cl | 3-OH | 3 |
| **63** | -Cl | -H | 3-OH | 3 |
| **64** | -F | $-CH_3$ | 3-OH | 3 |
| **65** | 4-$CH_3$ | -F | 3-OH | 3 |
| **66** | -H | -Cl | 3-OH | 4 |
| **67** | -Cl | -H | 3-OH | 4 |
| **68** | -F | $-CH_3$ | 3-OH | 4 |
| **69** | 4-$CH_3$ | -F | 3-OH | 4 |
| **70** | -H | -Cl | 3,5--$CH_3$ | 3 |
| **71** | -Cl | -H | 3,5--$CH_3$ | 3 |
| **72** | -H | -Cl | 3,5--$CH_3$ | 4 |
| **73** | -Cl | -H | 3,5--$CH_3$ | 4 |

Reagents and condition: (ii) DIPEA, EDC.HCl, HOBt, DMF, heat at 120 ºC, 8 h.

### 6.3.5.3 General procedure for the synthesis of sulphonamide intermediates using different aminoacids (5-12)

Aromatic biphenyl sulfonylchlorides (**1-4**) (0.0143 mol, 1 equivalent) were dissolved in acetone (2 ml). The mixture was added to water (2 ml) containing 6-aminocaproic acid/5-aminovaleric acid (0.0143 mol, 1 equivalent) and potassium carbonate (0.0429 mol, 3 equivalents). The final reaction mixture was stirred at room temperature (rt) for 24 h. The reaction was monitored by TLC using ethylacetate and methanol (8:2) as the mobile phase. The acetone was evaporated under reduced pressure and reaction mixture was neutralized with 1N HCl to get the product. The product was filtered and recrystallized with methanol to obtain the pure compounds.

**6.3.5.4 General procedure for the synthesis of adamantyl analogues (16-27)**

Sulphonamide intermediates (1.5mM, 1 equivalent) (**5-12**) were dissolved in dry DMSO containing substituted adamantly amine analogues (1.5 mM, 1 equivalent) (**13-15**), N,N-Diisopropylethylamine (DIPEA) (4 mM, 2.5 equivalent), N′-ethylcarbodi-imide hydrochloride (EDC.HCl) (2.5 mM, 1.5 equivalent) and hydroxybenzotriazole (HOBt) (2.55 mM, 1.5 equivalent). The reaction mixture was heated up to 120 ºC for 8 h, followed by workup with water ethyl acetate system. The organic layer was evaporated and product was purified by column chromatography using ethyl acetate and hexane (2:3) as mobile phase.

*5-([1,1'-biphenyl]-4-sulfonamido)-N-(3-hydroxyadamantan-1-yl)pentanamide* (**16**): It was synthesized as per general procedure described earlier in section (6.3.5.4) using 5-([1,1'-biphenyl]-4-sulfonamido)pentanoic acid (**5**) (0.5g) and 3-aminoadamantan-1-ol (**14**) (0.25g) to get compound **16** as white powder, yield 78%; mp 215-218 ºC; FTIR (KBr) $cm^{-1}$: 3124 (Ar-str.), 1710 (C=O-str.), 1171 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.95 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.75 (d, 2H, *J* = 10 Hz, biphenyl-$C_2$-$C_6$), 7.64 (d, 2H, *J* = 10 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.52 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.45 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, biphenyl-$C_{4'}$), 5.25 (s, 1H, -$SO_2$NH), 4.88 (s, 1H, -NH), 3.04-2.95 (m, 3H, 1-$CH_2$, -OH), 2.31-2.28 (m, 2H, 4-$CH_2$), 2.10 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, adamantyl-$C_6$), 2.02 (s, 2H, adamantyl-$C_2$), 1.95-1.86 (m, 6H, adamantyl-$C_4$,-$C_9$,-$C_{10}$), 1.73-1.69 (m, 4H, adamantyl-$C_5$,-$C_7$,-$C_8$), 1.59-1.52 (m, 4H, 2-$CH_2$, 3-$CH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 173.48 (-CONH), 148.49 (biphenyl-$C_4$), 145.70 (biphenyl-$C_1$), 140.41 (biphenyl-$C_{1'}$), 129.85 (biphenyl-$C_3$,-$C_5$), 129.02 (biphenyl-$C_2$,-$C_6$), 128.66 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.40 (biphenyl-$C_{3'}$,-$C_{5'}$), 127.10 (biphenyl-$C_{4'}$) 68.89 (1-$CH_2$), 53.51 (adamantyl-$C_3$), 47.42 (adamantyl-$C_1$), 46.25

(adamantyl-$C_2$, -$C_4$, -$C_{10}$), 45.10 (adamantyl-$C_5$, -$C_7$), 43.58 (adamantyl-$C_6$), 37.96 (adamantyl-$C_8$), 36.81 (adamantyl-$C_9$), 29.46 (4-$CH_2$), 28.98 (3-$CH_2$), 23.90 (2-$CH_2$); MS (ESI): *m/z* found 482.9 [$M^+$]; calculated for $C_{27}H_{34}N_2O_4S$ 482.2.

*5-((4'-chloro-[1,1'-biphenyl])-4-sulfonamido)-N-(3-hydroxyadamantan-1yl)pentane-mide* (**17**): It was synthesized as per general procedure described earlier in section 6.3.5.4 using 5-((4'-chloro-[1,1'-biphenyl])-4-sulfonamido)pentanoic acid (**6**) (0.5g) and 3-aminoadamantan-1-ol (**14**) (0.25g) to get compound **17** as white powder, yield 75%; mp 225-227 ºC; FTIR (KBr) $cm^{-1}$: 3129 (Ar-str.), 1672 (C=O-str.), 1158 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.95 (d, 2H, *J* = 10 Hz, biphenyl-$C_3$-$C_5$), 7.70 (d, 2H, *J* = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.56 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.48 (d, 2H, $J_1$ = 10 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.30 (s, 1H, -$SO_2$NH), 5.24 (s, 1H, -NH), 3.03-2.94 (m, 3H, 1-$CH_2$, -OH), 2.32-2.21 (m, 2H, 4-$CH_2$), 2.15 (t, 2H, $J_1$, $J_2$ = 5 Hz, adamantyl-$C_6$), 2.01 (s, 2H, adamantyl-$C_2$), 1.93-1.83 (m, 6H, adamantyl-$C_4$,-$C_9$,-$C_{10}$), 1.70-1.63 (m, 4H, adamantyl-$C_5$,-$C_7$,-$C_8$), 1.56-1.55 (m, 4H, 2-$CH_2$, 3-$CH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.15 (-CONH), 149.45 (biphenyl-$C_4$), 147.74 (biphenyl-$C_{4'}$), 143.15 (biphenyl-$C_1$), 138.14 (biphenyl-$C_{1'}$), 131.54 (biphenyl-$C_3$,-$C_5$), 130.02 (biphenyl-$C_{3'}$,-$C_{5'}$), 128.45 (biphenyl-$C_2$,-$C_6$), 127.57 (biphenyl-$C_{2'}$,-$C_{6'}$), 70.56 (1-$CH_2$), 62.54 (adamantyl-$C_3$), 51.54 (adamantyl-$C_1$), 48.45 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 46.54 (adamantyl-$C_5$, -$C_7$), 42.74 (adamantyl-$C_6$), 38.54 (adamantyl-$C_8$), 37.95 (adamantyl-$C_9$), 28.41 (4-$CH_2$), 28.17 (3-$CH_2$), 24.64 (2-$CH_2$); MS (ESI): *m/z* found 518.2 [$M^+$]; calculated for $C_{27}H_{33}ClN_2O_4S$ 517.0.

*5-((4'-fluoro-[1,1'-biphenyl])-4-sulfonamido)-N-(3-hydroxyadamantan-1-yl)pentan-amide* (**18**): The compounds was synthesized as per general procedure described earlier in section 6.3.5.4 using 5-((4'-fluoro-[1,1'-biphenyl])-4-sulfonamido)pentanoic acid (**7**)

(0.52g) and 3-aminoadamantan-1-ol (**14**) (0.25g) to get compound **18** as white powder, yield 82%; mp 231-233 ºC; FTIR (KBr) $cm^{-1}$: 3161 (Ar-str.), 1674 (C=O-str.), 1164 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.21 (d, 2H, *J* = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.85 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.61 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.51 (d, 2H, $J_1$ = 10 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.32 (s, 1H, -$SO_2$NH), 5.22 (s, 1H, -NH), 3.01-2.92 (m, 3H, 1-$CH_2$, -OH), 2.31-2.20 (m, 2H, 4-$CH_2$), 2.18 (t, 2H, $J_1$, $J_2$ = 5 Hz, adamantyl-$C_6$), 2.14 (s, 2H, adamantyl-$C_2$), 1.95-1.85 (m, 6H, adamantyl-$C_4$,-$C_9$,-$C_{10}$), 1.72-1.65 (m, 4H, adamantyl-$C_5$,-$C_7$,-$C_8$), 1.55-1.53 (m, 4H, 2-$CH_2$, 3-$CH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.51 (-CONH), 158.51 (biphenyl-$C_4$), 148.61 (biphenyl-$C_{4'}$), 143.51 (biphenyl-$C_1$), 138.54 (biphenyl-$C_{1'}$), 131.36 (biphenyl-$C_3$,-$C_5$), 130.21 (biphenyl-$C_{3'}$,-$C_{5'}$), 128.61 (biphenyl-$C_2$,-$C_6$), 127.54 (biphenyl-$C_{2'}$,-$C_{6'}$), 68.25 (1-$CH_2$), 62.51 (adamantyl-$C_3$), 52.51 (adamantyl-$C_1$), 48.52 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 46.51 (adamantyl-$C_5$, -$C_7$), 42.25 (adamantyl-$C_6$), 37.41 (adamantyl-$C_8$), 37.01 (adamantyl-$C_9$), 28.51 (4-$CH_2$), 28.12 (3-$CH_2$), 24.54 (2-$CH_2$); MS (ESI): *m/z* found 500.9 [$M^+$]; calculated for $C_{27}H_{33}FN_2O_4S$ 500.2.

*6-([1,1'-biphenyl]-4-sulfonamido)-N-(3-hydroxyadamantan-1-yl)hexanamide* (**19**): It was synthesized as per general procedure described earlier in section 6.3.5.4 using 5 6-([1,1'-biphenyl]-4-sulfonamido)hexanoic acid (**9**) (0.52g) and 3-aminoadamantan-1-ol (**14**) (0.25g) to get compound **19** as white powder, yield 74%; mp 195-197 ºC; FTIR (KBr) $cm^{-1}$: 3151 (Ar-str.), 1683 (C=O-str.), 1181 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.94 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.71 (d, 2H, *J* = 10 Hz, biphenyl-$C_2$-$C_6$), 7.65 (d, 2H, *J* = 10 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.55 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.39 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, biphenyl-$C_{4'}$), 5.34 (s, 1H, -$SO_2$NH), 4.85 (s, 1H, -NH), 3.02-2.93 (m, 3H, 1-$CH_2$, -OH), 2.30-2.27 (m, 2H, 5-$CH_2$), 2.8 (t,

2H, $J_1$ = 5, $J_2$ = 10 Hz, adamantyl-$C_6$), 2.12 (s, 2H, adamantyl-$C_2$), 1.97-1.89 (m, 6H, adamantyl-$C_4$,-$C_9$,-$C_{10}$), 1.72-1.67 (m, 4H, adamantyl-$C_5$,-$C_7$,-$C_8$), 1.62-1.56 (m, 6H, 2-$CH_2$, 3-$CH_2$, 4-$CH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 173.54 (-CONH), 148.52 (biphenyl-$C_4$), 145.84 (biphenyl-$C_1$), 140.51 (biphenyl-$C_{1'}$), 129.88 (biphenyl-$C_3$,-$C_5$), 129.56 (biphenyl-$C_2$,-$C_6$), 128.16 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.51 (biphenyl-$C_{3'}$,-$C_{5'}$), 127.21 (biphenyl-$C_{4'}$) 68.51 (1-$CH_2$), 55.92 (adamantyl-$C_3$), 47.61 (adamantyl-$C_1$), 46.36 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 44.92 (adamantyl-$C_5$, -$C_7$), 43.14 (adamantyl-$C_6$), 38.56 (adamantyl-$C_8$), 37.51 (adamantyl-$C_9$), 31.25 (5-$CH_2$), 29.65 (4-$CH_2$), 28.54 (3-$CH_2$), 23.58 (2-$CH_2$); MS (ESI): *m/z* found 497.6 [$M^+$]; calculated for $C_{28}H_{36}N_2O_4S$ 496.2.

*6-((4'-fluoro-[1,1'-biphenyl])-4-sulfonamido)-N-(3-hydroxyadamantan-1-yl)hexan-amide* (**20**): It was synthesized as per general procedure described earlier in section 6.3.5.4 using 6-((4'-fluoro-[1,1'-biphenyl])-4-sulfonamido)hexanoic acid (**11**) (0.54g) and 3-aminoadamantan-1-ol (**14**) (0.25g) to get compound **20** as white powder, yield 79%; mp 189-190 ºC; FTIR (KBr) $cm^{-1}$: 3156 (Ar-str.), 1664 (C=O-str.), 1164 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.31 (d, 2H, *J* = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.87 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.64 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.56 (d, 2H, $J_1$ = 10 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.34 (s, 1H, -$SO_2$NH), 5.25 (s, 1H, -NH), 3.04-2.94 (m, 3H, 1-$CH_2$, -OH), 2.33-2.23 (m, 2H, 5-$CH_2$), 2.21 (t, 2H, $J_1$, $J_2$ = 5 Hz, adamantyl-$C_6$), 2.16 (s, 2H, adamantyl-$C_2$), 1.93-1.83 (m, 6H, adamantyl-$C_4$,-$C_9$,-$C_{10}$), 1.75-1.67 (m, 4H, adamantyl-$C_5$,-$C_7$,-$C_8$), 1.60-1.57 (m, 4H, 2-$CH_2$, 3-$CH_2$, 4-$CH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.54 (-CONH), 158.45 (biphenyl-$C_4$), 148.57 (biphenyl-$C_{4'}$), 143.56 (biphenyl-$C_1$), 138.84 (biphenyl-$C_{1'}$), 131.58 (biphenyl-$C_3$,-$C_5$), 130.58 (biphenyl-$C_{3'}$,-$C_{5'}$), 128.85 (biphenyl-$C_2$,-$C_6$), 127.45 (biphenyl-$C_{2'}$,-$C_{6'}$), 68.84 (1-

$CH_2$), 62.85 (adamantyl-$C_3$), 52.65 (adamantyl-$C_1$), 48.47 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 46.45 (adamantyl-$C_5$, -$C_7$), 42.85 (adamantyl-$C_6$), 37.65 (adamantyl-$C_8$), 37.45 (adamantyl-$C_9$), 38.41 (5-$CH_2$) , 30.25 (4-$CH_2$), 28.11 (3-$CH_2$), 24.42 (2-$CH_2$); MS (ESI): *m/z* found 515.4 [$M^+$]; calculated for $C_{27}H_{33}FN_2O_4S$ 514.2.

*6-([1,1'-biphenyl]-4-sulfonamido)-N-(adamantan-1-yl)hexanamide* (**21**): It was synthesized as per general procedure described earlier in section 6.3.5.4 using 6-([1,1'-biphenyl]-4-sulfonamido)hexanoic acid (**9**) (0.52g) and adamantan-1-amine (**13**) (0.22g) to get compound **21** as white powder, yield 76%; mp 179-181 ºC; FTIR (KBr) $cm^{-1}$: 3154 (Ar-str.), 1689 (C=O-str.), 1131 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.95 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.74 (d, 2H, *J* = 10 Hz, biphenyl-$C_2$-$C_6$), 7.63 (d, 2H, *J* = 10 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.51 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.50 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, biphenyl-$C_{4'}$), 5.12 (s, 1H, -$SO_2$NH), 4.89 (s, 1H, -NH), 3.04-3.00 (m, 2H, 1-$CH_2$), 2.19-2.06 (m, 2H, 5-$CH_2$), 2.05 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, adamantyl-$C_6$), 1.99 (s, 2H, adamantyl-$C_2$), 1.60-1.57 (m, 6H, adamantyl-$C_4$,-$C_9$,-$C_{10}$), 1.55-1.53 (m, 5H, adamantly-$C_3$,-$C_5$,-$C_7$,-$C_8$), 1.52-1.51 (m, 6H, 2-$CH_2$, 3-$CH_2$, 4-$CH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 171.93 (-CONH), 145.48 (biphenyl-$C_4$), 139.38 (biphenyl-$C_1$), 138.65 (biphenyl-$C_{1'}$), 129.06 (biphenyl-$C_3$,-$C_5$), 128.45 (biphenyl-$C_2$,-$C_6$), 127.72 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.59 (biphenyl-$C_{3'}$,-$C_{5'}$), 127.33 (biphenyl-$C_{4'}$) 51.89 (1-$CH_2$), 42.95 (adamantyl-$C_3$), 41.68 (adamantyl-$C_1$), 37.18 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 36.35 (adamantyl-$C_3$, -$C_5$, -$C_7$), 29.71 (adamantyl-$C_6$), 29.44 (adamantyl-$C_8$), 29.22 (adamantyl-$C_9$), 25.85 (5-$CH_2$), 24.71 (2, 3, 4-$CH_2$); MS (ESI): *m/z* found 481.4 [$M^+$]; calculated for $C_{28}H_{36}N_2O_3S$ 480.2.

