HETEROCYCLES, Vol. 86, No. 1, 2012, pp. 165 - 170. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 26th June, 2012, Accepted, 6th August, 2012, Published online, 14th August, 2012
DOI: 10.3987/COM-12-S(N)56

FACILE SYNTHESIS AND ESTROGENIC ACTIVITY OF ARYLPYRROLE-BASED BISPHENOL DERIVATIVES

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Abstract – Novel estrogen candidates **6a** and **6b** incorporating arylpyrrole bisphenol structure were synthesized in only three steps from commercially available materials by means of McMurry coupling and an unexpected BBr_3-mediated aromatization. These compounds showed ERα-binding affinity in competitive binding assay and estrogenic activity in MCF-7 cell proliferation assay.

17β-Estradiol (E2, **1**) is an endogenous estrogen that plays important roles in the female and male reproductive systems, as well as in bone maintenance, in the central nervous system, and in the cardiovascular system (Figure 1a).[1] Most estrogenic signaling is mediated through estrogen receptors (ERs) α and β, which are members of the nuclear receptor superfamily of transcription factors.[2] Compounds that either induce or inhibit cellular estrogen responses have potential value as biochemical tools and candidates for drug development.[3] Since the discovery of non-steroidal estrogens, many estrogen agonists, antagonists, and selective estrogen receptor modulators (SERMs) have been developed as agents for regulating fertility, preventing and controlling hormone-responsive breast cancer, post-menopausal hormone replacement, and treating osteoporosis.[4] Binding of the ligands to the ER ligand binding domain (LBD) generally requires a phenolic ring, which forms hydrogen bonds with amino acid residues Glu353 and Arg394 of the hERα LBD (Figure 1a).[5] It is also well known that the secondary alcohol group of E2 interacts with His524 of hER.[5] The hydrophobic group should closely match the hydrophobic surface of the ER. Raloxifen (**2**), which is a well-known SERM, has a rigid and flat skeleton with two phenolic hydroxyl groups for hydrogen bond formation, and a basic side chain that affords partial agonistic activity (Figure 1b).

Dedicated to Professor Dr Ei-ichi Negishi on the occasion of his 77th birthday.

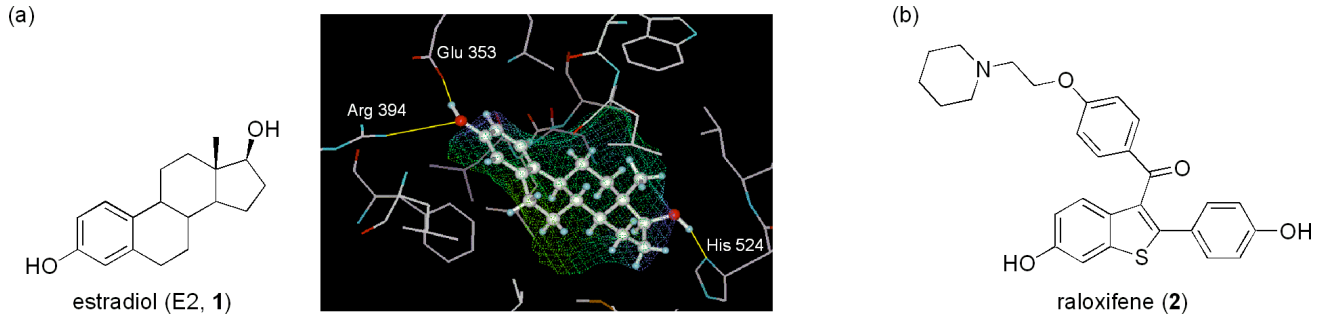


Figure 1. (a) Structure of E2 and binding mode of E2 with ERα. (b) Structure of raloxifene, a widely used SERM.

