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Estrogen Pyrazoles: Defining the Pyrazole Core Structure and the Orientation of Substituents in the Ligand Binding Pocket of the Estrogen Receptor

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Abstract—Previously, we reported that certain tetrasubstituted 1,3,5-triaryl-4-alkyl-pyrazoles bind to the estrogen receptor (ER) with high affinity (Fink, B. E.; Mortenson, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. A. *Chem. Biol.* **1999**, *6*, 205–219; Stauffer, S. R.; Katzenellenbogen, J. A. *J. Comb. Chem.* **2000**, *2*, 318–329; Stauffer, S. R.; Coletta, C. J.; Sun, J.; Tedesco, R.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2000**, submitted). To investigate how cyclic permutation of the two nitrogen atoms of a pyrazole might affect ER binding affinity, we prepared a new pyrazole core isomer, namely a 1,3,4-triaryl-5-alkyl-pyrazole (**2**), to compare it with our original pyrazole (**1**). We also prepared several peripherally matched core pyrazole isomer sets to investigate whether the two pyrazole series share a common binding orientation. Our efficient, regioselective synthetic route to these pyrazoles relies on the acylation of a hydrazone anion, followed by cyclization, halogenation, and Suzuki coupling. We found that the ER accommodates 1,3,4-triaryl-pyrazoles of the isomeric series only somewhat less well than the original 1,3,5-triaryl series, and it appears that both series share a common binding mode. This preferred orientation for the 1,3,5-triaryl-4-alkyl-pyrazoles is supported by binding affinity measurements of analogues in which the phenolic hydroxyl groups were systematically removed from each of the three aryl groups, and the orientation is consistent, as well, with molecular modeling studies. These studies provide additional insight into the design of heterocyclic core structures for the development of high affinity ER ligands by combinatorial methods.
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Introduction

The estrogen receptor (ER) binds a remarkably wide range of non-steroidal ligands,[1] and the diverse core structures of these ligands span a wide range of synthetic accessibility.[2] We have been intrigued, in particular, by the design of non-steroidal ligand cores that might be easily prepared and thus would be well suited to combinatorial expansion. As part of this investigation, we identified pyrazoles as favorable heterocyclic core building blocks,[3] and we found that by attaching a sufficient number of appropriate substituents onto this core system, we could obtain high affinity ligands for the ER.[3–5]

An issue which had interested us initially about these systems was whether the heterocyclic core structure itself plays an active role in ligand–receptor interaction, or whether it acts merely as a inert scaffold, simply displaying groups in a geometry appropriate for filling the various subpockets that make up the ligand cavity of ER.[3] Interestingly, we found that there were large differences in binding affinity (up to 50-fold) for ligands that had identical peripheral substitution patterns but different core structures (e.g. the two diazoles, imidazoles versus pyrazoles; Figure 1).[3] Clearly, our initial thought that the ligand core structure might be acting as a passive entity—simply to position peripheral substituents—was not true. In the case shown below, the lower ER binding affinity for the imidazoles compared to the pyrazoles was attributed, at least in part, to the significantly greater dipole moment of the imidazoles.[3]

In further consideration, we wondered whether the distribution of heteroatoms within the same heterocyclic system would also have a significant effect on ER binding affinity. In the two *imidazoles* shown in Figure 1, the different position of the nitrogen atoms had little effect on their binding affinity. However, we were curious whether the related cyclic permutation of the two nitrogen atoms of a *pyrazole* might have a more significant effect on ER binding affinity.

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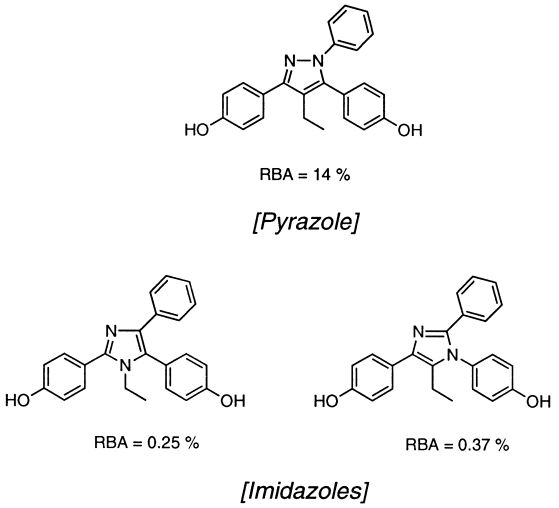


Figure 1. Effect of different core structures of selected five-member heterocycles (diazoles) on their estrogen receptor relative binding affinity (RBA).

To investigate this issue, we have prepared a new pyrazole core isomer, namely a 1,3,4-triaryl-5-alkyl-pyrazole (**2**), to compare it with our original 1,3,5-triaryl-4-alkyl-pyrazole (**1**) (Fig. 2). This new compound (**2**) represents the only other possible pyrazole system capable of displaying the same relative substitution pattern of aryl, alkyl, aryl, and phenyl groups as does our original pyrazole **1**. To extend this investigation further, we synthesized several other peripherally matched core pyrazole isomer sets, in which some of the phenolic hydroxyl groups are systematically deleted, to establish more definitively which core isomer is most favored and to investigate whether they share a common binding orientation.

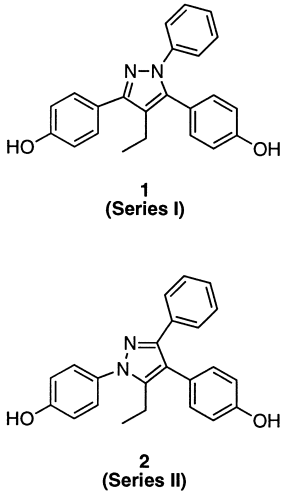


Figure 2. Original 1,3,5-triaryl-pyrazole **1** (the basis of Series I) and the new 1,3,4-triaryl-pyrazole isomer **2** (the basis of Series II).

Results and Discussion

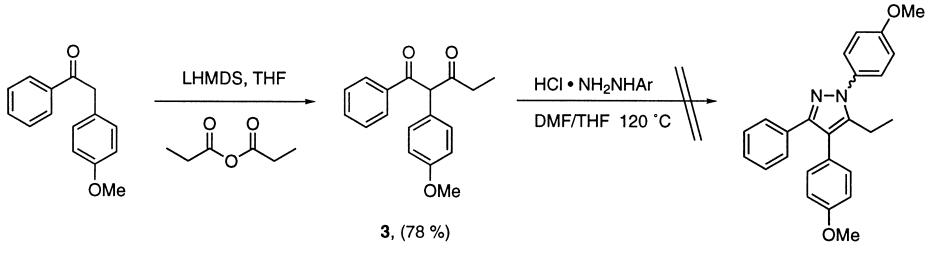
Synthesis of 1,3,4-triaryl-5-alkyl-pyrazoles

Our initial attempts to synthesize the pyrazole isomer **2** involved conditions similar to those used in previous studies (Scheme 1).[3] We first prepared diketone **3** in high yield, starting from the deoxybenzoin and propionic anhydride. However, our attempts to generate the pyrazole by condensation of the dione with 4-methoxyphenylhydrazine were unsuccessful and resulted in a complex mixture that contained the two possible retro-Claisen condensation products from cleavage of the 1,3-dione.

