ABSTRACT

The synthetic chemistry has gained much attention because of the broad spectrum of biological activities related to structural features of various synthesized molecules. The synthetic chemistry has prominent application in the field of pharmaceutical or medicinal chemistry regarding new drug candidates. In this regard, the three concerned functionalities; 1,3,4-oxadiazole, azomethine and benzo-2-pyrone; have gained much attention because of their notable biological activities. The current research work was an effort to synthesize different molecules bearing these functionalities; 1,3,4-oxadiazole derivatives bearing azomethine functionality and benzo-2-pyrone derivatives bearing acetamide functionality; and to evaluate their antibacterial and enzyme inhibition potential.

Eight (8) different carboxylic acids (**I_{1-8}**) were employed to synthesize one hundred thirty three (133) azomethine compounds (**$VIII_{1-133}$**, Scheme-1) by converting them to corresponding ethyl esters (**II_{1-8}**) by ethanol on reflux, carbohydrazides (**III_{1-8}**) by hydrazine on stirring at RT (room temperature) or reflux, 1,3,4-oxadiazoles (**IV_{1-8}**) by carbon disulfide on reflux, ethyl esters (**V_{1-8}**) by ethyl 2-bromoethanoate (EBE) on stirring at RT, again carbohydrazides (**VI_{1-8}**) with hydrazine on stirring at RT and finally azomethine derivatives (**$VIII_{1-133}$**) with aryl carboxaldehydes (**VII_{1-19}**) on stirring at RT. 2,4-Dimethylphenol (**IX**) was also converted to thirteen (13) compounds (**XV_{1-13}**, Scheme-2) of such type through the same steps except first one for the synthesis of ethyl ester (**X**) by ethyl 2-bromoethanoate (EBE) on reflux.

4-Chloro-1,3-dihydroxybenzene (**XVI**) was converted to heterocyclic 6-chloro-7-hydroxy-4-methylbenzo-2-pyrone (coumarin, **XVII**) by reaction with ethyl 2-ethanoylethanoate (EEE) in concentrated sulfuric acid. The synthesized benzo-2-pyrone molecule was *O*-substituted by alkyl halides (**$XVIII_{1-9}$**) to synthesize **XIX_{1-9}** and by acyl halides (**XX_{1-8}**) to synthesize **XXI_{1-8}** (Scheme-3). The different alkyl/aralkyl/aryl amines (**$XXII_{1-27}$**) were made to react with 2-bromoethanoyl bromide (BEB) on stirring to synthesize a number of new electrophiles (**$XXIII_{1-27}$**, Scheme-4). These synthesized electrophiles were subjected to react with **XVII** to synthesize *N*-substituted acetamide derivatives (**$XXIV_{1-26}$**, Scheme-5) and then with 4-hydroxybenzo-2-pyrone (**XXV**) to synthesize **$XXVI_{1-18}$** (Scheme-6) on stirring at RT. The *N*-substituted 1,3,4-oxadiazole acetamide derivatives (**XXX_{1-27}**, Scheme-7) of benzo-2-pyrone were synthesized by stirring **$XXIII_{1-27}$** with 5-{[(6-chloro-4-

methylbenzo-2-pyron-7-yl)oxy]methyl}-1,3,4-oxadiazol-2-thiol (**XXIX**), prepared by the same steps as that for 5-[(2,4-Dimethylphenoxy)methyl]-1,3,4-oxadiazol-2-thiol (**XII**) in Scheme-2.

All the proposed structures of synthesized compounds were characterized by IR (Infra Red), PNMR (Proton Nuclear Magnetic Resonance) and EIMS (Electron Impact Mass Spectrometry) spectral data. Ring formation of 1,3,4-oxadiazole and benzo-2-pyrone was confirmed through CNMR (Carbon-13 Nuclear Magnetic Resonance). The compounds have been enriched by their physical data also. All the synthesized compounds were screened against two Gram-positive and three Gram-negative bacteria to evaluate their antibacterial potential with reference of Ciprofloxacin, the reference drug. Along with antibacterial potential, these were also evaluated for their LOX (Lipoxygenase) inhibition potential with reference to Baicalein.

Among the 1,3,4-oxadiazole bearing azomethine compounds (Scheme-1 and Scheme-2), $\mathbf{VIII}_{5,7,48,53}$ & $\mathbf{XV}_{1,8\text{-}10}$, were the most active against both of the Gram-positive bacterial strains and the compounds, $\mathbf{VIII}_{5,53,90,124}$, were the most active against all the three Gram-negative bacterial strains. Also against all the five bacterial strains, $\mathbf{VIII}_{5,53}$, were the best inhibitors. Against LOX, the compound, $\mathbf{XV}_{9}$ bearing 5-[(2,4-Dimethylphenoxy)methyl]-1,3,4-oxadiazol-2-yl and 3-nitrobenzylidene, was better inhibitor even than Baicalein, as evident from its four times low IC_{50} value.

Among the benzo-2-pyrone derivatives (Scheme-3 to Scheme-7), the compounds obtained after alkylation ($\mathbf{XIX}_{1\text{-}9}$) of benzo-2-pyrone were relatively more efficient against the bacterial strains taken into account than the acylated ($\mathbf{XXI}_{1\text{-}8}$) ones. The compounds, $\mathbf{XIX}_{1,2,8,9}$, were the active inhibitors of all the bacterial strains. The acetamidic compounds, $\mathbf{XXIV}_{4,15,23,26}$ presented notably valuable inhibitory potential for all the bacterial strains. The LOX inhibition potential was too much low for these compounds. All the compounds, $\mathbf{XXVI}_{1\text{-}18}$, were notably active against all the strains but two compounds, $\mathbf{XXVI}_{16,17}$, were the most efficient ones. Among the compounds, $\mathbf{XXX}_{1\text{-}27}$, the Gram-negative strains were efficiently inhibited than Gram-positive ones. The best activity was presented by $\mathbf{XXX}_{5,6,10,22}$. Among the acetamidic 1,3,4-oxadiazole compounds, the molecules bearing alkyl substituted phenyl rings and aralkyl groups with long aliphatic chain resulted in moderate to good activity. The molecules bearing *ortho* substituted phenyl rings remained active against all the strains, also good to excellent and more efficient against the Gram negative strains. The *meta* substituted phenyl rings were also good against negative strains but the *para*

substituted ones presented varying moderate activities. For the LOX inhibition, the most of compounds remained inactive and the active ones depicted too much low potential.

The structure activity relationship (SAR) is discussed in detail in discussion section (Chapter-4) for all the series of compounds. Overall a number of compounds among all the series executed valuable antibacterial potential and a few ones with valuable anti-enzymatic potential. The most active compounds might be subjected to *in vivo* study for further analysis as drug candidates. The pharmacological industries may consider these compounds as new drug candidates for drug discovery pathway.