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Synthesis and evaluation of aryl-substituted diarylpropionitriles, selective ligands for estrogen receptor β, as positron-emission tomographic imaging agents

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ABSTRACT

We have investigated halogen-substituted non-steroidal estrogens with selective binding affinity for the estrogen receptor β (ERβ that might be used for imaging the levels of this ER-subtype in breast tumors by positron emission tomography (PET). Based on diarylpropionitrile (DPN, **1a**), a compound previously reported that has a 72-fold binding selectivity for ERβ, we developed a series of DPN analogs having methyl-, hydroxyl-, and halogen substituents, including fluoroethyl and fluoropropyl groups. In competitive radiometric binding assays with [^{3}H]estradiol, all of these DPN analogs showed high ERβ/ERα selectivity; while the selectivity varied, in some cases it reached nearly 300-fold (RBA: ERα, 0.023%; ERβ, 6.25%). The absolute ERβ binding affinities, however, were not sufficient to merit further consideration for developing these ligands as PET imaging agents.

1. Introduction

The estrogen receptor (ER) cloned in 1986[1] was believed to be the only ER that mediated the actions of estrogens, and for many years the clinical management of breast cancer was guided, to a large extent, by the status (presence or absence) of this estrogen receptor. A second form of the ER, with its variant isoforms, was unexpectedly discovered by Gustafsson and co-workers in 1996, during a search for novel androgen receptors in a rat prostate cDNA library.[2] This gene was called ERβ to distinguish it from the long-known ER, which was then re-termed ERα. The discovery of ERβ made definition of the ER status of breast cancers more complex, because, potentially, the phenotype of breast tumors might be controlled by either or both ER-subtypes.[3] In fact, the approximately 30% of breast cancers classified as ER negative by immunohistochemical assays for ERα, might actually be positive for ERβ expression. The potential for ERβ to be a diagnostic or therapeutic target of importance provided motivation to define its physiological role in mediating estrogen action, and consequently, much attention has been given to understanding the structures of the two ERs and the respective roles that they play in both normal estrogen-regulated physiology as well as in various diseases, such as breast cancer, prostate cancer, endometriosis, and inflammation.[4] Recent findings that ERα is generally more active in driving breast cancer cell proliferation, with ERβ often having a moderating effect on the ERα activity, have added further interest.[5]

ERα and ERβ have different tissue distributions and appear to mediate different physiological functions. Although widely found in many tissues, ERα is predominantly expressed in reproductive tissues, kidney, liver, and central nervous system, whereas ERβ is expressed in bone, lungs, bladder, ovaries, endothelium, and prostate. The two ERs have modest overall sequence identity, differing primarily in their N-terminus domains, with higher sequence conservation in their DNA-binding domains (about 95% identity) and moderate (58% amino acid sequence identity) in their ligand binding domains (LBDs).[2b] Despite only moderate homology in their LBDs, X-ray structures have shown that the ligand binding pockets of ERα and ERβ are remarkably similar, with only 2 out of 24 residue different (ERα Leu384→ERβ Met_{336}; ERα Met421→ERβ Ile_{373}).[6,7] Overall, however, the ERβ ligand binding pocket is smaller than that of ERα, a difference that appears to be an important factor in the binding of ER-subtype selective ligands.[6,8] Despite the structural similarity of the ERα and ERβ ligand binding sites,

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it has proved possible to develop ER ligands that bind to and activate either ERα or ERβ with impressive selectivity, and a reasonable pharmacophore model has been advanced to guide the design of such subtype-selective ligands.[7,9]

The pharmacological use of ER-subtype-selective ligands is under active investigation, but radioisotope-labeled versions of these ligands for imaging the levels of ERα and ERβ in various target tissues by positron emission tomography (PET) or single photon emission computed tomography (SPECT) might also be very useful in assessing these receptors as targets for various estrogen therapies. In breast tumors, the level of ERβ relative to ERα declines with disease progression, as one might expect with transition of the cancer to a more proliferative and malignant state.[10] Thus, if it were possible to measure ERα and ERβ levels non-invasively by PET or SPECT, using radioisotope-labeled versions of ligands that were highly selective for ERα and ERβ, one might obtain information regarding disease stage and prognosis, and might even be able to predict tumor response to endocrine therapies.

Among the various ERβ pharmacophores, diarylpropionitrile (DPN, **1a**, Table 1) has good selectivity (72-fold ERβ affinity preference) with full agonistic character.[9d] A number of variants on the DPN pharmacophore have been studied, and some of these (e.g., **1b**, **1c**) had increased ERβ binding affinity though reduced selectivity. On the basis of this structure–activity relationship, the F-18 labeled DPN analogue, FEDPN (**1d**), was prepared previously and studied as a potential agent for PET imaging in rats and in ERα or ERβ knockout mice.[11] Its ER-specific uptake in ERβ target tissues such as the ovary, however, was only modest, not enough for [^{18}F]FEDPN to be useful for imaging ERβ.[11] Thus, there was a clear need to develop PET imaging agents that would be more optimized in terms of ERβ binding affinity and selectivity than [^{18}F]FEDPN. In this regard, one ring-substituted DPN analog, the *ortho*-methyl analog **1e**, looked promising in terms of its in vitro receptor binding profile (Table 1). To extend this work, we describe in this report the design, synthesis and preliminary biological evaluation of a series of DPN analogs substituted in the synthetically more accessible *meta*-position with several substituents of varying size and polarity. Some of these are fluoroalkylated DPN analogs in which it would be possible to introduce F-18, producing products that might be candidate for ERβ-selective PET tracers.

2. Results and discussion

2.1. Chemical synthesis

The routes for the preparation of the methyl-, hydroxy-, halo- (F, Cl, and Br) and fluoroalkyl diarylpropionitriles (DPNs) (**6a**, **6b**, **6d**–**f**, and **11a**–**b**) are shown in Scheme 1. Various α-cyanostilbenes (**4a**, **c** and **d**–**f**) were prepared in 32–92% yield by the condensation of 3-substituted 4-methoxybenzaldehyde analogues (**2a, 2c**–**f**) and 4-methoxyphenylacetonitrile (**3**) with NaOMe in EtOH at room temperature for 12 h.[12] In case of **2b**, the hydroxy-α-cyanostilbene could not be obtained without MEM protection. Bis-(methoxyphenyl)-propionitriles (**5a**, **c** and **d**–**f**) were obtained in excellent yield upon reduction of the corresponding acrylonitriles with $NaBH_4$ in EtOH at 70 °C for 12 h. Subsequent deprotection of the methyl ethers with BBr_3 afforded the desired methyl, hydroxy and halogen-substituted bisphenolic propionitriles (**6a**, **b** and **d**–**f**) in 94–98% yields. The methyl ether of **6b** was completely removed by treatment with BBr_3 after deprotection of MEM group with 1 N HCl in CH_3CN at 70 °C for 1 h, giving material with high yield and purity.

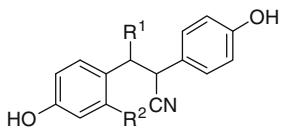
To prepare the fluoroalkylated DPN analogs (**11a**–**b**), bisphenolic nitrile (**6f**) was reprotected with MOMCl and NaH to give the MOM-protected analog **7** in 82% yield. This change of protecting groups was important, because in previous studies done on methyl ether-protected materials, we found that the final methyl ether-deprotection step, needed to obtain the desired fluoroalkyl bisphenol products, also caused cleavage the C–F bond.[11,13] The MOM group was selected because it is stable to the type of basic conditions used in the fluorination step, yet can easily be cleaved under mild acidic conditions.

To prepare the allyl-, vinyl-substituted intermediates **8a**–**b**, the MOM-protected **7** was treated with allyl or vinyl tributylstannane and Pd(II)$(PPh_3)_2Cl_2$ in anhydrous 1,4-dioxane at 90 °C for 12 h, thus giving the *meta*-allyl or vinyl bisphenyl nitrile **8a**–**b** in 44–64% yields. Hydroboration of alkenes **8a**–**b** using a borane–THF complex in THF at −10 °C for 12 h (for **9a**) or room temperature for 6 h (for **9b**), and subsequent oxidation with aqueous NaOH/H_2O_2, gave the terminal alcohols **9a–b** (36–68%), which were converted in high yields to the tosylates **10a–b**, precursors of fluorination, by treatment with toluenesulfonic anhydride and triethylamine in CH_2Cl_2 at room temperature for 30 min. The ether-protected fluoroethyl and fluoropropyl DPN analogs were obtained from the tosylates **10a**–**b** using CsF in *tert*-butanol at 100 °C for 16 h (>65%),[13,14] followed by deprotection of the MOM group with 1 N HCl/CH_3CN at 70 °C for 1 h, to give designed fluoroalkyl DPN analogues (**11a**–**b**).