Because of these difficulties and the fact that this route was not likely to be regioselective, we investigated an alternative, potentially regioselective approach that involved a one-pot acylation and cyclization procedure starting from an appropriate hydrazone, as illustrated in Figure 3. Unfortunately, we could not isolate the hydrazone (**4**), because it rapidly underwent Fischer indole cyclization to the 2,3-diaryl-indole product (**5**). Even under mild conditions, we obtained only starting material or indole product, but no hydrazone. Apparently, the 4-methoxyphenyl substituent in the deoxybenzoin starting material facilitates the [3,3]-sigmatropic cyclization of the ene-phenylhydrazole intermediate by stabilizing the transition state through a stilbene-like structure (Fig. 3).

We wondered whether we could avoid this competing cyclization by omitting the 4-methoxyphenyl substituent during the synthesis of the pyrazole (Fig. 4). Of course, this approach would entail adding an aryl group later to the completed heterocycle, but this could presumably be done using an appropriate Pd(0)-mediated coupling reaction. This synthetic strategy was also attractive because it allows for the introduction of additional structural diversity into these systems at a late stage, just before phenol deprotection, an attractive feature for combinatorial library expansion.[5]

According to this approach, we were able to successfully synthesize pyrazole **2** as well as analogues **10a–d** (Scheme 2). Initial formation of hydrazones **6a–c** by reaction of



Scheme 1. Attempted synthesis of MeO-protected pyrazole isomer.

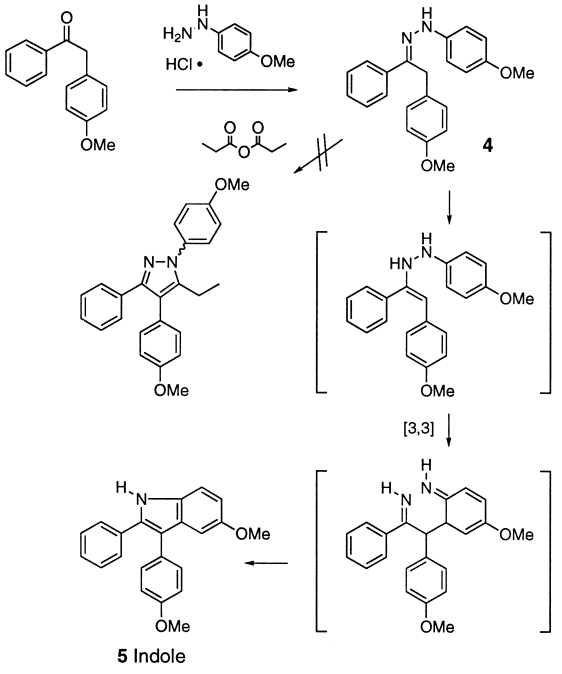


Figure 3. Attempted synthesis of pryazole isomer using an acylation–cyclization.

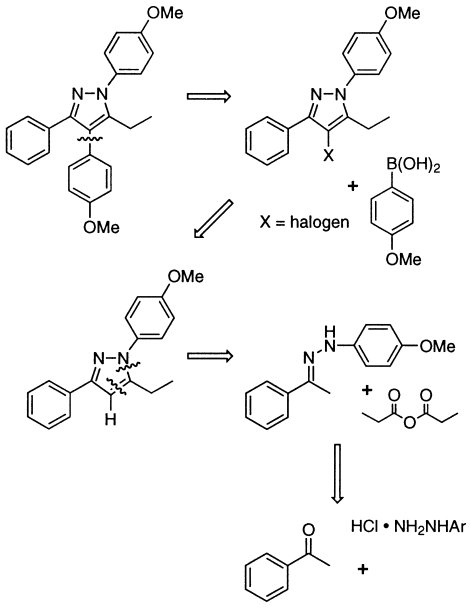


Figure 4. Retro-synthetic strategy for Pd(0)-mediated coupling approach to pyrazoles.

the acetophenone compounds with either the hydrochloride salt of 4-methoxyphenylhydrazine or phenylhydrazine occurred in moderate yields, and as we had hoped, no competing cyclization to the indole occurred with this less stabilized system. Hydrazones **6a–c** were then treated with butyllithium to form the corresponding dianion, which was acylated with an alkyl anhydride and then cyclized upon addition of HCl.[6] The yields shown for pyrazole formation are based on the anhydride and are typical for this reaction.

To introduce the last aromatic substituent, the tri-substituted pyrazoles **7a–d** were iodinated by treatment with a solution of KI and I_2,[7] and then subjected to Suzuki coupling conditions with either phenylboronic acid or *p*-methoxyphenylboronic acid. Initial conditions involved using $Pd(PPh_3)_4$ as a Pd(0) catalyst and DME/H_2O as solvent (**9c** 52%, 72 h); however, by using $Pd(OAc)_2$ as a pre-catalyst and an *n*-$PrOH/H_2O$ solvent mixture, we were able to obtain the tetra-substituted pyrazoles (**9a,b,d,e**) with slightly improved yields (60–71%) and shorter reaction times (1–14 h).[8] The protected pyrazole isomers were subsequently demethylated using BBr_3 to afford the desired phenolic products **10a–d** and **2**.

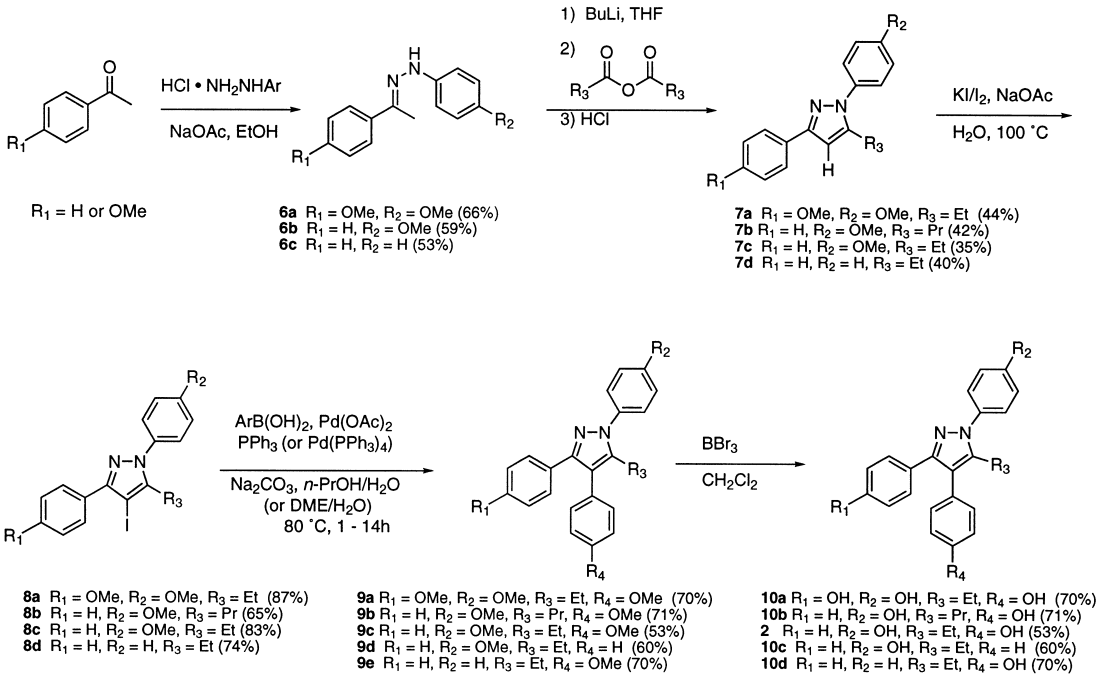
Comparison of the estrogen receptor binding affinities of the isomeric 1,3,4-triaryl-pyrazoles (Series II) and the original 1,3,5-triaryl-pyrazoles (Series I)

