Design, Synthesis, and SAR of New Pyrrole-Oxindole Progesterone Receptor Modulators Leading to 5-(7-Fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (WAY-255348)

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We have continued to explore the 3,3-dialkyl-5-aryloxindole series of progesterone receptor (PR) modulators looking for new agents to be used in female healthcare: contraception, fibroids, endometriosis, and certain breast cancers. Previously we reported that subtle structural changes with this and related templates produced functional switches between agonist and antagonist properties (Fensome et al. *Biorg. Med. Chem. Lett.* **2002**, *12*, 3487; **2003**, *13*, 1317). We herein report a new functional switch within the 5-(2-oxoindolin-5-yl)-1*H*-pyrrole-2-carbonitrile class of compounds. We found that the size of the 3,3-dialkyl substituent is important for controlling the functional response; thus small groups (dimethyl) afford potent PR antagonists, whereas larger groups (spirocyclohexyl) are PR agonists. The product from our optimization activities in cell-based systems and also for kinetic properties in rodents and nonhuman primates was 5-(7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile **27** (WAY-255348), which demonstrated potent and robust activity on PR antagonist and contraceptive end points in the rat and also in cynomolgus and rhesus monkeys including ovulation inhibition, menses induction, and reproductive tract morphology.

Introduction

The control and regulation of progesterone (**1**, Figure 1) and the progesterone receptor (PR)[a] has been a well-recognized drug target for female reproductive health for the past four decades. The PR is a member of the nuclear transcription factor superfamily.[1] PR agonists have been used in contraception (either alone or in combination with an estrogen), in postmenopausal hormone therapy in combination with estrogens, and also in high dose treatments for endometriosis and uterine fibroids. Antagonists have been studied clinically for contraception,[2,3] for the treatment of uterine fibroids,[4–8] and for the termination of pregnancy.[9] Ligands for this receptor display a spectrum of activities from full agonist (e.g., progesterone **1** and medroxyprogesterone acetate **2**) to antagonist (e.g., mifepristone **3** and ORG-33628[10] **4**). Newer compounds, such as asoprisnil[11] **5**, fall somewhere in between and are described as selective progesterone receptor modulators (SPRM). What is notable about the clinically studied PR ligands is the common steroidal platform. This platform brings with it potential to cross-react with other members of the steroid family (androgen receptor (AR), glucocorticoid receptor (GR), mineralocorticoid receptor (MR), and estrogen receptor (ER)), which can result in unwanted side effects, which potentially limit the benefits of the desired therapy. Analogous to the estrogen receptor field, where great advances have been made with nonsteroidal modulators,[12–15] more recent work in the PR modulator field has been applied to nonsteroidal templates.[16,17]

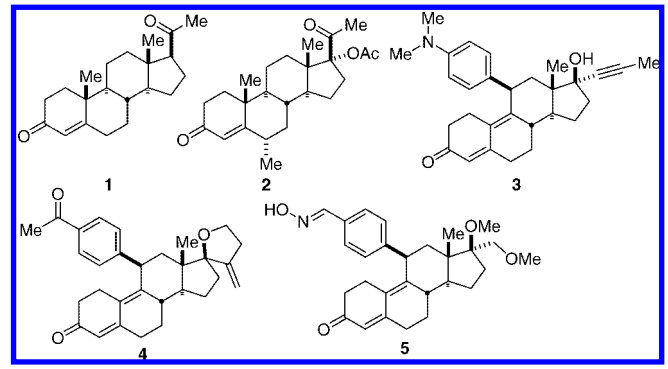

Figure 1. Steroidal PR modulators: progesterone **1**, medroxyprogesterone acetate **2**, mifepristone **3**, **4**, asoprisnil **5**.

Over the past few years, we have published new PR agonist templates such as the thio-oxindoles[18] **6** and cyanopyrrole carbamates **7**,[19] and the synergistic combination of both features (tanaproget **8**),[20] as well as PR antagonists such as the oxindoles **9** and **10**.[21] What has become apparent during the course of this work is the subtle structure–activity relationship (SAR) that controls the functional outcome from agonist to antagonist, without relying upon the larger structural changes necessary for their steroidal counterparts (e.g., the 11-β-aryl moiety present in **3**–**5**). In this paper, we describe a recent SAR exploration of

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[a] Abbreviations: PR, progesterone receptor; AR, androgen receptor; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; ER, estrogen receptor; RLM, CMLM, and HLM, rat, cynomolgus monkey, and human liver microsomes, respectively.

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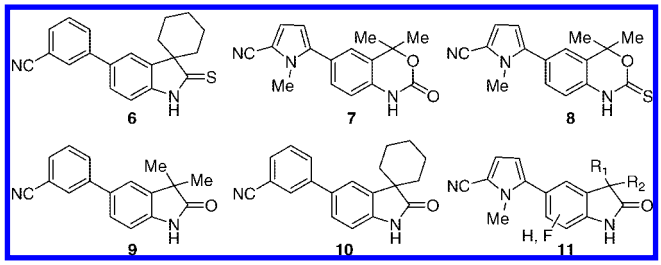


Figure 2. Nonsteroidal PR modulators.

Table 1. Optimization of Coupling Reaction To Prepare **27** from Bromide **36c** and Boronic Acid **16**

	catalyst	ligand	ratio Pd/P	base	solvent	yield (%)
1	$Pd(Ph_3P)_4$			K_2CO_3	DMF	19
2	$Pd_2(dba)_3 \cdot CHCl_3$	$(o\text{-tol})_3P$		KF	dioxane	0
3	$Pd_2(dba)_3 \cdot CHCl_3$	$(C_6H_{11})_2PPh$		KF	dioxane	58
4	$Pd_2(dba)_3 \cdot CHCl_3$	Q-phos[a]		KF	dioxane	64
5	$Pd_2(dba)_3 \cdot CHCl_3$	Q-phos[a]		KF	toluene	30
6	$Pd_2(dba)_3 \cdot CHCl_3$	$(t\text{-Bu})_3P$	1:3	KF	dioxane	30
7	$Pd_2(dba)_3 \cdot CHCl_3$	$Pd((t\text{-Bu})_3P)_2$	1:3	KF	dioxane	28
8	$Pd_2(dba)_3 \cdot CHCl_3$	$(t\text{-Bu})_3P$	1:2	KF	THF	80

[a] Q-phos = di-*tert*-butylphosphinopentaphenylferrocene.

a series of pyrrole-oxindoles **11** (Figure 2), their synthesis, and their biological activities. The work described herein led to the potent orally active PR antagonist 5-(7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2- carbonitrile **27** (WAY-255348).[22]

Chemistry

The 3,3-unsubstituted oxindole derivatives **12** and **13** were prepared according to Scheme 1. Palladium-catalyzed coupling of the bromide **14** with *N*-Boc-pyrrole-2-boronic acid gave the pyrrole **15**. Installation of the nitrile to provide target compound **12** was accomplished by treatment with chlorosulfonyl isocyanate followed by *N*,*N*-dimethylformamide (DMF) quench, and subsequent Boc group removal was achieved by thermolysis in dimethylacetamide (DMA). The analogous *N*-methyl derivative **13** was prepared via a palladium-catalyzed coupling of **14** with the boronic acid **16**, which was prepared by treatment of the pyrrole **17** with lithium di-isopropyl amide (LDA) and tri-isopropyl borate in tetrahydrofuran (THF).

The *des*-fluoro 3,3-dialkylated compounds **18**–**21** were prepared following Scheme 2.

Oxindole **22** was treated with 2 equiv of *n*-BuLi in THF at −25 °C in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (*N*,*N*,*N*′,*N*′-TMEDA) to generate the dianion, which was subsequently quenched with either an alkyl iodide to prepare the intermediates **23a**,**b** for targets **18** and **19** or an alkyl di-iodide for the preparation of the intermediates **23c**,**d** needed for the spirocyclic targets **20** and **21**.[23] The products were then brominated under standard conditions (Br_2, NaOAc, AcOH) to give the 5-bromo oxindoles **24a**−**d** respectively. The bromides **24a**−**d** were then coupled with the pyrrole boronic acid **16**, either in the isolated state or generated *in situ* from the treatment of pyrrole **17** with LDA and tri-isopropyl borate, to provide the target compounds **18**–**21**.

The fluorinated analogs **25**–**30** of general target **11** were prepared via a malonate route, Scheme 3.

Reaction of the 2-fluoro-nitrobenzenes **31a**−**c** with dimethyl malonate in DMF in the presence of potassium carbonate afforded malonates **32a**−**c**, which were subsequently hydrolyzed and decarboxylated in refluxing 6 N HCl to afford the acetic acids **33a**−**c**. Hydrogenolysis over Pd−C was followed by acid-catalyzed ring closure (*p*-TsOH in EtOH) to afford the fluorinated oxindoles **34a**−**c**. Alkylation of the 3-position was effected by generation of the dianion under the action of *n*-BuLi−LiCl in THF, followed by reaction with either an alkyl iodide to form the intermediates for targets **25**–**28** or an alkyl di-iodide for the spirocycles **29** and **30**. Compounds **35a**−**f** were then brominated under standard conditions to afford coupling partners **36a**−**f**. The 4-, 6-, and 7-fluoro-3,3-dimethyl targets **25**, **26**, and **27** were initially prepared via coupling with boronic acid **16** under traditional coupling conditions ($Pd(Ph_3P)_4$, K_2CO_3, THF, reflux); however the yields were low (5–28%).

Compound **27** was selected for optimization of the coupling chemistry between the bromide **36c** and boronic acid **16**, Table 1. We selected *tris*-dibenzylideneacetone dipalladium(II) as the metal source, and a range of phosphines were surveyed. KF was used as the base. Reactions were poor with the nonhindered phosphines (entries 1 and 2); however the bulkier phosphines, such as dicyclohexyl phenylphosphine (entry 3) and Q-phos (entry 4), gave more promising results. We observed a solvent effect and found that THF and dioxane gave better yields than did toluene (entry 4 and 5). Following the work of Fu and coworkers,[24] we then examined tri-*tert*-butylphosphine as the ligand (entries 6–8) and found the stoichiometry between the $Pd_2(dba)_3$ and the phosphine to be important; the optimal conditions found were a ratio of 1:2 between the $Pd_2(dba)_3 \cdot CHCl_3$ and the tri-*tert*-butylphosphine in THF giving **27** in an isolated yield of 84%. Under these optimized conditions, the diethyl derivative **28** and the 3,3-spirocycloalkyl compounds **29** and **30** were prepared from their corresponding bromides **36a**−**c**.

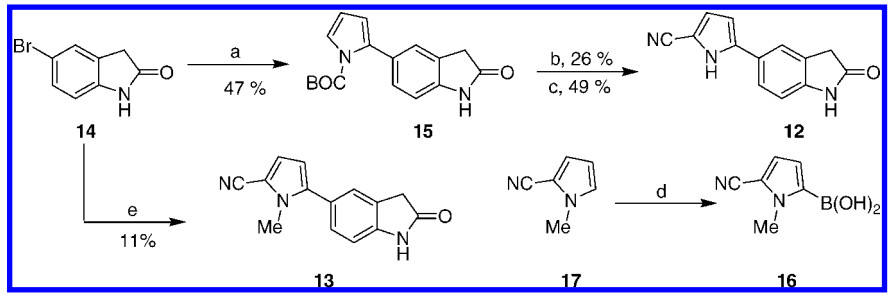
We then further sought to expand the oxindole template by incorporating functionality on N-1 through alkylation of **27** to afford compounds **37**–**48**, Scheme 4. Treating **27** with potassium *tert*-butoxide in THF and reacting the anion with the respective electrophile afforded the desired products.

Results and Discussion

The compounds synthesized were tested for functional activity in the human T47D cell alkaline phosphatase assay.[25] In the agonist mode, stimulation of alkaline phosphatase is reported as an EC_{50} value. In the antagonist mode, the compound is tested for its ability to antagonize the alkaline phosphatase induced by progesterone (1 nM) and is reported as an IC_{50}. Compounds were then assayed in a T47D whole cell competition-binding assay displacing tritiated R5020, the activity being reported as an IC_{50}.

