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ER_β Ligands. Part 1: The Discovery of ER_β Selective Ligands which Embrace the 4-Hydroxy-biphenyl Template

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Abstract—The synthesis and structure–activity relationships of a series of simple biphenyls is described. Optimization of the 4-hydroxy-biphenyl template led to compounds with ERβ selectivity on the order of 20–70-fold.

Introduction

The estrogen receptor (ER) mediates the activity of estrogens in a variety of organs, including those in the reproductive, cardiovascular, skeletal, immune, and central nervous systems. Estrogen-mediated events were originally thought to be regulated by only one estrogen receptor, a protein that was first cloned in the late 1980s.[1] However, in 1996, a second form of the ER receptor (ERβ) was unexpectedly discovered,[2,3] suggesting that some of the actions of estrogens might be mediated by this newly discovered form. Indeed, there has been much speculation about the possible therapeutic utility of an ERβ selective ligand.[4]

Both ERs share distinct domains associated with transactivation, DNA binding, and hormone binding. ERα and ERβ both have modest overall sequence identity, differing greatly at the N-terminal domains, but having sequence conservation among the DNA and ligand-binding domains.[5] Crystal structures of the ERα and ERβ binding pockets have been reported to have relatively invariant tertiary architecture.[6–8] This, as well as the size, shape, and plasticity of the receptor's component elements, may explain why ERs embrace a range of ligands containing a variety of structural motifs.[9] As previously reported,[10] many of the phytoestrogens, including genistein (**1**), were found to have modest selectivity for ERβ. This selectivity may be due to the two distinct differences in the amino acid contacting the ligand in the binding pocket: the leucine present at 384 in ERα is replaced by a methionine in ERβ (i.e., Met336), and the methionine at position 421 in ERα is replaced by an isoleucine in ERβ (i.e., Ile373).[8] Recently a number of groups have disclosed their attempts toward finding selective ERβ ligands within several classes of molecules (i.e., tetrahydrochrysenes,[11] diarylpropionitriles,[12] arylbenzthiophenes[13] and triazines[14]). With the exception of the diarylpropionitriles, which had selectivities up to 70-fold for ERβ, typical selectivities were on the order of 10–30-fold.

Though the clinical utility of ER ligands is well established (e.g., estrogen replacement therapy, contraception, breast cancer therapeutics), it is presently unknown whether these activities are exerted primarily via ERα or ERβ. However, recent work, using the ERα selective ligand propylpyrazole triol, suggests that many of the classical effects of estrogens are mediated via ERα.[15] Therefore, there is a pressing need for ERβ selective ligands to better define the biology and therapeutic utility of this newly discovered receptor.

The design and synthesis of nonsteroidal ligands having two phenols has been a common design strategy to obtain highly potent estrogens. The classical estradiol (**2**) pharmacophore was first described in 1950 as two hydroxyl groups separated by a hydrophobic spacer.[16] It is now known that the 3-OH group of the A-ring of estradiol (**2**) contributes an average of 1.9 kcal/mol to the binding free energy versus only 0.6 kcal/mol for the 17β-OH group.[16] Therefore, estradiol's B-, C- and D-ring

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orientations are strongly influenced by that of the A-ring, which itself must maintain a certain orientation to make key hydrogen bonding interactions. A variety of templates have been investigated as surrogates for the steroid backbone, including the simple biphenyl scaffold. Korach et al.[17] reported a limited study on polychlorinated 4-OH-biphenyls that can interact effectively with the estrogen receptor. More recently, Lesuisse et al.[18] reported a series of 4-hydroxy-4′-hydroxymethylbiphenyl derivatives (**3**), in which several analogues demonstrated excellent binding to the estrogen receptor. However, their investigation focused only on ERα, as well as predominately 2,6-disubstituted biphenyl derivatives. In Lesuisse's study, the hydroxymethyl group was conserved throughout their series as a mimic to the less essential 17β-OH group in the D-ring of estradiol.

As part of our search for potent and selective ERβ ligands, we decided to re-examine the potential use of the biphenyl template by preparing a series of analogues conserving the one crucial phenolic group that mimics the A-ring of **1** and **2**. The biphenyl is a typical drug-like scaffold found in 2.1% of reference drug molecules[19] and can be rapidly assembled and structure–activity relationships (SAR) quickly established if only one phenolic group is maintained within the biphenyl motif. Docking the simple unsubstituted 4-OH-biphenyl structure into the ligand-binding domain (Fig. 2) revealed how the B-ring is able to approach ERβMet336 more closely than the corresponding Leu384 residue in ERα. Thus, the ability of the 4-OH-biphenyl's B-ring to rotate relative to the A-ring could potentially induce some ERβ selectivity by allowing a closer approach and more favorable interaction with Met336. This is in contrast to estradiol's more rigid framework, whose B, C and D ring orientations are dictated by its A-ring as discussed above. Figure 3 clearly shows that the B-ring of 4-OH-biphenyl overlays well with that of genistein (**1**) and appears to have several opportunities to probe selectivity. An appealing feature of the 4-OH-biphenyl scaffold is its ability to present a variety of functional groups to the ligand-binding domain from different angles that would not be possible with the genistein scaffold. Therefore, one would expect that the 4-OH-biphenyl template may be able to mimic or even surpass the ERβ selectivity of genistein (**1**).

In our study we herein disclose the most thorough SAR investigation reported to date based on the biphenyl template with respect to both ERα and ERβ. This investigation led to over a dozen 4-OH-biphenyl derviatives

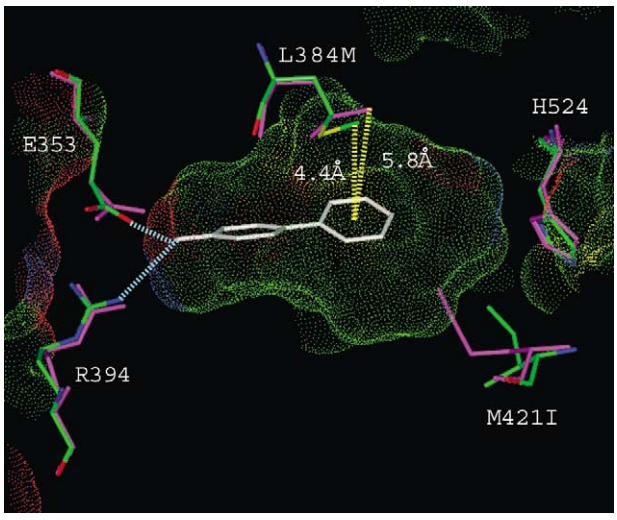


Figure 2. 4-Hydroxy-biphenyl (white), docked to the ERβ/genistein pocket (colored by atom type), and overlayed with ERα/diethylstilbestrol[7] (magenta). Only key residues, including a Connolly surface of the ERα binding site, are shown for simplicity. The residue numbering scheme for ERα has been used, also for simplicity. Distance monitors show that the biphenyl 'B' ring is in proximity to L384M.

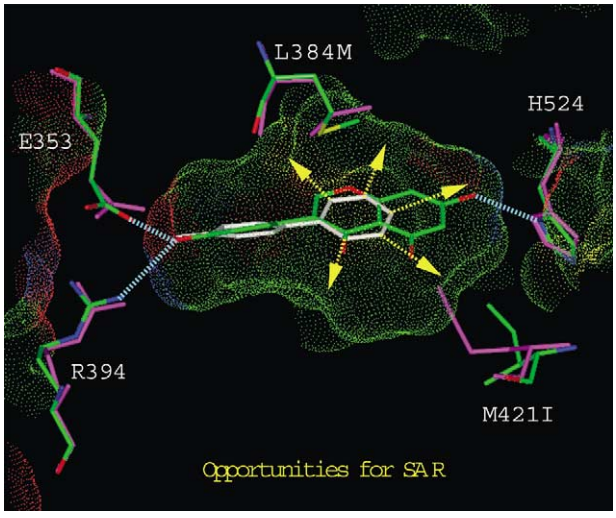


Figure 3. Overlay with genistein ligand included. Arrows indicate opportunities for exploration.

(**4**) that were identified as having ERβ selectivity (i.e., 20–70-fold) based on a conventional radioligand binding assay. The initial foundation of SAR within this series of 4-OH-biphenyls (**4**) is being further exploited in other series of biaryl ERβ selective ligands soon to be reported.

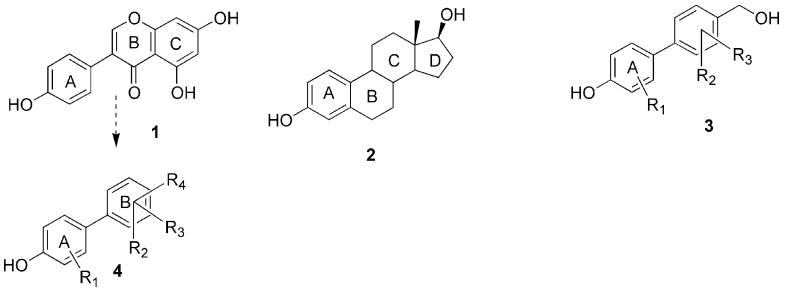


Figure 1. Compounds of interest.

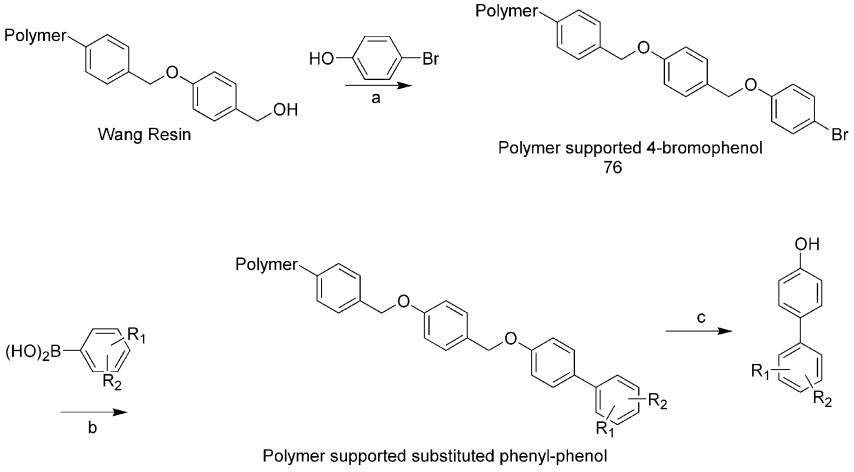
Chemistry

The biphenyl ligands were synthesized by utilizing two main methods. In order to quickly generate a wide variety of ligands to develop an initial SAR, 17 of the target molecules containing a modification to the B-ring were synthesized in parallel fashion using solid phase organic synthesis methods. As shown in Scheme 1, 4-bromophenol was linked to the Wang resin, reacted with the corresponding boronic acid, and then cleaved from the resin with a TFA/CH_2Cl_2 solution. This methodology allowed for the rapid synthesis and isolation of a significant number of targets in acceptable yields. In the cases where the solid-phase reaction was unsuccessful, or when modifications to the A-ring were desired, a solution-phase Suzuki[20] reaction was performed (Scheme 2). The intermediate 4-*tert*-butyldimethylsiloxyphenylboronic acid was utilized in a solution-phase Suzuki reaction to yield those ligands whose B-ring subunit moieties were not available as boronic acids (Scheme 3). The 3-fluoro-substituted ligands were obtained in a similar fashion by first synthesizing the 3-fluoro-4-methoxy phenyl boronic acid intermediate, coupling to the appropriate B-ring, and then removing the methyl ether protecting group (Scheme 4). As depicted in Scheme 5, 2-fluoro-4-bromophenol served as the starting point for the 2-fluoro-substituted ligands. The bromide was converted to the corresponding methoxy derivative and then converted to a triflate before being coupled to the appropriate boronic acid. Demethylation afforded the final product.

The intermediate 2,6-dichloro-4-methoxy-benzaldehyde (**90**) was synthesized as described by Karl et al.[21] and was a key intermediate in the synthesis of a number of the 3′,5′-dichloro-4′-substituted analogues (Scheme 6). Dichlorination of 4-bromophenol with NCS yielded the key intermediate 4-bromo-2,5-dichlorophenol, which was then coupled to the appropriate A-ring moiety to yield the corresponding 4,4′-biphenols (Scheme 7). 4-Phenylphenol (**5**) and 4,4′-biphenol (**20**) were commercially available and purchased from Aldrich.

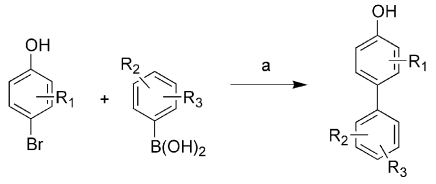
Results and Discussion

4-OH-Biphenyl derivatives have already been demonstrated to achieve good affinity for ERα as reported in a limited SAR study by Lesuisse et al.[18] The dihalogenated phenyl substitution pattern was shown to be an important feature to achieve high potency in their study as well as in other estrogenic agents.[22] Though much similarity exists in the ligand binding domain of ERα and ERβ, a systematic SAR study was still needed to discern the type of substituents and substitution patterns necessary for the biphenyls to achieve ERβ selectivity.



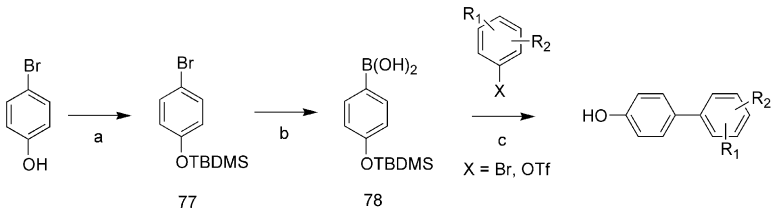
Compound	R1	R2
12	2'-F	H
13	3'-F	H
14	4'-F	H
15	2'-Cl	H
17	4'-Cl	H
21	2'-CH_3	H
22	3'-CH_3	H
23	4'-CH_3	H
26	4'-OCH_3	H
27	2'-OCF_3	H
28	3'-OCF_3	H
30	2'-Phenyl	H
37	3'-CN	H
41	4'-CH_3CH_3	H
43	2'-Cl	4'-Cl
51	2'-Cl	3'-Cl
54	2'-Cl	5'-Cl

Scheme 1. Reagents and conditions: (a) DIAD, PPh_3, THF; (b) $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 80 °C; (c) 50% TFA/CH_2Cl_2.