The binding affinities of the pyrazoles for ER were assayed in a competitive radiometric binding assay; this assay has been described previously,[9] and affinities are expressed as relative binding affinity (RBA) values, where estradiol has an affinity of 100% (Table 1). The 1,3,4-triaryl-pyrazole **2,** which is the nitrogen ring isomer of our original 1,3,5-triaryl-pyrazole **1**, has a very significant affinity of 5.8%, but is 2.6-fold less than the original pyrazole **1**. To determine whether the 1,3,4-triaryl-pyrazole binds to ER in the same mode as pyrazole **1**, we investigated the binding affinity of several other 1,3,4-triaryl-pyrazoles (**10a–d**) and compared their affinities with those of their corresponding 1,3,5-triaryl-pyrazole isomers (**11a,b**[4] and **11c,d**[10]).

When examining the first three sets of isomeric pyrazoles (the other two are discussed below), the pyrazoles in the new isomeric Series II (1,3,4-triaryl-pyrazoles) have somewhat lower affinity than those in the original Series I (1,3,5-triaryl-pyrazoles), but only by an average of 2-fold. Within the original pyrazole series (Series I), certain changes to the peripheral substituents resulted in an increase in RBA. For example, when a hydroxyl group is added to the N(1)-phenyl substituent (i.e. from pyrazole **1** to **11a**), a slight increase in affinity occurs. A similar increase in RBA upon hydroxyl substitution is observed in the isomeric Series II, going from pyrazole **2** to **10a**.

Previously, we also showed that modification of the alkyl chain at C(4)-position of the initial pyrazole Series I from an ethyl **1** to a propyl substituent **11b** results in a 1.6-fold increase in affinity, indicating a more favorable hydrophobic interaction. However, this favorable interaction ended at propyl, as the *n*-butyl isomer experienced a significant drop in binding affinity.[4] In Series II, going from $R_3 = Et$ (**2**) to *n*-propyl (**10b**) results in a similar but somewhat larger increase in affinity than it does in Series I (2.7-fold versus 1.6-fold).

Because the structure–binding affinity patterns observed for both pyrazole isomers (Series I and II) are quite similar, we postulated that these distinct core structure pyrazole isomers would be binding in the same orientation in the ER binding pocket.



Scheme 2. Synthesis of 1,3,4-triaryl-5-alkyl-pyrazoles.

Table 1. Binding affinity data for pyrazole isomers and original pyrazole series

R_1	R_2	R_3	R_4	Compound (I)	RBA (I)[a]	Compound (II)	RBA (II)[a]
H	OH	Et	OH	**1**	15.3±3	**2**	5.8±0.3
OH	OH	Et	OH	**11a**	20.3±3	**10a**	7.8±4
H	OH	*n*-Pr	OH	**11b**	25±0.01	**10b**	16.0±1
H	OH	Et	H	**11c**	0.46	**10c**	0.43±0.07
H	H	Et	OH	**11d**	0.007	**10d**	0.008±0.005

[a]Competitive radiometric binding assays were done using 10 nM [^{3}H]E_2 as tracer and lamb uterine cytosol as receptor source; for details, see Experimental. Compounds **11a–d** were prepared as described elsewhere.[4,10]

Elucidation of the aryl group in the pyrazole that mimics the A-ring of estradiol: Inferring pyrazole orientation in the ligand binding pocket from the binding affinity of isomeric monophenols

To further support the hypothesis that both pyrazole isomers have the same binding mode and to more confidently establish which phenolic group is playing the role of the A-ring phenol in estradiol, we prepared the individual monophenolic derivatives of pyrazole **1** (Table 1, Series I, **11c** and **11d**) and pyrazole **2** (Table 1, Series II, **10c** and **10d**). Systematic phenol deletion is a standard approach that has been used in the past to determine which phenol in an unsymmetrical bisphenolic non-steroidal ER ligand mimics the crucial A-ring phenol of estradiol (E_2).[11,12] The monophenolic analogue having the highest affinity is then presumed to have preserved the phenol that is acting as the estradiol A-ring mimic, because the hydroxyl substituent at this position is known to be essential for high affinity binding to the ER.[13] (At the outset, it is of note that removal of one of the phenols from the R_1 position (pyrazole **1** versus **11a** in Series I, and pyrazole **2** versus **10a** in Series II) has little effect on binding affinity, suggesting that these rings are not the ones that correspond to the A-ring of estradiol.)

The route in Scheme 2 was used to prepare both the N(1) and the C(4) monophenolic pyrazole Series II analogues **10c** and **10d**, regioselectively and in good yield. The RBA of pyrazole isomer **10c** is 0.43%, whereas that of pyrazole isomer **10d** is only 0.008%. When these affinities are compared to that of the bisphenolic pyrazole **2** (5.8%) (Table 1), one can see that removal of the phenolic hydroxyl from the N(1) phenyl ring results in a 725-fold decrease in affinity, whereas removal of the hydroxyl from the C(4) phenyl group results in only a 13-fold decrease. Thus, the 56-fold greater decrease in affinity that results from deleting the phenolic hydroxyl from the N(1) phenyl group versus from the C(4) phenyl group strongly suggests that the N(1)-phenolic substituent in the Series II pyrazoles is acting as the A-ring mimic (Fig. 5).

Initial attempts to prepare the C(3) and C(5) monophenol pyrazole analogues for Series I (**11c** and **11d**) regioselectively using the acylation–cyclization strategy were unsuccessful. However, these compounds could successfully be prepared via the corresponding pyrazolines by a new regioselective route (not shown) that will be described elsewhere.[10] The binding affinities for the Series I monophenolic isomers **11d** and **11c** are 0.007% and 0.46%, respectively. Compared to the corresponding bisphenolic pyrazole **1** (15.3%) (Table 1), a much greater decrease in binding affinity results when the hydroxyl group is removed from C(3) phenol (2185-fold, **11d**) than from the C(5) phenol (33-fold, **11c**). The difference in affinity loss that results from the alternative hydroxy group deletion in this series (i.e. 2185/33- or 66-fold) is comparable to that found in Series II (56-fold). This result indicates that in Series I the C(3) phenol is

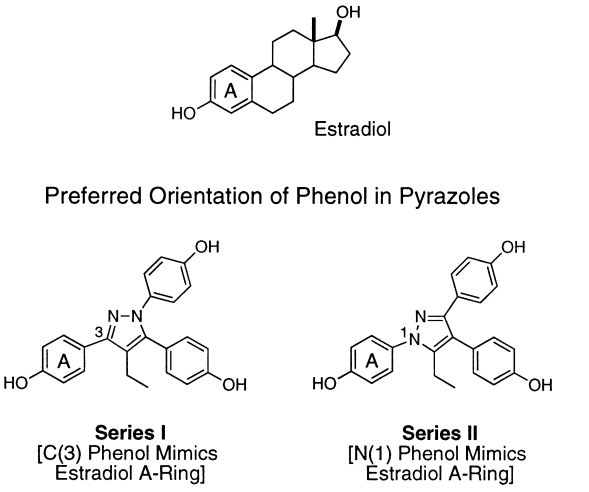


Figure 5. Preferred orientation and proposed A-ring mimic for Series I and Series II pyrazoles.

