UNIVERSITI TEKNOLOGI MARA

SYNTHESIS OF BENZIMIDAZOLE DERIVATIVES, BIOLOGICAL EVALUATION AND MOLECULAR DOCKING STUDIES

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ABSTRACT

Benzimidazoles which form a vital part of vitamin B_{12} are of wide interest because of their diverse biological activity and clinical application. This privileged structure has gained our interest to explore some new benzimidazole derivatives by combining with other biologically active moieties such as hydrazone, oxadiazole and thiourea. The first part of our work was to synthesize and characterize a total of 61 benzimidazole derivatives bearing different substituents such as hydrazone, oxadiazole and thiourea, by reacting benzimidazole benzoyl hydrazide and various aromatic aldehydes, aromatic acids or phenylisothiocyanates under certain conditions. The second part is to evaluate the synthesized compounds for their cytoprotective activity against cytokine-induced apoptosis in β-cells (20 compounds), α-glucosidase (43 compounds) or β-glucuronidase (18 compounds) inhibition activities. The final part is to construct a structure-activity relationship (SAR) and molecular docking studies in order to understand the mechanism of inhibition. For the first series, twenty six benzimidazole bearing hydrazone derivatives were synthesized and evaluated for cytoprotective activity against cytokine-induced apoptosis in β-cells and Baker's yeast α-glucosidase inhibitory activities. In the presence of pro-inflammatory cytokines, compounds **208**, **211** and **217** were the most potent among all the analogues, in which they increased the cellular ATP levels, inhibited caspase-3 activity, decreased nitrite production and restored GSIS in a dose-dependent manner. These results show that benzimidazole derivatives may protect pancreatic *β*-cells against cytokine-induced apoptosis. Meanwhile for α-glucosidase inhibitory activity, compounds **208**, **209**, **210**, **211**, **212** and **217** showed significant inhibitory effects than the rest of the derivatives with IC_{50} values between 8.40 ± 0.76 - 9.99 ± 0.69 μM when compared with standard acarbose (IC_{50} = 774.5 ± 1.94 μM). From SAR and docking studies, we concluded that the attachment of the atom at *meta-para* position over the phenyl ring might be one of the best clues for good interaction network and good inhibitory activity. For the second series, eighteen benzimidazole bearing 2,5-disubstituted-1,3,4-oxadiazole derivatives were synthesized and screened for β-glucuronidase inhibitory potential. Amongst the derivatives, compounds **222**, **234**, **227** and **232** exhibited single digit micromolar β-glucuronidase inhibition potential with IC_{50} values in the range of 2.14 ± 0.03 - 8.14 ± 0.29 μM, which is superior to the standard D-saccharic acid 1,4-lactone (IC_{50} = 48.4 ± 1.25 μM). From the docking conformations of compounds **222**, **234**, **227** and **232**, it was observed that all the active compounds are able to adopt suitable orientations within the binding pocket of *β*-D-glucuronidase with some specific functional groups at *ortho*, *meta* or *para* position over the phenyl ring, that interact to the important residues of the enzyme. For the last series, seventeen benzimidazole bearing thiourea derivatives were also evaluated for their α-glucosidase inhibitory potential. Compounds **246** and **250** showed significant inhibitory effects with IC_{50} values 50.57 ± 0.81 and 35.83 ± 0.66 μM, respectively, compared to the rest of the derivatives and standard acarbose. The docking results showed that the position of electron withdrawing moieties at *ortho, meta* and *para* over the phenyl ring are more favorable for the interactions with active site residues. Based on the above results, we concluded that benzimidazole derivatives possess great potential as antidiabetic drugs that need further investigation in order to establish these findings.

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