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Letters

Estrogen Receptor Ligands. II. Discovery of Benzoxathiins as Potent, Selective Estrogen Receptor α Modulators

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Abstract: The discovery and synthesis of dihydrobenzoxathiins as potent, ERα subtype selective ligands are described. The most active analogue, **4-D**, was found to be 50-fold selective in a competitive binding assay and 100-fold selective in a transactivation assay in HEK-293 cells. The α selectivity was postulated to lie in the interaction of the sulfur atom of the benzoxathiin ring with the two discriminating residues in the binding pocket of the receptor isoforms.

The selective estrogen receptor modulators (SERMs)[1] have been developed owing to the potential ability to antagonize the detrimental effects of estrogen on uterine and breast tissue while producing estrogen-like effects on bone and the cardiovascular system.[2] The utility of SERMs is exemplified by the use of tamoxifen[3] for the prevention and treatment of breast cancer and raloxifene[4] for the treatment and prevention of osteoporosis. Over recent years, several additional SERMs[5] have entered late stages of clinical trials for a variety of indications. Although the current SERMs have clear advantages over conventional HRT, they retain some of the disadvantages as well.

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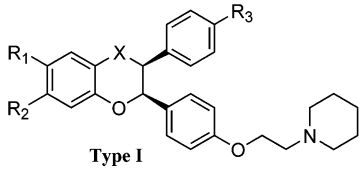

Figure 1.

The recent discovery of a second estrogen receptor subtype (ERβ)[6] provided an additional approach for the identification of "ideal SERMs" with improved side effect profiles. Whereas tamoxifen and raloxifene are tissue selective SERMs, they bind with comparable affinity to both receptor subtypes and thereby raise the possibility that there may be advantages to receptor subtype selective compounds.

In a previous communication,[7] we identified ERα subtype selective SERMs or SERAMs that centered on the isoflavanone core structure. Although these compounds, exemplified by compound **1**, type I (where R_1 = H, R_2 = R_3 = OH, X = CO; Figure 1), exhibited a greater affinity for ERα over ERβ (~70-fold selectivity), only modest binding and in vivo potency were observed. Our search for more potent subtype selective SERMs or SERSMs[1c] prompted an expanded structure−activity relationship (SAR) evaluation of the series. We report the results of this investigation leading to the discovery of the benzoxathiin core, type I (X = S).

A representative synthesis of the key compounds is described in Scheme 1. The thioketone **9** underwent reductive cyclization with Et_3SiH/TFA in dichloromethane at 0 °C to yield only the *cis*-dihydrobenzoxathiin **10**, as we have previously described.[8] The Mitsunobu alkylation of the phenol **10** with 1-(2-hydroxyethyl)-piperidine was utilized for the installation of the basic side chain. Sequential deprotection of the benzyl group, under transfer hydrogenation conditions, followed by desilylation with TBAF in the presence of HOAc, yielded the desired compound **4**. The trans isomer **14** and benzoxathiin **16** were prepared according to literature procedures with minor modifications.[9] Thus, reduction of **9** with $LiEt_3BH$, followed by acid (Amberlyst-15) catalyzed cyclization in toluene at room temperature, af-

