A New Series of Estrogen Receptor Modulators: Effect of Alkyl Substituents on Receptor-Binding Affinity

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New types of selective estrogen receptor modulators (SERMs) were synthesized and evaluated for their binding affinity and biological effect on reproductive cells. A proposed lead structure (B) was derivatized to provide compounds 30 and 44, which showed good estrogen-receptor binding affinity (K_i values: 6.3 and 10 nM, respectively), as well as minimal impact on mammary and uterine carcinoma cells. Introduction of an alkyl group in the core structure considerably enhanced receptor-binding affinity of the compounds tested. Synthesis and structure–activity relationships of these compounds are described.

Key words estrogen; selective estrogen receptor modulator (SERM); receptor-binding affinity

The menopausal syndrome has a significant negative impact on the quality of life of many older women.[1] A decline in estrogen production results in discomforts such as hot flushes, urogenital atrophy and mental disorders. Decreased levels of circulating estrogen also elicit changes in the metabolic pathways of several organs. In the skeletal system, low levels of circulating estrogen result in the loss of essential bone minerals, leading to osteoporosis and an increased incidence of fracture.[2] Estrogen also plays an important role in the maintenance of healthy blood-vessels and blood-lipid profiles[3,4]; a reduction in estrogen levels has often been associated with an increased risk of cardiovascular disease. Additionally, a decline in mental function has been associated with a decrease in estrogen production.[5—8]

To alleviate these symptoms, estrogen has been administered to menopausal women to offset reduced estrogen production. Such hormone replacement therapy[9—11] (HRT) has been used for decades, and has relieved the suffering of millions of patients.[12] However, the agonistic characteristics of HRT in mammary and uterine tissues have provoked concerns relating to the increased risk of proliferation in estrogen-receptor-dependent breast and uterine cancers.[13,14] Therefore, alternative methods of HRT have attracted the attention of the pharmaceutical industry.

In the 1960's, Tamoxifen[15,16] (Fig. 1) was discovered and subsequently marketed as an anti-breast cancer drug.[17—19] Interestingly, Tamoxifen exerts an antagonistic effect on mammary tissues, but adversely acts as an agonist on other tissues such as skeletal[20,21] and cardiovascular systems.[22—24] This unexpected discovery provided the impetus for pursuit of tissue-selective agonistic estrogen alternatives, which have beneficial effects on osteoporosis and cardiovascular diseases, and minimal effects on mammary and uterine tissues. Following extensive investigation, novel types of non-steroidal, estrogen receptor partial agonists, termed as selective estrogen receptor modulators (SERMs), have been identified.[25—27] (Fig. 1)

The common feature of SERM structures is the combination of a non-steroidal core and a basic side chain (Fig. 2, compound (**A**)). The core structure is comprised of an aromatic ring containing a phenolic-OH connected to another aromatic ring by a spacer group. The basic side chain consists of an aryl moiety and an alkyl amine. On the basis of the structural features described above, development of SERMs as pharmaceutical products was initiated, and several compounds such as Raloxifene[28,29] (on market, osteoporosis), Lasofoxifene[30] (ph III, osteoporosis), Pipendoxifene[31] (ph III, osteoporosis) and Bazedoxifene[31] (ph II, breast cancer) have been identified as valuable tools or candidates for treatment of menopausal symptoms.

In our drug discovery program, we have pursued a novel structural type of SERM compound. Subsequent to review of the SAR of known SERMs, we deduced several types of supposed SERM compounds carrying novel combinations of core structures and side chains. Among them, we were interested in a compound (**B**) (Fig. 2). On comparison with existing SERMs, compound (**B**) contains the requisite topology for a SERM, but the side chain is attached in a different position. It is well established that the topology of a side chain plays an important role in determination of the tissue-selective agonist/antagonist profile in SERMs[32,33]; therefore we reasoned that derivatization of compound (**B**) could result in

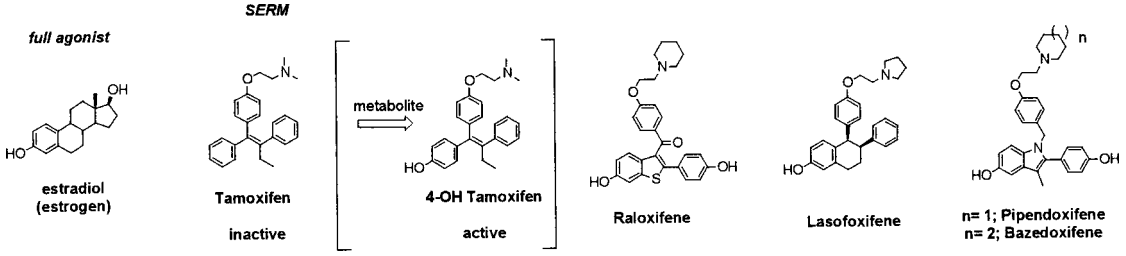

Fig. 1

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the identification of a novel SERM with beneficial effects with respect to tissue selectivity. In order to evaluate the suitability of compound (**B**) as a new SERM candidate, synthesis of the target compounds mentioned below was required to permit biological testing. Here we report the synthesis and the preliminary SAR results of our compounds.

Chemistry

The synthetic routes to compounds **6a**, **6b** and **10** are shown in Chart 1.

Compound **1** was coupled with 3-methoxybenzoyl chloride *via* Fries rearrangement and subsequent selective monomethylation afforded **3a**. According to a reported procedure,[34] **3a** was treated with methyl chloroformate followed by $NaBH_4$ to provide the decarbonylated product **4a**. Copper-promoted phenolic-OH arylation[35] of **4a** with 4-*tert*-butyldimethylsiloxyphenylboronic acid followed by desilylation produced **5a**. Introduction of an ethylpiperidine moiety on **5a** and subsequent demethylation furnished target compound **6a**. Starting from **7**,[36] **6b** was synthesized in a similar manner as described for **6a**. For the synthesis of **10**, the common intermediate **4a** was treated with trifluoromethanesulfonic anhydride, and the produced triflate was subjected to Suzuki–Miyaura coupling followed by hydrogenolysis to provide **9**. The attachment of an amine side chain and subsequent demethylation afforded **10**.

Compound **16** was synthesized by the procedures given in Chart 2. Aldehyde **12**, derivatized from **11**, was reacted with Grignard reagent to give **13**. Deoxygenation with silane followed by hydrolytic deprotection afforded **14**. Compound **14** was subjected to copper-promoted arylation and subsequent debenzylation to produce **15**, which was treated in a similar manner as described for **6a** to afford **16**.

Chart 3 illustrates the synthetic routes to compounds **22**, **25a**, **25b** and **30**. For the synthesis of **22**, compound **18** was selectively demethylated using carbonyl-assisted demethylation promoted by $CeCl_3$–NaI[37] under mild conditions. Decarbonylation of **19** using $NaBH_4$–methyl chloroformate gave complex mixtures. Alternatively, hydrogenolysis of **19** was successfully performed to provide **20**, which was converted to target compound **22** in a similar manner as described for **6a**. Syntheses of **25a** and **25b** were carried out following the procedures described for compound **10**. For the synthesis of **30**, introduction of a dimethyl moiety into **18** and subsequent application of the aforementioned procedures were effectively conducted. In this case, $NaBH_4$–methyl chloroformate decarbonylation could be performed without incurring significant problems.

Aniline type compounds **36a** and **36c** were synthesized as shown in Chart 4. The Mizoroki–Heck reaction product **32** was hydrogenated to give aniline 33. Introduction of the side chain moiety using amide formation followed by AlH_3 reduction afforded **35**. With or without the prior introduction of methyl group on the aniline moiety of **35**, deprotection was effected utilizing EtSH–$AlCl_3$ to provide target compounds **36a** and **36c**.

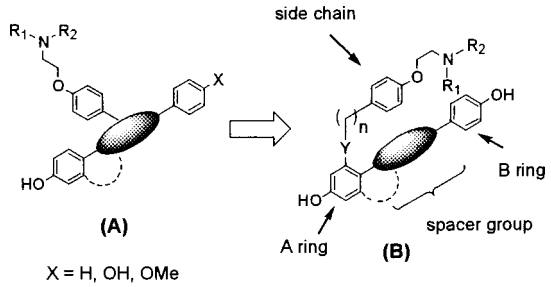
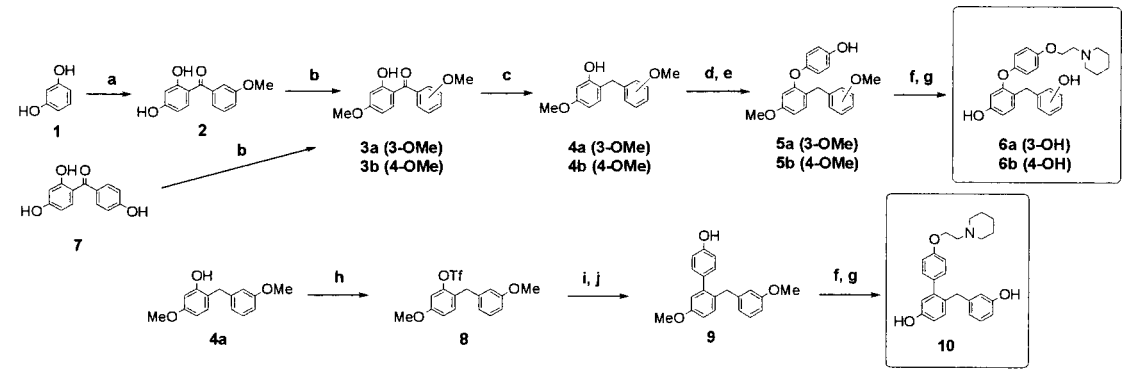
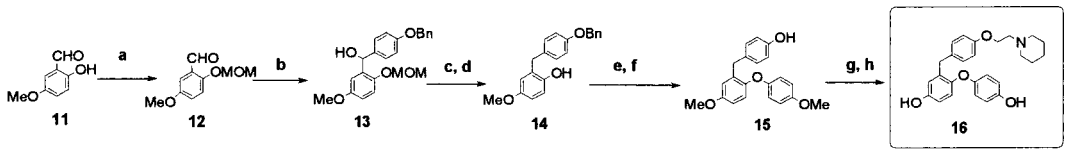


Fig. 2



Reagents: (a) 3-methoxybenzoyl chloride, $AlCl_3$; (b) MeI, K_2CO_3; (c) (1) methyl chloroformate, Et_3N, (2) $NaBH_4$; (d) 4-*tert*-butyldimethylsiloxyphenylboronic acid, $Cu(OAc)_2$, Et_3N, MS-4A; (e) TBAF; (f) 1-(2-chloroethyl)piperidine.HCl, NaH; (g) Py.HCl; (h) Tf_2O, Py.; (i) 4-benzyloxyphenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3; (j) H_2, Pd/C

