SUPPORTING INFORMATION

Regioselective Synthesis of 1,3,5-Triaryl-4-Alkyl Pyrazoles, Novel Ligands for the Estrogen Receptor

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EXPERIMENTAL SECTION

All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were recorded on 400 MHz and 500 MHz spectrometers. The spectra were recorded in parts per million from internal deutrated solvents specified on the δ scale. Mass spectra were obtained on instruments at an ionization energy of 70eV. Compounds for which exact masses are reported exhibited no significant peaks at *m/z* greater than that of the parent.

Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran, diethyl ether and benzene were distilled from sodium metal, dichloromethane, triethylamine, dimethylformamide and dimethylsulfoxide were distilled from calcium hydride. Reactions requiring an inert atmosphere were run under argon or nitrogen. Analytical thin-layer chromatography was conducted using EM Laboratories 0.25 mm thick precoated silica gel 60F-254 plates. Column chromatography was performed over EM laboratory silica gel (70-130 mesh).

3-(4-methoxyphenyl)-1,5-diphenyl-1*H*-pyrazole (12): A mixture of 131 mg (0.55 mmol) of 1-(4-methoxyphenyl)-3-phenylpropenone **10** and 0.50 mL (0.55 g, 5.1 mmol) of phenylhydrazine in 5 mL of dimethylsulfoxide was heated in air in an preequilibriated oil bath at 85 °C for 16 h. The reaction solution was cooled to room temperature and partitioned with 15 mL of diethyl ether and 5 mL of water. The organic layer was separated and washed with four 5-mL portions of water. The aqueous layers were combined, extracted with three 10-mL portions of diethyl ether. The organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over a 1 x 8 cm silica gel column (eluted with ethyl acetate-hexanes, 1:8) to give 96 mg (59%) of the desired pyrazole **12** as a yellow foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.82

(s, 3H, OCH_3), 6.78 (s, 1H, H_4), 6.98 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.2-7.4 (m, 10H, ArH), 7.83 (AA'XX', *J* = 8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 55.3, 104.8, 114.0, 125.3, 125.8, 127.1, 127.3, 128.2, 128.4, 128.7, 128.9, 130.7, 140.2, 144.3, 151.8, 159.6; exact mass calcd. for $C_{22}H_{18}N_2O$ *m/e*, 326.1419, found *m/e* 326.1421.

4-Iodo-3-(4-methoxyphenyl)-1,5-diphenyl-1H-pyrazole (10): To 285 mg (0.87 mmol) of pyrazole **12** in 5 mL of DMF was added 295 mg (1.31 mmol) of *N*-iodosuccinamide (NIS). After the resulting brown solution was stirred at room temperature under nitrogen for 40 h, 50 mg (0.22 mmol) of the NIS was added and resulting mixture was stirred for another 24 h. The progress of the reaction was followed by monitoring disappearance of the singlet at δ 6.78 in the ^1H NMR spectra. The reaction mixture was then diluted with 60 mL of ethyl acetate and washed with two portions of 15 mL of 10% $Na_2S_2O_3$. The aqueous layers were combined and extracted with three portions of 20-mL of ethyl acetate. The organic layers were combined, washed with 20 mL of brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over a 1.5 x 15 cm silica gel column (eluted with ethyl acetate-hexanes, 1:7) to give 342 mg (87%) off-white solid as the desired iodide **14**. The material was further recrystallized from dichloromethane and hexanes to give 257 mg of white crystal. **14**: mp 172-173 °C, ^1H NMR ($CDCl_3$, 400 MHz) δ 3.83 (s, 3H, OCH_3), 7.00 (AA'XX', *J* = 8.7 Hz, 2H, ArH), 7.2-7.3 (m, 6H, ArH), 7.30-7.36 (m, 2H, ArH), 7.36 - 7.42 (m, 2H, ArH), 7.88 (AA'XX', *J* = 8.7 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.3, 113.7, 124.7, 125.3, 127.4, 128.5, 128.8, 129.0, 129.9, 130.3, 130.5, 139.9, 145.2, 152.8, 159.8, one aromatic carbon is not resolved probably due to overlapping; exact mass calcd. for $C_{22}H_{17}IN_2O$ *m/e* 452.0387, found *m/e* 452.0380.

3-(4-Methoxyphenyl)-1,5-diphenyl-4-(trimethylsilanylethynyl)-1*H*-pyrazole (15): To 92 mg (0.20 mmol) of the iodide **14** in 10 mL of degassed benzene was added 19.2 mg

(0.017 mmol, 8.5%) of tetrakis(triphenylphosphios)palladium. The resulting mixture was stirred at room temperature for 30 min. To the stirring slurry 115 μL (80 mg, 0.81 mmol) of trimethylsilyl acetylene was added, followed by addition of 0.5 mL of triethylamine and 4 mg (0.02 mmol, 10%) of copper iodide. The resulting green mixture was heated in a 60 °C oil bath for 40 h. The reaction mixture was partitioned between 50 mL of ethyl acetate and 10 mL of saturated NH_4Cl. The aqueous layer was separated and extracted with two 15-mL portions of EtOAc. The combined organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over a 1 x 10 cm silica gel column (eluted with ethyl acetate-hexanes, 1:20) to give 38.4 mg (45%) of the desired product as a white solid: mp 135-136 °C; ^{1}H NMR δ 0.21 (s, 9H, CH_3), 3.87 (s, 3H, OCH_3), 6.97 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.27-7.37 (m, 8H, ArH), 7.40-7.42 (m, 2H, ArH), 8.20 (AA'XX', *J* = 8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ –0.2, 53.0, 55.3, 98.5, 99.1, 113.6, 125.2, 125.3, 127.6, 128.1, 128.4, 128.7, 128.9, 129.6, 139.7, 146.2, 152.2, 159.8, one aromatic carbon was not observed; exact mass calcd. for $C_{27}H_{26}N_2OSi$ *m/e* 422.1814, found *m/e* 422.1811.

3-(4-Methoxyphenyl)-4,5-dihydro-1,5-diphenyl-1*H*-pyrazole (11) A mixture of 238.2 (1.00 mmol) of 1-(4-methoxylphenyl)-3-phenylpropenone **10** and 723 mg (4.14 mmol) of phenylhydrazine hydrochloride salt in 10 mL of DMSO was heated at 85 °C (oil bath temperature) under nitrogen for 5 h. The resulting brown solution was cooled to room temperature and partitioned between 50 mL of diethyl ether and 10 mL of water. The organic layer was separated and washed with three 10 mL-portions of water. The aqueous layers were combined and extracted with three 25 mL-portions of diethyl ether. The organic layers were combined, dried ($MgSO_4$), and concentrated in *vacuo*. The residue was chromatographed over a 1 x 6 inch silica gel column (eluted with ethyl acetate-hexanes, 1:15) to give 199 mg (61%) of the desired pyrazoline **11** as a fluffy yellow solid. An analytically pure sample was prepared by recrystallization from

dichloromethane/hexanes: mp 172-173 °C; ^{1}H NMR δ 3.10 (dd, *J* = 17.0, 7.3 Hz, 1H, H_{4a}), 3.80 (dd, *J* = 16.8, 12.3 Hz, 1H, H_{4b}), 3.83 (s, 3H, OCH_3), 5.21 (dd, *J* = 12.3, 7.3 Hz, 1H, H_5), 6.78 (t, *J* = 7.4 Hz, 1H, ArH), 6.92 (AA'XX', *J* = 8.5 Hz, 2H, ArH), 7.07 (AA'XX', *J* = 8.5 Hz, 2H, ArH), 7.18 (ddm, J = 8.5, 7.4 Hz, 2H, ArH), 7.24-7.34 (m, 5H, ArH), 7.67 (AA'XX', *J* = 8.5 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 43.8, 55.3, 64.4, 113.2, 114.0, 118.8, 125.5, 125.9, 127.2, 127.5, 128.9, 129.1, 142.8, 145.2, 146.7, 160.1; exact mass calcd. for $C_{22}H_{20}N_2O$ *m/e* 328.1576, found *m/e* 328.1573.

