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INTERROGATING NOVEL COMPOUNDS FOR IMPROVED ANTI-DENGUE THERAPIES VIA INHIBITION OF HUMAN HEXOKINASE II (HKII)

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Dengue is one of the most fatal infectious diseases in the world, which is caused by dengue virus (DENV). Regrettably until now, specific treatment for the disease has not been established. It has been reported that a human glycolytic enzyme, the human hexokinase II (HKII) has a great impact in supporting viral replication in the host cell, thus the enzyme has been proposed as an anti-DENV drug target. The main aim of this research is to identify novel anti-DENV agents for the treatment of dengue disease through in silico screening and HKII enzymatic inhibition studies. In silico screening comprises of ligand-based and structure-based screening approaches, where the former analysis was performed by using Ultrafast Shape Recognition with CREDO Atom Types (USRCAT) programme, utilizing both HKII substrate and product; alpha-D-glucose (GLC), and beta-D-glucose-6-phosphate (BG6), as well as a known inhibitor of HKII, 2- deoxyglucose (2-DG) as the query molecules. The analogues were subsequently docked against the HKII crystal structure (PDB ID: 2NZT) by using AutoDock Vina programme on Chain A and B, where the active sites and strong bonds were located. The docking hits, which were molecules similar to GLC, BG6 and 2-DG possessed binding energy ranging from -6.1 to -6.4 kcal/mol, -6.2 to -6.8 kcal/mol and -6.9 to 7.0kcal/mol, respectively with strong H bond around the catalytic residues (Thr620, Glu629, Lys621, Asn656, Asp657, Ser893, Asn683, Phe623 Gln739 and Glu742). The top dockedposes compounds were then further analysed through Molecular Dynamics (MD) simulation studies. Inhibition analysis was subsequently conducted via a coupled enzyme assay, where chitin; the analogue of 2-DG, has shown 35% inhibition on HKII activity. Meanwhile, 2- (2,3,4,5,6 pentahydroxyhexanoylamino acetic and 4R,5R)-9-[(2S,3R,4S,5S)-3,4-dihydroxy5-(hydroxymethyl) tetrahydrofuran-2-yl]-4,5-dihydro-1H-purin-6; both are analogues of BG6, had exhibited 30% inhibition on HKII activity. Another compound; 3-Fluoro-3-deoxyD-glucopyranose, an analogue of GLC, showed 18% inhibition on the enzyme's activity. In a nut shell, selected compounds from virtual screening were proven to affect the activity of human HKII, which have future potentials to be developed as anti-dengue therapeutics and through the aid of nanotechnology for a better therapeutic performance.