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

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We have developed a number of pyrimidine and cyclobutane-core small molecules that directly disrupt the interaction between the estrogen and androgen nuclear receptors and their coactivators. These compounds are the first step in developing a new class of novel breast and prostate cancer therapeutics that act by disrupting the protein/protein interaction necessary for receptor-mediated transcription and consequent tumor progression. This model differs from the traditional approach of nuclear receptor inhibition, which involves the allosteric disruption of the coactivator binding groove caused by binding of an antagonist at the internal ligand binding pocket, and may prove a promising alternative for overcoming hormone-refractory cancers.