Photochemical Synthesis of Cyclophanes Containing Tethered Benzofuran Rings

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The design and synthesis of macrocyclic compounds attract current interest in view of supramolecular chemistry.[1] In particular, cyclophanes, macrocycles containing aromatic groups, represent the central class of synthetic receptors in molecular recognition because of the hydrophobicity and π-stacking interactions of their aromatic groups.[2] Recently, we prepared a novel class of cyclophane containing two benzo[*b*]furan rings, **1a**, based upon the photocyclization reaction via intramolecular δ-hydrogen abstraction.[3] X-ray analysis of **1a** has shown that it has a rectangular cavity,[3] rendering this cyclophane as an attractive candidate for a synthetic receptor. Thus, efficient preparation of this novel type of cyclophane with various tethering groups and functionalities would be interesting not only because it widens a pool of artificial receptors but also because it broadens photochemical synthetic applications. Here, we report the facile synthetic procedure for the cyclophanes containing two benzo[*b*]furan rings connected by various tethering groups, **1a**−**f** (Scheme 1).

Reaction of 2,4-dihydroxybenzophenone, **2**, with a 0.60 molar ratio of α,ω-dihaloalkane (X−R−X) in acetone at room temperature in the presence of potassium carbonate afforded the products **3**−**6** with ca. 80% yield, which indicates that the alkylation occurs exclusively at the *p*-hydroxyl group of **2**. Further reaction of α,ω-bis(4-benzoyl-3-hydroxyphenoxy)alkanes **3**−**6** with a slight molar excess of α,ω-dihaloalkane (X−R′−X) in acetone at reflux or in DMF at 80−90 °C in the presence of potassium carbonate gave the macrocycles **7a**−**f** with 30−40% yield. The differential reactivity between the two hydroxyl groups in 2,4-dihydroxybenzophenone, **2**, seems to arise from less reactivity of the *o*-hydroxyl group because of its hydrogen bonding to the carbonyl, which enables us to introduce a desired tethering group selectively at the ortho or para position of **2**. Similar selective alkylation of the non-hydrogen-bonded phenolic hydroxyl groups has been reported;[4,5] the 3-OH and 6-OH positions of 1,3,6,8-tetrahydroxyanthraquinone[4] or the 3-OH position of 1,3-dihydroxyacridone[5] was selectively alkylated.

It is well-known that *o*-alkoxybenzophenones photocyclize readily to benzofuranols via intramolecular δ-hydrogen abstraction.[6,7] The photocyclization of two *o*-alkoxybenzophenone moieties of **7a**−**f** followed by dehydration produced a novel type of cyclophane containing two benzo[*b*]furan rings, **1a**−**f**. A 1 mM benzene[8] solution of **7a**−**f** was irradiated under nitrogen with a 350 nm mercury lamp using a RPR-100 photochemical reactor in a Pyrex glass vessel. After 6−7 h of irradiation, the reaction mixture showed virtually no starting material remaining. Because so many stereoisomers are possible for the dihydrobenzofuranol derivatives **8a**−**f**, a dehydration reaction was carried out, without attempting the isolation and separation of the intermediates, by treating the concentrated reaction mixture with a few drops of 1 M HCl in acetone or DMF. Silica gel column chromatography afforded the desired cyclophanes with 20−58% yields. The results are summarized in Table 1. A lower concentration of **7a** in the photocyclization reaction gave a better yield of **1a**; the yields in 16 mM, 10 mM, and 1 mM benzene solution were 21%,[3] 25%, and 50%, respectively.

The structure of the cyclophanes **1a**−**f** was characterized by ^{1}H and ^{13}C NMR spectrometry and elemental analysis. The number of ^{1}H and ^{13}C NMR peaks confirmed the symmetrical nature of the compounds **1a**−**f**. The numbers of the peaks observed in their ^{13}C NMR spectra are included in Table 1, and they exactly match with the expected numbers based on 2-fold symmetry of the compounds except for **1e** having one less peak because of overlapping. The structure of **1a** was further determined by single-crystal X-ray analysis;[3] the cyclophane has 2-fold symmetry along the *b*-axis, the dihedral angle between a benzofuran ring and the benzene ring of *p*-xylyl group is 85.9°, and the two benzofuran rings are almost parallel to each other with a dihedral angle of 171.8°, making the molecule form a rectangular cavity.

