Indazole Estrogens: Highly Selective Ligands for the Estrogen Receptor β

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The estrogen receptors, ERα and ERβ, are important pharmaceutical targets. To develop ERβ-selective ligands, we synthesized a series of nonsteroidal compounds having a phenyl-2*H*-indazole core with different groups at C-3. Several of these show high affinity and good ERβ selectivity, especially those with polar and/or polarizable substituents at this site (halogen, CF_3, nitrile); the best compounds have affinities for ERβ comparable to estradiol, with ERβ affinity selectivity >100. This potency and ERβ selectivity is also seen in cell-based transcriptional assays, where several compounds showed ERβ efficacies equivalent to that of estradiol with ERβ potency selectivities of 100. These compounds might prove useful as selective pharmacological probes to study the biological actions of estrogens mediated through ERβ, and they might lead to the development of useful pharmaceuticals. These findings also contribute to an evolving pharmacophore that characterizes certain nonsteroidal ligands having high ERβ subtype affinity and potency selectivity.

Introduction

Estrogens are hormones that have many important physiological and pharmacological activities that include critical roles in the development and function of the female reproductive system, in the maintenance of bone mineral density,[1,2] and in control of blood lipid levels.[3,4] Moreover, recent data show that estrogens can also exert neuroprotective effects.[5,6] The mediators of the actions of estrogenic hormones are the estrogen receptors (ERs), of which there are two subtypes encoded by different genes: ERα, the first discovered, and ERβ, which was only discovered in 1996.[7,8] The overall amino acid sequence identity of the two ER subtypes is 44%; the DNA-binding domain is very well conserved, but the amino acid sequence identity of the ligand-binding domain (LBD) is less conserved (59%). Despite these differences, the two ligand-binding pockets are almost identical, the principal difference being a somewhat smaller internal volume for ERβ and the substitution of just two amino acids, with Met421 in ERα being replaced by Ile in ERβ and Leu384 in ERα being replaced by Met in ERβ.[9]

The tissue distributions of ERα and ERβ are quite different: ERα is predominant in the uterus, liver, mammary gland, bone, and cardiovascular systems, whereas ERβ is highly expressed in the prostate, ovary, and urinary tract.[10] Both receptors are also present in many tissues, including the brain, although in this organ they are not always expressed in the same regions.[11,12] There is also evidence that the two ER subtypes have distinct patterns of gene regulation.[13−15]

The discovery of the second estrogen receptor, together with its distinct tissue distribution and patterns of transcriptional regulation, has aroused strong interest in the scientific community, because it opens new possibilities for the synthesis of interesting tissue- and cell-selective estrogen pharmaceutical agents. In fact, ERβ-selective ligands might maintain some of the benefits of traditional hormone therapy without the undesired stimulatory effects on uterine and breast tissues.

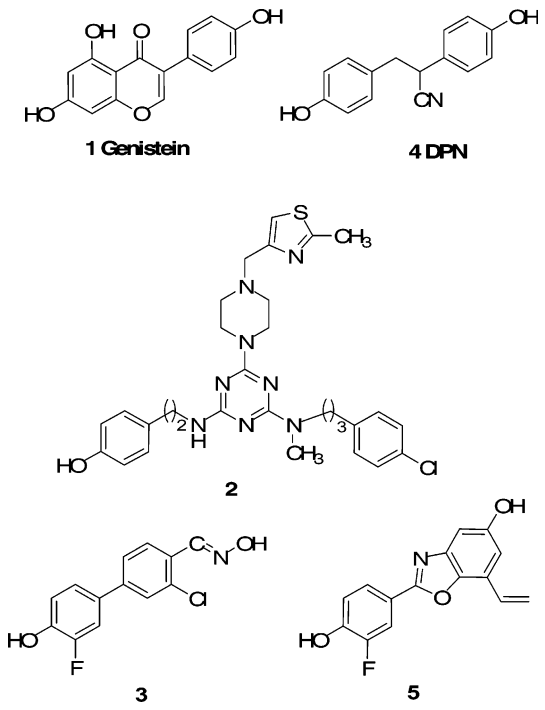

Figure 1.

Although there are a number of estrogens with good selectivity for ERα,[16,17] relatively few ERβ-selective compounds are known. Among natural products, the isoflavone phytoestrogen genistein (**1**, Figure 1) is notable for having a 20-fold ERβ selectivity;[18] it was one of the first ERβ-selective compounds characterized.[18] Among synthetic estrogens, a 30-fold selectivity is reported for compound **2**,[19] 50-fold for derivative **3**,[20] and 70-fold for the nitrile compound **4** (DPN), the last being

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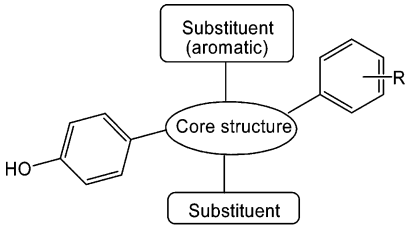


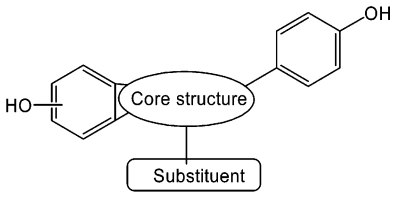


Figure 2.

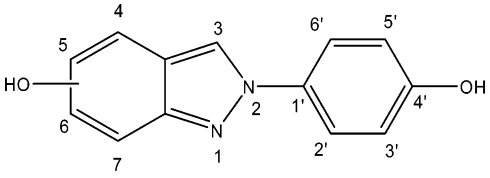


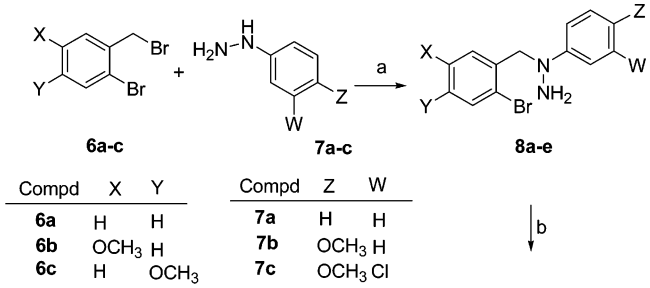
Figure 3. Indazole system for ERβ ligands.

a compound developed in our laboratories.[21] Recently, a number of new molecules bearing benzothiophene or benzofuran scaffolds have also emerged as ERβ-selective agents.[22,23] Further investigations on similar structures, such as benzothiazoles,[24] benzimidazoles,[25] and benzoxazoles,[26] have provided very promising results, as in the case of derivative **5**, which shows high binding affinity and a 200-fold selectivity for ERβ.[26] In these last derivatives, the increase in ERβ selectivity is achieved through the introduction of different polar and polarizable groups in the two phenyl rings, but for obvious structural reasons, no substitution could be made in the central part of the heterocyclic system.

We have developed a pharmacophore model for nonsteroidal estrogen receptor ligands in which two or three aryl substituents (of which one or two are *p*-hydroxyphenyl rings) are attached to a central core structure bearing various other substituents (Figure 2A).[27] Using this model as a guide, we were able to generalize ER ligand development and to synthesize very good ERα-selective ligands. The smaller ligand binding pocket of ERβ, the substitution of Met421 and Leu384 in ERα with Ile373 and Met336 in ERβ, and the observation that variation of substituents on the central core could lead to good ERβ-selective compounds, particularly when certain polar or polarizable groups were introduced,[21] lead us to develop a different pharmacophore model for ERβ (Figure 2B). The major differences between the two pharmacophores are the lack of the third aromatic substituent so that the ligand is smaller in volume. To reduce ligand size further, one of the two phenol rings has been fused to the heterocycle, although this last feature is not essential, as demonstrated by the activity shown by DPN (**4**). The nature of the substituent in pharmacophore B should be such that it would interact favorably with Ile373 or Met336 and/or unfavorably with Met421 and Leu384, in this way engendering better selectivity for ERβ.

Following this pharmacophore model, then, we decided to prepare compounds having a phenyl-2*H*-indazole core structure (Figure 3). An attractive feature of this particular heterocyclic system is that it is possible to introduce different steric and polar groups at an *internal* position of the heterocyclic system (C-3) and thereby to further investigate the validity of our pharmacophore model for ERβ-selective ligands, noted above.

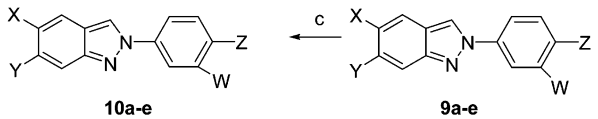
Scheme 1[a]



Compd	X	Y
6a	H	H
6b	OCH_3	H
6c	H	OCH_3

Compd	Z	W
7a	H	H
7b	OCH_3	H
7c	OCH_3	Cl

b



Compd	W	X	Y	Z
10a	H	H	H	OH
10b	H	OH	H	H
10c	H	OH	H	OH
10d	H	H	OH	OH
10e	Cl	OH	H	OH

Compd	W	X	Y	Z
8a, 9a	H	H	H	OCH_3
8b, 9b	H	OCH_3	H	H
8c, 9c	H	OCH_3	H	OCH_3
8d, 9d	H	H	OCH_3	OCH_3
8e, 9e	Cl	OCH_3	H	OCH_3

[a] (a) NAHMDS, THF; (b) $Pd(OAc)_2$, dppf, NaO*t*-Bu, toluene; (c) $BF_3{\cdot}SMe_2$, CH_2Cl_2.

In this report, we describe the synthesis and biological evaluation of a series of indazole compounds as potential ERβ-selective ligands, and we identify a number of these that show very good selectivity for ERβ in receptor binding and potency in transcription assays.

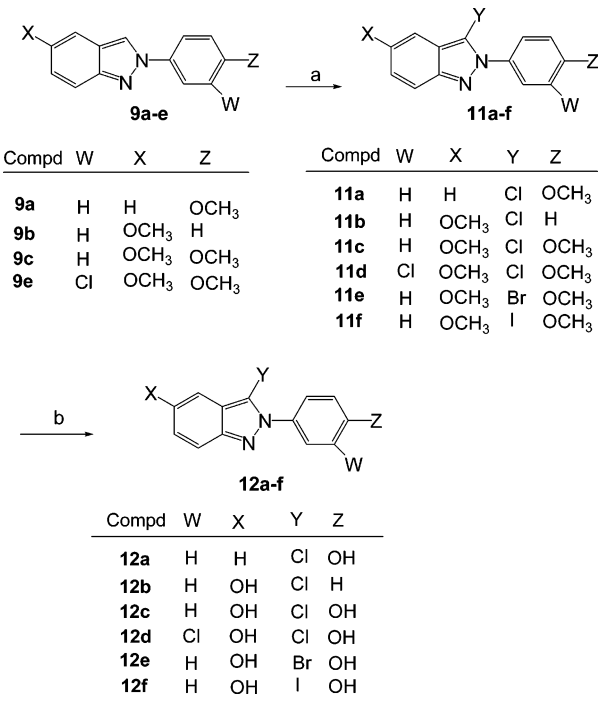
Results

Chemical Synthesis. Synthesis of the indazole core structure was accomplished following a known procedure, as outlined in Scheme 1.[28] Treatment of phenylhydrazines **7a**−**c** with sodium hexamethyl disilyl amide followed by the *o*-bromobenzyl bromides **6a**−**c** provided the alkylated derivatives **8a**−**e**. These were cyclized in a palladium-catalyzed coupling reaction and were then oxidized in situ to furnish the protected indazole derivatives **9a**−**e** (derivatives **9a,b** and their precursors are known compounds[28]). Deprotection gave the final products indazole phenols **10a**−**e**. Compound **6c** is not commercially available, but it was obtained as previously reported.[29]

All the compounds presented herein can be divided into two groups: analogues of 2-(4-hydroxyphenyl)-2*H*-indazol-5-ol (**10c**), having the indazole hydroxyl on C-5, and analogues of 2-(4-hydroxyphenyl)-2*H*-indazol-6-ol (**10d**), having the indazole hydroxyl on C-6. As will be noted below, analogues in the former class (**10c**) proved to be more interesting for our purpose.

