**Hybrid organometallic galectin inhibitors**

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# Hybrid organometallic galectin inhibitors

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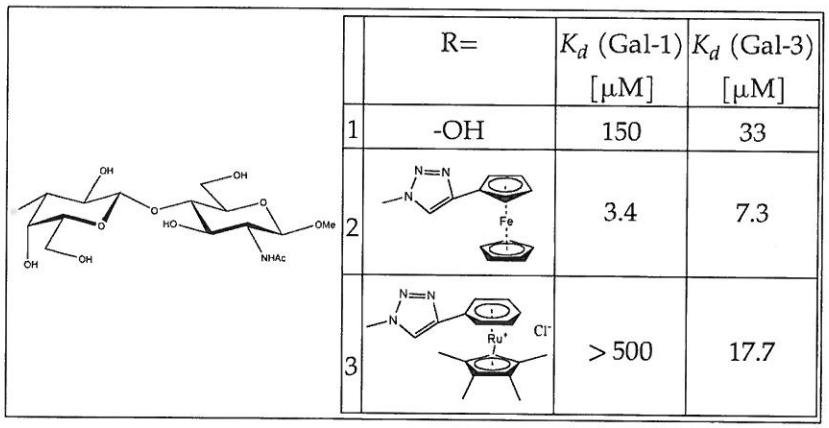
Galectins are lectin-type proteins defined by their sequence homology and the ability to bind β-galactosides. Human galectin-1 (Gal-1) and galectin-3 (Gal-3) are involved in tumor progression. Elevated Gal-1 levels are reported for many tumor tissues and Gal-1 contributes to tumor progression including cell migration and tumor immune escape. Gal-3 is characteristically overexpressed in many cancers and an elevated Gal-3 level is associated with increased invasiveness, metastatic spreading, immunosuppression and angiogenesis. Galectins are also implicated in progression of serious diseases other than cancer e.g., cardiovascular ones, diabetes mellitus, fibrosis, and others. These properties make galectins promising therapeutic targets.[1]

Natural ligands of galectins include galactose, lactose, *N*-acetyllactosamine and their glycosylated and sulfated forms. Modifications of these carbohydrate ligands can create non-natural structures (or glycomimetics) with enhanced binding to galectins, thus acting as their potent inhibitors. The most common type of alternation is to introduce an aromatic substituent instead of carbohydrate hydroxyl which do not participate in the binding.

In this project, we replace the aromatic substituent with arene-containing organometallic structure – ferrocenes[2] and ruthenium arenes[3] with known antitumor or antimetastatic properties. This creates a hybrid molecule, that acts both as a galectin inhibitor and a cytotoxic and/or antimetastatic agent. We have confirmed that both ferrocenes and ruthenium arenes moieties are viable bioisosteric replacement for planar arenes in the context of glycomimetic galectin inhibitors. Prepared organometallic inhibitors have a comparable or even better binding affinity to galectins than their nonmetallic counterparts. We have also established, that galactose bearing two ferrocenes moieties at positions C1 and C3 is selectively cytotoxic to resistant ovarian cancer cell line SK-OV-3 with about 100× higher cytotoxicity (expressed as $IC_{50}$) than currently used drug *cisplatin*.




| | R= | $K_d$ (Gal-1) [μM] | $K_d$ (Gal-3) [μM] |
|---|---|---|---|
| 1 | -OH | 150 | 33 |
| 2 | | 3.4 | 7.3 |
| 3 | | > 500 | 17.7 |

**Figure 1:** Structures of N-Acetyllactosamine (LacNAc) (**1**), 3′-LacNAc-ferrocene complex (**2**) and 3′-LacNAc-ruthenium-arene complex and their dissociation constants ($K_d$) to human Galectin 1 (Gal-1) and human Galectin 3 (Gal-3).

*References*

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2. Bartosik, M.; Koubková, L.; Karban, J.; Červenková Šťastná, L.; Hodík, T.; Lamač, M.; Pinkas, J.; Hrstka, R. *Analyst*, **2015**, *140*, 5864–5867.
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