Synthesis, Spectral Evaluation and *in Silico* Studies of *S*-Aralkylated 5-(4-methoxyphenyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiols: As suitable Alzheimer's disease drug candidates

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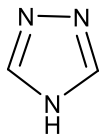
Summary: Our efforts lay emphasis on synthesis of *S*-aralkylated 5-(4-$OMeC_6H_5$)-4-phenyl-4*H*-1,2,4-triazol-3-thiols like pharmacologically active candidates to counter neurodegenerative disorder; Alzheimer's disease. A synthetic strategy was instigated by esterifying 4-methoxybenzoic acid through Fisher esterification's methodology. Hydrazinolysis of corresponding ester was performed under reflux with methanolic hydrated hydrazine to afford 4-methoxybenzohydrazide (**I**) which refluxing with phenyl isothiocyanate (**II**) in MeOH to yield a reactive intermediate (**III**). The later underwent base-catalyzed intermolecular cyclization to furnish 5-(4-$OMeC_6H_5$)-4*H*-1,2,4-triazol-3-thiol (**IV**). Ultimately, **IV** was aralkylated at thiol position with aralkyl halides **V(a-l)** in polar aprotic solvent and catalytic amounts of LiH to provide *S*-aralkylated 5-(4- $OMeC_6H_5$)-4-phenyl-4*H*-1,2,4-triazol-3-thiols **VI(a-l)**. Modern spectral analysis data explicitly established all the substitutions on nucleophilic *S*-atom of parent 1,2,4-triazol-3-thiol ring. Effective anti-cholinesterase potential depicted in 3-(phenylpropylthio)-5-(4-$OMeC_6H_5$)-4-phenyl-4*H*-1,2,4-triazole**; VIc** (IC_{50}; 3.26±0.35 μM) against acetyl cholinesterase; AChE and 3-(phenethylthio)-5-(4-$OMeC_6H_5$)-4-phenyl-4*H*-1,2,4-triazole; **VIb** (IC_{50}; 8.52±0.54 μM) against butyrylcholinesterase; BChE enzyme as compared to standard Eserine for both enzymes ($IC_{50;}$ 0.04±0.01 μM). Molecular modelling analyses had been conducted to recognize the interconnection of these compounds with enzymes that suggested key interactions (Docking is made to untie the active binding sites). Anti-proliferative activity results showed **VIg** and **VIj** with -Cl groups on benzylic ring as promising candidates with HCT-116 cell viability of 14.83 % and 3.09 % respectively.

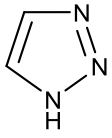
Keywords: 1,2,4-Triazole; Aralkyl halide; Spectral analysis; Cholinesterase abstinence.

Introduction

Triazoles gained importance after successful application of imidazoles as medicinal compounds. The 1,2,4-triazole ring, an isoester of imidazole, comprises of 5-membered heterocyclic ring having 3-N and 2-C atoms fused in a way that *C*-atoms took place at non-adjacent position in the ring. The simplest member of the family, the triazole (Fig. 1), exists as white crystalline solid with feeble distinctive odor soluble in alcohol, chloroform and water. Triazole and its derivatives display numerous biological activities [1, 2] e.g. anti-viral, anti-bacterial [3-5] anti-tuberculosis [6] and anti-fungal [7]. Per beneficence in pharmaceutical industry, 1,2,4-triazoles are very important (Fig. 1; I & II) in terms of biological activities spectrum. 1,2,4-Triazole heterocyclic symmetrical ring is notified as the most important biological active moiety among the two forms.



4*H*-1,2,4-Triazole **(I)**



1*H*-1,2,3-Triazole **(II)**

Fig. 1: Isomers of 1,2,4-Triazole.

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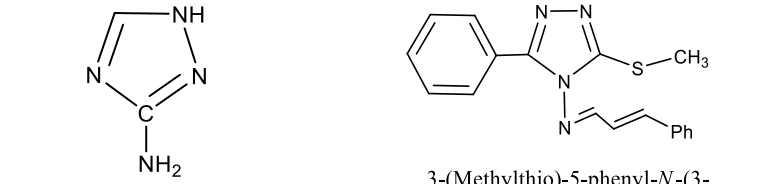
Bioisosterism is a phenomenon in which *O*-atom of oxadiazole nucleus is replaced with *N*-atom to yield triazole and its various analogues. 1,2,4-Triazole have widespread diversity of activity when 1,2,3 and 1,2,4-triazoles are compared. Amitrole is the first clinical synthetic compound based on 1,2,4-triazole nucleus (Fig. 2; **III**). Nitric oxide synthase in rat plasma and urine is inhibited by some innovative 1,2,4-triazoles (Fig. 2; **IV**).

1,2,4-Triazoles and quinoline based triazoles (**Fig. 3; V-XI**) are known to possess anti-bacterial and anti-fungal activities [8,9].

(1-*H*-1,2,4-Triazol-1-yl-CH_3)phenols, anilines, *N*-alkylanilines and *N,N*-dialkylanilines have bactericidal and fungicidal characteristics [10]. Some novel 1,2,4-triazoles were studied for surface activity [11]. The 1,2,4-triazole scaffolds bearing benzothiophene nucleus [12,13] were also found to possess anti-microbial potential. Similarly, 1,2,4-triazolo-thiol & aminonitriles possess anti-fungal activities [14]. 4-(1*H*-1,2,4-Triazol-1-yl-CH_3)phenol showed genotoxic activity [15]. Alzheimer's is neurodegenerative disease globally spread. Support therapy for it includes use of sedatives and inhibition of acetylcholinesterase (AChE) to raise conc. of acetylcholine in synaptic fissure [16-18]. In scheming of novel active drug candidates, computational chemistry aligned with biological ability is helpful with quick-chased drug discovery system. Operative molecular docking is used to explore drug-ligand interactions, in understanding of drug's binding alignment & attraction for targeted protein [19, 20]. Commonly, in living system, proteins are accountable for operative activity of numerous drugs that justified over the binding of characteristic proteins-drug affinity. Clue about the effectiveness of drug is connected with the protein-drug binding interaction and hence make it active research area [21].

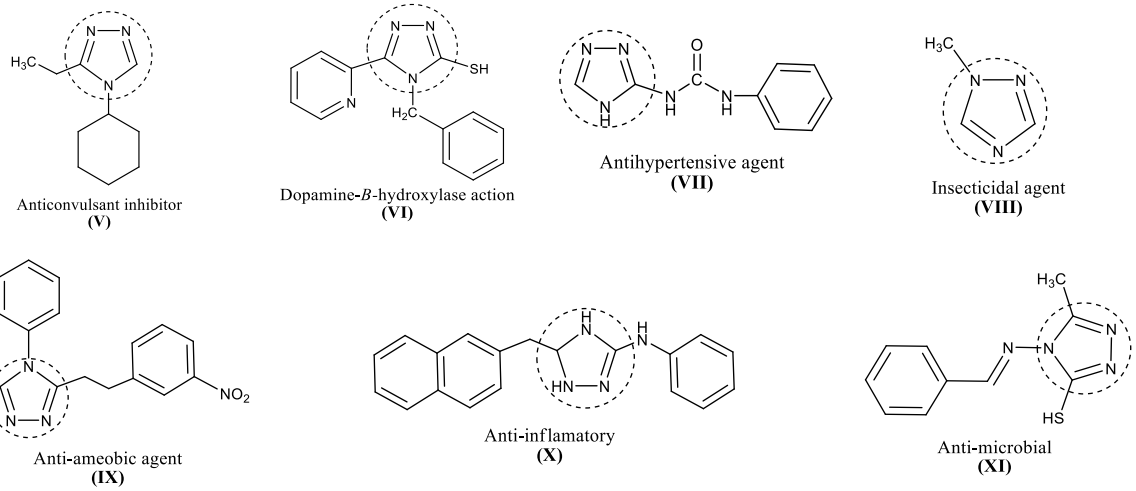
Based on our current research work and literature [22, 23] mentioned on 1,2,4-triazoles and their cholinesterase inhibition studies, range of pharmaceutically significant 1,2,4-triazols scaffolds incorporating 4-methoxyphenyl fraction made, their *in vitro* & *in silico* studies were determined.



1*H*-1,2,4-Triazol-3-amine **(III)**

3-(Methylthio)-5-phenyl-*N*-(3-phenylallylidene)-4*H*-1,2,4-triazol-4-amine **(IV)**

Fig. 2: Structure of clinical synthetic compounds.