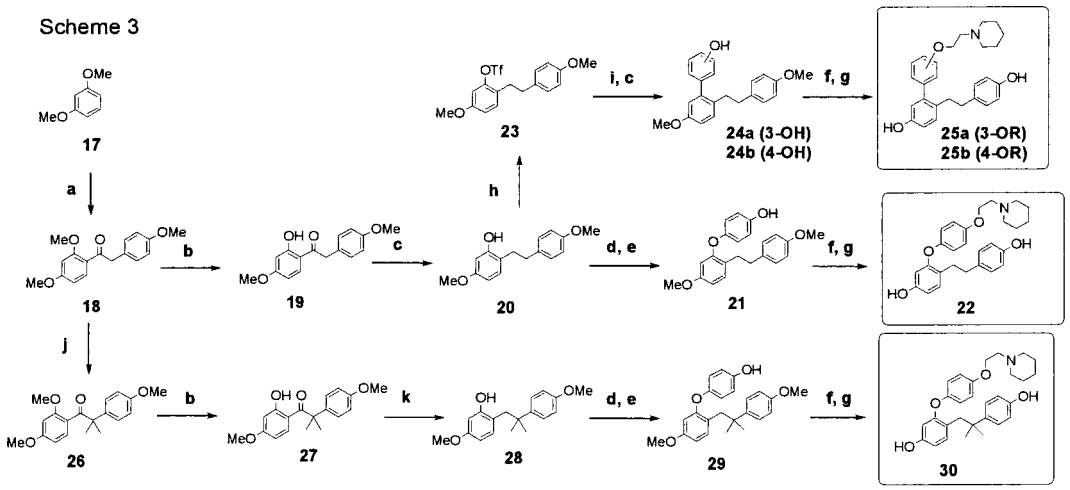
Chart 1



Reagents: (a) MOMCl, iPr_2NEt; (b) 4-benzyloxyphenylmagnesium bromide; (c) Et_3SiH, TFA; (d) 4N HCl- dioxane; (e) 4-methoxyphenylboronic acid, $Cu(OAc)_2$, Et_3N, MS-4A; (f) H_2, Pd/C; (g) 1-(2-chloroethyl)piperidine.HCl, NaH; (h) Py.HCl

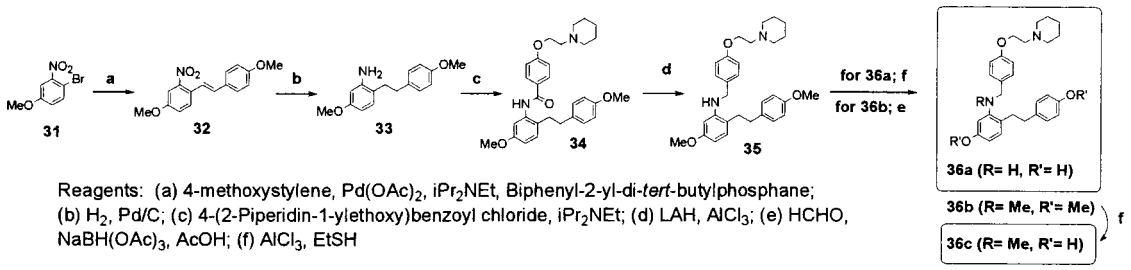
Chart 2

Finally, compounds **44** and **51** were synthesized according to Chart 5. Compound **37**[38] was subjected to intramolecular Friedel–Crafts acylation to give **38**. Application of Buchwald's arylation[39] permitted the smooth conversion of **38** to **39**. $CeCl_3$-promoted demethylation, $NaBH_4$-reduction and acid-promoted dehydration produced **41**. Compound **41** was



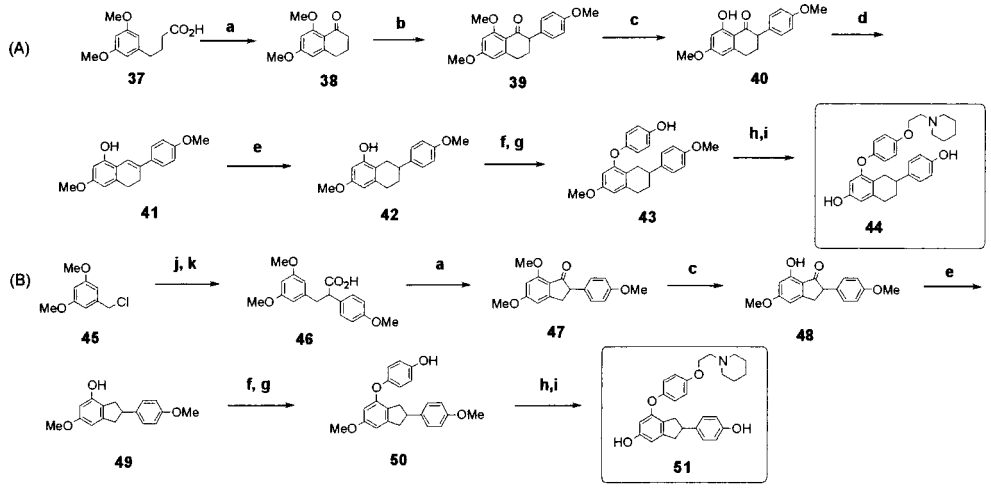
Reagents: (a) 4-methoxyphenylacetyl chloride, $AlCl_3$; (b) $CeCl_3.7H_2O$, NaI; (c) H_2, Pd/C; (d) 4-*tert*-butyldimethyl siloxyphenylboronic acid, $Cu(OAc)_2$, Et_3N, MS-4A; (e) TBAF; (f) 1-(2-chloroethyl)piperidine.HCl, NaH; (g) Py.HCl; (h) Tf_2O, Py.; (i) 3- or 4-benzyloxyphenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3; (j) MeI, KOtBu; (k) (1) methyl chloroformate, Et_3N; (2) $NaBH_4$

Chart 3



Reagents: (a) 4-methoxystylene, $Pd(OAc)_2$, iPr_2NEt, Biphenyl-2-yl-di-*tert*-butylphosphane; (b) H_2, Pd/C; (c) 4-(2-Piperidin-1-ylethoxy)benzoyl chloride, iPr_2NEt; (d) LAH, $AlCl_3$; (e) HCHO, $NaBH(OAc)_3$, AcOH; (f) $AlCl_3$, EtSH

Chart 4



Reagents: (a) $(COCl)_2$, $SnCl_4$; (b) 4-bromoanisole, $Pd_2(dba)_3$, BINAP, NaO^tBu; (c) $CeCl_3.7H_2O$, NaI; (d) (1) $LiBH_4$, (2) aq.HCl; (e) H_2, Pd/C; (f) 4-*tert*-butyldimethylsiloxyphenylboronic acid, $Cu(OAc)_2$, Et_3N, MS-4A; (g) TBAF; (h) 1-(2-chloroethyl)piperidine.HCl, NaH; (i) Py.HCl; (j) methyl 4-methoxyphenylacetate, NaH; (k) aq. NaOH

Chart 5

hydrogenated to provide **42**, which was converted to **44** in a similar manner for **6a**. For the synthesis of **51**, compound **45**[40] was converted to **47**, which was transformed to **51** in a similar manner as described above.

Results and Discussion

The synthesized compounds were tested for their ability to compete with ^{3}H-estradiol for binding to the estrogen receptor.[41] The compounds with a K_i value of double-figures or lower were selected for further evaluation of their agonistic activity on mammary and uterine tissues. Specifically, the selected compounds were examined for their agonistic activity in estrogen-receptor dependent proliferation of MCF-7 breast adenocarcinoma cells.[42] Estrogen-receptor dependent production of alkali phosphatase (ALP) by Ishikawa cells[43] was used for measurement of the agonistic effect of the tested compounds on uterine tissue. Additionally, the antagonistic effect of tested compounds against estradiol (E2) was evaluated. Tamoxifen and Raloxifene were used for comparative purposes. Biological data is presented in Table 1. The principal aim of this study was to clarify whether compound (**B**) was suitable for further derivatization studies directed toward the identification of novel SERM compounds. Initially, optimization of the spacer length was pursued.

Variation of the spacer length between A ring and B ring influenced the binding affinity of the tested compounds to the estrogen receptor. Compounds with a one-methylene spacer, such as **6a** and **6b**, exhibited a significant decrease in binding affinity. Carbon–oxygen exchange in the connecting section, presented in compound **16**, conferred no beneficial effect. In contrast, introduction of a two-methylene carbon spacer improved the receptor-binding affinity (RBA) of the compounds tested. Thus, the RBA of compound **22** was over seven times higher than that of compound **6b** (Table 1, Fig. 3). A similar relationship was noted between compound **10** and compound **25b**; the former showed a decreased binding affinity when compared to the latter (Table 1). In addition, a predominance of two-carbon unit spacers is noticeable in known SERMs, so our synthetic effort was concentrated on production of compounds that contained two-methylene spacers between A ring and B ring. Incidentally, compound **25a**, which contained a *meta*-alkylamine substituent, showed an improved binding affinity over compound **25b**, which contained a *para*-alkylamine substituent. This phenomenon indicated that a subtle change in the topology of the side chain could significantly affect the binding mode to the estrogen receptor.[44] Accordingly, we set out to synthesize and evaluate derivatives containing different side chain topologies.

The spacer between the core structure and the side chain ("Y" in Fig. 2) was another target of optimization. A biphenyl type (no spacer) compound **25b** showed weak affinity to the estrogen receptor. Introduction of at least one atom enhanced binding affinity to the estrogen receptor as shown in the case of compounds **22** and **36c**. Interestingly, the presence of a hydrogen donor in the vicinity of the core structure lowered the RBA. As for Y, oxygen, nitrogen (aniline) and carbon could be candidates for further synthetic studies. In light of the RBA, there were no obvious differences between them, so we selected an oxygen spacer for synthetic convenience.

At this point, we turned our attention again to the spacer group, between A ring and B ring, for further optimization of compound **22**. Introduction of ring structures to drug-like substances has often had beneficial impact on their affinity to biomolecules, so compounds **44** and **51** were synthesized with the aim of enhancing binding affinity to the estrogen receptor (Fig. 3). As expected, compound **44** (obtained following introduction of the "ethyl" moiety) had an enhanced K_i value of 10. However, compound **51** (obtained following introduction of the "methyl" moiety) did not exhibit a distinct improvement in binding affinity. With this data, it was reasoned that a certain level of "bulkiness" of an alkyl substituent was required in the spacer group in order to enhance receptor-binding affinity. This hypothesis led to the synthesis of compound **30**, which showed the strongest RBA among our compounds (Fig. 3). To the best of our knowledge, there is no explicit report, which states that the introduction of a dimethyl moiety to the spacer confers a considerable impact on the binding affinity of a SERM to the estrogen receptor. At present, we have no rationale to explain this phenomenon, but we are sure that this discovery should facilitate the identification novel types of SERMs.

