Structure−Activity Relationship Study To Understand the Estrogen Receptor-Dependent Gene Activation of Aryl- and Alkyl-Substituted 1*H*-Imidazoles

Thomas Wiglenda and Ronald Gust*

Institute of Pharmacy, Free University of Berlin, Königin-Luise Strasse 2+4, D-14195 Berlin, Germany

Received September 22, 2006

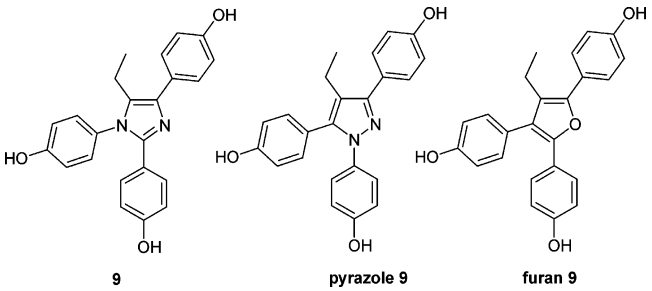
A series of C5-substituted 1,2,4-triaryl-1*H*-imidazoles was synthesized. Their gene-activating properties were determined on estrogen receptor alpha positive MCF-7 breast cancer cells, stably transfected with the plasmid ERE_{wtc}luc (MCF-7-2a cells). The influence of 4-OH and 2-Cl substituents on the phenyl rings as well as the significance of a methyl, ethyl, or phenyl group at C5 on the estrogen receptor binding and the resulting gene activation in MCF-7-2a cells was studied. The alkyl and aryl groups at C5 of 1,2,4-tris(4-hydroxyphenyl)-1*H*-imidazole **1** increased the transactivation, while chlorine atoms on the phenyl rings diminished this effect. 5-Ethyl-1,2,4-tris(4-hydroxyphenyl)-1*H*-imidazole **9** was identified as the most active compound. Its excellent transcriptional activity did not only depend on the C5 ethyl group, but also on the three hydroxyl groups of the phenyl rings. Compounds (**11**−**14**) with a reduced number of hydroxyl groups displayed distinctly lower gene activation.

Introduction

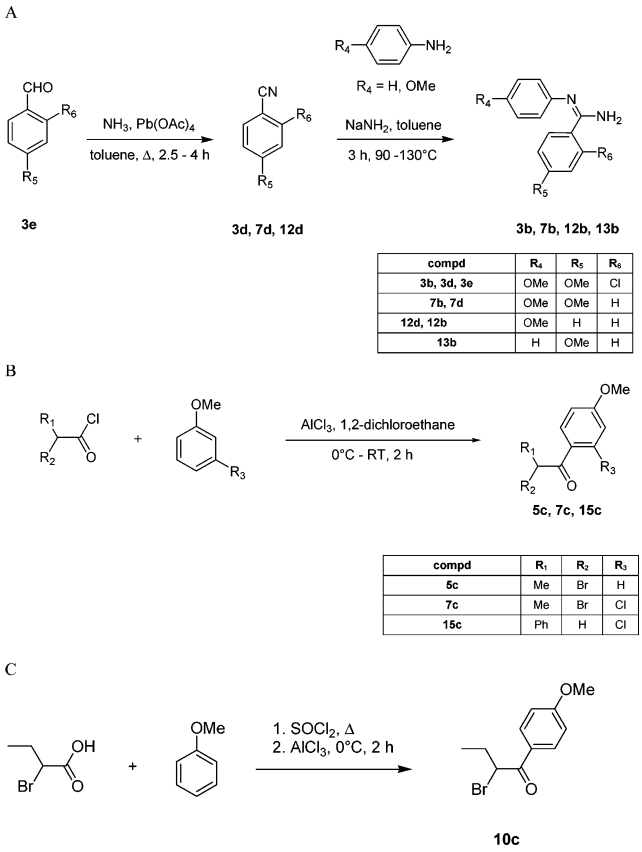
The estrogen receptor (ER) is an important transcription factor and regulates physiological processes, which are involved, for example, in the development and function of the reproductive and cardiovascular systems or in the bone density changes.[1−3] The regulatory properties become evident through the interaction with its native ligands such as estradiol (E2).

Nonsteroidal estrogenic (e.g., diethylstilbestrol) and antiestrogenic (e.g., raloxifene) ligands have been developed to regulate these processes or their pathological dysfunction, including breast cancer, osteoporosis, and infertility. New possibilities of treatment opened the discovery of selective estrogen receptor modulators (SERMs) which exert tissue- and cell-selective activity. It was demonstrated in various structure−activity relationship (SAR) studies that aromatic[4−7] and nonaromatic[6,7] heterocycles as well as cycloalkanes can act as potent SERMs. Their activity clearly depended on the arrangement of phenolic substituents at the core molecule. Intensive studies on 4-alkyl-1,3,5-tris(4-hydroxyphenyl)-1*H*-pyrazoles (e.g., **pyrazole 9**),[4] 3-alkyl-2,4,5-tris(4-hydoxyphenyl)furans (e.g., **furan 9**)[5] (formulas see Scheme 1), and on *N*-alkyl-substituted 4,5-bis-(4-hydroxyphenyl)-2-imidazolines[8] and 2,3-bis(4-hydroxyphenyl)piperazines[9] demonstrated the significance of the kind of the heteroatoms as well as the presence of alkyl substituents on the ER binding affinity and/or ER subtype selectivity.

Scheme 1



Scheme 2



compd	R_4	R_5	R_6
3b, 3d, 3e	OMe	OMe	Cl
7b, 7d	OMe	OMe	H
12d, 12b	OMe	H	H
13b	H	OMe	H

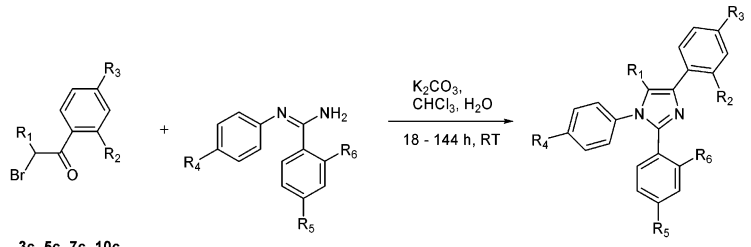
compd	R_1	R_2	R_3
5c	Me	Br	H
7c	Me	Br	Cl
15c	Ph	H	Cl

This observation induced us to optimize 1*H*-imidazoles[6,10] for a specific receptor−ligand interaction. Because of the negative results obtained with 4,5-bis(4-hydroxyphenyl)-1*H*-imidazoles[11] and 2,4,5-tris(4-hydroxyphenyl)imidazoles[12] the arrangement of the substituents at the imidazole core was changed to a 1,2,4-tris(4-hydroxyphenyl)-1*H*-imidazole scaffold[13] corresponding to the hormonally active **pyrazole 9** and **furan 9**. Indeed, the lead structure 5-ethyl-1,2,4-tris(4-hydroxyphenyl)-1*H*-imidazole **9** (for structure, see Scheme 1) was hormonally active but to a lesser extent than **pyrazole 9** and

* Corresponding author. Phone: (030) 838 53272; Telefax: (030) 838 56906; E-mail: rgust@zedat.fu-berlin.de.

10.1021/jm061106t CCC: $37.00
Published on Web 03/13/2007

Scheme 3

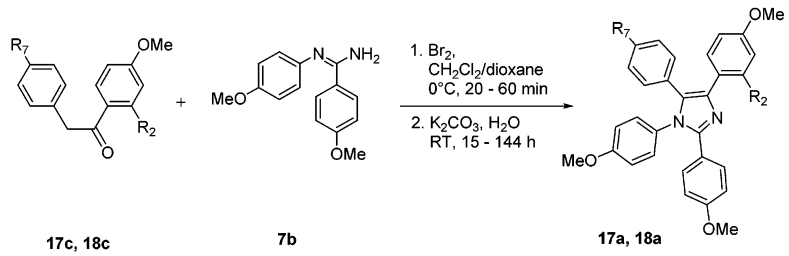


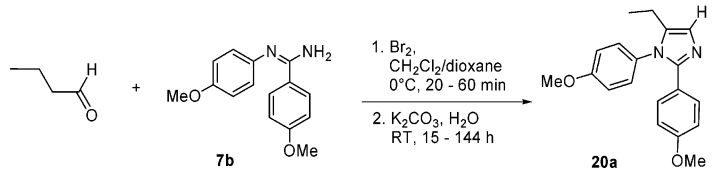
compd	R_1	R_2	R_3
3c	H	H	OMe
5c	Me	H	OMe
7c	Me	Cl	OMe
10c	Et	H	OMe
11c	Et	H	H
15c	Ph	H	OMe

compd	R_4	R_5	R_6
3b	OMe	OMe	Cl
7b	OMe	OMe	H
12b	OMe	H	H
13b	H	OMe	H

compd	R_1	R_2	R_3	R_4	R_5	R_6
3a	H	H	OMe	OMe	OMe	Cl
5a	Me	H	OMe	OMe	OMe	H
6a	Me	H	OMe	OMe	OMe	Cl
7a	Me	Cl	OMe	OMe	OMe	H
8a	Me	Cl	OMe	OMe	OMe	Cl
10a	Et	H	OMe	OMe	OMe	Cl
11a	Et	H	H	OMe	OMe	H
12a	Et	H	OMe	OMe	H	H
13a	Et	H	OMe	H	OMe	H
14a	Et	H	H	H	OMe	H
15a	Ph	H	OMe	OMe	OMe	H
16a	Ph	H	OMe	OMe	OMe	Cl

compd		R_2	R_7
17c	**17a**	H	OMe
18c	**18a**	Cl	H





furan 9. Interestingly, gene expression induced by **9** in estrogen receptor alpha (ERα) positive MCF-7-2a cells (routinely used in our laboratory for the evaluation of hormonally active compounds) depended on the presence of the C5 ethyl group. 1,2,4-Tris(4-hydroxyphenyl)-1*H*-imidazole **1** was completely inactive. In contrast to our investigations on meso-configurated 4,5-diaryl-2-imidazolines,[6,11] which can also be interpreted as 2,3-dihydro-1*H*-imidazoles, chlorine substituents on the phenolic rings did not increase the transcriptional activity. These results document the relevance of an alkyl chain at the imidazole core for estrogenic activity.

In this structure−activity relationship study we investigated the influence of alkyl chains at C5, the influence of the substituents on the aromatic rings, and the significance of the C4 aryl ring on the hormonal profile of 1,2,4-triaryl-1*H*-imidazoles.

Results and Discussion

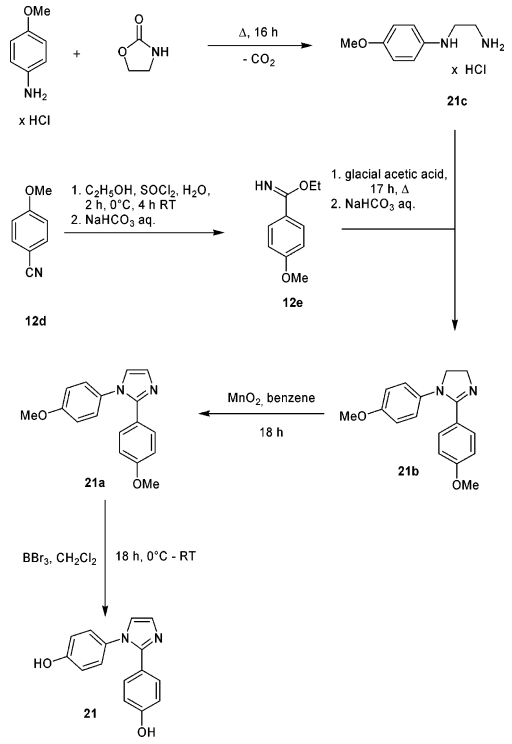
Chemistry. The synthesis of the 1,2-diaryl-, 1,2,4-triaryl-, and 5-alkyl-1,2,4-triaryl-1*H*-imidazoles was performed by cyclization of *N*-arylbenzamidines and α-bromoketones as described earlier.[13] The *N*-arylbenzamidines (**3b**, **7b**, **12b**, **13b**) were obtained by reaction of aryl nitriles (**3d**, **7d**, **12d**) with anisidine or aniline according to Gautier[14] or Daoust[15] using sodium amide as reaction agent (Scheme 2A). 2-Chloro-4-methoxybenzonitrile (**3d**), which was not commercially available, was prepared by reaction of 2-chloro-4-methoxybenzaldehyde (**3e**) with gaseous ammonia and lead(IV) acetate as oxidant.[16] The α-bromoketones **5c**, **7c**, **10c**, and **15c** were produced by Friedel−Crafts acylation of anisoles with α-bromo-substituted acid chlorides (Scheme 2B and 2C). The subsequent ring formation between α-bromoketones (**3c**, **5c**, **7c**, **10c**, **11c**, **15c**) and *N*-arylbenzamidines (**3b**, **7b**, **12b**, **13b**) was carried out at room temperature in a mixture of $CHCl_3/H_2O$ (6:1) utilizing K_2CO_3 as base (Scheme 3). Ring formation occurred in each case with high regioselectivity and yield. No regioisomers of **3a**, **5a**−**8a**, and **10a**−**16a** could be separated from the reaction mixture.

