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Structure–activity relationships of SERMs optimized for uterine antagonism and ovarian safety

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Abstract—Structure–activity relationship studies are described, which led to the discovery of novel selective estrogen receptor modulators (SERMs) for the potential treatment of uterine fibroids. The SAR studies focused on limiting brain exposure and were guided by computational properties. Compounds with limited impact on the HPO axis were selected using serum estrogen levels as a biomarker for ovarian stimulation.

Uterine fibroids (leiomyomas) are non-cancerous growths that develop from the smooth muscle cells and fibrous connective tissue of the uterine wall.[1] Although most are asymptomatic, in some women, fibroids cause abnormal menstrual bleeding and pain, which have a profoundly negative effect on quality of life. For these women hysterectomy is the most definitive solution accounting for over 200,000 surgeries a year in the US.[2] Pathological evaluation of hysterectomy specimens reveals a similar incidence in both postmenopausal and premenopausal women (84% and 74%, respectively).[3] However, in premenopausal women these growths are more numerous and of larger size. Hysterectomy is unacceptable for a woman who desires a future pregnancy. Other invasive surgical procedures, which preserve the uterus, such as myomectomy (fibroid removal with uterine retention), laser ablation, or emolization are effective; however, these treatments are associated with a high rate of fibroid recurrence.

The current pharmaceutical treatment for uterine fibroids involves the use of gonadotropin-releasing hormone (GnRH) agonists. These peptides stimulate the pituitary gland resulting in down-regulation of the hypothalamic–pituitary–ovarian (HPO) axis, decreasing the release of gonadotropins (FSH and LH), and a subsequent reduction in the amount of estrogen (E2) produced in the ovaries. This hypoestrogenic state causes a reduction in uterine volume and fibroid size.[4] Unfortunately, there are unacceptable side effects, most notably bone loss, associated with this therapy and once discontinued, the fibroids return. As a result, GnRH agonists are primarily used to reduce fibroid size prior to surgical removal.

Since uterine fibroids exhibit E2 dependence, the estrogen receptors (ERα and ERβ) are viable targets for pharmaceutical treatment. The ERs are ligand-dependent transcription factors that belong to the nuclear hormone receptor (NHR) superfamily. Selective estrogen receptor modulators (SERMs) exhibit tissue type functional selectivity, acting as agonists in some tissues but antagonists in others.[5,6] Tamoxifen (**1**) has been clinically evaluated for the treatment of fibroids but it lacks sufficient efficacy due to its agonist activity in uterine

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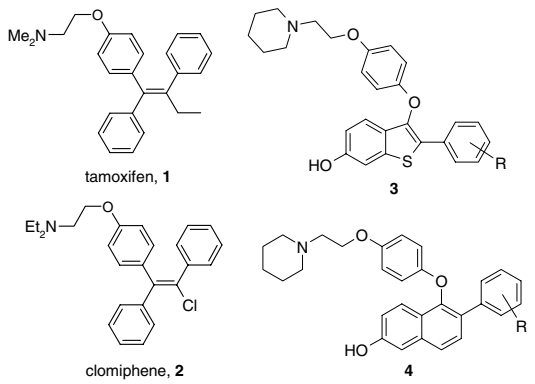
tissues.[7,8] It also causes ovarian cysts, an unacceptable side effect that limits its use in premenopausal women. This ovarian stimulatory effect has been attributed to inhibition of the HPO axis due to the antagonist activity exhibited by tamoxifen in the hypothalamus. Inhibition of the HPO axis results in overproduction of gonadotropins (LH and FSA) and hyper-stimulation of the ovaries. This activity is also exhibited by clomiphene (**2**), which has been used to induce ovulation.[9]