*N-(adamantan-1-yl)-6-((4'-chloro-[1,1'-biphenyl])-4-sulfonamido)hexanamide* (**22**): This compound was also synthesized as per general procedure described earlier in

section (6.3.5.4) using 6-((4'-chloro-[1,1'-biphenyl])-4-sulfonamido)hexanoic acid (**10**) (0.57g) and adamantan-1-amine (**13**) (0.22g) to get compound **22** as white powder, yield 84%; mp 209-211 ºC; FTIR (KBr) $cm^{-1}$: 3164 (Ar-str.), 1654 (C=O-str.), 1194 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.93 (d, 2H, *J* = 10 Hz, biphenyl-$C_3$-$C_5$), 7.74 (d, 2H, *J* = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.58 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.46 (d, 2H, $J_1$ = 10 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.22 (s, 1H, -$SO_2$NH), 4.84 (s, 1H, -NH), 3.00-2.90 (m, 2H, 1-$CH_2$), 2.32-2.28 (m, 2H, 5-$CH_2$), 2.12 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, adamantyl-$C_6$), 2.15 (s, 2H, adamantyl-$C_2$), 1.98-1.83 (m, 6H, adamantyl-$C_4$,-$C_9$,-$C_{10}$), 1.70-1.65 (m, 5H, adamantly-$C_3$,-$C_5$,-$C_7$,-$C_8$), 1.60-1.55 (m, 6H, 2-$CH_2$, 3-$CH_2$, 4-$CH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.16 (-CONH), 149.51 (biphenyl-$C_4$), 146.51 (biphenyl-$C_1$), 141.54 (biphenyl-$C_{1'}$), 129.61 (biphenyl-$C_3$,-$C_5$), 129.61 (biphenyl-$C_2$,-$C_6$), 127.64 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.41 (biphenyl-$C_{3'}$,-$C_{5'}$), 127.14 (biphenyl-$C_{4'}$) 68.84 (1-$CH_2$), 53.54 (adamantyl-$C_3$), 47.44 (adamantyl-$C_1$), 46.21 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 45.10 (adamantyl-$C_3$, -$C_5$, -$C_7$), 43.58 (adamantyl-$C_6$), 37.96 (adamantyl-$C_8$), 36.81 (adamantyl-$C_9$), 29.46 (5-$CH_2$), 29.46 (4-$CH_2$), 28.94 (3-$CH_2$), 23.94 (2-$CH_2$); MS (ESI): *m/z* found 481.4 [$M^+$]; calculated for $C_{28}H_{36}N_2O_3S$ 480.2.

*5-([1,1'-biphenyl]-4-sulfonamido)-N-(3,5-dimethyladamantan-1-yl)pentanamide* (**23**): It was synthesized as per general procedure described earlier in section 6.3.5.4 using 5-([1,1'-biphenyl]-4-sulfonamido)pentanoic acid (**5**) (0.50g) and 3,5-dimethyladamantan-1-amine (**15**) (0.26g) to get compound **23** as white powder, yield 70%; mp 188-191 ºC; FTIR (KBr) $cm^{-1}$: 3115 (Ar-str.), 1691 (C=O-str.), 1164 ($SO_2$-str.); $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.93 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.72 (d, 2H, *J* = 10 Hz, biphenyl-$C_2$-$C_6$), 7.63 (d, 2H, *J* = 10 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.55 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.44 (t, 1H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_{4'}$), 5.11 (s, 1H, -

$SO_2NH$), 4.64 (s, 1H, -NH), 3.00 (q, 2H, $J_1$ = 10, $J_2$ = 5 , $J_3$ = 5 Hz, 1-$CH_2$), 2.17-2.13 (m, 2H, 4-$CH_2$), 2.09-2.08 (m, 2H, adamantyl-$C_6$), 1.85 (s, 2H, adamantyl-$C_2$), 1.69-1.62 (m, 6H, adamantyl-$CH_3$ at -$C_3$,-$C_5$), 1.60-1.58 (m, 4H, adamantly -$C_9$,-$C_{10}$), 1.42-1.29 (m, 5H, adamantyl-$C_4$,-$C_7$,-$C_8$), 1.18-1.12 (m, 4H, 2-$CH_2$, 3-$CH_2$,);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 178.12 (-CONH), 150.51 (biphenyl-$C_4$), 147.64 (biphenyl-$C_1$), 144.41 (biphenyl-$C_{1'}$), 134.81 (biphenyl-$C_3$,-$C_5$), 129.54 (biphenyl-$C_2$,-$C_6$), 129.52 (biphenyl-$C_{2'}$,-$C_{6'}$), 128.51 (biphenyl-$C_{3'}$,-$C_{5'}$), 127.95 (biphenyl-$C_{4'}$) 68.84 (1-$CH_2$), 58.85 (adamantyl-$C_3$), 48.52 (adamantyl-$C_1$), 45.54 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 45.84 (adamantyl-$C_5$, -$C_7$), 45.54 (adamantyl-$C_6$), 39.84 (adamantyl-$C_8$), 38.85 (adamantyl-$C_9$), 38.74 (adamantyl-2$CH_3$), 30.54 (4-$CH_2$), 29.85 (3-$CH_2$), 25.62 (2-$CH_2$); MS (ESI): *m/z* found 495.6 [$M^+$]; calculated for $C_{29}H_{38}N_2O_3S$ 494.2.

*6-([1,1'-biphenyl]-4-sulfonamido)-N-(3,5-dimethyladamantan-1-yl)hexanamide* (**24**): This was synthesized as per general procedure described earlier in section 6.3.5.4 using 6-([1,1'-biphenyl]-4-sulfonamido)hexanoic acid (**9**) (0.52g) and 3,5-dimethyladamantan-1-amine (**15**) (0.26g) to get compound **24** as white powder, yield 75%; mp 197-198 ºC; FTIR (KBr) $cm^{-1}$: 3128 (Ar-str.), 1748 (C=O-str.), 1145 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.95 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.75 (d, 2H, *J* = 10 Hz, biphenyl-$C_2$-$C_6$), 7.64 (d, 2H, *J* = 10 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.52 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.46 (t, 1H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_{4'}$), 5.12 (s, 1H, -$SO_2NH$), 4.67 (s, 1H, -NH), 3.05 (q, 2H, $J_1$ = 10, $J_2$ = 5 , $J_3$ = 5 Hz, 1-$CH_2$), 2.16-2.13 (m, 2H, 5-$CH_2$), 2.07-2.05 (m, 2H, adamantyl-$C_6$), 1.83 (s, 2H, adamantyl-$C_2$), 1.67-1.60 (m, 6H, adamantyl-$CH_3$, -$C_3$,-$C_5$), 1.59-1.51 (m, 4H, adamantly -$C_9$,-$C_{10}$), 1.40-1.28 (m, 7H, adamantyl-$C_4$,-$C_5$,-$C_8$, 4-$CH_2$), 1.19-1.13 (m, 4H, 2-$CH_2$, 3-$CH_2$,); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 173.74 (-CONH), 149.58 (biphenyl-$C_4$),

147.15 (biphenyl-$C_1$), 144.24 (biphenyl-$C_{1'}$), 130.51 (biphenyl-$C_3$,-$C_5$), 129.58 (biphenyl-$C_2$,-$C_6$), 128.81 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.74 (biphenyl-$C_{3'}$,-$C_{5'}$), 127.74 (biphenyl-$C_{4'}$) 68.74 (1-$CH_2$), 58.46 (adamantyl-$C_3$), 47.81 (adamantyl-$C_1$), 45.94 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 45.51 (adamantyl-$C_5$, -$C_7$), 44.62 (adamantyl-$C_6$), 39.51 (adamantyl-$C_8$), 37.51 (adamantyl-$C_9$), 38.52 (adamantyl-2$CH_3$), 30.41 (4-$CH_2$, 5-$CH_2$), 29.51 (3-$CH_2$), 24.52 (2-$CH_2$); MS (ESI): *m/z* found 509.1 [$M^+$]; calculated for $C_{30}H_{40}N_2O_3S$ 508.2.

*5-((4'-chloro-[1,1'-biphenyl])-4-sulfonamido)-N-(3,5-dimethyladamantan-1-yl)pentan-amide* (**25**): It was synthesized as per general procedure described earlier in section 6.3.5.4 using 5-((4'-chloro-[1,1'-biphenyl])-4-sulfonamido)pentanoic acid (**6**) (0.55g) and 3,5-dimethyladamantan-1-amine (**15**) (0.26g) to get compound **25** as white powder, yield 75%; mp 168-170 ºC; FTIR (KBr) $cm^{-1}$: 3151 (Ar-str.), 1684 (C=O-str.), 1194 ($SO_2$-str.); $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.98 (d, 2H, *J* = 10 Hz, biphenyl-$C_3$-$C_5$), 7.78 (d, 2H, *J* = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.56 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.47 (d, 2H, $J_1$ = 10 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.14 (s, 1H, -$SO_2$NH), 4.68 (s, 1H, -NH), 3.14 (q, 2H, $J_1$ = 10, $J_2$ = 5 , $J_3$ = 5 Hz, 1-$CH_2$), 2.19-2.15 (m, 2H, 4-$CH_2$), 2.07-2.05 (m, 2H, adamantyl-$C_6$), 1.87 (s, 2H, adamantyl-$C_2$), 1.67-1.61 (m, 6H, adamantyl-$CH_3$, -$C_3$,-$C_5$), 1.61-1.57 (m, 4H, adamantly -$C_9$,-$C_{10}$), 1.43-1.31 (m, 4H, adamantyl-$C_4$,-$C_8$), 1.17-1.14 (m, 4H, 2-$CH_2$, 3-$CH_2$,);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 178.45 (-CONH), 150.45 (biphenyl-$C_4$), 147.15 (biphenyl-$C_1$), 144.56 (biphenyl-$C_{1'}$), 134.94 (biphenyl-$C_3$,-$C_5$), 129.94 (biphenyl-$C_2$,-$C_6$), 129.51 (biphenyl-$C_{2'}$,-$C_{6'}$), 128.65 (biphenyl-$C_{3'}$,-$C_{5'}$), 127.51 (biphenyl-$C_{4'}$) 68.58 (1-$CH_2$), 58.61 (adamantyl-$C_3$), 48.94 (adamantyl-$C_1$), 45.54 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 44.14 (adamantyl-$C_5$, -$C_7$), 44.10 (adamantyl-$C_6$), 39.56 (adamantyl-$C_8$), 38.64 (adamantyl-$C_9$), 37.61 (adamantyl-2$CH_3$), 31.65 (4-$CH_2$),

29.15 (3-$CH_2$), 26.56 (2-$CH_2$); MS (ESI): *m/z* found 529.2 [$M^+$]; calculated for $C_{29}H_{37}ClN_2O_3S$ 528.2.

*6-((4'-chloro-[1,1'-biphenyl])-4-sulfonamido)-N-(3,5-dimethyladamantan-1-yl)hexan-amide* (**26**): It was synthesized as per general procedure described earlier in section 6.3.5.4 using 6-((4'-chloro-[1,1'-biphenyl])-4-sulfonamido)hexanoic acid (**10**) (0.57g) and 3,5-dimethyladamantan-1-amine (**15**) (0.26g) to get compound **26** as white powder, yield 79%; mp 168-170 ºC; FTIR (KBr) $cm^{-1}$: 3164 (Ar-str.), 1725 (C=O-str.), 1164 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.98 (d, 2H, *J* = 10 Hz, biphenyl-$C_3$-$C_5$), 7.76 (d, 2H, *J* = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.55 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.49 (d, 2H, $J_1$ = 10 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 4.95 (s, 1H, -$SO_2$NH), 4.52 (s, 1H, -NH), 3.12 (q, 2H, $J_1$ = 10, $J_2$ = 5 , $J_3$ = 5 Hz, 1-$CH_2$), 2.18-2.15 (m, 2H, 5-$CH_2$), 2.10-2.08 (m, 2H, adamantyl-$C_6$), 1.88 (s, 2H, adamantyl-$C_2$), 1.68-1.63 (m, 6H, adamantyl-$CH_3$, -$C_3$,-$C_5$), 1.60-1.55 (m, 4H, adamantly -$C_9$,-$C_{10}$), 1.37-1.25 (m, 7H, adamantyl-$C_4$,-$C_5$,-$C_8$, 4-$CH_2$), 1.20-1.15 (m, 4H, 2-$CH_2$, 3-$CH_2$,);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 175.45 (-CONH), 150.21 (biphenyl-$C_4$), 148.25 (biphenyl-$C_1$), 144.64 (biphenyl-$C_{1'}$), 130.94 (biphenyl-$C_3$,-$C_5$), 129.64 (biphenyl-$C_2$,-$C_6$), 128.94 (biphenyl-$C_{2'}$,-$C_{6'}$), 128.05 (biphenyl-$C_{3'}$,-$C_{5'}$), 127.61 (biphenyl-$C_{4'}$) 68.81 (1-$CH_2$), 58.25 (adamantyl-$C_3$), 47.98 (adamantyl-$C_1$), 45.85 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 45.94 (adamantyl-$C_5$, -$C_7$), 44.94 (adamantyl-$C_6$), 39.62 (adamantyl-$C_8$), 37.81 (adamantyl-$C_9$), 38.81 (adamantyl-2$CH_3$), 30.84 (4-$CH_2$, 5-$CH_2$), 29.41 (3-$CH_2$), 24.51 (2-$CH_2$); MS (ESI): *m/z* found 543.1 [$M^+$]; calculated for $C_{30}H_{39}ClN_2O_3S$ 542.2.

*N-(adamantan-1-yl)-5-((4'-methyl-[1,1'-biphenyl])-4-sulfonamido)pentanamide* (**27**): The compound was synthesized as per general procedure described earlier in section 6.3.5.4 using 5-((4'-methyl-[1,1'-biphenyl])-4-sulfonamido)pentanoic acid (**8**) (0.52g)

and adamantan-1-amine (**13**) (0.22g) to get compound **27** as white powder, yield 68%; mp 164-166 ºC; FTIR (KBr) $cm^{-1}$: 3125 (Ar-str.), 1656 (C=O-str.), 1156 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.81 (d, 2H, *J* = 10 Hz, biphenyl-$C_3$-$C_5$), 7.65 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.42 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.32 (d, 2H, $J_1$ = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 4.84 (s, 1H, -$SO_2$NH), 3.72 (s, 1H, -NH), 3.05-2.97 (m, 2H, 1-$CH_2$), 2.25 (s, 3H, biphenyl-$CH_3$, $C_{4'}$), 2.30-2.25 (m, 2H, 4-$CH_2$), 2.18 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, adamantyl-$C_6$), 2.13 (s, 2H, adamantyl-$C_2$), 1.96-1.80 (m, 6H, adamantyl-$C_4$,-$C_9$,-$C_{10}$), 1.74-1.68 (m, 5H, adamantly-$C_3$,-$C_5$,-$C_7$,-$C_8$), 1.62-1.57 (m, 6H, 2-$CH_2$, 3-$CH_2$, 4-$CH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 167.45 (-CONH), 149.51 (biphenyl-$C_4$), 146.51 (biphenyl-$C_1$), 141.54 (biphenyl-$C_{1'}$), 129.61 (biphenyl-$C_3$,-$C_5$), 129.61 (biphenyl-$C_2$,-$C_6$), 127.64 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.41 (biphenyl-$C_{3'}$,-$C_{5'}$), 127.14 (biphenyl-$C_{4'}$) 68.84 (1-$CH_2$), 53.54 (adamantyl-$C_3$), 47.44 (adamantyl-$C_1$), 46.21 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 45.10 (adamantyl-$C_3$, -$C_5$, -$C_7$), 43.58 (adamantyl-$C_6$), 37.96 (adamantyl-$C_8$), 36.81 (adamantyl-$C_9$), 29.46 (4-$CH_2$), 28.94 (3-$CH_2$), 23.94 (2-$CH_2$); MS (ESI): *m/z* found 481.6 [$M^+$]; calculated for $C_{28}H_{36}N_2O_3S$ 480.2.

**6.3.5.5 General procedure for the synthesis of propargyl derivatives of amino acids (28-29):** 6-aminocaproic acid/5-aminovaleric acid (0.0143 mol, 1 equivalent) was dissolved in dry DMSO containing dry potassium carbonate (0.0715 mol 5 equivalent) in Nitrogen environment. Propargyl bromide (0.0429 mol 3 equivalent) was added to the reaction mixture and refluxed for 6 h. The reaction was monitored by TLC using ethylacetate and methanol (8:3) as mobile phase. The products were extracted from water by ethylacetate and used for second step.

**6.3.5.6 General procedure for the synthesis of propargyl derivatives of biphenyl sulfonamides (30-37):** Aromatic biphenyl sulfonylchlorides (**1-4**) (0.0143 mol, 1

equivalent) were dissolved in the acetone (2 ml). The mixture was added to water (2 ml) containing 6-(prop-2-yn-1-ylamino)hexanoic acid/ 6-(prop-2-yn-1-ylamino)hexanoic acid (0.0143 mol, 1 equivalent) and potassium carbonate (0.0429 mol, 3 equivalent). The final reaction mixture was stirred at room temperature (rt) for 24 h. The reaction was monitored by TLC using ethylacetate and methanol (8:2) as the mobile phase. The acetone was evaporated under reduced pressure and reaction mixture was neutralized with 1N HCl to get the product. The product was filtered and recrystallized with methanol to get the pure compounds.

**6.3.5.7 General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles (46-53):** To a mixture of compounds **30**-**37** (0.5 mmol, 1 equiv) and $Et_3N$ (2 equiv, 134 mL, 1 mmol) in water butanol mixture (2:1) (10 mL) was added with copper metal (5 mg, 0.025 mmol, 5 mol%). The suitable phenylazide **42-45** (1 mmol, 2 equiv) derivatives were added to the reaction mixture. The reaction mixture was stirred at room temprature for 6-8 h. The reaction was monitored by TLC using hexane and ethylacetate (6:4) as the mobile phase. The products were purified by column chromatography (cyclohexane/EtOAc 7:3).

**6.3.5.8 General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles analogues of adamantyl (54-73):** 1,2,3-triazoles analogues (1.5mM, 1 equivalent) (**46-53**) were dissolved in dry DMSO containing substituted adamantly amine analogues (1.5 mM, 1 equivalent) (**13-15**), N,N-Diisopropylethylamine (DIPEA) (4 mM, 2.5 equivalent), N′-ethylcarbodi-imide hydrochloride (EDC.HCl) (2.5 mM, 1.5 equivalent) and hydroxybenzotriazole (HOBt) (2.55 mM, 1.5 equivalent). The reaction mixture was heated up to 120 ºC for 8 h, followed by workup with water ethyl acetate system. The

organic layer was evaporated and product was purified by column chromatography using ethylacetate and hexane (2:3) as mobile phase.

