Synthesis of new 1,2-disubstituted benzimidazole analogs as potent inhibitors of b-Glucuronidase and in silico study

ABSTRACT

New benzimidazole analogues (1–18) were synthesized and characterized through differ- ent spectroscopic techniques such as 1H NMR, 13C NMR and HREI-MS. All analogues were screened for b-glucuronidase inhibitory potential. All analogues showed varied degree of inhibitory potentials with IC50 values ranging between 1.10 – 0.10 to 39.60 – 0.70 lM when compared with standard D-saccharic acid-1,4- lactone having IC50 value 48.30 lM. Analogues 17, 11, 9, 6, 1 and 13 having IC50 values 1.10 – 0.10, 1.70 – 0.10, 2.30 – 0.10, 5.30 – 0.20, 6.20 – 0.20 and 8.10 – 0. 20 lM respectively, showed excellent b-glucuronidase inhibitory potential many folds better than the standard. All other analogues also showed good inhibitory potential better as compared to stan- dard. Structure activity relationships (SAR) has been established for all compounds. The results from molecular docking studies supports the established SAR and developed a strong correlation with the results from into vitro assay. The molecular docking results clearly highlighted how sub- stituents like nitro and chloro affect the binding position of the active compounds in the active site. The docking results were also used to properly establish the effect of bulky substituents of least active compounds on reduced b-glucuronidase inhibitory activity. Compounds 1–18 were found non-toxic.