A High-Throughput Screen for Small Molecule Disruptors of RNA-Protein Binding in Type I Myotonic Dytrophy

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Myotonic Dystrophy Type I (DM1) is the most prevalent form of inherited muscular dystrophy, affecting 1 in 8000 adults. Patients experience a host of symptoms ranging from myotonia (loss of muscle relaxation) and insulin resistance to severe muscle wasting and ultimately death. At the heart of this disease is an aberrant binding interaction between muscleblind-like protein 1 (MBNL1) and triplet-repeat-expanded poly(CUG)RNA; the RNA sequesters MBNL1 in the nucleus, preventing it from performing its function as a regulator of pre-mRNA splicing. The poly(CUG)RNA expansion, meanwhile, serves no beneficial purpose, and so is uniquely positioned as a target for drug discovery.

Using a photonic crystal (PC) biosensor assay, a high-throughput screen of ~200,000 compounds was carried out as an effort to identify small molecules that would bind the poly(CUG)RNA and inhibit poly (CUG)RNA-MBNL1 binding. Hit compounds from this screen are being assessed as inhibitors, both in vitro and in cell culture.

Apart from the immediate goal of drug discovery as suggested by the disease model, our lab is also interested in small molecule binders for RNA in general. Since the poly(CUG)RNA is characterized by a repeating motif of 1x1 internal loops (arising from the U-U mismatches) we hope to arrive at a general binding module for RNA internal loops.

Design and Synthesis of Small Molecule Ligands for ER-Mediated Suppression of Inflammation

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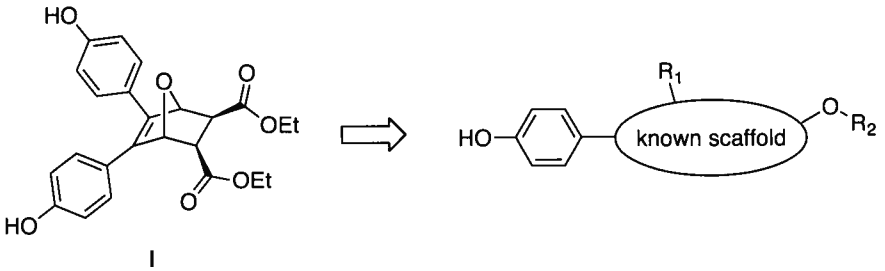
A relatively new facet of estrogen receptor research is the design of small molecules that selectively promote ER-mediated suppression of inflammation by down-regulating NFκB transcriptional cascades. Luciferase-based transcriptional assays have shown that oxabicyclic compound **I** inhibits NFκB transcription without activating traditional ER function. Further structural studies have suggested a mechanism whereby one of the ethyl ester displaces a histidine residue from the binding pocket, altering a hydrogen-bonding network crucial in ER transcriptional activation. We have set out on an aggressive campaign to develop high-potency functional analogs of **I** based on previously known high-affinity scaffolds altered to displace the histidine implicated in the proposed mechanism of action.



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