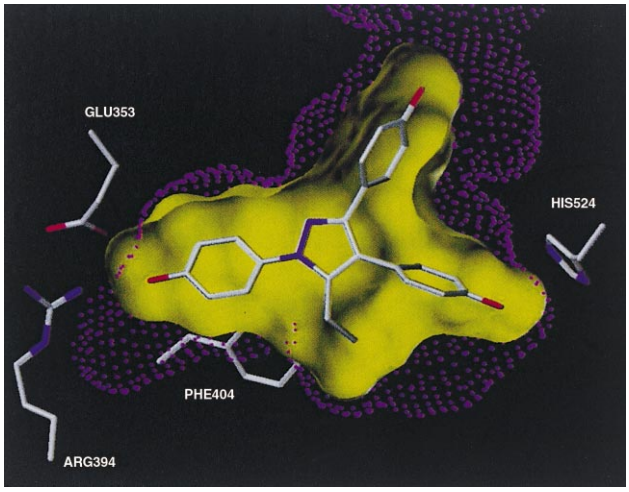


Figure 6. A model for pyrazole **10a** docked and minimized in the DES-ERα-LBD. The surface of the ligand is shown in yellow, and the solvent accessible surface of ER as purple dots.

mimicking the A-ring of E_2. Thus, because the C(3) phenol in Series I and the N(1) phenol in Series II are positioned in a congruent fashion, we believe that the pyrazoles of both Series I and II share a single common binding mode, as illustrated in Figure 5. According to this mode, the other two aryl groups are displayed within a region of the binding pocket resembling the C/D region of E_2, which is known to tolerate a large number of substituents.[13]

Modeling pyrazole orientation in the ligand binding pocket

In our original study of pyrazole **1**, we used molecular modeling to show that this compound could bind in an orientation in which the C(5) phenol mimicked the A-ring of estradiol;[3] this is different from that shown in Figure 5. However, in this earlier study, we had based our model on the ERα crystal structure with the antagonist ligand raloxifene.[14] Upon further consideration, we now think that the ERα crystal structure we used previously was not an appropriate one for modeling ligands like pyrazole **1**, because unlike raloxifene, these pyrazoles are ERα agonists, not antagonists.[4,15]

We have recently completed a more extensive modeling of a pyrazole triphenol that corresponds to pyrazole *di*phenol **11b**,[4] using as a starting point an X-ray structure of ERα complexed with the agonist diethylstilbestrol, a non-steroidal estrogen agonist with an RBA of 98%.[16] In this study, we considered six possible starting orientations (the three phenols placed in the A-ring pocket and in each case the two alternative orientations of the remaining two phenols that come from rotation about the bond linking the A-ring phenol and the pyrazole core). From this recent study,[4] the orientation in which the C(3) phenol of the Series I pyrazole mimics the A-ring of estradiol gave the lowest energy structure and appeared to be quite reasonable on steric grounds, although it is difficult to rigorously eliminate some of the other possible orientations. This is the orientation shown in Figure 5 for the Series I pyrazole.

In the present study, we have used this approach to examine the six possible binding orientations of the ethyl triphenol Series II pyrazole **10a**. Again, the orientation in which the N(1) phenol is the mimic of the A-ring of estradiol (cf. Fig. 5) is well accommodated by the structure and has a reasonable binding energy, although an alternative orientation with the C(4) phenol in this position cannot be ruled out by binding energy considerations. Nevertheless, this latter orientation seems unlikely, given the much higher experimental binding affinity of monophenol **10c** versus **10d** (Table 1).

Thus, on the basis of the experimental determinations of monophenol binding affinities and molecular modeling, we suggest that the preferred binding modes of the pyrazoles in the estrogen receptor correspond to those illustrated in Figure 5. A pictorial representation of pyrazole **10a** in this orientation is shown in Figure 6.

Conclusions

To explore the effect of core structure on the ability of pyrazole ligands to bind to ER, we developed an efficient, regioselective, and flexible route to a new isomeric series of pyrazoles (1,3,4-triaryl-5-alkyl-pyrazoles), and we evaluated their binding affinity to ER. The synthesis relies on the acylation of a hydrazone anion, followed, after cyclization and halogenation, by a Pd(0) Suzuki coupling strategy. We found that the ER accommodates 1,3,4-triaryl-pyrazoles of the new isomeric series (Series II) only slightly less well than the original 1,3,5-triaryl series (Series I), and on the basis of the binding affinity of the corresponding monophenols and molecular modeling studies, both isomers appear to share a common binding mode. In this binding mode, the putative A-ring mimic is the C(3) phenol in Series I and the N(1) phenol in Series II. Thus, as in the case of the imidazoles discussed earlier (Fig. 1), it does appear possible to permute the position of heteroatoms in the azole ring without having a major effect on the ER binding

affinity, provided that the peripheral substituents remain disposed with the same geometry and provided that one remains in the same azole series (i.e. 1,2-azoles [pyrazoles] not 1,3-azoles [imidazoles]), so that compounds with equivalent dipole moments and polarities are being compared. These studies provide additional insight into the design of heterocyclic core structures for the development of high affinity ER ligands by combinatorial methods.

Experimental

General

Melting points were determined on a Thomas-Hoover UniMelt capillary apparatus and are uncorrected. All reagents and solvents were obtained from Aldrich, Fisher or Mallinckrodt. Tetrahydrofuran was freshly distilled from sodium/benzophenone. Dimethylformamide was vacuum distilled prior to use, and stored over 4 Å molecular sieves. *n*-Butyllithium and *t*-butyllithium were titrated with *N*-pivaloyl-*o*-toluidine. Et_3N was stirred with phenylisocyanate, filtered, distilled, and stored over 4 Å molecular sieves. All reactions were performed under a dry N_2 atmosphere unless otherwise specified. Reaction progress was monitored by analytical thin-layer chromatography using GF silica plates purchased from Analtech. Visualization was achieved by short wave UV light (254 nm) or potassium permanganate. Flash column chromatography was performed using Woelm 32–63 μm silica gel packing.[17]

^1H and ^{13}C NMR spectra were recorded on either a Varian Unity 400 MHz or 500 MHz spectrometer using $CDCl_3$, MeOD or $(CD_3)_2SO$ as solvent. Chemical shifts were reported as parts per million downfield from an internal tetramethylsilane standard (δ 0.0 for ^1H) or from solvent references. NMR coupling constants are reported in Hertz. ^{13}C NMR spectra were determined using either the Attached Proton Test (APT) or standard ^{13}C pulse sequence parameters. Low resolution and high resolution electron impact mass spectra were obtained on Finnigan MAT CH-5 or 70-VSE spectrometers. Elemental analyses were performed by the Microanalytical Service Laboratory of the University of Illinois. Hydrazones **6a–c** are prone to decomposition and therefore could only be stored for 2–3 days at 0 °C. Once the hydrazone products were confirmed by ^1H NMR they were typically used directly in the acylation–cyclization step without further characterization.