Anticonvulsant inhibitor **(V)**

Dopamine-*B*-hydroxylase action **(VI)**

Antihypertensive agent **(VII)**

Insecticidal agent **(VIII)**

Anti-ameobic agent **(IX)**

Anti-inflamatory **(X)**

Anti-microbial **(XI)**

Fig. 3: Pharmaceutical agents commercially available bearing 1,2,4-triazole core (**V-XI**).

Experimental

Materials

Aldrich & Alfa Aesar were used to procure solvents and analytical grade chemicals and solvents. The path was checked & scrutinized for completion by chromatography (TLC) utilizing various percentage of (*n*-C_6H_{14}: $C_4H_8O_2$) as mobile medium, 254 nm UV spectral lines were used as visualizing agent. Griffin & George apparatus was utilized to verify melting points of compounds. IR spectra were recorded by Jasco-320-A spectrophotometric instrument ($\bar{\upsilon}$; cm^{-1}). Jeol MS 600 H-1 instrument was utilized to measure EIMS. Structure of synthesized products were elucidate by ^1H & ^{13}C (600 & 150 MHz) NMR done on Bruker setup.

Procedure

5-(4-OMeC_6H_5)-4-phenyl-4H-1,2,4-triazol-3-thiol **(IV)**

0.1 mol 4-Methoxybenzohydrazide (**I**) was reacted with 0.1 mol phenyl isothiocyanate (**II**) in methanol for 15 min. to hasten 2-(4-methoxybenzoyl)-*N*-phenylhydrazinecarbothioamide (**III**). Aftrer filtering & washing with methanol, ppts were dried in air to achieve transitional compound, that was further cyclized further by refluxing in alkaline medium (30 mL, 10 % NaOH) for 6 h. Limited aliquots of HCl was utilized to attain pH 2-3 to accomplish 5-(4-OMeC_6H_5)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (**IV**) that bathed by plenty dist. H_2O & sort out from pure C_2H_5OH.

S-Aralkylated 5-(4-OMeC_6H_5)-4-phenyl-4H-1,2,4-triazol-3-thiols **VI(a-l)**

0.7 mmol 5-(4- OMeC_6H_5)-4-phenyl-4*H*-1,2,4-triazol-3-thiol (**IV**) dissolved in DMF along with LiH (0.0008 g; 0.1 mmol) & then 0.7 mmol aralkyl halides (**V(a-l)**) were introduced to rex. that agitated for 7.0-8.0 h at RT. Ultimately, products were precipitated with ice and $CHCl_3$ utilized for extraction like an organic media in certain circumstances to give *S*-aralkylated 5-(4- OMeC_6H_5)-4-phenyl-4*H*-1,2,4-triazol-3-thiol **VI(a-l)** in upright vintages.

Cholinesterase Assays

Following equation was used to calculate % age inhibition values by performing cholinesterase (acetyl/butyryl) assay [24].

$$\% \text{ age Inhibition} = [(\text{Blank} - \text{Sample})/\text{Blank}] \times 100$$

whereas,

Blank and samples's absorbance read at 405nm. The IC_{50} of active samples was determined by assaying the suitable dilutions of the samples and data obtained was enamurated.

Anti-proliferation activity evaluation

Compounds were studied for anti-proliferation against HCT 116 human colon cancer *lines* assayed by Sulforhodamine B (SRB) method [25, 26]. Following formula was used to measure the % age activity:

$$\text{Anti} - \text{proliferation } (\%) = \frac{\text{Absorbance (Control)} - \text{Absorbance (Sample)}}{\text{Absorbance (Control)}} \times 100$$

Molecular Docking

In order to perform the docking of the scaffolds, construction of 3D forms of all scafflods done by means of Chem3D, kept in pdb setup and energy was lessened exploiting Avogadro. Human AChE (PDB accession code: *4pqe*, resolution 2.9 A through X-ray diffraction) and BChE cystal structures (PDB accession code: *1p0i*, resolution 2.0 A through X-ray diffraction) recovered from protein databank. Water particles detached from these structures using PyMol and MGLTools used for addition of hydrogen atoms. Both AChE and BChE Experimentally, synthesized scaffolds were docked against AChE & BChE using Auto-Dock Vina. The search space of 62 x 71 x 53 in x, y, and z dimensions was used for AChE and a search space 62 x 56 x 72 in x, y, and z dimensions were used for BChE. Discovery Studio Visualizer utilized to envisage docking results[27-31].

Results and Discussion

Chemistry

This research work is planned to discover biologically active compounds having potent anticholinesterase action beside with valuable anti-proliferative action. In experimental section, synthetic methodology and reaction conditions are documented for preparation of *S*-aralkylated 5-(4-OMeC_6H_5)-4-phenyl-4*H*-1,2,4-triazol-3-thiols **(VIa-l; Schem 1** & Table-1**)**. Contemporary spectral techniques were used to characterize synthesized compds., e.g., FTIR, EI-MS, ^1H & ^{13}C-NMR to elucidate their structures. Furthermore, these compounds have been analysed for anticholinesterase activities in terms of IC_{50} figures. Mostly they were potent in comparison to standard; Eserine and were docked to substantiate the results.

(Benzylthio)-5-(4-OMeC_6H_5)-4-phenyl-4H-1,2,4-triazole **(VIa)**

Amorp. residue; Y(%): 76; M.Pt.: 182 ^{0}C; Mol. formula: $C_{22}H_{19}N_3OS$; Mol. wt.(g/mol): 373; IR (ῡ; 1/cm): 2940, 1606, 1437, 1255, 1174, 1025, 835; ^{1}H-NMR with frequency 600x10^6 hertz: δ 7.48-7.43 (m. 3 $_1H^+$, H/3‴-5‴), 7.35 (d., J = 10.5, 2 $_1H^+$, H/2′,6′), 7.31-7.26 (m., 5 $_1H^+$, H/2‴-6‴), 7.09 (d., J = 8.7, 2 $_1H^+$, H/2‴,6‴), 6.80 (d., J = 10.5, 2 $_1H^+$, H/3′,5′), 4.49 (s., 2 $_1H^+$, -CH_2/7‴), 3.79 (s., 3 $_1H^+$, -OCH_3/1″); ^{13}C-NMR with frequency 150x10^6 hertz: δ 160.64 (C/4′), 154.80 (C/2), 151.96 (C/1), 136.57 (C/1‴), 134.40 (C/1⁗), 129.80 (C/2′,6′), 129.65 (C/4‴), 129.58 (C/3‴,5‴), 129.18 (C/3⁗,5⁗), 128.58 (C/2‴,6⁗), 127.63 (C/4⁗), 127.44 (C/2‴,6‴), 119.15 (C/1′), 113.93 (C/3′,5′), 55.01 (C/1″), 37.44 (C/7⁗); Analytical Cal.: $C_{22}H_{19}N_3OS$ (373.12): C: 70.75; H: 5.13; N: 11.25; O: 4.28; S: 8.59. Exact: C: 70.73; H: 5.10; N: 11.23; O: 4.25; S: 8.61; EI-MS: m /z 373 $[C_{22}H_{19}N_3OS]^{\bullet+}$ $[M]^{\bullet+}$, 282 $[C_{15}H_{12}N_3OS]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

3-(Phenethylthio)-5-(4-OMeC_6H_5)-4-phenyl-4H-1,2,4-triazole **(VIb)**

Amorp. residue: Y(%): 79; M.Pt.: 130 ^{0}C; Mol. formula: $C_{23}H_{21}N_3OS$; Mol. Wt.((g/mol)): 387 gmol^{-1}; IR (ῡ; 1/cm): 2929, 1606, 1437, 1255, 1137, 1018, 836; ^{1}H-NMR with frequency 600x10^6 hertz: δ 7.52-7.48 (m., 3 $_1H^+$, H/3‴,5‴), 7.37 (d., J = 8.8, 2 $_1H^+$, H/2′,6′), 7.30 (d., J = 7.4, 2 $_1H^+$, H/2‴,6‴), 7.27-7.22 (m., 5 $_1H^+$, H/2⁗,6⁗), 6.81 (d., J = 8.8, 2 $_1H^+$, H/3′,5′), 3.80 (s., 3 $_1H^+$, -OCH_3/1″), 3.51 (t., J = 7.5, 2 $_1H^+$, -CH_2/8⁗), 3.12 (t., J = 7.8, 2 $_1H^+$, -CH_2/7⁗); ^{13}C-NMR with frequency 150x10^6 hertz: δ 160.59 (C/4′), 154.79 (C/2), 152.24 (C/1), 139.75 (C/1‴), 134.48 (C/1⁗), 129.87 (C/2′ to C/6′), 129.73 (C/4‴), 129.58 (C/3⁗,5⁗), 128.69 (C/3⁗,5⁗), 128.46 (C/2⁗,6⁗), 127.43 (C/2⁗,6⁗), 126.50 (C/4⁗), 119.18 (C/1′), 113.94 (C/3′,5′), 55.24 (C/1″), 35.84 (C/8⁗), 33.69 (C/7⁗); Analytical Cal.: $C_{23}H_{21}N_3OS$ (387.14): C: 71.29; H: 5.46; N: 10.84; O: 4.13; S: 8.27. Exact: C: 71.31; H: 5.44; N: 10.82; O: 4.11; S: 8.25; EI- MS: m /z 387 $[C_{23}H_{21}N_3OS]^{\bullet+}$ $[M]^{\bullet+}$, 250 $[C_{15}H_{12}N_3O]^+$, 224 $[C_{14}H_{12}N_2O]^+$, 210 $[C_{14}H_{12}NO]^+$, 133 $[C_8H_7NO]^+$, 105 $[C_8H_9]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

