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FACILE SYNTHESIS OF HIGH AFFINITY STYRYLPYRIDINE SYSTEMS AS INHERENTLY FLUORESCENT LIGANDS FOR THE ESTROGEN RECEPTOR

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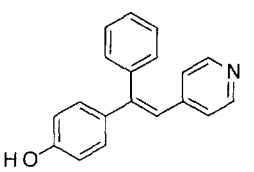
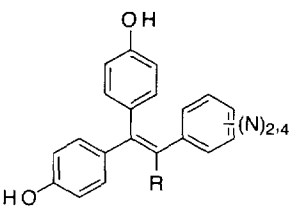
Abstract: A series of styrylpyridine derivatives containing two phenols was prepared via an efficient two-step synthesis. These compounds were designed to maximize the estrogen receptor binding affinity of a known series of inherently fluorescent styrylpyridines. While significant improvements were achieved in receptor affinity, the fluorescence intensity of this series of compounds is poor.

In our efforts to develop high affinity ligands for the estrogen receptor (ER), which serve as probes for receptor structure and function, we have prepared inherently fluorescent ligands. Such probes could be used to assay the binding of other ER ligands and to measure ER levels; potentially they could be used to identify ER-positive breast cancers, measuring the ER content of individual cells using flow cytometry[1] or fluorescence microscopy.[2] To be useful in this last application,[3–5] a probe must exhibit a high relative binding affinity (RBA) for the ER, fluorescence at wavelengths greater than 500 nm (in order to be distinguishable from cell autofluorescence), high quantum yield, and, ideally, an enhanced fluorescence when bound to the receptor.

Recently, we have shown derivatives of 2- and 4-styrylpyridines to be promising inherently fluorescent ligands with substantial affinity for the ER.[6,7] Lead compound **1** exhibits desirable fluorescence characteristics and high sensitivity to solvent polarity and pH, due to the donor-acceptor character provided by the nitrogen and hydroxyl functionalities.[7] This makes this series potentially useful as biological probes, since changes in spectral characteristics may be observed due to the interaction of the fluorophore with a biological molecule or to a change in the structure or environment of the receptor to which it is bound.[8,9] Since **1** has only a modest binding affinity for the ER (5.4% relative to estradiol),[7] we have prepared a series of 4'-hydroxyl analogs of **1**.[10] Compounds **2a–f** were envisioned to have higher RBAs than **1**, due to the 4'-hydroxyl substitution and increased alkyl bulk in the vinylic-position.



1



2a N-4 R = H **2d** N-2 R = H
2b N-4 R = Me **2e** N-2 R = Me
2c N-4 R = Et **2f** N-2 R = Et

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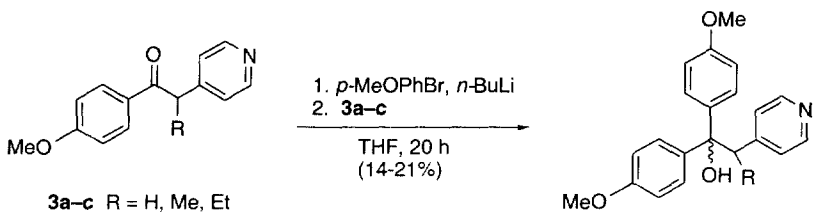
Synthesis

The initial synthetic strategy employed paralleled our previous work, in which an appropriate ketone precursor (**3a–c**) was treated with an aryl lithium reagent (Scheme 1).[7] The ketone precursor was prepared as previously described.[7] However, the addition of the aryl lithium reagent proceeded only in very low yields, probably due to competing enolization of the activated, sterically hindered ketone.[7] Other attempts to avoid enolization by converting ketone **3c** to the vinyl triflate,[11] followed by Suzuki, organozinc, and Stille coupling methodologies, were unsuccessful.

