ABSTRACT

Synthetic chemistry is well recognized field because of inauguration of different biologically active molecules as active drug candidate in pharmaceutical industry. In this regard, the considered functionalities; 1,3,4-oxadiazole, 1,2,4-triazole, piperidine, sulfonamide and acidamides; have gained much attention because of their notable biological activities. The current research work was an effort to synthesize different molecules bearing these functionalities collectively. The 2,5-disubstituted-1,3,4-oxadiazole and 3,4,5-trisubstituted-1,2,4-triazole derivatives bearing piperidine scaffold were evaluated for different pharmacological activities including antimicrobial, enzyme inhibition, hemolytic, Brine shrimp lethality and anti-inflammatory potential.

One hundred and seventeen compounds were synthesized and are presented in this thesis and the multistep protocol is described in eight schemes.

Ethyl piperidine-3-carboxylate **I** and 4-chlorophenylsulfonyl chloride **II** were employed to synthesize Ethyl-1-[(4-chlorophenyl)sulfonyl] piperidine-3-carboxylate **III** that was subsequently converted into corresponding carbohydrazide **IV** by hydrated hydrazine in methanol under reflux. 5-(1-(4-chlorophenylsulfonyl)-3-piperidinyl)-1,3,4-oxadiazole-2-thiol **V** was synthesized from compound **IV** by reflux in ethanol in presence of carbon disulfide in basic media. Twenty one alkyl/aralkyl derivatives of 1,3,4-oxadiazole bearing piperidine moiety were synthesized (**VII_{1-21}, Scheme-1**). *N*-substituted alkyl/aralkyl/aryl amines **IX_{1-23}** were made to react with Bromoacetyl bromide **VIII** to synthesize *N*-substituted alkyl/aralkyl/aryl 2-bromoacetamides **X_{1-23}**. Parent 1,3,4-oxadiazole **V** was further derivatized to synthesize twenty three *N*-aryl/aralkyl/alkyl substituted acetamide **XI_{1-23}** derivatives as described in **Scheme-2.** Seventeen *N*-aryl/aralkyl/alkyl substituted propanamide derivatives of 1,3,4-oxadiazole bearing piperidine nucleus (**XIV_{1-17}, Scheme-3**) were synthesized by reaction of compound **V** with *N*-substituted alkyl/aryl 3-bromopropanamides **$XIII_{1-7,17-26}$** in aprotic media. *N*-substituted alkyl/aryl 3-bromopropanamides **$XIII_{1-7,17-26}$** were synthesized by gearing up *N*-substituted alkyl/aralkyl/aryl amines **$IX_{1-7,17-26}$** with 3-bromopropionyl chloride **XII.** *N*-substituted aryl 4-bromobutanamides **$XVI_{1-6,10,19}$** were synthesized from *N*-substituted aryl amines **$IX_{1-6,10,19}$** and 4-bromobutyryl chloride **XV** in basic aquoues media. Eight *N*-aryl substituted butanamide derivatives of 1,3,4-oxadiazole bearing piperidine nucleus **$XVII_{1-8}$** was synthesized as depicted in **Scheme-4.** 1-[(4-