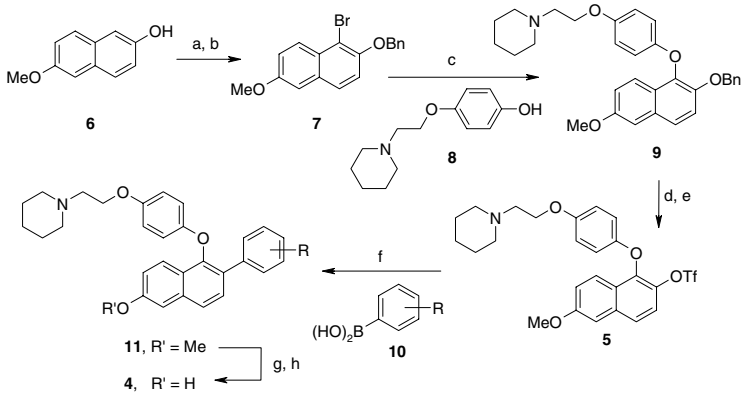
Here, we describe SAR studies that led to the discovery of SERMs that have antagonistic effects in the uterus with limited impact on the HPO axis and do not stimulate the ovaries.[10] We began our search for novel ovarian selective SERMs by pursuing structure–activity relationship (SAR) studies at the 2-aryl positions of the benzothiophene (**3**) and the naphthalene (**4**) ring systems, since it is known that this area of the ER pharmacophore is tolerant to functional group diversity.[11] Also since it has been demonstrated that an oxygen linker confers a substantial increase in estrogen antagonist potency, we focused our efforts on the oxygen linked derivatives of **3** and **4**.[12] Our primary strategy was to explore functional groups that might limit brain penetration with the hypothesis that restricting brain exposure would limit impact on the HPO axis.

Our first goal was to develop syntheses of common intermediates that would facilitate SAR studies. For the naphthalene series (**4**) we developed a synthesis of aryl triflate **5**, which could be coupled to commercially available aryl boronic acids using Suzuki conditions (Scheme 1). The synthesis of **5** began with selective bromination at C1 of 2-hydroxy-6-methoxynaphthalene (**6**) by treatment with *N*-bromosuccinimide. Protection of the phenol at C2 with benzyl bromide gave **7** in 86% yield. Copper-mediated Ullman diaryl ether coupling with catalytic quantities of copper triflate and 1.2 equivalents of **8**[12] gave **9** in low (30%) but reproducible yields. Hydrogenolysis of the benzyl group of **9**, followed by triflate formation, delivered the desired common intermediate **5** in good yield. Palladium-mediated cross-coupling of aryl triflate **5** with a wide variety of aryl boronic acids **10** provided a diverse array of 2-aryl-naphthalenes **11**. The methyl ether protecting group at C6 could be removed with boron tribromide followed by purification and treatment with HCl to give the final naphthalene analogs **4** suitable for biological assays.

We made further modifications to the C2 position of the naphthalene core by the preparation of saturated analogs of **4** (Scheme 2). However, as these boron containing coupling partners were not commercially available, independent syntheses were required to prepare coupling partners for triflate **5**. We targeted ketones **12** and **15** as starting points, envisioning that vinyl boronic esters **14** and **17** would serve as the cross-coupling components. Ketone **12** is commercially available, while **15** could be prepared in a single step by the cycloaddition of methylvinylsulfone and 2-(trimethylsiloxy)butadiene. Enol triflates **13** and **16** were prepared and transformed into **14** and **17** using standard conditions. The coupling of **14** and **17** with **5** was conducted using conditions as before with **5** and **10**. The coupling product of **14** and **5** was oxidized with oxone. The coupled products were deprotected using boron tribromide in the presence of isobutene as a scavenger to prevent substrate olefin bromination. The double bond of **19** was reduced using palladium black in an alcoholic solvent mixture. Following additional purification, the HCl salts of compounds **19** and **20** were prepared for evaluation.