3-(Phenylpropylthio)-5-(4-OMeC_6H_5)-4-phenyl-4H-1,2,4-triazole **(VIc)**

Amorp. residue; Y(%): 72; M.Pt.: 127 ^{0}C; Mol. formula: $C_{24}H_{23}N_3OS$; Mol. wt.(g/mol): 401; IR (ῡ; 1/cm): 2934, 1607, 1434, 1249, 1179, 1024, 835; ^{1}H-NMR with frequency 600x10^6 hertz: δ 7.53-7.49 (m., 3 $_1H^+$, H/3‴-5‴), 7.35 (d., J = 8.7, 2 $_1H^+$, H/2′,6′), 7.28 (d., J = 7.0, 2 $_1H^+$, H/2‴,6‴), 7.24-7.18 (m., 5 $_1H^+$, H/2⁗-6⁗), 6.80 (d., J = 8.76, 2 $_1H^+$, H/3′,5′), 3.79 (s., 3 $_1H^+$, -OCH_3/1″), 3.26 (t., J = 7.2, 2 $_1H^+$, -CH_2/9⁗), 2.76 (t., J = 7.5, 2 $_1H^+$, -CH_2/7⁗), 2.12(quint., J = 7.4, 2 $_1H^+$, -CH_2/8⁗); ^{13}C-NMR with frequency 150x10^6 hertz: δ 160.59 (C/4′), 154.77 (C/2), 152.27 (C/1), 141.02 (C/1‴), 134.55 (C/1⁗), 129.86 (C/2′-6′), 129.76 (C/4‴), 129.59 (C/3‴,5‴), 128.52 (C/3⁗,5⁗), 128.39 (C/2⁗,6⁗), 127.46 (C/2‴,6‴), 125.98 (C/4⁗), 119.19 (C/1′), 113.93 (C/3′,5′), 55.23 (C/1″), 34.61 (C/9⁗), 31.99 (C/7⁗), 30.88 (C/8⁗); Analytical Cal.: $C_{24}H_{23}N_3OS$ (401.16): C: 71.79; H: 5.77; N: 10.47; O: 3.98; S: 7.99. Exact: C: 71.77; H: 5.75; N: 10.45; O: 3.95; S: 7.96; EI- MS: m /z 401 $[C_{24}H_{23}N_3OS]^{\bullet+}$ $[M]^{\bullet+}$, 224 $[C_{14}H_{12}N_2O]^+$, 210 $[C_{14}H_{12}NO]^+$, 133 $[C_8H_7NO]^{\bullet+}$, 119 $[C_9H_{11}]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

3-(2-Methylbenzylthio)-5-(4-OMeC_6H_5)-4-phenyl-4H-1,2,4-triazole **(VId)**

Amorp. residue; Y(%): 72; M.Pt.: 124 ^{0}C; Mol. formula: $C_{23}H_{21}N_3OS$; Mol. wt.(g/mol): 387; IR (ῡ; 1/cm): 2938, 1621, 1436, 1251, 1176, 1023, 835; ^{1}H-NMR with frequency 600x10^6 hertz: δ 7.48-7.42 (m., 3 $_1H^+$, H/3‴-5‴), 7.35 (d., J = 8.6, 2 $_1H^+$, H/2′-6′), 7.27 (dist.t., J = 7.5, 1 $_1H^+$, H/5⁗), 7.18 (t., J = 7.3, 1 $_1H^+$, H/4⁗), 7.15-17.10 (d.-merged, J = 7.6, 2 $_1H^+$, H/3⁗,6⁗), 7.05 (d., J = 7.6, 2 $_1H^+$, H/2⁗,6⁗), 6.80 (d., J = 8.6, 2 $_1H^+$, H/3′,5′), 4.49 (s., 2 $_1H^+$, -CH_2/7⁗), 3.79 (s., 3 $_1H^+$, -$OCH_3$1″), 2.33 (s., 3 $_1H^+$, -CH_3/1⁗); ^{13}C-NMR with frequency 150x10^6 hertz: δ 160.63 (C/4′), 154.82 (C/2), 152.04 (C/1), 137.13 (C/1‴), 134.4 (C/1⁗), 134.06 (C/2⁗), 130.52 (C/3⁗), 130.21 (C/6⁗), 129.73 (C/2′,6′), 129.52 (C/3⁗-5⁗), 128.06 (C/4⁗), 127.44 (C/2‴,6‴), 126.17 (C/5⁗), 119.14 (C/1′), 113.93 (C/3′,5′), 55.23 (C/1″), 35.89 (C/7⁗), 19.03 (C/1⁗); Analytical Cal.: $C_{23}H_{21}N_3OS$ (387.14): C: 71.29; H: 5.46; N: 10.84; O: 4.13; S: 8.27. Exact: C: 71.31; H: 5.48; N: 10.82; O: 4.11; S: 8.25; EI- MS: m /z 387 $[C_{23}H_{21}N_3OS]^{\bullet+}$ $[M]^{\bullet+}$, 282 $[C_{15}H_{12}N_3OS]^+$, 210 $[C_{14}H_{12}NO]^+$, 133 $[C_8H_7NO]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

3-(3-Methylbenzylthio)-5-(4-OMeC_6H_5)- 4-phenyl-4H-1,2,4-triazole **(VIe)**

Amorp. residue; Y(%): 74; M.Pt.: 117 ^{0}C; Mol. formula: $C_{23}H_{21}N_3OS$; Mol. wt.(g/mol): 387; IR (ῡ; 1/cm): 2936, 1620.27, 1435, 1250, 1175, 1022, 835; ^{1}H-NMR with frequency 600x10^6 hertz: δ 7.49-7.43 (m., 3 $_1H^+$, H/3‴-5‴), 7.35 (d., J = 7.8, 2 $_1H^+$, H/2′,6′), 7.19-7.13 (m., 3 $_1H^+$, H/4⁗-6⁗), 7.09 (s., 1 $_1H^+$, H/2⁗), 7.08 (d., J = 6.4, 2 $_1H^+$, H/2⁗,6⁗), 6.80 (d., J = 7.8, 2 $_1H^+$, H/3′,5′), 4.45 (s., 2 $_1H^+$, -CH_2/7⁗), 3.79 (s., 3 $_1H^+$, -OCH_3/1″), 2.32 (s., 3 $_1H^+$, -CH_3/1⁗); ^{13}C-NMR with frequency 150x10^6 hertz: δ 160.62 (C/4′), 154.79 (C/2), 152.05 (C/1), 138.29 (C/1‴), 136.34 (C/1⁗), 134.42

(C/3‴″), 129.87 (C/5‴″), 129.74 (C/2′,6′), 129.63 (C/4‴″), 129.59 (C/3‴-5‴″), 128.40 (C/2‴″), 127.44 (C/2‴,6‴″), 126.22 (C/6‴″), 119.16 (C/1′), 113.93 (C/3′,5′), 55.23 (C/1‴), 37.50 (C/7‴″), 21.25 (C/1‴″); Analytical Cal.: $C_{23}H_{21}N_3OS$ (387.14): C: 71.29; H: 5.46; N: 10.84; O: 4.13; S: 8.27. Exact: C: 71.27; H: 5.44; N: 10.82; O: 4.12; S: 8.29; EI- MS: *m /z* 387 $[C_{23}H_{21}N_3OS]^{\bullet+}$ $[M]^{\bullet+}$, 282 $[C_{15}H_{12}N_3OS]^+$, 210 $[C_{14}H_{12}NO]^+$, 133 $[C_8H_7NO]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

