A novel heparin-like heparanase inhibitor hexasaccharide: synthesis and activity evaluation

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Heparanase (HPSE) is an β-endo-D-glucuronidase capable of cleaving the glycosaminoglycan chains of heparan sulfate (HS) at specific sites and thereby to modulate the biological function of this proteoglycan.

Deregulation of HPSE appeared in numerous pathological processes such as inflammation, metastasis, and angiogenesis [1], therefore, its inhibition is a good target for new therapeutic agents [2]. The development of non-anticoagulant heparin derivatives was a found promising strategy to develop HPSE inhibitors and among these compounds, Roneparstat was the first HPSE inhibitor reaching clinical trials [3]. It is obtained from heparin after N-desulfation, N-acetylation, periodate oxidation and borohydride reduction, originating the so called glyco-split residue (abbreviated as gs) in the heparin chain. It was later found that, when the primary alcohols of these gs units of heparin are replaced by carboxylic acids (gs/ox) heparanase inhibitory activity increased, thus resulting in a new drug (H1710), now in preclinical stage [4].

In the present work we synthesized a defined hexasaccharide containing a gs/ox uronic acid to check whether similar structural modifications on a hexasaccharide would result in similar effects. Surprisingly, we found that the synthetic derivative shows similar activity of Roneparstat (IC_{50} 70 nM), in spite its lower molecular weight.

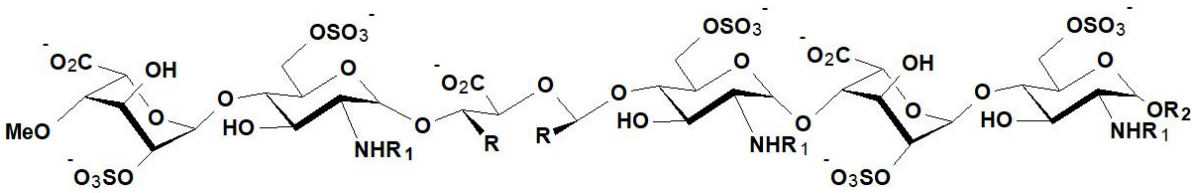

Figure 1, R = CH2OH, CO2H, R1 =Ac, SO3H, R2 = alkyl

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