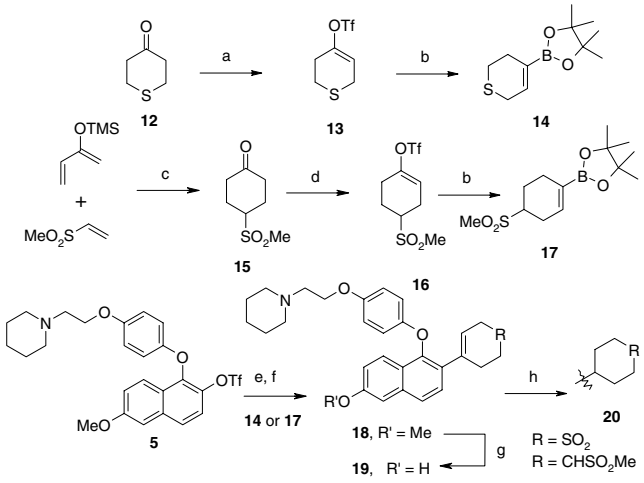
For the benzothiophene (**3**) series we developed a synthesis of 2-bromobenzothiophene **26**, which like aryl triflate **5** could also be coupled to commercially available aryl boronic acids using Suzuki conditions (Scheme 3). The synthesis of **26** began with 6-methoxybenzothiophene (**22**).[13] Attempts to di-brominate this material selectively at the required 2- and 3-positions produced the undesired 2,7-dibrominated product. Switching the methyl protecting group to the sterically bulky, electron-withdrawing pivalate group allowed selective bromination at the 2- and 3-positions to give compound **23**. The basic side chain at the 3-position was then installed using a conjugate addition–elimination protocol as previously described.[12] Since the pivalate protecting group proved labile under these conditions, it was exchanged for a benzyl group. Then the benzothiophene was oxidized to the corresponding sulfoxide using hydrogen peroxide and TFA (62% yield) to obtain **24**. Under basic conditions (*t*-BuOK in THF) the phenolic oxygen of **8** displaces the bromide at C3 to give coupled product **25**. After initial attempts to reduce the sulfoxide of **25** using BBr_3 or LAH failed to cleanly deliver the desired product in reasonable yields, we found that treatment with aqueous $TiCl_3$ in a mixture of methanol and chloroform gave the desired common intermediate 2-bromobenzothiophene **26** in good yield. Suzuki cross-coupling of aryl boronic acids **10** with **26** followed by debenzylation and HCl salt formation delivered the final benzothiophene analogs **3** for evaluation.

Very few compounds met our demanding criteria for ovarian safety. We began by evaluating their activities in a series of in vitro assays to determine their ability to bind the estrogen receptors and act as functional antagonists of E2 with little or no agonism in uterine tissue. We determined the binding affinity of our compounds to full-length, recombinant human ERα and ERβ using competitive radioligand binding assays. As shown in Table 1, all compounds in this study bind to ERα with good to excellent affinity



Scheme 1. Synthesis of naphthalene SERMs. Reagents: (a) NBS; (b) BnBr; (c) $Cu(OTf)_2$, **8**; (d) NH_4HCO_2, $Pd(OH)_2$; (e) Tf_2O; (f) $Pd(OAc)_2$, PCy_3, CsF, **10**; (g) BBr_3; (h) HCl.

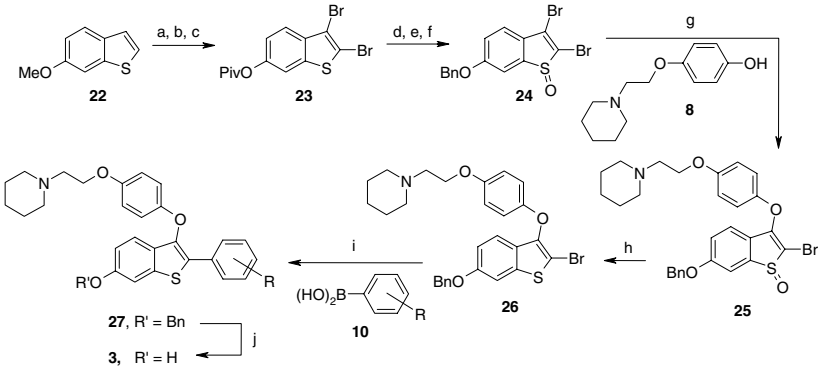
(K_i = 1.89–0.09 nM) and range from good to moderate to non-selective for ERα over ERβ (0.8- to 33-fold). The potential for estrogen stimulation and antagonism in uterine tissue was assessed in vitro by alkaline phosphatase quantitation in the Ishikawa human endometrial tumor cell line. All compounds in Table 1 exhibit maximum agonist stimulation in the absence of E2 of less than 30% at 1 μM in this assay. By comparison 4-hydroxytamoxifen, the active metabolite of tamoxifen, a known uterine agonist,[6] exhibits stimulation of 123% under the same conditions.[10] In the antagonist mode, these compounds block the stimulatory response of 1 nM E2 by at least 88% with IC_{50} values that range from 2.1–22 nM.



