Convergent Synthesis of 1,1′-Biisoquinolines Tethered to Calamitic Subunits

Elisabeth Kapatsina, Marie Lordon, Angelika Baro, Sabine Laschat*

Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany
E-mail: sabine.laschat@oc.uni-stuttgart.de

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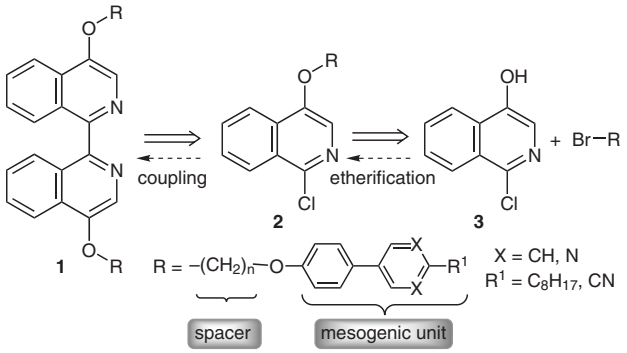
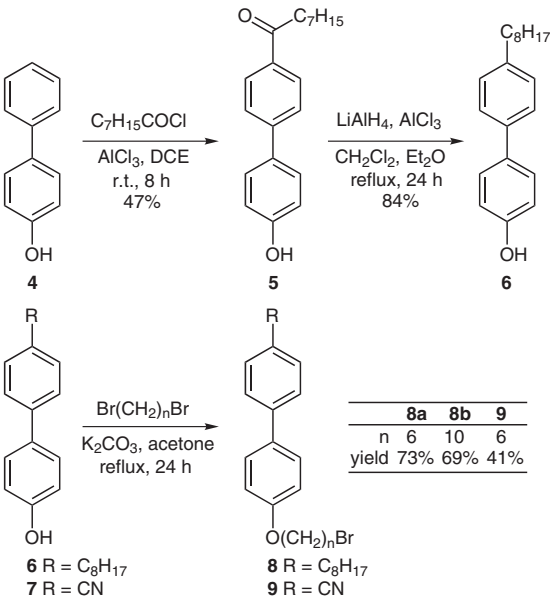
Abstract: A convergent synthesis of a series of 4,4′-functionalized 1,1′-biisoquinolines via 1-chloro-4-hydroxyisoquinoline and substituted biphenyl- and phenylpyrimidine ethers as building blocks is described. The latter were prepared by Williamson etherification of the respective 4-hydroxybiphenyl and -phenylpyrimidine precursors with dibromoalkanes, allowing variation of the spacer lengths. 1-Chloro-4-hydroxyisoquinoline was obtained from *N*-phthalimidoglycine ethyl ester through a Gabriel–Colman reaction as a key step. Linkage of the building blocks by etherification in the presence of potassium carbonate gave the isoquinolines, which were submitted to a nickel(II) chloride mediated homocoupling to yield the ligand systems.

Key words: biisoquinolines, biphenyls, ligands, homocoupling, Williamson etherification

Metallomesogens, that is, metal-containing thermotropic liquid crystals, have gained increasing interest because they combine the unique properties of transition-metal complexes (redox reactivity, luminescence and magnetism) with those of liquid crystals such as anisotropy of physical properties, self-aggregation and orientation in electric and magnetic fields.[1] Pyridines, bipyridines and phenanthrolines are widespread coordinating ligands in such metallomesogens. The corresponding biisoquinolines,[2] however, have only been rarely employed for this purpose although they might offer access to helically twisted metal complexes.[1] We thus investigated ligands of type **1** with a 1,1′-biisoquinoline binding unit as potential precursors for metallomesogens (Scheme 1). As mesogenic unit, we chose *p*-alkyl-1,1′-biphenyl, 2-alkyl-5-phenylpyrimidine and *p*-cyanobiphenyl,[3] due to their capability to form nematic and smectic mesophases. In order to allow easy modification of both tether lengths and calamitic moiety, a convergent synthetic approach was envisaged, in which the central aryl–aryl bond is formed in the last step (Scheme 1). The details of the synthesis are reported below.



Scheme 1



Scheme 2

As depicted in Scheme 2, the 4-alkyl-1,1′-biphenyl moiety **8** was prepared starting from 4-hydroxybiphenyl (**4**), which was submitted to Friedel–Crafts acylation with octanoic chloride in dichloroethane at room temperature.[4a] The obtained ketone **5**[4b] was reduced with lithium aluminium hydride and aluminium(III) chloride in dichloromethane/diethyl ether, under reflux following a procedure by Gray,[5] to give 4-hydroxy-4′-octylbiphenyl (**6**) in 84% yield. The latter was submitted to Williamson etherification[6] with the respective dibromoalkane in the presence of potassium carbonate in acetone under reflux, yielding the alkyl-substituted biphenylethers **8a** and **8b** in 73% and 69%, respectively. Analogously, the commercially available 4-cyano-4-hydroxybiphenyl (**7**) was etherified with 1,6-dibromohexane to provide derivative **9** in 41% yield.

Next, 2-octyl-5-phenylpyrimidine derivative **14** was prepared (Scheme 3). According to a procedure by Liepa,[7] 4-

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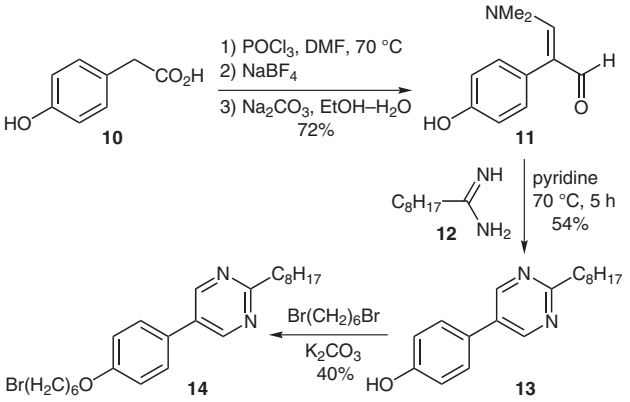
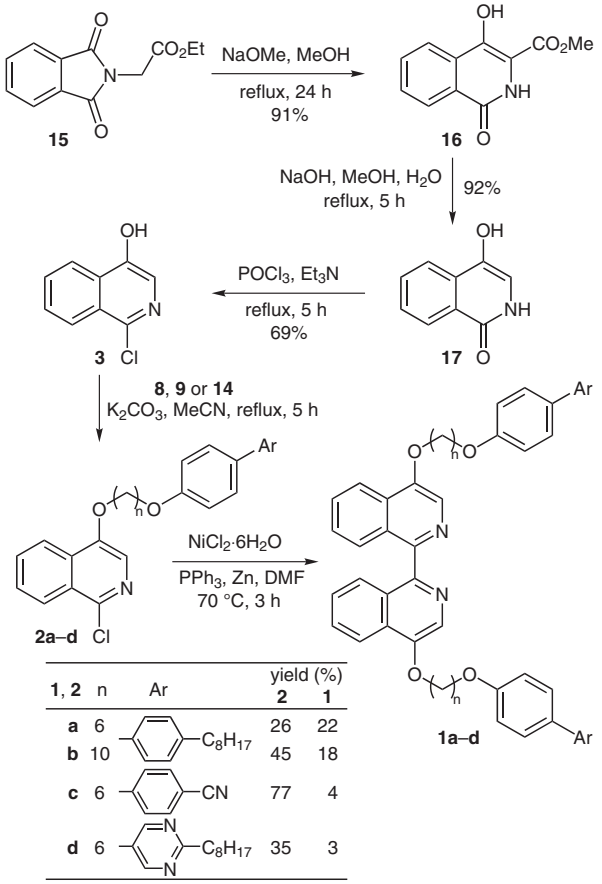


Scheme 3

hydroxyphenylacetic acid (**10**) was treated with phosphorus oxychloride ($POCl_3$) and *N*,*N*-dimethylformamide followed by addition of sodium fluoroborate ($NaBF_4$) and subsequent hydrolysis with sodium carbonate in aqueous ethanol to yield 3-dimethylamino-2-(hydroxyphenyl)propenal (**11**) in 72% overall yield. This Vilsmeier procedure was found to be more reliable in terms of product purification than the method by Reichardt.[8] Cyclocondensation of **11** with the known amidine **12**[9–11] in pyridine, following a method by Sugita, yielded phenylpyrimidine **13**[12] in 54% yield. Subsequent Williamson etherification with 1,6-dibromohexane under the conditions described above provided the ether **14** in 40% yield.