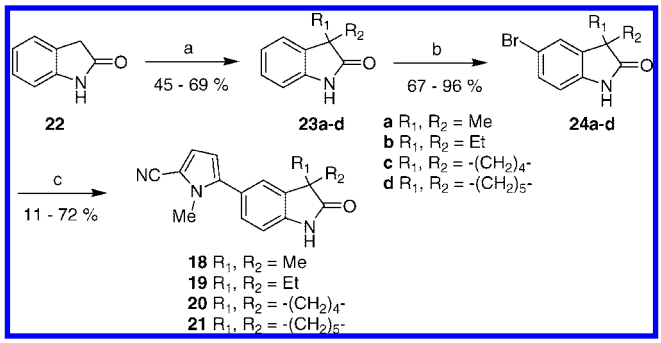
The SAR in the oxindole series is described below, Table 2. The unsubstituted oxindole **12** was a functional antagonist in the T47D alkaline phosphatase assay (IC_{50} = 300 nM). Addition of a methyl group to the pyrrole nitrogen afforded a 10-fold increase in activity (**13**, 20 nM). Further addition of substituents to the 3-position of the oxindole again increased potency; for example, the 3,3-dimethyl derivative (**18**, IC_{50} = 10 nM) and the 3,3-diethyl compound (**19**, IC_{50} = 3.3 nM) were also potent PR antagonists. We then chose to prepare the larger spirocyclic derivatives. The spirocyclopentyl derivative **20** was found to have a biphasic curve in the T47D alkaline phosphatase assay with approximate IC_{50} = 30 nM and EC_{50} = 300 nM. The next higher homologue, the spirocyclohexyl derivative **21**, was found to be a potent and efficacious agonist (T47D EC_{50} = 2.3 nM). It is interesting to compare the cyano-pyrrole series with the previously reported 5-aryl derivatives, the dimethyl derivative **9** and spirocyclohexyl derivative **10**, where the compounds were functional antagonists regardless of the size of the 3,3-alkyl

Scheme 1[a]



[a] Reagents and conditions: (a) *N*-Boc-pyrrole-2-boronic acid, Na_2CO_3, $Pd(Ph_3P)_4$, THF, reflux; (b) (i) $ClSO_2NCO$, DCM, −78 °C, (ii) DMF, rt; (c) DMA, 175 °C; (d) LDA, $(^iPrO)_3B$, THF, −78 °C; (e) $Pd(Ph_3P)_4$, K_2CO_3, **16**, THF, reflux.

Scheme 2[a]



[a] Reagents and conditions: (a) *n*-BuLi, *N*,*N*,*N*′,*N*′-TMEDA, THF, −25 °C, alkyl iodide; (b) Br_2, NaOAc, AcOH, rt; (c) $Pd(Ph_3P)_4$, K_2CO_3, **16**, THF, reflux.

substituent (T47D IC_{50} = 27 and 14.7 nM for **9** and **10**, respectively).[21] In comparison with mifepristone **3**, the most potent of the unsubsitituted oxindole derivatives, the diethyl analog **19** was approximately 1 order of magnitude less active in the T47D functional activity.

In the whole cell-binding assay the unsubstituted oxindole **13** was a competitive ligand for the hPR (IC_{50} = 80 nM). Similarly, compounds **18** and **19** were also competitive (IC_{50} = 22 and 35 nM, respectively) but gained potency due to the 3,3-dialkyl substitution, commensurate with the increase in potency seen in the functional alkaline phosphatase assay. The agonist **21** displayed potent displacement of the radioligand (IC_{50} = 3.3 nM), in close agreement with its functional activity. In the same whole cell binding assay, mifepristone **3** was approximately 2 orders of magnitude more potent than the oxindole antagonists (T47D whole cell binding assay IC_{50} = 0.6 nM).

As part of the characterization of the compounds, female rat, human, and cynomolgus monkey microsome stability data was obtained for a subset of compounds, Table 3.

While compound **13** was found to be stable across all three species tested, the 3,3-dimethyl **18** and 3,3-diethyl **19** derivatives were found to have low stability in the rat liver microsomes and moderate stability in cynomolgus monkey microsomes. No metabolic stability issues were noted for any of the compounds tested in human liver microsomes.

Controlling metabolic stability of compounds, either by blocking a site of metabolism or by reducing the electron density of a ring system through induction, can affect pharmacokinetic properties.[26] We selected the dimethyl oxindole **18** to conduct our studies and selectively installed a fluorine atom at the 4-, 6-, and 7-positions of the benzo-fused ring system, Table 4.

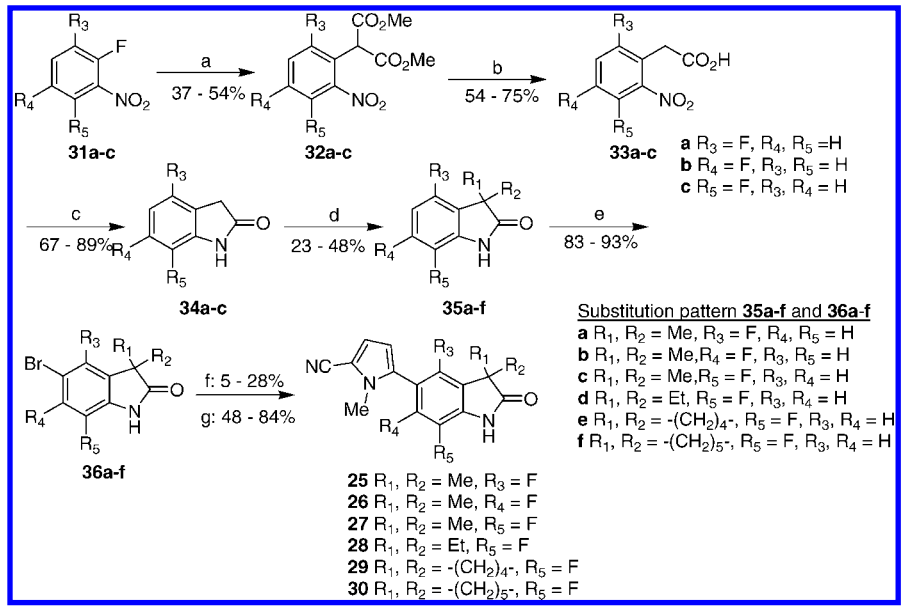
Addition of fluorine to either the 4- or 7-positions of the dimethyl derivative **18** afforded a small increase in potency in the alkaline phosphatase assay (IC_{50} = 10, 5.9, and 5.0 nM for **18**, **25**, and **27**, respectively). Similarly in the whole-cell binding assay, a small increase in potency was noted for both compounds **25** and **27** (IC_{50} = 5.5 and 4.1 nM, respectively). In comparison with mifepristone **3**, **27** was approximately 10-fold less active on both T47D alkaline phosphatase and whole cell binding assays. In contrast, the 6-fluoro derivative **26** was slightly less active than the parent **18** (T47D alkaline phosphatase IC_{50} = 20 nM). In the microsome stability assay, the 4-fluoro derivative **25** lost RLM stability in comparison with the des-fluoro homologue **18** (RLM $t_{1/2}$ = 2 and 6 min, respectively, for **18** and **25**). The 6- and 7-fluoro derivatives **26** and **27** did show significant improvements in rat liver microsome data over compound **18** (RLM $t_{1/2}$ = 30 and 26 min, respectively, for **26** and **27**). Compound **27** showed a small improvement in cynomolgus monkey microsome stability over the des-fluoro homologue **18**.

The 7-fluoro-3,3-diethyl derivative **28** had similar functional potency when compared with its des-fluoro congener **19** (T47D IC_{50} = 4.9 and 3.3 nM for **28** and **19**, respectively). Addition of the 7-fluorine substituent to the spirocyclopentyl derivative **20** shifted the mixed agonist/antagonist functional activity in favor of the antagonist mode (IC_{50} = 3.2 nM, 85% inhibition, compound **29**), while the 7-fluoro-3,3-spirocyclohexyl derivative **30** remained a relatively potent agonist (EC_{50} = 1.3 nM).

To further capitalize upon the pyrrole-oxindole series, we selected compound **27** as a platform from which to explore the nature of the oxindole nitrogen substituent, Table 5. In general, small substituents gave the most potent antagonists in the T47D alkaline phosphatase assay. Thus the methyl derivative **37** gave comparable functional activity to the N−H congener **27** (IC_{50} = 7.4 nM). The ethyl, *n*-propyl, and iso-butyl derivatives all lost between 2- and 4-fold in potency (IC_{50} = 29, 27, 13, and 30 nM for compounds **38**, **39**, **40**, and **41**, respectively). A size limitation was observed in the cycloalkyl compounds, where the cyclopentane **42** was similar in activity to the smaller alkyl substituents but the cyclohexyl derivative **43** lost approximately 40-fold in potency relative to the N−H derivative **27** (IC_{50} = 25 and 194 nM for **42** and **43**, respectively). We found that this series of molecules would also tolerate unsaturation, thus the allyl **44** and propargyl **45** derivatives were similar in potency to the smaller alkyl compounds (T47D alkaline phosphatase IC_{50} = 4.5 and 30 nM, respectively). Larger aromatic functionalities (benzyl **46** and phenethyl **47**) were only poorly tolerated. We also prepared one more functionalized derivative, the acetate **48**, which had modest potency in the functional activity assay (IC_{50} = 48 nM).

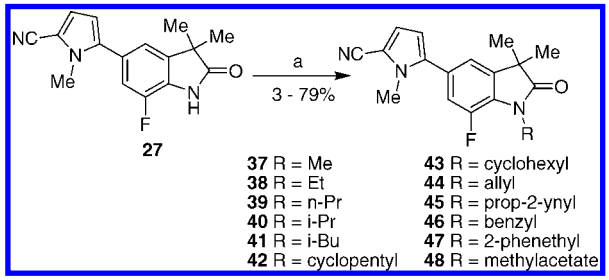
To further profile **27**, the ability of the compound to cross-react with other members of the steroid receptor family was evaluated in a Gal4 mammalian one-hybrid assay,[27] Table 6.

Scheme 3[a]



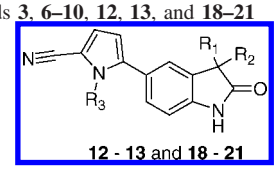
[a] Reagents and conditions: (a) K_2CO_3, $CH_2(CO_2Me)_2$, DMF, 65 °C; (b) 6 N HCl, reflux; (c) (i) H_2, Pd−C, AcOH, (ii) *p*-TsOH, EtOH, reflux; (d) *n*-BuLi, LiCl, THF, −78 °C, then alkyl iodide; (e) Br_2, CH_2Cl_2−AcOH; (f) $Pd(Ph_3P)_4$, K_2CO_3, **16**, THF, reflux for **25**–**27** or (g) $Pd_2(dba)_3$·$CHCl_3$, *t*-Bu_3P, KF, **16**, THF, rt for **27**–**30**.

Scheme 4[a]



[a] Reagents and conditions: (a) *t*-BuOK, THF, electrophile.

Table 2. Alkaline Phosphatase and Whole Cell Binding Data in T47D Cells for Compounds **3**, **6**–**10**, **12**, **13**, and **18**–**21**



				T47D alk phos[a]		T47D whole-cell binding
compd	R_1	R_2	R_3	IC_{50} (nM)	EC_{50} (nM)	IC_{50} (nM)
3				0.2		0.6
6					2.0	*b*
7					1.1	4.9
8					0.15	0.5
9				27		*b*
10				15		25
12	H	H	H	300		*b*
13	H	H	Me	20		80
18	Me	Me	Me	10		22
19	Et	Et	Me	3.3		36
20	$-CH_2CH_2CH_2CH_2-$		Me	~30	~300	8.1
21	$-CH_2CH_2CH_2CH_2CH_2-$		Me		2.3	3.3

[a] T47D cell alkaline phosphatase functional activity assay. Values represent the average of at least duplicate determinations. The standard deviation for the assay was typically ±20% of mean or less. [b] Not determined.

In comparison with mifepristone **3** and asoprisnil **5**, **27** is a relatively weak androgen receptor (AR) antagonist in the Gal4 mammalian one-hybrid assay (IC_{50} = 6.9, 6.1, and 196 nM, respectively, for **3**, **5**, and **27**). However in terms of the PR/AR selectivity ratio, **27** and **3** are equivalent (PR/AR = 39- and 34-fold, respectively, for **27** and **3**). In the glucocorticoid receptor (GR) assay, the well-characterized antagonist activity of **3** was apparent (IC_{50} = 0.6 nM); asoprisnil **5** was somewhat less potent (IC_{50} = 85 nM), whereas **27** was inactive as either an agonist or antagonist of this receptor, a characteristic not shared by the steroidal PR antagonists. Against both the mineralocortocoid (MR) and estrogen receptors (ER), **27** had no agonist activity and only weak antagonist activity (IC_{50} = 1600 and 1900 nM for hMR and hER, respectively).

