ABSTRACT

The chemistry of life has been extensively and effectively elaborated by organic chemists. No doubt, scientists belong to all the disciplines of science are striving for the wellbeing of humanity but the synthetic chemists are one step ahead in their quest for excellence. A wide library of compounds is under the process of synthesis in search of new drug candidates that may help the humanity to defeat the deadly disease by the synthetic chemists with great passion and excitement to guarantee comfort to humanity. The observed rise in inefficiency of pharmaceuticals used to treat a variety of disorders points out the significance of this recent trend of drugs discovery. Hence the synthesis of novel compounds in search of new drug candidates against different diseases is an ever green process.

The aforementioned was the motivating feature of the synthetic chemistry research review that prompted us to design novel compounds and assess their biological potential. The bioactivity potential of N-based heterocyclic moieties impelled us to design such type of heterocyclic compounds bearing more than one such heterocyclic moieties. These considered heterocyclic moieties included piperidine and 1,2,4-triazole. The aim of submerging different heterocyclic functionalities into one core was to boost up their bioactivity potential. Furthermore, the variation in some part of final molecules was also processed in order to acquire new potent drug candidates. The pharmacological evaluation included enzyme inhibition, biofilm inhibition and hemolysis for the purpose of cytotoxicity. The enzyme inhibition results were further substantiated through molecular docking analysis. The *in silico* analysis was further proceeded for the investigation of physicochemical properties as well as the ADME and the toxicity of the compounds.

The presented research work has been distributed into four solid schemes for the synthesis of sixty seven (67) compounds. Ethyl isonipecotate (2) was treated with 4-chloro-benzene sulfonyl chloride (1) in 5% sodium carbonate at pH of 9-10 to get ethyl-1-[(4-chloro-phenyl)sulfonyl]piperidine-4-carboxylate (3). Compound 3 and hydrazine monohydrate were refluxed in methanol to acquire 1-[(4-chlorophenyl)sulfonyl]piperidine-4-carbohydrazide (4). Compound 4 was refluxed with phenyl iso-thiocyanate and ethyl iso-thiocyanate in methanol resulting in 5-{1-[(4-chlorophenyl)sulfonyl]-4-piperidinyl}-4-phenyl-4*H*-1,2,4-triazole-3-thiol (5) and 5-{1-[(4-chlorophenyl)sulfonyl]-4-piperidinyl}-4-ethyl-4*H*-1,2,4-triazole-3-thiol (5a). The two different parent compounds 5 & 5a were stirred with different aralkyl halides (6a-o) in the presence of NaH and DMF. 3-Aralkylthio-5-{1-[(4-

chlorophenyl)sulfonyl]-4-piperidinyl}-4-phenyl-4*H*-1,2,4-triazole (7a-q) and 3-Aralkylthio-5-{1-[(4-chlorophenyl)sulfonyl]-4-piperidinyl}-4-ethyl-4*H*-1,2,4-triazole (8a-n) were obtained through filtration from aqueous medium. The compound 5 and 5a was treated with equimolar *N*-substituted-2-bromopropionamide (11a-s) to acquire *N*-alkyl/aralkyl/aryl/phenyl-2-[(5-{1-[(4-chlorophenyl) sulfonyl]-4-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]propanamide (12a-s) and *N*-alkyl /aralkyl/ aryl/phenyl-2-[(5-{1-[(4-chlorophenyl)sulfonyl]-4-piperidinyl} -4-phenyl-4*H*-1,2,4-triazo-3-yl)sulfanyl]propanamide (13a-q). The electrophiles, as were synthesized by the reaction of alkyl/aralkyl/aryl/phenyl amines (11a-s) and 2-bromopropionyl bromide (10) in 5% sodium carbonate solution. The synthesized compounds were initially verified through TLC and stored for further analysis.

The synthesized compounds were spectroscopically characterized by using IR, 1H-NMR, 13C-NMR, HMQC, HMBC and EIMS spectral information to justify the available main functional groups, hydrogen atoms, carbon atoms and the fragmentation pattern of the structures of synthesized compounds.

The synthesized compounds were screened for enzyme inhibition activity against three different enzymes and also for antioxidant activity. The different three enzymes included acetyl cholinesterase (AChE), butyryl cholinesterase (BChE) and urease. Almost all the compounds were found to have excellent potential against these enzymes. Biofilm inhibition of all the synthesized molecules was also tested in search of some unique drug candidates. The chemistry of active sites and different

functionalities responsible for the best pharmacological potential of all the synthesized compounds was verified through docking studies. In addition to it, the evaluation of protein drug interaction assisted us in understanding the various binding sites and binding constant to justify the stay of the drugs in the body, their circulation, metabolism, elimination and pharmacodynamics. The computational analysis enabled the compounds to pay their way for their enlistment as the drug as they mentioned all the physicochemical properties and ADMET and toxicity of the synthesized compounds.The sketched compounds in the four schemes were synthesized efficiently with high yield and purity through environment friendly protocol with minimum cost and time. The following synthetic as well as biological screening studies resulted into the identification of a number of compounds being active against the considered enzymes. The SAR study indicated that phenyl triazole has better biological activity as well as toxicity as compared to the ethyl triazole while the compounds with propionamide substitution as compared to the alkaryl halides had better enzymatic activities. These enzymes are responsible for different kind of diseases and so the bioactive potent compounds may be considered as new drug candidates for the concerned diseases. The active compounds for the enzymes with least toxicity from the four synthesized series can be undergone through further *in vitro* studies that may lead us to acquire the prominent compound against specific biological problem that may further can be use in *in vivo* trials.