In summary, we have developed a general facile route for a novel type of cyclophane, **1a**−**f**, having two benzo[*b*]furan rings connected through various tethering groups by photocyclization of the macrocycles **7a**−**f** followed by a dehydration reaction. Macrocycles **7a**−**f** were prepared by utilizing differential reactivity between two hydroxyl groups in 2,4-dihydroxybenzophenone; the first alkylation occurs selectively at the *p*-hydroxyl group at room temperature, and the second alkylation proceeds at the *o*-hydroxyl group at higher temperature.

Experimental Section

All reagents were purchased from Aldrich Chemical Co. and used as received. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained at 200/50 or 400/100 MHz using tetramethylsilane as an internal standard. High-field NMR

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(8) Benzene is a toxic solvent and should be handled with appropriate care. Using toluene instead of benzene lowered the yields.

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Scheme 1

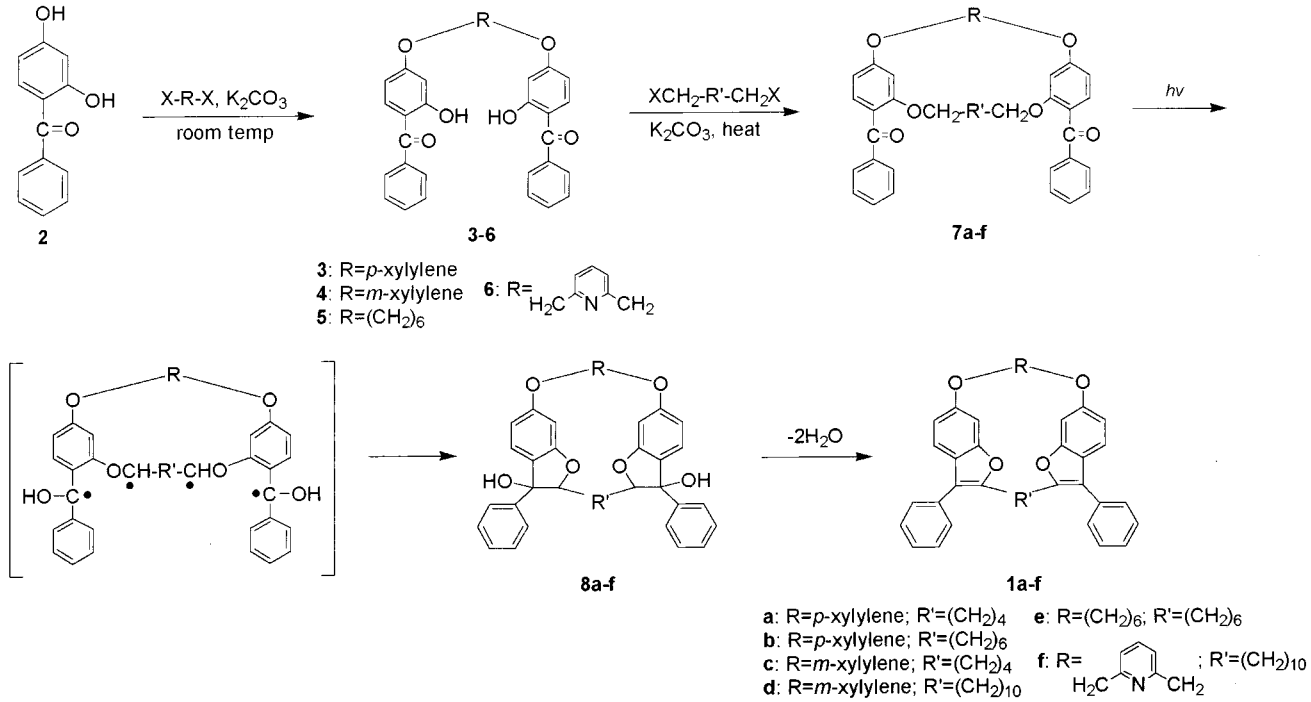
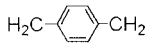
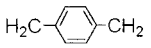
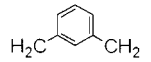
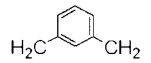
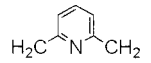


Table 1. Synthesis of Cyclophanes 1a−f by Photoirradiation[a] of 7a−f Followed by Dehydration[b]