Table 3. Rat, Cynomolgus Monkey and Human Liver Microsome Stability Data for **13**, **18**–**26**, and **27**

compound	RLM[a] $t_{1/2}$ (min)	CMLM[b] $t_{1/2}$ (min)	HLM[c] $t_{1/2}$ (min)
13	>30	>30	>30
18	6	13	>30
19	10	15	>30
25	2	*d*	*d*
26	30	*d*	*d*
27	26	19	>30

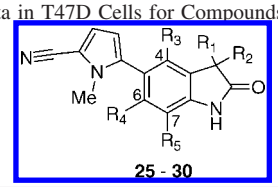
[a] Rat liver microsome. [b] Cynomolgus monkey liver microsome. [c] Human liver microsome. [d] Not determined.

***In Vivo* Pharmacology.** Compounds **18** from the des-fluoro series and **27** from the 7-fluoro series were chosen for further *in vivo* characterization. These compounds were selected based upon their similar potency in the T47D alkaline phosphatase assay and to examine the effect of the 7-fluorine present in **27**.

Pharmacokinetic parameters for both compounds **18** and **27** were obtained in female Sprague–Dawley rats, Table 7.

Compounds **18** and **27** were dosed in separate 1 in 4 iv cassette studies in female rats. It can be seen from the data that **27** in comparison to **18** achieves a higher exposure (AUC_{0-inf} = 937 and 1978 ng·h/mL for **18** and **27**, respectively) with a longer half-life ($t_{1/2}$ = 3.0 and 9.5 h for **18** and **27**, respectively). These effects are probably due to the lower clearance for the latter compound, which is in agreement with what would be expected from the increased rat metabolic stability observed for **27**. The discrete iv study for **27** was in close agreement with

Table 4. Alkaline Phosphatase and Whole Cell Binding Data in T47D Cells for Compounds **3** and **25–30**

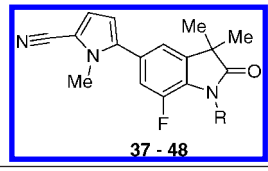


25 - 30

						T47D alk phos[a]		T47D whole cell binding
compd	R_1	R_2	R_3	R_4	R_5	IC_{50} (nM)	EC_{50} (nM)	IC_{50} (nM)
3						0.2		0.6
25	Me	Me	F	H	H	5.9		5.5
26	Me	Me	H	F	H	20.3		*b*
27	Me	Me	H	H	F	5.0		4.1
28	Et	Et	H	H	F	4.9		*b*
29	$-CH_2CH_2CH_2CH_2-$		H	H	F	3.2 (85%)[c]	~3000	14.7
30	$-CH_2CH_2CH_2CH_2CH_2-$		H	H	F		1.3	3.6

[a] T47D cell alkaline phosphatase functional activity assay. Values represent the average of at least duplicate determinations. The standard deviation for the assay was typically ±20% of mean or less. [b] Not determined. [c] Inhibition (percent) relative to R5020 as reference.

Table 5. Alkaline Phosphatase T47D Cell Data for Compounds **27** and **37–47**



37 - 48

compound	R	T47D alk phos[a] IC_{50} (nM)
3		0.2
27	H	5
37	Me	15
38	Et	29
39	*n*-Pr	27
40	*i*-Pr	13
41	*i*-Bu	30
42	cyclopentyl	25
43	cyclohexyl	194
44	allyl	4.5
45	prop-2-ynyl	30
46	benzyl	164
47	2-phenethyl	351
48	methylacetate	48

[a] T47D cell alkaline phosphatase functional activity assay. Values represent the average of at least duplicate determinations. The standard deviation for the assay was typically ± 20% of mean or less.

Table 6. Steroid Receptor Cross Reactivity Data for Compounds **3**, **5**, and **27**[a]

	hAR[b]		hGR[c]		hMR[d]		hER[e]	
compd	EC_{50} (nM)	IC_{50} (nM)	EC_{50} (nM)	IC_{50} (nM)	EC_{50} (nM)	IC_{50} (nM)	EC_{50} (nM)	IC_{50} (nM)
3	*f*	6.9	*f*	0.6	*g*	*g*	*g*	*g*
5	*f*	6.1	*f*	85	*f*	1600	*f*	1900
27	*f*	196	*f*	*f*	*f*	3700	*f*	*f*

[a] Steroid receptor cross-reactivity determined in a Gal4 mammalian hybrid assay. Values represent the average of at least duplicate determinations. The standard deviation for the assay was typically ±20% of mean or less. [b] hAR = human androgen receptor; antagonist mode run in the presence of 5α-dihydrotestosterone (10 nM). [c] hGR = human glucocorticoid receptor; antagonist mode run in the presence of dexamethasone (5 nM). [d] hMR = human mineralocorticoid receptor; antagonist mode in the presence of aldosterone (3 nM). [e] hER = human estrogen receptor; antagonist mode run in the presence of 17β-estradiol (5 nM). [f] Not statistically active. [g] Not determined.

the data obtained from the cassette study, allowing for differences in the dose administered. Following oral dosing, **27** showed good exposure (AUC_{0-inf} = 7149 ng·h/mL), a long half-life ($t_{1/2}$ = 9.3 h), and moderate bioavailability (F = 31%).

Compounds **18** and **27** were evaluated in the female rat decidual model. This model measures the ability of a compound to antagonize the progesterone-induced decidualization response in the stromal cells of the uterus.[28] In this assay, both compounds dose-dependently inhibited the decidual response produced by progesterone following oral administration in an aqueous vehicle (0.5% methyl cellulose/2% Tween 80) with potencies comparable to the reference compound mifepristone **3** (ED_{50} = 0.2, 0.3, and 0.7 mg/kg for **18**, **27**, and **3**, respectively).

To establish efficacy markers for pursuing contraception as our primary clinical indication, we examined both compounds **18** and **27** in the menses induction assay in female cynomolgus monkeys. A successful outcome in this assay was used as a screen prior to establishing efficacy in the rhesus macaque ovulation inhibition and reproductive tract model.

In mature normal cycling female cynomolgus monkeys, administration of a PR antagonist, mifepristone **3**, during the midluteal phase (days 19–22 of the menstrual cycle) causes premature menstruation indicating PR antagonist activity.[29] The clinical relevance of menses induction to a contraceptive regimen has been reported for **4** and a second steroidal antagonist 11-[4-(dimethylamino)phenyl]-4′,5′-dihydro-6-methyl-(6β,11β,17β)-spiro[estra-4,9-diene-17,2′(3′*H*)-furan]-3-one (ORG-31710), where administration of a single dose of this compound to women taking the 75 μg desogestrel progestin only pill during the luteal phase of the menstrual cycle was effective at inducing early menstruation.[30]

A typical menstrual cycle in cynomolgus monkeys is between 28 and 33 days in length. In an animal treated with an active PR antagonist for 4 days starting on day 19–22 of the menstrual cycle, the cycle length is reduced to 22–24 days. Steroidal PR antagonists mifepristone **3** and **4**, in our own hands, dosed at 5 mg/kg orally, induced early menses in 60% (3 out of 5 animals) and 50% (2 out of 4 animals), respectively, Table 8. Compound **18** following an oral dose of 5 mg/kg was inactive (0 out of 2 animals). In contrast, compound **27** at 5 mg/kg po induced early menses in 75% (3 out of 4 animals) of cycling monkeys.

To help understand the difference in activities seen in the menses induction assay between compounds **18** and **27**, the female cynomolgus monkey pharmacokinetic parameters were measured, Table 9.

In the monkey dosed at 0.25 mg/kg iv (1 in 4 cassette dosed in the same study), compound **27** had a longer half-life ($t_{1/2}$ = 8.8 and 2.1 h for **27** and **18**, respectively), lower clearance, higher volume of distribution, and higher exposure than did desfluoro analog compound **18**. Dosed orally at 5 mg/kg, compound **27** had a good exposure (AUC_{0-inf} = 5738 ng·h/mL) and good bioavailability (F = 49%) in this species. Although both compounds have similar potency in the T47D cell alkaline

Table 7. Pharmacokinetic Properties for Compounds **18** and **27**[a]

compound	study design[b]	route	dose (mg/kg)	C_0 (ng/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	Clp (mL/(min·kg))	V_{ss} (L/kg)	AUC_{0-inf} (ng·h/mL)	%F
18	1 in 4	iv[c]	0.5	288		3.0	9	2.2	937	
27	1 in 4	iv	0.5	385		9.5	4	2.9	1978	
	discrete	iv	1	528		9.4	4	2.4	4650	
	discrete	po[d]	5		414	9.3			7149	31

[a] Pharmacokinetic properties generated in female Sprague–Dawley rats. [b] Compounds were dosed as 1 in 4 cassette studies or in discrete studies. [c] Compounds dosed iv in DMSO/PEG200 20:80 vehicle. [d] Compounds dosed po in aqueous 2% Tween 80/0.5% methyl cellulose vehicle.

Table 8. Cynomolgus Monkey Menses Induction Data for **3**, **4**, **18**, and **27**[a]

compound	**3**	**4**	**18**	**27**
animals with early menstruation (%)	60	50	0	75

[a] Compounds dosed orally at 5 mg/(kg·day) on days 19–22 of the menstrual cycle. A positive result was given if menses occurred on days 22–24. Compounds were dosed in aqueous 2% Tween 80/0.5% methyl cellulose vehicle.

phosphatase assay and also in the rat decidualization assay, the lack of activity for compound **18** in the cynomolgus monkey menses induction assay and positive response for compound **27** can probably be attributed to the pharmacokinetic differences between the two compounds in the primate.

The ability of PR antagonists to block ovulation in humans has been demonstrated with mifepristone and with other steroids.[31] At higher doses, inhibition of follicular development occurs by suppressing the gonadotropin surge. At lower doses however, a delay in ovulation is induced rather than complete inhibition, which is also accompanied by a disruption of endometrial development.[32] Our nonhuman primate ovulation inhibition assay was based upon the model published by Hodgen and co-workers, who demonstrated that mifepristone **3** inhibited ovulation in 5 out of 6 normally cycling cynomolgus monkeys (1 mg/kg im).[33]

To determine the effect of compound **27** on ovulation in the nonhuman primate, normal cycling cynomolgus monkeys were treated orally with **27** for 30 days starting on day 2 of the menstrual cycle (day 1 = first day of menses), Figure 3. The compound (10, 3, or 1 mg/kg) was given daily in 2% Tween 80/0.5% methylcellulose vehicle. Blood samples were taken 3 times per week (Monday, Wednesday, and Friday), and ovulation was monitored through the measurement of serum progesterone levels. Animals treated with vehicle showed elevated progesterone levels during luteal phase, indicating the formation of a functional corpus luteum after ovulation. In contrast, all four animals treated with 10 mg/kg of **27** showed only basal levels of progesterone throughout the entire treatment cycle, suggesting complete inhibition of ovulation. Among the six animals treated with 3 mg/kg of **27**, only one monkey had a luteal phase progesterone surge. The other five animals showed only basal levels of progesterone, indicating that no ovulation occurred. Among the four monkeys treated with 1 mg/kg of **27**, one monkey showed inhibition of ovulation. Ordinary least-squares analysis of this data indicates an ED_{50} for ovulation inhibition of approximately 1.6 mg/kg.

Compound **27** was further evaluated in the rhesus macaque to study its effect upon ovulation and upon the reproductive tract. For this study, three adult female rhesus macaques with regular menstrual cycles were assigned and allowed to complete one full menstrual cycle. Beginning on day 2 of the next cycle (day 1 = first day of menses), the animals were treated with **27** (10 mg/(kg·day), po, 2% Tween 80/0.5% methylcellulose with artificial cherry flavoring) for 28 days. Blood was collected every 3 days (mid-day), and serum was assayed for estradiol and progesterone to monitor ovarian function. Additional samples were collected as needed to identify the midcycle surge of estradiol. Ovulation was monitored by blood ovarian steroid profile. The reproductive tract was collected at the end of study for histological and immunocytochemical analyses.