4-Ethyl-3-(4-methoxyphenyl)-1,5-diphenyl-4,5-dihydro-1*H*-pyrazole (16) To a solution of lithium diisopropylamide in THF [prepared from addition of 0.52 mL of 1.6 M (0.83 mmol) *n*-BuLi in hexanes to a solution of 0.12 mL (0.86 mmol) of diisopropylamine in 4.5 mL of dry THF] was added a solution of 162 mg (0.49 mmol) of pyrazoline **11** in 1.5 mL of THF *via* syringe under nitrogen at –78 °C. The resulting dark red solution was stirred at –78 °C for 1 h, and to it was added 58 μL (0.72 mmol) of ethyl iodide. The resulting solution was stirred at –78 °C for 30 min, then warmed up to room temperature and stirred for 20 h. The reaction solution was diluted with 3.5 mL of brine and 25 mL of CH_2Cl_2, and stirred for 20 min. The aqueous layer was separated and extracted with three 10 mL-portions of dichloromethane. The organic layers were combined, dried ($MgSO_4$), and concentrated in *vacuo*. The residue was chromatographed over a 2 x 15 cm silica gel column (eluted with ethyl acetate-hexanes, 1:20) to give, in sequence, 101.5 mg (63%) of the desired pyrazoline **16** as a yellow oil and 34.0 mg (21%) of pyrazole **12**. **16**: ^{1}H NMR (C_6D_6, 500 MHz) δ 0.78 (t, *J* = 7.5 Hz, 3H, CH_3), 1.42 (m, 1H, CH_2), 1.56 (m, 1H, CH_2), 3.20 (td, *J* = 8.4, 3.5 Hz, 1H, H_4), 3.27 (s, 3H, OCH_3), 4.85 (d, *J* = 3.5 Hz, 1H, H_5), 6.76 (a doublet on top of a doublet of a doublet, 3H, ArH), 6.96 (ddm, *J* = 7.3, 6.7 Hz, 1H, ArH), 7.02 (dd, *J* = 7.7, 7.1 Hz, 2H, ArH), 7.13 (d, *J* = 7.5 Hz, 2H, ArH), 7.18 (dd, *J* = 8.4, 7.4 Hz, 2H, ArH), 7.35 (d, *J* = 7.9 Hz, 2H, ArH), 7.62 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C NMR (C_6D_6, 125.8 MHz) δ 10.5, 25.5, 54.8, 57.7,

69.1, 113.3, 114.4, 118.9, 125.5, 125.9, 127.6, 127.9, 129.3, 129.4, 142.4, 144.7, 149.4, 160.4; exact mass calcd. for $C_{24}H_{24}N_2O$ *m/e* 356.1889, found *m/e* 356.1886.

4-Ethyl-3-(4-methoxyphenyl)-1,5-diphenyl-1*H*-pyrazole (9) A mixture of 50.6 mg (0.14 mmol) of pyrazoline **16** and 122.4 mg (1.44 mmol) of MnO_2 in 6 mL of benzene was heated at 100 °C (oil bath temperature) with a Dean-Stark trap for 3.5 days. The resulting mixture was cooled to room temperature and filtered through a plug of Celite. The filtrate was concentrated in vacuo, and the residue was chromatographed over a 1 x 10 cm silica gel column (eluted with ethyl acetate-hexanes, 1:20, followed by 1:10) to give, in sequence, 5.1 mg (10%) starting pyrazoline **16** and 33.0 mg (66%) of the desired pyrazole **9** as a white solid: mp 104-106 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (t, *J* = 7.5 Hz, 3H, CH_3), 2.64 (q, *J* = 7.5 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 7.00 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 7.19 (dd, *J* = 7.2, 7.1 Hz, 1H, ArH), 7.2-7.3 (m, 6H, ArH), 7.34-7.4 (m, 3H, ArH), 7.72 (AA'XX', *J* =8.6 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 15.5, 17.1, 55.3, 113.9, 120.6, 124.6, 126.5, 126.7, 128.2, 128.5, 128.6, 129.1, 130.0, 131.1, 140.1, 141.1, 150.7, 159.2; exact mass calcd. for $C_{24}H_{22}N_2O$ *m/e* 354.1732, found *m/e* 354.1730.

4-Ethyl-3-(4-hydroxyphenyl)-1,5-diphenyl-1*H*-pyrazole (3) To 21.4 mg (0.06 mmol) of pyrazole **9** in 0.5 mL of dichloromethane at –78 °C was added 0.62 mL of 1.0 M (0.62 mmol) BBr_3 in CH_2Cl_2 solution dropwise *via* syringe under nitrogen. The reaction mixture was stirred from –78 °C to room temperature for a total of 16 h. The reaction was quenched by careful addition of 2 mL of methanol, and the resulting solution was concentrated in vacuo. The residue was chromatographed over a 1 x 12 cm silica gel column (eluted with methanol-methylene chloride, 1:20) to give 21.0 mg (100%) of the desired product **3** as an off-white solid. An analytically pure sample was obtained by recrystallization from MeOH/CH_2Cl_2 to give fluffy white crystals: mp 212-213 °C; ^{1}H

NMR (CD_3OD, 500 MHz) δ 0.87 (t, *J* = 7.6 Hz, 3H, CH_3), 2.42 (q, *J* = 7.6 Hz, 2H, CH_2), 6.36 (d, *J* = 8.0 Hz, 1H, ArH), 6.84 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 6.92 (tm, *J* = 7.3 Hz, 1H, ArH), 7.08 (dd, *J* = 7.6, 6.6 Hz, 1H, ArH), 7.32 (AA'XX', *J* = 6.6 Hz, 2H, ArH), 7.4-7.5 (m, 2H, ArH), 7.5-7.6 (m, 5H, ArH), the phenolic proton was not observed in the spectrum; ^{13}C NMR (CD_3OD, 125.8 MHz) δ 15.4, 17.0, 115.6, 120.7, 124.8, 126.1, 126.8, 128.3, 128.5, 128.7, 129.4, 130.1, 130.9, 139.8, 141.1, 150.9, 155.7; exact mass calcd. for $C_{23}H_{20}N_2O$ *m/e* 340.1576, found *m/e* 340.1579.

5-(4-Methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole (**18**) A mixture of 475 mg (2.0 mmol) of 3-(4-methoxylphenyl)-1-phenylpropenone (**17**) and 1.48 g (10.2 mmol) of phenylhydrazine hydrochloride salt in 20 mL of dimethylsulfoxide was heated at 80 °C (oil bath temperature) under for nitrogen for 4 h. The solution was cooled to room temperature and partitioned between 75 mL of diethyl ether and 15 mL of water. The organic layer was separated and washed with three 15 mL–portions of water. The aqueous layers were combined, extracted with three 25 mL-portions of diethyl ether. The organic layers were combined, dried ($MgSO_4$) and concentrated in *vacuo*. The residue was chromatographed over a 2 x 16 cm silica gel column (eluted with ethyl acetate-hexanes, 1:8) to give 459 mg (70%) of the desired pyrazoline **18** as a yellow foam: ^1H NMR (C_6D_6, 500 MHz) δ 2.63 (dd, *J* = 16.8, 7.1 Hz, 1H, H_{4a}), 3.06 (dd, *J* = 17.0, 12.3 Hz, 1H, H_{4b}), 3.16 (s, 3H, OCH_3), 4.73 (dd, *J* = 12.3, 7.1 Hz, 1H, H_5), 6.60 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 6.76 (AA'XX', *J* = 7.3 Hz, 1H, ArH), 6.95 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.06 (dd, *J* = 7.5, 7.1 Hz, 1H, ArH), 7.1-7.2 (m, 4H, ArH), 7.34 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.64 (AA'XX', *J* = 8.8 Hz, 2H, ArH); ^{13}C NMR (C_6D_6, 125.8 MHz) δ 43.4, 54.6, 64.1, 114.0, 114.7, 119.5, 126.1, 127.2, 128.6, 128.7, 129.2, 133.5, 134.9, 145.5, 146.7, 159.4; exact mass calcd. for $C_{22}H_{20}N_2O$ *m/e* 328.1574, found *m/e* 328.1574.