For the synthesis of the 1*H*-imidazoles **17a**, **18a**, and **20a**, the desoxybenzoins **17c** and **18c** or butyraldehyde were used. In the first step the educts were brominated with Br_2 in a mixture of dry CH_2Cl_2 and dioxane, followed by the well-known cyclization without prior purification (Scheme 3).

The synthesis of the 1,2-diaryl-1*H*-imidazole **21a** is depicted in Scheme 4. A ring closing reaction of N^1-(4-methoxyphenyl)-ethane-1,2-diamine hydrochloride **21c** with 4-methoxybenzimidic acid ethyl ester **12e** in glacial acid gave the 1,2-bis(4-methoxyphenyl)-2-imidazoline (**21b**), which was oxidized to **21a** with MnO_2 in benzene under reflux.

N^1-(4-Methoxyphenyl)ethane-1,2-diamine hydrochloride (**21c**) was obtained by melting of oxazolidin-2-one and anisidine at a temperature between 170−190 °C. 4-Methoxybenzimide acid

Scheme 4



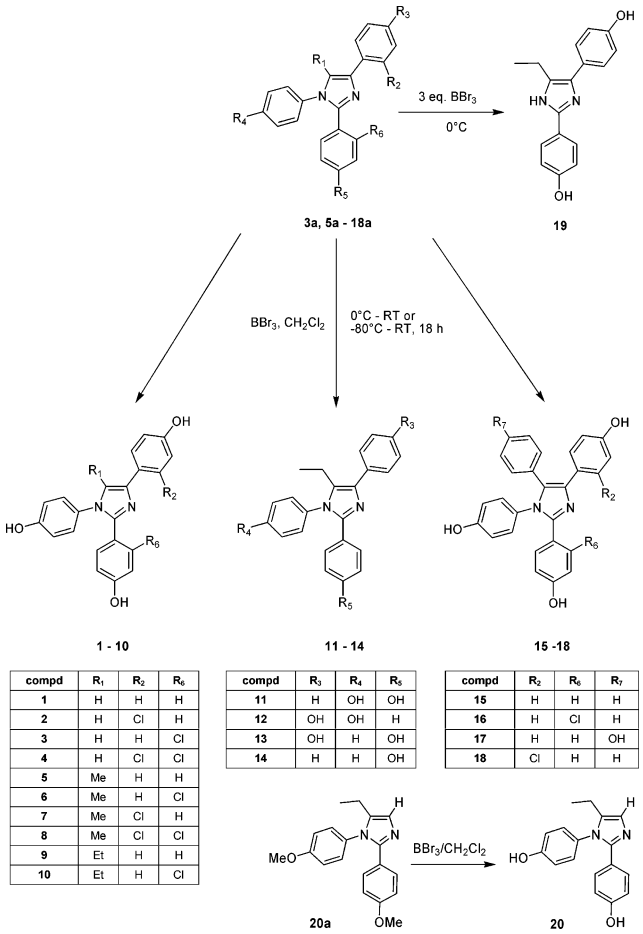
ethyl ester (**12e**) was obtained from 4-methoxybenzonitrile (**12d**) with $SOCl_2$ in a mixture of ethanol and water at about 0 °C.

The ether cleavage to afford the free phenols **1**−**18**, **20**, **21** was performed with boron tribromide (Scheme 5; for **21**, see Scheme 4) at −80 °C. Interestingly, if this reaction was carried out with 5-ethyl-2,4-bis(4-methoxyphenyl)-1-phenyl-1*H*-imidazole **13a**, a loss of the phenyl group at N1 (⇒ **19**, Scheme 5) was observed.

The structural characterization of the 1*H*-imidazoles was performed by double resonance nuclear Overhauser enhancement experiment (NOESY). It was confirmed that all oxo group standing substituents took position C4.

As an example, Figure 1 presents the section 5.8−8.0 ppm and 0.7−3.6 ppm of the NOESY spectrum of compound **10** (DMSO-d_6). All protons at the C2′ position of the phenyl rings showed NOEs to their neighboring protons at the C3′ position

Scheme 5



compd	R_1	R_2	R_6
1	H	H	H
2	H	Cl	H
3	H	H	Cl
4	H	Cl	Cl
5	Me	H	H
6	Me	H	Cl
7	Me	Cl	H
8	Me	Cl	Cl
9	Et	H	H
10	Et	H	Cl

compd	R_3	R_4	R_5
11	H	OH	OH
12	OH	OH	H
13	OH	H	OH
14	H	H	OH

compd	R_5	R_6	R_7
15	H	H	H
16	H	Cl	H
17	H	H	OH
18	Cl	H	H

(NOEs 1, 2, and 3). Furthermore, saturation transfers were observed between the methylene (NOEs b and d, Figure 1) and methyl protons (NOEs a and c, Figure 1) of the ethyl chain to the H-C2′ protons of the N1- and C4-standing phenyl rings. This is only possible if the ethyl group is located between these rings at C5 of the imidazole ring.

Estrogen Receptor Binding and Transcriptional Activity. The interaction of the 1*H*-imidazoles **1**−**21** with ERα was tested in a competition experiment with [^{3}H]E2 using calf uterine cytosol as source of ERα and in a luciferase assay[17] using ERα

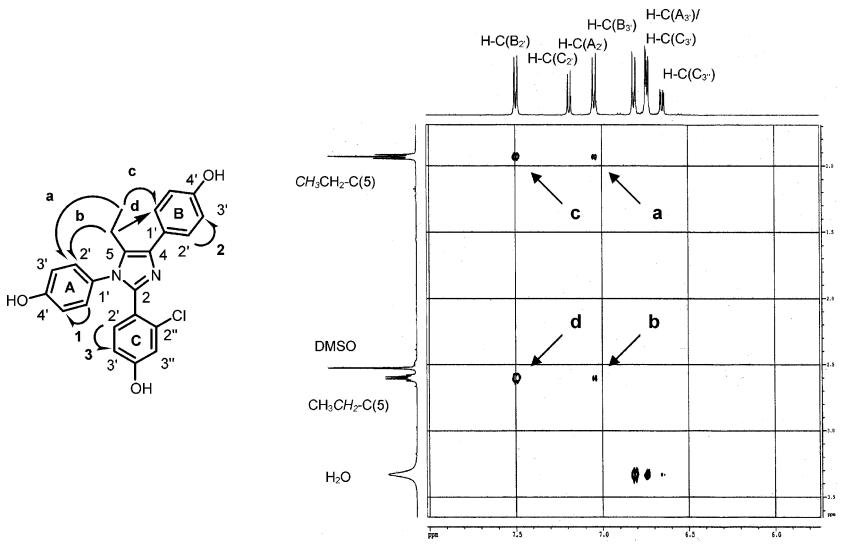


Figure 1. NOESY-spectrum of compound **10** in DMSO-d_6 (300 K). The saturation transfer of the methyl (a, c) and methylene (b, d) protons of the ethyl group to the protons at C($A_{2'}$) (a, b) and C($B_{2'}$) (c, d) of the phenyl rings A and B.

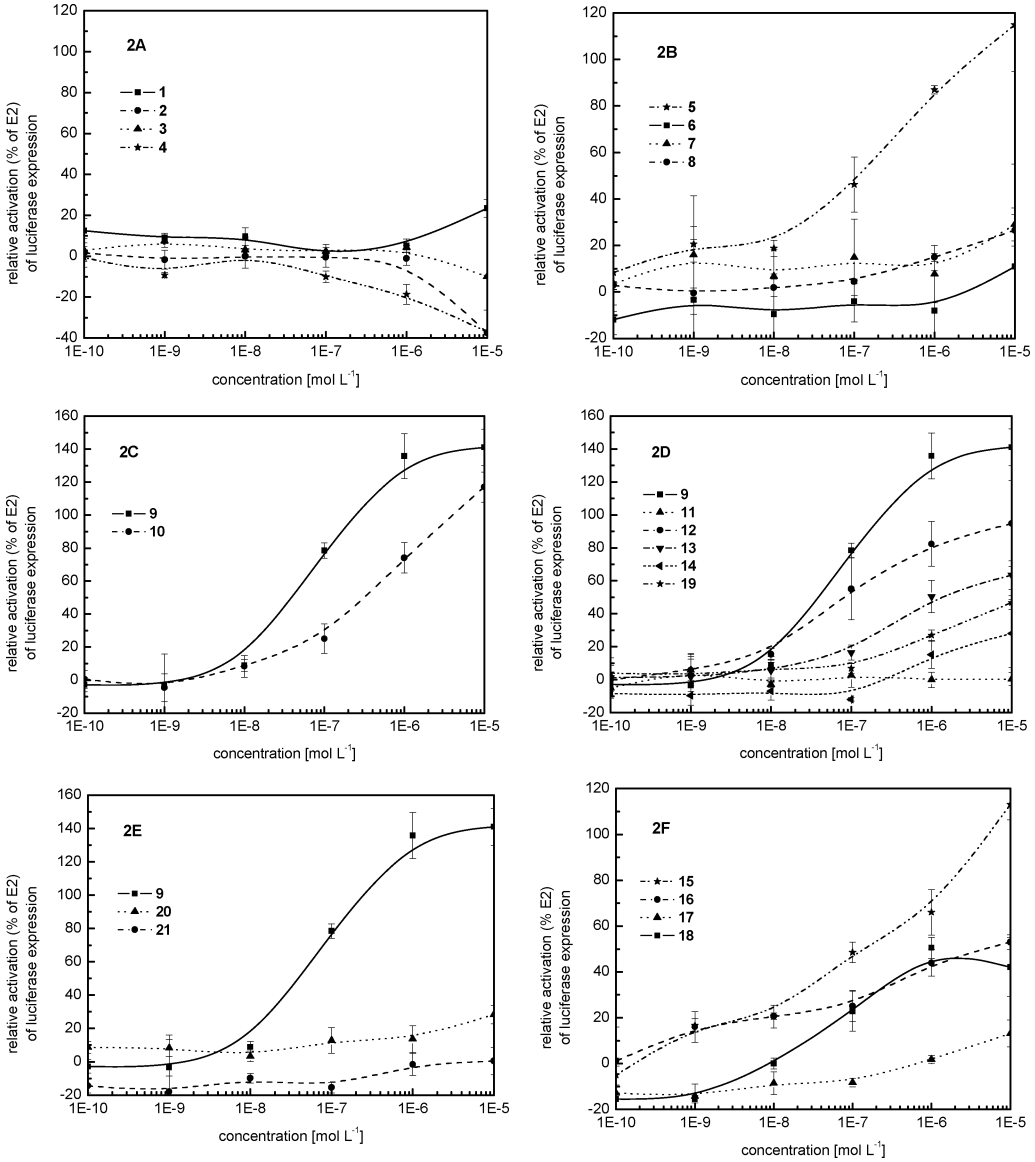


Figure 2. Activation (%) of the luciferase gene expression in MCF-7-2a cells by 1*H*-imidazoles **1**−**21**. Values expressed are the means ± SE of 3-fold determination in a single experiment.

positive MCF-7 breast cancer cells stably transfected with the plasmid ERE_{wtc}luc (MCF-7-2a cells). It is well accepted that the binding of hormonal drugs to the ERα leads to a conformational change of the receptor and subsequently to a dimerization of the ER/drug conjugates. The binding of the dimers to the estrogen response element (ERE) of the plasmid ERE_{wtc}-luc in MCF-7-2a cells causes the expression of luciferase, which correlates well with the estrogenic potency of the drug.[18]

The respective relative binding affinity (RBA) of the 1,2,4-triaryl-1*H*-imidazoles was very low. Only **4** (RBA = 0.09%), **8** (RBA = 0.11%), **9** (RBA = 0.11%), and **10** (RBA = 0.19%) possessed RBA values >0.05%. Nevertheless, gene activation measured strongly depended on the substituents of the aromatic rings and the C5 alkyl chain.