To prepare analogues in the 5-OH (**10c**) series, we developed methods to introduce substituents at C-3 that

Scheme 2[a]



Compd	W	X	Z
9a	H	H	OCH_3
9b	H	OCH_3	H
9c	H	OCH_3	OCH_3
9e	Cl	OCH_3	OCH_3

Compd	W	X	Y	Z
11a	H	H	Cl	OCH_3
11b	H	OCH_3	Cl	H
11c	H	OCH_3	Cl	OCH_3
11d	Cl	OCH_3	Cl	OCH_3
11e	H	OCH_3	Br	OCH_3
11f	H	OCH_3	I	OCH_3

Compd	W	X	Y	Z
12a	H	H	Cl	OH
12b	H	OH	Cl	H
12c	H	OH	Cl	OH
12d	Cl	OH	Cl	OH
12e	H	OH	Br	OH
12f	H	OH	I	OH

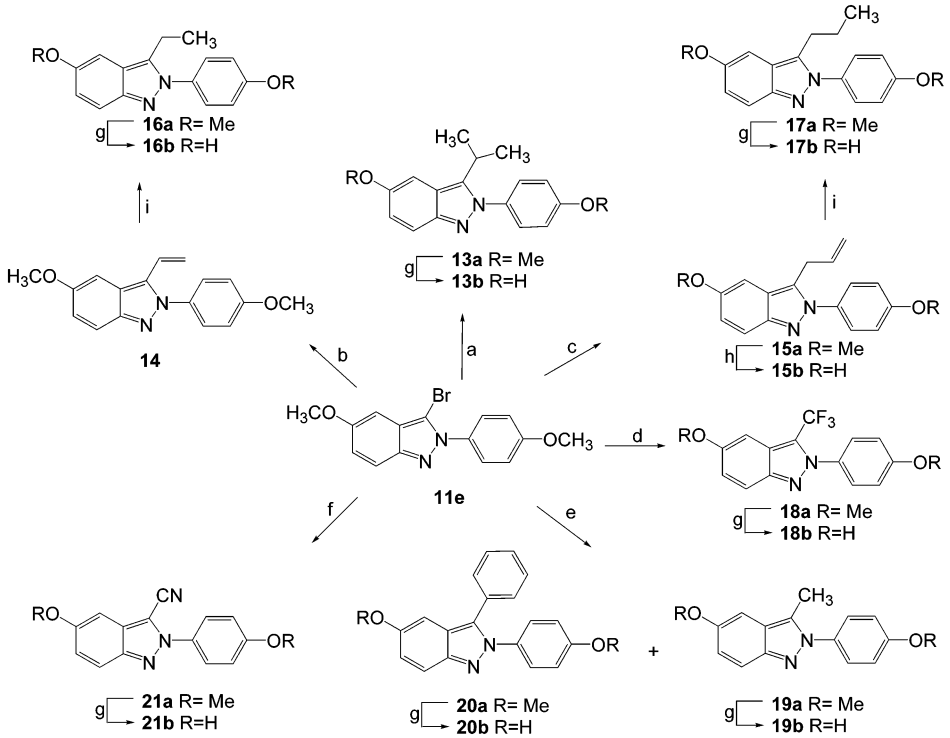
[a] **(a) NCS, CH_3CO_2H** (for **11a**−**d**); Br_2, CH_3CO_2H (for **11e**); I_2, KOH, DMF (**11f**); (b) BF_3·SMe_2, CH_2Cl_2.

would contribute steric bulk and polarity at this position in the heterocyclic system (Scheme 2). Since this position could be halogenated easily, a series of halo derivatives (**11a**−**f**) were synthesized. All of these compounds were obtained following classical procedures (NCS or Br_2 in acetic acid for derivatives **11a**−**e**, and I_2/sodium hydroxide in DMF for derivative **11f**[30,31]) and with yields that varied from 20 to 85%. These derivatives were then deprotected with BF_3·SMe_2 to give the final products, **12a**−**f**.

Compound **11e** can be considered a key intermediate because, through various palladium coupling reactions, it was possible to replace the bromine group with many substituents (Scheme 3). The isopropyl group (**13a**) was introduced through a nickel-catalyzed Kumada reaction,[32] but curiously, all attempts to employ the same reaction conditions for the synthesis of the corresponding ethyl and propyl derivatives failed. For this reason, we turned to the Stille coupling reaction to prepare the vinyl and allyl derivatives (**14**, **15a**)[33] that in turn were reduced to obtain the ethyl and propyl compounds (**16a**, **17a**). For the synthesis of product **18a**, we followed a literature procedure described for the displacement of an aromatic bromine group with the trifluoromethyl moiety using an unusual fluorosulfonylfluoroacetate reagent as a precursor for the in situ generation of trifluoromethide species.[34] Although examples of this reaction have never been reported for our particular heterocyclic system, we were able to obtain the desired compound in moderate yield within a few hours.

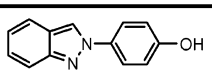
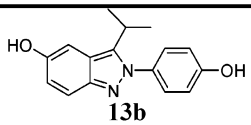
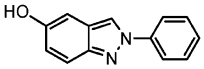
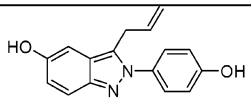
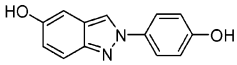
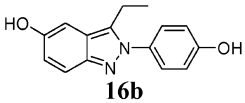
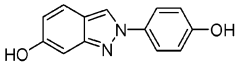
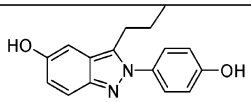
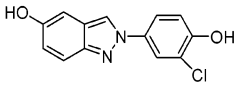
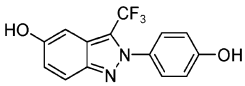
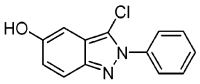
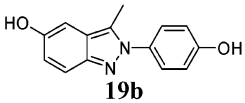
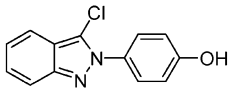
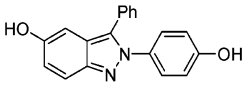
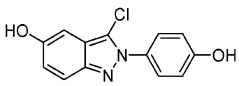
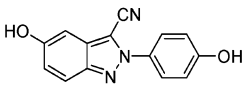
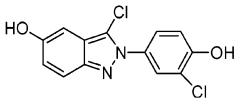
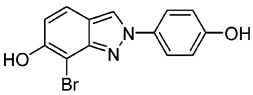
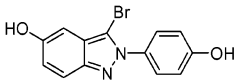
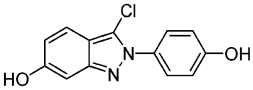
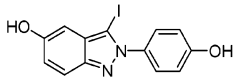
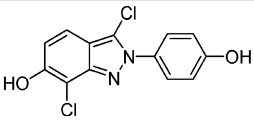
In an initial study, derivative **20a** was synthesized through a Stille coupling reaction using phenyltrimethyl tin as a source of the phenyl substituent. Although we obtained the desired phenyl-substituted compound (**20a**) as the major product, we observed significant formation of the methyl-substituted product (**19a**). We tried to increase the yield of **20a** by reducing the reaction temperature or changing the concentration of catalytic system, but we continued to observe the formation of **19a**, albeit in smaller amounts. We were able to obtain derivatives **20a** without the formation of any other byproducts, how-

Scheme 3[a]



[a] (a) $NiCl_2$(dppp), ^{i}PrMgCl, THF; (b) vinylSnBu_3, CsF, Pd_2(dba)$_3$, P(*t*-Bu)$_3$, dioxane; (c) allylSnBu_3, CsF, Pd_2(dba)$_3$, P(*t*-Bu)$_3$, dioxane; (d) $FSO_2CF_2CO_2CH_3$, CuI, DMF; (e) PhSn$(Me)_3$, P(*o*-Tol)$_3$, Pd_2(dba)$_3$, P(*t*-Bu)$_3$, DMF (f) Pd_2(dba)$_3$, Dppf, $Zn(CN)_2$, DMA; (g) BF_3·SMe_2, CH_2Cl_2; (h) BBr_3, CH_2Cl_2; (i) $Pd(OH)_2$/C, H_2 (1 atm), EtOH.

Table 1. Relative Binding Affinity (RBA) Values for ERα and ERβ and the Selectivity for ERβ As Determined by β/α Ratio[a]

Compound	ERα	ERβ	β/α	Compound	ERα	ERβ	β/α
 **10a**	0.020 ± 0.003	0.020 ± 0.004	1	 **13b**	0.14 ± 0.02	1.38 ± 0.33	9.9
 **10b**	<0.004	<0.004	1	 **15b**	0.06 ± 0.02	0.80 ± 0.22	13
 **10c**	0.049 ± 0.012	0.53 ± 0.16	11	 **16b**	0.08 ± 0.02	3.24 ± 0.92	41
 **10d**	0.008 ± 0.003	0.19± 0.06	24	 **17b**	0.04 ±0.001	0.48 ± 0.11	12
 **10e**	0.07 ± 0.01	0.06 ± 0.01	0.9	 **18b**	3.9 ± 0.8	69 ± 15	18
 **12a**	0.014 ± 0.004	0.038 ± 0.006	2.7	 **19b**	0.03 ± 0.01	0.97 ± 0.21	32
 **12b**	0.030 ± 0.006	0.077 ± 0.001	2.6	 **20b**	0.04 ±0.006	0.46 ± 0.11	12
 **12c**	0.30 ±0.03	32.1 ± 9.0	107	 **21b**	1.4 ± 0.39	30.1 ± 6.6	22
 **12d**	0.023 ± 0.00	0.68 ± 0.19	30	 **24**	0.02 ±0.004	0.14 ± 0.03	7
 **12e**	0.18 ± 0.05	18.4 ± 1.7	102	 **30**	0.08 ± 0.02	6.31 ± 0.24	79
 **12f**	0.17 ± 0.01	8.5 ± 2.5	50	 **31**	0.07 ± 0.02	1.37 ± 0.11	20

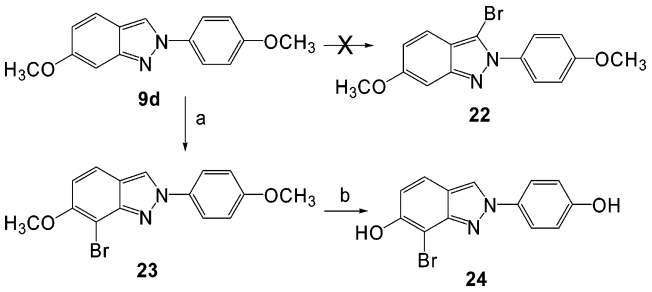
[a] Relative binding affinity (RBA) values are determined by competitive radiometric binding assays and are expressed as $IC_{50}^{compound}/IC_{50}^{estradiol} \times 100$ (RBA, estradiol = 100%). In these assays, the K_d for estradiol is 0.2 nM on ERα and 0.5 nM on ERβ. For details, see the Experimental Section.

ever, through a Suzuki coupling reaction between compound **11e** and phenylboronic acid (see the Experimental Section).