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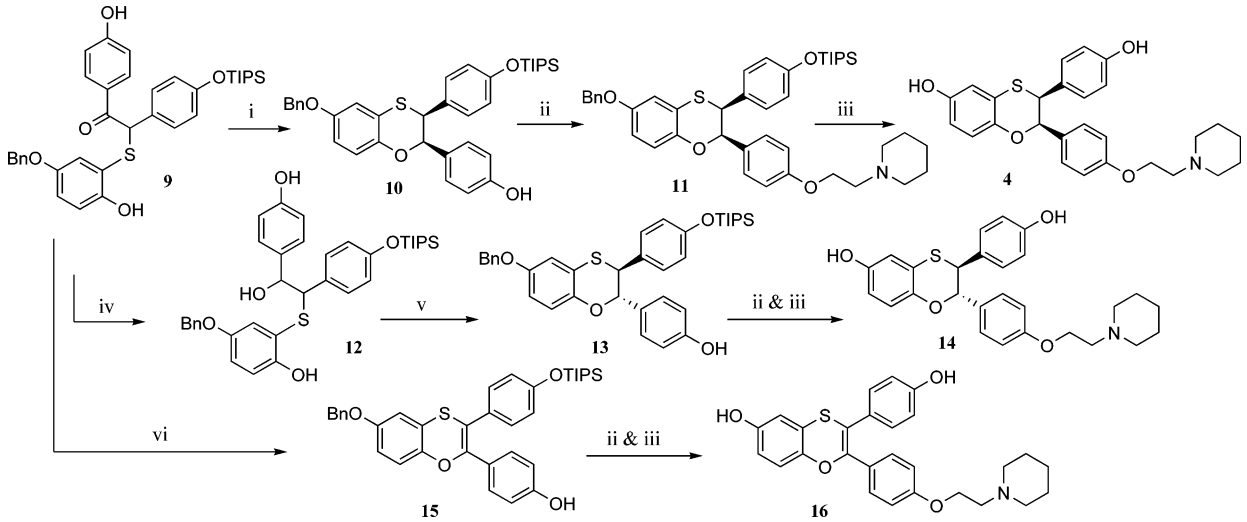
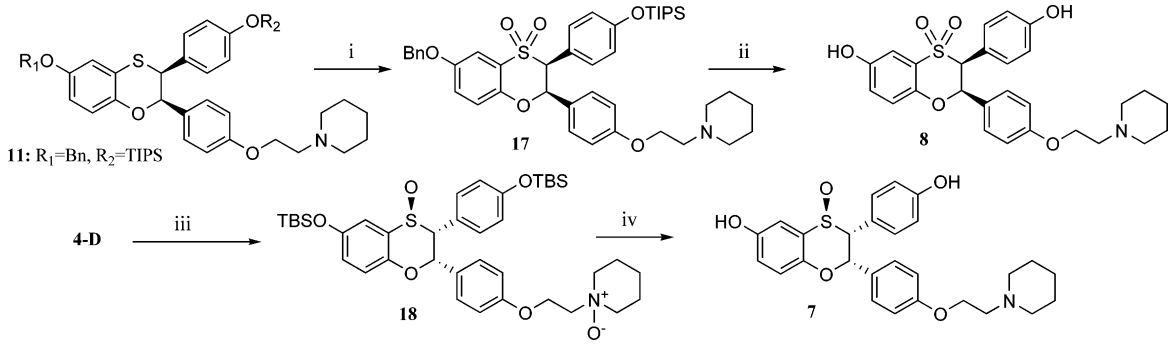
Scheme 1[a]



[a] Reagents: (i) Et_3SiH, TFA, 0 °C, 90%; (ii) PPh_3, DIAD, 1-(2-hydroxyethyl)piperidine, THF, 40 °C, 65−75%; (iii) (a) Pd, HCO_2NH_4, (b) TBAF, HOAc, THF, room temp, 43−55% for two steps (a and b); (iv) $LiEt_3BH$, THF, 0 °C; (v) Amberlyst-15, toluene, room temp, 93% for two steps (iv and v); (vi) TsOH, toluene, reflux, 40%.

Scheme 2[a]



[a] Reagents: (i) (a) excess mCPBA, CH_2Cl_2, room temp, (b) saturated $NaHSO_3$, saturated $NaHCO_3$, room temp, 1 h, 75% (steps a and b); (ii) (a) Pd, HCO_2NH_4, (b) TBAF, HOAc, THF, room temp, 64% for two steps (a and b); (iii) (a) TBSCl, $EtN(i\text{-}Pr)_2$, DMF, 89%, (b) 2 equiv of mCPBA, CH_2Cl_2, −10 °C, 2 h, 78%; (iv) (a) saturated $NaHSO_3$, saturated $NaHCO_3$, room temp, 1 h, 65%, (b) TBAF, HOAc, THF, room temp, 80%.

forded **13** in 93% yield. Conversion of thioketone **9** into thiin **15** was achieved by dehydrative cyclization with TsOH in refluxing toluene. Both **13** and **15** were converted to **14** and **16**, respectively, as described above. As shown in Scheme 2, exhaustive oxidation of **11** with excess mCPBA at room temperature provided the sulfone *N*-oxide (not shown), which was then selectively reduced back to the corresponding free amine **17** in 75% yield. The deprotection tactics described above afforded sulfone **8**. Similarly, sulfoxide **7** was synthesized from **4-D**.