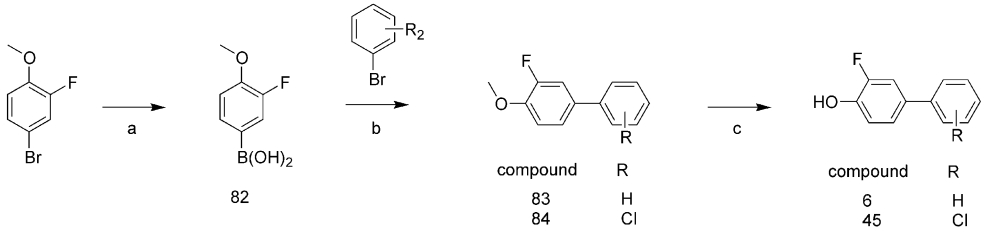
Compound	R_1	R_2	R3
7	3-Cl	H	H
8	3-CH_3	H	H
10	2-Cl	H	H
11	2-CH_3	H	H
24	H	2'-OCH_3	H
25	H	3'-OCH_3	H
29	H	4'-OCF_3	H
32	H	4'-Phenyl	H
34	H	3'-CF_3	H
39	H	2'-CH_2CH_3	H
46	3-Cl	3'-Cl	H
47	3-CH_3	3'-Cl	H
49	2-Cl	3'-Cl	H
50	2-CH_3	3'-Cl	H
52	H	3'-Cl	4'Cl
53	H	H	5'-Cl
63	2-F	3'-Cl	5'-Cl

Scheme 2. Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 95 °C.

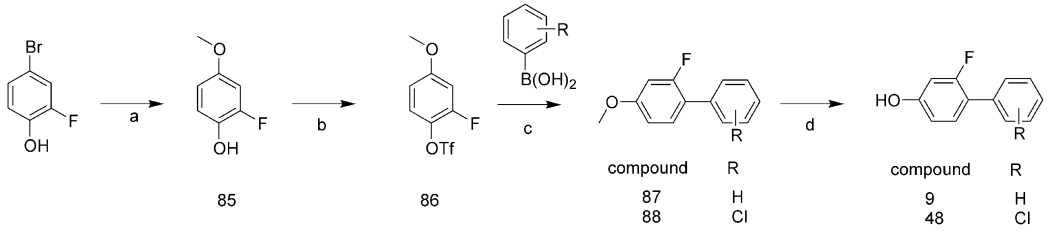


Compound	R_1	R_2
16	3'-Cl	H
18	2'-OH	H
19	3'-OH	H
31	3'-phenyl	H
33	2'-CF_3	H
35	4'-CF_3	H
36	2'-CN	H
38	4'-CN	H
40	3'-CH_2CH_3	H
42	3'-CH_2CH_3	4'-Cl
44	2'-Cl	6'-Cl
55	3'-Cl	4'-F
56	3'-Cl	4'-CH_3
57	3'-Cl	4'-OH
58	3'-Cl	4'-NH_2
59	3'-Cl	4'-CN
67	3'-CF_3	2'-F
68	3'-CF_3	2'-Cl
69	3'-CF_3	4'-F
70	3'-CF_3	4'-Cl
71	3'-CF_3	4'-NH_2
72	3'-CF_3	4'-$N(CH_3)_2$
73	3'-CF_3	5'-CF_3
74	5'-CF_3	2'-F
75	5'-CF_3	2'-Cl

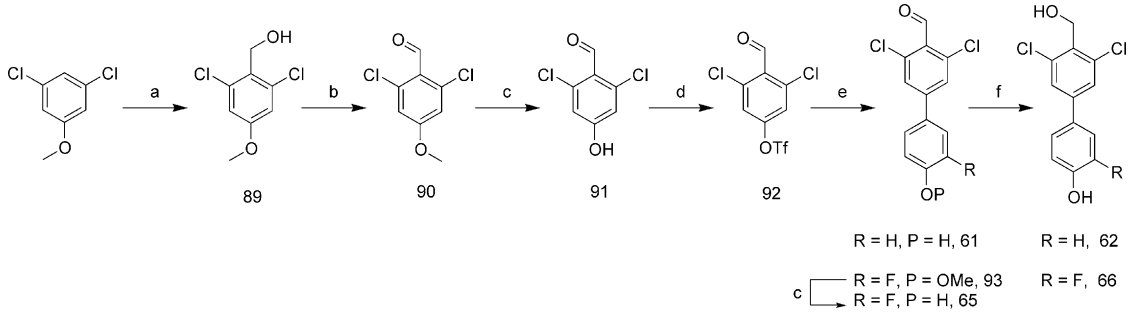
Scheme 3. Reagents and conditions: (a) TBDMS-Cl, imidazole, DMF; (b) (1) *n*-butyllithium, −78 °C; (2) triisopropyl borate; (3) HCl (c) $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 95 °C.



Scheme 4. Reagents and conditions: (a) (1) *n*-butyllithium, −78 °C; (2) triisopropylborate (3) HCl; (b) $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 95 °C; (c) pyridine hydrochloride, 190 °C.

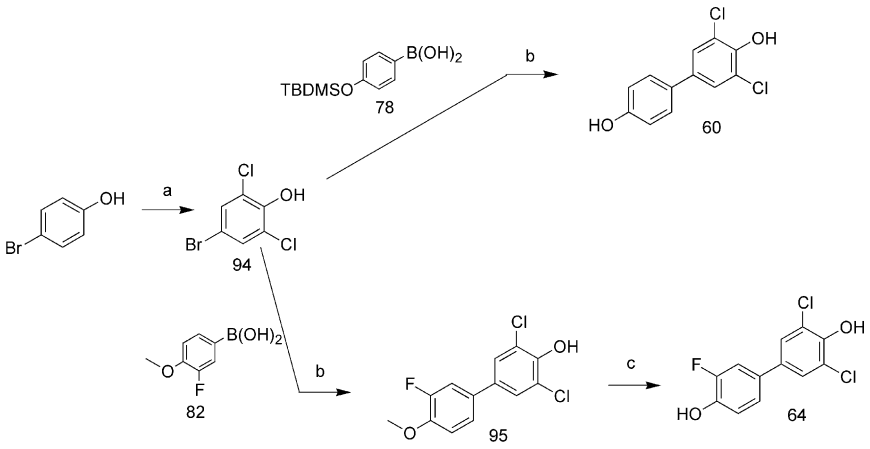


Scheme 5. Reagents and conditions: (a) CuBr, NaOMe, DMF; (b) Tf_2O, C_6H_5N, CH_2Cl_2 (c) $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 95 °C; (d) pyridine hydrochloride, 190 °C.



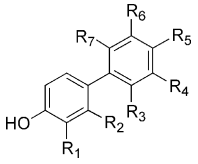
Scheme 6. Reagents and conditions: (a) (1) paraformaldehyde, HCl, H_2SO_4; (2) NaOH; (b) MnO_2, C_6H_6; (c) BBr_3, CH_2Cl_2; (d) Tf_2O, C_6H_5N, CH_2Cl_2 (e) $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 95 °C; (f) $NaBH_4$, EtOH.

The three- dimensional structure of the ERβ–genistein complex does not easily reconcile its ERβ selectivity.[8] However, it was suggested that a migration of the weakly polar methionine from the α- to the β-face of the cavity enables ERβ to accommodate more polar substituents, such as the intramolecular hydrogen bonding hydroxyl/carbonyl group array of genistein (**1**), which may influence ERβ selectivity. Superimposition of the biphenyl template (**4**) onto genistein (**1**) suggested that the B-ring of the biphenyl framework would have the most influence



Scheme 7. Reagents and conditions: (a) NCS, CH_3CN; (b) $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 95 °C; (c) pyridine hydrochloride, 190 °C.

Table 1. Substituted biphenyl derivatives of interest



Compd	R1	R2	R3	R4	R5	R6	R7	ER_β IC_{50} (nM)[a]	ER_α IC_{50} (nM)[b]	Ratio (ER_α/ER_β)	CLogP
1								9.7±4.3	395±181	41	2.40
2								3.6±1.6	3.20±1.0	1	3.784
5	H	H	H	H	H	H	H	8415±5070	78,000	9	3.36
6	F	H	H	H	H	H	H	3330±467	27,000	8	3.60
7	Cl	H	H	H	H	H	H	3110	12,000	4	4.04
8	Me	H	H	H	H	H	H	15,000	Inactive	—	3.86
9	H	F	H	H	H	H	H	2010±948	13,000	6	3.80
10	H	Cl	H	H	H	H	H	605±98	2277±881	4	4.12
11	H	Me	H	H	H	H	H	4000±141	13,890±5812	4	3.56
12	H	H	F	H	H	H	H	4097±1819	>23,000	—	3.56
13	H	H	H	F	H	H	H	1220±182	15,000	—	3.56
14	H	H	H	H	F	H	H	4337±765	>23,000	—	3.56
15	H	H	Cl	H	H	H	H	1018±303	6700±976	7	3.88
16	H	H	H	Cl	H	H	H	401±305	7230±2390	18	4.14
17	H	H	H	H	Cl	H	H	1343±386	12,433±7474	10	4.14
18	H	H	OH	H	H	H	H	>23,000	Inactive	—	2.20
19	H	H	H	OH	H	H	H	2187±598	>20,000	—	2.70
20	H	H	H	H	OH	H	H	2640±737	41,500±51,619	16	2.70
21	H	H	Me	H	H	H	H	1373±464	12,755±4589	9	3.56
22	H	H	H	Me	H	H	H	1312±523	7433±3173	6	3.86
23	H	H	H	H	Me	H	H	1392±870	21,000	11	3.86
24	H	H	OMe	H	H	H	H	4587±3076	>20,000	—	2.76
25	H	H	H	OMe	H	H	H	2335±1591	>20,000	—	3.32
26	H	H	H	H	OMe	H	H	2413±968	>23,000	—	3.32
27	H	H	OCF_3	H	H	H	H	145±21	1215±322	8	3.87
28	H	H	H	OCF_3	H	H	H	134±6	2115±177	16	4.423
29	H	H	H	H	OCF_3	H	H	641±253	3920±14	6	4.43
30	H	H	Ph	H	H	H	H	168±3	1355±233	8	4.65
31	H	H	H	Ph	H	H	H	1270±14	10,200±6788	8	5.25
32	H	H	H	H	Ph	H	H	16,000	>23,000	—	5.25
33	H	H	CF_3	H	H	H	H	532±182	2375±78	5	4.35
34	H	H	H	CF_3	H	H	H	109±42	2270±421	21	4.35
35	H	H	H	H	CF_3	H	H	519±156	5385±177	10	4.35
36	H	H	CN	H	H	H	H	1845±587	>23,000	—	2.93
37	H	H	H	CN	H	H	H	2620±511	8200±2121	3	2.93
38	H	H	H	H	CN	H	H	8790±1771	>20,000	—	2.93
39	H	H	Et	H	H	H	H	393±180	1810±141	5	4.09
40	H	H	H	Et	H	H	H	261±1	4690±1640	18	4.39
41	H	H	H	H	Et	H	H	566±342	4185±615	7	4.39
42	H	H	H	Et	Cl	H	H	64.5±50	703±81	11	5.16
43	H	H	Cl	H	Cl	H	H	153±10	1585±205	10	4.62
44	H	H	Cl	H	H	H	Cl	326±134	2525±148	8	4.37

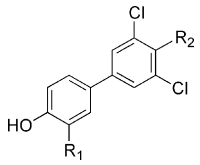
[a]IC_{50} values are the means of at least two experiments ±SEM (performed in triplicate, determined from eight concentrations).
[b]Values without SEM are for a single determination only.

on selectivity (Fig. 3). Based on this superimposition and rationale described in our introduction, modifications were predominately performed on the B-ring of the 4-OH-biphenyl template.

Shown in Tables 1–4 are the affinities for target molecules **5**–**75** for ERα and ERβ which were determined in a radioligand binding assay with [^{3}H]-17β-estradiol as previous described.[23] Three factors which appeared to be playing a significant role in determining affinity and selectivity were (1) the specific substituent appended, (2) their position on the biphenyl template, and (3) the ClogP values.[24] Since the majority of the binding pocket is hydrophobic, it is not surprizing that increasing lipophilicity would be expected to improve affinity. However, since the binding pocket has a specific shape, it is also quite reasonable to expect that the relationship between ClogP and affinity would eventually diverge when detrimental steric interactions start to predominate. Shown in Figure 4 is a graph of pIC_{50} versus ClogP which shows that though a trend exists between affinity and lipophilicity, other factors such as complementary electronic and steric effects are also playing a role in binding. Interestingly, docking calculations confirmed that compounds **7**, **8**, **31**, **32**, **46**, and **47** had poor fits within the binding pocket and were also observed as outliers in this graph. In general, we found that molecules substituted with lipophilic groups that also have a high degree of shape complementarity with the binding pocket were the most potent binders.

The simple unsubstituted 4-OH-biphenyl (**5**), having a ClogP of only 3.36, had little affinity for ERβ. Halogens placed at either the 2- or 3- position (A-ring) of the biphenyl-4-ol template increased affinity from 2-12-fold (i.e., **6**, **7**, **9**, **10**). However, substituents on the B-ring of the biphenyl template had a more dramatic influence on both affinity and selectivity. In general, substituents placed at the 3′-position resulted in a beneficial influence on both affinity and selectivity. The most selective compounds in Table 1 embraced the 3′ substitution pattern (i.e. **16**, **28**, **34**, and **40**), had affinities ranging from 109 to 401 nM and ERβ selectivities ranging from 16–21 fold. Table 2 shows a series of 3′-chloro-substituted 4-OH-biphenyl derivatives that were prepared to attempt to further optimize this substitution pattern. In general, substituents on the A-ring only led to a minor improvement in ERβ affinity (vs **16**) and all modifications led to a loss in selectivity with the exception of the 2-fluoro derivative (i.e., **45**). Attaching another chloro group to the B-ring led to several dichloro analogues with significant improvement in ERβ affinity (i.e., **51**–**54**) versus **16**. Selectivity was also slightly improved with dichloro derivatives **52** (25-fold) and **53** (24-fold). Attaching a OH group at the 4′ position (i.e., **57**) also improved selectivity versus **16**. In an attempt to

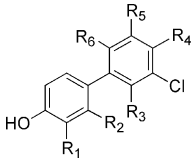
Table 3. 1-OH-3′,5′-Dichloro-biphenyl motif



Compd	R1	R2	ER_β IC_{50} (nM)	ER_α IC_{50} (nM)[a]	Ratio (ER_α/ER_β)[a]	CLogP
53	H	H	83±25	2013±356	24	4.87
60	H	OH	107±18	3823±457	36	3.89
61	H	CHO	69±18	5007±1729	72	4.44
62	H	CH_2OH	122±35	2529±950	21	3.83
63	F	H	173±89	2595±346	15	5.06
64	F	OH	136±34	3820	28	4.11
65	F	CHO	89±26	>5000	—	4.60
66	F	CH_2OH	82±3	3765±191	46	4.02

[a]See footnotes in Table 1.