Similar to the cynomolgus study above none of the animals treated with **27** showed a rise in luteal phase progesterone, indicating that ovulation was blocked. Only one animal in this group showed a significant midcycle estradiol surge. Laparoscopic examination revealed no evidence of an ovulatory site on the ovaries of this animal. No laparoscopic examination was conducted on the other two animals because there was no evidence of an estradiol surge or increase in serum progesterone indicative of a functional corpus luteum.

The effect of **27** on the uterus was evaluated at necropsy (day 28), Table 10. All the animals treated with **27** had thin-atrophied endometria relative to the endometrium from animals collected during the normal luteal phase (2.2 ± 0.33 mm and 60 ± 21 mg for **27** treated animals; 4.6 ± 0.7 mm and 430 ± 26 mg for luteal-phase vehicle control). Compared with luteal phase animals, which have secretory endometria with sacculated glands, the endometrium of **27** treated animals was generally proliferative in appearance with tubular glands. Myometrial compaction is also apparent for **27** treated animals (1760 ± 517 mg and 2213 ± 177 mg for **27** and luteal-phase control animals, respectively).

The menses induction, ovulation inhibition, and reproductive tract histology are consistent with compound **27** behaving as a progesterone antagonist in the primate.

In summary, we have further explored the SAR in the 5-aryloxindole class of progesterone receptor modulators. We found a subseries of cyano-pyrroles that possess an additional functional motif, the size of the 3,3-substituent, which determines the functional activity (agonist or antagonist) of the compound *in vitro*. Selected examples were found that have excellent *in vivo* properties in the rat decidualization model, possessing potencies similar to the steroidal comparator mifepristone **3**. The pharmacokinetic properties of these compounds support the observed *in vivo* activity. Compound **27** was found to be an active PR antagonist in the cynomolgus monkey and in the rhesus macaque. Compound **27** was advanced into phase 0 studies to be studied as a contraceptive agent in women.

Experimental Procedures

Chemistry. Solvents were purchased as anhydrous grade and used without further purification. Reagents were purchased from commercial suppliers and used without purification. 1H NMR spectra were recorded on a Varian Inova 400 instrument with chemical shifts reported in d values (parts per million, ppm) relative to an internal standard (tetramethylsilane). High-resolution mass spectra were obtained on an Agilent TOF. Low-resolution electrospray (ESI) mass spectra were recorded on a Waters Alliance ZMD instrument. Low-resolution electron impact (EI, EE = 70 eV) mass spectra were recorded on a Finnigan Trace mass spectrometer. Analytical thin layer chroimatography (TLC) were performed on precoated glass plates (silica gel F-254) and visualized under UV light.

Table 9. Female Cynomolgus Monkey Pharmacokinetic Parameters for Compounds **18** and **27**[a]

compound	study design[b]	route	dose (mg/kg)	C_0 (ng/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	Clp (mL/(min·kg))	V_{ss} (L/kg)	AUC_{0-inf} (ng·h/mL)	%F
18	1 in 4	iv[c]	0.25	241		2.1	12	1.6	343	
27	1 in 4	iv[c]	0.25	178		8.8	7	3.9	578	
	discrete	iv[c]	1	856		7.8	7	3.4	2358	
	discrete	po[d]	5		179	15.7			5738	49

[a] Pharmacokinetic properties generated in female cynomolgus monkeys. [b] Compounds were dosed as 1 in 4 cassette studies or in discrete studies. [c] Compounds dosed iv in DMSO/PEG200 20:80 vehicle. [d] Compounds dosed po in aqueous 2% Tween 80/0.5% methyl cellulose vehicle.

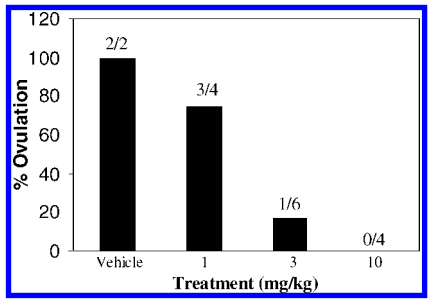


Figure 3. Ovulation inhibition data for **27** in cycling cynomolgus monkeys. Ovulation is determined by a luteal phase progesterone surge. The number of animals in each treatment group and those experiencing ovulation are indicated above the bars.

Table 10. Effect of **27** on Ovulation, Uterine and Oviductal Morphometrics, and Cell Proliferation in Naturally Cycling Macaques[a]

	27 ($n = 3$)	luteal-phase control ($n = 5$)
ovulation rate	0/3	5/5
endometrial weight (mg)[b]	60 ± 21	430 ± 26
endometrial thickness (mm)	2.2 ± 0.33	4.6 ± 0.7
myometrial weight (mg)	1760 ± 517	2213 ± 177
functionalis KI-67[c]	105 ± 34.0	0
functionalis mitotic index[d]	2.2 ± 1.0	0
basalis mitotic index	0	5.5 ± 1.15
basalis KI-67[c]	0	39 ± 5

[a] Luteal-phase animals represent values from animals used under other studies.[34,35] Unless otherwise indicated values represent mean ± SE. [b] Endometrial and myometrial weight indicate the weight of 1/2 of the uterus. [c] KI-67 index represents the number of KI-67 labeled cells per 1000 cells counted. [d] Mitotic index represents the number of mitotic cells per 1000 cells counted.

5-(2-Oxoindolin-5-yl)-1*H*-pyrrole-2-carbonitrile (12). Step 1. *tert*-Butyl 2-(2-oxoindolin-5-yl)-1*H*-pyrrole-1-carboxylate. A mixture of 5-bromo-oxindole (1.34 g, 6.35 mmol), 1-(*tert*-butoxycarbonyl)-1*H*-pyrrol-2-ylboronic acid (2.67 g, 12.7 mmol), and sodium carbonate (2.70 g, 25.4 mmol) in THF (75 mL) and water (25 mL) was degassed by passage of nitrogen gas. To this mixture was added tetrakis(triphenylphoshine)palladium(0) (0.30 g), and the mixture heated under reflux (16 h). The reaction mixture was cooled to room temperature, then poured into water and extracted into EtOAc, dried ($MgSO_4$), and evaporated. The residue was then purified by silica gel column chromatography (hexanes/acetone 100:0−50:50) to afford the product (0.89 g, 47%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (br s, 1H), 7.24 (dd, $J = 3.3$ and 1.8 Hz), 7.09 (s, 1H), 7.05 (dd, $J = 7.9$ and 1.8 Hz, 1H), 6.75 (d, $J = 7.9$ Hz, 1H), 6.18 (t, $J = 3.3$ Hz, 1H), 6.10 (dd, $J = 3.3$ and 1.8 Hz), 3.43 (s, 2H), and 1.27 (s, 9H). MS (ESI, $[M + H]^+$) 299.1.

Step 2. *tert*-Butyl 2-cyano-5-(2-oxoindolin-5-yl)-1*H*-pyrrole-1-carboxylate. To a solution of the last cited product (0.85 g, 2.89 mmol) in dry CH_2Cl_2 (30 mL) at −78 °C was added chlorosulfonyl isocyanate (0.21 mL, 2.38 mmol) dropwise. After 1 h, dry DMF (1.3 mL) was added dropwise; the reaction was allowed to warm up to room temperature. After 1 h, the mixture was poured into saturated sodium hydrogen carbonate solution, washed with water, dried ($MgSO_4$), and evaporated. The residue was then purified by silica gel column chromatography (hexanes/acetone 100:0−0:100) to afford the product (0.25 g, 26%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (br s, 1H), 7.23 (d, $J = 3.7$ Hz, 1H), 7.19 (s, 1H), 7.15−7.13 (m, 1H), 6.80 (d, $J = 7.9$ Hz, 1H), 6.32 (d, $J = 3.8$ Hz, 1H), 3.45 (s, 2H), and 1.30 (s, 9H). MS (ESI, $[M + H]^+$) 324.0. HRMS calculated for $C_{18}H_{17}N_3O_3 + H^+$ 324.1343; found (ESI, $[M + H]^+$) 324.1347.

Step 3. 5-(2-Oxoindolin-5-yl)-1*H*-pyrrole-2-carbonitrile (12). A solution of *tert*-butyl 2-cyano-5-(2-oxoindolin-5-yl)-1*H*-pyrrole-1-carboxylate (0.23 g, 0.71 mmol) in dry DMA (5 mL) was heated to 175 °C under nitrogen (30 min). After cooling to room temperature, the mixture was poured into water and extracted with EtOAc (×2), washed with water (×2), dried ($MgSO_4$), and evaporated. The residue was then purified by silica gel column chromatography (hexanes/acetone 100:0−0:100) to afford the title compound **12** (0.80 g, 49%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 10.49 (s, 1H), 7.59 (s, 1H), 7.55 (dd, $J = 8.1$ and 1.8 Hz, 1H), 6.95 (d, $J = 3.8$ Hz, 1H), 6.85 (d, $J = 8.1$ Hz, 1H), 6.57 (d, $J = 3.8$ Hz, 1H), and 3.53 (s, 2H). HRMS calculated for $C_{13}H_{10}N_3O + H^+$ 224.0828; found (ESI, $[M + H]^+$) 224.0818.

1-Methyl-5-(2-oxo-2,3-dihydro-1H-indol-5-yl)-1H-pyrrole-2-carbonitrile (13). 1-Methyl-1*H*-pyrrole-2-carbonitrile (0.5 g, 4.8 mmol) and tri-*iso*-propylborate (1.1 mL, 4.8 mmol) were dissolved in THF (12 mL) and cooled to 0 °C. LDA (2.5 mL, 5 mmol, 2 M) was added over 10 min. The reaction was stirred (30 min) and then allowed to warm up to room temperature.

In a separate flask, 5-bromoindolin-2-one (0.30 g, 1.42 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.030 g) were dissolved in THF (12 mL) and stirred under nitrogen (15 min). The above prepared boron complex was transferred (via syringe) to this solution, followed by addition of potassium carbonate (0.70 g, 5 mmol) and water (6 mL). The mixture was then heated under reflux (3 h). The reaction mixture was cooled to room temperature, then poured into water and extracted into EtOAc, dried ($MgSO_4$), and evaporated. The residue was then purified by silica gel column chromatography (hexanes/EtOAc 8/2 then 6/4) to afford the title compound (**13**) (0.035 g, 11%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 7.35 (s, 1H) 7.32 −7.29 (m, 1H), 7.00 (d, $J = 4.0$ Hz, 1H), 6.91 (d, $J = 8.0$ Hz, 1H), 6.25 (d, $J = 4.0$ Hz, 1H), 3.69 (s, 3H), and 3.54 (s, 2H). HRMS calculated for $C_{14}H_{11}N_3O + H^+$ 238.09749; found (ESI, $[M + H]^+$) 238.0985.

5-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrrole-2-carbonitrile (18). Step 1. 3,3-Dimethylindolin-2-one. Dimethylindolin-2-one was prepared according to a reported procedure.[23] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (br s, 1H), 7.21 (d, $J = 7.4$ Hz, 1H), 7.10 (dt, $J = 7.7$ and 1.3 Hz, 1H), 7.08 (dt, $J = 7.4$ and 0.9 Hz, 1H), 6.78 (d, $J = 7.7$ Hz, 1H), and 1.18 (s, 6H).

Step 2. 5-Bromo-3,3-dimethylindolin-2-one. 3,3-Dimethylindol-2-one (0.65 g, 4.03 mmol) and sodium acetate (0.33 g, 4.07 mmol) were stirred in acetic acid (5 mL); then bromine (0.66 g, 4.13 mmol) in acetic acid (5 cm^3) was added dropwise to the reaction mixture. The reaction was stirred for 50 min and then poured into water. The mixture was basified with sodium carbonate and then extracted with ethyl acetate (×3), dried ($MgSO_4$), filtered, and evaporated to provide the title compound, which required no further purification (0.89 g, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (br s, 1H), 7.47 (d, $J = 2.0$ Hz, 1H), 7.28 (dd, $J = 8.2$ and 2.0 Hz, 1H), 6.75 (d, $J = 8.2$ Hz, 1H), and 1.20 (s, 6H).