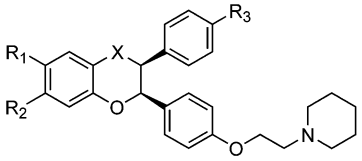
Chiral resolution of the dihydrobenzoxathiin **10** was realized by HPLC, using a Chiracel AD column and 30% IPA/hexane as the eluant, to provide the dextrorotatory enantiomer **10-D** and the levorotatory enantiomer **10-L**. Both chiral precursors were converted to **4-D** and **4-L**, respectively,[10] utilizing the same procedures as described in Scheme 1.

The ligand binding domain of ERα (residues 307−554) in complex with **4-D** was crystallized in space group $P6_5$-22, with cell dimensions $a = b = 58.48$ Å, $c = 276.08$ Å. Data to 1.9 Å resolution were measured at beamline 17-ID of the Advance Photon Source. The data were processed with program X-GEN, which yielded an R_{merge} of 0.070 for the data from 10.0 to 1.9 Å and 0.356 for the data from 2.02 to 1.90 Å. The structure was refined using program SHELXL, with final values for R_{work} and R_{free} of 0.218 and 0.272 for the data from 10.0 to 1.90 Å resolution. 99.1% of the residues in the refined model were in the most favorable and additionally allowed regions of a Ramachandran plot. The rms errors for bond distances and angles were 0.005 and 0.020, respectively. Coordinates and structure factors have been deposited with the Protein Data Bank (entry 1SJ0.

Our compounds were primarily tested for intrinsic activity in an ER binding assay.[11] Potency and selectivity of selected compounds were further assessed in a cellular transactivation assay utilizing HEK 293 cells stably cotransfected with either human ERα or ERβ and the alkaline phosphatase reporter gene. The inhibition of the proliferative activity of estradiol along with the estrogenic activity was measured in vivo using an immature rat uterine weight gain assay.[12]

The binding affinities of **1**−**8** to the human ERα and ERβ receptors are summarized in Table 1. Given the previous hypothesis[7] that the crucial difference responsible for the α selectivity of lead **1** lies in the interaction of its carbonyl with the two discriminating residues in the binding pocket of the two receptor isoforms (Leu 384 for ERα, Met 354 for ERβ),[13] our initial efforts were focused on the examination of point changes directed at the carbonyl region of the isoflavanone. Replacement

Table 1. Estrogen Receptor Binding Affinities, IC_{50}[11]



					IC_{50} (nM)[11]	
compd[a]	X	R_1	R_2	R_3	ERα	ERβ
1	CO	H	OH	OH	39	2732 ($n = 3$)
2	CH_2	H	OH	OH	6.7	8.9
3	S	H	OH	OH	1.6	45
4	S	OH	H	OH	3.0	143 ($n = 5$)
5	S	OH	H	H	6.2	183
6	S	H	H	OH	10	70
7[b]	SO	OH	H	OH	$>10^4$	$>10^4$
8	SO_2	OH	H	OH	1090	5950
E-2					1.3	1.1
ralox					1.8	12 ($n = 7$)

[a] All compounds are racemates. [b] Chiral.

of the carbonyl moiety with CH_2 (**2**)[7] significantly improved the ERβ binding affinity (8.9 nM) but had little effect on the ERα binding, thereby reducing its selectivity to about 1-fold. This result supported our hypothesis that a smaller group might enhance binding to the ERβ receptor by eliminating the proposed unfavorable steric and electronic interactions that the Met 354 residue presents. Conversely, α selectivity was regained by incorporation of the larger, more polar sulfur atom (**3**), which also resulted in increased receptor affinity compared to **1**. Within the limits of the binding assay, switching the hydroxyl from position 7 to 6 (**4**) was without consequence; however, this change had a profound effect on the pharmacokinetics.[14] To confirm the structural basis for the selectivity profile of **4**, molecular modeling of multiple conformers of each of the two cis enantiomers was evaluated in the context of hERα and hERβ ligand binding domains. The docking and energy minimization approach, which will be described elsewhere, identified a binding mode of **4** with the absolute configuration of [*2S*,*3R*] as being the most likely to explain the SAR and would assign that absolute stereochemistry to **4-D**. This binding mode posits the dihydrobenzoxathiin ring system of **4-D** in the benzothiophene location of raloxifene as it is bound to hERα determined crystallographically (PDB entry 1ERR), which is depicted in Figure 2. From the modeled results, the conjecture that the out-of-plane pucker of the sp^3-hybridized sulfur in the dihydrobenzoxathiin ring is responsible for the same interactions described above