Scheme 1

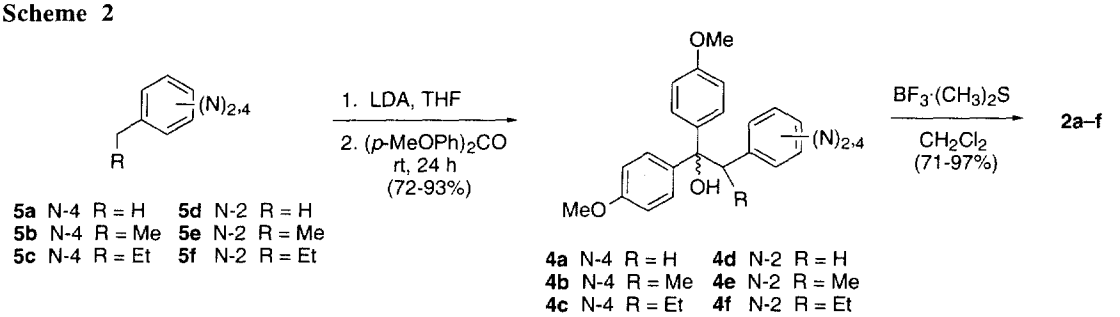


3a–c R = H, Me, Et

4a–c R = H, Me, Et

A much simpler and more efficient strategy, which took advantage of the symmetric nature of the targeted compounds, proved to be quite satisfactory (Scheme 2). The picoline anions generated from the appropriate commercially available alkylpyridines (**5a–f**) were successfully added to 4,4'-dimethoxybenzophenone to generate alcohols **4a–f** in excellent yield. Deprotection and dehydration was effected in a single step with boron trifluoride dimethyl sulfide complex in CH_2Cl_2 to give the desired products **2a–f** in excellent yields.

Scheme 2



5a N-4 R = H **5d** N-2 R = H
5b N-4 R = Me **5e** N-2 R = Me
5c N-4 R = Et **5f** N-2 R = Et

4a N-4 R = H **4d** N-2 R = H
4b N-4 R = Me **4e** N-2 R = Me
4c N-4 R = Et **4f** N-2 R = Et

Receptor Binding

The ER relative binding affinity (RBA)[12,13] of styrylpyridines **2a–f** is summarized in Table 1. As expected, the RBAs are better than for **1**. In general, an increase in RBA is observed as the alkyl steric bulk is increased, although for **2f** a small decrease is noted. Positioning of the nitrogen in the 4-position gives ligands having RBA values two to four times greater on average than those with the nitrogen in the 2-position. This may be due to rotational and steric factors or the ability of the nitrogen to participate in hydrogen bonding with residues

within the receptor binding pocket.[14] The binding affinities of the methyl- and ethyl- substituted compounds **2b** and **2c** are similar to that of estradiol itself.

Table 1. Relative Binding Affinity of Styrylpyridines for the ER

Compound	Position of N	R	RBA[a]
Estradiol	-	-	100
2a	4	H	20 ± 4
2b	4	Me	80 ± 5
2c	4	Et	81 ± 30
2d	2	H	7 ± 2
2e	2	Me	30 ± 1
2f	2	Et	21 ± 4

[a]RBAs determined relative to estradiol-17β in a competitive radiometric assay using lamb uterine cytosol at 0 °C.[12]

Spectroscopic Characterization

The wavelengths of maximum UV absorbance and fluorescence emission in a variety of solvents and at various pH for the highest affinity styrylpyridine (**2c**) are recorded in Table 2. As previously reported for simpler styrylpyridines,[6,7] an emission red-shift is observed in both acidic and basic conditions relative to neutrality. Compound **2c** does not appear to exhibit the increased red-shift expected for increasing solvent polarity, however.[6] The position of the fluorescence emission band under most conditions is greater than the 500 nm required, sufficiently red-shifted to avoid cell autofluorescence. However, the emission intensities of all the ligands are extremely weak, especially in water. This is thought to be due to the aryl and pyridyl rings being twisted out of the plane of the chromophore into the propeller-like conformation found in tamoxifen.[15] This was confirmed by molecular modeling using SPARTAN.