*N-(adamantan-1-yl)-5-(N-((1-(4-chlorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonamido)pentanamide* (**54**): It was synthesized as per general procedure described earlier in section 6.3.5.8 using 5-(N-((1-(4-chlorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonami-do)pentanoic acid (**46**) (0.78g) and adamantan-1-amine (**13**) (0.22g) to get compound **54** as yellowish powder, yield 49%; mp 155-157 ºC; FTIR (KBr) $cm^{-1}$: 3214 (Ar-str.), 1690 (C=O-str.), 1165 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.11 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.84 (d, 2H, *J* = 10 Hz, -chlorophenyl -$C_3$-$C_5$), 7.60 (d, 2H, *J* = 10 Hz, chlorophenyl -$C_2$-$C_6$), 7.43 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.36 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, biphenyl-$C_{4'}$), 7.22 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.05 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.48 (s, 1H, triazol-$N_2$), 4.84 (s, 1H, triazol-$C_5$), 3.93 (s, 2H, triazolyl methyl-$CH_2$), 3.90 (s, 1H, CONH), 3.33 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 2.35 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 4-$CH_2$), 2.13 (s, 1H, triazol-$N_3$), 2.02-1.98 (m, 9H, adamantyl-$C_2$,-$C_3$, -$C_5$, -$C_7$,-$C_8$,- $C_9$), 1.72-1.67 (m, 6H, adamantyl-$C_4$,-$C_6$, -$C_{10}$), 1.65-1.60 (m, 2H, 3-$CH_2$), 1.58-1.54 (m, 2H, 2-$CH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.25 (-CONH), 149.54 (biphenyl-$C_4$), 149.31 (-chlorophenyl-$C_4$), 148.79 (-chlorophenyl-$C_1$), 148.24 (-chlorophenyl-$C_3$,-$C_5$), 147.52 (-chlorophenyl-$C_2$,-$C_6$),146.81 (biphenyl-$C_1$), 144.14 (biphenyl-$C_{1'}$), 132.48 (biphenyl-$C_3$,-$C_5$), 130.52 (biphenyl-$C_2$,-$C_6$), 128.45 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.62 (biphenyl-$C_{3'}$,-$C_{5'}$), 125.54 (biphenyl-$C_{4'}$) 98.57 (triazol-$C_5$), 93.07 (triazol-$C_1$), 70.25 (triazolyl methyl-C), 68.45 (1-$CH_2$), 51.64 (adamantyl-$C_1$), 46.51 (adamantyl-$C_3$), 45.12 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.14 (adamantyl-$C_5$, -$C_7$), 41.26 (adamantyl-$C_6$), 36.52 (adamantyl-$C_8$), 35.74

(adamantyl-$C_9$), 28.54 (4-$CH_2$), 27.25 (3-$CH_2$), 24.54 (2-$CH_2$); MS (ESI): *m/z* found 659.9 [$M^+$]; calculated for $C_{36}H_{42}ClN_5O_3S$ 659.2.

*N-(adamantan-1-yl)-5-((4'-chloro-N-((1-phenyl-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)pentanamide* (**55**): This was synthesized as per general procedure described earlier in section 6.3.5.8 using 5-((4'-chloro-N-((1-phenyl-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)pentanoic acid (**47**) (0.78g) and adamantan-1-amine (**13**) (0.22g) to get compound **55** as buff yellowish powder, yield 52%; mp 165-166 ºC; FTIR (KBr) $cm^{-1}$: 3212 (Ar-str.), 1664 (C=O-str.), 1164 ($SO_2$-str.); $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.10 (d, 2H, *J* = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.83 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.54 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.45 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.17 (d, 2H, *J* = 10 Hz, -phenyl –$C_2$-$C_6$), 7.03 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, phenyl –$C_3$-$C_5$), 6.83 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, phenyl-$C_4$), 5.00 (s, 1H, triazol-$N_2$), 4.27 (s, 1H, triazol-$C_5$), 4.02 (s, 2H, triazolyl methyl-$CH_2$), 3.77 (s, 1H, CONH), 3.24 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 3.14 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 4-$CH_2$), 2.28 (s, 1H, triazol-$N_3$), 2.04-1.96 (m, 9H, adamantyl-$C_2$,-$C_3$, -$C_5$, -$C_7$,-$C_8$,- $C_9$), 1.72-1.71 (m, 6H, adamantyl-$C_4$,-$C_6$,-$C_{10}$), 1.71-1.53 (m, 2H, 3-$CH_2$), 1.53-1.52 (m, 2H, 2-$CH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 173.48 (-CONH), 147.65 (biphenyl-$C_{4'}$), 144.81 (biphenyl-$C_4$), 137.08 (phenyl-$C_1$), 130.63 (phenyl-$C_2$,-$C_6$), 130.19 (phenyl-$C_3$,-$C_5$), 130.18 (biphenyl-$C_1$), 128.10 (biphenyl-$C_{1'}$), 128.19 (phenyl-$C_4$), 119.29 (biphenyl-$C_3$,-$C_5$), 119.28 (biphenyl-$C_{3'}$,-$C_{5'}$), 107.75 (biphenyl-$C_{2'}$,-$C_{6'}$, biphenyl-$C_2$,-$C_6$), 91.27 (triazol-$C_1$), 52.57 (triazol-$C_5$), 49.65 (triazolyl methyl-C), 43.69 (1-$CH_2$), 43.68 (adamantyl-$C_1$), 40.47 (adamantyl-$C_3$), 37.96 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 37.76 (adamantyl-$C_5$,-$C_7$), 37.75 (adamantyl-$C_6$),

28.07 (adamantyl-$C_8$), 27.90 (adamantyl-$C_9$), 27.89 (4-$CH_2$), 24.08 (2, 3-$CH_2$); MS (ESI): *m/z* found 660.2 [$M^+$]; calculated for $C_{36}H_{42}ClN_5O_3S$ 659.2.

*N-(adamantan-1-yl)-5-((4'-fluoro-N-((1-(p-tolyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)pentanamide* (**56**): It was synthesized as per general procedure described earlier in section 6.3.5.8 using 5-((4'-fluoro-N-((1-(p-tolyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)pentanoic acid (**48**) (0.78g) and adamantan-1-amine (**13**) (0.22g) to get compound **56** as buff yellowish powder, yield 60%; mp 170-171 ºC; FTIR (KBr) $cm^{-1}$: 3264 (Ar-str.), 1663 (C=O-str.), 1165 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.30 (d, 2H, *J* = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.89 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.70 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.55 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.48 (d, 2H, *J* = 10 Hz, -phenyl -$C_2$-$C_6$), 7.34 (d, 2H, $J_1$ = 10 Hz, phenyl-$C_3$-$C_5$), 5.44 (s, 1H, triazol-$N_2$), 4.75 (s, 1H, triazol-$C_5$), 3.94 (s, 2H, triazolyl methyl-$CH_2$), 3.83 (s, 1H, CONH), 3.36 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 2.28 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 4-$CH_2$), 2.20 (s, 3H, phenyl-$CH_3$), 2.16 (s, 1H, triazol-$N_3$), 2.02-1.99 (m, 9H, adamantyl-$C_2$,-$C_3$, -$C_5$, -$C_7$,-$C_8$,- $C_9$), 1.73-1.45 (m, 6H, adamantyl-$C_4$,-$C_6$,-$C_{10}$), 1.65-1.60 (m, 2H, 3-$CH_2$), 1.55-1.51 (m, 2H, 2-$CH_2$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 175.13 (-CONH), 150.64 (biphenyl-$C_{4'}$), 148.64 (biphenyl-$C_4$), 146.21(phenyl-$C_1$), 145.21 (phenyl-$C_2$,-$C_6$), 146.85 (phenyl-$C_3$,-$C_5$), 146.32 (biphenyl-$C_1$), 144.32 (biphenyl-$C_{1'}$), 143.51 (phenyl-$C_4$), 132.62 (biphenyl-$C_3$,-$C_5$), 131.24 (biphenyl-$C_{3'}$,-$C_{5'}$), 129.64 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.62 (biphenyl-$C_2$,-$C_6$), 98.52 (triazol-$C_5$), 92.57 (triazol-$C_1$), 70.64 (triazolyl methyl-C), 67.25 (1-$CH_2$), 52.61 (adamantyl-$C_1$), 47.64 (adamantyl-$C_3$), 45.94 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.35 (adamantyl-$C_5$,-$C_7$), 42.54 (adamantyl-$C_6$), 36.64 (adamantyl-$C_8$), 35.64

(adamantyl-$C_9$), 31.21 (-$CH_3$), 28.94 (4-$CH_2$), 26.61 (3-$CH_2$), 24.64 (2-$CH_2$); MS (ESI): *m/z* found 658.3 [$M^+$]; calculated for $C_{37}H_{44}FN_5O_3S$ 657.3.

*N-(adamantan-1-yl)-5-((N-((1-(4-fluorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-4'-methyl-[1,1'-biphenyl])-4-sulfonamido)pentanamide* (**57**): The compound was synthesized as per general procedure described earlier in section 6.3.5.8 using 5-((N-((1-(4-fluorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-4'-methyl-[1,1'-biphenyl])-4-sulfonamido)pentanoic acid (**49**) (0.78g) and adamantan-1-amine (**13**) (0.22g). The compound **57** was obtained as white powder, yield 56%; mp 145-147 ºC; FTIR (KBr) $cm^{-1}$: 3215 (Ar-str.), 1694 (C=O-str.), 1164 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.07 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.91 (d, 2H, *J* = 10 Hz, phenyl-$C_3$,-$C_5$), 7.64 (d, 2H, *J* = 10 Hz, phenyl -$C_2$-$C_6$), 7.37 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_2$-$C_6$), 7.18 (d, 2H, *J* = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.00 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.21 (s, 1H, triazol-$N_2$), 4.82 (s, 1H, triazol-$C_5$), 3.91 (s, 2H, triazolyl methyl-$CH_2$), 3.84 (s, 1H, CONH), 3.38 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 2.32 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 4-$CH_2$), 2.21 (s, 3H, $CH_3$), 2.05-2.00 (m, 9H, adamantyl-$C_2$,-$C_3$, -$C_5$, -$C_7$,-$C_8$,- $C_9$), 1.73-1.46 (m, 6H, adamantyl-$C_4$,-$C_6$, -$C_{10}$), 1.71-1.67 (m, 2H, 3-$CH_2$), 1.59-1.55 (m, 2H, 2-$CH_2$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 175.64 (-CONH), 149.57 (biphenyl-$C_4$), 149.35 (phenyl-$C_4$), 148.74 (phenyl-$C_1$), 148.54 (phenyl-$C_3$,-$C_5$), 147.54 (phenyl-$C_2$,-$C_6$), 146.54 (biphenyl-$C_1$), 144.54 (biphenyl-$C_{1'}$), 132.15 (biphenyl-$C_3$,-$C_5$), 130.65 (biphenyl-$C_2$,-$C_6$), 128.56 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.54 (biphenyl-$C_{3'}$,-$C_{5'}$), 125.48 (biphenyl-$C_{4'}$) 98.56 (triazol-$C_5$), 87.28 (triazol-$C_1$), 70.56 (triazolyl methyl-C), 68.16 (1-$CH_2$), 64.14 (-$CH_3$), 51.84 (adamantyl-$C_1$), 46.64 (adamantyl-$C_3$), 45.64 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.54 (adamantyl-$C_5$, -$C_7$), 41.94 (adamantyl-$C_6$), 36.61

(adamantyl-$C_8$), 35.64 (adamantyl-$C_9$), 28.54 (4-$CH_2$), 27.64 (3-$CH_2$), 24.64 (2-$CH_2$); MS (ESI): *m/z* found 658.3 [$M^+$]; calculated for $C_{37}H_{44}FN_5O_3S$ 657.3.

*N-(adamantan-1-yl)-6-(N-((1-(4-chlorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonamido)hexanamide* (**58**)**:** It was synthesized as per general procedure described earlier in section 6.3.5.8 using 6-(N-((1-(4-chlorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonamido)hexanoic acid (**50**) (0.78g) and adamantan-1-amine (**13**) (0.22g) to get compound **58** as buff powder, yield 60%; mp 158-160 ºC; FTIR (KBr) $cm^{-1}$: 3264 (Ar-str.), 1714 (C=O-str.), 1164 ($SO_2$-str.); $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.10 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.85 (d, 2H, *J* = 10 Hz, phenyl -$C_3$-$C_5$), 7.62 (d, 2H, *J* = 10 Hz, phenyl -$C_2$-$C_6$), 7.44 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.36 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, biphenyl-$C_{4'}$), 7.23 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.04 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.47 (s, 1H, triazol-$N_2$), 4.86 (s, 1H, triazol-$C_5$), 3.96 (s, 2H, triazolyl methyl-$CH_2$), 3.92 (s, 1H, CONH), 3.36 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 2.36 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 5-$CH_2$), 2.00-1.97 (m, 9H, adamantyl-$C_2$,-$C_3$, -$C_5$, -$C_7$,-$C_8$,- $C_9$), 1.71-1.65 (m, 6H, adamantyl-$C_4$,-$C_6$, -$C_{10}$), 1.63-1.56 (m, 2H, 4-$CH_2$, 3-$CH_2$), 1.52-1.46 (m, 2H, 2-$CH_2$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.28 (-CONH), 149.56 (biphenyl-$C_4$), 149.36 (phenyl-$C_4$), 148.64 (phenyl-$C_1$), 148.26 (phenyl-$C_3$,-$C_5$), 147.56 (phenyl-$C_2$,-$C_6$), 146.86 (biphenyl-$C_1$), 144.19 (biphenyl-$C_{1'}$), 132.47 (biphenyl-$C_3$,-$C_5$), 130.53 (biphenyl-$C_2$,-$C_6$), 129.64 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.64 (biphenyl-$C_{3'}$,-$C_{5'}$), 126.64 (biphenyl-$C_{4'}$) 98.64 (triazol-$C_5$), 90.41 (triazol-$C_1$), 70.64 (triazolyl methyl-C), 68.64 (1-$CH_2$), 51.66 (adamantyl-$C_1$), 46.54 (adamantyl-$C_3$), 45.31 (adamantyl-$C_2$, -$C_4$,-$C_{10}$), 43.16 (adamantyl-$C_5$, -$C_7$), 41.24 (adamantyl-$C_6$), 36.56 (adamantyl-$C_8$), 35.78

(adamantyl-$C_9$), 28.64 (5-$CH_2$), 27.64 (3-$CH_2$, 4-$CH_2$), 24.54 (2-$CH_2$); MS (ESI): *m/z* found 674.6 [$M^+$]; calculated for $C_{37}H_{44}ClN_5O_3S$ 673.2.

*N-(adamantan-1-yl)-6-((4'-chloro-N-((1-phenyl-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)hexanamide* (**59**): It was synthesized as per general procedure described earlier in section 6.3.5.8 using 6-((4'-chloro-N-((1-phenyl-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)hexanoic acid (**51**) (0.78g) and adamantan-1-amine (**13**) (0.22g) to get compound **59** as buff yellowish powder, yield 54%; mp 158-160 ºC; FTIR (KBr) $cm^{-1}$: 3221 (Ar-str.), 1615 (C=O-str.), 1125 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.18 (d, 2H, *J* = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.86 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.60 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.56 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.41 (d, 2H, *J* = 10 Hz, -phenyl -$C_2$-$C_6$), 7.39 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, phenyl -$C_3$-$C_5$), 7.28 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, phenyl-$C_4$), 5.45 (s, 1H, triazol-$N_2$), 4.73 (s, 1H, triazol-$C_5$), 3.92 (s, 2H, triazolyl methyl-$CH_2$), 3.86 (s, 1H, CONH), 3.31 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 2.28 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 5-$CH_2$), 2.20 (s, 1H, triazol-$N_3$), 2.02-1.97 (m, 9H, adamantyl-$C_2$,-$C_3$, -$C_5$, -$C_7$,-$C_8$,- $C_9$), 1.69-1.65 (m, 6H, adamantyl-$C_4$,-$C_6$,-$C_{10}$), 1.60-1.58 (m, 2H, 4-$CH_2$, 3-$CH_2$), 1.53-1.50 (m, 2H, 2-$CH_2$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.45 (-CONH), 149.64 (biphenyl-$C_{4'}$), 148.84 (biphenyl-$C_4$), 147.61 (phenyl-$C_1$), 147.15 (phenyl-$C_2$,-$C_6$), 146.91 (phenyl-$C_3$,-$C_5$), 146.15 (biphenyl-$C_1$), 144.64 (biphenyl-$C_{1'}$), 144.48 (phenyl-$C_4$), 132.45 (biphenyl-$C_3$,-$C_5$), 131.48 (biphenyl-$C_{3'}$,-$C_{5'}$), 129.42 (biphenyl-$C_{2'}$,-$C_{6'}$), 128.14 (biphenyl-$C_2$,-$C_6$), 98.48 (triazol-$C_5$), 90.24 (triazol-$C_1$), 71.16 (triazolyl methyl-C), 68.45 (1-$CH_2$), 52.56 (adamantyl-$C_1$), 46.45 (adamantyl-$C_3$), 45.64 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.84 (adamantyl-$C_5$,-$C_7$), 41.94 (adamantyl-$C_6$), 36.47 (adamantyl-$C_8$),

34.87 (adamantyl-$C_9$), 28.68 (5-$CH_2$), 27.48 (4-$CH_2$, 3-$CH_2$), 26.45 (2-$CH_2$); MS (ESI): *m/z* found 674.3 [$M^+$]; calculated for $C_{37}H_{44}ClN_5O_3S$ 673.2.