The MCF-7 breast adenocarcinoma cell assay and Ishikawa cell assay indicated that the tested compounds exhibited weak agonistic activity. This fully exemplifies that our synthetic compounds are true SERMs, which show mini-

Table 1. Binding Affinity and Effect on Reproductive Cells

	ER binding K_i (nM)	MCF-7 (%)	Ishikawa cell (%)	Antagonistic effect on MCF-7 (against 10 pM E2) IC_{50} (nM)
Estradiol	0.11	200 (1 nM)	300 (1 nM)	—
Tamoxifen	140	130 (10 nM)	136 (100 nM)	86.1
Raloxifene	0.59	104 (1 μM)	102 (1 μM)	0.46
6a	190	—	—	—
6b	>307	—	—	—
10	240	—	—	—
16	240	—	—	—
22	41	122 (100 nM)	122 (1 μM)	43.38
25a	50	135 (100 nM)	128 (1 μM)	13.31
25b	180	—	—	—
30	6.3	111 (1 μM)	157 (100 nM)	3.89
36a	>235	—	—	—
36c	31	143 (100 nM)	157 (1 μM)	228.85
44	10	125 (100 nM)	104 (1 μM)	12.09
51	50	104 (1 μM)	89 (1 μM)	11.20

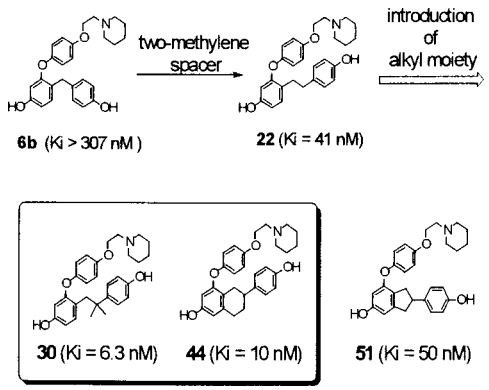


Fig. 3

mal effect on mammary and uterine tissues. Antagonistic effect against estrogen-promoted cell growth was rather in accord with RBA of tested compounds.

Conclusion

In summary, new types of SERMs were identified, which contain novel combinations of core structures and side chains. The introduction of an alkyl moiety with "requisite bulkiness" into the spacer between A ring and B ring considerably enhances the affinity of those compounds to the estrogen receptor. It was also evident that a hydrogen donor in the spacer in the vicinity of the core structure confers a deleterious effect on the affinity to the estrogen receptor.

We are now conducting further research in this area, and our results will be reported in future publications.

Experimental

Melting points were measured using a Yanako melting-point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian Unity 400 (400 MHz) spectrometer, and chemical shifts are expressed in ppm downfield from tetramethylsilane (δ=0) as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. ^{13}C-NMR spectra were obtained on a Varian Unity 400 (400 MHz) spectrometer. High-resolution mass spectra (HR-MS) were obtained on a Q-Tof Ultima global mass spectrometer. Elemental analysis was performed with a Heraeus Elemental Analyzer CHN-O-RAPID. Materials were used as bought without any special purification. Silica gel (Kieselgel 60, Merck) was used for column chromatography, and silica gel (Kieselgel 60 F_{254}, layer thickness 0.25 mm, Merck) for analytical thin layer chromatography (TLC).

(2,4-Dihydroxyphenyl)-(3-methoxyphenyl)methanone (2) To an ice-cooled, stirred suspension of aluminum chloride ($AlCl_3$) (14.0 g, 105 mmol) in dichloroethane (100 ml) were added 3-methoxybenzoyl chloride (18.8 g, 110 mol) and 2,4-dihydroxybenzene **1** (11.0 g, 100 mmol). The resultant mixture was heated at 60 °C for 3 h, at 90 °C for 2 h 30 min, and at 70 °C overnight. After cooling, the reaction mixture was poured into ice-water, and the resultant mixture was extracted with ethyl acetate (AcOEt)–tetrahydrofuran (THF) (2 : 1). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (30—70% AcOEt in hexane) to afford **2** (20.4 g, 84%) as a pale yellow solid. mp 161—163 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.79 (3H, s), 6.33—6.39 (2H, m), 7.10—7.18 (3H, m), 7.37 (1H, d, J=8.0 Hz), 7.43 (1H, dd, J=8.0, 8.0 Hz), 10.76 (1H, br s), 12.19 (1H, s).

(2-Hydroxy-4-methoxyphenyl)-(3-methoxyphenyl)methanone (3a) To a stirred solution of **2** (14.7 g, 60 mmol) in acetone (200 ml) were added potassium carbonate (12.4 g, 90 mmol) and iodomethane (9.37 g, 66 mmol). The resultant mixture was stirred for 23 h at room temperature (rt), and then evaporated under reduced pressure. The residue was partitioned between AcOEt and water, and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (10% AcOEt in hexane) to afford **3a** (10.3 g, 67%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.858 (3H, s), 3.864 (3H, s), 6.41 (1H, dd, J=2.4, 8.8 Hz), 6.52 (1H, d, J=2.4 Hz), 7.09 (1H, dd, J=2.4, 8.0 Hz), 7.15—7.22 (2H, m), 7.39 (1H, dd, J=8.0, 8.0 Hz), 7.53 (1H, d, J=8.8 Hz), 12.66 (1H, s).

5-Methoxy-2-(3-methoxybenzyl)phenol (4a) To an ice-cooled, stirred solution of **3a** (5.16 g, 20 mmol) in THF (100 ml) were added successively triethylamine (3.04 g, 30 mmol) and methyl chloroformate (2.17 g, 23 mmol). The resultant mixture was stirred for 48 min at the same temperature, and filtered. The filtrate was added to an ice-cooled, stirred solution of sodium borohydride (3.03 g, 80 mmol) in water (50 ml), and the stirring was continued for 2 h 10 min. The reaction mixture was evaporated, partitioned between AcOEt and water, and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (20% AcOEt in hexane) to afford **4a** (4.78 g, 98%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.75 (3H, s), 3.76 (3H, s), 3.90 (2H, s), 4.95 (1H, s), 6.38 (1H, d, J=2.4 Hz), 6.45 (1H, dd, J=2.4, 8.4 Hz), 6.72—6.82 (3H, m), 7.01 (1H, d, J=8.4 Hz), 7.18—7.23 (1H, m).

4-[5-Methoxy-2-(3-methoxybenzyl)phenoxy]phenol (5a) To a stirred solution of **4a** (977 mg, 4.0 mmol) in dichloromethane (50 ml) were added successively 4-*tert*-butyldimethylsilyloxyphenylboronic acid (1.51 g, 4.0 mmol), copper acetate (727 mg, 4.0 mmol), powdered molecular shieves 4A (5 g) and triethylamine (2.02 g, 20.0 mmol). The resultant mixture was stirred overnight at rt. The reaction mixture was filtered, and the filtrate was absorbed on silica gel under reduced pressure. The gel was charged upon a column of silica gel, and eluted with 10% AcOEt in hexane to give colorless oil. The oily residue was dissolved in THF (10 ml), and to this was added 1 N tetrabutylammonium fluoride in THF (4.0 ml, 4.0 mmol), and the resultant mixture was stirred for 20 min at rt. The reaction mixture was evaporated and partitioned between AcOEt and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (15—20% AcOEt in hexane) to afford **5a** (740 mg, 55%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.68 (3H, s), 3.74 (3H, s), 3.92 (2H, s), 4.96 (1H, s), 6.33 (1H, d, J=2.4 Hz), 6.55 (1H, dd, J=2.4, 8.4 Hz), 6.69—6.83 (7H, m), 7.08 (1H, d, J=8.4 Hz), 7.17 (1H, dd, J=8.0, 8.0 Hz). HR-MS (ESI) m/z: Calcd for $C_{21}H_{19}O_4$: 335.1283 Found: 335.1319.

4-(3-Hydroxybenzyl)-3-[4-(2-piperidin-1-ylethoxy)phenoxy]phenol (6a) To an ice-cooled, stirred solution of **5a** (430 mg, 1.28 mmol) in *N*,*N*-dimethylformamide (DMF) (4 ml) were added sodium hydride (118 mg, 60% in mineral oil, 2.95 mmol), 1-(2-chloroethyl)piperidine hydrochloride (306 mg, 1.66 mmol). The resultant mixture was stirred overnight at rt. The reaction mixture was quenched with water, partitioned between AcOEt and water. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on NH silica gel (5% AcOEt in hexane) to afford a pale yellow oil. To the residual oil was added pyridine hydrochloride (1.2 g), and the mixture was heated at 190 °C for 1 h 30 min. After cooling to rt, the resultant solid was partitioned between THF and saturated sodium hydrogen carbonate solution, and the resultant mixture was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on NH silica gel (2% MeOH in AcOEt) to afford **6a** (170 mg, 32%) as a colorless solid. mp 141—142 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.43 (2H, br s), 1.57—1.66 (4H, m), 2.52 (4H, br s), 2.71 (2H, t, J=6.0 Hz), 3.85 (2H, s), 3.95 (2H, t, J=6.0 Hz), 6.18 (1H, d, J=2.8 Hz), 6.45 (1H, dd, J=2.8, 8.4 Hz), 6.57—6.62 (4H, m), 6.67—6.71 (2H, m), 6.73—6.78 (1H, m), 7.00 (1H, d, J=8.4 Hz), 7.06 (1H, dd, J=7.6, 8.8 Hz). ^{13}C-NMR (DMSO-d_6): δ (ppm) 26.20, 35.21, 55.08, 58.61, 66.62, 105.06, 105.13, 110.61, 110.70, 113.30, 113.38, 115.99, 116.08, 116.29, 119.84, 119.92, 120.81, 121.89, 129.76, 132.01, 143.39, 150.53, 155.27, 156.82, 157.53, 157.91. *Anal.* Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.27; H, 7.06; N, 3.25. **6a** was dissolved in THF and the solution was treated with 4 N solution of hydrogen chloride in AcOEt (4 N HCl–AcOEt) to give the corresponding hydrochloride (HCl) salt as an amorphous for biological evaluation.

(2-Hydroxy-4-methoxyphenyl)-(4-methoxyphenyl)methanone (3b) To a stirred solution of **7**[36] (9.68 g, 42.0 mmol) in acetone (200 ml) were added potassium carbonate (14.5 g, 105 mmol) and iodomethane (13.1 g, 92.4 mmol), and the resultant mixture was stirred for 12 h 30 min at rt. The reaction mixture was partitioned between AcOEt and water, and the organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (5—15% THF in hexane) to afford **3b** (7.00 g, 64%) as a pale yellow solid. mp 111—113 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.87 (3H, s), 3.89 (3H, s), 6.42 (1H, dd, J=2.4, 8.8 Hz), 6.52 (1H, d, J=2.4 Hz), 6.96—7.01 (2H, m), 7.55 (1H, d, J=8.8 Hz), 7.64—7.69 (2H, m), 12.68 (1H, s).

5-Methoxy-2-(4-methoxybenzyl)phenol (4b) Starting from **3b** (7.00 g, 27.1 mmol), **4b** (5.02 g, 76%) was obtained as a colorless oil in a similar manner as described for **4a**. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.75 (3H, s), 3.77 (3H, s), 3.86 (2H, s), 4.94 (1H, s), 6.38 (1H, d, J=2.4 Hz), 6.45 (1H, dd, J=2.4, 8.4 Hz), 6.80—6.86 (2H, m), 6.99 (1H, d, J=8.4 Hz), 7.09—7.15 (2H, m).

