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Human Estrogen Receptor α Antagonists. Part 1: 3-D QSAR-Driven Rational Design of Innovative Coumarin-Related Antiestrogens as Breast Cancer Suppressants through Structure-Based and Ligand-Based Studies

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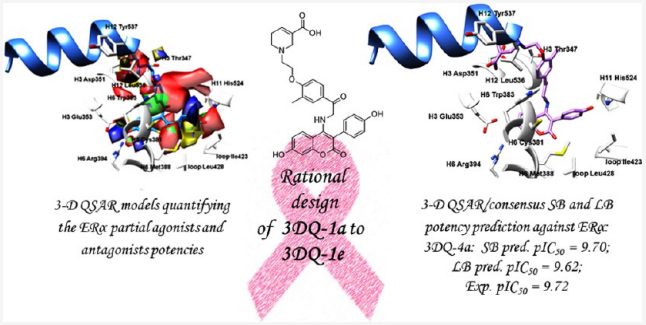
ABSTRACT: The estrogen receptor α (ERα) represents a 17β-estradiol-inducible transcriptional regulator that initiates the RNA polymerase II-dependent transcriptional machinery, pointed for breast cancer (BC) development *via* either genomic direct or genomic indirect (*i.e.*, tethered) pathway. To develop innovative ligands, structure-based (SB) three-dimensional (3-D) quantitative structure−activity relationship (QSAR) studies have been undertaken from structural data taken from partial agonists, mixed agonists/antagonists (selective estrogen receptor modulators (SERMs)), and full antagonists (selective ERα downregulators (SERDs)) correlated with either wild-type or mutated ERα receptors. SB and ligand-based (LB) alignments allow us to rule out guidelines for the SB/LB alignment of untested compounds. 3-D QSAR models for ERα ligands, coupled with SB/LB alignment, were revealed to be useful tools to dissect the chemical determinants for ERα-based anticancer activity as well as to predict their potency. The herein developed protocol procedure was verified through the design and potency prediction of 12 new coumarin-based SERMs, namely, **3DQ-1a** to **3DQ-1e**, that upon synthesis turned to be potent ERα antagonists by means of either *in vitro* or *in vivo* assays (described in the second part of this study).



INTRODUCTION

Estrogen receptors (ERs) are class I members of the nuclear receptor (NR) superfamily and represent 17β-estradiol (E_2)-inducible transcriptional regulators.[1] E_2 is normally produced within the female ovaries' follicles and also in other endocrine and nonendocrine tissues.[2] E_2's bioactivity is mediated by two estrogen NRs, α (ERα) and β (ERβ).[3] ERα, the predominant isoform, regulates estrogens' activity in mammary gland development, mating behavior, the hormonal regulation of glucose metabolism, cardiovascular system, and hypothalamic−pituitary axis while maintaining the bone mineral density.[4] As a key factor in breast cancer (BC) development, E_2 initiates a series of ERα-associated molecular events, mostly regulated by transcriptional factors. In this scenario, BC suffering patients are mainly treated with antiestrogens to block ERα activity.[5] However, the side effects due to off-target activity and the development of drug resistance in chronic treatment imply continuous demand for novel and more potent ERα antagonists.[1]

A survey through the Protein Data Bank (https://www.rcsb.org/) revealed that no full three-dimensional (3-D) ERα structure has yet been deposited. On the other hand, crystal structures of the DNA-binding domain (DBD), complexed with a specific human estrogen response element (*h*ERE) sequence,[6−8] and ligand-binding domain (LBD), cocrystallized with a series of partial agonists, mixed agonists/antagonists, and full antagonists (Figure 1), are available (Tables 1−3 and S1). LBD is of particular importance since it conveys partial agonists' and antagonists' potency on the transcription *via* either genomic direct or indirect (*i.e.*, the tethered) pathway: both pathways are initiated with the agonist-induced dimerization of ERα.[6−8] As any rational drug design approach focused on antagonism implies a deep knowledge of the understudy biochemistry scenarios, for the sake of manuscript length and clarity, further information and references that could be useful to the reader are reported in the Supporting Information.

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