Reversible Inhibition of Retinoic Acid Synthesizing Enzyme ALDH1A2 With WIN18,446 Derivatives in Male Contraception

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Almost half of the pregnancies around the globe are unplanned. The associated risks related to unexpected pregnancy include both physical and mental stress. A wide range of contraceptive methods has been utilized to prevent unexpected pregnancy. Female sterilization, oral contraceptive pills, and long-acting reversible contraception are the most popular. However, increasing research centralizes the negative experiences with detrimental side effects when using female contraceptives such as nausea and mood swings. While various female contraceptive methods are available, there is currently a lack of commercialized male contraception other than male condoms and vasectomy. As gender equality movements advance, there is an urgent need for an effective and reversible male contraceptive method to reduce unplanned pregnancy and the side effects of female contraceptives. WIN18,446, a recently studied molecule that inhibits the enzymatic reaction of retinoic acid synthesizing enzyme ALDH1A2 in male testicles, is a promising candidate for blocking male sperm production. Aiming at optimizing the binding of ALDH1A2 and WIN18,446 with the rational design of WIN18,446's chemical structure, this study presents four derivatives of WIN18,446 to optimize the binding with ALDH1A2. The quantitative results and crystal structures of the molecular binding sites show that all four refined structures of WIN18,446 achieve higher binding energy than the original structure. Remarkably, one of the derivatives, Ana_2, exhibits strong interaction with the enzyme through extra pi-pi stacking interactions, covalent adduct, and hydrogen bond in the binding sites. Potentially, Ana_2 could be further developed into effective male contraceptives.

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