The iodinated DPN analog **13** was prepared as shown in Scheme 2. The MOM-protected aryl stannane **12** was obtained in 70% yield from MOM-protected **7** by treatment with bis(tributyltin) and Pd(II)$(PPh_3)_2Cl_2$ at 100 °C. Iodination of stannane **12** with 1 M ICl/CH_2Cl_2, followed by deprotection of the MOM group with 1 N HCl/CH_3CN at 70 °C for 1 h, gave phenolic iodo-DPN **13** in 78% yield.

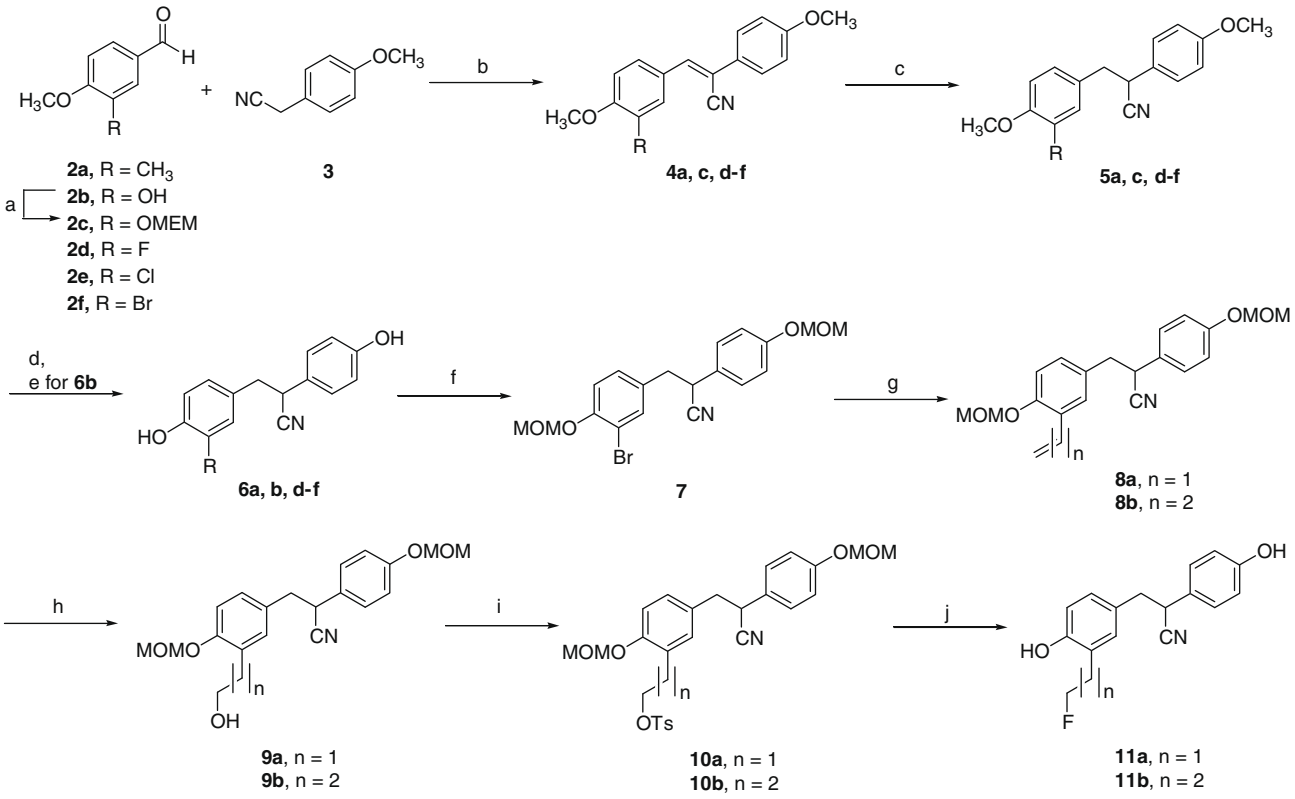
The hydroxymethyl analogue of DPN (**20**) was prepared as outlined in Scheme 3. Methyl ether-protected methyl-α-cyanostilbene (**4a**) was deprotected with BBr_3, affording the desired bisphenolic nitrile (**14**) in 94% yield. For the reasons described above, the free phenol groups in **14** were then reprotected with MOMCl and NaH to give the MOM-protected analog **15** in 74% yield. α-Cyanostilbene brominated in the benzylic position (**16**) was prepared in 61% yield by treatment with NBS and benzoyl peroxide in CCl_4 at reflux, and the bromide was then substituted by treatment with TBAF-3H_2O to give the fluoromethyl-α-stilbene moiety (**17**) in 74% yield. After conjugate reduction of unsaturated nitrile with $NaBH_4$ in EtOH (**18**, 96%), removal of the MOM group was attempted. Deprotection of MOM, however, with various reagents, such as 1 N HCl in MeOH, pyridinium *p*-toluenesulfonate in *tert*-BuOH, AcCl in MeOH CF_3COOH in CH_2Cl_2, or other conditions gave only the hydroxymethyl DPN analogue (**20**). We suspect that the sensitivity of this system is the result of its propensity for the 1,4-elimination of HF to form an orthoquinone methide species,

Table 1
Relative binding affinity (RBA) of DPN estrogen ligands for the ERα and ERβ

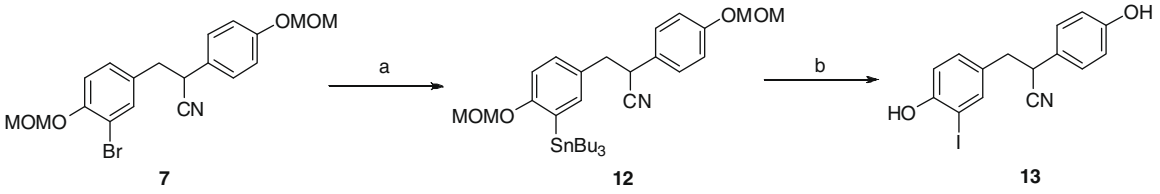


Compound	R^1	R^2	RBA (E_2 = 100)		ERβ/ERα ratio
			ERα	ERβ	
1a	H	H	0.25 ± 0.15	18 ± 2	72
1b	CH_3	H	1.7 ± 0.3	48 ± 3	11
1c	CH_2CH_3	H	17 ± 5	75 ± 6	4
1d	CH_2CH_2F	H	0.42 ± 0.09	8.74 ± 1.87	21
1e	H	CH_3	0.87 ± 0.18	60 ± 11	69

Data are taken from Refs. 9d and 11.



Scheme 1. Reagents and conditions: (a) DIEA, MEMCl, CH_2Cl_2, reflux, 6 h; (b) NaOMe, EtOH, rt, 12 h; (c) $NaBH_4$, EtOH, 70 °C, 12 h; (d) BBr_3, CH_2Cl_2, −10 °C to rt, 12 h; (e) (i) 1 N HCl, CH_3CN, 70 °C, 1 h; (ii) BBr_3, CH_2Cl_2, −10 °C to rt, 12 h; (f) NaH, MOMCl, THF, −10 °C to 70 °C, 2 h; (g) allyltributyltin (or vinyltributyltin), Pd(II)$(PPh_3)_2Cl_2$, 1,4-dioxane, 12 h; (h) BH_3–THF complex, 4 N NaOH, 30% H_2O_2, THF, −10 °C, 12 h for **9a**; −10 °C to rt, 6 h for **9b**; (i) Ts_2O, TEA, CH_2Cl_2, rt, 30 min; (j) (i) CsF, *tert*-BuOH, 100 °C, 16 h; (ii) 1 N HCl, CH_3CN, 70 °C, 1 h.



Scheme 2. Reagents and conditions: (a) Bistributyltin, Pd(II)$(PPh_3)_2Cl_2$, 1,4-dioxane, 100 °C, 12 h; (b) (i) ICl, CH_2Cl_2, rt, 10 min; (ii) 1 N HCl, CH_3CN, 70 °C, 1 h.