The cyano derivative **21a** was also prepared using a palladium coupling reaction, with good results being obtained with $Pd_2(dba)_3$, dppf, and $Zn(CN)_2$.[35] All compounds synthesized from derivative **11e** were deprotected with $BF_3 \cdot SMe_2$ (**13b**, **16b**−**21b**) except for derivatives **14** and **15a**, which were cleaved using BBr_3. Although it was possible to isolate the deprotected allyl derivative **15b**, we were unable to characterize the dihydroxy analogue of the vinyl derivative **14**, presumably because it decomposed under acidic conditions.

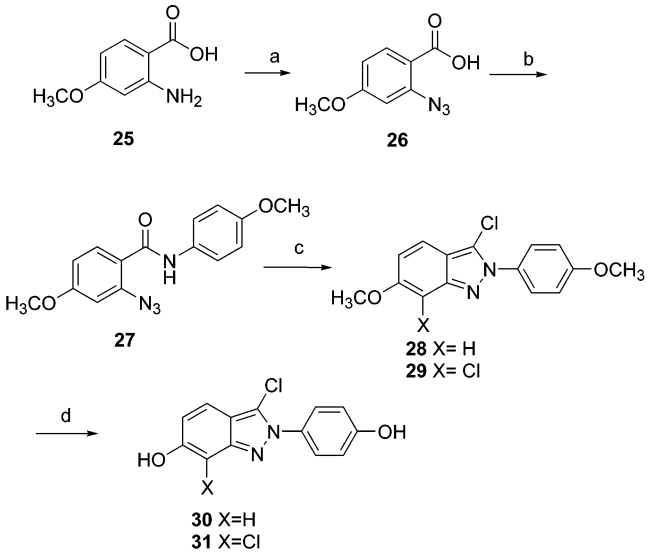
For the synthesis of the 6-OH series (**10d**) analogues, we initially followed the same synthetic strategy: bromination at C-3 of derivative **9d** and then introduction of

Scheme 4[a]



[a] (a) Br_2, CH_3CO_2H; (b) $BF_3{\cdot}SMe_2$, CH_2Cl_2.

Scheme 5[a]



[a] (a) TfN_3, $CuSO_4$, CH_2Cl_2, MeOH; (b) $SOCl_2$, *p*-anisidine; (c) benzene, $SOCl_2$; (d) $BF_3{\cdot}SMe_2$, CH_2Cl_2.

different alkyl and polar groups. The bromination of derivative **9d**, however, did not give the 3-bromo derivative **22**, but resulted, rather, in the formation of the 7-bromo compound **23**, which was subsequently deprotected to give **24** (Scheme 4).

To introduce a halogen group in the desired position, we followed a different synthetic strategy. It is known from the literature that 2-azido-*N*-phenyl-benzamide, when treated with a large excess of thionyl chloride, undergoes cyclization to form 3-chloro-2-phenyl-2*H*-indazole.[36] Following this procedure, we treated compound **27** (Scheme 5) with $SOCl_2$ in benzene, and we obtained the desired 3-chloro derivative **28** as well as the 3,7-dichloro compound **29** as a byproduct. Compound **27**, the key intermediate for this synthesis, is not commercially available but was readily synthesized as indicated in Scheme 5. Starting from the methoxyanthranilic acid **25**,[37] we prepared the corresponding azide (**26**) according to a literature precedent[38] that avoided traditional diazonium salt formation and strong acid hydrolysis. By this alternative method, we could produce the azide **26** in good yield within 1 h. The desired anilide **27** was easily prepared from derivative **26** by standard methods. The chloro compounds **28** and **29** were deprotected as previously reported to give the 6-OH isomeric derivatives **30** and **31**. Because these products showed lower ER binding affinities and lower ERβ selectivity when compared to their corresponding 5-hydroxy isomers (Table 1), no further 6-OH derivatives were prepared.

Biological Results

Estrogen Receptor Binding Assays. The indazole analogues were evaluated in competitive radiometric binding assays to determine their affinities for human ERα and ERβ. Binding affinities, expressed relative to that of estradiol (100%), gave relative binding affinity (RBA) values that are summarized in Table 1.

The nonsubstituted indazole derivatives (**10a**−**d**) show, in general, low affinities for both ER subtypes, with RBA values not exceeding 0.5% and selectivity for ERβ less than 20-fold. The monohydroxyl derivatives **10a,b** and **12a,b** were prepared to investigate which one of two phenyl rings mimicked the A-ring of estradiol; the expectation was that deletion of the phenolic hydroxyl from the ring that mimicked the A-ring of estradiol would result in a more marked reduction of binding affinity. According to the results we obtained, however, deletion of either hydroxy caused a large loss of binding affinity (compare ERβ values of **10c** with **10a** and **10b**; **12c** with **12a** and **12b**). Thus, both hydroxy groups appear to play important roles in the ERβ binding affinity of these indazoles, although, based on the somewhat larger binding decrement that occurs with deletion of the 4′-hydroxyl from the N-1 pendant phenol (cf. Figure 2), it appears that it is the *N*-(4-hydroxylphenyl) moiety that is the mimic of the A-ring of estradiol.

A large number of 5-hydroxyl derivatives with different C-3 substituents—alkyl, aryl, and polar groups—on the 1-(*p*-hydroxyphenyl)indazole core were investigated. Introduction of halogen groups (compounds **12c,e,f**) led to an increase in the affinity for ERβ, with RBA values ranging from 8% to 32%, whereas their affinity for ERα is always less than 0.3%. These derivatives are, therefore, strongly affinity selective for ERβ: compound **12f** is 50-fold selective with an 8.5% ERβ RBA, derivative **12e** is 102 times more selective with an 18% ERβ RBA, and compound **12c** is 107-fold selective with a 32% ERβ RBA. The introduction of other polar groups such trifluoro methyl (**18b**) and cyano (**21b**) also gave a large increase in activity, but with some reduction in ERβ affinity selectivity. Nevertheless, it should be pointed out that the trifluoromethyl derivative **18b**, with a 69% ERβ RBA, is the highest affinity compound of this series.

The substitution of the indazole system at C-3 with alkyl or aryl—rather than polar—groups, led to a dramatic reduction in affinity and sometimes also in selectivity. Usually bulky substituents, such as isopropyl (**13b**), propyl (**17b**), allyl (**15b**), and phenyl (**20b**), are not well-tolerated inside the ligand-binding pocket of ERβ; in fact, all of these compounds show RBA values that are less than 1% and generally have low ERβ affinity selectivity (9−13-fold). The C-3 methyl (**19b**) and ethyl (**16b**) derivatives are different and are ca. 40-fold affinity selective for ERβ, with RBA values between 1 and 3%, the ethyl derivative **16b** being the better of the two.

The binding data for a few 6-hydroxyl analogues (**10d**, **24**, **30**, and **31**) are also reported in Table 1. In general, these derivatives are of lower affinity and sometimes lower selectivity compared to their 5-hydroxyl counterparts (**10d** vs **10c**, and **30** vs **12c**). The best compound of this series is the 3-chloro analogue (**30**), but its ERβ

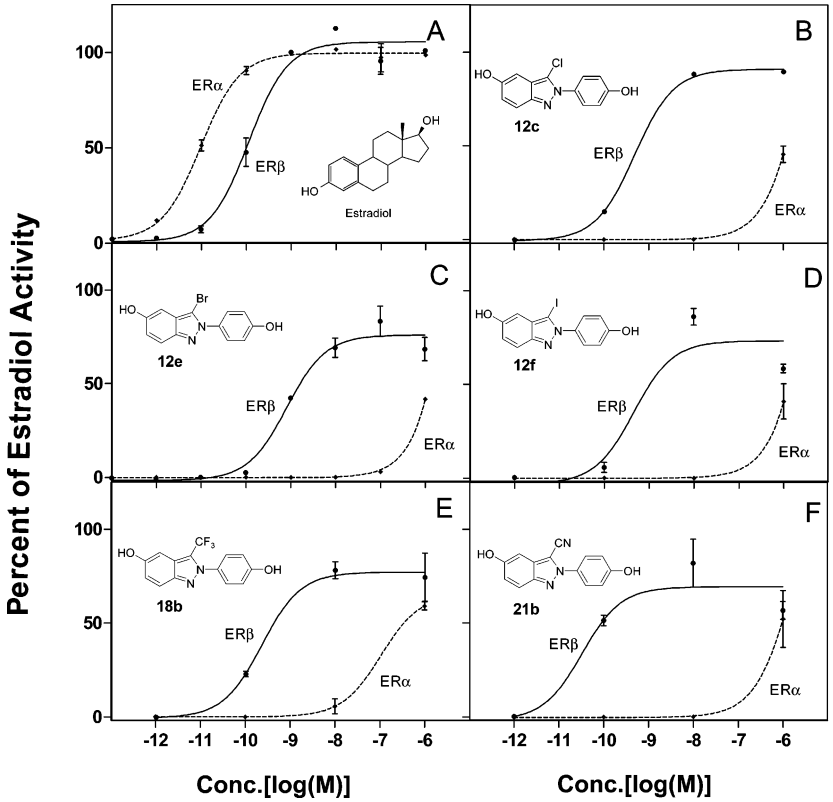


Figure 4. Transcriptional activation by ERα and ERβ in response to estradiol (E2), **12c,e,f**, **18b**, and **21b**. Human endometrial cancer (HEC-1) cells were transfected with expression vectors for ERα or ERβ and the estrogen responsive gene 2EREp-S2-Luc and were incubated with the indicated concentrations of estradiol or ligands **12c,e,f**, **18b**, and **21b** for 24 h. Value are expressed as percent of the ERα or ERβ response with 10^{-6} M estradiol.

affinity is still 5 times lower than that of its 5-hydroxyl analogue **12c**.

The following conclusions can be drawn from these data: (1) Only small C-3 alkyl groups are tolerated by ERβ; (2) C-5 is the favored position for the hydroxyl group on the indazole system; (3) high affinity and particularly high ERβ selectivity are found with polar and/or polarizable groups at the C-3 position, with the best examples being the halogenated derivatives **12c** and **12e**, which have ERβ affinity selectivities of over 100-fold and RBA values of ca. 20−30%. Although these two can be considered lead compounds in this series, it is important to note that a large number of other indazole compounds show very pronounced ERβ affinity selectivity, even though their absolute affinities are lower than those reported for **12c** and **12e**.

Activity of Indazole Compounds on Gene Transcription. The transcriptional activities of some indazole derivatives were assayed in human endometrial cancer (HEC-1) cells transfected with expression plamids for ERα and ERβ and an estrogen-responsive reporter gene. Activities were normalized to that reported for 10^{-6} M estradiol, which is set to 100. Eleven derivatives were selected for this transcriptional assay (**12c,e,f**, **16b**, **18b**, **19b**, **20b**, **21b**, and **24**). In an initial screening study, the efficacy of these compounds was determined at two different concentrations, 10^{-8} and 10^{-6} M; the results of these assays are summarized in Table 2. In general, compound potency and ERβ selectivity in these assays nicely reflected their behavior in the binding assays.

All of the compounds tested showed agonist activity at 10^{-8} M, as expected from their affinity in the binding assay: the most active derivatives on ERβ are **12c**,**e**,**f**, **18b**, and **21b**; these have an efficacy level that is close to that reported for estradiol, but they show weak or negligible activity on ERα. Good potency for ERβ is also observed for the derivatives **10c**, **16b**, and **19b**, whereas derivatives **10d**, **20b**, and **24** were the least potent and selective compounds of this series.