4-[5-Methoxy-2-(4-methoxybenzyl)phenoxy]phenol (5b) Starting from **4b** (977 mg, 4.0 mmol), **5b** (544 mg, 40%) was obtained as a colorless oil in a similar manner as described for **5a**. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.69 (3H, s), 3.77 (3H, s), 3.89 (2H, s), 4.97 (1H, s), 6.33 (1H, d, J=2.4 Hz), 6.55 (1H, dd, J=2.4, 8.4 Hz), 6.74—6.83 (6H, m), 7.06 (1H, d, J=8.4 Hz), 7.10—7.15 (2H, m). HR-MS (ESI) m/z: Calcd for $C_{21}H_{19}O_4$: 335.1283 Found: 335.1302.

4-(4-Hydroxybenzyl)-3-[4-(2-piperidin-1-ylethoxy)phenoxy]phenol (6b) Starting from **5b** (361 mg, 1.07 mmol), **6b** (262 mg, 58%) was obtained as a colorless solid in a similar manner as described for **6a**. mp 210—212 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.30—1.39 (2H, m), 1.43—1.51 (4H, m), 2.40 (4H, br s), 2.61 (2H, t, J=6.0 Hz), 3.69 (2H, s), 4.00 (2H, t,

J=6.0 Hz), 6.09 (1H, d, J=2.4 Hz), 6.40 (1H, dd, J=2.4, 8.4 Hz), 6.59—6.64 (m, 2H), 6.79—6.84 (m, 2H), 6.88—6.98 (5H, m). ^{13}C-NMR (DMSO-d_6): δ (ppm) 24.58, 26.21, 34.43, 55.08, 58.07, 66.63, 105.15, 105.23, 110.62, 110.72, 115.63, 115.69, 116.29, 120.69, 122.75, 130.07, 131.87, 132.05, 150.63, 155.21, 155.95, 156.63, 157.37. *Anal.* Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.33; H, 7.25; N, 3.22. **6b** was dissolved in THF and the solution was treated with 4 N HCl–AcOEt to give the corresponding HCl salt as an amorphous for biological evaluation.

Trifluoromethanesulfonic Acid 5-Methoxy-2-(3-methoxybenzyl)phenyl Ester (8) To an ice-cooled, stirred solution of **4a** (3.34 g, 13.7 mmol) and pyridine (2.16 g, 27.3 mmol) in dichloromethane (50 ml) was added trifluoromethanesulfonic anhydride (4.63 g, 16.4 mmol) for 5 min, and the stirring was continued for 20 min at the same temperature. The reaction mixture was partitioned between dichloromethane and water, and the organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (5% AcOEt in hexane) to afford **8** (3.90 g, 76%) as a yellow oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.77 (3H, s), 3.80 (3H, s), 3.97 (2H, s), 6.69—6.72 (1H, m), 6.74—6.79 (2H, m), 6.80—6.85 (2H, m), 7.09 (1H, d, J=8.8 Hz), 7.21 (1H, dd, J=8.0, 8.0 Hz).

5′-Methoxy-2′-(3-methoxybenzyl)biphenyl-4-ol (9) To a stirred solution of **8** (376 mg, 1.00 mmol) in 1,4-dioxane (10 ml) under nitrogen atmosphere were added 4-benzyloxyphenylboronic acid (251 mg, 1.10 mml), potassium carbonate (207 mg, 1.50 mmol) and tetrakis(triphenylphosphine)-palladium (35 mg, 0.03 mmol), and the resultant mixture was heated at 80 °C for 4 h 40 min. The reaction mixture was cooled to rt and partitioned between AcOEt and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (5—6% AcOEt in hexane) to afford a colorless oil. The residual oil was dissolved in THF (10 ml) and the solution was charged with palladium charcoal (Pd/C, 100 mg) and hydrogenolyzed under atmospheric pressure for 1 h at rt. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (30% AcOEt in hexane) to afford **9** (167 mg, 52%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.72 (3H, s), 3.80 (3H, s), 3.85 (2H, s), 5.16 (1H, s), 6.50—6.53 (m, 1H), 6.58 (1H, d, J=8.0 Hz), 6.68 (1H, dd, J=2.4, 8.0 Hz), 6.77—6.85 (4H, m), 7.09—7.15 (4H, m). HR-MS (ESI) m/z: Calcd for $C_{21}H_{19}O_3$: 319.1334 Found: 319.1360.

6-(3-Hydroxybenzyl)-4′-(2-piperidin-1-ylethoxy)biphenyl-3-ol (10) Starting from **9** (154 mg, 0.48 mmol), **10** (70 mg, 44%) was obtained as a colorless oil in a similar manner as described for **6a**. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.45 (2H, br s), 1.58—1.68 (4H, m), 2.56 (4H, br s), 2.75 (2H, t, J=6.0 Hz), 3.75 (2H, s), 4.00 (2H, t, J=6.0 Hz), 6.24 (1H, s), 6.51—6.61 (4H, m), 6.62 (1H, d, J=2.8 Hz), 6.76 (1H, dd, J=2.8, 8.4 Hz), 6.85—6.90 (2H, m), 7.03 (1H, dd, J=8.0, 8.0 Hz), 7.08 (1H, d, J=8.4 Hz). ^{13}C-NMR ($CDCl_3$): δ (ppm) 14.40, 21.29, 23.92, 25.00, 38.30, 54.94, 57.80, 60.75, 64.76, 113.32, 114.06, 115.04, 116.19, 117.41, 120.58, 129.54, 129.66, 130.27, 132.01, 134.24, 143.08, 144.17, 154.77, 156.54, 157.45. HR-MS (ESI) m/z: Calcd for $C_{26}H_{30}NO_3$: 404.2226 Found: 404.2189. **10** was dissolved in THF and the solution was treated with 4 N HCl–AcOEt to give the corresponding HCl salt as an amorphous for biological evaluation.

5-Methoxy-2-methoxymethoxybenzaldehyde (12) To a stirred solution of **11** (25.2 g, 166 mmol) and *N*,*N*-diisopropylethylamine (42.8 g, 332 mmol) in DMF (100 ml) and THF (100 ml) was added chloromethyl methyl ether (20.0 g, 248 mmol), and the resultant mixture was stirred overnight at rt. The reaction mixture was partitioned between AcOEt and water, and the organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (10% AcOEt in hexane) to afford **12** (29.8 g, 92%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.52 (3H, s), 3.81 (3H, s), 5.24 (2H, s), 7.13—7.14 (1H, m), 7.16—7.20 (1H, m), 7.32—7.34 (1H, m), 10.47 (1H, s).

(4-Benzyloxyphenyl)-(5-methoxy-2-methoxymethoxyphenyl)methanol (13) To a stirred suspension of fine-ground magnesium (1.44 g, 59.2 mmol) in THF (20 ml) was added dropwise a solution of 1-benzyloxy-4-bromobenzene (14.5 g, 55.1 mmol) in THF (80 ml) for 15 min. After the addition, the resultant mixture was heated at 60 °C for 1 h. After cooling in ice bath, a solution of **12** (9.81 g, 50.0 mol) in THF (50 ml) was added to the Grignard solution for 20 min and the resultant mixture was stirred for 50 min at the same temperature. The reaction mixture was poured into saturated ammonium chloride solution-ice, and the resultant mixture was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (20—30% AcOEt in hexane) to afford **13** (10.2 g, 54%) as a yellow oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.31 (3H, s), 3.75 (3H, s), 4.98—5.05 (4H, m), 6.00 (1H, s), 6.75 (1H, dd, J=3.2, 8.8 Hz), 6.90—6.95 (3H, m), 7.00 (1H, d, J=8.8 Hz), 7.27—7.44 (7H, m).

2-(4-Benzyloxybenzyl)-4-methoxyphenol (14) To an ice-cooled, stirred solution of **13** (4.62 g, 12.1 mmol) in dichloromethane (50 ml) were added successively trifluoroacetic acid (2.77 g, 24.3 mmol) and triethylsilane (2.12 g, 18.2 mmol), and the resultant mixture was stirred for 54 min at the same temperature. The reaction mixture was partitioned between AcOEt and 1 N sodium hydroxide solution, and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was dissolved in THF (40 ml), and to the solution were added 4 N solution of HCl in 1,4-dioxane (10 ml) and five drops of water. After stirred overnight, the reaction mixture was evaporated under reduced pressure. The residue was chromatographed on silica gel (20—30% AcOEt in hexane) to afford **14** (2.70 g, 70%) as a pale yellow solid. mp 108—109 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.73 (3H, s), 3.89 (2H, s), 4.40 (1H, s), 5.02 (2H, s), 6.63—6.73 (3H, m), 6.87—6.92 (2H, m), 7.10—7.15 (2H, m), 7.28—7.43 (5H, m).

4-[5-Methoxy-2-(4-methoxyphenoxy)benzyl]phenol (15) To a stirred solution of **14** (481 mg, 1.50 mmol) in dichloromethane (30 ml) were added successively 4-methoxyphenylboronic acid (342 mg, 2.25 mmol), copper acetate (272 mg, 4.0 mmol), powdered molecular shieves 4A (3 g) and triethylamine (759 mg, 7.50 mmol). The resultant mixture was stirred for 16 h at rt. The reaction mixture was filtered, and the filtrate was absorbed on silica gel under reduced pressure. The dried gel was charged upon a column of silica gel, and eluted with 5% AcOEt in hexane to give colorless oil. The oily residue was dissolved in THF (15 ml), and the solution was charge with palladium charcoal (Pd/C, 150 mg) and hydrogenolyzed under atmospheric pressure for 20 h 30 min at rt. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (15—20% AcOEt in hexane) to afford **15** (398 mg, 79%) as colorless oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.74 (3H, s), 3.78 (3H, s), 3.86 (2H, s), 4.91 (1H, s), 6.67—6.74 (4H, m), 6.77—6.84 (5H, m), 7.03—7.08 (2H, m). HR-MS (ESI) m/z: Calcd for $C_{21}H_{19}O_4$: 335.1283 Found: 335.1285.

3-[4-(2-Cyclohexylethoxy)benzyl]-4-(4-hydroxyphenoxy)phenol (16) Starting from **15** (290 mg, 0.86 mmol), **16** (235 mg, 65%) was obtained as a pink solid in a similar manner as described for **6a**. mp 204—212 °C (decomp.) ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.30—1.38 (2H, m), 1.42—1.49 (4H, m), 2.39 (4H, br s), 2.60 (2H, t, J=6.0 Hz), 3.70 (2H, s), 3.98 (2H, t, J=6.0 Hz), 6.51—6.56 (2H, m), 6.61—6.70 (5H, m), 6.78—6.83 (2H, m), 7.02—7.07 (2H, m), 9.11 (2H, s). HR-MS (ESI) m/z: Calcd for $C_{26}H_{29}N_4O_4$: 420.2175 Found: 420.2179. **16** was dissolved in THF and the solution was treated with 4N HCl–AcOEt to give the corresponding HCl salt as an amorphous for biological evaluation.