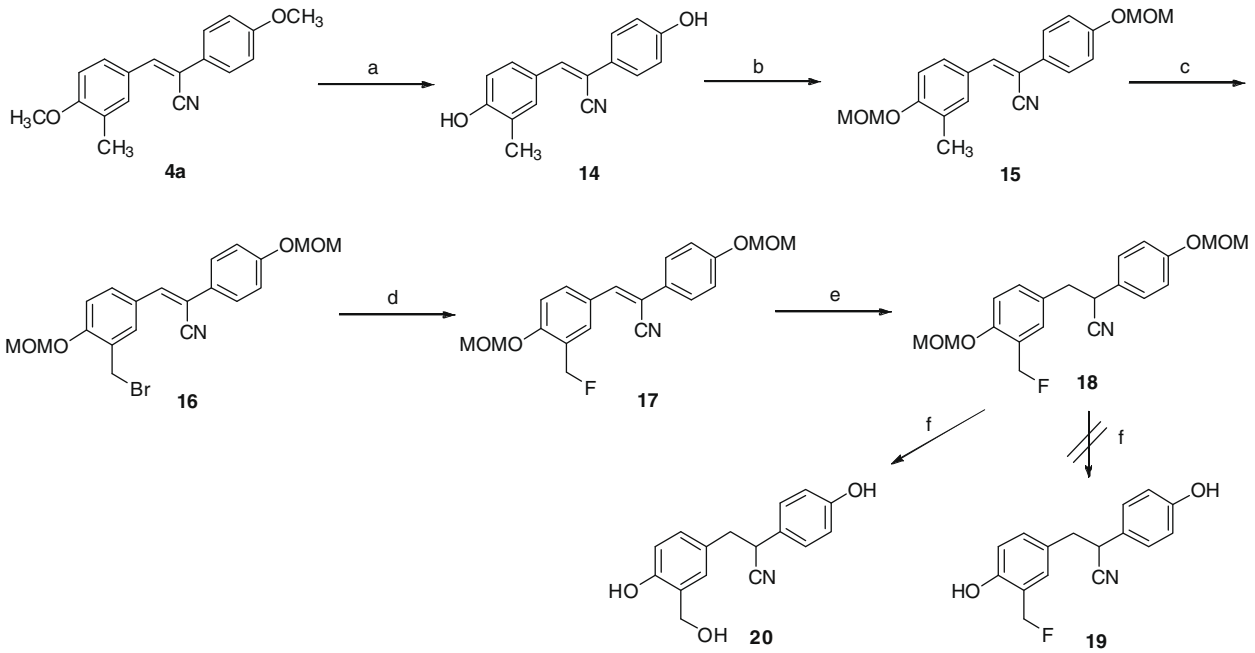
which then becomes hydrated, forming the hydroxy byproduct. Because of these difficulties, no further efforts toward fluoromethyl DPN (**19**) were made.

2.2. Relative binding affinity

The smaller substituted diarylpropionitrile estrogen analogues (**6a–b**, **6d–f**, **11a–b**, **13**, and **20**) were evaluated in competitive radiometric binding assays by previously described methods to measure their affinities for human ERα and ERβ.[15,16] Affinities obtained with these competitive binding assays are expressed as relative binding affinity (RBA) values, that is, relative to the that of [^{3}H]estradiol, which is 100% by definition. The binding affinities for the new DPN analogues we prepared and their ERβ/ERα affinity ratios are summarized in Table 2.

Analogues of the ERβ-selective ligand diarylpropionitrile (DPN, **1a**) containing substituents in the *meta*-position were investigated to establish the tolerance that ERβ has at this position for small substituents such as CH_3, OH, F, Cl, Br, and I. The lead compound, DPN (**1a**), has high ERβ binding selectivity, with a 72-fold preference for this ER-subtype, and all of the DPN analogues we have investigated share this ERβ selectivity to varying degrees. Although the addition of a methyl group at the *ortho*-position of DPN (**1e**, Table 1) results in a significantly increased affinity for ERβ with maintenance of high selectivity (60 ± 11 for ERβ and 0.87 ± 0.18 for ERα, β/α = 69-fold), we found that changing the position of this substituent from the *ortho*- to the *meta*-position (compound **6a**, Table 2) resulted in a 36-fold loss in ERβ binding affinity but, surprisingly, a two-fold increase in β/α selectivity. In fact, all of the aryl ring *meta*-substituted DPN analogues (**6a–b**, **6d–f**, **13**) showed lower binding affinities for both ERα and ERβ subtypes than estradiol, and also than DPN. While the ERβ binding affinities of the analogues having small substituents (namely, compounds **6a–b**, **6d–f**, **13**) are around 1–6% that of estradiol (100%), because their ERα affinities are all less than 0.025% that of estradiol, their ERβ/ERα selectivities range from 106 to 272. The size and electronic nature of these six substituents had relatively little effect on both their ERα and ERβ binding affinities.

Among the *meta*-halogen-substituted systems that might be radiolabeled for PET or SPECT imaging, fluoro-DPN (**6d**), which



Scheme 3. Reagents and conditions: (a) BBr_3, CH_2Cl_2, −10 °C to rt, 12 h; (b) NaH, MOMCl, THF, −10 °C to 70 °C, 2 h; (c) NBS, Bz_2O_2, CCl_4, 70 °C, 2 h; (d) TBAF-$3H_2O$, CH_3CN, 70 °C, 30 min; (e) $NaBH_4$, EtOH, 70 °C, 12 h; (f) 1 N HCl, MeOH or pyridinium *p*-toluenesulfonate, *tert*-BuOH, or AcCl, MeOH or CF_3COOH, CH_2Cl_2.

might be labeled with fluorine-18, has the most favorable binding affinities, 6.25% for ERβ and 0.023% for ERα, giving an ERβ/ERα ratio of 272-fold. Iodo-DPN (**13**), which might be labeled with iodine-123 or 124, showed 2.95% for ERβ and 0.021% for ERα, giving a selectivity of 140-fold, and bromo-DPN (**6f**), which could be labeled with bromine-76 or 77, had somewhat lower ERβ binding affinity and selectivity. None of these, however, would be particularly favorable for in vivo imaging.

Therefore, we investigated the *meta*-fluoroalkyl-DPN analogues, fluoromethyl- (**19**), fluoroethyl- (**11a**), or fluoropropyl-DPN (**11b**), into which it might be possible to introduce fluorine-18 relatively easily by nucleophilic aliphatic substitution. By contrast, the methods to label the fluorophenol unit in **6d** with fluorine-18 are relatively inefficient. Despite numerous attempts, we were unable to prepare fluoromethyl-DPN (**19**); all of the various deprotection conditions we used gave only hydroxymethyl DPN (**20**), an analog which has very low affinity for both ERα (0.002%) and ERβ (0.037%), and a modest ERβ/ERα selectivity (19-fold). The affinity of fluoroethyl-DPN (**11a)** for ERα 0.024%) was similar to that of fluoropropyl-DPN **11b**, 0.020%), while its affinity for ERβ 1.38%) was slightly higher than that of **11b** (0.896%); the ERβ/ERα ratios of these two compounds were 58- and 45-fold, respectively. In terms of both ERβ binding affinity and selectivity, the fluoroethyl-DPN (**11a**) is the better of the two fluoroalkyl derivatives.

Overall, although some of the DPN analogues we prepared had very high ERβ/ERα selectivities, one reaching almost 300-fold, none of them showed an affinity for ERβ that was better than that of DPN itself. From previously reported results,[9d] it is known that some DPNs with more optimized ERβ binding affinity and selectivity need to contain a linear core functional group, for example, nitriles or acetylenes, with relatively few other changes in the DPN structure. The fact that the binding affinity of the DPN analogues bearing small substituents in the *meta*-position, as characterized in this study, showed a several-fold drop in affinity is, unfortunately, consistent with these trends. Thus, the binding characteristics of these DPN analogs are not sufficiently promising for them to be considered further as potential PET or SPECT imaging radiotracers.

3. Conclusions

In conclusion, in an exploration to prepare ligands with good binding affinity and selectivity for the estrogen receptor β (ERβ) that might be explored further as PET imaging agents, we prepared nine new derivatives of the known ERβ-selective ligand, diarylpropionitrile (DPN), bearing substituents in the *meta*-position of the distal phenol ring. These included ones having fluoroethyl and fluoropropyl groups as well as methyl, hydroxymethyl, and halo-substituted DPN analogs to explore the structure–binding affinity relationship at this site. In competitive radiometric binding assays with [^{3}H]estradiol, most DPN derivatives showed greater ERβ/ERα selectivity than that of DPN. Among these, the *meta*-fluoro analog, **6d**, had the greatest ERβ/ERα selectivity 272-fold, with affinities that were 0.023% for ERα and 6.25% for ERβ relative to that of estradiol. Despite the good ERβ binding selectivities of many members of this series, their absolute binding affinities for ERβ are not good enough for them to be considered useful as potential PET or SPECT imaging agents for ERβ. In addition, preparation of the *ortho*-fluoro phenol unit in the most favorable compound (**6d**) in fluorine-18 labeled form would be challenging. Thus, ligands with more optimized ERβ binding affinity and adequate selectivities are likely be required for in vivo imaging of this estrogen receptor subtype.