Table 2. Transcriptional Efficacy of Estradiol (E2) and Some Indazole Derivatives at 10^{-8} and 10^{-6} M on ERα, ERβ

	% efficacy on ERα		% efficacy on ERβ	
compd	10^{-8} M	10^{-6} M	10^{-8} M	10^{-6} M
E2	77	100	83	100
10c	0.6	1.5	47	90
10d	0.23	0.18	1.7	75
12c	0.06	45	88	89
12e	0.03	42	66	67
12f	0.01	40	85	58
16b	0.6	20	63	100
18b	5.6	58	78	74
19b	0.6	0.5	57	87
20b	0.3	1.7	11	28
21b	0.02	52	82	56
24	0.08	0.5	1.4	29

When these derivatives were tested at 10^{-6} M, all of the compounds show efficacy through ERβ, with the low-affinity compounds **20b** and **24** being least efficacious. At this concentration, considerable ERα activity is found, but only with the compounds that have significant affinity for ERα (**12c,e,f**, **18b**, and **21b**).

More extensive dose−response curves were then obtained for some of the most interesting compounds (**12c,e,f**, **18b**, **21b**; Figure 4). From these data one can clearly see that all of these compounds have high ERβ

potency selectivity: With four of them (**10c,d**, **12c,e,f**, **21b**), full activation of ERβ is achieved at concentrations 30−100-fold below that at which one begins to see activation of ERα. Thus, these agents are clean pharmaceutical modulators of the ERβ subtype, capable—at an appropriate dose—of full activation of ERβ with no activation of ERα.

Conclusion

In summary, we have prepared novel ligands for the estrogen receptor β (ERβ) having a phenyl-2-*H*-indazole core structure. Most of the compounds prepared showed good selectivity for ERβ in terms of binding affinity and transcriptional potency; in particular, derivatives **12c** and **12e** can be considered the lead compounds of this series (RBA for ERβ between 18 and 32% and affinity selectivity over 100-fold). In the transcriptional assay, all the active compounds tested are agonists. Because of their good potency and efficacy through ERβ, coupled with their weak-to-negligible potency through ERα, these compounds are very promising agents for the selective activation of the ERβ. As such, they should prove to be useful pharmacological probes to define the biological importance and physiological roles of ERβ. This study also advances further our pharmacophore model for ERβ-selective ligands (Figure 2B) that embodies a structurally slender core having phenolic hydroxyl groups at both ends and incorporating polar or polarizable groups in the interior of the ligand; it highlights, in particular, the importance of the electronic nature of the internal substituent. While this pharmacophore is clearly not the only one capable of encompassing ERβ-selective ligands, it appears to be a valid one and thus can serve as a productive basis for the design of ligands having high selectivity for this ER subtype.

Experimental Section

Materials and Methods. All reagents and solvents were obtained from Aldrich or Fisher. Tetrahydrofuran, diethyl ether, toluene, and dichloromethane were dried by the solvent delivery system (SDS) (neutral alumina columns) designed by Meyer. Glassware was oven-dried, assembled while hot, and cooled under an inert atmosphere. Unless otherwise stated, all reactions were conducted in an inert atmosphere. Reactions using moisture- or air-sensitive reagents were performed in anhydrous solvents. Reaction progress was monitored using analytical thin-layer chromatography (TLC) on 0.25 mm Merck F-254 silica gel glass plates. Visualization was achieved by either UV light (254 nm) or potassium permanganate indicator. Flash chromatography was performed with Woelm silica gel (0.040−0.063 mm) packing.

^{1}H NMR and ^{13}C NMR spectra were obtained on a 400 or 500 MHz instrument. The chemical shifts are reported in ppm and are referenced to either tetramethylsilane or the solvent. Mass spectra were recorded under electron impact conditions at 70 eV. Melting points were obtained on a Thomas-Hoover MelTemp apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Service Laboratory of the University of Illinois. Those final components that did not give satisfactory combustion analysis gave satisfactory exact mass determinations and were found to be at least 96% pure by HPLC analysis.

General Procedure for the Synthesis of the 2-Arylindazole Ring System. Compounds **9a** and **9b** are known,[28] and derivatives **9c**−**e** were synthesized following the same procedure: to a solution of NaHMDS (30 mmol) at 0 °C was added phenylhydrazine hydrochloride (15 mmol). The reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 1 h. The reaction mixture was recooled at 0 °C and methoxy-2-bromobenzyl bromide (15 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and then quenched with water. The mixture was extracted with ethyl acetate (three times), and the organic extracts were dried over Na_2SO_4 and concentrated in a vacuum. The crude product was purified by flash chromatography (30% EtOAc/hexanes). The purified product (1.2 mmol) was dissolved in toluene (4 mL), and $Pd(OAc)_2$ (5 mol %), dppf (7.5 mol %), and NaO^{t}Bu (1.5 mmol) were added. The reaction mixture was stirred at 90 °C in a sealed tube for 15 h. The reaction mixture was filtered off, and the crude product purified by flash chromatography (30% EtOAc/hexanes).

***N*-(2-Bromo-5-methoxybenzyl)-*N*-(4-methoxyphenyl)-hydrazine (8c).** Product **8c** was obtained as orange oil that solidified on standing (630 mg, 3.6 mmol, 55% yield). The product was then recrystallized in ethyl acetate/hexane to give a pale yellow solid (mp 53−54 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.5, 1H), 7.02 (AA′ of AA′XX′ J_{AX} = 6.9, $J_{AA'}$ = 2.4, 2H), 6.95 (d, J = 3.0, 1H), 6.85 (XX′ of AA′XX′ J_{AX} = 6.9, $J_{XX'}$ = 2.4, 2H), 6.72 (dd, J = 8.8, 2.9, 1H), 4.51 (s, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 3.63 (bs, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.3, 153.4, 146.3, 138.0, 133.6, 115.7, 115.1, 114.6, 114.5, 114.1, 62.7, 55.8, 55.6; MS (EI) *m/z* 337 (M^+, 15).

***N*-(2-Bromo-6-methoxybenzyl)-*N*-(4-methoxyphenyl)-hydrazine (8d).** Product **8d** was obtained as orange oil that solidified on standing (700 mg, 2.5 mmol, 44% yield). The product was then recrystallized in ethyl acetate/hexane to give a pale yellow solid (mp 83−84 °C): ^{1}H NMR (400 MHz, $CDCl_3$)-δ 7.24 (d, J = 8.8, 1H), 7.14 (d, J = 2.8, 1H), 7.045 (AA′ of AA′XX′ J_{AX} = 6.8, $J_{AA'}$ = 2, 2H), 6.86−6.81 (m, 3H), 4.73 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.54 (bs, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.4, 153.4, 146.3, 130.6, 128.6, 124.4, 118.3, 116.0 114.5, 113.7; MS (EI) *m/z* 337 (M^+, 10).

***N*-(2-Bromo-5-methoxybenzyl)-*N*-(3-chloro-4-methoxyphenyl)hydrazine (8e).** Product **8e** was obtained as orange oil that solidified on standing (1.55 g, 4.1 mmol, 48% yield). The product was then recrystallized in ethyl acetate/hexane to give a pale yellow solid (mp 99−100 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.8, 1H), 7.19 (d, J = 2.0, 1H), 6.88−6.84 (m, 3H), 6.72 (dd, J = 8.8, 2.8, 1H), 4.51 (s, 2H), 3.84 (s, 3H), 3.71(s, 3H), 3.63 (bs, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.4, 148.4, 146.6, 137.4, 133.8, 116.5, 115.0, 114.5, 114.0, 113.4, 113.0; 61.9, 56.9, 55.6; MS (EI) *m/z* 371 (M^+, 10).

5-Methoxy-2-(4-methoxyphenyl)-2*H*-indazole (9c). Product **9c** was obtained as a white solid (122 mg, 0.48 mmol, 40% yield) recrystallized from EtOAc/hexanes (mp 154−155 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.74 (AA′ of AA′XX′ J_{AX} = 6.7, $J_{AA'}$ = 2.4, 2H), 7.66 (d, J = 9.6, 1H), 7.03−6.98 (m, 3 H), 6.87 (d, J = 2.4, 1H), 3.84 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$), δ 159.1, 155.5, 146.5, 134.3, 122.7, 122.1, 121.6, 119.3, 119.2, 114.6, 96.4, 55.6, 55.4; MS (EI) *m/z* 254 (M^+, 100).

6-Methoxy-2-(4-methoxyphenyl)-2*H*-indazole (9d). Product **9d** was obtained as a white solid (260 mg, 1.02 mmol, 50% yield) recrystallized from EtOAc/hexanes (mp 143−144 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.76 (AA′ of AA′XX′ J_{AX} = 6.5, $J_{AA'}$ = 2, 2H), 7.56 (d, J = 8.5, 1H), 7.02−7.00 (m, 3H), 6.80 (dd, J = 9, 2, 1H), 3.88 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.3, 159.1, 150.8, 134.3, 122.1, 121.2, 120.4, 118.5, 117.6, 114.7, 94.7, 55.7, 55.3; MS (EI) *m/z* 254 (M^+, 100).

5-Methoxy-2-(3-chloro-4-methoxyphenyl)-2*H*-indazole (9e). Product **9e** was obtained as a white solid (100 mg, 0.35 mmol, 35% yield) that was recrystallized from EtOAc/hexanes (mp 175−177 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.09 (d, J = 2.4, 1H), 7.67−7.63 (m, 2H), 7.02−6.69 (m, 2H), 6.84 (d, J = 2.4, 1H), 3.92 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.6, 154.4, 146.7, 134.3, 123.3, 122.9, 122.7, 122.2, 119.7, 119.2, 112.3, 96.2, 56.5, 55.4; MS (EI) *m/z* 288 (M^+, 100).

General Method for Deprotection of Methoxy Groups with BF_3·SMe_2. The methyl ether protected compound (0.5 mmol) was dissolved in CH_2Cl_2 (1 mL), and BF_3·SMe_2 (15 mmol) was added. The reaction mixture was stirred at room

temperature for 24 h. If after that time starting material was not totally consumed, an additional amount of $BF_3{\cdot}SMe_2$ (15 mmol) was added and the reaction mixture was stirred for another 24 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in a vacuum.

4-Indazol-2-ylphenol (10a). Compound **10a** was purified by flash chromatography (40% EtOAc/hexanes) to give a white solid (63 mg, 0.30 mmol, 96% yield) that was recrystallized from EtOAc (mp 193−194 °C): ^{1}H NMR (400 MHz, acetone-d_6) δ 8.77 (s, OH), 8.71 (s, 1H), 7.90 (AA′ of AA′XX′ $J_{AX} = 6.9$, $J_{AA'} = 3.4$, 2H), 7.72 (d, $J = 8.5$, 1H), 7.66 (d, $J = 8.8$, 1H), 7.28−7.24 (m, 1H), 7.07−7.00 (m, 3H);); ^{13}C NMR (400 MHz, acetone-d_6) δ 158.0, 150.1, 134.2, 126.9, 123.7, 122.8, 122.6, 121.4, 121.1, 118.3, 116.7; MS (EI) *m/z* 210 (M^+, 100); HRMS (EI) calcd for $C_{13}H_{10}N_2O$ 210.0793, found 210.0800. Anal. ($C_{13}H_{10}N_2O$) C, H, N.

2-Phenyl-2*H*-indazol-5-ol (10b). Compound **10b** was purified by flash chromatography (30% EtOAc/hexanes) to give a white solid (40 mg, 0.19 mmol 86% yield) that was recrystallized from EtOAc/hexanes (mp 168−169 °C, dec): ^{1}H NMR (400 MHz, acetone-d_6) δ 8.62 (s, 1H), 8.30 (bs, OH), 8.05 (AA′ of AA′XX′ $J_{AX} = 7.1$, $J_{AA'} = 3.4$, 2H), 7.61−7.54 (m, 3H), 7.42−7.38 (m, 1H), 7.03−6.97 (m, 2H); ^{13}C NMR (400 MHz, MeOH-d_4) δ 153.7, 147.6, 141.7, 130.7, 128.8, 124.7, 123.1, 121.7, 121.2, 119.2, 100.8; MS (EI) *m/z* 210 (M^+, 100); HRMS (EI) calcd for $C_{13}H_{10}N_2O$ 210.0793, found 210.0800. Anal. ($C_{13}H_{10}N_2O$) C, H, N.