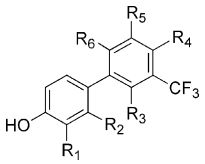
Table 2. 1-OH-3′-Chloro-biphenyl motif



Compd	R1	R2	R3	R4	R5	R6	ER_β IC_{50} (nM)[a]	ER_α IC_{50} (nM)[a]	Ratio (ER_α/ER_β)	cLogP
16	H	H	H	H	H	H	401±305	7230±2390	18	4.14
45	F	H	H	H	H	H	271±30	6670±110	25	4.34
46	Cl	H	H	H	H	H	1325±247	4780±28	4	4.78
47	Me	H	H	H	H	H	2065±1039	6890±297	3	4.58
48	H	F	H	H	H	H	199±30	1794±518	9	4.54
49	H	Cl	H	H	H	H	209±154	722±212	4	4.78
50	H	Me	H	H	H	H	416±37	1565±49	4	4.33
51	H	H	Cl	H	H	H	220±71	1890±368	9	4.50
52	H	H	H	Cl	H	H	73±16	1800±415	25	4.75
53	H	H	H	H	Cl	H	83±25	2013±356	24	4.87
54	H	H	H	H	H	Cl	83.5±1	977±160	12	4.62
55	H	H	H	F	H	H	509±107	6020±2150	12	4.23
56	H	H	H	Me	H	H	166±23	2575±1237	9	4.63
57	H	H	H	OH	H	H	305±35	8900±4389	29	3.39
58	H	H	H	NH_2	H	H	2950±211	>20,000	—	3.15
59	H	H	H	CN	H	H	455±191	12,000±0	26	3.54

[a]See footnotes in Table 1.

Table 4. 1-OH-3′-CF_3-Biphenyl motif



Compd	R1	R2	R3	R4	R5	R6	ER_β IC_{50} (nM)[a]	ER_α IC_{50} (nM)[a]	Ratio (ER_α/ER_β)	CLogP
34	H	H	H	H	H	H	109±42	2270±421	21	4.35
67	H	H	F	H	H	H	79±6	1095±629	14	4.51
68	H	H	Cl	H	H	H	60±20	453±173	8	4.63
69	H	H	H	F	H	H	107±37	3364±1955	32	4.51
70	H	H	H	Cl	H	H	41±11	693±163	17	4.88
71	H	H	H	NH_2	H	H	906±415	13,000	14	3.54
72	H	H	H	NMe_2	H	H	454±134	1555±346	3	3.74
73	H	H	H	H	CF_3	H	24±17	309±59	13	5.27
74	H	H	H	H	H	F	206±162	1458±810	7	4.51
75	H	H	H	H	H	Cl	64.5±49	502±315	8	4.83

[a]See footnotes in Table 1.

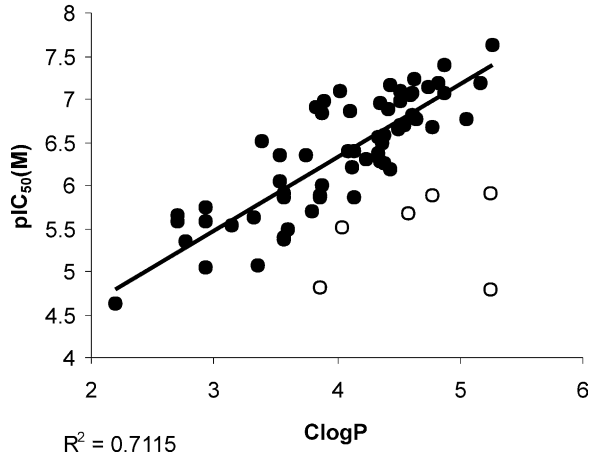


Figure 4. pIC_{50} (ERβ) versus ClogP. Compounds in open circles (i.e., **7**, **8**, **31**, **32**, **46**, and **47**) are outliers where detrimental steric factors are significantly influencing affinity.

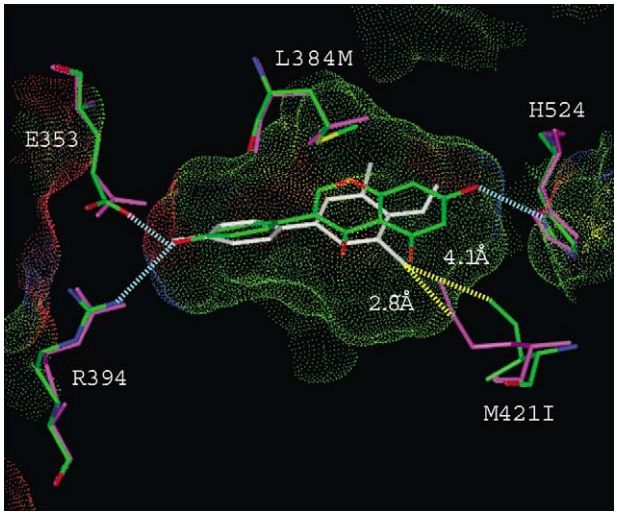


Figure 5. Compound **61** (white), docked to the ERβ/genistein pocket (including the ligand and colored by atom type), overlayed with ERα/diethylstilbestrol[7] (magenta). As in Figure 1, only key residues and a Connolly surface of the ERβ binding site are shown for simplicity. Again, the residue numbering scheme for ERα has been used. Distance monitors show that the 3′-Cl is in close proximity to M421I.

further optimize **53**, a small group of 4′-substituted-3′,5′-dichloro derivatives were prepared (Table 3). Interestingly, aldehydes **61** and **65** had the highest ERβ selectivity in this investigation (>56-fold), while maintaining similar ERβ affinity to that of **53**. In an attempt to mimic the 17β-OH group in the D-ring of estradiol (**2**) similar to that reported by Lesuisse,[18] the hydroxymethyl group was attached to **53** (i.e., **62**). Both **53** and **62** had similar affinities and selectivities, suggesting that the hydroxymethyl group could not effectively mimic the 17β-OH group of estradiol. Nevertheless, attaching a 2-fluoro substituent (i.e., **66**) improved both affinity and selectivity versus **62**. Table 4 shows a limited SAR study performed by maintaining the 3′-trifluoromethyl-4-OH-biphenyl motif based around **34**. The bis(trifluoromethyl) derivative (**73**), which had one of the highest ClogP values (5.27), was observed to be the most potent biphenyl identified in this study (24 nM). Though several compounds in Table 4 were found to have a slight improvement in ERb affinity, no improvement in selectivity was achieved.

Figure 5 shows 4-OH-dichloro biphenyl **61** docked into the ERβ pocket, and overlaid with genistein (**1**). As discussed earlier, only two residues are different within the ligand binding pockets of ERα and ERβ. ERαLeu384 in helix-5 corresponds to ERβMet336 and ERαMet421in helix-7 corresponds to ERβIle373. The 3′-Cl group is clearly in close proximity to ERαMet421/ERβIle373. In particular, it appears likely that the 2.8 Å distance between the 3′-Cl and the sulfur of ERαMet421 represents a repulsive interaction, which may be mimicking the behavior of the genistein 5′-OH group. In contrast, at a distance of 4.1 Å, neither electronic nor steric repulsion is expected to have a significant effect between the 3′-Cl group and ERβIle373. Although it may be possible for ERαMet421 to adopt an alternative rotamer state that would reduce the repulsive interaction described above, the restricted total number

of available side-chain rotamers would still represent an unfavorable change in free energy. Worth mentioning is that even if the energy difference for the interaction between the 3′-Cl group and ERαMet421 versus ERβIle373 is small, only 1.23 kcal/mol would be necessary to take the 9-fold selective 4-OH-biphenyl **5** to the 72-fold selective 4-OH-3′,5′-dichloro-biphenyl **61**.

Conclusions

In this report, we have described a systematic SAR study based around the 4-OH-biphenyl motif towards identifying ERβ selective ligands. The most selective compounds fell into the 4-OH-3′-substituted biphenyl motif. Similar to previous invesitigations,[18,22] the most effective substituents were the chloro and trifluoromethyl groups. However, in contrast to Leuisse's work[18] which focused on ERα, our study revealed the 4-OH-biphenyls prefer a different substitution pattern to achieve ERβ selectivity. The biphenyl scaffold could be further optimized by increasing lipophilicity and employing the 1-OH-3′,5′-disubstituted biphenyl motif which led to the most potent compound (i.e., **73**; $IC_{50} = 24$ nM). Also embracing the 3′,5′-disubstituted biphenyl motif were the aldehydes **61** and **65** which had ERβ selectivity on the order of 70-fold. Modeling studies indicated that the chlorine atom at the 3′ position of the biphenyl scaffold was playing a key role in the enhanced ERβ selectivity. Attempts to use the hydroxymethyl moiety (i.e., **62** and **63**) as a mimic for the 17β-OH group of estradiol (**2**) did not improve affinity. Further optimization and exploitation of this SAR to provide more potent and selective 4-OH-biphenyl analogues is currently being performed in our laboratories and will be reported shortly in Part 2 of this series.

Experimental

General

Melting points were measured on a Mel-Temp II (Laboratory Device Inc., USA) 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 $CDCl_3$ 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. Solvents and reagents were used as purchased.

(4-Bromo-phenoxy)-*tert*-butyl-dimethyl silane (77). A solution of 4-bromophenol (7.42 g, 42.9 mmol), imidazole (8.7 g, 127 mmol), and *tert*-butyl-dimethylsilane (9.0 g, 59.4 mmol) in DMF (100 mL) was stirred overnight at room temperature. The solution was poured into water (500 mL) and extracted with EtOAc (2×200 mL). The combined organic layers were washed with water, washed with brine, dried over sodium sulfate, and filtered. The solvent was evaporated and the residue was purified on silica (98% hexanes–2% EtOAc) to yield 12.29 g (100%) of a clear oil: ^{1}H NMR ($CDCl_3$): δ 0.16 (6H, s), 0.95 (9H, s), 6.79 (2H, d, $J = 8.81$ Hz), 7.29 (2H, d, $J = 8.81$ Hz); MS (EI) m/z 286/288 (M^+). Anal. calcd for $C_{13}H_{11}FO$: C:50.17H:6.67; Found: C:50.09H:6.91.

Method A: synthesis of boronic acids

4-*tert*–Butyl-dimethylsilyloxyphenylboronic acid (78). To a solution of (4-bromo-phenoxy)-*tert*-butyl-dimethylsilane (**77**) (11.20 g, 39.02 mmol) in THF (200 mL) at −78 °C was added *n*-butyl lithium (17.1 mL of 2.5 N solution, 42.9 mmol). The resulting solution was stirred at −78 °C for 30 min. Triisopropyl borate (36.7 g, 195 mmol) was added and the solution was stirred at −78 °C for 2 h before being warmed to room temperature overnight. The reaction was cooled to 0 °C and 250 mL of 1 N HCl was added and the mixture was stirred for 5 min at 0 °C. The mixture was then extracted with EtOAc (2×200 mL). The solvent was evaporated and the residue was taken up in a minimum of EtOAc–hexanes. A minor solid impurity was removed by filtration and the product was obtained by concentrating and cooling the solution. 3.55 g of a white solid (65%) was obtained by filtration. Analysis indicated that the compound was in the form of the boronic acid anhydride (reacted as the acid for cross-coupling reactions): ^{1}H NMR (DMSO-d_6): δ 0.16 (6H, s), 0.95 (9H, s), 6.79 (2H, d, $J = 8.81$ Hz), 7.29 (2H, d, $J = 8.81$ Hz); MS (ESI) m/z 485 ($[M-H]^-$). Anal. calcd for $C_{24}H_{40}B_2O_5Si_2$: C:59.27H:8.29; Found: C:59.18H:8.20.

3-Fluoro-4-methoxyphenylboronic acid (82). To a solution of 4-bromo-2-fluoroanisole (30.2 g, 147.3 mmol) in THF (500 mL) at −78 °C was added *n*-butyl lithium (65 mL of 2.5 N solution, 162 mmol). The resulting solution was stirred at −78 °C for 30 min. Triisopropyl borate (141 g, 750 mmol) was added and the solution was stirred at −78 °C for 4 h before being warmed to 0 °C. 500 mL of 2 N HCl was added and the mixture was stirred for 30 min at 0 °C and extracted with EtOAc (3×500 mL). The solvent was evaporated from the combined organic layers and the residue was taken up in a minimum of EtOAc. Trituration with hexanes yielded 16.1 g (64%) of a white solid. Preparative HPLC yielded an analytical sample as a white solid: mp 192–198 °C; ^{1}H NMR (DMSO-d_6): δ 3.84 (3H, s), 7.10–7.16 (1H, m), 7.51–7.60 (2H, m); ^{19}F NMR (DMSO-d_6): δ −138 (m); MS (ESI) m/z 169 ($[M-H]^-$). Anal. calcd for $C_7H_8BFO_3$: C:49.47H:4.74; Found: C:49.41H:4.63.

Wang resin linked 4-bromophenol (76). To a suspension of 17.07 g of Wang resin (0.83 mmol/g; 14.16 mmol

equiv), triphenylphosphine (11.14 g, 42.5 mmol), and 4-bromophenol (7.35 g, 42.5 mmol) in THF (100 mL) in a solid-phase synthesis vessel was added DIAD (8.58 g, 42.5 mmol). The reaction vessel was shaken overnight at room temperature and filtered dry. The resin was then washed successively with THF (×2), DMF (×2), and methanol (×3). The resin was dried under vacuum to yield 19.14 g of resin-linked 4-bromophenol (0.74 g/mmol).

Method B: solid-phase synthesis of biphenyls

2′-Fluoro-1,1′-biphenyl-4-ol (12). A suspension of resin-linked 4-bromophenol (**76**) (2.10 g, 1.55 mmol), 2-fluorophenylboronic acid (0.65 g, 4.5 mmol), tetrakis(triphenylphosphine)palladium(0) (0.090 g, 0.078 mmol), dimethoxyethane (6 mL) and sodium carbonate (3 mL of a 2 N aqueous solution) was place in a 20 mL vial, sealed, and shaken overnight at 80 °C. The suspension was cooled to room temperature and filtered into a polyethylene solid-phase vessel. The resin was washed successively with water (×2), methanol (×2), and CH_2Cl_2 (×2).

The desired product was then cleaved from the resin by shaking with TFA/CH_2Cl_2 (10 mL) for 10 min. The resin was filtered and retreated with 50% TFA/CH_2Cl_2 (10 mL) for 10 min. The solvent was evaporated from the combined TFA solution filtrates to yield 0.12 g of product (57%) which was further purified by reverse-phase HPLC to yield the title compound as a white solid: mp 124–126 °C; ^{1}H NMR (DMSO-d_6): δ 6.86 (2H, d, J = 8.58 Hz), 7.23–7.27 (2H, m), 7.31–7.38 (3H, m), 7.44–7.48 (1H, m), 9.62 (1H, s); ^{19}F NMR (DMSO-d_6): δ −119 (m); MS (EI) m/z 188.06 (M^+). Anal. calcd for $C_{12}H_9FO$ 0.10H_2O: C:75.86H:4.88; Found: C:75.89H:4.47.

3′-Fluoro-1,1′-biphenyl-4-ol (13). The title compound was prepared using Method B as above to yield 0.12 g (46%) of product which was further purified by reverse phase HPLC to yield a white solid: mp 122–123 °C; ^{1}H NMR (DMSO-d_6): δ 6.85 (2H, d, J = 8.71 Hz), 7.05–7.13 (1H, m), 7.38–7.45 (3H, m), 7.53 (2H, d, J = 8.71 Hz), 9.63 (1H, s); ^{19}F NMR (DMSO-d_6): δ −113−−114 (m); MS (EI) m/z 188.06 (M^+). Anal. calcd for $C_{12}H_9FO$: C:76.58H:4.82; Found: C:76.15H:4.47.