Step 3. 5-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrrole-2-carbonitrile (18). The title compound was prepared from 5-bromo-3,3-dimethylindolin-2-one (14.4 g, 60 mmol) according to the procedure described for compound (**13**) and purified by silica gel column chromatography (hexanes/EtOAc 3:1−1:1) to afford the title compound (**18**) (1.76 g, 11%). ^{1}H NMR

(400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 7.47 (s, 1H), 7.30 (dd, J = 8.0 and 1.9 Hz, 1H), 7.02 (d, J = 3.8 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.35 (d, J = 3.7 Hz, 1H), 3.71 (s, 3H), and 1.30 (s, 6H). HRMS calculated for $C_{16}H_{15}N_3O + H^+$ 266.12934; found (ESI, $[M + H]^+$) 266.1298.

5-(3,3-Diethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (19). Step 1. 3-Ethyl-indol-2-one. A solution of oxindole (40 g, 0.3 mol) in dry THF (400 mL) under N_2 was cooled to −25 °C and treated dropwise with *n*-butyl lithium (2.5 M in hexanes, 240 mL, 0.6 mol). To the resulting solution was added *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (90.4 mL, 0.6 mol). After 30 min, iodoethane (48 mL, 0.6 mol) was added, and the reaction mixture was allowed to warm to room temperature. After 16 h, the reaction was quenched (saturated NH_4Cl solution), extracted with EtOAc, washed with diluted HCl, water, and brine, dried ($MgSO_4$), and evaporated. The residual oil was triturated with hexane to afford the crude product (24.5 g, 51%). A sample (3 g) was recrystallized from EtOAc/hexane to obtain the title compound (1.4 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.3 (s, 1H), 7.22 (m, 1H), 7.15 (m, 1H), 6.93 (dt, J = 7.45 and 1.10 Hz, 1H), 6.8 (dt, J = 7.69 and 0.45 Hz, 1H), 3.38 (t, J = 5.7 Hz, 3H), 1.8–2.0 (m, 2H), and 0.76 (t, J = 7.5 Hz, 3H). MS (ESI, $[M + H]$) *m*/*z* 270.

Step 2. 3,3-Diethyl-indol-2-one. 3-Ethylindol-2-one (16 g, 0.1 mol) was resubjected to the conditions described in the preceding experiment to afford the title product (9.0 g, 45%), mp 156–159 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s,1H), 7.70−7.69 (t, 1H), 7.62−7.59 (m, 1H), 7.58 (d,1H J = 1.7 Hz), 7.53–7.50 (m, 1H), 7.45−7.41 (t,1H), 7.36−7.35 (m, 1H), 7.34−7.33 (m, 1H), 6.91−6.89 (d, 1H J = 8.2 Hz), 1.87−1.80 (m, 2H), 1.77−1.70 (m, 2H), and 0.54−0.50 (t, 6H). MS (+ESI, $[M + H]$) *m*/*z* 190. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (br s, 1H), 7.18−7.14 (m, 2H), 6.99 (dt, J = 10.7 and 1.0 Hz, 1H), 6.83 (dd, J = 7.9 and 0.8 Hz, 1H), 1.76–1.67 (m, 4H), and 0.50 (t, J = 7.4 Hz, 6H). MS (+ESI, $[M + H]^+$) *m*/*z* 190.

Step 3. 5-Bromo-3,3-diethyl-1,3-dihydro-indol-2-one. 5-Bromo-3,3-diethyl-1,3-dihydro-indol-2-one was prepared following the procedure for compound **18** step 2, from 3,3-diethyl-1,3-dihydro-indol-2-one (0.5 g, 2.6 mmol) affording the product, which was used without further purification (0.6 g, 85%), as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-δ_6) d 10.45 (s, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.34−7.31 (m, 1H), 6.77 (d, 1H J = 8.2 Hz, 1H), 1.78–1.65 (m, 4H), and 0.50−0.46 (m, 6H). MS (−ESI [M − H]) *m*/*z* 266/268.

Step 4. 5-Cyano-1-methyl-1*H*-pyrrol-2-ylboronic acid (16). To a solution of 1-methyl-1*H*-pyrrole-2-carbonitrile (1.20 g, 11.3 mmol) in dry THF (35 mL) at 0 °C was added tri-iso-propyl borate (2.6 mL, 11.3 mmol) and lithium di-iso-propylamine (7.3 mL, 14.7 mmol 2.0 M, in THF/hexane/ethylbenzene). The reaction was allowed to warm to room temperature and stirred (2 h). The mixture was quenched (saturated aq NH_4Cl) and extracted with EtOAc (3×). The organic layer was dried (Na_2SO_4), and evaporated (<25 °C) to give the product, which was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37 (bs, 2H), 6.87 (d, J = 4.0 Hz, 1H), 6.77 (d, J = 4.1 Hz, 1H), and 3.88 (s, 3H).

Step 5. 5-(3,3-Diethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (19). To a solution of 5-bromo-3,3-diethyl-1,3-dihydro-indol-2-one (0.6 g, 0.20 mmol) in dry THF (55 mL) was added tetrakis(triphenylphosphine)palladium(0) (0.26 g) after evacuation and purging with nitrogen. After 20 min, potassium carbonate (1.5 g, 11.1 mmol) and the above-prepared boronic acid were added, followed by water (13 mL). The mixture was heated under reflux (16 h). The reaction mixture was cooled and filtered through Celite, which was washed with EtOAc. The combined organic layers were washed with water and brine, then dried (Na_2SO_4) and evaporated. The residue was then purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:99–4:99) followed by further purification by silica gel column chromatography (hexanes/EtOAc 5:1−2:1) to give the title compound (**19**) (320 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (bs, 1H), 7.23 (dd, J = 7.9 and 1.8 Hz, 1H), 7.12 (s, 1H), 6.96 (d, J = 7.9 Hz, 1H), 6.85 (d, J = 4.0 Hz, 1H), 6.21 (d, J = 4.0 Hz, 2H), 3.72 (s, 3H), 1.98−1.93 (m, 2H), 1.86–1.77 (m, 2H), and 0.69 (t, J = 7.3 Hz, 6H). HRMS calculated for $C_{18}H_{19}N_3O + H^+$ 294.16009; found (ESI, $[M + H]^+$) 294.1616.

1-Methyl-5-(2′-oxo-1′,2′-dihydrospiro[cyclopentane-1,3′-indol]-5′-yl)-1*H*-pyrrole-2-carbonitrile (20). Step 1. Spiro[cyclopentane-1,3′-[3*H*]indol]-2′(1′*H*)-one. Spiro[cyclopentane-1,3′-[3*H*]indol]-2′(1′*H*)-one was prepared according to a described procedure[23] from oxindole (2.0 g, 15.0 mmol) to afford the product (1.4 g, 50%) as a tan solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (br s, 1H), 7.25−7.14 (m, 2H), 7.01 (dd, J = 7.5 and 1.0 Hz, 1H), 6.94 (dd, J = 7.5 and 1.0 Hz, 1H), and 2.2−1.80 (m, 8H).

Step 2. 5-Bromo-spiro[cyclopentane-1,3′-[3*H*]indol]-2′(1′*H*)-one. Prepared following the procedure for compound **18**, step 2, from spiro[cyclopentane-1,3′-[3*H*]indol]-2′(1′*H*)-one (0.27 g, 1.4 mmol) to afford the title compound (0.37 g, 96%) as an off-white solid, which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (br s, 1H), 7.39–7.30 (m, 2H), 6.79 (d, J = 8.0 Hz, 1H), and 2.27−1.80 (m, 8H).

Step 3. 1-Methyl-5-(2′-oxo-1′,2′-dihydrospiro[cyclopentane-1,3′-indol]-5′-yl)-1*H*-pyrrole-2-carbonitrile (20). Compound **20** was prepared according the procedure for compound **19**, step 5, from 5-bromo-spiro[cyclopentane-1,3′-[3*H*]indol]-2′(1′*H*)-one (0.30 g, 1.12 mmol) and purified by silica gel column chromatography (hexanes/acetone 100:0−0:100) to afford the title compound **20** (0.23 g, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 7.36 (d, J = 1.6 Hz, 1H), 7.28 (dd, J = 7.9 and 1.7 Hz, 1H), 7.00 (d, J = 4.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.29 (d, J = 4.0 Hz, 1H), 3.70 (s, 3H), 2.02−1.93 (m, 6H), and 1.84−1.80 (m, 2H). HRMS calculated for $C_{18}H_{17}N_3O + H^+$ 292.1444; found (ESI, $[M + H]^+$) 292.1463.

5-(Spiro[cyclohexane-1,3′-[3*H*]indole]-2′-oxo-5′-yl)-1*H*-pyrrole-1-methyl-2-carbonitrile (21). Step 1. Spiro[cyclohexane-1,3′-[3*H*]indol]-2′-(1′*H*)one. Spiro[cyclohexane-1,3′-[3*H*]indol]-2′-(1′*H*)one was prepared according to a described procedure[23] from oxindole (25.0 g, 0.19 mol) to afford the product (26.3 g, 69.6%) as colorless crystals, mp 110–114 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.3 (br s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 8 Hz, 7.17 (t, 1H, J = 8 Hz), 6.94 (t, J = 8.0 Hz, 1H), 6.84 (d, 1H, J = 8.0 Hz, 1H), and 1.67 (m, 10H).

Step 2. 5′-Bromospiro[cyclohexane-1,3′-[3*H*] indol]-2′(1′*H*)-one. 5′-Bromospiro[cyclohexane-1,3′-[3*H*] indol]-2′(1′*H*)-one was prepared following the procedure for compound **18**, step 2, from spiro[cyclohexane-1,3′-[3*H*]indol]-2′(1′*H*)-one (17.6 g, 0.09 mol) to afford the product (16.5 g, 67%) as off-white crystals, mp 196 −199 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.62 (m, 10H), 6.8 (d, 1H, J = 6.8 Hz), 7.36 (d, 1H, J = 8.2, 1.8 Hz), 7.58 (dd, 1H, J = 8.2, 1.8 Hz), 10.44 (S, 1H), 10.44 (s, 1H), 7.58 (dd, J = 8.2 and 1.8 Hz, 1H), 7.36 (d, J = 8.2 and 1.8 Hz, 1H), 6.80 (d, J = 6.8 Hz, 1H), and 1.62 (m, 10H).

Step 3. 5-(Spiro[cyclohexane-1,3′-[3*H*]indole]-2′-oxo-5′-yl)-1*H*-pyrrole-1-methyl-2-carbonitrile (21). The title compound was prepared from 5′-bromospiro[cyclohexane-1,3′-indolin]-2′-one (0.51 g, 1.8 mmol) according to the procedure for compound **12** and purified by silica gel column chromatography (hexanes/acetone 100:0−0:100) to afford the product (**21**) (0.38 g, 68%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 7.55 (d, J = 1.7 Hz, 1H), 7.31 (dd, J = 8.0 and 1.8 Hz), 7.01 (d, J = 4.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.29 (d, J = 4.0 Hz), 3.71 (s, 3H), 1.88−1.85 (m, 2H), and 1.72−1.57 (m, 8H). MS (ESI, $[M + H]^+$) *m*/*z* 304.

5-(4-Fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (25). Step 1. 2-(2-Fluoro-6-nitro-phenyl)-malonic Acid Dimethyl Ester. To a solution of 2,3-difluoronitrobenzene (9.0 g, 56 mmol) in DMF was added potassium carbonate (13.8 g, 100 mmol) and dimethylmalonate (6.88 mL, 60 mmol), and the reaction was heated to 65 °C (24 h.). After cooling to room temperature, the mixture was neutralized (dilute HCl) and extracted with Et_2O; the organic layers were dried ($MgSO_4$) and evaporated. The crude product was crystallized from hexanes/EtOAc (95:5) to afford the product (6.60 g, 43%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96−7.94 (m, 1H), 7.78–7.71 (m, 1H), 5.52 (s, 1H),

and 3.70 (s, 6H). HRMS calculated for $C_{11}H_{10}FNO_6 + H^+$ 272.05649; found (ESI, $[M + H]^+$) 272.0576.

Step 2. (2-Fluoro-6-nitrophenyl)acetic acid. 2-(2-Fluoro-6-nitro-phenyl)-malonic acid dimethyl ester (6.50 g, 23.98 mmol) and hydrochloric acid (200 mL, 6 N) were heated under reflux (24 h). After the mixture was cooled to room temperature, the solid was collected, washed with water, and dried *in vacuo* to give the product (3.30 g, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) 12.76 (br s, 1H), 7.95 (dd, $J = 8.1$ and 1.2 Hz, 1H), 7.72−7.59 (m 2H), and 3.91 (s, 2H). HRMS calculated for $C_{11}H_{10}FNO_6 + H^+$ 272.05649; found (ESI, $[M + H]^+$) 272.0576.

