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In This Issue

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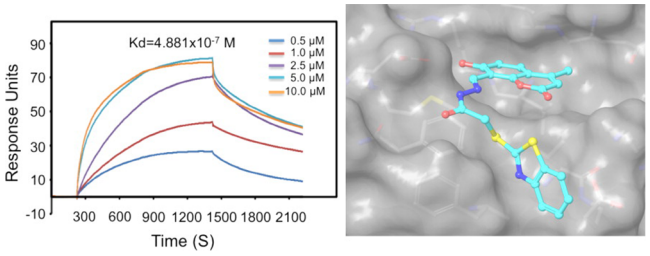
TARGETING RXRα'S COREGULATOR-BINDING SITE

Retinoid X receptor alpha (RXRα) is a key regulator of many signal transduction pathways. RXR ligands and modulators have shown promising chemopreventive and chemotherapeutic activities. One ligand, bexarotene, has been approved by FDA for treating cutaneous T-cell lymphoma. Consequently, great attention has been focused on developing new ligands and RXRα modulators for cancer and disease treatment. While drug discovery efforts have mostly been focused on targeting RXRα's classical ligand binding pocket, the current compounds suffer from unwanted side effects.

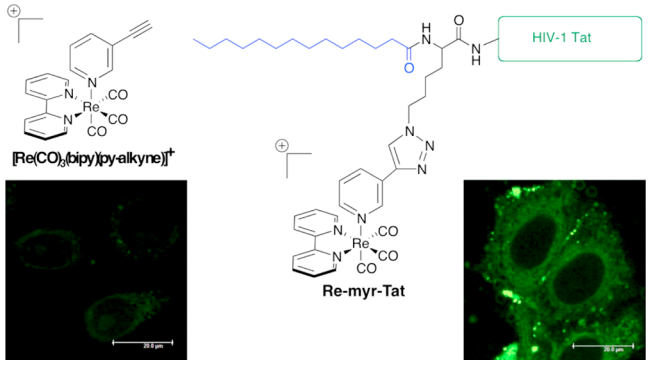
The coregulator-binding site located on the surface of RXRα offers an opportunity to identify such new RXRα modulators. In this issue, our Featured Letter authors, Chen et al. (DOI: 10.1021/ml5000405) report the identification and characterization of a small molecule that binds to the coregulator-binding site of RXRα, instead of the ligand binding pocket. The compound binds and inhibits RXRα's transcription activity. Further, this compound could potently inhibit RXRα-dependent activation of the PI3K/AKT signaling pathway in cancer cells by preventing the interaction of tRXRα with the p85α subunit of PI3K. This compound represents the first of a class of small molecules that bind to the coregulator-binding site of RXRα to regulate RXRα-dependent biological activities.



"CLICKABLE" LUMINESCENT RHENIUM COMPLEX

Since the discovery and phenomenal success of cisplatin, medicinal inorganic chemistry continued to grow as a field of research at the interface between inorganic chemistry, biology, and medicine. Surprisingly, while ruthenium organometallic compounds remain widely investigated, interest in the antiproliferative activity of rhenium organometallic complexes is relatively new.

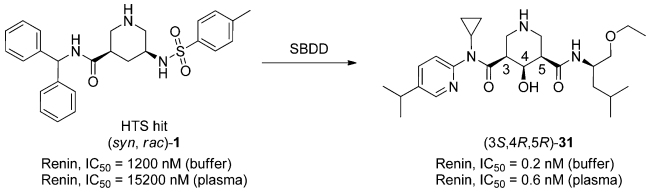
Here, Leonidova et al. (DOI: 10.1021/ml500158w) report the preparation and biological study of a luminescent Re(I)−peptide bioconjugate. The authors show that the complex is moderately cytotoxic toward cervical cancer cells and mainly localizes in the cytoplasm. The organometallic complex was coupled to a cell-penetrating peptide using click chemistry methodology, increasing its cytotoxicity and cellular uptake. This study illustrates how conjugation of a probe to a cellular penetrating peptide is a feasible method to enrich its biological properties.



NEW ORAL RENIN INHIBITORS

Hypertension, or high blood pressure, is the leading cause of cardiovascular mortality. The renin−angiotensin−aldosterone system has long been established as being the key cascade in the regulation of blood pressure and homeostasis of body fluid volume. Thus, renin inhibition has been considered to be a highly attractive model to treat hypertension. As such, vast medicinal chemistry efforts have been focused on the discovery of orally efficacious direct renin inhibitors.

In this issue, Ehara et al. (DOI: 10.1021/ml500137b) conducted structure-based design by utilizing X-ray crystal structure information to identify novel high affinity P3 scaffold, which has culminated in the discovery of 4-hydroxy-3,5-substituted piperidine inhibitor. The inhibitor demonstrates high *in vitro* potency toward human renin with excellent off-target selectivity as well as high oral bioavailability and efficacy in rat.



SBDD = Structure-based Drug Design

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