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New clicked full agonists of the estrogen receptor β†

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A click chemistry approach was used to synthesize a series of 1,4-diaryl-substituted 1,2,3-triazoles designed to behave as estrogen receptor (ER) ligands. We studied their affinities for both receptors α and β, their agonist activities in a cell-based luciferase reporter assay and their effect on the proliferation of the hormone-dependent MCF-7 cell line. We found two compounds (**3a** and **3c**) that behave as selective full agonists for ERβ at a 20 μM concentration, and one of them (**3c**) showed no proliferative effect on MCF-7 cells.

Introduction

The estrogen receptor (ER) is a member of the nuclear receptor gene family binding the steroid hormone estradiol.[1] Two subtypes are known of ER, designated ERα and ERβ. Both ER subtypes have overlapping but also unique roles in estrogen-dependent action and are important targets in the pharmaceutical industry. Additionally, ERα and ERβ have different transcriptional activities in certain ligand, cell-type, and promoter contexts.

The low expression level of ERβ in reproductive tissues such as the uterus suggests that a selective ERβ agonist may maintain the beneficial effects of estrogen, without the increased risk of breast and endometrial cancer. A number of selective ligands have been already identified.[2] ERβ selective agonist ERB-041 (226-fold selective for β) has been used to demonstrate that this receptor may be a useful target for certain inflammatory processes.[3] Other non-steroidal scaffolds which have been developed as ERβ ligands are diarylpropanenitriles (DPN),[4] 2-phenylnaphthalenes (WAY-202196),[2,5] and aryl-2*H*-indazoles.[6] We have described a series of benzonaphthofuran- and naphthothiophene-based ligands which behave as ERβ agonists and ERα antagonists,[7] and present interesting antitumor activity against two pancreatic cell lines.[8] Introduction of a basic side chain in these scaffolds has led to full antagonists of ERβ, with potency in the low micromolar concentration in a cell-based luciferase reporter assay, and completely devoid of activity against the ERα at the same concentration range.[9]

Click chemistry has had a profound effect on the design and development of novel compounds for therapeutic applications.[10] In particular, the Copper-Catalyzed reaction between an Azide and an Alkyne (CuAAC) has been widely used in fragment-based drug design, and target-guided synthesis (*in situ* click chemistry).[11]

Tron and co-workers[12] used CuAAC click chemistry to obtain a series of 1,4-diaryl-substituted 1,2,3-triazoles **1** (Fig. 1) and evaluated their effect on the proliferation of the hormone-dependent MCF-7 cell line. The only active compound promoted proliferation at a 100 pM concentration and possessed the two hydroxy groups in the *meta* position. This compound was capable of promoting transcriptional activation in HeLa cells expressing higher levels of ERβ than ERα at low concentrations. These data suggest ER-β selectivity, but further studies on the affinity and transcriptional response on both receptors are required to establish the subtype selectivity of this type of compound.

In the search for new and selective ligands of both estrogen receptor isoforms, we were interested in the observation of the authors that the introduction of a triazole ring is compatible with binding to the estrogen receptor, and the possibility to apply this efficient synthetic procedure to obtain analogues with additional substituents on the aromatic rings that could favour the interactions with one of the receptor subtypes.

Thus, we have synthesized two series of 1,4-bis(hydroxyphenyl)-1*H*-1,2,3-triazoles **2a–h**, **3a–f** and **3h** (Fig. 2), where methyl, trifluoromethyl, fluoro, carboxy and methoxycarbonyl groups have been introduced in *ortho* and *meta* positions of

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