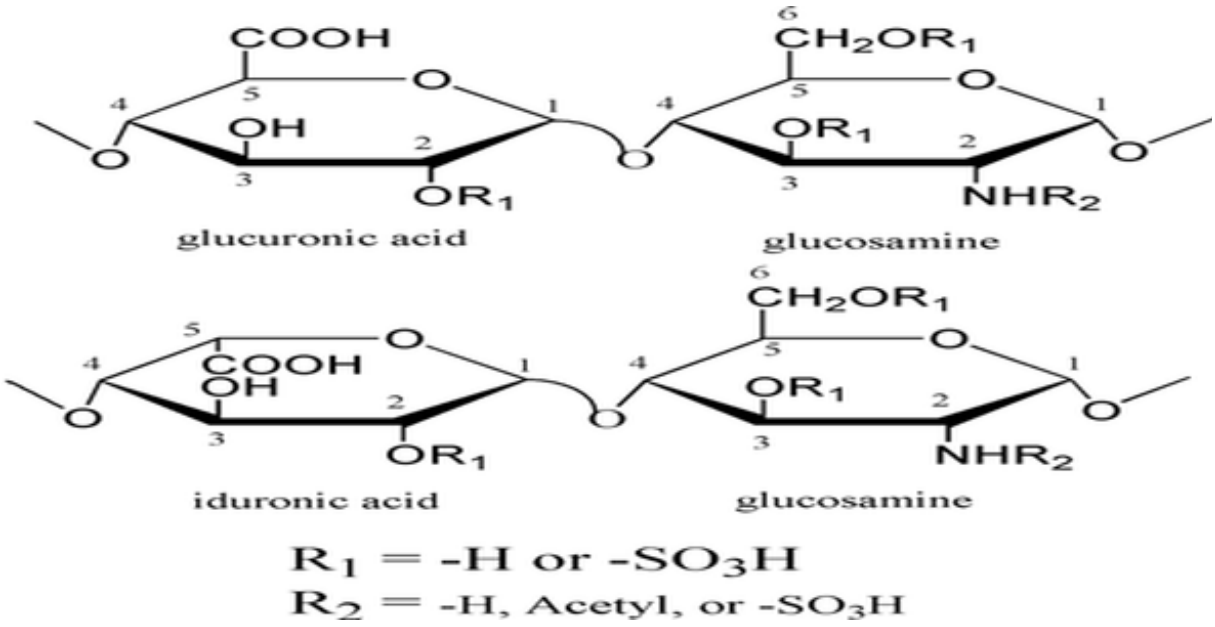
THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Chemistry

Enzymatic Approach to Synthesize UltraLow Molecular Weight (ULMW) Heparins



Heparin is a naturally occuring polysaccharide that has been used as an anticoagulant drug for more than 50 years. Heparin is marketed in three forms: unfractionated (UF) heparin (molecular weight of 14000); low molecular weight (LMW) heparin (molecular weight of 6000); and ultralow molecular weight (ULMW) heparin (molecular weight of 3000). UF heparin is used in surgery and kidney dialysis, but the anticoagulation effects and animal sourcing of UF heparin are unpredictable. In contrast, synthetic LMW and ULMW heparins have a more subtle regulation of coagulation, reduced side effects and have played an increasingly important role in anticoagulation therapy. Researchers at UNC have developed a method to produce two new ULMW heparins using an enzymatic approach and readily available disaccharide building blocks. This method provides a revolutionized approach to prepare ULMW heparin anticoagulant drugs.

Benefits

1. Significantly shorter synthesis process compared to existing chemical- and enzymatic-based approaches (10 steps rather than 50 steps).
2. Reduced cost of synthesis.
3. Improved selectivity/purity over other ULMW heparin anticoagulant drugs.
4. Improved yield compared to existing synthesis approaches (40% rather than 0.1%).

carolina blue™ opportunity

For More Information

If you would like more information about this technology or UNC - Chapel Hill's technology transfer program, please contact:

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The Technology

Heparin leads to the inactivation of Thrombin and Factor Xa, which are enzymes involved in blod clotting. The inactivation of Thrombin requires full length heparin, while Factor Xa inactivation only needs a pentasaccharide version of heparin and still displays excellent anticoagulant activity. This realization led to the development of LMW and ULMW heparins as pharmaceutical anticoagulants. For the past decade, synthetic ULMW heparin anticoagulants, such as Arixtra (GlaxoSmithKline), have been widely used. However, chemical-based methods to synthesize these ULMW heparins suffer from high costs, low yields, and have been subject to contamination issues. An enzyme-based approach for ULMW heparin synthesis, developed by researchers at UNC, eliminates these issues and offers a much better alternative.

This chemoenzymatic approach relies on a series of biosynthetic enzymes and mimics the biosynthesis of heparin and heparin sulfate. The synthesis is performed by: providing a disaccharide substrate; elongating the disaccharide substrate to form a saccharide of predetermined length; performing an epimerization reaction on the elongated saccharide; and, then, performing one or more sulfation reactions on the epimerized saccharide. The chemoenzymatic approach demonstrates that targeted, scalable, and efficient synthesis of heparin oligosaccharides is possible.

The ULMW heparin products of this enzyme-based synthesis have the most notable application as potent anticoagulants. This enzymatic-based approach could also facilitate the creation of a library of LMW and ULMW heparin varients. The heparin varient library could be screened to discover heparin structures with other therapeutic potentials, such as anticancer or antiviral activity.

Opportunity

UNC's Office of Technology Development seeks to stimulate development and commercial use of UNC-developed technologies. UNC is flexible in its agreements, and opportunities exist for joint development, academic or commercial licensing (exclusive, non-exclusive, and field-of-use), publishing, or other mutually beneficial relationships. UNC is pursuing U.S. and international intellectual property protection for this innovation.