Entry	Starting material	R	R'	Product	Yield %	mp °C	# of ^{13}C NMR peaks[c]
1	**7a**		$(CH_2)_4$	**1a**	50 (16.25)[d]	271[e]	17
2	**7b**		$(CH_2)_6$	**1b**	40	214-216	18
3	**7c**		$(CH_2)_4$	**1c**	55	210	19
4	**7d**		$(CH_2)_{10}$	**1d**	58	124-126	22
5	**7e**	$(CH_2)_6$	$(CH_2)_6$	**1e**	32	134-136	17
6	**7f**		$(CH_2)_{10}$	**1f**	20	179	21

[a] A 1 mM benzene solution of **7** was photoirradiated. [b] Acetone (entries 1−5) or DMF (entry 6) was used as a solvent for dehydration. [c] They exactly match with the expected numbers based on 2-fold symmetry of **1** except for **1e** having one less peak because of overlapping. [d] The yields obtained from 16 mM (ref 3) and 10 mM benzene solution are 16% and 25%, respectively. [e] Reference 3.

measurements and elemental analyses were performed at the Central Research Facilities of Chungnam National University.

General Procedure for the Synthesis of α,ω-Bis(4-benzoyl-3-hydroxyphenoxy)alkanes, 3−6. The procedure described for 1,4-bis(4-benzoyl-3-hydroxyphenoxymethyl)benzene[3] was followed with slight modification. An acetone solution (30 mL) of the corresponding α,ω-dihaloakane (5.60 mmol; α,α′-dibromo-*p*-xylene, α,α′-dibromo-*m*-xylene, 1,6-diiodohexane, or 2,6-bis(bromomethyl)pyridine) was added slowly to a mixture of 2,4-dihydroxybenzophenone (2.00 g, 9.34 mmol) and potassium carbonate (3.87 g, 28.0 mmol) in 50 mL of acetone, and the reaction mixture was stirred at room temperature for 25−70 h. After the reaction was complete, distilled water (200 mL) was added to dissolve the potassium carbonate. The remaining precipitate was filtered and washed with acetone to afford the corresponding α,ω-bis(4-benzoyl-3-hydroxyphenoxy)alkanes.

1,4-Bis(4-benzoyl-3-hydroxyphenoxymethyl)benzene, 3: yield, 87%; mp 175−176 °C (lit.[3] mp 175−176 °C).

1,3-Bis(4-benzoyl-3-hydroxyphenoxymethyl)benzene, 4: yield, 84%; mp 172−173 °C; ^{1}H NMR (DMSO-d_6) δ 5.23 (s, 4H, −O*CH*$_2$−C$_6$H$_4$−*CH*$_2$O−), 6.55−6.7 (m, 4H, Ar−H ortho or para to −OH), 7.4−7.7 (m, 16H, Ar−H), 11.99 (br s, 2H, Ar−OH).

1,6-Bis(4-benzoyl-3-hydroxyphenoxy)hexane, 5: yield, 79%; mp 148−149 °C; ^{1}H NMR ($CDCl_3$) δ 1.35−2.0 (m, 8H, −OCH$_2$(*CH*$_2$)$_4$CH$_2$O−), 3.96 (t, 4H, J = 6 Hz, −O*CH*$_2$(CH$_2$)$_4$-*CH*$_2$O−), 6.25−6.45 (m, 4H, Ar−H ortho or para to −OH), 7.3−7.65 (m, 12H, Ar−H), 12.59 (br s, 2H, Ar−OH).

2,6-Bis(4-benzoyl-3-hydroxyphenoxymethyl)pyridine, 6: yield, 79%; mp 173−174 °C; ^{1}H NMR ($CDCl_3$) δ 5.19 (s, 4H, −O*CH*$_2$−C$_5$H$_3$N-*CH*$_2$O−), 6.35−6.55 (m, 4H, Ar−H ortho or para to −OH), 7.3−7.8 (m, 15H, Ar−H), 12.52 (br s, 2H, Ar−OH).

