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Novel 3-Aryl Indoles as Progesterone Receptor Antagonists for Uterine Fibroids

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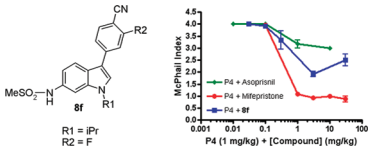
ABSTRACT We report the synthesis and characterization of novel 3-aryl indoles as potent and efficacious progesterone receptor (PR) antagonists with potential for the treatment of uterine fibroids. These compounds demonstrated excellent selectivity over other steroid nuclear hormone receptors such as the mineralocorticoid receptor (MR). They were prepared from 2-bromo-6-nitro indole in four to six steps using a Suzuki cross-coupling as the key step. Compound **8f** was orally active in the complement 3 model of progesterone antagonism in the rat uterus and demonstrated partial antagonism in the McPhail model of progesterone activity.

KEYWORDS Progesterone, progesterone receptor, NR3C3, progesterone receptor antagonist, uterine fibroids, Suzuki cross-coupling reaction



Uterine fibroids (leiomyomas) are benign tumors that develop from smooth muscle cells and fibrous connective tissues of the uterus.[1−3] Although most are asymptomatic, in some women fibroids cause abnormal menstrual bleeding, pelvic pain, and reproductive dysfunction.[4] The incidence of fibroids increases with age during the reproductive years and peaks between 35 and 40 years old.[5] For those women whose quality of life is negatively impacted, hysterectomy is often necessary. As a result, fibroids are the primary indication for over 200,000 hysterectomies in the U.S. per year.[6,7]

An evaluation of hysterectomy cases revealed a similar incidence (77%) in both post- and premenopausal women.[8] The fertility of premenopausal women can be decreased by the presence of submucosal myomas, which are fibroids partially in the cavity and partially in the wall of the uterus.[9] Since hysterectomy is unacceptable for a woman who desires a future pregnancy, surgical procedures have been developed that preserve the uterus, such as myomectomy (fibroid removal with uterine retention), laser ablation, or embolization. Removal of fibroid growths can restore fertility.[9] However, these treatments are invasive, expensive, and associated with a high rate of fibroid recurrence.[10] Therefore, there is an unmet medical need for a noninvasive, pharmaceutical treatment of uterine fibroids in both post- and premenopausal women.

Currently the only pharmaceutical treatment for uterine fibroids involves the use of gonadotropin-releasing hormone (GnRH) agonists such as Lupron. These peptide hormones act on the pituitary gland, resulting in a down-regulation of the hypothalamic-pituitary-ovarian (HPO) axis, which decreases the release of gonadotropins (FSH and LH) and subsequently reduces the production of the ovarian hormones estrogen and progesterone. Withdrawal of ovarian hormone stimulation reduces uterine volume and fibroid size.[11] Unfortunately, this benefit is accompanied by side effects, most notably bone loss, which limits treatment duration. Once therapy is discontinued, fibroids usually return. As a result, GnRH agonists are primarily used to reduce fibroid size prior to surgical removal.

Clinically, fibroids enlarge in women treated with norethynodrel, a steroidal progesterone agonist.[12] Progestins also block the decrease in uterine size associated with GnRH agonists.[13] Furthermore, it has been demonstrated preclinically that progestins increase the mitotic index of myomas and myometrial cells both *in vitro* and *in vivo*.[14] Conversely, clinical studies with the steroidal antiprogestin mifepristone have demonstrated a decrease in fibroid volume by 50% after 12 weeks of therapy.[15] Another steroidal antiprogestin, Proellex (CDB-4124), has been in clinical trials for uterine fibroids, associated anemia, and endometriosis.[16−19]

The progesterone receptor (PR, NR3C3) is a member of the nuclear receptor superfamily of ligand-dependent transcription factors. Two isoforms, PR-A and PR-B, have been described.[20] The PRs can be modulated by a wide variety of ligands, ranging from full agonists such as progesterone (**1**) and promegestone (R-5020, **2**) to full antagonists such as mifepristone (RU-486, **3**) and Proellex (CDB-4124, **4**). See