1-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)ethanone (18) To an ice-cooled, stirred suspension of $AlCl_3$ (7.58 g, 56.8 mmol) in dichloroethane (100 ml) were added 4-methoxyphenylacetyl chloride (10.0 g, 54.2 mmol) and **17** (8.23 g, 59.6 mmol). The resultant mixture was stirred at the same temperature for 20 min, then at rt for 1 h. The reaction mixture was poured into ice-water, and the resultant mixture was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (20—30% AcOEt in hexane) to afford **18** (8.02 g, 52%) as a pale yellow solid. mp 76.5—78 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.78 (3H, s), 3.84 (3H, s), 3.89 (3H, s), 4.21 (2H, s), 6.44 (1H, d, J=2.4 Hz), 6.51 (1H, dd, J=2.4, 8.8 Hz), 6.81—6.86 (2H, m), 7.10—7.15 (2H, m), 7.78 (1H, d, J=8.8 Hz).

1-(2-Hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)ethanone (19) To a stirred solution of **18** (2.76 g, 10.1 mmol) in acetonitrile (150 ml) were added sodium iodide (3.04 g, 20.2 mmol) and cerium chloride heptahydrate (5.66 g, 15.2 mmol), and the resultant mixture was heated under reflux for 20 h 30 min. An additional portion of sodium iodide (0.76 g, 5.1 mmol) and cerium chloride heptahydrate (1.89 g, 5.1 mmol) was added to the reaction mixture, and the reflux was continued for another 22 h 30 min. After cooling to rt, the reaction mixture was partitioned between AcOEt and water, and the resultant mixture was filtered. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (10—30% AcOEt in hexane) to afford **19** (2.46 g, 94%) as a colorless solid. mp 100—102 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.79 (3H, s), 3.83 (s, 3H), 4.16 (s, 2H), 6.42 (1H, d, J=2.4 Hz), 6.44 (1H, dd, J=2.4, 8.8 Hz), 6.85—6.90 (2H, m), 7.16—7.21 (2H, m), 7.75 (1H, d, J=8.8 Hz), 12.7 (1H, s).

5-Methoxy-2-[2-(4-methoxyphenyl)ethyl]phenol (20) A solution of **19** (3.53 g, 13.0 mmol) in THF (40 ml) and acetic acid (10 ml) was hydro-

genated over Pd/C (750 mg) under atmospheric pressure for 20 h at rt. Another portion of Pd/C (500 mg) was added and the resultant mixture was hydrogenated under 4 atm for 8 h 30 min at rt. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (10—30% AcOEt in hexane) to afford **20** (2.74 g, 77%) as a colorless solid. mp 123—126 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.81 (4H, br s), 3.76 (3H, s), 3.79 (3H, s), 4.69 (1H, s), 6.35 (1H, d, J=2.4 Hz), 6.43 (1H, dd, J=2.4, 8.8 Hz), 6.80—6.85 (2H, m), 6.97 (1H, d, J=8.8 Hz), 7.07—7.12 (2H, m).

4-{5-Methoxy-2-[2-(4-methoxyphenyl)ethyl]phenoxy}phenol (21) Starting from **20** (1.09 g, 4.2 mmol), **21** (644 mg, 44%) was obtained as a colorless solid in a similar manner as described for **5a**. mp 78—80.5 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.79—2.89 (4H, m), 3.70 (3H, s), 3.78 (3H, s), 4.93 (1H, s), 6.34 (1H, d, J=2.4 Hz), 6.55 (1H, dd, J=2.4, 8.4 Hz), 6.76—6.86 (6H, m), 7.03—7.08 (3H, m). HR-MS (ESI) *m/z*: Calcd for $C_{22}H_{21}O_4$: 349.1440 Found: 349.1475.

4-[2-(4-Hydroxyphenyl)ethyl]-3-[4-(2-piperidin-1-ylethoxy)-phenoxy]phenol (22) Starting from **21** (519 mg, 1.48 mmol), **22** (111 mg, 34%) was obtained as a colorless solid in a similar manner as described for **6a**. **22** was dissolved in THF and the solution was treated with 4 N HCl–AcOEt to give the corresponding HCl salt as a colorless solid for analytical and biological evaluation. mp 169—170 °C. ^{1}H-NMR (CD_3OD): δ (ppm) 1.69 (2H, br s), 1.80—1.95 (4H, m), 2.65—2.77 (4H, m), 3.30 (4H, br s), 3.53 (2H, t, J=5.2 Hz), 4.33 (2H, t, J=5.2 Hz), 6.20 (1H, d, J=2.4 Hz), 6.46 (1H, dd, J=2.4, 8.0 Hz), 6.58—6.64 (2H, m), 6.82—6.90 (4H, m), 6.94—7.02 (3H, m). ^{13}C-NMR (CD_3OD): δ (ppm) 21.41, 22.89, 32.06, 36.06, 53.66, 56.04, 62.48, 105.77, 105.85, 110.28, 110.36, 114.72, 114.76, 115.76, 119.12, 123.59, 129.22, 131.16, 133.10, 152.59, 153.55, 155.18, 155.98, 156.67. HR-MS (ESI) *m/z*: Calcd for $C_{27}H_{32}NO_4$: 434.2331 Found: 434.2325.

Trifluoromethanesulfonic Acid 5-Methoxy-2-[2-(4-methoxyphenyl)-ethyl]phenyl Ester (23) Starting from **20** (2.67 g, 10.3 mmol), **23** (3.31 g, 82%) was obtained as a yellow oil in a similar manner as described for **8**. ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.79—2.92 (4H, m), 3.79 (3H, s), 3.80 (3H, s), 6.78—6.85 (4H, m), 7.06—7.15 (3H, m).

5′-Methoxy-2′-[2-(4-methoxyphenyl)ethyl]biphenyl-3-ol (24a) Starting from **23** (586 mg, 1.5 mmol), **24a** (184 mg, 37%) was obtained as a colorless oil in a similar manner as described for **9**. ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.61—2.67 (2H, m), 2.74—2.80 (2H, m), 3.76 (3H, s), 3.80 (3H, s), 5.09 (1H, br s), 6.59—6.62 (1H, m), 6.72—6.77 (3H, m), 6.80—6.88 (5H, m), 7.18 (1H, d, J=8.4 Hz), 7.25 (1H, dd, J=8.0, 8.0 Hz).

6-[2-(4-Hydroxyphenyl)ethyl]-3′-(2-piperidin-1-yl-ethoxy)biphenyl-3-ol (25a) Starting from **24a** (184 mg, 0.55 mmol), **25a** (122 mg, 53%) was obtained as a colorless oil in a similar manner as described for **6a**. **25a** was dissolved in THF and the solution was treated with 4 N HCl–AcOEt to give the corresponding HCl salt as a colorless solid for analytical and biological evaluation. mp 213—215 °C. ^{1}H-NMR (CD_3OD): δ (ppm) 1.54 (2H, br s), 1.72—2.00 (4H, m), 2.49—2.56 (2H, m), 2.65—2.72 (2H, m), 3.05 (2H, br s), 3.52—3.64 (4H, m), 4.32—4.38 (2H, m), 6.54—6.60 (3H, m), 6.65—6.75 (3H, m), 6.86—6.91 (1H, m), 6.97—7.02 (1H, m), 7.09 (1H, d, J=8.4 Hz), 7.35 (1H, dd, J=8.0, 8.0 Hz). ^{13}C-NMR (CD_3OD): δ (ppm) 21.35, 22.85, 34.82, 37.10, 53.68, 56.00, 61.92, 112.82, 114.37, 114.69, 114.73, 115.47, 115.52, 116.15, 116.24, 122.73, 129.07, 129.18, 130.18, 130.48, 132.97, 142.69, 144.04, 155.05. 155.14, 157.64. HR-MS (ESI) *m/z*: Calcd for $C_{27}H_{32}NO_3$: 418.2382 Found: 418.2368.

5′-Methoxy-2′-[2-(4-methoxyphenyl)ethyl]biphenyl-4-ol (24b) Starting from **23** (586 mg, 1.5 mmol), **24b** (417 mg, 83%) was obtained as a colorless solid in a similar manner as described for **9**. mp 115—119 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.58—2.65 (2H, m), 2.74—2.79 (2H, m), 3.76 (3H, s), 3.81 (3H, s), 5.11 (1H, s), 6.72—6.78 (2H, m), 6.81—6.90 (6H, m), 7.13—7.20 (3H, m). HR-MS (ESI) *m/z*: Calcd for $C_{22}H_{21}NO_3$: 333.1491 Found: 333.1528.

6-[2-(4-Hydroxyphenyl)ethyl]-4′-(2-piperidin-1-yl-ethoxy)biphenyl-3-ol (25b) Starting from **24b** (208 mg, 0.62 mmol), **25b** (98 mg, 38%) was obtained as a colorless oil in a similar manner as described for **6a**. **25b** was dissolved in THF and the solution was treated with 4 N HCl–AcOEt to give the corresponding HCl salt as a colorless solid for analytical and biological evaluation. mp 236—242 °C (decomp.). ^{1}H-NMR (CD_3OD): δ (ppm) 1.70 (2H, br s), 1.89 (4H, br s), 2.49—2.55 (2H, m), 2.65—2.71 (2H, m), 3.39 (4H, br s), 3.57 (2H, t, J=4.8 Hz), 4.41 (2H, t, J=4.8 Hz), 6.55—6.59 (3H, m), 6.67—6.73 (3H, m), 7.02—7.08 (3H, m), 7.16—7.20 (2H, m). ^{13}C-NMR (CD_3OD): δ (ppm) 21.46, 22.95, 34.91, 36.99, 53.74, 56.10, 62.04, 110.40, 114.08, 114.69, 116.45, 116.52, 129.02, 130.29, 130.42, 132.98, 136.03, 142.49, 155.01, 155.14, 156.93. HR-MS (ESI) *m/z*: Calcd for $C_{27}H_{32}NO_3$: 418.2382 Found: 418.2376.

1-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-2-methylpropan-1-one (26) To a stirred solution of potassium *tert*-butoxide (7.97 g, 71.0 mmol) and 18-crown-6 (626 mg, 2.37 mmol) in THF (200 ml) was added a solution of **18** (6.78 g, 23.7 mmol) and iodomethane (13.4 g, 94.4 mmol) in THF (50 ml), and the resultant mixture was stirred for 28 min at rt. The reaction mixture was filtered and the filtrate was absorbed on silica gel under reduced pressure. The gel was charged upon a column of silica gel, and eluted with 15—25% AcOEt in hexane and the eluent was evaporated under reduced pressure. To a stirred solution of the residue and iodomethane (8.40 g, 59.2 mmol) was added a solution of potassium *tert*-butoxide (6.64 g, 59.2 mmol) in THF (60 ml) at once and the resultant mixture was stirred for 20 min at rt. The reaction mixture was filtered and the filtrate was absorbed on silica gel under reduced pressure. The gel was charged upon a column of silica gel, and eluted with 15—20% AcOEt in hexane and the eluent was evaporated under reduced pressure to afford **26** (6.22 g, 84%) as a colorless solid. mp 85—88 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.52 (6H, s), 3.68 (3H, s), 3.74 (3H, s), 3.81 (3H, s), 6.19 (1H, dd, J=2.0, 8.4 Hz), 6.35 (1H, d, J=2.0 Hz), 6.42 (1H, d, J=8.4 Hz), 6.82—6.90 (2H, m), 7.22—7.30 (2H, m).