4. Experimental

4.1. Chemistry

4.1.1. General

All commercial reagents and solvents were used without further purification unless otherwise specified. Reagents and solvents were commercially purchased from Sigma–Aldrich (USA), Merck (Germany) and TCI (Japan). Reaction progress was monitored by

Table 2
Relative binding affinity (RBA)[a] values for ERα and ERβ and the selectivity for ERβ as determined by β/α ratio

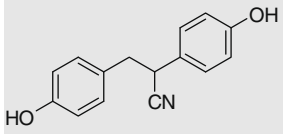
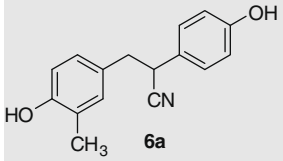
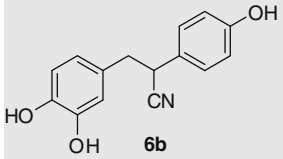
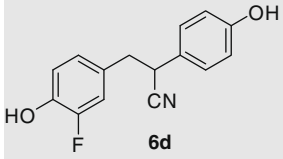
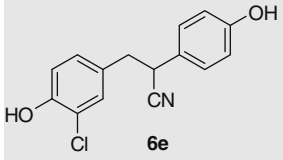
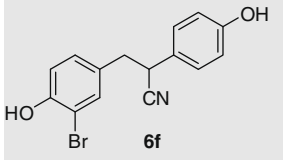
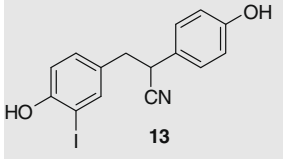
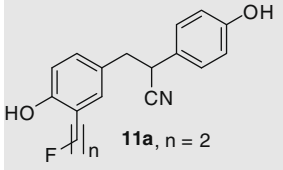
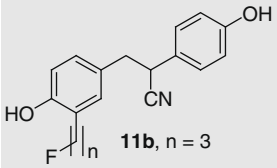
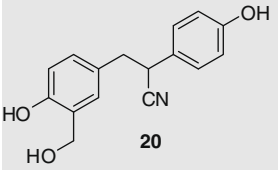
Compound	RBA (%)		β/α ratio
	hERα	hERβ	
 **1a, DPN**	0.25 ± 0.15	18 ± 2	72
 **6a**	0.012 ± 0.001	1.67 ± 0.32	139
 **6b**	0.012 ± 0.004	1.27 ± 0.31	106
 **6d**	0.023 ± 0.003	6.25 ± 1.4	272
 **6e**	0.010 ± 0.001	1.12 ± 0.04	112
 **6f**	0.012 ± 0.004	1.30 ± 0.13	108
 **13**	0.021 ± 0.001	2.95 ± 0.34	140
 **11a**, n = 2	0.024 ± 0.001	1.38 ± 0.33	58

Table 2 (*continued*)

Compound	RBA (%)		β/α ratio
	hERα	hERβ	
 **11b**, n = 3	0.020 ± 0.004	0.896 ± 0.19	45
 **20**	0.002 ± 0.00	0.037 ± 0.008	19

[a] Determined by a competitive radiometric binding assay with [^{3}H]estradiol and full length human ERα and ERβ. The RBA of estradiol (E_2) is defined as 100 and the measured RBA values are reported as the mean ± range or SD (n = 2 or 3).

analytical thin layer chromatography (TLC) with Merck 60 F-254 silica plates and visualized by UV light (254 nm) or phosphomolybdic acid indicator. Flash column chromatography was performed on silica gel (Merck, 230–400 mesh ASTM). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-300 instrument, and chemical shifts (δ, ppm) are reported in parts per million downfield from tetramethylsilane. Low- and high-resolution electron impact (EI) and chemical ionization (CI) mass spectra were obtained on a JMS700 spectrometer (JEOL Co., Japan).

4.1.2. 3-Methoxyethoxymethyl-4-methoxybenzaldehyde (2c)

Methoxyethoxymethyl chloride (1.12 mL, 9.86 mmol) was added dropwise to a CH_2Cl_2 (40 mL) containing 3-hydroxy-4-methoxybenzaldehyde (1.0 g, 6.57 mmol) and DIEA (3.43 mL, 19.7 mmol) at −10 °C. The reaction mixture was refluxed at 60 °C for 6 h and then cooled to room temperature. After the mixture was extracted with CH_2Cl_2, the organic layer was dried over sodium sulfate. The crude product was purified by flash column chromatography (40% EtOAc/hexane) to give **2c** (1.39 g, 88%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (br s, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.54 (dd, J = 8.4, 1.8 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 5.36 (s, 2H), 3.95 (s, 3H), 3.88–3.85 (m, 2H), 3.57–3.54 (m, 2H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 155.1, 146.9, 130.2, 126.5, 116.0, 111.2, 94.4, 71.5. 68.2, 59.1, 56.2; MS (EI) m/z: 240, 165, 151, 137, 109, 90 (100), 59 (100). HRMS (EI) calcd for $C_{12}H_{16}O_5$ (M^+) 240.0998, found 240.0998.

4.1.3. General method for (*Z*)-2-(3-methyl (4a)-, methoxyethoxymethyl (4c)-, fluoro (4d)-, chloro (4e)-, bromo (4f)-4-methoxyphenyl)-3-(4-methoxyphenyl)acrylonitrile

α-Cyanostilbenes (**4a**, **c**–**f**) were prepared by the condensation of arylaldehydes (**2a**, **c**–**f**) and arylacetonitriles (**3**) according to a reported method with little modification.[1] Briefly, for **4f**, a solution of 3-bromo-4-methoxybenzaldehydes (**2f**, 2.0 g, 9.3 mmol) and 4-methoxyphenylacetonitrile (**3**, 1.26 mL, 9.3 mmol) in absolute EtOH (6.5 mL, 0.7 mL/mmol) was treated with 0.5 N NaOMe (1.86 mL, 0.93 mmol) portionwise and then stirred at room temperature for 12 h. The reaction mixture was placed in a −24 °C freezer for 1 h, and the precipitate was collected by filtration. The precipitate was washed with cold ethanol to give **4f** (2.9 g, 91%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.92 (m, 2H), 7.56 (d, J = 9.0 Hz, 2H), 7.27 (s, 1H), 6.98–6.93 (m, 3H), 3.95 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 157.1, 138.0,

134.5, 129.2, 128.0, 127.2, 126.9, 118.2, 114.5, 112.0, 111.8, 110.0, 56.4, 55.5; MS (EI) *m/z*: 345 (M^++2, 100), 343 (M^+, 100), 330, 328, 221. HRMS (EI) calcd for $C_{17}H_{14}NO_2Br$ (M^+) 343.0207, found 343.0200.

4.1.3.1. (*Z*)-2-(3-Methyl-4-methoxyphenyl)-3-(4-methoxyphenyl)acrylonitrile (4a). This material was prepared by a procedure similar to that used for the preparation of **4f**, described above (yellow solid, 32%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, J = 8.4, 2.4 Hz, 1H), 7.66 (d, J = 2.4 Hz, 1H), 7.57 (d, J = 8.7 Hz, 2H), 7.33 (s, 1H), 6.94 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.4 Hz, 1H), 3.89 (s, 3H). 3.85 (s, 3H), 2,26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 159.4, 140.3, 131.7, 128.5, 127.6, 127.2, 127.0, 126.3, 118.8, 114.4, 110.0, 107.9, 55.5, 55.4, 16.3; MS (EI) *m/z*: 279 (M^+), 220, 191, 177, 163, 135 (100), 121, 107, 95. HRMS (EI) calcd for $C_{18}H_{17}O_2$ N (M^+) 279.1259, found 279.1261.

4.1.3.2. (*Z*)-2-(3-Methoxyethoxymethyl-4-methoxyphenyl)-3-(4-methoxyphenyl)acrylonitrile (4c). This material was prepared by a procedure similar to that used for the preparation of **4f**, described above. The purification of **4c**, however, was achieved by flash column chromatography (40% EtOAc/hexane) to give **4c** (92%) as a pale green oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.64 (m, 4H), 7.57 (d, J = 9.0 Hz, 1H), 6.97–6.93 (m, 3H), 5.23 (s, 2H), 3.92–3.89 (m, 5H), 3.84 (s, 3H), 3.60–3.57 (m, 2H), 3.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 151.44, 146.4, 139.8, 127.3, 127.14, 127.10, 123.9, 118.5, 117.7, 114.4, 111.7, 109.1, 94.7, 71.53, 68.0, 59.0, 56.0, 55.4; MS (EI) *m/z*: 369 (M^+, 100), 339, 293, 281, 89. HRMS (EI) calcd for $C_{21}H_{23}NO_5$ (M^+) 369.1576, found 369.1573.

4.1.3.3. (*Z*)-2-(3-Fluoro-4-methoxyphenyl)-3-(4-methoxyphenyl)acrylonitrile (4d). This material was prepared by a procedure similar to that used for the preparation of **4f**, described above (pale yellow solid, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.56 (m, 4H), 7.29–7.26 (m, 1H), 7.04–6.93 (m, 3H), 3.94 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 152.1 (d, J = 245.5 Hz), 149.2 (d, J = 10.9 Hz), 138.5 (d, J = 2.3 Hz), 127.2, 127.1, 126.9, 126.1 (d, J = 3.3 Hz), 118.2, 116.4 (d, J = 19.4 Hz), 114.5, 113.2 (d, J = 2.2 Hz), 109.9, 56.3, 55.5; MS (EI) *m/z*: 283 (M^+, 100), 268, 225, 208, 196, 142. HRMS (EI) calcd for $C_{17}H_{14}NO_2F$ (M^+) 283.1008, found 283.1009.

