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Design, synthesis and biological evaluation of novel triaryl (*Z*)-olefins as tamoxifen analogues

Khaled R. A. Abdellatif [a,*], Amany Belal [b], Hany A. Omar [c]

[a] Department of Pharmaceutical Organic Chemistry, Beni-Suef University, Beni-Suef 62514, Egypt
[b] Department of Medicinal Chemistry, Beni-Suef University, Beni-Suef 62514, Egypt
[c] Department of Pharmacology, Faculty of Pharmacy, Beni-Suef University, Beni-Suef 62514, Egypt

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ABSTRACT

Tamoxifen (TAM) is used for the treatment and prevention of estrogen receptor positive breast cancer. However, the limited activity, toxicity and the development of resistance raised the current need for new potent nontoxic antiestrogen. Six novel TAM analogues **5a**–**f** were synthesized using McMurry olefination reaction. Replacement of the dimethylamino group in TAM by piperidino, piperazino or *N*-methyl piperazino, substituting the phenyl ring with florine atom at *p*-position and changing the ethyl group by methyl, afforded compounds showing comparable activity to TAM (**1**). Compounds **5c** and **5e** showed significant increase in antiproliferative activity in two breast cancer cell lines (MCF-7 and MDA-MB-231) compared to tamoxifen, while other compounds showed similar activity. The increased anticancer activity of compounds **5c** and **5e** was attributed to their ability to induce ER-independent cell death.

Breast cancer is the most leading cause of death and the most frequent cancer in women. Estrogens are the most known stimulator of breast cancer cell growth so antiestrogens are considered good candidates for the treatment.[1,2] Tamoxifen (TAM, **1**), the nonsteroidal antiestrogenic drug is one of the most extensively used drugs to treat hormone-responsive human breast cancers since 1970.[3–6] The mode of action of TAM (**1**) in cancer therapy and in preventing breast cancer in high risk women is believed to be partially through competing with estrogens for binding to estrogen receptors.[7] High concentrations of TAM activates caspases and trigger apoptotic cell death independently of its estrogen receptors (ER) binding activity.[8,9] Both ER-dependent and ER-independent pathways for tamoxifen-induced programmed cell death are critical for successful therapy. The accumulative risk-benefit assessment of TAM therapy and comparative studies with other new types of drugs established its efficacy and safety.[10] Therefore, the development of new tamoxifen—type drugs are significantly required.

The aminoalkyloxy moiety present in TAM ($OCH_2CH_2NMe_2$, Fig. 1) plays a major role in determining receptor binding affinity.[11] Decreasing the basicity of the protonated amino group (cationic site) is believed to diminish the binding interaction with Asp 351 (anionic carboxylate site) on the estrogen receptors.[12] Although replacement of the $-CH_2CH_3$ substituent in tamoxifen (**1**) by a $-CH_3$ substituent does not change the antiproliferative data for MCF-7 human breast cancer cells.[13,14] Accordingly, it was anticipated that replacement of the dimethylamino group of aminoalkyloxy moiety with piperidino, piperazino and *N*-methylpiperazino to elevate the basic characters of the amino group may provide a new tamoxifen analogs of potential high antiproliferative activity. Accordingly, here we describe the synthesis of novel TAM analogs, molecular modeling studies, and their antiproliferative effect on MCF-7 and MDA-MB-231 human breast cancer cells.

The synthetic pathways adopted for the preparation of the desired new compounds are illustrated in Scheme 1. The (*Z*)-1-[4-(2-chloroethoxy)phenyl]-1,2-diphenylprop-1-ene (**4a**) was synthesized using a McMurry olefination reaction by Zn–$TiCl_4$ catalzyed reductive cross-coupling of 4-(2-chloroethoxy)benzophenone (**2**) with acetophenone (**3a**) in 38% yield. The **4a** product was the sole

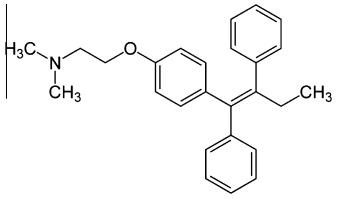

Figure 1. Chemical structure of Tamoxifen (**1**).