Step 3. 4-Fluoro-1,3-dihydro-2*H*-indol-2-one. 2-Fluoro-6-nitrophenyl)acetic acid (3.30 g, 16.6 mmol) was dissolved in acetic acid (20 mL) and hydrogenated (50 psi) over palladium on carbon (10%, 0.5 g). After 24 h, the catalyst was removed by filtation through Celite, the filter pad was washed with methanol, and the combined organics were evaporated. The mixture was then dissolved in ethanol (100 mL), treated with *para*-toluenesulfonic acid (0.05 g), and heated under reflux (1 h). The cooled mixture was poured into water, extracted with EtOAc, dried ($MgSO_4$), and evaporated. The solid was triturated (hexanes/EtOAc 95:5) to afford the product (1.70 g, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H, NH), 7.19–7.13 (m, 1H), 6.72 (t, $J = 8.59$, 1H), 6.61 (d, $J = 7.81$, 1H), and 3.48 (s, 2H). HRMS calculated for $C_8H_6FNO + H^+$ 152.05062; found (ESI, $[M + H]^+$) 152.0525.

Step 4. 4-Fluoro-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one. 4-Fluoro-1,3-dihydro-2*H*-indol-2-one (3.40 g, 22.5 mmol) and lithium chloride (2.7 g, 60 mmol) were dissolved in THF (100 mL). The solution was cooled (−78 °C), and *n*-butyl lithium (7 mL, 2.5 M in hexanes, 15 mmol) was added slowly over 15 min. Methyl iodide (3.1 mL, 50 mmol) was added, and the mixture allowed to warm up to room temperature. After 16 h, the mixture was poured into water and extracted with EtOAc; the organic layer was dried ($MgSO_4$) and evaporated. The resiude was purified by silica gel column chromatography (hexanes/EtOAc 90:10−80:20) to afford the product (1.00 g, 25%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 7.20–7.15 (m, 1H), 6.72 (t, $J = 8.84$, 1H), 6.67 (d, $J = 7.66$, 1H), and 1.29 (s, 6H). HRMS calculated for $C_{10}H_{10}FNO + H^+$ 180.08192; found (ESI, $[M + H]^+$) 180.0816.

Step 5. 5-Bromo-4-fluoro-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one. 4-Fluoro-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one (1.00 g, 22.9 mmol) was dissolved in CH_2Cl_2 (50 mL) and acetic acid (2 mL) was added. Bromine (0.38 mL, 7.5 mmol) was added dropwise, and the solution was allowed to stir (16 h). The reaction mixture was poured into saturated sodium thiosulfate solution, extracted with Et_2O, dried ($MgSO_4$), and evaporated. The residue was washed with hexane to afford the product (1.25 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 7.5 (dd, $J = 7.15$ and 1.04 Hz, 1H), 6.69 (d,$J = 8.31$ Hz, 1H), and 1.34 (s, 6H). HRMS calculated for $C_{10}H_9BrFNO + H^+$ 257.99243; found (ESI, $[M + H]^+$) 257.9936.

Step 6. 5-(4-Fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (25). 5-Bromo-4-fluoro-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one (1.25 g, 4.86 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.4 g) were dissolved in ethylene glycol dimethyl ether (40 mL) and stirred 15 min. *N*-Methyl-5-cyanopyrroleboronic acid (2.00 g, 13.33 mmol) and potassium carbonate (3.48 g, 25 mmol) were added, followed by water (20 mL), and the mixture was heated under reflux (16 h). After cooling to room temperature, the mixture was poured into water, neutralized (dilute HCl), and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and evaporated. The product was purified by silica gel column chromatography (hexanes/THF 90:10−70:30) to afford the title compound (**25**) (0.060 g, 5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 7.25 (t, $J = 7.8$, 1H), 7.01 (d, $J = 4.1$, 1H), 6.79 (d, $J = 7.9$ Hz, 1H), 6.26 (d, $J = 4.00$ Hz, 1H), 3.56 (s, 3H), and 1.34 (s, 6H). HRMS calcd for $C_{16}H_{14}FN_3O + H^+$ 284.11937; found (ESI, $[M + H]^+$) 284.1193.

5-(6-Fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (26). Step 1. Dimethyl 2-(4-Fluoro-2-nitrophenyl)malonate. Dimethyl 2-(4-fluoro-2-nitrophenyl)malonate was prepared according to the procedure for compound **25**, step 1, from 2,5-difluoronitrobenzene (7.95 g, 70 mmol). The product was recrystallized from hexanes/CH_2Cl_2 to afford the product (7.10 g, 37%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (dd, $J = 8.7$ and 2.7 Hz, 1H), 7.70 (dt, $J = 7.9$ and 2.9 Hz, 1H), 7.62 (dd, $J = 8.7$ and 5.6 Hz, 1H), 5.50 (s, 1H), and 3.70 (s, 6H). HRMS calculated for $C_{11}H_{10}FNO_6 + H^+$ 272.05649; found (ESI, $[M + H]^+$) 272.0561.

Step 2. 2-(4-Fluoro-2-nitrophenyl)acetic acid. 2-(4-Fluoro-2-nitrophenyl)acetic acid was prepared according to the procedure for compound **25**, step 2, from dimethyl 2-(4-fluoro-2-nitrophenyl)malonate (7.10 g, 26.1 mmol). The isolated product (3.94 g, 75%) was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H), 7.99 (dt, $J = 8.0$ and 2.2 Hz, 1H), 7.67−7.60 (m, 2H), and 3.99 (s, 2H).

Step 3. 6-Fluoroindolin-2-one. 6-Fluoroindolin-2-one was prepared according to the procedure for compound **25**, step 3, from 2-(4-fluoro-2-nitrophenyl)acetic acid (3.94 g, 19.79 mmol). The isolated product (2.67 g, 89%) was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 7.22−7.18 (m, 1H), 6.72 (dt, $J = 9.1$ and 2.5 Hz, 1H), 6.61 (dd, $J = 9.4$ and 2.5 Hz), and 3.44 (s, 2H). HRMS calculated for $C_8H_6FNO + H^+$ 152.05062; found (ESI, $[M + H]^+$) 152.0567.

Step 4. 6-Fluoro-3,3-dimethylindolin-2-one. 6-Fluoro-3,3-dimethylindolin-2-one was prepared according to the procedure for compound **25**, step 4, from 6-fluoroindolin-2-one (1.52 g, 10 mmol). The residue was purified by silica gel column chromatography (hexanes/EtOAc 80:20) to afford the product (0.47 g, 23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 7.29 (dd, $J = 8.2$ and 5.6 Hz, 1H), 6.78−6.72 (m, 1H), 6.65 (dd, $J = 9.3$ and 2.5 Hz, 1H), and 1.23 (s, 6H).

Step 5. 5-Bromo-6-fluoro-3,3-dimethylindolin-2-one. 5-Bromo-6-fluoro-3,3-dimethylindolin-2-one was prepared according to the procedure for compound **25**, step 5, from 6-fluoro-3,3-dimethylindolin-2-one (0.67 g, 3.76 mmol). The isolated product (0.88 g, 90%) was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 7.66 (d, $J = 6.9$ Hz, 1H), 6.82 (d, $J = 9.0$ Hz, 1H), and 1.25 (s, 6H). HRMS calculated for $C_{10}H_{10}FNO$ 179.07464; found (ESI, M^+) 179.0742.

Step 6. 5-(6-Fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (26). Compound **26** was prepared following the procedure for compound **12** from 5-bromo-6-fluoro-3,3-dimethylindolin-2-one (0.88 g, 3.40 mmol). The residue was purified by silica gel column chromatography (hexanes/EtOAc 80:20−75:25) to afford the title compound **26** (0.27 g, 28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 7.41 (d, $J = 7.4$ Hz, 1H), 7.04 (d, $J = 4.0$ Hz, 1H), 6.81 (d, $J = 10.1$ Hz, 1H), 6.29 (d, $J = 4.0$ Hz, 1H), 3.59 (d, $J = 1.2$ Hz, 3H), and 1.28 (s, 6H). HRMS calculated for $C_{16}H_{14}FN_3O + H^+$ 284.11937; found (ESI, $[M + H]^+$) 284.1206.

5-(7-Fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (27). Step 1. 2-(3-Fluoro-2-nitro-phenyl)-malonic acid dimethyl ester. 2-(3-Fluoro-2-nitrophenyl)-malonic acid dimethyl ester was prepared following the procedure for compound **25**, step 1, from 2,6-difluoronitrobenzene (5.00 g, 31.44 mmol). Crystallization from hexanes/EtOAc (95:5) afforded the product (4.60 g, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81–7.75 (m, 1H), 7.69–7.64 (m, 1H,), 7.43 (d, $J = 7.93$, 1H), 5.32 (s, 1H), and 3.71 (s, 6H). HRMS calculated for $C_{11}H_{10}FNO_6$ 271.0492; found (ESI, $[M + H]^+$) 272.0576.

Step 2. (3-Fluoro-2-nitro-phenyl)-acetic acid. (3-Fluoro-2-nitrophenyl)-acetic acid was prepared following the procedure for compound **25**, step 2, from 2-(3-fluoro-2-nitro-phenyl)-malonic acid dimethyl ester (12.00 g, 44 mmol). Crystallization from hexanes/EtOAc (95:5) gave the product (7.60 g, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (s, 1H), 7.62–7.67 (m, 1H), 7.47–7.52 (m, 1H), 7.35 (d, $J = 7.80$, 1H), and 3.84 (s, 2H). MS (ESI, $[M - H]^-$) *m*/*z* 197.9.

Step 3. 7-Fluoro-1,3-dihydro-indol-2-one. 7-Fluoro-1,3-dihydro-indol-2-one was prepared following the procedure for compound **25**, step 3, from (3-fluoro-2-nitro-phenyl)-acetic acid (9.60 g, 48 mmol). The residue was triturated with hexanes/EtOAc (95:5) to afford the product (6.00 g, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H, NH), 7.05–7.10 (m, 2H, ArH), 6.91–6.96 (m, 1H, ArH), and 3.56 (s, 2H). HRMS calculated for $C_8H_6FNO + H^+$ 151.0433; found (ESI, $[M + H]^+$) 152.0515.

Step 4. 7-Fluoro-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one. 7-Fluoro-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one was prepared following the procedure for compound **25**, step 4, from 7-fluoro-1,3-dihydro-indol-2-one (7.30 g, 48 mmol). The residue was purified by silica gel column chromatography (hexanes/EtOAc 90:10−80:20) to afford the product (4.10 g, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 7.15 (d, J = 7.1, 1H), 7.05−7.10 (m, 1H), 6.95−7.00 (m, 1H), and 1.26 (s, 6H). HRMS calculated for $C_{10}H_{10}FNO + H^+$ 180.08192; found (ESI, $[M + H]^+$) 180.0831.

Step 5. 5-Bromo-7-fluoro-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one. 5-Bromo-7-fluoro-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one was prepared following the procedure for compound **25**, step 5, from 7-fluoro-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one (4.1 g, 22.9 mmol). The residue was triturated with hexanes to afford the product (4.84 g, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 7.45 (d, J = 1.6 Hz, 1H), 7.41 (dd, J = 9.7 and 1.6 Hz, 1H), and 1.27 (s, 6H). HRMS calculated for $C_{10}H_9BrFNO - H^+$ 255.97788; found (ESI, $[M - H]^-$) 255.9781.

Step 6. 5-(7-Fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (27). Compound **27** was prepared following the procedure for compound **19** from 5-bromo-7-fluoro-3,3-dimethyl-1,3-dihydro-2*H*-indol-2-one (3.60 g, 14 mmol) replacing THF with DMF (140 mL) as the solvent. The residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 98:2) to afford the title compound **27** (0.75 g, 19%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 7.36 (d, J = 1.4 Hz, 1H), 7.29 (dd, J = 11.2 and 1.4 Hz, 1H), 7.02 (d, J = 4.0 Hz, 1H), 6.35 (d, J = 4.0 Hz, 1H), 3.73 (s, 3H), and 1.31 (s, 6H). HRMS calculated for $C_{16}H_{14}FN_3O - H^+$ 282.10481; found (ESI, $[M - H]^-$) 282.1034.