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Chart 1. Structures of Progestins, Antiprogestins, and SPRMs

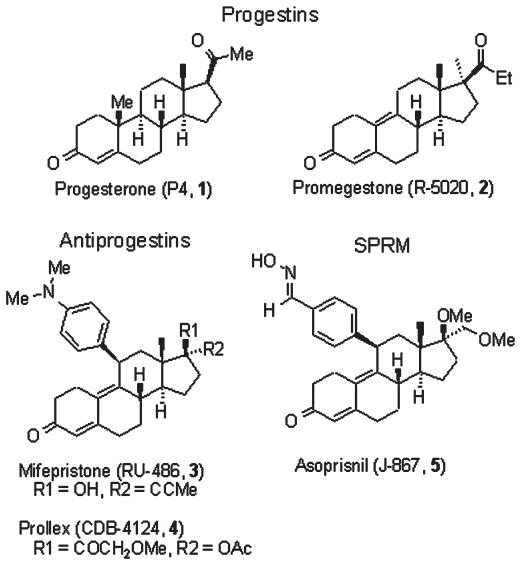

Chart 1. In between these two extremes are selective progesterone receptor modulators (SPRMs). Like their cousins, the selective estrogen receptor modulators (SERMs), these compounds elicit functional activities that depend on the cell context in which ligand induced receptor conformations recruit an ensemble of coactivators, resulting in promoter-specific interactions and subsequent selective gene activations.[21] Results from a recent phase III clinical study with the steroidal SPRM asoprisnil (J-867, **5**) suggest that PR modulation can affect dysfunctional bleeding and reduce fibroid size.[22]

We have recently described the development of SERMs for the treatment of uterine fibroids in premenopausal women.[23−25] Since clinical experience with GnRH agonists demonstrates that both estrogen and progesterone promote fibroid growth, we have also pursued the development of SPRMs for this indication. Here we describe for the first time a novel series of 3-aryl indoles as nonsteroidal, highly selective PR ligands.

Through screening efforts, we discovered that 3-[(4-methoxyphenyl)phenylmethyl]indole binds weakly across the steroidal nuclear hormone class of receptors (**6**, Figure 1). We recently described a selective Mineralocorticoid Receptor (MR, NR3C2) antagonist **7a** based on this same nonsteroidal indole scaffold.[26] We embarked on an extensive SAR study around compound **7a**, with the primary goal being the removal of the tetrasubstituted, chiral carbon atom at C3 on the indole ring. During the course of this work, we unexpectedly discovered the highly selective PR ligands **8**.

Figure 1 shows the previously described crystal structure of **7a** overlaid with a representative of the new, achiral PR selective series (**8c**). The compounds are easily superimposable; however, in order to place the three common substituents (alkyl, aryl, and methylsulfonamide) in the same positions in chemical space, the indole rings must be rotated significantly with respect to each other. The resulting compounds showed reduced MR binding, increased PR binding,

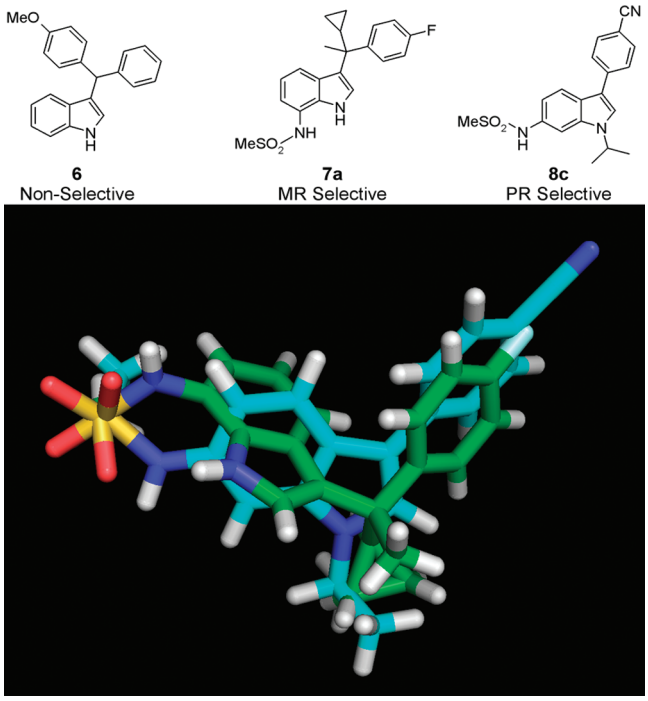

Figure 1. MR selective **7a** overlaid with PR selective **8c**.

and even greater selectivity for PR over the androgen (AR, NR3C4) and glucocorticoid (GR, NR3C1) receptors.

