Articles

ERβ Ligands. 3. Exploiting Two Binding Orientations of the 2-Phenylnaphthalene Scaffold To Achieve ERβ Selectivity

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The 2-phenylnaphthalene scaffold was explored as a simplified version of genistein in order to identify ER selective ligands. With the aid of docking studies, positions 1, 4, and 8 of the 2-phenylnaphthalene template were predicted to be the most potentially influential positions to enhance ER selectivity using two different binding orientations. Both orientations have the phenol moiety mimicking the A-ring of genistein. Several compounds predicted to adopt orientations similar to that of genistein when bound to ERβ were observed to have slightly higher ER affinity and selectivity than genistein. The second orientation we exploited, which was different from that of genistein when bound to ERβ, resulted in the discovery of several compounds that had superior ER selectivity and affinity versus genistein. X-ray structures of two ER selective compounds (i.e., **15** and **47**) confirmed the alternate binding mode and suggested that substituents at positions 1 and 8 were responsible for inducing selectivity. One compound (i.e., **47**, WAY-202196) was further examined and found to be effective in two models of inflammation, suggesting that targeting ER may be therapeutically useful in treating certain chronic inflammatory diseases.

Introduction

Estrogens are a family of naturally occurring steroid hormones that play a central role in the growth, development, and maintenance of a diverse range of tissues. Their actions are mediated by estrogen receptors (ER), which are members of a superfamily of nuclear receptors that function as ligand-activated gene transcription factors. Prior to 1996, estrogen-mediated events had been assumed to be regulated by only one estrogen receptor (now called ERα).[1] However, the discovery of a second estrogen receptor subtype (ERβ) in 1996 led to an intense interest in elucidating ERβ function[2,3] and determining which aspects of estrogen biology it mediated. Significant sequence homology is observed in the DNA and ligand binding domains (LBDs) of ERα and ERβ; however, the expression pattern of the two subtypes is different. Although widely found in many tissues, ERβ is predominately expressed in ovarian granulosa cells, lung, bladder, and prostate, whereas ERα is the predominant ER expressed in the uterus, kidney, and ovarian theca cells.[4−6] Over the last several years our laboratories and others have been focused on identifying selective ERβ ligands from several classes of molecules, e.g., biphenyls,[7,8] tetrahydrochrysenes,[9] diarylpropionitriles,[10] arylbenzthiophenes,[11] and triazines.[12] The challenge to identify highly selective compounds has stifled progress to probe the physiological function of ERβ. Only a small group of molecules has been reported to have ERβ selectivities above 40-fold.[13] However, with the recent identification of the highly ERβ selective agonist ERB-041, our company discovered that one function of ERβ may be to modulate the inflammatory response.[14,15]

In an effort to continue to identify novel nonsteroidal ER agonists, our group initially focused on the modestly selective structure of genistein (**1**) as a starting point.[16] In the three-dimensional structure of human ER complexed with genistein (**1**),[17] the phenolic hydroxyl group interacts with a Glu−Arg−water triad at one end of the cavity through hydrogen-bonding interactions, while the chromenone hydroxyl at C(7) forms a hydrogen bond with a His side chain at the other end of the cavity. The remaining hydroxyl at C(5) is believed to be hydrogen bonded to the adjacent carbonyl group[18−23] and does not interact with the protein. Our initial efforts focused on whether the isoflavone framework of genistein could be mimicked with an appropriately substituted biphenyl scaffold (Figure 1). Though we showed that incorporating only a single phenolic group (i.e. **2**) within the 4-OH-biphenyl motif produced ERβ selective ligands, only modest affinity and selectivity could be achieved.[8] To further mimic the key pharmacophoric groups of genistein, an oxime moiety was appended to the 4-OH-biphenyl scaffold, resulting in the identification of a 4-OH-

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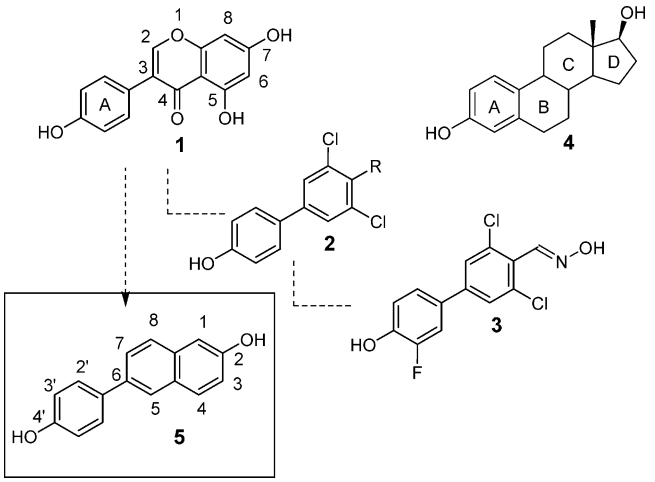


Figure 1. Compounds of interest.

biphenyl oxime derivative (i.e. **3**) having affinity and selectivity similar to that of genistein (**1**).[7] In this paper, we will disclose further efforts at creating a new template that can embrace similar spatial and chemical features of genistein (**1**) that fulfill the ER pharmacophoric requirements, while exploring how to enhance ERβ selectivity. The classical ER pharmacophore basically consists of an A-ring phenol linked by a hydrophobic core to a second hydroxyl group placed approximately 11 Å from the A-ring phenolic OH to mimic the 17-hydroxy group of estradiol (**4**).[24] The phenol group appears to be the key pharmacophoric group needed to achieve ligand recognition and high affinity for ER. One such scaffold that conforms to this design strategy is the 6-phenylnaphthalene framework (i.e. **5**). In fact, the 6-phenylnaphthalene motif has been previously employed in the anti-estrogen field.[25]

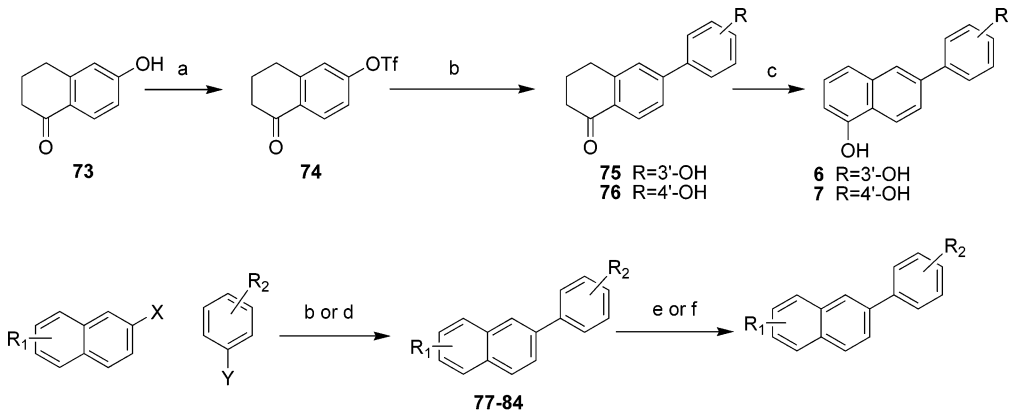
The 6-phenylnaphthalene scaffold can present similar spatial and conformational requirements as genistein (**1**), while at the same time provide the synthetic chemist a platform to expedite structural modifications. The 6-phenylnaphthalene moiety actually represents a simplified version of genistein, in which the heteroatoms in the B and C rings of genistein (**1**) have been removed, providing us with a further understanding of their role in ERβ binding and selectivity. Furthermore, although the 6-phenylnaphthalene scaffold was initially intended to serve as a "stripped-down" version of genistein, we present evidence to support our hypothesis that two of the binding orientations, one genistein-like and another that is flipped relative to the genistein binding mode, provide opportunities to enhance ERβ selectivity beyond that of genistein. We now report the design, synthesis, and structure−activity relationships (SAR) of a new class of ERβ selective ligands that embrace the 6-phenylnaphthalene scaffold to achieve superior ER affinity and selectivity to that of genistein (**1**).

Chemistry

Synthesis. All target molecules prepared as depicted in Schemes 1−10 are described in detail in the Experimental Section. Synthesis of the 1-hydroxy-6-phenylnaphthalenes (**6** and **7**) began with commercially available 6-hydroxytetralone, which was converted to the triflate and coupled to the appropriate phenyl derivative, followed by aromatization (Scheme 1). Compounds **5**, **8**−**14** were prepared by coupling the bromo or triflate derivatives (i.e., **77**−**84**) to the appropriately substituted boronic acid (method a) or Grignard reagent (method b), followed by demethylation using either boron tribromide or pyridinium hydrochloride (methods c or d, respectively). Chlorination or bromination led to **85** and **86**, respectively (Scheme 2). Bromide **86** was converted to the 1-substituted derivatives (**87**−**90**), which were subsequently demethylated. Bromide **16** was converted to the corresponding methoxy derivative (**21**) using cuprous bromide and sodium methoxide. Nitration followed by Suzuki coupling and deprotection led to **22**. Suzuki coupling of the appropriately substituted naphthalenes and phenyl derivatives followed by deprotection led to the 6-phenylnaphthalene derivatives (i.e., **23**, **25**, **27**, **29**, **31**, **32**, **34**, **36**, **38**) as depicted in Scheme 3. Subsequent chlorination with NCS (method E) of the appropriate 6-(4-hydroxyphenyl)-2-naphthols led to the 1-chloro-6-phenylnaphthalenes (**24**, **26**, **28**, **30**, **33**, **35**, **37**, **39**). Shown in Scheme 4 is the rather lengthy route used to prepare the 8-fluoro-6-phenylnaphthalenes **40**−**43**, beginning with commercially available 1-amino-7-hydroxynaphthalene (**106**). A three-step sequence was used to methylate **106** to afford the methoxy derivative **109**. Diazoniation and demethylation gave naphthol **111**, which was dibrominated to afford **112**. Selective debromination with $SnCl_2$ afforded **113**, which when reacted under Suzuki conditions led to **116** and **117**. The methoxy derivatives (i.e., **116**, **117**) could either be demethylated with boron tribromide to afford **40** and **41** or further reacted with NCS, followed by demethylation, to produce **42** and **43**. The 8-chloro-6-phenylnaphthalene derivatives **44** and **45** were prepared from intermediate **109** in a straightforward manner as depicted in Scheme 5. Target molecules **46**−**50** were prepared from commercially available tetralone **129** (Scheme 6). Briefly, tetralone **129** was converted to the cyano derivative **130**, which was aromatized with palladium in cymene followed by demethylation with pyridinium hydrochloride to produce naphthol **132**. Dibromination followed by selective debromination led to the key intermediate **133**, which when coupled under Suzuki conditions led to the phenylnaphthalenes **134** and **135**. Subsequent modifications of **134** and **135** in a straightforward manner afforded **46**−**50**. As shown in Scheme 7, naphthol **133** was converted to **51** in four steps. Further elaboration of the 8-cyano group of **47** led to the corresponding aldehyde, vinyl, ethyl, and alkynyl analogues (**52**−**56**). Several fluoro-subsituted analogues (i.e., **57**−**60**) were prepared using the appropriately substituted phenylboronic acids under Suzuki conditions (Scheme 8). The 4-cyano-6-phenylnaphthalenes (i.e., **61** and **62**) were prepared in four steps (Scheme 9) from key intermediate **133**. Subsequent modification of **61**, **62**, and **152** led to the 1,4-disubstituted-6-phenylnaphthalenes (**63**−**67**). Finally, the 4-cyano derivative **62** was modified (Scheme 10) to afford the corresponding 4-substituted derivatives **68**−**72** by employing similar chemistry as previous shown in Scheme 7.

Crystallography. The overall structures of ERβ LBD complexed with **15** and with **47** are similar to those

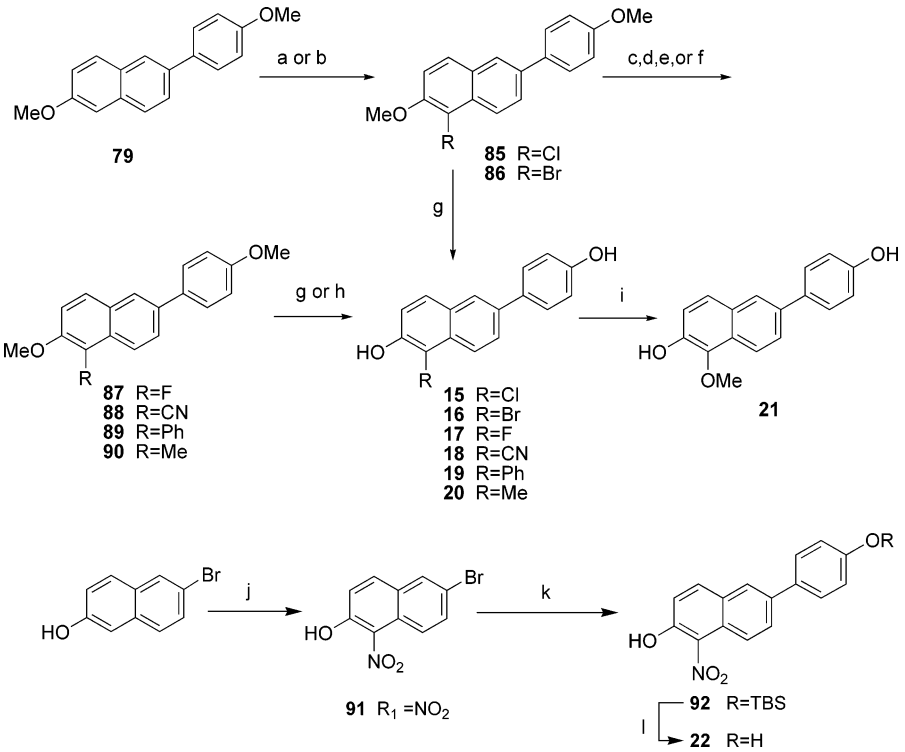
Scheme 1[a]



compound	R_1	R_2	X	Y	Method		R_1	R_2
77	2-OH	2'-OMe	Br	$B(OH)_2$	a	**8**	2-OH	2'-OH
78	2-OMe	3'-OMe	Br	$B(OH)_2$	a	**9**	2-OH	3'-OH
79	2-OMe	4'-OMe	Br	MgBr	b	**5**	2-OH	4'-OH
80	2-OMe	H	Br	MgBr	b	**10**	2-OH	H
81	3-OMe	4'-OMe	OTf	$B(OH)_2$	b	**11**	3-OH	4-'OH
82	3-OMe	3'-OMe	OTf	$B(OH)_2$	a	**12**	3-OH	3'-OH
83	3-OMe	H	OTf	$B(OH)_2$	a	**13**	3-OH	H
84	H	4'-OMe	Br	MgBr	b	**14**	H	4'-OH

[a] Reagents: (a) Tf_2O, C_6H_5N, CH_2Cl_2, 0 °C; (b) $Pd[P(Ph)_3]_4$, Na_2CO_3, DME/H_2O, 85 °C (method A); (c) 10% Pd/C, *p*-cymene, reflux; (d) ArMgBr, $Pd[P(Ph)_3]_4$, (method B); (e) C_6H_5N·HCl, 190 °C (method D); (f) BBr_3, CH_2Cl_2, 0 °C (method C).

Scheme 2[a]

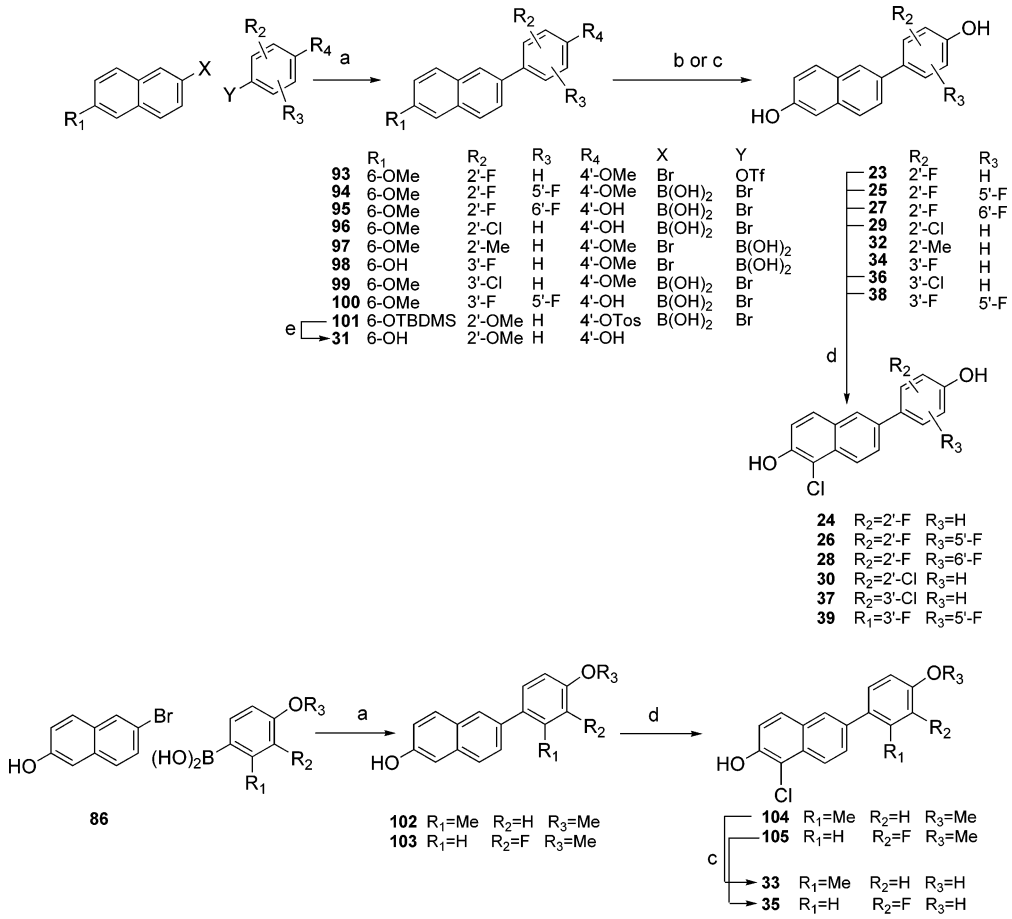


[a] Reagents: (a) NCS (method E) (b) Br_2/AcOH; (c) n-BuLi, NFSI; (d) CuCN, DMF, 120 °C; (e) PhMgBr, $Pd[P(Ph)_3]_4$ (method A); (f) n-BuLi, MeI; (g) C_6H_5N·HCl, 190 °C (method D); (h) BBr_3, CH_2Cl_2, 0 °C (method C); (i) CuBr, NaOMe, DMF; (j) 4-NO_2-4-Me-2,3,5,6-Br_4-2,5-cyclohexadien-1-one; (k) $Pd[P(Ph)_3]_4$, Na_2CO_3, DME/H_2O, 85 °C (method A); (l) TBAF.

previously reported by our group[14,26] and by others[17,27−29] and thus they will not be described in detail here. We point out that in both cases the helix-12 conformation corresponds to that observed for other bound agonists, consistent with the observed functional activity within this series (see below). When helix-12 adopts an "agonist-like" conformation, the ligand becomes completely encapsulated by the protein, as a result of the helix "closing" over the binding pocket. The closing of helix-12 also forms a cavity on the surface of the ER LBD, formed by helices H3, H4, H5, and H12, and the turn between H3 and H4. In our structures, a coactivator fragment binds to this cavity in a α-helical conformation, in a manner similar to what has been previously described for other ERα and ER*β* LBD complexes (see Figure 2).

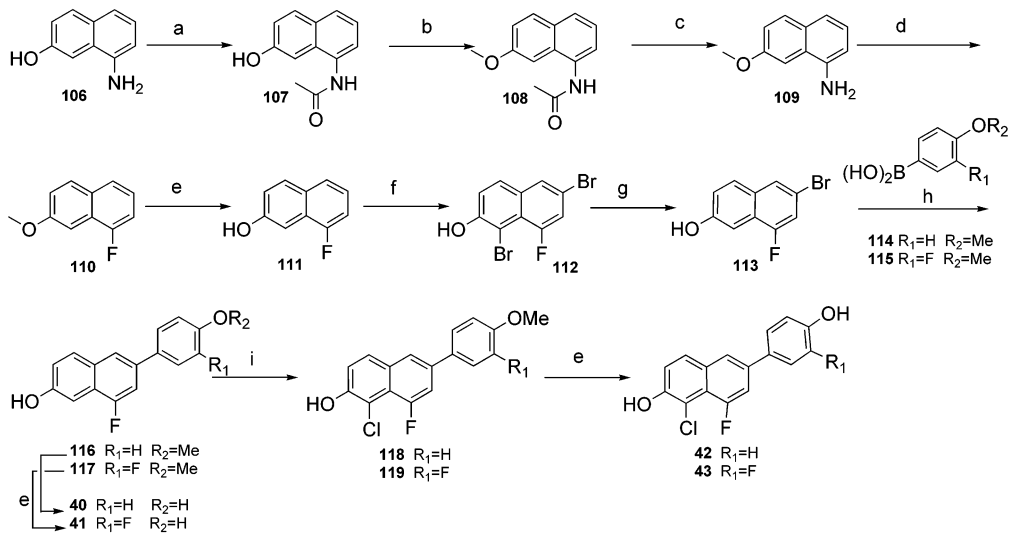
Crystal structures of the ERα and ER*β* binding pockets have been reported to have relatively consistent

Scheme 3[a]



[a] Reagents: (a) $Pd[P(Ph)_3]_4$, Na_2CO_3, DME/H_2O, 85 °C (method A); (b) $C_6H_5N{\cdot}HCl$, 190 °C (method D); (c) BBr_3, CH_2Cl_2, 0 °C (method C); (d) NCS (method E); (e) KOH/H_2O/EtOH, 90 °C.

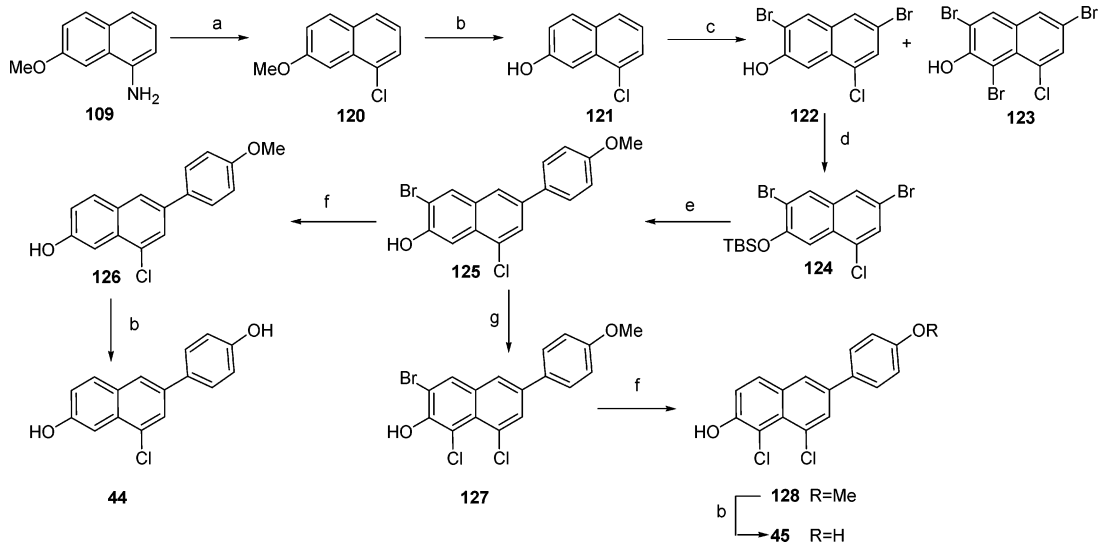
Scheme 4[a]



[a] Reagents: (a) Ac_2O (b) MeI, K_2CO_3; (c) 1N HCl; (d) (i) $NaNO_2$ (ii) HBF_4; (iii) xylenes, reflux; (e) BBr_3, CH_2Cl_2, 0° (method C); (f) Br_2/AcOH; (g) $SnCl_2$; (h) $Pd[P(Ph)_3]_4$, Na_2CO_3, DME/H_2O, 85 °C (method A); (i) NCS (method E).

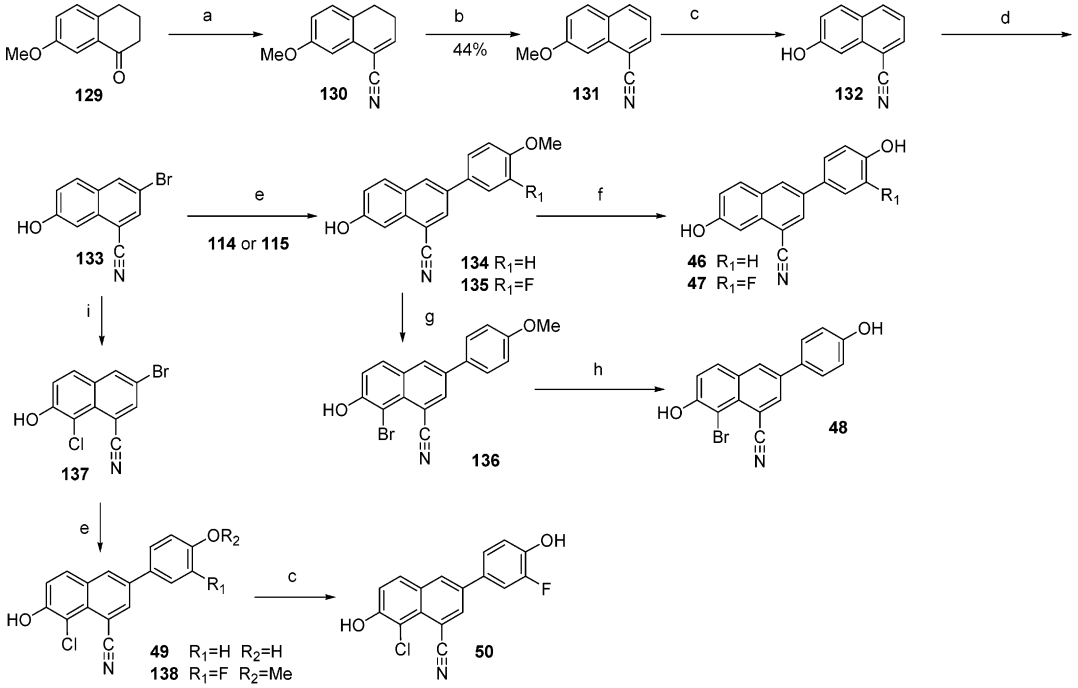
tertiary architecture. Comparing X-ray cocrystal structures of ERα and ERβ complexed with agonists[14,17,26–29] reveals only two residue substitutions within 5 Å of the bound ligand. The leucine present at position 384 in ERα is replaced by a methionine in ERβ (i.e., Met_{336}), and the methionine at position 421 in ERα is replaced by an isoleucine in ERβ (i.e. Ile_{373}). It has been hypothesized from modeling studies in our labs[7,8,14,26] and others[12] that there exist an opportunity to achieve enhanced selectivity for ERβ by identifying a ligand that could differentiate the substitution of ERα Met_{421} to ERβ Ile_{373}, which lies at the α-face of ER-bound estradiol. Briefly, the substitution of Met_{421} by Ile_{373} may impart the ability of certain appropriately placed func-

Scheme 5[a]



[a] Reagents: (a) CuCl, *tert*-butyl nitrite, MeCN; (b) BBr_3, CH_2Cl_2, 0 °C (method C); (c) Br_2/AcOH; (d) TBSCl; (e) ArMgBr, $Pd[P(Ph)_3]_4$, (method B); (f) (i) t-BuLi, (ii) H_2O; (g) NCS (method E).