1-(2-Hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)-2-methyl-propan-1-one (27) Starting from **26** (6.22 g, 19.8 mmol), **27** (4.86 g, 82%) was obtained as a pale yellow solid in a similar manner as described for **19**. mp 86—89 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.60 (6H, s), 3.75 (3H, s), 3.78 (3H, s), 6.06 (1H, dd, J=2.4, 9.2 Hz), 6.36 (1H, d, J=2.4 Hz), 6.83—6.88 (2H, m), 7.08 (1H, d, J=9.2 Hz), 7.13—7.18 (2H, m), 13.14 (1H, s).

5-Methoxy-2-[2-(4-methoxyphenyl)-2-methylpropyl]phenol (28) Starting from **27** (2.94 g, 9.8 mmol), **28** (1.94 g, 69%) was obtained as a colorless solid in a similar manner as described for **4a**. mp 101—102.5 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.36 (6H, s), 2.76 (2H, s), 3.72 (3H, s), 3.80 (3H, s), 4.02 (s, 1H), 6.25 (1H, d, J=2.4 Hz), 6.36 (1H, dd, J=2.4, 8.4 Hz), 6.74 (1H, d, J=8.4 Hz), 6.82—6.88 (2H, m), 7.20—7.26 (2H, m).

4-{5-Methoxy-2-[2-(4-methoxyphenyl)-2-methylpropyl]phenoxy}phenol (29) Starting from **28** (1012 mg, 3.53 mmol), **29** (375 mg, 28%) was obtained as a colorless oil in a similar manner as described for **5a**. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.33 (6H, s), 2.87 (2H, s), 3.66 (3H, s), 3.80 (3H, s), 4.80 (1H, s), 6.24 (1H, d, J=2.4 Hz), 6.39 (1H, dd, J=2.4, 8.4 Hz), 6.62 (1H, d, J=8.4 Hz), 6.76—6.84 (6H, m), 7.22—7.28 (2H, m). HR-MS (ESI) *m/z*: Calcd for $C_{24}H_{25}O_4$: 377.1753 Found: 377.1767.

4-[2-(4-Hydroxyphenyl)-2-methylpropyl]-3-[4-(2-piperidin-1-ylethoxy)phenoxy]phenol (30) Starting from **29** (201 mg, 0.53 mmol), **30** (119 mg, 49%) was obtained as a colorless oil in a similar manner as described for **6a**. **30** was dissolved in THF and the solution was treated with 4 N HCl–AcOEt to give the corresponding HCl salt as a colorless solid for analytical and biological evaluation. mp 213—214 °C. ^{1}H-NMR (CD_3OD): δ (ppm) 1.27 (6H, s), 1.56 (2H, br s), 1.89 (4H, br s), 2.77 (2H, s), 3.08 (2H, br s), 3.54 (2H, t, J=4.8 Hz), 3.66 (2H, br s), 4.34 (2H, t, J=4.8 Hz), 6.10 (1H, d, J=2.4 Hz), 6.29 (1H, dd, J=2.4, 8.4 Hz), 6.54 (1H, d, J=8.4 Hz), 6.62—6.69 (2H, m), 6.78—6.85 (2H, m), 6.95—7.01 (2H, m), 7.06—7.12 (2H, m). ^{13}C-NMR (CD_3OD): δ (ppm) 21.39, 22.86, 27.85, 38.49, 43.06, 53.65, 56.00, 62.46, 104.45, 104.53, 109.16, 109.25, 114.28, 115.73, 119.69, 120.51, 127.05, 132.92, 133.00, 140.52, 151.92, 153.65, 154.84, 156.57, 156.93. *Anal.* Calcd for $C_{29}H_{36}NO_4Cl$: C, 69.93; H, 7.29; N, 2.81. Found: C, 69.65; H, 7.30; N, 2.74.

4-Methoxy-1-[2-(4-methoxyphenyl)vinyl]-2-nitrobenzene (32) To a stirred solution of **31** (6.96 g, 30.0 mmol) in acetonitrile (60 ml) were added 4-methoxystylene (4.23 g, 31.5 mmol), *N*,*N*-diisopropylethylamine (11.6 g, 89.7 mmol), biphenyl-2-yl-di-*tert*-butylphosphane (537 mg, 1.80 mmol) and palladium acetate (404 mg, 1.80 mmol), and the resultant mixture was heated at 80 °C for 11 h under nitrogen atmosphere. After cooling to rt, the reaction mixture was partitioned between AcOEt and water, and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (10% AcOEt in hexane–10% AcOEt–10% THF in hexane) to afford **32** (6.46 g, 76%) as a yellow solid. mp 108—110.5 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.84 (3H, s), 3.88 (3H, s), 6.88—6.93 (2H, m), 6.95 (1H, d, J=16.0 Hz), 7.14 (1H, dd, J=2.8, 8.8 Hz), 7.41 (1H, d, J=16.0 Hz), 7.42—7.48 (3H, m), 7.66 (1H, d, J=8.8 Hz).

5-Methoxy-2-[2-(4-methoxyphenyl)ethyl]phenylamine (33) A solution of **32** (1.40 g, 4.91 mmol) in THF (50 ml) was hydrogenated over Pd/C (400 mg) under atmospheric pressure for 20 h 50 min at rt. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (10—20% AcOEt in hexane) to afford **33** (1.01 g, 80%) as a pink solid. mp 108—114 °C. ^{1}H-NMR (DMSO-

d_6): δ (ppm) 2.54—2.60 (2H, m), 2.64—2.71 (2H, m), 3.61 (3H, s), 3.69 (3H, s), 4.84 (2H, s), 6.03 (1H, d, J=2.4, 8.0 Hz), 6.19 (1H, d, J=2.4 Hz), 6.75 (1H, d, J=8.0 Hz), 6.78—6.86 (2H, m), 7.12—7.18 (2H, m).

***N*-{5-Methoxy-2-[2-(4-methoxyphenyl)ethyl]phenyl}-4-(2-piperidin-1-ylethoxy)benzamide (34)** To a stirred solution of **33** (643 mg, 2.50 mmol) in 1,4-dioxane (20 ml) was added *N*,*N*-diisopropylethylamine (3 ml) and 4-(2-piperidin-1-ylethoxy)benzoyl chloride hydrochloride (989 mg, 3.25 mmol), and the resultant mixture was heated at 100 °C for 50 min. After cooling to rt, the reaction mixture was evaporated, and the residue was partitioned between AcOEt and saturated sodium hydrogen carbonate solution. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on NH silica gel (50% AcOEt in hexane) to afford **34** (1.18 g, 97%) as a pale yellow solid. mp 103.5—104.5 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.43—1.50 (2H, m), 1.58—1.67 (4H, m), 2.48—2.57 (4H, m), 2.78—2.86 (6H, m), 3.76 (3H, s), 3.81 (3H, s), 4.17 (2H, t, J=6.0 Hz), 6.74 (1H, dd, J=2.8, 8.4 Hz), 6.75—6.80 (2H, m), 6.90—6.98 (4H, m), 7.06 (1H, br s), 7.13 (1H, d, J= 8.4 Hz), 7.47 (1H, d, J=2.8 Hz), 7.53—7.58 (2H, m). HR-MS (ESI) m/z: Calcd for $C_{30}H_{37}N_2O_4$: 489.2753 Found: 489.2788.

{5-Methoxy-2-[2-(4-methoxyphenyl)ethyl]phenyl}-[4-(2-piperidin-1-ylethoxy)benzyl]amine (35) To an ice-cooled suspension of lithium aluminum hydride (607 mg, 16.0 mmol) and aluminum chloride (2.13 g, 16.0 mmol) in THF (100 ml) was added dropwise a solution of **34** (1.95 g, 4.00 mmol) in THF (20 ml), and the resultant mixture was stirred at the same temperature for 3 h 7 min. The reaction mixture was diluted with THF and quenched with 28% aqueous ammonia solution. The resultant suspension was filtered off, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on NH silica gel (10—30% AcOEt in hexane) to afford **35** (1.70 g, 90%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.40—1.48 (2H, m), 1.57—1.65 (4H, m), 2.47—2.55 (4H, m), 2.63—2.69 (2H, m), 2.77 (2H, t, J=6.0 Hz), 2.81—2.87 (2H, m), 3.75 (3H, s), 3.78 (3H, s), 4.10 (2H, t, J=6.0 Hz), 4.18 (2H, s), 6.21—6.27 (2H, m), 6.77—6.82 (2H, m), 6.85—6.90 (2H, m), 6.95 (1H, d, J=8.0 Hz), 7.02—7.08 (2H, m), 7.20—7.26 (2H, m). HR-MS (ESI) m/z: Calcd for $C_{30}H_{39}N_2O_3$: 475.2961 Found: 475.2954.

4-[2-(4-Hydroxyphenyl)ethyl]-3-[4-(2-piperidin-1-ylethoxy)benzylamino]phenol (36a) To a stirred solution of **35** (474 mg, 1.00 mmol) in dichloromethane (20 ml) was added $AlCl_3$ (666 mg, 5.00 mmol) and ethanethiol (0.37 ml, 5.00 mmol) and the resultant mixture was stirred for 27 min at rt. The reaction mixture was diluted with THF and quenched with 28% aqueous ammonia solution. The resultant suspension was filtered off, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on NH silica gel (100% AcOEt–2% MeOH in AcOEt) to afford **36a** (330 mg, 74%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.45 (2H, br s), 1.59—1.68 (4H, m), 2.60 (2H, br s), 2.64 (2H, t, J=6.8 Hz), 2.73—2.81 (4H, m), 3.65 (1H, br s), 4.05—4.13 (2H, m), 6.09 (1H, d, J=2.4 Hz), 6.16 (1H, dd, J=2.4, 8.0 Hz), 6.57—6.63 (2H, m), 6.74—6.79 (2H, m), 6.86—6.92 (3H, m), 7.06—7.10 (2H, m). ^{13}C-NMR ($CDCl_3$): δ (ppm) 24.06, 25.27, 32.96, 35.05, 47.88, 55.09, 57.86, 65.19, 99.06, 104.46, 114.81, 115.73, 118.12, 128.85, 129.64, 130.12, 131.59, 133.53, 147.06, 154.68, 155.86, 157.86. HR-MS (ESI) m/z: Calcd for $C_{28}H_{35}N_2O_3$: 447.2648 Found: 447.2638. **36a** was dissolved in THF and the solution was treated with 4 N HCl–AcOEt to give the corresponding HCl salt as an amorphous for biological evaluation.

{5-Methoxy-2-[2-(4-methoxyphenyl)ethyl]phenyl}methyl-[4-(2-piperidin-1-ylethoxy)benzyl]amine (36b) To a stirred solution of **35** (712 mg, 1.50 mmol) in THF (30 ml) were added successively acetic acid (675 mg, 11.25 mmol), 37% aqueous formaldehyde (0.27 ml, 3.38 mmol) and sodium triacetoxyborohydride (699 mg, 3.30 mmol), and the resultant mixture was stirred for 13 h 40 min at rt. The reaction mixture was partitioned between AcOEt and 1 N sodium hydroxide solution, and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on NH silica gel (10—30% AcOEt in hexane) to afford **36b** (733 mg, 73%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.41—1.49 (2H, m), 1.57—1.65 (4H, m), 2.48—2.54 (4H, m), 2.53 (3H, s), 2.78 (2H, t, J=6.0 Hz), 2.83—2.90 (2H, m), 2.92—2.99 (2H, m), 3.79 (6H, s), 3.92 (2H, s), 4.10 (2H, t, J=6.0 Hz), 6.60 (1H, dd, J=2.4, 8.8 Hz), 6.72 (1H, d, J=2.4 Hz), 6.79—6.87 (4H, m), 7.08—7.15 (3H, m), 7.23—7.28 (2H, m).