As depicted in Figure 2A, the 1*H*-imidazoles **1**−**4** without C5 alkyl substituents did not induce gene activation. In the case of the Cl-substituted compounds **2**−**4**, a significant reduction of the relative activation (% E2) of the luciferase expression was observed at the highest concentration.

C5 alkyl chains enhanced the transcriptional activity. The methyl derivative **5** reached the 100% E2 activation at a concentration of 10 μM and showed an EC_{50} = 0.14 μM. Hydrophobic chlorine substituents on the C2 and/or the C4 aryl ring abolished the gene activation (compounds **6**−**8**, Figure 2B). In contrast, enhancement of the hydrophobicity by elongation of the C5 alkyl chain increased the hormonal potency (Figure 2C). The 1*H*-imidazole **9** bearing a C5 ethyl residue showed a distinctly lower EC_{50} value (0.077 μM) than **5** but a maximum activation of 140%. Interestingly, the ethyl chain compensated the negative effect of the chlorine on the aromatic rings. Compound **10** activated the luciferase expression (EC_{50} = 0.48 μM) despite the Cl atom on the C2 aryl ring.

In the next step we studied the significance of the OH groups on the phenyl rings of **9**. Each modification, the exchange of an OH group by H reduced the transcriptional potency. None of the compounds **11**−**14** reached the maximum effect of E2 (100%) within the specified concentration range (Figure 2D). An EC_{50} = 0.061 μM was determined for compound **12**.

Nevertheless, a structure−activity relationship can be deduced from these results. Hydroxyl groups on the N1/C4 aryl rings (**12:** rel activation at 10 μM: 90%) were more effective than on the C2/C4 rings (**13:** rel activation at 10 μM: 60%). Compound **11** with OH groups on the N1/C2 rings was completely inactive. The 5-ethyl-2,4-bis(4-hydroxyphenyl)-1*H*-

imidazole **19** showed a slightly lower activation of luciferase expression than **13** (which confirmed the ER binding mainly by the C2/C4 phenolic rings) but with a clearly higher activation than compound **14** which had only one OH group.

Exchange of the C4 aryl ring (compound **20**) and the C5 ethyl chain (compound **21**) led to inactive compounds (Figure 2E). The comparison with the results for compound **9** showed that the C4 phenolic ring is not only essential to achieve H bonds in the ligand binding domain but also for hydrophobic contacts.

Therefore, in the next step of this SAR study the C5 ethyl chain in **9** was replaced by an aromatic ring. The resulting 1,2,4-tris(4-hydroxyphenyl)-5-phenyl-1*H*-imidazole **15** showed lower hormonal activity than **9** but reached the 100% relative activation at a concentration of 10 μM (Figure 2F). The $EC_{50} = 0.35$ μM was comparable to that of the methyl derivative **5**. Chlorine substituents either on the C2 or the C4 phenolic ring of **15** reduced the luciferase expression. At the highest concentration of 10 μM, **16** and **18** achieved relative activation levels of 50% and 40%, respectively (Figure 2F).

The introduction of an OH group on the C5 phenyl ring led to a strong decrease of activity. The 1*H*-imidazole **17** was nearly inactive. This might be the consequence of hindered hydrophobic contacts by the hydrophilic OH group indicating a well defined orientation of the 1*H*-imidazoles in the ligand binding domain (LBD).

The results of the transcriptional assay depended on the interaction of the drugs with the ERα, because the MCF-7-2a cells contain this ER subtype. The binding mode of hormones at the ERα is well-known from X-ray crystallographic studies and molecular modeling.[19−21] Estradiol is attached to Arg394, Glu353, and a water molecule by hydrogen bonds from the 3-OH group as well by an H bridge from the 17β-OH group to His524. This orientation is stabilized by van der Waals contacts of the steroidal skeleton to hydrophobic amino acids. This binding mode is realized for all linear hormones (type I or class I estrogens).[6,22,23]

During the last years a lot of angular hormones were developed, which cannot bind in the LBD in the same orientation.[6,8,24] In a previous SAR study, we investigated *meso*-4,5-bis(4-hydroxyphenyl)-2-imidazolines as new SERMs.[6,8,25] The prerequesite for their ER binding were the two OH groups in a distance of 6.8 Å and *o*-chloro substituents on the aromatic rings to intensify the hydrophobic contacts. For this and related compounds, an interaction between the OH groups and the guanidinium residue of Arg394 and the carboxylate group of Glu353 as well as an incorporated water molecule on the one hand and Asp351 or Thr347 residue in the 11β cannel at ERα on the other hand was proposed.[19]

The 1*H*-imidazoles presented in this paper can be assigned to type I or type II estrogens, because linear (N1/C4 rings and C2/C4 rings) and angular pharmacophores (N1/C2 rings) can be realized. From the data of the luciferase assay, however, a type II estrogen like orientation can be excluded. Compounds **20** and **21** are completely inactive.

The variation of the substituents on the phenyl rings showed that mainly the N1/C4 rings act as pharmacophores and should be bound in the linear way in the LBD. The insertion of a hydrophobic alkyl residue or a phenyl ring at C5 in the 1,2,4-tris(4-hydroxyphenyl)-1*H*-imidazole **1** enhanced the estrogenic effect, while the C5 phenolic residue abolished the gene activation. These findings point to strong hydrophobic interactions and to a well defined orientation of the 1*H*-imidazoles in the LBD.[26]

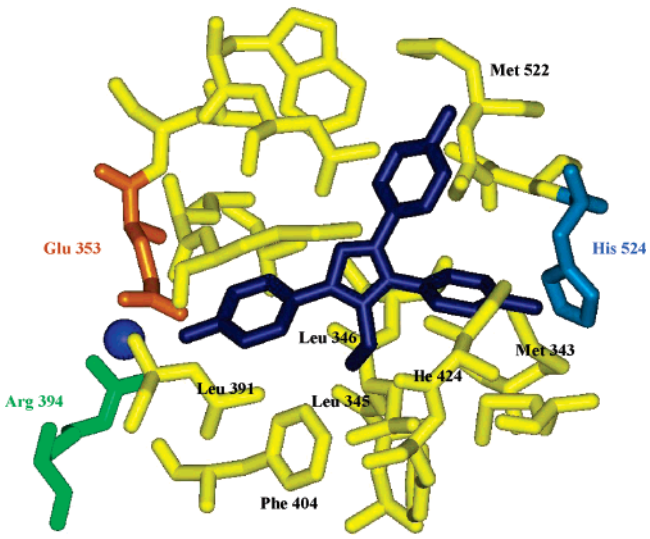


Figure 3. Model of the interaction of 5-ethyl-1,2,4-tris(4-hydroxyphenyl)-1*H*-imidazole **9** with the estrogen receptor α binding site. Compound **9**, generated by Tripos SYBYL software and energy minimized with MM3, was inserted in the LBD of the 1ERE crystal structure image from the pdb data base. The physiological ligand estradiol was removed and replaced by compound **9**. (The ligand was fitted out of the E2 molecule plane. The C2−C1′ bond was aligned in the plane of the E2 C13-Me group.) The C4 phenolic group was oriented to the guanidinium residue of Arg394 and the carboxylate group of Glu353 as well as an incorporated water molecule. The phenolic substituent at N1 was oriented towards His524 to develop a second hydrogen bond. The third C2 phenolic ring was directed towards Met522. The C5 ethyl residue was embeded in a lipophilic pocket formed by Phe404, Leu346, and Ile424.

The binding model of **9** is depicted in Figure 3. In view of the fact that a hydroxyl group was more effective on the N1/C4 rings than on the C2/C4 rings (**12** more active than **13**) and, moreover, totally ineffective on the N1/C2 rings (**11**), we assume that the C4 phenolic ring is directed to Arg394 and Glu353 and mimics ring A of E2. The OH group of the N1 phenolic ring is oriented to His524. The third phenolic ring contacts Met522. The importance of Met522 for the binding of hormonally active compounds was already detected by Danielian et al. They generated mutant mouse estrogen receptors, which differ in their sensitivity to estrogens. Mutation of Gly525 and Met522 virtually abolished the ability of the receptor to bind estradiol and to stimulate transcription.[27]

The C5-standing residue is oriented toward a hydrophobic pocket well-known from the X-ray structrure of ERα co-crystallized with DES.[20] This pocket tolerates the ethyl chain but also a C5 aryl ring. Van der Waals contacts are possible to Phe404, Leu391, Ile 424, and Leu346. Hydrophilic groups such as those in **17** (C5 phenolic ring) disturb these contacts, leading to a reorientation of the drug in the LBD and a reduction of gene activation.

The decreased efficacy of chlorine-bearing compounds might be a result of steric repulsion during the ER binding. Only if the hydrophobic character of the entire molecule is high enough, can this obstacle be overcome as demonstrated for **3** and **16** as well as **2** and **18**.

Finally some comments are necessary regarding the curve of **9** and those of the chlorine-substituted compounds **2** and **4** depicted in Figure 2A. Compound **9** exceeded the transactivation level of E2. This might be the consequence of a distinct mode of action. The additional contacts of **9** in the LBD might induce a conformation of the ER, which is different to that of E2. As a consequence co-activator or co-repressor recruitment might

be different. Other reasons would be the interaction with an additional binding site, which can be the explanation for the low RBA value, or an influence on the ER turnover rate. Investigations on these topics are in the planning stage and will be performed in the future.

The negative activations at 10 μM displayed by both compounds **2** and **4** were the results of inhibition of the MCF-7-2a cell growth. This cytotoxic effect was verified in the hormone-dependent MCF-7 and the hormone-independent MDA-MB 231 cell lines.[13] Therefore, it was deduced that the ER was not involved in the cytotoxic activity. Furthermore, the cyclooxygenase enzymes (COX) were identified as targets for this class of drugs. The inhibition of the cell growth correlates very well with the inhibition of the COX enzymes.[13]

Inhibition of cell growth and reduced COX activity were only observed with compounds **2** and **4** bearing an *o*-Cl on the C4 phenolic ring. Compound **3** (Cl substituent on the C2 phenolic ring) showed neither cytotoxicity nor COX-inhibition (data not shown).

To get more information about the structural requirement for cytotoxicity and COX inhibition, an SAR study was initiated. The results will be presented in a forthcoming paper.

Experimental Section

General Methods. All reagents and solvents were purchased from Acros Organics, Fluka Chemie, Lancaster, Merck, or Sigma-Aldrich. All reactions were monitored by TLC, performed on silica gel plates 60 F_{254} (Merck, Darmstadt/Germany). Visualization on TLC was achieved by UV light. Column chromatography was performed with Merck silica gel 60H, grain size <0.063 mm, 230 mesh ASTM (Darmstadt/Germany). Melting points: 510 Büchi (Flawil/Schweiz) capillary melting point apparatus. IR spectra (KBr pellets): Perkin-Elmer Model 580 A (Rodgau-Jügesheim/Germany). ^{1}H NMR: Avance DPX-400 spectrometer (Bruker, Karlsruhe/Germany) at 400 MHz, AMX 500 spectrometer (Bruker, Karlsruhe/Germany) at 500.14 MHz (internal standard: TMS). Elemental analyses: Microlaboratory of the Free University of Berlin. EI-MS spectra: CH-7A-Varian MAT, 70 eV (Melbourne/Australia). FAB spectra: CH5 DF (Varian MAT, Bremen, Germany) modified with focused FAB-gun (AMD-Intectra). Microlumat: Victor^2 1420 Multilabel Counter (Wallac, Perkin-Elmer, Life sciences, Turku/Finnland). Microplate reader: FLASHscan S12 (analytikjena AG/Germany).