4′-Fluoro-1,1′-biphenyl-4-ol (14). The title compound was prepared using Method B as above to yield 0.10 g (39%) of product which was further purified by reverse-phase HPLC to yield a white solid: mp 161–164 °C; ^{1}H NMR (DMSO-d_6): δ 6.84 (2H, d, J = 8.71 Hz), 7.19–7.25 (2H, m), 7.45 (2H, d, J = 8.58 Hz), 7.57–7.62 (2H, m), 9.54 (1H, s); ^{19}F NMR (DMSO-d_6): δ −117 to −118 (m); MS (EI) m/z 188.06 (M^+). Anal. calcd for $C_{12}H_9FO$ 0.20H_2O: C:75.15H:4.94; Found: C:75.00H:4.87.

2′-Chloro-1,1′-biphenyl-4-ol (15). The title compound was prepared using Method B as above to yield 0.35 g (85%) of product which was further purified by reverse-phase HPLC to yield a yellow solid: mp 54–56 °C; ^{1}H NMR (DMSO-d_6): δ 6.84 (2H, d, J = 8.58 Hz), 7.25 (2H, d, J = 8.59 Hz), 7.31–7.40 (3H, m), 7.50–7.53 (1H, m), 9.60 (1H, s); MS (EI) m/z 204.3/206.3 (M^+). Anal. calcd for $C_{12}H_9ClO$: C:70.43H:4.43; Found: C:70.24H:4.35.

4′-Chloro-1,1′-biphenyl-4-ol (17). The title compound was prepared using Method B as above to yield 0.25 g (66%) of product which was further purified by reverse-phase HPLC to yield a yellow solid: mp 123–126 °C; ^{1}H NMR (DMSO-d_6): δ 6.85 (2H, d, J = 8.71 Hz), 7.44 (2H, d, J = 8.59 Hz), 7.49 (2H, d, J = 8.72 Hz), 7.60 (2H, d, J = 8.59 Hz), 9.60 (1H, s); MS (EI) m/z 204.0/206.0 (M^+). Anal. calcd for $C_{12}H_9ClO$: C:70.43H:4.43; Found: C:68.70H:4.12.

2′-Methyl-1,1′-biphenyl-4-ol (21). The title compound was prepared using Method B as above to yield 0.15 g (52%) of product which was further purified by reverse-phase HPLC to yield a white solid: mp 70–71 °C; ^{1}H NMR ($CDCl_3$): δ 2.27 (3H, s), 4.71 (1H, s), 6.90 (2H, d, J = 8.52 Hz), 7.18–7.26 (6H, m); MS (EI) m/z 184.09 (M^+). Anal. calcd for $C_{13}H_{12}O$·0.10H_2O: C: 83.93H:6.61; Found: C:84.00H:6.43.

3′-Methyl-1,1′-biphenyl-4-ol (22). The title compound was prepared using Method B as above to yield 0.061 g (21%) of product which was further purified by reverse phase HPLC to yield a white solid: mp 71–72 °C; ^{1}H NMR ($CDCl_3$): δ 2.40 (3H, s), 4.75 (1H, s), 6.89 (2H, d, J = 6.58 Hz), 7.30–7.35 (3H, m), 7.47 (2H, d, J = 8.58 Hz); MS (EI) m/z 184.09 (M^+). Anal. calcd for $C_{13}H_{12}O$·0.30H_2O: C:82.34H:6.70; Found: C:82.77H:6.61.

4′-Methyl-1,1′-biphenyl-4-ol (23). The title compound was prepared using Method B as above to yield 0.18 g (62%) of product which was further purified by reverse-phase HPLC to yield a white solid: mp 140–143 °C; ^{1}H NMR ($CDCl_3$): δ 2.38 (3H, s), 4.73 (1H, s), 6.89 (2H, d, J = 8.55 Hz), 7.22 (2H, d, J = 7.92 Hz), 7.42–7.47 (4H, m); MS (EI) m/z 184.09 (M^+). Anal. calcd for $C_{13}H_{12}O$·0.20H_2O: C:83.13H:6.65; Found: C:83.44H:6.32.

4′-Methoxy-1,1′-biphenyl-4-ol (26). The title compound was prepared using Method B as above to yield 0.21 g (57%) of product which was further purified by reverse phase HPLC to yield an off-white solid: mp 168–171 °C; ^{1}H NMR (DMSO-d_6): δ 3.77 (3H, s), 6.81 (2H, d, J = 8.59 Hz), 6.96 (2H, d, J = 8.54 Hz), 7.41 (2H, d, J = 8.58 Hz), 7.49 (2H, d, J = 8.72 Hz), 9.42 (1H, s); MS (EI) m/z 200.08 (M^+). Anal. calcd for $C_{13}H_{12}O_2$: C:77.98H:6.04; Found: C:75.71H:5.71.

2′-(Trifluoromethoxy)-1,1′-biphenyl-4-ol (27). The title compound was prepared using Method B as above to yield 0.31 g (68%) of product which was further purified by reverse-phase HPLC to yield a tan solid: mp 45–49 °C; ^{1}H NMR (DMSO-d_6): δ 6.85 (2H, d, J = 8.72 Hz), 7.28 (2H, d, J = 8.58 Hz), 7.40–7.49 (4H, m), 9.62 (1H, s); ^{19}F NMR (DMSO-d_6): δ −56.5 (s); MS (EI) m/z 254.05 (M^+). Anal. calcd for $C_{13}H_9F3O_2$·0.10H_2O: C:60.99H:3.62 Found: C:60.93H:3.37.

3′-(Trifluoromethoxy)-1,1′-biphenyl-4-ol (28). The title compound was prepared using Method B as above to yield 0.34 g (70%) of product which was further purified by reverse-phase HPLC to yield a tan solid: mp 36–37 °C; ^{1}H NMR (DMSO-d_6): δ 6.87 (2H, d, J = 8.71 Hz), 7.25–7.28 (1H, m), 7.50–7.56 (4H, m), 7.62–7.64 (1H, m), 9.67 (1H, s); ^{19}F NMR (DMSO-d_6): δ −57.03 (s); MS (EI) m/z 254.05 (M^+). Anal. calcd for $C_{13}H_9F_3O_2$: C:61.42H:3.57; Found: C:61.13H:3.34.

1,1′:2′,1″-Terphenyl-4-ol (30). The title compound was prepared using Method B as above to yield 0.19 g (44%) of product which was further purified by reverse-phase HPLC to yield a white solid: mp 109–110 °C; ^{1}H NMR (DMSO-d_6): δ 6.60 (2H, d, J = 8.59 Hz), 6.88 (2H, d, J = 8.58 Hz), 7.06–7.11 (2H, m), 7.18–7.27 (3H, m), 7.33–7.43 (4H, m), 9.34 (1H, s); MS (EI) m/z 246.1 (M^+). Anal. calcd for $C_{18}H_{14}O{\cdot}0.30H_2O$: C:85.89H:5.85; Found: C:86.16H:5.56.

4′-Hydroxy-1,1′-biphenyl-3-carbonitrile (37). The title compound was prepared using Method B as above to yield 0.34 g (91%) of product which was further purified by reverse-phase HPLC to yield a yellow solid: mp 172–176 °C (decomp); ^{1}H NMR (DMSO-d_6): δ 6.88 (2H, d, J = 8.71 Hz), 7.60 (2H, d, J = 8.84 Hz), 7.78–7.86 (4H, m), 9.79 (1H, s); MS (EI) m/z 195.07 (M^+). Anal. calcd for $C_{13}H_9NO$: C:79.98H:4.65 N:7.17 Found: C:73.16H:4.95 N:4.78.

4′-Ethyl-1,1′-biphenyl-4-ol (41). The title compound was prepared using Method B as above to yield 0.25 g (66%) of product which was further purified by reverse-phase HPLC to yield an off-white solid: mp 137–139 °C; ^{1}H NMR (DMSO-d_6): δ 1.19 (3H, t, J = 7.63), 2.61 (2H, q, J = 7.59 Hz), 6.82 (2H, d, J = 8.71 Hz), 7.24 (2H, d, J = 8.45 Hz), 7.44 (2H, d, J = 8.71 Hz), 7.47 (2H, d, J = 8.20), 9.47 (1H, s); MS (EI) m/z 198.1 (M^+). Anal. calcd for $C_{14}H_{14}O$: C:84.81H:7.12; Found: C:81.87H:6.68.

2′,4′-Dichloro-1,1′-biphenyl-4-ol (43). The title compound was prepared using Method B as above to yield 0.33 g (76%) of product which was further purified by reverse-phase HPLC to yield a tan solid: mp 64–67 °C; ^{1}H NMR (DMSO-d_6): δ 6.84 (2H, d, J = 8.58 Hz), 7.24 (2H, d, J = 8.58 Hz), 7.38 (1H, d, J = 8.33 Hz), 7.46 (1H, dd, J = 8.32 Hz, J = 2.18 Hz), 7.68 (1H, d, J = 2.05 Hz), 9.66 (1H, s); MS (EI) m/z 238/240/242 (M^+). Anal. calcd for $C_{12}H_8Cl_2O{\cdot}0.30H_2O$: C:58.95H:3.55; Found: C:58.52H:3.44.

2′,3′-Dichloro-1,1′-biphenyl-4-ol (51). The title compound was prepared using Method B as above to yield 0.37 g (79%) of product which was further purified by reverse-phase HPLC to yield a yellow solid: mp 74–76 °C; ^{1}H NMR (DMSO-d_6): δ 6.85 (2H, d, J = 8.71 Hz), 7.24 (2H, d, J = 8.59 Hz), 7.32 (1H, dd, J = 7.68 Hz, J = 1.66 Hz), 7.37–7.41 (1H, m), 7.60 (1H, dd, J = 7.95 Hz, J = 1.66 Hz), 9.67 (1H, s); MS (EI) m/z 238/240/242 (M^+). Anal. calcd for $C_{12}H_8Cl_2O$: C:60.28H:3.37; Found: C:60.03H:3.28.

2′,5′-Dichloro-1,1′-biphenyl-4-ol (54). The title compound was prepared using Method B as above to yield 0.31 g (68%) of the title compound which was further purified by reverse-phase HPLC to yield a yellow solid: mp 74–78 °C; ^{1}H NMR (DMSO-d_6): δ 6.84 (2H, d, J = 8.71 Hz), 7.27 (2H, d, J = 8.71 Hz), 7.37–7.43 (2H, m), 7.54–7.57 (1H, m), 9.69 (1H, s); MS (EI) m/z 238/240/242 (M^+). Anal. calcd for $C_{12}H_8Cl_2O$: C:60.28H:3.37; Found: C:60.13H:3.24.

Method C: normal phase Suzuki reactions

3-Chloro-1,1′-biphenyl-4-ol (7). A suspension of 2-chloro-4-bromophenol (0.52 g, 2.21 mmol), phenylboronic acid (0.37 g, 3.0 mmol), tetrakis(triphenylphosphine) palladium(0) (0.14 g, 0.12 mmol), sodium carbonate (3.5 mL of a 2 N aqueous solution), and dimethoxyethane (10 mL) was stirred under nitrogen overnight at 95 °C. The suspension was cooled, poured into 100 mL of 1 N NH_4Cl solution, and extracted with EtOAc (2×100 mL). The combined organic layers were washed with brine, dried with sodium sulfate, and filtered. The solvent was removed by evaporation and the residue was purified on a silica column (20% EtOAc–80% hexanes) to yield 0.51 g (99%) of a white solid. This material was further purified by reverse-phase HPLC to yield the title compound as a white solid: mp 61–63 °C; ^{1}H NMR (DMSO-d_6): δ 7.05 (1H, d, J = 8.40 Hz), 7.29–7.33 (1H, s), 7.40–7.48 (3H, m), 7.58–7.63 (3H, m), 10.29 (1H, s); MS (EI) m/z 204.0/206.1 (M^+). Anal. calcd for $C_{12}H_9ClO{\cdot}0.10H_2O$: C:69.81H:4.49; Found: C:69.97H:4.53.

3-Methyl-1,1′-biphenyl-4-ol (8). The title compound was prepared by reacting 4-bromo-2-methylphenol (0.49 g, 2.62 mmol) with phenylboronic acid (0.38 g, 3.1 mmol) according to Method C to yield 0.45 g (94%) of a white solid: mp 103–104 °C; ^{1}H NMR ($CDCl_3$): δ 2.32 (3H, s), 4.71 (1H, s), 6.84 (1H, d, J = 8.20 Hz), 7.26–7.43 (5H, m), 7.52–7.55 (2H, m); MS (EI) m/z 184.1 (M^+). Anal. calcd for $C_{13}H_{12}O{\cdot}0.10H_2O$: C:83.93H:6.61; Found: C:84.07H:6.61.

2-Chloro-1,1′-biphenyl-4-ol (10). The title compound was prepared by reacting 3-chloro-4-bromophenol (0.50 g, 2.41 mmol) with phenylboronic acid (0.35 g, 2.9 mmol) according to Method C to yield 0.27 g (55%) of a clear, colorless oil: ^{1}H NMR (DMSO-d_6): δ 6.82 (1H, dd, J = 8.41 Hz, J = 2.46 Hz), 6.92 (1H, d, J = 2.46 Hz), 7.21 (1H, d, J = 8.40 Hz), 7.32–7.38 (3H, m), 7.40–7.44 (2H, m), 9.98 (1H, s); MS (EI) m/z 204.0/206.0 (M^+). Anal. calcd for $C_{12}H_9ClO{\cdot}0.20H_2O$: C:69.21H:4.55 Found: C:68.98H:4.71.

2-Methyl-1,1′-biphenyl-4-ol (11). The title compound was prepared by reacting 4-bromo-3-methylphenol (0.53 g, 2.83 mmol) with phenylboronic acid (0.41 g, 3.4 mmol) according to Method C to yield 0.52 g (100%) of a clear, colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.23 (3H, s), 4.73 (1H, s), 6.69–6.76 (2H, m), 7.11 (1H, d, J = 8.14 Hz), 7.27–7.34 (3H, m), 7.37–7.42 (2H, m); MS (EI) m/z 184.1 (M^+). Anal. calcd for $C_{13}H_{12}O{\cdot}0.20H_2O$: C:83.13H:6.65 Found: C: 82.96H: 6.80.

3′-Chloro-1,1′-biphenyl-4-ol (16). The title compound was prepared by reacting 3-bromochlorobenzene (2.46 g, 12.85 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (4.5 g, 18.0 mmol) according to Method C to yield 2.46 g (94%) of a light yellow solid: mp 59–60 °C; ^{1}H NMR (DMSO-d_6): δ 6.85 (2H, d, J = 8.71 Hz), 7.31–7.34 (1H, m), 7.41–7.45 (1H, m), 7.50–7.56 (3, m), 7.61–7.62 (1H, m), 9.64 (1H, s); MS (ESI) m/z 203/205 ([M−H]−). Anal. calcd for $C_{12}H_9ClO{\cdot}0.10H_2O$: C:69.81H:4.49; Found: C:69.71H:4.29.

