8. CONCLUSION

A series of novel benzimidazole derivative containing isoxazolin-5-one, pyrazoline-5-one and pyrazolidine-3,5-dione have been synthesized. The structures of these compounds were characterized by TLC, UV, IR, 1H NMR and mass spectral analysis. Compounds were evaluated for anti-inflammatory as well as gastric ulcerogenic effects, antimicrobial properties and *in vitro* anti-oxidant effects.

In the acute toxicity studies, the examined compounds did not show toxic effects at doses up to 2000 mg/kg b.w. Therefore, 1/10\(^{\text{th}}\) of the tolerated dose was chosen for the pharmacological evaluation.

N-Phenyl pyrazolone derivative 7i showed better anti-inflammatory activity and other compounds 8c, 7h and 7f, exhibited comparable activity in carrageenan-induced rat paw edema in rat, with low ulcerogenicity compared with the standard drug Indomethacin. Since GI problems due to NSAID continue to be the major impediment to their use in therapeutics, GI protection of the new anti-inflammatory derivatives proves them useful lead molecules for the development of better NSAID with greatly improved therapeutic index. Molecular docking studies using Hex and auto dock of these derivatives with COX-2 and COX-1 receptors are also showed minimum binding energy for all the compounds and may be considered as good inhibitors of COX-2. A Lamarckian genetic algorithm method implemented in the program Auto dock 4.0, was employed.
The newly synthesized compounds were also screened for their antibacterial activity and antifungal activity against gram positive bacteria (*B. subtilis* and *S. aureus*), gram negative bacteria (*E. coli* and *P. aeruginosa*) and *A. niger* and *S. cerevisiae* fungal strains respectively by cup plate method. Minimum inhibitory concentration also reported. Among the test compounds, the compounds 6e, 7d and 8d have emerged as active against all tested microorganisms and all other compounds showed moderate activity whereas 6a, 7b, 7i, 7f and 8a did not show any activity. Further, the anti fungal evaluation result of the synthesized compounds indicated that compounds 8c and 6e have the potential to be selective as lead compounds.

The enhanced antibacterial and antifungal activities of the 6e, 8d and 7d could be attributed to the presence of o-hydroxy phenyl and cinnamoyl or styryl groups in benzimidazole moiety. With *in vitro* anti microbial results in hand it is thought worth-while to do *in silico* studies to support the *in vitro* activities .Theoretically all the compounds showed very good binding energy. So, it can be predicted as the activity may be due to inhibition of enzyme either β-keto acyl acyl carrier protein or peptide deformylase or heptosyl WaaC enzymes in case of anti bacterial activities and either 14-α demethylase or glucosamine-6-Phospahe synthatase enzyme for antifungal activity to confirm these studies. Further enzyme assays are required to confirm these studies.
Hence, this study widened the scope of developing these benzimidazole containing isoxazoline-5-one, pyrazoline-5-one and pyrazolidine-3,5-dione as promising anti-bacterial and anti-fungal agents.

In *in-vitro* anti-oxidant activities, most of the compounds assayed showed excellent reducing power and free radical scavenging activities. Compounds 6e, 6c, 8b, 7c, 7d and 7h are the most active among the series showing high reducing power and hydrogen peroxide scavenging activities.

The drug likeness properties synthesized compounds were predicted by calculating Lipinski rule-5 that satisfies the rule of 5 for potent inhibitors except 7h, 7i, and 7j.

These results and previous experimental and docking studies strongly suggest that most of molecules synthesized in this study may indeed be promising drug candidates with interesting pharmacological profile and most of these derivatives could be a fruitful pharmacophore for further development of better anti inflammatory, antimicrobial and anti-oxidant agents.
9. REFERENCES


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