Synthesis. The 1*H*-imidazoles **1**, **2**, **4**, and **9** and the benzaldehyde **3e** were synthesized as previously published.[13,28] Compounds **7d** and **12d** were commercially available.

General Procedure for the Preparation of Benzonitrile. Through a stirred solution of the respective benzaldehyde and lead(IV) acetate in toluene (30 mL) was passed gaseous ammonia for 3 h while heating to reflux. The solution was then poured onto a mixture of crushed ice (200 g) and 36% HCl (50 mL) and was subsequently extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over Na_2SO_4 and removed under reduced pressure to provide the product.

2-Chloro-4-methoxybenzonitrile (3d). From 2-chloro-4-methoxybenzaldehyde **3e** (1.00 g, 5.86 mmol) and lead(IV) acetate (5.20 g, 11.72 mmol). Yield: 0.92 g (5.49 mmol, 94%) of colorless crystals (mp: 75 °C). ^{1}H NMR (DMSO-d_6): δ = 7.89 (d, 1H, J = 8.7 Hz, Ar*H*), 7.35 (d, 1H, J = 2.5 Hz, Ar*H*), 7.11 (dd, 1H, J = 2.5 Hz, J = 8.7 Hz, Ar*H*), 3.88 (s, 3H, OCH_3).

General Procedure for the Preparation of *N*-Arylbenzamidines. A solution of anisidine or aniline in dry toluene (20−40 mL) was treated with $NaNH_2$ under N_2 atmosphere. The respective benzonitrile was then added after stirring for 3 h at 120−140 °C. The mixture was held at this temperature for 3 h and then cooled overnight to room temperature without stirring.

***N*-(4-Methoxyphenyl)-2-chloro-4-methoxybenzamidine (3b).** From anisidine (2.59 g, 21.07 mmol), $NaNH_2$ (986 mg, 25.27 mmol), and benzonitrile **3d** (3.53 g, 21.06 mmol). Water (150 mL) was added to the crude mixture, and it was repeatedly extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuum. The crude product was purified by chromatography with stepwise gradient elution (CH_2Cl_2/methanol 95:5, 90:10) to give **3b** (1.08 mg, 18%) as violet amorphous solid (mp: 79 °C). ^{1}H NMR (DMSO-d_6): δ = 9.50 (bs, 2H, NH_2), 7.72 (bs, 1H, Ar*H*), 7.28 (bs, 3H, Ar*H*), 7.09 (bs, 3H, Ar*H*), 3.85 (bs, 3H, OCH_3), 3.73 (bs, 3H, OCH_3).

***N*-(4-Methoxyphenyl)-4-methoxybenzamidine (7b).** From anisidine (2.43 g, 19.76 mmol), $NaNH_2$ (924 mg, 23.70 mmol), and 4-methoxybenzonitrile (**7d**) (2.63 g, 19.75 mmol). The crude product was separated by vacuum filtration, washed with toluene, and suspended in H_2O (150 mL). After being stirred for 30 min, the slurry was extracted with CH_2Cl_2 (3 × 60 mL). The organic layers were combined and dried over Na_2SO_4. Evaporation gave the product **7b** (2.70 g, 53%) as a colorless solid (mp: 150 °C). ^{1}H NMR (DMSO-d_6): δ = 7.92 (d, 2H, J = 8.8, Ar*H*), 6.96 (d, 2H, J = 8.8, Ar*H*), 6.88 (d, 2H, J = 8.8, Ar*H*), 6.76 (d, 2H, J = 8.7, Ar*H*), 6.07 (s, 2H, NH_2), 3.79 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3).

***N*-(4-Methoxyphenyl)benzamidine (12b).** From anisidine (1.85 g, 15.03 mmol), $NaNH_2$ (586 mg, 15.03 mmol), and benzonitrile **12d** (1.55 g, 15.03 mmol). Water (150 mL) was added to the crude mixture, and it was repeatedly extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuum. The crude product was purified by chromatography with stepwise gradient elution (CH_2Cl_2/methanol 95:5, 90:10) to give **12b** (470 mg, 14%) as colorless amorphous solid (mp: 86 °C). ^{1}H NMR (DMSO-d_6): δ = 7.97−7.93 (m, 2H, Ar*H*), 7.48−7.41 (m, 2H, Ar*H*), 6.92−6.82 (m, 5H, Ar*H*), 6.46 (bs, 2H, NH_2), 3.73 (s, 3H, OCH_3).

***N*-Phenyl-4-methoxybenzamidine (13b).** From aniline (3.77 g, 40.48 mmol), $NaNH_2$ (1.58 g, 40.50 mmol), and 4-methoxybenzonitrile (**7d**) (5.40 g, 43.87 mmol). The crude product was separated by vacuum filtration, washed with toluene, and suspended in H_2O (150 mL). After being stirred for 30 min, the slurry was extracted with CH_2Cl_2 (3 × 60 mL). The organic layers were combined and dried over Na_2SO_4. Evaporation gave the product **13b** (4.32 g, 19.1 mmol, 47%) as a colorless solid (mp: 138 °C). ^{1}H NMR (DMSO-d_6): δ = 7.93 (d, 2H, J = 8.6, Ar*H*), 7.30 (pt, 2H, J = 7.6, Ar*H*), 6.96 (pt, 3H, J = 7.4, Ar*H*), 6.83 (d, 2H, J = 7.6, Ar*H*), 6.12 (s, 2H, NH_2), 3.81 (s, 3H, OCH_3).

General Procedure of the Preperation of Ketones. The respective acid chloride was added to a cooled solution of $AlCl_3$ in 1,2-dichlorethane (250 mL). Subsequently, the anisole was added at a rate that maintained the temperature at 0−5 °C. The mixture was allowed to warm to room temperature, and stirring was continued for 1.5 h. Then the reaction mixture was poured onto a mixture of crushed ice (400 g) and 36% HCl (10 mL), the organic layer was separated, and the aqueous solution was subsequently extracted with CH_2Cl_2 (3 × 50−80 mL). The organic layers were combined and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The products were separated if necessary by column chromatography on SiO_2.

2-Bromo-1-(4-methoxyphenyl)propan-1-one (5c). From 2-bromopropionic acid chloride (3.00 mL, 29.75 mmol), $AlCl_3$ (5.95 g, 44.63 mol), and anisole (3.24 mL, 29.75 mmol). Column chromatography with stepwise gradient elution: petroleum ether/diethyl ether 5:2, 4:1, 2:1. Yield: 2.30 g (32%) of colorless oil. After standing at room temperature the oil crystallized (mp = 57 °C). ^{1}H NMR (DMSO-d_6): δ = 8.03 (d, 2H, J = 8.9, Ar*H*), 7.05 (d, 2H, J = 9.0, Ar*H*), 5.79 (q, 1H, J = 6.5, C*H*BrCH$_3$), 3.86 (s, 3H, OCH_3), 1.76 (q, 3H, J = 6.5, CHBrCH_3).

2-Bromo-1-(2-chloro-4-methoxyphenyl)propan-1-one (7c). From 2-bromopropionic acid chloride (3.00 mL, 29.75 mmol), $AlCl_3$ (5.95 g, 44.63 mol), and 3-chloroanisole (3.66 mL, 29.75 mmol). Column chromatography with stepwise gradient elution: petroleum ether, petroleum ether/diethyl ether 5:2, 1:1. Yield: 2.88 g (35%) of colorless oil. After standing at room temperature, the oil solidified to gelatinous needles. ^{1}H NMR (DMSO-d_6): δ = 7.85 (d, 1H, J =

8.7, Ar*H*), 7.15 (d, 1H, $J = 2.5$, Ar*H*), 7.04 (d, 1H, $J = 2.5$, Ar*H*), 5.65 (q, 1H, $J = 6.5$, C*H*BrCH$_3$), 3.86 (s, 3H, OC*H*$_3$), 1.76 (d, 3H, $J = 6.5$, CHBrC*H*$_3$).

2-Bromo-1-(4-methoxyphenyl)butan-1-one (10c). 2-Bromobutyric acid (3.21 mL, 29.94 mmol) was heated with $SOCl_2$ (3.26 mL, 44.91 mmol) under reflux for 40 min. To the reaction mixture was added 1,2-dichlorethane (80 mL), and the solution was cooled with an ice bath. $AlCl_3$ (5.99 g, 44.91 mmol) was added gradually. Under ice cooling, anisole (3.24 mL, 29.94 mmol) was added dropwise (30 min) and the mixture was stirred for 0.75−1.5 h. Separation by column chromatography with stepwise gradient elution: petroleum ether, petroleum ether/diethyl ether 4:1, 1:1; Yield: 3.30 g (43%) of colorless oil. ^{1}H NMR (DMSO-d_6): $\delta =$ 8.04 (d, 2H, $J = 8.9$, Ar*H*), 7.08 (d, 2H, $J = 9.0$, Ar*H*), 5.62 (pq, 1H, $J = 7.6$, C*H*BrCH$_2$CH$_3$), 3.89 (s, 3H, OC*H*$_3$), 2.15−2.07 (m, 2H, CHBrC*H*$_2$CH$_3$), 1.00 (t, 3H, $J = 7.3$, CHBrCH$_2$C*H*$_3$).

1-(2-Chloro-4-methoxyphenyl)-2-phenylethan-1-one (15c). From phenylacetyl chloride (6.00 g, 38.81 mmol), $AlCl_3$ (7.76 g, 58.20 mol), and 3-chloroanisole (4.77 mL, 38.80 mmol). Column chromatography with stepwise gradient elution: petroleum ether/diethyl ether 5:1, 4:1. ^{1}H NMR (DMSO-d_6): $\delta = 7.83$ (d, 2H, $J = 8.7$, Ar*H*), 7.56 (m, 2H, $J = 8.4$, Ar*H*), 7.30 (d, 2H, $J = 8.8$, Ar*H*), 7.22 (d, 1H, $J = 1.8$, Ar*H*), 7.08 (dd, 1H, $J = 1.9$, $J = 8.0$, Ar*H*), 4.24 (s, 2H, C*H*$_2$), 3.93 (s, 3H, OC*H*$_3$).

General Procedure for the Preparation of Substituted 1*H*-Imidazoles. Method A: K_2CO_3 and the α-bromoketone were subsequently added to a stirred solution of the *N*-arylbenzamidine in $CHCl_3$ (3.00 mL) and H_2O (0.50 mL) at room temperature. The reaction was kept at room temperature for 18−56 h, quenched with H_2O (50 mL), and stirred for additional 20 min. The solution was extracted with CH_2Cl_2 (3 × 20 mL), and the organic layer was separated, dried over Na_2SO_4, and evaporated under reduced pressure, to give a crude product, which was purified by chromatography on silica gel.

Method B: Br_2 in dry CH_2Cl_2 (3.00 mL) was added over a period of 20−60 min to a cooled solution of the ketone in a mixture of dry CH_2Cl_2/dioxane (1:1, 5.00 mL) under nitrogen atmosphere. After decolorization, *N*-arylbenzamidine, K_2CO_3 and H_2O (1.00 mL) were added and the reaction mixture was stirred at room temperatur for 15−49 h. The reaction was quenched with H_2O (50 mL) and stirred for an additional 20 min. The solution was extracted with CH_2Cl_2 (3 × 20 mL), and the organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure, to give a crude product, which was purified by chromatography on silica gel.

2-(2-Chloro-4-methoxyphenyl)-1,4-bis(4-methoxyphenyl)-1*H*-imidazole (3a). From amidine **3b** (200 mg, 0.69 mmol), K_2CO_3 (143 mg, 1.03 mmol), and α-bromoketone **3c** (237 mg, 1.04 mmol). Method A; reaction time: 20 h; column chromatography with CH_2Cl_2/methanol 98:2. Yield: 250 mg (86%) of a colorless solid (mp: 76 °C). ^{1}H NMR (DMSO-d_6): $\delta = 7.88$ (s, 1H, 5-*H*), 7.78 (d, 2H, $J = 8.7$, Ar*H*), 7.48 (d, 1H, $J = 8.5$, Ar*H*), 7.16 (d, 2H, $J = 8.8$, Ar*H*), 7.02 (d, 1H, $J = 2.5$, Ar*H*), 6.98−6.92 (m, 5H, Ar*H*), 3.79 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 3.74 (s, 3H, OC*H*$_3$).