General Procedure for the Synthesis of Macrocycles 7a−f. The procedure described for the macrocycle **7a**[3] was followed with slight modification. To the suspension of α,ω-bis-(4-benzoyl-3-hydroxyphenoxy)alkane (2.00 mmol) and potassium carbonate (1.66 g, 12.0 mmol) in acetone (200 mL) at reflux was added a solution of the corresponding α,ω-dihaloalkane (2.10 mmol; 1,6-diiodohexane, 1,8-diiodooctane, or 1,12-dibromododecane) in acetone (45 mL) very slowly, and reflux was continued

for 48−72 h. In the case of **7e**,**f**, DMF was used as a solvent instead of acetone and the mixture was heated at 80−90 °C for 16−70 h. When the α,ω-dihaloakane is dibromide, a catalytic amount of KI was added to the reaction mixture. After most of the starting material, α,ω-bis(4-benzoyl-3-hydroxyphenoxy)-alkane, was used up, potassium carbonate was removed by filtration, and the concentrated filtrate was purified by silica gel column chromatography eluting with dichloromethane and then 40:1 dichloromethane/ethyl acetate to give macrocycles **7a**−**f**.

7a: yield, 32%; mp 172 °C (lit.[3] mp 172 °C).

7b: yield, 30%; mp 170 °C; ^{1}H NMR ($CDCl_3$) δ 1.0−1.2 (m. 8H, $-O(CH_2)_2-(CH_2)_4-(CH_2)_2O-$), 1.38 (quintet, 4H, J = 7 Hz, $-OCH_2CH_2(CH_2)_4CH_2CH_2O-$), 3.67 (t, 4H, J = 7 Hz, $-OCH_2-(CH_2)_6-CH_2O-$), 5.19 (s, 4H, $-OCH_2-C_6H_4-CH_2O-$), 6.32 (d, 2H, J = 2 Hz, Ar−H ortho to $-O(CH_2)_8-$), 6.67 (dd, 2H, J = 8, 2 Hz, Ar−H para to $-O(CH_2)_8-$), 7.3−7.55 (m, 12H, Ar−H), 7.7−7.75 (m, 4H, Ar−H ortho to C═O in two benzoyl groups).

7c: yield, 40%; mp 124 °C; ^{1}H NMR ($CDCl_3$) δ 1.1−1.2 (m. 4H, $-O(CH_2)_2-(CH_2)_2-(CH_2)_2O-$), 1.4−1.55 (m, 4H, $-OCH_2CH_2-(CH_2)_2CH_2CH_2O-$), 3.83 (t, 4H, J = 7 Hz, $-OCH_2-(CH_2)_4-CH_2O-$), 5.20 (s, 4H, $-OCH_2-C_6H_4-CH_2O-$), 6.53 (d, 2H, J = 2 Hz, Ar−H ortho to $-O(CH_2)_6-$), 6.62 (dd, 2H, J = 8, 2 Hz, Ar−H para to $-O(CH_2)_6-$), 7.3−7.55 (m, 11H, Ar−H), 7.65 (s, 1H, Ar−H ortho to both CH_2- in the *m*-xylyl group), 7.72−7.76 (m, 4H, Ar−H ortho to C═O in two benzoyl groups).

7d: yield, 30%; mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 1.05−1.3 (m. 16H, $-O(CH_2)_2-(CH_2)_8-(CH_2)_2O-$), 1.43 (quintet, 4H, J = 7 Hz, $-OCH_2CH_2(CH_2)_8CH_2CH_2O-$), 3.84 (t, 4H, J = 7 Hz, $-OCH_2-(CH_2)_{10}-CH_2O-$), 5.15 (s, 4H, $-OCH_2-C_6H_4-CH_2O-$), 6.61 (d, 2H, J = 2 Hz, Ar−H ortho to $-O(CH_2)_{12}-$), 6.65 (dd, 2H, J = 8, 2 Hz, Ar−H para to $-O(CH_2)_{12}-$), 7.35−7.55 (m, 11H, Ar−H), 7.67 (s, 1H, Ar−H ortho to both CH_2- in the *m*-xylyl group), 7.74 (d, 4H, J = 7 Hz, Ar−H ortho to C═O in two benzoyl groups).

7e: yield, 33%; mp 123−125 °C; ^{1}H NMR ($CDCl_3$) δ 1.1−2.0 (m, 20H, $-OCH_2-(CH_2)_6-CH_2O-$ and $-OCH_2-(CH_2)_4-CH_2O-$), 3.83 (t, 4H, J = 7 Hz, $-OCH_2-(CH_2)_nCH_2O-$), 4.07 (t, 4H, J = 6 Hz, $-OCH_2-(CH_2)_nCH_2O-$), 6.47 (d, 2H, J = 2 Hz, Ar−H ortho to $-O(CH_2)_{12}-$), 6.56 (dd, 2H, J = 8, 2 Hz, Ar−H para to $-O(CH_2)_{12}-$), 7.3−7.55 (m, 8H, Ar−H), 7.71−7.76 (m, 4H, Ar−H ortho to C═O in two benzoyl groups).