Scheme 6[a]



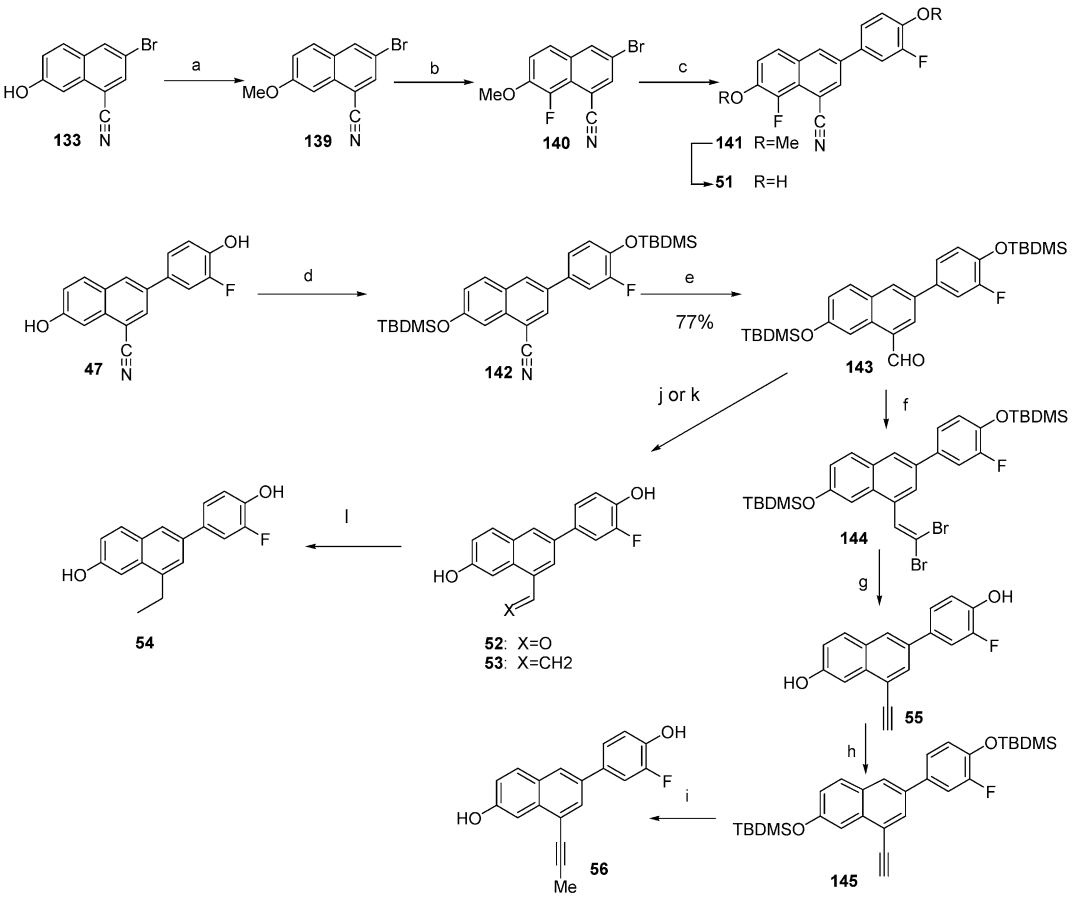
[a] Reagents: (a) (i) TMSCN/ZnI_2 (ii) $POCl_3$, AcOH (b) 10% Pd/C, *p*-cymene, reflux; (c) $C_6H_5N{\cdot}HCl$, 190 °C (method D); (d) (i) Br_2/AcOH (ii) $SnCl_2$; (e) $Pd[P(Ph)_3]_4$, Na_2CO_3, DME/H_2O, 85 °C (method A); (f) $C_6H_5N{\cdot}HCl$, 190 °C (method D); (g) NBS; (h) BBr_3, CH_2Cl_2, 0° (method C); (i) NCS (method E).

tional groups to achieve stereoelectronic differentiation between these two residue side chains, leading to enhanced ERβ selectivity.

ERβ Selectivity

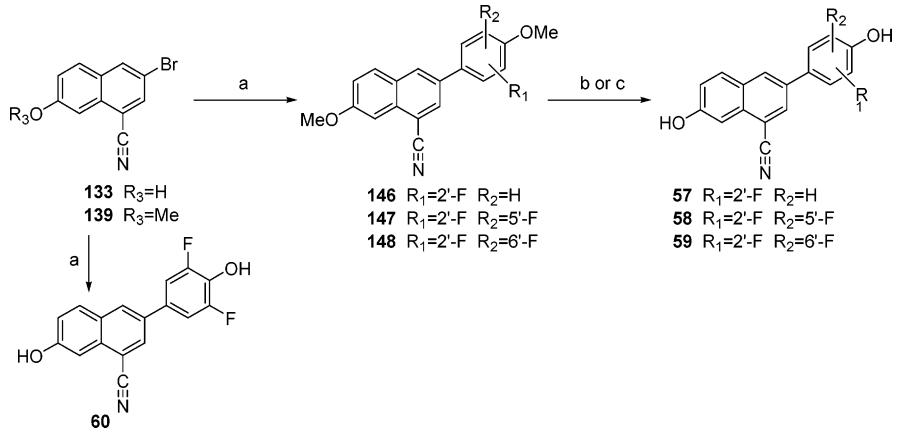
Optimization of Key Hydroxyl Groups. Shown in Tables 1−6 are the affinities (as measured by IC_{50}s) and selectivities for human ERα or ERβ of all compounds of interest using a competitive radioligand binding assay.[30] Since the ER has been reported to have some tolerance for the oxygen−oxygen distance[24] (D_1) (e.g., genistein D_1 = 12.2Å; estradiol D_1 = 10.9Å), a better understanding of the roles of the crucial hydroxyl groups, with respect to ERβ affinity and selectivity, needed to be addressed within the phenylnaphthalene scaffold. As shown in Table 1, compound **5** (D_1 = 12.0Å), having its hydroxyl groups in comparable positions to that of genistein (**1**), was also observed to have similar affinity. However, the ERβ selectivity of **5** decreased 3-fold versus **1**, suggesting that one or more of the other three oxygens of **1**, not present in **5**, plays a significant role in determining ERβ selectivity. Naphthalene **7** (D_1 = 10.7Å) was observed to have the highest affinity for ERβ; however, selectivity decreased 10-fold versus **1**. The 4′-OH phenyl group was always observed to be the most potent derivative within its respective group of 1-, 2- or 3-OH substituted naphthalenes (i.e., **6** vs **7**; **8** vs **5**; **9** vs **5**; **11** vs **12**). Removal of

Scheme 7[a]



[a] Reagents: (a) MeI, K_2CO_3; (b) Selectfluor; (c) $Pd[P(Ph)_3]_4$, Na_2CO_3, DME/H_2O, 85 °C (method A); (d) TBSCl; (e) DIBAL; (f) CBr_4, Zn, $P(Ph)_3$; (g) (i) n-BuLi, (ii) TBAF; (h) TBDSCl, (i) n-BuLi, MeI; (j) $P(Ph_3)CH_3Br$, n-BuLi; (k) TBAF; (l) H_2 10% Pd/C.

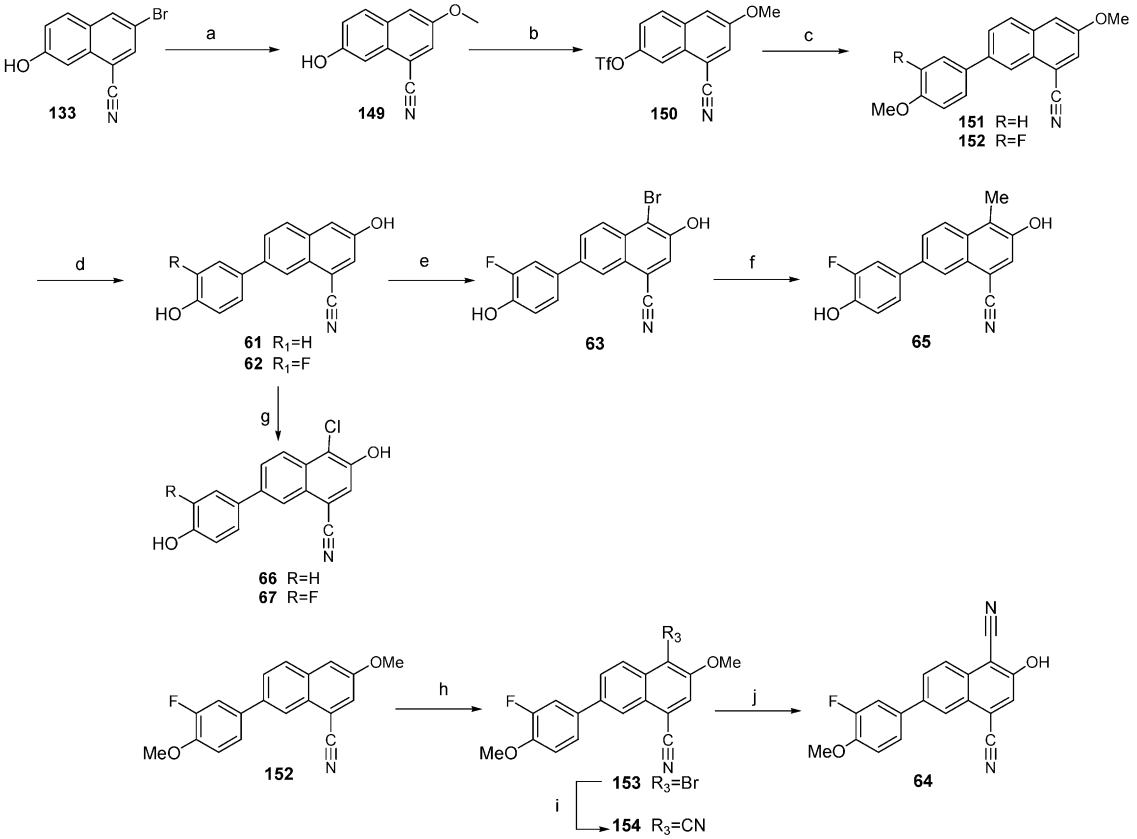
Scheme 8[a]



[a] Reagents: (a) $Pd[P(Ph)_3]_4$, Na_2CO_3, DME/H_2O, 85 °C (method A); (b) C_6H_5N·HCl, 190 °C (method D); (c) BBr_3, CH_2Cl_2, 0 °C (method C).

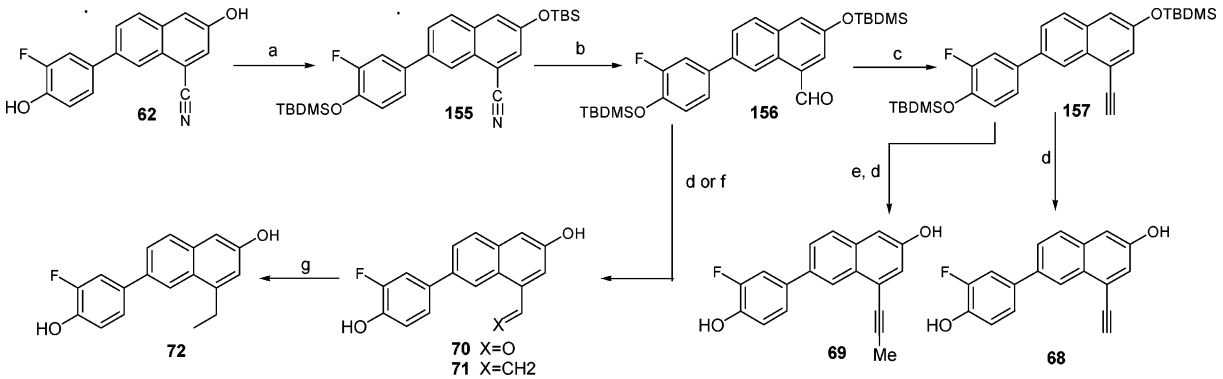
one of the hydroxyl groups of **5** led to a 19−29-fold loss in affinity (i.e., **5** vs **10**, and **5** vs **14**), confirming the importance of having two hydrogen bonding groups within the 6-phenylnaphthalene scaffold. However, the monohydroxyl derivatives **10**, **13**, and **14** were still more potent than the dihydroxyl analogue **8**, suggesting that the 2′-OH phenyl group was playing no role in hydrogen bonding (D_1 = 8−8.4 Å) and was actually having a detrimental effect. Also worth mentioning are that monohydroxyl derivatives **10** and **14** had similar ERβ affinities. Since it is known that the phenolic A-ring of estrogens participates in key hydrogen bonds with the receptor,[24] this suggests that the hydroxyl groups of **10** and **14** are involved in the essential hydrogen-bond network that mimics the A-ring of estradiol using two completely different binding orientations of the phenylnaphthalene scaffold. In the case of **10**, the naphthol moiety is mimicking the A-ring of estradiol, whereas in **14** the phenolic ring mimics the A-ring of estradiol. This supports the notion that the phenylnaphthalene scaffold is capable of what we term "A−C-ring flipping" or "horizontal flipping," due prima-

Scheme 9[a]



[a] Reagents: (a) NaOMe, CuBr (method F); (b) Tf_2O, C_6H_5N, CH_2Cl_2, 0 °C; (c) $Pd[P(Ph)_3]_4$, Na_2CO_3, DME/H_2O, 85 °C (method A); (d) C_6H_5N·HCl, 190 °C (method D); (e) NBS; (f) $SnMe_4$, $PdCl_2P(o\text{-tolyl})_3$; (g) NCS (method E); (h) Br_2/AcOH; (i) Pd(0), $Zn(CN)_2$; (j) C_6H_5N·HCl, 190 °C (method D).

Scheme 10[a]



[a] Reagents: (a) TBDSCl; (b) DIBAL; (c) (i) CBr_4, Zn, $P(Ph)_3$; (ii) n-BuLi; (d) TBAF; (e) n-BuLi, MeI; (f) $P(Ph)_3CH_3Br$, n-BuLi; (g) H_2 10% Pd/C.

rily to the pseudosymmetry of this simplified scaffold (see below).

Opportunities To Enhance Selectivity. To be able to fully understand how to exploit the residue substitutions in ERβ relative to ERα, it is necessary to have an understanding of the binding orientation that is favored by the chosen template. As discussed above in the case of estradiol, the phenol ring is involved in a hydrogen-bonding interaction with Glu_{305} and Arg_{346}, and the 17β-OH group forms a hydrogen bond to His_{475}. In this case, one of the primary determinants of the ligand-binding mode appears to be the shape and asymmetry of the estradiol steroidal scaffold. Similarly, in the case of genistein the phenol ring mimics the A-ring of estradiol, while the second phenolic hydroxyl group on the chromenone ring mimics the 17β-OH group of estradiol. Again, the ability of ER to differentiate the two phenolic groups and ultimately determine the true binding mode must rely on the structural (i.e. geometric) features of the genistein framework. On the other hand, a simplified template, such as phenylnaphthalene **5**, may have no obvious means to allow ER to differentiate one potential binding mode from another. In fact, one could argue that **5** possesses pseudo D_{2h} symmetry, and thus there appear to be essentially four reasonable binding orientations that **5** can adapt when bound to ER (Figure 3). While these orientations all seem to yield similar interactions with the receptor, docking studies also sug-

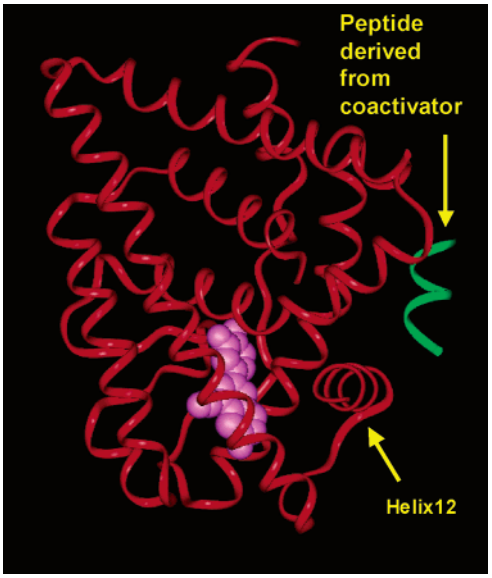
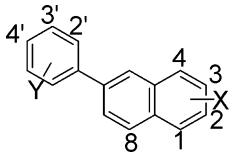


Figure 2. Ribbon diagram of the X-ray structure of **47** complexed to ERβ.

Table 1. Optimizing Hydroxyl Groups



compd	X	Y	ERβ (nM)[a]	ERα (nM)[a]	ratio
1			9.7 ± 4.3	395 ± 181	41
4			3.6 ± 1.6	3.2 ± 1.0	1
5	2-OH	4′-OH	16.3 ± 7	211 ± 74	13
6	1-OH	3′-OH	205 ± 100	1452 ± 718	7
7	1-OH	4′-OH	5.8 ± 0.7	22 ± 5	4
8	2-OH	2′-OH	2000	>5000	–
9	2-OH	3′-OH	30 ± 9	230 ± 91	8
10	2-OH	H	374 ± 119	1345 ± 64	4
11	3-OH	4′-OH	44 ± 13	442 ± 229	10
12	3-OH	3′-OH	566 ± 63	2642 ± 1692	5
13	3-OH	H	527 ± 95	3405 ± 1846	6
14	H	4′-OH	245 ± 163	638 ± 295	3

[a] IC_{50} values are the means of at least two experiments ± SD, determined from eight concentrations (performed in triplicate). Values without SDs are for a single determination only.

gest that orientations a ("genistein-like") and b ("vertically flipped", i.e., about the longest axis of the molecule) may provide the greatest opportunity to take advantage of the ERβ Ile_{373} → ERα Met_{421} residue substitution, by introducing functional groups that interact less favorably with ERα Met_{421} relative to ERβ Ile_{373}. In contrast, the two "horizontally flipped" orientations c and d may be less desirable, because the phenyl ring can easily rotate to achieve more favorable interactions with ERα Met_{421}. In addition, interactions between the B-ring and ERβ Met_{336}, which previous studies suggest may contribute to ERβ selectivity,[8] appear to be more difficult to maintain in these orientations. In the light of this discussion, the most likely positions to influence ERβ selectivity on the phenylnaphthalene template would be the 4 position, using the genistein-like orientation, and positions 1 and 8, using the vertically flipped orientation. Interestingly, even though we initially intended to mimic the genistein scaffold, we were most successful at enhancing ERβ selectivity beyond that of genistein by taking advantage of the vertically flipped orientation. It is to these results that we now turn our attention.

Selectivity Enhancements Obtained Utilizing the Vertically Flipped Orientation. As shown in Table 2, attaching a chlorine substituent (i.e. **15**) to the 1 position led to a 6.5-fold increase in ERβ affinity versus **5** and 36-fold selectivity for ERβ. Docking studies predicted **15** to adopt a vertically flipped binding mode, which was verified by an X-ray cocrystal structure of **15** bound to the ERβ LBD (see Figure 4a). As predicted, the 1-chloro substituent is directed at the ERβ Ile_{373} → ERα Met_{421} residue substitution, consistent with the selectivity improvement seen for **15** relative to **5.** We also point out that the chloro group was found to be an effective substituent in our earlier work within the biphenyl series.[8]

Shown in Table 3 is a summary of the substituent effects on the phenolic ring with respect to **5** and **15**. In general, with the exception of **31**, all modifications of the phenolic ring of **5** led to an improvement in ERβ affinity, with very little effect on ERβ selectivity. However, this trend was not observed when attaching substituents to the phenolic ring of **15**. Only in the case of attaching a 2′-fluoro group to **15** (i.e. **24**) did a slight increase in both ERβ affinity and selectivity occur. Attachment of a second chloro group ortho to the phenol hydroxyl of **15** (i.e. **37**) led to over a 12-fold loss in ERβ affinity. The fact that this trend was not observed when comparing **5** to **36**, in terms of a loss in ERβ affinity, suggests that **36** may be binding in a different orientation than **15**. Since it is known that the A-ring of estradiol is not very tolerant toward *o*-chloro groups,[24] we hypothesize that **36** may be maintaining its affinity using the naphthol moiety as the A-ring mimic (i.e. horizontally flipped binding mode), whereas dichloro **37** does not have this alternative orientation to exploit, since both of its hydroxyl groups are flanked by chloro groups, which thus results in a diminished ER affinity. Addition of a single 2′-F or 3′-F group to the phenolic ring of **15** either maintained or slightly improved ERβ affinity and selectivity (i.e. **24** and **35**). Attaching two *o*-fluoro groups to the phenol of **15** (i.e. **39**) led to a slight increase in ERβ selectivity, with the concurrent loss in ERβ affinity. This loss in affinity can be explained by electrostatic repulsion between one of these fluoro groups and the side chain of Glu_{305}.[14]

As mentioned above, docking calculations predicted that position 8 might have a potentially beneficial effect on ERβ selectivity. As shown in Table 4, several compounds were indeed identified to possess enhanced ERβ selectivity when exploiting this position. For example, the cyano derivative **46** was found to be 46-fold selective for ERβ and could be further improved to achieve 78-fold selectivity by the addition of a 3′-fluoro group (i.e. **47**). An X-ray cocrystal structure of **47** complexed to ERβ was obtained (Figures 2 and 4b) in order to confirm the predicted binding mode (Figure 3b). In particular, the 8-cyano group is directed toward ERβ Ile_{373}, which may represent a more favorable interaction than with the corresponding ERα Met_{421}.[26] However, this difference is a subtle one, given that the 3.5-fold difference in selectivity observed when comparing **5** to **46** corresponds to only a 0.75 kcal/mol binding free

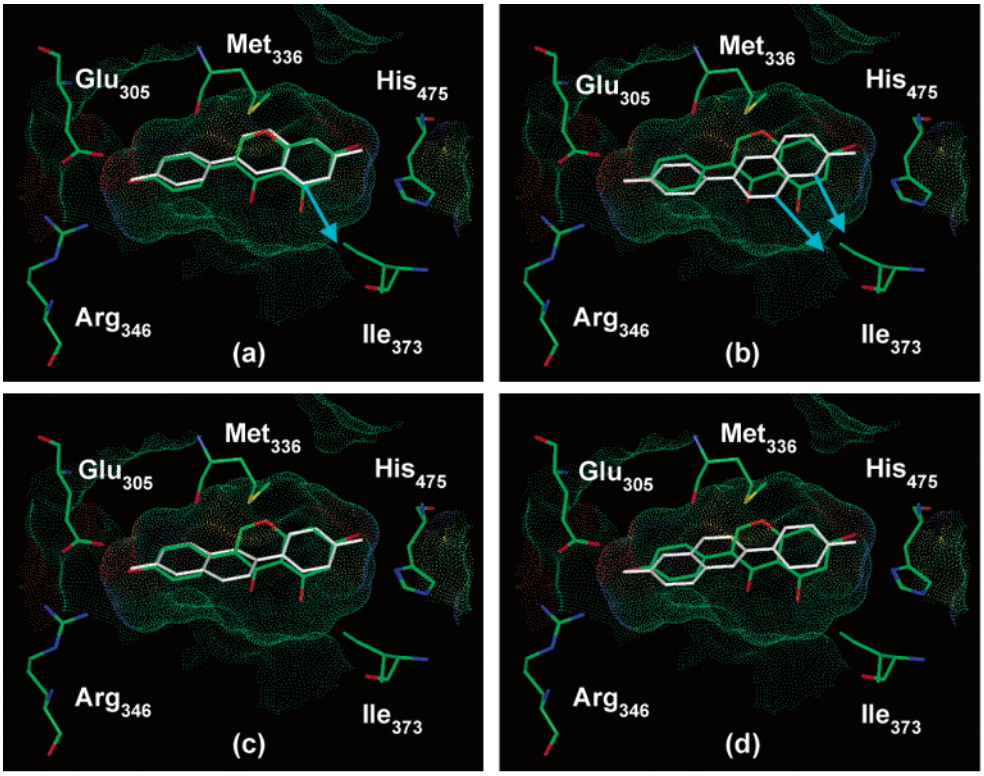
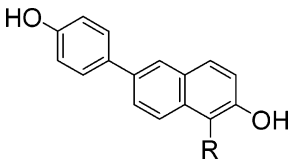


Figure 3. Four potential binding motifs (orientations a−d) identified by docking compound **5** to the ERβ LBD.

Table 2. SAR at the 1 Position



compd	R	ERβ (nM)[a]	ERα (nM)[a]	ratio
5	H	16.3 ± 7	211 ± 74	13
15	Cl	2.52 ± 1.3	91 ± 37	36
16	Br	13.0 ± 5	266 ± 62	20
17	F	7.0 ± 3	77 ± 28	11
18	CN	81 ± 27	1402 ± 805	17
19	Ph	748 ± 129	1231 ± 692	2
20	Me	17 ± 2	282 ± 46	17
21	OMe	114 ± 26	884 ± 192	8
22	NO_2	199 ± 11	709 ± 132	4

[a] IC_{50} values are the means of at least two experiments ± SD, determined from eight concentrations (performed in triplicate).

energy difference at room temperature. We also point out that, in addition to direct interaction with ERα Met_{421}/ERβ Ile_{373}, 8-position substituents may indirectly modulate the electronic interaction between the B-ring and ERβ Met_{336} relative to ERα Leu_{384}. The even more subtle selectivity effect induced by the 3′-fluoro substituent was also observed within the 4-OH-biphenyl series reported in parts 1 and 2,[8] as well as within a 2-phenyl benzoxazole series reported previously.[14,26] A structure-based explanation for this effect has been provided elsewhere.[26]

Several other analogues were also observed to be more selective than genistein. In particular, the ethyl analogue **54** was 98-fold selective for ERβ. Docking calculations on **54** suggest a vertically flipped binding mode, similar to that observed for **47** complexed to ERβ, placing the ethyl group near ERα Met_{421}/ERβ Ile_{373}. Thus, the selectivity enhancement due to the ethyl moiety can be explained by a favorable dispersive interaction with ERβ Ile_{373}, relative to a less favorable or unfavorable (i.e. steric) interaction with ERα Met_{421} (which may translate to increased strain of either the ethyl group, the protein, or both). However, the docking calculations also suggest the possibility that **54** might adopt a genistein-like binding mode when bound to ERα and/or ERβ. In this case, the enhanced selectivity of **54** relative to **5** can also be rationalized by more favorable contact (and thus more favorable dispersive interactions) with ERβ Met_{336} relative to ERα Leu_{384}, resulting from the ethyl projecting ∼90° out of the naphthalene plane. As with the 8-cyano substituent, we cannot discount the possibility that the 8-ethyl group modulates the differential interaction between the B-ring and ERβ Met_{336} relative to ERα Leu_{384} in either binding mode.

