Abstract

Potent and Selective Estrogen Receptor-Beta Agonists Which Enhance Memory Consolidation in an Ovariectomized Mouse Model †

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Estrogen receptor-beta (ER-beta) is a drug target for memory consolidation in postmenopausal women, while estrogen receptor-alpha (ER-alpha) is linked with the proliferation of certain breast cancer cell lines. While the ligand-binding domains of ER-beta and ER-alpha share less than 60% sequence homology, the ligand-binding pockets of the two subtypes have only minor differences in structure and composition. Nonetheless, these minor differences make the ER-beta binding pocket smaller in volume (282 Å³) compared to the ER-alpha binding pocket (379 Å³). We report a series of potent and selective ER-beta agonists with in vivo efficacy that are A–C estrogens, lacking the B and D rings of the endogenous ligand, estradiol (E2). The most potent and selective A–C analog activates the ER-beta isoform over the ER-alpha isoform by 750-fold, with an EC50 of 27 ± 4 nM in cell-based functional assays. The compound exhibits in vivo efficacy for memory consolidation for object placement and object recognition in an ovariectomized mouse model at a 0.5 mg/kg dose by intraperitoneal injection and by oral gavage. This analog does not activate seven other nuclear hormone receptors, does not inhibit CYP1A2 or CYP2D6 and has only weak inhibition of CYP2C9 and CYP3A4, and does not cause significant proliferation of MDF-7 breast cancer cells at doses up to 1000 nM.

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