Table 2. UV Absorbance and Fluorescence Characteristics of Styrylpyridine 2c

Solvent[a]	Conditions[b]	λ_{max} absorbance (nm)	λ_{max} emission(nm)
THF	neutral	350	483
	acidic	388	516
	basic	306	-
CH_3CN	neutral	384	512
	acidic	382	526
	basic	368	544
EtOH	neutral	312	431
	acidic	396	517
	basic	366	566
H_2O	neutral	300	420/512
	acidic	368	425
	basic	350	-

[a]Samples prepared from EtOH stock solution (1 x 10^{-3} M) diluted with the appropriate solvent to 1 x 10^{-5} M. [b]Acidic solutions prepared by adding 6 M HCl to make 0.1 N HCl; basic solutions prepared by adding 6 M KOH to make 0.1 N KOH.

Compounds **2c** and **2e** were chosen for ER binding fluorescence studies on the basis of their high binding affinities within the respective 2- and 4-styrylpyridine classes. By comparing the fluorescence of the ligands (100 nM to 5000 nM) in buffer (50 mM tris, 10% glycerol, pH 7.5) with their fluorescence after being allowed to bind ER (100 nM) in buffer, it was found that the maximum excitation and emission are essentially the same regardless of whether the ligands were bound to the ER or not.[16] However, the fluorescence intensity is

three and a half to four times greater when the ligands are bound to the receptor rather than free. This may be due to the protein limiting the rotation of the aryl and pyridyl rings when the compound is bound. There is very little difference in fluorescence characteristics for the 2-N versus the 4-N compounds. Unfortunately, the intensity of the bound ligands was approximately 1000 times lower than the fluorescent tetrahydrochrysene class of ER ligands we have previously described.[3,5] Thus, further characterization of the fluorescence of this class of compounds is not being pursued.

Conclusions

The styrylpyridine series described was synthesized utilizing an efficient two-step route. Although many of the styrylpyridine compounds have very good binding affinities for the ER and exhibit desirable fluorescence characteristics, the intensity of their fluorescence is inadequate. Molecular modeling suggests that this may be due to the increased bulk contributed by the alkyl side chain, which subsequently shifts the pyridyl and aryl rings out of the plane of the chromophore.

Experimental Procedure

General Procedure for Alkylpyridine Additions. LDA (1.1 equiv) was prepared from the dropwise addition of *n*-butyllithium (1.0 equiv) to a stirred solution of diisopropylamine (1.1 equiv) in THF (0.3 M) at -78 °C. The solution was stirred for 10 min, allowed to warm to room temperature for 25 min, then cooled back to -78 °C. The appropriate alkylpyridine (1.0 equiv) was added dropwise and the solution stirred an additional 45 min at -78 °C before warming to 0 °C for 25 min. A solution of 4,4'-dimethoxybenzophenone (1.0 equiv) in THF (0.2 M) was added dropwise and the solution stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl and extracted repeatedly with EtOAc. The combined organic layers were washed with water and brine. Subsequent drying over Na_2SO_4, concentration under reduced pressure, and recrystallization (benzene/pentane) or flash chromatography (5% MeOH/CH_2Cl_2) yielded products **4a–f** in 72–93% yield.

1,1'-Bis(4-methoxyphenyl)-2-(4-pyridyl)ethanol (4a). mp 161–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 ppm (bs, 1H), 3.52 (bs, 2H), 3.78 (s, 6H), 6.81 (m, 6H), 7.25 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.6 Hz, 4H), 8.25 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.7 ppm, 55.2, 77.4, 113.3, 126.3, 127.4, 138.5, 146.6, 148.4, 158.5; MS (CI, 130 eV) *m/z* 336 (M + H^+). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.08; H, 6.26; N, 4.18.