The synthesis of the desired biisoquinolines **1** commenced with a Gabriel–Colman reaction[13] of *N*-phthalimidoglycine ethylester (**15**) and sodium methoxide in refluxing methanol, yielding isoquinolone ester **16** in 91% yield (Scheme 4). Ester **16** was converted into 4-hydroxyisoquinolone (**17**) in 92% yield. Subsequent treatment with $POCl_3$ and triethylamine under reflux provided 1-chloro-4-hydroxyisoquinoline (**3**). Etherification with the calamitic subunits **8**, **9** and **14** gave the coupling precursors **2** in moderate to good yields. Finally, the chlorides **2** were coupled to the fully functionalized 1,1′-biisoquinolines **1** in the presence of $NiCl_2{\cdot}6H_2O$ (1.1 equivalents), PPh_3 (4.1 equivalents) and zinc (1.2 equivalents) in DMF at 70 °C, analogously to a method by Bolm.[14] However, the reaction suffered from tedious chromatographic purification of the biisoquinolines with two hydrophobic tails, giving the desired products **1** in low yields (Scheme 4). When $NiBr_2(PPh_3)_2$ and zinc in the presence of tetraethylammonium iodide (Et_4NI)[15] were used as catalyst, no conversion at all was observed.

The presence of a strongly coordinating bipyridine subunit in the target molecules **1** may cause catalyst deactivation due to irreversible binding, thus decreasing the yields. To check this issue, a series of alkoxy-substituted biisoquinolines **21** with various alkyl chain lengths were prepared from precursors **19** (Scheme 5). All compounds **21** were obtained in good yield regardless of the alkyl chain lengths. Even 4,4′-bis(octadecyloxy)-1,1′-biisoquinoline (**21m**) was isolated in 74% yield.[16] These results indicate that neither the electron-donating substituents in the 4,4′-



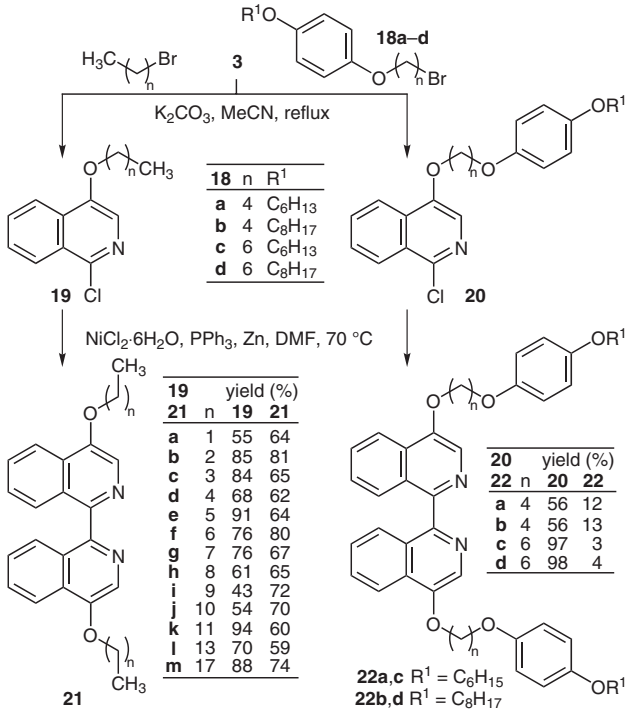
1, 2	n	Ar	yield (%) 2	1
a	6	C_8H_{17}	26	22
b	10	C_8H_{17}	45	18
c	6	CN	77	4
d	6	C_8H_{17}	35	3

Scheme 4

position, nor the biisoquinoline moiety itself, are responsible for the decreased yields in series **1**. In order to study whether an additional aryl moiety in the side chain influences the heteroaryl coupling, we synthesized a series of biisoquinolines **22** (Scheme 5).

The bromides **18a–d** were prepared in 67–77% yield by etherification of 4-hexyl- and 4-octyloxyphenol with dibromobutane and dibromohexane, respectively. Reaction with **3** gave the precursor isoquinolines **20**, which were coupled under the conditions described above to give biisoquinolines **22**. In contrast to the alkyloxy-substituted biisoquinolines **21**, the yields of derivatives **22** were much lower, decreasing from 13% for compounds **22a** and **22b** (with butyl spacer) to trace amounts of 3–4% for compounds **22c** and **22d** (with hexyl spacer). Thus, the additional aryl moiety in the side chain seems to have a deleterious effect on the nickel-mediated homocoupling.

In conclusion, a convergent synthetic route to 1,1′-biisoquinolines **1** tethered to different calamitic units via a Gabriel–Colman reaction and a nickel-mediated homocoupling as key steps was achieved. The latter coupling reaction could also be successfully applied to the synthesis of 4,4′-bis(alkyloxy)-1,1′-biisoquinolines **21** with various alkyl chain lengths. However, when 4-alkyloxyphenyloxy units were attached, the yields of biisoquinolines **22** were significantly decreased. Further conversion of these novel ligands into transition-metal complexes and



18	n	R^1
a	4	C_6H_{13}
b	4	C_8H_{17}
c	6	C_6H_{13}
d	6	C_8H_{17}

19 / 21	n	yield (%) 19	21
a	1	55	64
b	2	85	81
c	3	84	65
d	4	68	62
e	5	91	64
f	6	76	80
g	7	76	67
h	8	61	65
i	9	43	72
j	10	54	70
k	11	94	60
l	13	70	59
m	17	88	74

20 / 22	n	yield (%) 20	22
a	4	56	12
b	4	56	13
c	6	97	3
d	6	98	4

Scheme 5

investigation of their mesomorphic properties are under investigation and will be reported elsewhere.

Melting points were measured on a Mettler–Toledo DSC822e calorimeter and are uncorrected. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 or a Bruker Avance 500 spectrometer with TMS as an internal standard. Mass spectra were obtained using a Finnigan MAT 95 or a Varian MAT 711 spectrometer. Flash chromatography was performed using Kieselgel 60, 40–63 μm (Fluka). All solvents were dried, and reactions were performed in dried glassware. Petroleum ether (PE), where used, had a boiling range of 30–75 °C. Compound **10** was purchased from Fluka, and compounds **5**,[4a] **11**[7] and **12**[11] were prepared according to literature procedures.

4′-Octyl-1,1′-biphenyl-4-ol (6)

A solution of $AlCl_3$ (15.6 g, 117 mmol) in Et_2O (60 mL) followed by a solution of **5** (6 g, 20.2 mmol) in anhydrous CH_2Cl_2 (150 mL) was added slowly to a suspension of $LiAlH_4$ (2.76 g, 72.7 mmol) in anhydrous Et_2O (60 mL), and the reaction mixture was heated under reflux for 24 h. The cooled mixture was poured very carefully into H_2O and the precipitate of aluminium hydroxide was dissolved in 2 N HCl (~600 mL). After separation of the layers, the aqueous layer was extracted with EtOAc (4 × 200 mL) and the combined organic layers were washed with H_2O (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed under vacuum and the residue was purified by chromatography on SiO_2 (PE–EtOAc, 5:1) to give **6**.

Yield: 4.20 g (70%); colorless crystals; mp 140 °C; R_f = 0.46 (PE–EtOAc, 5:1).

FT-IR (ATR): 3414 (m, br), 2955 (m), 2917 (s), 2847 (m), 1609 (m), 1597 (m), 1498 (s), 1464 (m), 1375 (m), 1263 (s), 1242 (m), 1205 (m), 1179 (m), 1137 (m), 1002 (m), 840 (m), 813 (s), 784 (s), 721 (m), 682 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.4 Hz, 3 H, CH_3), 1.27–1.32 (m, 10 H, CH_2), 1.57–1.69 (m, 2 H, 4′-CH_2CH_2), 2.60–2.65 (m, 2 H, 4′-CH_2), 4.73 (s, 1 H, OH), 6.87–6.90 (m, 2 H, H-3, H-5), 7.21–7.23 (m, 2 H, H-3′, H-5′), 7.43–7.48 (m, 4 H, H-2, H-6, H-2′, H-6′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 29.3, 29.4, 29.5, 31.9 (CH_2), 31.5 (4′-CH_2CH_2), 35.6 (4′-CH_2), 115.6 (C-3, C-5), 126.5, 128.2 (C-2, C-6, C-2′, C-6′), 128.6 (C-3′, C-5′), 134.1, 138.1 (C-1, C-1′), 141.5 (C-4′), 154.8 (C-4).

HRMS (ESI, +): m/z [M + H$^+$] calcd for $C_{20}H_{27}O$: 283.2056; found: 283.2046.

Anal. Calcd for $C_{20}H_{26}O$: C, 85.06; H, 9.28. Found: C, 85.16; H, 9.16.

(Bromoalkyloxy)biphenyl Derivatives 8a, 9 and 14; General Procedure

K_2CO_3 (3 equiv) and dibromohexane (2.4 equiv) were added to a solution of **6**, **7** or **13** in acetone (50 mL) under an N_2 atmosphere, and the reaction mixture was heated under reflux for 24 h. After cooling to r.t., the solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2–H_2O (2:1, 75 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers were washed with H_2O (2 × 25 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by chromatography on SiO_2 (PE–EtOAc, 50:1→5:1) in the case of **9**, or by recrystallization from EtOH for **8a** and **14**.

