Insights Into the Effect of Scaffold Structure on Estrogen Receptor Binding Affinity and Subtype Selectivity

Christopher G. Mayne and John A. Katzenellenbogen.

A member of the nuclear receptor superfamily, the estrogen receptor (ER) is a ligand regulated transcription factor responsible for the regulation of hundreds of genes and is involved in a number of disease states. The discovery of a second ER subtype, ERβ, has sparked substantial interest in the development of subtype-selective ligands as chemical probes of ER pharmacology and potential anticancer or hormone replacement therapeutics. While the ligand binding domain of these two ER subtypes share only 59% amino acid sequence homology, the interior of the binding pocket is nearly identical. Only two amino acid residues are substituted between the two binding pockets, Met421→Ile and Leu483→Met in the transformation from ERα to ERβ, and the ERβ pocket volume is approximately 100Å^3 (~20%) smaller.

The reduced binding volume of ERβ serves as a handle for the design of ERα-selective ligands based on size exclusion; these ligands are typified by pharmacophore **I**. The principles behind designing ERβ selective ligands, however, are much less well understood. Only a handful of high affinity, highly ERβ-selective ligands have been reported in the literature, which are generally described by pharmacophore **II**. Previous work based on an indazole core scaffold (**III**) has highlighted that the nature of the R-substituent profoundly affects both affinity and selectivity. Using this ERβ-selective indazole core as a reference, we set out to investigate the nitrogen isomer imidazo[1,2-*a*]pyridine (**IV**) as a scaffold replacement in order to probe how the identity of the heterocyclic core scaffold specifically affects ligand binding to ER. Herein, we will report the synthesis, biological evaluation, and computational analysis of imidazo[1,2-*a*]pyridines as high affinity ERβ-selective ligands, and how subtle perturbations of scaffold structure can significantly change the observed ligand binding properties.