2-(4-Hydroxyphenyl)-2*H*-indazol-5-ol (10c). Compound **10c** was purified by flash chromatography (50% EtOAc/hexanes) to give a white solid (13 mg, 0.06 mmol, 97% yield) that was recrystallized from EtOAc (mp >230 °C dec): ^{1}H NMR (400 MHz, acetone-d_6) δ 8.70 (bs, OH), 8.44 (s, 1H), 8.18 (bs, OH), 7.83 (AA′ of AA′XX′ $J_{AX} = 6.9$, $J_{AA'} = 3.4$, 2H), 7.55 (d, $J = 8.8$, 1H), 7.00−6.95 (m, 4H); ^{13}C NMR (400 MHz, acetone-d_6) δ 157.7, 153.1, 146.8, 134.4, 124.2, 122.4, 121.4, 119.6, 119.1. 116.6, 100.4; MS (EI) *m/z* 226 (M^+, 100); HRMS (EI) calcd for $C_{13}H_{10}N_2O_2$ 226.0742, found 216.0745. Anal. ($C_{13}H_{10}N_2O_2{\cdot}0.2\ H_2O$) C, H, N.

2-(4-Hydroxyphenyl)-2*H*-indazol-6-ol (10d). Compound **10d** was purified by flash chromatography (30% EtOAc/hexanes) to give a white solid (50 mg, 0.22 mmol, 94% yield) that was recrystallized from EtOAc (mp >200 °C dec): ^{1}H NMR (400 MHz, acetone-d_6) δ 8.71 (bs, OH), 8.58 (s, 1H), 8.45 (s, OH), 7.82 (d, $J = 9$, 2H), 7.60 (d, $J = 9$, 1H), 7.00−6.92 (m, 3H), 6.77 (d, $J = 1.9$, 1H); ^{13}C NMR (400 MHz, acetone-d_6) δ 157.6, 156.9, 151.4, 134.3, 122.4, 122.3, 120.9, 119.2, 117.2, 116.6, 98.3; MS (EI) *m/z* 226 (M^+, 100); HRMS (EI) calcd for $C_{13}H_{10}N_2O_2$ 226.0742, found 216.0745. Anal. ($C_{13}H_{10}N_2O_2$) C, H, N.

2-(3-Chloro-4-hydroxyphenyl)-2*H*-indazol-5-ol (10e). Compound **10e** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (30 mg, 0.11 mmol, 82% yield) that was recrystallized from EtOAc (mp >250 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.54 (s, 1H), 8.03 (d, $J = 3$, 1H), 7.83 (dd, $J = 8.8$, 2.6, 1H), 7.56 (d, $J = 8.8$, 1H), 7.17 (d, $J = 8.8$, 1H), 7.00 (dd, $J = 9.2$, 2.2, 1H), 6.95 (d, $J = 2.1$, 1H); ^{13}C NMR (500 MHz, acetone-d_6) δ 153.3, 153.2, 134.8, 124.4, 122.5, 122.0, 121.6, 120.6, 119.7, 119.4, 117.9, 100.4; MS (EI) *m/z* 260 (M^+, 100); HRMS (EI) calcd for $C_{13}H_9ClN_2O_2$ 260.0353, found 260.0352. Anal. ($C_{13}H_9ClN_2O_2$) C, H, N.

3-Chloro-2-(4-methoxyphenyl)-2*H*-indazole (11a). Compound **9a** (45 mg, 0.2 mmol) was dissolved in acetic acid (2 mL), and *N*-chlorosuccinimide (27 mg, 0.2 mmol) was added. The reaction mixture was heated under reflux overnight. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 × 5 mL). The organic extracts were washed twice with NaOH (1 M), dried over Na_2SO_4, and concentrated in a vacuum. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to give a white solid (45 mg, 0.17 mmol, 87% yield) that was recrystallized from EtOAc/hexanes (mp 105−106 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, $J = 8.8$, 1H), 7.63−7.59 (m, 3H), 7.36−7.33 (m, 1H), 7.17−7.14 (m, 1H), 7.05 (d, $J = 8.8$, 2H), 3.88 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.2, 148.5, 131.6, 127.5, 127.1, 122.7, 119.8, 119.7, 119.1, 118.2, 114.4, 55.7; MS (EI) *m/z* 258 (M^+, 100).

3-Chloro-5-methoxy-2-phenyl-2*H*-indazole (11b). Compound **9b** (45 mg, 0.2 mmol) was dissolved in acetic acid (2 mL), and *N*-chlorosuccinimide (26 mg, 0.2 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 × 5 mL). The organic extracts were washed twice with NaOH (1 M), dried over Na_2SO_4, and concentrated in a vacuum. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to give a white solid (11 mg, 0.04 mmol, 22%) that was essentially pure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.47 (m, 5H), 7.06 (dd, $J =$ 8.4, 2.4, 1H); 6.77 (d, $J = 2.4$, 1H), 3.89 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 156.04, 145.6, 138.7, 129.2, 129.0, 125.7, 123.1, 120.0, 119.8, 94.7, 55.6; MS (EI) *m/z* 258 (M^+, 100).

3-Chloro-5-methoxy-2-(4-methoxyphenyl)-2*H*-indazole (11c). Compound **9c** (100 mg, 0.4 mmol) was suspended in acetic acid (4 mL), and *N*-chlorosuccinimide (53 mg, 0.4 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were washed twice with NaOH (1 M), dried over Na_2SO_4, and concentrated in a vacuum. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to give a white solid (50 mg, 0.17 mmol, 44%) that was recrystallized from EtOAc/hexanes (mp 134−135 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61−7.56 (m, 3H), 7.07−7.03 (m, 3H), 6.76 (d, $J = 2.4$, 1H), 3.88 (s, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.1, 156.0, 145.0, 131.5, 127.0, 123.1, 119.7, 119.5, 118.6, 114.4, 94.7, 55.7, 55.6; MS (EI) *m/z* 288 (M^+, 100).

3-Chloro-5-methoxy-2-(3-chloro-4-methoxyphenyl)-2*H*-indazole (11d). Compound **9e** (100 mg, 0.35 mmol) was dissolved in acetic acid (3 mL), and *N*-chlorosuccinimide (47 mg, 0.35 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were washed twice with NaOH (1 M), dried over Na_2SO_4, and concentrated in a vacuum. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to give a white solid (40 mg, 0.12 mmol, 35%) that was recrystallized from EtOAc/hexanes (mp 179−181 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, $J = 2.4$, 1H), 7.59−7.53 (m, 2H), 7.035 (AA′ of AA′XX′ $J_{AX} = 8.4$, $J_{AA'} = 2.4$, 2H), 6.73 (d, $J = 2$, 1H), 3.97 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 156.0, 155.5, 145.5, 131.9, 127.6, 125.0, 123.3, 122.9, 119.8, 119.7, 118.2, 111.8, 94.6, 56.6, 55.6; MS (EI) *m/z* 323 (M^+, 16).

3-Bromo-5-methoxy-2-(4-methoxyphenyl)-2*H*-indazole (11e). Compound **9c** (60 mg, 0.23 mmol) was suspended in acetic acid (1 mL), and a solution of bromine (12 μL, 0.23 mmol) in acetic acid (1.5 mL) was added dropwise at room temperature for 4 h. After the addition was complete, the reaction mixture was stirred at room temperature for another 12 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were washed twice with NaOH (1 M), dried over Na_2SO_4, and concentrated in a vacuum. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to give a white solid (47 mg, 0.14 mmol, 61%) that was recrystallized from EtOAc/hexanes (mp 148−149 °C): ^{1}H NMR (400 MHz, $CDCl_3$)-δ 7.62 (d, $J = 9.2$, 1H), 7.55 (AA′ of AA′XX′ $J_{AX} = 7.0$, $J_{AA'} =$ 2.0, 2H), 7.06−7.01 (m, 3H), 6.71 (d, $J = 2.4$, 1H), 3.88 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.0, 156.0, 145.9, 132.5, 127.4, 122.8, 122.7, 119.6, 114.2, 104.8, 95.4, 55.7, 55.6; MS (EI) *m/z* 333 (M^+, 18).

3-Iodo-5-methoxy-2-(4-methoxyphenyl)-2*H*-indazole (11f). Iodine (190 mg, 0.75 mmol) and KOH in pellets (42 mg, 0.75 mmol) were added at room temperature to a solution of compound **9c** (50 mg, 0.19 mmol) in DMF (1 mL). The reaction mixture was stirred at the same temperature for another 12 h. The reaction mixture was quenched with 10 mL of $NaHCO_3$

(sat. solution) and extracted with diethyl ether (3 × 10 mL). The organic extracts were dried over Na_2SO_4 and concentrated in a vacuum. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to give a white solid (43 mg, 0.11 mmol, 60%) that was recrystallized from EtOAc/hexanes (mp 150−151 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 9.5, 1H), 7.52 (AA′ of AA′XX′ J_{AX} = 6.8, $J_{AA'}$ = 2.3, 2H), 7.07−7.02 (m, 3H), 6.63 (d, J = 2.5, 1H), 3.90 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.1, 156.3, 146.7, 133.8, 128.2, 128.0, 122.7, 119.7, 114.7, 114.2, 97.0, 74.6, 55.7, 55.6; MS (EI) *m/z* 380 (M^+, 100).

4-(3-Chloroindazol-2-yl)phenol (12a). Compound **11a** (40 mg, 0.15 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **12a** was purified by flash chromatography (50% EtOAc/hexanes) to give a white solid (25 mg, 0.1 mmol, 68%) that was recrystallized from EtOAc/hexanes (mp 194−195 °C): ^{1}H NMR (500 MHz, acetone-d_6) δ 9.01 (bs, OH), 7.67−7.62 (m, 2H), 7.57 (dd, J = 6.7, J = 3.4, 2H), 7.38−7.35 (m, 1H), 7.20−7.17 (m, 1H), 7.06 (dd, J = 6.8, 3.2, 2H); ^{13}C NMR (500 MHz, acetone-d_6) δ 159.1, 149.0, 131.5, 128.1, 127.9, 123.4, 120.3, 119.5, 118.9, 116.4; MS (EI) *m/z* 244 (M^+, 100); HRMS (EI) calcd for $C_{13}H_9ClN_2O$ 244.0403, found 244.0409. Anal. ($C_{13}H_9ClN_2O$) C, H, N.

3-Chloro-2-phenyl-2*H*-indazol-5-ol (12b). Compound **11b** (8 mg, 0.03 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **12b** was purified by flash chromatography (40% EtOAc/hexanes) to give a white solid (5 mg, 0.02 mmol, 68% yield, mp >200 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.57 (bs, OH), 7.73−7.56 (m, 6H), 7.07 (d, J = 9.2, 1H), 6.82 (d, J = 2, 1H); ^{13}C NMR (500 MHz, acetone-d_6) δ 153.9, 145.9, 139.7, 129.9, 129.7, 126.3, 123.0, 121.0, 120.5, 98.1; MS (EI) *m/z* 244 (M^+, 100); HRMS (EI) calcd for $C_{13}H_9ClN_2O$ 244.0403, found 244.0405. Anal. ($C_{13}H_9ClN_2O$) C, H, N.