3-(4-Methylbenzylthio)-5-(4-OMeC_6H_5)- 4-phenyl-4H-1,2,4-triazole **(VIf)**

Amorp. residue; Y(%): 71; M.Pt.: 190 ^{0}C; Mol. formula: $C_{23}H_{21}N_3OS$; Mol. wt.(g/mol): 387; IR (ῡ; 1/cm): 2939, 1622, 1437, 1252, 1177, 1024, 834; ^{1}H-NMR with frequency 600x10^6 hertz: δ 7.48-7.43 (m., 3 $_1H^+$, H/3‴-5‴), 7.35 (d., J = 9.5, 2 $_1H^+$, H/2′,6′), 7.25 (d., J = 8.8, 2 $_1H^+$, H/2‴,6‴), 7.12-7.11 (m., 4 $_1H^+$, H/2‴,6‴,3‴,5‴), 6.80 (d., J = 9.5, 2 $_1H^+$, H/3′,5′), 4.46 (s., 2 $_1H^+$, -CH_2/7‴″), 3.79 (s., 3 $_1H^+$, -OCH_3/1″), 2.33 (s., 3 $_1H^+$, -CH_3/1‴″); ^{13}C-NMR with frequency 150x10^6 hertz: δ 160.62 (C/4′), 154.75 (C/2), 152.12 (C/1), 137.40 (C/1‴), 134.45 (C/4‴″), 133.42 (C/1‴″), 129.74 (C/2′,6′), 129.62 (C/4‴″), 129.58 (C/3‴-5‴″), 129.09 (C/3‴″,5‴″), 127.44 (C/2‴,6‴″), 129.26 (C/2‴″,6‴″), 119.19 (C/1′), 113.92 (C/3′,5′), 55.22 (C/1″), 37.13 (C/7‴″), 21.08 (C/1‴″); Analytial Cal.: $C_{23}H_{21}N_3OS$ (387.14): C: 71.29; H: 5.46; N: 10.84; O: 4.13; S: 8.27. Exact: C: 71.28; H: 5.44; N: 10.86; O: 4.10; S: 8.28; EI-MS: *m /z* 387 $[C_{23}H_{21}N_3OS]^{\bullet+}$ $[M]^{\bullet+}$, 282 $[C_{15}H_{12}N_3OS]^+$, 210 $[C_{14}H_{12}NO]^+$, 133 $[C_8H_7NO]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

3-(2-Chlorobenzylthio)-5-(4-OMeC_6H_5)-4-phenyl-4H-1,2,4-triazole **(VIg)**

Amorp. residue; Y(%): 75; M.Pt.: 130 ^{0}C; Mol. formula: $C_{22}H_{18}ClN_3OS$; Mol. wt.(g/mol): 407; IR (ῡ; 1/cm): 2937, 1610, 1435, 1249, 1175, 1033, 841; ^{1}H-NMR with frequency 600x10^6 hertz: δ 7.57 (d., J = 7.2, 1 $_1H^+$, H/3‴), 7.49-7.43 (m., 3 $_1H^+$, H/3‴-5‴), 7.36-7.33 (d.-merged, J = 7.2, 3 $_1H^+$, H/2′,6′,6‴), 7.24-7.19 (m., 2 $_1H^+$, H/4‴,5‴), 7.08 (d., J = 7.7, 2 $_1H^+$, H/2‴,6‴), 6.80 (d., J = 8.5, 2 $_1H^+$, H/3′,5′), 4.60 (s., 2 $_1H^+$, -CH_2/7‴), 3.79 (s., 3 $_1H^+$, -OCH_3/1″); ^{13}C-NMR with frequency 150x10^6 hertz: δ 160.63 (C/4′), 154.93 (C/2), 151.81 (C/1), 134.71 (C/1‴), 134.37 (C/1‴″), 134.31 (C/6‴″), 131.57 (C/2‴″), 129.80 (C/2′,6′), 129.68 (C/5‴″), 129.57 (C/3‴-5‴″), 129.11 (C/4‴″), 127.44 (C/2‴,6‴″), 126.93 (C/3‴″), 119.12 (C/1′), 113.93 (C/3′,5′), 55.23 (C/1″), 35.03 (C/7‴″); Analytical Cal.: $C_{22}H_{18}ClN_3OS$ (407.09): C: 64.78; H: 4.45; Cl: 8.69; N: 10.30; O: 3.92; S: 7.86. Exact: C: 64.80; H: 4.43; Cl: 8.67; N: 10.29; O: 3.90; S: 7.84; EI- MS: *m /z* 407 $[C_{22}H_{18}ClN_3OS]^{\bullet+}$ $[M]^{\bullet+}$, 224 $[C_{14}H_{12}N_2O]^+$, 210 $[C_{14}H_{12}NO]^+$, 133 $[C_8H_7NO]^+$, 125 $[C_7H_6Cl]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

3-(4-Chlorobenzylthio)-5-(4-OMeC_6H_5)-4-phenyl-4H-1,2,4-triazole **(VIh)**

Amorp. residue; Y(%): 69; M.Pt.: 178 ^{0}C; Mol. formula: $C_{22}H_{18}Cl\ N_3OS$; Mol. wt.(g/mol): 407; IR (ῡ; 1/cm): 2936, 1611, 1434, 1248, 1176, 1034, 842; ^{1}H-NMR with frequency 600x10^6 hertz: δ 7.49-7.45 (m., 3 $_1H^+$, H/3‴-5‴), 7.34 (d., J = 8.6, 2 $_1H^+$, H/2′,6′), 7.31 (d., J = 8.3, 2 $_1H^+$, H/3‴,5‴), 7.25 (d., J = 8.3, 2 $_1H^+$, H/2‴,6‴), 7.11 (d., J = 7.4, 2 $_1H^+$, H/2‴,6‴), 6.80 (d., J = 8.6, 2 $_1H^+$, H/3′,5′), 4.44 (s., 2 $_1H^+$, -CH_2/7‴), 3.79 (s., 3 $_1H^+$, -OCH_3/1″); ^{13}C-NMR with frequency 150x10^6 hertz: δ 160.67 (C/4′), 154.91 (C/2), 151.56 (C/1), 135.35 (C/1‴), 134.31 (C/1‴″), 133.52 (C/4‴″), 130.54 (C/2‴″,6‴″), 129.83 (C/2′,6′), 129.74 (C/4‴″), 129.56 (C/3‴″,5‴″), 128.71 (C/3‴″,5‴″), 127.37 (C/2‴″,6‴″), 119.02 (C/1′), 113.95 (C/3′,5′), 55.23 (C/1″), 36.46 (C/7‴″); Analytical Cal.: $C_{22}H_{18}Cl\ N_3OS$ (407.09): C: 64.78; H: 4.45; Cl: 8.69; N: 10.30; O: 3.92; S: 7.86. Exact: C: 64.76; H: 4.43; Cl: 8.67; N: 10.28; O: 3.90; S: 7.84; EI- MS: *m /z* 407 $[C_{22}H_{18}ClN_3OS]^{\bullet+}$ $[M]^{\bullet+}$, 224 $[C_{14}H_{12}N_2O]^+$, 210 $[C_{14}H_{12}NO]^+$, 133 $[C_8H_7NO]^+$, 125 $[C_7H_6Cl]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