4-[2-(4-Hydroxyphenyl)ethyl]-3-{methyl-[4-(2-piperidin-1-ylethoxy)benzyl]amino}phenol (36c) Starting from **36b** (471 mg, 0.97 mmol), **36c** (410 mg, 92%) was obtained as a colorless oil in a similar manner as described for **36a**. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.42—1.50 (2H, m), 1.62—1.70 (4H, m), 2.54 (3H, s), 2.61 (4H, br s), 2.76—2.89 (6H, m), 3.88 (2H, s), 4.09 (2H, t, J=6.0 Hz), 6.49 (1H, dd, J=2.4, 8.4 Hz), 6.59 (1H, d, J=2.4 Hz), 6.61—6.66 (2H, m), 6.67—6.72 (2H, m), 6.84—6.89 (2H, m), 7.05 (1H, d, J=8.4 Hz), 7.07—7.12 (3H, m). ^{13}C-NMR ($CDCl_3$): δ (ppm) 24.06, 25.31, 32.53, 36.22, 42.14, 55.22, 57.92, 60.93, 65.47, 108.68, 110.89, 114.40, 115.54, 128.76, 129.52, 129.70, 130.62, 131.43, 134.09, 153.57, 154.41, 154.93, 157.59. HR-MS (ESI) m/z: Calcd for $C_{29}H_{37}N_2O_3$: 461.2804 Found: 461.2817. **36c** was dissolved in THF and the solution was treated with 4 N HCl–AcOEt to give the corresponding HCl salt as an amorphous for biological evaluation.

6,8-Dimethoxy-3,4-dihydro-2H-naphthalen-1-one (38) To a stirred suspension of **37**[38] (18.1 g, 80.7 mmol) in toluene (100 ml) was added oxalyl chloride (15.4 g, 121 mmol), and the resultant mixture was stirred for 3 h 30 min at rt. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in dichloromethane (100 ml), and to this was added a solution of stannic chloride in dichloromethane (1.0 M, 89.0 ml, 89.0 mmol) for 20 min with ice-cooling. After stirred for 2 h, the reaction mixture was quenched with water and the resultant mixture was extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (80% AcOEt in hexane–100% AcOEt) to afford **38** (16.0 g, 96%) as a pale yellow solid. mp 61—62 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.98—2.06 (2H, m), 2.58 (2H, t, J=6.0 Hz), 2.87 (2H, t, J=6.0 Hz), 3.84 (3H, s), 3.88 (3H, s), 6.31—6.35 (2H, m).

6,8-Dimethoxy-2-(4-methoxyphenyl)-3,4-dihydro-2*H*-naphthalen-1-one (39) To a stirred solution of **38** (11.9 g, 57.7 mmol) in THF (200 ml) were added 4-bromoanisole (16.2 g, 86.6 mmol), sodium *tert*-butoxide (11.1 g, 115 mmol), *rac*-BINAP (1.29 g, 2.07 mmol) and tris(dibenzylideneacetone)palladium (792 mg, 8.65 mmol), and the resultant mixture was heated for 1 h 30 min at 75 °C under nitrogen atmosphere. After cooling to rt, the reaction mixture was partitioned between AcOEt and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue crystallized on standing, and the crude crystal was triturated in diethyl ether and filtered to give **39**. The filtrate was evaporated under reduced pressure, and the residue was chromatographed on silica gel (50—60% AcOEt in hexane) to give another portion of **39**. In total, 14.2 g (79%) of **39** were obtained as an off-white solid. mp 115—117 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.22—2.36 (2H, m), 2.92—3.02 (2H, m), 3.69 (1H, dd, J=5.6, 10.0 Hz), 3.78 (3H, s), 3.85 (6H, s), 6.29—6.37 (2H, m), 6.80—6.86 (2H, m), 7.06—7.12 (2H, m).

8-Hydroxy-6-methoxy-2-(4-methoxyphenyl)-3,4-dihydro-2*H*-naphthalen-1-one (40) Starting from **39** (16.4 g, 52.5 mmol), **40** (8.68 g, 55%) was obtained as a colorless solid in a similar manner as described for **19**. mp 144.5—147 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.26—2.36 (2H, m), 2.90—2.98 (2H, m), 3.76 (1H, dd, J=6.4, 9.2 Hz), 3.77 (3H, s), 3.83 (3H, s), 6.27—6.31 (2H, m), 6.86—6.91 (2H, m), 7.08—7.13 (2H, m), 12.88 (1H, s).

3-Methoxy-7-(4-methoxyphenyl)-5,6-dihydronaphthalen-1-ol (41) To an ice-cooled, stirred suspension of lithium borohydride (1.10 g, 50.5 mmol) in THF (60 ml) was added a solution of **40** (6.19 g, 20.7 mmol) in THF (130 ml) for 10 min, and the resultant mixture was stirred for 20 min at the same temperature. The reaction mixture was quenched with 2 N hydrochloric acid solution and the resultant mixture was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (10—25% THF in hexane) to afford **41** (5.56 g, 95%) as a purple oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.64—2.72 (2H, m), 2.84—2.92 (2H, m), 3.78 (3H, s), 3.83 (3H, s), 4.97 (1H, br s), 6.23 (1H, d, J=2.4 Hz), 6.37 (1H, d, J=2.4 Hz), 6.88—6.94 (2H, m), 6.98 (1H, s), 7.46—7.52 (2H, m).

3-Methoxy-7-(4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-1-ol (42) A solution of **41** (5.56 g, 19.7 mmol) in THF (50 ml) and MeOH (50 ml) was hydrogenated over Pd/C (560 mg) under atmospheric pressure for 12 h 40 min at rt. Another portion of Pd/C (280 mg) was added and the resultant mixture was hydrogenated under atmospheric pressure for another 25 h 30 min at rt. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (10—20% THF in hexane) to afford **42** (4.67 g, 83%) as a colorless solid. mp 132—133.5 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.80—1.93 (1H, m), 2.02—2.11 (1H, m), 2.45—2.57 (1H, m), 2.80—2.98 (4H, m), 3.76 (3H, s), 3.80 (3H, s), 4.77 (1H, s), 6.25 (1H, d, J=2.0 Hz), 6.29 (1H, d, J=2.4 Hz), 6.83—6.89 (2H, m), 7.16—7.22 (2H, m).

4-[3-Methoxy-7-(4-methoxyphenyl)-5,6,7,8-tetra-hydronaphthalen-1-yloxy]phenol (43) Starting from **42** (569 mg, 2.0 mmol), **43** (362 mg, 48%) was obtained as a pale yellow oil in a similar manner as described for **5a**. ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.82—1.95 (1H, m), 2.04—2.14 (1H, m), 2.58 (1H, dd, J=11.2, 16.8 Hz), 2.84—3.01 (3H, m), 3.11 (1H, dd, J=4.8,

16.8 Hz), 3.71 (3H, s), 3.79 (3H, s), 6.20 (1H, d, J=2.4 Hz), 6.43 (1H, d, J=2.4 Hz), 6.74—6.80 (2H, m), 6.81—6.88 (4H, m), 7.17—7.22 (2H, m). HR-MS (ESI) m/z: Calcd for $C_{24}H_{23}O_4$: 375.1596 Found: 375.1615.

6-(4-Hydroxyphenyl)-4-[4-(2-piperidin-1-ylethoxy)phenoxy]-5,6,7,8-tetrahydronaphthalen-2-ol (44) Starting from **43** (189 mg, 0.50 mmol), **44** (104 mg, 45%) was obtained as a colorless solid in a similar manner as described for **6a**. **44** was dissolved in THF and the solution was treated with 4 N HCl–AcOEt to give the corresponding HCl salt as a colorless solid for analytical and biological evaluation. mp 197—198 °C. ^{1}H-NMR (CD_3OD): δ (ppm) 1.69 (2H, br s), 1.78—1.92 (5H, m), 1.96—2.05 (1H, m), 2.42 (1H, dd, J=11.2, 16.4 Hz), 2.72—2.94 (4H, m), 3.20 (4H, br s), 3.44—3.50 (2H, m), 4.27—4.32 (2H, m), 6.07 (1H, d, J=2.4 Hz), 6.36 (1H, d, J=2.4 Hz), 6.67—6.72 (2H, m), 6.85—6.90 (2H, m), 6.94—6.99 (2H, m), 7.01—7.06 (2H, m). ^{13}C-NMR (DMSO-d_6): δ (ppm) 21.85, 23.01, 30.31, 30.44, 32.08, 49.27, 53.30, 55.44, 63.35, 103.41, 103.47, 110.84, 110.93, 115.73, 116.60, 118.33, 120.01, 128.19, 137.52, 139.41, 151.49, 153.91, 156.02, 156.22, 156.43. HR-MS (ESI) m/z: Calcd for $C_{29}H_{34}NO_4$: 460.2488 Found: 460.2489.

3-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)propionic acid (46) To an ice-cooled, stirred suspension of sodium hydride (2.40 g, 60% in mineral oil, 60.0 mmol) in DMF (40 ml) was added dropwise a solution of **45**[40] (7.47 g, 40.0 mmol) and methyl 4-methoxyphenylacetate (7.93 g, 44.0 mmol) in DMF (40 ml) for 6 min, and the resultant mixture was stirred for 30 min at the same temperature. The reaction mixture was poured into 1 N hydrochloric acid solution-ice, and the resultant mixture was extracted with AcOEt. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel (10% AcOEt in hexane) to afford a pale yellow oil. To a stirred solution of the residual oil in THF (60 ml) and MeOH (40 ml) was added 5 N sodium hydroxide solution (15.0 ml, 60.0 mmol), and the resultant mixture was stirred for 1 h at 60 °C. The reaction mixture was quenched with 5 N hydrochloric acid solution (20.0 ml), and the resultant mixture was partitioned between AcOEt and water. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give a white solid. The crude solid was triturated in *tert*-butyl methyl ether and filtered to afford **46** (8.23 g, 65%) as a white solid. mp 119—120 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.94 (1H, dd, J=7.2, 14.0 Hz), 3.32 (1H, dd, J=8.0, 14.0 Hz), 3.70 (6H, s), 3.78 (3H, s), 3.75—3.84 (1H, m), 6.24—6.30 (3H, m), 6.82—6.87 (2H, m), 7.20—7.25 (2H, m).