3-Chloro-2-(4-hydroxyphenyl)-2*H*-indazol-5-ol (12c). Compound **11c** (45 mg, 0.15 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **12c** was purified by flash chromatography (70% EtOAc/hexanes) to give a white solid (38 mg, 0.13 mmol, 95%) that was recrystallized from EtOAc (mp >195 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.92 (bs, OH), 8.50 (bs, OH), 7.55−7.03 (m, 3H), 7.04−7.02 (m, 3H), 6.8 (d, J = 2.2, 1H); ^{13}C NMR (500 MHz, acetone-d_6) δ 159.0, 153.9, 145.1, 131.4, 127.9, 123.0, 120.7, 120.1, 117.6, 116.4, 98.4; MS (EI) *m/z* 260 (M^+, 100); HRMS (EI) calcd for $C_{13}H_9ClN_2O_2$ 260.0353, found 260.0353. Anal. ($C_{13}H_9ClN_2O_2$) C, H, N.

3-Chloro-2-(3-Chloro-4-hydroxyphenyl)-2*H*-indazol-5-ol (12d). Compound **11d** (50 mg, 0.15 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **12d** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (40 mg, 0.13 mmol, 90% yield; mp 204−205 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 9.0 (bs, OH), 7.74 (d, J = 2.4, 1H), 7.57−7.53 (m, 2H), 7.23 (d, J = 8.5, 1H), 7.07 (dd, J = 9.2, J = 2.1, 1H), 6.81 (d, J = 2.4, 1H); ^{13}C NMR (500 MHz, acetone-d_6) δ 154.5, 153.9, 145.7, 132.2, 128.1, 126.4, 123.1, 121.137, 120.8, 120.4, 117.4, 117.1, 98.2; MS (EI) *m/z* 294 (M^+, 100); HRMS (EI) calcd for $C_{13}H_9ClN_2O$ 293.9963, found 293.9955. Anal. ($C_{13}H_9ClN_2O$·$0.7H_2O$) C, H, N.

3-Bromo-2-(4-hydroxyphenyl)-2*H*-indazol-5-ol (12e). Compound **11e** (45 mg, 0.13 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **12e** was purified by flash chromatography (70% EtOAc/hexanes) to give a white solid (35 mg, 0.11 mmol, 85%) that was recrystallized from EtOAc (mp 195−196 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 9.0 (bs, OH), 7.56 (d, J = 9, 1H), 7.49 (AA′ of AA′XX′ J_{AX} = 6.8, $J_{AA'}$ = 2, 2H), 7.06−7.01 (m, 3H), 6.77 (d, J = 2, 1H); ^{13}C NMR (500 MHz, acetone-d_6) δ 158.9, 153.9, 146.2, 132.5, 128.3, 132.8, 122.6, 120.3, 116.2, 103.7, 99.1; MS (EI) *m/z* 305 (M^+, 20); HRMS (EI) calcd for $C_{13}H_9CBrN_2O$: 303.9847, found 303.9853. Anal. $C_{13}H_9BrN_2O$ C, H, N.

3-Iodo-2-(4-hydroxyphenyl)-2*H*-indazol-5-ol (12f). Compound **11f** (35 mg, 0.09 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **12f** was purified by flash chromatography (70% EtOAc/hexanes) to give a white solid (25 mg, 0.07 mmol, 79%) that was recrystallized from EtOAc (mp 170−174 °C dec): ^{1}H NMR (400 MHz, acetone-d_6) δ 8.9 (bs, 1H), 8.3 (bs, OH), 7.55 (d, J = 9.2, 1H), 7.46 (AA′ of AA′XX′ J_{AX} = 6.6, $J_{AA'}$ = 2.2, 2H), 7.05−7.01 (m, 3H), 6.70 (d, J = 2.4, 1H); ^{13}C NMR (400 MHz, acetone-d_6) δ 158.9, 154.0, 147.0, 134.0, 129.4, 128.8, 122.4, 120.3, 116.1, 100.9, 74.4; MS (EI) *m/z* 352 (M^+, 100); HRMS (EI) calcd for $C_{13}H_9IN_2O$ 351.9709, found 351.9711; purity > 96% (HPLC).

3-Isopropyl-5-methoxy-2-(4-methoxyphenyl)-2*H*-indazole (13a). Compound **11e** (66 mg, 0.2 mmol) was dissolved in THF (1 mL), and Ni(dppp)Cl_2 (11 mg, 10 mol %) was added. The reaction mixture was cooled at 0 °C, and ^{i}PrMgBr (2 M solution in THF, 0.28 mmol) was added. The reaction mixture was gently allowed to reach room temperature and stirred at this temperature for 30 min. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were dried over Na_2SO_4 and concentrated in a vacuum. The crude product was purified by flash chromatography (30% EtOAc/hexanes) to give a white solid (15 mg, 0.05 mmol, 26%) that was recrystallized from EtOAc/hexanes (mp 181−185 °C): ^{1}H NMR (500 MHz, $CDCl_3$)-δ 7.61 (d, J = 9.3, 1H), 7.38 (AA′ of AA′XX′ J_{AX} = 6.7, $J_{AA'}$ = 2.3, 2H), 7.03−6.99 (m, 4H), 3.88 (s, 3H), 3.87 (s, 3H), 3.88−3.28 (m, 1H), 1.44 (d, J = 7.1, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.9, 154.1, 154.7, 140.8, 133.3, 127.7, 121.1, 119.3, 118.6, 114.3, 97.4, 55.7, 55.5, 26.9, 22.2; MS (EI) *m/z* 296 (M^+, 70).

3-Vinyl-5-methoxy-2-(4-methoxyphenyl)-2*H*-indazole (14). Compound **11e** (100 mg, 0.3 mmol) was dissolved in dioxane (2.5 mL), and the following reagents were added: $Pd_2(dba)_3$ (12 mg, 4.5 mol %), P^tBu_3 (11 mg, 18 mol %), CsF (100 mg, 0.66 mmol), and vinyltributyltin (87 μL, 0.3 mmol). The reaction mixture was heated in a sealed tube at 100 °C for 2 h. The reaction mixture was filtered, the solvent removed in a vacuum, and the crude product purified by flash chromatography (30% EtOAc/hexanes) to give a white solid (63 mg, 0.22 mmol, 75%) that was recrystallized from EtOAc/hexanes (mp 86−88 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 9.2, 1H), 7.47 (d, J = 8.8, 2H), 7.08−7.01 (m, 4H), 6.76 (dd, J = 17.8, 11.6, 1H), 5.87 (dd, J = 17.9, 1H), 5.45 (d, J = 11.8, 1H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (400 MHz) δ 159.8, 156.1, 145.5, 133.0, 132.3, 127.4, 125.4, 121.3, 120.2, 119.5, 116.2, 114.3, 97.2, 55.7, 55.5; MS (EI) *m/z* 280 (M^+, 100).

3-Allyl-5-methoxy-2-(4-methoxyphenyl)-2*H*-indazole (15a). Compound **11e** (100 mg, 0.3 mmol) was dissolved in dioxane (2.5 mL), and the following reagents were added: $Pd_2(dba)_3$ (12 mg, 4.5 mol %), P^tBu_3 (11 mg, 18 mol %), CsF (100 mg, 2.2 mmol), and allyltributyltin (92 μL, 0.3 mmol). The reaction mixture was heated in a sealed tube at 100 °C for 2 h. The reaction mixture was filtered off, the solvent removed in a vacuum, and the crude product purified by flash chromatography (30% EtOAc/hexanes) to give a white solid (70 mg, 0.23 mmol, 79%) that was recrystallized from EtOAc/hexanes (mp 96−97 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 9.5, 1H), 7.44 (AA′ of AA′XX′ J_{AX} = 6.8, $J_{AA'}$ = 2.3, 2H), 5.98−592 (m, 1H), 5.12 (d, J = 10.3, 1H), 4.99 (d, J = 17.1, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.71−3.69 (m, 2H); ^{13}C NMR (500 MHz) δ 159.8, 154.7, 145.4, 134.0, 133.0, 132.0, 127.1, 121.5, 121.2, 119.1, 117.0, 114.2, 96.2, 55.6, 55.4, 29.6; MS (EI) *m/z* 294 (M^+, 100).

5-Methoxy-2-(4-methoxyphenyl)-3-ethyl-2*H*-indazole (16a). Compound **14** (70 mg, 0.25 mmol) was dissolved in EtOH (2 mL), and $Pd(OH)_2$ (20 mg) was added. The reaction mixture was stirred at room temperature under hydrogen atmosphere (1 atm), for 24 h. The reaction mixture was filtered off, the organic solvent removed in a vacuum, and the crude product purified by flash chromatography (20% EtOAc/hexanes) to give a white solid (55 mg, 0.19 mmol, 78% yield) that was recrystallized from EtOAc/hexanes (mp 134−136 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 9.2, 1H), 7.41 (AA′ of AA′XX′ J_{AX} = 6.8, $J_{AA'}$ = 2.2, 2H), 7.03−7.00 (m, 3H), 6.84 (d, J = 2.0, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.98 (q, J = 7.7, 2H),

1.23 (t, $J = 7.7$, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.8, 154.4, 145.4, 136.8, 133.2, 127.2, 121.4, 120.1, 119.0, 114.3, 96.3, 55.6, 55.5, 18.7, 14.0; MS (EI) *m/z* 282 (M^+, 98).

5-Methoxy-2-(4-methoxyphenyl)-3-propyl-2*H*-indazole (17a). Compound **15a** (60 mg, 0.2 mmol) was dissolved in EtOH (2 mL), and $Pd(OH)_2$ (13 mg) was added. The reaction mixture was stirred at room temperature under hydrogen atmosphere (1 atm), for 15 h. The reaction mixture was filtered off, the organic solvent removed in a vacuum, and the crude product purified by flash chromatography (20% EtOAc/hexanes) to give a white solid (40 mg, 0.13 mmol, 66% yield) that was recrystallized from EtOAc/hexanes (mp 95−97 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, $J = 9.3$, 1H), 7.40 (AA′ of AA′XX′ $J_{AX} = 6.8$, $J_{AA'} = 2.2$, 2H), 7.03−7.00 (m, 3H), 6.82 (d, $J = 2.1$, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.92 (t, $J = 7.7$, 2H), 1.63 (m, 2H), 0.89 (t, $J = 7.4$, 3H); ^{13}C NMR (500 MHz, $CDCl_3$)δ 159.8, 154.5, 145.3, 135.7, 133.2, 127.4, 121.4, 120.6, 119.0, 114.3, 96.5, 55.6, 55.5, 27.2, 22.7, 14.0; MS (EI) *m/z* 296 (M^+, 90).

5-Methoxy-2-(4-methoxyphenyl)-3-trifluoromethyl-2*H*-indazole (18a). Compound **11e** (66 mg, 0.2 mmol) was dissolved in DMF (1 mL), and $FSO_2CF_2CO_2CH_3$ (127 μL, 1 mmol), followed by the addition of CuI (38 mg, 0.2 mmol), was added. The reaction mixture was heated at 80 °C and stirred at this temperature for 2 h. The reaction mixture was filtered off, the DMF solvent removed in a vacuum, and the crude product purified by flash chromatography (30% EtOAc/hexanes) to give a white solid (22 mg, 0.06 mmol, 34%) that was recrystallized from EtOAc/hexanes (mp 128−129 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, $J = 9.5$, 1H), 7.47 (AA′ of AA′XX′ $J_{AX} = 6.7$, $J_{AA'} = 2.3$, 2H), 7.10 (dd, $J = 9.2$, 2.4, 1H), 7.01 (XX′ of AA′XX′ $J_{AX} = 6.8$, $J_{XX'} = 2.2$, 2H), 6.95 (d, $J = 2.1$, 1H), 3.89 (s, 3H), 3.88 (s, 3H); ^{19}F NMR (500 MHz, $CDCl_3$) δ −54.9; MS (EI) *m/z* 322 (M^+, 100).