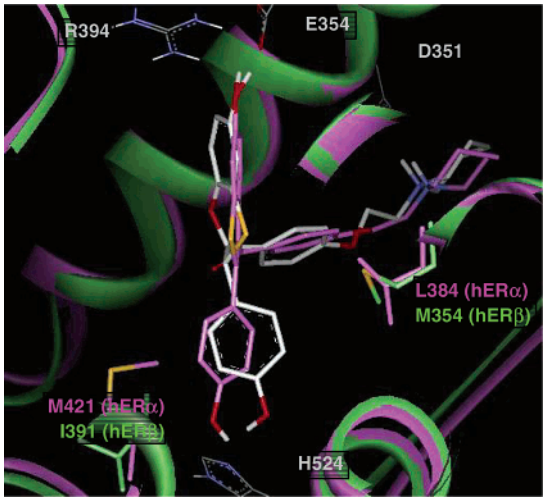


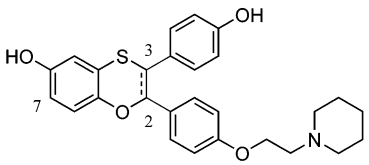
Figure 2. Molecular modeling of **4-D** (white) against raloxifene (purple). HERα is depicted in purple and hERβ in green. Residue numbering is hERα unless otherwise indicated.

is consistent with the prior observation. This pucker clearly directs the sulfur toward one of the two selectivity regions that line the binding cavity, whereas the sp^2-hybridized sulfur of raloxifene is directed away from this selectivity region. The proposed binding mode and absolute stereochemistry were later confirmed crystallographically as shown in Figure 3.

In contrast to the isoflavanone series[7] where both hydroxyls at R_2 and R_3 were required for optimal binding and selectivity, only modest decreases were observed upon removal of the hydroxyl at R_3 (**5**). The relative importance of the benzoxathiin ring hydroxyl, R_1, is measured by the more dramatic impact on these parameters observed with **6**.[16] A similar trend was also reported for raloxifene derivatives.[17] The incorporation of a polar group, like sulfoxide **7**, had a detrimental effect on the binding affinity, implying that a negative charge on oxygen is not tolerated at all in this hydrophobic region of the receptor.[18] A similar effect was also observed with the sulfone moiety (**8**). From these data, it is clear that activity and selectivity correlate well with the nature of the X moiety.

To enhance the SAR of the benzoxathiin core, the stereochemistry at $C_{2,3}$ was investigated, and these results are described in Table 2. As observed with isoflavanones,[7] the cis stereochemistry at $C_{2,3}$ proved to be an absolute requirement for the maintenance of an optimal antagonist/agonist activity profile in vivo,

Table 2. Binding Affinities and in Vivo Data



		binding affinity, IC_{50} (nM)[11]		HEK 293 cells, IC_{50} (nM)		uterine weight assay (sc),[12]
compd	$C_{2,3}$	human ERα	human ERβ	ERα	ERβ	% inhibition @ 1mpk/% control @ 1 mpk
4	(±)-*cis*	3.0	143 ($n = 5$)	9.6	52	77/5.0
4-D[b]	cis-[2*S*,3*R*]	0.8	45 ($n = 36$)	0.8	97	92/0.4[a]
4-L	*cis*-[2*R*,3*S*]	23	287	353	3876	16/1.0
14	(±)-*trans*	17	276	188	1404	18/20
16	olefin	1.6	5.1	5.1	159	55/45

[a] At a po dose of 0.3 mpk (1.0 mpk), 80% (99%) inhibition and 11.4% (9.0%) agonism was observed. [b] The absolute configuration was confirmed by X-ray crystallography of **4-D** complexed with ERα-LBD307-554.

