Biological evaluation of heparin octadecasaccharides as iduronate-2-sulphatase inhibitors with chaperone effect

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ABSTRACT

Introduction: Mucopolysaccharidoses Type II (MPS II) is an X-linked lysosomal storage disorder characterised by IDS mutations leading to iduronate-2-sulphatase (IDS) deficiency and glycosaminoglycan substrate accumulation. Due to the limitations of currently available treatments, pharmacological chaperone (PC) has been suggested as a potential alternative therapy to MPS II. Here, we describe the biological characteristics of heparin octadecasaccharides (HO18) as an IDS inhibitor and the potential of PC in treating the disease. **Methods:** The chaperone effect of HO18 was evaluated using recombinant IDS protein for kinetic, inhibition, thermal stability, dose-dependent, and cell viability studies. **Results:** A kinetic study through the Lineweaver-Burk plot indicated that HO18 may act as a competitive inhibitor attached to the substrate binding site with the Michaelis-Menten constant (Km) of 1703.67 µM with a Vmax of 1666.67 µmolh-1. The higher affinity of HO18 for IDS was observed at neutral pH (Half maximal inhibitory concentration, IC50=29.5 µM, pH 7.0) compared to acidic (lysosomal) pH (IC50=97.9 µM, pH 5.0) which suggests that it is a potent inhibitor. Furthermore, HO18 significantly improved the stability of IDS at 67oC ($p<0.05$) as well as increased IDS activity in a dose-dependent manner. In addition, HO18 at the concentration of 18.82 µM reduces cell viability by 50%. **Conclusion:** These findings strongly suggest that HO18 could be used as a potential PC for MPS II. Further in vitro studies utilising the expression of IDS-mutated enzymes can be carried out for further validation.