3-(2,4-Dichlorobenzylthio)-5-(4-OMeC_6H_5)-4-phenyl-4H-1,2,4-triazole **(VIi)**

Amorp. residue: Y(%): 78; M.Pt.: 148 ^{0}C; Mol. formula: $C_{22}H_{17}Cl_2N_3OS$; Mol. wt.(g/mol): 441; IR (ῡ; 1/cm): 2942, 1605, 1442, 1250, 1176, 1035, 837; ^{1}H-NMR with frequency 600x10^6 hertrz: δ 7.59 (d., J = 8.3, 1 $_1H^+$, H/6‴), 7.50-7.45 (m., 3 $_1H^+$, H/3‴-5‴), 7.37 (d., J = 1.9, 1 $_1H^+$, H/3‴), 7.34 (d., J = 8.7, 2 $_1H^+$, H/2′,6′), 7.19 (dd., J = 1.9, 8.2, 2 $_1H^+$, H/5‴), 7.12 (d., J = 7.5, 2 $_1H^+$, H/2‴,6‴), 6.80 (d., J = 8.76, 2 $_1H^+$, H/3′,5′), 4.55 (s., 2 $_1H^+$, -CH_2/7‴), 3.79 (s., 3 $_1H^+$, -OCH_3/1″); ^{13}C-NMR with frequency 150x10^6 hertz: δ 160.68 (C/4′), 155.03 (C/2), 151.51 (C/1), 134.99 (C/1‴), 134.24 (C/2‴), 134.21 (C/4‴), 133.51 (C/6‴), 132.42 (C/1‴), 129.85 (C/2′,6′), 129.77 (C/4‴), 129.55 (C/3‴,5‴), 129.36 (C/3‴), 127.33 (C/2‴,6‴), 127.18(C/5‴), 119.0 (C/1′), 113.96 (C/3′,5′), 55.23 (C/1″), 34.13 (C/7‴); Analytical Cal.: $C_{22}H_{17}Cl_2N_3OS$ (441.05): C: 59.73; H: 3.87; Cl: 16.03 N: 9.50; O: 3.62; S: 7.25. Exact: C: 59.73; H: 3.89; Cl: 16.01; N: 9.48; O: 3.60; S: 7.23; EI- MS: *m /z* 441 $[C_{22}H_{17}Cl_2N_3OS]^{\bullet+}$ $[M]^{\bullet+}$, 282 $[C_{15}H_{12}N_3OS]^+$, 250 $[C_{15}H_{12}N_3O]^+$, 210 $[C_{14}H_{12}NO]^+$, 159 $[C_7H_5Cl_2]^+$, 133 $[C_8H_7NO]^+$, 89 $[C_7H_5]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

3-(3,4-Dichlorobenzylthio)-5-(4-OMeC_6H_5)-4-phenyl-4H-1,2,4-triazole **(VIj)**

Amorp. solid: Y(%): 71; M.Pt.: 110 ^{0}C; Mol.

formula: $C_{22}H_{17}Cl_2N_3OS$; Mol. wt.(g/mol): 441; IR (ῡ; 1/cm): 2941, 1608, 1440, 1251, 1175, 1036, 838; ^{1}H-NMR with frequency 600x10^6 hertz: δ 7.50 (d., J = 7.1, 1 $_1H^+$, H/5‴), 7.49-7.46 (m., 3 $_1H^+$, H/3‴-5‴), 7.36 (s., J = 1.9, 1 $_1H^+$, H/2‴), 7.34 (d., J = 8.4, 2 $_1H^+$, H/2′,6′), 7.24 (dd., J = 1.8, 8.2, 1 $_1H^+$, H/6‴), 7.12 (d., J = 7.4, 2 $_1H^+$, H/2‴,6‴), 6.80 (d., J = 8.4, 2 $_1H^+$, H/3′,5′), 4.41 (s., 2 $_1H^+$, -CH_2/7‴), 3.79 (s., 3 $_1H^+$, -OCH_3/1″); ^{13}C-NMR with frequency 150x10^6 hertz: δ 160.71 (C/4′), 155.03 (C/2), 151.19 (C/1), 137.22 (C/1‴), 134.20 (C/1⁗), 132.53 (C/3⁗), 131.75 (C/4⁗), 131.00 (C/5⁗), 130.44 (C/2⁗), 129.88 (C/2′,6′), 129.83 (C/4‴), 129.57 (C/3‴,5‴), 128.60 (H/6⁗), 127.31 (C/2‴,6‴), 118.91 (C/1′), 113.97 (C/3′,5′), 55.24 (C/1″), 35.91 (C/7⁗); Analytical Cal.: $C_{22}H_{17}Cl_2N_3OS$ (441.05): C: 59.73; H: 3.87; Cl: 16.03 N: 9.50; O: 3.62; S: 7.25. Exact: C: 59.71; H: 3.85; Cl: 16.05; N: 9.52; O: 3.60; S: 7.26; EI-MS: *m /z* 441 $[C_{22}H_{17}Cl_2N_3OS]^{\bullet+}$ $[M]^{\bullet+}$, 282 $[C_{15}H_{12}N_3OS]^+$, 250 $[C_{15}H_{12}N_3O]^+$, 210 $[C_{14}H_{12}NO]^+$, 159 $[C_7H_5Cl_2]^+$, 133 $[C_8H_7NO]^+$, 89 $[C_7H_5]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

3-(4-Bromobenzylthio)-5-(4-OMeC_6H_5)-4-phenyl-4H-1,2,4-triazole **(VIk)**

Amorp. residue: Y(%): 68; M.Pt.: 180 ^{0}C; Mol. formula: $C_{22}H_{18}Br\ N_3OS$; Mol. wt.(g/mol): 45; IR (ῡ; 1/cm): 2940, 1606, 1437, 1251, 1176, 1021, 833; ^{1}H-NMR with frequency 600x10^6 hertz: δ 7.50-7.45 (m., 3 $_1H^+$, H/3‴-5‴), 7.42 (d., J = 8.2, 2H, H/2′,6′), 7.34 (d., J = 8.6, 2 $_1H^+$, H/3⁗,5⁗), 7.26 (d., J = 8.2, 2 $_1H^+$, H/2⁗,6⁗), 7.11 (d., J = 7.6, 2 $_1H^+$, H/2‴,6‴), 6.80 (d., J = 8.7, 2 $_1H^+$, H/3′,5′), 4.43 (s., 2 $_1H^+$, -CH_2/7⁗), 3.79 (s., 3 $_1H^+$, -OCH_3/1″); ^{13}C-NMR with frequency 150x10^6 hertz: δ 160.67 (C/4′), 154.92 (C/2), 151.54 (C/1), 135.58 (C/1‴), 134.29 (C/1⁗), 131.68 (C/3⁗,5⁗), 130.88 (C/2⁗,6⁗), 129.84 (C/2′,6′), 129.75 (C/4⁗), 129.57 (C/3‴-5‴), 127.36 (C/2‴,6‴), 121.62 (C//4⁗), 119.00 (C/1′), 113.95 (C/3′,5′), 55.24 (C/1″), 36.5 (C/7⁗); Analytical Cal.: $C_{22}H_{18}Br\ N_3OS$ (451.04): C: 58.41; H: 4.01; Br: 17.66 N: 9.29; O: 3.54; S: 7.09. Exact: C: 58.39; H: 3.99; Br: 17.64; N: 9.31; O: 3.52; S: 7.07; EI- MS: *m /z* 451 $[C_{22}H_{18}BrN_3OS]^{\bullet+}$ $[M]^{\bullet+}$, 372 $[C_{22}H_{18}N_3OS]^+$, 346 $[C_{15}H_{11}BrN_3S]^+$, 250 $[C_{15}H_{12}N_3O]^+$, 210 $[C_{14}H_{12}NO]^+$, 201 $[C_7H_6BrS]^+$, 155 $[C_6H_4Br]^+$, 133 $[C_8H_7NO]^+$, 122 $[C_7H_6S]^+$, 107 $[C_7H_7O]^+$, 90 $[C_7H_6]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

3-(4-Fluorobenzylthio)-5-(4-OmeC$_6H_5$)-4-phenyl-4H-1,2,4-triazole **(VIl)**

Ampop. residue; Y(%): 72; M.Pt.: 127 ^{0}C; Mol. formula: $C_{22}H_{18}FN_3OS$; Mol. wt.(g/mol): 391; IR (ῡ; 1/cm): 2936, 1609, 1438, 1250, 1172, 1025, 835; ^{1}H-NMR with frequency 600x10^6 hertz: δ 7.51-7.45 (m., 3 $_1H^+$, H/3‴-5‴), 7.36-7.34 (d.-merged, J = 8.3, 4 $_1H^+$, H/2′,6′,2⁗,6⁗), 7.34 (dist. Dd., $J_{(a,\ b\ \&\ a,\ ^{19}F)}$ = 3.4, 5.2, 8.6, 2 $_1H^+$, H/2⁗,6⁗), 7.11 (d., J = 7.6, 2 $_1H^+$, H/2‴,6″), 6.98 (t., $J_{(b,\ a\ \&\ b,\ ^{19}F)}$ = 8.5, 2 $_1H^+$, H/3⁗,5⁗), 6.80 (d., J = 8.7, 2 $_1H^+$, H/3′,5′), 4.46 (s., 2 $_1H^+$, -CH_2/7⁗), 3.79 (s., 3 $_1H^+$, -OCH_3/1″); ^{13}C-NMR with frequency 150x10^6 hertz: δ 161.45 (C/4⁗), 160.67 (C/4′), 154.87 (C/2), 151.72 (C/1), 134.36 (C/1‴), 132.50 (C/1⁗), 130.89 (C/2⁗), 130.83 (C/6⁗), 129.86 (C/2′,6′), 129.73 (C/4‴), 129.57 (C/3‴-5‴), 127.38 (C/2‴, 6‴), 119.05 (C/1′), 115.51 (C/3⁗), 115.36 (C/5⁗), 113.95 (C/3′,5′), 55.25 (C/1″), 36.46 (C/7⁗); Analytical Cal.: $C_{22}H_{18}FN_3OS$ (391.12): C: 67.50; H: 4.63; F: 4.85 N: 10.73; O: 4.09; S: 8.19. Exact: C: 67.48; H: 4.61; F: 4.83; N: 10.71; O: 4.11; S: 8.17; EI- MS: *m /z* 391 $[C_{22}H_{18}FN_3OS]^{\bullet+}$ $[M]^{\bullet+}$, 282 $[C_{15}H_{12}N_3OS]^+$, 210 $[C_{14}H_{12}NO]^+$, 109 $[C_7H_6F]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

Spectral characteristics of representative compound **(VIk)**

Among the whole series, structural elucidation of compound **VIk** has been argumented inclusively. Absorption peaks of IR spectrum appeared at 2940, 1606, 14379, 1251, 1176, 1021, 833. Furthermore, ^{1}H & ^{13}C-NMR information established structure *via* counting no. of protons and carbon atoms in spectra.