1,1'-Bis(4-methoxyphenyl)-2-(4-pyridyl)propanol (4b). mp 156.5–158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (d, J = 7.1 Hz, 3H), 2.69 (bs, 1H), 3.69 (s, 3H), 3.80 (s, 3H), 3.81 (q, J = 6.9 Hz, 1H), 6.64 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.7 Hz, 2H), 6.88 (AA'XX', J_{AX} = 8.9 Hz, $J_{AA'}$ = 2.7 Hz, 2H), 7.01 (d, J = 6.3 Hz, 2H), 7.09 (AA'XX', J_{AX} = 8.9 Hz, $J_{AA'}$ = 2.7 Hz, 2H), 7.44 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.7 Hz, 2H), 8.29 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 47.7, 55.1, 55.2, 79.8, 113.0, 113.5, 125.1, 126.9, 127.4, 137.7, 138.1, 148.3, 152.5, 157.9, 158.3; MS (CI, 130 eV) *m/z* 350 (M + H^+). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.80; H, 6.67; N, 4.00.

1,1'-Bis(4-methoxyphenyl)-2-(4-pyridyl)butanol (4c). mp 163–165 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (t, J = 7.3 Hz, 3H), 1.78 (ddq, J = 13.7, 11.5, 7.3 Hz, 1H), 1.87 (dqd, J = 13.6, 7.6, 2.7 Hz, 1H), 2.50 (bs, 1H), 3.46 (dd, J = 11.5, 2.7 Hz, 1H), 3.68 (s, 3H), 3.81 (s, 3H), 6.61 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.6 Hz, 2H), 6.89 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.6 Hz, 2H), 7.02 (d, J = 6.3 Hz, 2H), 7.04 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.7 Hz, 2H), 7.41 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.7 Hz, 2H), 8.31 (d, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 23.3, 55.1, 55.2, 56.3, 80.2, 113.1, 113.6, 125.8, 126.8, 127.4, 137.9, 138.2, 148.5, 150.6, 157.9, 158.5; MS (CI, 130 eV) *m/z* 364 (M + H^+). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 75.69; H, 6.88; N, 3.88.

1,1'-Bis(4-methoxyphenyl)-2-(2-pyridyl)ethanol (4d). mp 106–107 °C (lit. mp 111–112 °C)[17]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (bs, 2H), 3.74 (s, 6H), 6.77 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.6 Hz, 4H), 7.03 (d, J = 7.7 Hz, 1H), 7.06 (ddd, J = 7.6, 5.0, 1.2 Hz, 1H), 7.34 (AA'XX', J_{AX} = 9.1 Hz, $J_{AA'}$ = 2.6 Hz, 4H), 7.53 (td, J = 7.7, 1.8 Hz, 1H), 8.39 (ddd, J =^4.9, 1.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.3, 55.1, 77.9, 113.1, 121.5, 124.7, 127.4, 137.0, 139.7, 148, 158.0, 159.4; MS (CI, 130 eV) *m/z* 336 (M + H^+). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 74.83; H, 6.25; N, 3.93.

1,1'-Bis(4-methoxyphenyl)-2-(2-pyridyl)propanol (4e). mp 126–128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, J = 6.9 Hz, 3H), 3.64 (s, 3H), 3.76 (s, 3H), 3.91 (q, J = 6.9 Hz, 1H), 6.61 (AA'XX', J_{AX} = 8.8 Hz, $J_{AA'}$ = 2.6 Hz, 2H), 6.84 (AA'XX', J_{AX} = 8.7 Hz, $J_{AA'}$ = 2.6 Hz, 2H), 6.99 (ddd, J = 7.6, 5.0, 0.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.35 (AA'XX', J_{AX} = 8.4 Hz, $J_{AA'}$ = 2.5

Hz, 2H), 7.43 (bs, 1H), 7.50 (AA'XX', J_{AX} = 8.4 Hz, $J_{AA'}$ = 2.5 Hz, 2H), 7.51 (td, J = 7.4, 1.9 Hz, 1H), 8.32 (ddd, J = 4.9, 1.8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 47.4, 54.9, 55.1, 79.4, 112.9, 113.2, 121.1, 124.0, 126.6, 126.9, 136.9, 139.0, 141.1, 148.0, 157.3, 157.7, 165.1; MS (CI, 130 eV) *m/z* 350 (M + H$^+$). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.63; H, 6.64; N, 4.08.