1,2,4-Tris(4-methoxyphenyl)-5-methyl-1*H*-imidazole (5a). From amidine **7b** (691 mg, 2.70 mmol), K_2CO_3 (495 mg, 3.58 mmol), and α-bromoketone **5c** (580 mg, 2.39 mmol). Method A; reaction time: 48 h; column chromatography with CH_2Cl_2/methanol 98:2. Yield: 310 mg (29%) of a colorless solid (mp: 78 °C). ^{1}H NMR (DMSO-d_6): $\delta =$ 7.49 (d, 2H, $J = 8.9$, Ar*H*), 7.28 (d, 2H, $J =$ 8.8, Ar*H*), 7.07−7.03 (m, 4H, Ar*H*), 6.88 (d, 2H, $J = 8.9$, Ar*H*), 6.82 (d, 2H, $J = 8.8$, Ar*H*), 3.82 (s, 3H, OC*H*$_3$), 3.71 (s, 6H, OC*H*$_3$), 1.90 (s, 3H, C*H*$_3$).

2-(2-Chloro-4-methoxyphenyl)-1,4-bis(4-methoxyphenyl)-5-methyl-1*H*-imidazole (6a). From amidine **3b** (202 mg, 0.69 mmol), K_2CO_3 (128 mg, 0.93 mmol), and α-bromoketone **5c** (150 mg, 0.62 mmol). Method A; reaction time: 72 h; column chromatography with CH_2Cl_2/methanol 98:2. Yield: 292 mg (97%) of a colorless solid (mp: 196−198 °C). ^{1}H NMR (DMSO-d_6): $\delta = 7.64$ (d, 2H, $J = 8.7$, Ar*H*), 7.39 (d, 1H, $J = 8.6$, Ar*H*), 7.19 (d, 2H, $J = 8.9$, Ar*H*), 7.01−6.98 (m, 3H, Ar*H*), 6.95 (d, 2H, $J = 8.9$, Ar*H*), 6.89 (dd, 1H, $J = 2.5$, $J = 8.6$, Ar*H*), 3.79 (s, 3H, OC*H*$_3$), 3.76 (s, 3H, OC*H*$_3$), 3.75 (s, 3H, OC*H*$_3$), 2.20 (s, 3H, C*H*$_3$).

4-(2-Chloro-4-methoxyphenyl)-1,2-bis(4-methoxyphenyl)-5-methyl-1*H*-imidazole (7a). From amidine **7b** (104 mg, 0.41 mmol), K_2CO_3 (75 mg, 0.54 mmol) and α-bromoketone **7c** (100 mg, 0.35 mmol). Method A; reaction time: 80 h; column chromatography with CH_2Cl_2/methanol 98:2. Yield: 59 mg (33%) of a colorless solid (mp: 65−70 °C). ^{1}H NMR (DMSO-d_6): $\delta = 7.46$ (d, 1H, $J =$ 8.6, Ar*H*), 7.29 (d, 2H, $J = 8.8$, Ar*H*), 7.26 (d, 2H, $J = 8.8$, Ar*H*), 7.12 (d, 2H, $J = 2.5$, Ar*H*), 7.07 (d, 2H, $J = 8.9$, Ar*H*), 7.00 (dd, 1H, $J = 2.5$, $J = 8.7$, Ar*H*), 6.83 (d, 1H, $J = 8.8$, Ar*H*), 3.82 (s, 3H, OC*H*$_3$), 3.72 (s, 6H, OC*H*$_3$), 1.92 (s, 3H, C*H*$_3$).

2,4-Bis(2-chloro-4-methoxyphenyl)-1-(4-methoxyphenyl)-5-methyl-1*H*-imidazole (8a). From amidine **3b** (344 mg, 0.41 mmol), K_2CO_3 (257 mg, 1.86 mmol), and α-bromoketone **7c** (301 mg, 0.35 mmol). Method A; reaction time: 72 h; column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5. Yield: 363 mg (66%) of a colorless solid (mp: 74 °C). ^{1}H NMR (DMSO-d_6): $\delta = 8.11$ (d, 1H, $J = 8.4$, Ar*H*), 7.49 (d, 1H, $J =$ 8.5, Ar*H*), 7.20−7.16 (m, 3H, Ar*H*), 7.06 (dd, 1H, $J = 2.0$, $J =$ 8.3, Ar*H*), 7.03 (d, 1H, $J = 2.5$, Ar*H*), 6.97 (dd, 1H, $J = 2.5$, $J =$ 8.6, Ar*H*), 6.93 (d, 2H, $J = 8.9$, Ar*H*), 3.95 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 3.74 (s, 3H, OC*H*$_3$), 1.96 (s, 3H, C*H*$_3$).

2-(2-Chloro-4-methoxyphenyl)-5-ethyl-1,4-bis(4-methoxyphenyl)-1*H*-imidazole (10a). From amidine **3b** (513 mg, 1.76 mmol), K_2CO_3 (366 mg, 2.65 mmol), and α-bromoketone **10c** (454 mg, 1.77 mmol): Method A; reaction time: 144 h; column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 99:1, 98:2. Yield: 342 mg (43%) of a vitreous brownish solid (mp: 65−68 °C). ^{1}H NMR (DMSO-d_6): $\delta = 7.63$ (d, 2H, $J = 8.8$, Ar*H*), 7.38 (d, 1H, $J = 8.6$, Ar*H*), 7.23 (d, 2H, $J = 8.9$, Ar*H*), 7.00 (d, 2H, $J = 8.9$, Ar*H*), 6.97 (d, 1H, $J = 2.6$, Ar*H*), 6.95 (d, 2H, $J =$ 8.9, Ar*H*), 6.86 (dd, 1H, $J = 2.5$, $J = 8.6$, Ar*H*), 3.79 (s, 3H, OC*H*$_3$), 3.75 (s, 6H, OC*H*$_3$), 2.61 (q, 2H, $J = 7.4$, C*H*$_2$CH$_3$), 1.43 (t, 3H, $J = 7.4$, CH$_2$C*H*$_3$).

5-Ethyl-1,2-bis(4-methoxyphenyl)-4-phenyl-1*H*-imidazole (11a). From amidine **7b** (677 mg, 2.64 mmol), K_2CO_3 (1.09 g, 7.92 mmol), and α-bromoketone **11c** (600 mg, 2.64 mmol). Method A; reaction time: 60 h; column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5. Yield: 321 mg (32%) of a colorless solid (mp: 150 °C). ^{1}H NMR (DMSO-d_6): $\delta = 7.65$ (d, 2H, $J = 8.8$, Ar*H*), 7.57−7.54 (m, 3H, Ar*H*), 7.41−7.39 (m, 2H, Ar*H*), 7.23 (d, 2H, $J = 8.9$, Ar*H*), 7.01 (d, 2H, $J = 8.8$, Ar*H*), 6.80 (d, 2H, $J = 8.9$, Ar*H*), 3.80 (s, 3H, OC*H*$_3$), 3.71 (s, 3H, OC*H*$_3$), 2.58 (q, 2H, $J = 7.4$, C*H*$_2$CH$_3$), 0.92 (t, 3H, $J = 7.4$, CH$_2$C*H*$_3$).

5-Ethyl-1,4-bis(4-methoxyphenyl)-2-phenyl-1*H*-imidazole (12a). From amidine **12b** (457 mg, 2.02 mmol), K_2CO_3 (838 mg, 6.06 mmol), and α-bromoketone **10c** (727 mg, 2.83 mmol). Method A; reaction time: 48 h; column chromatography with CH_2Cl_2/methanol 98:2. Yield: 234 mg (30%) of a colorless solid (mp: 103 °C). ^{1}H NMR (DMSO-d_6): $\delta = 7.66$ (d, 2H, $J = 7.8$, Ar*H*), 7.34 (d, 4H, $J = 7.0$, Ar*H*), 7.25 (bs, 3H, Ar*H*), 7.07 (d, 2H, $J = 7.7$, Ar*H*), 7.02 (d, 2H, $J = 7.7$, Ar*H*), 3.83 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 2.60 (q, 2H, $J = 7.1$, C*H*$_2$CH$_3$), 0.95 (t, 3H, $J = 7.2$, CH$_2$C*H*$_3$).

5-Ethyl-2,4-bis(4-methoxyphenyl)-1-phenyl-1*H*-imidazole (13a). From amidine **13b** (500 mg, 2.21 mmol), K_2CO_3 (916 mg, 6.62 mmol), and α-bromoketone **10c** (795 mg, 3.09 mmol). Method A; reaction time: 72 h; column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5. Yield: 84 mg (10%) of a colorless solid (mp: 121 °C). ^{1}H NMR (DMSO-d_6): $\delta = 7.65$ (d, 2H, $J = 8.8$, Ar*H*), 7.57−7.54 (m, 3H, Ar*H*), 7.42−7.39 (m, 2H, Ar*H*), 7.23 (d, 2H, $J = 8.9$, Ar*H*), 7.01 (d, 2H, $J = 8.8$, Ar*H*), 6.80 (d, 2H, $J = 8.8$, Ar*H*), 3.80 (s, 3H, OC*H*$_3$), 3.71 (s, 3H, OC*H*$_3$), 2.60 (q, 2H, $J = 7.4$, C*H*$_2$CH$_3$), 0.92 (t, 3H, $J = 7.4$, CH$_2$C*H*$_3$).

5-Ethyl-2-(4-methoxyphenyl)-1,4-diphenyl-1*H*-imidazole (14a). From amidine **13b** (1.00 g, 4.41 mmol), K_2CO_3 (1.83 g, 13.26 mmol) and α-bromoketone **11c** (1.59 g, 7.00 mmol). Method A ($CHCl_3$ (5.00 mL) and H_2O (1.00 mL)); reaction time: 72 h; column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5. Yield: 302 mg (19%) of a colorless solid (mp: 114−116 °C). ^{1}H NMR (DMSO-d_6): $\delta = 7.74$ (d, 2H, $J = 7.3$, Ar*H*),

7.57−7.55 (m, 3H, Ar*H*), 7.46−7.41 (m, 4H, Ar*H*), 7.28 (t, 1H, *J* = 8.0, Ar*H*), 7.24 (d, 2H, *J* = 8.9, Ar*H*), 6.81 (d, 2H, *J* = 8.8, Ar*H*), 3.71 (s, 3H, OCH_3), 2.64 (q, 2H, *J* = 7.5, CH_2CH$_3$), 0.94 (t, 3H, *J* = 7.4, CH$_2$CH_3).

1,2,4-Tris(4-methoxyphenyl)-5-phenyl-1*H*-imidazole (15a). From amidine **7b** (300 mg, 1.17 mmol), K_2CO_3 (214 mg, 1.55 mmol), and α-bromoketone **15c** (470 mg, 1.54 mmol). Method A; reaction time: 67 h; column chromatography with petroleum ether/diethyl ether 1:1. Yield: 206 mg (38%) of a colorless solid (mp: 176−180 °C). ^{1}H NMR (DMSO-d_6): δ = 7.38 (d, 2H, *J* = 8.9, Ar*H*), 7.33−7.28 (m, 5H, Ar*H*), 7.23−7.20 (m, 2H, Ar*H*), 7.16 (d, 2H, *J* = 8.8, Ar*H*), 6.86 (d, 4H, *J* = 8.9, Ar*H*), 6.81 (d, 2H, *J* = 8.9, Ar*H*), 3.73 (s, 3H, OCH_3), 3.71 (s, 6H, OCH_3).

2-(2-Chloro-4-methoxyphenyl)-1,4-bis(4-methoxyphenyl)-5-phenyl-1*H*-imidazole (16a). From amidine **3b** (675 mg, 2.32 mmol), K_2CO_3 (285 mg, 2.06 mmol), and α-bromoketone **15c** (514 mg, 1.68 mmol). Method A; reaction time: 17 h; column chromatography with stepwise gradient elution: petroleum ether/diethyl ether 1:1, 1:2. Yield: 479 mg (42%) of a colorless solid (mp: 153 °C). ^{1}H NMR (DMSO-d_6): δ = 7.46 (d, 2H, *J* = 8.5, Ar*H*), 7.37 (d, 2H, *J* = 9.0, Ar*H*), 7.32−7.30 (m, 3H, Ar*H*), 7.22−7.19 (m, 2H, Ar*H*), 7.05−7.01 (m, 2H, Ar*H*), 6.90 (dd, 1H, *J* = 2.7, *J* = 8.6, Ar*H*), 6.81 (d, 2H, *J* = 9.0, Ar*H*), 6.74 (d, 2H, *J* = 9.0, Ar*H*), 3.77 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3).