Scheme 2. Synthesis of saturated analogs. Reagents and condition: (a) LDA, THF, $PhNTf_2$; (b) bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf); (c) toluene, heat; then TFA, MeOH; (d) Tf_2O, CH_2Cl_2, 2,6-di-*tert*-butyl-4-methylpyridine; (e) $Pd(OAc)_2$, PCy_3; CsF, **14** or **17**; (f) R = S → SO_2 oxone, MeOH; (g) BBr_3, CH_2Cl_2, isobutene; (h) Pd black, THF/EtOH, H_2.

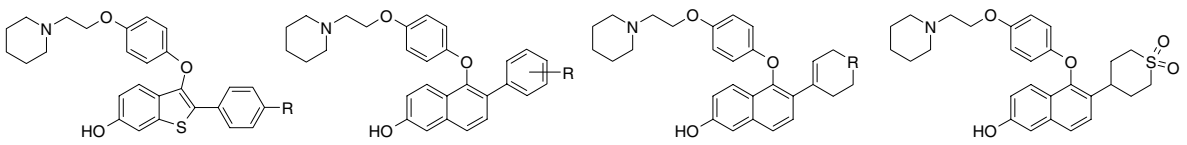
Having identified compounds with good to excellent estrogen antagonism in vitro, we next determined their ability to oppose E2 driven proliferative effects on uterine tissue in vivo. Uterine antagonism was measured in immature (3-week-old) female rats, which have low circulating E2 levels and therefore are highly sensitive to E2 stimulation of the uterus. Ethynyl estradiol (EE) produces a 3- to 4-fold increase in uterine wet weight when administered to these animals at 0.1 mg/kg. As shown in Table 1 all compounds in this study were found to be potent uterine antagonists, inhibiting E2 stimulation by at least 83% at 10 mg/kg with ED_{50} values less than 1 mg/kg.

Our primary goal was to find compounds with little or no impact on the HPO axis. We therefore designed compounds that would have restricted access to the hypo-



Scheme 3. Synthesis of benzothiophene SERMs. Reagents: (a) NaSEt; (b) PivCl; (c) Br_2; (d) KOH; (e) NaH, BnBr; (f) H_2O_2, TFA; (g) KO^{t}Bu; **8**; (h) $TiCl_3$, HCl; (i) $Pd(OAc)_2$, PCy_3, CsF, **10**; (j) NH_4HCO_2, $Pd(OH)_2$; HCl.

Table 1. Binding affinity (K_i), functional activity (Ishikawa antagonist IC_{50} and efficacy and agonist efficacy), in vivo rat uterine antagonist potency (ED_{50}), E2 ratio, Exposure: brain, plasma and log BB, calculated properties: C log *P* and polar surface area (PSA) for naphthalene and benzothiophene SERMs[a]



