Poster No. B-04

Bioevaluation Of Heparin Oligosaccharides In Correcting Iduronate-2-Sulfatase Deficiency

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INTRODUCTION

Mucopolysaccharidoses Type II is caused by an X-linked mutation in IDS gene which produce an enzyme called iduronate 2-sulfatase (IDS) that is essential for the breakdown of glycosaminoglycans. Lack of IDS enzyme activity leads to the accumulation of heparan sulfate and dermatan sulfate within the lysosomes. Apart from enzyme replacement therapy, current treatments of MPS II have been a challenge especially in finding donor for bone marrow transplantation. Thus, this study aims to evaluate the various heparin oligosaccharides (HO) on IDS activities as potential pharmacological chaperone (PC).

MATERIALS & METHOD

HO (H004, H008, H010, H012, H014, H016, H018 and H020) in several concentrations were used in this study. Enzyme inhibition assay is as illustrated in Figure 1. All HO candidates were also tested on ATCC cell for specificity testing.

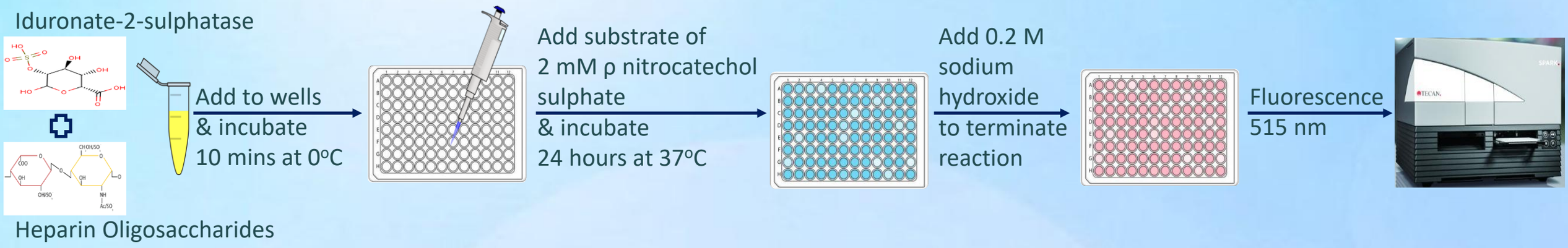

Figure 1: Schematic enzyme inhibition assay

RESULTS

- The results of this study is summarized in Table 1. Three selected inhibition profiling of potential small molecules are depicted in Figure 2.
- No significant difference ($p>0.05$) was observed in the inhibition of IDS activity in ATCC cells which proves its specificity on IDS.

Table 1: Inhibition assay results

Heparin Oligosaccharides	IC_{50} (µM)$_a$	Ki value
H004	59.27	19.40
H008	34.40	95.51
H010	11.38	24.17
H012	9.26	20.98
H014	8.44	13.54
H016	7.26	9.19
H018	11.55	7.19
H020	7.54	7.95