Abbreviations: TAM, tamoxifen; ER, estrogen receptor; MOE, molecular operating environment; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide; DMEM/F12, Dulbecco's modified Eagle medium nutrient mixture F-12; FBS, fetal bovine serum.

* Corresponding author. Tel.: +20 100 2535444; fax: +20 82 2317958.
E-mail address: khaled.ahmed@pharm.bsu.edu.eg (K.R.A. Abdellatif).

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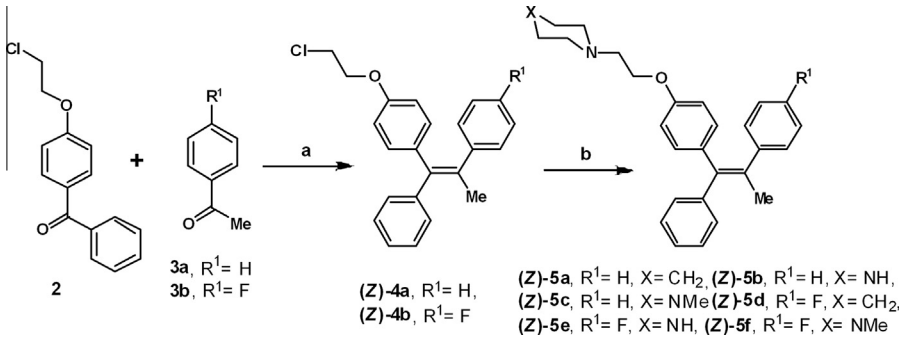

Scheme 1. Reagents and conditions: (a) Zn, $TiCl_4$, THF, reflux 3.5 h; (b) piperidine, piperazine or *N*-methylpiperazine, EtOH, reflux 24 h.

stereoisomer obtained after silica gel column chromatography and recrystallization from *n*-hexane. A similar cross-coupling reaction of the benzophenone analog **2** with 4-floroacetophenone (**3b**) afforded the (*Z*)-1-[4-(2-chloroethoxy)phenyl]-1-(4-florophenyl)-2-phenylprop-1-ene (**4b**) (40%). Subsequent reaction of the chloroethoxy **4a** and **4b** with piperidine, piperazine or *N*-methylpiperazine in EtOH at reflux afforded the target compounds **5a**–**f** in high yields (72–85%). Stereoisomer assignments were made based on ^{1}H NMR chemical shifts from published information.[15–19] 4-(2-Chloroethoxy)benzophenone (**2**) was prepared according to the reported procedure.[20]

The rational for the design of the new tamoxifen analogs (**5a**–**f**) was based on the expectation that replacement of a dimethyl amino moiety in TAM (**1**) by other secondary amine moieties such as piperidino, piperazino and *N*-methylpiperazino would furnish novel tamoxifen analogs with high antiproliferative activity. Changing the ethyl group with methyl one and substituting the *para* position of the phenyl ring with florine atom were also performed to study its impact on activity. Docking experiments for the prepared compounds **5a**–**f** in the ligand binding domain (LBD), derived from the structure of ERα crystallized with OH-Tam, showed that all compounds showed score energy less than or closely similar to tamoxifen (Table 1), docking tamoxifen into ERα presented in Figure 2. Furthermore, compounds **5c** and **5e** showed a hydrogen bonding to Asp-351 amino acid (Figs. 3 and 4). The antiproliferative effect of increasing concentrations of the synthesized compounds compared to tamoxifen in the presence and absence of estradiol on MCF-7 and MDA-MB-231 cells was estimated using MTT assay. Compounds **5c** and **5e** showed about twofold increase in the antiproliferative activity compared to tamoxifen (Table 2), while other compounds like **5a** and **5f** showed similar activities like tamoxifen. To figure out if the increased antiproliferative activity of test compounds is ER-dependent or not, the antiproliferative activity was estimated in an ER-negative breast cancer cell line, MDA-MB-231 cells. In addition, the ability of these compounds to antagonize estradiol-induced cell growth in MCF-7 cells was tested. Both compounds **5c** and **5e** showed similar potency in antagonizing estradiol-induced breast cancer cell growth and