4-[(6-Bromohexyl)oxy]-4′-octyl-1,1′-biphenyl (8a)

Mp 67 °C (EtOH); R_f = 0.56 (PE–EtOAc, 20:1).

FT-IR (ATR): 2917 (m), 2848 (m), 1606 (m), 1500 (m), 1465 (m), 1274 (m), 1243 (s), 1213 (m), 1033 (s), 996 (s), 842 (m), 813 (s), 784 cm^{-1} (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3 H, CH_3), 1.23–1.36 (m, 10 H, CH_2), 1.51–1.56 (m, 4 H, $OCH_2CH_2CH_2CH_2$), 1.60–1.66 (m, 2 H, 4′-CH_2CH_2), 1.79–1.85 (m, 2 H, CH_2CH_2Br), 1.88–1.94 (m, 2 H, OCH_2CH_2), 2.61–2.64 (m, 2 H, 4′-CH_2), 3.43 (t, J = 6.8 Hz, 2 H, CH_2Br), 4.00 (t, J = 6.4 Hz, 2 H, OCH_2), 6.94–6.96 (m, 2 H, H-3, H-5), 7.21–7.23 (m, 2 H, H-3′, H-5′), 7.45–7.50 (m, 4 H, H-2, H-6, H-2′, H-6′).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 25.3, 27.9, 29.1, 29.3, 29.4, 31.9, 32.7 (CH_2), 31.6 (4′-CH_2CH_2), 32.7 (CH_2CH_2Br), 33.8 (CH_2Br), 35.6 (4′-CH_2), 67.8 (OCH_2), 114.7 (C-3, C-5), 126.6, 127.9 (C-2, C-6, C-2′, C-6′), 128.8 (C-3′, C-5′), 133.7, 138.2 (C-1, C-1′), 141.4 (C-4′), 158.4 (C-4).

MS (EI, +): m/z (%) = 444.2 (100) [M$^+$], 364.2 (2), 345.0 (7), 282.2 (36) [M + H – $(CH_2)_6Br$]$^+$, 209.1 (3), 196.1 (5), 183.1 (70), 154.1 (4), 83.1 (3), 55.0 (4), 43.0 (3) [C_3H_7]$^+$.

HRMS (EI, +): m/z [M$^+$] calcd for $C_{26}H_{37}BrO$: 444.2028; found: 444.2038.

4′-[(6-Bromohexyl)oxy]-1,1′-biphenyl-4-carbonitrile (9)

Mp 62 °C; R_f = 0.23 (PE–EtOAc, 50:1).

FT-IR (ATR): 2935 (m), 2921 (m), 2226 (m), 1600 (m), 1493 (m), 1468 (m), 1286 (m), 1267 (m), 1240 (m), 1215 (m), 1199 (m), 1181 (m), 1076 (m), 980 (m), 854 (m), 814 (s), 727 (m), 710 (m), 659 (m), 644 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48–1.55 (m, 4 H, CH_2), 1.77–1.98 (m, 4 H, CH_2), 3.43 (t, J = 6.6 Hz, 2 H, CH_2Br), 4.02 (t, J = 6.3 Hz, 2 H, OCH_2), 6.95–7.02 (m, 2 H, H-3′, H-5′), 7.49–7.56 (m, 2 H, H-3, H-5), 7.61–7.72 (m, 4 H, H-2, H-6, H-2′, H-6′).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.3, 27.9, 29.0, 32.7 (CH_2), 33.8 (CH_2Br), 67.9 (OCH_2), 110.1 (C-4), 115.1 (C-3′, C-5′), 119.1 (CN), 127.1, 128.4 (C-2, C-6, C-2′, C-6′), 131.4 (C-1′), 132.6 (C-3, C-5), 145.3 (C-1), 159.7 (C-4′).

MS (ESI, +): m/z = 380.1 [M + Na]$^+$, 360.1, 301.1, 149.0.

HRMS (ESI, +): *m/z* [M + Na^+] calcd for $C_{19}H_{20}BrNNaO$: 380.0620; found: 380.0606.

5-{4-[(6-Bromohexyl)oxy]phenyl}-2-octylpyrimidine (14)
Mp 115 °C (EtOH); R_f = 0.86 (PE–EtOAc, 1:1).

FT-IR (ATR): 2916 (m), 2848 (m), 1586 (m), 1536 (m), 1515 (m), 1445 (s), 1247 (s), 1180 (m), 1116 (m), 1011 (m), 994 (m), 838 (s), 651 (m), 608 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.21–1.45 (m, 10 H, CH_2), 1.49–1.58 (m, 4 H, CH_2), 1.79–1.98 (m, 6 H, CH_2), 2.96–3.01 (m, 2 H, 2-CH_2), 3.44 (t, *J* = 6.6 Hz, 2 H, CH_2Br), 4.02 (t, *J* = 6.4 Hz, 2 H, OCH_2), 6.99–7.03 (m, 2 H, H-3, H-5), 7.46–7.50 (m, 2 H, H-2, H-6), 8.83 (s, 2 H, H-4, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 25.3, 27.9, 28.9, 29.0, 29.2, 29.4, 31.9, 32.7 (CH_2), 33.8 (CH_2Br), 39.2 (2-CH_2), 67.9 (OCH_2), 115.2 (C-3′, C-5′), 128.0 (C-2′, C-6′), 126.7, 130.8 (C-1, C-5), 154.8 (C-4, C-6), 159.9 (C-4), 169.5 (C-2).

MS (EI, +): *m/z* (%) = 446.1 (100) [M^+], 361.0 (20) [$M^+ - C_6H_{13}$], 348.0 (78) [$M^+ - C_7H_{15}$ + H], 199.0 (10), 186.0 (28).

HRMS (ESI, +): *m/z* [M + H^+] calcd for $C_{24}H_{36}BrN_2O$: 447.2006; found: 447.1984.

4-[(10-Bromodecyl)oxy]-4′-octyl-1,1′-biphenyl (8b)
NaOH (67 mg, 1.68 mmol) in H_2O (0.5 mL) was added dropwise to a solution of **6** (500 mg, 1.77 mmol) and 1,10-dibromodecane (669 mg, 2.23 mmol) in H_2O (5 mL) under an N_2 atmosphere, and the reaction mixture was heated under reflux for 7 h. After cooling, CH_2Cl_2 (10 mL) and H_2O (5 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with H_2O (2 × 5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by recrystallization from EtOAc to give **8b**.

Yield: 400 mg (45%); colorless solid; mp 71 °C (EtOH); R_f = 0.33 (PE–EtOAc, 100:1).

FT-IR (ATR): 2917 (vs), 2849 (s), 1607 (m), 1500 (s), 1473 (m), 1464 (m), 1274 (m), 1253 (s), 1214 (m), 1180 (m), 1037 (m), 1009 (m), 811 (s), 784 (m), 720 (m), 645 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H, CH_3), 1.19–1.55 (m, 22 H, CH_2), 1.60–1.71 (m, 2 H, CH_2), 1.74–1.93 (m, 4 H, CH_2), 2.59–2.68 (m, 2 H, $C_6H_4CH_2$), 3.41 (t, *J* = 6.8 Hz, 2 H, CH_2Br), 3.99 (t, *J* = 6.5 Hz, 2 H, OCH_2), 6.91–6.98 (m, 2 H, H-3, H-5), 7.21–7.23 (m, 2 H, H-3′, H-5′), 7.42–7.53 (m, 4 H, H-2, H-6, H-2′, H-6′).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.1, 28.2, 28.8, 29.3, 29.4, 29.5, 31.9, 32.8 (CH_2), 31.6 (4′-CH_2CH_2), 34.1 (CH_2Br), 35.6 (4′-CH_2), 68.0 (OCH_2), 114.7 (C-3, C-5), 126.5, 127.9 (C-2, C-6, C-2′, C-6′), 128.8 (C-3′, C-5′), 133.6, 138.2 (C-1, C-1′), 141.4 (C-4′), 158.5 (C-4).

MS (ESI, +): *m/z* = 523.3 [M + Na]$^+$, 461.3, 399.2.

HRMS (ESI, +): *m/z* [M + Na^+] calcd for $C_{30}H_{45}BrNaO$: 523.2546; found: 523.2546.

Alkylation of 1-Chloro-4-hydroxyisoquinoline (3) to Products 2, 19, 20; General Procedure
K_2CO_3 (3 equiv) and the respective alkylbromide **8**, **9**, **14** or **18** (1.1 equiv) were added to a solution of **3** (1 equiv) in MeCN (30 mL) under an N_2 atmosphere, and the reaction mixture was heated under reflux for 5 h. After cooling to r.t., the solvent was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (25 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with H_2O (2 × 25 mL), dried (Na_2SO_4) and evaporated. The crude product was purified either by chromatography on SiO_2 and/or by recrystallization from EtOAc.

