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ESTROGEN RECEPTOR LIGANDS. PART 15: SYNTHESIS OF BENZOTHIOPYRAN-BASED SELECTIVE ESTROGEN RECEPTOR ALPHA MODULATORS (SERAM)

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Abstract – Benzothiopyran (**2**) was prepared and the bioactive (+)-**2** was found to exhibit a reduced affinity toward the estrogen receptors (ER α / β) when compared to the corresponding dihydrobenzoxathiin (+)-**1**.

In a previous communication,¹ we identified ER α subtype selective ligands or Selective Estrogen Receptor Alpha Modulators (SERAMs) that centered on the dihydrobenzoxathiin core structure.² This compound, as exemplified by **1**, exhibited low nanomolar binding affinity and sub-nanomolar functional activity, as well as *in vivo* efficacy for the suppression of estradiol-driven uterine proliferation, with minimal uterotropic activity. Subsequent expanded structure-activity relationship³ eventually led to a potential developmental candidate.⁴

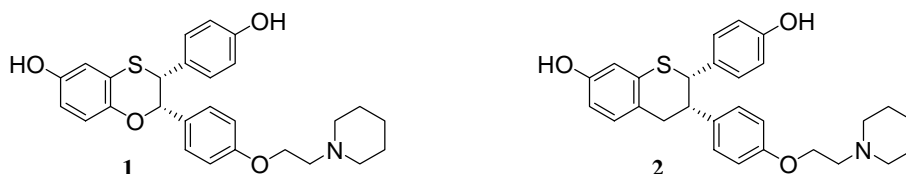


Figure 1

Although dihydrobenzoxathiin (**1**) had excellent potency and selectivity for ER α , it was judged to be unacceptably prone to oxidative metabolism, with subsequent formation of covalent protein adducts.⁵ We initially identified that an iminium ion resulting from oxidation of the piperidine residue present in the side chain of **1** was a significant contributor to the formation of covalent adducts.⁶ Meanwhile,

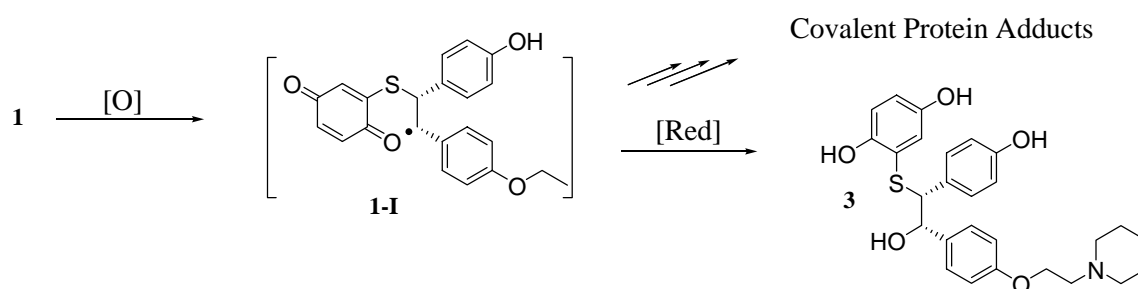
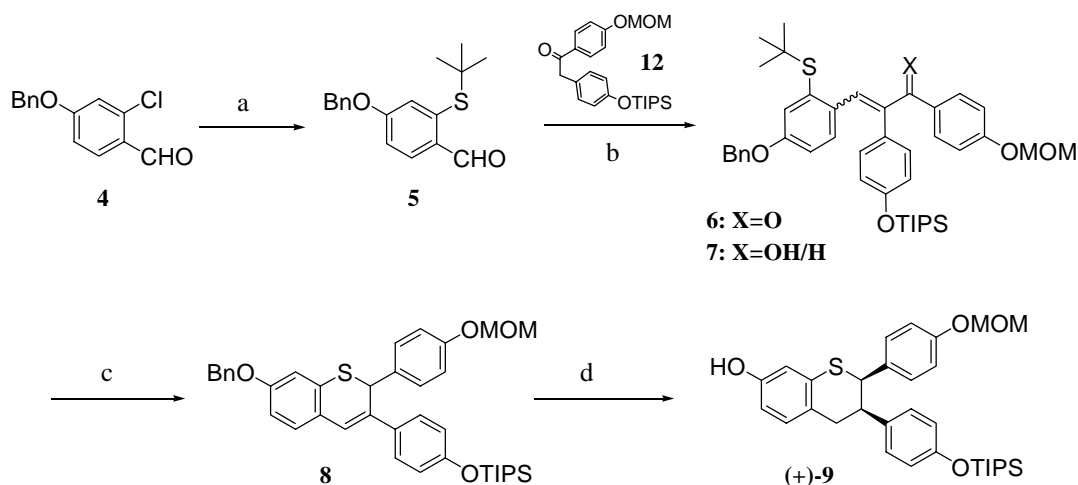