Table 1
Docking energy score results. Tamoxifen (TAM) was docked in the active site of ERα receptor (3ERT.pdb) with $S = -30.1209$ kcal/mol (Fig. 2), the novel six tamoxifen analogs were docked against the same receptor using the same method

Compounds	Docking energy score (kcal/mol)
5a	−31.8890
5b	−31.7390
5c	−31.0242
5d	−31.1929
5e	−28.9745
5f	−31.4630
TAM	−30.1209

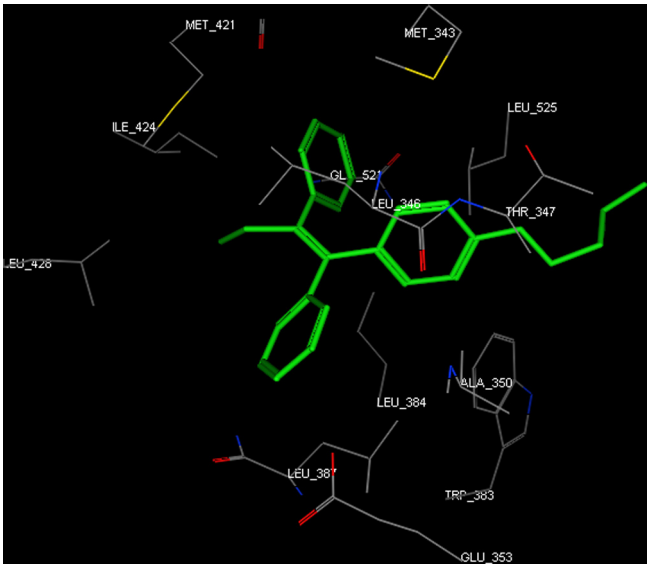

Figure 2. Docking of Tamoxifen in the active site of ERα (3ERT), $S = -30.12$ kcal/mol.

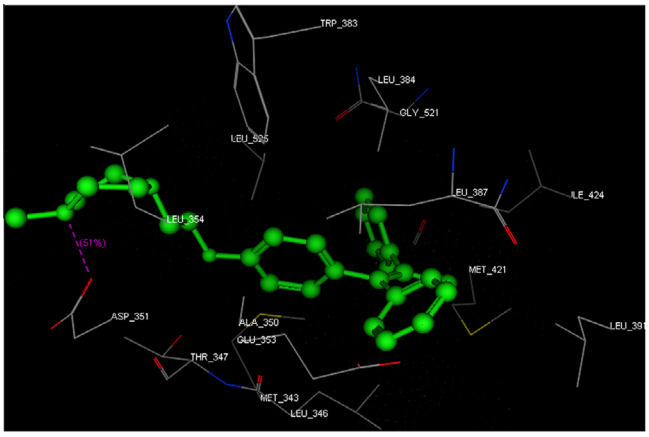

Figure 3. Docking of **5c** (green colored) in the active site of 3ERT ($S = -31.02$ kcal/mol) exhibiting interaction with Asp-351, hydrogen bond 2.34 Å.

inhibiting the proliferation of MDA-MB-231 cells which indicates that the increased anticancer activities is ER-independent (Table 2, Fig. 5). To explain the increased anticancer activity of compounds **5c** and **5e**, their ability to induce ER-independent cell death was tested. Both compounds showed relatively high ability to trigger classic caspase-dependent apoptosis as indicated by increased caspase 3/7 activities in MCF-7 treated cells compared to TAM (Fig. 6).