The syntheses of compounds **8a−h** are outlined in Scheme 1. In addition to being achiral, a significant advantage of this platform was the ease with which a three point SAR could be executed in rapid fashion. Therefore, several flexible routes were developed.

The initial route began with 3-bromo-6-nitroindole (**9**),[27] which was deprotonated with LiHMDS followed by alkylation with alkyl halides to give 1-alkyl-3-bromo-6-nitroindoles **10**. Alternatively, the indole nitrogen could be alkylated with alkyl alcohols using standard Mitsunobu conditions. Although many aryl coupling methods were effective with the bromoindoles **10**, Suzuki conditions using the air-stable trialkylphosphonium tetrafluoroborate salt[28,29] and tris(dibenzylideneacetone) dipalladium proved most versatile, allowing for a wide variety of aryl substitutions at C3 on the indole ring. Thus, 1-alkyl-3-bromo-6-nitroindoles **10** were coupled to aryl boronic acids to give 1-alkyl-3-aryl-6-nitroindoles **11**. The nitro group was then reduced using standard conditions [hydrogenation or tin(II) chloride] followed by reaction with methanesulfonyl chloride to give final compounds **8** for biological assays.

Alternatively, the indole nitrogen could be protected as the phenyl sulfonamide **12** followed by Suzuki coupling and then deprotection of the phenyl sulfonamide with TBAF to give 3-aryl-indoles **14**. The indole nitrogen of **14** could then be alkylated followed by reduction of the nitro group and sulfonylation of the subsequent amine to give final compounds **8**.

In a third approach, 3-bromo-6-nitroindole was converted to the pinacolboryl derivative **15**. This allowed direct coupling of more readily available aryl bromides without conversion to

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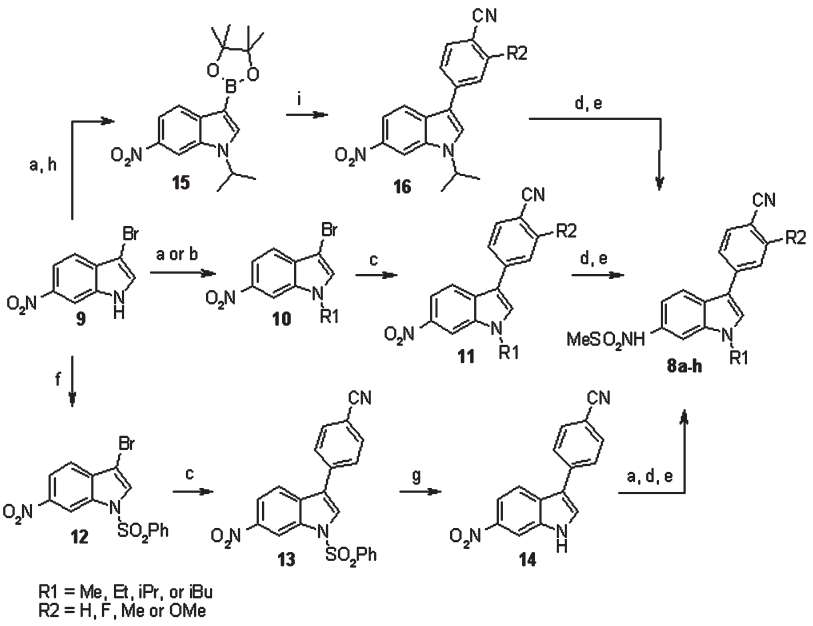
Scheme 1[a]



