ABSTRACT

The chemistry of life has been extensively and effectively elaborated by organic chemists. No doubt, all the fields of science are struggling for the benefit of human beings and the chemists are well known in this regard. The organic or medicinal chemists are the main worker of improving the health. A number of compounds have been synthesized in search of new drug candidates by the orgnic chemists and also they have been successful up to much extent in this regard. The importance of this process can be realized from the increasing inactivity of the running drugs against different diseases. Hence the synthesis of new molecules in search of new drug candidates against different diseases is an ever green process.

This was the motivating aspect of the literature survey of synthetic chemistry which encouraged us to design new molecules and evaluate their biological potential. The bioactivity potential of some heterocyclic moieties (as discussed in introduction and review of literature) prompted has to design such type of molecules which bear more than one 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, antioxidant activity and bovine serum albumin (BSA) binding analysis. The enzyme inhibition results were further substantiated through molecular docking analysis.

The presented research work has been distributed into eight solid schemes for the synthesis of ninety six compounds. Ethyl isonipecotate (**2**) was treated with 4-methoxybenzene sulfonyl chloride (**1**) in 5% sodium carbonate at pH of 9-10 to get ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine-4-carboxylate (**3**). Compound **3** and hydrazine monohydrate were refluxed in methanol to acquire 1-[(4-methoxyphenyl)sulfonyl]piperidine-4-carbohydrazide (**4**). Compound **4** was refluxed with phenyl isothiocyanate in methanol to acquire an intermediate compound (2-({1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}carbonyl)-*N*-phenyl-1-hydrazinecarbothio amide) which was refluxed in basic medium to get 5-{1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}-4-phenyl-4*H*-1,2,4-triazole-3-thiol (**5**). Compound **5** was stirred with

different aralkyl halides (**6a-j**) in the presence of NaH and DMF using conventional and microwave assisted methods. 3-Aralkylthio-5-{1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}-4-phenyl-4*H*-1,2,4-triazole (**7a-j**) were obtained through filtration from aqueous medium. The compound **5** was treated with equimolar *N*-substituted-2-bromoacetamides (**10a-t**) to acquire *N*-alkyl/aralkyl/aryl/phenyl-2-[(5-{1-[(4-methoxyphenyl) sulfonyl]-4-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl] acetamide (**11a-t**). The electrophiles, **10a-t**, were synthesized by the reaction of alkyl/aralkyl/aryl/phenyl amines (**8a-t**) and bromoacetyl bromide (**9**) in 5% sodium carbonate solution. The compound **5** was treated with equimolar *N*-substituted-2-bromopropanamides (**13a-r**) to acquire *N*-alkyl/aralkyl/aryl/phenyl-2-[(5-{1-[(4-methoxyphenyl) sulfonyl]-4-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl] propanamide (**14a-r**). The electrophiles, **13a-r**, were synthesized by the reaction of alkyl/aralkyl/aryl/phenyl amines (**8a-i, k, m-t**) and 2-bromopropionyl bromide (**12**) in 5% sodium carbonate solution. Compound **4** was refluxed with methyl isothiocyanate in methanol to acquire an intermediate compound (2-({1-[(4-methoxyphenyl) sulfonyl]-4-piperidinyl}carbonyl)-*N*-methyl-1-hydrazinecarbothioamide) which was refluxed in basic medium to get 5-{1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}-4-methyl-4*H*-1,2,4-triazole-3-thiol (**15**). Compound **15** was stirred with different aralkyl halides (**6a-j**) in the presence of NaH and DMF using conventional and microwave assisted methods. 3-Aralkylthio-5-{1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}-4-methyl-4*H*-1,2,4-triazole (**16a-j**) were obtained through filtration from aqueous medium. The compound **15** was treated with equimolar *N*-substituted-2-bromoacetamides (**10a-t**) to acquire *N*-alkyl/aralkyl/aryl/phenyl-2-[(5-{1-[(4-methoxyphenyl) sulfonyl]-4-piperidinyl}-4-methyl-4*H*-1,2,4-triazol-3-yl)sulfanyl] acetamide (**17a-t**). The compound **15** was treated with equimolar *N*-substituted-2-bromopropanamides (**13a-r**) to acquire *N*-alkyl/aralkyl/aryl/phenyl-2-[(5-{1-[(4-methoxyphenyl) sulfonyl]-4-piperidinyl}-4-methyl-4*H*-1,2,4-triazol-3-yl)sulfanyl] propanamide (**18a-r**). The synthesized compounds were initially verified through TLC and stored for further analysis.

The synthesized compounds were spectroscopically characterized by using IR, ^{1}H-NMR, ^{13}C-NMR, HMQC, HMBC, COSY, NOESY 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 six different enzymes and also for antioxidant activity. The different six enzymes included acetyl cholinesterase (AChE), butyryl cholinesterase (BChE), α-glucosidase, urease, lipoxygenase and carbonic anhydrase II enzyme. Almost all the compounds were found to be excellent active agents against these enzymes. Antioxidant activity 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 sketched compounds in the eight schemes were synthesized efficiently with high yield and purity through environment friendly protocol with minimum cost and time. The time of synthesis and the yield were compared for two modes of synthetic methods including conventional and microwave assisted ones. The following synthetic as well as biological screening studies resulted into the identification of a number of compounds being active against the considered enzymes. 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.