Biological procedures: relative binding affinity assay

Ligand binding affinities (RBAs) using lamb uterine cytosol as a receptor source were determined by a competitive radiometric binding assay using 10 nM [^3H]estradiol as tracer and dextran-coated charcoal as an adsorbent for free ligand.[9] All incubations were done at 0 °C for 18–24 h. Binding affinities are expressed relative to estradiol (RBA = 100%) and are reproducible with a coefficient of variation of 0.3.

Molecular modeling of pyrazole 10a

The protocol for modeling followed that recently described for a related pyrazole triphenol.[4] The starting conformation for pyrazole **10a** used for receptor docking studies was generated from a random conformational search performed using the MMFF94 force field as implemented in Sybyl 6.6. The resulting lowest energy conformer was then used for docking studies. Charge calculations were determined using the MMFF94 method and molecular surface properties displayed using MOLCAD module in Sybyl 6.6.

Pyrazole **10a**, generated as noted above, was pre-positioned in the DES-ERα-LBD crystal structure[16] using a least squares multifitting of select atoms within the DES ligand. Once pre-positioned, DES was deleted and ligand **10a** was optimally docked in the ERα binding pocket in six orientations (as specified in the text) using the Flexidock routine within Sybyl (Tripos). Both hydrogen-bond donors and acceptors within the pocket surrounding the ligand (Glu_{353}, Arg_{394}, and His_{524}), the ligand itself and select torsional bonds were defined. The docked receptor ligand complexes from Flexidock then underwent a three step minimization. First, non-ring torsional bonds of the ligand were minimized in the context of the receptor using the torsmin command. This was followed by minimization of the side chain residues within 8 Å of the ligand, while holding the backbone and residues Glu_{353} and Arg_{394} fixed. A final third minimization of both the ligand and receptor was conducted using the Anneal function (hot radius 8 Å, interesting radius 16 Å from pyrazole **10a**) to afford the final model.

Chemical syntheses

5-Ethyl-1,4-bis-(4-methoxyphenyl)-3-phenyl-1H-pyrazole (2). A stirred solution of **9e** (46 mg, 0.16 mmol) in CH_2Cl_2 (15 mL) was treated with BBr_3 (1.62 mL, 1.62 mmol) according to the general demethylation procedure. After work up and an SiO_2 plug (30% EtOAc/hexanes) a white solid was isolated (40 mg, 94%): mp 220–225 °C; ^1H NMR (MeOD-d_4, 400 MHz) δ 0.90 (t, 3H, $J = 7.5$), 2.62 (q, 2H, $J = 7.5$), 6.79 (XX′ of AA′XX′, 2H, $J_{AX} = 8.3$, $J_{XX} = 2.3$), 6.94 (XX′ of AA′XX′, 2H, $J_{AX} = 8.6$, $J_{XX} = 2.7$), 7.04 (AA′ of AA′XX′, 2H, $J_{AX} = 8.2$, $J_{AA'} = 2.4$), 7.20–7.27 (m, 2H), 7.34 (AA′ of AA′XX′, 2H, $J_{AX} = 8.8$, $J_{AA'} = 2.6$), 7.37–7.44 (m, 3H); ^{13}C NMR (MeOD-d_4, 100 MHz) δ 12.4, 17.2, 114.8, 115.2, 118.5, 124.3, 126.9, 127.4, 127.5, 127.6, 131.0, 131.0, 132.9, 144.1, 148.9, 156.2, 157.8; MS (EI, 70 eV) *m*/*z* (relative intensity, %): 356 (M^+, 100); Anal calcd for $C_{23}H_{20}N_2O_2 \cdot H_2O$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.82; H, 5.95; N, 7.69.

4′-Methoxyacetophenone-4-methoxyphenylhydrazone (6a). An EtOH (40 mL) solution of 4-methoxyacetophenone (1 g, 6.67 mmol), sodium acetate (1.09 g, 13.34 mmol), and 4-methoxyphenylhydrazine hydrochloride (1.74 g, 10.0 mmol) was heated to 80 °C for 3.0 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in ethyl

acetate (30 mL) and washed with water (40 mL) and brine (2×40 mL). After drying over $MgSO_4$ and solvent concentration a red and white heterogeneous solid formed. The product was collected by filtration and rinsed with cold ethanol (20 mL) to afford **6a** as a white solid (1.18 g, 66%) which was used directly in the next step.

Acetophenone-4-methoxyphenylhydrazone (6b). A solution of acetophenone (250 mg, 2.00 mmol) and 4-methoxyphenylhydrazine hydrochloride (349 mg, 2.00 mmol) was reacted similarly to conditions used for **6a** to afford a red and white heterogeneous sold. Cold ethanol (20 mL) was added and the remaining solid collected via vacuum filtration to afford **6b** as a white solid (1.41 g, 59%) which was used directly in the next step.

Acetophenonephenylhydrazone (6c). A solution of acetophenone (1.8 g, 15 mmol), phenylhydrazine hydrochloride (2.17 g, 15 mmol), and sodium acetate (1.23 g, 15.0 mmol), in anhydrous ethanol (40 mL), was reacted similarly to conditions used for **6a** to afford a yellow and white heterogeneous solid. Cold ethanol (20 mL) was added to the solid and the product collected via vacuum filtration to afford **6c** as a white solid (1.67 g, 53%) which was used directly in the next step.

General acylation–cyclization procedure (7a–d). To a stirred solution of hydrazone (3.05 mmol) in THF (10 mL) at 0 °C was added 1.29 M BuLi (4.73 mL, 6.10 mmol) dropwise. The resulting deep red solution was allowed to stir at 0 °C for 0.25 h, then room temperature for 0.25 h, and re-cooled to 0 °C, whereupon a THF solution (2.0 mL) of the appropriate alkyl anhydride (1.53 mmol) was added dropwise. This mixture was stirred at 0 °C for 0.25 h, then treated with 3 M HCl (6 mL, 18 mmol) and refluxed for 1.5 h. The biphasic mixture was cooled to room temperature and the aqueous layer separated and neutralized with saturated $NaHCO_3$. The neutralized solution was extracted with ethyl acetate (3×20 mL) and the organic layers combined with the THF layer from the reaction mixture. The final organic layers were washed with satd $NaHCO_3$ (3×20 mL), dried over $MgSO_4$, and concentrated to afford a red oil. The crude oil was purified by flash chromatography.