1-Chloro-4-({6-[(4′-octyl-1,1′-biphenyl-4-yl)oxy]hexyl}oxy)isoquinoline (2a)
Purified by recrystallization from EtOAc.

Mp 74 °C (EtOAc); R_f = 0.64 (PE–EtOAc, 1:5).

FT-IR (ATR): 2920 (m), 2850 (m), 1578 (m), 1562 (m), 1499 (m), 1453 (m), 1383 (m), 1311 (s), 1271 (s), 1247 (vs), 1177 (m), 1099 (s), 997 (m), 952 (m), 818 (m), 763 (s), 726 (s), 659 (s), 611 (m), 593 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H, CH_3), 1.21–1.40 (m, 10 H, CH_2), 1.60–1.71 (m, 6 H, CH_2), 1.83–2.09 (m, 4 H, CH_2), 2.59–2.65 (m, 2 H, $C_6H_4CH_2$), 4.03 (t, *J* = 6.5 Hz, 2 H, $C_6H_4OCH_2$), 4.22 (t, *J* = 6.3 Hz, 2 H, 4-OCH_2), 6.92–6.98 (m, 2 H, H-3′, H-5′), 7.19–7.25 (m, 2 H, H-3″, H-5″), 7.43–7.53 (m, 4 H, H-2′, H-6′, H-2″, H-6″), 7.65–7.76 (m, 2 H, H-6, H-7), 7.80 (s, 1 H, H-3), 8.21–8.28 (m, 2 H, H-5, H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 25.9, 26.0, 29.2, 29.3, 29.4, 29.5, 31.6 (CH_2), 31.9 ($C_6H_4CH_2CH_2$), 35.6 ($C_6H_4CH_2$), 67.8, 68.8 (OCH_2), 114.7 (C-3′, C-5′), 121.9, 126.0, 128.7, 130.3 (C-5, C-8, C-6, C-7, C-3), 126.5, 128.0 (C-2′, C-6′, C-2″, C-6″), 127.0, 130.5 (C-4a, C-8a), 128.8 (C-3″, C-5″), 133.7, 138.2, 141.5 (C-1′, C-1″, C-4″), 142.4, 150.0 (C-1, C-4), 158.4 (C-4′).

MS (EI, +): *m/z* = 543.2 (100) [M^+].

HRMS (ESI, +): *m/z* [M + H^+] calcd for $C_{35}H_{43}ClNO_2$: 544.2977; found: 544.2952.

1-Chloro-4-({10-[(4′-octyl-1,1′-biphenyl-4-yl)oxy]decyl}oxy)isoquinoline (2b)
Purified by chromatography (PE–EtOAc, 5:1) and recrystallization from EtOAc.

Mp 78 °C (EtOAc); R_f = 0.42 (PE–EtOAc, 5:1).

FT-IR (ATR): 2918 (vs), 2851 (s), 1608 (m), 1500 (s), 1486 (m), 1451 (m), 1385 (m), 1312 (m), 1274 (s), 1248 (vs), 1177 (m), 1099 (s), 1045 (m), 1003 (m), 981 (m), 951 (m), 845 (m), 813 (s), 780 (m), 764 (vs), 720 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H, CH_3), 1.18–1.51 (m, 22 H, CH_2), 1.61–1.71 (m, 2 H, CH_2), 1.75–1.87 (m, 2 H, CH_2), 1.88–2.01 (m, 2 H, CH_2), 2.57–2.70 (m, 2 H, $C_6H_4CH_2$), 3.99 (t, *J* = 6.5 Hz, 2 H, $C_6H_4OCH_2$), 4.19 (t, *J* = 6.4 Hz, 2 H, 4-OCH_2), 6.92–6.99 (m, 2 H, H-3′, H-5′), 7.20–7.23 (m, 2 H, H-3″, H-5″), 7.41–7.55 (m, 4 H, H-2′, H-6′, H-2″, H-6″), 7.66–7.76 (m, 2 H, H-6, H-7), 7.79 (s, 1 H, H-3), 8.23–8.27 (m, 2 H, H-5, H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.1, 29.2, 29.3, 29.4, 29.5, 31.6 (CH_2), 31.9 ($C_6H_4CH_2CH_2$), 35.6 ($C_6H_4CH_2$), 68.0, 69.0 (OCH_2), 114.7 (C-3′, C-5′), 121.9, 126.0, 128.7, 130.3 (C-5, C-8, C-6, C-7, C-3), 126.5, 128.0 (C-2′, C-6′, C-2″, C-6″), 127.0, 130.5 (C-4a, C-8a), 128.8 (C-3″, C-5″), 133.6, 138.2, 141.5 (C-1′, C-1″, C-4″), 142.3, 150.0 (C-1, C-4), 158.5 (C-4′).

MS (ESI, +): *m/z* = 600.3 [M + H^+], 318.2, 180.0.

HRMS (ESI, +): *m/z* [M + H^+] calcd for $C_{39}H_{51}ClNO_2$: 600.3603; found: 600.3593.

4′-({6-[(1-Chloroisoquinolin-4-yl)oxy]hexyl}oxy)-1,1′-biphenyl-4-carbonitrile (2c)
Purified by chromatography (PE–EtOAc, 5:1).

Mp 121 °C; R_f = 0.24 (PE–EtOAc, 5:1).

FT-IR (ATR): 2943 (m), 2867 (m), 2222 (m), 1600 (m), 1576 (m), 1493 (m), 1477 (m), 1450 (m), 1384 (m), 1312 (m), 1270 (s), 1248 (s), 1173 (m), 1163 (m), 1098 (s), 1035 (m), 1026 (m), 1008 (m),

999 (m), 983 (m), 947 (m), 852 (m), 823 (s), 802 (m), 759 (m), 728 (m), 657 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.61–1.74 (m, 4 H, CH_2), 1.83–1.94 (m, 2 H, CH_2), 1.95–2.05 (m, 2 H, CH_2), 4.05 (t, *J* = 6.4 Hz, 2 H, 4′-OCH_2), 4.22 (t, *J* = 6.4 Hz, 2 H, 4-OCH_2), 6.95–7.02 (m, 2 H, H-3′, H-5′), 7.49–7.55 (m, 2 H, H-3″, H-5″), 7.60–7.77 (m, 6 H, H-6, H-7, H-2′, H-6′, H-2″, H-6″), 7.80 (s, 1 H, H-3), 8.21–8.28 (m, 2 H, H-5, H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.8, 25.9, 29.1, 29.2 (CH_2), 67.9, 68.7 (OCH_2), 110.2 (C-4″), 115.0 (C-3′, C-5′), 119.2 (CN), 121.8, 121.9, 126.0 (C-5, C-8, C-3), 127.1, 128.4 (C-2′, C-6′, C-2″, C-6″), 127.0, 130.4 (C-4a, C-8a), 132.6 (C-3″, C-5″), 131.4, 142.5, 145.3, 150.0 (C-1′, C-1″, C-1, C-4, C-4′).

MS (ESI, +): *m*/*z* = 479.2 $[M + Na]^+$, 457.2 $[M + H]^+$.

HRMS (ESI, +): *m*/*z* $[M + Na^+]$ calcd for $C_{28}H_{25}ClN_2NaO_2$: 479.1497; found: 479.1480.

1-Chloro-4-({6-[4-(2-octylpyrimidin-5-yl)phenoxy]hexyl}oxy)isoquinoline (2d)
Purified by recrystallization from EtOAc.

Mp 142 °C (EtOAc); R_f = 0.83 (PE–EtOAc, 1:1).

FT-IR (ATR): 2942 (m), 2915 (m), 2848 (m), 1586 (m), 1536 (m), 1516 (m), 1445 (s), 1394 (m), 1289 (m), 1247 (s), 1179 (m), 1116 (m), 1025 (m), 1011 (m), 995 (m), 839 (s), 721 (m), 709 (m), 652 (m), 608 (m), 561 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.90 (m, 3 H, CH_3), 1.23–1.46 (m, 10 H, CH_2), 1.57–1.71 (m, 4 H, CH_2), 1.79–1.94 (m, 4 H, CH_2), 1.95–2.03 (m, 2 H, CH_2), 2.94–3.03 (m, 2 H, 2″-CH_2), 4.03 (t, *J* = 6.4 Hz, 2 H, 4′-OCH_2), 4.23 (t, *J* = 6.2 Hz, 2 H, 4-OCH_2), 6.98–7.03 (m, 2 H, H-3′, H-5′), 7.45–7.52 (m, 2 H, H-2′, H-6′), 7.64–7.78 (m, 2 H, H-6, H-7), 7.80 (s, 1 H, H-3), 8.20–8.31 (m, 2 H, H-5, H-8), 8.82 (s, 2 H, H-4″, H-6″).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 25.9, 28.9, 29.2, 29.5, 31.9 (CH_2), 39.2 (2-CH_2), 68.0 (4′-O*C*H_2CH_2), 68.7 (4-O*C*H_2), 115.4 (C-3′, C-5′), 121.9, 126.0 (C-3, C-5, C-8), 126.8, 130.8 (C-1′, C-5″), 127.9 (C-2′, C-6′), 128.7, 130.2 (C-6, C-7), 127.0, 130.8 (C-4a, C-8a), 143.2, 149.7, 154.6 (C-6″, C-2″), 159.6, 169.7 (C-1, C-4, C-4″).