Compound	Structure	Binding		Antagonism		Agonism	In vivo		Exposure			Calculated	
	R	ERa K_i[b] (nM)	ERb K_i[b] (nM)	Ishi IC_{50}[c] (nM)	Ishi % inhib[d]	Ishi % eff[e]	ED_{50} (mpk)[f]	E2 ratio[g]	Brain[h]	Plasma[h]	log BB[i]	C log *P*[j]	PSA[k]
4a	4-SO_2NMe_2	0.40 ± 0.11	1.69 ± 0.46	2.8 ± 0.8	99 ± 3	27 ± 14	0.44 ± 0.19	1.83	46	108	-0.37	6.52	87.7
4b	4-SO_2Me	0.47 ± 0.21	1.32 ± 0.34	10.7 ± 6.8	88 ± 6	29 ± 4	0.071 ± 0.055	1.1	103	660	-0.81	5.69	84.5
4c	4-SO_2Et	1.22 ± 0.54	4.19 ± 1.51	6.1 ± 2.1	95 ± 2	19 ± 1	0.14 ± 0.02	1.75	43	357	-0.92	6.22	84.5
4d	4-SO_2*i*-Pr	0.73 ± 0.51	2.17 ± 0.89	4.9 ± 0.9	96 ± 2	11 ± 7	0.37 ± 0.05	1.06	NA	NA	NA	6.52	84.5
4e	3-CN	0.24 ± 0.08	0.35 ± 0.21	18.5 ± 6.1	94 ± 4	23 ± 10	0.37	5.62	529	360	0.17	6.76	65.7
4f	3-OH	0.21 ± 0.10	0.36 ± 0.24	2.1 ± 0.7	100 ± 4	26 ± 19	0.13 ± 0.03	1.28	57	211	-0.57	6.66	62.2
4g	4-OH	0.32 ± 0.13	0.48 ± 0.18	4.7 ± 1.0	96 ± 2	13 ± 5	0.3	2.94	47	277	-0.77	6.66	62.2
4h	4-$CONMe_2$	0.57 ± 0.38	1.16 ± 0.66	6.7 ± 1.4	95 ± 7	25 ± 18	0.19 ± 0.06	5.67	NA	NA	NA	5.79	62.2
4i	4-F	0.24 ± 0.09	0.28 ± 0.11	3.2 ± 1.2	93 ± 4	21 ± 9	0.015	4.6	2690	151	1.25	7.47	41.9
4j	3-F	0.18 ± 0.07	0.16 ± 0.05	4.8 ± 1.2	97 ± 5	15 ± 8	0.23 ± 0.08	7.44	730	137	0.73	7.47	41.9
4k	3,4-diF	0.20 ± 0.02	0.29 ± 0.05	3.9 ± 1.5	96 ± 5	13 ± 10	0.058	5.59	3490	418	0.92	7.54	41.9
4l		1.03 ± 0.21	2.10 ± 0.15	7.2 ± 2.2	98 ± 4	19 ± 12	0.25 ± 0.11	8.64	NA	NA	NA	4.74	84.5
4m		1.89 ± 0.17	4.11 ± 0.36	15.7 ± 2.7	93 ± 3	27 ± 11	0.34 ± 0.16	2.81	NA	NA	NA	4.44	84.5
4n[l]		1.09	2.69	8.0 ± 4.2	99 ± 2	24 ± 7	0.26 ± 0.08	1.94	NA	NA	NA	5.49	84.5
3a	*i*-Pr	0.091 ± 0.016	0.63 ± 0.04	16.2 ± 5.0	95 ± 3	29 ± 8	0.16 ± 0.07	4.5	NA	NA	NA	8.98	41.9
3b	SO_2Me	0.63 ± 0.31	13.6 ± 5.4	22.2 ± 6.3	97 ± 4	24 ± 21	0.62 ± 0.12	2.19	NA	NA	NA	5.95	84.5
3c	SO_2Et	0.48 ± 0.31	15.7 ± 5.1	14.5 ± 4.7	95 ± 5	16 ± 13	0.56 ± 0.15	2.85	NA	NA	NA	6.48	84.5

[a] Experimental values represent the average with the standard deviation ± SD for multiple determinations (at least $n = 2$) between the assay values. Values without SD notation were run once ($n = 1$). NA means data not available.

[b] K_i values determined by radioligand binding assay using ^{3}H-estradiol.

[c] Ishikawa antagonism IC_{50} values are the compound concentration needed to block 50% of 1 nM E2 stimulation as determined by alkaline phosphatase quantitation.

[d] Ishikawa antagonism is the efficacy (%) of blocking 1 nM E2 stimulation.

[e] Ishikawa agonism is the % increase in alkaline phosphatase compared to control.

[f] Female Sprague–Dawley rats, 6 per group and 19–21 days of age, were orally treated with ethynyl estradiol (0.1 mg/kg) and 10, 1.0, 0.1 or 0.01 mg/kg of SERM for 3 days.

[g] The ratio of serum E2 levels (the ratio of treated to vehicle control) after oral dosing with compound for 10 days at a dose of 30 times that of the immature rat ED_{50}.

[h] Brain (ng/g) and plasma (ng/mL) exposure at the 6 h time point following a 10 mg/kg oral dose.

[i] $\log BB = \log(C_{brain}/C_{blood})$.

[j] The calculated logarithm of the *n*-octanol/water partition.

[k] Polar surface area (Å^2).