*N-(adamantan-1-yl)-6-((4'-fluoro-N-((1-(p-tolyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)hexanamide* (**60**): It was synthesized as per general procedure described earlier in section 6.3.5.8 using 6-((4'-fluoro-N-((1-(p-tolyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)hexanoic acid (**52**) (0.78g) and adamantan-1-amine (**13**) (0.22g) to obtain compound **60** as buff powder, yield 64%; mp 180-178 ºC; FTIR (KBr) $cm^{-1}$: 3254 (Ar-str.), 1684 (C=O-str.), 1194 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.22 (d, 2H, *J* = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.76 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.72 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.58 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.51 (d, 2H, *J* = 10 Hz, -phenyl -$C_2$-$C_6$), 7.28 (d, 2H, $J_1$ = 10 Hz, phenyl-$C_3$-$C_5$), 5.48 (s, 1H, triazol-$N_2$), 4.74 (s, 1H, triazol-$C_5$), 3.96 (s, 2H, triazolyl methyl-$CH_2$), 3.75 (s, 1H, CONH), 3.34 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 2.31 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 5-$CH_2$), 2.24 (s, 3H, phenyl-$CH_3$), 2.15 (s, 1H, triazol-$N_3$), 2.00-1.97 (m, 9H, adamantyl-$C_2$,-$C_3$, -$C_5$, -$C_7$,-$C_8$,- $C_9$), 1.71-1.42 (m, 6H, adamantyl-$C_4$,-$C_6$,-$C_{10}$), 1.64-1.58 (m, 4H, 4-$CH_2$, 3-$CH_2$), 1.56-1.53 (m, 2H, 2-$CH_2$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 176.15 (-CONH), 152.45 (biphenyl-$C_{4'}$), 147.45 (biphenyl-$C_4$), 146.23 (phenyl-$C_1$), 145.45 (phenyl-$C_2$,-$C_6$), 146.57 (phenyl-$C_3$,-$C_5$), 146.42 (biphenyl-$C_1$), 144.51 (biphenyl-$C_{1'}$), 143.74 (phenyl-$C_4$), 132.74 (biphenyl-$C_3$,-$C_5$), 131.31 (biphenyl-$C_{3'}$,-$C_{5'}$), 129.65 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.69 (biphenyl-$C_2$,-$C_6$), 98.54 (triazol-$C_5$), 93.18 (triazol-$C_1$), 70.45 (triazolyl methyl-C), 67.54 (1-$CH_2$), 52.65 (adamantyl-$C_1$), 47.45 (adamantyl-$C_3$), 45.84 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.54 (adamantyl-$C_5$,-$C_7$), 42.58 (adamantyl-$C_6$), 36.65 (adamantyl-$C_8$),

35.45 (adamantyl-$C_9$), 31.45 (-$CH_3$), 29.84 (5-$CH_2$), 26.54 (4-$CH_2$, 3-$CH_2$), 25.54 (2-$CH_2$); MS (ESI): *m/z* found 672.3 [$M^+$]; calculated for $C_{38}H_{46}FN_5O_3S$ 671.3

*N-(adamantan-1-yl)-6-((N-((1-(4-fluorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-4'-methyl-[1,1'-biphenyl])-4-sulfonamido)hexanamide* (**61**): It was synthesized as per general procedure described earlier in section 6.3.5.8 using 6-((N-((1-(4-fluorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-4'-methyl-[1,1'-biphenyl])-4-sulfonamido)hexanoic acid (**53**) (0.78g) and adamantan-1-amine (**13**) (0.22g) to get compound **61** as white powder, yield 64%; mp 159-161 ºC; FTIR (KBr) $cm^{-1}$: 3264 (Ar-str.), 1645 (C=O-str.), 1194 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.10 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.96 (d, 2H, *J* = 10 Hz, phenyl-$C_3$,-$C_5$), 7.69 (d, 2H, *J* = 10 Hz, phenyl -$C_2$-$C_6$), 7.38 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_2$-$C_6$), 7.16 (d, 2H, *J* = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.05 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.24 (s, 1H, triazol-$N_2$), 4.86 (s, 1H, triazol-$C_5$), 3.87 (s, 2H, triazolyl methyl-$CH_2$), 3.75 (s, 1H, CONH), 3.36 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 2.31 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 5-$CH_2$), 2.29 (s, 3H, $CH_3$), 2.16 (s, 1H, triazol-$N_3$), 2.09-2.03 (m, 9H, adamantyl-$C_2$,-$C_3$, -$C_5$, -$C_7$,-$C_8$,-$C_9$), 1.71-1.64 (m, 6H, adamantyl-$C_4$,-$C_6$, -$C_{10}$), 1.58-1.54 (m, 4H, 4-$CH_2$, 3-$CH_2$), 1.52-1.50 (m, 2H, 2-$CH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.94 (-CONH), 149.61 (biphenyl-$C_4$), 149.25 (phenyl-$C_4$), 148.75 (phenyl-$C_1$), 148.25 (phenyl-$C_3$,-$C_5$), 147.32 (phenyl-$C_2$,-$C_6$), 146.61 (biphenyl-$C_1$), 144.69 (biphenyl-$C_{1'}$), 132.65 (biphenyl-$C_3$,-$C_5$), 130.94 (biphenyl-$C_2$,-$C_6$), 128.91 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.71 (biphenyl-$C_{3'}$,-$C_{5'}$), 125.35 (biphenyl-$C_{4'}$) 98.85 (triazol-$C_5$), 90.48 (triazol-$C_1$), 70.84 (triazolyl methyl-C), 68.68 (1-$CH_2$), 64.51 (-$CH_3$), 51.54 (adamantyl-$C_1$), 46.51 (adamantyl-$C_3$), 45.81 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.51 (adamantyl-$C_5$, -$C_7$), 41.94 (adamantyl-$C_6$), 36.74

(adamantyl-$C_8$), 35.59 (adamantyl-$C_9$), 28.64 (5-$CH_2$), 28.14 (4-$CH_2$, 3-$CH_2$), 24.84 (2-$CH_2$); MS (ESI): *m/z* found 672.3 [$M^+$]; calculated for $C_{38}H_{46}FN_5O_3S$ 671.3.

*5-(N-((1-(4-chlorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonamido)-N-(3-hydroxyadamantan-1-yl)pentanamide* (**62):** It was synthesized as per general procedure described earlier in section 6.3.5.8 using 5-(N-((1-(4-chlorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonamido)pentanoic acid (**46**) (0.78g) and 3-aminoadamantan-1-ol (**14**) (0.22g) to get compound **62** as yellowish powder, yield 51%; mp 182-184 ºC; FTIR (KBr) $cm^{-1}$: 3215 (Ar-str.), 1664 (C=O-str.), 1146 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.08 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.74 (d, 2H, *J* = 10 Hz, -chlorophenyl -$C_3$-$C_5$), 7.65 (d, 2H, *J* = 10 Hz, chlorophenyl -$C_2$-$C_6$), 7.48 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.37 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, biphenyl-$C_{4'}$), 7.27 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.12 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.44 (s, 1H, triazol-$N_2$), 4.87 (s, 1H, triazol-$C_5$), 3.54 (s, 2H, triazolyl methyl-$CH_2$), 3.94 (s, 1H, CONH), 3.38 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 3.14 (s, 1H, -OH), 2.37 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 4-$CH_2$), 2.20 (s, 1H, triazol-$N_3$), 2.05-1.21 (m, 8H, adamantyl-$C_2$,-$C_5$,-$C_7$,-$C_8$,-$C_9$), 1.73-1.51 (m, 6H, adamantyl-$C_4$,-$C_6$, -$C_{10}$), 1.67-1.63 (m, 2H, 3-$CH_2$), 1.56-1.52 (m, 2H, 2-$CH_2$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.45 (-CONH), 149.74 (biphenyl-$C_4$), 149.61 (-chlorophenyl-$C_4$), 148.54 (-chlorophenyl-$C_1$), 148.41 (phenyl-$C_3$,-$C_5$), 147.61 (-chlorophenyl-$C_2$,-$C_6$),146.94 (biphenyl-$C_1$), 144.23 (biphenyl-$C_{1'}$), 132.51 (biphenyl-$C_3$,-$C_5$), 130.54 (biphenyl-$C_2$,-$C_6$), 128.57 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.71 (biphenyl-$C_{3'}$,-$C_{5'}$), 125.81 (biphenyl-$C_{4'}$) 98.61 (triazol-$C_5$), 91.85 (triazol-$C_1$), 70.71 (triazolyl methyl-C), 68.84 (1-$CH_2$), 55.45 (adamantyl-$C_3$), 46.51 (adamantyl-$C_1$), 45.45 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.45 (adamantyl-$C_5$, -$C_7$), 41.84 (adamantyl-$C_6$), 36.62

(adamantyl-$C_8$), 35.77 (adamantyl-$C_9$), 28.57 (4-$CH_2$), 27.45 (3-$CH_2$), 25.44 (2-$CH_2$); MS (ESI): *m/z* found 675.8 [$M^+$]; calculated for $C_{36}H_{42}ClN_5O_4S$ 675.2.

*5-((4'-chloro-N-((1-phenyl-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)-N-(3-hydroxyadamantan-1-yl)pentanamide* (**63**): It was synthesized as per general procedure described earlier in section 6.3.5.8 using 5-((4'-chloro-N-((1-phenyl-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)pentaneic acid (**47**) (0.78g) and 3-aminoadamantan-1-ol (**14**) (0.22g). The compound **63** was obtained as buff yellowish powder, yield 58%; mp 172-174 ºC; FTIR (KBr) $cm^{-1}$: 3264 (Ar-str.), 1684 (C=O-str.), 1145 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.10 (d, 2H, *J* = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.75 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.54 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.50 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.45 (d, 2H, *J* = 10 Hz, -phenyl –$C_2$-$C_6$), 7.39 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, phenyl -$C_3$-$C_5$), 7.37 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, phenyl-$C_4$), 5.47 (s, 1H, triazol-$N_2$), 4.75 (s, 1H, triazol-$C_5$), 3.94 (s, 2H, triazolyl methyl-$CH_2$), 3.82 (s, 1H, CONH), 3.34 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 2.48 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 4-$CH_2$), 2.27 (s, 1H, triazol-$N_3$), 2.02-1.96 (m, 8H, adamantyl-$C_2$,-$C_7$,-$C_5$,-$C_8$,-$C_9$), 1.72-1.43 (m, 6H, adamantyl-$C_4$,-$C_6$,-$C_{10}$), 1.66-1.61 (m, 2H, 3-$CH_2$), 1.57-1.55 (m, 2H, 2-$CH_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 175.55 (-CONH), 149.57 (biphenyl-$C_{4'}$), 149.64 (biphenyl-$C_4$), 147.46 (phenyl-$C_1$), 147.10 (phenyl-$C_2$,-$C_6$), 147.07 (phenyl-$C_3$,-$C_5$), 146.94 (biphenyl-$C_1$), 144.57 (biphenyl-$C_{1'}$), 144.52 (phenyl-$C_4$), 132.57 (biphenyl-$C_3$,-$C_5$), 131.63 (biphenyl-$C_{3'}$,-$C_{5'}$), 129.55 (biphenyl-$C_{2'}$,-$C_{6'}$), 128.31 (biphenyl-$C_2$,-$C_6$), 98.41 (triazol-$C_5$), 90.75 (triazol-$C_1$), 71.04 (triazolyl methyl-C), 68.51 (1-$CH_2$), 52.31 (adamantyl-$C_1$), 46.64 (adamantyl-$C_3$), 45.64 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.51 (adamantyl-$C_5$,-$C_7$), 41.67 (adamantyl-$C_6$),

36.68 (adamantyl-$C_8$), 34.87 (adamantyl-$C_9$), 28.61 (4-$CH_2$), 27.67 (3-$CH_2$), 24.24 (2-$CH_2$); MS (ESI): *m/z* found 676.3 [$M^+$]; calculated for $C_{36}H_{42}ClN_5O_4S$ 675.2.`

*5-((4'-fluoro-N-((1-(p-tolyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)-N-(3-hydroxyadamantan-1-yl)pentanamide* (**64**): It was synthesized as per general procedure described earlier in section 6.3.5.8 using 5-((4'-fluoro-N-((1-(p-tolyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)pentanoic acid (**48**) (0.78g) and 3-aminoadamantan-1-ol (**14**) (0.22g) to get compound **64** as buff yellowish powder, yield 59%; mp 164-166 ºC; FTIR (KBr) $cm^{-1}$: 3265 (Ar-str.), 1665 (C=O-str.), 1168 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.19 (d, 2H, *J* = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.88 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.72 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.52 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.45 (d, 2H, *J* = 10 Hz, -phenyl -$C_2$-$C_6$), 7.38 (d, 2H, $J_1$ = 10 Hz, phenyl-$C_3$-$C_5$), 5.46 (s, 1H, triazol-$N_2$), 4.76(s, 1H, triazol-$C_5$), 3.98 (s, 2H, triazolyl methyl-$CH_2$), 3.85 (s, 1H, CONH), 3.37 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 3.36 (s, 1H, -OH), 2.27 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 4-$CH_2$), 2.22 (s, 3H, phenyl-$CH_3$), 2.14 (s, 1H, triazol-$N_3$), 2.03-1.97 (m, 8H, adamantyl-$C_2$,-$C_7$, -$C_5$,-$C_8$,- $C_9$), 1.71-1.43 (m, 6H, adamantyl-$C_4$,-$C_6$,-$C_{10}$), 1.64-1.60 (m, 2H, 3-$CH_2$), 1.52-1.48 (m, 2H, 2-$CH_2$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.23 (-CONH), 150.45 (biphenyl-$C_{4'}$), 148.64 (biphenyl-$C_4$), 146.61(phenyl-$C_1$), 145.64 (phenyl-$C_2$,-$C_6$), 146.48 (phenyl-$C_3$,-$C_5$), 146.64 (biphenyl-$C_1$), 144.32 (biphenyl-$C_{1'}$), 143.64 (phenyl-$C_4$), 132.84 (biphenyl-$C_3$,-$C_5$), 131.32 (biphenyl-$C_{3'}$,-$C_{5'}$), 129.95 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.85 (biphenyl-$C_2$,-$C_6$), 98.68 (triazol-$C_5$), 91.52 (triazol-$C_1$), 70.54 (triazolyl methyl-C), 67.64 (1-$CH_2$), 52.84 (adamantyl-$C_1$), 47.32 (adamantyl-$C_3$), 45.84 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.94 (adamantyl-$C_5$,-$C_7$), 42.54 (adamantyl-$C_6$), 36.64 (adamantyl-$C_8$),

35.84 (adamantyl-$C_9$), 31.68 (-$CH_3$), 28.84 (4-$CH_2$), 26.61 (3-$CH_2$), 24.45 (2-$CH_2$); MS (ESI): *m/z* found 674.3 [$M^+$]; calculated for $C_{37}H_{44}FN_5O_4S$ 673.3.

*5-((N-((1-(4-fluorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-4'-methyl-[1,1'-biphenyl])-4-sulfonamido)-N-(3-hydroxyadamantan-1-yl)pentanamide* (**65**): This was synthesized as per general procedure described earlier in section 6.3.5.8 using 5-((N-((1-(4-fluorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-4'-methyl-[1,1'-biphenyl])-4-sulfonamido)pentanoic acid (**49**) (0.78g) and 3-aminoadamantan-1-ol (**14**) (0.22g) to get compound **65** as white powder, yield 58%; mp 159-161 ºC; FTIR (KBr) $cm^{-1}$: 3264 (Ar-str.), 1646 (C=O-str.), 1146 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.09 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.83 (d, 2H, *J* = 10 Hz, phenyl-$C_3$,-$C_5$), 7.64 (d, 2H, *J* = 10 Hz, phenyl-$C_2$,-$C_6$), 7.35 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_2$-$C_6$), 7.20 (d, 2H, *J* = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.04 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.24 (s, 1H, triazol-$N_2$), 4.84 (s, 1H, triazol-$C_5$), 3.84 (s, 2H, triazolyl methyl-$CH_2$), 3.83 (s, 1H, CONH), 3.34 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 3.31 (s, 1H, -OH), 2.33 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 4-$CH_2$), 2.27 (s, 3H, $CH_3$), 2.10 (s, 1H, triazol-$N_3$), 2.04-2.00 (m, 8H, adamantyl-$C_2$,-$C_5$,-$C_7$,-$C_8$,-$C_9$), 1.72-1.44 (m, 6H, adamantyl-$C_4$,-$C_6$, -$C_{10}$), 1.70-1.66 (m, 2H, 3-$CH_2$), 1.58-1.54 (m, 2H, 2-$CH_2$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.56 (-CONH), 149.46 (biphenyl-$C_4$), 149.46 (phenyl-$C_4$), 148.84 (phenyl-$C_1$), 148.43 (phenyl-$C_3$,-$C_5$), 147.56 (phenyl-$C_2$,-$C_6$), 146.53 (biphenyl-$C_1$), 144.14 (biphenyl-$C_{1'}$), 132.12 (biphenyl-$C_3$,-$C_5$), 130.54 (biphenyl-$C_2$,-$C_6$), 128.57 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.58 (biphenyl-$C_{3'}$,-$C_{5'}$), 125.44 (biphenyl-$C_{4'}$) 98.64 (triazol-$C_5$), 90.74 (triazol-$C_1$), 70.84 (triazolyl methyl-C), 68.64 (1-$CH_2$), 64.64 (-$CH_3$), 51.83 (adamantyl-$C_1$), 46.41 (adamantyl-$C_3$), 45.66 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.57 (adamantyl-$C_5$, -$C_7$), 41.82 (adamantyl-$C_6$), 36.81 (adamantyl-$C_8$), 35.24 (adamantyl-$C_9$), 28.61 (4-$CH_2$), 27.84 (3-

$CH_2$), 24.94 (2-$CH_2$); MS (ESI): *m/z* found 674.3 [$M^+$]; calculated for $C_{37}H_{44}FN_5O_4S$ 673.3.