Interestingly, the chloro group, which induced modest selectivity from the 1 position (i.e. **15**), has virtually no effect on ERβ selectivity relative to **5** when placed at the 8-position (i.e. **44**; 13-fold selective), demonstrating that certain substituents can only induce ERβ selectivity from appropriate positions of the phenylnaphthalene scaffold, even though they may have a similar trajectory within the ligand binding cavity. Also, no synergistic effect was observed by having both the 1-chloro and 8-cyano substituents (i.e. **49**) placed onto the phenylnaphthalene template, which actually had a detrimental effect on ERβ affinity and selectivity. This appears to be a consequence of the fact that any given functional group can modulate the interactions between the rest of the ligand and the protein. For example, the interaction of the 8-cyano of **49** with nearby residues can

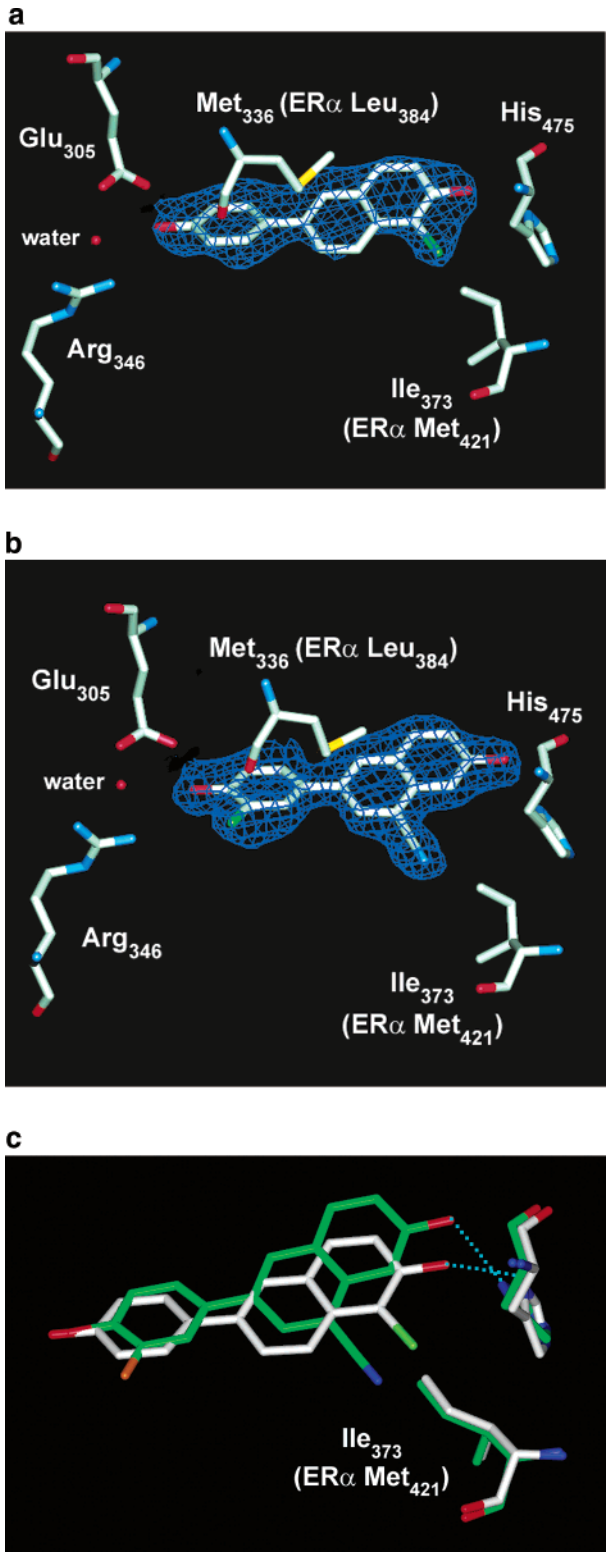
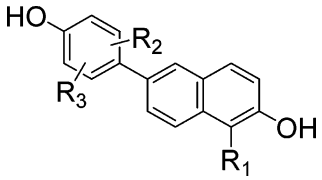


Figure 4. Unbiased $2F_o - F_c$ maps for **15** and **47** complexed to the ERβ LBD unambiguously define the ligand binding modes of (a) **15** and (b) **47**. For both ligands, the phenol mimics the estradiol A-ring, with the phenolic hydroxyl (4′-OH) involved in a hydrogen-bonding network between ERβ residues Glu_{305} and Arg_{346} (ERα residues Glu_{353} and Arg_{394}) and a highly ordered water molecule. Another hydrogen bond is formed between the naphthalene hydroxyl (2-OH) and $N_{\delta 1}$ of ERβ His_{475} (ERα His_{524}). The core scaffold, consisting of the A-ring phenyl and the naphthalene B and C rings, fills the remainder of the primarily hydrophobic pocket. (c) An overlay of **15** and **47** in the ligand binding pocket.

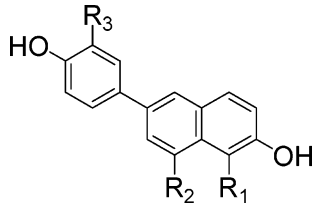
Table 3. A-Ring Substituent Effects



compd	R_1	R_2	R_3	ERβ (nM)[a]	ERα (nM)[a]	ratio
5	H	H	H	16.3 ± 7	211 ± 74	13
15	Cl	H	H	2.52 ± 1.3	91 ± 37	36
23	H	2′-F	H	2 ± 0.3	24 ± 0.8	12
24	Cl	2′-F	H	1.2 ± 0.3	58 ± 6	48
25	H	2′-F	5′-F	2.8 ± 0.1	27 ± 13	10
26	Cl	2′-F	5′-F	8.5 ± 4	118 ± 40	14
27	H	2′-F	6′-F	2.3 ± 0.1	10.3 ± 2.4	4
28	Cl	2′-F	6′-F	3.4 ± 1.3	35 ± 5	10
29	H	2′-Cl	H	1.4 ± 0.6	10 ± 5	7
30	Cl	2′-Cl	H	3.3 ± 2	36 ± 23	11
31	H	2′-OMe	H	27 ± 6	174 ± 26	6
32	H	2′-Me	H	10 ± 1	40 ± 1	4
33	Cl	2′-Me	H	13	40	11
34	H	3′-F	H	5 ± 1	92 ± 25	17
35	Cl	3′-F	H	4.0 ± 1	143 ± 28	36
36	H	3′-Cl	H	11 ± 1.4	107 ± 30	10
37	Cl	3′-Cl	H	32 ± 3	356 ± 65	11
38	H	3′-F	5′-F	8.4 ± 3.6	92 ± 52	11
39	Cl	3′-F	5′-F	10.6 ± 0	519 ± 126	47

[a] IC_{50} values are the means of at least two experiments ± SD, determined from eight concentrations (performed in triplicate). Values without SDs are for a single determination.

Table 4. SAR at the 1, 8, and 3′ Positions

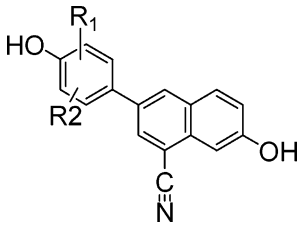


compd	R_1	R_2	R_3	ERβ (nM)[a]	ERα (nM)[a]	ratio
5	H	H	H	16.3 ± 7	211 ± 74	13
40	H	F	H	1.6 ± 0.7	22 ± 1	14
41	H	F	F	1.5 ± 0.6	21 ± 6	14
42	Cl	F	H	1.1 ± 0.5	40 ± 11	36
43	Cl	F	F	2.5 ± 1	125 ± 24	50
44	H	Cl	H	2.3 ± 1.7	30 ± 1	13
45	Cl	Cl	H	9	43	5
46	H	CN	H	2.3 ± 1.3	105 ± 47	46
47	H	CN	F	2.7 ± 1.9	210 ± 122	78
48	Br	CN	H	12 ± 4	131 ± 50	11
49	Cl	CN	H	6.0 ± 3.3	109 ± 29	18
50	Cl	CN	F	11 ± 6	299 ± 147	27
51	F	CN	F	5.6 ± 2.7	312 ± 75	56
52	H	CHO	F	3.4 ± 0.5	231 ± 91	68
53	H	$CH{=}CH_2$	F	4.4 ± 3.7	254 ± 112	58
54	H	ethyl	F	2.4 ± 1	235 ± 31	98
55	H	C≡CH	F	6.3 ± 1.3	247 ± 190	40
56	H	$C{\equiv}CCH_3$	F	10 ± 6	343 ± 61	34

[a] IC_{50} values are the means of at least two experiments ± SD, determined from eight concentrations (performed in triplicate). Values without SDs are for a single determination.

modify the trajectory groups at the 1-position (e.g. chloro), leading to reduced affinity and selectivity. This can be understood by overlaying the X-ray structures of ERβ complexed with **15** and **47**, which clearly demonstrates that steric interactions between the 8-nitrile of **46** and the protein contribute to a shift of the 1-position relative to **15** (see Figure 4c).

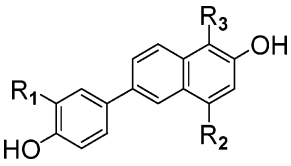
Table 5. A-Ring Substituent Effect Based on 46



compd	R_1	R_2	ERβ (nM)[a]	ERα (nM)[a]	ratio
46	H	H	2.3 ± 1.3	105 ± 47	46
47	3′-F	H	2.7 ± 1.9	210 ± 122	78
57	2′-F	H	0.5 ± 0.5	26 ± 3	55
58	2′-F	5-F	6.9 ± 1	186 ± 16	27
59	2′-F	6-F	2.2 ± 1.1	45 ± 17	20
60	3′-F	5-F	58 ± 45	548 ± 225	9

[a] IC_{50} values are the means of at least two experiments ± SD, determined from eight concentrations (performed in triplicate).

Table 6. SAR at the 1, 4, and 3′ Positions



compd	R_1	R_2	R_3	ERβ (nM)[a]	ERα (nM)[a]	ratio
5	H	H	H	16 ± 7	211 ± 74	13
61	H	CN	H	2.0 ± 1.5	84 ± 33	42
62	F	CN	H	2.1 ± 0.9	96 ± 42	46
63	F	CN	Br	4.5 ± 1.8	116 ± 47	26
64	F	CN	CN	28 ± 5	877 ± 48	31
65	F	CN	Me	6.0 ± 0.1	406 ± 136	68
66	H	CN	Cl	3.0 ± 2.6	98 ± 12	32
67	F	CN	Cl	2.6 ± 2.7	55 ± 49	21
68	F	CCH	H	1.2 ± 0.7	73 ± 73	61
69	F	CCMe	H	5.5 ± 4.0	180 ± 91	33
70	F	CHO	H	1.1 ± 0.2	73 ± 23	67
71	F	$CH{=}CH_2$	H	7.3 ± 7.5	527 ± 607	72
72	F	ethyl	H	2.5 ± 1.2	113 ± 82	45

[a] IC_{50} values are the means of at least two experiments ± SD, determined from eight concentrations (performed in triplicate).

Attempts to further optimize cyano analogue **46** by various fluorine substitutions showed again that the 2′-fluoro group (i.e., **57**) resulted in an increase ERβ affinity at the expense of a slight loss in ERβ selectivity (Table 5). In contrast to the 3′,5′-difluoro analogue **39** (Table 3), the 3′,5′-difluoro substitutents pattern resulted in a dramatic loss in ERβ affinity and selectivity when incorporated with the 8-cyano group (**46** vs **60**). As previously discussed,[14] this loss in affinity can be explained by electrostatic repulsion between one of these fluoro groups and the side chain of Glu_{305}.

Selectivity Enhancements Obtained Utilizing a Genistein-Like Orientation. To attempt to exploit a second "genistein-like" binding mode (i.e., orientation a in Figure 2), the 4-position of the naphthalene scaffold was focused on. As shown in Table 6, several 4-substituted naphthalene derivatives (i.e., **61**, **62**, **65**, **68**, **70**, **71**, and **72**) were all observed to have higher affinity and selectivity for ERβ than that of genistein (**1**). Shown in Figure 5a,b is **62** docked into the binding site of ERβ, showing how the cyano group might enhance ERβ selectivity by accessing the ERβ Ile_{373} → ERα Met_{421} residue substitution. The overlay with genistein in Figure 5a illustrates that this compound

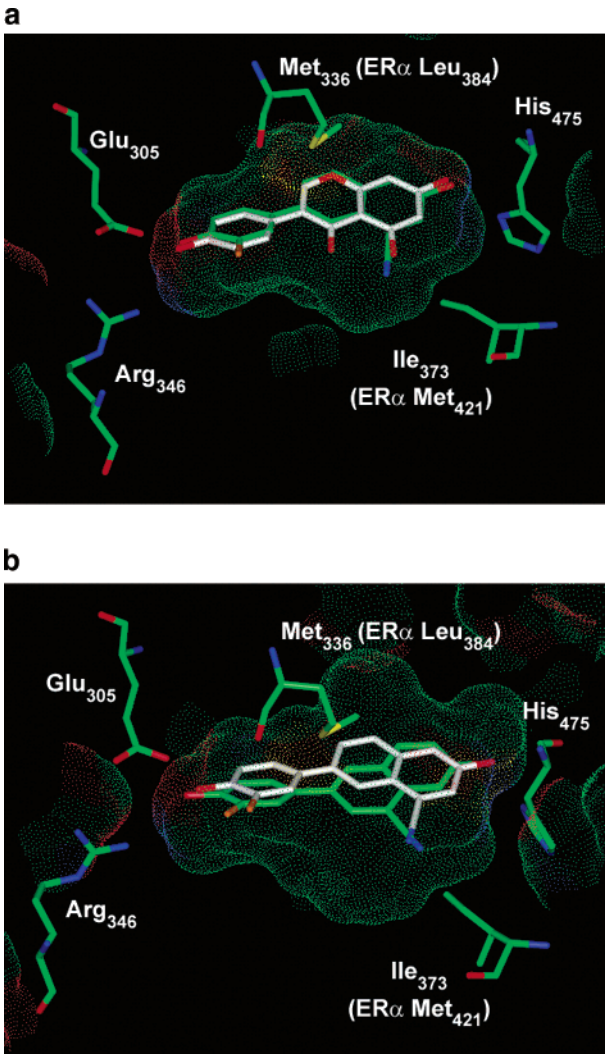


Figure 5. (a) **62** overlayed with genistein and docked to the ERβ/genistein binding site and (b) **62** docked to the ERβ/**47** binding site, colored by atom type. For **62**, carbon atoms were colored white for clarity. A Connolly surface of the binding site is also shown.

may be taking advantage of the genistein-like binding mode, while Figure 5b shows how the docked binding mode of **62** compares to that of **47** bound to ERβ. Clearly, **47** and **62** appear to use two different orientations to enhance ERβ selectivity, by directing the common cyano functional group toward the ERβ Ile_{373} → ERα Met_{421} residue substitution but at different angles.

Several compounds were prepared with substitutions at both the 1 and 4 positions (i.e. **63**−**67**). Interestingly, these compounds have the potential of adopting either the genistein-like or vertically flipped orientations. For example, if compounds **63**−**67** exploit a genistein-like orientation, the 4-cyano group would be directed toward the ERβ Ile_{373} → ERα Met_{421} residue substitution. In contrast, if **63**−**67** exploit a vertically flipped orientation, the 1-bromo, cyano, methyl, and chloro groups would be directed toward the ERβ Ile_{373} → ERα Met_{421} residue substitution. Since we have learned that placing a cyano group at the 1 position had no significant effect on ERβ selectivity (i.e. **5** vs **18**, Table 2), this suggests that **64** may be using a genistein-like orientation to achieve its 30-fold selectivity. Since it was also observed

Table 7. Regulation of IGFBP-4 mRNA in SAOS-2 Cells

compound[a]	% activity relative to 10 nM 17β-estradiol
15 (WAY-169122)	106
20	100
35	90
42	88
43	100
46	103
47 (WAY-202196)	120
49	143
50	100
39	100

[a] Compounds were tested at 1 μM, except for **15**, which was tested at 0.2 μM.

Table 8. Uterine Weights of Immature Rats after 3 days of Treatment

compound	mean uterine wt (mg) ± SEM
vehicle (50% DMSO/50% 1× Dulbecco's PBS)	21.4 ± 1.6
17α-ethinyl-17β-estradiol (0.06 μg/rat/day)	85.5 ± 3.1[a]
47 (2 mg/rat/day)	23.3 ± 1.3
47 + 17α-ethinyl-17β-estradiol	81.9 ± 4.2[b]

[a] Significantly greater than vehicle, $p < 0.05$. [b] Not significantly different from 17α-ethinyl-17β-estradiol alone, $p > 0.05$.

that attaching a methyl group to the 1 position (i.e. **20**) had no effect of affinity or selectivity, this suggests that **65** may also be achieving its 68-fold ERβ selectivity by exploiting a genistein-like orientation. The methyl group of **65** may be introducing some steric bulk, thus redirecting the 4-cyano group more optimally toward the ERβ Ile_{373} → ERα Met_{421} residue substitution, leading to an improvement in ERβ selectivity with respect to **62**. No improvement in ERβ selectivity was observed when the 3′-fluoro group was attached to the phenolic moiety (i.e., **61** vs **62**, and **66** vs **67**), which suggests the enhanced ERβ selectivity from a 3′-fluoro group is only manifested via the vertically flipped binding orientation.

Biological Evaluation

Cell-Based Transcriptional Assay. To assess whether compounds were ERβ agonists, a cell-based transcriptional assay was conducted. Insulin-like growth factor binding protein-4 (IGFBP4) is upregulated by 17β-estradiol in human osteosarcoma cells expressing ERβ.[31] Ten compounds were evaluated for their ability to upregulate this mRNA at a single dose (typically 1 μM). As shown in Table 7, each of the 10 compounds tested was essentially a full agonist in this assay.

Rat Uterotrophic Assay. The uterus of the sexually immature rat is highly responsive to estrogens, and this model is commonly used as an estrogenic bioassay.[32,33] Compounds such as 17α-ethynyl-17β-estradiol (e.g. 0.06 μg/~50 g rat, given subcutaneously) increase organ weight by about 4-fold. Because the rat uterus expresses essentially only ERα and little or no ERβ, this model can be used to assess the in vivo ER selectivity of compounds. Cyano derivative **47** was evaluated in this model at high doses given subcutaneously each day for three consecutive days. Specifically, **47** was dosed at 2 mg/~50 g rat, a >30 000-fold excess over the reference compound. No increase in organ weight was seen (Table 8). Moreover, when given in combination, organ weights were not reduced, indicating no antagonistic effect. The ERα-selective ligand propylpyrazoletriol (PPT) is fully uterotrophic,[31] suggesting ERα activation is necessary and sufficient for a full uterine response to nonreceptor subtype selective estrogens. **47** was also tested in an analogous model using sexually immature mice. Doses as high as 50 mg/kg were tested subcutaneously for 4 days. Consistent with the data from the rat model, organ weight did not increase (data not shown). Finally, **47** was also nonuterotrophic following 28 days of oral dosing, and this regimen achieved blood exposure substantially higher than those needed for efficacy in the Lewis rat adjuvant-induced model discussed below (data not shown).

HLA-B27 Transgenic Rat Model. The HLA-B27 transgenic rat expresses two human proteins (HLA-B27 and β2 microglobulin) that, over time, provoke a misdirected immune response.[34] One of the first phenotypes these rats manifest is chronic intestinal inflammation, and thus they provide a model of inflammatory bowel disease. A later phenotype to appear is joint inflammation, and they are also used as a model of arthritis. Daily oral administration of **47** rapidly converted the chronic diarrhea these rats experienced to a normal stool. Efficacy was seen as low as 0.1 mg/kg, dosed daily, but the response was slower at this dose compared to higher doses. A composite graph of these data is shown in Figure 6. Upon euthanasia, the colons were examined histologically for quantification of four disease parameters, which were then summed to calculate a total disease score. As shown in Table 9, all doses of **47** significantly reduced total disease score. However, as seen with the stool scores, the 0.1 mg/kg dose was slightly less effective than the higher doses. As mentioned above, the joints of the HLA-B27 transgenic rat become inflamed as they age. One of the studies looking at intestinal endpoints was extended to cover the period of time when swelling occurred in the vehicle-treated rats. Thus, this was a preventative study. Joint swelling was evaluated by visual inspection each day, with a possible maximum score of 12. As shown in Figure 7, rats treated with **47** (10 mg/kg, po) had less swelling than those treated with vehicle. The difference in the two curves is significantly different ($p < 0.05$).

Lewis Rat Adjuvant-Induced Arthritis Model. Because positive joint data were seen in the HLA-B27 transgenic rat, **47** was evaluated in a second model of arthritis. When immunized with Complete Freund's Adjuvant, the joints of Lewis rats swell dramatically over a period of 8 days. After maximal swelling occurred, rats received an oral daily dose of **47**. Thus, this was a full treatment regimen. Joint swelling was evaluated every day, and upon euthanasia, histological analysis was performed. As shown in the Figure 8, a composite graph of two studies, joint swelling was rapidly and dramatically reduced in rats treated with **47**. The first study evaluated doses of 10, 5, and 1 mg/kg and the second study tested doses of 1, 0.3, and 0.1 mg/kg. The 1 mg/kg dose was tested in both studies to illustrate the consistency of the data. Efficacy on this endpoint is seen with the lowest dose tested, 0.1 mg/kg. Serum from some of these rats was analyzed for haptoglobin, an acute phase protein that is elevated in many inflammatory conditions. **47**, at doses of 1 and 0.3 mg/kg, reduced haptoglobin levels by >70% (Table 10). Joints of the rats from this study were assessed for histological evidence

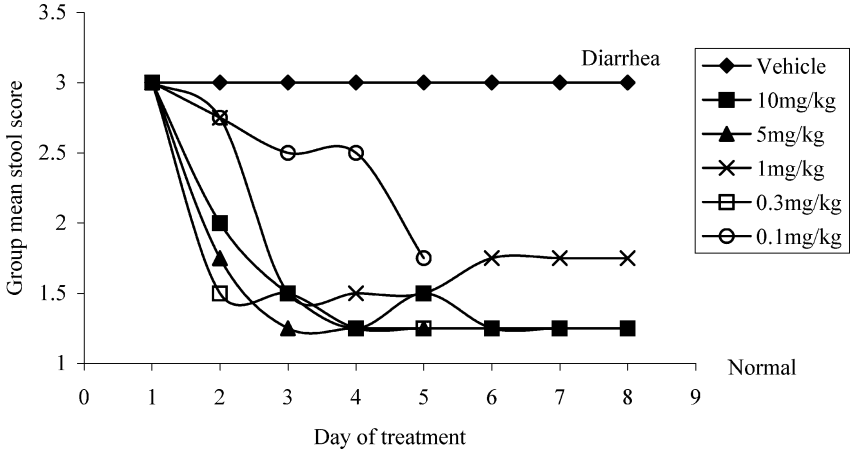


Figure 6. Effect of **47** on stool character of HLA-B27 transgenic rats. Fully diseased male rats were treated with oral daily doses of compound and stool character assessed daily according to following scale: diarrhea = 3; soft stool = 2; normal = 1.

Table 9. Effect of **47** on Colon Histology of HLA-B27 Transgenic Rats

group	ulceration (0−2)	inflammation (0−3)	lesion depth (0−3)	fibrosis (0−2)	total score (0−10)
vehicle	1.81 ± 0.24	2.75 ± 0.20	2.38 ± 0.32	1.69 ± 0.32	8.63 ± 0.85
47					
10 mg/kg	0.25 ± 0.35[a]	1.19 ± 0.52[a]	0.20 ± 0.28[a]	0.06± 0.13[a]	1.75 ± 1.10[a]
5 mg/kg	0.75 ± 0.41[a]	1.13 ± 0.72[a]	0.50 ± 0.12[a]	0.31 ± 0.32[a]	2.69 ± 1.52[a]
1 mg/kg	0.31 ± 0.38[a]	1.00 ± 0.29[a]	0.19 ± 0.24[a]	0.13 ± 0.14[a]	1.63 ± 1.00[a]
vehicle	1.81 ± 0.24	2.81 ± 0.24	1.81 ± 0.24	1.81 ± 0.24	8.25 ± 0.74
47					
0.3 mg/kg	1.00 ± 0.50	0.83 ± 0.29[a]	0.58 ± 0.14[a]	0.17 ± 0.29[a]	2.58 ± 0.52[a]
0.1 mg/kg	1.65 ± 0.55	1.85 ± 0.60[a]	0.95 ± 0.11[a]	0.45 ± 0.45[a]	4.90 ± 1.63[a]

[a] Significantly less than vehicle ($p < 0.05$).

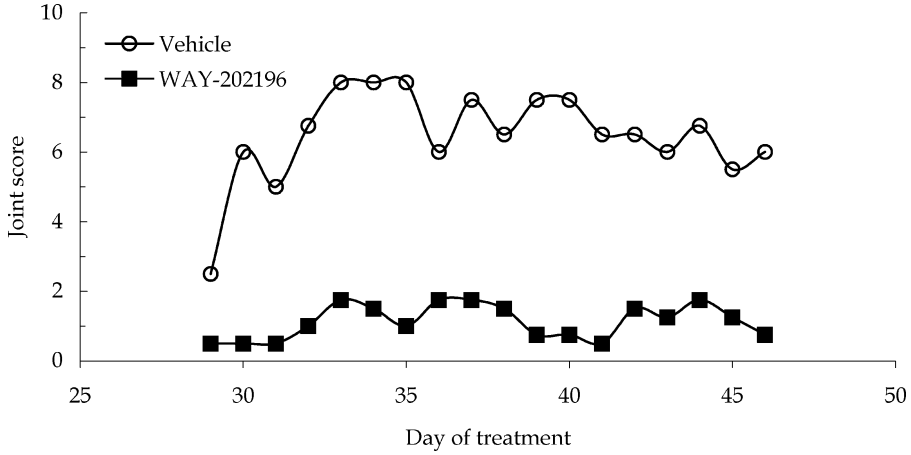


Figure 7. Effect of **47** on preventing arthropathy in HLA-B27 transgenic rats. Eight to 10 week old rats were treated with oral daily doses of 10 mg/kg, and joint redness and swelling were assessed on days 28−46 of treatment.

of disease (synovitis and Mankin scores). Each category of these disease indices was significantly reduced for the 10, 5, 1, and 0.3 mg/kg dose of **47**. At 0.1 mg/kg, although total synovitis scores were reduced, there was no difference in the Mankin scores (Table 11).

Receptor Selectivity Assays. To assess the receptor selectivity of **47**, several assays were conducted. **47** was tested in three cell-based assays to evaluate its ability to direct transcription of genes via the progesterone (PR), glucocorticoid receptors (GR), or androgen receptors (AR). First, progestins upregulate alkaline phosphatase activity in T47D cells, and this in vitro assay has been used to characterize new progestins.[35] When tested alone, **47** (8 nM to 5 μM) did not upregulate alkaline phosphatase activity, indicating that the compound does not have PR agonist activity in this assay. When tested in combination with 1 nM progesterone, a decrease in alkaline phosphatase activity was seen at 5 μM, and the ED_{50} was estimated to be between 1 and 5 μM. Second, A549 lung carcinoma cells express GR, and a hormone response element luciferase reporter system was used to test for cross-reactivity on this receptor. **47** (0.3 nM to 10 μM) had little to no effect (≤5% of the positive control) on reporter gene activity when tested alone. In combination with 10 nM dexamethasone, no inhibitory effect was seen. Third, L929 cells express AR, and a hormone response element luciferase reporter system was used to test for cross-reactivity with this receptor. When tested alone, **47** (0.1 nM to 10 μM) did not upregulate reporter gene activity,

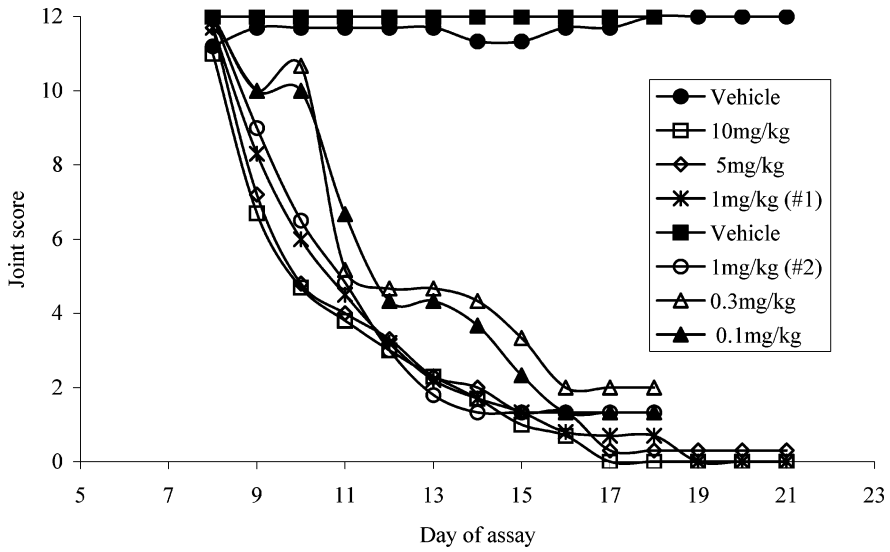


Figure 8. Effect of **47** on gross joint scores in the Lewis rat adjuvant-induced arthritis model. Data are a composite of two studies, both of which included a 1 mg/kg dose. Treatment began 8 days after adjuvant injection, when maximal redness and swelling developed in all rats.

Table 10. Effect of **47** on Colon Histology of HLA-B27 Transgenic Rats

	mean [haptoglobin] (mg/mL) ± SD
vehicle	1.55 ± 0.74
47 (1 mg/kg)	0.45 ± 0.16[a]
47 (0.3 mg/kg)	0.35 ± 0.09[a]

[a] Significantly less than vehicle; $p < 0.05$.

indicating that the compound does not have AR agonist activity in this assay. When tested in combination with 3 nM 5α-dihydrotestosterone, reporter gene activity was decreased by 42% at 10 μM, thus the IC_{50} of this compound in this assay is predicted to be ≥10 μM. Finally, **47** was tested for binding to human sex hormone binding globulin (SHBG) in a competition binding assay using [^{3}H]-5α-dihydrotestosterone (DHT) as the tracer. **47** (10 nM to 10 μM) did compete for binding at concentrations above 1 μM, and the IC_{50} was estimated to be ~10 μM. For comparison, radioinert DHT had an IC_{50} value of 1.3 nM.