5,7-Dimethoxy-2-(4-methoxyphenyl)indan-1-one (47) To a stirred suspension of **46** (7.68 g, 24.3 mmol) in toluene (150 ml) was added oxalyl chloride (4.62 g, 36.4 mmol), and the resultant mixture was stirred for 1 h 10 min at rt. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in dichloromethane (100 ml), and to this was added a solution of stannic chloride in dichloromethane (1.0 M, 26.0 ml, 26.0 mmol) for 3 min with ice-cooling, and the stirring was continued for 1 h at the same temperature. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was absorbed on silica gel under reduced pressure. The gel was charged upon a column of silica gel, and eluted with AcOEt–hexane (50—100%) and subsequently with THF to give **47** (6.78 g, 94%) as a colorless solid. mp 121—123 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.08 (1H, dd, J=4.0, 17.2 Hz), 3.54 (1H, dd, J=8.4, 17.2 Hz), 3.77 (3H, s), 3.79 (1H, dd, J=4.0, 8.4 Hz), 3.90 (6H, s), 6.34 (1H, d, J=1.2 Hz), 6.52 (1H, d, J=1.2 Hz), 6.80—6.86 (2H, m), 7.07—7.13 (2H, m).

7-Hydroxy-5-methoxy-2-(4-methoxyphenyl)indan-1-one (48) Starting from **47** (6.62 g, 22.1 mmol), **48** (2.81 g, 45%) was obtained as a brown solid in a similar manner as described for **19**. mp 116—119 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.12 (1H, dd, J=4.0, 17.6 Hz), 3.58 (1H, dd, J=8.0, 17.6 Hz), 3.79 (s, 3H), 3.87 (s, 3H), 6.34 (1H, s), 6.51 (1H, s), 6.84—6.90 (2H, m), 7.08—7.13 (2H, m), 9.12 (1H, s).

6-Methoxy-2-(4-methoxyphenyl)indan-4-ol (49) Starting from **48** (1.86 g, 6.5 mmol), **49** (1.04 g, 59%) was obtained as a colorless oil in a similar manner as described for **20**. ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.84 (1H, dd, J=8.0, 14.8 Hz), 3.00 (1H, dd, J=8.4, 15.6 Hz), 3.23 (1H, dd, J=8.0, 14.8 Hz), 3.27 (1H, dd, J=8.4, 15.6 Hz), 3.60—3.72 (1H, m), 3.77 (3H, s), 3.80 (3H, s), 4.82 (1H, s), 6.26 (1H, d, J=2.0 Hz), 6.43 (1H, d, J=2.0 Hz), 6.82—6.88 (2H, m), 7.18—7.24 (2H, m).

4-[6-Methoxy-2-(4-methoxyphenyl)indan-4-yloxy]phenol (50) Starting from **49** (780 mg, 2.89 mmol), **50** (379 mg, 38%) was obtained as a colorless solid in a similar manner as described for **5a**. mp 113—113.5 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.81 (1H, dd, J=8.4, 15.6 Hz), 3.02 (1H, dd, J=8.4, 15.6 Hz), 3.21 (1H, dd, J=8.4, 15.6 Hz), 3.33 (1H, dd, J=8.4, 15.6 Hz), 3.58—3.68 (m, 1H), 3.73 (3H, s), 3.79 (3H, s), 4.71 (1H, br s), 6.26 (1H, d, J=2.0 Hz), 6.56 (1H, d, J=2.0 Hz), 6.75—6.80 (2H, m), 6.81—6.90 (4H, m), 7.17—7.21 (2H, m). HR-MS (ESI) m/z: Calcd for $C_{23}H_{21}O_4$: 361.1440 Found: 361.1469.

2-(4-Hydroxyphenyl)-7-[4-(2-piperidin-1-ylethoxy)phenoxy]indan-5-ol (51) Starting from **50** (290 mg, 0.80 mmol), **51** (84 mg, 24%) was obtained as a colorless solid in the same manner as described for **6a**. **51** was dissolved in THF and the solution was treated with 4 N HCl in AcOEt to give the corresponding HCl salt as a colorless solid for analytical and biological evaluation. mp 203—205 °C. ^{1}H-NMR (CD_3OD): δ (ppm) 1.68 (2H, br s), 1.82—1.95 (4H, m), 2.62 (1H, dd, J=8.4, 15.6 Hz), 2.91 (1H, dd, J=8.4, 15.6 Hz), 3.04 (1H, dd, J=8.4, 15.6 Hz), 3.19 (1H, dd, J=8.4, 15.6 Hz), 3.34 (4H, br s), 3.45—3.56 (3H, m), 4.32 (2H, t, J=4.8 Hz), 6.13 (1H, d, J=2.0 Hz), 6.47 (1H, d, J=2.0 Hz), 6.65—6.70 (2H, m), 6.88—6.93 (2H, m), 6.95—7.00 (2H, m), 7.02—7.07 (2H, m). ^{13}C-NMR (CD_3OD): δ (ppm) 21.38, 22.85, 37.37, 41.20, 44.94, 53.65, 56.01, 62.42, 103.62, 103.69, 106.45, 106.54, 114.91, 114.88, 115.67, 119.22, 123.69, 127.60, 136.49, 146.87, 152.15, 153.55, 153.68, 155.49, 157.73. *Anal.* Calcd for $C_{28}H_{32}NO_4Cl$: C, 69.77; H, 6.69; N, 2.91. Found: C, 69.53; H, 6.76; N, 2.66.

Estrogen Receptor Binding Assay. Materials and Methods [2,4,6,7,16,17-^{3}H] Estradiol, specific activity 143 Ci/mmol (TRK587) was purchased from Amersham LIFE SCIENCE. Charcoal, dextran coated (C-6197) and diethylstilbestrol (D-4628) were purchased from SIGMA. Bovine uteri were obtained from a nearby slaughterhouse.

Estrogen receptor binding assay was done according to the method of S. G. Korenman.[41] Cytosol was obtained from a homogenate of bovine uterus by centrifugation at 105000×$\boldsymbol{g}$ for 30 min in 3 volumes of Buffer A (20 mM Tris/HCl, pH 7.5, containing 10% glycerol, 1 mM EDTA, 1 mM dithiothreitol and 100 μM *p*-APMSF). ^{3}H-Estradiol (10000 dpm) and competing compounds were mixed in a total volume of 80 μl Buffer A. Then 20 μl of uterine cytosol was added and incubated for 1 h at 23 °C. 100 μl of a charcoal, dextran coated suspension (2% W/V) was added and mixed, incubated at 23 °C for 10 min. The charcoal was then removed by centrifugation at 2000×$\boldsymbol{g}$ for 10 min. The radioactivity of the bound ^{3}H-Estradiol remaining in 150 μl of the supernatant (total binding, dpm) was measured by liquid scintillation counter (LSC-6100, Aloka). Nonspecific binding (dpm) in the supernatant was measured in the presence of 10 μM diethylstilbestrol. Specific binding (dpm) was calculated by subtracting nonspecific binding (dpm) from total binding (dpm). IC_{50} value (nM) was calculated as a concentration of the compound, which shows 50% replacement of ^{3}H-estradiol bound to the estrogen receptors. Binding activity of the compound was shown as a K_i value. The K_i value was obtained from the calculation; $K_i = IC_{50}/(1+(C/K_d))$. C and K_d are concentration (nM) of ^{3}H-Estradiol and dissociation constant (nM) in the binding assay, respectively. The K_d value was calculated 0.3 nM by the Scatchard analysis (data not shown).

Effect on Reproductive Cells. Materials and Methods Cell Culture: Response to estrogen was assessed by cell proliferation of MCF-7 cell, a human breast adenocarcinoma cell line, and expression of alkaline phosphatese in Ishikawa cell, a human endometrial tumor cell line. MCF-7 cells and Ishikawa cells (subclone 3-H-12, No. 50, gifted by Dr. Nishida, University of Tsukuba, Japan) were maintained in minimum essential medium with Earles's salts without phenol red (Invitrogen Corp., CA, U.S.A.) and 10% fetal bovine serum, supplemented with 10% fetal bovine serum (FBS) (V/V), 2 mM L-glutamine (Invitrogen Corp., CA, U.S.A.), 1 mM sodium pyruvate (Invitrogen Corp., CA, U.S.A.), non-essential amino acids solution (1 : 100, Invitrogen Corp., CA, U.S.A.), and antibiotics–antimycotics (1 : 100, penicillin G, streptomycin, and amphotericin B, Invitrogen Corp., CA, U.S.A.). The cells were maintained in 75-cm^2 culture flasks at 37 °C in a 5% CO_2 humidified incubator and were subcultured at a 1 : 20 to 40 ratio once a week. The cells were used for assay before 100% confluence. The culture media were switched to assay media which was the same as maintenance medium except supplemented with 10% "stripped" FBS in place of 10% FBS, one day prior to plating. Stripped FBS was obtained by treating the serum with dextran-coated charcoal to remove steroid hormones and was used throughout all assays. The cells were removed from flasks using 0.05% Trypsin/0.53 mM EDTA (Invitrogen Corp., CA, U.S.A.). After neutralizing of trypsin with assay media, the cells were pelleted and the trypsin/EDTA was removed by washing. The cells were re-suspended with assay medium. MCF-7 cells were plated on 96-well plate at 5000 cells/100 μl/well for cell proliferation assay. Ishikawa cells were plated on 96-well plate at 20000 cells/100 μl/well for alkaline phosphatase assay. After 24-h incubation, the whole culture media were changed to 100 μl of fresh assay media. The testing compounds were applied from 1 pM to 1 uM at final concentration. The group of cells treated with 1 nM β-estradiol (Sigma, St. Louis, MO, U.S.A.) was set up as positive control for each assay plate. For evaluation of antago-

nistic effect against β-estradiol of testing compounds, 10 pM of β-estradiol was applied at the same time.

Cell Proliferation Assay[45] Cell proliferation of MCF-7 cells was assessed by MTT reduction assay 3 d after compound application. Briefly, the reaction was started by adding MTT (8 mg/ml, 10 μl, Sigma, St. Louis, MO, U.S.A.) to each well and terminated by adding a solution containing 50% dimethylformamide and 20% sodium dodecyl sulphate (pH 4.8). The amount of formazan product was determined by measuring absorbance at 590 nm. The MCF-7 proliferation score, which was calculated as ((sample−control)/(1 nM β-estradiol−control)×100+100), was used as an index for comparison of potency of MCF-7 proliferation effect of compounds. IC_{50} value (nM) was calculated as a concentration of the compound, which inhibits 50% cell growth of 10 pM β-estradiol.

Alkaline Phosphatase Assay[46] Alkaline phosphate activity in Ishikawa cell was assessed by the method of Bessey–Lowry, using *p*-nitrophenylphosphate as substrate (Alkaline phospha B-test WAKO kit, Wako Pure Chemical Industries, Ltd., Osaka). Briefly, The cultured cells were rinsed with Dulbecco's phosphate-buffered saline and were incubated for 2 h in 37 °C CO_2 incubator with 100 μl of the 6.7 mM *p*-nitrophenylphosohate solution (6.7 mM). The relative phosphatase activity was determined by measuring absorbance at 405 nm. The relative alkaline phosphatase activity was expressed by using "alkaline phosphatase (ALP) score" as index. ALP score was calculated as ((sample−control)/(1 nM estradiol−control)×200+100).

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