4.1.3.4. (*Z*)-2-(3-Chloro-4-methoxyphenyl)-3-(4-methoxyphenyl)acrylonitrile (4e). This material was prepared by a procedure similar to that used for the preparation of **4f**, described above (pale green solid, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.7, 2.4 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.27 (s, 1H), 7.00 (d, J = 8.7 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H), 3.95 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 156.3, 138.2, 131.3, 128.6, 127.5, 127.2, 126.9, 122.9, 118.2, 114.5, 112.0, 110.0, 56.3, 55.5; MS (EI) *m/z*: 301 (M^++2, 47), 299 (100), 284, 221, 206, 178, 151. HRMS (EI) calcd for $C_{17}H_{14}NO_2Cl$ (M^+) 299.0713, found 299.0712.

4.1.4. General method for the 2-(3-methyl (5a)-, methoxyethoxymethyl (5c)-, fluoro (5d)-, chloro (5e)-, bromo (5f)-4-methoxyphenyl)-3-(4-methoxyphenyl)propionitrile

Bismethoxyphenyl nitriles (**5a**, **c**–**f**) were prepared by the conjugate reduction of unsaturated nitriles with $NaBH_4$ in EtOH. Briefly, for **5f**, $NaBH_4$ (576 mg, 15.2 mmol) was added to a solution of α-cyanostilbene **4f** (2.6 g, 7.61 mmol) in 40 mL of anhydrous EtOH under argon atmosphere. After the reaction mixture was warmed to 70 °C for 12 h, the solution was cooled to room temperature. The mixture was extracted with ethyl acetate (×3), and the organic layer was dried over sodium sulfate and purified by flash column chromatography (30% EtOAc/hexane) to give **5f** (2.51 g, 95%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 2.1 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 7.03 (dd, J = 8.4, 2.1 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.4 Hz, 1H), 3.93–3.87 (m, 4H), 3.80 (s, 3H), 3.11–2.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 155.1, 133.9, 129.8, 129.4, 128.6, 126.8, 120.4, 114.4, 111.8, 111.5, 56.2, 55.3, 41.0, 39.0; MS (EI) *m/z*: 347 (M^++2, 9.1) 345 (M^+, 9.8), 201 (100), 199 (100), 146, 121, 105, 90, 77. HRMS (EI) calcd for $C_{17}H_{14}NO_2Br$ (M^+) 345.0364, found 345.0367.

4.1.4.1. 2-(3-Methyl-4-methoxyphenyl)-3-(4-methoxyphenyl)propionitrile (5a). This material was prepared by a procedure similar to that used for the preparation of **5f**, described above (pale yellow solid, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J = 8.7 Hz, 2H), 6.94–6.85 (m, 4H), 6.73 (d, J = 7.8 Hz, 1H), 3.92–3.85 (m, 1H), 3.81 (s, 6H), 3.11–2.99 (m, 2H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 157.0, 131.5, 128.6, 128.1, 127.5, 126.7, 120.8, 114.3, 109.9, 55.4, 55.3, 41.6, 39.4, 16.2; MS (EI) *m/z*: 281 (M^+), 146, 135 (100), 120, 91. HRMS (EI) calcd for $C_{18}H_{19}NO_2$ (M^+) 281.1416, found 281.1416.

4.1.4.2. 2-(3-Methoxyethoxymethyl-4-methoxyphenyl)-3-(4-methoxyphenyl)propionitrile (5c). This material was prepared by a procedure similar to that used for the preparation of **5f**, described above (white oily solid, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 1.5 Hz, 1H), 6.87–6.73 (m, 4H), 5.25 (s, 2H), 3.90 (t, J = 7.4 Hz, 1H), 3.85–3.82 (m, 5H), 3.78 (s, 3H), 3.55–3.52 (m, 2H), 3.36 (s, 3H), 3.10–2.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 148.9, 146.4, 129.0, 128.7, 127.3, 123.2, 120.7, 117.3, 114.3, 111.6, 94.4, 71.5, 67.7, 59.0, 55.9, 55.3, 41.7, 39.2; MS (EI) *m/z*: 371 (M^+), 296, 225 (100), 195, 151, 137, 89, 59. HRMS (EI) calcd for $C_{21}H_{25}NO_5$ (M^+) 371.1732, found 371.1730.

4.1.4.3. 2-(3-Fluoro-4-methoxyphenyl)-3-(4-methoxyphenyl)propionitrile (5d). This material was prepared by a procedure similar to that used for the preparation of **5f**, described above (white solid, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 8.7 Hz, 2H), 6.89–6.79 (m, 5H), 3.91 (t, J = 7.4 Hz, 1H) 3.87 (s, 3H), 3.80 (s, 3H), 3.12–2.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 152.1 (d, J = 244.7 Hz), 146.9 (d, J = 10.4 Hz), 129.1 (d, J = 6.2 Hz), 128.6, 126.8, 125.1 (d, J = 3.5 Hz), 120.5, 116.9 (d, J = 18.3 Hz), 114.4, 113.3 (d, J = 2.0 Hz), 56.2, 55.3, 41.3, 38.9; MS (EI) *m/z*: 285 (M^+), 139 (100), 105, 96, 77. HRMS (EI) calcd for $C_{17}H_{16}NO_2F$ (M^+) 285.1165, found 285.1166.

4.1.4.4. 2-(3-Chloro-4-methoxyphenyl)-3-(4-methoxyphenyl)propionitrile (5e). This material was prepared by a procedure similar to that used for the preparation of **5f**, described above (white solid, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 2.1 Hz, 1H), 6.98 (dd, J = 8.7, 2.1 Hz, 1H), 6.89–6.82 (m, 3H), 3.93–3.83 (m, 4H), 3.80 (s, 3H), 3.11–2.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 154.3, 130.9, 129.4, 128.7, 128.6, 126.8, 122.3, 120.4, 114.4, 112.0, 56.1, 55.4, 41.1, 39.0; MS (EI) *m/z*: 303 (M^++2, 3.0)301 (M^+, 8.9), 157 (41), 155 (100), 146, 105, 91, 77. HRMS (EI) calcd for $C_{17}H_{16}NO_2Cl$ (M^+) 301.0869, found 301.0870.

4.1.5. General method for the 2-(3-methyl (6a)-, hydroxy (6b)-, fluoro (6d)-, chloro (6e)-, bromo (6f)-4-hydroxyphenyl)-3-(4-hydroxyphenyl)propionitrile

Bisphenolic nitriles (**6a**, **b**, **d**–**f**) were prepared by removal of methyl ether with 1 M BBr_3/CH_2Cl_2. Briefly, for **6f**, boron tribromide (1.0 M in CH_2Cl_2, 41.6 mL) was added slowly dropwise to a stirred solution containing bismethoxyphenylacrylonitrile **5** (2.4 g, 6.9 mmol) in CH_2Cl_2 (80 mL) at −10 °C. After stirring for

30 min, the ice bath was removed, and stirring was continued for 12 h. The solution was cooled in an ice bath, and then slowly quenched with small amounts of water. The mixture solution was extracted with ethyl acetate (×3) and washed with brine. The organic layer was dried over sodium sulfate and purified by flash column chromatography (50% EtOAc/hexane) to give **6f** (2.15 g, 98%) as a white oily solid: ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.25 (d, J = 2.1 Hz, 1H), 7.08 (d, J = 8.7 Hz, 2H), 6.93 (dd, J = 8.1, 2.1 Hz, 1H), 6.79–6.73 (m, 3H), 4.10 (t, J = 7.4 Hz, 1H), 3.00 (d, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 157.1, 153.1, 133.5, 129.4, 129.3, 128.5, 126.1, 120.8, 115.6, 115.3, 109.2, 40.3, 38.2; MS (CI) *m/z*: 320 (MH^++2, 55.3), 318 (MH^+, 56.1), 293 (99.0), 291 (100), 240, 213. HRMS (CI) calcd for $C_{15}H_{13}NO_2Br$ (MH^+) 318.0129, found 318.0131.

4.1.5.1. 2-(3-Methyl-4-hydroxyphenyl)-3-(4-hydroxyphenyl)propionitrile (6a). This material was prepared by a procedure similar to that used for the preparation of **6f**, described above (pale yellow solid, 97%): ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.08 (d, J = 8.7 Hz, 2H), 6.85–6.72 (m, 4H), 6.62 (d, J = 8.1 Hz, 1H), 4.04 (t, J = 7.5 Hz, 1H). 2.95 (d, J = 7.5 Hz, 2H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 157.0, 154.2, 131.4, 128.4, 127.6, 127.2, 126.6, 124.1, 121.1, 115.2, 114.0, 41.1, 38.6; MS (CI) *m/z*: 254 (MH^+), 227 (100), 121. HRMS (CI) calcd for $C_{16}H_{16}NO_2$ (MH^+) 254.1181, found 254.1185.