In aromatic region of ^{1}H-NMR, a merged signal in form of multiplet resonated downfield at 7.51-7.45 in favor of 3Hs (H/3‴-5‴) with a doublet at 7.11 for 2Hs at H/2⁗,6‴ confirming the presence of -C_6H_5 ring. At δ 7.42 a doublet appeared for 2Hs (H/2′,6′) & one another doublet appeared at 6.80; 2Hs (H/3′,5′) confirming the *para*-substitution of one of the phenyl rings. Similarly, another A_2B_2 spin resonated as *diortho*-coupled doublets one at 7.34 for H/3⁗,5⁗ & other at 7.26 for H/2⁗,6⁗ protons confirmed presence of another C_6H_5 ring which is also *para*-substituted. In aliphatic region, 2 singlets appeared one at 4.42 for -CH_2 protons flanged between 4-methoxyphenyl-1,2,4-triazole and 4-bromophenyl moiety and other at δ 3.79 for methoxy protons (-OCH_3) attached to 4-position of phenyl ring, verified the estimated structure (Fig. 4a & Fig. 4b; extended) that as well substantiated by ^{13}C-NMR spectra (Fig. 5). Quaternary carbon of 1,2,4-triazole mediety showed signals at 154.3 (C/2), 151.5 (C/1) in spectrum. Remaining carbons exhibited peaks at 160.7(C/4′), 135.9(C/1‴), 134.3(C/1⁗), 131.7(C/3⁗,5⁗), 130.9(C/2⁗,6⁗), 129.8(C/2′,6′), 129.75(C/4‴), 129.57(C/3‴,5‴), 127.4(C/2‴,6‴), 121.6(C/4⁗), 119(C/1′), 113.95(C/3′,5′), 55.2(C/1″) and 36.5(C/7⁗) correspondingly. EIMS provided valuable information in calculation of molecular mass *via* molecular formula which was established by appearance of $[M]^{\bullet+}$ signal at *m/z* 451 $[C_{22}H_{18}BrN_3OS]^{\bullet+}$. Someother important fragment signals at 201 (bromobenzylthio

cation), 107 (methoxyphenyl cation), 90 for tropylium radical cation, 77 for phenyl ring and 51 for cyclobutadiene cation assisted in ascertaining VIk structure (Fig. 6 & Fig. 7). The cumulative spectral data established compound as 3-(4-bromobenzylthio)-5-(4-$OMeC_6H_5$)-4-phenyl-4*H*-1,2,4-triazole **(VIk)**.

In same way, remaining *S*-substituted scaffolds were characterized. The spectral data besides morphology of scaffolds was vindicated their structures.

Biological Assays

Acetyl/ButyrylCholinesterase assay

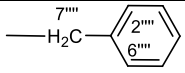
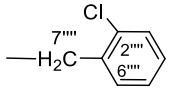
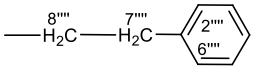
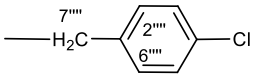
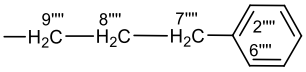
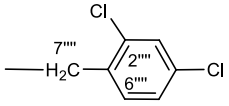
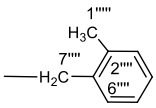
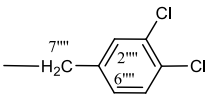
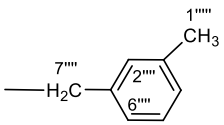
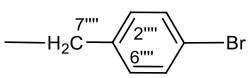
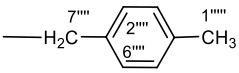
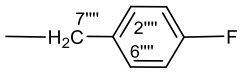
Synthesized *S*-substituted scaffolds 5-(4-$OMeC_6H_5$)-4-phenyl-4*H*-1,2,4-triazol-3-thiols; **VI(a-l)** screened alongside AChE enzyme to evaluate inhibition potency and consequences are tabularized as %age inhibition & IC_{50} figures (Table-2). Thrice experiments were conducted on a single sample to compile the results. This has been construed that 3-(phenylpropylthio)-5-(4- $OMeC_6H_5$)-4-phenyl-4*H*-1,2,4-triazole revealed excellent IC_{50} (3.26±0.35 μmol; **VIc)** where Eserine (0.04±0.001 μmol) was used as reference standard. 3-(Phenethylthio)-5-(4- $OMeC_6H_5$)-4-phenyl-4*H*-1,2,4-triazole presented brilliants results (19.25±0.53 μM; **VIb)**. 3-(4-Methylbenzylthio)-5-(4-$OMeC_6H_5$)-4-phenyl-4*H*-1,2,4-triazole revealed outstanding results (36.82±0.42 μmol; **VIf)**. Compounds **VId**,**g**,**h**,**i**,**j** were also found to be potent having IC_{50} range of (45.17±0.48 to 62.53±0.37 μmol). Similarly, **VIa**,**e**,**k ,l** exhibited modrate potency having IC_{50} range of (95.24±0.53 to 165.43±0.52 μmol).

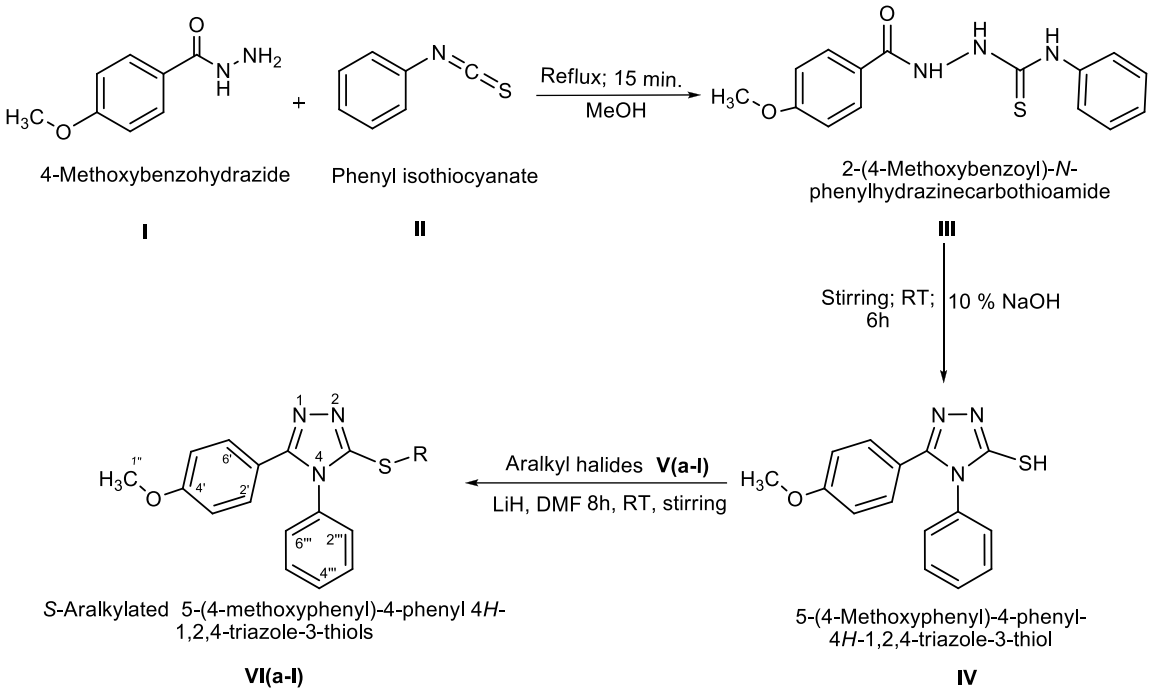
Against butyrylcholinesterase (BChE) enzyme for **VI(a-l)** the enzymatic potency and consequences has been charted as %age inhibition & IC_{50} figures (**Table 2)**. This has been exposed that 3-(phenethylthio)-5-(4-$OMeC_6H_5$)-4-phenyl-4*H*-1,2,4-triazole portrayed exceptional inhibition potency (8.52±0.54 μmol; **VIb**) compared Eserine (0.04 ± 0.001 μmol). Other compounds **VIg**,**h,j** exhibited good results. Remaining compounds exhibited moderate activity in range of (259.43±0.48 to 307.53±0.57 μmol) except **VIa**,**e**,**f**,**i**,**k** which showed no activity against BChE enzyme.