[l] The more potent enantiomer was tested but the configuration was not assigned.

thalamus in the brain. A common measure of blood–brain barrier (BBB) penetration is log BB, the log of the ratio of plasma to brain concentration at a single time point. Since it is time consuming and resource-intensive to measure log BB, several methods to predict blood–brain barrier (BBB) penetration have been proposed.[14] These methods are based on molecular descriptors that can be readily calculated, with the most important being C log *P*, polar surface area (PSA), and the number of rotatable bonds.[15] Since our efforts were limited to the 2-aryl positions of the benzothiophene (**3**) and naphthalene (**4**) ring systems, we focused on the addition of polar functional groups that would be tolerated by the receptor at this location, increase PSA, and therefore lower C log *P*. As can be seen in Table 1, on the naphthalene scaffold **4**, the addition of sulfone functional groups (**4b**, **4c**, and **4d**) on the 2-aryl ring produced compounds with higher PSAs (84.5 Å^2) than the corresponding fluoro substituents (compounds **4i**, **4j**, **4k**; PSA = 42 Å^2). As expected, higher PSA translated into lower C log *P* for the sulfone substituted analogs (C log *P* = 5.69–6.52) compared to the fluoro analogs (C log *P* = 7.47–7.54). These data correlate nicely with measured log BB. The sulfone substituted analogs had log BB < 0, while the fluoro analogs had log BB > 0, indicating that the sulfone analogs might have less propensity to antagonize the HPO axis compared to the fluoro analogs.

Inhibition of the HPO axis results in overproduction of LH and FSH which in turn stimulate the ovaries to produce E2, therefore plasma E2 levels are a sensitive biomarker for ovary stimulation. In order to screen for ovarian stimulation, mature intact female rats were given compound once daily for 10 days with an oral dose 30 times the ED_{50} in the immature rat assay. As can be seen in Table 1, for the extreme cases of sulfone and fluoro substitution, plasma E2 levels correlate well with log BB. For the sulfone analogs (**4b**, **4c**, **4d**), the ratio of serum E2 levels compared to vehicle control was between 1.06 and 1.75, indicating minimal ovarian stimulation. By contrast, the fluoro analogs (**4i**, **4j**, **4k**) produced plasma levels of E2 that were 4.6–7.4 times that of vehicle control. The calculated molecular properties of sulfonamide **4a** were similar to those of the sulfone analogs. It also did not raise E2 levels although its overall plasma exposure was lower as well indicating it may have poor overall absorption or higher metabolism.

The cyano and amide substituted compounds (**4e** and **4h**) possess PSAs (66 and 62 Å^2) that are intermediate between the sulfone and fluoro analogs. The corresponding C log *P*s (6.8–5.8) are closer to the sulfones. For these intermediate cases, we observed some compounds that stimulated E2 with the same propensity as the fluoro analogs and others that behaved more like the sulfones. The amide analog **4h** for example has a C log *P* similar to sulfone **4b** but stimulated E2 levels to the same extent as difluoro **4k**. The cyano compound **4e**, with nearly equal levels of brain and plasma exposure, produced an E2 plasma concentration that was 5.62 times vehicle control.

The phenol isomers **4f** and **4g** are particularly interesting. Since the calculated molecular descriptor PSA does not take into account differences between isomers, both of these possess the same value for PSA. The C log *P*s for the *meta* and *para* isomers are also identical and the corresponding brain to plasma ratios are nearly the same as well. For these two, the *meta* isomer **4f** behaved more like the sulfones, while the *para* isomer **4g** was stimulatory. The saturated analogs **4l**, **4m**, and **4n** all have calculated PSA values similar to the aryl sulfones (**4b**, **4c**, **4d**) and even have C log *P* values that are lower. Unfortunately, these favorable calculated properties did not translate into superior performance in the E2 stimulation assay. We observed a dramatic difference between the dihydrothiopyran **4l**, one of the most stimulatory compounds (8.6-fold), and its fully saturated analog **4m**, which caused only 2.8-fold stimulation. The 4-(methylsulfonyl)-cyclohexene analog **4n** performed almost as well as the ethyl sulfone **4c**. The 2-aryl analogs of the benzothiophene scaffold showed similar trends compared to the naphthalenes. The lipophilic isopropyl compound **3a** has a low PSA and correspondingly high C log *P*. Not surprisingly, it produced high levels of E2 compared to vehicle control. The sulfone analogs **3b**

