Abstract

Five membered heterocyclic compounds and their derivatives have gained much attraction of synthetic chemists due to their valuable biological activities. Especially 1,3,4-oxadiazole have shown remarkable broad spectrum biological activities which prompted us to synthesize its different 2,5-disubstituted-1,3,4-oxadiazole derivatives. Benzodioxole moiety has also shown numerous biological activities. It was assumed that 2,5-disubstituted-1,3,4-oxadiazole ring along with the potential benzodioxole moiety might boost up the pharmacological activities of the synthesized molecules. Sulfamoyl derivatives were also prepared to evaluate them for their various biological activities. Many incurable fatal diseases can be made curable to much extent by the help of latest and advanced research. So the presented research work comprises of the synthesis of some novel multifunctional compounds followed by the characterization of these compounds and biological evaluation including antibacterial studies as well as enzyme inhibition studies. The selection of these moieties was made on the basis of their known remarkable pharmacological activities.

The compounds presented in this particular work were synthesized according to the protocol available in the literature and has been mentioned in respective schemes in detail. In **Scheme-37 & 38**, 5-substituted-1,2,4-triazol-3-thiol **(4, 21)** were synthesized, starting from *p*-chlorophenoxyacetic acid through formation of corresponding esters converted into hydrazides and ultimately 5-substituted-1,2,4-triazol-3-thiol were obtained through an intermolecular cyclization mechanism. Moreover, the reaction of 5-[(*p*-chlorophenoxy)methyl]-4-phenyl-4*H*-1,2,4-triazol-3-thiol **(4)** **Scheme-29-32**, with electrophiles, alkyl/aralkyl halides **(5a-o)**, 2-bromo-*N*-substitutedphenylacetamides **(9a-j)**, 3-bromo-*N*-substitutedphenylpropanamides **(13a-k)** and 4-chloro-*N*-substitutedphenylbutanamides **(17a-l),** yielded fifteen **(15)** *S*-aralkylated/alkylate 3-(alkylthio)-5-((4-chlorophenoxy)methyl)-4-phenyl-4*H*-1,2,4-triazole **6(a-o)**, ten **(10)** 3-{5-[(*p*-Chlorophenoxy)methyl]-4-phenyl-4*H*-1,2,4-triazol-3-ylthio}-*N*-(substitutedphenyl)acetamides **10(a-j)**, eleven **(11)** 3-{5-[(*p*-Chlorophenoxy)methyl]-4-phenyl-4*H*-1,2,4-triazol-3-ylthio}-*N*-(substitutedphenyl) propanamides **14(a-k)** and twelve **(12)** 3-{5-[(*p*-Chlorophenoxy)methyl]-4-phenyl-4*H*-1,2,4-triazol-3-ylthio}-*N*-(substitutedphenyl)butanamides **18(a-l)** respectively in the presence of *N,N*-dimethylformamide and lithium hydride. In **Scheme-33-36,** the reaction of 5-[(*p*-chlorophenoxy)methyl]-4-ethyl-4*H*-1,2,4-triazol-3-thiol **(21)** with electrophiles, alkyl/aralkyl halides **(22a-i)**, 2-bromo-*N*-substitutedphenylacetamides **(9a-i)**, 3-bromo-*N*-14

substitutedphenylpropanamides **(13a-e)** and 4-chloro-*N*-substitutedphenylbutanamides **(17a-g),** yielded nine **(9)** *S*-aralkylated/alkylate 3-(alkylthio)-5-((4-chlorophenoxy)methyl)-4-ethyl-4*H*-1,2,4-triazole **23(a-i)**, nine **(9)** 3-{5-[(*p*-chlorophenoxy)methyl]-4-ethyl-4*H*-1,2,4-triazol-3-ylthio}-*N*-(substituted phenyl)acetamides **26(a-i)**, five **(5)** 3-{5-[(*p*-chlorophenoxy)methyl]-4-ethyl-4*H*-1,2,4-triazol-3-ylthio}-*N*-(substitutedphenyl) propanamides **28(a-e)** and seven **(7)** 3-{5-[(*p*-chlorophenoxy)methyl]-4-ethyl-4*H*-1,2,4-triazol-3-ylthio}-*N*-(substitutedphenyl)butanamides **30(a-g)** respectively in the presence of *N,N*-dimethylformamide and lithium hydride.

