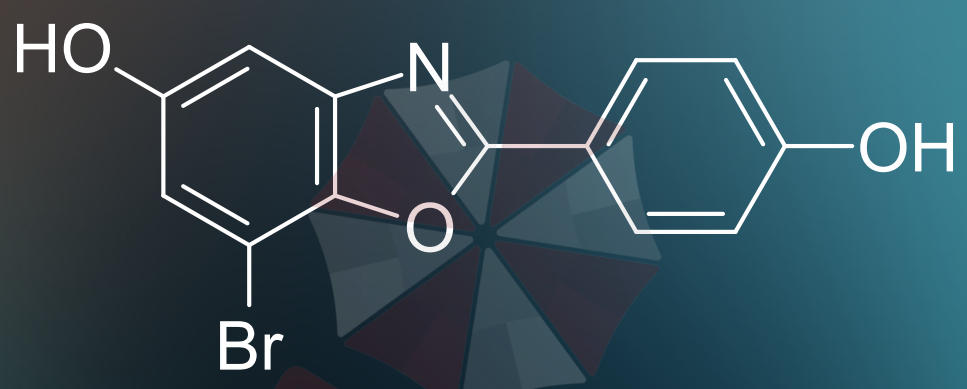

WAY-200070: A Selective Estrogen Receptor Beta Agonist with Potential Neuroprotective, Metabolic, and Anticancer Applications

History

WAY-200070 (also sometimes known as WAY 200070–3) was first described in a publication in 2004, where itself and several other members of its class were first synthesized and their receptor affinities towards the estrogen alpha (ERα) and beta receptor (ERβ) characterized.[1] Afterwards, it has been used as research compound in a variety of academic studies.

Mechanism of Action

WAY-200070 is an estrogen receptor agonist, which is mostly selective for the beta receptor subtype. The affinity for the ERα is 75-fold smaller (2 nM for ERβ vs 155 nM for ERα). Due to its selectivity for ERβ, WAY-200070 is does not have an effect like classics estrogens. For example, WAY-200070 does not affect luteinizing hormone or follicle-stimulating hormone or inhibit ovulation.

Preclinical Trials

In some ground laying studies it was discovered that estrogen has an anti-depressant effect in animals in some cases. WAY-200070 was hence examined in its role of ERβ activation on brain neurochemistry and activity in antidepressant and anxiolytic models in male mice. Within 15 min of administration, WAY-200070 (30 mg/kg s.c.) caused more ERβ receptors to be present on the surface of brain neurons. The absenceof these effects in the Erβ knockout mice confirmed that WAY-200070 was targeting ERβ . Administration of WAY-200070 (30 mg/kg s.c.) produced a delayed 50% increase in dopamine in the brains of wild type mice. The effect was significant and maintained from 90 to 240 min. In wild type mice, WAY-200070 (30 mg/kg s.c.) also produced a delayed and transient 100% increase in serotonin. To further investigate the role of ERβ receptors on serotonergic function, 5-HTP (a precursor to serotonin) accumulation was measured. WAY-200070 (3–30 mg/kg s.c.) was also tested in behavioural models. WAY-200070 (30 mg/kg s.c.) reduced showed an anti- depressant like effect in the wild type mice. WAY-200070 (30 mg/kg) showed anxiolytic-like effects in the four-plate test (increased punished crossings) and stress- induced hyperthermia (attenuation of hyperthermic response).[2]

In a different study on the anxiolytic properties of WAY-200070, it was shown that the compound significantly altered the light/dark choice behaviour of zebrafish larvae, which indicates that these larvae hat a less pronounced fear of the dark.

Further investigation showed WAY-200070 treatment caused a reduction of crh expression level in the hypothalamus, suggesting activation of ERβ signalling attenuates the stress response. Interestingly, WAY-200070 treatment caused marked increase of c- fos (a marker for ER acitvation) expression in specific brain areas of fish larvae.[3] In rats, a moderate stress reducing effect of WAY-200070 was also described in an additional study.[4]

In a behavioral study in mice, results show that in male and female mice, WAY- 200070 increased agonistic behaviours such as pushing down intruders and aggressive grooming, while leaving attacks unaffected. Overall, the detailed behavioural analysis suggested that in healthy male and female mice, ERβ mediates patterns of behaviour that are not directly involved in attacks. This suggests that specific aspects of aggressive behaviour are acutely mediated by ERβ in adult mice.[5]

WAY200070 was also shown to enhance glucose-stimulated insulin secretion both in mouse and human isolated pancreatic cells. In vivo mice experiments showed that a single administration of WAY200070 leads to an increase in plasma insulin levels. Two-week treatment administration increased glucose-induced insulin release and pancreatic β-cell mass and improved glucose and insulin sensitivity. In addition, induced diabetic mice treated with WAY200070 exhibited a significant improvement in plasma insulin levels and glucose tolerance as well as a regeneration of pancreatic β-cell mass. Studies performed in diabetic mice demonstrated that this compound restored first-phase insulin secretion and enhanced pancreatic β-cell mass.[6]

From previous studies, it was known that estrogens can protect cells from apoptosis during ischemic events, such as a stroke. The ERα-selective agonist propyl pyrazole triol (PPT, 10 mg/kg) and ERβ-selective agonist WAY 200070 (1 mg/kg) produced nearly complete protection of CA1 neurons in approximately 50% of the animals. PPT, but not WAY 200070, at doses used for protection, elicited lordosis, induced negative feedback inhibition of LH release, and reduced weight gain. These findings establish the efficacy of the PPT dose in neuroendocrine assays and specificity of WAY 200070 for ERβ . Due to the fact that ERβ selective agonist produce less side effects, this also shows that this class is more interesting to prevent stroke related cell death compared to ERα agonists.[7]

It was also found that WAY-200070 can inhibit the growth of human breast cancer cell lines in vitro if it is used together with the estrogen receptor modulator tamoxifen.

Alone, it did not have an effect on the cells.[8,9] In ovarian cancer cell lines, WAY-200070 and other ERβ agonists showed a slowdown of cancer cell growth in vitro.[10]

Conclusion

Since its discovery, WAY 200070 has been sporadically used in a variety of preclinical studies to investigate specific effects of the ERβ receptor. It was found to be potentially useful to treat conditions like strokes, diabetes and renal fibrosis, but it also has effects in the behaviour of animals. Due to its selectivity to the ERβ receptor, it lacks some specific side effects of estrogen, like increased bone density and effects on the female cycle.

However, there is no evidence no human clinical trial were performed so far with WAY-200070. Other ERβ selective agonists like LY3201 and Erteberel were chosen for clinical development and entered Phase II trials, but their development was ultimately discontinued.

Typical dosing in animal studies ranged between 1-30 mg/kg bodyweight as subcutaneous injection.

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