MS (ESI, +): *m*/*z* = 568.3 $[M + Na]^+$, 546.3 $[M + H]^+$.

HRMS (ESI, +): *m*/*z* $[M + H^+]$ calcd for $C_{33}H_{41}ClN_3O_2$: 546.2882; found: 546.2875.

1-Chloro-4-propoxyisoquinoline (19b)
Purified by chromatography (PE–EtOAc, 10:1).

Mp 56 °C; R_f = 0.48 (PE–EtOAc, 10:1).

FT-IR (ATR): 2971 (m), 2942 (m), 1580 (m), 1562 (m), 1454 (m), 1381 (m), 1313 (s), 1277 (s), 1256 (m), 1098 (m), 996 (s), 956 (s), 901 (m), 871 (s), 799 (m), 759 (s), 727 (s), 660 (s), 640 (m), 609 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.96 (qt, *J* = 6.4, 7.5 Hz, 2 H, $OCH_2CH_2CH_3$), 4.15 (t, *J* = 6.4 Hz, 2 H, $OCH_2CH_2CH_3$), 7.65–7.76 (m, 2 H, H-6, H-7), 7.78 (s, 1 H, H-3), 8.22–8.23, 8.25–8.26 (2 × m, 2 H, H-5, H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.6 (CH_3), 22.6 ($OCH_2CH_2CH_3$), 70.4 ($OCH_2CH_2CH_3$), 121.9, 126.0 (C-3, C-5, C-8), 128.7, 130.2 (C-6, C-7), 127.0, 130.5 (C-4a, C-8a), 142.3, 150.0 (C-1, C-4).

GC-MS (EI): *m*/*z* (%) = 221 (30) $[M^+]$, 179 (100) $[M^+ + H - C_3H_7]$.

Anal. Calcd for $C_{12}H_{12}ClNO$: C, 65.02; H, 5.46; N, 6.33; Cl, 15.99. Found: C, 64.90; H, 5.47; N, 6.22; Cl, 16.24.

1-Chloro-4-(octyloxy)isoquinoline (19g)
Purified by chromatography (PE–EtOAc, 10:1).

Mp 67 °C; R_f = 0.52 (PE–EtOAc, 10:1).

FT-IR (ATR): 2914 (m), 1580 (m), 1455 (m), 1307 (m), 1282 (s), 1096 (m), 983 (m), 948 (m), 867 (m), 762 (s), 728 (s), 660 (s), 610 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.25–1.45 (m, 8 H, CH_2), 1.50–1.60 (m, 2 H, CH_2), 1.88–1.97 (m, 2 H, CH_2), 4.18 (t, *J* = 6.4 Hz, 2 H, OCH_2), 7.67 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1 H, H-6 or H-7), 7.72 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1 H, H-6 or H-7), 7.78 (s, 1 H, H-3), 8.21–8.23, 8.24–8.25 (2 × m, 2 H, H-5, H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.1, 29.2, 29.3, 29.4, 31.8 (CH_2), 68.9 (OCH_2), 121.9, 125.9 (C-3, C-5, C-8), 126.9, 130.4 (C-4a, C-8a), 128.6, 130.1 (C-6, C-7), 142.3, 150.0 (C-1, C-4).

GC-MS (EI): *m*/*z* (%) = 291 (30) $[M^+]$, 179 (100) $[M^+ + H - C_8H_{17}]$.

Anal. Calcd for $C_{17}H_{22}ClNO$: C, 69.97; H, 7.60; N, 4.80; Cl, 12.15. Found: C, 69.86; H, 7.57; N, 4.71; Cl, 12.09.

1-Chloro-4-(nonyloxy)isoquinoline (19h)
Purified by chromatography (PE–EtOAc, 10:1).

Mp 57 °C; R_f = 0.52 (PE–EtOAc, 10:1).

FT-IR (ATR): 1576 (m), 1313 (m), 1272 (m), 1166 (w), 1100 (m), 949 (m), 853 (m), 773 (s), 750 (m), 728 (s), 660 (s), 614 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.25–1.45 (m, 10 H, C*H*$_2$), 1.50–1.60 (m, 2 H, CH_2), 1.88–1.97 (m, 2 H, CH_2), 4.18 (t, *J* = 6.4 Hz, 2 H, OCH_2), 7.66–7.77 (m, 2 H, H-6, H-7), 7.79 (s, 1 H, H-3), 8.22–8.24, 8.24–8.26 (2 × m, 2 H, H-5, H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.1, 29.2, 29.3, 29.4, 29.5, 31.9 (CH_2), 68.9 (OCH_2), 121.9, 126.0 (C-3, C-5, C-8), 126.9, 130.4 (C-4a, C-8a), 128.7, 130.2 (C-6, C-7), 142.3, 150.0 (C-1, C-4).

GC-MS (EI): *m*/*z* (%) = 305 (20) $[M^+]$, 179 (100) $[M^+ + H - C_9H_{19}]$.

Anal. Calcd for $C_{18}H_{24}ClNO$: C, 70.69; H, 7.91; N, 4.58; Cl, 11.59. Found: C, 70.55; H, 7.81; N, 4.51; Cl, 11.77.

1-Chloro-4-(octadecyloxy)isoquinoline (19m)
Purified by chromatography (PE–EtOAc, 15:1).

Mp 67 °C; R_f = 0.43 (PE–EtOAc, 15:1).

FT-IR (ATR): 2922 (s), 2848 (s), 1575 (m), 1464 (m), 1448 (m), 1308 (m), 1275 (s), 1099 (m), 948 (m), 848 (m), 771 (s), 726 (s), 659 (m), 613 cm^{-1} (m).

^1H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.3 Hz, 3 H, CH_3), 1.26–1.47 (m, 28 H, CH_2), 1.50–1.62, 1.88–1.99 (2 × m, 4 H, CH_2), 4.19 (t, *J* = 6.4 Hz, 2 H, OCH_2), 7.66–7.78 (m, 2 H, H-6, H-7), 7.79 (s, 1 H, H-3), 8.23–8.28 (m, 2 H, H-5, H-8).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.1, 29.2, 29.4, 29.6, 29.7, 31.9 (CH_2), 69.0 (OCH_2), 121.89, 121.90, 126.0 (C-3, C-5, C-8), 128.7 and 130.2 (C-6, C-7), 127.0 and 130.4 (C-4a, C-8a), 142.3, 150.0 (C-1, C-4).

MS (EI, +): *m*/*z* (%) = 431.3 (16) $[M^+]$, 396.4 (100) $[M^+ - Cl]$, 179 (92) $[M^+ - C_{18}H_{37} + H]$.

Anal. Calcd for $C_{27}H_{42}ClNO$: C, 75.05; H, 9.80; N, 3.23; Cl, 8.21. Found: C, 75.16; H, 9.71; N, 3.19; Cl, 8.37.

1-Chloro-4-{4-[4-(hexyloxy)phenoxy]butoxy}isoquinoline (20a)
Purified by recrystallization from EtOAc.

Mp 80 °C; R_f = 0.86 (PE–EtOAc, 1:1).

FT-IR (ATR): 1510 (m), 1448 (m), 1386 (m), 1310 (m), 1273 (m), 1221 (s), 1098 (m), 1033 (m), 987 (m), 947 (m), 830 (s), 760 (m), 728 (m), 658 (m), 613 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.29–1.51 (m, 6 H, CH_2), 1.70–1.81 [m, 2 H, Ph(4′)OCH_2CH_2], 1.99–2.19 [m, 4 H, Ph(1′)$OCH_2CH_2CH_2$], 3.90 (t, *J* = 6.6 Hz, 2 H, $PhOCH_2$), 4.04 (t, *J* = 6.0 Hz, 2 H, $PhOCH_2$), 4.27 [t, *J* = 5.9 Hz, 2 H, isoquinoline(4)OCH_2], 6.82–6.85 (m, 4 H, H-2′, H-3′, H-5′, H-6′), 7.66–7.76 (m, 2 H, H-6, H-7), 7.76 (s, 1 H, H-3), 8.19–8.29 (m, 2 H, H-5, H-8).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6, 25.7, 26.1, 26.2, 29.4, 31.6 (CH_2), 67.9, 68.5 ($PhOCH_2$), 68.6 [isoquinoline(4)OCH_2], 115.4 (C-2′, C-3′, C-5′, C-6′), 121.8, 121.9, 126.0 (C-3, C-5, C-8), 127.0, 130.4 (C-4a, C-8a), 128.7, 130.3 (C-6, C-7), 142.5, 149.9 (C-1, C-4), 152.9, 153.4 (C-1′, C-4′).