*6-(N-((1-(4-chlorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonamido)-N-(3-hydroxyadamantan-1-yl)hexanamide* (**66**): It was synthesized as per general procedure described earlier in section 6.3.5.8 using 6-(N-((1-(4-chlorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonami-do)hexanoic acid (**50**) (0.78g) and 3-aminoadamantan-1-ol (**14**) (0.22g) to get compound **66** as buff powder, yield 62%; mp 161-163 ºC; FTIR (KBr) $cm^{-1}$: 3264 (Ar-str.), 1764 (C=O-str.), 1194 ($SO_2$-str.); $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.09 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.84 (d, 2H, *J* = 10 Hz, phenyl -$C_3$-$C_5$), 7.66 (d, 2H, *J* = 10 Hz, phenyl -$C_2$-$C_6$), 7.43 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.34 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, biphenyl-$C_{4'}$), 7.25 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.03 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.43 (s, 1H, triazol-$N_2$), 4.84 (s, 1H, triazol-$C_5$), 3.95 (s, 2H, triazolyl methyl-$CH_2$), 3.95 (s, 1H, CONH), 3.34 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 3.30 (s, 1H, -OH), 2.32 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 5-$CH_2$), 2.08 (s, 1H, triazol-$N_3$), 2.03-1.99 (m, 8H, adamantyl-$C_2$, -$C_5$, -$C_7$,-$C_8$,- $C_9$), 1.73-1.45 (m, 6H, adamantyl-$C_4$,-$C_6$, -$C_{10}$), 1.67-1.64 (m, 4H, 4-$CH_2$, 3-$CH_2$), 1.57-1.54 (m, 2H, 2-$CH_2$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.94 (-CONH), 149.64 (biphenyl-$C_4$), 149.64 (phenyl-$C_4$), 148.25 (phenyl-$C_1$), 148.20 (phenyl-$C_3$,-$C_5$), 147.54 (phenyl-$C_2$,-$C_6$), 146.84 (biphenyl-$C_1$), 144.64 (biphenyl-$C_{1'}$), 132.84 (biphenyl-$C_3$,-$C_5$), 130.65 (biphenyl-$C_2$,-$C_6$), 129.51 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.54 (biphenyl-$C_{3'}$,-$C_{5'}$), 126.51 (biphenyl-$C_{4'}$) 98.84 (triazol-$C_5$), 91.64 (triazol-$C_1$), 70.58 (triazolyl methyl-C), 68.57 (1-$CH_2$), 51.45 (adamantyl-$C_1$), 46.94 (adamantyl-$C_3$), 45.84 (adamantyl-$C_2$, -$C_4$,-$C_{10}$), 43.54 (adamantyl-$C_5$, -$C_7$), 41.21 (adamantyl-$C_6$), 36.74 (adamantyl-$C_8$), 35.37 (adamantyl-$C_9$), 29.85 (5-$CH_2$), 26.84 (3-

$CH_2$, 4-$CH_2$), 24.54 (2-$CH_2$); MS (ESI): *m/z* found 690.3 [$M^+$]; calculated for $C_{37}H_{44}ClN_5O_4S$ 689.2.

*6-((4'-chloro-N-((1-phenyl-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)-N-(3-hydroxyadamantan-1-yl)hexanamide* (**67**): The compound was synthesized as per general procedure described earlier in section 6.3.5.8 using 6-((4'-chloro-N-((1-phenyl-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)hexanoic acid (**51**) (0.78g) and 3-aminoadamantan-1-ol (**14**) (0.22g) to get compound **67** as yellowish powder, yield 60%; mp 148-150 ºC; FTIR (KBr) $cm^{-1}$: 3264 (Ar-str.), 1684 (C=O-str.), 1194 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.13 (d, 2H, *J* = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.85 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.57 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.52 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.42 (d, 2H, *J* = 10 Hz, -phenyl -$C_2$-$C_6$), 7.41 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, phenyl -$C_3$-$C_5$), 7.30 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, phenyl-$C_4$), 5.41 (s, 1H, triazol-$N_2$), 4.72 (s, 1H, triazol-$C_5$), 3.95 (s, 2H, triazolyl methyl-$CH_2$), 3.85 (s, 1H, CONH), 3.32 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 3.28 (s, 1H, -OH), 2.26 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 5-$CH_2$), 2.22 (s, 1H, triazol-$N_3$), 2.03-1.99 (m, 8H, adamantyl-$C_2$, -$C_5$, -$C_7$,-$C_8$,- $C_9$), 1.69-1.64 (m, 6H, adamantyl-$C_4$,-$C_6$,-$C_{10}$), 1.60-1.57 (m, 4H, 4-$CH_2$, 3-$CH_2$), 1.54-1.52 (m, 2H, 2-$CH_2$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.64 (-CONH), 149.57 (biphenyl-$C_{4'}$), 148.85 (biphenyl-$C_4$), 147.64 (phenyl-$C_1$), 147.11 (phenyl-$C_2$,-$C_6$), 146.74 (phenyl-$C_3$,-$C_5$), 146.17 (biphenyl-$C_1$), 144.63 (biphenyl-$C_{1'}$), 144.46 (phenyl-$C_4$), 132.51 (biphenyl-$C_3$,-$C_5$), 131.49 (biphenyl-$C_{3'}$,-$C_{5'}$), 129.84 (biphenyl-$C_{2'}$,-$C_{6'}$), 128.27 (biphenyl-$C_2$,-$C_6$), 98.49 (triazol-$C_5$), 91.74 (triazol-$C_1$), 71.27 (triazolyl methyl-C), 68.57 (1-$CH_2$), 52.41 (adamantyl-$C_1$), 46.71 (adamantyl-$C_3$), 45.67 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.94 (adamantyl-$C_5$,-$C_7$), 41.74 (adamantyl-$C_6$), 36.44 (adamantyl-$C_8$), 34.74 (adamantyl-$C_9$), 28.69 (5-$CH_2$),

27.45 (4-$CH_2$, 3-$CH_2$), 26.47 (2-$CH_2$); MS (ESI): *m/z* found 690.3 [$M^+$]; calculated for $C_{37}H_{44}ClN_5O_3S$ 689.2.

*6-((4'-fluoro-N-((1-(p-tolyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)-N-(3-hydroxyadamantan-1-yl)hexanamide* (**68**): This was synthesized as per general procedure described earlier in section 6.3.5.8 using 6-((4'-fluoro-N-((1-(p-tolyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido) hexanoic acid (**52**) (0.78g) and 3-aminoadamantan-1-ol (**14**) (0.22g) to get compound **68** as buff powder, yield 61%; mp 174-176 ºC; FTIR (KBr) $cm^{-1}$: 3294 (Ar-str.), 1720 (C=O-str.), 1185 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.12 (d, 2H, *J* = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.75 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.71 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.55 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.52 (d, 2H, *J* = 10 Hz, -phenyl -$C_2$-$C_6$), 7.24 (d, 2H, $J_1$ = 10 Hz, phenyl-$C_3$-$C_5$), 5.47 (s, 1H, triazol-$N_2$), 4.75 (s, 1H, triazol-$C_5$), 3.97 (s, 2H, triazolyl methyl-$CH_2$), 3.77 (s, 1H, CONH), 3.36 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 3.24 (s, 1H, -OH), 2.32 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 5-$CH_2$), 2.27 (s, 3H, phenyl-$CH_3$), 2.17 (s, 1H, triazol-$N_3$), 2.05-1.20 (m, 6H, adamantyl-$C_2$, -$C_5$, -$C_7$,-$C_8$,- $C_9$), 1.70-1.51 (m, 6H, adamantyl-$C_4$,-$C_6$,-$C_{10}$), 1.66-1.62 (m, 4H, 4-$CH_2$, 3-$CH_2$), 1.57-1.55 (m, 2H, 2-$CH_2$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 175.43 (-CONH), 152.45 (biphenyl-$C_{4'}$), 147.64 (biphenyl-$C_4$), 146.84 (phenyl-$C_1$), 145.48 (phenyl-$C_2$,-$C_6$), 146.53 (phenyl-$C_3$,-$C_5$), 146.45 (biphenyl-$C_1$), 144.84 (biphenyl-$C_{1'}$), 143.54 (phenyl-$C_4$), 132.84 (biphenyl-$C_3$,-$C_5$), 131.64 (biphenyl-$C_{3'}$,-$C_{5'}$), 129.63 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.67 (biphenyl-$C_2$,-$C_6$), 98.67 (triazol-$C_5$), 91.74 (triazol-$C_1$), 70.47 (triazolyl methyl-C), 67.53 (1-$CH_2$), 52.67 (adamantyl-$C_1$), 47.74 (adamantyl-$C_3$), 45.83 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.56 (adamantyl-$C_5$,-$C_7$), 42.55 (adamantyl-$C_6$), 36.68 (adamantyl-$C_8$), 35.42 (adamantyl-$C_9$), 31.51 (-$CH_3$), 29.87 (5-$CH_2$), 26.52 (4-

$CH_2$, 3-$CH_2$), 25.45 (2-$CH_2$); MS (ESI): *m/z* found 688.3 [$M^+$]; calculated for $C_{38}H_{46}FN_5O_4S$ 687.3

*6-((N-((1-(4-fluorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-4'-methyl-[1,1'-biphenyl])-4-sulfonamido)-N-(3-hydroxyadamantan-1-yl)hexanamide* (**69**): The compound was synthesized as per general procedure described earlier in section (6.3.5.8) using 6-((N-((1-(4-fluorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-4'-methyl-[1,1'-biphen-yl])-4-sulfonamido)hexanoic acid (**53**) (0.78g) and 3-aminoadamantan-1-ol (**14**) (0.22g) to get compound **69** as white powder, yield 57%; mp 153-155 ºC; FTIR (KBr) $cm^{-1}$: 3254 (Ar-str.), 1684 (C=O-str.), 1184 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.12 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.96 (d, 2H, *J* = 10 Hz, phenyl-$C_3$,-$C_5$), 7.65 (d, 2H, *J* = 10 Hz, phenyl -$C_2$-$C_6$), 7.32 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_2$-$C_6$), 7.20 (d, 2H, *J* = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.11 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.27 (s, 1H, triazol-$N_2$), 4.88 (s, 1H, triazol-$C_5$), 3.83 (s, 2H, triazolyl methyl-$CH_2$), 3.78 (s, 1H, CONH), 3.37 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 3.27 (s, 1H, -OH), 2.32 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 5-$CH_2$), 2.32 (s, 3H, $CH_3$), 2.20 (s, 1H, triazol-$N_3$), 2.09-2.03 (m, 8H, adamantyl-$C_2$, -$C_5$, -$C_7$,-$C_8$,- $C_9$), 1.73-1.69 (m, 6H, adamantyl-$C_4$,-$C_6$, -$C_{10}$), 1.62-1.58 (m, 4H, 4-$CH_2$, 3-$CH_2$), 1.54-1.50 (m, 2H, 2-$CH_2$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.81 (-CONH), 149.51 (biphenyl-$C_4$), 149.21 (phenyl-$C_4$), 148.45 (phenyl-$C_1$), 148.15 (phenyl-$C_3$,-$C_5$), 147.45 (phenyl-$C_2$,-$C_6$), 146.58 (biphenyl-$C_1$), 144.84 (biphenyl-$C_{1'}$), 132.61 (biphenyl-$C_3$,-$C_5$), 130.92 (biphenyl-$C_2$,-$C_6$), 128.54 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.84 (biphenyl-$C_{3'}$,-$C_{5'}$), 125.84 (biphenyl-$C_{4'}$) 98.87 (triazol-$C_5$), 91.24 (triazol-$C_1$), 70.94 (triazolyl methyl-C), 68.64 (1-$CH_2$), 64.52 (-$CH_3$), 51.84 (adamantyl-$C_1$), 46.54 (adamantyl-$C_3$), 45.84 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.82 (adamantyl-$C_5$, -$C_7$), 41.94 (adamantyl-$C_6$), 36.78 (adamantyl-$C_8$), 35.82 (adamantyl-

$C_9$), 30.84 (5-$CH_2$), 29.64 (4-$CH_2$, 3-$CH_2$), 25.64 (2-$CH_2$); MS (ESI): *m/z* found 688.6 [$M^+$]; calculated for $C_{38}H_{46}FN_5O_3S$ 687.3.

*5-(N-((1-(4-chlorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonamido)-N-(3,5-dimethyladamantan-1-yl)pentanamide* (**70**): It was synthesized as per general procedure described earlier in section 6.3.5.8 using 5-(N-((1-(4-chlorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonamido)pentanoic acid (**46**) (0.78g) and 3,5-dimethyladamantan-1-amine (**15**) (0.26g) to get compound **70** as white powder, yield 45%; mp 144-146 ºC; FTIR (KBr) $cm^{-1}$: 3284 (Ar-str.), 1694 (C=O-str.), 1194 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.15 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.81 (d, 2H, *J* = 10 Hz, phenyl -$C_3$-$C_5$), 7.68 (d, 2H, *J* = 10 Hz, chlorophenyl -$C_2$-$C_6$), 7.47 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.34 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, biphenyl-$C_{4'}$), 7.19 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.09 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.50 (s, 1H, triazol-$N_2$), 4.87 (s, 1H, triazol-$C_5$), 3.96 (s, 2H, triazolyl methyl-$CH_2$), 3.98 (s, 1H, CONH), 3.28 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 2.54 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 4-$CH_2$), 2.14 (s, 1H, triazol-$N_3$), 2.05-1.23 (m, 7H, adamantyl-$C_2$, -$C_7$,-$C_8$,- $C_9$), 1.70-1.66 (m, 6H, adamantyl-$C_4$,-$C_6$, -$C_{10}$), 1.62-1.54 (m, 2H, 3-$CH_2$), 1.57-1.53 (m, 2H, 2-$CH_2$), 1.40 (s, 6H, -2$CH_3$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 168.45 (-CONH), 148.46 (biphenyl-$C_4$), 147.46 (phenyl-$C_4$), 146.49 (phenyl-$C_1$), 145.47 (phenyl-$C_3$,-$C_5$), 145.22 (phenyl-$C_2$,-$C_6$),144.81 (biphenyl-$C_1$), 144.45 (biphenyl-$C_{1'}$), 132.84 (biphenyl-$C_3$,-$C_5$), 130.84 (biphenyl-$C_2$,-$C_6$), 128.84 (biphenyl-$C_{2'}$,-$C_{6'}$), 128.28 (biphenyl-$C_{3'}$,-$C_{5'}$), 125.94 (biphenyl-$C_{4'}$) 98.64 (triazol-$C_5$), 91.94 (triazol-$C_1$), 70.84 (triazolyl methyl-C), 68.94 (1-$CH_2$), 51.94 (adamantyl-$C_1$), 47.61 (adamantyl-$C_3$), 46.94 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.94 (adamantyl-$C_5$, -$C_7$), 41.94 (adamantyl-$C_6$), 36.94 (adamantyl-$C_8$), 35.64 (adamantyl-$C_9$), 32.58 (adamantly-

3, 5 -$CH_3$), 28.89 (4-$CH_2$), 27.94 (3-$CH_2$), 23.65 (2-$CH_2$); MS (ESI): *m/z* found 688.2 [$M^+$]; calculated for $C_{38}H_{46}ClN_5O_3S$ 687.3.

*5-((4'-chloro-N-((1-phenyl-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)-N-(3,5-dimethyladamantan-1-yl)pentanamide* (**71**): This was synthesized as per general procedure described earlier in section 6.3.5.8 using 5-((4'-chloro-N-((1-phenyl-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)pent-anoic acid (**47**) (0.78g) and 3,5-dimethyladamantan-1-amine (**15**) (0.26g) to get compound **71** as buff yellowish powder, yield 50%; mp 141-143 ºC; FTIR (KBr) $cm^{-1}$: 3261 (Ar-str.), 1664 (C=O-str.), 1194 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.15 (d, 2H, *J* = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.83 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.68 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.61 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.41 (d, 2H, *J* = 10 Hz, -phenyl –$C_2$-$C_6$), 7.35 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, phenyl -$C_3$-$C_5$), 7.28 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, phenyl-$C_4$), 5.64 (s, 1H, triazol-$N_2$), 4.76 (s, 1H, triazol-$C_5$), 3.94 (s, 2H, triazolyl methyl-$CH_2$), 3.88 (s, 1H, CONH), 3.38 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 2.32 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 4-$CH_2$), 2.12 (s, 1H, triazol-$N_3$), 2.02-1.97 (m, 7H, adamantyl-$C_2$,-$C_7$,-$C_8$,-$C_9$), 1.71-1.63 (m, 6H, adamantyl-$C_4$,-$C_6$,-$C_{10}$), 1.60-1.58 (m, 2H, 3-$CH_2$), 1.54-1.50 (m, 2H, 2-$CH_2$), 1.46 (s, 6H, 3,5 –$CH_3$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 175.15 (-CONH), 149.94 (biphenyl-$C_{4'}$), 148.84 (biphenyl-$C_4$), 147.65 (phenyl-$C_1$), 147.20 (phenyl-$C_2$,-$C_6$), 147.14 (phenyl-$C_3$,-$C_5$), 146.82 (biphenyl-$C_1$), 144.94 (biphenyl-$C_{1'}$), 144.21 (phenyl-$C_4$), 132.94 (biphenyl-$C_3$,-$C_5$), 130.95 (biphenyl-$C_{3'}$,-$C_{5'}$), 129.64 (biphenyl-$C_{2'}$,-$C_{6'}$), 128.84 (biphenyl-$C_2$,-$C_6$), 98.34 (triazol-$C_5$), 92.52 (triazol-$C_1$), 71.51 (triazolyl methyl-C), 68.47 (1-$CH_2$), 52.61 (adamantyl-$C_1$), 46.15 (adamantyl-$C_3$), 45.50 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.57 (adamantyl-$C_5$,-$C_7$), 41.45 (adamantyl-$C_6$), 36.37 (adamantyl-$C_8$), 34.74 (adamantyl-

$C_9$), 32.28 (3, 5 -$CH_3$), 28.94 (4-$CH_2$), 27.64 (3-$CH_2$), 24.97 (2-$CH_2$); MS (ESI): *m/z* found 688.1 [$M^+$]; calculated for $C_{38}H_{46}ClN_5O_3S$ 687.3.