4-Ethyl-5-(4-methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole (19) To a solution of lithium diisopropylamide in THF at –78 °C [prepared from addition of 0.18 mL of 1.6 M *n*-BuLi (0.29 mmol) in hexanes to a solution of 42 μL (0.30 mmol) diisopropylamine in 1.5 mL THF] was added a solution of 58 mg (0.18 mmol) of pyrazoline **18** in 1 mL of THF under nitrogen over a period of 2 min *via* syringe. The resulting red solution was stirred at –78 °C for 1 h, and 21 μL (0.26 mmol) of ethyl iodide was added *via* syringe. The resulting mixture was stirred at –78 °C for 30 min then warmed up to room temperature and stirred for 16 h. To the resulting brown solution was added 1 mL of brine solution. The aqueous layer was separated and extracted with two 5 mL-portions of diethyl ether. The combined organic layer was dried ($MgSO_4$) and concentrated in *vacuo*. The residue was chromatographed over a 1 x 12 cm silica gel column (eluted with ethyl acetate-hexanes, 1:20) to give 61 mg (97%) of the desired pyrazoline **19** as a yellow oil: ^{1}H NMR δ 1.04 (t, *J* = 7.4 Hz, 3H, CH_3), 1.68 (m, 1H, CH_2), 1.86 (m, 1H, CH_2), 3.38 (dt, *J* = 8.4, 3.7 Hz, 1H, H_4), 3.78 (s, 3H, OCH_3), 4.97 (d, *J* = 3.7 Hz, 1H, H_5), 6.75 (tm, *J* = 6.4 Hz, 1H, ArH), 6.82 (AA'XX', *J* = 8.4 Hz, 2H, ArH), 7.07 (AA'XX', *J* = 8.2 Hz, 2H, ArH), 7.14 (AA'XX', *J* = 8.2 Hz, 2H, ArH), 7.18 (dd, *J* = 8.7, 7.7 Hz, 2H, ArH), 7.30 (ddm, *J* = 7.7, 6.4 Hz, 1H, ArH), 7.37 (dd, *J* = 7.7, 7.7 Hz, 2H, ArH), 7.73 (AA'XX', *J* = 8.2 Hz, 2H, ArH); ^{13}C NMR (C_6D_6, 125.8 MHz) δ 10.5, 25.3, 54.6, 57.5, 68.7, 113.5, 114.8, 119.2, 126.3, 127.0, 128.3, 128.8, 129.4, 133.0, 134.0, 144.5, 149.4, 159.5; exact mass calcd. for $C_{24}H_{24}N_2O$ *m/e* 356.1889, found *m/e* 356.1891.

4-Ethyl-5-(4-methoxyphenyl)-1,3-diphenyl-1*H*-pyrazole (20) A mixture of 40 mg (0.11 mmol) of pyrazoline **19** and 0.42 g of MnO_2 in 0.4 mL of dichloromethane was stirred under nitrogen at room temperature for 4.6 days. The resulting black slurry was filtered through a plug of Celite. The filtrate was concentrated in *vacuo*. The residue was chromatographed over a 1 x 12 cm silica gel column (eluted with ethyl acetate-hexanes,

1:20) to give, in sequence, 4.3 mg (11%) of the starting pyrazoline **19** and 33.8 mg (85%) of the desired pyrazole **20** as a yellow foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (t, *J* = 7.6 Hz, 3H, CH_3), 2.65 (q, *J* = 7.6 Hz, 2H, CH_2), 3.02 (s, 3H, OCH_3), 6.90 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 7.17 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.19 (m, 1H, ArH), 7.2-7.3 (m, 4H, ArH), 7.36 (ddm, *J* = 8.6, 7.6 Hz, 1H, ArH), 7.44 (dd, *J* = 7.8, 7.3 Hz, 2H, ArH), 7.79 (AA'XX', *J* = 7.6 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 15.6, 17.1, 55.2, 114.0, 120.8, 123.2, 124.7, 126.6, 127.6, 128.0, 128.4, 128.6, 131.3, 134.3, 140.2, 141.1, 150.8, 159.5; exact mass calcd. for $C_{24}H_{22}N_2O$ *m/e* 354.1732, found *m/e* 354.1731.

4-Ethyl-5-(4-hydroxyphenyl)-1,3-diphenyl-1*H*-pyrazole (4). To 32 mg (0.09 mmol) of pyrazole **20** in 1.5 mL of dichloromethane at 0 °C was added 0.25 mL of 1.0 M (0.25 mmol) of BBr_3 in CH_2Cl_2 under nitrogen *via* syringe. The resulting brown solution was stirred at 0 °C for 30 min, then warmed up to room temperature and stirred for 20 h. The mixture was taken up with 2 mL of methanol cautiously, and stirred for 10 min. The solution was concentrated in vacuo and the residue was chromatographed over a 1 x 10 cm silica gel column (eluted with MeOH-CH_2Cl_2, 1:10) to give 25.4 mg (79%) of the desired pyrazole **4** as an off-white solid. An analytically pure sample was obtained by recrystallization with CH_2Cl_2: mp 210-212 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 0.82 (t, *J* = 7.8 Hz, 3H, CH_3), 2.42 (q, *J* = 7.8 Hz, 2H, CH_2), 6.52 (d, *J* = 8.1 Hz, 1H, ArH), 6.92 (AA'XX', *J* = 8.1 Hz, 2H, ArH), 6.99 (ddm, *J* = 7.6, 7.6 Hz, 1H, ArH), 7.10 (t, *J* = 7.1 Hz, 1H, ArH), 7.24 (AA'XX', *J* = 8.1 Hz, 2H, ArH), 7.32 (AA'XX', *J* = 7.6 Hz, 1H, ArH), 7.35-7.46 (m, 4H, ArH), 7.69 (AA'XX', *J* = 8.1 Hz, 2H, ArH), the phenolic proton was not visible in the spectrum; ^{13}C NMR (CD_3OD, 125.8 MHz) δ 15.5, 17.5, 115.5, 117.2, 120.4, 125.6, 127.7, 129.1, 129.7, 130.3, 131.5, 132.2, 132.6, 141.7, 142.4, 149.5, 160.7; exact mass calcd. for $C_{23}H_{20}N_2O$ *m/e* 340.1576, found *m/e* 340.1577.

3-(4-Hydroxyphenyl)-1-(4-methoxayphenyl)propenone (**21**): A mixture of 13.3 g (88.5 mmol) of 4-methoxyacetophenone, 10.6 g (86.8 mmol) of *p*-hydroxybenzaldehyde and 6.33 g (158 mmol) of sodium hydroxide in 140 mL of ethanol and 80 mL of water was heated at 75 °C (oil bath temperature) for three days. The reaction mixture was cooled to room temperature and concentrated in *vacuo* to remove most of the ethanol. The aqueous layer was diluted with 100 mL of 1 N aqueous NaOH and 50 mL of Et_2O. The basic aqueous layer was separated and washed with five 50-mL portions of Et_2O. The aqueous layer was then brought to pH 6 by addition of 1N HCl. The acidic aqueous layer was extracted with three 150-mL portions of ethyl acetate. The EtOAc extracts were combined, dried ($MgSO_4$), decolorized with charcoal, and filtered through a pad of silica gel (eluted with ethyl acetate-hexanes, 1:3). The filtrate was concentrated in *vacuo* and recrystallized from EtOAc to give 3.45 g (15%) of desired enone **21** as a yellow solid: mp 177-179 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (s, 3H, OCH_3), 6.88 (AA'XX', *J* = 8.5 Hz, 2H, ArH), 6.98 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.42 (d, *J* = 15.6 Hz, 1H, CH=CH), 7.56 (AA'XX', *J* = 8.5 Hz, 2H, ArH), 7.76 (d, *J* = 15.6 Hz, 1H, CH=CH), 8.03 (AA'XX', *J* = 8.7 Hz, 2H, ArH), the phenolic hydrogen was not observed.

