Design and Synthesis of Selective Estrogen Receptor Agonists

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Dissertation

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Abstract

Estrogens are hormone that regulates many different physiological functions. A decline in estrogen leads to significant issues that decrease the quality of life. Past treatments of menopausal symptoms included the administration of estrogen. However, side effects such as an increased risk of breast cancer, made this an unattractive therapeutic option. When a new estrogen receptor (ERβ) was discovered, it provided new hope for hormone replacement therapy (HRT). ERβ was shown to inhibit tumor growth, whereas ERα regulates breast cancer proliferation in certain types of breast cancer. The therapeutic benefits of targeting ERβ is vast, herein we focus on the benefits HRT has on memory and general cognitive functions. Several research groups have reported selective ERβ agonists (DPN, WAY). Our lab previously reported two of the most selective ERβ agonists to date, ISP 173 and EGX 358. Analogues of EGX 358 were then explored, along with an improved stereo-selective synthesis. In addition to these compounds, several additional compounds were explored that altered the cyclohexane core of EGX 358. EAW 999, which contains an adamantyl substitution on the phenol ring, showed improved potency, but lowered the selectivity relative to EGX 358. Additionally, EAW 854, which contains a spiro[3,5]cyclononane substitution, both improves the potency and selectivity for ERβ.