1,1′-Biphenyl-2,4′-diol (18). The title compound was prepared by reacting 2-bromophenol (0.42 g, 2.43 mmol) with 4-*tert*-butyldimethylsilyloxyphenyl-boronic acid (**78**) (0.85 g, 3.4 mmol) according to Method C to yield to yield 0.42 g (96%) of a white solid: mp 150–155 °C; ^{1}H NMR (DMSO-d_6): δ 6.77 (2H, d, J = 8.71 Hz), 6.79–6.84 (1H, m), 6.89 (1H, dd, J = 8.07 Hz, J = 1.16 Hz), 7.06–7.10 (1H, m), 7.18 (1H, dd, J = 7.56 Hz, J = 1.66 Hz), 7.35 (2H, d, J = 8.71 Hz), 9.32 (1H, s), 9.35 (1H, s); MS m/z 186.06 (M^+). Anal. calcd for $C_{12}H_{10}O_2{\cdot}0.10H_2O$: C:76.66H:5.47; Found: C:76.76H:5.34.

1,1′-Biphenyl-3,4′-diol (19). The title compound was prepared by reacting 3-bromophenol (0.82 g, 4.74 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (1.67 g, 6.6 mmol) according to Method C to yield 0.80g (91%) of a white solid: mp 179–183 °C; ^{1}H NMR (DMSO-d_6): δ 6.66–6.69 (1H, m), 6.82 (2H, d, J = 8.71 Hz), 6.92–6.93 (1H, m), 6.96–6.98 (1H, m), 7.16–7.20 (1H, m), 7.40 (2H, d, J = 8.71 Hz), 9.40 (1H, s), 9.49 (1H, s); MS (EI) m/z 186.06 (M^+). Anal. calcd for $C_{12}H_{10}O_2{\cdot}0.10H_2O$: C: 76.66H:5.47; Found: C:76.64H:5.48.

2′-Methoxy-1,1′-biphenyl-4-ol (24). The title compound was prepared by reacting 4-bromophenol (0.54 g, 3.12 mmol) with 2-methoxyphenylboronic acid (0.66 g, 4.4 mmol) according to Method C to yield 0.58 g (93%) of a white solid: mp 89–93 °C; ^{1}H NMR (DMSO-d_6): δ 3.74 (3H, s), 6.78 (2H, d, J = 8.71 Hz), 6.96–7.00 (1H, m), 7.06 (1H, dd, J = 8.26 Hz, J = 0.83 Hz), 7.22 (1H, dd, J = 7.49 Hz, J = 1.73 Hz), 7.25–7.30 (3H, m), 9.41 (1H, s); MS (EI) m/z 200.08 (M^+). Anal. calcd for $C_{13}H_{12}O_2{\cdot}0.10H_2O$: C:77.28H:6.09; Found: C:77.35H:6.06.

3′-Methoxy-1,1′-biphenyl-4-ol (25). The title compound was prepared by reacting 4-bromophenol (0.61 g, 3.53 mmol) with 3-methoxyphenylboronic acid (0.75 g, 4.9 mmol), according to Method C to yield 0.31 g (44%) of a white solid: mp 79–81 °C; ^{1}H NMR (DMSO-d_6): δ 3.80 (3H, s), 6.82–6.86 (3H, m), 7.08–7.09 (1H, m), 7.12–7.15 (1H, m), 7.29–7.33 (1H, m), 7.48 (2H, d, J = 8.71 Hz), 9.53 (1H, s); MS (EI) m/z 200.08 (M^+). Anal. calcd for $C_{13}H_{12}O_2$: C: 77.98 H: 6.04; Found: C: 77.56 H: 5.91.

4′-(Trifluoromethoxy)-1,1′-biphenyl-4-ol (29). The title compound was prepared by reacting 4-bromophenol (0.52 g, 3.01 mmol) with 4-trifluoromethoxyphenylboronic acid (0.87 g, 4.2 mmol) according to Method C to yield 0.53 g (69%) of a white solid: mp 124–127 °C; ^{1}H NMR (DMSO-d_6): δ 6.86 (2H, d, J = 8.71 Hz), 7.37–7.40 (2H, m), 7.50 (2H, d, J = 8.71 Hz), 7.68 (2H, d, J = 8.84 Hz), 9.62 (1H, s); ^{19}F NMR (DMSO-d_6): δ −57.2 (s); MS (EI) m/z 254.02 (M^+). Anal. calcd for $C_{13}H_9F_3O_2$: C: 61.42H: 3.57; Found: C: 61.40H: 3.49.

1,1′:3′,1″-Terphenyl-4-ol (31). The title compound was prepared by reacting 3-bromobiphenyl (0.50 g, 2.15 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (0.76 g, 3.0 mmol) according to Method C to yield 0.48 g (91%) of a white solid: mp 78–85 °C; ^{1}H NMR (DMSO-d_6): δ 6.87 (2H, d, J = 8.71 Hz), 7.46–7.52 (3H, m), 7.55–7.60 (4H, m), 7.74 (2H, d, J = 7.05 Hz), 7.80 (1H, m), 9.56 (1H, s); MS (EI) m/z 246.1 (M^+). Anal. calcd for $C_{18}H_{14}O{\cdot}0.30H_2O$: C:85.89H:5.85; Found: C:85.58H:5.80.

1,1′:4′,1″-Terphenyl-4-ol (32). The title compound was prepared by reacting 4-bromophenol (0.49 g, 2.83 mmol) with 4-biphenylboronic acid (0.79 g, 4.0 mmol) according to Method C to yield 0.30 g (43%) of a white solid: mp > 250 °C; ^{1}H NMR (DMSO-d_6): δ 6.87 (2H, d, J = 8.71 Hz), 7.34–7.38 (1H, m), 7.46–7.49 (2H, m), 7.55 (2H, d, J = 8.58 Hz), 7.66–7.72 (6H, m), 9.57 (1H, s); MS (EI) m/z 246.1 (M^+). Anal. calcd for $C_{18}H_{14}O{\cdot}0.10H_2O$: C:87.14H:5.77; Found: C:87.30H:5.59.

2′-(Trifluoromethyl)-1,1′-biphenyl-4-ol (33). The title compound was prepared by reacting 2-bromobenzotrifluoride (0.61 g, 2.71 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (0.96 g, 3.8 mmol) according to Method C to yield 0.37 g (57%) of a white solid: mp 47–49 °C; ^{1}H NMR (DMSO-d_6): δ 6.8.1 (2H, d, J = 8.58 Hz), 7.11 (2H, d, J = 8.33 Hz), 7.36 (1H, d, J = 7.68 Hz), 7.53–7.57 (1H, m), 7.65–7.69 (1H, m), 7.77–7.79 (1H, m), 9.58 (1H, s); ^{19}F NMR (DMSO-d_6): δ −55.8 (s); MS (EI) m/z 238.06 (M^+). Anal. calcd for $C_{13}H_9F_3O$: C:65.55H:3.81; Found: C:65.30H:3.93.

3′-(Trifluoromethyl)-1,1′-biphenyl-4-ol (34). The title compound was prepared by reacting 4-bromophenol (0.54 g, 3.12 mmol) with 3-trifluoromethylphenylboronic acid (0.83 g, 4.4 mmol) according to Method C to yield 0.44 g (59%) of a white solid: mp 52–56 °C; ^{1}H NMR (DMSO-d_6): δ 6.88 (2H, d, J = 8.71 Hz), 7.58 (2H, d, J = 8.71 Hz), 7.61–7.67 (2H, m), 7.86–7.91 (2H, m), 9.68 (1H, s); MS (EI) m/z 238.06 (M^+). Anal. calcd for $C_{13}H_9F_3O$: C:65.55H:3.81; Found: C:65.53H:3.78.

4′-(Trifluoromethyl)-1,1′-biphenyl-4-ol (35). The title compound was prepared by reacting 4-bromobenzotrifluoride (0.60 g, 2.67 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (0.94 g, 3.7 mmol) according to Method C to yield 0.40 g (63%) of a white solid: mp 129–132 °C; ^{1}H NMR (DMSO-d_6): δ6.89 (2H, d, J = 8.71 Hz), 7.58 (2H, d, J = 8.72 Hz), 7.74 (2H, d, J = 8.32 Hz), 7.80 (2H, d, J = 8.20 Hz), 9.72 (1H, s); ^{19}F NMR (DMSO-d_6): δ −61.2 (s); MS (EI) m/z 238.05 (M^+). Anal. calcd for $C_{13}H_9F_3O$: C:65.55H:3.81; Found: C:65.11H:3.74.

4′-Hydroxy-1,1′-biphenyl-2-carbonitrile (36). The title compound was prepared by reacting 2-bromobenzonitrile

(0.41 g, 2.25 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (0.85 g, 3.4 mmol) according to Method C to yield 0.42 g (96%) of a white solid: mp 166–167 °C; ^{1}H NMR (DMSO-d_6): δ 6.91 (2H, d, J = 8.71 Hz), 7.41 (2H, d, J = 8.71 Hz), 7.48–7.52 (1H, m), 7.56 (1H, dd, J = 7.88 Hz, J = 0.70 Hz), 7.72–7.76 (1H, m), 7.89 (1H, dd, J = 7.82 Hz, J = 0.90 Hz), 9.79 (1H, s); MS (EI) m/z 188.2 (M^+). Anal. calcd for $C_{13}H_9NO$: C:79.98H:4.65 N:7.17; Found: C:79.62H:4.51 N:7.16.

4′-Hydroxy-1,1′-biphenyl-4-carbonitrile (38). The title compound was prepared by reacting 4-bromobenzonitrile (0.67 g, 3.68 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (1.30 g, 5.2 mmol) according to Method C to yield 0.65 g (91%) of a white solid: mp 182–186 °C; ^{1}H NMR (DMSO-d_6): δ 6.89 (2H, d, J = 8.71 Hz), 7.60 (2H, d, J = 8.71 Hz), 7.79 (2H, d, J = 8.71 Hz), 7.85 (2H, d, J = 8.58 Hz), 9.79 (1H, s); MS (EI) m/z 195.07 (M^+). Anal. calcd for $C_{13}H_9NO{\cdot}0.10H_2O$: C:79.25H:4.71 N:7.11 Found: C:79.48H:4.61 N:7.18.

2′-Ethyl-1,1′-biphenyl-4-ol (39). The title compound was prepared by reacting 4-bromophenol (0.68 g, 3.93 mmol) with 2-ethylphenylboronic acid (0.83 g, 5.5 mmol) according to Method C to yield 0.63 g (81%) of a white solid: mp 59–62 °C; ^{1}H NMR (DMSO-d_6): δ 1.02 (3H, t, J = 7.49 Hz), 2.54 (2H, q, J = 7.56 Hz), 6.81 (2H, d, J = 8.58 Hz), 7.07–7.11 (3H, m), 7.17–7.30 (3H, m), 9.44 (1H, s); MS (EI) m/z 198.1 (M^+). Anal. calcd for $C_{14}H_{14}O$: C:84.81H:7.12; Found: C:84.69H:6.95.

3′-Ethyl-1,1′-biphenyl-4-ol (40). The title compound was prepared by reacting 3-ethylbromobenzene (0.47 g, 2.54 mmol) with 4-tert-butyldimethylsilyloxyphenylboronic acid (**78**) (0.90 g, 3.6 mmol) according to Method C to yield 0.49 g (97%) of a white solid: mp 40–48 °C; ^{1}H NMR ($CDCl_3$): δ 1.28 (3H, t, J = 7.60 Hz), 2.70 (2H, q, J = 7.60 Hz), 4.50 (1H, bs), 6.90 (2H, d, J = 8.59 Hz), 7.15 (1H, d, J = 6.36 Hz), 7.30–7.37 (3H, m), 7.48 (2H, d, J = 8.59 Hz); MS (EI) m/z 198.1 (M^+). Anal. calcd for $C_{14}H_{14}O{\cdot}0.10H_2O$: C:84.05H:7.15; Found: C:84.15H:7.21.

4′-Chloro-3′-ethyl-1,1′-biphenyl-4-ol (42). The title compound was prepared by reacting 4-chloro-3-ethyl-phenyl trifluoromethanesulfonate (**79**) (0.41 g, 1.42 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (0.39 g, 1.6 mmol) according to Method C to yield 0.15 g (45%) of a white solid: mp: 77–81 °C; ^{1}H $CDCl_3$): δ 1.27 (3H, t, J = 7.52 Hz), 2.78 (2H, q, J = 7.54 Hz), 4.82 (1H, s), 6.90 (2H, d, J = 8.64 Hz), 7.29 (1H, dd, J = 8.28 Hz, J = 2.25 Hz), 7.35–7.39 (2H, m), 7.44 (2H, d, J = 8.64 Hz); MS (EI) m/z 232.07/234.07 (M^+). Anal. calcd for $C_{14}H_{13}ClO{\cdot}0.10H_2O$: C:71.70H:5.67; Found: C:71.58H:5.67.

2′,6′-Dichloro-1,1′-biphenyl-4-ol (44). The title compound was prepared by reacting 2,6-dichlorobromobenzene (0.79 g, 3.50 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (1.23 g, 4.9 mmol) according to Method C to yield 0.79 g (94%) of a white solid: mp 80–81 °C; ^{1}H NMR (DMSO-d_6): δ 6.85 (2H, d, J = 8.58 Hz), 7.05 (2H, d, J = 8.71 Hz), 7.36–7.40 (1H, m), 7.53–7.55 (2H, m), 9.63 (1H, s); MS (EI) m/z 238/240/242 (M^+). Anal. calcd for $C_{12}H_8Cl_2O$: C:60.28H:3.37; Found: C:59.93H:3.43.

5,3′-Dichloro-1,1′-biphenyl-4-ol (46). The title compound was prepared by reacting 2-chloro-4-bromophenol (0.52 g, 2.51 mmol) with 3-chlorophenylboronic acid (0.47 g, 3.0 mmol) according to Method C to yield 0.43 g (60%) of a clear oil which formed a white solid upon standing. Mp <40 °C; ^{1}H NMR (DMSO-d_6): δ 7.05 (1H, d, J = 8.41 Hz), 7.35–7.38 (1 H, m), 7.42–7.46 (1H, m), 7.50 (1H, dd, J = 8.48 Hz, J = 2.28 Hz) 7.57–7.60 (1H, m), 7.67–7.70 (2H, m), 10.41 (1H, s); MS (EI) m/z 238/240/242 (M^+). Anal. calcd for $C_{12}H_8Cl_2O$: C:60.28H:3.37; Found: C:60.30H:3.56.

