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Letter

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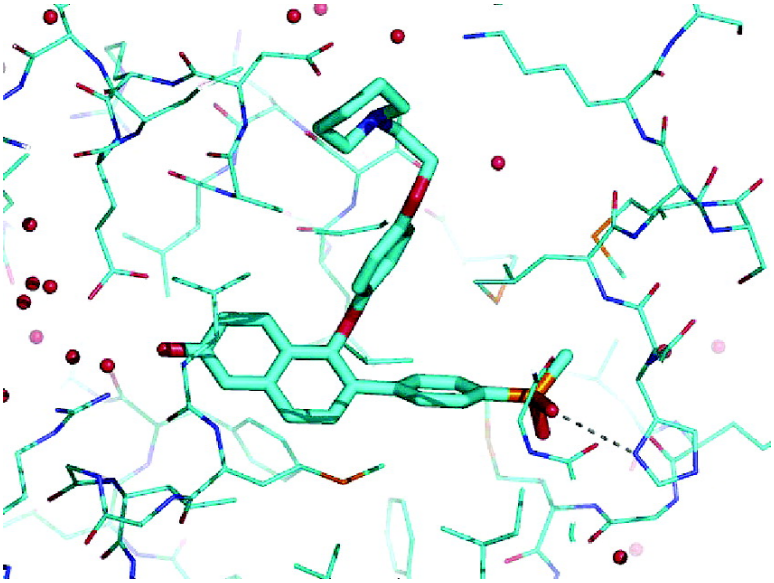

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# A Selective Estrogen Receptor Modulator Designed for the Treatment of Uterine Leiomyoma with Unique Tissue Specificity for Uterus and Ovaries in Rats

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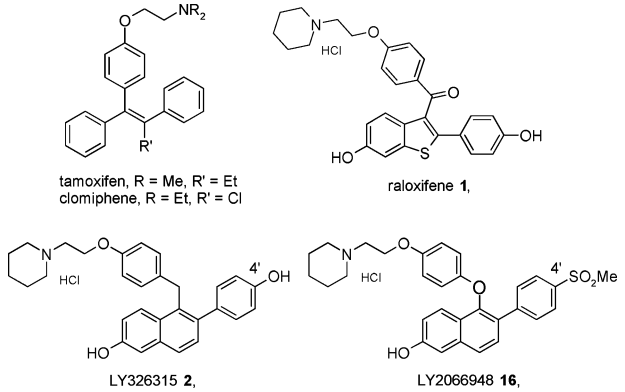
**Abstract:** The design of a novel selective estrogen receptor modulator (SERM) for the potential treatment of uterine leiomyoma is described. **16** (LY2066948−HCl) binds with high affinity to estrogen receptors α and β (ERα and ERβ, respectively) and is a potent uterine antagonist with minimal effects on the ovaries as determined by serum biomarkers and histologic evaluation.