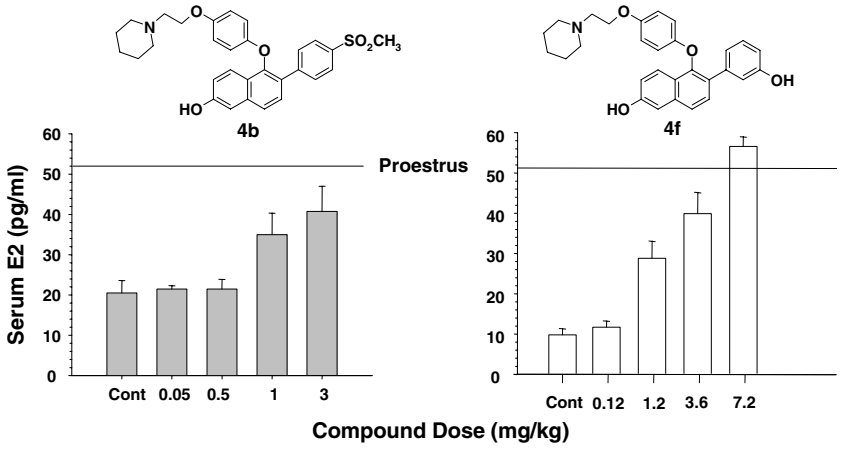


Figure 1. Serum E2 levels in rats treated with **4b** or **4f** for 35 days: error bars = SEM.

and **3c** possess PSA and C log *P* values very similar to the corresponding naphthalene analogs **4b** and **4c**. Although these did not stimulate E2 to the same extent as isopropyl analog **3b**, unfortunately, their ED_{50}s in the immature rat uterine assay were 4–8 times that of the naphthalenes. As a result, they were dosed higher in the 10-day E2 assay, and although the trends are similar, the best benzothiophenes produced E2 levels that were twice vehicle control. The lower activity of the benzothiophenes in the immature rat uterine assay may be due to overall lower absorption and/or higher metabolism than the corresponding naphthalenes (data not available).

The effects of lead compounds on the uterus and ovaries were studied in 6-month-old ovary-intact female rats treated with oral doses of compound at 1, 10, 30, and 60 times the ED_{50} in the immature rat assay (Fig. 1). Dose-dependent decreases in uterine wet weight (data not shown) were observed with the total area of uterine wall reduced in both the endometrium and myometrium, confirming that the compounds are potent antagonists in both compartments of the uterus in the presence of E2 over several estrous cycles. The extent of ovarian stimulation was determined by measuring serum E2 levels. As shown in Figure 1, treatment with compounds **4b** and **4f** resulted in serum E2 levels that are similar to vehicle-treated animals. Even at the highest doses, the E2 levels are within the normal proestrus range for Sprague–Dawley rats (52 ng/mL).

In conclusion, SAR studies on the 2-aryl positions of the benzothiophene (**3**) and the naphthalene (**4**) ring systems produced novel SERMs that are potent antagonist in uterine tissue but cause limited ovarian stimulation, as judged by increased plasma E2 levels in rats. We identified a loose correlation between calculated properties (C log *P* and PSA) and measured properties (log BB and plasma E2). Substituents that confer high PSA and low C log *P*, such as aryl sulfones, produced compounds that caused slight or no increases in serum E2 levels, while the corresponding fluoro analogs with low PSA and high C log *P* increased plasma E2 significantly. For intermediate cases such as phenols or amides, the relationship was not as predictive. We cannot rule out the possibility that stimulatory compounds such as cyano **4e** and amide **4f** have a direct effect on the ovaries. Although saturated sulfone analogs possess favorable calculated properties, they did not behave as well as the aryl sulfones. These results demonstrate it is possible to obtain a wide therapeutic window between desired antagonistic effects on the uterus and undesirable effects on the ovaries in a rodent animal model. As such, compounds such as sulfone **4b** and *meta*-phenol **4f** may have therapeutic potential for the treatment of leiomyomas in premenopausal women.

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