3′-Chloro-3-methyl-1,1′-biphenyl-4-ol (47). The title compound was prepared by reacting 4-bromo-2-methylphenol (0.48 g, 2.57 mmol) with 3-chlorophenylboronic acid (0.48 g, 3.1 mmol) according to Method C to yield 0.38 g (68%) of a clear, colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.31 (3H, s), 4.78 (1H, s), 6.84 (1H, d, J = 8.22 Hz), 7.24–7.35 (4H,m), 7.39–7.42 (1H, m), 7.51–7.52 (1H, m); MS (EI) m/z 218.1/220.1 (M^+). Anal. calcd for $C_{13}H_{11}ClO{\cdot}0.20H_2O$: C:70.24H:5.17; Found: C:70.25H:5.16.

2,3′-Dichloro-1,1′-biphenyl-4-ol (49). The title compound was prepared by reacting 3-chloro-4-bromophenol (0.50 g, 2.41 mmol) with 3-chlorophenylboronic acid (0.45 g, 2.9 mmol) according to Method C to yield 0.30 g (52%) of a white solid: mp 71–73 °C; ^{1}H NMR (DMSO-d_6): δ 6.84 (1H, dd, J = 8.40 Hz, J = 2.46 Hz), 6.94 (1H, d, J = 2.46 Hz), 7.25 (1H, d, J = 8.40 Hz), 7.33–7.36 (1H, m), 7.41–7.48 (3H, m), 10.08 (1H, s); MS (EI) m/z 238/240/242 (M^+). Anal. calcd for $C_{12}H_8Cl_2O$: C:60.28H:3.37 Found: C:59.98H:3.70.

3′-Chloro-2-methyl-1,1′-biphenyl-4-ol (50). The title compound was prepared by reacting 4-bromo-3-methylphenol (0.53 g, 2.83 mmol) with 3-chlorophenylboronic acid (0.53 g, 3.4 mmol) according to Method C to yield 0.19 g (31%) of a clear, colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.22 (3H, s), 4.82 (1H, s), 6.69–6.75 (2H, m), 7.07 (1H, d, J = 8.14 Hz), 7.14–7.18 (1H, m), 7.28–7.34 (3H, m); MS (EI) m/z 218.1/220.1 (M^+). Anal. calcd for $C_{13}H_{11}ClO{\cdot}0.20H_2O$: C:70.24H:5.17; Found: C:70.25H:5.09.

3′,4′-Dichloro-1,1′-biphenyl-4-ol (52). The title compound was prepared by reacting 4-bromophenol (0.45 g, 2.60 mmol) with 3,4-dichlorophenylboronic acid (0.70 g, 3.6 mmol) according to Method C to yield 0.54 g (87%) of a white solid: mp 81–83 °C; ^{1}H NMR (DMSO-d_6): δ (6.85 (2H, d, J = 8.81 Hz), 7.55 (2H, d, J = 8.81 Hz), 7.58 (1H, dd, J = 8.45 Hz, J = 2.18H), 7.64 (1H, d, J = 8.46 Hz), 7.83 (1H, d, J = 2.18 Hz), 9.70 (1H, s); MS (EI) m/z 238/240/242 (M^+). Anal. calcd for $C_{12}H_8Cl_2O$: C:60.28H:3.37; Found: C:60.08H:3.47.

3′,5′-Dichloro-1,1′-biphenyl-4-ol (53). The title compound was prepared by reacting 4-bromophenol (0.64 g,

3.52 mmol) with 3,5-dichlorophenylboronic acid (0.94 g, 4.4 mmol) according to Method C to yield 0.63 g (75%) of a white solid: mp 108–109 °C; ^{1}H NMR (DMSO-d_6): δ 6.85 (2H, d, J = 8.84 Hz), 7.47–7.48 (1H, m), 7.58 (2H, d, J = 8.84 Hz), 7.63 (2H, d, J = 1.92 Hz), 9.75 (1H, s); MS (EI) m/z 238/240/242 (M^+). Anal. calcd for $C_{12}H_8Cl_2O$: C:60.28H:3.37; Found: C:60.14H:3.24.

3′-Chloro-4′-fluoro-1,1′-biphenyl-4-ol (55). The title compound was prepared by reacting 4-bromo-2-chlorofluorobenzene (0.53 g, 2.52 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (0.83 g, 3.3 mmol) according to Method C to yield 0.46 g (82%) of a white solid: mp 78–83 °C; ^{1}H NMR (DMSO-d_6): δ 6.84 (2H, d, J = 8.80 Hz), 7.41–7.45 (1H, m), 7.50 (2H, d, J = 8.66 Hz), 7.56–7.60 (1H, m), 7.76 (1H, dd, J = 7.11 Hz, J = 2.33 Hz), 9.64 (1H, s)Hz) Hh; ^{19}F NMR (DMSO-d_6): δ −120.8 (m); MS (EI) m/z 222.0/224.0 (M^+). Anal. calcd for $C_{12}H_8ClFO$: C:64.74H:3.62; Found: C:64.71H:3.95.

3′-Chloro-4′-methyl-1,1′-biphenyl-4-ol (56). The title compound was prepared by reacting 4-bromo-2-chlorotoluene (0.52 g, 2.53 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (0.83 g, 3.3 mmol) according to Method C to yield 0.34 g (61%) of a white solid: mp 87–90 °C; ^{1}H NMR ($CDCl_3$): δ 2.39 (3H, s), 4.80 (1H, s), 6.89 (2H, d, J = 8.64 Hz), 7.24–7.34 (2H, m), 7.44 (2H, d, J = 8.65 Hz), 7.52 (1H, d, J = 1.79 Hz); MS (EI) m/z 218/220 (M^+). Anal. calcd for $C_{13}H_{11}ClO{\cdot}0.4H_2O$: C:69.12H:5.27; Found: C:69.06H:5.13.

2-Chloro-4,4′-biphenol (57). The title compound was prepared by reacting 4-bromo-2-chlorophenol (0.53 g, 2.55 mmol) with 4-*tert*-butyldimethylsilyloxy-phenylboronic acid (**78**) (0.83 g, 3.3 mmol) according to Method C to yield 0.50 g (89%) of a white solid: mp 134–136 °C; ^{1}H NMR (DMSO-d_6): δ 6.80 (2H, d, J = 8.80 Hz), 6.99 (1H, d, J = 8.41 Hz), 7.34 (1H, dd, J = 8.40 Hz, J = 2.33 Hz), 7.40 (2H, d, J = 8.81 Hz), 7.50 (1H, d, J = 2.33 Hz), 9.46 (1H, s), 10.12 (1H, s); MS (EI) m/z 220/222 (M^+). Anal. calcd for $C_{12}H_9ClO_2{\cdot}0.20H_2O$: C:64.27H:4.22; Found: C:64.38H:4.23.

4′-Amino-3′-chloro-1,1′-biphenyl-4-ol (58). The title compound was prepared by reacting 4-bromo-2-chloroaniline (0.53 g, 2.57 mmol) with 4-*tert*-butyldimethylsilyloxy-phenylboronic acid (**78**) (0.83 g, 3.3 mmol) according to Method C to yield 0.48 g (85%) of a white solid: mp 148–160 °C; ^{1}H NMR (DMSO-d_6): δ 6.78 (2H, d, J = 8.66 Hz), 6.84 (1H, d, J = 8.27 Hz), 7.26 (1H, dd, J = 8.41 Hz, J = 2.20 Hz), 7.36 (2H, d, J = 8.79 Hz, 7.38 (1H, d, J = 2.07 Hz), 9.37 (1H, s); MS (EI) m/z 219/221 (M^+). Anal. calcd for $C_{12}H_{10}ClNO{\cdot}0.40$ $C_2HF_3O_2$: C:57.95H:3.95 N:5.28 Found: C:57.52H:3.96 N:5.07.

3-Chloro-4′hydroxy-1,1′-biphenyl-4-carbonitrile (59). The title compound was prepared by reacting 4-bromo-2-chlorobenzonitrile (0.56 g, 2.59 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (0.85 g, 3.4 mmol) according to Method C to yield 0.46 g (77%) of a white solid: mp 194–195 °C; ^{1}H NMR (DMSO-d_6): δ 6.89 (2H, d, J = 8.66 Hz), 7.67 (2H, d J = 8.80 Hz), 7.78 (1H, dd, J = 8.22 Hz, J = 1.75 Hz), 7.96–7.98 (2H, m), 9.91(1H, s); MS (EI) m/z 229/231 (M^+). Anal. calcd for $C_{13}H_8ClNO$: C:67.99H:3.51 N:6.10; Found: C:67.70H:3.64 N:5.98.

3′,5′-Dichloro-2-fluoro-1,1′-biphenyl-4-ol (63). The title compound was prepared by reacting 4-bromo-2-fluorophenol (0.51 g, 2.67 mmol) with 3,5–dichlorophenyl boronic acid (0.71 g, 3.7 mmol) according to Method C to yield 0.48 g (70%) of a white solid: mp 93–96 °C; ^{1}H NMR (DMSO-d_6): δ 7.0–7.05 (1H, m), 7.41–7.44 (1H, m), 7.52 (1H, t, J = 1.88 Hz), 7.62 (1H, dd, J = 12.74 Hz, J = 2.26 Hz), 7.70 (2H, d, J = 1.94 Hz), 10.20 (1H, s); ^{19}F NMR (DMSO-d_6): δ −136.1 (m); MS (EI) m/z 256/258/260 (M^+). Anal. calcd for $C_{12}H_7Cl_2FO{\cdot}0.2H_2O$: C:54.33H:2.86 Found: C:54.75H:2.82.

2′-Fluoro-3′-trifluoromethyl-1,1′-biphenyl-4-ol (67). The title compound was prepared by reacting 2-fluoro-3-trifluoro-phenyl trifluoromethanesulfonate (**82**) (0.42 g, 1.35 mmol) with 4-*tert*-butyldimethylsilyloxyphenyl boronic acid (**78**) (0.38 g, 1.5 mmol) according to Method C to yield 0.18 g (52%) of a white solid: mp 41–42 °C; ^{1}H NMR (DMSO-d_6): δ 6.90 (2H, d, J = 8.67 Hz), 7.40–7.42 (2H, m), 7.44–7.48 (1H, m), 7.69–7.73 (1H, m), 7.78–7.82 (1H, m), 9.78 (1H, s); ^{19}F NMR (DMSO-d_6): δ −122.3 (m), −60.4 (s); MS (EI) m/z 256.06 (M^+). Anal. calcd for $C_{13}H_8F_4O{\cdot}0.2H_2O$: C:60.10H:3.26; Found: C:60.15H:3.11.

2′-Chloro-3′-trifluoromethyl-1,1′-biphenyl-4-ol (68). The title compound was prepared by reacting 2-chloro-3-trifluoro-phenyl trifluoromethanesulfonate (**81**) (0.41 g, 1.25 mmol) with 4-*tert*-butyldimethylsilyloxyphenyl boronic acid (**78**) (0.35 g, 1.4 mmol) according to Method C to yield 0.25 g (73%) of a white solid: mp 84–86 °C; ^{1}H NMR (DMSO-d_6): δ 6.80 (2H, d, J = 8.67 Hz), 7.25 (2H, d, J = 8.67 Hz), 7.56–7.60 (1H, m), 7.66 (1H, dd, J = 7.76 Hz, J = 1.55 Hz), 7.83 (1H, dd, J = 7.76 Hz, J = 1.68 Hz), 9.71 (1H, s); ^{19}F NMR (DMSO-d_6): δ −61.3 (s); MS (EI) m/z 272.03/274.03 (M^+). Anal. calcd for $C_{13}H_8ClF_3O$: C:57.27H:2.96; Found: C:57.13H:2.95.

4′-Fluoro-3′-trifluoromethyl-1,1′-biphenyl-4-ol (69). The title compound was prepared by reacting 5-bromo-2-fluorobenzotrifluoride (0.57 g, 2.35 mmol) with 4-*tert*-butyldimethylsilyloxyphenyl boronic acid (**78**) (0.77 g, 3.0 mmol) according to Method C to yield 0.37 g (62%) of a white solid: mp 99–101 °C; ^{1}H NMR (DMSO-d_6): δ 6.87 (2H, d, J = 8.67 Hz), 7.52–7.56 (3H, m), 7.85–7.88 (1H, m), 7.92–7.96 (1H, m), 9.68 (1H, s); ^{19}F NMR (DMSO-d_6): δ −120.5–−120.6 (m);−60.4 (d, J = 12.76 Hz); MS (EI) m/z 265.0 (M^+). Anal. calcd for $C_{13}H_8F4_3O{\cdot}0.10H_2O$: C:60.52H:3.20; Found: C:60.44H:2.99.

4′-Chloro-3′-trifluoromethyl-1,1′-biphenyl-4-ol (70). The title compound was prepared by reacting 5-bromo-2-chlorobenzotrifluoride (0.54 g, 2.09 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (0.68 g, 2.7 mmol) according to Method C to yield 0.36 g (63%) of a white solid: mp 80–82 °C; ^{1}H NMR (DMSO-d_6): δ 6.88 (2H, d, J = 8.80 Hz), 7.59 (2H, d, J = 8.67 Hz), 7.74 (1H, d, J = 8.40 Hz), 7.90 (1H, dd, J = 8.41 Hz, J = 2.20 Hz),

7.95 (1H, d, $J=2.20$ Hz), 9.75 (1H, s); ^{19}F NMR (DMSO-d_6): δ −61.6 (s); MS (EI) m/z 272.0/274.0 (M^+). Anal. calcd for $C_{13}H_8ClF_3O\cdot0.2H_2O$: C:56.52H:3.06; Found: C:56.54H:3.09.

4′-Amino-3′-trifluoromethyl-1,1′-biphenyl-4-ol (71). The title compound was prepared by reacting 4-bromo-2-(trifluoromethyl)aniline (0.56 g, 2.33 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (0.76 g, 3.0 mmol) according to Method C to yield 0.33 g (56%) of a white solid: mp 119–124 °C; ^{1}H NMR (DMSO-d_6): δ 6.79 (2H, d, $J=8.66$ Hz), 6.89 (1H, d, $J=8.54$ Hz), 7.37 (2H, d, $J=8.67$ Hz), 7.46 (1H, d, 2.20 Hz), 7.51 (1H, dd, $J=8.53$ Hz, $J=1.94$ Hz), 9.40 (1H, s); ^{19}F NMR (DMSO-d_6): δ −61.78 (s); MS (EI) m/z 253 (M^+). Anal. calcd for $C_{13}H_{10}F_3NO\cdot0.1H_2O$: C:61.23H:4.03 N:5.49; Found: C:60.94H:3.90 N:5.49.