7f: yield, 31%; mp 126−129 °C; ^{1}H NMR ($CDCl_3$) δ 1.05−1.25 (m, 16H, $-O(CH_2)_2-(CH_2)_8-(CH_2)_2O-$), 1.41 (quintet, 4H, J = 7 Hz, $-OCH_2CH_2(CH_2)_8CH_2CH_2O-$), 3.81 (t, 4H, J = 7 Hz, $-OCH_2-(CH_2)_{10}-CH_2O-$), 5.28 (s, 4H, $-OCH_2-C_5H_3N-CH_2O-$), 6.61 (d, 2H, J = 2 Hz, Ar−H ortho to $-O(CH_2)_{12}-$), 6.69 (dd, 2H, J = 8, 2 Hz, Ar−H para to $-O(CH_2)_{12}-$), 7.35−7.55 (m, 10H, Ar−H), 7.71−7.75 (m, 4H, Ar−H ortho to C═O in two benzoyl groups), 7.83 (t, 1H, J = 7 Hz, C_4−H of the pyridine ring).

General Procedure for the Synthesis of Benzofuran-Containing Cyclophanes, 1a−f. A 1 mM benzene[8] solution of macrocycle **7** (350 mL) contained in a Pyrex glass vessel was purged with nitrogen for 1 h and then irradiated under nitrogen with a 350 nm mercury lamp for 6−7 h using a RPR-100 photochemical reactor (Southern New England Ultraviolet Company). After the reaction was complete, the solvent was removed under reduced pressure, and the residue was dissolved in 10 mL of acetone. The acetone solution was treated with a few drops of 1 M HCl, stirred for 1 h, and then concentrated and subjected to silica gel column chromatography (eluent, 1:1 CH_2Cl_2/hexane) to afford the cyclophanes.

For the cyclophane **1f**, dehydration and workup procedures were modified. DMF was used instead of acetone as a solvent for dehydration; the residue obtained from the photoreaction was dissolved in DMF, treated with a few drops of 1 M HCl, stirred for 1 h, and then neutralized with 5% KOH aqueous solution. After removal of the solvent in vacuo, the residue was taken up in water and extracted with ethyl ether. The ether layer was purified by column chromatography (eluent: dichloromethane) to give **1f**.

Photoirradiation of a 10 mM benzene solution of **7a** followed by dehydration gave the product with 25% yield, much lower yield compared with 50% obtained with a 1 mM solution.

1a: yield, 50%; mp 271 °C (lit.[3] mp 271 °C).

1b: yield, 40%; mp 214−216 °C; ^{1}H NMR ($CDCl_3$) δ 1.1−1.3 (m, 4H, $-(CH_2)_2-(CH_2)_2-(CH_2)_2-$), 1.55−1.75 (m, 4H, $-CH_2CH_2-(CH_2)_2CH_2CH_2-$), 2.75 (t, 4H, J = 7 Hz, $-CH_2(CH_2)_4CH_2-$), 5.28 (s, 4H, $-OCH_2-C_6H_4-CH_2O-$), 6.70 (d, 2H, J = 2 Hz, C_7−H of benzofuran ring), 6.99 (dd, 2H, J = 9, 2 Hz, C_5−H of benzofuran ring), 7.3−7.5 (m, 16H, Ar−H); ^{13}C NMR δ 26.31, 27.25, 28.72, 69.13, 96.17, 113.35, 117.08, 119.76, 121.94, 126.35, 126.84, 128.64, 129.00, 132.93, 136.85, 153.69, 154.47, 155.65. Anal. Calcd for $C_{42}H_{36}O_4$: C, 83.42; H, 6.00. Found: C, 83.28; H, 6.17.

1c: yield, 55%; mp 210 °C; ^{1}H NMR ($CDCl_3$) δ 1.70 (br s, 4H, $-CH_2-(CH_2)_2-CH_2-$), 2.82 (br s, 4H, $-CH_2(CH_2)_2CH_2-$), 5.26 (s, 4H, $-OCH_2-C_6H_4-CH_2O-$), 6.70 (d, 2H, J = 2 Hz, C_7−H of benzofuran ring), 6.97 (dd, 2H, J = 8, 2 Hz, C_5−H of benzofuran ring), 7.3−7.5 (m, 16H, Ar−H); ^{13}C NMR δ 25.80, 26.27, 70.58, 97.26, 113.72, 117.12, 119.53, 122.40, 124.19, 125.54, 126.84, 128.64, 128.96, 129.49, 132.92, 138.55, 153.32, 154.57, 156.05. Anal. Calcd for $C_{40}H_{32}O_4$: C, 83.31; H, 5.59. Found: C, 83.41; H, 5.50.