We have found that a simple 1,2-bis(4-hydroxyphenyl)-*o*-carborane, BE360 (**3**), exhibited high binding affinity for ERα and ERβ.[6] Furthermore, in vivo evaluation indicated that **3** exhibited estrogenic action in bone, ameliorating bone loss without showing estrogenic action in uterus of ovariectomized (OVX) and orchiectomy (ORX) mice, suggesting its possible application as a new type of SERM to treat osteoporosis.[7] Therefore, we next designed BE1060 (**4**) and BE1054 (**5**), which have three-dimensional hydrocarbon units as new hydrophobic pharmacophores.[8] Interestingly, bicyclo[2,2,2]octane-based bisphenol **4** showed potent estrogenic activity but tetramethylcyclohexene-based bisphenol **5** acted as a partial agonist, like **2**. A vicinal bisphenol structure and a hydrophobic moiety should provide a basis for development of various ER ligands with agonistic, partial agonistic or antagonistic activities.

Therefore, we have focused on the development of novel bisphenol derivatives. Compound **2** has a phenol ring on the opposite side of benzothiophene ring, which plays an important role for ER binding. In consideration of raloxifene-like geometry between two phenol rings and synthetic advantages such as

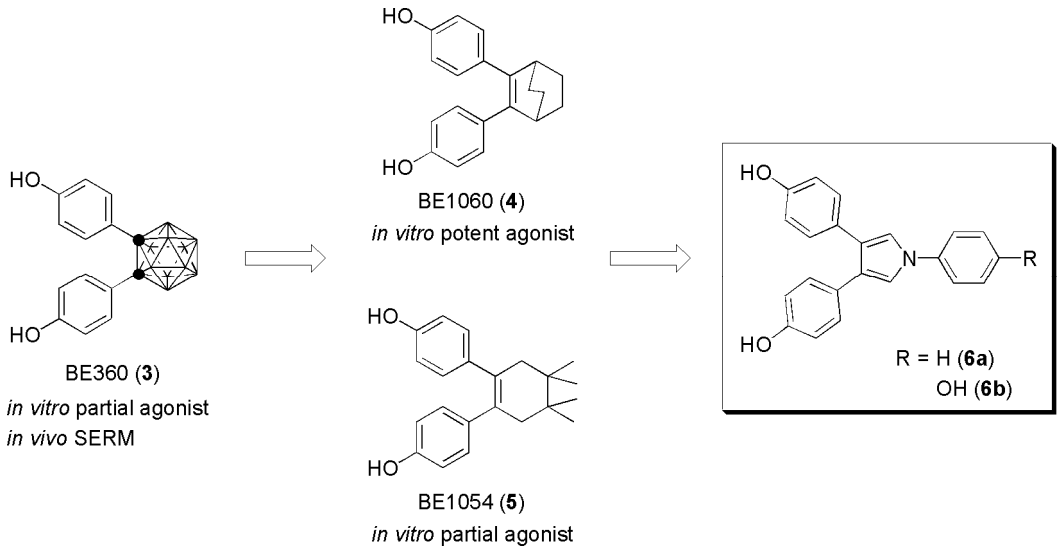
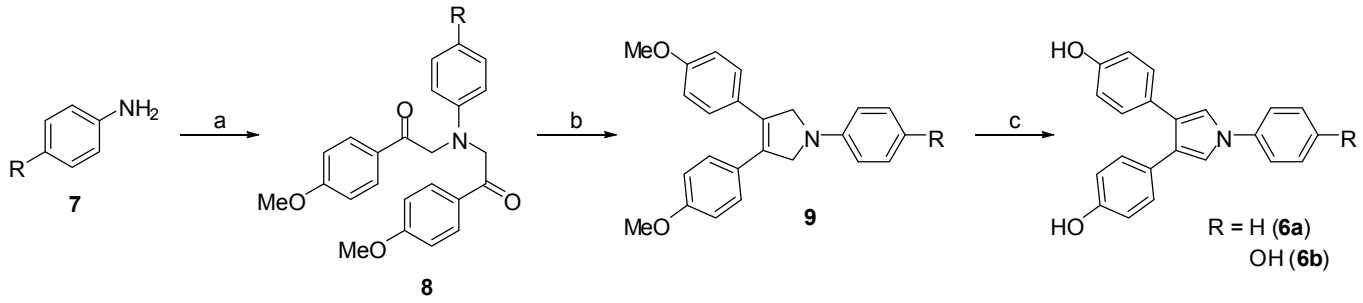


Figure 2. Structures of ER modulators and newly designed ER modulator candidates based on a bisphenol structure.

symmetric structure and simple synthesis, we chose a pyrrole ring as a central core structure and designed compounds (**6**) as novel ER modulators. In this paper, we describe the facile synthesis and biological activities of the novel pyrrole-based vicinal bisphenol compounds **6a** and **6b**.