4′-Dimethylamino-3′-trifluoromethyl-1,1′-biphenyl-4-ol (72). The title compound was prepared by reacting 4-bromo-*N*,*N*-dimethyl-3-(trifluoromethyl)aniline (0.57 g, 2.13 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (0.70 g, 2.8 mmol) according to Method C to yield 0.36 g (60%) of a white solid: mp 94–98 °C; ^{1}H NMR (DMSO-d_6): δ 2.97 (6H, s), 6.76 (2H, d, $J=8.36$ Hz), 6.95–6.98 (2H, m), 7.04 (2H, d, $J=8.28$ Hz), 7.14 (1H, d, $J=8.27$ Hz), 9.42 (1H, bs); ^{19}F NMR (DMSO-d_6): δ −55.91 (s); MS (EI) m/z 281.1 (M^+). Anal. calcd for $C_{15}H_{14}F_3NO\cdot0.3C_2HF_3O_2$: C:59.39H:4.57 N:4.44; Found: C:59.61H:4.57 N:4.42.

3′,5′-Bis-trifluoromethyl-1,1′-biphenyl-4-ol (73). The title compound was prepared by reacting 3,5-bis(trifluoromethyl) bromobenzene (0.70 g, 2.39 mmol) with 4-*tert*-butyldimethylsilyloxyphenyl boronic acid (**78**) (0.84 g, 3.3 mmol) according to Method C to yield 0.72 g (98%) of a white solid: mp 102–104 °C; ^{1}H NMR (DMSO-d_6): δ 6.90 (2H, d, $J=8.66$ Hz), 7.97 (1H, s), 8.22 92H, s), 9.83 (1H, s); ^{19}F NMR (DMSO-d_6): δ −61.7 (s); MS (EI) m/z 305.9 (M^+). Anal. calcd for $C_{14}H_8F_6O$: C:54.92H:2.63; Found: C:54.95H:2.75.

2′-Fluoro-5′-trifluoromethyl-1,1′biphenyl-4-ol (74). The title compound was prepared by reacting 3-bromo-4-fluoro-benzotrifluoride (0.67 g, 2.75 mmol) with 4-*tert*-butyldimethylsilyloxyphenyl boronic acid (**78**) (0.90 g, 3.6 mmol) according to Method C to yield 0.61 g (87%) of a white solid: mp 76–77 °C; ^{1}H NMR (DMSO-d_6): δ 6.89 (2H, d, $J=8.79$ Hz), 7.44 (2H, dd, $J=8.60$ Hz, $J=1.75$ Hz), 7.49–7.54 (1H, m), 7.71–7.75 (1H, m), 7.80 (1H, dd, $J=7.18$ Hz, $J=2.26$ Hz), 9.77 (1H, s); ^{19}F NMR (DMSO-d_6): δ −112.8 (m), −60.8 (s); MS (EI) m/z 256.1 (M^+). Anal. calcd for $C_{13}H_8F_4O$: C:60.95H:3.15; Found: C:60.93H:3.05.

2′-Chloro-5′-trifluoromethyl-1,1′-biphenyl-4-ol (75). The title compound was prepared by reacting 3-bromo-4-chloro-benzotrifluoride (0.47 g, 1.81 mmol) with 4-*tert*-butyldimethylsilyloxyphenyl boronic acid (**78**) (0.55 g, 2.2 mmol) according to method C to yield 0.39 g (78%) of a white solid: mp 66–68 °C; ^{1}H NMR (DMSO-d_6): δ 6.87 (2H, d, $J=8.67$ Hz), 7.31 (2H, d, $J=8.66$ Hz), 7.66 (1H, d, $J=2.32$ Hz), 7.70 (1H, dd, $J=8.40$ Hz, $J=1.81$ Hz), 7.78 (1H, d, $J=8.40$ Hz), 9.73 (1H, s); ^{19}F NMR (DMSO-d_6): δ −61.4 (s); MS (EI) m/z 272.06/274.06 (M^+). Anal. calcd for $C_{13}H_8ClF_3O\cdot0.2H_2O$: C:56.52H:3.06; Found: C:56.63H:2.81.

3-Fluoro-4-methoxy-1,1′-biphenyl (83). The title compound was prepared by reacting bromobenzene (2.77 g, 17.6 mmol) with 3-fluoro-4-methoxyphenylboronic acid (**82**) (4.2 g, 24.7 mmol) according to Method C to yield 3.00 g (84%) of a white solid: mp 76–77 °C; ^{1}H NMR ($CDCl_3$): δ 3.93 (3H, s), 7.00–7.05 (1H, m), 7.29–7.35 (3H, m), 7.40–7.44 (2H,m), 7.51–7.54 (2H, m); ^{19}F NMR ($CDCl_3$): δ δ136 (m); MS (EI) m/z 202.2 (M^+). Anal. calcd for $C_{13}H_{11}FO$: C:77.21H:5.48; Found: C:76.96H:5.33.

3′-Chloro-3-fluoro-1,1′-biphenyl-4-yl methyl ether (84). The title compound was prepared by reacting 3-bromochlorobenzene (2.22 g, 11.59 mmol) with 3-fluoro-4-methoxyphenylboronic acid (**82**) (2.8 g, 16.2 mmol) according to Method C to yield 2.55 g (84%) of a clear oil: ^{1}H NMR ($CDCl_3$): δ 3.93 (3H, s), 6.99–7.04 (1H, m), 7.25–7.36 (4H, m), 7.38–7.40 (1H, m), 7.50–7.51 (1H, m); ^{19}F NMR ($CDCl_3$): δ −135 (m); MS (EI) m/z 236/238 (M^+). Anal. calcd for $C_{13}H_{10}ClFO$: C:65.97H:4.26; Found: C:65.90H:3.95.

2-Fluoro-4-methoxy-1,1′-biphenyl (87). The title compound was prepared by reacting 2-fluoro-4-methoxyphenyl trifluoromethanesulfonate (**86**) (0.44 g, 1.61 mmoles) with phenylboronic acid (0.25 g, 2.1 mmol) according to Method C to yield a clear oil: ^{1}H NMR ($CDCl_3$): δ 3.84 (3H, s), 6.69–6.79 (2H, m), 7.32–7.45 (4H, m), 7.50–7.53 (2H,m); ^{19}F NMR ($CDCl_3$): δ −116 (m); MS (EI) m/z 202.1 (M^+). Anal. calcd for $C_{13}H_{11}FO$: C:77.21H:5.48; Found: C:77.59H:5.49.

3′-Chloro-2-fluoro-1,1′-biphenyl-4-yl methyl ether (88). The title compound was prepared by reacting 2-fluoro-4-methoxyphenyl trifluoromethanesulfonate (**86**) (0.42 g, 1.53 mmoles) with 3-chloro-phenylboronic acid (0.31 g, 2.0 mmol) according to Method C to yield a clear oil: ^{1}H NMR ($CDCl_3$): δ 3.83 (3H,s), 6.68–6.78 (2H, m), 7.27–7.41 (4H, m), 7.49 (1H, d, $J=1.34$ Hz); ^{19}F NMR ($CDCl_3$): δ −116 (m); MS (EI) m/z 236/238 (M^+). Anal. calcd for $C_{13}H_{10}ClFO$: C:65.97H:4.26; Found: C:66.16H:4.13.

Method D: Pyridine hydrochloride demethylation

3-Fluoro-1,1′-biphenyl-4-ol (6). To 30 g of pyridine hydrochloride at 190 °C was added 3-fluoro-4-methoxy-1,1′-biphenyl (**83**) (2.05 g, 10.13 mmol). The resulting solution was stirred at 190 °C for 4 h and poured into 300 mL water. The resulting mixture was extracted with EtOAc (3×100 mL). The combined organic layers were washed with water, washed with brine, dried over sodium sulfate, and filtered. The solvent was removed by evaporation and the residue was purified on silica (10% EtOAc–hexanes) to yield 1.54 g (81%) of a white solid: mp 102–105 °C; ^{1}H NMR (DMSO-d_6): δ 7.00–7.05 (1H, m), 7.28–7.34 (2H, m), 7.39–7.44 (2H, m), 7.47 (1H, dd, $J=12.82$ Hz, $J=2.18$

Hz), 7.59–7.62 (2H, m), 9.96 (1H, s); ^{19}F NMR (DMSO-d_6): δ −136 (m); MS (ESI) m/z 187 ([M−H]). Anal. calcd for $C_{12}H_9FO$: C:76.58H:4.82; Found: C:76.44H:4.67.

2-Fluoro-1,1′-biphenyl-4-ol (9). The title compound was prepared by reacting 2-fluoro-4-methoxy-1,1′-biphenyl (**87**) (0.20 g, 0.99 mmol) with pyridine hydrochloride (12 g) according to Method D to yield 0.070 g (38%) of a white solid: mp 136–137 °C; ^{1}H NMR (DMSO-d_6): δ 6.64–6.73 (2H, m), 7.31–7.35 (2H, m), 7.41–7.48 (5H, m), 10.01 (1H, d, J = 1.03 Hz); ^{19}F NMR (DMSO-d_6): δ −117.3 (m); MS (EI) m/z 188 (M^+). Anal. calcd for $C_{12}H_9FO{\cdot}0.3H_2O$: C:74.45H:5.00; Found: C:74.06H:4.82.

3′-Chloro-3-fluoro-1,1′-biphenyl-4-ol (45). The title compound was prepared by reacting 3′-chloro-3-fluoro-1,1′-biphenyl-4-yl methyl ether (**84**) (2.15 g, 9.07 mmol) with pyridine hydrochloride hydrochloride (30 g) according to Method D to yield 1.87 g (92%) of a white waxy solid. HPLC purification yielded the title compound as a white solid: mp 50–51 °C; ^{1}H NMR (DMSO-d_6): δ 7.00–7.06 (1H, m), 7.35–7.39 (2H, m), 7.41–7.47 (1H, m), 7.55 (1H, dd, J = 12.95 Hz, J = 2.35 Hz), 7.59 (1H, d, J = 7.80 Hz), 7.67–7.69 (1H, m), 10.1 (1H, s); ^{19}F NMR (DMSO-d_6): δ −136 (m); MS (ESI) m/z 221/223 ([M−H]). Anal. calcd for $C_{12}H_8ClFO$: C:64.74H:3.62; Found: C:64.45H:3.72.

3′-Chloro-2-fluoro-1,1′-biphenyl-4-ol (48). The title compound was prepared by reacting 3′-chloro-2-fluoro-4-methoxy-biphenyl (**88**) (0.21 g, 0.89 mmol) with pyridine hydrochloride (12 g) to yield 0.18 g (91%) of a white solid: mp 62–64 °C; ^{1}H NMR (DMSO-d_6): δ 6.66–6.74 (2H, m), 7.35–7.41 (2H, m), 7.42–7.49 (2H, m), 7.51 (1H, d, J = 1.29 Hz), 10.14 (1H, d, J = 0.77 Hz); ^{19}F NMR (DMSO-d_6): δ −117.1 (m); MS (EI) m/z 222/224 (M^+). Anal. calcd for $C_{12}H_8ClFO$: C:64.74H:3.62; Found: C:60.58H:3.42.

Method E: conversion of phenols to triflates

4-Chloro-3-ethyl-phenyl trifluoromethanesulfonate (79). To a solution of 4-chloro-3-ethyl-phenol (0.72 g, 4.60 mmol) and pyridine (0.87 g, 11.0 mmol) in CH_2Cl_2 (30 mL) at 0 °C was slowly added trifluoromethanesulfonic anhydride (2.6 g, 9.2 mmol). The solution was allowed to warm to room temperature while stirring overnight and was then quenched by the addition of saturated sodium bicarbonate solution (50 mL). The resulting mixture was poured into water (100 mL) and extracted with EtOAc (1×100 mL). The layers were separated and the organic layer was washed with brine, dried over sodium sulfate, and filtered. The solvent was removed by evaporation and the residue was purified on silica (90% hexanes–10% EtOAc) to yield a clear oil: ^{1}H NMR (DMSO–d_6): δ 1.25 (3H, t, J = 7.54 Hz), 2.78 (2H, q, J = 7.53 Hz), 7.06 (1H, dd, J = 8.74 Hz, J = 2.94 Hz), 7.15 (1H, d, J = 2.94 Hz), 7.41 (1H, d, J = 8.76 Hz); ^{19}F NMR (DMSO–d_6): δ −73.2 (s); MS (EI) m/z 287.9/289.9 (M^+). Anal. calcd for $C_9H8_6ClF_3O_3S$: C:37.45H:2.79 Found: C:37.9H:2.77.

2 - Fluoro - 3 - trifluoro - phenyl trifluoromethanesulfonate (80). The title compound was prepared by reacting 2-fluoro-3-trifluoromethyl phenol (0.69 g, 3.83 mmol) with trifluoromethanesulfonic anhydride (2.2 g, 7.7 mmol) according to method E to yield a clear oil: ^{1}H NMR (DMSO–d_6): δ 7.50–7.60 (2H, m), 7.76 (1H, dd, J = 7.80 Hz, J = 1.30 Hz); ^{19}F NMR (DMSO-d_6): δ −61.6 (s), −73.4 (s), −128.9 (m).

2 - Chloro - 3 - trifluoro - phenyl trifluoromethanesulfonate (81). The title compound was prepared by reacting 2-chloro-3-trifluoromethyl phenol (0.71 g, 3.61 mmol) with trifluoromethanesulfonic anhydride (2.0 g, 7.2 mmol) according to Method E to yield a clear oil: ^{1}H NMR (DMSO–d_6): δ 7.33–7.39 (1H, m), 7.55–7.61 (1H, m), 7.64–7.69 (1H, m); ^{19}F NMR (DMSO-d_6): δ −63.0 (s), −73.6 (s), −128.9 (m); MS (EI) m/z 327.99/329.99 (M^+).

2-Fluoro-4-methoxy-phenol (85). A mixture of 4-bromo-2-fluorophenol (11.13 g, 58.3 mmol), CuBr (9.2 g, 64 mmol), sodium methoxide (50 mL of 25% in methanol), and DMF (75 mL) was stirred at reflux overnight. The suspension was cooled to room temperature and poured into HCl solution (300 mL of 2 N). The resulting suspension was extracted with EtOAc (3×200 mL). The combined organic layers were washed with water, dried over sodium sulfate, and filtered. The solvent was removed by evaporation and the residue was purified on silica (80% hexanes–20% EtOAc) to yield the title compound as a brown oil: ^{1}H NMR (DMSO-d_6): δ 3.67 (3H, s), 6.56–6.59 (1H, m), 6.78 (1H, dd, J = 12.94 Hz, J = 2.92 Hz), 6.83–6.88 (1H, m), 9.22 (1H, s); MS (EI) m/z 141.9 ([M]$^+$).

2 - Fluoro - 4 - methoxyphenyl trifluoromethanesulfonate (86). The title compound was prepared by reacting 2-fluoro-4-methoxy-phenol (**85**) (4.58 g, 32.25 mmol) with trifluoromethanesulfonic anhydride (10.0 g, 35.5 mmol) according to Method E to yield a clear oil: ^{1}H NMR (DMSO-d_6): δ 3.82 (3H, s), 6.90–6.94 (1H, m), 7.23 (1H, dd, J = 12.57 Hz, J = 3.05 Hz), 7.57–7.62 (1H, m); MS (EI) m/z 273.9 (M^+). Anal. calcd for $C_8H_6F_4O_4S$: C:35.04H:2.21 Found: C:35.34H:1.95.