1,1'-Bis(4-methoxyphenyl)-2-(2-pyridyl)butanol (4f). mp 133–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.67 (t, J = 7.5 Hz, 3H), 1.72 (dqd, J = 13.8, 7.6, 3.0 Hz, 1H), 1.91 (ddq, J = 14.1, 11.0, 7.4 Hz, 1H), 3.58 (dd, J = 10.9, 2.9 Hz, 1H), 3.62 (s, 3H), 3.76 (s, 3H), 6.59 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.6 Hz, 2H), 6.85 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.6 Hz, 2H), 6.99 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.05 (dt, J = 7.8, 1.0 Hz, 1H), 7.31 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.6 Hz, 2H), 7.40 (bs, 1H), 7.47 (td, J = 7.7, 1.8 Hz, 1H), 7.53 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.6 Hz, 2H), 8.37 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 23.7, 54.9, 55.1, 55.3, 79.7, 112.9, 113.3, 121.3, 125.9, 126.5, 126.7, 136.1, 139.2, 141.2, 148.2, 157.2, 157.7, 163.0; MS (CI, 130 eV) *m/z* 364 (M + H$^+$). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 75.91; H, 6.86; N, 3.84.

General Procedure for Dehydrations and Deprotections. A solution of the appropriate alcohol (1 equiv) in CH_2Cl_2 (0.25 M) was cooled to 0 °C. Boron trifluoride dimethyl sulfide complex (50 equiv) was added dropwise to the stirring solution. After stirring overnight at room temperature, the dimethyl sulfide was removed with a steady stream of nitrogen for several hours, followed by quenching with water and the addition of EtOAc. Saturated $NaHCO_3$ was added carefully until the solution was neutralized. The solution was partitioned between water and EtOAc and the aqueous layer was extracted repeatedly with EtOAc. Combined organic layers were washed with water, brine, and Celite and then dried over Na_2SO_4. Concentration under reduced pressure and purification by flash chromatography (20% MeOH/CH_2Cl_2) and recrystallization (MeOH) yielded final products **2a–f** in 71–97% yield.

1,1'-Bis(4-hydroxyphenyl)-2-(4-pyridyl)ethene (2a). mp 141–144 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 6.74 (AA'XX', J_{AX} = 8.6 Hz, $J_{AA'}$ = 2.5 Hz, 2H), 6.78 (s, 1H), 6.79 (AA'XX', J_{AX} = 8.6 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 6.95 (AA'XX', J_{AX} = 8.6 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 6.97 (d, J = 6.6 Hz, 2H), 7.19 (AA'XX', J_{AX} = 8.7 Hz, $J_{AA'}$ = 2.5 Hz, 2H), 8.20 (d, J = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 115.2, 115.8, 121.7, 123.3, 128.9, 129.7, 130.8, 132.9, 145.0, 146.4, 149.3, 157.3, 157.9; MS (EI, 70 eV) *m/z* 289 (M$^+$). HRMS calcd for $C_{19}H_{15}NO_2$: 289.1103, found 289.1102.

1,1'-Bis(4-hydroxyphenyl)-2-(4-pyridyl)propene (2b). mp 298–299 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.07 (s, 3H), 6.48 (AA'XX', J_{AX} = 8.6 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 6.64 (AA'XX', J_{AX} = 8.6 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 6.77 (AA'XX', J_{AX} = 8.6 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 7.00 (AA'XX', J_{AX} = 8.6 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 7.09 (d, J = 6.2 Hz, 2H), 8.34 (d, J = 6.1 Hz, 2H), 9.33 (bs, 1H), 9.50 (bs, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 22.3, 114.6, 114.9, 124.2, 130.4, 130.8, 131.6, 133.1, 133.3, 140.9, 149.2, 152.2, 155.9, 156.4; MS (EI, 70 eV) *m/z* 303 (M$^+$). HRMS calcd for $C_{20}H_{17}NO_2$: 303.1259, found 303.1258.

