

Abstract

Five membered heterocyclic compounds and their derivatives have gained much attraction of synthetic chemists due to their valuable biological activities. Especially 1,3,4-oxadiazole have shown remarkable broad spectrum biological activities which prompted us to synthesize its different 2,5-disubstituted-1,3,4-oxadiazole derivatives. Benzodioxole moiety has also shown numerous biological activities. It was assumed that 2,5-disubstituted-1,3,4-oxadiazole ring along with the potential benzodioxole moiety might boost up the pharmacological activities of the synthesized molecules. Sulfamoyl derivatives were also prepared to evaluate them for their various biological activities. Many incurable fatal diseases can be made curable to much extent by the help of latest and advanced research. So the presented research work comprises of the synthesis of some novel multifunctional compounds followed by the characterization of these compounds and biological evaluation including antibacterial studies as well as enzyme inhibition studies. The selection of these moieties was made on the basis of their known remarkable pharmacological activities.

The compounds presented in this particular work were synthesized according to the protocol available in the literature and has been mentioned in respective schemes in detail. In Scheme-1, twenty four (24) various 5-substituted-1,3,4-oxadiazole-2-thiol 4a-x were synthesized, starting from different carboxylic acids through formation of corresponding esters converted into hydrazides and ultimately 5-substituted oxadiazoles were obtained through an intermolecular cyclization mechanism. Moreover, the reaction of different 5-substituted-1,3,4-Oxadiazol-2-thiols 4a-x Scheme-2, 3 & 4, with electrophiles, 6-chloro-3,4-methylenedioxybenzylchloride 5, 6-bromo-3,4-methylene dioxybenzylbromide 7 and 2-bromo-*N*-(3,4-methylene dioxybenzyl)acetamide 11, yielded twenty four (24) 5-(aryl/aralkyl)-2-((6-chloro-3,4-methylenedioxybenzyl)thio)-1,3,4-Oxadiazoles 6a-x, twenty four (24) 5-(aryl/aralkyl)-2-((6-bromo-3,4-methylenedioxybenzyl)thio)-1,3,4-Oxadiazole 8a-x, and twenty (20) *N*-[3,4-methylenedioxybenzyl]-2-[(5-substituted-1,3,4-oxadiazol-2-yl)thio]acetamide 12a-t, respectively in the presence of *N,N*-dimethylformamide and sodium hydride. According to the Scheme-5, twenty (20) different electrophiles, *N*-substituted-2-bromoacetamides 14a-t, were synthesized in aqueous basic conditions on simple shaking. Twenty (20) *N*-substituted-2-((5-(3,4-methylenedioxy)phenyl)-1,3,4-Oxadiazol-2-yl) sulfanyl)acetamide derivatives 15a-t, were also produced by the

reaction of twenty presynthesised electrophiles, 14a-t with 5-(3,4-methylenedioxyphenyl)-1,3,4-Oxadiazol-2-thiol 4a in *N,N*-dimethylformamide and sodium hydride Scheme-6. In Scheme-7, twenty one (21) different 2-alkyl/aralkylthio-5-(3,4-methylenedioxyphenyl)-1,3,4-Oxadiazole derivatives 17a-u were synthesized on treating 5-(3,4-methylenedioxyphenyl)-1,3,4-Oxadiazol-2-thiol 4a with twenty one aryl/aralkyl halides (16a-u). Scheme-8 comprises of the synthesis of fourteen (14) sulfonamide derivatives of paroxetine 20a-k,m-o by the usual method of stirring in basic aqueous medium with fourteen different sulfonyl chlorides 19a-k,m-o. Twelve (12) 3,4-methylenedioxyphenylsulfonohydrazide derivatives 21a-l, were prepared by the reaction of 3,4-methylenedioxybenzohydrazide 3a with different sulfonyl chlorides 19a-l by the continuous stirring in basic aqueous conditions using sodium carbonate solution.

