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Original article

Design and synthesis of azaisoflavone analogs as phytoestrogen mimetics

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ABSTRACT

A series of azaisoflavone analogs were designed and synthesized and their transactivation activities and binding affinities for ERα and ERβ were investigated. Among these compounds, **2b** and **3a** were the most potent with 6.5 and 1.1 μM of EC_{50}, respectively. Molecular modeling study showed putative binding modes of the compound **3a** in the active site of ERα and ERβ, which were similar with that of genistein and provided insight of the effect of *N*-alkyl substitution of azaisoflavones on ERβ activity. Also, a biphasic effect of azaisoflavone analogs on MCF-7 cell growth depending on their concentrations was investigated.

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1. Introduction

Estrogen receptors (ERs), a member of the steroid nuclear hormone receptor family, are ligand-activated transcription factor which play a crucial role in the development, maintenance, and function of the female reproductive system as well as other tissues such as colon, prostate, bone, cardiovascular system and central nervous systems [1]. There are two isoforms, ERα and ERβ. ERα is expressed in nearly all tissues whereas ERβ is mainly expressed in the ovaries, uterus and oviduct of the female reproductive tract but not in breast tissue [2]. ERα and ERβ have different biological functions including a tissue-specific regulation as well as their different gene expression patterns [3].

The hormone 17β-estradiol (E2) binds to ligand binding domain (LBD) of ERs, enters the nucleus of the cell, and regulates the target gene expression related to proliferation and differentiation of the cell by recruiting a various co-regulators. A deficiency of estrogen is associated with hot flashes, sweating, heart attacks and bone loss and hormone replacement therapy (HRT) is a medical treatment for older postmenopausal women in order to reduce these symptoms [4]. However, Women's Health Initiative (WHI) study showed beneficial effects of estrogen could increase risk of certain cancers such as breast [5]. Selective ER modulators (SERMs) are therapeutic agents for treating osteoporosis and breast cancer by modulating both ERs [6]. Tamoxifen, the first clinically relevant SERM, antagonizes the ER in breast tissue via active metabolite, hydroxytamoxifen and inhibits estrogenic effects such as proliferation of cancer cell [7].

Recently, a number of researches have been demonstrated ERα is more active in driving breast cancer cell proliferation than ERβ [8]. Meanwhile, it has been demonstrated that ERβ has anti-proliferative effect in breast cancer cells [9] and preventive effects for prostate adenocarcinoma [10] and also modulates the immune response [11]. Therefore, discovery of selective ERβ agonists may provide high potential to develop therapeutic agents for the various diseases such as breast cancer, prostate cancer, endometriosis, and inflammation. Recently, non-steroidal selective ERβ agonists SERBA-1, ERB-041 and WAY-202196 have been reported their anti-inflammatory activities and estrogenic activities (Fig. 1).

Phytoesterogens, naturally occurring estrogenic plant compounds, have been considered as an alternative method of menopause treatment. Among them, isoflavones are the well-known ER agonistic phytoestrogens and exhibit a number of biological properties including the prevention of cancers [12], coronary heart diseases [13], and osteoporosis [14]. Genistein is one of the potent

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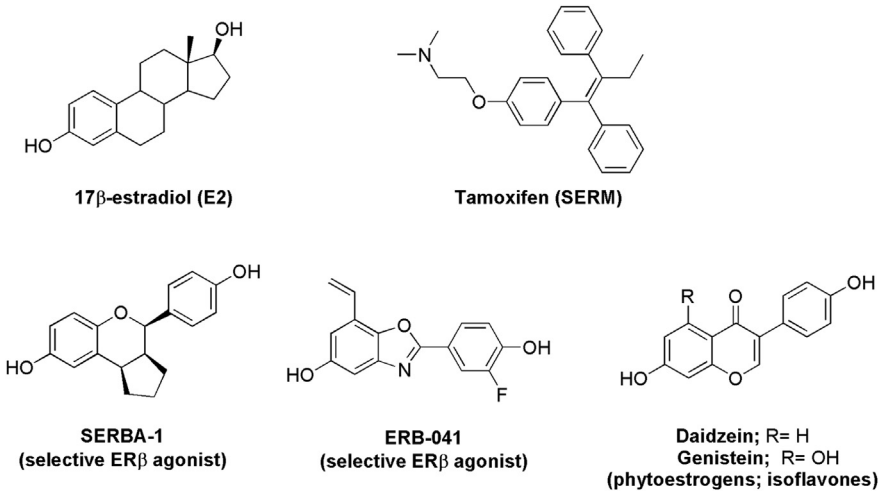

Fig. 1. Structures of ER modulators.

phytoestrogenic isoflavone, reveals 10–40 fold greater affinity for ERβ than for ERα [15], and inhibits cell proliferation in various breast cancer cell lines including MCF-7, T47D, BT20, MD-MBA-231, and SKBR3 [16]. The biphasic effect of genistein on cell growth has been reported in several studies in which genistein increased the MCF-7 cell growth at low concentrations but inhibited at higher concentrations [16a,17].