Chlorophenyl)sulfonyl]piperidine-3-carbohydrazide **IV** was made to react with phenyl isothiocyanate **XVIII** to synthesize 2-({1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}carbonyl)-*N*-phenyl-1-hydrazinecarbothioamide **XIX** that was subsequently converted into 5-{1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazole-3-thiol **XX** under reflux in basic aqueous media. Twenty alkyl/aralkyl derivatives of 3,4,5-trisubstituted-1,2,4-triazole bearing piperidine moiety $\mathbf{XXI_{1-20}}$ were synthesized by reaction of alkyl halide $\mathbf{VI_{1-11,13-17,19-20,22,23}}$ with 5-{1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazole-3-thiol **XX** as described by **Scheme-5.** The synthesized compound **XX** was *S*-substituted by alkyl halide $\mathbf{VI_{1-11,13-17,19-20,22,23}}$ in polar aprotic solvent. Seventeen *N*-aryl/aralkyl/alkyl substituted acetamide derivatives of 3,4,5-trisubstituted-1,2,4-triazole bearing piperidine nucleus $\mathbf{XXII_{1-17}}$ were synthesized by derivatization with *N*-substituted aralkyl/aryl 2-bromoacetamides $\mathbf{X_{1-7,10,13,17-21,23,24,27}}$ in **Scheme-6.** Six *N*-aryl/aralkyl/alkyl substituted propanamide derivatives of 3,4,5-trisubstituted-1,2,4-triazole bearing piperidine nucleus were synthesized by following the same conditions as earlier. *N*-aralkyl/aryl substituted-3-bromopropamides $\mathbf{XIII_{4,15,18,19,22,23}}$ were synthesized in basic media by reacting *N*-substituted aralkyl/aryl amines $\mathbf{IX_{4,15,18,19,22,23}}$ with bromopropionyl chloride **XII.** Resulting electrophiles were used to synthesize target compound **($\mathbf{XXIII_{1-6}}$, Scheme-7).** Five (5) *N*-aryl/aralkyl/alkyl substituted butanamide derivatives of 3,4,5-trisubstituted-1,2,4-triazole bearing piperidine nucleus **($\mathbf{XXIV_{1-5}}$, Scheme-8)** were synthesized by following the same protocol as above.

Structures of all target compounds were corroborated by Infra Red, Proton Nuclear Magnetic Resonance, Carbon-13 Nuclear Magnetic Resonance spectroscopy and Electron Impact Mass Spectrometry data. Ring formation of 1,3,4-oxadiazole and 1,2,4-triazole was confirmed through Carbon-13 Nuclear Magnetic Resonance spectroscopy. Physical properties of all the target compounds have also been determined. The synthesized compounds were screened for antimicrobial potential (against Gram-positive, Gram-negative bacterial strains and *Aspergilus flavus* as fungal strain), enzyme inhibition potential (against Cholinesterases, Urease, Lipoxygenase and α-Glucosidase), Cytotoxicity (hemolytic potential, Brine Shrimp lethality and anti-cancer potential) and anti-inflammatory activity. Antibacterial potential was evaluated with reference to standard drug ciprofloxacin and streptomycin while antifungal activity was analyzed with reference to standard fluconazole. LOX inhibition potential was evaluated with reference to baicalein

reference standard while serine was used as reference standard against cholinesterases. Acarbose was used as reference drug for α-Glucosidase inhibitory activity. PBS and Triton-X100 were used as negative and positive control for hemolytic screening of the synthesized derivatives. Etoposide was used as reference drug for Brine Shrimp lethality bioassay while Ibuprofen was used for anti-inflammatory activity.