5-Ethyl-1,3-bis-(4-methoxyphenyl)-1H-pyrazole (7a). Following the general procedure above hydrazone **6a** (824 mg, 3.05 mmol) was acylated with propionic anhydride (198 mg, 0.20 mL, 1.53 mmol) and cyclized with HCl. Flash chromatography (25% EtOAc/hexanes) afforded an inseparable mixture of 4-methoxyacetophenone and **7a** (474 mg). The phenone was reduced by the dropwise addition of a solution of $NaBH_4$ (27.3 mg, 0.72) in H_2O (5 mL) to a solution of the product mixture in ethanol (5 mL). The solution was stirred for 18 h at room temperature and poured over 1 M HCl (20 mL). Upon product isolation (EtOAc, satd $NaHCO_3$, brine) and solvent removal under reduced pressure an orange oil was isolated, which upon addition of 25% EtOAc/hexanes resulted in selective crystallization of pyrazole **7a** as fine white crystals (200 mg, 44%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, 3H, J=7.6), 2.64 (q, 2H, J=7.5), 3.83 (s, 3H) 6.45 (s, 1H), 3.85 (s, 3H), 6.98 (XX′ of AA′XX′, 2H, J_{AX}=8.9, J_{XX}=2.4), 7.09 (XX′ of AA′XX′, 2H, J_{AX}=9.0, J_{XX}=2.7), 7.39 (AA′ of AA′XX′, 2H, J_{AX}=8.9, $J_{AA'}$=2.7), 7.79 (AA′ of AA′XX′, 2H, J_{AX}=8.9, $J_{AA'}$=2.8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.0, 19.6, 55.1, 55.4, 101.2, 113.7, 114.1, 126.2, 126.8, 126.8, 133.0, 146.5, 150.8, 158.9, 159.1.

1-(4-Methoxyphenyl)-3-phenyl-5-propyl-1H-pyrazole (7b). Following the general procedure above hydrazone **6a** (1.37 g, 5.71 mmol) was acylated with butyric anhydride (452 mg, 0.47 mL, 2.86 mmol) and cyclized with HCl. Flash chromatography (30% EtOAc/hexanes) afforded the title compound as a yellow oil (710 mg, 42%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, 3H, J=7.5) 1.66 (sext, 2H, J=7.5), 2.61 (t, 2H, J=7.7), 3.85 (s, 3H), 6.54 (s, 1H), 6.99 (XX′ of AA′XX′, 2H, J_{AX}=8.7, J_{XX}=2.7), 7.31 (app tt, 1H, J=7.3, 1.5), 7.38–7.43 (m, 4H), 7.89 (AA′ of AA′XX′, 2H, J_{AX}=7.2, $J_{AA'}$=1.3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 21.9, 27.1, 55.4, 102.2, 114.1, 125.5, 126.9, 127.5, 128.4, 132.9, 133.4, 145.2, 150.9, 159.1; HRMS (EI, M^+) calcd for $C_{19}H_{20}N_2O$: 292.1576. Found: 292.1569.

5-Ethyl-1-(4-methoxyphenyl)-3-phenylpyrazole (7c). Following the general procedure above hydrazone **6b** (4.50 g, 18.75 mmol) was acylated with propionic anhydride (1.22 g, 1.20 m L, 9.38 mmol) and cyclized with HCl. Upon solvent removal a crude orange solid was isolated. The crude solid was recrystallized from 20% ethyl acetate/hexanes to afford the title compound as pale yellow needles (1.82 g, 35%): mp 70–75 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, 3H, J=7.5), 2.65 (q, 2H, J=7.5), 6.53 (s, 1H), 3.86 (s, 3H), 6.99 (AA′XX′, 2H, J=8.6, 2.6), 7.28–7.33 (m, 1H), 7.37–7.43 (m, 4H), 7.85–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.0, 19.6, 55.4, 101.6, 114.2, 125.5, 126.8, 127.5, 128.4, 132.9, 133.3, 146.6, 151.0, 159.0; MS (EI, 70 eV) m/z (relative intensity, %): 278 (M^+, 100). Anal. calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.62; H, 6.49; N, 10.05.

1,3-Diphenyl-5-propyl-1H-pyrazole (7d). Following the general procedure above hydrazone **6c** (1.30 g, 6.19 mmol) was acylated with propionic anhydride (403 mg, 0.40 mL, 3.10 mmol) and cyclized with HCl. Flash chromatography (20% diethyl ether/hexanes) afforded the title compound as a yellow oil (600 mg, 40%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28 (t, 3H, J=7.4), 2.72 (q, 2H, J=7.4), 6.58 (s, 1H), 7.32–7.53 (m, 8H), 7.91 (d, 2H, J=7.5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.2, 19.9, 102.3, 125.7, 127.8, 127.9, 128.8, 129.1, 133.4, 140.0, 146.7, 151.5; HRMS (EI, M^+) calcd for $C_{17}H_{16}N_2$: 248.1313. Found: 248.1312.

General iodination procedure (8a–d). To a refluxing solution of pyrazole (0.59 mmol) and sodium acetate (107 mg, 1.13 mmol) in H_2O (4.00 mL) was added a solution of KI (591 mg, 3.56 mmol) and I_2 (301 mg, 1.19 mmol) in H_2O (4 mL) dropwise. The resulting dark brown solution was allowed to reflux for 3 h and then was cooled to room temperature and the product extracted with diethyl ether (3×25 mL). The organic

layers were combined, washed with NaS_2O_2 (3×20 mL), $NaHCO_3$ (2×20 mL), brine (2×20 mL) and then dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude iodo-pyrazoles. The products were purified by recrystallization from hexanes or by flash chromatography on silica gel.

5-Ethyl-4-iodo-1,3-bis-(4-methoxyphenyl)-1H-pyrazole (8a). Pyrazole **7a** (153 mg, 0.59 mmol) was iodinated according to the general procedure above. A crude tan solid was isolated and recrystallized from hexanes to afford the title compound as a white solid (224 mg, 87%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, 3H, J=7.4), 2.73 (q, 2H, J=7.5), 3.84 (s, 3H), 3.85 (s, 3H), 6.94–7.02 (m, 4H), 7.36 (AA′XX′, 2H, J=9.0, 2.7), 7.83 (AA′XX′, 2H, J=8.8, 2.5); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.1, 20.1, 55.1, 55.4, 60.1, 113.4, 114.2, 125.4, 126.9, 129.4, 132.6, 147.2, 151.4, 159.4, 159.5.

4-Iodo-1-(4-methoxyphenyl)-3-phenyl-5-propylpyrazole (8b). Pyrazole **7b** (660 mg, 2.26 mmol) was iodinated according to the general procedure above. A crude oil was isolated and purified by flash chromatography (25% ethyl acetate/hexanes) to afford a mixture of unreacted pyrazole **7b** and product **8b** as a pale-yellow oil (yield as determined by NMR: 65%; resonances listed for product only): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, 3H, J=7.4) 1.56 (sext, 2H, J=7.6), 2.70 (t, 2H, J=7.8), 3.86 (s, 3H), 6.99 (XX′ of AA′XX′, 2H, J_{AX}=8.7, $J_{XX'}$=2.8), 7.90 (AA′ of AA′XX′, 2H, J_{AX}=8.3, $J_{AA'}$=1.6), 7.26–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 21.9, 28.4, 55.4, 60.9, 114.2, 127.1, 128.0, 128.0, 128.2, 132.8, 146.2, 151.5, 159.5; HRMS (EI, M^+) calcd for $C_{19}H_{19}N_2OI$: 418.0542. Found: 418.0550.