1,2,4,5-Tetrakis(4-methoxyphenyl)-1*H*-imidazole (17a). From desoxybenzoine **17c** (250 mg, 0.80 mmol) with Br_2 (128 mg. 0.80 mmol; 60 min). Method B (amidine **7b** (259 mg, 1.01 mmol), K_2CO_3 (124 mg, 0.90 mmol)); reaction time: 15 h; column chromatography with stepwise gradient elution: petroleum ether/diethyl ether 1:1, 1:2. Yield: 498 mg (30%) of a colorless solid (mp: 209 °C). ^{1}H NMR (DMSO-d_6): δ = 7.40 (d, 2H, *J* = 8.9, Ar*H*), 7.30 (d, 2H, *J* = 8.9, Ar*H*), 7.15 (pt, 4H, *J* = 8.3, Ar*H*), 6.88−6.81 (m, 8H, Ar*H*), 3.73 (s, 9H, OCH_3), 3.71 (s, 3H, OCH_3).

4-(2-Chloro-4-methoxyphenyl)-1,2-bis(4-methoxyphenyl)-5-phenyl-1*H*-imidazole (18a). From ketone **18c** (900 mg, 3.45 mmol) with Br_2 (180 mg, 1.13 mmol; 60 min). Method B (amidine **7b** (870 mg, 3.39 mmol), K_2CO_3 (480 mg, 4.84 mmol)); reaction time: 48 h; column chromatography with CH_2Cl_2/methanol 98:2. Yield: 448 mg (27%) of a colorless solid (mp: 139 °C). ^{1}H NMR (DMSO-d_6): δ = 7.35 (d, 1H, *J* = 8.6, Ar*H*), 7.28 (d, 2H, *J* = 8.8, Ar*H*), 7.19−7.14 (m, 5H, Ar*H*), 6.99 (d, 1H, *J* = 2.6, Ar*H*), 6.95−6.90 (m, 5H, Ar*H*) 6.85 (d, 2H, *J* = 8.9, Ar*H*), 3.77 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3).

5-Ethyl-1,2-bis(4-methoxyphenyl)-1*H*-imidazole (20a). From butanal (500 μL, 5.55 mmol) and Br_2 (887 mg, 5.55 mmol, 20 min). Method B (amidine **7b** (500 mg, 1.95 mmol), K_2CO_3 (0.77 g, 11.94 mmol)); reaction time: 48 h; column chromatography with CH_2Cl_2/methanol 95:5. Yield: 373 mg (58%) of brownish high viscous oil. ^{1}H NMR (DMSO-d_6): δ = 7.23 (d, 2H, *J* = 8.9, Ar*H*), 7.20 (d, 2H, *J* = 9.0, Ar*H*), 7.04 (d, 2H, *J* = 8.9, Ar*H*), 6.86 (s, 1H, 4-*H*), 6.81 (d, 2H, *J* = 8.9, Ar*H*), 3.81 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 2.32 (q, 2H, *J* = 7.5, CH_2CH$_3$), 1.05 (t, 3H, *J* = 7.5, CH$_2$CH_3).

Preparation of 1,2-Bis(4-methoxyphenyl)-1*H*-imidazole 21a. 4-Methoxybenzimidic Acid Ethyl Ester (12e). $SOCl_2$ (5.14 mL, 70.59 mmol) was added over a period of 30 min to a stirred solution of 4-methoxybenzonitrile (**12d**) (10 g, 75.11 mmol), ethanol (4.37 mL, 75.11 mmol), diethyl ether (4.40 mL), and water (1.10 mL) at 0−5 °C. The reaction mixture was stirred for 4 h at room temperature and then stored in a refrigerator overnight and cooled to −30 °C. The solution was kept at this temperature to provide a colorless amorphous solid. The crude product was separated by vacuum filtration, washed with diethyl ether, and treated for a short time with 15% aqueous $NaHCO_3$ solution (200 mL). The resulting emulsion was extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuum to obtain a colorless oil (6.53 g, 40%). ^{1}H NMR (DMSO-d_6): δ = 8.66 (s, 1H, C═N*H*), 7.78 (d, 2H, *J* = 9.0, Ar*H*), 6.97 (d, 2H, *J* = 8.8, Ar*H*), 4.22 (q, 2H, *J* = 7.1, OCH_2CH$_3$), 3.80 (s, 3H, OCH_3), 1.31 (t, 3H, *J* = 7.1, OCH$_2$CH_3).

***N*^{1}-(4-Methoxyphenyl)ethane-1,2-diamine Hydrochloride (21c).** Oxazolidin-2-one (6.75 g, 77.52 mmol) and anisidine hydrochloride (3.68 g, 23.13 mmol) were heated to 170−190 °C for 16 h. The melt was cooled to room temperature and dissolved in a mixture of methanol/diethyl ether (3:2). After being refluxed for 30 min, the product was allowed to crystallize at 7 °C. The precipitate was separated by vacuum filtration and washed with methanol/diethyl ether (3:2). Yield: 2.75 g (59%) of a gray amorphous powder (mp: 185 °C). ^{1}H NMR (DMSO-d_6): δ = 7.44 (d, 2H, *J* = 9.0, Ar*H*), 6.88 (d, 2H, *J* = 9.0, Ar*H*), 6.77 (s, 1H, N*H*), 3.79 (t, 2H, *J* = 7.8, CH$_2$CH$_2$), 3.71 (s, 3H, OCH_3), 3.37 (t, 2H, *J* = 7.9, CH_2CH_2), 3.31 (s, 3H, NH_3).

1,2-Bis(4-methoxyphenyl)-2-imidazoline (21b). Ethane-1,2-diamine hydrochloride **21c** (1.00 g, 4.98 mmol) was stirred with the iminoethyl ether **12e** (900 mg, 2.25 mmol) in glacial acetic acid (15 mL) for 1 h and then heated to reflux for 17 h. The reaction mixture was added to a 15% aqueous $NaHCO_3$ solution (200 mL), stirred for 15 min, and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure to give a crude product which was purified by column chromatography using stepwise gradient elution with CH_2Cl_2/methanol 98:2, 95:5, and 90:10. Compound **21b** (631 mg, 45%) was isolated from the main fraction as colorless vitreous solid (mp: 97−102 °C). ^{1}H NMR (DMSO-d_6): δ = 7.35 (d, 2H, *J* = 8.8, Ar*H*), 6.98 (d, 2H, *J* = 8.9, Ar*H*), 6.90 (d, 2H, *J* = 8.9, Ar*H*), 6.85 (d, 2H, *J* = 9.0, Ar*H*), 4.03 (t, 2H, *J* = 9.0, CH_2CH_2), 3.90 (t, 2H, *J* = 9.2, CH_2CH_2), 3.75 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3).

1,2-Bis(4-methoxyphenyl)-1*H*-imidazole (21a). The 2-imidazoline **21b** (282 mg, 1.01 mmol) was dissolved in dry benzene (30 mL) and heated to reflux for 3 h to remove water using a Dean−Stark trap. MnO_2 (508 mg, 5.84 mmol) was added to this solution and was heated for additional 18 h. The solution was filtered, the residue was washed with toluene, and the organic layers were combined. 1*H*-Imidazole **21a** (0.28 g, 98%) was isolated from the solution as colorless solid. ^{1}H NMR (DMSO-d_6): δ = 7.34 (d, 1H, *J* = 1.0, C*HCH*), 7.24 (d, 2H, *J* = 8.9, Ar*H*), 7.21 (d, 2H, *J* = 8.9, Ar*H*), 7.10 (d, 1H, *J* = 1.2, C*HCH*), 7.00 (d, 2H, *J* = 8.9, Ar*H*), 6.86 (d, 2H, *J* = 8.9, Ar*H*), 3.79 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3).

General Procedure for the Ether Cleavage with BBr_3. A solution of the methyl ether (1.00 mmol) in 15 mL of dry CH_2Cl_2 was cooled to 0 °C. BBr_3 (4.5 mmol) in 5 mL of dry CH_2Cl_2 was added at this temperature under N_2 atmosphere. Then the reaction mixture was allowed to warm up to room temperature and was stirred for further 18 h. After the reaction mixture was cooled with an ice bath, the excess BBr_3 was hydrolyzed with three portions of a mixture of methanol and Cl_2CH_2 and then methanol. The phenolic product was dissolved in 10% aqueous $NaHCO_3$ (50 mL), and the solution was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude product was purified by chromatography on silica gel.

2-(2-Chloro-4-hydroxyphenyl)-1,4-bis(4-hydroxyphenyl)-1*H*-imidazole (3). From **3a** (296 mg, 0.70 mmol) and BBr_3 (266 μL, 2.81 mmol). Column chromatography with CH_2Cl_2/methanol 9:1. Yield: 250 mg (94%) of a colorless solid (mp: 262 °C). ^{1}H NMR (DMSO-d_6): δ = 10.16 (s, 1H, O*H*), 9.68 (s, 1H, O*H*), 9.35 (s, 1H, O*H*), 7.72 (s, 1H, 5-*H*), 7.63 (d, 2H, *J* = 8.6, Ar*H*), 7.30 (d, 1H, *J* = 8.1, Ar*H*), 7.00 (d, 2H, *J* = 8.7, Ar*H*), 6.78−6.74 (m, 4H, Ar*H*), 6.71 (d, 2H, *J* = 8.7, Ar*H*). Anal. ($C_{21}H_{15}ClN_2O_3$) C, H, N.

1,2,4-Tris(4-hydroxyphenyl)-5-methyl-1*H*-imidazole (5). From **5a** (687 mg, 1.72 mmol) and BBr_3 (162 μL, 1.71 mmol). Column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 99:1, 95:5, 90:10. Yield: 223 mg (36%) of a colorless solid (mp: 185 °C). ^{1}H NMR (DMSO-d_6): δ = 9.90 (s, 1H, O*H*), 9.58 (s, 1H, O*H*), 9.36 (s, 1H, O*H*), 7.53 (d, 2H, *J* = 8.4, Ar*H*), 7.28 (d, 2H, *J* = 8.7, Ar*H*), 7.13 (d, 4H, *J* = 8.9, Ar*H*), 6.88 (d, 2H, *J* = 8.4, Ar*H*), 6.83 (d, 2H, *J* = 8.7, Ar*H*), 2.12 (s, 3H, CH_3). Anal. ($C_{22}H_{18}N_2O_3$) C, H, N.

2-(2-Chloro-4-hydroxyphenyl)-1,4-bis(4-hydroxyphenyl)-5-methyl-1*H*-imidazole (6). From **6a** (220 mg, 0.51 mmol) and BBr_3

(215 μL, 2.27 mmol). Column chromatography with CH_2Cl_2/methanol 9:1. Yield: 132 mg (67%) of a colorless solid (mp: 260 °C). ^{1}H NMR (DMSO-d_6): δ = 10.13 (s, 1H, O*H*), 9.78 (s, 1H, O*H*), 9.40 (s, 1H, O*H*), 7.50 (d, 2H, *J* = 8.6, Ar*H*), 7.22 (d, 1H, *J* = 8.4, Ar*H*), 7.02 (d, 2H, *J* = 8.7, Ar*H*), 6.82 (d, 2H, *J* = 8.7, Ar*H*), 6.74 (d, 3H, *J* = 8.7, Ar*H*), 6.68 (dd, 1H, *J* = 2.4, *J* = 8.5, Ar*H*), 2.17 (s, 3H, C*H*$_3$). Anal. ($C_{22}H_{17}ClN_2O_3$) C, H, N.

4-(2-Chloro-4-hydroxyphenyl)-1,2-bis(4-hydroxyphenyl)-5-methyl-1*H*-imidazole (7). From **7a** (246 mg, 0.57 mmol) and BBr_3 (241 μL, 2.55 mmol). Reaction time after reaching room temperature: 48 h. Column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5, 90:10. Yield: 182 mg (85%) of a colorless solid (mp: 263 °C). ^{1}H NMR (DMSO-d_6): δ = 9.92 (s, 2H, O*H*), 9.60 (s, 1H, O*H*), 7.36 (bs, 1H, Ar*H*), 7.17 (bs, 4H, Ar*H*), 6.95−6.82 (m, 4H, Ar*H*), 6.66 (bs, 2H, Ar*H*), 1.91 (s, 3H, C*H*$_3$). Anal. ($C_{22}H_{17}ClN_2O_3$) C, H, N.