3-[4-(*tert*-Butyldiphenylsilanyloxy)phenyl)-1-(4-methoxyphenyl)propenone (**22**): To a solution of 0.78 g (3.07 mmol) of phenol **21** and 256 mg (3.76 mmol) of imidazole in 12 mL of DMF was added 1.0 mL (1.06 g, 3.84 mmol) of *tert*-butylchlorodiphenylsilane *via* syringe dropwise over a period of 5 min. The resulting yellow solution was stirred at room temperature for 16 h. The solution was partitioned with 50 mL of diethyl ether and 10 mL of water. The organic layer was separated and washed with three 10-mL portions of water. The aqueous layer was extracted with three 25-mL portions of diethyl ether. The organic layers were combined, dried ($MgSO_4$) and concentrated in *vacuo*. The residue was chromatographed over a silica gel column (eluted with ethyl acetate-hexanes,

1:20 followed by 1:10 to give 0.97 g (64%) fluffy white solid as the desired product **22**: mp 98-100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (s, 9H, CH_3), 3.88 (s, 3H, CH_3), 6.78 (AA'XX', *J* = 8.5 Hz, 2H, ArH), 6.95 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.32-7.48 (m, 9H, ArH and CH=), 7.64-7.74 (m, 5H, ArH and CH=), 8.00 (AA'XX', *J* = 8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 19.1, 26.1, 55.2, 113.5, 119.4, 119.9, 127.6, 127.9, 129.6, 129.8, 130.4, 131.1, 132.1, 135.2, 143.6, 157.6, 162.9, 188.5; exact mass calcd. for $C_{32}H_{32}O_3Si$ *m/e* 492.2121, found *m/e* 492.2120; elemental analysis calcd. for $C_{32}H_{32}O_3Si$ C 78.01, H 6.72, found C 77.92, H 6.72.

5-[4-(*tert*-Butyldiphenylsilanyloxy)phenyl]-1,3-bis(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole (23): A slurry of 5.0 g (10.2 mmol) of α,β–unsaturated ketone **22** and 8.9 g (51.0 mmol) of 4-methoxyphenylhydrazine hydrochloride salt in 120 mL of DMF was heated at 85 °C (oil bath temperature) under argon for 20 h. The dark brown solution was cooled to room temperature and partitioned between 200 mL of Et_2O and 100 mL of water. The organic layer was separated and washed with three 100-mL portions of water. The aqueous layers were combined and extracted with three times with 100 mL of CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated in *vacuo*. The residue was chromatographed over a 5.5 x 22 cm silica gel column (eluted with ethyl acetate-hexanes, 1:15) to give 4.61 g (74%) of the desired pyrazoline **23** as a yellow foam: ^{1}H NMR (C_6D_6, 500 MHz) δ 1.15 (s, 9H, CH_3), 2.58 (dd, *J* = 17.1, 8.8 Hz, 1H, CH_2), 3.04 (dd, *J* = 17.1, 12.0 Hz, 1H, CH_2), 3.28 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 4.59 (dd, *J* = 12.0, 8.8 Hz, 1H, CH), 6.76–6.84 (m, 6H, ArH), 6.90 (AA'XX', *J* = 9.4 Hz, 2H, ArH), 7.74 –7.78 (two sets of dm overlapping on each other, 4H, ArH); ^{13}C NMR (C_6D_6, 125.8 MHz) δ 19.6, 26.6, 43.9, 54.8, 55.1, 65.6, 114.2, 114.7, 115.4, 120.5, 126.5, 127.5, 127.6, 128.1, 130.2, 133.2, 135.8, 136.2, 140.7, 146.2, 153.9, 155.2, 160.4; exact mass calcd. For $C_{39}H_{40}N_2O_3Si$ *m/e* 612.2808, found *m/e* 612.2813.

5-[4-(*tert*-Butyldiphenylsilanyloxy)phenyl]-4-methyl-1,3-bis(4-methoxy-phenyl)-4,5-dihydro-1*H*-pyrazole (**24**): To a solution of lithium diisopropylamide in 20 mL of THF [prepared by dropwise addition of 2.1 mL of 1.6 M *n*-BuLi (3.36 mmol) in hexanes to 0.48 mL (346 mg, 3.42 mmol) of diisopropylamine in 20 mL of THF] was added a solution of 1.24 g (2.03 mmol) of pyrazoline **23** in 6 mL of THF dropwise *via* syringe under argon at –78 °C over a period of 2 min. The resulting dark red solution was stirred at –78 °C for 1 h. To the resulting solution, 190 μL (4.15 mmol) of iodomethane was added in one portion. The resulting yellow solution was warmed up to room temperature slowly overnight. To the solution 10 mL of brine was added. The aqueous layer was separated and extracted with two 25-mL portions of ethyl acetate. The organic layers were combined, dried ($MgSO_4$), and concentrated in *vacuo*. The residue was chromatographed over a silica gel column (eluted with ethyl acetate-hexanes, 1:20) to give 648 mg (51%) of white foam as the desired product **24** and 298 mg (24%) recovered starting material. **24**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (s, 9H, CH_3), 1.37 (d, *J* = 7.1 Hz, 3H, CH_3), 3.38 (dq, *J* = 7.1, 5.6 Hz, 1H, CH), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.59 (d, *J* = 5.6 Hz, 1H, CH), 6.70 (d, *J* = 8.6 Hz, 2H, ArH), 6.76 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 6.91 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 6.94 (AA'XX', *J* = 9.1 Hz, 2H, ArH), 7.00 (AA'XX', *J* = 8.5 Hz, 2H, ArH), 7.36 (dd, *J* = 7.3, 7.3, 4H, ArH), 7.42 (AA'XX', *J* = 8.9 Hz, 2H, ArH), 7.64 (AA'XX', *J* = 8.7 Hz, 2H, ArH), 7.70 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 19.4, 26.5, 50.8, 55.3, 55.6, 72.9, 114.0, 114.2, 114.3, 120.6, 125.0, 126.7, 127.3, 127.7, 129.8, 132.8, 134.4, 135.5, 139.5, 150.3, 152.7, 154.9, 159.6; exact mass cacld. for $C_{40}H_{42}N_2O_2Si$ *m/e* 626.2965, found *m/e* 626.2958.