Conclusion

Our goal was to design a selective ligand for ERβ because we expected that such a compound would exhibit a radically different pharmacologic profile from nonselective estrogens, such as 17β-estradiol. We have shown that, though the possibility of multiple binding modes may present a greater challenge toward the rational design of ERβ selective ligands, introducing the proper substituent at the appropriate position of the phenylnaphthalene scaffold can allow a single orientation to predominate, while at the same time allowing us to exploit the ERβ Ile_{373} → ERα Met_{421} residue substitution to afford ERβ selective compounds. Within the phenylnaphthalene scaffold, we learned that both hydroxyl groups were optimized when placed at either the 1 or 2 positions of the naphthalene framework and 4′ position of the phenyl ring (Table 1). ERβ selectivity could be achieved by exploiting two different orientations using the appropriate substituents attached to the 1, 4, or 8 position of the 6-(4′-hydroxyphenyl)naphthalen-2-ol template (**5**). An *o*-fluoro substituent slightly improved ERβ selectivity when the phenylnaphthalene scaffold exploited orientation b, an effect which was not observed for orientation a. One of the most selective compounds (i.e., **47**) showed no evidence of activity via ERα in vivo and had little or no effect on GR, PR, or AR activity in vitro. However, **47** was observed to be active in two inflammation models (i.e., HLA-B27 transgenic rat and Lewis rat adjuvant-induced arthritis models), which suggests it may have utility in treating chronic inflammatory diseases such as inflammatory bowel disease or rheumatoid arthritis. Efforts to further improve ERβ selectivity by exploiting multiple binding modes as well as evolving from the phenylnaphthalene motif to other new scaffolds will be reported shortly.

Experimental Section

Melting points were measured on a Mel-Temp II (Laboratory Device Inc.) melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DPX300, Varian INOVA 400, or Varian INOVA 500 instrument. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of tetramethylsilane in $CDCl_3$, acetone-d_6, or DMSO-d_6. Electrospray (ESI) mass spectra were recorded using a Hewlett-Packard 5989B MS engine or Waters Alliance-ZMD mass spectrometer. Electron impact ionization (EI, EE = 70 eV) mass spectra were recorded on a Finnigan Trace mass spectrometer. Elemental analyses were carried out on a modified Perkin-Elmer model 2400 series II CHN analyzer or sent to Robertson Microlit. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F-254), and spots were visualized with UV light and stained in iodine. Preparative HPLC purifications were performed on a preparative Gilson HPLC system using a CombiPrep Pro C18 column with acetonitrile (0.1% TFA) and water (0.1% TFA) as solvents at a flow rate of 20 mL/min.

6-Trifluoromethanesulfonic Acid 5-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl Ester (74). A solution of commercially available 6-hydroxy-1-tetralone (4.8 g, 29.6 mmol, Aldrich) in anhydrous CH_2Cl_2 (220 mL) was azeotroped with xylenes to remove any residual water. The solution was then cooled to 0 °C and anhydrous pyridine (3.35 mL, 41.4 mmol) was added followed by triflic anhydride (10.0 g, 35.5 mmol). After 0.5 h at 0 °C the reaction was quenched with saturated aqueous bicarbonate and washed with water. The organic layer was passed through a silica plug and concentrated to 8.39 g (96%)

Table 11. Effect of WAY-202196 on Histology Scores of Lewis Rats with Adjuvant-Induced Arthritis

Synovitis Scores

group	synovial structure (0−3)	fibroplasia (0−3)	inflammatory cells (0−3)	pannus (0−2)	total score (0−11)
vehicle	2.75 (0.27	2.67 ± 0.26	3.00 ± 0.00	2.00 ± 0.00	10.5 ± 0.45
47					
10 mg/kg	1.50 ± 0.32[a]	1.08 ± 0.67[a]	1.08 ± 0.59[a]	0.50 ± 0.55[a]	4.00 ± 1.41[a]
5 mg/kg	2.08 ± 0.38[a]	1.42 ± 0.49[a]	1.33 ± 0.41[a]	0.83 ± 0.75[a]	5.67 ± 1.72[a]
1 mg/kg	2.25 ± 0.52	1.50 ± 0.45[a]	1.33 ± 0.41[a]	1.00 ± 0.89[a]	6.08 ± 2.18[a]
vehicle	2.92 ± 0.2	2.58 ± 0.38	2.92 ± 0.2	2 ± 0	10.42 ± 0.59
47					
1 mg/kg	1.25 ± 0.52[a]	0.75 ± 0.61[a]	0.75 ± 0.42[a]	0 ± 0[a]	2.75 ± 1.41[a]
0.3 mg	1.67 ± 0.41[a]	1.42 ± 0.38[a]	1.25 ± 0.42[a]	0.5 ± 0.55[a]	4.83 ± 1.47[a]
0.1 mg	2.25 ± 0.69[a]	1.92 ± 0.59[a]	1.67 ± 0.41[a]	0.67 ± 0.82[a]	6.5 ± 2.15[a]

Mankin Scores

group	cartilage structure (0−6)	cartilage cells (0−3)	Safranin-o/Fast Green staining (0−4)	tidemark integrity (0−1)	total score (0−14)
vehicle	2.83 ± 0.26	2.58 ± 0.38	2.83 ± 0.26	0	8.25 ± 0.42
47					
10 mg/kg	1.83 ± 0.68[a]	1.58 ± 0.49[a]	1.75 ± 0.82[a]	0	5.17 ± 1.81[a]
5 mg/kg	2.33 ± 0.26[a]	1.58 ± 0.20[a]	2.00 ± 0.45[a]	0	5.92 ± 0.74[a]
1 mg/kg	2.08 ± 0.38[a]	1.75 ± 0.42[a]	1.83 ± 0.4[a]	0	5.67 ± 0.98[a]
vehicle	3.58 ± 0.59	2.75 ± 0.42	3 ± 0	0	9.33 ± 0.88
47					
1 mg/kg	1.08 ± 0.2[a]	0.92 ± 0.49[a]	1.67 ± 0.41[a]	0	3.67 ± 0.88[a]
0.3 mg	2.17 ± 0.68[a]	1.58 ± 0.49[a]	2.25 ± 0.42[a]	0	6.0 ± 1.23[a]
0.1 mg	3.31 ± 0.41	2.58 ± 0.49	2.58 ± 0.49	0	8.5 ± 1.27

[a] Significantly less than vehicle ($p < 0.05$).

product as a pale yellow oil: ^{1}H NMR (DMSO-d_6) δ 2.07 (2H, m), 2.65 (2H, t, J = 6.5 Hz), 3.03 (2H, t, J = 6.0 Hz), 7.47 (1H, dd, J = 8.7 Hz, 2.3 Hz), 7.57 (1H, d, J = 1.9 Hz), 8.03 (1H, d, J = 8.7 Hz).

6-(3-Hydroxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (75). Method A. A solution of **74** (1.01 g, 3.43 mmol), 3-hydroxyphenyl boronic acid (0.56 g, 4.1 mmol), sodium carbonate (7 mL of 2 N aqueous, 14 mmol), and tetrakis-(triphenylphosphine)palladium (0.20 g, 0.17 mmol) in DME (20 mL) were stirred at reflux overnight. The reaction mixture was cooled to room temperature, poured into 100 mL of 1 N NH_4Cl, and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with water, washed with brine, dried over sodium sulfate, concentrated, and purified on silica to yield 0.68 g (83%) of a white solid: mp 156−160 °C; ^{1}H NMR (DMSO-d_6) δ 1.99−2.10 (2H, m), 2.62 (2H, t, J = 5.95 Hz), 3.01 (2H, t, J = 6.08 Hz), 6.81−6.89 (1H, m), 7.07−7.08 (1H, m), 7.12−7.15 (1H, m), 7.56−7.58 (2H, m), 7.92 (1H, d, J = 8.15 Hz), 9.60 (1H, bs); MS (ESI) *m/z* 239; MS (ESI) *m/z* 237.

6-(4-Hydroxyphenyl)-1-tetralone (76). A mixture of **74** (5.0 g, 17.0 mmol), 4-[[*tert*-butyl(dimethyl)silyl]oxy]phenylboronic acid[7,8] (5.45 g, 20.4 mmol), sodium carbonate (4.56 g as 2 N aqueous, 42.5 mmol), and tetrakis(triphenylphosphine)-palladium (0.98 g, 0.85 mmol) in DME (200 mL) was reacted according to method A to yield 3.68 g (92%) of a tan solid: mp 208−210 °C; ^{1}H NMR (DMSO-d_6) δ 2.06 (2H, m), 2.60 (2H, t, J = 6.5 Hz), 2.99 (2H, t, J = 5.9 Hz), 6.87 (2H, d, J = 8.6 Hz), 7.57 (4H, m), 7.86 (1H, d, J = 8.7 Hz), 9.74 (1H, s); MS (ESI) *m/z* 237 $(M + H^+)^+$. Anal. ($C_{16}H_{14}O_2 \cdot 0.25H_2O$) C, H.

6-(3-Hydroxyphenyl)-1-naphthol (6). A mixture of **75** (0.51 g) and 10% Pd/C (0.61 g) in *p*-cymene (50 mL) was heated to reflux overnight. The reaction was cooled to room temperature and filtered through Celite. The Celite was rinsed with ethyl acetate, and the combined organics were removed under vacuum and purified on silica to yield 0.38 g (75%) of a white solid: mp 137−140 °C; ^{1}H NMR (DMSO-d_6) δ 6.79−6.82 (1H, m), 6.87 (1H, dd, J = 7.44 Hz, J = 0.97 Hz), 7.15−7.16 (1H, m), 7.19−7.22 (1H, m), 7.28−7.34 (2H, m), 7.42 (1H, d, J = 8.28 Hz), 7.69 (1H, dd, J = 8.79 Hz, J = 1.94 Hz), 8.04 (1H, d, J = 1.81 Hz), 8.19 (1H, d, J = 8.79 Hz), 9.55 (1H, bs), 10.11 (1H, bs); MS (ESI) *m/z* 237 $(M + H^+)^+$. Anal. ($C_{16}H_{12}O_2 \cdot 0.3H_2O$) C, H.

6-(4-Hydroxyphenyl)-1-naphthol. (7) A mixture of **76** (500 mg, 2.12 mmol), 10% palladium on carbon (510 mg), and *p*-cymene (15 mL) was reacted according to the procedure used to prepare **6** to afford 260 mg (53%) of product as a brown solid: mp above 200 °C (dec); ^{1}H NMR (DMSO-d_6) δ 6.82 (1H, d, J = 7.5 Hz), 6.87 (2H, d, J = 8.1 Hz), 7.29 (1H, t, J = 7.5 Hz), 7.38 (1H, d, J = 7.5 Hz), 7.63 (2H, d, J = 8.2 Hz), 7.70 (1H, d, J = 8.5 Hz), 7.99 (1H, s) 8.14 (1H, d, J = 8.5 Hz), 9.59 (1H, s), 10.09 (1H, s); MS (ESI) *m/z* 235 $(M - H^+)^-$. Anal. ($C_{16}H_{12}O_2$) C, H.

2-Methoxy-6-(4-methoxyphenyl)naphthalene (79). Method B. To a mixture of 2-bromo-6-methoxynaphthalene (23.79 g, 100.3 mmol, Aldrich) and tetrakis(triphenylphosphine)palladium (5.8 g, 5 mmol) was added a solution of 4-methoxyphenylmagnesium bromide in THF (400 mL of 0.5 N solution, 200 mmol). The solution was heated to reflux for 3 h, cooled to room temperature, and poured into 200 mL of 1 N HCl. The mixture was extracted with dichloromethane and filtered through a short silica plug with dichloromethane. The solvent was removed to yield a crude yellow solid that was further purified by silica chromatography (20−50% ethyl acetate−hexanes) to yield 25.7 g (97%) of the title compound as a white solid: mp 190 °C; ^{1}H NMR ($CDCl_3$): δ 3.86 (3H, s), 3.93 (3H, s), 7.01 (2H, d, J = 8.57 Hz), 7.14−7.18 (2H, m), 7.63 (2H, d, J = 8.50 Hz), 7.67 (1H, dd, J = 1.68 Hz, J = 8.73 Hz), 7.76−7.80 (2H, m), 7.91 (1H, d, J = 0.94 Hz); MS (ESI) *m/z* 265 $(M + H)^+$. Anal. ($C_{18}H_{16}O_2$) C, H.

7-Methoxy-2-naphthyl Trifluoromethanesulfonate. Treatment of commercially available 7-methoxy-2-naphthol (4.75 g, 27.27 mmol) with trifluoromethanesulfonic anhydride (10.0 g, 35 mmol) according to the procedure used to prepare **74** afforded 8.08 g (97%) of 7-methoxy-2-naphthyl trifluoromethanesulfonate as a clear colorless oil: ^{1}H NMR (DMSO-d_6) δ 3.92 (3H, s), 7.30 (1H, dd, J = 2.58 Hz, J = 8.93 Hz), 7.42 (1H, dd, J = 2.59 Hz, J = 8.93 Hz), 7.52 (1H, d, J = 2.38 Hz), 7.96 (1H, d, J = 9.12 Hz), 8.00 (1H, d, J = 2.38 Hz), 8.06 (1H, d, J = 8.73 Hz); MS (EI) *m/z* 306 $(M\bullet)^+$. Anal. ($C_{12}H_9F_3O_4S$) C, H.

2-Methoxy-7-(4-methoxyphenyl)naphthalene (81). The title compound was prepared by reacting 7-methoxy-2-naphthyl trifluoromethanesulfonate (3.15 g, 10.3 mmol), prepared above, with 4-methoxyphenylboronic acid (2.2 g, 14 mmol) according to method A to afford 2.17 g (79%) of **81** as a white

solid: mp 154 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (3H, s), 3.94 (3H, s), 7.02 (2H, d, J = 8.72 Hz), 7.13 (1H, dd, J = 2.54 Hz, J = 9.09 Hz), 7.18 (1H, d, J = 2.55 Hz), 7.56 (1H, dd, J = 1.82 Hz, J = 8.36 Hz), 7.65 (2H, d, J = 8.72 Hz), 7.74 (1H, d, J = 9.09 Hz), 7.81 (1H, d, J = 8.36 Hz), 7.89 (1H, d, J = 1.09 Hz); MS (EI) *m/z* 264 (M·). Anal. ($C_{18}H_{16}O_2$) C, H.

2-Methoxy-7-phenylnaphthalene (83). The title compound was prepared by reacting 7-methoxy-2-naphthyl trifluoromethanesulfonate (3.01 g, 9.83 mmol) with phenylboronic acid (1.4 g, 12 mmol) according to method A to yield 1.95 g (85%) of a white solid: mp 62−64 °C; ^{1}H NMR ($CDCl_3$) δ 3.95 (3H, s), 7.15 (1H, dd, J = 2.56 Hz, J = 8.79 Hz), 7.20 (1H, d, J = 2.56 Hz), 7.36−7.39 (1H, m), 7.46−7.50 (2H, m), 7.60 (1H, dd, J = 1.83 Hz, J = 8.42 Hz), 7.70−7.73 (2H, m), 7.76 (1H, d, J = 8.79 Hz), 7.84 (1H, d, J = 8.42 Hz), 7.94 (1H, d, J = 1.46 Hz); MS (EI) *m/z* 234 (M•)$^+$. Anal. ($C_{17}H_{14}O{\cdot}0.1H_2O$) C, H.

6-(2-Hydroxyphenyl)-2-naphthol (8). Method C. To a solution of **77** (0.38 g, 1.52 mmol) in dichloromethane (20 mL) at 0 °C was slowly added BBr_3 (4.5 mL of 1 N, 4.5 mmol). The solution was allowed to warm to room temperature overnight with stirring and was poured into 100 mL of water. The mixture was extracted with 100 mL of ethyl acetate and the organic layer was washed with water and with brine, dried over sodium sulfate, filtered, and concentrated, and the product was purified on silica (25% ethyl acetate/hexanes) to yield 0.29 g (81%) of an off-white solid: mp 179−180 °C; ^{1}H NMR (DMSO-d_6) δ 6.87−6.91 (1H, m), 6.96 (1H, dd, J = 8.14 Hz, J = 1.04 Hz), 7.08 (1H, dd, J = 8.72 Hz, J = 2.40 Hz), 7.12−7.18 (2H, m), 7.33 (1H, dd, J = 7.63 Hz, J = 1.68 Hz), 7.61 (1H, dd, J = 8.48 Hz, J = 1.74 Hz), 7.68 (1H, d, J = 8.80 Hz), 7.78 (1H, d, J = 8.92 Hz), 7.90 (1H, D, J = 0.91 Hz), 9.48 (1H, bs), 9.70 (1H, bs); MS (ESI) *m/z* 235 (M − H)$^-$. Anal. ($C_{16}H_{12}O_2{\cdot}0.1H_2O$) C, H, N.

6-(4-Hydroxyphenyl)-2-naphthol (5). Method D. Compound **79** (5.61 g, 21.2 mmol) was added to pyridinium HCl (30 g) at 190 °C for 2 h, and the mixture cooled to room temperature and was stirred with 200 mL of 1 N HCl. The resulting suspension was filtered and dissolved ethyl acetate (500 mL). The combined organic layers were washed with water (200 mL), dried over anhydrous magnesium sulfate, and filtered; the solvent was removed under vacuum; and the product was purified by silica chromatography (40% ethyl acetate−hexanes) to yield 4.88 g (98%) of a white solid: mp >220 °C(discolors above 200 °C); ^{1}H NMR (DMSO-d_6) δ 6.87 (2H, d, J = 8.54 Hz), 7.08 (1H, dd, J = 2.34 Hz, J = 8.76 Hz), 7.11 (1H, d, J = 2.14 Hz), 7.58 (2H, d, J = 8.54 Hz), 7.65 (1H, dd, J = 1.92 Hz, J = 8.76 Hz), 7.71 (1H, d, J = 8.54 Hz), 7.79 (1H, d, J = 8.97 Hz), 7.95 (1H, s), 9.56 (1H, bs), 9.70 (1H, bs); MS (ESI) *m/z* 235 (M − H)$^-$. Anal. ($C_{16}H_{12}O_2$) C, H.

1-Chloro-2-methoxy-6-(4-methoxyphenyl)naphthalene (85). Method E. A suspension of **79** (0.51 g, 1.93 mmol) and NCS (0.28 g, 2.13 mmol) in acetonitrile (20 mL) was heated to reflux for 3 h. The resulting solution was cooled to room temperature and the resulting solid was collected by filtration and rinsed with acetonitrile to yield 0.41 g (72%) of a white solid: mp 158−164 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (3H, s), 4.05 (3H, s), 7.03 (2H, d, J = 8.62 Hz), 7.32 (1H, d, J = 9.02 Hz), 7.65 (2H, d, J = 8.55 Hz), 7.82 (2H, d, J = 9.01 Hz), 7.95 (1H, d, J = 1.36 Hz), 8.27 (1H, d, J = 8.81 Hz); MS (EI) *m/z* 298 (M·)$^+$. Anal. ($C_{18}H_{15}ClO_2$) C, H.

1-Bromo-2-methoxy-6-(4-methoxyphenyl)naphthalene (86). To a mixture of **79** (9.68 g, 36.6 mmol) and glacial acetic acid (150 mL) was slowly added a solution of bromine (5.85 g, 36.6 mmol) in glacial acetic acid (20 mL). The mixture was stirred for 1 h and the resulting suspension was poured into water (200 mL) and the solid product was collected by filtration. The solid was triturated with water and then with ethyl acetate to yield 11.25 g (90%) of a white solid: mp 172−174 °C; ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 4.05 (3H, s), 7.04 (2H, d, J = 8.56 Hz), 7.30 (1H, d, J = 9.01 Hz), 7.67 (2H, d, J = 8.65 Hz), 7.81 (1H, dd, J = 1.61 Hz, J = 8.84 Hz), 7.87 (1H, d, J = 9.04 Hz), 7.94 (1H, d, J = 1.47 Hz), 8.27 (1H, d, J = 8.92 Hz); MS (EI) *m/z* 343 (M•)$^+$. Anal. ($C_{18}H_{15}BrO_2$) C, H.

2-Methoxy-6-(4-methoxyphenyl)-1-fluoronaphthalene (87). To a solution of **86** (1.28 g, 3.72 mmol) in THF (25 mL) at −78 °C was slowly added *n*-butyllithium (1.9 mL of 2.5 N in hexanes). The resulting solution was stirred at −78 °C for 0.5 h and a solution of *N*-fluorobenzenesulfonimide (1.40 g, 4.5 mmol) in THF (10 mL) was added. After an additional 2 h at −78 °C, the reaction was warmed to room temperature, poured into water, and extracted with ethyl acetate (2 × 250 mL). The combined organic layers were washed with water, dried over sodium sulfate, filtered, and concentrated, and the product was purified by silica chromatography (5% THF−hexanes) to yield 0.66 g (63%) of a white solid: mp 150−155 °C; ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 4.04 (3H, s), 7.02 (2H, d, J = 8.69 Hz), 7.28−7.34 (1H, m), 7.62−7.67 (3H, m), 7.74 (1H, dd, J = 1.60 Hz, J = 8.79 Hz), 7.93 (1H, s), 8.09 (1H, d, J = 8.77 Hz). Anal. ($C_{18}H_{15}O_2F$) C, H.

2-Methoxy-6-(4-methoxyphenyl)-1-naphthonitrile (88). A mixture of **86** (0.76 g, 2.21 g), CuCN (0.24 g, 2.66 mmol), and DMF (10 mL) was stirred at 120 °C for 4 h. The reaction mixture was cooled to room temperature, triturated with ethyl acetate, filtered through silica, and concentrated, and the product was purified by silica column chromatography (20% ethyl acetate−hexanes) to yield 0.19 g (30%) of a pale yellow solid: mp 182−185 °C; ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 4.09 (3H, s), 7.03 (2H, d, J = 8.73 Hz), 7.29 (1H, d, J = 9.12 Hz), 7.63 (2H, d, J = 8.73 Hz), 7.88 (1H, dd, J = 1.98 Hz, J = 8.73 Hz), 7.97 (1H, d, J = 1.98 Hz), 8.09 (1H, d, J = 9.12 Hz), 8.14 (1H, d, J = 8.73 Hz).

2-Methoxy-6-(4-methoxyphenyl)-1-phenylnaphthalene (89). The title compound was prepared by reacting **86** (0.80 g, 2.33 mmol) with phenylmagnesium bromide (2.2 mL of 3 N in ether) according to method B to yield 0.42 g (53%) of a gray solid: mp 157−160 °C; ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s), 3.87 (3H, s), 7.01 (2H, d, J = 8.64 Hz), 7.38−7.46 (4H, m), 7.49−7.57 (4H, m), 7.64 (2H, d, J = 8.64 Hz), 7.92 (1H, d, J = 9.05 Hz), 7.97 (1H, s); MS (ESI) *m/z* 341 (M + H)$^+$. Anal. ($C_{24}H_{20}O_2{\cdot}0.5H_2O$) C, H.

2-Methoxy-6-(4-methoxyphenyl)-1-methylnaphthalene (90). To a solution of **86** in THF (25 mL) at 0 °C were slowly added *n*-butyllithium (2 mL of 2.5N) and TMEDA (0.60 g, 5.13 mmol, freshly distilled from KOH). After 0.5 h at 0 °C, iodomethane (7.3 g, 51.3 mmol, passed through basic alumina) was added and the solution was allowed to warm to room temperature overnight. The reaction was poured into water (100 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered, and concentrated, and the product purified by silica column chromatography (5% THF−hexanes) to yield 0.63 g (88%) of a white solid: mp 136−138 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (3H, s), 3.96 (3H, s), 7.02 (2H, d, J = 8.74 Hz), 7.29 (1H, d, J = 9.01 Hz), 7.60−7.80 (4H, m), 7.95 (1H, d, J = 1.76 Hz), 8.00 (1H, d, J = 8.86 Hz); MS (ESI) *m/z* 279 (M + H)$^+$. Anal. ($C_{19}H_{18}O_2{\cdot}0.3H_2O$) C, H.

1-Chloro-6-(4-hydroxyphenyl)-2-naphthol (15). The title compound was prepared by reacting **85** (0.32 g, 1.07 mmol) with pyridinium HCl (7 g) at 190 °C according to method D to yield 0.12 g (41%) of an off-white solid: mp 222−224 °C (dec); ^{1}H NMR (DMSO-d_6) δ 6.88 (2H, d, J = 8.46 Hz), 7.29 (1H, d, J = 8.88 Hz), 7.63 (2H, d, J = 8.50 Hz), 7.81−7.88 (2H, m), 8.02−8.08 (2H, m), 9.59 (1H, s), 10.43(1H, s); MS (ESI) *m/z* 269/271 (M − H)$^-$. Anal. ($C_{16}H_{11}ClO_2$) C, H.

1-Bromo-6-(4-hydroxyphenyl)-2-naphthol (16). To a solution of **5** (4.02 g, 17.0 mmol) in acetonitrile (150 mL) at 0 °C was added NBS (3.03 g, 17.0 mmol). The reaction was stirred at 0 °C for 3 h and then poured into water (200 mL) and extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with water, dried over sodium sulfate, filtered, and concentrated, and the product was purified by silica column chromatography (20% ethyl acetate−hexanes) to yield 5.33 g (100%) of a tan solid. Further purification by reverse phase HPLC yielded a white solid: mp 208−210 °C; ^{1}H NMR (DMSO-d_6) δ 6.89 (2H, d, J = 8.47 Hz), 7.28 (1H, d, J = 8.80 Hz), 7.63 (2H, d, J = 8.50 Hz), 7.85

(2H, d, J = 8.84 Hz), 8.02−8.06 (2H, m), 9.60 (1H, s), 10.54 (1H, s); MS (ESI) *m/z* 313/315 $(M - H)^-$. Anal. ($C_{16}H_{11}BrO_2$) C, H.

1-Fluoro-6-(4-hydroxyphenyl)-2-naphthol (17). The title compound was prepared by reacting **87** (0.250 g, 0.886 mmol) with boron tribromide (2.7 mL of 1 N solution, 2.7 mmol) according to method C to yield 0.13 g (15%) of a white solid: mp 219−224 °C; ^{1}H NMR (DMSO-d_6) δ 6.89 (2H, d, J = 8.49 Hz), 7.22−7.28 (1H, m), 7.61 (2H, d, J = 8.53 Hz), 7.65 (1H, d, J = 9.12 Hz), 7.79 (1H, d, J = 8.77 Hz), 7.92 (1H, d, J = 8.73 Hz), 8.05 (1H, s), 9.63 (1H, bs), 10.00 (1H, bs); MS (ESI) *m/z* 253 $(M - H)^-$. Anal. ($C_{16}H_{11}FO_2$) C, H: calcd, 75.58; found, 75.13.

2-Hydroxy-6-(4-hydroxyphenyl)-1-naphthonitrile (18). The title compound was prepared by reacting **88** (0.115 g, 0.397 mmol) with pyridinium HCl (4 g) at 190 °C according to method D to yield 0.025 g (24%) of a tan solid: mp >220 °C; ^{1}H NMR (DMSO-d_6) δ 6.89 (2H, d, J = 8.37 Hz), 7.28 (1H, d, J = 9.07 Hz), 7.63 (2H, d, J = 8.42 Hz), 7.88−7.98 (2H, m), 8.12−8.16 (2H, m), 9.63 (1H, s), 11.65 (1H, bs); MS (ESI) *m/z* 260 $(M - H)^-$. Anal. ($C_{17}H_{11}NO_2 \cdot 0.4H_2O$) C, H, N.