1d: yield, 58%; mp 124−126 °C; ^{1}H NMR ($CDCl_3$) δ 1.15−1.35 (m, 12H, $-(CH_2)_2-(CH_2)_6-(CH_2)_2-$), 1.71 (quintet, 4H, J = 7 Hz, $-CH_2CH_2(CH_2)_6CH_2CH_2-$), 2.81 (t, 4H, J = 7 Hz, $-CH_2-(CH_2)_8-CH_2-$), 5.21 (s, 4H, $-OCH_2-C_6H_4-CH_2O-$), 6.92 (dd, 2H, J = 8, 2 Hz, C_5−H of benzofuran ring), 7.03 (d, 2H, J = 2 Hz, C_7−H of benzofuran ring), 7.3−7.5 (m, 16H, Ar−H); ^{13}C NMR δ 26.61, 28.20, 28.60, 28.81, 29.39, 70.34, 97.88, 111.84, 116.68, 119.48, 122.64, 125.39, 126.02, 126.84, 128.64, 128.80, 128.94, 132.98, 137.91, 154.38, 154.69, 156.37. Anal. Calcd for $C_{46}H_{44}O_4$: C, 83.60; H, 6.71. Found: C, 83.81; H, 6.67.

1e: yield, 32%; mp 134−136 °C; ^{1}H NMR ($CDCl_3$) δ 1.3−1.4 (m, 4H, $-(CH_2)_2-(CH_2)_2-(CH_2)_2-$), 1.5−1.6 (m, 4H, $-O(CH_2)_2-(CH_2)_2-(CH_2)_2O-$), 1.75−1.85 (m, 8H, two $-CH_2-CH_2-(CH_2)_2-CH_2-CH_2-$), 2.81 (t, 4H, J = 7 Hz, $-CH_2-(CH_2)_4-CH_2-$), 4.09 (t, 4H, $-OCH_2-(CH_2)_4-CH_2O-$), 6.85 (dd, 2H, J = 8, 2 Hz, C_5−H of benzofuran ring), 7.02 (d, 2H, J = 2 Hz, C_7−H of benzofuran ring), 7.3−7.5 (m, 12H, Ar−H); ^{13}C NMR δ 24.93, 26.20, 27.15, 28.09, 68.35, 97.67, 111.57, 116.74, 119.39, 122.30, 126.81, 128.64, 128.95, 133.06, 154.00, 154.86, 156.62. Anal. Calcd for $C_{40}H_{40}O_4$: C, 82.16; H, 6.89. Found: C, 82.32; H, 6.96.

1f: yield, 20%; mp 179 °C; ^{1}H NMR ($CDCl_3$) δ 1.2−1.4 (m. 12H, $-(CH_2)_2-(CH_2)_6-(CH_2)_2$), 1.73 (quintet, 4H, J = 7 Hz, $-CH_2CH_2-(CH_2)_6-CH_2CH_2-$), 2.79 (t, 4H, J = 7 Hz, $-CH_2-(CH_2)_8-CH_2-$), 5.38 (s, 4H, $-OCH_2-C_5H_3N-CH_2O-$), 7.02 (dd, 2H, J = 8, 2 Hz, C_5−H of benzofuran ring), 7.06 (d, 2H, J = 2 Hz, C_7−H of benzofuran ring), 7.3−7.5 (m, 14H, Ar−H), 7.63 (t, 1H, J = 8 Hz, C_4−H of the pyridine ring); ^{13}C NMR δ 26.78, 28.32, 28.55, 28.71, 29.07, 71.23, 96.73, 113.20, 116.48, 119.64, 119.75, 122.52, 126.89, 128.71, 128.93, 132.96, 137.61, 154.47, 154.64, 156.19, 157.39. Anal. Calcd for $C_{45}H_{43}NO_4$: C, 81.67; H, 6.55; N, 2.12. Found: C, 81.53; H, 6.58; N, 2.31.

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