5-[4-(*tert*-Butyldiphenylsilanyloxy)phenyl]-4-ethyl-1,3-bis(4-methoxyphenyl)-4, 5-dihydro-1*H*-pyrazole (**25**): Proceeded as described above for the preparation of pyrazoline **24**. 1.65 g (2.69 mmol) of pyrazoline **23** in 7 mL of THF was added to a LDA

solution prepared from mixing 2.8 mL of 1.6 M *n*-BuLi and 0.63 mL of *I*-Pr_2NH. 0.33 mL of ethyl iodide was used for alkylation. 619 mg (36%) of white foam was isolated as the desired product **25**: ^1H NMR (C_6D_6, 500 MHz) δ 0.73 (t, *J* = 7.5 Hz, 3H, CH_3), 1.12 (s, 9H, CH_3), 1.45 (dq, *J* = 15.8, 7.4 Hz, 1H, CH_2), 1.51 (dqd, *J* = 15.8, 7.4, 3.6 Hz, 1H, CH_2), 3.16 (dt, *J* = 3.9, 1.5 Hz, 1H, CH), 3.28 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 4.71 (d, *J* = 3.9 Hz, 1H, CHAr), 6.77 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 6.79 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 6.81 (AA'XX', *J* = 9.1 Hz, 2H, ArH), 6.91 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.07 – 7.16 (m, 6H, ArH), 7.19 –7.25 (m, 2H, ArH), 7.59 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 7.78 (AA'XX' and m, *J* = 8.8 Hz, 4H, ArH); ^{13}C NMR (C_6D_6, 125.7 MHz) δ 10.4, 19.5, 25.3, 26.5, 54.8, 55.1, 57.6, 69.4, 114.3, 114.5, 114.9, 120.5, 125.9, 127.2, 127.7, 130.2, 133.2, 135.2, 135.6, 135.8, 139.4, 148.5, 153.5, 155.2, 160.1; exact mass calcd. for $C_{41}H_{44}N_2O_3Si$ *m/e* 640.3121, found *m/e* 640.3120.

5-[4-*tert*-Butyldiphenylsilanyloxy)phenyl]-4-propyl-1,3-bis(4-methoxy-phenyl)-4,5-dihydro-1*H*-pyrazole (**26**): Proceeded as describe for the preparation of pyrazoline **24.** 1.76 g (2.88 mmol) of pyrazoline **23** in 8 mL of THF was added to a LDA solution prepared from 3.0 mL of 1.6 M *n*-BuLi and 0.68 mL of *i*Pr_2NH. 0.42 mL of propyl iodide was used for alkylation. The desired product **26** was isolated as a white foam (952.4 mg, 36%): ^1H NMR (C_6D_6, 500 MHz) δ 0.65 (t, *J* = 8.5 Hz, 3H, CH_3), 1.09 (s, 9H, CH_3), 1.26 (m, 1H, CH_2), 1.30 (m, 1H, CH_2), 1.35 (m, 1H, CH_2), 1.47 (m, 1H, CH_2), 3.20 (dt, *J* = 3.1, 1.5 Hz, 1H, CH), 3.21 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 4.72 (d, *J* = 3.1 Hz, 1H, CHAr), 6.73-6.78 (m, 4H, ArH), 6.80 (AA'XX', *J* = 8.5 Hz, 2H, ArH), 6.88 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.04-7.10 (m, 6H, ArH), 7.22 (AA'XX', *J* = 8.5 Hz, 2H, ArH), 7.60 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.7 (m, 4H, ArH); ^{13}C NMR (C_6D_6, 125.8 MHz) 14.1, 19.5, 19.7, 26.6, 34.8, 54.8, 55.1, 56.3, 69.8, 114.3, 114.5, 115.0, 120.5, 125.9, 127.2, 127.7, 128.3, 130.2, 133.2, 135.5, 135.8, 139.5, 148.8, 153.5, 155.3, 160.1; exact mass calcd. for $C_{42}H_{46}N_2O_3Si$ *m/e* 654.3278, found *m/e* 654.3284.

5-[4-*tert*-(Butyldiphenylsilanyloxy)phenyl]-4-methyl-1,3-bis(4-methoxy-phenyl) 1*H*-pyrazole (**27**): A mixture of 615 mg (1.02 mmol) of pyrazoline **24** and 352 mg (1.55 mmol) of dichlorodicyanoquinone in 30 mL of benzene was heated to reflux for 16 h. The mixture was cooled to room temperature and filtered through a plug of Celite with diethyl ether. The filtrate was concentrated in vacuo and the residue was chromatographed over a 2.8 cm x 12 cm silica gel column (eluted with ethyl acetate-hexanes, 1:10, then 1:5) to give 539 mg (86%) of white foam as the desired pyrazole **27:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.14 (s, 9H, CH_3), 2.18 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.74 (AA'XX', *J* = 8.9 Hz, 2H, ArH), 6.75 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 6.94 (AA'XX', *J* = 8.9 Hz, 2H, ArH), 6.98 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 7.12 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 7.38 (ddm, *J* = 7.5, 7.5 Hz, 4H, ArH), 7.44 (ddm, *J* = 7.3, 7.3, Hz, 2H, ArH), 7.71 (m, 6H, ArH); ^{13}C NMR δ 10.5, 19.7, 26.7, 55.5, 55.6, 113.1, 113.95, 114.05, 120.2, 123.8, 126.2, 127.0, 128.0, 129.3, 130.2, 131.3, 133.0, 133.9, 135.8, 141.5, 150.7, 155.7, 158.3, 159.3; exact mass calcd. for $C_{40}H_{40}N_2O_3Si$ *m/e* 624.2808, found *m/e* 624.2817.

5-[4-*tert*-Butyldiphenylsilanyloxy)phenyl]-4-ethyl-1,3-bis(4-methoxyphenyl) 1*H*-pyrazole (**28**): A black slurry of 2.06 g (3.22 mmol) of pyrazoline **25** and 2.8 g (32.2 mmol) of MnO_2 in 40 mL of benzene was sonicated at room temperature for 25 h. The mixture was filtered through a plug of Celite (rinsed with EtOAc). The filtrate was concentrated *in vacuo* and the residue was chromatographed over a 3 x 16 cm silica gel column (eluted with ethyl acetate-hexanes, 1:25, then 1:8) to give 494 mg (24%) of starting material and 1.49 g (72%) of white foam as the desired product **28**. The recovered starting material was treat with MnO_2 again to afford 321 mg (16%) of desired product **28**. **28**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98 (t, *J* = 7.5 Hz, 3H, CH_3), 1.11 (s, 9H, CH_3), 2.56 (q, *J* = 7.5 Hz, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.72

(AA'XX', *J* = 9.0 Hz, 2H, ArH), 6.75 (AA'XX', *J* = 8.7 Hz, 2H, ArH), 6.94 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 6.96 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 7.11 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 7.37 (dd, *J* = 7.5, 6.7 Hz, 4H, ArH), 7.44 (tt, *J* =7.3, 2.9 Hz, 2H, ArH), 7.67 (AA'XX', *J* = 8.9 Hz, 2H, ArH), 7.70 (d and m, *J* = 6.6 Hz, 4H, ArH); ^{13}C NMR ($CDCl_3$, 127.8 MHz) δ 15.4, 17.0, 19.4, 26.4, 55.2, 55.3, 113.6, 113.8, 119.8, 120.0, 123.8, 125.9, 126.8, 127.7, 129.0, 129.9, 131.1, 132.7, 133.5, 135.5, 140.9, 150.0, 155.6, 158.0, 159.1; exact mass calcd. for $C_{41}H_{42}N_2O_3Si$ *m/e* 638.2965, found *m/e* 638.2968.

5-[4-*tert*-Butyldiphenylsilanyloxy)phenyl]-4-propyl-1,3-bis(4-methoxyphenyl) 1*H*-pyrazole (**29**): Proceeded as described for the preparation of pyrazole **28** from 1.3 g (1.99 mmol) of pyrazoline **26** and 1.8 g of MnO_2, chromatographed over a 3 cm x 18 cm silica gel column (eluted with ethyl acetate-hexanes, 1:15, then 1:5) to give 821 mg (63%) of white foam as the desired product: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.74 (t, *J* = 7.2 Hz, 3H, CH_3), 1.11 (s, 9H, CH_3), 1.35 (ddt, *J* = 7.9, 7.9, 7.5 Hz, 2H, CH_2), 2.50 (dd, *J* = 7.9 Hz, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.72 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 6.75 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 6.93 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 6.96 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 7.12 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 7.36 (tm, *J* = 7.8 Hz, 4H, ArH), 7.44 (tm, *J* = 7.5 Hz, 2H, ArH), 7.65 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.70 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.1, 18.4, 22.8, 24.9, 25.4, 54.1, 54.3, 112.6, 112.7, 117.3, 119.0, 123.0, 124.8, 125.9, 126.7, 128.0, 128.9, 120.1, 131.7, 132.5, 134.5, 140.1, 149.2, 154.5, 156.9, 158.0; exact mass calcd. for $C_{42}H_{44}N_2O_3Si$ *m/e* 652.3121, found *m/e* 652.3129.