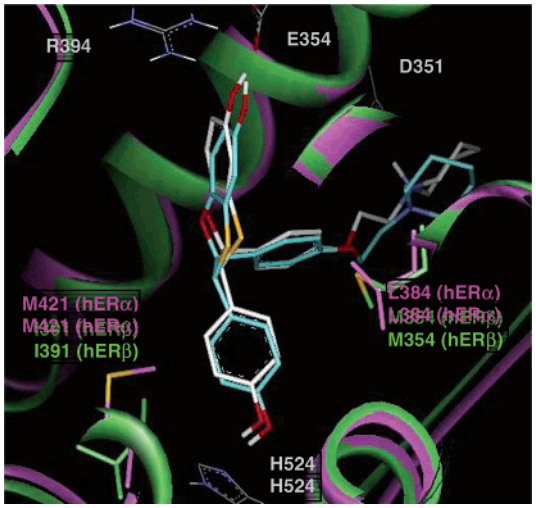


Figure 3. Comparison of crystallographic (cyan) to molecular modeling results for **4-D** (white). HERα is depicted in purple and hERβ in green.

as evidenced by a comparison of the uterine weight data for **4** and the trans **14** (77% inhibition and 5.0% agonism versus 18% inhibition and 20% agonism). The poor activity exhibited by **14** paralleled the weak estradiol antagonism observed in the functional assay (HEK ERα = 188 nM). Interestingly, the planar thiin **16**, with receptor affinity and functional activity comparable to those of **4**, produced a significant increase in uterine weight (45% agonism) along with a modest antiproliferative effect (55% inhibition). These results suggested that the coplanar orientation of the side chain present in **16** may contribute to uterine stimulation, as seen with tamoxifen and raloxifene derivatives where the carbonyl hinge has been excised to similarly generate a coplanar orientation of the side chain.[19]

As suggested by molecular modeling, only the single enantiomer **4-D** reproduced the activities exhibited by the racemate **4**.[20] Thus, when dosed sc, **4-D** potently inhibited the estradiol-driven uterine growth in immature rats (92% inhibition), while only weak uterotropism (0.4%) was observed. Even at a lower oral dose of 0.3 mpk, **4-D** suppressed nearly 80% of the estrogen stimulus on the uterus and the agonist activity did not appear to be dose-dependent (ca. 10% agonism at both 0.3 and 1.0 mpk).[14]

In addition, **4-D**, in the appropriate rat models, was shown to effectively inhibit ovariectomy-induced bone resorption, lower serum cholesterol levels, and estradiol-driven endometrial explant growth. Such a profile of activities clearly establish this new class of compounds as potent SERAMs that warrant further investigation and will be the subject of future communications from these laboratories.

In summary, we have disclosed herein a novel ERα selective SERM (**4-D**) or SERAM that displays low-nanomolar binding affinity and subnanomolar functional activity. This compound exhibited excellent in vivo efficacy for the suppression of estradiol-driven uterine proliferation, with minimal uterotropic activity. The molecular modeling of **4-D** suggested that the sulfur moiety may be crucial to maintaining subtype selectivity.

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Supporting Information Available: Characterization (^{1}H NMR, LC/MS, and HRMS) of **4-D**, **5**, **7**, **8**, **14**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) **4-D**: $[\alpha]_D$ +276.8° (*c* 0.49, MeOH). **4-L**: $[\alpha]_D$ −263.3° (*c* 0.515, MeOH). **10-D**: $[\alpha]_D$ +184.4° (*c* 0.725, MeOH). **10-L**: $[\alpha]_D$ −188.5° (*c* 0.740, MeOH).

(11) The IC_{50} values were generated in an estrogen receptor ligand binding assay. This scintillation proximity assay was conducted in NEN Basic Flash plates using tritiated estradiol and full-length recombinant human ERα and ERβ proteins with incubation times of 3−23 h. In our experience, this assay provides IC_{50} values that are reproducible to within a factor of 2−3. Most

compounds are single-point determinations. The binding results for **4-D** reflect an average of 36 determinants at 3 h of incubation. For estradiol, the binding data reflect an average of over 100 determinants at 3 h of incubation.

(12) Twenty-day-old intact female Sprague-Dawley rats were treated (sc) with test compounds for 3 days at 1 mpk. The uteri wet weights were determined on day 4, and dry weights were determined after air-drying the tissue samples for 3 days. The antiestrogenic activity of the compounds was determined by coadministration of the compound with a subcutaneous injection of 17-β-estradiol and reported as % inhibition. The estrogenic activity (partial agonism) of the compounds was determined by administering the test compound without estradiol and reported as % control.

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(14) Compound **3** exhibited no oral bioavalibility in female Sprague-Dawley rats dosed at 2 mpk. In contrast, **4** was markedly improved; $F = 31\%$. As observed with lasofoxifene,[15] the active enantiomer **4-D** exhibited greater oral bioavailability than **4-L**: $F = 62\%$ vs $F = 11\%$, respectively.

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