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Estrogen receptor ligands. Part 6: Synthesis and binding affinity of dihydrobenzodithiins

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Abstract—Dihydrobenzodithiin compounds (**1**–**6**) were prepared to explore the expansion of the dihydrobenzoxathiin lead compounds **I**–**III** as SERAMs (Selective Estrogen Receptor Alpha Modulators). The dihydrobenzodithiin compounds generally maintained a high degree of selectivity for ERα over ERβ, however, they lacked the in vivo antagonism/agonism activity exhibited by the lead class in an immature rat uterine growth model.

The estrogen receptor is a nuclear hormone receptor, which plays an important role in regulating the female reproductive system, bone tissue, cardiovascular system, and CNS. The concept of selective estrogen receptor modulators (SERMs) has been widely explored as low-risk yet an effective means to treat reproductive disorders, estrogen-sensitive cancers, and osteoporosis.[1,2] The recent discovery of a new subtype of estrogen receptor, ERβ,[3] and the anticipation of it possessing unique biological functions has prompted a new wave of effort searching for subtype selective SERMs, or SERSMs (Selective Estrogen Receptor Subtype Modulators).[1c] Previously we reported on a new class of dihydrobenzoxathiin-based ERα selective SERMs or SERAMs (Selective Estrogen Receptor Alpha Modulators) (e.g. **I**–**III**).[4] Since then, we have been engaged in expanding the SAR of the class and now wish to report the results obtained by replacing the dihydrobenzoxathiin core with a dihydrobenzodithiin core (**1**–**6**) (Fig. 1).

These compounds[4e] were synthesized utilizing the same general strategy reported by Kim et al.[4a,c,5] for the preparation of dihydrobenzoxathiins, which is outlined in Scheme 1. To this end, treatment of dithioketal ketone **7** with NBS induced a series of tandem sulfur bromination-migration, ring bromination, and aromatization reactions leading to dithiin **8**. Reductive cleavage of the alkyl group provided the previously unknown, and pivotal synthon, 3,4-dimercaptophenol (**9**). One of the freely exposed thiol groups in **9** was selectively protected by a trityl group to give **10**, whose structure was confirmed by NOE experiments. We found that the best conditions to influence this conversion was the use of rotary evaporation under reduced pressure to remove both the solvent (methylene chloride) and the HCl generated in situ in order to drive the reaction to completion. A possible explanation for the selectivity of the reaction is that in the absence of base and presence of HCl, the thiol groups remain nonionized and the inductively more nucleophilic one, *para* to the phenol OH, reacted preferentially.

Coupling of the unprotected thiol group in **10** with α-bromoketone **16**[6] afforded **11**. Utilization of the Kim protocol (TFA–triethyl silane) led to the release of the free thiol group and subsequent stereoselective, reductive cyclization gave rise to **12**, the desired dihydrobenzodithiin core, as judged by the small coupling constant ($J = 3.4$ Hz @ $\delta = 4.67$ and 4.65 ppm) between the two *cis* protons on the dithiin ring. Finally,

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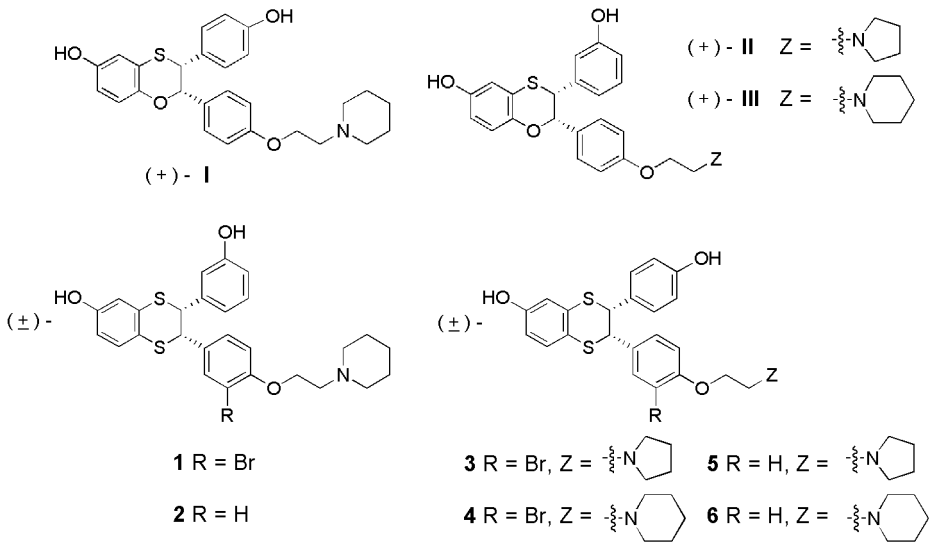
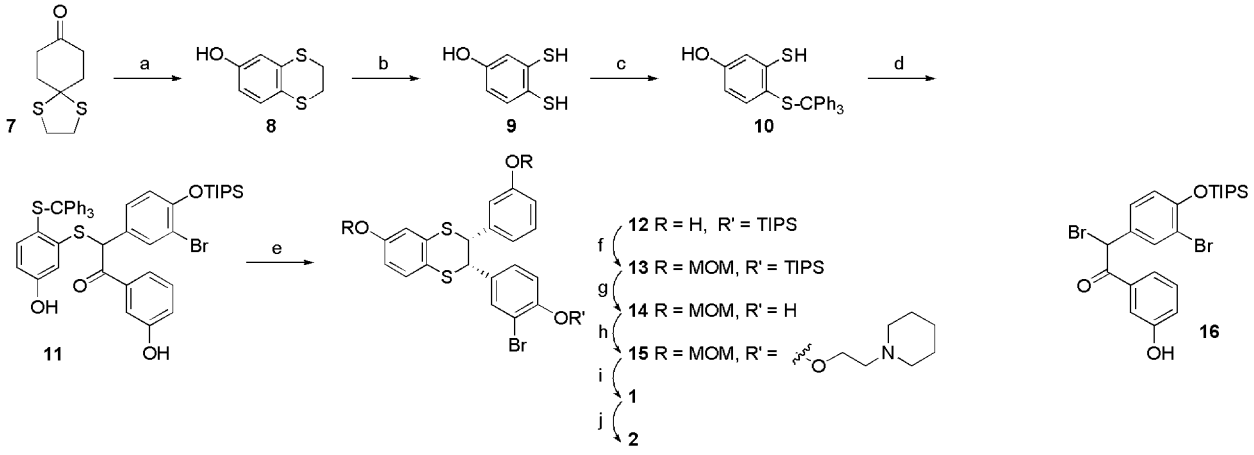