Aromatic rings can be introduced into a pyrrole ring by means of Cu-mediated[9] or Pd-catalyzed[10] coupling reaction, but we chose pyrrole ring synthesis using McMurry coupling[11,12] because of the easily oxidizable character of pyrrole derivatives. The synthesis of the target compounds **6a** and **6b** is summarized in Scheme 1. Commercially available 2-bromo-4'-methoxyacetophenone (**7**) was reacted with aniline or *p*-anisidine to afford tertiary amines (**8**). Intramolecular McMurry coupling of **8** using $TiCl_4$ and Zn powder afforded dihydropyrrole derivatives (**9**) in low yields. We suggested that the low yields of coupling products **9** are due to a property of a dihydropyrrole ring, which is susceptible to oxidation. When the methoxy groups were deprotected with BBr_3, an unexpected aromatization proceeded simultaneously to afford the target compounds **6a** and **6b** in high yields. In general, the oxidation of dihydropyrroles to pyrroles is achieved under oxidative conditions using metal or organic oxidants.[13] During this reaction, dihydropyrrole derivatives could not be observed on TLC and were not isolated. Although the mechanisms involved are not clear, we suspected that the driving forces may be extension of the π-conjugated system and activation of α-hydrogen of the dihydropyrrole ring by coordination of the amine with BBr_3.



Scheme 1. Synthesis of bisphenol derivatives **6a** and **6b**; Reagents and conditions: (a) aniline or *p*-anisidine, $Na_2CO_3 \cdot 10H_2O$, EtOH, reflux, 70% (for R = H) and quant (for R = OMe); (b) $TiCl_4$, Zn, THF, reflux, 21% (for R = H) and 28% (for R = OMe); (c) BBr_3, CH_2Cl_2, rt, 88% (for **6a**) and 61% (for **6b**).

Figure 3 shows dose-response curves for competitive binding of compounds **6a** and **6b** with [2,4,6,7-^{3}H]E2 using human recombinant ERα and ERβ.[14] Both bisphenols **6a** and **6b** bound to ERα, but not to ERβ, and acted as ERα-selective ligands. Unfortunately, their potencies were around 100 times weaker than that of E2. Since there was no significant difference between compounds **6a** and **6b** in ERα-binding properties, the phenolic hydroxyl group in the *N*-substituent of **6b** appears not participate in secondary hydrogen bond formation with His524 or hydrogen-bonding amino acid residues around His524. On the other hand, compound **6b** has three phenolic hydroxyl groups and its binding mode to

ERα might be quite different from that of **6a**. In that case, these compounds might show different biological activities.

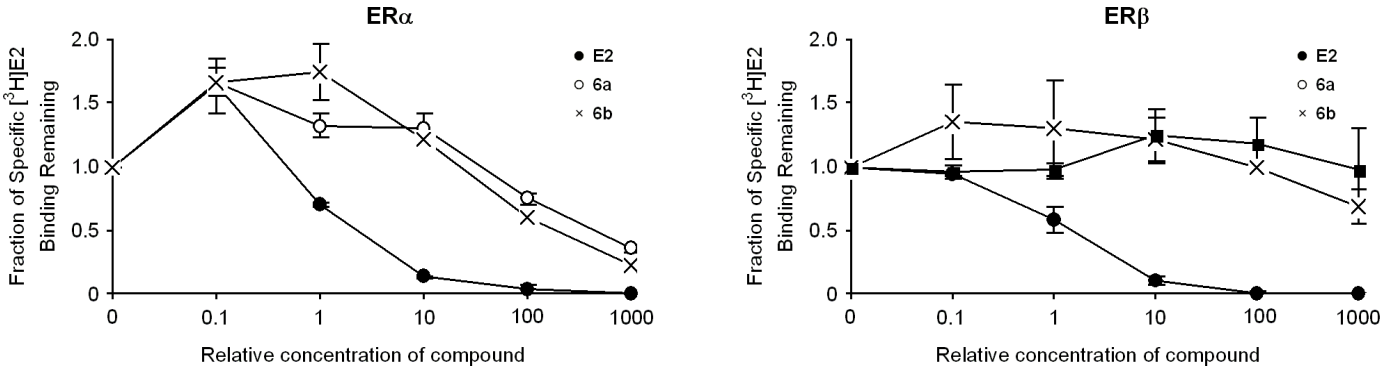


Figure 3. Competitive binding assay of compounds **6a** and **6b** with [^{3}H]E2 (4 nM), using ERα and ERβ.

