Flexible Etherified and Esterified Triphenylethylene Derivatives and Their Evaluation on ER positive and Triple Negative Breast Cancer Cell Lines

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Abstract

Tamoxifen (TAM) is a selective estrogen receptor modulator (SERM). It is currently the endocrine treatment of choice for all stages of breast cancer and a prophylactic for women with high risk of breast cancer. TAM is majorly metabolized by to more potent 4-hydroxytamoxifen and endoxifen *via* CYP2D6 and CYP3A4/5 enzymes. CYP2D6 is a polymorphic enzyme and has around 63 alleles; this remarkably affects the clinical outcome of tamoxifen treatment.

Herein we report novel TAM analogues that are hydrolyzed *via* esterases to avoid the genetic polymorphism of the CYP2D6. The novel compounds bear an element of flexibility, *via* insertion of a methylene group between ring **A** and the ethylene backbone. Ring **A** bears a *para* methoxy substituent whereas ring **B** bears different alkoxyamino side chains. In series 1, ring **C** bears either a propionate or a decanoate ester. In series 2, Ring **B** and **C** bear homo dialkoxyamino groups. Compound **VII** bearing an OH group on ring **C** showed highest relative anti-estrogenic activity of 0.52 in presence of 1 nM estradiol (E2). Compound **VI** bearing an OH group on ring **C** showed highest growth inhibitory activity on MCF-7 cells (GI_{50} = 0.15 µM) which is ten-fold more potent than TAM (GI_{50} = 1.58 µM) whereas it showed growth inhibitory activity on MDA-MB-231 cells (GI_{50} = 1.71 µM) which is fivefold more potent than TAM (GI_{50} = 6.31 µM) . Compound **XIII** was the most potent among homo diaminoalkoxy derivatives (GI_{50} = 0.44) on both MCF-7 and MDA-MB-231 cell lines, respectively. It showed no estrogen receptor alpha (ERα) anti-estrogenic activity in yeast estrogen screen assay (YES). Furthermore, the COMPARE analysis using NCI-60 cancer cell line suggested that it has different molecular modes of action compared to some of the current anti-cancer drugs including tamoxifen, highest correlation was observed with tamoxifen followed by a reported autophagy inducer N-(6-Chloro-2-methoxyacridin-9-yl)-N',N'-diethylbutane-1,4-diamine. These results indicate that compound **XIII** is an interesting candidate for novel anti-cancer agents with unique modes of action.

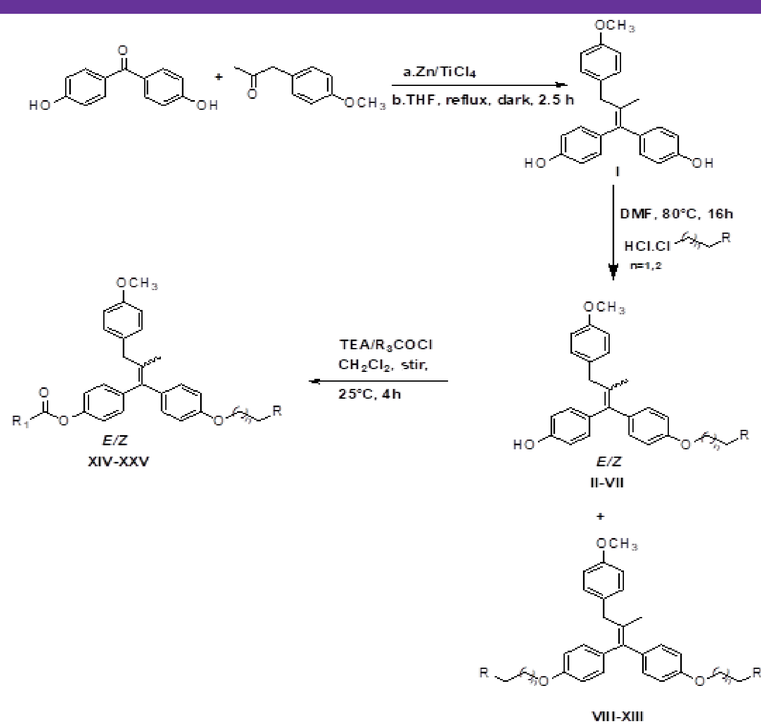
Introduction

Tamoxifen is a revolutionary drug in medical oncology that has saved many lives over the past fifty years. The story of development of tamoxifen is perceived as a case study in pharmaceutical innovation. A drug that started as a failure contraceptive pill ended up as a blockbuster in the field of breast cancer treatment.(1) Tamoxifen is a prodrug; it requires the intrinsic metabolizing enzymes (CYP2D6 and CYP3A4) to be converted to the more anti-estrogenic metabolites, 4-hydroxytamoxifen and endoxifen.(2)CYP3A4/5 and CYP2D6 are major isozymes involved in tamoxifen metabolism and are known to display several genotypes that may lead to different enzyme activities and personal variation in therapeutic effects. 14 Despite being a key player in the treatment of ER-positive breast cancer and a chemopreventive agent in women with high risk for breast cancer. The most challenging issue with tamoxifen use is the development of resistance in patients who were initially responsive to tamoxifen. Although the molecular mechanisms of resistance to tamoxifen remains vague, various mechanisms have been proposed. Some of those mechanisms involved differential metabolic activation of tamoxifen, loss of ER function/expression, alterations in crosstalk between ER and growth factor-mediated signaling pathways, the presence of ER-negative cancer stem cells, and dynamic responses to oxidative stress.(3) Many approaches were studied to overcome tamoxifen resistance. For instance, our research group worked on development of novel analogues that can bypass CYP2D6 metabolism, these analogues were metabolized *via* esterases.(4–6)