Uterine leiomyomas, or fibroids, are the most common type of solid tumor in adult women, clinically apparent in at least 25% of those of reproductive age.[1−3] In those women that experience symptoms, abnormal menstrual bleeding, pelvic pain, and infertility are the most common. Diagnosis of uterine fibroids is the leading cause of hysterectomies in the United States, accounting for over 200,000 of these procedures each year. Other invasive surgical interventions include myomectomy and uterine artery embolization. Leiomyomas are estrogen responsive tumors that can be treated with gonadotropin-releasing hormone (GnRH) agonists. These injectable peptides inhibit estrogen synthesis and result in the reduction of uterine volume and fibroid size.[4] However, GnRH therapy can result in hot flushes and osteoporosis, a side effect that restricts use for chronic treatment. Because leiomyomas depend on estrogen for growth, antagonism of this steroid hormone receptor is a viable therapeutic approach. Along these lines, selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene (**1**) have been clinically evaluated for the treatment of leiomyoma. Tamoxifen lacks sufficient efficacy to reduce tumor size in premenopausal women, in part because of the uterine agonist characteristics exhibited by this SERM.[5,6] In addition, treatment with tamoxifen has resulted in ovarian cysts, an undesired side effect that severely limits the use of this compound for the treatment of fibroids in ovulatory women. These stimulatory effects on the ovaries have been attributed to the inhibitory properties that tamoxifen has on the hypothalamic−pituitary−ovarian (HPO) axis; i.e., this SERM acts as an estrogen antagonist at the hypothalamus, resulting in increased gonadotropins levels (luteinizing hormone, follicle stimulating hormone) and, ultimately, hyperstimulation of the ovaries. In fact, inhibition of the HPO axis by SERMs such as clomiphene has been clinically exploited to induce ovulation in women.[7] Raloxifene, a more complete uterine antagonist than tamoxifen or clomiphene, significantly reduces leiomyoma size in postmenopausal women[8] yet is less efficacious at reducing tumor volume in premenopausal women.[9] This result has been attributed to the poor pharmacokinetic properties of this compound in which extensive conjugative metabolism of the phenol(s) limits the circulating levels of the parent drug. In addition, clinical outcomes in premenopausal women treated with raloxifene have suggested that this compound, like tamoxifen and clomiphene, can affect the ovaries via the HPO axis.[10] These data, taken collectively, indicate that current SERMs lack the efficacy, pharmacokinetic, and ovarian safety properties needed to treat leiomyoma in ovulatory women. Therefore, we sought to improve the potency and efficacy of this class of molecules while simultaneously addressing the issue of ovarian safety. We hypothesized that limiting access of a SERM to the estrogen receptors in the hypothalamus would diminish their inhibitory effects on the HPO axis, thereby minimizing unwanted stimulation of the ovaries. Here, we describe the discovery of such a SERM, **16** (LY2066948−HCl, Chart 1), a new chemical entity currently under clinical evaluation for the potential treatment of uterine leiomyoma in premenopausal women.

**Chart 1**




Initially we investigated the naphthalene SERM **2** (LY326315)[11] because this compound has been shown to reduce the incidence of spontaneous leiomyomas in the Eker rat model.[12] Unfortunately, when **2** was given to normal female rats for 35 days at doses of 1 mpk and greater, histologic effects on the ovaries (decreased corpora lutea and follicular prominence) were seen, as well as a greater than 3-fold increase in serum estradiol levels, a sensitive biomarker for ovarian stimulation. Moreover, the uterine antagonism of **2** in rats is similar to that of **1** (0.36 vs 0.55 mg/kg, respectively; see Table 1), a result that we felt would be less than optimal for the treatment of uterine tumors based on the clinical outcomes observed with **1** in premenopausal women.

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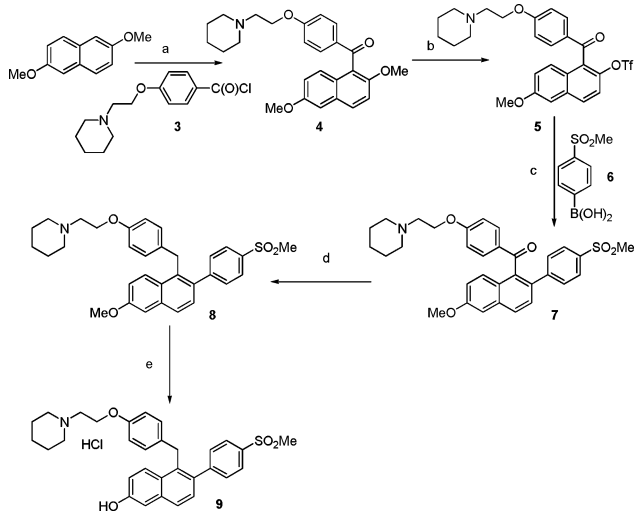
**Table 1.** Binding Affinity ($K_i$), Functional Activity ($IC_{50}$), and in Vivo Uterine Antagonist Potency ($ED_{50}$) for SERMs[a]