5-Ethyl-4-iodo-1-(4-methoxyphenyl)-3-phenyl-1H-pyrazole (8c). Pyrazole **7c** (500 mg, 1.80 mmol) was iodinated according to the general procedure above to afford the title compound as a white solid (603 mg, 83%): mp 70–73 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.14 (t, 3H, J=7.5), 2.74 (q, 2H, J=7.5), 3.86 (s, 3H), 6.99 (AA′XX′, 2H, J=8.6, 2.9), 7.34–7.47 (m, 5H), 7.86–7.92 (m, 2H); MS (EI, 70 eV) m/z (relative intensity, %): 404 (M^+, 100). Anal. calcd for $C_{18}H_{17}N_2OI$: C, 53.48; H, 4.24; N, 6.93. Found: C, 53.66; H, 4.24; N, 6.89.

5-Ethyl-4-iodo-1,3-diphenyl-1H-pyrazole (8d). Pyrazole **7d** (248 mg, 1.13 mmol) was iodinated according to the general procedure above to afford a crude orange solid. Recrystallization from hexanes afforded **8d** as small white crystals (312 mg, 74%): mp 82–85 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.61 (t, 3H, J=7.5), 2.78 (q, 2H, J=7.5), 7.35–7.55 (m, 8H), 7.86–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.3, 20.3, 61.1, 125.6, 128.2, 128.3, 128.4, 128.6, 129.3, 132.9, 139.9, 147.3, 152.1; HRMS (EI, M^+) calcd for $C_{17}H_{15}N_2I$: 374.0280. Found: 374.0277.

General procedure for Suzuki coupling (9a,b,d,e). To a stirred solution of iodo-pyrazole (0.43 mmol) in *n*-propanol (2 mL) were added the appropriate boronic acid (0.45 mmol), $Pd(OAc)_2$ (3 mg, 0.013 mmol), PPh_3 (10 mg, 0.039 mmol), 2 M Na_2CO_3 (0.47 mL, 0.95 mmol), and H_2O (0.5 mL). The heterogeneous solution was heated to reflux for 5 h, cooled to room temperature, and filtered through Celite (EtOAc 4×5 mL). The filtrate was concentrated and partitioned in diethyl ether and water and the aqueous layer separated and extracted twice more with ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The tetrasubstituted pyrazoles were subsequently purified by flash chromatography.

5-Ethyl-1,3,4-tris-(4-methoxyphenyl)-1H-pyrazole (9a). Iodo-pyrazole **8a** (187 mg, 0.43 mmol) was coupled with 4-methoxyphenylboronic acid (68 mg, 0.45 mmol) according to the general procedure above to afford a crude brown oil. Flash chromatography (40% ethyl acetate/hexanes) furnished the title compound as a clear oil (124 mg, 70%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, 3H, J=7.5), 2.63 (q, 2H, J=7.5), 3.77 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 6.78 (AA′XX′, 2H, J=8.9, 2.5), 6.93 (AA′XX′, 2H, J=8.7, 2.5), 7.01 (AA′XX′, 2H, J=8.9, 2.6), 7.20 (AA′XX′, 2H, J=8.6, 2.5), 7.43 (AA′XX′, 2H, J=8.8, 2.4), 7.46 (AA′XX′, 2H, J=8.9, 2.6); ^{13}C NMR (CD_3OD, 100 MHz) δ 13.7, 17.8, 54.9, 55.0, 55.4, 113.3, 113.8, 114.1, 125.9, 126.4, 127.1, 127.4, 128.9, 131.3, 133.1, 143.5, 148.7, 158.3, 158.7, 159.1; HRMS (EI, M^+) calcd for $C_{26}H_{26}N_2O_3$: 414.1943. Found: 414.1937.

1,4-Bis-(4-methoxyphenyl)-3-phenyl-5-propyl-1H-pyrazole (9b). Iodo-pyrazole **8b** (300 mg, 0.72 mmol) was coupled with 4-methoxyphenylboronic acid (115 mg, 0.75 mmol) according to the general procedure above. Flash chromatography (25% EtOAc/hexanes) afforded the title compound as a glassy solid (203 mg, 71%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.70 (t, 3H, J=7.4), 1.31 (sext, 2H, J=7.6), 2.59 (t, 2H, J=7.9), 3.84 (s, 3H), 3.86 (s, 3H), 6.92 (AA′XX′, 2H, J=8.4, 2.4), 7.00 (AA′XX′, 2H, J=8.5, 2.5), 7.16–7.27 (m, 5H), 7.45 (AA′XX′, 2H, J=8.7, 2.4), 7.48–7.54 (m, 2H); ^{13}C NMR (MeOD-d_4, 100 MHz) δ 13.8, 22.2, 26.5, 55.2, 55.5, 113.9, 114.3, 114.6, 126.4, 127.2, 127.3, 127.9, 128.1, 131.5, 133.3, 133.4, 142.6, 149.0, 158.5, 159.3; HRMS (EI, M^+) calcd for $C_{26}H_{27}N_2O_2$: 398.1994. Found: 398.1991.

5-Ethyl-1,4-bis-(4-methoxyphenyl)-3-phenyl-1H-pyrazole (9c). To a degassed solution of 2 M Na_2CO_3 (0.55 mL, 1.09 mmol; 0.5 mL H_2O), and DME (3.0 mL) was added 4-methoxyphenylboronic acid (83 mg, 0.55 mmol) and pyrazole **8c** (200 mg, 0.45 mmol). To this solution $Pd(Ph_3P)_4$ (27 mg, 0.025 mmol) was added and the mixture heated to 80 °C for 72 h. The reaction mixture was then cooled to room temperature and filtered through Celite. The filtrate was transferred to a separatory funnel and the aqueous layers extracted with Et_2O (3×5 mL). The organic layers were combined and concentrated under reduced pressure. Flash chromatography (25% EtOAc/hexanes) afforded **9c** as a white solid (100 mg, 53%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, 3H, J=7.5), 2.64 (q, 2H, J=7.6), 3.85 (s, 3H), 3.86 (s, 3H), 6.93 (AA′XX′, 2H, J=8.7, 2.4), 7.00 (AA′XX′, 2H, J=9.2, 2.7), 7.18–7.27 (m, 5H), 7.46 (AA′XX′, 2H, J=9.0, 2.7), 7.49–7.53 (m, 2H); HRMS (EI, M^+) calcd for $C_{25}H_{24}N_2O_3$: 384.1834. Found: 384.1838.

5-Ethyl-1-(4-methoxyphenyl)-3,4-diphenyl-1H-pyrazole (9d). Iodo-pyrazole **8c** (400 mg, 0.99 mmol) was coupled with phenylboronic acid (144 mg, 1.04 mmol) according to the general procedure above to afford a crude brown oil. Flash chromatography (15% THF/hexanes) furnished the product and a mixture of the product and unreacted starting material. The mixture was treated to a second column under the same conditions to afford additional **9d** (50 mg combined, 14% isolated yield; 217 mg for remaining mixture, 60% total yield as determined by NMR): ^{1}H NMR (MeOD-d_4, 500 MHz) δ 0.94 (t, 3H, J = 7.4), 2.66 (q, 2H, J = 7.5), 7.02 (AA′XX′, 2H, J = 8.9, 2.7), 7.17–7.53 (m, 12H); ^{13}C NMR (MeOD-d_4, 100 MHz) δ 13.7, 17.8, 55.4, 114.1, 118.7, 126.6, 127.2, 127.9, 127.9, 128.3, 130.2, 132.8, 133.1, 133.9, 143.7, 148.8, 159.3.