[a] Reagents and conditions: (a) LiHMDS, alkyl halide, DMF, 0 °C to RT; (b) alkyl alcohol, DIAD, PPh_3, CH_2Cl_2, 0 °C to RT; (c) aryl boronic acid, $Pd_2(dba)_3$, $[(tBu)_3PH]BF_4$, KF, THF, 40 °C; (d) H_2, Pd/C or PtO_2, THF or $SnCl_2 \cdot 2H_2O$, DMF, 60 °C; (e) MsCl, pyr, CH_2Cl_2; (f) $PhSO_2Cl$, DMAP, Et_3N, CH_2Cl_2; (g) TBAF, THF; (h) bis(pinacolato)diboron, $PdCl_2(dppf)_2 \cdot CH_2Cl_2$, KOAc, DMSO, 90 °C; (i) aryl bromide, $Pd(PPh_3)_4$, Na_2CO_3, LiOH, H_2O, toluene, EtOH.

the corresponding boronic acids. Coupling of aryl bromides to intermediate **15** worked well using standard, aqueous Suzuki conditions [tetrakis(triphenylphosphine) palladium(0), bicarbonate, and lithium chloride]. This was followed by reduction and sulfonylation to give final compounds **8**.

Biological data for compounds **8a**−**h** are shown in Table 1. The binding affinity data were generated using appropriate tritium labeled standards and recombinant, full-length human receptors in competitive binding assays. The functional activity was measured using a transcription assay with full-length human PR cotransfected into a HEK293 cell line.

In general, the more rigid achiral series displayed much higher selectivities than the chiral series with its flexible linker between the aryl group and the indole ring. The screening hit, indole **6**, possesses a binding affinity for PR of 478 nM but is 6- to 10-fold more potent at the other steroid receptors. It is nearly a full antagonist of PR but with a relatively weak IC_{50} of about 4 μM. The previously reported chiral indole **7a** possesses a binding affinity for MR of 0.64 nM with 710-fold selectivity over PR while the new achiral indole **8c** possesses a binding affinity for PR of 0.795 nM with 1900-fold selectivity over MR. In the functional antagonist assays, the chiral indole **7a** is about 12-fold selective for MR while the achiral indole **8c** is greater than 1500-fold selective for PR. Indole **8c** displays similarly high selectivity for PR over AR and GR in both the binding and functional assays.

The alkyl substituent at N1 played a very important role in binding potency. Changing this substituent from methyl (**8a**) to ethyl (**8b**) and then from ethyl to isopropyl (**8c**) improved the binding affinity 7- and 5-fold, respectively. The functional activities follow this same trend. We also noted a preference for substitution of select small functional groups ortho to the cyano at the 4′ position on the aromatic ring at carbon 3 of the indole. For example, addition of a methyl group (**8d**) improved binding affinity by 3-fold. However, addition of a methoxy group at this position (**8e**) decreased binding affinity, while addition of fluorine (**8f**) improved affinity for PR. The same trend, although with somewhat muted differences, was also noted in the functional assays.

In our previous studies, we discovered a clear preference of MR for the *S*-enantiomers of compounds **7**. Compare, for example, **7b**, which has 5-fold better affinity than **7c**. We wondered if PR would have a similar preference for one enantiomer over the other if chiral substituents were placed at the N1 position of indoles **8**. In practice, substituting chiral groups at N1, such as the secondary butyl substituted indoles **8g** and **8h**, demonstrated a slight but consistent preference of PR for the *S*-enantiomers.

Compound **8f** was advanced to further testing *in vivo*. The ovariectomized rat complement C3 assay was used to evaluate its ability to reverse the progestin (R5020) dependent down-regulation of estrogen induced expression of complement C3 mRNA in the rat uterus (Figure 2).[30] In this model, when compound **8f** was dosed orally, it demonstrated potent antagonist activity, with an ED_{50} of 0.33 mg/kg, which is comparable to that of asoprisnil (ED_{50} = 0.31 mg/kg).

The activity of **8f** was also assessed in the McPhail model. Progesterone treatment of immature estrogen-primed rabbits induces endometrial transformation, which is scored using the McPhail Index (Figure 3).[31] The animals were dosed subcutaneously (sc) with or without progesterone to evaluate the agonist or antagonist activity of the compound. In the antagonist mode, mifepristone, asoprisnil, and **8f** antagonize the effects of progesterone dosed at 1 mg/kg.