6-(4-Hydroxyphenyl)-1-phenyl-2-naphthol (19). The title compound was prepared by reacting **89** (0.36 g, 1.06 mmol) with boron tribromide (3.2 mL of 1 N in CH_2Cl_2) according to method C to yield 0.14 g (42%) of a white solid: mp 142−146 °C; ^{1}H NMR (DMSO-d_6) δ 6.86 (2H, d, J = 8.50 Hz), 7.26−7.42 (5H, m), 7.48−7.61 (5H, m), 7.84 (1H, d, J = 8.96 Hz), 8.02 (1H, d, J = 1.46 Hz), 9.52 (2H, s); MS (ESI) *m/z* 311 $(M - H)^-$. Anal. ($C_{22}H_{16}O_2 \cdot 0.1H_2O$) C. H.

6-(4-Hydroxyphenyl)-1-methyl-2-naphthol (20). The title compound was prepared by reacting **90** (0.35 g, 1.26 mmol) with boron tribromide (3.8 mL of 1 N solution, 3.8 mmol) according to method C to yield 0.15 g (48%) of a white solid: mp >170 °C (dec); ^{1}H NMR (DMSO-d_6) δ 2.42 (3H, s), 6.87 (2H,k d, J = 8.33 Hz), 7.15 (1H, d, J = 8.81 Hz), 7.59 (2H, d, J = 8.35 Hz), 7.65 (1H, d, J = 8.93 Hz), 7.71 (1H, dd, J = 1.24 Hz, J = 8.90 Hz), 7.88 (1H, d, J = 8.87 Hz), 7.95 (1H, s), 9.49 (1H, s), 9.52 (1H, s); MS (ESI) 249 *m/z* $(M - H)^-$. Anal. ($C_{17}H_{14}O_2$) C, H.

6-(4-Hydroxyphenyl)-1-methoxy-2-naphthol (21). Method F. A mixture of **16** (0.41 g, 1.30 mmol), CuBr (0.19 g, 0.13 mmol), sodium methoxide (3 mL of 4.4 N in methanol), and DMF (6 mL) was heated to reflux for 3 h. The reaction mixture was cooled to room temperature, poured into HCl (50 mL of 1 N aqueous solution), and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with sodium bicarbonate solution, dried over sodium sulfate, and filtered; the solvent was removed under vacuum; and the product was purified by silica column chromatgraphy (40% ethyl acetate−hexanes) to yield 0.31 g (89%) of the title compound as a white solid: mp 204−206 °C; ^{1}H NMR (DMSO-d_6) δ 6.88 (2H, d, J = 8.47 Hz), 7.19 (1H, d, J = 8.81 Hz), 7.57−7.60 (3H, m), 7.71 (1H, dd, J = 1.41 Hz, J = 8.78 Hz), 7.94−7.98 (2H, m), 9.54 (2H, s); MS (ESI) *m/z* 265 $(M - H)^-$. Anal. ($C_{17}H_{14}O_3$) C, H.

6-Bromo-1-nitro-2-naphthol (91). Commercially available 4-nitro-4-methyl-2,3,5,6-tetrabromo-2,5-cyclohexadien-1-one (2.53 g, 4.95 mmol) was added to a solution of 6-bromo-2-naphthol (1 g, 4.5 mmol) in of dry ether (40 mL). The mixture was allowed to react for 1.5 h at room temperature. The solid byproduct, 2,3,5,6-tetrabromo-4-methylphenol (144 mg), was removed by filtration. The solution was then evaporated under vacuum and the crude mixture was dissolved in ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate and filtered, and the solvent was removed under vacuum. An additional batch of 2,3,5,6-tetrabromo-4-methylphenol (1.2 g) was separated by recrystallization of the crude product with ethyl acetate−hexane. The mother liquid was concentrated onto Florosil and purified on a silica column (15−20% ethyl acetate−hexane) to yield 0.731 g (61%) of the desired product as a yellow solid: mp 111−113 °C; ^{1}H NMR (DMSO-d_6) δ 7.39 (1H, d, J = 9.07 Hz), 7.54 (1H, d, J = 9.05 Hz), 7.75 (1H, dd, J = 9.05 Hz, J = 1.70 Hz), 8.03 (1H, d, J = 9.14 Hz), 8.29 (1H, d, J = 1.84 Hz), 11.65 (1H, s); MS (ESI) *m/z* 266/268 $(M - H)^-$; IR 1350 cm^{-1}, 1490 cm^{-1}. Anal. ($C_{10}H_6BrNO_3 \cdot 0.2H_2O$) C, H.

6-[4-(*tert*-Butyldimethylsilanyloxy)phenyl]-1-nitro-2-naphthol (92). The title compound was prepared by reacting **91** (560 mg, 2.1 mmol) with 4-*tert*-butyl-dimethylsilyoxyphenylboronic acid[8] (688 mg, 2.73 mmol) according to method A to yield 347 mg (42%) of yellowish solid: ^{1}H NMR (DMSO-d_6) δ 0.23 (6H, s), 0.98 (9H, s), 6.98 (2H, d, J = 8.47 Hz), 7.35 (1H, d, J = 9.05 Hz), 7.64 (1H, d, J = 8.86 Hz), 7.70 (2H, d, J = 8.51 Hz), 7.94 (1H, dd, J = 6.62 Hz, J = 1.25 Hz), 8.08 (1H, d, J = 9.16 Hz), 8.22(1H, s), 11.45 (1H, s); MS (ESI) *m/z* 394 $(M - H)^-$.

6-(4-Hydroxyphenyl)-1-nitro-2-naphthol (22). Method G. To a solution of **92** (302 mg, 0.764 mmol) in THF (12 mL) was added TBAF (0.92 mL, 0.917 mmol, 1.0 M solution in THF). The solution was stirred for 10 min at room temperature and poured into water, and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and filtered; the solvent was removed; and the product was purified on a silica column (20−40% ethyl acetate−hexane) to yield 130 mg (61%) of a orange solid. An analytical sample was further purified by recrystallization with ethyl acetate−hexane to yield the title compound as an orange solid: mp 199−201 °C; ^{1}H NMR (DMSO-d_6) δ 6.89 (2H, d, J = 8.51 Hz), 7.33 (1H, d, J = 9.05 Hz), 7.62 (1H, d, J = 8.94 Hz), 7.63(2H, d, 8.48 Hz), 7.91 (1H, dd, J = 8.87 Hz, J = 1.59 Hz), 8.06 (1H, d, 9.18 Hz), 8.17 (1H, d, J = 1.31 Hz), 9.64(1H, s), 11.40 (1H, s); MS (ESI) *m/z* 280 $(M - H)^-$. Anal. ($C_{16}H_{11}NO_4$) C, H, N.

6-Methoxy-2-naphthalenyl)boronic Acid. 2-Bromo-6-methoxynaphthalene (8.02 g, 33.8 mmol, Aldrich) was reacted with *sec*-butyllithium (56 mL of 1.3 N solution in hexanes, 72.8 mmol) in THF at −78 °C, followed by the addition of triisopropyl borate (47 mL, 203.7 mmol). The mixture was then stirred with aqueous HCl (200 mL of 1 N solution) for 10 min and then extracted with ethyl acetate and concentrated, and crystallization was induced with hexanes to afford a solid which was filtered and dried to give 7.01 g (∼100%) of 6-methoxy-2-naphthalenyl)boronic acid as a light orange powder: ^{1}H NMR (DMSO-d_6) δ 3.88 (3H, s), 7.15 (1H, dd, J = 8.9 Hz, 2.7 Hz), 7.29 (1H, d, J = 2.5 Hz), 7.75 (1H, d, J = 8.3 Hz), 7.83 (2H, appt), 8.30 (1H, s); MS (EI) *m/z* 202.17 (M^+).

2-(2-Fluoro-4-methoxyphenyl)-6-methoxynaphthalene (93). Reaction of trifluoromethanesulfonic acid 2-fluoro-4-methoxyphenyl ester [3.86 g, 14.0 mmol; prepared according to the procedure used for **74**, with 6-methoxy-2-naphthalenylboronic acid (2.97 g, 14.8 mmol)] according to method A yielded 2.27 g (58%) of white solid: mp 104−106 °C; ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s), 3.89 (3H, s), 6.92 (1H, dd, J = 8.46 Hz, J = 2.64 Hz), 6.98 (1H, dd, J = 12.92, J = 2.48 Hz), 7.19 (1H, dd, J = 8.94 Hz, J = 2.46 Hz), 7.35 (1H, J = 2.38 Hz), 7.53−7.63 (2H, m), 7.90 (2H, d, J = 8.72 Hz), 7.97 (1H, s); MS (ESI) *m/z* 283 $(M + H^+)$. Anal. ($C_{18}H_{15}FO_2$) C, H.

2-(2,5-Difluoro-4-methoxyphenyl)-6-methoxynaphthalene (94). The title compound was prepared according to method A by reacting 4-bromo-2,5-difluoroanisole (4.06 g, 18.3 mmol) with 6-methoxy-2-naphthalenylboronic acid (4.81 g, 23.8 mmol, prepared above) to yield 5.18 g (94.2%) of white solid: mp 153−155 °C; ^{1}H NMR (DMSO-d_6) δ 3.90 (3H, s), 3.91 (3H, s), 7.20 (1H, dd, J = 8.94 Hz, J = 2.50 Hz), 7.28 (1H, dd, J = 12.38 Hz, J = 7.47 Hz), 7.36 (1H, d, J = 2.42 Hz), 7.56 (1H, dd, J = 12.17 Hz, J = 7.53 Hz), 7.62−7.66 (1H, m), 7.89 (2 H, d, J = 8.67 Hz), 8.02 (1H, s); MS (ESI) *m/z* 301 $(M - H)^+$; HRMS calcd for $C_{18}H_{14}F_2O_2$ 300.0962, found 300.0872. Anal. ($C_{18}H_{14}F_2O_2$) C, H, N: calcd, 71.99; found, 73.00.

3-Chloro-4-(6-methoxy-2-naphthyl)phenol (96). The title compound was prepared by reacting 4-bromo-3-chlorophenol (3.8 g, 18.3 mmol) and 6-methoxy-2-naphthalenylboronic acid (4.81 g, 23.8 mmol, prepared above) according to method A to yield 5.09 g (98%) of white solid: mp 139−142 °C; ^{1}H NMR (DMSO-d_6) δ 3.89 (3H,s), 6.87 (1H, dd, J = 8.39 Hz, J = 2.45 Hz), 6.98 (1H, J = 2.40 Hz), 7.19 (1H, dd, J = 8.98 Hz, J = 2.46 Hz), 7.32 (1H, d, J = 8.39 Hz), 7.35 (1H, d, J = 2.38

Hz), 7.50 (1H, dd, J = 8.47 Hz, J = 1.73 Hz), 7.83−7.88 (3H, m), 10.04 (1H, s); MS (ESI) *m/z* 283/285 $(M - H)^-$. Anal. ($C_{16}H_{11}ClO$) C, H.

6-(4-Methoxy-2-methylphenyl)-2-naphthol (97). Reaction of 4-bromo-3-methylanisole (10 g, 0.050 mol) with *n*-butyllithium (24 mL of 2.5 M solution in hexane, 0.055 mol) followed by triisopropyl borate (57.7 mL, 47.02 g, 0.25 mol), according to the procedure described for 6-methoxy-2-naphthalenyl)boronic acid above, yielded 5.7 g (69%) of 4-methoxy-2-methylphenylboronic acid as a white solid: MS (ESI) *m/z* 313 $(2M - H_2O - H)^-$.

Treatment of 6-bromo-2-naphthol (1.8 g, 5.4 mmol) with 4-methoxy-2-methylphenylboronic acid (1.74 g, 7.0 mmol) according to method A afforded 1.56 g (73%) of yellowish solid: mp 124−126 °C; ^{1}H NMR (DMSO-d_6) δ 2.25 (3H,s), 3.78 (3H, s), 6.85 (1H, dd, J = 8.35 Hz, J = 2.56 Hz), 6.90 (1H, d, J = 2.37 Hz), 7.09 (1H, dd, J = 8.75 Hz, J = 2.25 Hz), 7.13 (1H, s), 7.20 (1H, d, J = 8.33 Hz), 7.35 (1H, dd, J = 8.39 Hz, J = 1.37 Hz), 7.67 (1H, s), 7.70 (1H, d, J = 8.53 Hz), 7.78 (1H, d, J = 8.78 Hz), 9.74 (1H, s); MS (ESI) *m/z* 263 $(M - H)^-$. Anal. ($C_{18}H_{16}O_2$) C, H.

4-(6-Hydroxy-2-naphthyl)-3-methoxyphenyl 4-methylbenzenesulfonate (101). 4-Bromo-3-methoxyphenyl 4-methylbenzenesulfonate. A mixture of 4-bromoresorcinol (4.92 g, 26.0 mmol), *p*-toluenesulfonic chloride (5.95 g, 31.2 mmol), potassium carbonate (23 g, 167 mmol), and acetone (300 mL) was refluxed for 16 h. Iodomethane (9.89 g, 70 mmol) was added and the mixture was refluxed for an additional 12 h. The mixture was cooled to room temperature, ether (200 mL) was added, and the suspension was filtered. The filtrate was concentrated and the product purified on a silica column (10% ethyl acetate−hexanes) to yield 6.49 g (70%) of 4-bromo-3-methoxyphenyl 4-methylbenzenesulfonate as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.45 (3H, s), 3.78 (3H, s), 6.40 (1H, dd, J = 2.45 Hz, J = 8.60 Hz), 6.59 (1H, d, J = 2.48 Hz), 7.33 (2H, d, J = 8.30 Hz), 7.40 (1H, d, J = 8.69 Hz), 7.71 (2H, d, J = 8.23 Hz); MS (ESI) *m/z* 355/357 $(M - H)^-$. Anal. ($C_{14}H_{13}BrO_4S$) C, H.

***tert*-Butyl[(6-bromo-2-naphthyl)oxy]dimethylsilane.** To a solution of 6-bromo-2-naphthol (13.68 g, 61.33 mmol) and TBDMS−Cl (11.09 g, 73.6 mmol) in DMF (50 mL) was added imidazole (10.2 g, 150 mmol). The solution was stirred for 3 h, mixed with sodium bicarbonate solution (250 mL), and extracted with 50% ethyl acetate−hexanes (3 × 250 mL). The combined organic layers were washed with water, dried over magnesium sulfate, and filtered, and the solvent was evaporated to yield an oil which was dried under vacuum to yield 19.9 g (97%) of the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.24 (6H, s), 1.01 (9H, s), 7.08 (1H, dd, J = 2.26 Hz, J = 8.81 Hz), 7.14 (1H, d, J = 2.15 Hz), 7.46 (1H, dd, J = 1.80 Hz, J = 8.77 Hz), 7.54 (1H, d, J = 8.77 Hz), 7.61 (1H, d, J = 8.81 Hz), 7.90 (1H, s); MS (EI) *m/z* 336/338 $(M\bullet)^+$. Anal. ($C_{16}H_{21}BrO_1Si\cdot0.25H_2O$) C, H, N.

***tert*-Butyl[(2-(6-naphthylboronic acid)oxy]dimethylsilane.** To a solution of *tert*-butyl[(6-bromo-2-naphthyl)oxy]-dimethylsilane (19.18 g, 56.9 mmol), prepared as described above, in THF (200 mL) at −78 °C was slowly added *n*-butyllithium (25 mL of 2.5 N solution in hexanes). The solution was stirred for 30 min followed by the addition of triisopropyl borate (53.5 g, 285 mmol). The solution was stirred for 1 h at −78 °C and then allowed to warm to room temperature overnight. The solution was then cooled to 0 °C and stirred with HCl (200 mL of 1 N solution) for 10 min. The mixture was extracted with ethyl acetate (3 × 250 mL). The combined organic layers were concentrated to a volume of 25 mL. Crystallization was induced with hexanes, and the solid product was collected by filtration and dried under vacuum to yield 13.5 g (79%) of an off-white solid: ^{1}H NMR (DMSO-d_6) δ 0.25 (6H, s), 0.99 (9H, s), 7.10 (1H, dd, J = 2.56 Hz, J = 8.97 Hz), 7.26 (1H, d, J = 2.56 Hz), 7.73 (1H, d, J = 8.54 Hz), 7.82 (1H, dd, J = 1.07 Hz, J = 8.33 Hz), 7.83 (1H, d, J = 8.97 Hz), 8.30 (1H, s); MS (ESI) *m/z* 303 $(M + H)^+$.

4-Bromo-3-methoxyphenyl 4-methylbenzenesulfonate (3.07 g, 8.60 mmol) and *tert*-butyl[(2-(6-naphthyl boronic acid)oxy]-dimethylsilane (2.86 g, 9.46 mmol) were reacted according to method A to yield 2.15 g (53%) of an orange solid: ^{1}H NMR ($CDCl_3$) δ 2.44 (3H, s), 3.65 (3H, s), 6.69 (1H, dd, J = 2.10 Hz, J = 8.29 Hz), 6.74 (1H, d, J = 2.10 Hz), 7.06−7.11 (2H, m), 7.36 (1H, d, J = 8.27 Hz), 7.45 69 (1H, dd, J = 1.32 Hz, J = 8.57 Hz), 7.51 (1H, d, J = 8.28 Hz), 7.67 (1H, d, J = 8.61 Hz), 7.77 (1H, d, J = 8.80 Hz), 7.80−7.85 (3H, m), 9.78 (1H, s); MS (ESI) *m/z* 419 $(M - H)^-$. Anal. ($C_{24}H_{20}O_5S\cdot0.25H_2O$) C, H.

6-(4-Hydroxy-2-methoxyphenyl)-2-naphthol (31). A solution of **101** (1.74 g, 4.05 mmol), potassium hydroxide (5 g), water (85 mL), and ethanol (85 mL) was stirred at 90 °C for 2 h. The reaction was cooled to room temperature and concentrated to 50% volume, neutralized with acetic acid, and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated, and the product was purified by silica column (25% ethyl acetate−hexanes) to yield 1.01 g (94%) of a tan solid. A sample was further purified by preparative reverse phase HPLC to yield a tan solid: mp 152−154 °C; ^{1}H NMR (DMSO-d_6) δ 3.72 (3H, s), 6.46 (1H, dd, J = 1.52 Hz, J = 8.20 Hz), 6.52 (1H, d, J = 1.77 Hz), 7.04−7.09 (2H, m), 7.16 (1H, d, J = 8.23 Hz), 7.47 (1H, d, J = 8.50 Hz), 7.63 (1H, d, J = 8.57 Hz), 7.72−7.75 (2H, m), 9.56 (1H, bs), 9.68 (1H, bs); MS (ESI) *m/z* 265 $(M - H)^-$. Anal. ($C_{17}H_{14}O_3$) C, H, N.

6-(2-Fluoro-4-hydroxyphenyl)-2-naphthol (23). Treatment of **93** (1.12 g, 3.97 mmol) with boron tribromide (23.8 mL of 1.0 M solution in CH_2Cl_2, 23.8 mmol) according to method C yielded 0.92 g (91%) of a white solid: mp 208−209 °C; ^{1}H NMR (DMSO-d_6) δ 6.66−6.75 (2H, m), 7.08−7.13 (2H, m), 7.41 (1H, dd, J = 9.37 Hz, J = 8.57 Hz), 7.49−7.53 (1H, m), 7.72 (1H, d, J = 8.64 Hz), 7.80 (1H, d, J = 8.76 Hz), 7.86 (1H, s), 9.79 (1H, s), 10.01 (1H, s); MS (ESI) *m/z* 255 $(M + H)^+$, MS (ESI) *m/z* 253 $(M - H)^-$. Anal. ($C_{16}H_{11}FO_2\cdot0.15H_2O$) C, H, N.

6-(3,5-Difluoro-4-hydroxyphenyl)-2-naphthol (38). Treatment of 6-bromo-2-naphthol (0.165 g, 0.74 mmol) with 3,5-difluoro-4-*tert*-butyldimethylsilyoxyboronic acid (0.25 g, 0.87 mmol) according to method A yielded 0.14 g (70%) of a tan solid. This material was further purified by preparative reverse phase HPLC to yield the title compound as a white solid: mp 216−220 °C; ^{1}H NMR (DMSO-d_6) δ 7.09−7.13 (2h, m), 7.50 (2H, d, J = 10.00 Hz), 7.73 (2H, s), 7.78 (1H, d, J = 8.58 Hz), 8.10 (1H, s), 9.83 (1H, s), 10.28 (1H, s); MS (ESI) *m/z* 271 $(M - H)^-$. Anal. ($C_{16}H_{10}F_2O_2\cdot0.25H_2O$) C, H.

1-Chloro-6-(2-fluoro-4-hydroxyphenyl)-2-naphthol (24). The title compound was prepared by reacting **23** (300 mg, 1.18 mmol) and NCS (191 mg, 1.43 mmol) in THF (30 mL) according to method E to yield 170 mg (50%) of yellowish solid: mp 179−180 °C; ^{1}H NMR (DMSO-d_6) δ 6.73 (1H, dd, J = 12.69 Hz, J = 2.44 Hz), 6.75 (1H, dd, J = 8.30 Hz, J = 2.44 Hz), 7.31 (1H, d, J = 8.79 Hz), 7.45 (1H, t, J = 9.28 Hz), 7.70−7.72 (1H, m), 7.83 (1H, d, J = 8.79 Hz), 7.97 (1H, s), 8.06 (1H, d, J = 7.79 Hz), 10.06 (1H, s), 10.48 (1H, s); MS (ESI) *m/z* 287/289 $(M - H)^-$. Anal. ($C_{16}H_{10}ClFO_2$) C, H.

1-Chloro-6-(3,5-difluoro-4-hydroxyphenyl)-2-naphthol (39). The title compound was prepared by reacting **38** (300 mg, 1.10 mmol) with NCS (155 mg, 1.16 mmol) in THF (30 mL) according to method E to yield 264 mg (78%) of gray solid: mp 209−210 °C; ^{1}H NMR (DMSO-d_6) δ 7.32 (1H, d, J = 8.89 Hz), 7.50−7.61 (2H, m), 7.83 (1H, d, J = 8.96 Hz), 7.92 (1H, dd. J = 8.94 Hz, J = 1.59 Hz), 8.05 (1H, d, J = 8.88 Hz), 8.22 (1H, d, J = 1.19 Hz), 10.36 (1H, s), 10.54 (1H, s); MS (ESI) *m/z* 305/307 $(M - H)^-$. Anal. ($C_{16}H_9ClF_2O_2$) C, H.

***N*-(7-Hydroxynaphthyl)acetamide (107).** To a solution of commercially available 8-amino-2-naphthol (149.1 g, 0.937 mol) in methanol (1 L) was added acetic anhydride (93 mL, 0.984 mol). The reaction was refluxed for 90 min and cooled to room temperature. The solvent was removed and the residue was filtered through a plug of silica with ethyl acetate. The solvent was removed to yield 175.8 g (93%) of the desired product as a dark purple solid. An analytical sample was further purified by reverse phase preparative HPLC to yield

a pink solid: mp 161−162 °C; ^{1}H NMR (DMSO-d_6) δ 2.15 (3H, s), 7.09 (1H, dd, J = 1.95 Hz, J = 8.79 Hz), 7.20−7.26 (2H, m), 7.49 (1H, d, J = 7.31 Hz), 7.63 (1H, d, J = 8.11 Hz), 7.77 (1H, d, J = 8.81 Hz), 9.76 (1H, s), 9.79 (1H, s), MS (ESI) *m/z* 202 $(M + H)^+$. Anal. ($C_{12}H_{11}NO_2$) C, H, N.

***N*-(7-Methoxynaphthyl)acetamide (108).** To a mixture of **107** (175.4 g, 0.872 mol), potassium carbonate (301 g, 2.18 mol), and acetone (1 l) was added iodomethane (270 mL, 4.36 mol). The reaction mixture was heated to reflux for 6 h and then cooled to room temperature, and the solvent was removed under vacuum. The residue was filtered through silica with ethyl acetate and triturated with ethyl acetate to yield 161.6 g (86%) of a gray solid. An analytical sample was further purified by preparative reverse phase HPLC to yield the title compound as a white solid: mp 154−155 °C; ^{1}H NMR (DMSO-d_6) δ 2.19 (3H, s), 3.90 (3H, s), 7.19 (1H, dd, J = 2.39 Hz, J = 8.94 Hz), 7.29−7.34 (2H, m), 7.39 (1H, d, J = 1.86 Hz), 7.75−7.68 (2H, m), 7.87 (1H, d, J = 8.96 Hz), 9.82 (1H, s); MS (ESI) *m/z* 216 $(M + H)^+$. Anal. ($C_{13}H_{13}NO_2$) C, H, N.

7-Methoxynaphthylamine (109). A mixture of **108** (160.6 g, 0.747 mol) and HCl (1.5 L of 1 N solution) was heated to reflux for 5 h. The reaction was allowed to cool to room temperature, neutralized with solid sodium bicarbonate, and extracted with dichloromethane. The combined organic layers were filtered through silica, and the solvent was removed under vacuum to yield 89.5 g (69%) of a brown solid. An analytical sample was prepared by preparative HPLC to yield the title compound as a white solid: mp 134−136 °C; ^{1}H NMR ($CDCl_3$) δ 3.94 (3H, s), 4.01 (2H, bs), 6.80 (1H, d, J = 7.26 Hz), 7.05 (1H, d, J = 2.20 Hz), 7.12−7.19 (2H, m), 7.28 (1H, d, J = 8.17 Hz), 7.71 (1H, d, J = 8.93 Hz); MS (ESI) *m/z* 174 $(M + H)^+$. Anal. ($C_{11}H_{11}NO\cdot CF_3CO_2H$) C, H, N.

1-Fluoro-7-methoxynaphthalene (110). To a mixture of **109** (10.94 g, 63.24 mmol), HCl (15.8 mL of 12 N solution, 190 mmol), and water (50 mL) cooled to 10 °C was added a solution of sodium nitrite (4.58 g, 66.40 mmol) in water (25 mL) over 10 min. The solution was stirred for 30 min and combined with fluoroboric acid (100 mL). The resulting green solid was collected by filtration and washed with water, with ethanol, and then with ether to yield 15.48 g (90%) of the diazonium fluoroborate salt intermediate as a yellow solid. This yellow solid was combined with xylenes (250 mL) and allowed to reflux for 1 h. The solvent was removed and the residue was partitioned between ethyl acetate and sodium bicarbonate solution. The organic layer was dried over sodium sulfate and filtered, the solvent was evaporated, and the product was purified on silica (hexanes) to yield a light yellow liquid: ^{1}H NMR ($CDCl_3$) δ 3.94 (3H, s), 7.10−7.28 (3H, m), 7.34 (1H, d, J = 2.50 Hz), 7.55 (1H, d, J = 8.12 Hz), 7.75 (1H, dd, J = 1.69 Hz, J = 9.00 Hz); MS (EI) *m/z* 176 $(M^{\bullet})^+$. Anal. ($C_{11}H_9FO$) C, H.

8-Fluoro-2-naphthol (111). The title compound was prepared by reacting **110** (7.99 g, 45.34 mmol) with boron tribromide (68 mL of 1 N solution, 68 mmol) according to method C to yield 3.99 g (54%) of a red solid. An analytical sample was prepared by preparative reverse phase HPLC to yield a white solid: mp 89−92 °C; ^{1}H NMR (DMSO-d_6) δ 7.16 (1H, dd, J = 2.42 Hz, J = 8.90 Hz), 7.21−7.25 (3H, m), 7.62−7.65 (1H, m), 7.85 (1H, dd, J = 1.72 Hz, J = 8.87 Hz), 10.08 (1H, s); MS (ESI) *m/z* 161$(M - H)^-$. Anal. ($C_{10}H_7FO$) C, H.