2,4-Bis(2-chloro-4-hydroxyphenyl)-1-(4-hydroxyphenyl)-5-methyl-1*H*-imid azole (8). From **8a** (281 mg, 0.60 mmol) and BBr_3 (255 μL, 2.69 mmol). Column chromatography with CH_2Cl_2/methanol 9:1. Yield: 200 mg (78%) of a colorless solid (mp: 254 °C). ^{1}H NMR (DMSO-d_6): δ = 10.04 (s, 1H, O*H*), 9.94 (s, 1H, O*H*), 9.76 (s, 1H, O*H*), 7.31 (d, 1H, *J* = 8.4, Ar*H*), 7.19 (d, 1H, *J* = 8.4, Ar*H*), 7.02 (d, 2H, *J* = 8.4, Ar*H*), 6.91 (d, 1H, *J* = 1.8, Ar*H*), 6.81 (dd, 1H, *J* = 1.8, *J* = 8.0, Ar*H*), 6.74 (pd, 3H, *J* = 9.0, Ar*H*), 6.67 (d, 1H, *J* = 8.4, Ar*H*), 1.96 (s, 3H, C*H*$_3$). Anal. ($C_{22}H_{16}Cl_2N_2O_3$) C, H, N.

2-(2-Chloro-4-hydroxyphenyl)-5-ethyl-1,4-bis(4-hydroxyphenyl-1*H*-imidazole (10). From **10a** (239 mg, 0.53 mmol) and BBr_3 (227 μL, 2.39 mmol). Column chromatography with CH_2Cl_2/methanol 9:1. Yield: 205 mg (95%) of a colorless solid (mp: 140−145 °C). ^{1}H NMR (DMSO-d_6): δ = 10.05 (s, 1H, O*H*), 9.75 (s, 1H, O*H*), 9.35 (s, 1H, O*H*), 7.49 (d, 2H, *J* = 8.6, Ar*H*), 7.20 (d, 1H, *J* = 8.4, Ar*H*), 7.05 (d, 2H, *J* = 8.7, Ar*H*), 6.80 (d, 2H, *J* = 8.6, Ar*H*), 6.74−6.72 (m, 3H, Ar*H*), 6.65 (dd, 1H, *J* = 2.3, *J* = 8.4, Ar*H*), 2.60 (q, 2H, *J* = 7.4, C*H*$_2$CH$_3$), 0.93 (t, 3H, *J* = 7.4, CH$_2$C*H*$_3$). Anal. ($C_{23}H_{19}ClN_2O_3$) C, H, N.

5-Ethyl-1,2-bis(4-hydroxyphenyl)-4-phenyl-1*H*-imidazole (11). From **11a** (256 mg, 0.67 mmol) and BBr_3 (188 μL, 2.00 mmol). Column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5. Yield: 219 mg (96%) of a colorless solid (mp: 250−255 °C). ^{1}H NMR (DMSO-d_6): δ = 9.93 (s, 1H, O*H*), 9.60 (s, 1H, O*H*), 7.72 (d, 2H, *J* = 7.3, Ar*H*), 7.42 (pt, 2H, *J* = 7.7, Ar*H*), 7.26 (t, 1H, *J* = 7.3, Ar*H*), 7.17 (d, 4H, *J* = 8.7, Ar*H*), 6.88 (d, 2H, *J* = 8.7, Ar*H*), 6.63 (d, 2H, *J* = 8.7, Ar*H*), 2.60 (q, 2H, *J* = 7.4, C*H*$_2$CH$_3$), 0.96 (t, 3H, *J* = 7.4, CH$_2$C*H*$_3$). Anal. ($C_{23}H_{20}N_2O_2$) C, H, N.

5-Ethyl-1,4-bis(4-hydroxyphenyl)-2-phenyl-1*H*-imidazole (12). From **12a** (215 mg, 0.56 mmol) and BBr_3 (159 μL, 1.68 mmol). Column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5. Yield: 128 mg (67%) of a colorless solid (mp: 285 °C). ^{1}H NMR (DMSO-d_6): δ = 9.94 (s, 1H, O*H*), 9.40 (s, 1H, O*H*), 7.53 (d, 2H, *J* = 8.6, Ar*H*), 7.36−7.33 (m, 2H, Ar*H*), 7.28−7.23 (m, 2H, Ar*H*), 7.18 (d, 3H, *J* = 8.6, Ar*H*), 6.88 (d, 2H, *J* = 8.6, Ar*H*), 6.83 (d, 2H, *J* = 8.6, Ar*H*), 2.57 (q, 2H, *J* = 7.4, C*H*$_2$CH$_3$), 0.94 (t, 3H, *J* = 7.4, CH$_2$C*H*$_3$). Anal. ($C_{23}H_{20}N_2O_2$) C, H, N.

5-Ethyl-2,4-bis(4-hydroxyphenyl)-1-phenyl-1*H*-imidazole (13). From **13a** (169 mg, 0.44 mmol) and BBr_3 (104 μL, 1.10 mmol). Addition of BBr_3 at −80 °C over 1 h, reaction time 18 h (−80 °C → RT). Column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5, 90:10. Yield: 148 mg (94%) of a colorless solid (mp: 149 °C). ^{1}H NMR (DMSO-d_6): δ = 9.55 (s, 1H, O*H*), 9.36 (s, 1H, O*H*), 7.55−7.51 (m, 5H, Ar*H*), 7.37−7.35 (m, 2H, Ar*H*), 7.10 (d, 2H, *J* = 8.7, Ar*H*), 6.82 (d, 2H, *J* = 8.6, Ar*H*), 6.59 (d, 2H, *J* = 8.7, Ar*H*), 2.57 (q, 2H, *J* = 7.5, C*H*$_2$CH$_3$), 0.90 (t, 3H, *J* = 7.4, CH$_2$C*H*$_3$). Anal. ($C_{23}H_{20}N_2O_2$) C, H, N.

5-Ethyl-1,4-diphenyl-2-(4-hydroxyphenyl)-1*H*-imidazole (14). From **14a** (100 mg, 0.28 mmol) and BBr_3 (98 μL, 1.04 mmol). Addition of BBr_3 at −80 °C over 1 h, reaction time 16 h (−80 °C → RT). Column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5. Yield: 57 mg (60%) of a colorless solid (mp: 119−125 °C). ^{1}H NMR (DMSO-d_6): δ = 9.58 (s, 1H, O*H*), 7.73 (d, 2H, *J* = 7.6, Ar*H*), 7.57−7.54 (m, 3H, Ar*H*), 7.45 (m, 4H, Ar*H*), 7.27 (t, 1H, *J* = 7.3, Ar*H*), 7.12 (d, 2H, *J* = 8.6, Ar*H*), 6.61 (d, 2H, *J* = 8.6, Ar*H*), 2.63 (q, 2H, *J* = 7.5, C*H*$_2$CH$_3$), 0.93 (t, 3H, *J* = 7.4, CH$_2$C*H*$_3$). Anal. ($C_{23}H_{20}N_2O$) C, H, N.

1,2,4-Tris(4-hydroxyphenyl)-5-phenyl-1*H*-imidazole (15). From **15a** (377 mg, 0.82 mmol) and BBr_3 (346 μL, 3.66 mmol). Column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5, 90:10. Yield: 255 mg (75%) of a colorless solid (mp: > 300 °C). ^{1}H NMR (DMSO-d_6): δ = 9.71 (s, 1H, O*H*), 9.63 (s, 1H, O*H*), 9.31 (s, 1H, O*H*), 7.29−7.25 (m, 5H, Ar*H*), 7.20 (d, 2H, *J* = 8.7, Ar*H*), 7.18−7.15 (m, 2H, Ar*H*), 6.98 (d, 2H, *J* = 8.7, Ar*H*), 6.66−6.61 (m, 6H, Ar*H*). Anal. ($C_{27}H_{20}N_2O_3$) C, H, N.

2-(2-Chloro-4-hydroxyphenyl)-1,4-bis(4-hydroxyphenyl)-5-phenyl-1*H*-imidazole (16). From **16a** (398 mg, 0.80 mmol) and BBr_3 (340 μL, 3.61 mmol). The solution was stirred for a period of 48 h after reaching room temperature. Column chromatography with CH_2Cl_2/methanol 9:1. Yield: 243 mg (67%) of a colorless solid (mp: 200−203 °C). ^{1}H NMR (DMSO-d_6): δ = 10.11 (s, 1H, O*H*), 9.58 (s, 1H, O*H*), 9.31 (s, 1H, O*H*), 7.28−7.23 (m, 6H, Ar*H*), 7.19−7.15 (m, 2H, Ar*H*), 6.86 (d, 2H, *J* = 8.7, Ar*H*), 6.80 (d, 1H, *J* = 2.4, Ar*H*), 6.69 (dd, 1H, *J* = 2.37, *J* = 8.4, Ar*H*), 6.61 (d, 2H, *J* = 8.7, Ar*H*), 6.53 (d, 2H, *J* = 8.6, Ar*H*). Anal. ($C_{27}H_{19}ClN_2O_3$) C, H, N.

1,2,4,5-Tetrakis(4-hydroxyphenyl)-1*H*-imidazole (17). From **17a** (400 mg, 0.81 mmol) and BBr_3 (460 μL, 4.87 mmol). Column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 9:1, 8:2. Yield: 218 mg (62%) of a colorless solid (mp: 200−203 °C). ^{1}H NMR (DMSO-d_6): δ = 9.69 (s, 1H, O*H*), 9.60 (s, 1H, O*H*), 9.52 (s, 1H, O*H*), 9.27 (s, 1H, O*H*), 7.29 (d, 2H, *J* = 8.6, Ar*H*), 7.18 (d, 2H, *J* = 8.6, Ar*H*), 6.97−6.93 (m, 4H, Ar*H*), 6.66−6.61 (m, 8H, Ar*H*). Anal. ($C_{27}H_{20}N_2O_4$) C, H, N.

4-(2-Chloro-4-hydroxyphenyl)-1,2-bis(4-hydroxyphenyl)-5-phenyl-1*H*-imidazole (18). From **18a** (140 mg, 0.28 mmol) and BBr_3 (96 μL, 1.02 mmol). Addition of BBr_3 at −80 °C over 1 h, reaction time 20 h (−80 °C → RT). Column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5, 90:10. Yield: 126 mg (98%) of a colorless solid (mp: >300 °C). ^{1}H NMR (DMSO-d_6): δ = 9.86 (s, 1H, O*H*), 9.77 (s, 1H, O*H*), 9.63 (s, 1H, O*H*), 7.22 (d, 1H, *J* = 8.3, Ar*H*), 7.18−7.13 (m, 5H, Ar*H*), 7.00 (d, 2H, *J* = 8.3, Ar*H*), 6.92−6.89 (m, 2H, Ar*H*), 6.78 (d, 1H, *J* = 2.0, Ar*H*), 6.72−6.68 (m, 3H, Ar*H*), 6.64 (d, 2H, *J* = 8.6, Ar*H*). Anal. ($C_{27}H_{19}ClN_2O_3$) C, H, N.