Anti-proliferation assay

Anti-proliferative activities of *S*-Aralkylated 5-(4-$OMeC_6H_5$)-4-phenyl-4*H*-1,2,4-triazol-3-thiols; **VI(a-l)** have been checked by utilizing HCT 116 cell line over 3-day SRB assay (Table-3). The scaffolds exhibited reasonable to very decent activities. Compounds with benzylic substitution at the *S*-atom of the moiety along with *para*-substitution of -CH_3 group were unfavorable for activity as compared to *ortho* and *meta*-substitution on the aromatic rings (**VId & VIe > VIf** for Me-substituent). Overall, best cell viability showed by **VIj** compound i.e., 3.09 % at 25 μmol and 0.51 % at 50 μmol and followed by **VIg** with 14.83 % at 25 μmol and 1.68 % at 50 μmol in tested library.

Table-1: Following list of aralkyl halides that's exploited in synthesis of **VI(a-l)** scaffolds.

Code	R	Code	R
VIa		**VIg**	
VIb		**VIh**	
VIc		**VIi**	
VId		**VIj**	
VIe		**Vik**	
VIf		**VIl**	



Scheme-1: Schematic sketch for synthesis of **VI(a-l).**

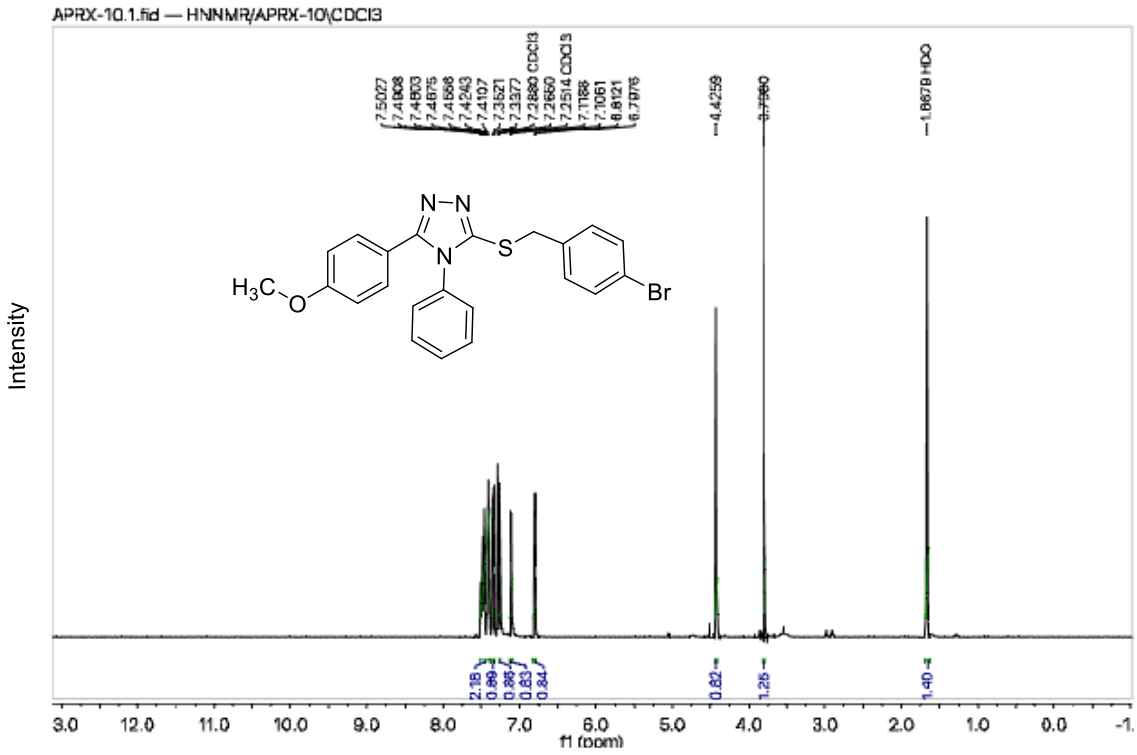


Fig. 4a: Complete ^{1}H-NMR spectrum of **VIk.**

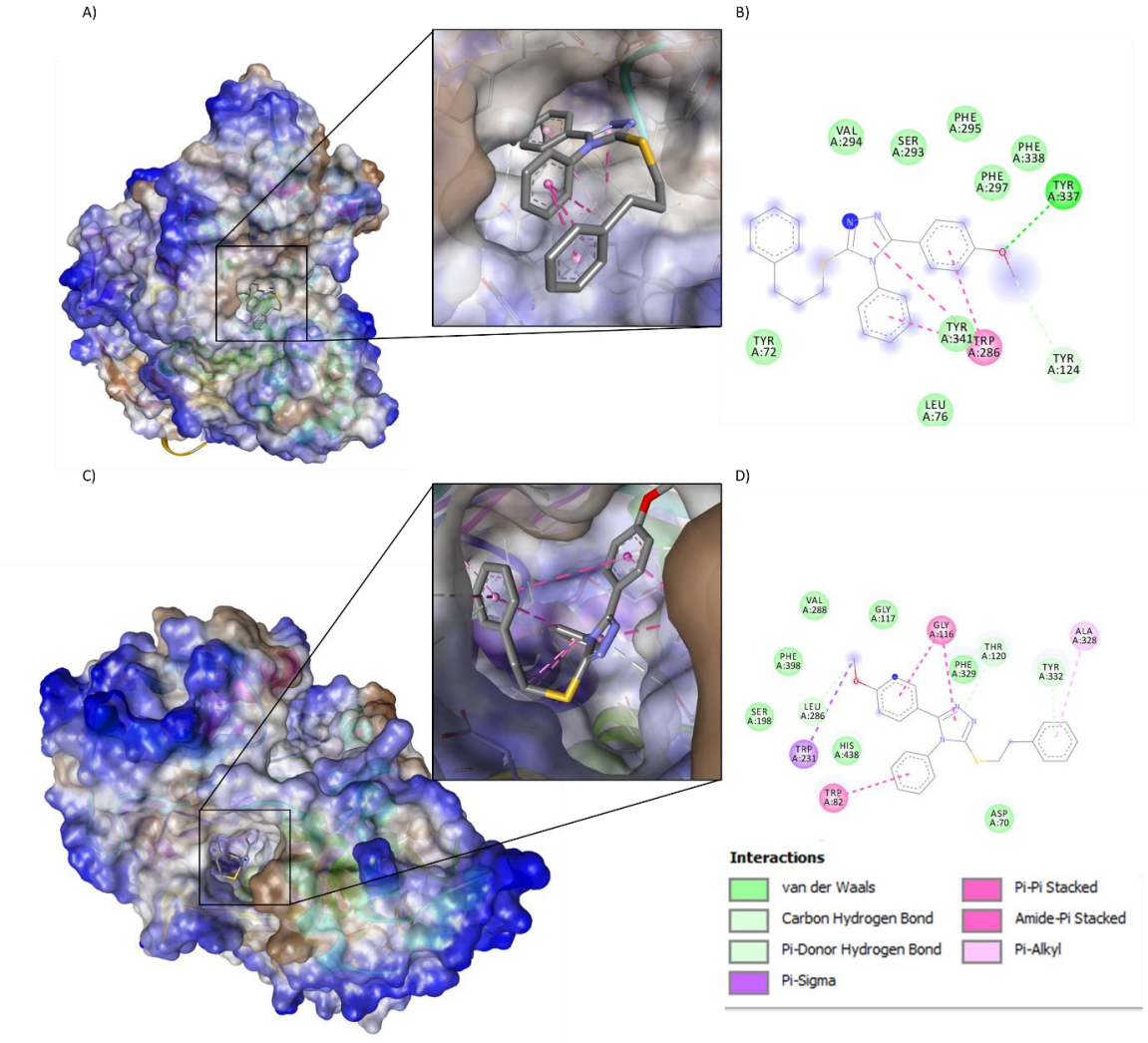


Fig. 8: Docking of **VIc** with AChE and **VIb** with BChE
A) 3D Docking of **VIc** with AChE
B) 2D interaction map of **VIc** with AChE at the binding site
C) 3D Docking of **VIb** with BChE
D) 2D interaction map of **VIb** with BChE at the binding site

Structure-Activity Relationship (SAR)

Compounds **VIa** (IC_{50} = 122.86±0.42), **VIb** (IC_{50} = 19.25±0.53 μM) & **VIc** (IC_{50} = 3.26±0.35 μM) possessed moderate to good inhibition bearing benzyl, phenethyl and phenylpropyl group at *S*-position of triazole moiety respectively. It is concluded that compound **6c** was found to be most active amongst benzyl, phenethyl and phenylpropyl substituents against AChE. Standard was Eserine (IC_{50} = 0.04±0.001 μM).