*6-(N-((1-(4-chlorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonamido)-N-(3,5-dimethyladamantan-1-yl)hexanamide* (**72**): It was synthesized as per general procedure described earlier in section 6.3.5.8 using 6-(N-((1-(4-chlorophenyl)-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl]-4-sulfonamido)hexanoic acid (**72**) (0.78g) and 3,5-dimethyladamantan-1-amine (**15**) (0.26g) to get compound **58** as buff powder, yield 62%; mp 159-161 ºC; FTIR (KBr) $cm^{-1}$: 3264 (Ar-str.), 1764 (C=O-str.), 1164 ($SO_2$-str.); $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.12 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.86 (d, 2H, *J* = 10 Hz, phenyl -$C_3$-$C_5$), 7.66 (d, 2H, *J* = 10 Hz, phenyl -$C_2$-$C_6$), 7.49 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.37 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, biphenyl-$C_{4'}$), 7.25 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.00 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 5.45 (s, 1H, triazol-$N_2$), 4.86 (s, 1H, triazol-$C_5$), 3.92 (s, 2H, triazolyl methyl-$CH_2$), 3.95 (s, 1H, CONH), 3.37 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 2.38 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 5-$CH_2$), 2.15 (s, 1H, triazol-$N_3$), 2.02-1.99 (m, 5H, adamantyl-$C_2$, -$C_7$,-$C_8$,- $C_9$), 1.71-1.65 (m, 6H, adamantyl-$C_4$,-$C_6$, -$C_{10}$), 1.63-1.58 (m, 2H, 4-$CH_2$, 3-$CH_2$), 1.57-1.54 (m, 2H, 2-$CH_2$), 1.45 (s, 6H, 3, 5-$CH_3$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.84 (-CONH), 149.84 (biphenyl-$C_4$), 149.64 (phenyl-$C_4$), 148.64 (phenyl-$C_1$), 148.22 (phenyl-$C_3$,-$C_5$), 147.54 (phenyl-$C_2$,-$C_6$), 146.94 (biphenyl-$C_1$), 144.27 (biphenyl-$C_{1'}$), 132.57 (biphenyl-$C_3$,-$C_5$), 131.42 (biphenyl-$C_2$,-$C_6$), 129.94 (biphenyl-$C_{2'}$,-$C_{6'}$), 127.61 (biphenyl-$C_{3'}$,-$C_{5'}$), 126.94 (biphenyl-$C_{4'}$) 98.65 (triazol-$C_5$), 91.33 (triazol-$C_1$), 70.91 (triazolyl methyl-C), 68.64 (1-$CH_2$), 51.64 (adamantyl-$C_1$), 46.31 (adamantyl-$C_3$), 45.84 (adamantyl-$C_2$, -$C_4$,-$C_{10}$), 43.94 (adamantyl-$C_5$, -$C_7$), 41.64 (adamantyl-$C_6$), 36.94 (adamantyl-$C_8$), 35.84 (adamantyl-$C_9$), 33.14 (3, 5-$CH_3$),

29.15 (5-$CH_2$), 27.94 (3-$CH_2$, 4-$CH_2$), 25.15 (2-$CH_2$); MS (ESI): *m/z* found 702.3 [$M^+$]; calculated for $C_{39}H_{48}ClN_5O_3S$ 701.3.

*6-((4'-chloro-N-((1-phenyl-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)-N-(3,5-dimethyladamantan-1-yl)hexanamide* (**73**): It was synthesized as per general procedure described earlier in section 6.3.5.8 using 6-((4'-chloro-N-((1-phenyl-2,3-dihydro-1H-1,2,3-triazol-4-yl)methyl)-[1,1'-biphenyl])-4-sulfonamido)hexanoic acid (**51**) (0.78g) and 3,5-dimethyladamantan-1-amine (**15**) (0.26g) to get compound **73** as yellowish powder, yield 56%; mp 157-159 ºC; FTIR (KBr) $cm^{-1}$: 3294 (Ar-str.), 1664 (C=O-str.), 1164 ($SO_2$-str.);$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.16 (d, 2H, *J* = 10 Hz, biphenyl-$C_{3'}$-$C_{5'}$), 7.84 (d, 2H, *J* = 5 Hz, biphenyl-$C_3$-$C_5$), 7.65 (d, 2H, *J* = 5 Hz, biphenyl-$C_{2'}$-$C_{6'}$), 7.52 (d, 2H, *J* = 5 Hz, biphenyl-$C_2$-$C_6$), 7.44 (d, 2H, *J* = 10 Hz, -phenyl -$C_2$-$C_6$), 7.35 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, phenyl -$C_3$-$C_5$), 7.22 (t, 1H, $J_1$ = 5, $J_2$ = 10 Hz, phenyl-$C_4$), 5.43 (s, 1H, triazol-$N_2$), 4.74 (s, 1H, triazol-$C_5$), 3.97 (s, 2H, triazolyl methyl-$CH_2$), 3.82 (s, 1H, CONH), 3.35 (t, 2H, $J_1$ = 10, $J_2$ = 5 Hz, 1-$CH_2$), 2.23 (t, 2H, $J_1$ = 5, $J_2$ = 10 Hz, 5-$CH_2$), 2.21 (s, 1H, triazol-$N_3$), 2.04-1.98 (m, 7H, adamantyl-$C_2$, -$C_7$, -$C_8$,- $C_9$), 1.72-1.68 (m, 6H, adamantyl-$C_4$,-$C_6$,-$C_{10}$), 1.62-1.59 (m, 4H, 4-$CH_2$, 3-$CH_2$), 1.52-1.48 (m, 2H, 2-$CH_2$), 1.42 (s, 6H, 3, 5 –$CH_3$);$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 174.64 (-CONH), 149.84 (biphenyl-$C_{4'}$), 148.62 (biphenyl-$C_4$), 147.51 (phenyl-$C_1$), 147.64 (phenyl-$C_2$,-$C_6$), 146.61 (phenyl-$C_3$,-$C_5$), 146.94 (biphenyl-$C_1$), 144.48 (biphenyl-$C_{1'}$), 144.58 (phenyl-$C_4$), 132.91 (biphenyl-$C_3$,-$C_5$), 131.51 (biphenyl-$C_{3'}$,-$C_{5'}$), 129.14 (biphenyl-$C_{2'}$,-$C_{6'}$), 128.45 (biphenyl-$C_2$,-$C_6$), 98.61 (triazol-$C_5$), 92.47 (triazol-$C_1$), 71.44 (triazolyl methyl-C), 68.91 (1-$CH_2$), 52.48 (adamantyl-$C_1$), 46.96 (adamantyl-$C_3$), 45.92 (adamantyl-$C_2$, -$C_4$, -$C_{10}$), 43.68 (adamantyl-$C_5$,-$C_7$), 41.57 (adamantyl-$C_6$), 36.84 (adamantyl-$C_8$), 34.72 (adamantyl-

$C_9$), 32.17 (3, 5 –$CH_3$), 29.48 (5-$CH_2$), 28.94 (4-$CH_2$, 3-$CH_2$), 27.64 (2-$CH_2$); MS (ESI): *m/z* found 702.3 [$M^+$]; calculated for $C_{39}H_{48}ClN_5O_3S$ 701.3.

### 6.3.6 *In-vitro* MMP-2 inhibition assay

Chapter 4 section 4.1.6.3 contain detail procedure of assay. Briefly seven different concentrations (0.1-1000 nM) of test compounds were used in the enzyme inhibition studies.

### 6.3.7 Inhibition assay of metal induced $A\beta_{1-42}$ aggregation

Aβ-redox active metal produces ROS causing neuronal cell death. Metal ions along with AChE were found to induce the Aβ aggregation(365). Thioflavin T (ThT) assay was performed to determine the inhibition potential of compounds against $Fe^{+2}$ induced $A\beta_{1-42}$ aggregation(415). $A\beta_{1-42}$ (Sigma) was dissolved in phosphate buffer (PBS, 10 mM, pH 7.5), compounds were dissolved in DMSO and diluted with PBS. The synthesized compounds were screened at the ratio of $A\beta_{1-42}$: Inhibitor 1:2. The selected compounds were further tested at different proportions of the $A\beta_{1-42}$: Inhibitor (1:0.5, 1:1, 1:2). The final concentration of $A\beta_{1-42}$ compounds and $Fe^{+2}$ was 10 μM (2μL), 0.5, 10, 20 μM (2μL) and 10 μM (16 μL) respectively. The mixtures were incubated at room temperature for 48h in dark. The fluorescence intensities of the incubated mixtures were measured at the end of experiment by adding 178 μL of 20 μM ThT at excitation and emission wavelengths of 485 and 528 nm respectively.

### 6.3.8 Confocal fluorescence imaging

The assay mentioned in section 6.3.7 was further used for the confocal fluorescence imaging. Fluorescence dye ThT; $A\beta_{1-42}$ and ThT; $A\beta_{1-42}$; $A\beta_{1-42}$ and $FeCl_3$; $A\beta_{1-42}$, $FeCl_3$ and ThT; $A\beta_{1-42}$, $FeCl_3$, compound **55** and ThT; compound **55** and ThT; compound **55** alone were incubated and mounted on the glass slide using DABCO

(Sigma, CAS-280-57-9) as fixing agent. The images were taken at 40X using FITC fluorescence cube at 494 nm excitation and 518 emission. Experiments containing 20 mM of compound **55** was used for confocal imaging(416).

**6.3.9 Antioxidant activity (DPPH assay)**

Chapter 4 section 4.1.6.8 contain detail procedure of assay. 100 µL of drug solutions of concentration ranges 20µM, 40 µM, 80µM and 160 µM were taken and assay protocol was followed as mentioned in chapter 3 section 4.1.6.8. The assays were performed in triplicate and in three independent runs and $EC_{50}$ was calculated. Ascorbic acid was used as the standard for the DPPH assay(370).

**6.3.10 MC65 neuroprotection assay**

The assay protocol used in chapter 4 section 4.1.6.6 was used for the neuroprotection study.

**6.3.11 Evaluation of Adamantyl analogy on different subtypes of glutamate and glycine mediated NMDA receptors.**

*Xenopus laevis's* oocyte of stage V or VI was selected and injected with cRNA of specific subunit to express hetromeric NMDA receptors. 10nL of GluN1-1a was injected along with 15nL and 13nL of GluN2A and GluN2B respectively. Electrophysiological readings were performed on $4^{th}$-$7^{th}$ day. Two-electrode voltage clamping was performed using a TurboTec-10CX amplifier (npi electronic) controlled by Pulse software (HEKA). Borosilicate glass capillaries (Harvard Instruments) were pulled to resistances of 0.1–1.0 MΩ and filled with 3 m KCl. Oocytes were clamped at 70 mV. All recordings were performed in barium Ringer's solution (BaR, in mm: 115 NaCl, 2.5 KCl, 1.8 BaCl2, 10 HEPES-NaOH, pH 7.2) supplemented with 250 mm niflumic acid (NFA) to prevent the

opening of endogenous calcium-induced chloride channels. The solutions of compounds were prepared with 10nM DMSO solution and final concentration was prepared with stock solution of 100 μm glutamate and 10 μm glycine. and the amound of current inhibited was recorded. Agonist solution was also supplemented with 0.01% DMSO and the recording was performed.

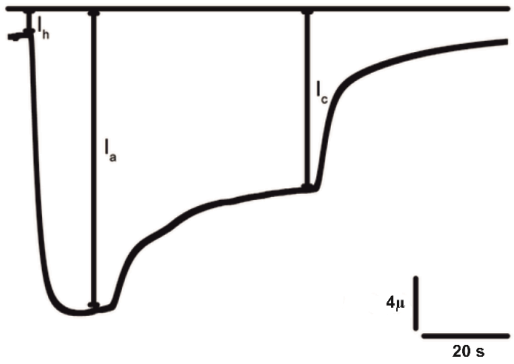
**Data analysis**

Data analysis was performed using OriginPro 2015. Current Inhibition was calculated using following formula-

$$Inhibition(\%) = (1 - \frac{I_c - I_h}{I_a - I_h}) \text{ X100}$$

Where, $I_h$ refers to holding current before adding agonist solution, $I_a$ is the current after adding agonist in the solution. $I_c$ is the resulting current in presence of compound (**Figure 6.7**).

**Figure 6.7** Method of identification of activity against different subtypes of NMDA.




Typical current curve during activation of GluN2B containing NMDA receptor. $I_h$ represents holding current, $I_a$ is the current produced due to agonist solution, and $I_c$ is the current resulting in presence of antagonist solution(417).

## 6.4 Results & discussion

### 6.4.1 Pharmacophore development and virtual screening

Pharmacophoric features *viz*. ring aromatic (A1 and A2), hydrophobic (HY), hydrogen-bond acceptor (HA), hydrogen-bond donor (HD) of co-crystalized ligand, ifenprodil (PDB id- 5EWJ) were identified. Shape based pharmacophore screening was performed on ZINC ligand database of 12,996,897 molecules. RMSD was set to 0.5 and the resultant search ligands were subjected to drug-likeliness and pains filters (**Figure 6.8, Table 6.1**).

**Figure 6.8** Pharmacophoric features of Ifenprodil used for screening (A1,A2-Aromatic, HY- Hydrophobic, HA-Hydrogen-bond acceptor, HD- Hydrogen-bond donor).

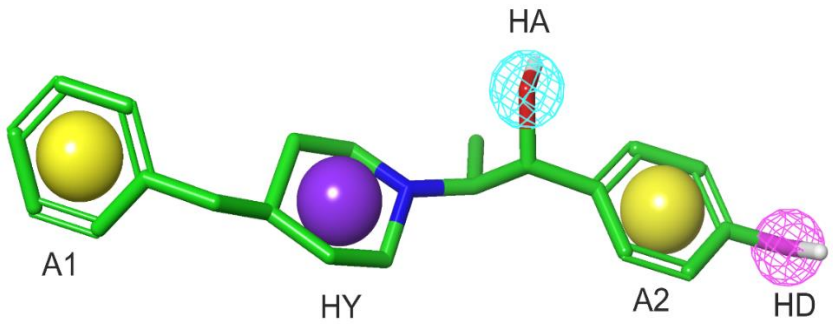



**Table 6.1** Distance between pharmacophoric features in Å

| **Pharmacophoric features** | **A1** | **HY** | **HA** | **A2** | **HD** |
|---|---|---|---|---|---|
| **A1** | - | 5.24 | 8.94 | 11.73 | 14.44 |
| **HY** | 5.24 | - | 4.29 | 6.53 | 9.22 |
| **HA** | 8.94 | 4.29 | - | 3.67 | 6.30 |
| **A2** | 11.73 | 6.53 | 3.67 | - | 2.67 |
| **HD** | 14.44 | 9.22 | 6.30 | 2.67 | - |

### 6.4.2 Drug-likeliness, ADME and toxicity Prediction

Synthesized compounds were evaluated for their ADME and toxicity predictions by using preADMET server. The predicted properties included 'Lipinski rule of 5 voilations', blood-brain barrier (BBB) permeability, buffer solubility, hERG inhibition, AMES test, and human intestinal absorption. The properties were calculated and the results are summarized in **Table 6.2**

### 6.4.3 Docking studies

#### 6.4.3.1 Homology modelling and validation

The missing residues of protein (PDB id 5EWJ) was filled using SWISS-MODEL accessible via ExPASy web server. The developed model of human GluN1-GluN2B subunit, containing NMDA receptor based on PDB 5EWJ, was validated by RAMPAGE and PROCHECK for overall stereochemical property of modelled protein using Ramachandran plot (**Figure 6.9)**.

The verified 3D results showed that 95.45% of residues have average 3D-1D score ≥ 0.2. Ramachandran plot also showed that about 90% of residues fall in favorable range. The model was built to add missing loops and side chain. GMQE (Global Model Quality Estimation), an important parameter to estimate the property of model with respect to template, was 0.99 indicating good reliability of model. QMEAN score estimated the overall quality of model based on structural features, both global and local. The score indicated degree of nativeness of the model and a score of zero indicated good agreement of model features with experimental structure of similar size. The score 0.64 for the developed model showed good agreement with the structural features of experimental model.