Synthesis of hydroxymethyl-biphenyl-ol

(2,6-Dichloro-4-methoxy-phenyl)-methanol (89). A mixture of 3,5 dichloroanisole (16.39 g, 92.59 mmol), HCl (250 mL of concentrated solution), and sulfuric acid (2.5 mL of concentrated solution) was stirred at 60 °C overnight. The mixture was cooled to room temperature and the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were washed with water and the solvent was removed by evaporation. To the remaining oil was added NaOH (180 mL of 1 N solution) and dioxane (85 mL). The mixture was stirred at reflux for 3 h and cooled to room temperature. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with water, washed with brine, dried over sodium sulfate, and filtered. The residue was purified on

silica (90% hexanes–10% EtOAc) to yield 5.82 g (30%) of the title compound as a white solid: mp 71–72 °C; ^{1}H NMR ($CDCl_3$): δ 1.88 (1H, s), 3.73 (3H, s), 4.81 (2H, s), 6.81 (2H, s); MS (EI) *m*/*z* 206/208/210 (M^+). Anal. calcd for $C_8H_8Cl_2O_2$: C:46.41H:3.89; Found: C:46.38H:3.69.

2,6-Dichloro-4-methoxy-benzaldehyde (90). A suspension of (2,6-dichloro-4-methoxy-phenyl)-methanol (**89**) (5.69 g, 27.49 mmol) and MnO_2 (15 g) in benzene (100 mL) was stirred at reflux, utilizing a Dean-Stark trap, overnight. The suspension was cooled to room temperature, filtered through Celite, and the solvent was removed by evaporation to yield 4.69 g (83%) of crude white solid. An analytical sample was obtained by recrystallization from methanol to yield white needle crystals: mp 104–106 °C; ^{1}H NMR (DMSO-d_6): δ 3.90 (3H, s), 7.21 (2H, s), 10.29 (1H, s); MS (EI) *m*/*z* 204/206/218 (M^+). Anal. calcd for $C_8H_6Cl_2O_2$: C:46.86H:2.95 Found: C:46.67H:2.89.

2,6-Dichloro-4-hydroxy-benzaldehyde (91). To a solution of 2,6-dichloro-4-methoxy-benzaldehyde (**90**) (3.44 g, 16.8 mmol) in CH_2Cl_2 (120 mL) at 0 °C was slowly added boron tribromide (42 mL of 1 N in CH_2Cl_2, 42 mmol). The solution was allowed to warm to room temperature while stirring overnight and was quenched with saturated sodium bicarbonate solution (250 mL). The resulting mixture was extracted with EtOAc (3×200 mL). The combined organic layers were washed with water, washed with brine, dried over sodium sulfate, and filtered. The solvent was removed by evaporation and the residue was purified on silica (70% hexanes–30% EtOAc) to yield 2.19 g (68%) of a pink solid. Trituration with EtOAc–hexanes yielded an analytical sample of the title compound as a white solid: mp: 214–217 °C; ^{1}H NMR (DMSO-d_6): δ 6.95 (2H, s), 10.26 (1H, s), 11.44 (1H, s); MS (EI) *m*/*z* 189.8/191.8/193.8 (M^+). Anal. calcd for $C_7H_4Cl_2O_2$: C:44.02H:2.11; Found: C:44.08H:2.07.

3,5-Dichloro-4-formyl-phenyl-trifluoromethanesulfonate (92). The title compound was prepared by reacting 2,6-dichloro-4-hydroxy-benzaldehyde (**91**) (2.35 g, 12.3 mmol) with trifluoromethanesulfonic anhydride (4.51 g, 16.0 mmol) according to Method E to yield 3.45 g (87%) of a clear yellow oil. TLC analysis of this oil indicated that it appeared to decompose into the starting phenol upon standing. ^{1}H NMR (DMSO-d_6): δ 8.03 (2H, s), 10.31 (1H, s).

3,5-Dichloro-4′-hydroxy-1,1′-biphenyl-4-carbaldehyde (61). The title compound was prepared by reacting 3,5-dichloro-4-formyl-phenyl trifluoromethanesulfonate (**92**) (0.73 g, 2.26 mmol) with 4-*tert*-butyldimethylsilyloxyphenyl boronic acid (**78**) (0.80 g, 3.2 mmol) according to Method C to yield 0.30 g (50%) of a yellow solid: mp: 178–180 °C; ^{1}H NMR (DMSO-d_6): δ 6.88 (2H, d, *J* = 8.84 Hz), 7.72 (2H, d, *J* = 8.71 Hz), 7.84 (2H, s), 9.95 (1H, s), 10.38 (1H, s); MS (EI) *m*/*z* 266.0/268.0/270.0 (M^+). Anal. calcd for $C_{13}H_8Cl_2O_2 \cdot 0.5H_2O$: C:56.55H:3.29 Found: C:56.36H:2.90.

Method F: sodium borohydride reduction

3′,5′-Dichloro-4′hydroxymethyl-1,1′-biphenyl-4-ol (62). To a suspension of 3,5-dichloro-4′hydroxy-biphenyl-4-carbaldehyde (**61**) (0.075g, 0.28 mmol) in ethanol (3 mL) was added a solution of $NaBH_4$ (0.011 g, 0.28 mmol) in ethanol (1 mL). The resulting solution was stirred at room temperature for 1 h and then poured into 1 N HCl (50 mL). The mixture was extracted with EtOAc (2×50 mL). The combined organic layers were washed with water, washed with brine, dried over sodium sulfate, and filtered. The solvent was removed by evaporation and the residue was purified on silica (70% hexanes–30% EtOAc) to yield 0.061 g (81%) of the title compound as a white solid: mp 187–188 °C; ^{1}H NMR (DMSO-d_6): δ 4.69 (2H, s), 5.18 (1H, s), 6.85 (2H, d, *J* = 8.80 Hz), 7.57 (2H, d, *J* = 8.79 Hz), 7.65 (2H, s), 9.74 (1H, s); MS (EI) *m*/*z* 267/269/271 (M^+). Anal. calcd for $C_{13}H_{10}Cl_2O_2$: C:58.02H:3.75 Found: C:57.63H:3.63.

3,5-Dichloro-3′-fluoro-4′-methoxy-1,1′-biphenyl-4-carbaldehyde (93). The title compound was prepared by reacting 3,5-dichloro-4-formyl-phenyl-trifluoromethanesulfonate (**92**) (1.94 g, 6.01 mmol) with 3-fluoro-4-methoxyphenylboronic acid (**82**) (1.12 g, 6.61 mmol) according to Method C to yield 0.70 g (39%) of a white solid: mp 113–117 °C; ^{1}H NMR ($CDCl_3$): δ 3.96 (3H, s), 7.03–7.09 (1H, m), 7.32–7.37 (2H, m), 7.55 (2H, s), 10.52 (1H, s); ^{19}F NMR ($CDCl_3$): δ −134 (m); MS (EI) *m*/*z* 298.02/300.01/302.01 (M^+). Anal. calcd for $C_{14}H_9Cl_2FO_2$: C:56.21H:3.03 Found: C:55.97H:2.82.

Method G: boron tribromide demethylation

3,5-dichloro-3′-fluoro-4′-hydroxy-1,1′-biphenyl-4-carbaldehyde (65). To a solution of 3,5-dichloro-3′-fluoro-4′-methoxy-1,1′-biphenyl-4-carbaldehyde (**93**) (0.64 g, 2.14 mmol) in CH_2Cl_2 (25 mL) at 0 °C was slowly added a solution of boron tribromide (5.4 mL of 1N in CH_2Cl_2). The reaction was allowed to warm to room temperature while stirring overnight. The reaction was quenched by the addition of saturated sodium bicarbonate solution (50 mL). The mixture was extracted with EtOAc (2×100 mL). The combined organic layers were washed with water, washed with brine, dried over sodium sulfate, and filtered. Evaporation of the solvent and purification by silica column yielded 0.52 g (85%) of the title compound as a white solid: mp 169–170 °C; ^{1}H NMR (DMSO-d_6): δ 7.03–7.08 (1H, m), 7.55–7.58 (1H, m), 7.78 (1H, dd, *J* = 12.74 Hz, *J* = 2.26 Hz), 7.90 (2H, s), 10.37 (1H, s), 10.40 (1H, s); ^{19}F NMR (DMSO-d_6): δ −135.8 (m); MS (EI) *m*/*z* 284/286/288 (M^+). Anal. calcd for $C_{13}H_7Cl_2FO_2$: C:54.77H:2.47 Found: C:54.57H:2.36.

3′,5′-Dichloro-3-fluoro-4′-(hydroxymethyl)-1,1′-biphenyl-4-ol (66). The title compound was prepared by reacting 3,5-dichloro-3′-fluoro-4′-hydroxy-1,1′-biphenyl-4-carbaldehyde (**65**) with sodium borohydride (24 mg, 0.596 mmol) according to Method F to yield 0.16 g (94%) of a white solid: mp 155–158 °C; ^{1}H NMR (DMSO-d_6): δ 4.68 (2H, d, *J* = 5.17 Hz), 5.20 (1H, t, *J* = 5.37 Hz),

7.00–7.04 (1H, m), 7.41–7.44 (1H,m), 7.62 (1H, dd, $J = 12.80$ Hz, $J = 2.33$ Hz), 7.72 (2H, s), 10.19 (1H, s); ^{19}F NMR (DMSO-d_6): δ −136 (m); MS (ESI) m/z 285 ([M−H]−). Anal. calcd for $C_{13}H_9Cl_2FO_2 \cdot 0.1H_2O$: C:53.71H:3.19 Found: C:53.84H:3.11.

4-Bromo-2,5-dichlorophenol (94). A solution of 4-bromophenol (3.25 g, 18.78 mmol), NCS (5.29 g, 39.5 mmol), and acetonitrile (100 mL) was stirred for 2 days at room temperature. The reaction solution was poured into water (400 mL) and extracted with EtOAc (2×150 mL). The combined organic layers were washed with water, washed with brine, dried over sodium sulfate, and filtered. Evaporation of the solvent and purification by reverse phase preparative HPLC yielded 2.37 g (52%) of the title compound as an off white solid: mp 54–58 °C; ^{1}H NMR (DMSO-d_6): δ 7.63 (2H, s), 10.49 (1H, s); MS (EI) m/z 240/242/244/246 (M^+). Anal. calcd for $C_6H_3BrCl_2O \cdot 0.1H_2O$: C:29.35H:1.31; Found: C:29.29H:1.54.

3,5-Dichloro-1,1′-biphenyl-4,4′-diol (60). The title compound was prepared by reacting 4-bromo-2,5-dichlorophenol (**94**) (0.17 g, 0.70 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (**78**) (0.19 g, 0.77 mmol) according to Method C to yield 0.040 g (22%) of a white solid: mp 130–135 °C; ^{1}H NMR (DMSO-d_6): δ 6.81 (2H, d, $J = 8.79$ Hz), 7.46 (2H, d, $J = 8.80$ Hz), 7.55 (2H, s), 9.57 (1H, s); MS (ESI) m/z 253/255/257 ([M + H]$^+$). Anal. calcd for $C_{12}H_8Cl_2O_2 \cdot 0.2H_20$: C:54.95H:3.23; Found: C:55.36H:3.62.

3′,5′-Dichloro-2-fluoro-4′-hydroxy-1,1′-biphenyl-4-yl methyl ether (95). The title compound was prepared by reacting 4-Bromo-2,5-dichlorophenol (**94**) (0.71 g, 2.93 mmol) with 3-fluoro-4-methoxyphenylboronic acid (**82**) (0.65 g, 3.8 mmol) according to Method C to yield 0.33 g (39%) of a white solid: mp 98–99 °C; ^{1}H NMR ($CDCl_3$): δ 3.93 (3H, s), 5.85 (1H, s), 6.99–7.03 (1H, m), 7.18–7.25 (2H, m), 7.42 (2H, s); ^{19}F NMR ($CDCl_3$): δ −134.8 (m); MS (ESI) m/z 85/287 [M−H]$^-$. Anal. calcd for $C_{13}H_9Cl_2FO_2$: C:54.38H:3.16; Found: C:54.13H:2.93.

3′,5′-Dichloro-2-fluoro-1,1′-biphenyl-4,4′-diol (64). The title compound was prepared by reacting 3′,5′-dichloro-2-fluoro-4′-hydroxy-1,1′-biphenyl-4-yl methyl ether (**95**) (0.22 g, 0.77 mmol) with pyridine hydrochloride (20 g) according to Method D to yield 0.12 g (57%) of white solid: mp 142–145 °C; ^{1}H NMR (DMSO-d_6): δ 6.96–7.00 (1H, m), 7.30–7.32 (1H, m), 7.50 91H, dd, $J = 12.88$ Hz, 2.26 Hz), 7.62 (2H, s), 10.00 (1H, s), 10.16 (1H, s) ^{19}F NMR (DMSO-d_6): δ −136.2 (m); MS (ESI) m/z 271 ([M−H]$^-$). Anal. calcd for $C_{12}H_7Cl_2FO_2 \cdot 0.6H_2O$: C:48.91H:2.80; Found: C:49.01H:2.91.

Ligand binding competition experiments. A solid phase radioligand binding assay was used to measure interaction of compounds with ERα and ERβ[23] Briefly, the ligand binding domains of human ERα and ERβ were expressed in E. coli and a crude lysate prepared. Using high binding microtiter plates, eight concentrations of compounds were combined with 2 nM [^{3}H]-17β-estradiol and specific binding measured to ERα and ERβ after incubation at room temperature for 5–18 h. The assay buffer was 1× Dulbecco's phosphate buffered saline (pH 7.4) supplemented with 1mM EDTA. The results were plotted as measured DPM versus concentration of test compound. For dose–response curve fitting, a four-parameter logistic model on the transformed, weighted data was fit and the IC_{50} was defined as the concentration of compound decreasing maximum [^{3}H]-17β-estradiol binding by 50%.

Computational methodology. Coordinates for ERα complexed with diethylstilbestrol were obtained from the protein data bank X-ray crystal structure 3ERD.[7] Coordinates for the ERβ–genistein complex were obtained from an in-house X-ray structure, which was found to be in good agreement with previously published results.[8,25] All docking calculations were performed using the QXP software package.[26] After adding explicit hydrogens using the hadd/hopt utilities, the X-ray ligand was minimized in the active site. The resulting structure was used as input to a series of 10 constrained simulated annealing dynamics calculations. This was done to relieve any artifacts of the X-ray refinement perceived as unfavorable interactions or strain by the QXP forcefield. During the dynamics simulation, all atoms were allowed to move in a 0.1 Å radius flat potential, after which a 20 kJ/mol/Å^2 quadratic constraint penalty was applied. Once the binding site model was generated, docking of analogues was performed using the QXP Monte Carlo docking algorithm mcdock. In general, 1000 Monte Carlo steps was sufficient for the poses and their energy scores to converge. Visualization of X-ray structures and docking results was performed using the InsightII software package (Accelrys, Inc., San Diego, CA, USA).

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