MS (EI, +): *m*/*z* (%) = 427.2 (100) $[M^+]$, 356.1 (10) $[M - C_5H_{11}]^+$, 249.2 (37), 234.1 (58) $[M - OC_6H_{13} - Ph - O]^+$, 192.0 (20) $[M - OC_6H_{13} - Ph - OC_3H_6]^+$, 123.0 (38), 110.0 (30), 55.1 (20), 43.0 (33).

HRMS (ESI, +): *m*/*z* [M + Na^+] calcd for $C_{25}H_{30}ClNNaO_3$: 450.1812; found: 450.1805.

1-Chloro-4-{4-[4-(octyloxy)phenoxy]butoxy}isoquinoline (20b)
Purified by recrystallization from EtOAc.

Mp 86 °C; R_f = 0.92 (EtOAc).

FT-IR (ATR): 1508 (s), 1475 (m), 1386 (m), 1310 (m), 1273 (m), 1231 (s), 1098 (m), 1048 (m), 1025 (m), 955 (m), 827 (s), 763 (s), 728 (m), 661 (m), 613 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.21–1.51 (m, 10 H, CH_2), 1.70–1.82 [m, 2 H, Ph(4′)OCH_2CH_2], 1.99–2.21 [m, 4 H, Ph(1′)$OCH_2CH_2CH_2$], 3.92 (t, *J* = 6.6 Hz, 2 H, $PhOCH_2$), 4.04 (t, *J* = 5.9 Hz, 2 H, $PhOCH_2$), 4.28 [t, *J* = 6.0 Hz, 2 H, isoquinoline(4)OCH_2], 6.79–6.87 (m, 4 H, H-2′, H-3′, H-5′, H-6′), 7.66–7.77 (m, 2 H, H-6, H-7), 7.81 (s, 1 H, H-3), 8.19–8.28 (m, 2 H, H-5, H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.1, 26.2, 29.3, 29.4, 31.8 (CH_2), 68.0, 68.6 ($PhOCH_2$), 68.7 [isoquinoline(4)OCH_2], 115.4 (C-2′, C-3′, C-5′, C-6′), 121.8, 121.9, 126.0 (C-3, C-5, C-8), 127.0, 130.4 (C-4a, C-8a), 128.7, 130.3 (C-6, C-7), 142.5, 149.9 (C-1, C-4), 152.9, 153.4 (C-1′, C-4′).

MS (ESI, +): *m*/*z* = 478.2 [M + Na^+], 456.2 [M + H^+].

HRMS (ESI, +): *m*/*z* [M + H^+] calcd for $C_{27}H_{35}ClNO_3$: 456.2305; found: 456.2282.

1-Chloro-4-({6-[4-(hexyloxy)phenoxy]hexyl}oxy)isoquinoline (20c)
Purified by recrystallization from EtOAc.

Mp 63 °C; R_f = 0.83 (EtOAc).

FT-IR (ATR): 2938 (m), 1508 (s), 1473 (m), 1453 (m), 1307 (m), 1287 (m), 1274 (m), 1224 (s), 1097 (m), 1033 (m), 999 (m), 949 (m), 825 (m), 768 (s), 729 (s), 660 (m), 613 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.27–1.54 (m, 6 H, CH_2), 1.57–1.68 (m, 4 H, CH_2), 1.69–1.88 (m, 4 H, CH_2), 1.91–2.03 (m, 2 H, CH_2), 3.90 (t, *J* = 6.1 Hz, 2 H, $PhOCH_2$), 3.94 (t, *J* = 5.8 Hz, 2 H, $PhOCH_2$), 4.21 [t, *J* = 6.3 Hz, 2 H, isoquinoline(4)OCH_2], 6.79–6.84 (m, 4 H, H-2′, H-3′, H-5′, H-6′), 7.69–7.75 (m, 2 H, H-6, H-7), 7.79 (s, 1 H, H-3), 8.21–8.28 (m, 2 H, H-5, H-8).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6, 25.7, 25.9, 26.0, 29.2, 29.3, 29.4, 31.6 (CH_2), 68.4, 68.6 ($PhOCH_2$), 68.8 [isoquinoline(4)OCH_2], 115.4 (C-2′, C-3′, C-5′, C-6′), 121.9, 122.0, 126.0 (C-3, C-5, C-8), 127.0, 130.4 (C-4a, C-8a), 128.7, 130.2 (C-6, C-7), 142.4, 149.9 (C-1, C-4), 153.1, 153.3 (C-1′, C-4′).

MS (ESI, +): *m*/*z* = 478.2 [M + Na^+], 456.2 $[M^+]$.

HRMS (ESI, +): *m*/*z* [M + H^+] calcd for $C_{27}H_{35}ClNO_3$: 456.2305; found: 456.2291.

1-Chloro-4-({6-[4-(octyloxy)phenoxy]hexyl}oxy)isoquinoline (20d)
Purified by chromatography (PE–EtOAc, 7:1)

Mp 73 °C; R_f = 0.92 (PE–EtOAc, 1:1).

FT-IR (ATR): 1508 (s), 1473 (m), 1310 (m), 1290 (m), 1274 (m), 1231 (s), 1099 (s), 1046 (m), 1033 (m), 951 (m), 823 (m), 813 (m), 766 (s), 730 (m), 661 (m), 612 (m), 524 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H, CH_3), 1.24–1.65 (m, 14 H, CH_2), 1.71–2.03 (m, 6 H, CH_2), 3.89 (t, *J* = 6.2 Hz, 2 H, $PhOCH_2$), 3.94 (t, *J* = 6.3 Hz, 2 H, $PhOCH_2$), 4.21 [t, *J* = 6.4 Hz, 2 H, isoquinoline(4)OCH_2], 6.78–6.83 (m, 4 H, H-2′, H-3′, H-5′, H-6′), 7.66–7.77 (m, 2 H, H-6, H-7), 7.79 (s, 1 H, H-3), 8.20–8.28 (m, 2 H, H-5, H-8).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 25.9, 26.0, 26.1, 29.1, 29.3, 31.9 (CH_2), 29.4 [Ph(1′)OCH_2CH_2, Ph(4′)OCH_2CH_2, isoquinoline(4)OCH_2CH_2], 68.4 [Ph(4′)OCH_2], 68.6 [Ph(1′)OCH_2], 68.8 [isoquinoline(4)OCH_2], 115.4 (C-2′, C-3′, C-5′, C-6′), 121.8, 121.9, 126.0 (C-3, C-5, C-8), 126.9, 130.4 (C-4a, C-8a), 128.7, 130.3 (C-6, C-7), 142.3, 150.0 (C-1, C-4), 153.1, 153.3 (C-1′, C-4′).

MS (ESI, +): *m*/*z* = 506.2 [M + Na^+], 484.4 $[M^+]$, 449.4 $[MH - Cl]^+$.

HRMS (ESI, +): *m*/*z* [M + Na^+] calcd for $C_{29}H_{38}ClNO_3$: 506.2438; found: 506.2437.

Coupling of Isoquinoline Derivatives 2, 19, 20 to Products 1, 21 and 22; General Procedure
A solution of $NiCl_2 \cdot 6H_2O$ (1.22 equiv) in degassed anhydrous DMF (8 mL) was heated at 70 °C (bath temperature) and Ph_3P (4.86 equiv) and Zn (1.31 equiv) were added. The mixture became brown and was heated at 70 °C for 1 h, then a solution of **2a–d**, **19** or **20** in degassed anhydrous DMF (5 mL) was added. The reaction mixture was stirred at 70 °C for 4 h (TLC monitoring). After cooling to r.t., the mixture was quenched with aq NH_3 (5%, 21 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2–Et_2O (2:1, 3 × 25 mL). The combined organic layers were concentrated under vacuum and the residue was taken up in CH_2Cl_2 (15 mL), washed with H_2O (4 × 8 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under vacuum. The crude products were purified by chromatography on SiO_2 and/or by recrystallization from EtOAc.

4,4′-Bis({6-[(4′-octyl-1,1′-biphenyl-4-yl)oxy]hexyl}oxy)-1,1′-biisoquinoline (1a)
Purified by chromatography (PE–EtOAc, 1:2) followed by recrystallization from EtOAc.

Mp 145 °C (EtOAc); R_f = 0.23 (PE–EtOAc, 1:2).