4.1.5.2. 2-(3-Hydroxy-4-hydroxyphenyl)-3-(4-hydroxyphenyl)propionitrile (6b). This material was prepared by a procedure similar to that used for the preparation of **6f**, described above. The preparation of **6b**, however, was achieved by 1 M BBr_3/CH_2Cl_2 after MEM deprotection with 1 N HCl in CH_3CN at 70 °C for 1 h: ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.07 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H), 6.65 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 2.1 Hz, 1H), 6.47 (dd, J = 8.1, 2.1 Hz, 1H), 4.03 (t, J = 7.4 Hz, 1H), 2.93 (d, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 156.9, 144.7, 144.0, 128.44, 128.40, 126.5, 121.1, 120.4, 116.1, 115.2, 114.9, 41.2, 38.5; MS (EI) *m/z*: 255 (M^+), 123, 105, 77. HRMS (EI) calcd for $C_{15}H_{13}NO_3$ (M^+) 255.0895, found 255.0892.

4.1.5.3. 2-(3-Fluoro-4-hydroxyphenyl)-3-(4-hydroxyphenyl)propionitrile (6d). This material was prepared by a procedure similar to that used for the preparation of **6f**, described above (white solid, 96%): ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.08 (d, J = 8.4 Hz, 2H), 6.88–6.73 (m, 5H), 4.10 (t, J = 7.4 Hz, 1H), 2.99 (d, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 157.1, 151.2 (d, J = 238.8 Hz), 143.7 (d, J = 13.0 Hz), 128.6 (d, J = 6.0 Hz), 128.4, 126.2, 125.1 (d, J = 3.2 Hz), 120.8, 117.1 (d, J = 3.0 Hz), 116.3 (d, J = 18.6 Hz), 115.2, 40.6, 38.2; MS (CI) *m/z*: 258 (MH^+), 231 (100), 125. HRMS (CI) calcd for $C_{15}H_{13}NO_2F$ (MH^+) 258.0930, found 258.0932.

4.1.5.4. 2-(3-Chloro-4-hydroxyphenyl)-3-(4-hydroxyphenyl)propionitrile (6e). This material was prepared by a procedure similar to that used for the preparation of **6f**, described above (white solid, 96%): ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.08–7.05 (m, 3H), 6.87 (dd, J = 8.4, 2.1 Hz, 1H), 6.81–6.75 (m, 3H), 4.05 (t, J = 7.4 Hz, 1H), 2.97 (d, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 157.0, 151.9, 130.4, 129.1, 128.7, 128.5, 126.1, 120.8, 120.0, 116.1, 115.3, 40.4, 38.2; MS (CI) *m/z*: 276 (MH^++2, 13.6), 274 (MH^+, 38.2), 249 (35.5), 247 (100), 141. HRMS (CI) calcd for $C_{15}H_{13}NO_2Cl$ (MH^+) 274.0635, found 274.0640.

4.1.6. 2-(3-Bromo-4-methoxymethoxyphenyl)-3-(4-methoxymethoxyphenyl)propionitrile (7)

Chloromethyl methyl ether (2.2 mL, 28.92 mmol) was added in solution of **6f** (2.3 g, 7.23 mmol) in anhydrous THF (80 mL) at −10 °C. After stirring for 5 min, NaH (60%, 1.15 g, 28.92 mmol) was added in several portions over 5 min. The reaction mixture was refluxed for 2 h and then quenched with small amounts of water in an ice bath. The solution was diluted with ethyl acetate and then washed with water. The combined organic layer was dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatography (25% EtOAc/hexane) to give **7** (2.4 g, 82%) as a white oily solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 2.1 Hz, 1H), 7.16 (d, 8.7 Hz, 2H), 7.06–7.01 (m, 4H), 5.23 (s, 2H), 5.18 (s, 2H), 3.93–3.88 (m, 1H), 3.5 (s, 3H), 3.48 (s, 3H). 3.06–3.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 153.1, 134.0, 131.2, 129.3, 128.6, 128.1, 120.3, 116.8, 116.1, 112.8, 95.1, 94.4, 56.4, 56.1, 41.1, 39.0; MS (EI) *m/z*: 407 (M^++2), 405 (M^+), 234, 232, 221 (100), 201, 191. HRMS (EI) calcd for $C_{19}H_{20}NO_4Br$ (M^+) 405.0575, found 405.0576.

4.1.7. 2-(3-Vinyl-4-methoxymethoxyphenyl)-3-(4-methoxymethoxyphenyl)propionitrile (8a)

$Pd(II)(PPh_3)_2Cl_2$ (86 mg, 0.123 mmol) and vinyltributyltin (1.08 mL, 3.69 mmol) was added to a solution of MOM protected propionitrile **7** (1.0 g, 2.46 mmol) in anhydrous 1,4-dioxane (40 mL) under argon atmosphere. The reaction mixture was heated to 100 °C for 2 h. The solution was removed in a vacuum and the crude product purified by flash chromatography (25% EtOAc/hexanes) to give vinyl **8a** (590 mg, 68%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.16 (m, 3H), 7.06–6.96 (m, 5H), 5.62 (dd, J = 18, 1.5 Hz, 1H), 5.25 (dd, J = 11.4, 1.5 Hz, 1H), 5.19 (s, 2H), 5.17 (s, 2H), 3.94–3.90 (m, 1H), 3.480 (s, 3H), 3.476 (s, 3H), 3.15–3.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 153.6, 131.3, 129.7, 129.6, 128.7, 128.5, 127.6, 127.3, 120.6, 116.7, 115.0, 114.9, 94.7, 94.4, 56.2, 56.1, 41.6, 39.2; MS (EI) *m/z*: 353 (M^+), 231, 221, 177, 145 (100), 117. HRMS (EI) calcd for $C_{21}H_{23}NO_4$ (M^+) 353.1627, found 353.1628.

4.1.8. 2-(3-Allyl-4-methoxymethoxyphenyl)-3-(4-methoxymethoxyphenyl)propionitrile (8b)

This material was prepared by a procedure similar to that used for the preparation of vinyl **8a**, described above, and obtained allyl **8b** (44%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 8.7 Hz, 2H), 7.02–7.00 (m, 4H), 6.86 (d, J = 1.8 Hz, 1H), 5.96–5.85 (m, 1H), 5.17 (s, 4H), 5.04–4.97 (m, 2H), 3.92–3.87 (m, 1H), 3.48 (s, 3H), 3.90 (s, 3H), 3.34 (d, J = 6.3 Hz, 2H), 3.08–2.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 154.2, 136.7, 130.9, 129.5, 129.3, 128.7, 128.6, 128.1, 120.6, 116.7, 115.6, 114.1, 94.4 (two), 56.1 (two), 41.6, 39.2, 34.2; MS (EI) *m/z*: 367 (M^+), 191 (100), 159. HRMS (EI) calcd for $C_{22}H_{25}NO_4$ (M^+) 367.1783, found 367.1783.

4.1.9. 2-(3-Hydroxyethoxy-4-methoxymethoxyphenyl)-3-(4-methoxymethoxyphenyl)propionitrile (9a)

BH_3–THF complex (1 M, 2.16 mmol, 2.16 mL) was added dropwise to an anhydrous tetrahydrofuran (30 mL) solution of vinyl **8a** (510 mg, 1.44 mmol) at −10 °C. The reaction mixture was stirred at 0 °C for 12 h under an argon atmosphere. The mixture was quenched with small amounts of water. Sodium hydroxide (4 M, 7 mL) and 30% H_2O_2 (8 mL) were added, and the resulting reaction mixture was stirred for 30 min more in an ice bath. The solution was extracted with ethyl acetate, and the combined organic layer was dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatography (50% EtOAc/hexane) to give hydroxyethoxy **9a** (196 mg, 36%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 8.7 Hz, 2H), 7.03–7.00 (m, 4H), 6.88 (d, J = 2.1 Hz, 1H), 5.19 (s, 2H), 5.17 (s, 2H), 3.91 (t, J = 7.2 Hz, 1H), 3.78 (t, J = 6.6 Hz, 2H), 3.48 (s, 3H), 3.47 (s, 3H), 3.07–3.03 (m, 2H), 2.85 (t, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 154.6, 132.0, 129.5, 128.7, 128.51, 128.47, 127.7, 120.6, 116.7, 114.1, 94.5, 94.4, 62.7, 56.2, 56.1, 41.5, 39.3, 33.9; MS (EI) *m/z*: 371 (M^+), 310, 221, 195, 163, 133 (100). HRMS (EI) calcd for $C_{21}H_{25}NO_5$ (M^+) 371.1732, found 371.1732.