| | ERα $K_i$ (nM) | ERβ $K_i$ (nM) | MCF-7 $IC_{50}$ (nM)[b] | Ishikawa $IC_{50}$ (nM)[c] | rat $ED_{50}$ (mg/kg)[d] |
|---|---|---|---|---|---|
| **1** | 0.37 ± 0.09 ($n$ = 3) | 2.74 ± 1.37 ($n$ = 3) | 0.37 ± 0.03 ($n$ = 2) | 4.32 ± 1.69 ($n$ = 8) | 0.55 ± 0.15 ($n$ = 15) |
| **2** | 0.2 ± 0.14 ($n$ = 8) | 0.70 ± 0.34 ($n$ = 8) | 0.2 ± 0.02 ($n$ = 2) | 1.14 ± 0.56 ($n$ = 2) | 0.36 ± 0.16 ($n$ = 7) |
| **9** | 1.15 ± 0.44 ($n$ = 2) | 24.1 ± 7.67 ($n$ = 2) | 3.4 ($n$ = 1) | 4.78 ± 3.22 ($n$ = 3) | 0.40 ± 0.09 ($n$ = 2) |
| **16** | 0.51 ± 0.21 ($n$ = 6) | 1.36 ± 0.34 ($n$ = 6) | 0.86 ± 0.27 ($n$ = 3) | 10.7 ± 6.82 ($n$ = 4) | 0.07 ± 0.02 ($n$ = 3) |
| **17** | 0.25 ± 0.09 ($n$ = 8) | 0.30 ± 0.11 ($n$ = 8) | 0.34 ± 0.14 ($n$ = 3) | 3.18 ± 1.18 ($n$ = 9) | 0.02 ($n$ = 1) |

[a] Experimental values represent the average for multiple determinations ($n$) along with the standard deviation (SD) between the assay values. Values without SD notation were run once. Efficacy values were >90% in all cases. [b] MCF-7 values are half-maximal inhibition concentrations that block growth stimulation by 10 pM E2. [c] Ishikawa $IC_{50}$ values are the compound concentration needed to block 50% of 1 nM E2 stimulation as determined by alkaline phosphatase quantitation. [d] Female Sprague-Dawley rats, six 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.

**Scheme 1.** Synthesis of **9**[a]

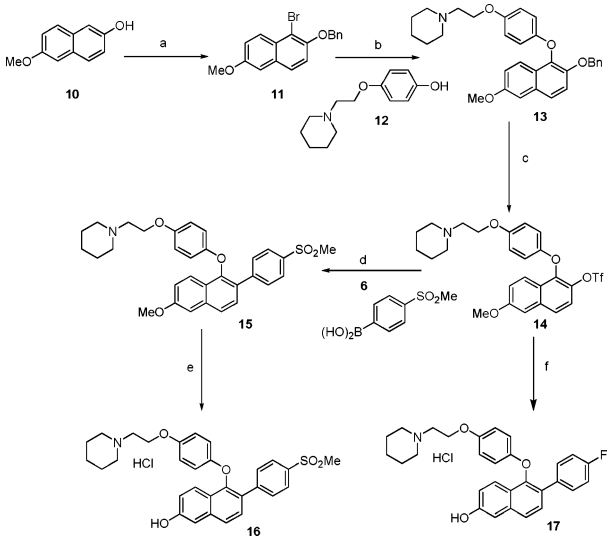



[a] Reagents: (a) $AlCl_3$, **3**; (b) (1) $BCl_3$; (2) $CF_3SO_2Cl$; (c) $Pd(OAc)_2$, $PPh_3$, **6**; (d) (1) LAH; (2) $Et_3SiH$, TFA; (e) (1) pyridine·HCl; (2) HCl.

To identify a SERM with the desired profile on the uterus and ovaries, we initiated structure−activity studies that included the para (4′) position of the 2-aryl ring in **2**.[13] A primary strategy was to replace the 4′-phenol with a single group that would serve two purposes: render the molecule less susceptible to metabolic conjugation and limit brain penetration. As part of this broad SAR effort, we identified analogues such as **9** in which the 4′-phenol has been replaced with a methyl sulfone moiety. The sulfone group, unlike a phenol, cannot undergo conjugative metabolism to the glucuronide and/or sulfate ester, a characteristic that we felt could enhance the pharmacokinetic properties ultimately resulting in more potent in vivo uterine antagonism. Moreover, we felt the relatively polar nature of the sulfone group might limit the brain penetration of this molecule.[14]

The synthesis of **9** is shown in Scheme 1. Friedel−Crafts acylation of 2,6-dimethoxynaphthalene with acid chloride **3**[13] provided intermediate **4**. Selective cleavage of the methoxy group proximal to the carbonyl with boron trichloride followed by conversion to the triflate gave **5**. Treatment of **5** with 4-methanesulfonylphenylboronic acid **6** under Suzuki cross-coupling conditions gave **7** in quantitative yield. Reduction of the ketone followed by treatment of the resulting alcohol with triethylsilane/trifluoroacetic acid gave **8**. Deprotection of the aryl methyl ether using pyridine hydrochloric acid followed by salt formation delivered **9**.