FT-IR (ATR): 2921 (m), 2852 (m), 1579 (m), 1498 (s), 1453 (m), 1374 (m), 1312 (m), 1273 (m), 1244 (s), 1174 (m), 1094 (m), 990 (m), 817 (m), 802 (m), 767 (m), 721 (m), 684 (m), 631 (m), 516 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 6 H, CH_3), 1.22–1.40 (m, 20 H, CH_2), 1.57–1.79 (m, 12 H, CH_2), 1.84–1.96 (m, 4 H, CH_2), 1.99–2.11 (m, 4 H, CH_2), 2.58–2.67 (m, 4 H, $C_6H_4CH_2$), 4.03 (t, *J* = 6.5 Hz, 4 H, $C_6H_4OCH_2$), 4.22 (t, *J* = 6.2 Hz, 4 H, 4-OCH_2), 6.95–6.99 (m, 4 H, H-3″, H-5″), 7.20–7.24 (m, 4 H, H-3‴, H-5‴), 7.44–7.52 (m, 10 H, H-2″, H-6″, H-2‴, H-6‴, H-6 or H-7), 7.63–7.70 (m, 2 H, H-6 or H-7), 7.72–7.76 (m, 2 H, H-5 or H-8), 8.24 (s, 2 H, H-3), 8.31–8.35 (m, 2 H, H-5 or H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.0, 26.1, 29.3, 29.4, 29.5, 31.6 (CH_2), 31.9 ($C_6H_4CH_2CH_2$), 35.6 ($C_6H_4CH_2$), 67.9,

68.7 (OCH_2), 114.7 (C-3″, C-5″), 121.3, 126.9 (C-5, C-8), 122.6 (C-3), 126.5, 127.9 (C-2″, C-6″, C-2‴, C-6‴), 127.6, 129.3 (C-6, C-7), 128.5, 129.1 (C-4a, C-8a), 128.8 (C-3‴, C-5‴), 133.6, 138.2, 141.4, 149.9, 150.6, 158.4 (C-1″, C-1‴, C-4‴, C-1, C-4, C-4″).

MS (ESI, +): *m*/*z* = 1017.7 [M + H^+], 653.4, 567.3, 289.1.

HRMS (ESI, +): *m*/*z* [M + H^+] calcd for $C_{70}H_{85}N_2O_4$: 1017.6504; found: 1017.6496.

4,4′-Bis({10-[(4′-octyl-1,1′-biphenyl-4-yl)oxy]decyl}oxy)-1,1′-biisoquinoline (1b)

Purified by chromatography (PE–EtOAc, 5:1) followed by recrystallization from EtOAc.

Mp 127 °C (EtOAc); R_f = 0.46 (PE–EtOAc, 5:1).

FT-IR (ATR): 2923 (m), 2852 (m), 1578 (m), 1500 (m), 1454 (m), 1300 (m), 1247 (m), 1176 (m), 1097 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 6 H, CH_3), 1.23–1.71 (m, 48 H, CH_2), 1.75–1.87 (m, 4 H, CH_2), 1.94–2.06 (m, 4 H, CH_2), 2.57–2.66 (m, 4 H, $C_6H_4CH_2$), 4.00 (t, *J* = 6.5 Hz, 4 H, $C_6H_4OCH_2$), 4.33 (t, *J* = 6.3 Hz, 4 H, 4-OCH_2), 6.92–6.98 (m, 4 H, H-3″, H-5″), 7.19–7.24 (m, 4 H, H-3‴, H-5‴), 7.43–7.52 (m, 10 H, H-2″, H-6″, H-2‴, H-6‴, H-6 or H-7), 7.66–7.75 (m, 4 H, H-5 or H-8, H-6 or H-7), 8.25 (s, 2 H, H-3), 8.33–8.38 (m, 2 H, H-5 or H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.1, 26.2, 29.2, 29.3, 29.4, 29.5, 29.7, 31.6 (CH_2), 31.9 ($C_6H_4CH_2CH_2$), 35.6 ($C_6H_4CH_2$), 68.1, 68.8 (OCH_2), 114.7 (C-3″, C-5″), 121.4, 126.9 (C-5, C-8), 122.6 (C-3), 126.5, 127.9 (C-2″, C-6″, C-2‴, C-6‴), 127.6, 129.3 (C-6, C-7), 128.5, 129.1 (C-4a, C-8a), 128.8 (C-3‴, C-5‴), 133.5, 138.2, 141.4, 150.0, 150.6, 158.5 (C-1″, C-1‴, C-4‴, C-1, C-4, C-4″).

MS (ESI, +): *m*/*z* = 1151.8 [M + Na^+], 1129.8 [M + H^+].

HRMS (ESI, +): *m*/*z* [M + H^+] calcd for $C_{78}H_{101}N_2O_4$: 1129.7756; found: 1129.7744.

4′-[(6-{[4′-({6-[(4′-cyano-1,1′-biphenyl-4-yl)oxy]hexyl}oxy)-1,1′-biisoquinolin-4-yl]oxy}hexyl)oxy]-1,1′-biphenyl-4-carbonitrile (1c)

Purified by chromatography (PE–EtOAc, 5:1).

Mp 186 °C; R_f = 0.22 (PE–EtOAc, 5:1).

FT-IR (ATR): 2922 (m), 2223 (m), 1580 (m), 1470 (m), 1379 (m), 1268 (s), 1245 (s), 1168 (m), 1094 (s), 1024 (m), 950 (m), 830 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60–1.75 (m, 10 H, CH_2), 1.83–1.95 (m, 6 H, CH_2), 4.10 (t, *J* = 6.4 Hz, 4 H, 4″-OCH_2), 4.35 (t, *J* = 6.4 Hz, 4 H, 4-OCH_2), 6.90–6.99 (m, 4 H, H-3″, H-5″), 7.52–7.59 (m, 4 H, H-3‴, H-5‴), 7.66–7.82 (m, 12 H, H-6, H-7, H-2″, H-6″, H-2‴, H-6‴), 7.86 (s, 2 H, H-3), 8.26 (s, 2 H, H-3), 8.24–8.38 (m, 2 H, H-5 or H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.8, 29.1, 29.2 (CH_2), 67.9, 68.7 (OCH_2), 110.3 (C-4‴), 115.0 (C-3″, C-5″), 119.2 (CN), 121.3, 126.9 (C-5, C-8), 122.8 (C-3), 127.1, 128.4 (C-2″, C-6″, C-2‴, C-3‴), 128.6, 129.2 (C-4a, C-8a), 132.6 (C-3‴, C-5‴), 131.4, 145.3, 150.0, 159.7 (C-1, C-4, C-1″, C-1‴, C-4″).

MS (ESI, +): *m*/*z* = 865.4 [M + Na^+], 843.4 [M + H^+].

HRMS (ESI, +): *m*/*z* [M + H^+] calcd for $C_{56}H_{51}N_4O_4$: 843.3905; found: 843.3900.

4,4′-Bis({6-[4-(2-octylpyrimidin-5-yl)phenoxy]hexyl}oxy)-1,1′-biisoquinoline (1d)

Purified by recrystallization from EtOAc.

Mp 147 °C; R_f = 0.19 (PE–EtOAc, 1:1).

FT-IR (ATR): 2921 (m), 2851 (m), 1607 (m), 1577 (m), 1539 (m), 1517 (m), 1503 (m), 1441 (s), 1417 (m), 1392 (m), 1377 (m), 1294 (s), 1246 (s), 1181 (m), 1159 (m), 1094 (s), 1059 (m), 1027 (m), 995 (m), 934 (m), 872 cm^{-1} (m).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.7 Hz, 6 H, CH_3), 1.20–1.48 (m, 20 H, CH_2), 1.61–1.78 (m, 8 H, CH_2), 1.77–1.99 (m, 8 H, CH_2), 1.99–2.13 (m, 4 H, CH_2), 2.93–3.04 (m, 4 H, 2‴-CH_2), 4.07 (t, *J* = 6.7 Hz, 4 H, 4″-OCH_2), 4.35 (t, *J* = 6.2 Hz, 4 H, 4-OCH_2), 6.99–7.09 (m, 4 H, H-3″, H-5″), 7.43–7.52 (m, 6 H, H-2″, H-6 or H-7), 7.63–7.71 (m, 2 H, H-6 or H-7), 7.71–7.78 (m, 2 H, H-5 or H-8), 8.24 (s, 2 H, H-3), 8.29–8.36 (m, 2 H, H-5 or H-8), 8.83 (s, 4 H, H-4‴, H-6‴).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 28.8, 29.2, 29.4, 31.9 (CH_2), 39.0 (2‴-CH_2), 67.8, 68.7 (OCH_2), 115.4 (C-3″, C-5″), 121.5, 126.9 (C-5, C-8), 122.7 (C-3), 126.8, 130.8 (C-1″, C-5‴), 127.9 (C-2″, C-6″), 127.5, 129.5 (C-6, C-7), 128.5, 129.1 (C-4a, C-8a), 143.2, 149.7, 159.8, 169.7 (C-1, C-4, C-2‴, C-4″), 154.4 (C-4‴, C-6‴).