4-[2,5-Bis-(4-methoxyphenyl)-4-methyl-2*H*-pyrazol-3-yl]-phenol (30): To 564 mg (0.90 mmol) of pyrazole **27** in 12 mL of THF was added 1.2 mL of 1.0 M TBAF (1.2 mmol) in THF solution under nitrogen. The resulting reaction solution was stirred at room temperature for 0.5 h and concentrated *in vacuo.* The residue was

chromatographed over a 2 x 18 cm silica gel column (eluted with ethyl acetate-hexanes, 1:3, to 1:1) to give 233 mg (67%) of white solid as the desired product. An analytically pure sample was obtained from recrystallization from ethyl acetate: mp 232-234 °C; ^{1}H NMR (500 MHz, THF-d_8) δ 2.01 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.74 (AA'XX', *J* = 8.4 Hz, 2H, ArH), 6.80 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 6.94 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.02 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 7.18 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.72 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 8.47 (s, 1H, OH); ^{13}C NMR (125.0 MHz, THF-d_8) δ 10.7, 55.3, 55.5, 113.3, 114.30, 114.34, 116.15, 122.9, 126.4, 128.2, 129.4, 132.2, 135.1, 142.1, 150.7, 158.6, 159.1, 160.1; exact mass calcd. for $C_{24}H_{22}N_2O_3$ 386.1630, found 386.1623, elemental analysis calcd. for $C_{24}H_{22}N_2O_3$ C 74.59, H 5.74, found C 74.05, H 5.69.

4-[4-ethyl-2,5-Bis-(4-methoxyphenol-2*H*-pyrazol-3-yl]-phenol (31): Prepared by following the same procedure described for that of **30** from 1.81 g (2.83 mmol) of starting pyrazole **28** to give 785 mg (69%) of white solid as the desired product **31**, which was then recrystallized from EtOAc. **31**: mp 233-234 °C; ^{1}H NMR (400 MHz, THF-d_8) δ 1.02 (t, *J* = 7.6 Hz, 3H, CH_3), 2.62 (q, *J* =7.6 Hz, 2H, CH_2), 3.73 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.75 (AA'XX', *J* = 8.5 Hz, 2H, ArH), 6.78 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 6.94 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.04 (AA'XX', *J* = 8.5 Hz, 2H, ArH), 7.17 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 7.69 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 8.50 (s, 1H, OH); ^{13}C NMR (100 MHz, THF-d_8) δ 15.9, 18.0, 55.3, 55.5, 114.2, 114.4, 116.2, 120.3, 123.0, 126.3, 128.4, 129.4, 135.2, 135.0, 141.9, 150.2, 158.8, 159.1, 160.2; exact mass calcd. for $C_{25}H_{24}N_2O_3$ 400.1789, found 400.1781; elemental analysis calcd. for $C_{25}H_{24}N_2O_3$ C 74.98, H 6.04, found C 74.71, H 6.06.

4-[2,5-Bis-(4-methoxyphenyl)-4-propyl-2*H*-pyrazol-3-yl]-phenol (32) Prepared from 1.20 g of **29** and 2.2 mL of 1.0 M TBAF, according to the procedure described for

preparation of **30**, to give 417.5 mg (55%) of desired product as a white solid. The solid was then recrystallized from EtOAc: mp 165-166 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.77 (t, *J* = 7.3 Hz, 3H, CH_3), 1.39 (qt, *J* = 7.8, 7.6 Hz, 2H, CH_2), 2.65 (dd, *J* = 8.1, 7.6 Hz, 2H, CH_2), 3.74 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.70 (AA'XX', *J* = 8.3 Hz, 2H, ArH), 6.75 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 6.96 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.01 (AA'XX', *J* = 8.5 Hz, 2H, ArH), 7.18 (AA'XX', *J* = 8.3 Hz, 2H, ArH), 7.66 (AA'XX', *J* = 8.5 Hz, 2H, ArH), the phenolic proton was not observed; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 23.9, 26.0, 55.2, 55.3, 113.7, 113.8, 115.5, 118.4, 122.7, 126.2, 126.6, 129.2, 131.3, 133.2, 141.5, 150.4, 155.9, 158.1, 159.1; exact mass calcd. for $C_{26}H_{26}N_2O_3$ 414.1943, found 414.1939; elemental analysis calcd. for $C_{26}H_{26}N_2O_3$ C 75.34, H 6.32, found C 74.84, H 6.29.

*General Procedure for Preparation of Compounds **33-40***:

To a solution of corresponding phenols **27-29** (1.0 eq), triphenylphosphine (4 eq) and corresponding alcohols (5 eq) in THF (2.5 mL/0.1 mmol) was added diisopropyldiazodicarboxylate (DIAD, 4 eq). The resulting solution was stirred at room temperature under N_2 for 4-16 h, and concentrated under reduced pressure. The residue was chromatographed over silica gel columns (eluted with mixtures of CH_3OH and CH_2Cl_2). The by-product from DIAD sometimes was difficult to remove entirely from the desired product. The products were dissolved in dichloromethane (2.5 mL/0.1mmol), and the resulting solution was added to the solution of $AlCl_3$ (9-10 eq) and EtSH (5 eq) in CH_2Cl_2 (1mL/0.1mmol). The reactions were usually finished in 0.5-3 h and were quenched by careful addition of MeOH. Silica gel was then added to the resulting solution. Solvents were removed under reduced pressure, and the dry silica gel was then loaded on top of silica gel columns. The columns were eluted with mixture of MeOH-CH_2Cl_2 (1:20-1:5) to give desired products **33-40** in 76%-100% yield for the two steps.

1,3-Bis(4-hydroxyphenyl)-4-methyl-5-[4-(2-piperidinylethoxy)phenol]-1*H*-pyrazole (**33**): mp 160-165 °C (decomposed); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.45 (m, 1H, CH_2), 1.75 (m, 3H, CH_2), 1.85 (dm, *J* = 13.1 Hz, 2H, CH_2), 2.09 (s, 3H, CH_3), 2.98 (t, 2H, CH_2), 3.47 (m, 2H, CH_2), 3.52 (dm, *J* = 12.5 Hz, 2H, CH_2), 4.30 (br s, 2H, CH_2), 6.69 (AA'XX', *J* = 8.2 Hz, 2H, ArH), 6.83 (AA'XX', *J* = 8.4 Hz, 2H, ArH), 6.96 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.06 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.17 (AA'XX', *J* = 8.4 Hz, 2H, ArH), 7.46 (AA'XX', *J* = 8.6 Hz, 2H, ArH), the two phenolic protons were not observed; ^{13}C NMR δ 10.5, 22.6, 24.1, 55.4, 57.5, 63.8, 114.8, 116.2, 116.7, 115.8, 122.0, 122.5, 129.3, 129.9, 131.0, 133.1, 145.6, 150.0, 159.6, 159.7, 159.8; exact mass calcd. for $C_{29}H_{31}N_3O_3$ *m/e* 469.2365, found *m/e* 469.2374.