**Scheme 2.** Synthesis of **16** and **17**[a]




[a] Reagents: (a) (1) NBS; (2) BnBr; (b) Cu $(OTf)_2$, **12**; (c) (1) $Pd(OH)_2$; (2) $Tf_2O$; (d) $Pd(OAc)_2$, $PCy_3$, **6**; (e) (1) HCl; (2) $BBr_3$; (3) HCl; (f) (1) $Pd(OAc)_2$, PCy3, 4-fluorophenylboronic acid; (2) $BBr_3$; (3) HCl.

In addition to modifying the 4′-position, we also replaced the diarylmethylene group with an ether linker. This was accomplished as shown in Scheme 2. Bromination of 2-hydroxy-6-methoxynaphthalene (**10**) by treatment with *N*-bromosuccinimide led to selective bromination of the 1-position in high yield. Protection of the phenol with benzyl bromide gave **11** in 86% yield. Copper-mediated Ullman diaryl ether coupling with catalytic quantities of copper triflate and 1.2 equiv of **12**[15] gave **13** in low (30%) but reproducible yields. Hydrogenolysis of the benzyl group of **13** followed by triflate formation delivered **14** in good yield. Palladium-catalyzed Suzuki cross-coupling of this triflate with **6** gave **15**. Removal of the aryl methyl ether with boron tribromide gave the free base, which was treated with HCl to give compound **16**.

Compounds **1**, **2**, **9**, and **16** were evaluated in a series of estrogen-dependent in vitro and in vivo assays that measured their affinity to the estrogen receptors and their ability to act as functional agonists or antagonists of estrogen. As shown in Table 1, sulfone analogue **9** binds with good affinity to estrogen receptor α (ERα) ($K_i$ = 1.15 nM), is moderately selective versus ERβ ($K_i$ = 24.1 nM), and inhibits estrogen-induced proliferation of breast (MCF-7, $IC_{50}$ = 3.4 nM) and uterine cells (Ishikawa, $IC_{50}$ = 4.8 nM). In addition, **9** is not an agonist in uterine cells in the absence of exogenous 17β-estradiol (E2, data not shown). In immature rats treated with ethynyl estradiol, **9** blocks the uterine weight gain in a dose-dependent manner with an $ED_{50}$ of 0.40 mg/kg after oral administration. Subsequent structure−activity studies led to replacement of the diarylmethylene linker in **9** with an oxygen.[15] This diaryl ether

analogue (**16**) binds with higher affinity than **9** to both estrogen receptors and is a potent inhibitor of MCF-7 cell proliferation ($IC_{50} = 0.86$ nM). The effects on uterine tissue were assessed at the in vitro level in Ishikawa cells in the presence (antagonism) and absence (agonism) of E2. In the antagonist mode, **16** blocks the effects of 1 nM E2 by >90% with an $IC_{50}$ of 10.7 nM (Table 1). The agonist activity of **16** was similar to that of **1** (29.0 ± 3.7% over control versus 28.6 ± 8.50% for **1**) and significantly less than that of 4-hydroxytamoxifen (123 ± 24%), a known uterine agonist. When tested in rodents, **16** proved to be a highly potent, orally active uterine antagonist with an $ED_{50}$ of 0.07 mg/kg at blocking estrogen-induced uterine hypertrophy in immature, ovary-intact rats. Significantly, this analogue is >5-fold more potent than **1** or **2** as a uterine antagonist. In addition, **16** does not have agonist properties in the uterus when administered to ovariectomized (OVX) rats for 4 days at all doses examined (0.01−10.0 mg/kg, data not shown) based on eosinophil peroxidase activity, a sensitive marker for determining the uterine agonist properties of SERMs.[16] Long-term treatment (42 days) of **16** to OVX rats does not cause uterine weight gain.[17] Taken together, the uterine data indicate that **16** is a potent estrogen antagonist without significant agonist properties in the uterus.