ERα and ERβ are similar in sequence with 58% identity and both ligand biding domains (LBDs) are nearly conserved differing by only two amino acids; Leu384 and Met421 in ERα are replaced by Met336 and Ile373 in ERβ, respectively (Fig. 2) [18]. The hydroxy groups in both ends of E2 and genistein essentially interact with key residues such as Glu353, Arg394 and His524 of ERα by hydrogen bonding within 2–3 Å (Glu305, Arg346 and His475 of ERβ). Their different residues Leu384/Met336 are positioned above the C-ring of genistein in the distance of 4–5 Å, and Met421/Ile373 are located below the A-ring near C-5 hydroxy group of genistein. These two pairs of amino acids within the LBD of ERα and ERβ make slight differences and mainly contribute to ligand selectivity [9c,19] (Fig. 3).

Regarding the previous findings, we became interested in modifying C-ring of isoflavone to identify a novel selective ER agonist. In this point of view, a previously reported compound azaisoflavone became the object of our attention. In fact, azaisoflavones were originally derived from isoflavone scaffold and designed as an iNOS inhibitor since inhibitory activity of several naturally occurring isoflavone for NO production was reported [20]. We supposed that the azaisoflavone analogs could function as phytoestrogens. Furthermore, *N*-substitution of azaisoflavone ring may give selectivity for ligand binding domains of ERα and ERβ. Herein we report synthesis of azaisoflavone analogs and their ERα/β transactivation activities. Structure activity relationship study was focused on the influence of phenolic OH of A and B-ring and *N*-substitution of C-ring of azaisoflavones. The effect of azaisoflevones on MCF-7 cell proliferation was also evaluated.

2. Chemistry

Synthetic routes for the preparation of azaisoflavones **1a**-**3d** are outlined in Scheme 1. Aniline or methoxyaniline was acylated with acetonitrile in the presence of boron trichloride and aluminum trichloride by Friedel–Craft's reaction. Condensation of the resulting ketones **4a**–**4c** with *p*-anisaldehyde resulted in 2'-aminochalcones **5a**–**5c** which were followed by *N*-acetylation to afford 2'-acetamidochalcones **6a**–**6c**. Rearrangement of 2'-acetamidochalcone **6a**–**6c** in the presence of thallium nitrate and trimethyl orthoformate gave β-ketoacetal **7a**–**7c** which were subsequently cyclized under acidic condition to yield quinolones **8a**–**10a**. The resulting quinolones **8a**–**10a** were alkylated with various alkyl halides in the presence of base to afford *N*-alkylated quinolones **8b**–**10d**. The final hydroxyquinolones **1a**–**3d** were obtained by deprotection of methoxyquinolones **8a**–**10d** under HBr and acetic acid conditions, respectively.

3. Results and discussion

3.1. ER transactivation activity and binding affinities

ER agonist activities of the prepared compounds were evaluated by in vitro transient transactivation assay and described in Table 1. The efficacy of the tested compounds was compared to the reference compounds E2 and genistein.

At first, an importance of phenolic OH on A and B-ring of azaisoflavones was investigated. Mono-hydroxy analogs **1a**–**d**, dihydroxy of daidzein analogs **2a**–**c** and tri-hydroxy of genistein analogs **3a**–**c** were compared with the corresponding methoxy compounds **8a, 9a**–**c** and **10a**–**c**, respectively. All methoxy compounds showed lower activities than the respective hydroxy compounds, and mono-hydroxy analog **1a** was less active than daidzein analog **2a** and genistein analog **3a** as expected.

When the oxygen of genistein was simply replaced with nitrogen as depicted in compound **3a**, both ER activities were dropped, whereas the selectivity for ERβ was increased. Genistein type analog **3a** showed the highest ERβ activity with 2.9 fold selectivity over ERα.

Effect of *N*-alkyl substituent of azaisoflavone on ER activity was evaluated. In the case of mono-hydroxy compounds **1a**–**d**, only *N*-propylated compound **1d** showed increased ERα and β activity than the parent compound **1a** while *N*-methyl or ethyl substitution vanished activity. In the daidzein analogs **2a**–**f**, introduction of alkyl substituent at nitrogen of C-ring enhanced ERβ activity and selectivity. Especially, *N*-methyl substituted compound **2b** showed promising ERβ activity with the highest ERβ selectivity at the ratio of 6.4:1. When the size of substituent was increased, the ERβ activity was decreased. In the genistein analogs **3a**–**c**, *N*-alkyl substitution lowered ERβ activity and selectivity. In contrast, *N*-alkyl

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