[a]IC_{50} values were measured in triplicate experiments

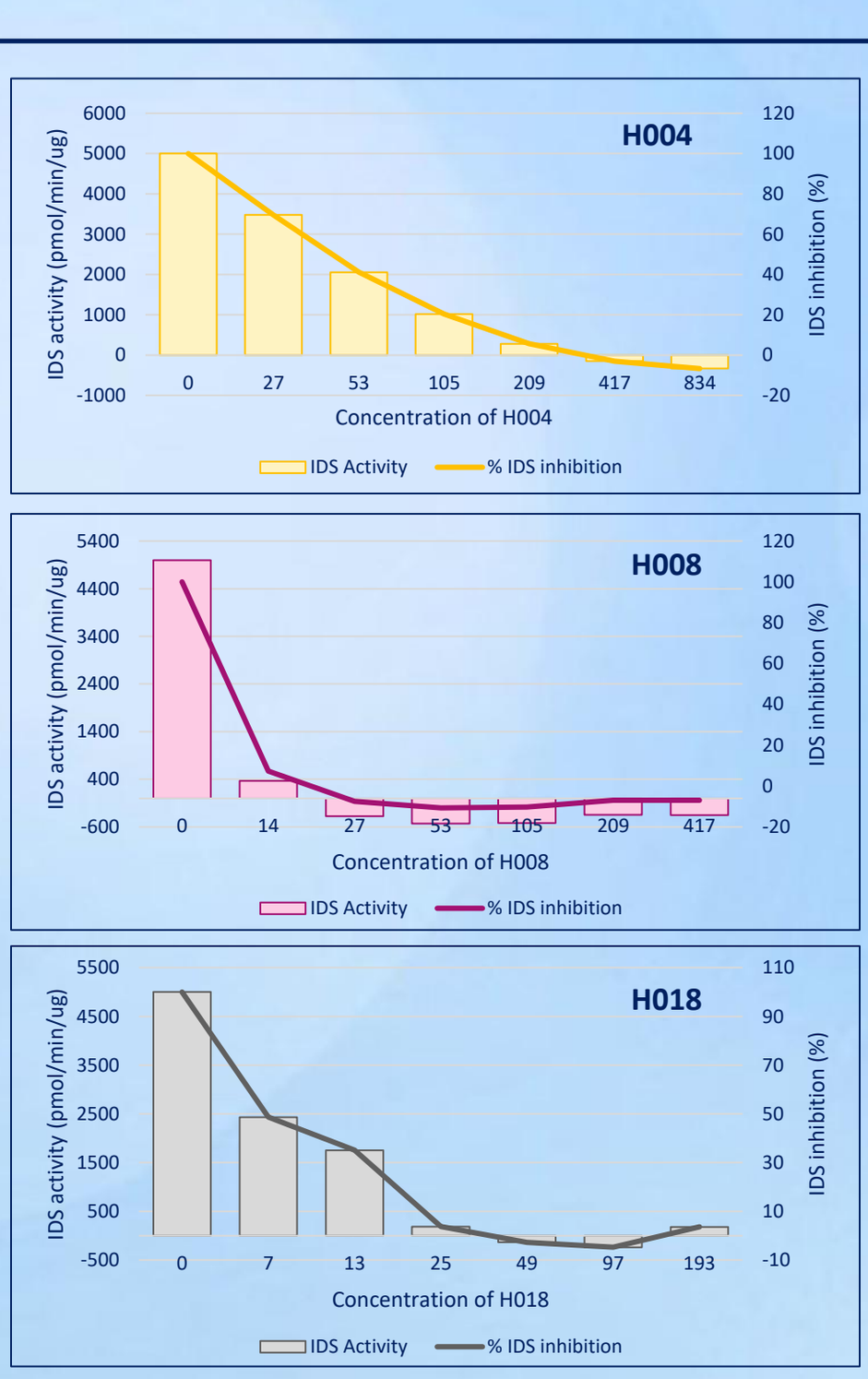

Figure 2 : Inhibition profiling of respective heparin oligosaccharides

DISCUSSION & CONCLUSION

- PCs are small molecules that have an affinity to mutant enzymes and directly bind to them which improve their folding, stability, and enzymatic activity (1)
- Ideal PC of potent inhibitor exhibits low concentration of 50% inhibition of enzyme activity (IC_{50}) with high inhibition constant (Ki) of the dissociation between the enzyme-inhibitor complex or the reciprocal of the binding affinity of the inhibitor to the enzyme (2).
- Out of eight species of HO tested, three demonstrate as PC with Ki and IC_{50} (µM) of 59.27 & 19.40; 34.40 & 95.51; and 11.55 & 7.19 for H004, H008 and H018, respectively.
- As conclusion, three potential small molecules (H004, H008 and H018) with high Ki with low IC_{50} have been identified as potential pharmacological chaperone. Future research will be done on thermal stability analysis and cell-based experiments.

REFERENCES

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2. Cheng Y., Prusoff W.H. Relationship between the inhibition constant (Ki) and the concentration of inhibitor which causes 50 percent inhibition (IC_{50}) of an enzymatic reaction. Biochem Pharmacol. (1973) 22: 3099–3108.

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