Pharmacokinetic analysis of **16** in rats following a single intravenous dose at 1 mg/kg or a single oral dose at 10 mpk indicated an oral bioavailability of 27%. The brain-to-plasma ratio of **16** was determined after a single oral dose of 10 mg/kg to female rats ($n = 3$). In this study we found that after 6 h, the concentration of **16** is >6-fold higher in rat plasma, 660 ± 82.8 ng/mL, than whole brain, 102 ± 28.0 ng/g. Overall, we felt that the potent uterine antagonist effects of **16** coupled with the favorable brain/plasma ratio provided an appropriate window for investigating whether this compound would antagonize the uterus at concentrations that minimally affect the ovaries

The effects of **16** on the uterus and ovaries were studied in 6-month-old ovary-intact female rats.[17] Oral administration of **16** for 35 days at doses of 0.05, 0.5, 1.0, and 3.0 mg/kg results in a dose-dependent decrease in uterine weight with a maximal inhibitory dose of 1 mg/kg (51% reduction in uterine wet weight) and an $ED_{50}$ of 0.15 mg/kg. Morphometric measurements at the 0.5 mg/kg dose group compared to the control group show that the total area of the uterine wall was significantly reduced by 53% with nearly equal contributions in reduction of endometrial (54%) and myometrial (51%) compartments. These data confirm substantial antagonist activity in both compartments of the uterus in the presence of circulating levels of E2 over several estrous cycles in the rat. The effects on the ovaries in this study were determined by measuring serum estradiol levels and histologic evaluation of ovarian cross sections. As shown in Figure 1, treatment with **16** results in serum E2 levels that are similar to vehicle-treated animals at doses that exceed the inhibitory effects on the uterus by greater than 60-fold. Statistically significant increases in serum E2 levels are observed at the high dose but are within the normal proestrus range for Sprague-Dawley rats. Histological evaluation of the ovaries of the rats treated with **16** indicates minimal ovarian stimulation relative to untreated controls, i.e., ovarian weights are decreased at doses >0.5 mg/kg, there are no ovarian cysts, and granulosa cell hyperplasia is observed in only a few animals and generally at a mild level. These data collectively indicate that **16** is a potent uterine antagonist with minimal ovarian stimulation in rats.

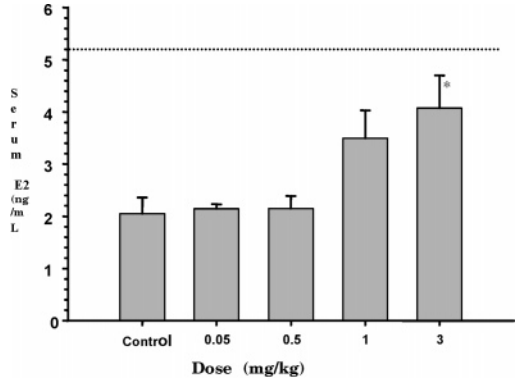



**Figure 1.** Serum E2 levels in rats treated with **16** for 35 days: error bars = SEM; (*) = $p < 0.05$ vs control, Dunett's *t*-test.