3-Methyl-5-methoxy-2-(4-methoxyphenyl)-2*H*-indazole (19a). Compound **19a** was obtained as a byproduct in the synthesis of product **20a**. Product **20a** was more conveniently synthesized by following the experimental procedure reported below (**20a**). Compound **11e** (80 mg, 0.24 mmol) was dissolved in DMF (2 mL), and the following reagents were added: $Pd_2(dba)_3$ (4 mg, 6 mol %), P(*o*-tolyl)$_3$ (8.8 mg, 12 mol %), and phenyltrimethyltin (87 μL, 0.48 mmol). The reaction mixture was stirred at 80 °C for 3 h. The reaction mixture was filtered off, the solvent removed in a vacuum, and the crude product purified by flash chromatography (30% EtOAc/hexanes) to give compound **19a** (19 mg, 0.07 mmol, 30% yield)-as white solid (mp 122−123 °C) and compound **20a** (26 mg, 0.07 mmol, 33% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, $J = 9.3$, 1H), 7.44 (AA′ of AA′XX′ $J_{AX} = 6.8$, $J_{AA'} = 2.4$, 2H), 7.04−7.01 (m, 3H), 6.79 (d, $J = 2.4$, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (400 MHz) δ 159.6, 154.6, 145.4, 133.2, 130.7, 126.9, 121.6, 121.1, 119.0, 114.3, 96.2, 55.6, 55.5, 11.1; MS (EI) *m/z* 268 (M^+, 100).

5-Methoxy-2-(4-methoxyphenyl)-3-phenyl-2*H*-indazole (20a). Compound **11e** (70 mg, 0.21 mmol) was dissolved in DMF (2 mL), and the following reagents were added: $Pd(PPh_3)_4$ (12 mg, 5 mol %), Cs_2CO_3 (96 mg, 0.3 mmol), and phenylboronic acid (31 mg, 0.25 mmol). The reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was filtered off, the solvent removed in a vacuum, and the crude product purified by flash chromatography (30% EtOAc/hexanes) to give a white solid (31 mg, 0.09 mmol, 45%) that was recrystallized from EtOAc/hexanes (mp 138−140 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, $J = 9.2$, 1H), 7.46−730 (m, 7H), 7.04 (dd, $J = 9$, 2.4, 1H), 6.90−6.86 (m, 3H), 3.83 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.3, 155.9, 145.8, 134.3, 133.6, 130.5, 129.7, 128.9, 128.1, 127.1, 121.9, 121.5, 119.2, 114.2, 96.4, 55.6, 55.6; MS (EI) *m/z* 330 (M^+, 35).

5-Methoxy-2-(4-methoxyphenyl)-2*H*-indazole 3-carbonitrile (21a). Compound **11e** (66 mg, 0.2 mmol) was dissolved in dimethylacetamide (1 mL), and the following reagents were added: $Pd_2(dba)_3$ (7.2 mg, 4 mol %), Dppf (8.8 mg, 8 mol %), Zn powder (1.5 mg, 24 mol %), and $Zn(CN)_2$ (23 mg, 0.2 mmol). The reaction mixture was stirred at 120 °C for 6 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were dried over Na_2SO_4 and concentrated in a vacuum. The crude product was purified by flash chromatography (30% EtOAc/hexanes) to give a white solid (30 mg, 0.1 mmol, 53%) that was recrystallized from EtOAc/hexanes (mp 147−148 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77−7.75 (m, 3H), 7.12−7.06 (m, 3H), 6.96 (d, $J = 2.3$, 1H), 3.91 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.5, 158.5, 145.3, 132.4, 128.4, 125.1, 123.0, 120.5, 114.8, 112.2, 105.4, 94.8, 55.8; MS (EI) *m/z* 279 (M^+, 100).

2-(4-Hydroxyphenyl)-3-isopropyl-2*H*-indazol-5-ol (13b). Compound **13a** (30 mg, 0.10 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **13b** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (20 mg, 0.07 mmol, 75% yield; mp >270 °C dec): ^{1}H NMR (500 MHz, methanol-d_4) δ 7.43 (d, $J = 9.1$, 1H), 7.27 (AA′ of AA′XX′ $J_{AX} = 6.7$, $J_{AA'} = 2.1$, 2H), 7.05 (d, $J = 2.2$, 1H), 6.97−6.93 (m, 3H), 3.21 (m, 1H), 1.41 (d, $J = 7.1$, 6H); ^{13}C NMR (500 MHz, methanol-d_4) δ 159.8, 152.2, 146.1, 142.0, 132.7, 129.0, 122.1, 120.2, 118.8, 116.6, 101.6, 28.2, 22.2; MS (EI) *m/z* 268 (M^+, 72); HRMS (EI) calcd for $C_{16}H_{16}N_2O_2$ 268.1212, found 268.1207; purity > 95% (HPLC).

3-Allyl-2-(4-hydroxyphenyl)-2*H*-indazol-5-ol (15b). Compound **15a** (20 mg, 0.07 mmol) was dissolved in CH_2Cl_2 (0.5 mL), and BBr_3 (3 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and then quenched with water (3 mL). The inorganic phase was extracted with EtOAc (3 × 5 mL), and the combined organic extracts were dried on Na_2SO_4 and concentrated in a vacuum. Compound **15b** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (13 mg, 0.04 mmol, 65% yield, mp 210 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.87 (bs, OH), 8.11 (bs, OH), 7.50 (d, $J = 9.0$ 1H), 7.40 (AA′ of AA′XX′ $J_{AX} = 6.7$, $J_{AA'} = 2.0$, 2H), 7.02−6.97 (m, 3H), 6.91 (d, $J = 2.3$, 1H), 5.99−5.91 (m, 1H), 5.06 (d, $J = 10.0$, 1H), 4.97 (d, $J = 17.0$), 3.72−3.70 (m, 2H); ^{13}C NMR (500 MHz, methanol-d_4) δ 159.7, 152.8, 145.9, 135.2, 133.7, 132.5, 128.5, 122.7, 122.5, 118.6, 117.2, 116.6, 100.7, 30.2; MS (EI) *m/z* 266 (M^+, 100); HRMS (EI) calcd for $C_{16}H_{14}N_2O_2$ 266.1055, found 266.1078. Anal. ($C_{16}H_{14}N_2O_2$·0.3H_2O) C, H, N.

2-(4-Hydroxyphenyl)-3-ethyl-2*H*-indazol-5-ol (16b). Compound **16a** (55 mg, 0.19 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **16b** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (42 mg, 0.16 mmol, 85%) that was recrystallized from EtOAc (mp >230 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.8 (bs, OH), 8.2 (bs, OH), 7.47 (d, $J = 9.2$, 1H), 7.39 (AA′ of AA′XX′ $J_{AX} = 6.7$, $J_{AA'} = 2.1$, 2H), 7.02−6.94 (m, 4H), 2.96 (q, $J = 7.6$, 2H), 1.17 (t, $J = 7.7$, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 158.5, 152.0, 145.7, 136.2, 133.3, 128.1, 121.5, 121.3, 119.3, 116.3, 100.3, 19.0, 14.0; MS (EI) *m/z* 254 (M^+, 100); HRMS (EI) calcd for $C_{15}H_{14}N_2O_2$ 254.1055, found 254.1061. Anal. ($C_{15}H_{14}N_2O_2$·0.2H_2O) C, H, N.

2-(4-Hydroxyphenyl)-3-propyl-2*H*-indazol-5-ol (17b). Compound **17a** (30 mg, 0.10 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **17b** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (22 mg, 0.08 mmol, 82%) that was recrystallized from EtOAc/acetone (mp >240 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.5 (bs, OH), 7.46 (d, $J = 9.2$, 1H), 7.36 (AA′ of AA′XX′ $J_{AX} = 6.7$, $J_{AA'} = 2.1$, 2H), 7.00 (XX′ of AA′XX′ $J_{AX} = 6.8$, $J_{XX'} = 2.2$, 2H), 6.96 (dd, $J = 9.2$, 2.2, 2H), 6.91 (d, $J = 2.2$, 1H), 2.91 (t, $J = 7.7$, 2H), 1.60−1.56 (m, 2H), 0.83 (t, $J = 7.3$, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 158.5, 152.0, 145.7, 134.8, 133.5, 128.2, 122.1, 121.2, 119.4, 116.3, 100.5, 27.5, 23.1, 14.0; MS (EI) *m/z* 268 (M^+, 66); HRMS (EI) calcd for $C_{16}H_{16}N_2O_2$ 268.1212, found 268.1210. Anal. ($C_{16}H_{16}N_2O_2$·0.1 H_2O) C, H, N.

2-(4-Hydroxyphenyl)-3-trifluoromethyl-2*H*-indazol-5-ol (18b). Compound **18a** (30 mg, 0.09 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **18b** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (23 mg, 0.08 mmol,

85%) that was recrystallized from EtOAc/hexanes (mp 224−225 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.98 (s, OH), 8.71 (s, OH), 7.68 (d, J = 9.4, 1H), 7.44 (XX′ of AA′XX′ J_{AX} = 6.8, $J_{XX'}$ = 2.2, 2H), 7.11 (dd, J = 9.2, 2.3, 1H), 7.04−7.02 (m, 3H); ^{19}F NMR (500 MHz, acetone-d_6) δ −55.4; MS (EI) m/z 294 (M^+, 100); HRMS (EI) calcd for $C_{14}H_9F_3N_2O_2$ 294.0616, found 294.0612. Anal. ($C_{14}H_9F_3N_2O_2$·0.1H_2O) C, H, N.

2-(4-Hydroxyphenyl)-3-methyl-2*H*-indazol-5-ol (19b). Compound **19a** (19 mg, 0.07 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **19b** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (14 mg, 0.05 mmol, 82% yield, mp >200 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.8 (bs, OH), 8.2 (bs, OH), 7.46−7.42 (m, 3H), 7.01 (AA′ of AA′XX′ J_{AX} = 6.6, $J_{AA'}$ = 2.2, 2H), 6.95 (dd, J = 9.2, 2.2, 1H), 6.86 (d, J = 2.1, 1H), 2.50 (s, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 158.2, 152.0, 145.7, 133.4, 130.0, 127.7, 121.3, 119.3, 116.3, 100.2, 10.9; MS (EI) m/z 240 (M^+, 100); HRMS (EI) calcd for $C_{14}H_{12}N_2O_2$ 240.0899, found 240.0901. Anal. ($C_{14}H_{12}N_2O_2$·0.3H_2O) C, H, N.

2-(4-Hydroxyphenyl)-3-phenyl-2*H*-indazol-5-ol (20b). Compound **20a** (30 mg, 0.09 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **20b** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (23 mg, 0.07 mmol, 77%) that was recrystallized from EtOAc (mp >250 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.5 (bs, OH), 7.59 (d, J = 9.3, 1H), 7.44−7.34 (m, 5H), 7.25 (AA′ of AA′XX′ J_{AX} = 6.8, $J_{AA'}$ = 2.1, 2H), 7.05 (dd, J = 9.2, 2.1, 1H), 6.95 (d, J = 1.8, 1H), 6.87 (XX′ of AA′XX′ J_{AX} = 6.7, $J_{XX'}$ = 2.1, 2H); ^{13}C NMR (500 MHz, acetone-d_6) δ 158.1, 153.6, 146.1, 133.7, 133.7, 131.6, 130.2, 129.5, 128.5, 128.1, 122.7, 121.6, 119.8, 116.1, 100.1; MS (EI) m/z 302 (M^+, 100); HRMS (EI) calcd for $C_{19}H_{14}N_2O_2$ 302.1055, found 302.1050. Anal. ($C_{19}H_{14}N_2O_2$·0.1H_2O) C, H, N.