5-Ethyl-2,4-bis(4-hydroxyphenyl)-1*H*-imidazole (19). From **13a** (140 mg, 0.36 mmol) and BBr_3 (104 μL, 1.10 mmol). Column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5, 90:10, 70:30. Yield: 44 mg (43%) of a colorless solid (mp: 180 °C). ^{1}H NMR (DMSO-d_6): δ = 12.40 (bs, 1H, N*H*), 9.83 (s, 1H, O*H*), 9.53 (s, 1H, O*H*), 7.81 (d, 2H, *J* = 8.6, Ar*H*), 7.40 (d, 2H, *J* = 8.5, Ar*H*), 6.87−6.83 (m, 4H, Ar*H*), 2.70 (q, 2H, *J* = 7.5, C*H*$_2$CH$_3$), 1.23 (t, 3H, *J* = 7.5, CH$_2$C*H*$_3$). Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

5-Ethyl-1,2-bis(4-hydroxyphenyl)-1*H*-imidazole (20). From **20a** (373 mg, 1.21 mmol) and BBr_3 (349 μL, 3.68 mmol). Column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5, 90:10. Yield: 181 mg (53%); colorless solid (mp: 235 °C). ^{1}H NMR (DMSO-d_6): δ = 9.84 (s, 1H, O*H*), 9.53 (s, 1H, O*H*), 7.09 (d, 2H, *J* = 8.7, Ar*H*), 7.05 (d, 2H, *J* = 8.6, Ar*H*), 6.83 (d, 2H, *J* = 8.6, Ar*H*), 6.79 (s, 1H, 4-*H*), 6.60 (d, 2H, *J* = 8.7, Ar*H*), 4.61 (q, 2H, *J* = 7.4, C*H*$_2$CH$_3$), 1.04 (t, 3H, *J* = 7.5, CH$_2$C*H*$_3$). Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

1,2-Bis(4-hydroxyphenyl)-1*H*-imidazole (21). From **21a** (200 mg, 0.71 mmol) and BBr_3 (337 μL, 3.57 mmol). Column chromatography with stepwise gradient elution: CH_2Cl_2/methanol 98:2, 95:5, 90:10. Yield: 60 mg (33%) of a colorless solid (mp: 279 °C). ^{1}H NMR (DMSO-d_6): δ = 9.78 (s, 1H, O*H*), 9.61 (s, 1H, O*H*), 7.26 (d, 1H, *J* = 1.3, C*H*=C*H*), 7.13 (d, 2H, *J* = 8.7, Ar*H*), 7.06 (d, 2H, *J* = 8.9, Ar*H*), 7.04 (d, 1H, *J* = 1.5, C*H*=C*H*), 6.80 (d, 2H, *J* = 8.64, Ar*H*), 6.65 (d, 2H, *J* = 8.61, Ar*H*). Anal. ($C_{15}H_{12}N_2O_2$) C, H, N.

Biological Methods. Transcriptional Binding Assay. The transactivation on the estrogen receptor was tested by using MCF-7-2a cells, stably transfected with the plasmid ERE_{wtc}luc. The cells were cultivated in DMEM supplemented with L-glutamine, antibiotics, and dextran/charcoal-treated BCS (ct-BCS, 50 mL/L) one week before starting the experiment. Cells from an almost confluent monolayer were removed by trypsinization and suspended to approximately 2.2×10^5 cells/mL in the growth medium mentioned above. The cell suspension was then cultured in six-well flat-bottomed plates (0.5 mL cell suspension and 1.5 mL medium per well) at growing conditions (see above). After 24 h, 20 μL of a stock solution of the test compounds were added to achieve concentrations ranging between 10^{-5} to 10^{-10} M, and the plates were incubated for 50 h. Before harvesting, the cells were washed twice with PBS and 200 μL of cell lysis reagent was added to each well. After 20 min lysis at room temperature, cells were transferred into reaction tubes and centrifuged. Luciferase was assayed using the Promega luciferase assay reagent. A 50 μL amount of each supernatant was mixed with 50 μL of substrate reagent. Luminescence (in relative light units, RLU) was measured for 10 s using a microlumat. Measurements were corrected by correlating the quantity of protein (quantified according to Bradford[29]) in each sample with the mass of luciferase. Estrogenic activity was expressed as % activation of a 10^{-8} M estradiol control (100%).

Estrogen Receptor Binding Assay. The relative binding affinity of the test compounds was determined by displacement of 17β-[^{3}H]estradiol. At 4 °C the test compounds were shaken with calf uterine cytosol and 17β-[^{3}H]estradiol for 16 h. To stop the incubation, dextran-coated charcoal was added, and after centrifugation, the radioactivity of a 200 μL supernatant aliquot was counted. On a semilog plot the percentage of bound labeled steroid vs concentration of the competitor was plotted. Six concentrations of each compound were chosen to get a linear graph. From the plot, the molar concentration of unlabeled estradiol and of the competitor that reduced the binding of the radioligand by 50% was determined.

Acknowledgment. The technical assistance of S. Bergemann and I. Schnautz is acknowledged. The presented study was supported by Grants Gu285/3-1 and Gu285/3-2 from the Deutsche Forschungsgemeinschaft.

Supporting Information Available: Elemental analyses of the target compounds **3** and **5**−**21** and additional analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Cosman, F.; Lindsay, R. Selective estrogen receptor modulators: Clinical spectrum. *Endocr. Rev.* **1999**, *20*, 418−434.
(2) Nuttali, M. E.; Stroup, G. B.; Fisher, P. W.; Nadeau, D. P.; Gowen, M.; Suva. L. J. Distinct mechanisms of action of selective estrogen receptor modulators in breast and osteoblastic cells. *Am. J. Physiol. Cell Physiol.* **2000**, *279*, C1550−C1557.
(3) Barrett-Conner, E.; Cox D. A.; Anderson, P. W. The potential of SERMs for reducing the risk of coronary heart disease. *Trends Endocrin. Met.* **1999**, *10*, 320−325.
(4) Stauffer, S. R.; Coletta C. J.; Tedesco R.; Nishiguchi G.; Carlson K.; Sun J.; Katzenellenbogen, B. S.; Katzenellenbogen J. A. Pyrazole ligands: Structure-affinity/activity relationship and estrogen receptor-α-selective agonists. *J. Med. Chem.* **2000**, *43*, 4934−4947.
(5) Mortensen, D. S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen J. A. Synthesis and biological evaluation of a novel series of furans: Ligands selective for estrogen receptor α. *J. Med. Chem.* **2001**, *44*, 3838−3848.
(6) Gust, R.; Keilitz, R.; Schmidt, K. Investigations of new lead structures for the design of selective estrogen receptor modulators. *J. Med. Chem.* **2001**, *44*, 1963−1970.
(7) Mull, E. S.; Sattigeri, V. J.; Rodriguez, A. L.; Katzenellenbogen, J. A. Aryl cyclopentadienyl tricarbonyl rhenium complexes: Novel ligands for the estrogen receptor with potential use as estrogen radiopharmaceuticals. *Bioorg. Med. Chem.* **2002**, *10*, 1381−1398.
(8) von Rauch, M.; Schlenk, M.; Gust, R. Effect of C2-akylation, N-alkylation and N,N′-dialkylation on the stability and estrogen receptor interaction of (*R,S)/(S,R)-4,5*-bis(4-hydroxyphenyl)-2-imidazolines. *J. Med. Chem.* **2004**, *47*, 915−927.
(9) Gust, R.; Keilitz R.; Schmidt, K.; Synthesis, structural evaluation, and estrogen receptor interaction of 2,3-diarylpiperazines. *J. Med. Chem.* **2002**, *45*, 2325−2337.
(10) Fink, B. E.; Mortensen, D. S.; Stauffer S, R.; Aron Z. D.; Katzenellenbogen J. A. Novel structural templates for estrogen-receptor ligands and prospects for combinatorial synthesis of estrogens. *Chem. Biol.* **1999**, *6*, 205−219.
(11) Gust, R.; Keilitz, R.; Schmidt, K.; von Rauch M. Synthesis, structural evaluation and estrogen receptor interaction of 4,5-bis(4-hydroxyphenyl)imidazoles. *Arch. Pharm. Pharm. Med. Chem.* **2002**, *335*, 463−471.
(12) Gust, R.; Busch, S.; Keilitz, R.; Schmidt, K.; von Rauch, M. Investigation on the influence of halide substituents on the estrogen receptor interaction of 2,4,5-tris(4-hydroxyphenyl)imidazoles. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 456−465.
(13) Wiglenda, T.; Ott, I.; Kircher, B.; Schumacher, P.; Schuster, D.; Langer, T.; Gust, R. Synthesis and pharmacological evaluation of *1H*-imidazoles as ligands of the estrogen receptor and cytotoxic inhibitors of the cyclooxygenase. *J. Med. Chem.* **2005**, *48*, 6516−6521.
(14) Gautier, J.-A.; Miocque, M.; Fauran, C.; Le Cloareg, A.-Y. Préparation d'amidines à partir de nitriles et d'amines aromatiques en solvant ammoniac liquide. *Bull. Soc. Chim. Fr.* **1970**, *1*, 200−207.
(15) Daoust, B.; Lessard, J. Eletrochemical behavior of amidine hydrochlorides and amidines. *Can. J. Chem.* **1995**, *73*, 362−374.
(16) Wen, J.; Chen, H.; Zhang, Z. Synthesis of 4-methoxy(polyfluoro)-benzonitriles. Patent CN 1190093, 1998.
(17) Hafner, F.; Holler, E.; von Angerer, E. Effect of growth factors on estrogen receptor mediated gene expression. *J. Steroid Biochem. Mol. Biol.* **1996**, *58*, 385−393.
(18) Biberger, C.; von Angerer, E. 1-Benzyl-2-phenylindole- and 1,2-diphenylindole-based antiestrogens. Estimation of agonist and antagonist activities in transfection assays. *J. Steroid. Biochem. Mol. Biol.* **1998**, *64*, 277−285.
(19) Brzozowski, A. M.; Pike, A. C. W.; Dauter, Z.; Hubbard, R. W.; Bonn, T.; Engström, O.; Öhman, L.; Greene, G. L.; Gustafsson, J.-Å.; Carlquist, M. Molecular basis of agonism and antagonism in the oestrogen receptor. *Nature* **1997**, *389*, 753−758.
(20) Shiau, A. K.; Barstad, D.; Loria, P. M.; Cheng, L.; Kushner, P. J.; Agard, D. A.; Greene, G. L. The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen. *Cell* **1998**, *95*, 927−937.
(21) Kekenes-Huskey, P. K.; Muegge, I.; Gust, R.; Knapp, W. E. A molecular docking study of estrogenically active compounds with 1,2-diarylethane and 1,2-diarylethene pharmacophores. *Bioorg. Med. Chem.* **2004**, *12*, 6527−6537.
(22) Jordan, V. C. Antiestrogens and selective estrogen receptor modulators as multifunctional medicines. Clinical considerations and new agents. *J. Med. Chem.* **2005**, *48*, 6516−6521.
(23) Jordan, V. C.; MacGregor Schafer, J. I.; Levenson, A. S.; Liu, H.; Pease, K. M.; Simons, L. A.; Zapf, J. W. Molecular classification of estrogens. *Cancer Res.* **2001**, *61*, 6619−6623.
(24) McCague, R.; Kuroda, R.; Leclercq, G.; Stoessel, S. Synthesis and estrogen receptor binding of 6,7-dihydro-8-phenyl-9-[4-[2-(dimethylamino)ethoxy]phenyl]-5*H*-benzocycloheptene, a nonisomerizable analogue of tamoxifen. X-ray crystallographic studies. *J. Med. Chem.* **1986**, *29*, 2053−2059.
(25) Gust, R.; Keilitz, R.; Schmidt, K.; von Rauch, M. (*R,S)/(S,R)-4,5*-Bis(4-hydroxyphenyl)-2-imidazolines: Ligands for the estrogen receptor with a novel binding mode. *J. Med. Chem.* **2002**, *45*, 3356−3365.
(26) Stauffer, S. R.; Huang, Y.; Coletta, C. J.; Tedesco, R.; Katzenellenbogen J. A. Estrogen pyrazoles: Defining the pyrazole core structure and the orientation of substituents in the ligand binding pocket of the estrogen receptor. *Bioorg. Med. Chem.* **2001**, *9*, 141−150.
(27) Danielian, P. S.; White, R.; Hoare, S. A.; Fawell, S. E.; Parker, M. G. Identification of residues in the estrogen receptor that confer differential sensitivity to estrogen and hydroxytamoxifen. *Mol. Endocrinol.* **1993**, *7*, 232−240.
(28) Gust, R.; Burgemeister, T.; Mannschreck, A.; Schönenberger, H. Aqua[1-(2,6-dichloro-4-hydroxyphenyl)-2-phenylethylenediamine]-sulfatoplatinum(II) complexes with variable substituents in the 2-phenyl ring. 1. Synthesis and antitumor and estrogenic properties. *J. Med. Chem.* **1990**, *33*, 2535−2544.
(29) Bradford, M.M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal. Biochem.* **1976**, *72*, 248−254.

JM061106T