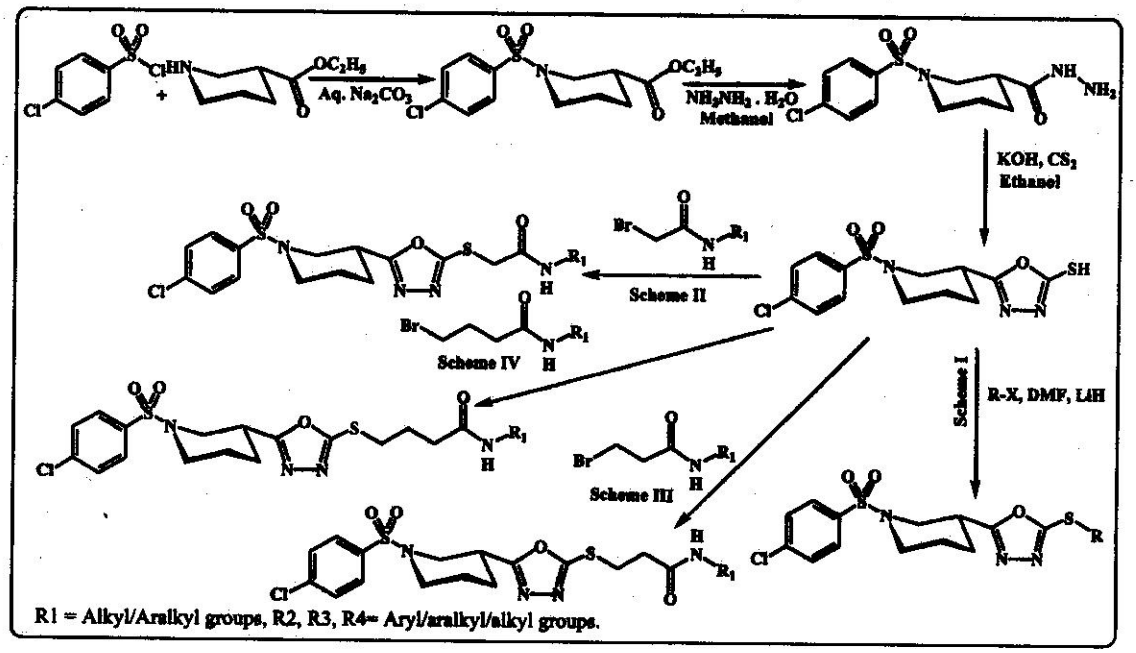
Among the *S*-substituted derivatives of 5-(1-(4-chlorophenylsulfonyl) piperidin-3-yl)-1,3,4-oxadiazole-2-thiol $\mathbf{VII_{1-21}}$, compound $\mathbf{VII_{6,7,15}}$ revealed better results than that of Baicalein standard as LOX inhibitory agents. Compound $\mathbf{VII_{2,4,5,6,9}}$ revealed comparable antibacterial results to standard against *S. typhi* while compound $\mathbf{VII_{2,4,6}}$ exhibited comparable antibacterial potential to reference against *B. subtilus*. *N*-substituted derivatives of 5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-1,3,4-oxadiazol-2-yl-2-sulfanyl acetamide $\mathbf{XI_{1-23}}$ were screened for different biological activities. Compounds $\mathbf{XI_{10,12}}$ revealed least hemolytic percentages and those were comparable to reference PBS. Compound $\mathbf{XI_{8,9}}$ exhibit antibacterial potential against *S. typhi*, compound $\mathbf{XI_{9,13,17}}$ showed MIC values against *E. coli* very close to reference standard. Compound $\mathbf{XI_8}$ exhibited *S. aureus* antibacterial potential that is very close to Ciprofloxacin. Compound $\mathbf{XI_{18}}$ revealed positive lethality against brine shrimp lethality bioassay. Compounds $\mathbf{XI_{11,18}}$ revealed anti-inflammatory potential comparable to the standard drug. From *N*-substituted derivatives of 5-{1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}-1,3,4-oxadiazol-2-yl-2-sulfanyl propanamide $\mathbf{XIV_{1-17}}$, compound $\mathbf{XIV_1}$ revealed positive lethality against brine shrimp lethality bioassay. Most of the *S*-substituted derivatives of 5-{1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazole-3-thiol $\mathbf{XXI_{1-20}}$ revealed excellent α-glucosidase inhibition potential that is much better than acarbose reference standard. Compound $\mathbf{XXI_{3,7,12,13,15,20}}$ showed much lower IC_{50} values than acarbose. *N*-aralkyl/aryl substituted derivatives of 2-[(5-{1-[(4-chlorophenyl) sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)thio]-acetamide $\mathbf{XXII_{1-17}}$ were analyzed for α-glucosidase inhibition potential and compound $\mathbf{XXII_{4,6,7,9,11-16}}$ showed better result than standard acarbose. Compound $\mathbf{XXII_{1,4,5}}$ showed comparable anti-inflammatory potential to ibuprofen. Most of the compounds remained inactive against different biological activities and some of the active compounds revealed much low potential.

The molecular docking studies have been discussed in Chapter-4. Overall a number of compounds exhibited valuable anti-enzymatic potential much better than

standards used and a few ones showed antibacterial potential and anti-inflammatory potential. Most of the active compounds might be suitable drug candidates for pharmaceutical industries to develop new potent drugs.

Overall Reaction Schemes

Synthesis of different 2,5-disubstituted-1,3,4-oxadiazole



Synthesis of different 3,4,5-trisubstituted-1,2,4-triazole