5-Hydroxy-2-(4-hydroxyphenyl)-2*H*-indazole-3-carbonitrile (21b). Compound **21a** (17 mg, 0.06 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **21b** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (14 mg, 0.05 mmol, 93%) that was recrystallized from EtOAc (mp >280 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 9.06 (bs, OH), 7.79 (d, J = 9.2, 1H), 7.72 (AA′ of AA′XX′ J_{AX} = 6.7, $J_{AA'}$ = 2.3, 2H), 7.16 (dd, J = 9.3, 2.2, 1H), 7.09 (XX′ of AA′XX′ J_{AX} = 6.7, $J_{XX'}$ = 2.1, 2H), 7.02 (d, J = 2.3, 1H);^{13}C NMR (500 MHz, acetone-d_6) δ 159.4, 156.7, 145.5, 132.3, 129.0, 126.3, 122.7, 121.4, 116.7, 112.4, 105.3, 98.5; MS (EI) m/z 251 (M^+, 100); HRMS (EI) calcd for $C_{14}H_9N_3O_2$ 251.0695, found 251.0696; purity > 96% (HPLC).

7-Bromo-6-methoxy-2-(4-methoxyphenyl)-2*H*-indazole (23). Compound **9d** (60 mg, 0.23 mmol) was suspended in acetic acid (1 mL) and a solution of bromine (12 μL, 0.23 mmol) in acetic acid (1.5 mL) was added dropwise at room temperature for 4 h. After the addition was complete, the reaction mixture was stirred at room temperature for another 12 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were washed twice with NaOH (1 M), dried over Na_2SO_4, and concentrated in a vacuum. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to give a white solid (65 mg, 0.19 mmol, 85%) that was recrystallized from EtOAc/hexanes (mp 147−148 °C): ^{1}H NMR (500 MHz, $CDCl_3$)-δ 8.34 (s, 1H), 7.80 (AA′ of AA′XX′ J_{AX} = 6.5, $J_{AA'}$ = 2.0, 2H), 7.63 (d, J = 9, 1H), 7.00 (XX′ of AA′XX′ J_{AX} = 6.5, $J_{XX'}$ = 2.0, 2H), 6.97 (dd, J = 9, 1H), 4.0 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.3, 154.6, 149.1, 133.8, 122.5, 121.6, 120.4, 119.4, 114.5, 112.4, 96.5, 57.5, 55.5; MS (EI) m/z 333 (M^+, 100).

7-Bromo-2-(4-hydroxyphenyl)-2*H*-indazol-6-ol (24). Compound **23** (60 mg, 0.18 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **24** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (35 mg, 0.11 mmol, 63%) that was recrystallized from EtOAc/hexanes (mp 160−165 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.7 (s, OH), 8.5 (s, OH), 7.86 (AA′ of AA′XX′ J_{AX} = 6.6, $J_{AA'}$ = 2.1, 2H), 7.60 (d, J = 8.8, 1H), 7.01 (XX′ of AA′XX′ J_{AX} = 6.8, $J_{XX'}$ = 2.3, 2H), 6.89 (d, J = 9.0, 1H); ^{13}C NMR (500 MHz, acetone-d_6) δ 157.3, 152.8, 149.0, 133.3, 122.0, 122.0, 120.9, 119.0, 116.3, 116.1, 92.6; MS (EI) m/z 305 (M^+, 3); HRMS (EI) calcd for $C_{13}H_9BrN_2O_2$ 303.9847, found 303.9844. Anal. ($C_{13}H_9BrN_2O_2$·0.5H_2O) C, H, N.

2-Azido-4-methoxybenzoic Acid (26). Compound **25** (500 mg, 3 mmol) was dissolved in CH_2Cl_2 (2 mL), and Et_3N (1.25 mL, 9 mmol) and $CuSO_4$ (24 mg, 5 mol %) were added. The reaction mixture was cooled at 0 °C and a freshly prepared solution of TfN_3 (9 mmol in 9 mL of CH_2Cl_2) was added. The solution was brought to homogeneity by adding MeOH (2 mL) and allowed to warm to room temperature. After 1 h of stirring at this temperature, the reaction mixture was quenched with water (10 mL), acidified with HCl (1 M), and extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were dried over Na_2SO_4 and concentrated in a vacuum. The crude product was purified by flash chromatography (90% CH_2Cl_2/MeOH) to give a pale brown solid (550 mg, 2.8 mmol, 94% yield) that was essentially pure (mp >140 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 7.94 (d, J = 8.5, 1H), 6.85 (dd, J = 8.7, 2.2, 1H), 6.81 (d, J = 2, 1H), 3.91 (s, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 165.8, 164.5, 142.9, 134.9, 115.9, 111.6, 106.8, 56.1; MS (EI) m/z 193 (M^+, 5).

2-Azido-4-methoxy-*N*-(4-methoxyphenyl)benzamide (27). Compound **26** (100 mg, 0.5 mmol), was dissolved in benzene (1 mL), and $SOCl_2$ (375 μL, 10 mmol) was added. The reaction mixture was stirred under refluxed for 2 h. After the removal of $SOCl_2$ by distillation, a solution of *p*-anisidine (63 mg, 0.5 mmol) in pyridine (1 mL) was added. After 15 min of stirring at room temperature, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were washed twice with HCl (1 M), dried over Na_2SO_4, and concentrated in a vacuum. The crude product was purified by flash chromatography (40% EtOAc/hexanes) to give a white solid (110 mg, 0.21 mmol, 71%) that was recrystallized from EtOAc/hexanes (mp 154−155 °C dec): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, NH), 8.19 (d, J = 9, 1H), 7.54 (d, J = 8.8, 2H), 6.87 (d, J = 8.8, 2H), 6.78 (dd, J = 8.8, 2.2, 1H), 6.66 (d, J = 2.1, 1H), 3.85 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 163.0, 162.3, 156.5, 138.3, 134.5, 131.3, 122.3, 117.9, 114.2, 110.6, 104.2, 55.7, 55.7; MS (EI) m/z 298 (M^+, 8).

3-Chloro-6-methoxy-2-(4-methoxyphenyl)-2*H*-indazole (28). Compound **27** (100 mg, 0.33) was dissolved in benzene (1.5 mL) and $SOCl_2$ (1 mL) was added. The reaction mixture was stirred under reflux for 3 h. After this time the excess of $SOCl_2$ was removed by distillation and the crude product dissolved in EtOAc. The organic phase was washed twice with $NaHCO_3$ (sat. solution), dried over Na_2SO_4, and concentrated in a vacuum. The crude product was purified by flash chromatography (30% EtOAc/hexanes) to give a white solid (50 mg, 0.17 mmol, 51%) that was recrystallized from EtOAc/hexanes (mp 97−100 °C dec): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 9.0, 1H), 7.45 (d, J = 9.2, 2H), 7.02 (d, J = 8.8, 2H), 6.90 (d, J = 1.9, 1H), 6.81 (dd, J = 9.1, 2.0, 1H), 3.86 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.96, 159.91, 149.5, 131.7, 126.9, 119.9, 119.7, 118.1, 115.6, 114.3, 94.7, 55.7, 55.4; MS (EI) m/z 288 (M^+, 100).

3,7-Dichloro-6-methoxy-2-(4-methoxyphenyl)-2*H*-indazole (29). Compound **29** was obtained as byproduct in the synthesis of derivative **28**. Using the same reaction conditions and the same purification method, it was possible to obtained **29** (40 mg, 0.12 mmol, 35% yield) as a white solid which was recrystallized from EtOAc/hexanes (mp 119−120 °C dec): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 9.1, 2H), 7.50 (d, J = 9.3, 1H), 7.03−7.00 (m, 3H), 3.99 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.2, 154.0, 146.8, 131.3, 127.3, 120.8, 118.5, 116.8, 114.4, 114.3, 113.0, 107.6, 57.7, 55.7; MS (EI) m/z 322 (M^+, 100).

3-Chloro-2-(4-hydroxyphenyl)-2*H*-indazol-6-ol (30). Compound **28** (95 mg, 0.33 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2.

Compound **30** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (70 mg, 0.26 mmol, 81%) that was recrystallized from EtOAc/hexanes (mp 236−238 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.7 (bs, OH), 7.53−7.48 (m, 3H), 7.03 (d, J = 8.8, 2H), 6.87−6.85 (m, 2H); ^{13}C NMR (500 MHz, acetone-d_6) δ 158.8, 157.8, 150.1, 131.5, 127.9, 120.5, 119.4, 118.2, 116.3, 115.8, 98.3; MS (EI) *m/z* 260 (M^+, 100); HRMS (EI) calcd for $C_{13}H_9ClN_2O_2$ 260.0353, found 260.0348. Anal. ($C_{13}H_9ClN_2O_2$) C, H, N

3,7-Chloro-2-(4-hydroxyphenyl)-2*H*-indazol-6-ol (31). Compound **29** (30 mg, 0.09 mmol) was deprotected according to the procedure described above with BF_3·SMe_2 in CH_2Cl_2. Compound **31** was purified by flash chromatography (60% EtOAc/hexanes) to give a white solid (17 mg, 0.05 mmol, 63% yield) that was essentially pure (mp >240 °C dec): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.7 (bs, OH), 7.56 (d, J = 8.8, 2H), 7.49 (d, J = 9.0, 1H), 7.06 (d, J = 8.6, 2H), 7.02 (d, J = 8.8, 2H); ^{13}C NMR (500 MHz, acetone-d_6) δ 159.0, 152.7, 147.3, 131.3, 128.0, 120.7, 119.0, 118.0, 116.6, 116.3, 104.2; MS (EI) *m/z* 294 (M^+, 100); HRMS (EI) calcd for $C_{13}H_8Cl_2N_2O_2$ 293.9963, found 293.9959. Purity > 96% (HPLC).

Estrogen Receptor Binding Affinity Assays. Relative binding affinities were determined by a competitive radiometric binding assay as previously described,[39,40] using 10 nM [^{3}H]-estradiol as tracer ([6,7-^{3}H]estra-1,3,5,(10)-triene-3,17-β-diol, 51−53 Ci/mmol, Amersham BioSciences, Piscataway, NJ), and purified full-length human ERα and ERβ were purchased from PanVera (Madison, WI). Incubations were for 18−24 h at 0 °C. Hydroxyapatite (Bio-Rad, Hercules, CA) was used to absorb the receptor−ligand complexes, and free ligand was washed away. The binding affinities are expressed as relative binding affinity (RBA) values with the RBA of estradiol set to 100%. The values given are the average ± range or SD of two or three independent determinations. Estradiol binds to ERα with a K_d of 0.2 nM and to ERβ×*e2* with a K_d of 0.5 nM.

Cell Culture and Transient Transfections. Human endometrial cancer (HEC-1) cells were maintained in minimum essential medium (MEM) plus phenol-red supplemented with 5% calf serum and 5% fetal calf serum. Cells were plated in phenol-red-free improved MEM and 5% charcoal dextran-treated calf serum (CDCS) and were given fresh medium 24 h before transfection. Transfection assays were performed in 24-well plates using a mixture of 0.35 mL of serum-free improved MEM medium and 0.15 mL of Hank's balanced salt solution containing 5 μL of lipofectin (Life Technologies, Inc., Gaithersburg, MD), 1.6 μg of transferrin (Sigma, St. Louis, MO), 200 ng of pCMV β-galactosidase as internal control, 1 μg of 2ERE-pS2-Luc, and 100 ng of ER expression vector per well. The cells were incubated at 37 °C in a 5% CO_2-containing incubator for 5 h. The medium was then replaced with fresh improved MEM supplemented with 5% CDCS plus the desired concentrations of ligands. Cells were harvested 24 h later. Luciferase and β-galactosidase activity were assayed as described.[41]

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Supporting Information Available: HPLC and elemental analysis of compounds **10a**−**e**, **12a**−**f**, **13b**, **15b**, **16b**−**21b**, **24**, **30**, **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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