ABSTRACT

The heterocyclic molecules have greatly influenced the pharmaceutical industries due to their bioactivity potential. The discovery of new drug candidates has been the burning issue of all the times owing to new emerging diseases. Heterocyclic Chemistry has been involved exlusively in the field of organo-pharmaceutical drug discovery program. Owing to the reported potential of piperazine, amide, sulfonamide, 1,3,4-oxadiazole and carbamate moieties, the present work was designed to synthesize some new multi-functional molecules encompassing different bioactive functionalties including furan, piperazine, acetamide, propanamide, hexanamide, sulfonamide, ether, ester, 1,3,4-oxadiazole and carbamates. The synthesized molecules have been subjected to evaluation of their antibacterial, antifungal, enzyme inhibition and hemolytic potential. Furthermore, enzyme inhibition potential results have been supported by computational docking in order to find the types of interactions with the active site of involved enzymes. Thirteen (13) schemes have been used to demonstrate the synthesis of one hundred and nine (109) compounds. In scheme-1 to 3, different substituted phenyl amines (**1a-t**) were stirred with 2-bromoacetyl bromide (**2**), 3-bromopropionyl bromide (**6**) and 6-bromohexanoyl bromide (**9**) in basic medium to yield 2-bromo-*N*-(substituted phenyl)acetamides (**3a-t**), 3-bromo-*N*-(substitutedphenyl)propanamides (**7a-q**) and 6-bromo-*N*-(substitutedphenyl)hexamides (**10a-g**) as electrophiles. The synthesized electrophiles were treated with 1-(2-furoyl)piperazine (**4**) to acquire final compounds as 2-[4-(2-furoyl)-1-piperazinyl]-*N*-(substitutedphenyl)acetamides (**5a-r**), 2-[4-(2-furoyl)-1-piperazinyl]-*N*-(substitutedphenyl)propanamides (**8a-q**) and 2-[4-(2-furoyl)-1-piperazinyl]-*N*-(substitutedphenyl)hexamides (**11a-g**). In scheme-4 and 5, different substituted phenyl amines (**1a-h**) were stirred with 4-chloromethylbenzoyl chloride (**12**) and 3-chloromethylbenzoyl chloride (**15**) in basic medium to yield 4-(chloromethyl)-*N*-(substitutedphenyl)benzamides (**13a-h**) and 3-(chloromethyl)-*N*-(substitutedphenyl)benzamides (**16a-h**) as electrophiles. The synthesized electrophiles were treated with **4** to acquire final compounds as 4-{[4-(2-furoyl)-1-piperazinyl] methyl}-*N*-(substitutedphenyl)benzamides (**14a-h**) and 3-{[4-(2-furoyl)-1-piperazinyl]methyl}-*N*-(substitutedphenyl)benzamides (**17a-h**). In scheme-6 to 8, {4-[(3,5-dichloro-2-hydroxyphenyl)sulfonyl]-1-piperazinyl}(2-furyl)methanone (**19**) was synthesized by stirring **4** and 3,5-dichloro-2-hydroxybenzenesulfonyl chloride (**18**) in

