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Galectin-3 is extensively involved in metabolic and disease processes, such as cancer metastasis, thus giving impetus for the design of specific inhibitors targeting this β-galactose-binding protein. Thiodigalactoside (TDG) presents a scaffold for construction of galectin inhibitors, and its inhibition of galectin-1 has already demonstrated beneficial effects as an adjuvant with vaccine immunotherapy, thereby improving the survival outcome of tumour-challenged mice. A novel approach--replacing galactose with its C2 epimer, talose--offers an alternative framework, as extensions at C2 permit exploitation of a galectin-3-specific binding groove, thereby facilitating the design of selective inhibitors. We report the synthesis of thioditaloside (TDT) and crystal structures of the galectin-3 carbohydrate recognition domain in complexes with TDT and TDG. The different abilities of galactose and talose to anchor to the protein correlate with molecular dynamics studies, likely explaining the relative disaccharide binding affinities. The feasibility of a TDT scaffold to enable access to a particular galectin-3 binding groove and the need for modifications to optimise such a scaffold for use in the design of potent and selective inhibitors are assessed.