All the synthesized compounds were characterized by using different spectroscopic techniques i.e. IR, 1H-NMR and 13C-NMR to support the structural analysis. Some of the 1H-NMR and 13C-NMR spectra of synthesized compounds are presented. The synthesized compounds were also evaluated for cytotoxicity, enzyme inhibition activities and molecular docking. All the eight schemes were put for cholinesterase assay anti-urease assay. Overall the synthesized compounds showed significant results. In **Scheme-29**, the compound 3-(2-chlorobenzylthio)-5-((4-CP)methyl)-4-C_6H_5-4*H*-1,2,4-triazole exhibited strong inhibitory potential (IC_{50}= 38.91±0.52; **6e**) showed overall maximum activity against AChE and 3-(2-bromoethylthio)-5-((4-CP)methyl)-4-C_6H_5-4*H*-1,2,4-triazole (IC_{50}= 138.74±0.42; **6l**) showed overall maximum activity against BChE among the compounds. In **Scheme-30**, the compound 2-(5-((4-chlorophenoxy)methyl)-4-C_6H_5-4*H*-1,2,4-triazol-3-ylthio)-*N*-(4-ethoxy-C_6H_5)acetamide (IC_{50}= 68.17±0.49 µM; **10e**) showed overall maximum activity against AChE and 2-(5-((4-CP)methyl)-4-C_6H_5-4*H*-1,2,4-triazol-3-ylthio)-*N*-*m*-tolylacetamide (IC_{50}= 107.32±0.54µM; **10f**) showed overall maximum activity against BChE among the compounds. In **Scheme-31**, the compound 3-(5-((4-CP)methyl)-4-C_6H_5-4*H*-1,2,4-triazol-3-ylthio)-*N*-(2,5-dimethyl-C_6H_5) propanamide (IC_{50}= 71.43±0.49µM; **14d**) showed overall maximum activity against AChE and 3-(5-((4-CP)methyl)-4-C_6H_5-4*H*-1,2,4-triazol-3-ylthio)-*N*-(4-ethyl-C_6H_5)propanamide (IC_{50}= 427.53±0.62µM; **14h**) showed overall maximum activity against BChE among the compounds. In **Scheme-32**, the compound 4-(5-((4-CP)methyl)-4-C_6H_5-4*H*-1,2,4-triazol-3-ylthio)-*N*-(3,5-dimethyl-C_6H_5) butanamide (IC_{50}= 158.93±0.49µM; **18f**) showed overall maximum activity against AChE and 4-(5-((4-CP)methyl)-4-C_6H_5-4*H*-1,2,4-triazol-3-ylthio)-*N*-(3,5-dimethyl- C_6H_5) butanamide (IC_{50}= 251.24±0.52µM; **18f**) showed overall maximum activity against BChE among the compounds. In **Scheme-33**, the compound 3-(3-bromobenzylthio)-5-((4-CP)methyl)-4-ethyl-4*H*-1,2,4-triazole (IC_{50}= 91.42±0.39 µM; **23g**) showed overall maximum activity against AChE and 3-(4-chlorobenzylthio)-5-((4-CP)methyl)-4-15

ethyl-4*H*-1,2,4-triazole (IC_{50} = 235.48±0.52µM; **23c**) showed overall maximum activity against BChE among the compounds. In **Scheme-34**, 2-(5-((4-CP)methyl)-4-ethyl-4*H*-1,2,4-triazol-3-ylthio)-*N*-*m*-tolylacetamide (IC_{50}= 149.63±0.39µM; **26h**) showed overall maximum activity against AChE and 2-(5-((4-CP)methyl)-4-ethyl-4*H*-1,2,4-triazol-3-ylthio)-*N*-(2-ethyl-C_6H_5) acetamide (IC_{50} = 325.76±0.49µM; **26g)** showed overall maximum activity against BChE among the compounds. In **Scheme-35**, 3-(5-((4-CP)methyl)-4-ethyl-4*H*-1,2,4-triazol-3-ylthio)-*N*-(2,5-dimethylphenyl) propanamide (IC_{50}= 18.92±0.38µM; **28b**) showed overall maximum activity against AChE and all the compounds of this series were found to be inactive against BChE enzyme. In **Scheme-36**, 4-(5-((4-CP)methyl)-4-ethyl-4*H*-1,2,4-triazol-3-ylthio)-*N*-(3,4-dimethyl- C_6H_5) butanamide (IC_{50}= 248.93±0.52µM; **30c**) showed overall maximum activity against AChE and all the compounds of this series were found to be inactive against BChE enzyme. Molecular docking studies were performed for active analogs.