

Structural Motifs for Developing Coactivator Binding Inhibitors for the Estrogen Receptor Alpha

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Molecules that directly interrupt the interaction of estrogen receptor alpha and steroid receptor coactivators could be useful as probes of estrogen receptor function and could have clinical importance in instances where conventional endocrine therapy fails (e.g. SERM and aromatase inhibitor resistance). We report here several structural classes of small molecule inhibitors of this interaction, compounds we term coactivator binding inhibitors (CBIs). These molecules, pyrimidines, amphipathic benzenes, and variants of a previously reported guanyldrazone, have been designed to mimic the steroid receptor coactivator's amphipathic leucine-rich alpha-helical consensus sequence that interacts with a shallow groove on the estrogen receptor alpha. These compounds are active at low micromolar concentrations in *in vitro* models of estrogen receptor action, as well as in cell-based assays of estrogen receptor-mediated coactivator interaction, transcription, and gene regulation.