Estrogens bind with and activate estrogen receptors (ERs) to modulate gene transcription and signaling, impacting cellular processes in various tissues, including bone, breast, and endometrium. ER-mediated activity has shown benefits for menopause-related conditions in women; however, estrogens are associated with proliferation in uterine tissue compartments. Consequently, traditional estrogen therapy for postmenopausal women with a uterus requires use of progestins, which via the progesterone receptor, inhibit cellular proliferation in the endometrium, counteracting estrogenic effects. Progestins, however, are associated with tolerability issues including breast pain and uterine bleeding. A newer approach to menopausal therapy, the tissue selective estrogen complex (TSEC), pairs a selective estrogen receptor modulator (SERM) with 1 or more estrogens. Because SERMs exhibit distinct profiles of gene and target-tissue activity, TSECs maintain the benefits of estrogens on menopausal symptoms without the stimulatory effects on breast and uterus. The components of a TSEC can form a heteroligand-estrogen receptor (ER) complex with distinct effects on gene expression and target tissues, compared with their individual SERM or estrogen components. Preclinically, the TSEC conjugated estrogens/bazedoxifene (CE/BZA) is associated with ER agonist effects on bone turnover and vasomotor function as well as concurrent antagonist effects in breast and endometrium resulting from the presence of the bazedoxifene SERM component. CE/BZA also promotes ER degradation somewhat tissue-selectively, further minimizing endometrial and breast estrogenic responses. Thus, via receptor binding competition, variable gene transcriptional activity associated with heteroliganded receptor dimers, and ER degradation, CE/BZA is mechanistically and pharmacologically distinct from its individual components.