6-Bromo-8-fluoro-2-naphthol (113). To a solution of **111** (3.24 g, 20.0 mmol) in glacial acetic acid (30 mL) was slowly added a solution of bromine (7.35 g, 46.0 mmol) in glacial acetic acid (30 mL). The solution was stirred at 100 °C for 1 h. The reaction was cooled to room temperature, poured into water (50 mL), and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with sodium bicarbonate solution, dried over sodium sulfate, and filtered; the solvent was evaporated; and the product was purified on a silica column (2.5% ethyl acetate−hexanes) to yield 3.96 g (12.4 mmol, 62%) of **112** as a yellow solid. This solid was combined with $SnCl_2$ (7.0 g, 31 mmol), glacial acetic acid (35 mL), and HCl (35 mL of 12 N) and heated to 100 °C for 1 h. The resulting solution was cooled to room temperature, poured into water (100 mL), and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with water, dried over sodium sulfate, filtered, and concentrated, and the product was purified on silica 2.5% ethyl acetate−hexanes) to yield 1.97 g (41%) a white solid: mp 124−126 °C; ^{1}H NMR (DMSO-d_6) δ 7.20 (1H, s), 7.23 (1H, d, J = 2.39 Hz), 7.48 (1H, dd, J = 1.78 Hz, J = 10.52 Hz), 7.84−7.88 (1H, m), 7.94 (1H, d, J = 0.79 Hz), 10.28 (1H, s); MS (ESI) *m/z* 239/241 $(M - H)^-$. Anal. ($C_{10}H_6BrFO$) C, H.

8-Fluoro-6-(4-methoxyphenyl)-2-naphthol (116). The title compound was prepared by reacting **113** (0.39 g, 1.62 mmol) with 4-methoxyphenyl boronic acid (0.34 g, 2.27 mmol) according to method A to yield 0.35 g (81%) of a white solid: mp 150−151 °C; ^{1}H NMR (DMSO-d_6) δ 3.81 (3H, s), 7.05 (2H, d, J = 8.75 Hz), 7.16−7.20 (2H, m), 7.57 (1H, dd, J = 1.21 Hz, J = 12.76 Hz), 7.74 (2H, d, J = 8.74 Hz), 7.89−7.92 (2H, m), 10.10 (1H, s); MS (ESI) *m/z* 269 $(M - H)^+$. Anal. ($C_{17}H_{13}FO_2\cdot 0.1H_2O$) C, H.

8-Fluoro-6-(3-fluoro-4-methoxyphenyl)-2-naphthol (117). The title compound was prepared by reacting **113** (0.66 g, 2.74 mmol) with 3-fluoro-4-methoxyphenyl boronic acid[7,8] (0.56 g, 3.3 mmol) according to method A to yield 0.67 g (85%) of a white solid: mp 138−140 °C; ^{1}H NMR (DMSO-d_6) δ 3.90 (3H, s), 7.17−7.30 (3H, m), 7.60−7.65 (2H, m), 7.71 (1H, dd, J = 2.19 Hz), J = 13.14 Hz), 7.90 (1H, d, J = 8.37 Hz), 7.99 (1H, bs), 10.15 (1H, bs); MS (ESI) *m/z* 285 $(M - H)^-$. Anal. ($C_{17}H_{12}F_2O_2$) C, H.

8-Fluoro-6-(4-hydroxyphenyl)-2-naphthol (40). The title compound was prepared by reacting **116** (0.10 g, 0.37 mmol) with boron tribromide (0.56 mL of 1 N solution, 0.56 mmol) according to method C to yield 0.10 g (100%) of a white solid: mp 236−238 °C; ^{1}H NMR (DMSO-d_6) δ 6.87 (2H, d, J = 8.57 Hz), 7.14−7.18 (2H, m), 7.52 (1H, dd, J = 1.18 Hz, J = 12.78 Hz), 7.61 (2H, d, J = 8.59 Hz, 7.86−7.89 (2H, m), 9.61 (1H, bs), 10.05 (1H, bs); MS (ESI) *m/z* 253 $(M - H)^-$. Anal. ($C_{16}H_{11}FO_2\cdot 0.1H_2O$) C, H.

8-Fluoro-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol (41). The title compound was prepared by reacting **117** (0.10 g, 0.35 mmol) with boron tribromide (0.7 mL of 1 N solution, 0.7 mmol) according to method C to yield 0.020 g (21%) of a white solid: mp 218−220 °C (dec); ^{1}H NMR (DMSO-d_6) δ 7.01−7.07 (1H, m), 7.16−7.19 (2H, m), 7.46 (1H, dd, J = 1.74 Hz, J = 8.40 Hz), 7.56−7.65 (2H, m), 7.88 (1H, d, J = 8.31 Hz), 7.93 (1H, bs), 10.04 (1H, s), 10.11 (1H, s); MS (ESI) *m/z* 271 $(M - H^+)^-$. Anal. ($C_{16}H_{10}F_2O_2\cdot 0.25H_2O$) C, H.

1-Chloro-8-fluoro-6-(4-methoxyphenyl)-2-naphthol (118). A solution of **116** (0.17 g, 0.63 mmol) and NCS (0.10 g, 0.76 mmol) in THF (20 mL) was stirred under nitrogen at room temperature overnight according to method E. The solution was concentrated onto Florosil and purified on a silica column (20% ethyl acetate−hexanes) to yield 0.16 g (84%) a yellow solid. An analytical sample was further prepared by preparative reverse phase HPLC to yield a light yellow solid: mp 120−124 °C; ^{1}H NMR (DMSO-d_6) δ 3.82 (3H, s), 7.06 (2H, d, J = 8.80 Hz), 7.34 (1H, d, J = 8.91 Hz), 7.67 (1H, dd, J = 1.69 Hz, J = 15.48 Hz), 7.78 (2H, d, J = 8.78 Hz), 8.01 (1H, d, J = 1.54 Hz), 10.62 (1H, s); MS (ESI) *m/z* 301/303 $(M - H^+)^-$. Anal. ($C_{17}H_{12}ClFO_2$) C, H.

1-Chloro-8-fluoro-6-(3-fluoro-4-methoxyphenyl)-2-naphthol (119). The title compound was prepared by reacting **41** (0.30 g, 1.05 mmol) and NCS (0.17 g, 1.26 mmol) according to method E to yield 0.21 g (62%) of a light orange solid: mp 126−128 °C; ^{1}H NMR (DMSO-d_6) δ 3.90 (3H, s), 7.25−7.31 (1H, m), 7.35 (1H, d, J = 8.91 Hz), 7.64−7.67 (1H, m), 7.70−7.78 (2H, m), 7.87 (1H, dd, J = 1.58 Hz, J = 9.04 Hz), 10.68 (1H, s); MS (ESI) *m/z* 319/321 $(M - H^+)^-$. Anal. ($C_{17}H_{11}ClF_2O_2$) C, H.

1-Chloro-8-fluoro-6-(4-hydroxyphenyl)-2-naphthol (42). The title compound was prepared by reacting **118** (0.14 g, 0.46 mmol) with boron tribromide (0.69 mL of 1 N solution, 0.69 mmol) according to method C to yield 0.050 g (38%) of a white solid mp 174−176 °C; ^{1}H NMR (DMSO-d_6) δ 6.88 (2H, d, J = 8.62 Hz), 7.33 (1H, d, J = 8.92 Hz), 7.60−7.67 (3H, m), 7.86 (1H, dd, J = 1.43 Hz, J = 9.02 Hz), 7.95 (1H, d, J = 1.37 Hz),

9.68 (1H, s), 10.59 (1H, s); MS (ESI) *m/z* 287/289 $(M - H^+)^-$. Anal. ($C_{16}H_{10}ClFO_2 \cdot 0.25H_2O$) C, H.

1-Chloro-8-fluoro-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol (43). The title compound was prepared by reacting **119** (0.13 g, 0.41 mmol) with boron tribromide (0.8 mL of 1 N solution, 0.8 mmol) according to method C to yield 0.070 g (56%) of a white solid: mp 198−200 °C; ^{1}H NMR (DMSO-d_6) δ 7.03−7.09 (1H, m) 7.34 (1H, d, J = 8.92 Hz), 7.49−7.52 (1H, m), 7.68 (2H, d, J = 15.0 Hz), 7.85−7.88 (1H, m), 8.02 (1H, d, J = 0.70 Hz), 10.13 (1H, s), 10.66 (1H, s); MS (ESI) *m/z* 305/307 $(M - H^+)^-$. Anal. ($C_{16}H_9ClF_2O_2$) C, H.

8-Chloro-2-methoxynaphthalene (120). $CuCl_2$ (4.6 g, 24.6 mmol) and *tert*-butyl nitrite (4.46 g, 43.3 mmol) were added to acetonitrile (125 mL) at 0 °C. To this mixture was slowly added a solution of **109** (4.99 g, 28.8 mmol) in acetonitrile (25 mL). The reaction was allowed to warm to room temperature, stirred with HCl (400 mL of 2 N solution), and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with 2 N HCl, dried over sodium sulfate, and filtered; the solvent was evaporated; and the product was purified on a silica column (hexanes) to yield 2.27 g (41%) of an orange liquid. An analytical sample was further purified by reverse phase preparative HPLC to yield the title compound as a yellow solid: mp 32−34 °C; ^{1}H NMR ($CDCl_3$) δ 3.98 (3H, s), 7.20 (1H, dd, J = 2.52 Hz, J = 8.96 Hz), 7.22−7.27 (1H, m), 7.52 (1H, d, J = 2.47 Hz), 7.55 (1h, d, J = 7.47 Hz), 7.69 (1H, d, J = 8.15 Hz), 7.75 (1H, d, J = 8.95 Hz); MS (ESI) *m/z* 191/193 $(M - H^+)^-$. Anal. ($C_{11}H_9ClO$) C, H.

8-Chloro-2-naphthol (121). The title compound was prepared by reacting **120** (10.25 g, 53.4 mmol) with boron tribromide (67 mL of 1 N solution, 67 mmol) according to method C to yield 8.76 g (92%) of a yellow solid. An analytical sample was further purified by reverse phase preparative HPLC to yield the title compound as a white solid: mp 95−100 °C; ^{1}H NMR (DMSO-d_6) δ 7.18 (1H, dd, J = 2.37 Hz, J = 8.85 Hz), 7.23−7.28 (1H, m), 7.41 (1H, d, J = 2.28 Hz), 7.59 (1H, d, J = 7.37 Hz), 7.81 (1H, d, J = 8.15 Hz), 7.87 (1H, d, J = 8.86 Hz), 10.17 (1H, s); MS (ESI) *m/z* 177/179 $(M - H^+)^-$. Anal. ($C_{10}H_7ClO$) C, H.

3,6-Dibromo-8-chloro-2-naphthol (122). To a solution of **121** (4.92 g, 27.6 mmol) in glacial acetic acid (40 mL) was slowly added a solution of bromine (9.7 g, 60.7 mmol) in glacial acetic acid (40 mL). The solution was stirred at 100 °C for 1 h, cooled to room temperature, poured into water (250 mL), and extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate, dried with sodium sulfate, and filtered; the solvent was evaporated; and the product was purified on a silica column (20% ethyl acetate−hexanes) to yield 4.61 g (50%) of a yellow solid. An analytical sample was further purified by reverse phase preparative HPLC to yield the title compound as a white solid: mp 156−158 °C; ^{1}H NMR (DMSO-d_6) δ 7.57 (1H, s), 7.82 (1H, d, J = 1.89 Hz), 8.11 (1H, d, J = 1.69 Hz), 8.31 (1H, s), 11.30 (1H, bs); MS (ESI) *m/z* 333/335/337 $(M - H)^-$. Anal. ($C_{10}H_5Br_2ClO$) C, H.

In addition, 1.80 g of **123** was isolated (16%) as a light orange solid: mp 166−170 °C; ^{1}H NMR (DMSO-d_6) δ 7.90 (1H, d, J = 2.07 Hz), 8.23 (1H, d, J = 2.08 Hz), 8.40 (1H, s), 10.54 (1H, bs); MS (ESI) *m/z* 411/413/415/417/419 $(M - H)^-$. Anal. ($C_{10}H_4Br_3ClO$) C, H calcd, 28.92; found: 30.15.

***tert*-Butyl[(3,6-dibromo-8-chloro-2-naphthyl)oxy]dimethylsilane (124).** The title compound was prepared by reacting **122** (3.00 g, 8.92 mmol) with TBDMSCl (1.75 g, 15.07 mmol), according to the experimental for **101**, to yield 3.36 g (84%) of a white solid: mp 58−64 °C; ^{1}H NMR ($CDCl_3$) δ 0.34 (6H, s), 1.08 (9H, s), 7.57 (1H, s), 7.62 (1H, d, J = 1.72 Hz), 7.75 (1H, d, J = 1.24 Hz), 7.97 (1H, s); MS (ESI) *m/z* 333/335/337 $(M - H)^-$. Anal. ($C_{16}H_{19}Br_2ClOSi$) C, H.

3-Bromo-8-chloro-6-(4-methoxyphenyl)-2-naphthol (125). Naphthalene **124** (1.95 g, 4.32 mmol) was reacted with with 4-methoxyphenylmagnesium bromide (13.8 mL of 0.5 N solution, 6.9 mmol) and tetrakis(triphenylphosphine)palladium (0.25 g, 0.21 mmol) in THF (10 mL) according to method B to yield 1.42 g (69%) of *tert*-butyl[(3-bromo-8-chloro-(4-methoxyphenyl)-2-naphthyl)oxy]dimethylsilane as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.36 (6H, s), 1.10 (9H, s), 3.87 (3H, s), 7.01 (2H, d, J = 8.78 Hz), 7.33 (1H, d, J = 1.36 Hz), 7.58 (2H, d, J = 8.75 Hz), 7.73 (1H, s), 7.78 (1H, d, J = 1.62 Hz), 8.10 (1H, s).

tert-Butyl[(3-bromo-8-chloro-(4-methoxyphenyl)-2-naphthyl)-oxy]dimethylsilane (0.50 g, 1.06 mmol) was reacted with TBAF (5 mL of 1 N solution in THF, 55 mmol), according to the preparation of compound **22** (method G), to yield 0.34 g (88%) of a white solid: mp 138−139 °C; ^{1}H NMR (DMSO-d_6) δ 3.82 (3H, s), 7.06 (2H, d, J = 8.76 Hz), 7.58 (1H, s), 7.73 (2H, d, J = 8.73 Hz), 7.94 (1H, d, J = 1.56 Hz), 8.07 (H, bs), 8.34 (1H, s), 11.05 (1H, s); MS (ESI) *m/z* 361/363/365 $(M - H)^-$. Anal. ($C_{17}H_{12}BrClO_2 \cdot 0.6H_2O$) C, H.

8-Chloro-6-(4-methoxyphenyl)-2-naphthol (126). Method H. To a solution of **125** (0.254 g, 0.698 mmol) in THF (25 mL) at −78 °C was slowly added *tert*-butyllithium (1.65 mL of 1.7 N solution, 2.8 mmol). The resulting solution was stirred for 20 min at −78 °C, 2.5 mL of water was added, and the mixture was warmed to room temperature slowly with stirring. The reaction was poured into 50 mL of water and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water, dried with sodium sulfate, filtered; the solvent was removed; and the product was purified on a silica column (10% ethyl acetate−hexanes) to yield 0.15 g (88%) of a yellow solid. An analytical sample was further prepared by reverse phase preparative HPLC to yield a light yellow solid: mp 116−118 °C; ^{1}H NMR (DMSO-d_6) δ 3.81 (3H, s), 7.05 (2H, d, J = 8.75 Hz), 7.19 (1H, dd, J = 2.34 Hz, J = 8.84 Hz), 7.40 (1H, d, J = 2.25 Hz), 7.74 (2H, d, J = 8.73 Hz), 7.89 (1H, d, J = 1.65 Hz), 7.92 (1H, d, J = 8.93 Hz), 8.07 (1H, s), 10.19 (1H, s); MS (ESI) *m/z* 283/285 $(M - H)^-$. Anal. ($C_{17}H_{13}ClO_2 \cdot 0.1H_2O$) C, H.

8-Chloro-6-(4-hydroxyphenyl)-2-naphthol (44). The title compound was prepared by reacting **126** (0.10 g, 0.35 mmol) with boron tribromide (0.9 mL of 1 N solution, 0.9 mmol) according to method C to yield 0.080 g (85%) of product that was further purified by reverse phase preparative HPLC to yield a white solid: mp 204−206 °C; ^{1}H NMR (DMSO-d_6) δ 6.87 (2H, d, J = 8.61 Hz), 7.17 (1H, dd, J = 2.34 Hz, J = 8.83 Hz), 7.38 (1H, d, J = 2.26 Hz), 7.62 (2H, d, J = 8.59 Hz), 7.85 (1H, d, J = 1.64 Hz), 7.90 (1H, d, J = 8.92 Hz), 8.01 (1H, bs), 9.62 (1H, s), 10.14 (1H, s); MS (ESI) *m/z* 269 $(M - H)^-$. Anal. ($C_{16}H_{11}ClO_2 \cdot 0.25H_2O$) C, H.

3-Bromo-1,8-dichloro-6-(4-methoxyphenyl)-2-naphthol (127). The title compound was prepared by reacting **125** (0.69 g, 1.90 mmol) and NCS (0.31 g, 2.3 mmol) in THF (25 mL) according to method E to yield 0.61 g (81%) of a yellow solid. An analytical sample was further prepared by reverse phase preparative HPLC to yield a white solid: mp 176−178 °C (dec); ^{1}H NMR (DMSO-d_6) δ 3.82 (3H, s), 7.08 (2H, d, J = 8.77 Hz), 7.77 (2H, d, J = 8.75 Hz), 8.00 (1H, d, J = 1.84 Hz), 8.19 (1H, d, J = 1.84 Hz), 8.39 (1H, s), 10.53 (1H, bs); MS (ESI) *m/z* 395/397/399 $(M - H)^-$. Anal. ($C_{17}H_{11}BrCl_2O_2$) C, H.

1,8-Dichloro-6-(4-methoxyphenyl)-2-naphthol (128). The title compound was prepared by reacting **127** (0.30 g, 0.754 mmol) with *tert*-butyl lithium (1.75 mL of 1.7 N solution, 3.0 mmol) and quenching with water according to the procedure used to prepare **126** (method H) to yield 0.19 g (79%) of a yellow solid. An analytical sample was further prepared by reverse phase preparative HPLC to yield a light yellow solid: mp 132−134 °C; ^{1}H NMR (DMSO-d_6) δ 3.82 (3H, s), 7.06 (2H, d, J = 8.77 Hz), 7.37 (1H, d, J = 8.90 Hz), 7.77 (2H, d, J = 8.75 Hz), 7.89−7.93 (2H, m), 8.15 (1H, d, J = 1.85 Hz), 10.68 (1H, s); MS (ESI) *m/z* 317/319/321 $(M - H)^-$. Anal. ($C_{17}H_{12}Cl_2O_2$) C, H.

1,8-Dichloro-6-(4-hydroxyphenyl)-2-naphthol (45). The title compound was prepared by reacting **128** (0.12 g, 0.38 mmol) with boron tribromide (0.75 mL of 1 N solution, 0.75 mmol) according to method C to yield 0.10 g (86%) which was further purified by reverse phase preparative HPLC to yield the title compound as a white solid: mp 172−174 °C (dec); ^{1}H NMR (DMSO-d_6) δ 6.89 (2H, d, J = 8.54 Hz), 7.36 (1H, d, J = 8.90 Hz), 7.65 (2H, d, J = 8.56 Hz), 7.88−7.91 (2H, m), 8.10

(1H, d, J = 1.63 Hz), 9.69 (1H, s), 10.64 (1H, s); MS (ESI) *m/z* 303/305/307 $(M - H)^-$. Anal. ($C_{16}H_{10}Cl_2O_2 \cdot 0.25H_2O$) C, H.

7-Methoxy-3,4-dihydronaphthalene-1-carbonitrile (130). To a mixture of commercially available 7-methoxy-1-tetralone (**129**) (39.65 g, 0.23 mol), zinc iodide (1.73 g, 5.4 mmol), and benzene (100 mLs) was added trimethylsilyl cyanide (25.0 g. 0.25 mol). The mixture was stirred overnight at room temperature. Pyridine (350 mL) was added and phosphorus oxychloride (100 mL) was then added dropwise. The mixture was heated to reflux for 6 h and then allowed to stir overnight at room temperature. The mixture was carefully poured onto ice/hydrochloric acid (1.5 L of 10% HCl) for a total volume of 2 L. This mixture was extracted with ethyl acetate (3 × 500 mL), and the organics were combined and washed with water (2 × 500 mL) and then brine (500 mL). The ethyl acetate layer was dried over magnesium sulfate and the solvent evaporated to provide a liquid that solidified upon standing. This crude solid was triturated in hexane and filtered to give 31.3 g (74%) of a tan solid. A portion of this material was purified by silica gel chromatography (10% ethyl acetate−hexanes) to provide a solid: mp 47−49 ° C; ^{1}H NMR (DMSO-d_6) δ 2.44−2.50 (2H, m), 2.72 (2H, t, J = 8.4 Hz), 6.81 (1 H, d, J = 2.6 Hz), 6.90 (1H, dd, J = 2.9 Hz, J = 8.2 Hz), 7.17−7.19 (2H, m); MS (ESI) *m/z* 168 $(M - H)^-$. Anal. ($C_{12}H_{11}NO$) C, H, N.

7-Methoxy-1-cyanonaphthalene (131). The title compound was prepared by reacting **130** (9.95 g, 53.1 mmol) with 10% Pd/C according to the procedure used to prepare naphthol **6** to yield a white solid (4.3 g, 44%). A portion was purified further by silica gel (10% ethyl acetate−hexanes) to produce a white solid: mp 77−78 °C; ^{1}H NMR (DMSO-d_6) δ 3.97 (3H, s), 7.36 (1H, s), 7.39 (1 H, d, J = 2.5 Hz), 7.52 (1H, t, J = 7.4 Hz), 8.04−8.13 (2H, m), 8.24 (1H, d, J = 8.2 Hz). Anal. ($C_{12}H_9NO$) C, H, N.

7-Hydroxy-1-naphthonitrile (132). The title compound was prepared by reacting **131** (1.19 g, 6.50 mmol) with pyridinium HCl (9 g) according to method D to yield 0.88 g (80%) of a white solid: mp 184−188 °C; ^{1}H NMR (DMSO-d_6) δ 7.25 (1H, dd, J = 2.30 Hz, J = 8.88 Hz), 7.38 (1H, d, J = 2.20 Hz), 7.39−7.44 (1H, m), 7.98 (1H, d, J = 8.91 Hz), 8.04 (1H, d, J = 7.14 Hz), 8.17 (1H, d, J = 8.19 Hz), 10.48 (1H, s); MS (ESI) *m/z* 170 $([M + H]^+)$; MS (ESI) *m/z* 168 $(M - H)^-$. Anal. ($C_{11}H_7NO$) C, H, N.

3-Bromo-7-hydroxy-1-naphthonitrile (133). To a mixture of **132** (26.03 g, 154.0 mmol) and glacial acetic acid (400 mL) was added bromine (51.8 g, 323 mmol). The mixture was stirred at 100 °C for 6 h, HCl (400 mL of 12 N solution) and $SnCl_2$ (69 g, 308 mmol) were added, and the mixture was allowed to stir at 100 °C for 1 h. The resulting solution was cooled to room temperature and poured into water (1 l). The resulting yellow precipitate was collected by filtration, dried under vacuum, and triturated with ethyl acetate to yield 14.68 g (38%) of an off-white solid. An analytical sample was prepared by preparative reverse phase HPLC to yield the desired product as a white solid: mp 222−224 °C; ^{1}H NMR (DMSO-d_6) δ 7.28−7.35 (2H, m), 7.97 (1H, d, J = 8.73 Hz), 8.26 (1H, s), 8.47 (1H, s), 10.65 (1H, s); MS (ESI) *m/z* 246/247 $(M - H)^-$. Anal. ($C_{11}H_6BrNO$): C, H, N, calcd, 5.65; found, 4.82.

7-Hydroxy-3-(4-methoxyphenyl)-1-naphthonitrile (134). The title compound was prepared by reacting **133** (0.249 g, 1.00 mmol) with 4-methoxyphenylboronic acid (0.21 g, 1.4 mmol) according to method A to yield 0.19 (69%) of a light yellow solid: mp 226 °C; ^{1}H NMR (DMSO-d_6) δ 3.82 (3H, s), 7.07 (2H, d, J = 8.82 Hz), 7.26 (1H, dd, J = 2.32 Hz, J = 8.90 Hz), 7.37 (1H, d, J = 2.27 Hz), 7.80 (2H, d, J = 8.80 Hz), 8.02 (1H, d, J = 8.96 Hz), 8.37 (1H, d, J = 1.85 Hz), 8.44 (1H, d, J = 1.43 Hz), 10.48 (1H, bs); MS (ESI) *m/z* 274 $(M - H)^-$. Anal. ($C_{18}H_{13}NO_2 \cdot 0.1H_2O$) C, H, N.

3-(3-Fluoro-4-methoxyphenyl)-7-hydroxy-1-naphthonitrile (135). The title compound was prepared by reacting **133** (0.208 g, 0.839 mmol) with 3-fluoro-4-methoxyphenylboronic acid[7,8] (0.18 g, 1.1 mmol) according to method A to yield 0.16 g (65%) of a light yellow solid. An analytical sample was prepared by preparative reverse phase HPLC to yield the title compound as a white solid: mp 214−216 °C; ^{1}H NMR (DMSO-d_6) δ 3.90 (3H, s), 7.23−7.32 (2H, m), 7.37 (1H, d, J = 2.24 Hz), 7.65−7.70 (1H, m), 7.79 (1H, dd, J = 2.22 Hz, J = 13.10 Hz), 8.03 (1H, d, J = 8.96 Hz), 8.41 (1H, d, J = 1.86 Hz), 8.50 (1H, d, J = 1.43 Hz), 10.55 (1H, s); MS (ESI) *m/z* 292 $(M - H)^-$. Anal. ($C_{18}H_{12}FNO_2 \cdot 0.1H_2O$) C, H, N.

7-Hydroxy-3-(4-hydroxyphenyl)-1-naphthonitrile (46) The title compound was prepared by reacting **134** (0.14 g, 0.51 mmol) with pyridinium HCl (3 g) according to method D to yield 0.10 g (75%) of a white solid: mp 254−257 °C; ^{1}H NMR (DMSO-d_6) δ 6.89 (2H, d, J = 8.53 Hz), 7.25 (1H, dd, J = 2.15 Hz, J = 8.88 Hz), 7.36 (1H, d, J = 1.86 Hz), 7.67 (2H, d, J = 8.55 Hz), 8.00 (1H, d, J = 8.94 Hz), 8.31−8.38 (2H, m), 9.70 (1H, bs), 10.44 (1H, bs); MS (ESI) *m/z* 260 $(M - H)^-$. Anal. ($C_{17}H_{11}NO_2 \cdot 0.25H_2O$) C, H, N.

3-(3-Fluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile (47). The title compound was prepared by reacting **135** (0.12 g, 0.41 mmol) with pyridinium HCl (3 g) according to method D to yield 0.085 g (74%) of a white solid: mp 265−269 °C; ^{1}H NMR (DMSO-d_6) δ 7.04−7.09 (1H, m), 7.26 (1H, dd, J = 2.31 Hz, J = 8.88 Hz), 7.36 (1H, d, J = 2.19 Hz), 6.52 (1H, d, J = 2.19 Hz), 6.52 (1H, dd, J = 1.76 Hz, J = 8.40 Hz), 6.71 (1H, dd, J = 2.22 Hz, J = 12.88 Hz), 8.01 (1H, d, J = 8.97 Hz), 8.37 (1H, d, J = 1.83 Hz), 8.45 (1H, d, J = 1.41 Hz), 10.33 (2H, bs); MS (ESI) *m/z* 278 $(M - H)^-$. Anal. ($C_{17}H_{10}FNO_2$) C, H, N.

8-Bromo-7-hydroxy-3-(4-methoxyphenyl)-1-naphthonitrile (136). The title compound was prepared by reacting **134** (0.160 g, 0.58 mmol) with NBS (0.12 g, 0.70 mmol) in THF (10 mL) according to the procedure used to prepare **16** to yield 0.080 g (39%) of a yellow solid: mp 145−146 °C; ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s), 7.08 (2H, d, J = 8.79 Hz), 7.42 (1H, d, J = 8.79 Hz), 7.84 (2H, d, J = 8.79 Hz), 8.04 (1H, d, J = 8.79 Hz), 8.42 (1H, d, J = 1.95 Hz), 8.53 (1H, d, J = 1.95 Hz), 11.21 (1H, s); MS (ESI) *m/z* 354/356 $(M + H^+)$; MS (ESI) *m/z* 352/354 $(M - H)^-$. Anal. ($C_{18}H_{12}BrNO_2 \cdot 0.25H_2O$) C, H, N.