Compound **VIb** (IC_{50} = 8.52±0.54 μM), **VIc** (IC_{50} = 81.47±0.67 μM) having phenethyl and phenylpropyl group at *S*-position of triazole moiety showed outstanding enzyme inhibition activity against BChE in reference to standard Eserine (IC_{50} = 0.62±0.08 μM) and **VIa** remained inactive (**Fig. 9**).

Compounds **VId** (IC_{50} = 58.72±0.37 μM), **VIe** (IC_{50} = 95.24±0.53 μM) & **VIf** (IC_{50} = 36.82±0.42 μM) possessing *o*-methylbenzyl ring, *m*-methylbenzyl ring & *p*-methylbenzyl ring substituted at *S*-position of triazole moiety respectively and concluded that *para*-position of substitution was more favorable than *ortho/meta*-substitution against AChE enzyme.

Compounds **VId** (IC_{50} = 259.43±0.48 μM) showed that *o*-methylbenzyl ring substitution at *S*-atom exhibited good inhibition activity but **VIe**, **VIf** remained inactive against BChE enzyme. (Fig. 10).

Compounds **VIg** (IC_{50} = 59.21±0.56 μM), **VIh** (IC_{50} = 62.53±0.37 μM), **VIi** (IC_{50} = 45.17±0.48 μM) & **VIj** (IC_{50} = 61.95±0.54 μM) possessing *o*/*p*-chlorobenzyl group and *ortho-para* / *meta-para* dichlorobenzyl part associated at *S*-location of triazole molecule respectively. All compounds **VIg,h,i,j** showed good inhibition against AChE enzyme.

Compounds **VIg** (IC_{50} = 63.51±0.57 μM), **VIh** (IC_{50} = 63.87±0.51 μM) & **VIj** (IC_{50} = 63.25±0.52 μM) showed that chlorobenzyl ring substitution at on *S*-atom of triazole ring exhibited outstanding inhibitory activity against BChE enzyme but 6i showed inactivity. (Fig. 11).

Compounds **VIk** (IC_{50} = 165.43±0.52 μM), **VIl** (IC_{50} = 142.35±0.43 μM) possessing *p*-bromobenzyl ring and *p*-fluorobenzyl part associated at *S*-location of triazole molecule respectively showed fair inhibition against AChE.

Compounds **VIl** (IC_{50} = 307.53±0.57 μM) showed that *p*-fluorobenzyl ring substitution at *S*-atom of triazole ring exhibited good inhibition against BChE but **VIk** showed inactivity. (**Fig. 12**).

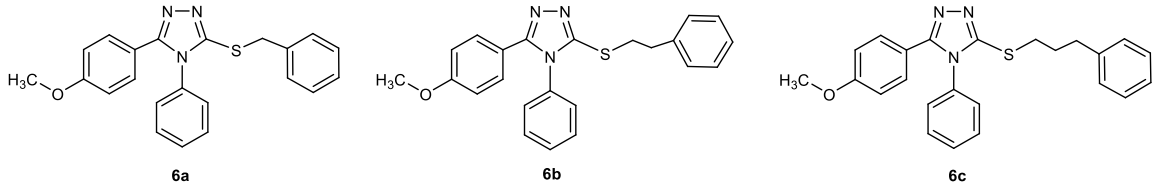


Fig. 9: SAR of compounds **VIa,b,c.**

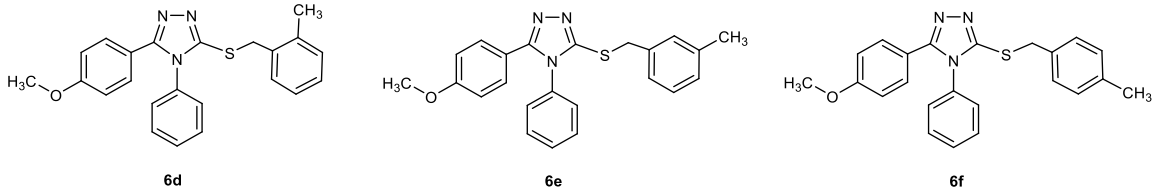


Fig. 10: SAR of compounds **VId**,**e**,**f.**

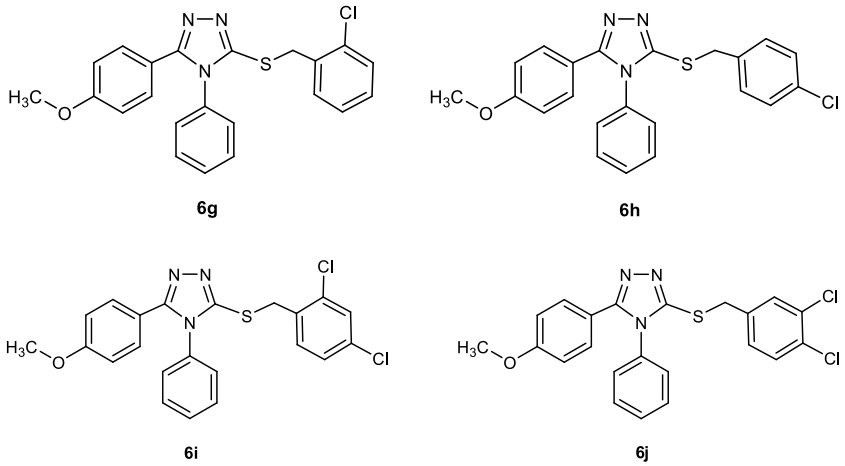


Fig. 11: SAR of compounds **VIg**,**h**,**i**,**j.**

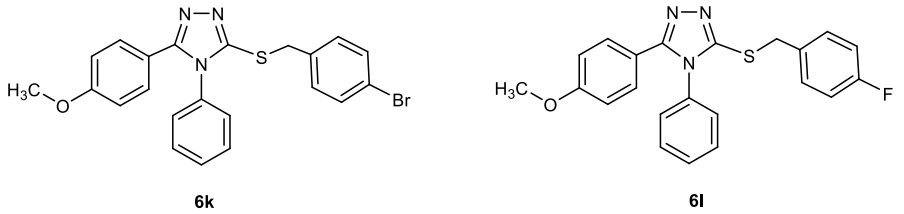


Fig. 12: SAR of compounds **VIk,l.**

Conclusion

S-aralkylated 5-(4-OMeC_6H_5)-4-phenyl-4*H*-1,2,4-triazol-3-thiols **VI(a-l)** have been produced as potent inhibitors for AChE and BChE which are drug targets in handling of Alzehimer's ailment. Up-to-date spectral practices have been utilized to elucidate these structures. Anti-cholinesterase results demonstrated that 3-(phenylpropylthio)-5-(4-OMeC_6H_5)-4-phenyl-4*H*-1,2,4-triazole (IC_{50} = 3.26±0.35; **VIc**), 3-(phenethylthio)-5-(4- OMeC_6H_5)-4-phenyl-4*H*-1,2,4-triazole (IC_{50} = 8.52±0.54; **VIb**) showed excellent acetyl/butyryl cholinesterase inhibitory potential and could be future potent candidate to counter this neurodegenerative disorder and asserts that insertion of phenylethyl and phenylpropyl moieties on the *S*-atom of the triazole ring have feasible results confirmed *via* docking studies. Moreover, in tested library, **VIj** is superlative composite having 3.09 % and 0.51 % cell viability at 25 and 50 µM concentrations in anti-proliferative activity.

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