4.1.10. 2-(3-Hydroxypropoxy-4-methoxymethoxyphenyl)-3-(4-methoxymethoxyphenyl)propionitrile (9b)

This material was prepared by a procedure similar to that used for the preparation of allyl **9a**, described above: 1 M BH_3–THF complex (2.12 mmol, 2.12 mL) was added in anhydrous tetrahydrofuran solution (30 mL) of vinyl **8b** (520 mg, 1.42 mmol) dropwise at −10 °C. The reaction mixture was stirred at 0 °C for 30 min and stirred for 6 h more at room temperature under an argon atmosphere. The solution was quenched with small amounts of water. Sodium hydroxide (4 M, 7.0 mL) and 30% H_2O_2 (8.0 mL) was added, and the resulting reaction mixture was stirred for 30 min more in an ice bath. The mixture was extracted with ethyl acetate, and the combined organic layer was dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatography (50% EtOAc/hexane) to give hydroxypropoxy **9b** (370 mg, 68%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 8.7 Hz, 2H), 7.03–6.94 (m, 4H), 6.85 (d, J = 2.1 Hz, 1H), 5.19 (s, 2H), 5.17 (s, 2H), 3.91 (t, J = 7.2 Hz, 1H), 3.55 (t, J = 6.0 Hz, 2H), 3.48 (s, 6H), 3.07–3.03 (m, 2H), 2.68 (t, J = 7.4 Hz, 2H), 1.83–1.74 (m, 3H, $-CH_2$, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 154.4, 131.5, 130.6, 129.5, 128.7, 128.6, 127.9, 120.6, 116.7, 114.0, 94.6, 94.4, 61.6, 56.2, 56.1, 41.5, 39.3, 32.6, 26.0; MS (EI) *m/z*: 385 (M^+), 292, 209, 177, 147 (100). HRMS (EI) calcd for $C_{22}H_{27}NO_5$ (M^+) 385.1889, found 385.1890.

4.1.11. 2-(3-*p*-Toluenesulfonyloxyethyl-4-methoxymethoxyphenyl)-3-(4-methoxymethoxyphenyl)propionitrile (10a)

p-Toluenesulfonic anhydride (237 mg, 0.73 mmol), TEA (203 μL, 1.46 mmol) were added to a CH_2Cl_2 (20 mL) solution of hydroxyethyl **9a** (180 mg, 0.49 mmol) and stirred 30 min. The solution was extracted with ethyl acetate and the combined organic layer was dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatography (35% EtOAc/hexane) to give tosylate **10a** (250 mg, 98%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 7.03–6.92 (m, 4H), 6.84 (d, J = 1.8 Hz, 1H), 5.17 (s, 2H), 5.07 (s, 2H), 4.18 (t, J = 7.0 Hz, 2H), 3.88 (t, J = 7.4 Hz, 1H), 3.47 (s, 3H), 3.37 (s, 3H), 3.03–3.01 (m, 2H), 2.94 (t, J = 7.1 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 154.5, 144.5, 133.2, 131.8, 129.7, 129.6, 129.1, 128.6, 128.5, 127.8, 125.1, 120.5, 116.7, 113.8, 94.4, 94.3, 69.4, 56.1, 41.4, 39.2, 30.5, 21.6; MS (EI) *m/z*: 525 (M^+), 462, 349, 221, 133 (100). HRMS (EI) calcd for $C_{28}H_{31}NO_7S$ (M^+) 525.1821, found 525.1822.

4.1.12. 2-(3-*p*-Toluenesulfonyloxypropyl-4-methoxymethoxyphenyl)-3-(4-methoxymethoxyphenyl)propionitrile (10b)

This material was prepared by a procedure similar to that used for the preparation of ethyl tosylate **10a**, described above, and produced tosylate **10b** (82%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.03–6.96 (m, 4H), 6.85 (d, J = 1.8 Hz, 1H), 5.17 (s, 2H), 5.15 (s, 2H), 4.08–3.98 (m, 2H), 3.92 (t, J = 7.4 Hz, 1H), 3.47 (s, 3H), 3.44 (s, 3H), 3.02–2.97 (m, 2H), 2.64 (t, J = 7.4 Hz, 2H), 2.43 (s, 3H), 1.95–1.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 154.4, 144.7, 131.1, 129.8, 129.6, 129.5, 128.7, 128.6, 128.3, 127.9, 120.6, 116.7, 113.9, 94.42, 93.37, 70.0, 56.08, 56.07, 41.6, 39.3, 29.0, 26.3, 21.6; MS (EI) *m/z*: 539 (M^+), 363, 147 (100). HRMS (EI) calcd for $C_{29}H_{33}NO_7S$ (M^+) 539.1978, found 539.1978.

4.1.13. 2-[3-(2-Fluoroethyl-4-hydroxyphenyl)-3-(4-hydroxyphenyl)]propionitrile (11a)

Tosylate **10a** (175 mg, 0.33 mmol) and CsF (506 mg, 3.30 mmol) were dissolved in anhydrous *tert*-butanol (15 mL) and stirred at 100 °C for 16 h. The reaction mixture was extracted with ethyl acetate, and the combined organic layer was dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatography (30% EtOAc/hexane) to give ether-protected **11a**. The collected compound was dissolved in CH_3CN (15 mL) and stirred with 1 N HCl (6 mL) for 1 h at 80 °C. The solution was extracted with ethyl acetate, and combined organic layer was dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatography (50% EtOAc/hexane) to give fluoroethylate **11a** (74 mg, 78%) as a white solid: ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.60 (d, J = 8.4 Hz, 2H), 6.87–6.83 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.7 Hz, 1H), 4.50 (dt, J = 47.4, 7.0 Hz, 2H), 4.06 (t, J = 7.4 Hz, 1H), 3.00–2.86 (m, 4H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 157.0, 154.4, 131.7, 128.43, 128.38, 127.6, 126.4, 122.9, 122.8, 121.0, 115.2, 114.4, 82.4 (d, J = 166.4 Hz), 41.0, 38.5, 31.2 (d, J = 20.9 Hz); MS (CI) *m/z*: 286 (MH^+), 266 (100), 259, 239, 153, 133. HRMS (CI) calcd for $C_{17}H_{17}O_2NF$ (MH^+) 286.1243, found 286.1243.

4.1.14. 2-[3-(3-Fluoropropyl-4-hydroxyphenyl)-3-(4-hydroxyphenyl)]propionitrile (11b)

This material was prepared by a procedure similar to that used for the preparation of fluoroethylate **11a**, described above, and produced fluoropropylate **11b** (83%) as a white solid: ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.06 (d, J = 8.7 Hz, 2H), 6.84–6.79 (m, 2H), 6.74 (d, J = 8.7 Hz, 2H), 6.65 (d, J = 8.1 Hz, 1H), 4.36 (dt, J = 41.4, 12.3 Hz, 2H), 4.06 (t, J = 7.2 Hz, 1H), 3.00 (d, J = 7.2 Hz, 2H), 2.61 (t, J = 7.5 Hz, 2H), 1.96–1.83 (m, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 157.0, 154.1, 131.0, 128.4, 127.7, 127.5, 127.3, 126.4, 121.0, 115.2, 114.4, 83.0 (d, J = 162.7 Hz), 41.0, 38.5, 30.2 (d, J = 19.4 Hz), 25.4 (d, J = 6.1 Hz); MS (CI) *m/z*: 300 (MH^+), 280 (100), 273, 253, 167, 147. HRMS (CI) calcd for $C_{18}H_{19}NO_2F$ (MH^+) 300.1400, found 300.1401.

4.1.15. 2-(3-Tributylstannyl-4-methoxymethoxyphenyl)-3-(4-methoxymethoxyphenyl)propionitrile (12)

MOM-protected **7** (500 mg, 1.23 mmol) was dissolved in anhydrous 1,4-dioxane (25 mL), and the following reagents were added: Pd(II)$(PPh_3)_2Cl_2$ (43 mg, 0.06 mmol) and bis(tributyltin) (925 μL, 1.85 mmol). The reaction mixture was heated at 100 °C for 12 h under an argon atmosphere. The reaction mixture was collected by filtration, and then the solvent removed in a vacuum. The crude product purified by flash chromatography (30% EtOAc/hexanes) to give **12** (530 mg, 70%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 8.7 Hz, 2H), 7.08–6.91 (m, 5H), 5.16 (s, 2H), 5.12 (s, 2H), 3.89 (t, J = 7.2 Hz, 1H), 3.48 (s, 3H), 3.45 (s, 3H), 3.15–3.01 (m, 2H), 1.53–1.47 (m, 6H), 1.34–1.27 (m 6H), 1.03–0.98 (m, 6H), 0.90–0.85 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 157.1, 137.8, 130.9, 130.6, 129.5, 128.73, 128.68, 120.7, 116.6, 112.0, 94.4, 94.2, 56.1, 55.9, 41.5, 39.3, 29.1, 27.3, 13.7, 9.8; MS (CI) *m/z*: 618 (MH^+, 100), 560, 530, 328, 296, 257. HRMS (CI) calcd for $C_{31}H_{46}NO_4Sn$ (MH^+) 618.2605, found 618.2602.

