ABSTRACT

In the presented research work sulfonamide, acetamide and oxadiazole functionalities were incorporated as appendants of piperidine. The aim of this work was to synthesize new compounds exhibiting diverse and improved pharmacological potential in search of new drug contenders with enhanced activity, might be helpful in controlling many degenerative diseases.

The present work was accomplished to synthesize 149 compounds having specific structural as well as chemical properties in six different schemes. The synthesized derivatives were evaluated for their enzyme inhibitory potential against different enzymes, that is, acetylcholinesterase, butyrylcholinesterase and lipoxygenase; antibacterial activity using different bacterial strains of gram positive and negative bacteria; and moreover molecular docking studies was also performed for the potent derivatives against AChE & BChE.

The **scheme-1** was based on the synthesis of twenty different *N*-substituted derivatives including *N*-alkyl-*N*-(piperidin-1-yl)benzenesulfonamide (**5a-f**) and *N*-aryl-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (**7a-n**) from 1-amino piperidine. In **scheme-2** ten 2-*O*-substituted derivatives (**9a-j**) of 1-[(3,5-dichloro-2-hydroxyphenyl)sulfonyl] piperidine (**8**) were synthesized by reacting 2-bromoacetamide electrophiles with **8**. In **scheme-3**, 4-(Piperidine-1-yl)aniline was subjected to react with different sulfonyl chlorides (**1a-k**) to form eleven alkyl/aralkyl sulfonamides (**10a-k**) which were substituted with ethyl iodide to generate eleven newfangled *N*-ethyl substituted sulfonamides (**11a–k**). **Schemes-4 & 5** were based on Ethyl isonipecotate as main piperidine based reactant which then treated differently to generate series of novel cholinesterase inhibitors. In series 4 Ethyl isonipecotate was firstly converted to ethyl 1-(phenylsulfonyl)piperidine-4-carboxylate (**12**) which then reacted with NH_2-NH_2 (hydrated) to form 1-(phenylsulfonyl)piperidin-4-carbohydrazide (**13**). By reacting **13** with different sulfonyl chlorides, fourteen *N'*-(1-(phenylsulfonyl)piperidine-4-carbonyl)sulfonohydrazide derivatives (**14a-n**) were synthesized. 5-(1-(Phenylsulfonyl)piperidin-4-yl)-1,3,4-Oxadiazol-2-thiol (**15**) was synthesized by refluxing carbohydrazide **13** with CS_2/KOH in ethanol. This 1,3,4-Oxadiazole **15**, was processed for the synthesis of *S*-substituted 1,3,4-Oxadiazol

derivatives (**16a-v**) (**Scheme-5**). This synthetic scheme involved the stirring of alkyl/aralkyl halides with **15** in the presence of NaH/DMF. The eleven aralkyl/aryl carboxylic acids (**18a-k**) were converted into corresponding ethyl esters (**19a-k**) through esterification with ethanol in the presence of small amount of conc. H_2SO_4 as catalyst. Ethyl esters (**19a-k**) were further converted into carbohydrazides (**20a-k**) by stirring with hydrazine in methanol. The eleven 1,3,4-Oxadiazoles (**21a-k**) were synthesized by refluxing carbohydrazides with CS_2/KOH in ethanol (**Scheme-6**). This scheme also included the formation of an electrophile, **22**, by stirring of piperidine with 4-(bromomethyl)benzenesulfonyl chloride in aqueous basic medium and then stirring of **22** with eleven 5-substituted-1,3,4-Oxadiazol-2-thiols in NaH/DMF to synthesize 5-aralkyl/aryl-1,3,4-Oxadiazol-2-yl 4-(piperidin-1-ylsulfonyl)benzyl sulfide (**23a-k**). All the compounds were corroborated through spectral analysis including ^{1}H-NMR, IR and EI-MS.

Scheme 1-4 & 6 derivatives were screened against AChE, BChE & LOX enzyme and showed excellent to moderate inhibitory potential and most potent inhibitors from each of above mentioned schemes were docked with AChE & BChE proteins to establish the binding models for structure activity relationship. **Scheme-5** derivatives were screened against both gram positive and gram negative bacterial strains *i.e. B. subtilis* (+), *S. aureus* (+) and *S. sonnei* (-), *E. coli* (-), *P. aeruginosa* (-) and *S. typhi* (-) using Ampicillin and Ciprofloxacin as reference standard. All compounds showed varying degree of antimicrobial activity.