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Structure based approach to identify potent tissue selective androgen receptor modulators

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The steroids testosterone and dihydrotestosterone (DHT) are androgens that play an important role in the development and maintenance of a variety of physiological responses such as male sexual function, bone density, muscle mass and strength. The androgen receptor is a nuclear hormone receptor that is expressed in many tissues and is responsible for mediating the actions of testosterone and DHT. Patients that have defects in the androgen receptor or have androgen deficiencies can be effectively treated with exogenous testosterone and other steroidal androgens as a hormone replacement therapy. The anabolic effects of testosterone have shown benefit in age related decline of bone density and muscle mass. However, the side effect profile of testosterone and other currently available anabolic steroids precludes their wide spread use and the chronic administration of steroidal androgens is associated with potential serious side effects such as hepatotoxicity, prostate hypertrophy and cancer. In addition, the oral bioavailability of testosterone is poor and the route of its administration is generally through topical formulations. We will describe our efforts to find novel series of oral tissue selective androgen receptor modulators (SARM) i.e., cyanopyrroles and indolines that selectively promote muscle growth while showing reduced androgenic effects on the prostate and seminal vesicles. Using a docking approach, we were able to delineate the binding mode of these series and further optimize the potency. An x-ray structure of a lead compound 7 bound to AR ligand binding domain revealed an interesting electrostatically unfavorable interaction of the 3-fluorophenol group with a carbonyl backbone of Leu704 residue. QM based intermolecular potential calculation performed to understand the strength of this interaction along with ligand strain energy calculations indicate a small energy penalty of ~0.6 kcal/mol paid by the ligand to adopt the bound state conformation.

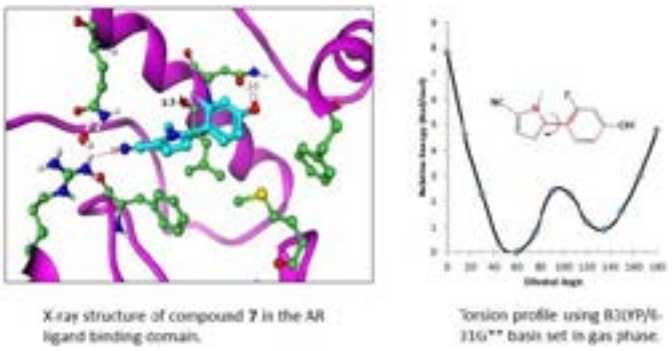

Figure 1: X-ray structure of compound 7 in AR LBD along with the calculated torsional profile from B3LYP/6-31G.

Recent Publications

1. Unwalla R et al., (2017) A structure-based approach to identify 5-[4-hydroxyphenyl]-pyrrole-2-carbonitrile derivatives as potent and tissue selective androgen receptor modulators. Journal of Medicinal Chemistry 60(14):6451-6457.
2. Saeed A et al., (2016) 2-Chloro-4[[(1R, 2R)-2-hydroxy-2-methyl-cyclopentyl]amino]-3-methyl-benzonitrile: A transdermal selective androgen receptor modulator (SARM) for muscle atrophy. Journal of Medicinal Chemistry 59(2):750-755.
3. Pollock J et al., (2015) Rational design of orthogonal multipolar interactions with fluorine in protein-ligand complexes. Journal of Medicinal Chemistry 58(18):7465-7474.

4. Chekler E et al., (2014) 1-(2-hydroxy-2-methyl-3-phenoxypropanoyl)indoline-4-carbonitrile derivatives as potent and tissue selective androgen receptor modulators. Journal of Medicinal Chemistry 57(6):2462-2471.
5. Bagatell C J (1996) Androgens in men – uses and abuses. New England Journal of Medicine 334(11):707-714.

Biography

Ray Unwalla is a computational chemist at Pfizer, USA working in the Inflammation and Immunology Department. He has several years of drug discovery experience and has expertise in the area of nuclear hormone receptors, kinases and GPCRs. He has an in depth knowledge of various computational tools and techniques to provide insightful design hypothesis and specific compound proposals that test design hypothesis. He was involved in project teams that successfully delivered two drug candidates i.e., Dutasteride for benign prostate hyperplasia, Duavee for hormone replacement therapy and six clinical candidates for the progesterone, ERα LXRβ, SARM, JAK1 and JAK3 targets.

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