Tetra-Aryl Cyclobutanes as Direct Inhibitors of the Nuclear Receptor/Coactivator Interaction

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In a continued effort to develop novel therapeutics for the management of hormone receptor-driven cancers, we have developed a set of 1,3-biphenyl-2,4-bipyrimidynyl-cyclobutanes that directly disrupt the interaction between the estrogen and androgen receptors and their coactivators. These compounds differ from traditional nuclear hormone receptor antagonists in that they bind to the surface of the receptors, as opposed to an internal hydrophobic pocket, and are active even in the presence of an agonist ligand. The cyclobutanes are active in both in vitro (time-resolved FRET) and cell-based (luciferase reporter gene) assays, and bind with affinities ranging from submicromolar to low micromolar. These preliminary results suggest that compounds with this mechanism of action may prove efficacious in the treatment of hormone-refractory breast and prostate cancers.

Design and Testing of Mechanochromic Spiropyran-Linked Polymers

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Mechanophores are molecules that utilize mechanical deformation to initiate chemical transformations. Recently, spiropyrans have been established as mechanophores in solid-state polymers. When covalently bound to a polymer of sufficient molecular weight, a visible color change can be observed when the polymeric material is subjected to mechanical deformation. This color change is attributed to a 6-π electrocyclic ring-opening of the spiropyran initiated by mechanochemical transduction of macroscopic forces to the molecular level. Herein, we seek to expand our knowledge of the mechanochemical activation of this mechanophore in the solid-state through the synthesis and mechanical testing of a variety of polymeric materials.