All the synthesized compounds were characterized by using different spectroscopic techniques i.e. IR, ¹H-NMR and mass spectral data. ¹³C-NMR technique was also used in some cases to elucidate and to support the structural analysis. A proposed mass fragmentation pattern of some of the compounds is also given. Some of the ¹H-NMR, ¹³C-NMR and EIMS spectra of synthesized compounds are presented. The synthesized compounds were also evaluated for antibacterial and enzyme inhibition activities. All the nine schemes were put for antibacterial assay. Overall the synthesized compounds showed significant results. In Scheme-2, the compound 5-(Pyridin-3-yl)-2-((6-chloro-3,4-methylenedioxybenzyl)thio)-1,3,4-Oxadiazole 6i showed overall maximum activity against *E.coli* (-), and *Bacillus subtilis* (+) among the compounds. The compound remained at the top with %age inhibition value, 76.17±5.00 for *E.coli*, and 70.12±3.65 for *Bacillus subtilis* (+), compared to the reference standard, Ciprofloxacin with the %age inhibition value 92.02±1.97. In Scheme-3, the compound, 8x expressed the highest %age inhibition value 79.19 ± 1.10 against *Escherichia coli* (-) relative to the reference standard, Ciprofloxacin with %age inhibition value 90.44±1.23. In Scheme-4, the compound, *N*-[3,4-methylenedioxybenzyl]-2-[(5-(4-chlorophenoxy)methyl)-1,3,4-Oxadiazol-2-yl]thio]acetamide 12m revealed the maximum activity against *Pseudomonas aeruginosa* with the %age inhibition value 76.45±0.70 relative to the reference standard, ciprofloxacin with the %age inhibition value 93.45±0.42. In Scheme-6 the compounds which seem as highly active within the series are 15r, 15a, 15m and 15b

among which *N*-[2,3-dimethylphenyl]-2-[(5-(3,4-methylenedioxyphenyl)-1,3,4-oxadiazol-2-yl)thio]acetamide 15a is the most active one with %age inhibition value 68.75 ± 0.68 against *E.coli* relative to the reference value 92.79 ± 0.83 . In Scheme-7, the compound, 2-(2-Phenylethyl)thio-5-(3,4-methylenedioxyphenyl)-1,3,4-Oxadiazole 17j, surprisingly, showed maximum excellent activity against all the bacterial strains used under analysis. Its %age inhibition values are 80.50 ± 2.64 , 88.11 ± 0.33 , 87.20 ± 1.65 , 83.86 ± 1.75 , 84.25 ± 0.58 and 87.46 ± 0.69 relative to the reference standard, ciprofloxacin whose inhibitory values are 90.85 ± 1.53 , 92.04 ± 1.07 , 91.83 ± 2.77 , 89.59 ± 2.00 , 89.25 ± 1.92 and 88.15 ± 1.23 against the bacterial strains *S. Typhi*, *E. Coli*, *K. Pneumoniae* and *P. aeruginosa*, *B. Subtilis*, *S. Aerus* respectively. In the Scheme-8, lipoxygenase enzyme inhibition assay, was carried out. The excellent inhibition in LOX assay was shown by the compound *N*-(4-chlorobenzenesulfonyl)paroxetine (20m) with %age inhibition value 98.01 ± 0.01 compared with the reference standard baicalien value 93.79 ± 1.27 . The Scheme-9, was tested for antibacterial activity and it was found that all the compounds were quite active against *E.coli*. The results are very close to the reference standard value. Amongst the compounds, 2-(1,3-Benzodioxol-5-ylcarbonyl)-3,5-dichloro-2-hydroxybenzenesulfonohydrazide (21i), was found to be the most active against all bacterial strains. Its % inhibition values are 70.35 ± 3.06 , 87.38 ± 1.75 , 89.33 ± 1.42 , 72.60 ± 2.20 and 85.35 ± 1.65 compared with reference values; 91.19 ± 2.10 , 90.44 ± 1.23 , 92.00 ± 2.76 , 89.98 ± 2.07 and 92.21 ± 1.59 against *S. typhi* (-), *E. coli* (-), *P. aeruginosa* (-), *B. subtilis* (+) and *S. aureus* (+) respectively. Overall it was observed that the compounds having electron donating substitutions within their structures exhibited good to excellent antibacterial results. Biological activity data in comparison with the reference standard drugs is presented in biological activity section.