Herein we report the design and synthesis of twenty-four novel compounds that are designed to bypass CYP2D6. A second series is designed to work in a non ER-dependent manner in a similar fashion to ridaifen. The analogues are designed to endure an element of flexibility to the rigid triphenylethylene backbone of tamoxifen. **Ring A** bears a *para* methoxy substituent**,** the effect of this electron donating, hydrophilic substituent on activity is investigated. Ring **B** bears different aminoalkoxy side chain, an essential feature for anti-estrogenic activity of tamoxifen analogues. Ring **C** bears a metabolically labile ester group, both a small and long chain propyl and decyl esters are prepared. In series 2, ring **B** and ring **C** bears identical aminoalkoxy.

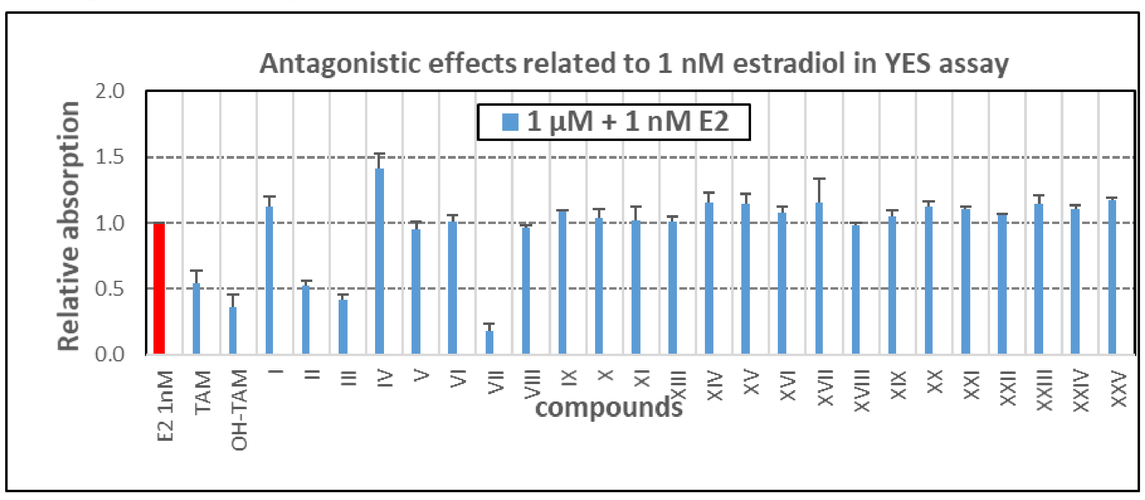
All synthesized compounds were tested for their relative activity in β-galactosidase yeast estrogen screen (YES) assay. All compounds were screened by the National Cancer Institute (NCI) for *in vitro* antitumor activity against 60 human tumor cell lines. Additionally, we used COMPARE algorithm enabled us to investigate potentially unique modes of action compared to current anticancer drugs.

Scheme



Results and Discussion

All compounds were investigated for their anti-estrogenic activity using Yeast Estrogenic Screening (YES assay). Tamoxifen and 4-OH-TAM were used as controls .



- Compounds **II**, **III**, **VII** are the most potent anti-estrogenic analogues, they showed relative β galactosidase activity =0.48, 0.42, 0.18, respectively.
- Compounds **VIII-XIII** are bis-alkoxyamino derivatives that showed no anti-estrogenic activity.
- Converting the hydroxyl group on ring **C** to decanoate or propionate ester group led to compounds that lack anti-estrogenic activity (**XIV-XVV)**.
- Among all hydroxylated analogues , only compound **VI** showed a mean growth inhibition of >100 % despite it lacks anti-estrogenic activity.
- Compound **VI** showed GI_{50}= 0.15 µM on MCF-7 cell lines, this is ten-fold more active than TAM (NSC-180973) GI_{50}= 1.58 µM.
- Compound **VI** showed GI_{50} values of 1.71, 1.69, 1.54 , 1.54 and 1.69 µM on TNBC namely MDA-MB-231/ATCC, MDA-MB-468, BT-549 and HS 578T.

Conclusions

- Results of COMPARE analysis showed that all tested compounds have activity which is moderately correlated to TAM (0.51-0.63)
- The novel analogues are active against ER+ breast cancer and other types of malignancies.
- The low to moderate correlation with the seed compounds suggest that the novel analogues are examples of a novel class of anti-cancer drug however; this needs to be verified by biological testing in the future .

References

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