**Table 6.2** Drug-likeliness, ADME and toxicity prediction of the compounds.

| Comp | Lipinski Rule of 5 Violations | BBB* | Buffer solubility (mg/L) | hERG Inhibition | AMES Test | Human intestinal absorption (%) |
|---|---|---|---|---|---|---|
| **16** | 0 | 0.172 | 79.77 | Negative | Non-Mutagen | 84.60 |
| **17** | 2 | 0.308 | 46.45 | Low-risk | Non-Mutagen | 94.60 |
| **18** | 1 | 0.21 | 149.198 | Low-risk | Non-Mutagen | 93.60 |
| **19** | 0 | 0.252 | 40.40 | Negative | Non-mutagen | 93.82 |
| **20** | 1 | 0.315 | 75.48 | Low-risk | Non-mutagen | 93.84 |
| **21** | 1 | 1.367 | 12.29 | Negative | Non-mutagen | 95.618 |
| **22** | 2 | 2.458 | 7.15 | Low-risk | Non-mutagen | 96.172 |
| **23** | 1 | 1.222 | 26.54 | Low-risk | Non-mutagen | 95.752 |
| **24** | 2 | 2.020 | 13.43 | Low-risk | Non-mutagen | 95.878 |
| **25** | 2 | 3.347 | 7.79 | Medium risk | Non-mutagen | 96.36 |
| **26** | 1 | 1.358 | 17.07 | Negative | Non-mutagen | 95.61 |
| **54** | 3 | 1.82 | 0 | Negative | Non-mutagen | 94.42 |
| **55** | 3 | 2.154 | 0 | Low-risk | Non-mutagen | 96.41 |
| **56** | 3 | 1.96 | 0 | Negative | Non-mutagen | 96.23 |
| **57** | 3 | 1.759 | 0 | Negative | Non-mutagen | 96.23 |
| **58** | 3 | 2.45 | 0 | Negative | Non-mutagen | 96.45 |
| **59** | 3 | 2.86 | 0 | Negative | Non-mutagen | 96.45 |
| **60** | 3 | 2.63 | 0 | Negative | Non-mutagen | 96.29 |
| **61** | 3 | 2.36 | 0 | Low-risk | Non-mutagen | 96.29 |
| **62** | 3 | 0.38 | 0 | Low-risk | Non-mutagen | 95.50 |
| **63** | 3 | 0.48 | 0 | Negative | Non-mutagen | 95.50 |
| **64** | 3 | 0.42 | 0 | Negative | Non-mutagen | 95.12 |
| **65** | 3 | 0.36 | 0 | Low-risk | Non-mutagen | 94.85 |
| **66** | 3 | 0.50 | 0 | Negative | Non-mutagen | 95.24 |
| **67** | 3 | 0.70 | 0 | Low-risk | Non-mutagen | 95.59 |
| **68** | 3 | 0.59 | 0 | Low-risk | Non-mutagen | 95.24 |
| **69** | 3 | 0.50 | 0 | Negative | Non-mutagen | 95.24 |
| **70** | 3 | 0.68 | 0 | Negative | Non-mutagen | 95.36 |
| **71** | 3 | 2.33 | 0 | Low-risk | Non-mutagen | 93.79 |
| **72** | 3 | 2.97 | 0 | Low-risk | Non-mutagen | 96.40 |
| **73** | 3 | 3.53 | 0 | Negative | Non-mutagen | 96.53 |

**Figure 6.9** Ramachandran plot for modeled protein.

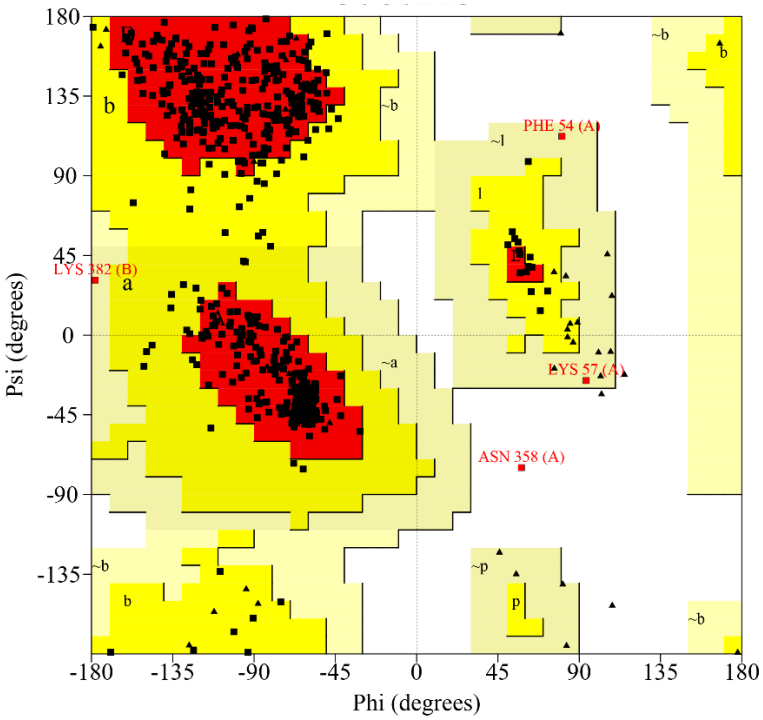



**Figure 6.10** Docking pose of compound **22**

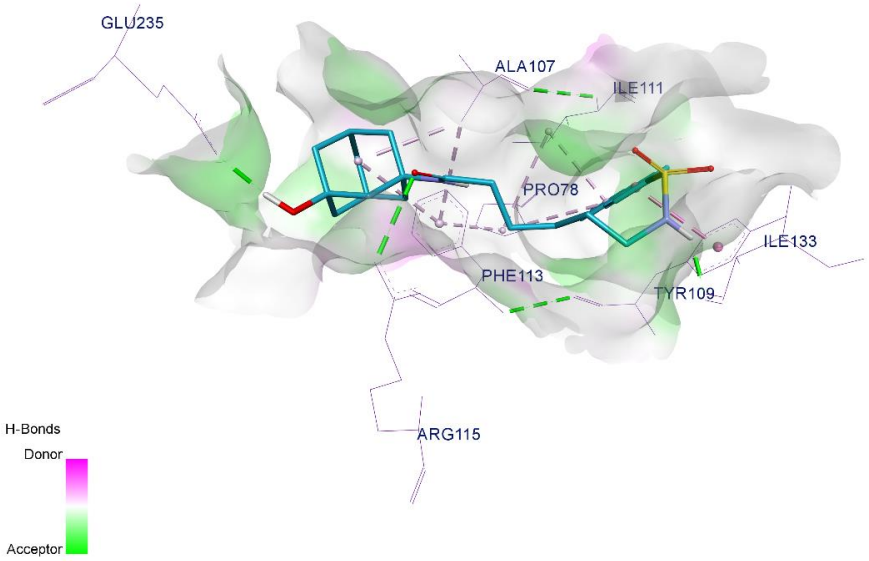


**Figure 6.11** Docking pose of compound **24**

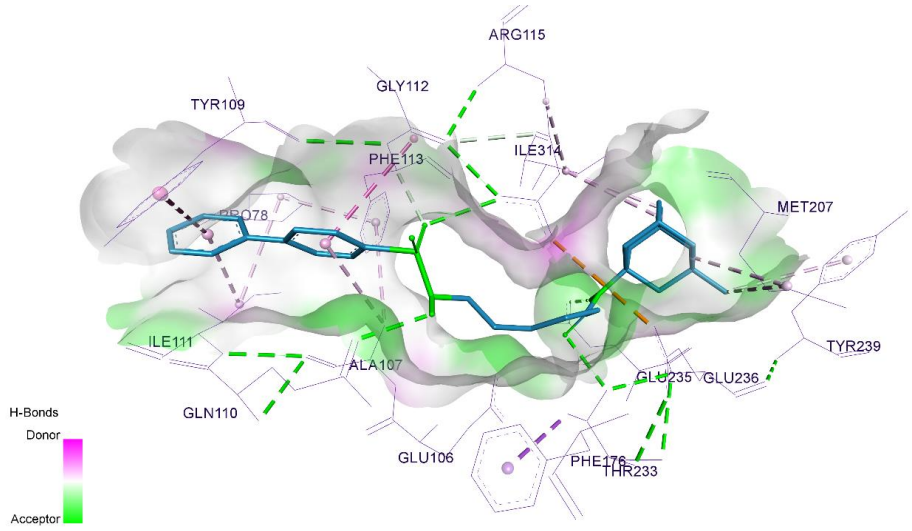
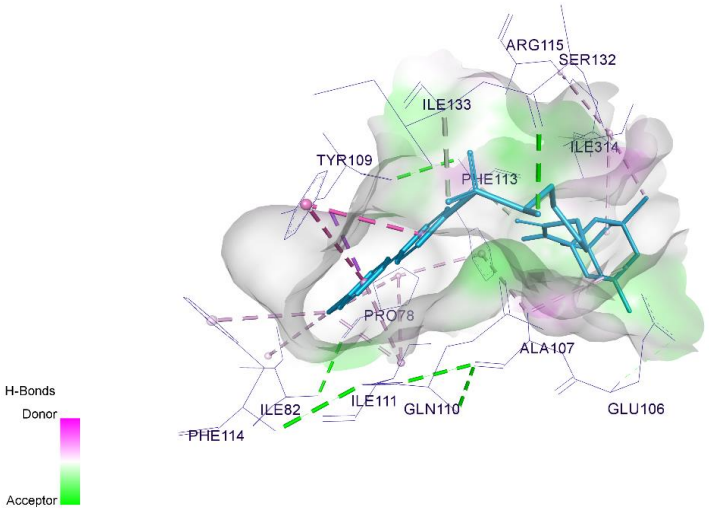



**Figure 6.12** Docking pose of compound **26**




### 6.4.4 *In-vitro* MMP-2 inhibition assay

The adamantyl analogues (scheme I), synthesized and screened for MMP-2 enzyme assay, showed moderate activity against MMP-2 ($IC_{50}$ 82.14 to 0.028 µM). The results also supported the *in-silico* study and increase in potency was expected upon making appropriate substitutions. The substitution of third and fifth hydrogens of adamantyl

with methyl group produces results in significant changes in the $IC_{50}$ values (compounds **23**-**26**, $IC_{50}$ 80.24±2.14, 57.04±2.63, 82.14±1.24, 68.24±1.51 µM, respectively). The replacement of third hydrogens of adamantyl led to minor improment in activity (compounds **16**-**20**, $IC_{50}$ 41.21±1.53, 27.51±1.58, 31.25±2.04, 33.52±2.17, 26.35±1.38 µM respectively). Further, the linker of compounds along with substitutions were explored and it was found that compounds containing five carbon linker had better activity in comparison to un-substituted adamantly ring and *p*-chloro substituted biphenyl ring (Compounds **21** and **22,** $IC_{50}$ 02.64±1.81, 00.28±0.04 µM). The adamantyl analogues (scheme I) provided strong support for the development of 1,4-disubstituted 1,2,3-triazoles (scheme II). The series was developed for better interactions with different amino acid residues of MMP-2 along with improving neuroprotection score of adamantyl analogues. S1 and S2 subsites of MMP-2 were found to interact with π cloud of aromatic groups leading to decrease in $IC_{50}$ of compound **55** (00.032±0.12 µM). Further, substitution of the adamantyl ring led to decrease in the activity and methyl substitution was most unfavorable (compounds **70**-**73**, $IC_{50}$ 43.25±1.28, 55.24±1.01, 61.53±1.08, 76.12±1.21). An un-substituted adamantyl ring along with four carbon linker and *p*-chloro substituted biphenyl ring was most promising (**Table 6.3**).

### 6.4.5 Inhibition assay of metal induced $A\beta_{1-42}$ aggregation and confocal fluorescence imaging:

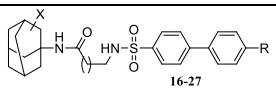
High concentrations of biometals (Fe, Cu, and Zn) are found to be related with Aβ in amyloid plaques in brain. Aβ-metal ion complexation effects the aggregation of Aβ and is shown to alleviate the toxic oligomeric form. Moreover, Aβ bound to redox-active metal ions ($Cu^{2+}$ and $Fe^{3+}$) produces ROS such as hydroxyl radicals, superoxide, and

$H_2O_2$ through Fenton-type reaction, which subsequently induces oxidative stress and eventually leading to neuronal death. Overall, the multifaceted toxicity induced by Aβ oligomers and aggregates, with or without metal inclusion, leads to neuronal cell death. Hence, a multifaceted approach to develop effective therapeutic agents for the treatment/management of AD is crucial(365).

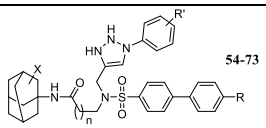
The designed compounds showed remarkable metal chelation property, so metal induced aggregation of $A\beta_{1-42}$ assay was performed to determine the potency. The adamantyl and 1,2,3-triazole analogues were screened for their anti $A\beta_{1-42}$ aggregation activity. The adamantly analogues showed 52 to 72% of $A\beta_{1-42}$ aggregation and the 1,2,3-triazole containing compounds were found to be better and showed 78 to 49 % of $A\beta_{1-42}$ aggregation (**Table 6.3**).

$A\beta_{1-42}$ when incubated with metal showed 100% aggregation. DNP, at a dose of 20 µM, showed significant inhibition of metal induced $A\beta_{1-42}$ aggregation. Compound **55**, found to be more effective than DNP and inhibited abov 50% $A\beta_{1-42}$ aggregation, when compared with $Fe^{+2}$+ $A\beta_{1-42}$ and $A\beta_{1-42}$ groups (**Figure 6.13A**). Confocal imaging was performed to understand the interaction of $A\beta_{1-42}$, $FeCl_3$ and compound **55** at molecular level. Fluorescent background was obtained when dye ThT was used (**Figure 6.13B**). $A\beta_{1-42}$ aggregate was obtained when it was incubated and treated with ThT (**Figure 6.13C**), whereas the fluorescence disappeared when $A\beta_{1-42}$ alone (**Figure 6.13D**) and $A\beta_{1-42}$ along with the metal were incubated without ThT (**Figure 6.13E**). The blank images ascertain that neither $A\beta_{1-42}$ and metal nor their combinations showed any background noises in absence of ThT. $A\beta_{1-42}$ incubated with metal showed aggregate plaque deposition (**Figure 6.13F**) while the plaques were disaggregated on treatment with compound **55** (**Figure 6.13G**).

**Table 6.3** Adamantyl (scheme I) and 1,4-disubstituted 1,2,3-triazoles (scheme II) analogues with inhibitory activities ($IC_{50}$) *viz.* MMP-2, $A\beta_{1-42}$ % aggregation, $EC_{50}$ of DPPH assay, and neuroprotection assay against MC65 cell line showing cell viability ±SE.