8-Bromo-7-hydroxy-3-(4-hydroxyphenyl)-1-naphthonitrile (48). The title compound was prepared by reacting **136** (0.13 g, 0.37 mmol) with boron tribromide (1.1 mL of 1 N solution, 1.1 mmol) according to method C to yield 0.050 g (40%) of an off white solid: mp 204−208 °C (dec); ^{1}H NMR (DMSO-d_6) δ 6.90 (2H, d, J = 8.30 Hz), 7.41 (1H, d, J = 8.79 Hz), 7.72 (2H, d, J = 8.79 Hz), 8.02 (1H, d, J = 9.23 Hz), 8.37 (1H, d, J = 1.95 Hz), 8.47 (1H, d, J = 2.44 Hz), 9.72 (1H, s), 11.16 (1H, s); MS (ESI) *m/z* 338/340 $(M - H)^-$. Anal. ($C_{17}H_{10}BrNO_2$) C, H, N.

3-Bromo-8-chloro-7-hydroxy-1-naphthonitrile (137). The title compound was prepared by reacting **133** (0.32 g, 1.28 mmol) with NCS (0.24 g, 1.8 mmol) in THF (25 mL) at 45 °C for 3 h according to method E to yield 0.30 g (83%) of a yellow solid. An analytical sample was prepared by preparative reverse phase HPLC to yield a white solid: mp 148−150 °C; ^{1}H NMR (DMSO-d_6) δ 7.47 (1H, d, J = 8.98 Hz), 7.95 (1H, d, J = 9.02 Hz), 8.32 (1H, d, J = 2.08 Hz), 8.55 (1H, d, J = 2.08 Hz), 11.33 (1H, s); MS (ESI) *m/z* 280/282/284 $(M - H)^-$. Anal. ($C_{11}H_5BrClNO \cdot 0.25H_2O$) C, H, N.

8-Chloro-3-(4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile (49). The title compound was prepared by reacting **137** (0.10 g, 0.37 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid[8] (0.13 g, 0.52 mmol) according to method A to yield 0.036 g (33%) of a white solid: mp 254−256 °C; ^{1}H NMR (DMSO-d_6) δ 6.90 (2H, d, J = 8.64 Hz), 7.43 (1H, d, J = 8.95 Hz), 7.72 (2H, d, J = 8.64 Hz), 7.99 (1H, d, J = 8.97 Hz), 8.38 (1H, d, J = 1.95 Hz), 8.47 (1H, d, J = 1.92 Hz), 9.73 (1H, s), 11.08 (1H, s); MS (ESI) *m/z* 294/296 $(M - H)^-$. Anal. ($C_{17}H_{10}ClNO_2$) C, H, N.

8-Chloro-3-(3-fluoro-4-methoxyphenyl)-7-hydroxy-1-naphthonitrile (138). The title compound was prepared by reacting **137** (0.20 g, 0.71 mmol) with 3-fluoro-4-methoxyphenylboronic acid[7,8] (0.17 g, 1.0 mmol) according to method A to yield 0.14 g (60%) of a yellow solid: mp 198−200 °C; ^{1}H NMR (DMSO-d_6) δ 3.91 (3H, s), 7.27−7.33 (1H, m), 7.45 (1H, d, J = 8.93 Hz), 7.71−7.74 (1H, m), 7.85 (1H, dd, J = 2.23 Hz, J = 13.09 Hz), 8.00 (1H, d, J = 9.08 Hz), 8.48 (1H, d, J = 1.97

Hz), 8.57 (1H, d, J = 1.95 Hz), 11.18 (1H, s); MS (ESI) *m/z* 326/328 $(M - H)^-$. Anal. ($C_{18}H_{11}ClFNO_2$) C, H, N.

8-Chloro-3-(3-fluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile (50). The title compound was prepared by reacting **138** (0.042 g, 0.13 mmol) with pyridinium HCl (1.8 g) according to method D to yield 0.033 g (78%) of a tan solid. This material was further purified by preparative reverse phase HPLC to yield the title compound as a white solid: mp 246−252 °C; ^{1}H NMR (DMSO-d_6) δ 7.04−7.10 (1H, m), 7.44 (1H, d, J = 8.94 Hz), 7.56 (1H, dd, J = 1.66 Hz, J = 8.37 Hz), 7.76 (1H, dd, J = 2.20 Hz, J = 12.88 Hz), 7.99 (1H, d, J = 9.09 Hz), 8.43 (1H, d, J = 1.98 Hz), 8.52 (1H, d, J = 1.94 Hz), 10.19 (1H, bs), 11.05 (1H, bs); MS (ESI) *m/z* 312/ 314 $(M - H)^-$. Anal. ($C_{17}H_9ClFNO_2 \cdot 0.25H_2O$) C, H, N.

3-Bromo-7-methoxy-1-naphthonitrile (139). The title compound was prepared by reacting **133** (3.01 g, 12.2 mmol) with iodomethane (8.62 g, 61 mmol) and K_2CO_3 (5.1 g, 37 mmol) in acetone (100 mL) overnight at reflux temperature with stirring. The solution was cooled to room temperature and poured into 300 mL of water. The resulting mixture was made slightly acidic and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with water, dried over sodium sulfate, and filtered, and the solvent was evaporated. Purification by silica column (95% hexanes/5% ethyl acetate) yielded 2.41 g (75%) of a white solid: mp 140−143 °C; ^{1}H NMR (DMSO-d_6) δ 3.97 (3H, s), 7.33 (1H, d, J = 2.37 Hz), 7.42 (1H, dd, J = 9.03 Hz, J = 2.45 Hz), 8.04 (1H, d, J = 9.08 Hz), 8.35 (1H, d, J = 2.00 Hz), 8.55 (1H, d, J = 1.86 Hz); MS (EI) *m/z* 261 $(M\bullet)^+$. Anal. ($C_{12}H_8BrNO$) C, H, N.

3-Bromo-8-fluoro-7-methoxy-1-naphthonitrile (140). To a mixture of **139** (0.93 g, 4.27 mmol) and Selectfluor (1.66 g, 4.70 mmol) in a sealed flask under nitrogen was added acetonitrile (30 mL) via syringe. The resulting solution was stirred at room temperature overnight and then poured into 200 mL of water. The resulting mixture was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and filtered; the solvent was evaporated; and the product waspurified on silica (80% hexanes/20% ethyl acetate) to yield 0.15 g (13%) of a white solid: mp 167−170 °C; ^{1}H NMR ($CDCl_3$) δ 4.07 (3H, d, J = 0.64 Hz), 7.41−7.45 (1H, m), 7.61 (1H, dd, J = 9.12 Hz, J = 1.62 Hz), 8.00 (1H, d, J = 1.81 Hz), 8.15−8.16 (1H, m); MS (EI) *m/z* 279. Anal. ($C_{12}H_7BrFNO \cdot 0.1H_2O$) C, H, N.

8-Fluoro-3-(3-fluoro-4-methoxyphenyl)-7-methoxy-1-naphthonitrile (141). The title compound was prepared by reacting **140** (0.13 g, 0.46 mmol) with 3-fluoro-4-methoxyphenylboronic acid[7,8] (0.11 g, 0.65 mmol) according to method A to yield 0.11 g (74%) of a tan solid: mp 170−172 °C; ^{1}H NMR ($CDCl_3$) δ 3.97 (3H, s), 4.09 (3h, s), 7.07−7.11 (1H, m), 7.37−7.46 (3H, m), 7.73 (1H, dd, J = 9.46 Hz, J = 1.70 Hz), 8.09−8.10 (1H, m), 8.14 (1H,d, J = 1.68 Hz); MS (EI) *m/z* 325.1 $(M\bullet)^+$. Anal. ($C_{19}H_{13}F_2NO_2 \cdot 0.2H_2O$) C, H, N.

8-Fluoro-3-(3-fluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile (51). Treatment of **141** (0.090 g, 0.28 mmol) with BBr_3 (1.1 mL of a 1 N solution, 1.1 mmol) according to method C yielded 0.074 g (90%) of a light yellow solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 7.05−7.09 (1H, m), 7.40−7.42 (1H, m), 7.53−7.58 (1H, m), 7.74 (1H, dd, J = 12.87 Hz, J = 2.27 Hz), 7.84 (1H, dd, J = 9.06 Hz, J = 1.04 Hz), 8.42 (1H, d, J = 1.81 Hz), 8.50−8.51 (1H, m), 10.15 (1H, bs), 10.69 (1H, bs); MS (ESI) *m/z* 296 $(M - H^+)^-$. Anal. ($C_{17}H_9F_2NO_2$) C, H, N: calcd, C: 68.69 N: 4.71; found, C: 64.07 N: 4.21.

7-[[*tert*-Butyl(dimethyl)silyl]oxy]-3-(4-[[*tert*-butyl(dimethyl)silyl]oxy]-3-fluorophenyl)-1-naphthonitrile (142). The title compound was prepared by reacting **47** (4.24 g, 15.20 mmol) with TBDMS−Cl (5.74 g, 38.0 mmol), according to the procedure used to prepare compound **101**, to yield 7.68 g (15.12 mmol) of a white solid: mp 104−105 °C; ^{1}H NMR ($CDCl_3$) δ 0.24 (3H, s), 0.25 (3h, s), 0.31 (6H, s), 1.03 (9H, s), 1.04 (9H, s), 7.02−7.05 (1H, m), 7.22 (1H, dd, J = 8.79 Hz, J = 2.33 Hz), 7.27−7.30 (1H, m), 7.36 (1H, dd, J = 11.64 Hz, J = 2.32 Hz), 7.56 (1H, d, J = 0.32 Hz), 7.84 (1H, d, J = 8.79 Hz), 8.04 (1H,d, J = 1.81 Hz), 8.10 (1H, s); MS (EI) *m/z* 507.4 $(M\bullet)^+$. Anal. ($C_{29}H_{38}FNO_2Si_2$) C, H: calcd, 68.59; found, 67.84.

7-[[*tert*-Butyl(dimethyl)silyl]oxy]-3-(4-[[*tert*-butyl(dimethyl)silyl]oxy]-3-fluorophenyl)-1-naphthaldehyde (143). To a solution of **142** (7.46 g, 14.69 mmol) in toluene (150 mL) at −78 °C was added DIBAL (14.7 mL of a 1 N solution, 14.7 mmol). The solution was allowed to stir for 1 h at −78 °C and then allowed to warm to room temperature slowly overnight. Methanol (5 mL) and water (5 mL) were added and the mixture was stirred for 30 min. The resulting suspension was filtered and the solid was washed well with ethyl acetate. The combined filtrates were washed with water and with brine and dried over sodium sulfate, the solvent was evaporated, and the product was purified on silica (1−2% ethyl acetate/hexanes) to yield the product as a yellow solid: mp 105−107 °C; ^{1}H NMR ($CDCl_3$) δ 0.24 (3H, s), 0.25 (3H, s), 0.34 (6H, s), 1.04 ((9H, s), 1.05 (9H, s), 7.01−7.06 (1H, m), 7.20 (H, dd, J = 8.79 Hz, J = 2.46 Hz), 7.34−7.37 (1H, m), 7.43 (1H, dd, J = 11.77 Hz, J = 2.20 Hz), 7.84 (1H, d, J = 8.93 Hz), 8.12 (1H, dd, J = 7.50 Hz, J = 1.81 Hz), 8.72 (1H, d, J = 2.33 Hz), 10.39 (1H, s); MS (EI) *m/z* 510.26 $(M^\bullet)^+$. Anal. ($C_{29}H_{39}FO_3Si_2$) C, H.

3-(3-Fluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthaldehyde (52). The title compound was prepared by reacting **143** (0.34 g, 0.67 mmol) with TBAF, according to method G, to yield 0.12 g (64%) of a yellow solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 7.07−7.11 (1H, m), 7.20 (1H, dd, J = 8.92 Hz, J = 2.46 Hz), 7.54−7.56 (1H, m), 7.72 (1H, dd, J = 12.80, J = 2.20 Hz), 7.97 (1H, d, J = = 9.06 Hz), 8.43−8.44 (1H, m), 8.54 (H, d, J = 2.46 Hz), 10.07 (1H, bs), 10.22 (1H, bs), 10.34 (1H, s); MS (ESI) *m/z* 281 $(M - H^+)^-$. Anal. ($C_{17}H_{11}FO_3 \cdot 0.1H_2O$) C, H.

6-(3-Fluoro-4-hydroxyphenyl)-8-vinyl-2-naphthol (53). To a suspension of methyltriphenylphosphonium bromide (2.1 g, 5.88 mmol) in THF (30 mL) at 0 °C was added *n*-butyllithium (2.35 mL of 2.5 N, 5.88 mmol). The mixture was stirred for 15 min at 0 °C. A solution of **143** (1.50 g, 2.94 mmol) in THF (15 mL) was added and stirred for 30 min at 0 °C. Water (5 mL) was added and the mixture was stirred for 10 min. The reaction was diluted with 100 mL of ethyl acetate and washed with 100 mL of 1 N HCl. The organic layer was concentrated and treated with TBAF in THF, according to method G, to yield 0.33 g (66%) of a tan solid: mp 132−136 °C; ^{1}H NMR (DMSO-d_6) δ 5.50 (1H, dd, J = 11.00 Hz, J = 1.96 Hz), 5.93−5.98 (1H, m), 7.03−7.07 (1H, m), 7.12 (1H, dd, J = 8.86 Hz, J = 2.26 Hz), 7.33−7.40 (2H, m), 7.45−7.47 (1H, m), 7.62 (1H, dd, J = 12.94 Hz, J = 2.20 Hz), 7.82−7.85 (2H, m), 8.00 (1H, d, J = 1.43 Hz), 9.93 (1H, s), 10.20 (1H, s); MS (ESI) *m/z* 279 $(M - H^+)^-$. Anal. ($C_{18}H_{13}FO_2 \cdot 0.20H_2O$) C, H.

8-Ethyl-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol (54). A mixture of **53** (0.16 g, 0.57 mmol) and 10% Pd/C (60 mg) in ethyl acetate (20 mL) was stirred under a balloon of hydrogen for 4 h. The mixture was filtered through Celite and the solvent evaporated. Purification by silica column (25% ethyl acetate/hexanes) yielded 0.13 g (71%) of the desired product as a white solid: mp 126−128 °C; ^{1}H NMR (DMSO-d_6) δ 1.33 (3H, t, J = 7.43 Hz), 2.99 (2H, q, J = 7.43 Hz), 7.02−7.09 (2H, m), 7.24 (1H, d, J = 2.18 Hz), 7.41 (1H, dd, J = 8.40 Hz, J = 1.60 Hz), 7.53−7.57 (2H, m), 7.80 (1H, d, J = 8.97 Hz), 7.86 (H, d, J = 1.40 Hz), 9.74 (1H, s), 9.89 (1H, s); MS (ESI) *m/z* 283; MS (ESI) *m/z* 281 $(M - H^+)^-$; HRMS (ESI−FT, $[M + H]^+$) calcd for $C_{18}H_{15}FO_2 + H^+$ 283.11288, found 283.11253. Anal. ($C_{18}H_{15}FO_2 \cdot 0.1H_2O$) C, H.

8-Ethynyl-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol (55). To a solution of CBr_4 (3.89 g, 11.7 mmol) in dichloromethane (30 mL) at 0 °C were added **143** (1.50 g, 2.94 mmol), zinc dust (0.76 g, 11.7 mmol), and triphenylphosphine (3.06 g, 11.7 mmol). The mixture was stirred at room temperature for 3 h and then filtered through silica. The silica was washed with dichloromethane, and the combined filtrates were concentrated and purified on silica (1.5% ethyl acetate−hexanes) to yield the intermediate **144** as a yellow oil.

To a solution of **144** (1.85 g, 2.77 mmol) in THF (25 mL) at −78 °C was slowly added *n*-butyllithium (4.4 mL of 2.5 N, 11.1 mmol). The resulting solution was stirred at −78 °C for 30 min and then allowed to warm to room temperature. Water (5 mL) was added, and the mixture was stirred at room

temperature for 3 h. TLC analysis indicated a mixture of products with one or both silyl groups removed. The reaction was poured into 150 mL of water. The resulting mixture was made slightly acidic and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with water and with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The resulting oil was treated with TBAF in THF according to method G to yield 0.61 g (86%) of the title compound as a white solid: mp 140−141 °C; ^{1}H NMR (DMSO-d_6) δ 4.60 (1H, s), 7.02−7.07 (1H, m), 7.15 (1H, dd, J = 8.86 Hz, J = 2.40 Hz), 7.43−7.45 (1H, m), 7.50 (1H, d, J = 2.46 Hz), 7.60 (1H, dd, J = 12.82 Hz, J = 2.32 Hz), 7.88 (1H, d, J = 8.79 Hz), 7.90 (1H, d, J = 1.94 Hz), 8.12 (1H, d, J = 1.55 Hz), 9.99 (1H, s), 10.06 (1H, s); MS (ESI) *m/z* 279 (M + H^+)$^+$; MS (ESI) *m/z* 277 (M − H^+)$^-$. Anal. ($C_{18}H_{11}FO_2$·1.0H_2O) C, H.

6-(3-Fluoro-4-hydroxyphenyl)-8-prop-1-ynyl-2-naphthol (56). Treatment of **55** (0.38 g, 1.36 mmol) with TBDMSCl (0.52 g, 3.4 mmol), according to the procedure used to prepare **101**, afforded 0.53 g (77%) of **145** as a yellow oil. To a solution of **145** (0.53 g, 1.05 mmol) in THF (20 mL) at −78 °C was added *n*-butyllithium (0.8 mL of 2.5 N, 2.1 mmol). The resulting solution was allowed to stir at −78 °C for 30 min. Iodomethane (2 mL, filtered through basic alumina) was added, and the reaction was allowed to warm to room temperature overnight. The solvent was removed by evaporation (in order to remove excess iodomethane) and the resulting oil was treated with TBAF in THF, according to method G, to yield 0.30 g (98%) of a yellow solid: mp 83−86 °C; ^{1}H NMR (DMSO-d_6) δ 2.22 (3H, s), 7.01−7.06 (1H, m), 7.12 (1H, dd, J = 8.80 Hz, J = 2.46 Hz), 7.42 (1H, dd, J = 8.34 Hz, J = 1.62 Hz), 7.50 (1H, d, J = 2.33 Hz), 7.58 (1H, dd, J = 12.93 Hz, J = 2.20 Hz), 7.79 (1H, d, J = 1.82 Hz), 7.84 (1H, d, J = 8.80 Hz), 8.02 (1H, d, J = 1.42 Hz), 9.96 (2H s); MS (ESI) *m/z* 293 (M + H^+)$^+$; MS (ESI) *m/z* 291 (M − H)$^-$.

3-(2-Fluoro-4-methoxyphenyl)-7-methoxy-1-naphthonitrile (146). A mixture of **139** (0.73 g, 2.79 mmol), bis-(pinacolato)diboron (1.06 g, 4.18 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.23 g, 0.28 mmol), and potassium acetate (0.55 g, 5.6 mmol) in DMF (15 mL) was stirred at 85 °C for 2 h. The mixture was cooled to room temperature; 2-fluoro-4-methoxyphenyl trifluoromethanesulfonate (1.52 g, 5.6 mmol, synthesized as described previously), sodium carbonate (2.8 mL of 2 N aqueous solution), and an additional 0.23 g of Pd(II) were added; and the mixture was heated to 85 °C for 6 h. The reaction was cooled to room temperature, dissolved in 100 mL of water, and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water, dried over sodium sulfate, and concentrated, and the product was purified on silica to yield 0.60 g (70%) a white solid: mp 144−146 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (3H, s), 4.01 (3H, s), 6.77 (1H, dd, J = 12.53 Hz, J = 2.47 Hz), 6.83 (1H, dd, J = 8.60 Hz, J = 2.69 Hz), 7.27 (1H, dd, J = 8.99 Hz, J = 2.43 Hz), 7.39−7.45 (1H, m), 7.47 (1H, d, J = 2.36), 7.84 (1H, d, J = 9.02 Hz), 8.05−8.06 (1H, m), 8.11 (1H, s); MS (EI) *m/z* 307 ($M^\bullet$)$^+$. Anal. ($C_{19}H_{14}FNO_2$) C, H, N.

3-(2,5-Difluoro-4-methoxyphenyl)-7-methoxy-1-naphthonitrile (147). The title compound was prepared by reacting **139** (0.67 g, 2.56 mmol) with 1-bromo-2,5-difluoro-4-methoxybenzene as described for **146** to yield 0.55 g (66%) of a white solid: mp 190−193 °C; ^{1}H NMR ($CDCl_3$) δ 3.95 (3H, s), 4.02 (3H, s), 6.84 (1H, dd, J = 11.68 Hz, 7.15 Hz), 7.20−7.30 (2H, m), 8.75 (1H, d, J = 2.36 Hz), 7.85 (1H, d, J = 9.02 Hz), 8.03−8.05 (1H, m), 8.10 (1H, s); MS (EI) *m/z* 325 ($M^\cdot$)$^+$. Anal. ($C_{19}H_{13}F_2NO_2$) C, H, N.

3-(2,6-Difluoro-4-methoxyphenyl)-7-methoxy-1-naphthonitrile (148). The title compound was prepared by reacting **139** (0.51 g, 1.94 mmol) with commercially available 2-bromo-1,3-difluoro-5-methoxybenzene as described for **146** to yield 0.44 g (74%) of a white solid: mp 203−208 °C; ^{1}H NMR ($CDCl_3$) δ 3.86 (3H, s), 4.02 (3H, s), 6.58−6.63 (2H, m), 7.26−7.30 (1H, m), 7.48 (1H, d, J = 2.35 Hz), 8.78 (1H, d, J = 9.02 Hz), 7.96 (1H, d, J = 1.38 Hz), 8.07 (1H, s); MS (EI) *m/z* 325 ($M^\bullet$)$^+$. Anal. ($C_{19}H_{13}F_2NO_2$) C, H, N.

3-(2-Fluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile (57). Treatment of **146** (0.55 g, 1.80 mmol) with pyridinium HCl according to method D yielded 0.35 g (67%) of a white solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 6.70 (1H, dd, J = 12.83 Hz, J = 2.29 Hz), 6.75 (1H, d, J = 8.40 Hz, J = 2.29 Hz), 7.25 (1H, dd, J = 8.86 Hz, J = 2.29 Hz), 7.36 (1H, d, J = 2.14 Hz), 7.46−7.50 (1H, m), 8.00 (1H, d, J = 9.01 Hz), 10.17 (1H, bs), 10.44 (1H, bs); MS (ESI) *m/z* 278 (M − H)$^-$. Anal. ($C_{17}H_{10}FNO_2$·0.2H_2O) C, H, N.

3-(2,5-Difluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile (58). Treatment of **147** (0.48 g, 1.48 mmol) with BBr_3 according to method C yielded 0.18 g (41%) of a white solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 6.90 (1H, dd, J = 11.83 Hz, J = 7.41 Hz), 7.26 (1H, dd, J = 8.93 Hz, J = 2.21 Hz), 7.37 (1H, d, J = 1.99 Hz), 7.55 (1Hk dd, J = 11.76 Hz, J = 7.63 Hz), 8.01 (1H, d, J = 8.85 Hz),l 8.16 (1H, s), 8.30 (1H, s), 10.57 (2H, bs); MS (ESI) *m/z* 296 (M − H)$^-$. Anal. ($C_{17}H_9F_2NO_2$·0.25H_2O) C, H, N.

3-(2,6-Difluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile (59). Treatment of **148** (0.32 g, 0.98 mmol) with BBr_3 according to method C yielded 0.15 g (51%) of a white solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 6.59−6.64 (2H, m), 7.27 (1H, dd, J = 8.85 Hz, J = 2.29 Hz), 7.39 (1H, d, J = 2.13 Hz), 8.01 (1H, d J = 9.01 Hz), 8.04 (1H, s), 8.19 (1H, s), 10.59 (1H, bs); MS (ESI) *m/z* 296 (M − H)$^-$. Anal. ($C_{17}H_9F_2NO_2$·0.25H_2O) C, H, N.

3-(3,5-Difluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile (60). 4-Bromo-2,6-difluorophenol (10.5 g, 50.4 mmol) was reacted with TBDMS−Cl (9.88 g, 150.7 mmol) according to the procedure used to prepare **101**, yielding 14.6 g (90%) of *tert*-butyl(4-bromo-2,6-difluorophenyloxy)-dimethylsilane a clear colorless, oil: ^{1}H NMR ($CDCl_3$) δ 0.17 (6H, s), 0.99 (9H, s), 7.02 (H, d, J = 7.13 Hz). This material (12.98 g, 40.19 mmol) was treated with *n*-butyllithium (27.6 mL of 1.6 N solution, 44.2 mmol) followed by triisopropyl borate (37.8 g, 200 mmol) according to the procedure used prepare **101** to afford 4.38 g (38%) of 3,5-difluoro-4-*tert*-butyldimethylsilyoxyboronic acid as a white solid: ^{1}H NMR (DMSO-d_6) δ 0.25 (6H, s), 1.06 (9H, s), 7.54 (2H, d, J = 7.93 Hz).

The title compound was prepared by reacting **133** (0.124 g, 0.50 mmol) with 3,5-difluoro-4-*tert*-butyldimethylsilyloxyphenylboronic acid (0.17 g, 0.59 mmol, prepared above) according to method A to yield 0.090 g (61%) of a yellow solid. An analytical sample was prepared by preparative reverse phase HPLC to produce a light yellow solid: mp 300−304 °C (dec); ^{1}H NMR (DMSO-d_6) δ 7.27 (1H, dd, J = 2.26 Hz, J = 8.88 Hz), 7.36 (1H, d, J = 2.12 Hz), 7.63−7.66 (2H, m), 8.00 (1H, d, J = 8.95 Hz), 8.43 (1H, d, J = 1.77 Hz), 8.52 (1H, s), 10.44 (1H, s), 10.54 (1H, s); MS (ESI) *m/z* 296 (M − H)$^-$. Anal. ($C_{17}H_9F_2NO_2$·0.3H_2O) C, H, N.

7-Hydroxy-3-methoxy-1-naphthonitrile (149). The title compound was prepared by reacting **133** (4.04 g, 16.3 mmol) with sodium methoxide in the presence of copper(I) bromide according to method F to yield 2.17 g (67%) of a yellow solid: mp 185−188 °C; ^{1}H NMR (DMSO-d_6) δ 3.88 (3H, s), 7.21 (1H, dd, J = 8.87 Hz, J = 2.39 Hz), 7.31 (1H, d, J = 2.34 Hz), 7.68 (1H, d, J = 2.52 Hz), 7.77 (1H, d, J = 0.60 Hz), 7.86 (1H, d, J = 8.96 Hz), 10.16 (1H, s); MS (ESI) *m/z* 198 (M − H)$^-$. Anal. ($C_{12}H_9NO_2$) C, H, N.

8-Cyano-6-methoxy-2-naphthyl Trifluoromethanesulfonate (150). The title compound was prepared by reacting **149** (2.07 g, 10.4 mmol) with trifluoromethanesulfonic anhydride according to the procedure used to prepare **74** to yield 3.25 g (94%) of a light yellow solid: mp 91−94 °C; ^{1}H NMR ($CDCl_3$) δ 3.97 (3H, s), 7.42 (1H, d, J = 2.40 Hz), 7.49 (1H, dd, J = 9.05 Hz, J = 2.46 Hz), 7.68 (1H, d, J = 2.47 Hz), 7.90 (1H, d, J = 9.04 Hz), 8.03 (1H, d, J = 2.39 Hz); MS (ESI) *m/z* 332 (M + H^+)$^+$. Anal. ($C_{13}H_8F_3NO_4S$) C, H, N.