The origin for the uterine−ovarian selectivity is not clear. One leading possibility is that the relatively low brain-to-plasma ratio (0.16) observed with **16** limits this compound's ability to act as an antagonist of the HPO axis at doses that also inhibit uterine growth. The higher brain-to-plasma ratio (0.9) observed for **2**, which is ovarian stimulatory, supports this hypothesis. To more fully test this hypothesis, we prepared (Scheme 2) and evaluated fluorine analogue **17**. This compound has a significantly lower polar surface area value (42 Å) than **16** (84 Å) and a correspondingly higher brain-to-plasma ratio, i.e., 18 versus 0.16, respectively. In addition, the overall concentration in rat brain is >25-fold higher for **17** than **16**, 2692 ± 211 ng/g compared to 102 ± 28.0 ng/g, respectively. As shown in Table 1, these SERMs have similar binding, functional, and in vivo uterine antagonist potencies. However, oral administration of **17** for 10 days to ovary-intact rats results in elevated estradiol levels that are > 4-fold that of **16** (4.6 over control compared to 1.1, respectively), indicating that **17** is causing stimulation of the ovaries. Elevations in estradiol levels have been observed for tamoxifen (2.2-fold) and raloxifene (4.5-fold) in this model.[17] In longer-term studies (35 days), daily oral administration of **17** (0.45 mg/kg) results in clear ovarian stimulation as indicated by a 43% increase in ovarian weight and nearly 3-fold increase in granulosa cell hyperplasia. While we cannot rule out the possibility that **17** has direct stimulatory effects on the ovaries, our data are consistent with the hypothesis that decreased brain concentrations of **16** at the hypothalamic loci responsible for gonadotropin production may be responsible for limiting HPO stimulation in **16** relative to **17**. However, because at least part of the hypothalamus is outside the blood−brain barrier, other factors that can lead to neutral HPO effects cannot be eliminated.

Another possibility for the selectivity observed with **16** is that the interaction of this ligand with the estrogen receptors may induce a unique receptor−ligand confirmation that results in tissue-specific pharmacology. To

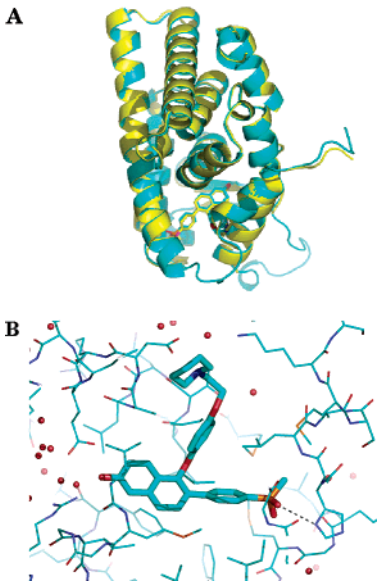



**Figure 2.** (A) Superimposed crystal structures of **16** (yellow) and **17** (teal) bound to the ligand binding domain of ERα. (B) Orientation of **16** in ERα.

investigate this possibility, we independently crystallized **16** and **17** in the ligand binding domain of ERα. As shown in the overlay for these two crystal structures (Figure 2A), the overall protein−ligand architectures of the ligand-bound monomers are very similar, including the position of helix 12, indicating that at the crystallographic level **16** does not induce a conformation that is substantially different from that of **17**. One particular note of interest (Figure 2B) is that the methyl sulfone in **16** interacts with the His 524 side chain via a H-bond (3.3 Å) and thus represents a novel phenol mimic among ER ligands.

In summary, we have identified a novel ovarian selective SERM (**16**) that demonstrates a wide therapeutic window between the desired antagonistic effects on the uterus and the undesirable side effects on the ovaries. In addition, bone studies demonstrate that **16** prevents ovariectomy-induced bone loss in OVX rats and does not cause bone loss in ovary-intact rats, data which support estrogen agonist effects on skeletal tissue.[17] As such, this compound has therapeutic potential for the treatment of leiomyomas in premenopausal women and is currently in clinical development.