16-27

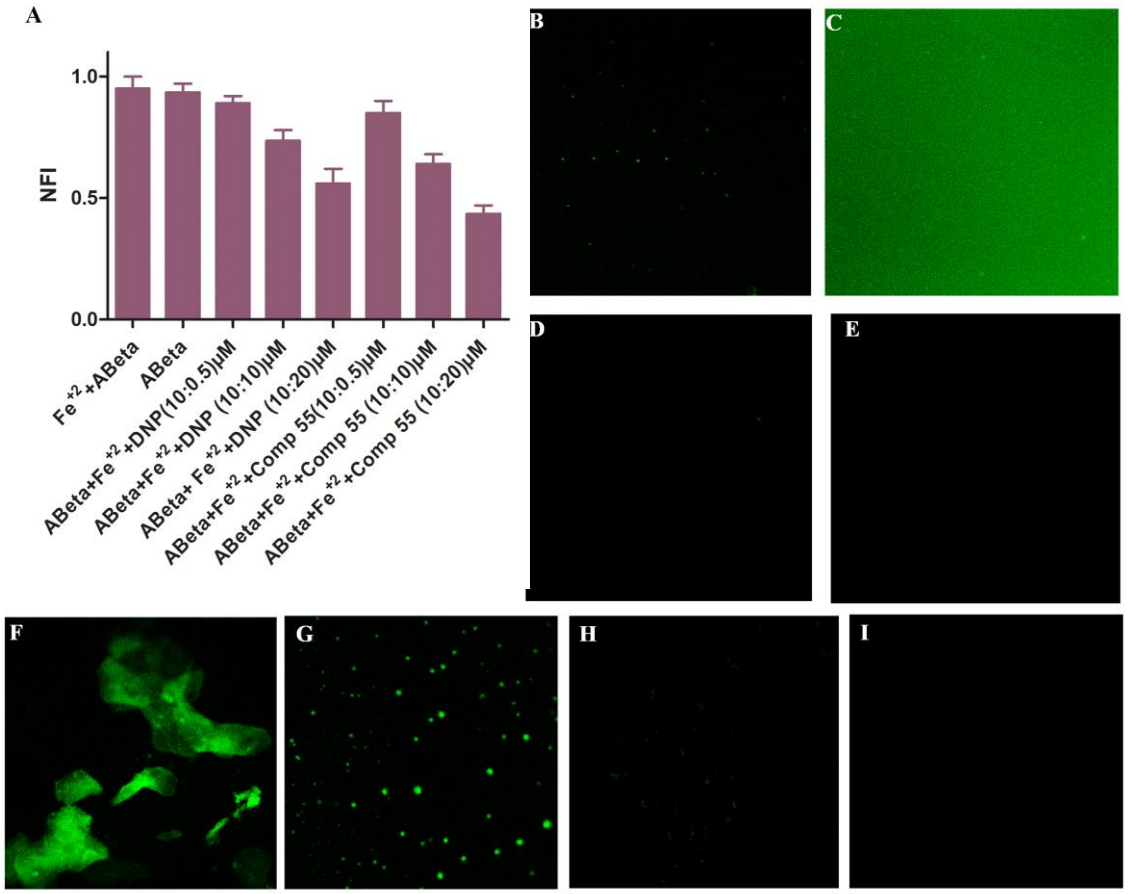



54-73

| Comp | R | R' | n | X | MMP-2 $IC_{50}$ ±SE (µM) | $A\beta_{1-42}$ % aggregation 10:20 µM | $EC_{50}$ (µM) DPPH assay | CV[a] % at 50 µM |
|---|---|---|---|---|---|---|---|---|
| 16 | -H | --- | 3 | 3-OH | 41.21±1.53 | 75.12±3.01 | 32.58±3.21 | 65.21±1.45 |
| 17 | -Cl | --- | 3 | 3-OH | 27.51±1.58 | 72.31±5.21 | 23.62±2.14 | 61.31±2.55 |
| 18 | -F | --- | 3 | 3-OH | 31.25±2.04 | 78.21±5.74 | 21.35±1.25 | 68.84±3.15 |
| 19 | -H | --- | 4 | 3-OH | 33.52±2.17 | 75.24±8.14 | 27.51±1.28 | 60.51±2.11 |
| 20 | -F | --- | 4 | 3-OH | 26.35±1.38 | 73.21±9.10 | 24.56±2.14 | 70.51±3.21 |
| 21 | -H | --- | 4 | 3-H | 02.64±1.81 | 80.21±14.2 | 38.51±2.51 | 55.21±2.15 |
| 22 | -Cl | --- | 4 | 3-H | 00.28±0.04 | 81.21±10.1 | 42.14±2.40 | 56.21±3.25 |
| 23 | -H | --- | 3 | 3,5-$CH_3$ | 22.24±2.14 | 90.48±9.01 | 53.55±2.54 | 68.24±4.00 |
| 24 | -H | --- | 4 | 3,5-$CH_3$ | 07.04±2.63 | 92.56±8.12 | 62.31±2.41 | 62.31±2.81 |
| 25 | -Cl | --- | 3 | 3,5-$CH_3$ | 38.14±1.24 | 95.81±9.15 | 58.21±1.54 | 59.62±2.14 |
| 26 | -Cl | --- | 4 | 3,5-$CH_3$ | 01.24±1.51 | 98.25±12.1 | 70.24±2.17 | 61.25±1.98 |
| 27 | -$CH_3$ | --- | 3 | 3-H | 23.51±1.24 | 92.65±5.14 | 62.17±1.28 | 63.28±1.85 |
| 54 | -H | -Cl | 3 | 3-H | 02.15±0.38 | 50.21±8.01 | 58.12±2.17 | 54.21±2.01 |
| 55 | -Cl | -H | 3 | 3-H | 0.32±0.12 | ------ | 70.15±2.21 | 98.51±2.01 |
| 56 | -F | -$CH_3$ | 3 | 3-H | 10.63±2.51 | 63.39±11.5 | 62.31±1.14 | 87.21±2.05 |
| 57 | -$CH_3$ | -F | 3 | 3-H | 15.28±2.54 | 78.85±10.2 | 08.54±1.24 | 95.01±1.51 |
| 58 | -H | -Cl | 4 | 3-H | 20.62±0.08 | 51.24±7.15 | 08.96±1.25 | 97.14±3.06 |
| 59 | -Cl | -H | 4 | 3-H | 32.25±0.04 | 52.36±9.15 | 14.25±2.14 | 88.21±2.04 |
| 60 | -F | -$CH_3$ | 4 | 3-H | 38.32±0.06 | 61.23±5.69 | 09.21±2.14 | 97.21±2.25 |
| 61 | -$CH_3$ | -F | 4 | 3-H | 23.15±1.51 | 68.59±6.21 | 10.24±1.25 | 98.15±2.15 |
| 62 | -H | -Cl | 3 | 3-OH | 18.24±1.21 | 49.58±9.63 | 11.01±1.51 | 89.25±2.14 |
| 63 | -Cl | -H | 3 | 3-OH | 15.84±1.42 | 50.21±6.24 | 18.21±1.28 | 92.14±2.94 |
| 64 | -F | -$CH_3$ | 4 | 3-OH | 31.25±1.25 | 51.24±8.22 | 04.62±1.85 | 92.01±2.39 |
| 65 | -$CH_3$ | -F | 3 | 3-OH | 42.84±0.94 | 55.21±6.25 | 06.32±1.24 | 93.21±2.51 |
| 66 | -H | -Cl | 4 | 3-OH | 21.56±0.54 | 52.61±5.61 | 04.15±2.10 | 95.12±3.07 |
| 67 | -Cl | -H | 4 | 3-OH | 29.38±0.41 | 52.84±6.01 | 09.21±1.28 | 96.31±2.14 |
| 68 | -F | -$CH_3$ | 4 | 3-OH | 38.25±0.71 | 56.14±12.5 | 06.32±1.85 | 93.21±3.05 |
| 69 | -$CH_3$ | -F | 4 | 3-OH | 33.21±0.84 | 56.32±8.21 | 03.21±1.28 | 96.01±2.08 |
| 70 | -H | -Cl | 3 | 3,5-$CH_3$ | 43.25±1.28 | 63.21±12.5 | 5.33±1.51 | 88.21±1.94 |
| 71 | -Cl | -H | 3 | 3,5-$CH_3$ | 55.24±1.01 | 68.32±8.12 | 07.14±1.24 | 97.26±2.14 |
| 72 | -H | -Cl | 4 | 3,5-$CH_3$ | 61.53±1.08 | 65.14±10.3 | 12.36±1.85 | 96.48±1.24 |
| 73 | -Cl | -H | 4 | 3,5-$CH_3$ | 76.12±1.21 | 69.21±6.21 | 23.14±1.65 | 96.21±3.02 |
| NNGH | ----- | ----- | --- | ---- | 0.014±0.01 | ----- | ----- | ----- |
| Control | ----- | ----- | ---- | ----- | ----- | 100±1.24 | ----- | ----- |
| Aa | ----- | ----- | ---- | ----- | ----- | ----- | 03.47±0.34 | ----- |
| TC+ | ----- | ----- | | ----- | ----- | ----- | ----- | 100±2.14 |
| TC- | ----- | ----- | | ----- | ----- | ----- | ----- | 28.21±2.18 |

Aa- Ascorbic acid; [a]Cell viability (CV) /Neuroprotection assay against MC65 cell line TC+ Tetracycline present, TC- Tetracycline absent.

**Figure 6.13** Inhibition assay of metal induced $A\beta_{1-42}$ aggregation and its confocal imaging: (A) metal induced $A\beta_{1-42}$ aggregation assay (One-way ANOVA followed by one-way analysis of variance*** $p < 0.0001$), error bars represent the standard deviation (SD) of the normalized fluorescence intensity (NFI), DNP; confocal image of (B) ThT (C) $A\beta_{1-42}$ along with ThT (D) $A\beta_{1-42}$ without fluorescence dye ThT (E) $A\beta_{1-42}$ along with $FeCl_3$ (F) $A\beta_{1-42}$ containing $FeCl_3$ and ThT (G) $A\beta_{1-42}$ containing $FeCl_3$, compound 55 and ThT (H) compound **55** and ThT (I) containing only compound **55**; (magnification 40X).



### 6.4.6 Antioxidant activity (DPPH assay)

DPPH assay measures the hydrogen atom/ electron donating capacity, and is based on reduction of DPPH (1, 1-Diphenyl-2-picrylhydrazyl), a stable free radical of purple color, to yellow colored of 1, 1,-diphenyl-2-picryl hydrazine. Adamantyl (scheme I) and 1,4-disubstituted 1,2,3-triazoles (scheme II) were screened for their antioxidant potential. Adamantyl containing compounds **17**, **18**, **19** and **20** were found to be most active in series ($EC_{50}$ 23.62±2.14, 21.35±1.25, 27.51±1.28, 24.56±2.14 µM, respectively). The possible reason behind the superior activity of these compounds among its series are the presence of hydroxyl group on third position of adamantly. 1,2,3-triazoles containing three nitrogen's have the better possibility to quench the free radicals generated in the DPPH assay and are having superior antioxidant potential for compounds **64**, **65**, **66**, **69** and **70** ($EC_{50}$ 04.62±1.85, 06.32±1.24, 04.15±2.10, 03.21±1.28, 5.33±1.51 µM). The other compounds **57**, **58**, **60**, **61** and **71** have moderate free radical quenching potential (08.54±1.24, 08.96±1.25, 09.21±2.14, 10.24±1.25, 07.14±1.24 µM) (**Table 6.3**).

### 6.4.7 Electrophysiological study on oocyte of *Xenopus laevis*

Effects on compounds **22**, **24** and **26** was observed on the electrophysiology of NMDA receptor and was recorded and displayed in **Figure 6.14**. Compounds were diluted in barium ringer solution and antagonists were tested in agonist solution. The hampening of agonist induced current by compound **22** is depctied at selected concentration in GluN1A/GluN2A heteromers. (**Figure 6.14)** Inhibitory effect of 1000 µM of Compound **26** on GluN1A/GluN2A (8) and GluN1A/GluN2B heteromers and also for compound **24** on GluN1A/GLuN2A heteromers (9) and GluN1A-GluN2B containing receptor were evaluated.

From the data, percentage of agonist induced current inhibition was recorded for various concentrations of the compound and data was plotted for activity against GluN1A/GluN2B subunit containing NMDA receptor **(Figure 6.15)**.

### 6.4.8 MC65 neuroprotection assay

The mutated neuronal cell line MC65 itself produces Aβ in the absence of tetracycline (TC-) leading to generation of ROS. The rational behind the use of 1,2,3-triazoles in series two was due to the neuroprotection by the moiety. Compounds **55**, **57**, **58**, **60**, **61**, **66**, **67**, **69**, **71**, **72** and **73** showed significant neuroprotection (98.51±2.01, 95.01±1.51, 97.14±3.06, 97.21±2.25, 98.15±2.15, 96.31±2.14, 96.01±2.08, 97.26±2.14, 96.48±1.24, 96.21±3.02 µM, respectively).

### 6.4.9 Molecular dynamics simulation

Molecular dynamics simulation of protein ligand complex of compound **22** was performed for 50 ns. It indicated that presence or absence of ligand in the active site of protein did not affect the global RMSD of protein. Further, the simulation of protein along with compound **22** also displayed similar RMSD in range of 1- 2.5 Å, which was acceptable for proteins. Molecular dynamics simulation indicated that presence of ligand stabilized the protein in 200-325 residue regions. The ligand RMSF of compound **22** revealed that the adamantyl group exhibited greater flexibility than other regions of molecule. It was also observed that compound **22** displayed hydrogen bond interaction with residues Glu and Arg for more than 50 percent of total run time. The hydrophobic interactions were also significant in contributing ligand-receptor stability through residues Tyr109, Phe133 and TYR239 for signification fraction of time. The compound also showed water mediated hydrogen bonding through residues Glu106, Arg115, and Glu236 (**Figure 6.16**).

**Figure 6.14** Effect of Compounds **22**, **24**, **26** on Glycine and glutamate evoked currents in GluN1/GluN2A containing receptor and GluN1A/GluN2B containing receptor.

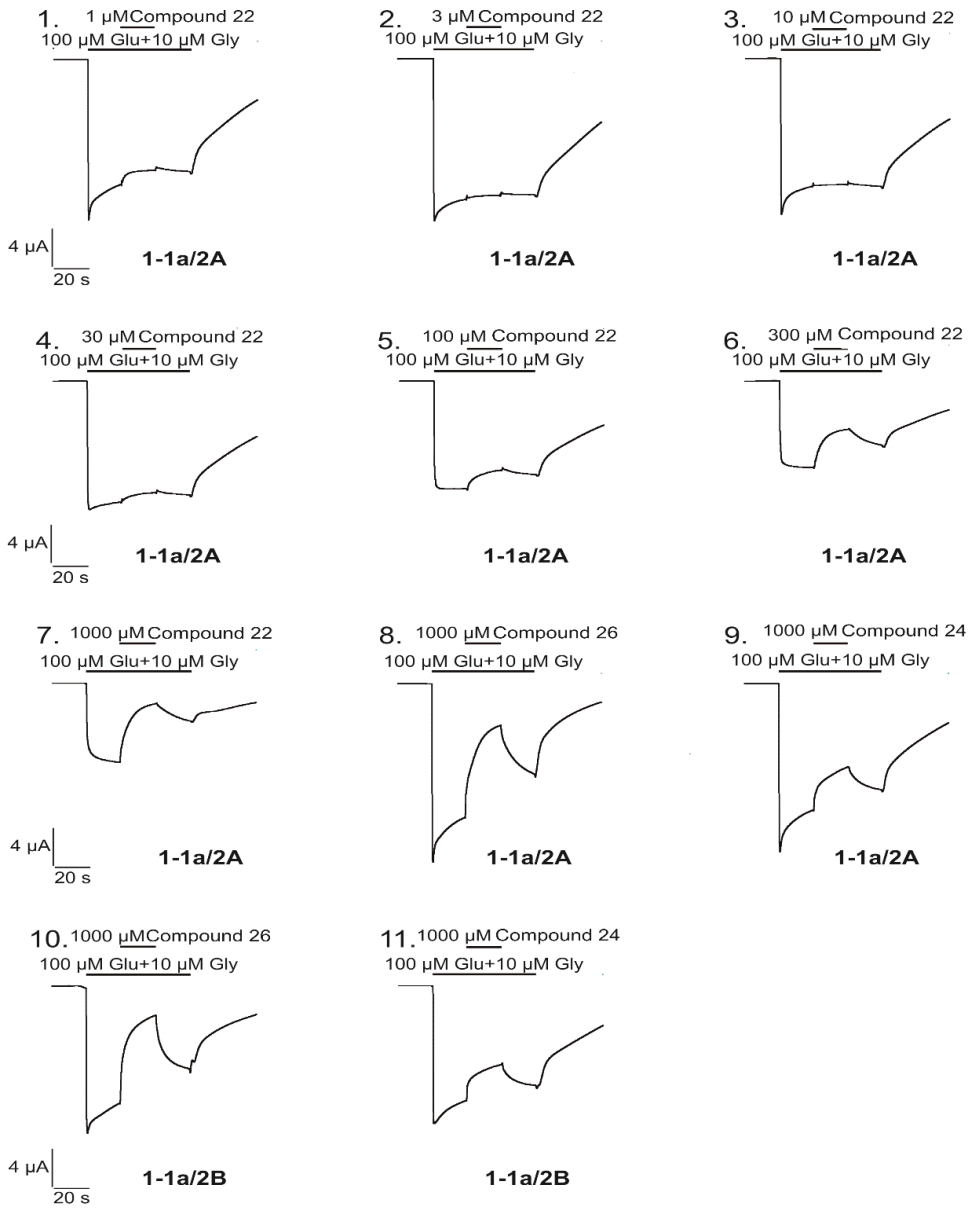


**Figure 6.15** Inhibition of current induced by 100 µM glutamate and 10µM glycine in presence of antagonists tested on GluN1A/ GluN2B containing receptor.

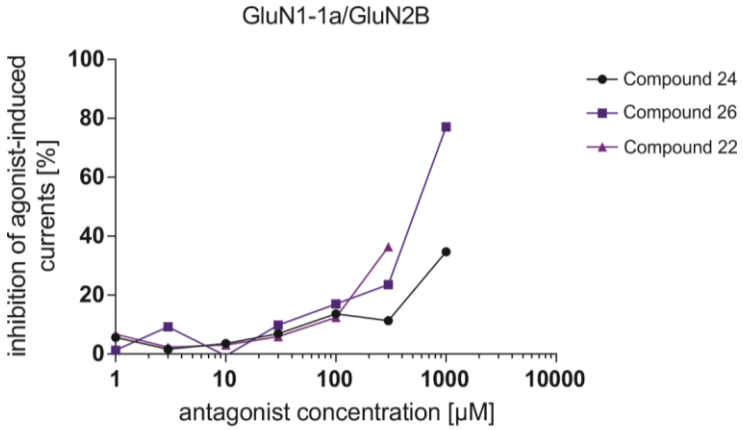
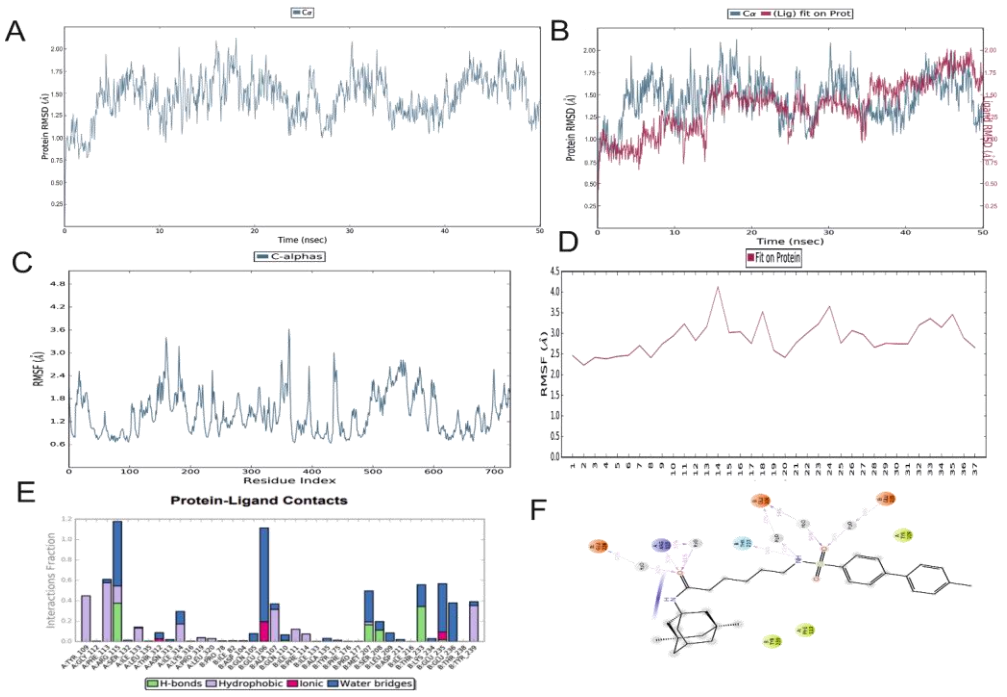



**Figure 6.16** (A) and (B) Protein RMSD and Protein Ligand RMSD respectively. (C) Root Mean Square Fluctuation (RMSF) of protein in presence of compound. (D) RMSF of ligand (E) Interaction fraction of Protein-Ligand Contacts (F) Protein ligand interaction.



## 6.5 Conclusion

Adamantyl (**16**-**27**) and their 1,4-disubstituted 1,2,3-triazole (**54**-**73**) derivatives were designed, synthesized and screened for its biological activity. The derivatives were substituted with biphenyl groups and various linkers. Compound **22** showed the maximum activity in the adamantyl (**16**-**27**) series. The results indicated that compounds containing unsubstituted amantadine (**21**, **22**) were better for the MMP-2 enzyme binding. Presence of five carbon linker along with substitution at para position of the biphenyl group increased the activity. Three, five di-substituted methyl containing compounds (**23**-**26**) were also found to be active but it was lower than the unsubstituted amantadines. Electron withdrawing groups at para position of biphenyl along with five carbon linker increased the activity in this series. Hydrogen bond donors at third position of amantadine decreased the activity. The detailed docking pose analysis of hydroxy group containing compounds (**17**-**20**) reveled that hydrophobic amino acid residues were present around the group. These residues showed favorable interactions with compounds (**23**-**26**) containing methyl at third and fifth positions. Triazoles containing compounds having electron withdrawing groups at para position of biphenyl group along with four carbon linker showed better activity (compound **55**). Displacement of chloro group from biphenyl para position to triazoleyl phenyl decreased the activity slightly (compound **54**). Further, increasing the carbon length of linker decreased the activity due to increase in free rotation and unfavorable receptor penetration (compound **58**-**61**). Three hydroxyl and three, five dimethyl containing compounds showed reduced enzyme activity (compound **62**-**73**). Although, the decrease in the activity of compounds **62**-**73** were observed, but still the compounds were produced descent $IC_{50}$ values (18-76 μM due to presence of triazole).

The $A\beta_{1-42}$ aggregation at ratio 10:20 µM for compounds **16**-**27** was in range of 72-92%. Most of the compounds (**16**-**20**) showed $A\beta_{1-42}$ aggregation in the range of 72-80 % range. Amantadine containing compounds (**16**-**27**) having hydroxyl group at third position showed better anti-aggregation activity against peptide due to the presence of lone pair on the hydroxyl group. Moderate antioxidant and neuroprotecting activity was in compounds **16**-**27**. Triazole group is reported for its antioxidant and neuroprotective activity. It was assumed that the activity by triazole will lead to disaggregation of $A\beta_{1-42}$. Compounds (**54**-**73**) containing triazole showed much better activity against $A\beta_{1-42}$ aggregation. These compounds also possessed superior antioxidant and cell viability potentials.