Alternative Preparation of 5-(7-Fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (27). 5-Bromo-7-fluoro-3,3-dimethyl-1,3-dihydro-indol-2-one (5.16 g, 20.0 mmol), 1-methyl-5-cyano-2-pyrroleboronic acid (5.4 g, 36 mmol), KF (3.83 g, 66 mmol), and $Pd_2(dba)_3$ monochloroform adduct (516 mg, 0.500 mmol) were added to a 200 mL round-bottom flask under nitrogen. The flask was sealed and purged with nitrogen for 5 min. THF (50 mL) was added, and the mixture was purged with nitrogen for an additional 5 min. A solution of tri-*tert*-butylphosphine (10 wt % in hexanes; 2.97 mL, 1.00 mmol) was added via syringe, and the mixture was stirred vigorously at 25 °C for 5 h. The mixture was diluted with 250 mL of EtOAc, filtered through a plug of silica gel, washed through with 200 mL of EtOAc, and concentrated to give a crude brown/black semisolid. Purification by flash chromatography (20% acetone/hexane) afforded the title compound **27** (4.5 g, 80%) as an off-white solid.

5-(7-Fluoro-3,3-diethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (28). Step 1. 7-Fluoro-3,3-diethyl-1,3-dihydro-2*H*-indol-2-one. 7-Fluoro-3,3-diethyl-1,3-dihydro-2*H*-indol-2-one was prepared following the procedure for compound **17**, step 4, from7-fluoro-1,3-dihydro-indol-2-one (1.00 g, 6.60 mmol). The residue was purified by silica gel column chromatography (hexanes/EtOAc 90:10−80:20) to afford the product (0.40 g, 29%). ^{1}H NMR (400 MHz, DMSO) δ 10.86 (s, 1H), 7.14−6.98 (m, 3H), 1.79−1.69 (m, 4H), and 0.51 (t, J = 7.5 Hz, 6H). HRMS calculated for $C_{12}H_{14}FNO + H^+$ 207.2477; found (ESI, $[M + H]^+$) 208.1134.

Step 2. 5-Bromo-7-fluoro-3,3-diethyl-1,3-dihydro-2*H*-indol-2-one. 5-Bromo-7-fluoro-3,3-diethyl-1,3-dihydro-2*H*-indol-2-one was prepared following the procedure for compound **25**, step 5, from 7-fluoro-3,3-diethyl-1,3-dihydro-2*H*-indol-2-one (0.38 g, 1.83 mmol). The crude residue was triturated with hexanes to afford the product (0.49 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H, NH), 7.44 (dd, J = 9.75 Hz and1.69 Hz, 1H), 7.36 (d, J = 1.7 Hz, 1H), 1.91−1.68 (m, 4H), and 0.51 (t, J = 7.4 Hz, 6H). HRMS calculated for $C_{12}H_{13}BrFNO + H^+$ 286.02373; found (ESI, $[M + H]^+$) 286.024.

Step 3. 5-(7-Fluoro-3,3-diethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (28). In a 40 mL septa cap vial, 5-bromo-7-fluoro-3,3-diethyl-1,3-dihydro-2*H*-indol-2-one (0.48 g, 1.67 mmol), tris(dibenzylideneacetone) dipalladium(0) chloroform (0.042 g, 0.042 mmol), *N*-methyl-5-cyanopyrrole-2-boronic acid (0.54 g, 3.6 mmol), and potassium fluoride (0.83 g, 6.6 mmol) were combined, and THF (5 mL) was added under a nitrogen atmosphere. Tri-*tert*-butyl phosphine (0.24 mL, 0.082 mmol, 10% in hexane) was added. After 3 h, hexanes/EtOAc (50:50) was added, and the reaction mixture was filtered through a pad of silica gel. The solvent was evaporated, and the solid was recrystallized from hexanes/EtOAc to give the title compound **28** (0.25 g, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (s, 1H), 7.32−7.29 (dd, J = 11.0 J = 1.5 Hz, 1H), 7.27 (d, J = 1.4 Hz, 1H), 7.02 (d, J = 4.1 Hz, 1H), 6.37 (d, J = 4.0 Hz, 1H), 3.72 (s, 3H), 1.68–1.87 (m, 4H), and 0.56 (t, J = 7.4 Hz, 6H). HRMS calculated for $C_{18}H_{18}FN_3O + H^+$ 312.15067; found (ESI, $[M + H]^+$) 312.1507.

5-(7′-Fluoro-2′-oxo-1′,2′-dihydrospiro[cyclopentane-1,3′-indol]-5′-yl)-1-methyl-1H-pyrrole-2-carbonitrile (29). Step 1. 7′-Fluorospiro[cyclopentane-1,3′-indolin]-2′-one. 7′-Fluorospiro[cyclopentane-1,3′-indolin]-2′-one was prepared following the procedure for compound **25**, step 4, from 7-fluoro-1,3-dihydro-indol-2-one (1.00 g, 6.61 mmol). The residue was purified by silica gel column chromatography (hexanes/EtOAc 100:0−0:100) to afford the product (0.59 g, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (br s, 1H), 7.04−6.98 (m, 2H), 6.93−6.88 (m, 1H), 1.96−1.84 (m, 6H), and 1.74−1.67 (m, 2H). MS (ESI, $[M + H]^+$) 206.1.

Step 2. 5′-Bromo-7′-fluorospiro[cyclopentane-1,3′-indolin]-2′-one. 5′-Bromo-7′-fluorospiro[cyclopentane-1,3′-indolin]-2′-one was prepared following the procedure for compound **25**, step 5, from 7′-fluorospiro[cyclopentane-1,3′-indolin]-2′-one (0.57 g, 2.77 mmol). The product (0.76 g, 91%) was used without further purification or characterization.

Step 3. 5-(7′-Fluoro-2′-oxo-1′,2′-dihydrospiro[cyclopentane-1,3′-indol]-5′-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (29). Compound 29 was prepared according to the procedure for compound **28**, step 3, from 5′-bromo-7′-fluorospiro[cyclopentane-1,3′-indolin]-2′-one (0.56 g, 1.96 mmol). The residue was purified by silica gel column chromatography (hexanes/EtOAc 80:20−0:100) to afford the title compound **29** (0.37 g, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.42 (d, J = 1.3 Hz, 1H), 7.30 (dd, J = 11.0 and 1.4 Hz, 1H), 7.02 (d, J = 4.0 Hz, 1H), 6.35 (d, J = 4.0 Hz, 1H), 3.73 (s, 3H), 1.88−1.86 (m, 2H), and 1.71−1.56 (m, 6H). HRMS calculated for $C_{18}H_{16}FN_3O + H^+$ 310.13502; found (ESI, $[M + H]^+$) 310.1363.

5-(7′-Fluoro-2′-oxo-1′,2′-dihydrospiro[cyclohexane-1,3′-indol]-5′-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (30). Step 1. 7′-Fluorospiro[cyclohexane-1,3′-indolin]-2′-one. 7′-Fluorospiro[cyclohexane-1,3′-indolin]-2′-one was prepared according to the procedure for compound **18**, step 2, from 7-fluoroindolin-2-one (1.00 g, 6.61 mmol). The residue was purified by silica gel column chromatography (hexanes/EtOAc 90:10) and then recrystallized from hexanes to afford the product (0.40 g, 40%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 7.30 (dd, J = 7.4 and 0.6 Hz, 1H), 7.12−7.07 (m, 1H), 6.99−6.94 (m, 1H), 1.89−1.82 (m, 2H), 1.89−1.62 (m, 5H), and 1.55−1.49 (m, 3H). HRMS calculated for $C_{13}H_{14}FNO + H^+$ 220.11322; found (ESI, $[M + H]^+$) 220.1159.

Step 2. 5′-Bromo-7′-fluorospiro[cyclohexane-1,3′-indolin]-2′-one. 5′-Bromo-7′-fluorospiro[cyclohexane-1,3′-indolin]-2′-one was prepared following the procedure for compound **11**, step 2, from 7′-fluorospiro[cyclohexane-1,3′-indolin]-2′-one (0.34 g, 1.57 mmol) to afford the product (0.39 g, 83%), which was used without further purification or characterization.

Step 3. 5-(7′-Fluoro-2′-oxo-1′,2′-dihydrospiro[cyclohexane-1,3′-indol]-5′-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (30). Compound **30** was prepared according to the procedure for compound

28, step 3, from 5′-bromo-7′-fluorospiro[cyclohexane-1,3′-indolin]-2′-one (0.39 g, 1.30 mmol). The residue was purified by silica gel column chromatography (hexanes/EtOAc 90:10) to afford the title compound **30** (0.078 g, 18%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.28 (dd, J = 11.0 and 1.6 Hz, 1H), 7.24 (d, J = 1.4 Hz, 1H), 7.02 (d, J = 4.0 Hz, 1H), 6.36 (d, J = 4.0 Hz, 1H), 3.72 (s, 3H), and 2.02−1.84 (m, 8H). HRMS calculated for $C_{19}H_{18}FN_3O$ + H^+ 324.15067; found (ESI, $[M + H]^+$) 324.1517.

5-(7-Fluoro-1,3,3-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (37). To 5-(7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile **27** (0.100 g, 0.35 mmol) in dry THF (2 mL) under nitrogen was added potassium *tert*-butoxide (0.5 mL, 1 N in THF, 0.5 mmol). After 15 min, methyl iodide (31 μL, 0.5 mmol) was added, and the mixture stirred (16 h). After evaporation, the residue was purified by silica gel column chromatography (hexanes/EtOAc 100:0−0:100) to afford the title compound **37** (0.083 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (d, J = 1.6 Hz, 1H), 7.36 (dd, J = 12.6 and 1.6 Hz, 1H), 7.03 (d, J = 4.0 Hz, 1H), 6.38 (d, J = 4.1 Hz, 1H), 3.74 (s, 3H), 3.33 (d, J = 2.7 Hz, 3H), and 1.33 (s, 6H). HRMS calculated for $C_{17}H_{16}FN_3O$ + H^+ 298.13502; found (ESI, $[M + H]^+$) 298.1366.

5-(1-Ethyl-7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (38). Compound **38** was prepared following the procedure for compound **37** using ethyl iodide (40 μL, 0.5 mmol) to afford the title compound **38** (0.072 g, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (d, J = 1.6 Hz, 1H), 7.37 (dd, J = 12.7 and 1.6 Hz, 1H), 7.03 (d, J = 4.0 Hz, 1H), 6.38 (d, J = 4.0 Hz, 1H), 3.81 (q, J = 14.1 and 7.3 Hz, 2H), 3.74 (s, 3H), 1.33 (s, 6H), and 1.21 (t, J = 6.9 Hz, 3H). HRMS calculated for $C_{18}H_{18}FN_3O$ + H^+ 312.15067; found (ESI, $[M + H]^+$) 312.1524.

5-(7-Fluoro-3,3-dimethyl-2-oxo-1-propyl-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (39). Compound **39** was prepared following the procedure for compound **37** using 1-iodopropane (49 μL, 0.5 mmol) to afford the title compound **39** (0.070 g, 58%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (d, J = 1.56 Hz, 1H), 7.36 (dd, J = 12.7 and 1.6 Hz, 1H), 7.03 (d, J = 4.0 Hz, 1H), 6.38 (d, J = 4.0 Hz, 1H), 3.77−3.74 (m, 5H), 1.68−1.62(m, 2H), 1.34 (s, 6H), and 0.87 (t, J = 7.4 Hz, 3H). HRMS calculated for $C_{19}H_{20}FN_3O$ + H^+ 326.16632; found (ESI, $[M + H]^+$) 326.1652.

5-(7-Fluoro-1-isopropyl-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (40). Compound **40** was prepared following the procedure for compound **37** using 2-iodopropane (50 μL, 0.5 mmol) to afford the title compound **40** (0.055 g, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 1.6 Hz, 1H), 7.37 (dd, J = 13.2 and 1.7 Hz, 1H), 7.04 (d, J = 4.1 Hz, 1H), 6.38 (d, J = 4.0 Hz, 1H), 4.76−4.73 (m, 1H), 3.75 (s, 3H), 1.39 (d, J = 7.0 Hz, 6H), and 1.32 (s, 6H). HRMS calculated for $C_{19}H_{20}FN_3O$ + H^+ 326.16632; found (ESI, $[M + H]^+$) 326.1661.