Figure 1.



Scheme 1. Synthesis of **1** and **2**. Reagents and conditions: (a) NBS, methylene chloride, 40%. (b) Li, liquid ammonia, 98%. (c) Trityl chloride, methylene chloride, then evaporate solvent 91%. (d) **16**, triethyl amine, 51%. (e) TFA, triethyl silane, 65%. (f) MOMCl, NaH, THF. (g) TBAF, THF, ca. 70% for two steps. (h) 1-Piperidineethanol, DIAD, triphenyl phosphine, THF. (i) 2 N HCl–MeOH–acetone, ca. 90% for two steps. (j) Mg, MeOH, ca. 30%.

the piperidino ethyl side chain was installed by the use of a Mitsunobu reaction, which in conjunction with protecting group manipulations provided **1**. Subsequent reduction of **1** provided **2**. Similarly prepared were compounds **3**–**6**. (For more information on the preparation of relevant structures, see Refs. 4 and 5.)

As indicated in Table 1, racemic compounds **1**–**6** exhibited good affinity for ERα with an ERα/β selectivity up to 40-fold, which is comparable to the dihydrobenzoxathiins **I**–**III**. Interestingly, the removal of the bromine atom resulted in a significant decrease in the binding affinity to ERα. Although compounds **1**–**6** do inhibit estrogen-dependent growth of the MCF-7 cells, they are substantially less potent than the dihydrobenzoxathiin class of compounds, and were found to be devoid of either *anti*-estrogenic or estrogen-like activity in an immature rat model designed to measure the stimulatory effects on uterine tissue in the presence and absence of estradiol.

In summary, the scope of the Kim protocol[5] was broadened by successfully applying it to the synthesis of *cis*-di-substituted dihydrobenzodithiins. As with dihydrobenzoxathiins,[4] the ERα selectivity of dihydrobenzodithiins is thought to arise from the interaction of the sulfur atom with the two discriminating residues of protein binding cavities in ERα and ERβ. However, the replacement of the oxygen atom with a sulfur atom significantly altered the size of the ring, which presumably contributed to the reduction in binding affinity and moreover, altered the native conformation of the aryl appendages, which in turn dramatically impacted the in vivo antagonism/agonism activity profile found in **I**–**III**. Such a result is testimony to the very sensitive nature of the estrogen receptor in response to the structural

Table 1. Human ER binding[a] and inhibition of MCF-7 cell growth

Compound[b]	Binding affinity, IC_{50} (nM) ERα/ERβ (fold selective for ERα)	MCF-7 inhibition IC_{50} (nM)
1	4/161 (40)	152
2	15/583 (39)	564
3	4/87 (22)	114
4	5/111 (22)	67
5	18/266 (15)	123
6	21/326 (16)	112
I[c]	0.8/45 (56)[d]	3.0[e]
II[c]	1.0/38 (38)[f]	0.6[g]
III[c]	4/115 (29)[h]	0.4[i]
Estradiol	1.3/1.1 (1)[j]	—

[a] The single IC_{50} values were generated in an estrogen receptor ligand binding assay. This scintillation proximity assay was conducted in NEN basic flashplates using tritiated estradiol and full length recombinant human ERα and ERβ proteins, with an incubation time of 3 h. In our experience, this assay provides IC_{50} values that are reproducible to within a factor of 2–3.

[b] All new dihydrobenzodithiins are racemic and were characterized spectroscopically.

[c] Chiral.

[d] Average of 36 measurements.

[e] Average of 7 measurements.

[f] Average of 101 measurements.

[g] Average of 5 measurements.

[h] Average of 2 measurements.

[i] Average of 2 measurements.

[j] Average of 130 measurements.

changes and has prompted future work toward understanding the SAR of the dihydrobenzoxathiin SERAM platform.

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