4-Ethyl-1,3-bis(4-hydroxyphenyl)-5-[4-(2-piperidinylethoxy)phenol]-1*H*-pyrazole (**34**): mp 155-160 °C (decomposed); ^{1}H NMR (CD_3OD, 500 MHz) δ 0.86 (t, *J* = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.42 (m, 2H, CH_2), 1.56 (m, 4H, CH_2), 2.48 (q, *J* = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 2.57 (br s, 4H, NCH_2), 2.79 (t, *J* = 5.1 Hz, 2H, $OCH_2C\underline{H}_2N$), 4.06 (t, *J* = 5.4 Hz, 2H, $OC\underline{H}_2CH_2N$), 6.58 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 6.76 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 6.84 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 6.94 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 7.00 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.37 (AA'XX', *J* = 8.6 Hz, 2H, Ar), the two phenolic protons were not observed; ^{13}C NMR (CD_3OD, 125.7 MHz) δ 14.9, 17.5, 22.4, 24.0, 54.9, 57.0, 63.3, 116.3, 117.1, 117.2, 118.7, 120.7, 122.2, 127.0, 130.0, 131.3, 133.0, 147.9, 148.0, 160.5, 161.0, 161.2; exact mass calcd. for $C_{30}H_{33}H_3O_3$ 483.2522, found 483.2519.

1,3-Bis(4-hydroxyphenyl)-4-propyl-5-[4-(2-piperidinylethoxy)phenol]-1*H*-pyrazole (**35**): mp 155-160 °C (decomposed); ^{1}H NMR (CD_3OD, 500 MHz) δ 0.59 (br s, 3H, CH_3), 1.22 (br s, 2H, CH_2), 1.40 (br s, 1H, CH_2), 1.6-1.8 (m, 5H, CH_2), 2.52 (br. s, 2H, CH_2), 2.95 (br s, 2H, CH_2), 3.3-3.6 (m, 4H, CH_2), 4.28 (br s, 2H, OCH_2), 6.68 (br s, 2H,

ArH), 6.83 (br s, 2H, ArH), 6.98 (br s, 2H, ArH), 7.1–7.3 (m, 4H, ArH), 7.42 (br s, 2H, ArH), the two phenolic protons were not observed; ^{13}C NMR (CD_3OD, 125.7 MHz) δ 14.3, 22.5, 24.0, 26.2, 55.1, 57.3, 63.7, 116.7, 117.1, 117.2, 118.9, 120.7, 126.7, 130.1, 131.5, 133.3, 148.0, 148.2, 160.4, 160.8, 161.0, one carbon in aliphatic region and one in aromatic region were not resolved; exact mass calcd. for $C_{31}H_{35}N_3O_3$ *m/e* 497.2678, found *m/e* 497.2678.

4-Ethyl-1,3-bis(4-hydroxyphenyl)-5-[4-(2-pyrrolidinylethoxyl)phenol]-1*H*-pyrazole (36): mp 160-162 °C (decomposed); ^{1}H NMR (CD_3OD, 500 MHz) δ 0.92 (t, *J* = 7.5, 3H, $CH_2C\underline{H}_3$), 1.95 (m, 2H, CH_2), 2.05 (m, 2H, CH_2), 2.48 (q, *J* = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 3.08 (br s, 2H, CH_2), 3.59 (m, 4H, CH_2), 4.23 (br s, 2H, CH_2), 6.64 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 6.82 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 6.96 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.18 (AA'XX', *J* = 9.2 Hz, 2H, ArH), 7.22 (AA'XX', *J* = 9.2 Hz, ArH, 2H), 7.42 (AA'XX', *J* = 9.0 Hz, 2H, ArH), the two phenolic protons were not observed; ^{13}C NMR (CD_3OD, 125.7 MHz), δ 14.9, 17.5, 23.9, 55.0, 55.8, 64.5, 116.3, 117.1, 117.3, 118.7, 120.7, 122.2, 127.0, 130.0, 131.3, 133.0, 147.9, 148.1, 160.6, 161.1, 161.3; exact mass found for $C_{29}H_{31}N_3O_3$ 469.2365, found, 469.2348.

4-Ethyl-1,3-bis(4-hydroxyphenyl)-5-[4-(2-diethylaminylethoxyl)phenol]-1*H*-pyrazole (37): mp 128-130 °C (decomposed); ^{1}H NMR (CD_3OD, 500 MHz) δ 0.86 (t, *J* = 7.3 Hz, 3H, CH_3), 1.13 (t, *J* = 7.3 Hz, 6H, CH_3), 2.49 (q, *J* = 7.3 Hz, 2H, CH_2), 2.92 (q, *J* = 7.3 Hz, 4H, CH_2), 3.17 (br s, 2H, CH_2), 4.13 (t, *J* = 5.1 Hz, 2H, CH_2), 6.58 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 6.77 (AA'XX', *J* = 8.4 Hz, 2H, ArH), 6.88 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 6.94 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.07 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 7.38 (AA'XX', *J* = 8.4 Hz, 2H, ArH), the two phenolic protons were not observed; ^{13}C NMR (CD_3OD, 125.7 MHz) 9.7, 15.3, 17.8, 22.3, 52.5, 64.1, 116.4, 117.06, 117.11, 118.8,

120.6, 122.1, 126.9, 130.3, 131.5, 133.4, 147.7, 148.0, 160.0, 160.7, 160.9; exact mass cacld. for $C_{29}H_{33}N_3O_3$ 471.2522, found 471.2520.

4-Ethyl-1,3-bis(4-hydroxyphenyl)-5-[4-(2-dimethylaminylethoxyl)phenol]-1*H*-pyrazole (38): mp 168-170 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 0.88 (t, *J* = 7.3 Hz, 3H, CH_3), 2.54 (q, *J* = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 2.87 (s, 6H, NCH_3), 3.50 (br s, 2H, CH_2), 4.27 (br s, 2H, CH_2), 6.65 (AA'XX', *J* = 7.3 Hz, 2H, ArH), 6.82 (AA'XX', *J* = 7.7 Hz, 2H, ArH), 6.97 (AA'XX', *J* = 7.3 Hz, 2H, ArH), 7.07 (AA'XX', *J* = 7.9 Hz, 2H, ArH), 7.19 (AA'XX', *J* = 7.5 Hz, 2H, ArH), 7.42 (AA'XX', *J* = 8.4 Hz, 2H, ArH), the two phenolic protons were not observed; ^{13}C NMR (CD_3OD, 125.7 MHz) δ 15.3, 17.7, 44.5, 57.8, 63.6, 116.2, 116.9, 117.0, 120.7, 121.8, 121.9, 128.5, 129.6, 131.2, 133.1, 146.5, 149.0, 160.0, 160.1, 160.4; exact mass calcd. for $C_{27}H_{29}N_3O_3$ m/e 443.5376, found HR FAB 444.2290 (M^++1).

4-Ethyl-1,3-bis(4-hydroxyphenyl)-5-[4-(2-morpholinylethoxyl)phenol]-1*H*-pyrazole (39): mp 144-146 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 0.89 (t, *J* = 7.5 Hz, 3H, CH_3), 2.58 (q, *J* = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 3.20 (m, 2H, CH_2), 3.49 (dm, *J* = 11.9 Hz, 2H, CH_2), 3.56 (t, *J* = 4.9 Hz, 2H, CH_2), 3.76 (ddm, *J* = 11.8, 11.6 Hz, 2H, CH_2), 3.95 (dd, *J* = 10.7, 2.8 Hz, 2H, OCH_2), 4.35 (t, *J* = 4.9 Hz, 2H, CH_2), 6.69 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 6.87 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 7.00 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 7.15 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.24 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 7.46 (AA'XX', *J* = 8.6 Hz, 2H, ArH), the two phenol protons were not observed; ^{13}C NMR (CD_3OD, 125.7 MHz) δ 14.9, 17.5, 53.7, 57.3, 63.2, 64.8, 116.2, 117.0, 117.1, 119.5, 121.2, 122.0, 127.6, 129.6, 131.2, 132.9, 147.4, 148.3, 160.3, 160.6, 160.9; exact mass calcd. for $C_{29}H_{31}N_3O_4$ *m/e* 485.2315, found *m/e* 485.2306.