3-Methoxy-7-(4-methoxyphenyl)-1-naphthonitrile (151). Treatment of **150** (0.71 g, 2.14 mmol) with 4-methoxyphenylboronic acid according to method A yielded 0.50 g (81%) a white

solid: mp 163−165 °C; ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 3.96 (3H, s), 7.01−7.06 (2H, m), 7.39 (1H, d, J = 2.40 Hz), 7.59 (1H, d, J = 2.50 Hz), 7.65−7.70 (2H, m), 7.81 (1H, dd, J = 8.59 Hz, J = 1.64 Hz), 7.85 (1H, d J = 8.51 Hz), 8.26 (1H, s). Anal. ($C_{19}H_{15}NO_2$) C, H, N.

7-(3-Fluoro-4-methoxyphenyl)-3-methoxy-1-naphthonitrile (152). Treatment of **150** (0.71 g, 2.14 mmol) with 3-fluoro-4-methoxyphenylboronic acid[7,8] according to method A afforded 0.48 g (73%) a white solid: mp 204−207 °C; ^{1}H NMR ($CDCl_3$) δ 3.97 (6H, s), 7.06−7.12 (1H, m), 7.40 (1H, d, J = 2.44 Hz), 7.45−7.50 (2H, m), 7.60 (1H, d, J = 2.55 Hz), 7.77 (1H, dd, J = 8.58 Hz, J = 1.80 Hz), 7.76 (1H, d, J = 9.57 Hz), 8.24−8.25 (1H, m). Anal. ($C_{19}H_{14}FNO_2$) C, H, N.

3-Hydroxy-7-(4-hydroxyphenyl)-1-naphthonitrile (61). Compound **151** (0.42 g, 1.45 mmol) was reacted with pyridinium HCl according to method D to yield 0.30 g (80%) of a light yellow solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 6.90−6.94 (2H, m), 7.53 (1H, d, J = 2.27 Hz), 7.60−7.64 (2H, m), 7.68 (1H, d, J = 2.39 Hz), 7.85 (1H, dd, J = 8.67 Hz, J = 1.72 Hz), 7.95 (1H, d, J = 8.68 Hz), 8.02 (1H, d, J = 0.68 Hz), 9.69 (1H, s), 10.43 (1H, s); MS (ESI) *m/z* 260 (M − H)$^-$. Anal. ($C_{17}H_{11}NO_2$) C, H, N.

7-(3-Fluoro-4-hydroxyphenyl)-3-hydroxy-1-naphthonitrile (62). Compound **152** (0.34 g, 1.11 mmol) was treated with pyridine HCl according to method D to afford 0.27 g (88%) of a light yellow solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 7.07−7.13 (1H, m), 7.45 (1H, dd, J = 8.38 Hz, J = 1.64 Hz), 7.54 (1H, d, J = 2.26 Hz), 7.61 (1H, dd, J = 12.70 Hz, J = 2.20 Hz), 7.69 (1H, d, J = 2.39 Hz), 7.87 (1H, dd, J = 8.68 Hz, J = 1.73 Hz), 7.96 (1H, d, J = 8.70 Hz), 8.04 (1H, d, J = 0.63 Hz), 10.26 (2H, bs); MS (ESI) *m/z* 278 (M − H)$^-$. Anal. ($C_{17}H_{10}FNO_2\cdot 0.3H_2O$) C, H, N.

4-Bromo-7-(3-fluoro-4-hydroxyphenyl)-3-hydroxy-1-naphthonitrile (63). A solution of **62** (0.82 g, 2.94 mmol) and NBS (0.55 g, 3.1 mmol) in THF (30 mL) was stirred overnight at room temperature, according to the procedure used to prepare **16**, to yield 0.82 g (78%) of a white solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 7.110−7.14 (1H, m), 7.48 (1H, d, J = 7.94 Hz), 7.64 (1H, d, J = 12.30 Hz), 7.79 (1H, s), 8.04−8.09 (2H, m), 8.21 (1H, d J = 8.84 Hz), 10.17 (1H, s), 11.32 (1H, s); MS (ESI) *m/z* 356 (M − H)$^-$. Anal. ($C_{17}H_9BrFNO_2\cdot 0.1H_2O$) C, H, N.

7-(3-Fluoro-4-hydroxyphenyl)-3-hydroxy-4-methyl-1-naphthonitrile (65). A solution of **63** (0.22 g, 0.61 mmol), tetramethyltin (0.16 g, 0.9 mmol), and dichlorobis(tri-*o*-tolylphosphine)palladium(II) (0.048 g, 0.006 mmol) in DMF (3 mL) was stirred overnight at 80 °C. The reaction was cooled to room temperature, poured into 50 mL of 1 N NH_4Cl, and extracted with ethyl acetate (2 × 75 mL). The combined organic layers were washed with water, dried over sodium sulfate, filtered, concentrated, and the product was purified on silica (30% ethyl acetate/hexanes) to yield 0.10 g (56%) of a white solid: mp >250 °C; ^{1}H NMR (acetone-d_6) δ 2.63 (3H, s), 7.15−7.19 (1H, m), 7.50−7.53 (1H, m), 7.60 (1H, dd, J = 12.43 Hz, J = 2.18 Hz), 7.72 (1H, s), 7.94 (1H, dd, J = 8.84 Hz, J = 1.92 Hz), 8.17 (1H, dd, J = 8.97 Hz, J = 0.51 Hz), 8.21 (1H, d, J = 1.54 Hz), 8.95 (2H, bs); MS (ESI) *m/z* 292 (M − H)$^-$. Anal. ($C_{18}H_{12}FNO_2\cdot 0.1H_2O$) C, H, N.

4-Chloro-3-hydroxy-7-(4-hydroxyphenyl)-1-naphthonitrile (66). Treatment of **61** (0.24 g, 0.92 mmol) with NCS (0.15 g, 1.10 mmol) in THF (10 mL) at room temperature according to method E yielded 0.15 g (56%) of a yellow solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 6.94 (2H, d, J = 8.59 Hz), 7.77 (2H, d, J = 8.61 Hz), 7.83 (1H, s), 8.04 (1H, dd, J = 8.89 Hz, J = 1.70 Hz), 8.08 (1H, d, J = 1.16 Hz), 8.22 (1H, d, J = 8.87 Hz), 9.75 (1H, bs), 11.24 (1H, bs); MS (ESI) *m/z* 294 (M − H)$^-$. Anal. ($C_{17}H_{10}ClNO_2\cdot 0.3H_2O$) C, H, N.

4-Chloro-7-(3-fluoro-4-hydroxyphenyl)-3-hydroxy-1-naphthonitrile (67). Reacting **62** (0.13 g, 0.47 mmol) with NCS (0.079 g, 0.6 mmol) in THF (10 mL) at room temperature according to method E produced 0.063 g (43%) of a white solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 7.10−7.12 (1H, m), 7.48 (1H, dd, J = 8.39 hz, J = 1.60 Hz), 7.64 (1H, dd, J = 12.62 Hz, J = 1.98 Hz), 7.83 (1H, s), 8.05 (1H, dd, J = 8.97 Hz, J = 1.41 Hz), 8.09 (1H, s), 8.21 (1H, d, J = 8.97 Hz), 10.18 (1H, bs), 11.25 (1H, bs); MS (ESI) *m/z* 312 (M − H)$^-$. Anal. ($C_{17}H_9ClFNO_2\cdot 0.1H_2O$) C, H, N.

4-Bromo-7-(3-fluoro-4-methoxyphenyl)-3-methoxy-1-naphthonitrile (153). A solution of **152** (0.98 g, 3.19 mmol) and bromine (0.56 g, 3.5 mmol) in acetic acid (10 mL) was heated to 100 °C overnight in a pressure flask. The flask was cooled to room temperature and the reaction was poured into 300 mL of water. The resulting dark yellow solid was collected by filtration and triturated with THF to yield 0.83 g (69%) of the product as a yellow solid: mp 192−194 °C; ^{1}H NMR ($CDCl_3$) δ 3.97 (3H, s), 4.07 (3H, s), 7.07−7.12 (1H, m), 7.46−7.50 (2H, m), 7.64 (1H, s), 7.87 (1H, dd, J = 8.92 Hz, J = 1.81 Hz), 8.26 (1H, d, J = 1.43 Hz), 8.35 (1H, d, J = 8.92 Hz); MS (EI) *m/z* 385 (M•)$^+$. Anal. ($C_{19}H_{13}BrFNO_2$) C, H, N.

6-(3-Fluoro-4-methoxyphenyl)-2-methoxynaphthalene-1,4-dicarbonitrile (154). A mixture of **153** (0.48 g, 1.24 mmol), $Zn(CN)_2$ (0.10 g, 0.87 mmol), tris(dibenzylideneacetone-)dipalladium(0) (0.11 g, 0.12 mmol), zinc dust (0.039 g, 0.62 mmol), and dppf (0.069 g, 0.12 mmol) in DMF (15 mL) was stirred for 3 h at 120 °C. The reaction was cooled to room temperature and poured into 200 mL of 1 N NaOH. The resulting dark gray solid was collected by filtration. The crude product was filtered through a silica pad (50%THF/hexanes) and the filtrate was concentrated. The product was further purified by trituration to yield 0.33 g (80%) of a yellow solid: mp >220 °C; ^{1}H NMR ($CDCl_3$) δ 3.98 (3H, s), 4.14 (3H, s), 7.09−7.13 (1H, m), 7.46−7.49 (2H, m), 7.69 (1H, s), 7.98 (1H, dd, J = 8.73 Hz, J = 1.36 Hz), 8.24 (1H, d, J = 8.79 Hz), 8.30 (1H, s); MS (EI) *m/z* 332 (M•)$^+$. Anal. ($C_{20}H_{13}FN_2O_2$) calcd, C: 72.28 N: 8.43; found, C: 70.26 N: 6.66.

6-(3-Fluoro-4-hydroxyphenyl)-2-hydroxynaphthalene-1,4-dicarbonitrile (64). Treatment of **154** (0.10 g, 0.31 mmol) with pyridinium HCl according to method D yielded 0.070 g (74%) of a yellow solid: ^{1}H NMR (DMSO-d_6) δ 7.10−7.14 (1H, m), 7.47−7.49 (1H, m), 7.65 (1H, dd, J = 12.60 Hz, J = 2.21 Hz), 7.81 (1H, s), 8.03 (1H, dd, J = 7.74 Hz, J = 1.76 Hz), 8.13−8.15 (2H, m), 10.19 (1H, s), 12.41 (1H, s); MS (ESI) *m/z* 303 (M − H)$^-$. Anal. ($C_{18}H_9FN_2O_2$) C, H, N: calcd, C: 71.05 N: 9.21; found, C: 66.20 N: 8.00.

3-[[*tert*-Butyl(dimethyl)silyl]oxy]-7-(4-[[*tert*-butyl(dimethyl)silyl]oxy]-3-fluorophenyl)-1-naphthonitrile (155). The title compound was prepared by reacting **62** (2.28 g, 8.17 mmol) with TBDMSCl (4.9 g, 32.7 mmol) according to the procedure used to prepared compound **101** to yield 2.44 g (59%) of a white solid: mp 112−114 °C; ^{1}H NMR ($CDCl_3$) δ 0.24 (3H, s), 0.25 (3H, s), 0.28 (6H, s), 1.03 (9H, s), 1.04 (9H, s), 7.00−7.05 (1H, m), 7.35−7.39 (1H, m), 7.41−7.46 (2H, m), 7.51 (1H,d, J = 2.38 Hz), 7.75 (1H, dd, J = 8.61 Hz, J = 1.66 Hz), 7.81 (1H, d, J = 8.61 Hz), 8.25 (1H, s); MS (EI) *m/z* 507.2 (M•)$^+$. Anal. ($C_{29}H_{38}FNO_2Si_2$) C, H, N: calcd, 68.59; found, 68.00.

3-[[*tert*-Butyl(dimethyl)silyl]oxy]-7-(4-[[*tert*-butyl(dimethyl)silyl]oxy]-3-fluorophenyl)-1-naphthaldehyde (156). The title compound was prepared by reacting **155** (2.27 g, 4.47 mmol) with DIBAL (4.9 mL of 1 N solution, 4.9 mmol) according to the procedure used to prepare compound **143** to yield 1.13 g (49%) of a yellow solid: mp 67−68 °C; ^{1}H NMR ($CDCl_3$) δ 0.24 (3H, s), 0.25 (3H, s), 0.30 (6H, s), 1.04 (9H, s), 1.05 (9H, s), 6.99−7.04 (1H, m), 7.38−7.41 (1H, m), 7.43−7.48 (2H, m), 7.58 (1H, d, J = 2.52 Hz), 7.74 (1H, dd, J = 8.59 Hz, J = 1.78 Hz), 7.81 (1H, d, J = 8.60 Hz), 9.32 (1H, d, J = 1.20 Hz), 10.36 (1H, s). Anal. ($C_{29}H_{39}FO_3Si_2$) C, H: calcd, 68.19; found, C: 67.65.

7-(3-Fluoro-4-hydroxyphenyl)-3-hydroxy-1-naphthaldehyde (70). The title compound was prepared by reacting **156** (0.21 g, 0.41 mmol) with TBAF in THF according to method G to yield 0.080 g (68%) of a yellow solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 7.07−7.11 (1H, m), 7.43−7.46 (1H, m), 7.50 (1H, d, J = 2.46 Hz), 7.58 (1H, dd, J = 12.81 Hz, J = 2.20 Hz), 7.74 (1H, d, J = 2.58 Hz), 7.82 (1H, dd, J = 8.61 Hz, J = 1.88 Hz), 7.91 (1H, d, J = 8.67 Hz), 9.17−9.18 (1H, m), 10.03 (1H, s), 10.24 (1H, s), 10.45 (1H, s); MS (ESI) *m/z* 281 (M − H)$^-$. Anal. ($C_{17}H_{11}FO_3\cdot 0.5H_2O$) C, H.

6-(3-Fluoro-4-hydroxyphenyl)-4-vinyl-2-naphthol (71). The title compound was prepared by reacting **156** (1.74 g, 3.41 mmol) with methyl triphenylphosphonium bromide (2.08 g, 5.8 mmol) according to the procedure for **53** to yield 0.68 g (71%) of a yellow solid: ^{1}H NMR (DMSO-d_6) δ 5.48 (1H, dd, J = 10.92 Hz, J = 1.43 Hz), 5.82 (1H, dd, J = 17.22 Hz, J = 1.50 Hz), 7.02−7.07 9H, m), 7.12 (1H, d, J = 2.34 Hz), 7.26 (1H, d, J = 1.56 Hz), 7.43−7.46 (1, m), 7.62 (1H, dd, J = 12.87 Hz, J = 2.20 Hz), 7.66−7.70 (2H, m), 7.75 (1H, d, J = 8.57 Hz), 8.17 (1H, s), 9.78 (1H, s), 9.93 (1H, s); MS (ESI) *m/z* 279 (M − H)$^-$. Anal. ($C_{18}H_{13}FO_2$·0.25H_2O) C, H.

4-Ethyl-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol (72). The title compound was prepared by reacting **71** (0.57 g, 2.03 mmol) with hydrogen and Pd/C according to the procedure for **54** to yield 0.42 g (73%) of a white solid: mp 126−127 °C; ^{1}H NMR (DMSO-d_6) δ 1.31 (2H, t, J = 7.54 Hz), 3.08 (3H, q, J = 7.41 hz), 6.96−6.98 (2H, m), 7.03−7.08 (1H, m), 7.41−7.43 (1H, m), 7.58 (1H, dd, J = 12.87 Hz, J = 2.20 Hz), 7.64 (1H, dd, J = 8.58 Hz, J = 1.82 Hz), 7.72 (1H, d, J = 8.58 Hz), 8.04 (1H, d, J = 1.42 Hz), 9.63 (1H, s), 9.92 (1H, s); MS (ESI) *m/z* 283 (M − H)$^-$; MS (ESI) *m/z* 281. Anal. ($C_{18}H_{15}FO_2$·0.1H_2O) C, H.

4-Ethynyl-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol (68). 3-(*tert*-Butyldimethylsilanyloxy)-7-[4-(*tert*-butyldimethylsilanyloxy)-3-fluorophenyl]-1-(2,2-dibromovinyl)naphthalene. A mixture of **156** (0.51 g, 1.00 mmol) CBr_4, zinc dust, and triphenylphosphine was reacted according to the procedure used to prepare **55** to yield 0.61 g (92%) of the intermediate 3-(*tert*-butyldimethylsilanyloxy)-7-[4-(*tert*-butyldimethylsilanyloxy)-3-fluorophenyl]-1-(2,2-dibromovinyl)naphthalene as a white solid.

Treatment of this 2,2-dibromovinyl intermediate (0.40 g, 0.61 mmol) with *n*-butyllithium followed by deprotection as described in the preparation of **55** afforded 0.060 g (35%) of the desired product as a tan solid: mp 83−85 °C; ^{1}H NMR (DMSO-d_6) δ 4.63 (1H, s), 7.06−7.10 (1H, m), 7.24 (1H, d, J = 2.33 Hz), 7.30 (1H, d, J = 2.32 Hz), 7.38−7.40 (1H, m), 7.52 (1H, dd, J = 12.67 Hz, J = 2.20 Hz), 7.74 (1H, dd, J = 8.60 Hz, J = 0.88 Hz), 7.82 (1H, d, J = 8.53 Hz), 8.20 (1H, m), 10.01 (2H, s); MS (ESI) *m/z* 279 (M − H)$^-$; MS (ESI) *m/z* 277. Anal. ($C_{18}H_{11}FO_2$·0.75H_2O) C, H.

6-(3-Fluoro-4-hydroxyphenyl)-4-prop-1-ynyl-2-naphthol (69). Treatment of **68** (0.25 g, 0.915 mmol) with TBDMS−Cl according to the procedure used to prepare compound **101** yielded 0.40 g (83%) of **157** as a white solid. The title compound was prepared by reacting **157** (0.40 g, 0.79 mmol) with *n*-butyllithium according to the procedure used to prepare **56** to yield 0.16 g (69%) of a gray solid: mp 124−126 °C; ^{1}H NMR (DMSO-d_6) δ 2.23 (3H, s), 7.05−7.10 (1H, m), 7.14 (1H, d, J = 2.20 Hz), 7.19 (1H, d, J = 2.46 Hz), 7.38−7.41 (1H, m), 7.52 (1H, dd, J = 12.68 Hz, J = 2.20 hz), 7.71 (1H, dd, J = 8.53 Hz, J = 1.94 Hz), 7.78 (1H, d, J = 8.53 Hz), 8.20 (1H), 9.89 (1H, s), 9.99 (1H, s); MS (ESI) *m/z* 291 (M − H)$^-$. Anal. ($C_{19}H_{13}FO_2$·0.75H_2O) C, H.

Biological Assay Methods. Competitive Radioligand Binding Assay. This assay was performed as previously described.[30] Briefly, Human ERα and ERβ ligand binding domains were expressed in *Escherichia coli*, and a crude cell lysate of these cells was used in a solid-phase binding assay. The radioligand was [^{3}H]-17β-estradiol, a ligand known to bind equally well to ERα and ERβ.

Cell-Based Transcriptional Assay. Regulation of IGFBP-4 mRNA was monitored in SAOS-2 cells engineered with an adenovirus to express human ERβ as previously described.[31] Briefly, cells were treated for 24 h with test compound (typically 1μM) or 10 nM 17β-estradiol and mRNA levels measured by real-time quantitative RT-PCR.

Rat Uterotrophic Assay. This assay was performed as previously described.[31] Briefly, sexually immature rats (19 days old) were treated with **47** daily for 3 days and euthanized 24 h after the last dose. The vehicle was 50% DMSO/50% 1× Dulbecco's phosphate-buffered saline, and doses were administered subcutaneously in 0.2 mL. The doses given are expressed in milligram or microgram per rat per day, because the rats typically grow from 38 to 55 g during the course of the study. Thus the dose of 2 mg/rat translates into ∼36−53 mg/kg and the 17α-ethynyl-17β-estradiol dose of 0.06 μg/rat ranges between 1.1 and 1.6 μg/kg.

HLA-B27 Transgenic Rat Model. Assessment of **47** effects on intestinal endpoints was performed as previously described.[15] To assess the ability of **47** to prevent joint swelling, 8−10 week old male rats were used. These rats were treated with daily oral doses of **47** (10 mg/kg) in a vehicle of 2% Tween-80/0.5% methylcellulose for 46 days. Gross evaluation of joint swelling was scored as previously described.[15]

Lewis Rat Adjuvant-Induced Arthritis Model. This model was performed as previously described.[15] Briefly, male Lewis rats were injected intradermally with Freunds Complete Adjuvant at the base of the tail. After full joint inflammation developed (8 days after adjuvant injection), vehicle or **47** was administered in daily oral doses. Joint redness and swelling were evaluated daily, and after euthanasia, joint histology was evaluated (synovitis and Mankin scores). At necropsy, blood samples were collected and serum prepared. Haptoglobin concentrations were assessed using a commercially available kit (TriDelta Diagnostics), which measures the inherent peroxidase activity of hemoglobin that is preserved at low pH when haptoglobin is present. The assay was performed according to the manufacturer's directions, except that a kinetic (V_{max}) rather than endpoint measurement was used. Plates were read in a microplate reader at A_{595} (Molecular Devices).

Cell-Based Selectivity Assays. These assays were performed as previously described.[35]

SHBG Binding Assay. Human blood was collected in SST VACUTAINER tubes (Becton-Dickenson) and kept at room temperature for 30 min before centrifugation at 1000*g* for 10 min (4 °C). The serum was aliquoted and stored at −80 °C. Human serum was diluted with TG buffer (10 mM Tris and 10% glycerol, pH 7.4, at room temperature) 20−100-fold to achieve a total binding signal of about 3000 cpm. Seven hundred microliters of dextran-coated charcoal (1% charcoal, 0.05% dextran 69K in Tris/EDTA buffer, pH 7.4) was added to every 1000 μL of diluted serum, and the mixture was incubated on ice for 1 h, followed by centrifugation at 2000*g* for 20 min. The SHBG binding assay was performed with 100 μL of this supernatant solution, 25 μL [1,2-N-^{3}H]-5α-dihydrotestosterone ([^{3}H]DHT; final concentration = 8 nM), and 25 μL of various concentrations of **47**. Following overnight incubation at 4 °C, free and bound [^{3}H]DHT were separated by using 100 μL of 0.5% dextran-coated charcoal followed by centrifugation at 1000*g* for 5 min. Bound [^{3}H]DHT (150 μL) was counted in a Beckman LS6500 scintillation counter (Beckman Instruments, Inc).

Crystallography. Human ERβ LBD was cloned, expressed, and purified as previously described.[14,26] The ERβ complexes were concentrated to approximately 10 mg/mL in a buffer containing 0.2 M NaCl, 1 mM EDTA, 5 mM DTT, and 10 mM Tris-HC1 at pH 7.5 and mixed with a nuclear receptor box peptide Biotin-SGSHKLVQLLTTT-COOH (derived from steroid receptor coactivator-1)[36,37] at a molar ratio of 1.5:1 peptide to protein−ligand complex. Screening of crystallization conditions was performed at 18 °C using the hanging drop vapor diffusion method.[38] Crystals were grown from a drop containing a mixture of protein−ligand solution and reservoir solution of 20% PEG3350 (v/v), 0.2 M Mg formate, pH 5.9.

X-ray data were collected at 100 K using Quantum-4 CCD area detector at the Advanced Light Source (ALS, Berkeley, CA) and processed using DENZO and Scalepack.[39] Crystal structures were solved by molecular replacement using the program AMORE.[40] All complex structures were solved using ERβ complexed with genistein as a search model. This ERβ/genistein structure was in turn solved in-house by molecular replacement, using ERα complexed with E2 as a model[41] (pdb code 1A52), and was later found to be in good agreement with the published structure[17] (pdb code 1QKM). To avoid model bias, the ligand, the loop connecting H8−H9, the C and N terminal helices, and the coactivator peptide were omitted from the search models. Structures were refined using the program

Table 12. X-ray Data Collection and Refinement Statistics for Ligands **15** and **47**

	15	**47**
Data Collection		
space group	$P2_12_12_1$	
wavelength (Å)	1.10	
unit cell dimensions		
a (Å)	51.970	52.075
b (Å)	87.677	88.504
c (Å)	99.760	100.139
maximal resolution (Å)	2.7	2.03
observations	12673	30401
completeness (%)	96.1	98.5
R_{merge}[a]	0.081	0.073
mean I/σ (I)	17.38	18.21
reflections used	12278	29584
reflections in working set	11652	28130
reflections in test set	626	1454
highest resolution bin (Å)	2.8−2.7	2.10−2.03
completeness (%)	89.5	95.7
R_{merge}[a]	0.357	0.489
mean I/σ (I)	3.38	2.80
mosaicity (deg)	0.947	0.467
Refinement		
no. of molecules per asymmetric unit	2	2
protein atoms[b]	3546	3575
other atoms		
ligand[b]	38	42
coactivator peptide[b]	142	162
water	102	219
resolution range (Å)	15−2.2	15−2.0
R_{work}[c]	0.208	0.222
R_{free}[d]	0.271	0.281
rms bond length[e] (Å)	0.006	0.0067
rms bond angles[e] (deg)	1.033	1.094
mean *B*-factor (Å^2)		
complex	36.2	26.1
main-chain atoms	35.9	24.9
side-chain atoms	37.0	27.8
ligand	35.7	21.0
water	31.2	28.7
rms backbone ΔB (Å^2)[f]	1.00	1.15
%A, B, L (a, b, l, p)[g]	100	100

[a] $R_{merge} = \sum_n\sum_{hkl}|I_{hkl}{}^n - \langle I_{hkl}{}^n\rangle|/\sum_n\langle I_{hkl}{}^n\rangle$, where $I_{hkl}{}^n$ is the *n*th observation of reflection *hkl*, and $\langle I_{hkl}{}^n\rangle$ denotes an average of reflection *hkl* over *n* observations. [b] Per monomer unit. [c] Crystallographic *R*-factors were computed using $R_{work} = \sum_{hkl}|F_{hkl}{}^{obs} - F_{hkl}{}^{calc}|/\sum_{hkl}F_{hkl}{}^{obs}$. [d] R_{free} values were calculated in the same manner as R_{work}, except over approximately 4% of the data excluded from the refinement. [e] Root-mean-square deviation in bond length and bond angle distances from the Engh and Huber ideal values. [f] Root-mean-square deviation between *B*-factors for bonded main chain atoms. [g] Percentage of residues located in most favored (additional) regions of the Ramachandran plot as determined by PROCHECK.[44]

CNS.[42] The resulting difference electron density maps show clear electron density for the compounds, residues within the binding site, helix 12, and the coactivator peptide. Cysteine modifications and some flexible loop residues were not included in the models due to poor electron density. Table 12 gives the data collection and refinement details for all of the complexes studied. Atomic coordinates for ERβ complexed with compounds **15** and **47** have been deposited in the Protein Data Bank, with accession codes 1YY4 and 1YYE, respectively.

Computational Methods. Docking calculations were performed using the QXP software package.[43] The QXP Monte Carlo docking algorithm mcdock was used to generate potential binding modes in the active site. In general, 1000 Monte Carlo steps was sufficient for the poses and their energy scores to converge. Constrained residue flexibility was utilized to take subtle movements of the pocket into account when necessary. Visualization of X-ray structures and docking results was performed using the InsightII and Quanta software packages (Accelrys, Inc., San Diego, CA). Protein overlays were performed using the homology module of the InsightII software package. After performing a preliminary structural alignment based on all alpha-carbons, the superimpose_aln command was used to generate matches based on fitting only α-carbons closer than 2.00 Å. This ensured that conformational changes in highly flexible regions such as loops did not exert an undesired influence on the overlays.

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Supporting Information Available: Experimental, analytical, and spectroscopic data for compounds **9**−**14**, **25**−**30**, **32**−**37**, **77**, **78**, **80**, **82**, **84**, **95**, **98**, **100**, **102**−**105** and elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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