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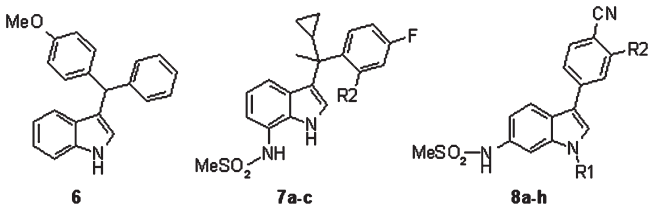
Table 1. PR Binding and Functional Activities of **6**, **7a**−**c**, and **8a**−**h**[a]



				binding				functional			
				PR	MR	AR	GR	PR		MR	
cmpd	R1	R2	isomer	K_i (nM)	K_i (nM)	K_i (nM)	K_i (nM)	IC50(nM)	% Inhib	IC50 (nM)	% Inhib
6				478 ± 287	86.8 ± 49.6	68.9 ± 16.8	50.2 ± 19.4	3720 ± 563	86.5 ± 2.26	>10000	40.8 ± 3.39
7a		H		454 ± 188	0.640 ± 0.864	220 ± 97.7	6.39 ± 3.43	765 ± 171	91.7 ± 4.59	64.1 ± 25.8	76.3 ± 12.8
7b		F	S	464 ± 158	0.319 ± 0.156	211 ± 99.4	5.93 ± 4.18	715 ± 61.9	89.7 ± 9.38	27.2 ± 13.7	62.9 ± 11.5
7c		F	R	1230 ± 260	1.51 ± 0.856	676 ± 306	54.4 ± 8.33	2020 ± 155	94.5 ± 0.141	306 ± 53.3	87.0 ± 2.12
8a	Me	H		28.0 ± 10.7	>4170	>4020	>4290	485 ± 214	87.8 ± 3.70	>10000	−2.2
8b	Et	H		4.23 ± 1.95	1770 ± 640	2590	927 ± 93.8	12.6 ± 2.47	97.0 ± 3.28	>10000	23.8 ± 7.23
8c	iPr	H		0.795 ± 0.286	1490 ± 123	>3900	1530 ± 156	6.81 ± 1.11	96.2 ± 1.34	>10000	36.6 ± 9.12
8d	iPr	Me		0.298 ± 0.150	126 ± 12.1	403 ± 212	157 ± 15.2	3.38 ± 0.698	95.8 ± 4.03	>10000	56.0 ± 7.37
8e	iPr	OMe		1.45 ± 0.760	1390 ± 403	490 ± 172	977 ± 65.7	7.28 ± 1.06	97.4 ± 0.726	2420	35.8 ± 2.31
8f	iPr	F		0.214 ± 0.0924	849 ± 223	648	523 ± 148	2.29 ± 0.860	94.9 ± 4.74	8150	50.2 ± 11.9
8g	sBu		S	0.320 ± 0.227	1000 ± 155	1740 ± 795	1860 ± 552	3.89 ± 1.04	96.8 ± 1.03	9800	43.4 ± 9.22
8h	sBu		R	0.834 ± 0.339	1440 ± 223	2550 ± 666	780 ± 147	9.92 ± 1.88	96.2 ± 0.635	>10000	39.2 ± 6.79

[a] Experimental values represent the average of at least duplicate determinations. Standard deviations are indicated by ± of the geometric mean.

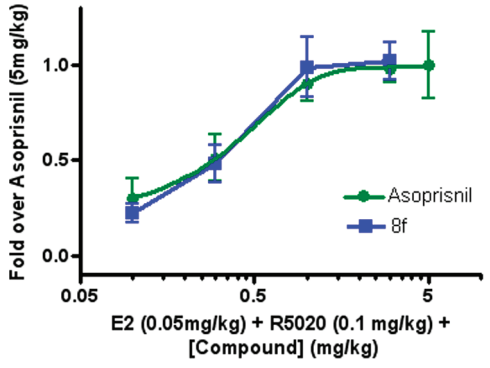


Figure 2. Dose response (mg/kg, po) of asoprisnil and **8f** in the ovariectomized rat complement C3 assay. E2 is estrogen. R5020 is promegestone. By comparison, the fold over asoprisnil (5 mg/kg) for vehicle control was 0.018 ± 0.011, while E2 (0.05 mg/kg) alone was 0.73 ± 0.05, and E2 (0.05 mg/kg) + R5020 (0.1 mg/kg) was 0.12 ± 0.03.

