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Extended Abstract

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# MD simulations of estrogen receptors (ER) and docking analysis of DPN analogues reveal insights about subtype-receptor selectivity

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Estrogen (17-estradiol) is essential for normal growth and differentiation in the mammary gland. In the last three decades previous investigations have revealed that estrogen receptor alpha (ERα) plays a critical role in breast cancer. More recently, observations regarding the widespread expression of ERβ-like proteins in normal and neoplastic mammary tissues have suggested that ERβ is involved in the mentioned pathology. Therefore, design of new drugs both steroidal and nonsteroidal that target ERβ represents a therapeutical promise to treat several diseases. In this work, we have proposed a new set of compounds that target effectively the estrogen receptors, and particularly the ERβ. They were designed based on the chemical structure of the ERβ-selective agonist diarylpropionitrile (DPN), then, these potential ligands were submitted in silico ADMET (absorption, distribution, metabolism, excretion, toxicity), from such analysis we could select the ones that showed better properties and they were used for docking studies on ERα and ERβ, employing snapshots at 0 ns and 100 ns retrieved from Molecular Dynamics (MD) Simulations. MD Simulations of the ligand binding domains (LBDs) of both estrogen receptors revealed important structural information and docking studies of the designed ligands provided useful information regarding the molecular basis in the binding of these ligands, for example, ligands that show polar functional groups, as well as aromatic groups, such as chlorobenzene exhibit higher affinity for ERα, whereas ligands that exhibit dinitrile functional groups, as well as ligands that show dinitrile groups combined with amino protonated groups ensure higher affinity and selectivity for ERβ. Moreover, from our structural results we could decipher structural differences between these nuclear receptors. Through an effort to develop novel ligands that have subtype selectivity for the estrogen receptors alpha (ERalpha) and beta (ERbeta), we have found that 2,3-bis(4-hydroxyphenyl)propionitrile (DPN) acts as an agonist on both ER subtypes, but has a 70-fold higher relative binding affinity and 170-fold higher relative potency in transcription assays with ERbeta than with ERalpha. To investigate the ERbeta affinity- and potency-selective character of this DPN further, we prepared a series of DPN analogues in which both the ligand core and the aromatic rings were modified by the repositioning of phenolic hydroxy groups and by the addition of alkyl substituents and nitrile groups. We also prepared other series of DPN analogues in which the nitrile functionality was replaced with acetylene groups or polar functions, to mimic the linear geometry or polarity of the nitrile, respectively. To varying degrees, all of the analogues show preferential binding affinity for ERbeta (i.e., they are ERbeta affinity-selective), and many, but not all of them, are also more potent in activating transcription through ERbeta than through ERalpha (i.e., they are ERbeta potency-selective). meso-2,3-Bis(4-hydroxyphenyl)succinonitrile and dl-2,3-bis(4-hydroxyphenyl)succinonitrile are among the highest ERbeta affinity-selective ligands, and they have an ERbeta potency selectivity that is equivalent to that of DPN. The acetylene analogues have higher binding affinities but somewhat lower selectivities than their nitrile counterparts. The polar analogues have lower affinities, and only the fluorinated polar analogues have substantial affinity selectivities. This study suggests that, in this series of ligands, the nitrile functionality is critical to ERbeta selectivity because it provides the optimal combination of linear geometry and polarity. Furthermore, the addition of a second nitrile group beta to the nitrile in DPN or the addition of a methyl substitutent at an ortho position on the beta-aromatic ring increases the affinity and selectivity of these compounds for ERbeta. These ERbeta-selective compounds may prove to be valuable tools in understanding the differences in structure and biological function of ERalpha and ERbeta. Estrogen (17β-estradiol) is essential for normal growth and differentiation in the mammary gland. In the last three decades, previous investigations have revealed that Estrogen Receptor Alpha (ERα) plays a critical role in breast cancer. More recently, observations regarding the widespread expression of ERβ-like proteins in normal and neoplastic mammary tissues have suggested that ERβ is also involved in the mentioned pathology. Design of new drugs both steroidal and nonsteroidal that target any of these receptors represents a promise to treat breast cancer although it remains a challenge due to the sequence similarity between their catalytic domains. In this work, we propose a new set of compounds that could effectively target the estrogen receptors ERα and ERβ. These ligands were designed based on the chemical structure of the ERβ-selective agonist Diarylpropionitrile (DPN). The designed ligands were submitted to in silico ADMET studies, yielding in a filtered list of ligands that showed better drug-like properties. Molecular dynamics simulations of both estrogen receptors and docking analysis were carried-out employing the designed compounds, from which two were chosen due to their promising characteristics retrieved from theoretical results (docking analysis or targeting receptor predictions).

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