Synthesis of High Affinity Estrogen Receptor PROTACs

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The estrogen receptor (ER) is a member of the nuclear hormone receptor superfamily and has been implicated in breast and ovarian cancers as well as osteoporosis, neurodegenerative diseases, and cardiovascular disease in women and men. Over the past few decades the incidence of breast cancer has risen worldwide and has been attributed to an increase in exposure to environmental estrogens; even with improvements in detection, prevention, and treatment, breast cancer continues to be a leading cause of death in women. Typical chemotherapy treatment using an ER antagonist, or more recently, an aromatase inhibitor, helps control receptor activity at the protein-small molecule interface. Conversely, control of cellular receptor concentration can be achieved at the post-translational level by using a small molecule-peptide conjugate called a PROteolysis TArgeting Chimeric molecule, or PROTAC. This conjugate consists of a high affinity ER ligand covalently linked to a ubiquitin ligase (E3) destruction sequence; the PROTAC recruits both ER and an E3, effectively ubiquitinating the ER and targeting it for destruction by the proteasome. The design and synthesis of a new high affinity PROTAC is presented.