SUBSTITUTED ADAMANTYL BENZENES AS SUB-TYPE SPECIFIC ESTROGEN RECEPTOR MODULATORS

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Abstract: Estrogen receptors (ER) belong to the nuclear receptor super family of ligand-triggered transcription factors. Estrogen binds to ER and mediates a cascade of cellular signaling events. Substituted phenolics affect the estrogenic signaling pathways through direct interactions with the ligand binding site of estrogen receptors (ERs). We have previously reported that adamantyl phenols are estrogenic and target human estrogen receptors just like Estrogen and diethylstilbesterol. Here we report the optimization of adamantyl phenols to target ER subtypes using a combination of structure-assisted compound optimization and fluorescence polarization (FP). Our hypothesis is that substituted adamantylphenols with the proper orientation to access Glutamate-353 and His-524 will mimic estrogen better than the ligands with other orientations will have poor binding properties. All the synthetic diphenols tested in the study are weaker than that of diethylstilbestrol for both ERs with the exception of substituted adamantlyldiphenols. We also found that most diphenols tested cause differential conformational changes in ERalpha and ERbeta, which result in altered affinities of the ERs for fluorescein-labeled estrogen response elements (EREs) using a direct binding FP assay. Our data suggest that substituted-adamantyl benzene/phenols with proper orientation may function as sub-type selective ligands for hER. Further optimization of synthetic adamantly benzene derivatives would open new avenues for drug development and would lead to advanced clinical studies of an entirely new breed of anticancer agents.

Key words: Estrogen receptor, Adamantyl phenol, anti-cancer drugs, drug discovery

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