1-2-{4-[4-Ethyl-2,5-bis-(4-hydroxyphenyl)-2*H*-pyrazol-3-yl]-phenoxy}-ethyl)-pyrrolidin-2-one (40): mp 175-180 °C (decomposed); ^{1}H NMR (CD_3OD, 500 MHz) δ 0.92 (t, *J* = 7.5 Hz, 3H, CH_3), 1.92 (tt, *J* = 7.9, 7.5 Hz, 2H, CH_2), 2.26 (t, *J* = 8.1 Hz, 2H, CH_2), 2.60 (q, *J* = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 3.48 (t, *J* =7.1 Hz, 2H, CH_2), 3.57 (t, *J* = 4.9 Hz, 2H, $NC\underline{H}_2CH_2$), 4.07 (t, *J* = 5.1 Hz, 2H, $NCH_2C\underline{H}_2O$), 6.72 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 6.80 (AA'XX', *J* =8.6 Hz, 2H, ArH), 6.91 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 7.17 (AA'XX', *J* = 8.6 Hz, 2H, ArH), 7.20 (AA'XX', *J* = 8.4 Hz, 2H, ArH), 7.41 (AA'XX', *J* = 8.6 Hz, 2H, ArH), the two phenolic protons were not observed; ^{13}C NMR (CD_3OD, 125.7 MHz) δ 15.3, 17.7, 19.1, 32.0, 43.4, 67.0, 116.0, 116.9, 117.0, 121.0, 121.3, 121.8, 128.9, 129.5, 131.2, 133.0, 146.7, 149.2, 160.5, 160.5, 161.0; exact mass calcd. for $C_{29}H_{29}N_3O_4$ *m/e* 483.2158 found *m/e* 483.2153.

5-(4-Allyloxyphenyl)-4-ethyl-1,3-bis-(4-methoxyphenyl)-1*H*-pyrazole (42) : To a mixture of 72 mg (0.18 mmol) of phenol **31**, 32 mg (0.8 mmol) of sodium hydroxide in 0.5 mL of water and 2 mL of ethanol was added 25 μL (0.29 mmol) of allyl bromide. After the reaction mixture was heated at ca. 70 °C for 24 h, 125 μL of allyl bromide was added. The reaction was complete after another 48 h at that temperature. The mixture was cool to room temperature and most of the solvent was removed under reduced pressure. The residue was taken up with 15 mL of ethyl acetate, and 1 N HCl was added to the solution to bring it to acidic. The aqueous layer was separated and extracted with two 10-mL portions of ethyl acetate. The organic layers were combined, dried ($MgSO_4$), and concentrated. The residue was chromatographed over a 2 x 16 cm silica gel column (eluted with EtOAc-hexanes, 1:10, then 1:5) to give 65.5 mg (85%) of white solid as the desired product **42**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (t, *J* = 7.5 Hz, 3H, CH_3), 2.63 (q, *J* = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 3.77 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.54 (dt, *J* = 4.1, 1.3 Hz, 2H, CH_2), 5.30 (dt, *J* =10.5, 1.3 Hz, 1H, $=CH_2$), 5.43 (dq, *J* = 17.1, 1.5 Hz, 1H, $=CH_2$), 6.06 (ddt, *J* = 17.1, 10.5, 4.1 Hz, 1H, =CH), 6.78 (AA'XX', *J* = 8.8 Hz, 2H,

ArH), 6.90 (AA'XX', *J* = 9.6 Hz, 2H, ArH), 6.98 (AA'XX', *J* = 9.6 Hz, 2H, ArH), 7.14 (AA'XX', *J* = 9.4 Hz, 2H, ArH), 7.19 (AA'XX', *J* = 10.0 Hz, 2H, ArH), 7.70 (AA'XX', *J* = 9.6 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 15.6, 17.1, 55.2, 55.3, 68.7, 113.7, 113.8, 114.6, 117.9, 119.9, 123.4, 126.1, 126.9, 129.1, 131.3, 133.0, 133.6, 140.9, 150.1, 158.1, 158.4, 159.1; exact mass calcd. for $C_{28}H_{28}N_2O_3$ *m/e* 440.2100, found *m/e* 440.2101.

3-{4-[4-Ethyl-2,5-bis-(4-methoxyphenyl)-2*H*-pyrazol-3-yl]-phenoxy}-propane-1,2-diol (43): To a solution of 65.5 mg (0.15 mmol) of allyl ether **42** and 21 mg (0.18 mmol) of *N*-methylmorpholine-*N*-oxide in 1.2 mL of acetone, 0.4 mL of water was added 150 mg (0.60 mmol) of osmium tetroxide. The reaction was complete in 6 h. The resulting black slurry was concentrated in *vacuo*, and the residue was filtered over a pad of silica gel (eluted with ethyl acetate). The filtrate was then concentrated, and the residue was chromatographed over a 1 x 8 cm silica gel column (eluted with ethyl acetate-hexanes, 1:1, followed by EtOAc) to give 59.2 mg (90%) of the desired diol **43**: mp 115-120 °C (decomposed); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (t, *J* = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 7.45 (t, *J* = 5.6 Hz, 1H, $CH_2O\underline{H}$), 2.61 (t, *J* = 7.5 Hz, 2H, CH_2CH_3), 2.93 (d, *J* = 4.5 Hz, 1H, $CHO\underline{H}$), 3.69 (m, 1H, $C\underline{H}_2OH$), 3.75 (s, 3H, OCH_3), 3.80 (m, 1H, $C\underline{H}_2OH$), 3.84 (s, 3H, OCH_3), 3.95–4.01 (m, 2H, CH_2O), 4.05 (m, 1H, $C\underline{H}OH$), 6.77 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 6.86 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 6.98 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.13 (AA'XX', *J* = 8.8 Hz, 2H, ArH), 7.17 (AA'XX', *J* = 9.0 Hz, 2H, ArH), 7.68 (AA'XX', *J* = 9.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 15.5, 17.1, 55.2, 55.3, 63.4, 68.9, 70.2, 113.80, 113.84, 114.4, 120.0, 123.7, 126.2, 126.7, 129.1, 131.3, 133.4, 140.8, 150.2, 158.17, 158.21, 159.1; exact mass calcd. for $C_{28}H_{30}N_2O_5$ *m/e* 474.2155 found *m/e* 474.2147.

3-{4-[4-Ethyl-2,5-bis-(4-methoxyphenyl)-2*H*-pyrazol-3-yl]-phenoxy}-propane-1,2-diol (41): The demethylation was carried out as describe above, chromatographed over a

1 x 10 cm silica gel column (eluted with MeOH:CH_2Cl_2, 1:20 followed by 1:10) to give 44.0 mg (76%) of a white solid as the desired product **41**: ^{1}H NMR (CD_3OD, 500 MHz) δ 0.92 (br s, 3H, CH_3), 2.54 (br s, 2H, C<u>H</u>$_2$CH$_3$), 3.58 (m, 2H, C<u>H</u>$_2$OH), 3.80 (m, 2H, C<u>H</u>$_2$O), 3.96 (m, 1H, CHOH), 6.62 (br s 2H, ArH), 6.82 (m, 4H, ArH), 7.08 (m, 4H, ArH), 7.42 (br s, 2H, ArH), the two hydroxy protons and the two phenolic protons were not observed; ^{13}C NMR (CD_3OD, 125.7 MHz) δ 14.8, 17.5, 63.9, 70.4, 71.5, 116.1, 117.2, 117.3, 118.7, 119.6, 122.1, 127.0, 129.8, 131.1, 132.7, 147.9, 148.3, 161.0, 161.3, 161.9; exact mass calcd. for $C_{26}H_{26}N_2O_5$ *m/e* 446.1842, found *m/e* 446.1839