The cell proliferative activity of compounds **6a** and **6b** was evaluated using human breast cancer MCF-7 cells, which show ER-dependent growth (Figure 4).[15] Neither of the bisphenols showed anti-proliferative activity. Compounds **6a** and **6b** showed dose-dependent enhancement of cell proliferation, although their activity was weaker than that of E2. These compounds acted as ER agonists and the EC_{50} values of compounds **6a** and **6b** were estimated to be 72 nM and 19 nM, respectively, from the dose-response curves.

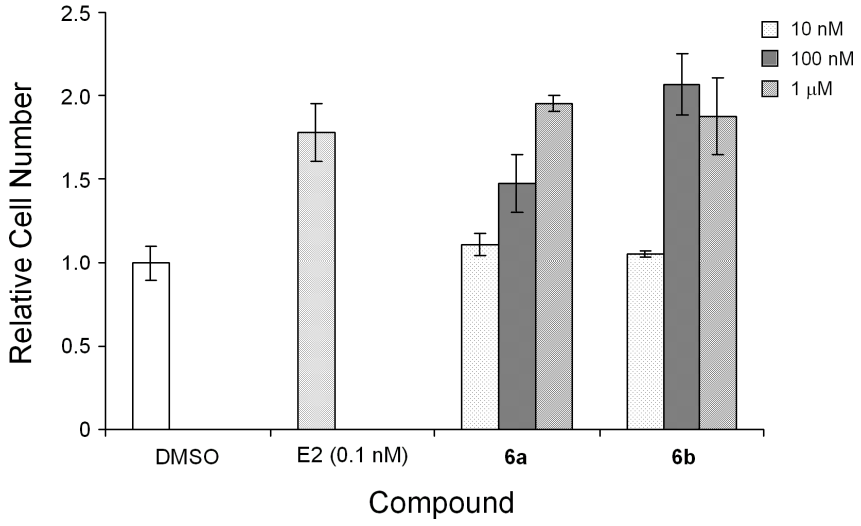


Figure 4. MCF-7 cell proliferation in the presence of compounds **6a** and **6b**.

Although the bisphenol compounds acted as moderately potent pure ER agonists, not partial agonists, in cell proliferation assay, the synthetic method allows convenient modification of the benzene and pyrrole rings, which might be effective to alter the activities. For example, it might be possible to produce a

partial agonist by the introduction of a basic side chain at a phenolic hydroxyl group of the bisphenol structure, as in the case of raloxifen. It seems that an agonistic activity is induced by a small and planar hydrophobic structure in the bisphenol derivatives. Therefore, an introduction of bulky hydrophobic substituents at the 2 and 5 positions on the pyrrole ring might conduct partial agonistic activity. These easily available compounds, **6a** and **6b**, are expected to be useful as lead compounds. Further derivatization and structure-activity relationship studies are in progress.

In conclusion, bisphenol derivatives **6a** and **6b** were prepared in short step synthesis from commercially available materials by using McMurry coupling as a key reaction, together with a unique BBr_3-mediated aromatization. Compounds **6a** and **6b** bound weakly to ERα and showed estrogenic activity in MCF-7 cell proliferation assay. Although their activities were not strong, there is scope for improvement by means of structural modifications on the nitrogen atom, benzene rings, and pyrrole ring. A triarylpyrrole structure might be a promising scaffold for drug discovery, because of the fixed structure in three different directions, availability of various substituted derivatives, and ease of synthesis.

ACKNOWLEDGEMENTS

This research was supported by a Grant-in-Aid for High Technology Research Program, a Grant-in-Aid for Scientific Research (B) (No. 20390035) and a Grant-in-Aid for Young Scientists (B) (No. 21790116) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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