Small-Molecule Inhibitors of the Estrogen and Androgen Receptor/Coactivator Binding Interaction

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Many breast and prostate cancers can be effectively treated with endocrine therapies, which have traditionally involved the administration of partial or full antagonists, ligands that bind to the internal ligand binding site of the estrogen (ER) or androgen (AR) receptor, inducing a conformation that prevents receptor interaction with key coactivator proteins required for hormone signaling. While this approach often causes an initial regression of the disease, the cancer cell eventually overcomes this antagonism through cellular adaptations, inducing a hormone-refractory state. We are developing an alternative approach to blocking estrogen and androgen action by the use of small molecules that directly disrupt the key ER and AR/steroid receptor coactivator (SRC) interactions necessary for gene activation. The direct nature of this disruption might provide a viable therapeutic for even hormone refractory breast and prostate tumors. Consequently, we have synthesized a pyrimidine-based library of moderate size, members of which effectively act as α-helix mimics to disrupt the interaction between the ER and AR ligand binding domains and their coactivators. As measured by *in vitro* time-resolved fluorescence resonance energy transfer (TR-FRET) and luciferase reporter gene assays, the most active members of this library selectively disrupt the ER/SRC and AR/SRC interactions with K_i's in the low micromolar range. These results support the feasibility of this direct protein/protein inhibitory approach as a possible new type of directed endocrine therapy.