a basic medium. The compound **19** was refluxed with different previously electrophiles, **13a-h, 16a-h** and acylhalides (**22a-g**) to synthesize 4-[(2,4-dichloro-6-{[4-(2-furoyl)-1-piperazinyl]sulfonyl}phenoxy)methyl]-*N*-(substituted phenyl) benzamides (**20a-h**), 3-[(2,4-dichloro-6-{[4-(2-furoyl)-1-piperazinyl]sulfonyl} phenoxy)methyl]-*N*-(substitutedphenyl)benzamides (**21a-h**) and *O*-acyl derivatives (**23a-g**). In scheme-9 and 10, different 5-substituted-1,3,4-oxadiazol-2-thiol (**28a-g**) were sytnthesized from corresponding aryl carboxylic acids (**25a-g**) through esterification and hydrazide formation. Two electrophiles, {4-[4-(chloromethyl)benzoyl]-1-piperazinyl}(2-furyl)methanone (**24**) and {4-[3-(chloromethyl)benzoyl]-1-piperazinyl}(2-furyl)methanone (**30**) were synthesized in basic medium by the reaction of **4** with **12** and **15**. The synthesized electrophiles, **24** and **30**, were refluxed with **28a-g** to prepare {4-[4-({[5-(substituted)-1,3,4-oxadiazol-2-yl]sulfanyl}methyl)benzoyl]-1-piperazinyl} (2-furyl) methanone (**29a-g**) and {4-[3-({[5-(substituted)-1,3,4-oxadiazol-2-yl]sulfanyl}methyl)benzoyl]-1-piperazinyl} (2-furyl) methanone (**31a-g**). In scheme-11, the secondary amines (**32a-h**) were stirred with 4-bromomethylbenzenesulfonyl chloride (**33**) in a basic medium to get sulfonamides, **34a-h**, as electrophiles. These electrophiles were refluxed with **4** in acetonitrile in the presence of K_2CO_3 to get a series of 1-{[1-(2-furoyl)piperazin-4-yl]methyl}phenyl-4-sulfonyl substituted secondary amines (**35a-h**). In scheme-12 and 13, bromoalkyl amines (**36** and **43**) were stirred with phenyl chloroformate (**22e**) in a basic medium to yield phenyl 2-bromoethylcarbamate (**37**) and phenyl 3-bromopropylcarbamate (**44**). These two compounds were subjected to nitration and bromination to acquire 2,4,6-trinitrophenyl 2-bromoethylcarbamate (**39**), 2,4,6-tribromophenyl 2-bromoethylcarbamate (**41**), 2,4,6-trinitrophenyl 3-bromopropylcarbamate (**46**) and 2,4,6-tribromophenyl 3-bromopropyl carbamate (**48**). All these electrophiles were refluxed with **4** to synthesize a series of carbamates, phenyl 2-[4-(2-furoyl)-1-piperazinyl]ethylcarbamate (**38**), 2,4,6-trinitrophenyl 2-[4-(2-furoyl)-1-piperazinyl]ethylcarbamate (**40**), 2,4,6-tribromophenyl 2-[4-(2-furoyl)-1-piperazinyl]ethylcarbamate (**42**), phenyl 3-[4-(2-furoyl)-1-piperazinyl]propyl carbamate (**45**), 2,4,6-trinitrophenyl 3-[4-(2-furoyl)-1-piperazinyl]propylcarbamate (**47**) and 2,4,6-tribromophenyl 3-[4-(2-furoyl)-1-piperazinyl]propylcarbamate (**49**). The synthesized compounds were initially checked through thin layer chromatography (TLC) and then finally corroborated through spectral data of IR (Infra Red), ^{1}H-NMR (Proton Nuclear Magnetic Resonance), ^{13}C-NMR (Carbon-13

Nuclear Magnetic Resonance) and EI-MS (Electron Impact Mass Spectrometry). Some spectra are also given for structural elucidation in the discussion section of chapter 4. The compounds are also characterized by the physical data of like color, state, yield, melting points (not for sticky solids), molecular formula and molecular mass. The pharmacological screening of synthesized molecules included the evaluation of their antibacterial and enzyme inhibition potential. The antibacterial potential against different bacterial strains was conducted through two methods including dilution and disc diffusion. Activity through dilution method was compared with Ciprofloxacin and that with disc diffusion method was compared with Rifamicin. Antifungal activity was also tested through disc diffusion method in comparison of Fluconazole. The enzyme inhibition potential was evaluated against α-glucosidase, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) with reference of Acarbose, Eserine and Eserine respectively. The pharmacological screening results were also aided by % hemolytic activity for toxicity of compounds with reference to PBS (phosphate buffer saline) and Triton X-100. Molecular docking study was also conducted for enzyme inhibition data in order to explain the types of interactions with the active site of the considered enzyme by the most active compounds. Among the synthesized one hudred and nine (109) compounds, a number of compounds have exhibited pharmacological activity potential. The structure activity relationship (SAR) of these compounds has been demonstrated explicatively in chapter 4 under discussion section. The most potent antibacterial agents and enzyme inhibitors with least toxicity might be subjected to *in vivo* study for further analysis as drug candidates. These compounds might be considerable for the pharmacological industries as new drug candidates for drug discovery program.