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**Supporting Information Available:** Experimental procedures for **9**, **16**, and **17**, elemental analysis results, protocols for all in vitro and in vivo assays, and crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Stewart, E. A. Uterine fibroids. *Lancet* **2001**, *357*, 293−298.
(2) Cramer, S. F.; Patel, A. The frequency of uterine leiomyomas. *Am. J. Clin. Pathol*. **1990**, 94, 435−438.
(3) Buttram, V. C., Jr.; Reuter, R. C. Uterine leiomyomata: etiology, symptomatology, and management. *Fertil. Steril.* **1981**, *36*, 433−445.
(4) Lethaby, A.; Vollenhoven, B.; Sowter, M. Efficacy of pre-operative gonadotrophin hormone releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy: a systematic review. *Br. J. Obstet. Gynecol*. **2002**, *109*, 1097−1108.
(5) Lumsden, M. A.; West, C. P.; Baird, D. T. Tamoxifen prolongs luteal phase in premenopausal women but has no effect on the size of uterine fibroids. *Clin. Endocrinol*. **1989**, *31*, 335−343.
(6) Sadan, O.; Ginath, S.; Sofer, D.; Rotmensch, S.; Debby, A.; Glezerman, M.; Zakut, H. The role of tamoxifen in the treatment of symptomatic uterine leiomyomata. A pilot study. *Eur. J. Obstet. Gynecol. Reprod. Biol*. **2001**, *96*, 183−186.
(7) Huppert, L. C. Induction of ovulation with clomiphene citrate. *Fertil. Steril.* **1979**, *31*, 1−8.
(8) Palomba, S.; Sammartino, A.; Di Carlo, C.; Affinito, P.; Zullo, F.; Nappi, C. Effects of raloxifene treatment on uterine leiomyomas in postmenopausal women. *Fertil. Steril*. **2001**, *76*, 38−43.
(9) Palomba, S.; Orio, F.; Morelli, M.; Russo, T.; Pellicano, M.; Zupi, E.; Lombardi, G.; Nappi, C.; Panici, P. L. B.; Zullo, F. Raloxifene administration in premenopausal women with uterine leiomyomas: a pilot study. *J. Clin. Endocrinol. Metab*. **2002**, *87*, 3603−3608.
(10) Plouffe, L.; Siddhanti, S. The effect of selective estrogen receptor modulators on parameters of the hypothalamic−pituitary−gonadal axis. *Ann. N. Y. Acad. Sci.* **2001**, *949*, 251−158.
(11) Dodge, J. A.; Ellis, K. K.; Hay, L. A.; Koenig, T. M.; Lugar, C.; Strouse, E. E.; Mitchell, D. Practical convergent synthesis of SERM 2. *ACS Symp. Ser.* **2002**, *817*, 133−140.
(12) Walker, C. L.; Burroughs, K.; Davis, B.; Sowell, K.; Everitt, J.; Fuchs-Young, R. Preclinical evidence for therapeutic efficacy of selective estrogen receptor modulators for uterine leiomyoma. *J. Soc. Gynecol. Invest*. **2000**, *7*, 249−256.
(13) Grese, T. A.; Cho, S.; Finley, D.; Godfrey, A. G.; Jones, C. D.; Lugar, C. W.; Martin, M. J.; Matsumoto, K.; Pennington, L. D.; Winter, M. W.; Adrian, M. D.; Cole, H. W.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Short, L. L.; Glasebrook, A. L.; Bryant, H. U. Structure−activity relationships of selective estrogen receptor modulators: modifications to the 2-arylbenzothiophene core of raloxifene. *J. Med. Chem.* **1997**, *40*, 146−167.
(14) Kelder, J.; Grootenhuis, P. D. J.; Bayada, D. M.; Delbressine, L. P. C.; Ploemen, J.-P. Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs. *Pharm. Res.* **1999**, *16*, 1514−1519.
(15) Palkowitz, A. D.; Glasebrook, A. L.; Thrasher, K. J.; Hauser, K. L.; Short, L. L.; Phillips, D. L.; Muehl, B. S.; Sato, M.; Shetler, P. K.; Cullinan, G. J.; Pell, T. R.; Bryant, H. U. Discovery and synthesis of [6-hydroxy-3[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[*b*]thiophene: a novel, highly potent, selective estrogen receptor modulator. *J. Med. Chem*. **1997**, *40*, 1407−1416.
(16) Lyttle, C. R.; DeSombre, E. R. Uterine peroxidase as a marker for estrogen action. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 3162−3166.
(17) Geiser, A. G.; Hummel, C. W.; Draper, M. W.; Henck, J. W. Cohen, I. R.; Rudmann, D. G.; Donnelly, K. B.; Adrian, M. D.; Shepherd, T. A.; Wallace, O. B.; McCann, D. J.; Oldham, S. W.; Bryant, H. U.; Sato, M.; Dodge, J. A. A new selective estrogen receptor modulator (SERM) with potent uterine antagonist activity, agonist activity in bone, and minimal ovarian stimulation *Endocrinology* **2005**, 10.1210/en2005-0024. See http://endo.endojournals.org for manuscript in Rapid Electronic Publication format.

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