Figure 2: Possible Metabolic Pathway leading to Protein Binding Adducts

formation of a quinone intermediate (**1-I**), generated from a phenolic-radical fragmentation process embedded in the dihydrobenzoxathiin core, had also been postulated as being responsible for the covalent adducts with biological proteins.⁵ Intuitively, the isolation of hydroquinone (**3**) from the *in vitro* incubation of **1** with human liver microsomes supported the plausibility of the above metabolic pathway (Figure 2).⁷ Therefore, it seemed prudent to replace the oxygen in the core with a methylene unit, thus eliminating the possible formation of the quinone intermediate and thereby ameliorating any potential for cytochrome P-450 mediated activation. Herein, we report the synthesis, estrogen/anti-estrogen activity, and metabolic stability of target (**2**).



Scheme 1 Reagents and Conditions: (a) 1.5 equiv. *t*-Butylthiol, 1.8 equiv. NaH, Diglyme, 95°C, 15 h, 72% ; (b) Piperidine, AcOH, 110°C, 2 days, 50%; (c) i. LiAlH₄, 0°C ii. 5% TFA, CH₂Cl₂, -5°C, 10 min, 90% for two steps; (d) 1 equiv. Pd black, H₂, EtOH, rt, 2 days, 75%

The synthesis began with the known compound (**4**), which was easily synthesized from *m*-chlorophenol by a Reimer-Tiemann reaction in 60-70% yield.⁸ Replacement of the chlorine atom with a *t*-butylthio group was initially problematic due, in part, to the lability of the benzyl group under the basic conditions.⁹ However, the best conversion was realized by using a minimum amount of the reagents at lower temperature. The resulting *t*-butylthiobenzaldehyde (**5**) was condensed with a properly protected ketone (**12**) in the presence of piperidine/HOAc to give a mixture of (*E/Z*)- α,β -unsaturated ketones (**6**).¹⁰ This

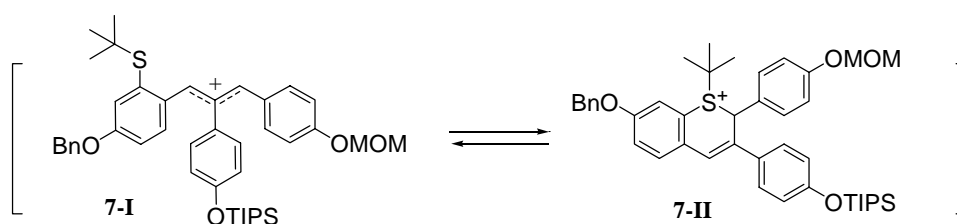
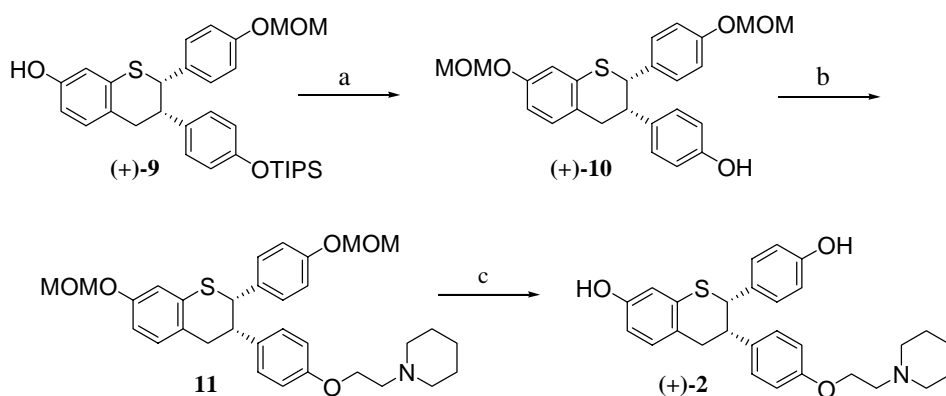


Figure 3

Knoevenagel reaction was very sluggish and reaction times of 2 days were necessary to ensure total consumption of the starting material. Selective 1,2-reduction of α,β -unsaturated ketones (**6**) with 1 equiv. LiAlH_4 in THF gave allylic alcohols (**7**), thus setting the stage for subsequent cyclization to the benzothiopyran.