5-(7-Fluoro-1-isobutyl-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (41). Compound **41** was prepared following the procedure for compound **37** using 2-methyliodopropane (60 μL, 0.5 mmol) to afford the title compound **41** (0.066 g, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 1.6 Hz, 1H), 7.36 (dd, J = 12.7 and 1.6 Hz, 1H), 7.03 (d, J = 4.1 Hz, 1H), 6.38 (d, J = 4.0 Hz, 1H), 3.75 (s, 3H), 3.59 (d, J = 6.6 Hz, 2H), 2.03−1.99 (m, 1H), 1.34 (s, 6H), and 0.89 (d, J = 6.6 Hz, 6H). HRMS calculated for $C_{20}H_{22}FN_3O$ + H^+ 340.18197; found (ESI, $[M + H]^+$) 340.1838.

5-(1-Cyclopentyl-7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (42). Compound **42** was prepared following the procedure for compound **37** using cyclopentyliodide (57 μL, 0.5 mmol) to afford the title compound **42** (0.034 g, 27%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 1.7 Hz, 1H), 7.36 (dd, J = 13.3 and 1.7 Hz, 1H), 7.04 (d, J = 4.0 Hz, 1H), 6.38 (d, J = 4.1 Hz, 1H), 4.89−4.84 (m, 1H), 3.75 (s, 3H), 1.88−1.82 (m, 6H), 1.67−1.62 (m, 2H), and 1.32 (s, 6H). HRMS calculated for $C_{21}H_{22}FN_3O$ + H^+ 352.18197; found (ESI, $[M + H]^+$) 352.184.

5-(1-Cyclohexyl-7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (43). Compound **43** was prepared following the procedure for compound **37** using cyclohexyl iodide (57 μL, 0.5 mmol) to afford the title compound **43** (0.004 g, 3%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (d, J = 1.7 Hz, 1H), 7.36 (dd, J = 13.4 and 1.6 Hz, 1H), 7.04 (d, J = 4.1 Hz, 1H), 6.38 (d, J = 4.0 Hz, 1H), 4.23−4.37 (m, 1H), 3.75 (s, 3H), 2.09−1.98 (m, 2H), 1.85−1.82 (m, 2H), 1.73−1.65 (m, 2H), 1.41−1.32 (m, 8H), and 1.27−1.14. HRMS calculated for $C_{22}H_{24}FN_3O$ + H^+ 366.19762; found (ESI, $[M + H]^+$) 366.1978.

5-(1-Allyl-7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (44). Compound **44** was prepared following the procedure for compound **37** using allyl iodide (45 μL, 0.5 mmol) to afford the title compound **44** (0.077 g, 68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J = 1.6 Hz, 1H), 7.34 (dd, J = 12.5 and 1.6 Hz, 1H), 7.03 (d, J = 4.1 Hz, 1H), 6.38 (d, J = 4.0 Hz, 1H), 5.99−5.91 (m, 1H), 5.16 (d, J = 1.3 Hz, 1H), 5.13 (d, J = 1.3 Hz, 1H), 4.41 (br d, J = 3.5 Hz, 2H), 3.74 (s, 3H), and 1.36 (s, 6H). HRMS calculated for $C_{19}H_{18}FN_3O$ + H^+ 324.15067; found (ESI, $[M + H]^+$) 324.1512.

5-(7-Fluoro-3,3-dimethyl-2-oxo-1-prop-2-yn-1-yl-2,3-dihydro-1*H*-indol-5-yl)-1- methyl-1*H*-pyrrole-2-carbonitrile (45). Compound **45** was prepared following the procedure for compound **37** using propargyl bromide (45 μL, 0.5 mmol) to afford the title compound **45** (0.050 g, 43%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (d, J = 1.6 Hz, 1H), 7.40 (dd, J = 12.2 and 1.4 Hz, 1H), 7.04 (d, J = 4.0 Hz, 1H), 6.39 (d, J = 4.1 Hz, 1H), 4.58 (d, J = 1.9 Hz, 2H), 3.75 (s, 3H), 3.29 (t, J = 2.2 Hz), and 1.36 (s, 6H). HRMS calculated for $C_{19}H_{16}FN_3O$ + H^+ 322.13502; found (ESI, $[M + H]^+$) 322.1350.

5-(1-Benzyl-7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (46). Compound **46** was prepared following the procedure for compound **37** using benzyl bromide (59 μL, 0.5 mmol) to afford the title compound **46** (0.077 g, 57%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (d, J = 1.6 Hz, 1H), 7.37−7.33 (m, 2H), 7.30−7.22 (m, 4H), 7.02 (d, J = 4.1 Hz, 1H), 6.36 (d, J = 4.0 Hz, 1H), 6.36 (s, 2H), 5.01 (s, 3H), 3.72 (s, 3H), and 1.41 (s, 6H). HRMS calculated for $C_{23}H_{20}FN_3O$ + H^+ 374.16632; found (ESI, $[M + H]^+$) 374.1685.

5-[7-Fluoro-3,3-dimethyl-2-oxo-1-(2-phenylethyl)-2,3-dihydro-1*H*-indol-5-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile (47). Compound **47** was prepared following the procedure for compound **37** using phenethyl bromide (67 μL, 0.5 mmol) to afford the title compound **47** (0.041 g, 28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (d, J = 1.6 Hz, 1H), 7.37 (dd, J = 12.6 and 1.6 Hz, 1H), 7.28−7.26 (m, 2H), 7.25−7.16 (m, 3H), 7.04 (d, J = 4.0 Hz), 6.39 (d, J = 4.1 Hz), 4.01 (t, J = 7.1 Hz, 2H), 3.75 (s, 3H), 2.93 (t, J = 7.1 Hz, 2H), and 1.24 (s, 3H). HRMS calculated for $C_{24}H_{22}FN_3O$ + H^+ 388.18197; found (ESI, $[M + H]^+$) 388.1806.

Methyl [5-(5-Cyano-1-methyl-1*H*-pyrrol-2-yl)-7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate (48). Compound **48** was prepared following the procedure for compound **37** using methyl bromo acetate (47 μL, 0.5 mmol) to afford the title compound **48** (0.087 g, 68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (d, J = 1.5 Hz, 1H), 7.35 (dd, J = 12.4 and 1.5 Hz, 1H), 7.04 (d, J = 4.0 Hz), 6.39 (d, J = 4.0 Hz), 4.66 (s, 1H), 3.75 (s, 3H), 3.72 (s, 3H), and 1.37 (s, 6H). HRMS calculated for $C_{19}H_{18}FN_3O_3$ + H^+ 356.14050; found (ESI, $[M + H]^+$) 356.1420.

Biology. T47D Cell Alkaline Phosphatase Assay. T47D Cell Culture. Frozen T47D cells are thawed in a 37 °C water bath and diluted to 280 000 cells/mL in culture medium (DMEM/F12 (1:1); GIBCO, BRL) supplemented with 5% (v/v) charcoal-stripped fetal bovine serum (not heat-inactivated), 100 U/mL penicillin, 100 μg/mL streptomycin, and 2 mM GlutaMax (GIBCO, BRL). To each well in a 96-well plate (Falcon, Becton Dickinson Labware), 180 μL of diluted cell suspension is added. Twenty microliters of reference or test compounds diluted in the culture medium is then added to each well. In the antagonist mode, reference antiprogestins

or test compounds are added in the presence of 1 nM progesterone. The cells are incubated at 37 °C in a 5% CO_2 humidified atmosphere for 24 h.

Alkaline Phosphatase Enzyme Assay. At the end of treatment, the medium is removed from the plate. Fifty microliters of 0.1 M Tris-HCl, pH 9.8, containing 0.2% Triton X-100 is added to each well. The plates are shaken in a titer plate shaker for 15 min. Then 150 μL of *p*-nitrophenyl phosphate (4 mM in 0.1 M Tris-HCl, pH 9.8) is added to each well. Optical density measurements are taken at 5 min intervals for 30 min at a test wavelength of 405 nM. Data is analyzed using JMP software (SAS Institute, Inc.) for both one-way analysis of variance and non-4 linear dose response analysis in both single dose and dose response studies.

Progesterone Receptor Whole Cell Competition Binding Assay. T47D Cell Culture. T47D cells are maintained in 10% RC media at 37 °C in a 5% CO_2 humidified atmosphere and needed to be split twice weekly for proper response. Cells are plated in 10% RC the day before the binding assay at 50 000 cells per well in the white, clear bottom plates.

Binding Assay. Cells plated the day prior to the assay in white clear bottom plates are used. A master compound plate is set up containing control and test compounds at 20× final desired concentration for the competition binding. Control compounds are typically run 10-fold lower than this and include a 0 or vehicle (50% DMSO/50% ethanol (v/v)) control well. A stock of 60 nM ^{3}H-progesterone (Perkin-Elmer Life Science, NET-381, typically around 102 Ci/mmol) (20×) is also prepared at a volume needed of 10 μL per well. Media on cells is replaced with 180 μL of 5% RC. Ten microliters (10 μL) of 60 nM ^{3}H-progesterone (for final concentration of 3 nM) is added immediately followed by 10 μL of 20X test or control compounds. Compounds are incubated for 3 h at 37 °C. Following incubation, media is carefully removed and cells are washed 3X with 200 μL 5% RC each wash. Fifty microliters of liquid scintillation cocktail (Beckman Coulter, Ready-Safe; cat# 141349) is added and the plates are shaken vigorously for a minimum of 15 min. Plates are read on the Wallac Microbeta 1450 plate reader.

Steroid Receptor (GAL-4) Cross Reactivity Assays. Plasmids and Cells. The ligand binding domains (LBD) of the GR (aa 485–777), MR (aa 669–984), ERα (aa 303–595), and AR (aa 644–920) were cloned into the pM GAL4-DBD vector (Clontech).

For the AR two-hybrid assay, SRC-2 (aa 620–1121) was cloned into the pVP16 vector (Clontech). For the $GAL4_{UAS}$−luciferase reporter, five copies of the 17bp GAL_{UAS} sequence along with the E1b minimal TATA promoter were cloned into the pG5basic luciferase vector (Promega). Experiments were performed in COS-7 African green monkey kidney fibroblast-like cells (ATCC no. CRL-1651) grown in phenol red free Dulbecco's modified minimum essential medium (Gibco) supplemented with 10% charcoal/dextran-treated fetal bovine serum (Hyclone).

GAL4 Fusion Assays.[27] The GAL4−steroid receptor LBD fusion plamid and $GAL4_{UAS}$−luciferase reporter plasmid (50 ng/well each) were transfected for 16 h into COS-7 cells using Fugene6 (0.5 μL/well) according to the manufacturer's protocol (Roche). In the AR assay, the addition of VP16−SRC-2 was necessary for optimal response. Cells were treated with compounds for 20 h, and luciferase activity was measured using Cell Culture Lysis Buffer and Luciferase Reagent (Promega) on a Victor2 luminometer (Perkin-Elmer).

Cynomolgus Monkey Ovulation Inhibition. The cynomolgus monkey ovulation inhibition assay was run at the Wyeth Primate Center in Pearl River, NY, following institutionally approved protocols. Regularly cycling cynomolgus monkeys were housed in individual cages. They were checked visually for menstrual status daily. Animals had experienced at least two normal menstrual cycles (27–32 days) before being enrolled into the study. The animals (n = 2–6 per group) were assigned to the following treatment groups: vehicle control (n = 2) and test compound at 1.0 (n = 4), 3.0 (n = 6), and 10.0 (n = 4) mg/(kg·day). Since some animals were used for more than one treatment, they were allowed to rest for at least two cycles before reassignment for the next treatment, except the vehicle-treated group in which animals were rested for one cycle. The monkeys were treated for 30 days (day 2–31; the first day of menses was designated as day 1 of menstrual cycle). The compounds (in 2% Tween 80/0.5% methyl cellulose, 2 mL/kg) were given orally once daily, and blood samples were collected by venipuncture before the first dose and every Monday, Wednesday, and Friday until next menses. Serum samples were collected and stored at –80 °C until analyzed for progesterone levels.

Serum progesterone levels were measured by radioimmunoassay.[36] The sensitivity of this assay was 2.5 pg/tube and the intra- and interassay percent coefficient of variation at approximately the IC_{50} value were 6.6% and 12.3%, respectively.

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Supporting Information Available: Analytical HPLC and low-resolution mass spectrometry data for compounds **12**−**21**, **25**−**26**, **27**, **28**–**30**, and **37**–**48**. This material is available free of charge via the Internet at http://pubs.acs.org.

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