Mifepristone reached full antagonism at 1 mg/kg, whereas asoprisnil and **8f** demonstrated only partial antagonism with a McPhail score of 3.1 for asoprisnil at 10 mg/kg and 2.0 for **8f** at 3 mg/kg. At 30 mg/kg, **8f** resulted in a McPhail score of 2.5 in the antagonist mode. In the agonist mode, mifepristone had no effect, but asoprisnil and **8f** increased the McPhail Index to 3.1 and 1.5, respectively, at 30 mg/kg.

The oral bioavailability of **8f** (dosed as a suspension) in rats was 31.4 ± 7.3 % with a t_{max} of 4 h and an elimination half-life ($t_{1/2}$) of 19.8 ± 5.0 h. The volume of distribution (V_d) was 2.3 ± 0.7 L/kg, while its clearance was 2.5 ± 0.6 mL/min/kg.

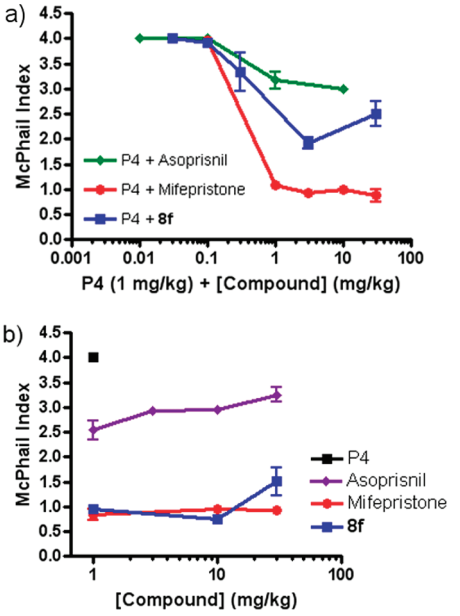


Figure 3. Dose responses (mg/kg, sc) of asoprisnil, mifepristone, and **8f** in the immature, estrogen-stimulated rabbit McPhail assay: (a) antagonist mode with 1 mg/kg progesterone (P4) + test compound at various doses; (b) agonist mode with progesterone (P4) alone at 1 mg/kg compared to test compound alone at 1, 10, and 30 mg/kg.

The indole **8f** is a potent, selective antagonist of PR *in vitro*. It is orally efficacious in an *in vivo* rat uterine model of PR

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antagonist activity. In the McPhail model, in the antagonist mode, it demonstrated activity less efficacious than the full antagonists mifepristone but more efficacious than the partial antagonist asoprisnil.

SUPPORTING INFORMATION AVAILABLE Synthesis procedures and characterization data for compounds **8a**−**h**, and a description of the biological assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions: T.I.R. designed and interpreted experiments, synthesized compounds, wrote the manuscript, and contributed to the Supporting Information; C.A.C. designed experiments, synthesized compounds, wrote the Supporting Information, and contributed to the manuscript; Y.K.Y., T.J.B., J.E.L., S.A.J., N.E.H., B.S.M., and C.W.L. designed experiments, synthesized compounds, and contributed to the Supporting Information; K.-L.Y. led the chemistry team, designed and interpreted experiments, synthesized compounds, and contributed to the Supporting Information; A.G.G., T.L.M. and P.K.S. designed, performed, and interpreted *in vivo* experiments; R.W.Z., J.J.O., and C.M.-R. designed, performed, and interpreted *in vitro* experiments and contributed to the Supporting Information; N.P. designed and interpreted animal exposure experiments, R.J.S.G. led the biology team, designed and interpreted experiments, and contributed to the manuscript and the Supporting Information; J.A.D. led the discovery team, designed and interpreted experiments, and contributed to the manuscript.

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