Scheme 2 Reagents and Conditions: (a) i. 3 equiv. NaH , MOMCl , DMF , rt ii. TBAF , HOAc , THF , 80% for two steps; (b) 2-Chloroethylpiperidine, Cs_2CO_3 , acetone, reflux; (c) 10% HCl , MeOH , reflux, 1 h, 81%

The allylic alcohols (**7**), without further purification, were then cyclized with TFA in dichloromethane to yield the 2,3-disubstituted $2H$ -1-benzothiopyran (**8**) in 90% yield.¹¹ An acid-mediated cyclization of the allylic carbocation **7-I** to **7-II** followed by loss of isobutylene was postulated as the reaction mechanism (Figure 3).¹¹ Hydrogenation of compound (**8**) with Pd black provided exclusively the racemic, *syn*-compound (**9**).¹² The *syn* relationship of the two phenyl groups was unambiguously established by the observed small coupling constant ($J = 3.5$ Hz, $\delta = 4.2$ ppm, see ref. 2), between H_2 - H_3 . Subsequent chiral resolution of the racemic benzothiopyran (**9**) was realized by HPLC, using a Chiracel AD column and 30% IPA/hexane as the eluant, to provide the dextrorotatory enantiomer ((+)-**9**).¹³

With (+)-**9** now readily available, protection of the hydroxyl group in the A-ring, followed by deprotection of TIPS group produced (+)-**10** in quantitative yield (Scheme 2). The phenol ((+)-**10**) was next converted to the respective ether (**11**) by reaction with 2-piperidinoethyl chloride in the presence of cesium carbonate in acetone. Removal of the two MOM groups with dilute acid resulted in the final

compound ((+)-**2**) in 81% yield.¹⁴ Similarly, in the racemic series, (**9**) was also converted to (**2**) by application of the same procedure.

It is clear from the data in Table 1 that the benzothiopyran (**2**) retained the ER α potency and the magnitude of receptor subtype selectivity (ER β /ER α ratio) exhibited by the dihydrobenzoxathiin (**1**) in an *in vitro* ER binding assay. However, the replacement of the oxygen atom with a methylene unit altered the size of the ring, which presumably contributed to the reduction of the binding affinity (ER α for (+)-**1**= 0.8 nM and (+)-**2**= 3.1 nM).¹⁵ This weaker potency paralleled the weaker estradiol antagonism observed in the immature rat uterine model (92% inhibition vs 76% inhibition).

Table 1. Binding affinities^a and *in vivo* data

Compd	Binding affinity		Uterine Assay (sc) ^c % inhib @ 1mpk / % control @ 1 mpk
	ER α	ER β (α selectivity)	
(+)- 1 ^b	0.8	45 (56)	92/0.4
(±)- 1 ^b	3.0	143 (48)	77/5.0
(+)- 2 ^d	3.1	130 (43)	76/4.7
(+)- 2	5.8	590 (101)	N.A.

^aUtilizing full length recombinant human ER α / β proteins; IC₅₀ (nM), n=>48-56, see ref 1. ^bAbsolute stereochemistry was determined by X-Ray crystallography, see ref 1 ^cSee ref 1 & 3; ^dThe absolute stereochemistry of (+)-**2** was assigned based on analogy with (+)-**1**, see ref 13 and 14

As with the dihydrobenzoxathiins, only the single enantiomer ((+)-**2**) reproduced the activity exhibited by the racemate (**2**). In addition, the metabolism of the tritium-labelled ((+)-**2**) was investigated and, in spite of the modification, was found to have a similar level of covalent protein adducts as (+)-**1** in incubations with rat liver microsomes. Further results in this area will be reported in future publications from this laboratory.

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12. *Ca.* 3% yield of *trans* isomer was also formed. See also ref. 2.
13. The absolute stereochemistry of (+)-**9** was assigned based on analogy with (+)-**1**, and confirmed later by biological data, see also ref. 1 and Table 1. (+)-**10**: $[\alpha]_{\text{D}} +227.6^{\circ}$ (*c* 0.69, MeOH)
14. (+)-**2**: $[\alpha]_{\text{D}} +193.2^{\circ}$ (*c* 0.49, MeOH); $^1\text{H NMR}$ (500 MHz, Acetone- d_6) δ (ppm) 7.00 (d, *J*=8.3 Hz, 1H), 6.82 (d, *J*=8.4 Hz, 2H), 6.76 (d, *J*=8.5 Hz, 2H), 6.68 (d, *J*=8.7 Hz, 2H), 6.68 (d, hidden, 1H), 6.60 (d, *J*=8.5 Hz, 2H), 6.58 (dd, *J*=2.5 Hz, 1H), 4.49 (d, *J*=3.7 Hz, 1H), 4.10 (t, 2H), 3.60 (m, 1H), 3.05 (dd, *J*=10.5 and 16.25 Hz, 1H), 2.90 (dd, *J*=3.6 and 16.00 Hz, 1H), 2.80 (br t, 2H), 2.60 (br s, 4H), 1.60 (m, 4H), 1.50 (br m, 2H); MS *m/z* 462.0 (M^+)
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