1,1'-Bis(4-hydroxyphenyl)-2-(4-pyridyl)butene (2c). mp 259–261 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.87 (t, J = 7.4 Hz, 3H), 2.45 (q, J = 7.4 Hz, 2H), 6.47 (AA'XX', J_{AX} = 8.7 Hz, $J_{AA'}$ = 2.3 Hz, 2H), 6.64 (AA'XX', J_{AX} = 8.6 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 6.78 (AA'XX', J_{AX} = 8.6 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 7.00 (AA'XX', J_{AX} = 8.5 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 7.08 (d, J = 6.0 Hz, 2H), 8.36 (d, J = 6.1 Hz, 2H), 9.30 (s, 1H), 9.50 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.3, 27.8, 114.5, 115.0, 124.7, 130.1, 131.5, 133.1, 133.4, 137.0, 140.4, 149.2, 150.7, 155.8, 156.4; MS (EI, 70 eV) *m/z* 317 (M$^+$). Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.39; H, 6.04; N, 4.40.

1,1'-Bis(4-hydroxyphenyl)-2-(2-pyridyl)ethene (2d). mp 234–236 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 6.75 (AA'XX', J_{AX} = 9.0 Hz, $J_{AA'}$ = 2.5 Hz, 2H), 6.76 (AA'XX', J_{AX} = 8.8 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 6.78 (m, 1H), 6.88 (s, 1H), 6.95 (AA'XX', J_{AX} = 8.6 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 7.08 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H), 7.19 (AA'XX', J_{AX} = 8.9 Hz, $J_{AA'}$ = 2.5 Hz, 2H), 7.42 (td, J = 7.8, 1.9 Hz, 1H), 8.41 (ddd, J = 5.1, 1.8, 1.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 115.2, 115.7, 120.9, 122.8, 125.3, 128.7, 130.0, 130.8, 133.2, 135.3, 145.0, 149.1, 156.6, 157.1, 157.7; MS (EI, 70 eV) *m/z* 289 (M$^+$). HRMS calcd for $C_{19}H_{15}NO_2$: 289.1103, found 289.1102.

1,1'-Bis(4-hydroxyphenyl)-2-(2-pyridyl)propene (2e). mp 271 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.11 (s, 3H), 6.44 (d, J = 8.5 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.6 Hz, 2H), 6.76 (dd, J = 7.9, 0.8 Hz, 1H), 6.98 (d, J = 8.4 Hz, 2H), 7.05 (dd, J = 7.4, 4.9 Hz, 1H), 7.39 (td, J = 7.7, 1.6 Hz, 1H), 8.50 (dt, J = 4.9, 0.8 Hz, 1H), 9.26 (s, 1H), 9.45 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.4, 114.5, 114.8, 120.9, 125.1, 130.9, 131.5, 133.2, 133.6, 135.4, 140.4, 148.7, 155.8, 156.2, 162.1; MS (EI, 70 eV) *m/z* 303 (M$^+$). HRMS calcd for $C_{20}H_{17}NO_2$: 303.1259, found 303.1258.

1,1'-Bis(4-hydroxyphenyl)-2-(2-pyridyl)butene (2f). mp 205.5–206.5 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.82 (t, J = 7.4 Hz, 3H), 2.53 (q, J = 7.4 Hz, 2H), 6.42 (AA'XX', J_{AX} = 8.7 Hz, $J_{AA'}$ = 2.5 Hz, 2H), 6.55 (AA'XX', J_{AX} = 8.7 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 6.74 (AA'XX', J_{AX} = 8.5 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 6.76 (d, J = 7.9 Hz, 1H), 6.98 (AA'XX', J_{AX} = 8.6 Hz, $J_{AA'}$ = 2.4 Hz, 2H), 7.06 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 7.40 (td, J = 7.7, 1.8 Hz, 1H), 8.51 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 9.24 (s, 1H), 9.44 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.5, 27.1, 114.5, 114.9, 121.0, 126.1, 130.2, 131.4, 133.6, 133.7, 135.3, 139.7, 139.9, 148.8, 155.8, 156.3, 160.8; MS (EI, 70 eV) *m/z* 317 (M$^+$). Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.09; H, 6.08; N, 4.29.

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References and Notes

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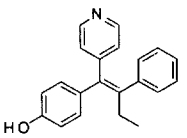

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