5-Ethyl-4-(4-methoxyphenyl)-1,3-diphenyl-1H-pyrazole (9e). Iodo-pyrazole **8d** (244 mg, 0.65 mmol) was coupled with 4-methoxyphenylboronic acid (105 mg, 0.69 mmol) according to the general procedure above to afford a yellow oil. Flash chromatography (15% EtOAc/hexanes) was performed to afford a pale yellow oil which was then recrystallized from hexanes to afford the title compound as white crystals (160 mg, 70%): ^{1}H NMR (MeOD-d_4, 500 MHz) δ 0.94 (t, 3H, J = 7.5), 2.70 (q, 2H, J = 7.5), 3.85 (s, 3H), 6.94 (AA′XX′, 2H, J = 8.8, 2.6), 7.19–7.28 (m, 5H), 7.43 (app tt, 1H, J = 7.4, 1.7), 7.48–7.55 (m, 4H), 7.55–7.60 (m, 2H); ^{13}C NMR (MeOD-d_4, 125 MHz) δ 13.7, 17.9, 55.1, 113.8, 118.8, 125.7, 126.1, 127.2, 127.8, 127.9, 129.0, 131.3, 133.2, 140.0, 143.6, 149.3, 158.4.

General procedure for demethylation using BBr_3 (2, 10a–d). To a stirred solution of pyrazole (**9a**–**e**, 0.28 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added BBr_3 (2.82 mL, 2.82 mmol) dropwise as a 1 M solution in CH_2Cl_2. The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched at 0 °C by the addition of H_2O (10 mL). The resulting solid was solubilized by the addition of ethyl acetate and the resulting biphasic solution transferred to a separatory funnel and the aqueous layer isolated. The aqueous layer was acidified with 3 M HCl (3 mL) and extracted with ethyl acetate (2×15 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the phenolic products purified by flash chromatography and/or crystallization.

5-Ethyl-1,3,4-tris-(4-hydroxyphenyl)-1H-pyrazole (10a). A stirred solution of **9a** (46 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) was treated with BBr_3 (1.10 mL, 1.10 mmol) according to the general demethylation procedure. After work up a reddish brown oil isolated. The oil was dissolved in methanol and concentrated under reduced pressure. No effort was made to remove trace amounts of methanol remaining in the sample. The residue was triturated by adding CH_2Cl_2 dropwise until a precipitate formed. The precipitate was isolated by vacuum filtration to afford **10a** as a white solid (40 mg, 93%): ^{1}H NMR (MeOD-d_4, 400 MHz) δ 0.89 (t, 3H, J = 7.6) 2.59 (q, 2H, J = 7.5), 6.65 (d, 2H, J = 8.4), 6.79 (d, 2H, J = 8.4), 6.93 (d, 2H, J = 8.8), 7.03 (d, 2H, J = 8.8), 7.21 (d, 2H, J = 8.4), 7.32 (d, 2H, J = 8.8); ^{13}C NMR (MeOD-d_4, 100 MHz) δ 12.4, 17.2, 114.3, 114.8, 115.1, 118.0, 124.2, 124.6, 127.4, 128.9, 131.0, 131.2, 143.9, 149.1, 156.0, 156.6, 157.7; HRMS (EI, M^+) calcd for $C_{23}H_{20}N_2O_3$: 372.1474. Found: 372.1468.

1,4-Bis-(4-hydroxyphenyl)-3-phenyl-5-propyl-1H-pyrazole (10b). A stirred solution of **9b** (100 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) was treated with BBr_3 (2.50 mL, 2.50 mmol) according to the general demethylation procedure. After work up a red solid was isolated. The solid was recrystallized from 10% $CH_3OH/CHCl_3$ to afford **10b** as small white crystals (75 mg, 81%): mp 233–236 °C; ^{1}H NMR (MeOD-d_4, 400 MHz) δ 0.67 (t, 3H, J = 7.3), 1.29 (sext, 2H, J = 7.5), 2.59 (t, 2H, J = 7.9), 6.79 (AA′XX′, 2H, J = 8.4, 2.2), 6.94 (AA′XX′, 2H, J = 8.6, 2.5), 7.03 (AA′XX′, 2H, J = 8.3, 2.1), 7.20–7.26 (m, 3H), 7.31–7.43 (m, 4H); ^{13}C NMR (MeOD-d_4, 100 MHz) δ 12.4, 21.5, 25.9, 114.9, 115.2, 119.1, 124.4, 127.0, 127.4, 127.5, 127.6, 131.1, 131.2, 132.9, 142.8, 148.9, 156.2, 157.8; HRMS (EI, M^+) calcd for $C_{24}H_{22}N_2O_2$: 370.1681. Found: 370.1685.

5-Ethyl-1-(4-hydroxyphenyl)-3,4-diphenyl-1H-pyrazole (10c). A stirred solution of **9c** (37 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) was treated with BBr_3 (1.00 mL, 1.00 mmol) according to the general demethylation procedure. After work up a brown oil was afforded. The crude oil was purified by flash chromatography (5% CH_3OH/CH_2Cl_2) to afford **10c** as a white solid (30 mg, 86%): mp 210–220 °C; ^{1}H NMR (MeOD-d_4, 400 MHz) δ 0.90 (t, 3H, J = 7.60 Hz), 2.65 (q, 2H, J = 7.4), 6.95 (AA′XX′, 2H, J = 9.1, 2.7), 7.19–7.26 (m, 5H), 7.31–7.42 (m, 7H); ^{13}C NMR (MeOD-d_4, 100 MHz) δ 13.8, 17.8, 116.5, 118.8, 126.8, 127.5, 127.6, 128.1, 128.1, 128.5, 130.3, 132.1, 132.9, 133.9, 144.2, 149.1, 156.5; HRMS (EI, M^+) calcd for $C_{23}H_{20}N_2O$: 340.1576. Found: 340.1576.

5-Ethyl-4-(4-hydroxyphenyl)-1,3-diphenyl-1H-pyrazole (10d). A stirred solution of **9e** (100 mg, 0.28 mmol) in CH_2Cl_2 (10 mL) was treated with BBr_3 (2.82 mL, 2.82 mmol) according to the general demethylation procedure. After work up a crude brown solid was isolated. The solid was purified by flash chromatography (5% CH_3OH/CH_2Cl_2) to afford **10d** as a white solid (89 mg, 93%): ^{1}H NMR (MeOD-d_4, 500 MHz) δ 0.93 (t, 3H, J = 7.5), 2.68 (q, 2H, J = 7.6), 6.78 (XX′ of XX′AA′, 2H, J_{AX} = 8.4, $J_{XX'}$ = 2.5), 7.10 (AA′ of AA′XX′, 2H, J_{AX} = 8.4, $J_{AA'}$ = 2.5), 7.21–7.28 (m, 3H), 7.40–7.52 (m, 6H), 7.53–7.58 (m, 2H); ^{13}C NMR (MeOD-d_4, 100 MHz) δ 13.7, 17.9, 115.6, 119.1, 125.8, 125.9, 127.4, 128.0, 128.1, 128.2, 129.2, 131.5, 133.0, 139.8, 143.9, 149.5, 154.9; HRMS (EI, M^+) calcd for $C_{23}H_{20}N_2O$: 340.1576. Found: 340.1571.

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