4.1.16. 2-[3-(3-Iodo-4-hydroxyphenyl)-3-(4-hydroxyphenyl)]-propionitrile (13)

The stannane **12** (140 mg, 0.23 mmol) and 1 M ICl in CH_2Cl_2 (230 μL, 0.23 mmol) were added to methylene chloride (15 mL) and stirred at room temperature for 10 min. The reaction was quenched by sodium sulfite solution and extracted with ethyl acetate, and combined organic layer was dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatography (30% EtOAc/hexane) to give MOM-protected **13**. The collected compound was dissolved in CH_3CN (15 mL) and stirred with 1 N HCl (6 mL) for 1 h at 70 °C. The solution was extracted with ethyl acetate, and combined organic layer was dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatography (50% EtOAc/hexane) to give the iodo compound **13** (65 mg, 78%) as a white solid: ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.45 (d, J = 2.1 Hz, 1H), 7.07 (d, J = 8.7 Hz, 2H), 6.94

(dd, J = 8.4, 2.1 Hz, 1H), 6.77–6.66 (m, 3H), 4.07 (t, J = 7.4 Hz, 1H), 2.96 (d, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 157.1, 155.7, 139.7, 130.2, 130.1, 128.5, 126.1, 120.8, 115.3, 114.8, 114.1, 40.1, 38.3; MS (CI) m/z: 366 (MH^+), 339 (100), 280, 240, 213, 107. HRMS (CI) calcd for $C_{15}H_{13}O_2NI$ (MH^+) 365.9991, found 365.9994.

4.1.17. (*Z*)-2-(3-Methyl-4-hydroxyphenyl)-3-(4-hydroxyphenyl)acrylonitrile (14)

This material was prepared by a procedure similar to that used for the preparation of **6f**, described above (yellow solid, 94%): ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.63–7.60 (m, 2H), 7.49–7.43 (m, 3H), 6.85–6.78 (m, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 157.9, 157.6, 140.1, 131.8, 128.0, 126.6, 126.2, 125.6, 124.8, 118.7, 115.4, 114.3, 106.5, 14.8; MS (EI) m/z: 252 (M^+), 233, 145, 131, 117 (100), 88. HRMS (EI) calcd for $C_{16}H_{14}O_2N$ (M^+) 252.1024, found 252.1027.

4.1.18. (*Z*)-2-(3-Methyl-4-methoxymethoxyphenyl)-3-(4-methoxymethoxyphenyl)acrylonitrile (15)

This material was prepared by a procedure similar to that used for the preparation of **7**, described above (white solid, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.68 (m, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.34 (s, 1H), 7.12–7.07 (m, 3H), 5.26 (s, 2H), 5.21 (s, 2H), 3.494 (s, 3H), 3.490 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 157.0, 140.5, 131.7, 128.54, 128.52, 127.8, 127.3, 127.1, 118.5, 116.6, 113.5, 108.4, 94.3, 94.1, 56.14, 56.10, 16.3; MS (EI) m/z: 339 (M^+), 309, 294, 279, 264, 239, 221, 209, 193, 179, 165, 141, 125, 111, 97, 71, 57. HRMS (EI) calcd for $C_{20}H_{21}O_4N$ (M^+) 339.1470, found 339.1470.

4.1.19. (*Z*)-2-(3-Bromomethyl-4-methoxymethoxyphenyl)-3-(4-methoxymethoxyphenyl)acrylonitrile (16)

A stirred solution of **15** (1.35 g, 3.97 mmol), *N*-bromosuccinimide (776 mg, 4.36 mmol) and benzoyl peroxide (64 mg) in carbon tetrachloride (60 mL) was heated at reflux under an argon atmosphere for 2 h. The suspension was then cooled to 0 °C, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (25% EtOAc/hexane) to give **16** as a slightly yellow solid mixed with methyl α-stilbene (**15**). Recrystallization from EtOAc/hexane gave pure bromoethyl α-stilbene **16** (1.02 g, 61%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.83 (m, 2H), 7.57 (d, J = 9.0 Hz, 2H), 7.34 (s, 1H), 7.17 (d, J = 9.3 Hz, 1H), 7.08 (d, J = 9.0 Hz, 2H), 5.33 (s, 2H), 5.22 (s, 2H), 4.59 (s, 2H), 3.53 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 156.3, 139.4, 131.9, 131.1, 128.2, 127.6, 127.3, 127.1, 118.2, 116.6, 114.3, 109.6, 94.3, 94.0, 56.5, 56.1, 28.2; MS (EI) m/z: 419 (M^++2, 18.8), 417 (M^+, 18.8), 338, 293, 261, 248, 232, 203, 190, 177. HRMS (EI) calcd for $C_{20}H_{20}O_4NBr$ (M^+) 417.0575, found 417.0575.

4.1.20. (*Z*)-2-(3-Fluoromethyl-4-methoxymethoxyphenyl)-3-(4-methoxymethoxyphenyl)acrylonitrile (17)

The bromomethyl α-stilbene **16** (600 mg, 1.43 mmol) and tetrabutylammonium fluoride-3H_2O (71 mg, 0.47 mmol) were dissolved in anhydrous CH_3CN (30 mL) and stirred at 70 °C for 30 min. The reaction mixture was extracted with ethyl acetate, and combined organic layer was dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatography (25% EtOAc/hexane) to give **17** (380 mg, 74%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 8.7 Hz, 1H), 7.84 (s, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.38 (s, 1H), 7.20 (d, J = 8.7 Hz, 1H), 7.10 (d, J = 8.7 Hz, 2H), 5.50 (d, J = 47.7 Hz, 2H), 5.28 (s, 2H), 5.21 (s, 2H), 3.49 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 156.1 (d, J = 4.1 Hz), 139.7, 130.6 (d, J = 2.6 Hz), 130.4 (d, J = 7.8 Hz), 128.2, 127.6, 127.2, 126.0 (d, J = 16.9 Hz), 118.3, 116.6, 114.1, 109.6, 94.3, 94.2, 80.0 (d, J = 165.2 Hz), 56.4, 56.1; MS (EI) m/z: 357 (M^+, 100), 327, 293, 261, 232, 190. HRMS (EI) calcd for $C_{20}H_{20}O_2NF$ (M^+) 357.1376, found 357.1374.

4.1.21. 2-(3-Fluoromethyl-4-methoxymethoxyphenyl)-3-(4-methoxymethoxyphenyl)propionitrile (18)

This material was prepared by a procedure similar to that used for the preparation of **5f**, described above (pale yellow oily solid, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.7 Hz, 2H), 7.16–7.01 (m, 5H), 5.42 (d. J = 47.7 Hz, 2H), 5.20 (s, 2H), 5.17 (s, 2H), 3.92 (t, J = 7.4 Hz, 1H), 3.48 (s, 3H), 3.47 (s, 3H), 3.11–3.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 154.1 (d, J = 4.4 Hz), 130.8 (d, J = 2.8 Hz), 129.8 (d, J = 7.4 Hz), 129.7, 128.6, 128.4, 125.7 (d, J = 17.0 Hz), 120.5, 116.7, 114.2, 94.4, 94.4, 80.2 (d, J = 164.1 Hz), 56.2, 56.1, 41.5, 39.2; MS (EI) m/z: 359 (M^+), 221, 191, 183 (100), 153, 119, 104, 91.HRMS (EI) calcd for $C_{20}H_{22}O_4NF$ (M^+) 359.1533, found 359.1533.

4.1.22. 2-(3-Hydroxymethyl-4-hydroxyphenyl)-3-(4-hydroxyphenyl)propionitrile (20)

The fluoromethyl DPN **18** (250 mg, 0.70 mmol) was dissolved in MeOH (10 mL). To this stirred mixture, 1 N HCl (3 mL) was added, and stirring was continued for 30 min at 70 °C. The reaction mixture was extracted with ethyl acetate, and combined organic layer was dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatography (60% EtOAc/hexane) to give **20** (156 mg, 82%) as a white solid: ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.12–7.08 (m, 3H), 6.88 (dd, J = 8.1, 2.1 Hz, 1H), 6.75 (d, J = 8.7 Hz, 2H), 6.87 (d, 8.1 Hz, 1H), 4.61 (s, 2H), 4.07 (t, J = 7.5 Hz, 1H), 3.00 (d, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 154.0, 128.94, 128.87, 128.4, 127.6, 127.1, 126.5, 121.1, 115.2, 114.5, 59.7, 41.1, 38.6; MS (CI) m/z: 268 (MH^+), 252 (100), 243, 137, 117, 88. HRMS (CI) calcd for $C_{16}H_{14}O_3N$ (MH^+) 268.0974, found 268.0971.

4.2. Relative binding affinity assay

Binding affinities of DPN derivatives were determined by a competitive radiometric binding assay with 2 nM [^{3}H]estradiol as tracer ([2,4,6,7-^{3}H]estra-1,3,5,(10)-triene-3,17β-diol, 70–120 Ci/mmol, GE Healthcare, Piscataway, NJ), using purified full-length human ERα and ERβ (PanVera/Invitrogen), as previously described.[15,16] Incubations were for 18–24 h at 0 °C. Hydroxyapatite (Bio-Rad, Hercules, CA) was used to absorb the receptor-ligand complexes, and free ligand was washed away. The binding affinities are expressed as RBA values, where the RBA of estradiol is 100%. The values given are the average ± range or SD of two or three independent determinations. Estradiol binds to ERα with a K_d of 0.2 nM and to ERβ with a K_d of 0.5 nM.

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