ORGANORUTHENIUM GLYCOMIMETICS AS NEXT-GENERATION GALECTIN-1 INHIBITORS

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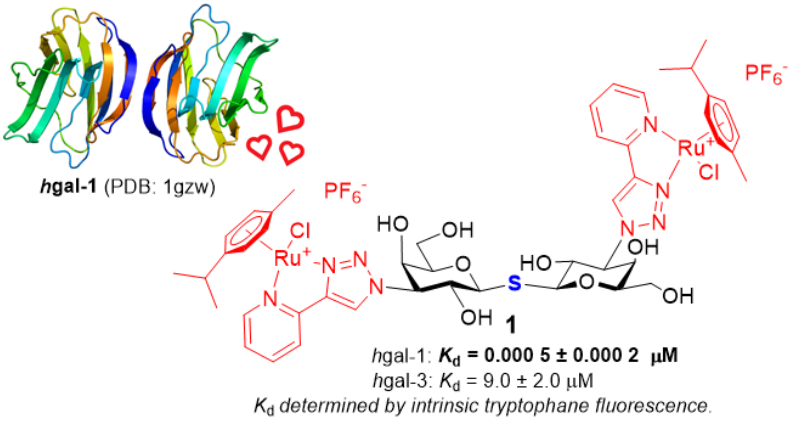
Galectins, a family of β-galactoside-binding lectins, play key roles in various biological processes, including tumor development and progression. Human galectin-1 (*h*gal-1) has been implicated in immune evasion, cell migration, and regulation of apoptosis, making it an attractive target for anticancer drug development [1]. Here, we introduce a novel class of ruthenium-based glycomimetic inhibitors designed to selectively target *h*gal-1. These inhibitors are based on *N*-acetyllactosamine and thiodigalactoside scaffolds, functionalized with organoruthenium piano-stool complexes.

Our ruthenium-functionalized glycomimetics (such as **1**) show nanomolar binding affinities for both human and mouse galectin-1, while exhibiting unprecedented selectivity—over 1000-fold preference for *h*gal-1 compared to human galectin-3 (*h*gal-3). Biological studies revealed that these inhibitors prevent *h*gal-1-induced apoptosis in Jurkat cells, a mechanism that may contribute to suppressing immune escape in certain cancers. Additionally, they selectively reduce the viability of *h*gal-1-expressing MDA-MB-231 breast cancer cells at low micromolar concentrations while displaying minimal toxicity toward galectin-1 null HEK-293 noncancerous cells. Furthermore, they effectively scavenge extracellular *h*gal-1, preventing its association with the cancer cell surface—a crucial property for disrupting *h*gal-1-mediated signaling pathways.



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References:

1. Perrotta, R. M.; Bach, C. A.; Salatino, M.; Rabinovich, G. A. *Biochem. J.* **2021**, 478 (3), 597–617.