Abstract

Estrogen receptor (ER) has been a therapeutic target to treat ER positive breast cancer, most notably by agents known as selective estrogen receptor modulators (SERMs). However, resistance and severe adverse effects of known drugs gave impetus to the search for newer agents with better therapeutic profile. ERα and ERβ are two isoforms sharing 56% identity, and having different physiological functions and expressions in various tissues. Only two residues differ in the active sites of the two isoforms motivating us to design isoform selective ligands. Guided by computational docking and molecular dynamics simulations, we have designed, synthesized and tested, substituted biphenyl-2,6-diethanones and their derivatives as potential agents targeting ERα. Four of the molecules synthesized exhibited preferential cytotoxicity in ERα+ cell line (MCF-7) compared to ERβ+ cell line (MDA-MB-231). Molecular dynamics (MD) in combination with molecular mechanics-generalized born surface area (MM-GBSA) methods could account for binding selectivity. Further co-treatment and *E-screen* studies with known ER ligands- estradiol (E_2) and tamoxifen (Tam) indicated isoform selective anti-estrogenicity in ERα+ cell line which might be ER mediated. ERα siRNA silencing experiments further confirmed the ER selective nature of ligands.