HRMS (ESI, +): *m*/*z* [M + H^+] calcd for $C_{66}H_{81}N_6O_4$: 1021.6314; found: 1021.6317.

Anal. Calcd for $C_{66}H_{80}N_6O_4$: C, 77.61; H, 7.89; N, 8.23. Found: C, 77.58; H, 8.00; N, 8.15.

4,4′-Bis(propyloxy)-1,1′-biisoquinoline (21b)

Purified by chromatography (PE–EtOAc, 1:1).

Mp 164 °C; R_f = 0.30 (PE–EtOAc, 1:1).

FT-IR (ATR): 2968 (m), 2934 (m), 1576 (m), 1502 (m), 1450 (m), 1369 (m), 1295 (s), 1276 (s), 1246 (s), 1159 (m), 1094 (s), 1057 (m), 1020 (m), 961 (m), 903 (m), 893 (m), 852 (m), 766 (s), 722 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.4 Hz, 6 H, CH_3), 1.97–2.08 (m, 4 H, CH_2), 4.29 (t, *J* = 6.4 Hz, 4 H, OCH_2), 7.47 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 2 H, H-6 or H-7), 7.68 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 2 H, H-6 or H-7), 7.74 (ddd, *J* = 8.4, 1.2, 0.8 Hz, 2 H, H-5 or H-8), 8.24 (s, 2 H, H-3), 8.35 (ddd, *J* = 8.4, 1.2, 0.8 Hz, 2 H, H-5 or H-8).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7 (CH_3), 22.7 (CH_2), 70.3 (OCH_2), 121.3, 126.9 (C-5, C-8), 122.8 (C-3), 127.6, 129.1 (C-6, C-7), 128.5, 129.2 (C-4a, C-8a), 149.8, 150.7 (C-1, C-4).

MS (ESI, +): *m*/*z* = 395.2 [M + Na^+], 373.2 [M + H^+].

Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.19; H, 6.48; N, 7.49.

4,4′-Bis(octyloxy)-1,1′-biisoquinoline (21g)

Purified by chromatography (PE–EtOAc, 5:1).

Mp 105 °C; R_f = 0.24 (PE–EtOAc, 5:1).

FT-IR (ATR): 2922 (m), 2853 (m), 1576 (m), 1502 (m), 1453 (m), 1296 (s), 1244 (m), 1173 (m), 1159 (m), 1096 (s), 1023 (m), 956 (m), 849 (m), 766 (s), 665 (m), 625 cm^{-1} (s).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.3 Hz, 6 H, CH_3), 1.31–1.47 (m, 16 H, CH_2), 1.58–1.64 (m, 4 H, CH_2), 1.97–2.02 (m, 4 H, CH_2), 4.32 (t, *J* = 6.5 Hz, 4 H, OCH_2), 7.47 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 2 H, H-6 or H-7), 7.67 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 2 H, H-6 or H-7), 7.73–7.75 (m, 2 H, H-5 or H-8), 8.23 (s, 2 H, H-3), 8.33–8.35 (m, 2 H, H-5 or H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.2, 29.3, 29.4, 31.8 (CH_2), 68.8 (OCH_2), 121.3, 126.9 (C-5, C-8), 122.8 (C-3), 127.6, 129.2 (C-6, C-7), 128.5, 129.1 (C-4a, C-8a), 149.8, 150.6 (C-1, C-4).

HRMS (ESI, +): *m*/*z* [M + H^+] calcd for $C_{34}H_{44}N_2O_2$: 513.3481; found: 513.3471.

Anal. Calcd for $C_{34}H_{44}N_2O_2$: C, 79.65; H, 8.65; N, 5.46. Found: C, 79.41; H, 8.62; N, 5.35.

4,4′-Bis(nonyloxy)-1,1′-biisoquinoline (21h)
Purified by chromatography (PE–EtOAc, 4:1).

Mp 110 °C; R_f = 0.31 (PE–EtOAc, 4:1).

FT-IR (ATR): 2925 (m), 1454 (m), 1297 (s), 1096 (m), 766 (s), 686 (m), 624 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.7 Hz, 6 H, CH_3), 1.26–1.50 (m, 20 H, CH_2), 1.56–1.66 (m, 4 H, CH_2), 1.95–2.04 (m, 4 H, CH_2), 4.32 (t, J = 6.4 Hz, 4 H, OCH_2), 7.44 (ddd, J = 8.4, 7.1, 1.2 Hz, 2 H, H-6 or H-7), 7.68 (ddd, J = 8.4, 7.1, 1.2 Hz, 2 H, H-6 or H-7), 7.74 (ddd, J = 8.4, 1.2, 0.8 Hz, 2 H, H-5 or H-8), 8.23 (s, 2 H, H-3), 8.34 (ddd, J = 8.4, 1.2, 0.8 Hz, 2 H, H-5 or H-8).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.2, 29.3, 29.4, 29.6, 31.9 (CH_2), 68.9 (OCH_2), 121.4, 126.9 (C-5, C-8), 122.8 (C-3), 127.6, 129.2 (C-6, C-7), 128.6, 129.1 (C-4a, C-8a), 149.9, 150.7 (C-1, C-4).

Anal. Calcd for $C_{36}H_{48}N_2O_2$: C, 79.96; H, 8.95; N, 5.18. Found: C, 79.70; H, 8.92; N, 5.04.

4,4′-Bis(octadecyloxy)-1,1′-biisoquinoline (21m)
Purified by chromatography (PE–EtOAc, 2:1).

Mp 99 °C; R_f = 0.40 (PE–EtOAc, 2:1).

FT-IR (ATR): 2914 (s), 2849 (s), 1471 (m), 1456 (m), 1297 (s), 1274 (m), 1102 (m), 759 (s), 715 (m), 689 (m), 624 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.7 Hz, 6 H, CH_3), 1.21–1.50 (m, 56 H, CH_2), 1.56–1.66 (m, 4 H, CH_2), 1.95–2.04 (m, 4 H, CH_2), 4.32 (t, J = 6.4 Hz, 4 H, OCH_2), 7.48 (ddd, J = 8.4, 7.1, 1.2 Hz, 2 H, H-6 or H-7), 7.69 (ddd, J = 8.4, 7.1, 1.2 Hz, 2 H, H-6 or H-7), 7.74 (ddd, J = 8.4, 1.2, 0.8 Hz, 2 H, H-5 or H-8), 8.24 (s, 2 H, H-3), 8.34 (ddd, J = 8.4, 1.2, 0.8 Hz, 2 H, H-5 or H-8).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.2, 29.1, 29.3, 29.4, 29.6, 29.7, 31.9 (CH_2), 68.8 (OCH_2), 121.4, 126.9 (C-5, C-8), 122.7 (C-3), 127.6, 129.2 (C-6, C-7), 128.3, 129.1 (C-4a, C-8a), 149.9, 150.6 (C-1, C-4).

Anal. Calcd for $C_{54}H_{84}N_2O_2$: C, 81.76; H, 10.67; N, 3.53. Found: C, 81.49; H, 10.71; N, 3.43.

4,4′-Bis{4-[4-(hexyloxy)phenoxy]butoxy}-1,1′-biisoquinoline (22a)
Purified by chromatography (PE–EtOAc, 1:1) and recrystallization from EtOAc.

Mp 139 °C; R_f = 0.30 (PE–EtOAc, 1:1).

FT-IR (ATR): 1505 (s), 1469 (m), 1303 (m), 1225 (s), 1095 (m), 1035 (m), 831 (m), 818 (m), 771 (m), 750 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.1 Hz, 6 H, CH_3), 1.27–1.51 (m, 12 H, CH_2), 1.69–1.83 [m, 4 H, Ph(4′)OCH_2CH_2], 2.03–2.27 [m, 8 H, Ph(1′)$OCH_2CH_2CH_2$], 3.91 (t, J = 6.6 Hz, 4 H, $PhOCH_2$), 4.08 (t, J = 6.1 Hz, 4 H, $PhOCH_2$), 4.40 [t, J = 5.9 Hz, 4 H, isoquinoline(4)OCH_2], 6.79–6.91 (m, 8 H, H-2′, H-3′, H-5′, H-6′), 7.47 (ddd, J = 8.4, 6.9, 1.3 Hz, 2 H, H-6 or H-7), 7.66 (ddd, J = 8.4, 6.9, 1.3 Hz, 2 H, H-6 or H-7), 7.74 (ddd, J = 8.4, 1.3, 0.8 Hz, 2 H, H-5 or H-8), 8.24 (s, 2 H, H-3), 8.31 (ddd, J = 8.4, 1.3, 0.8 Hz, 2 H, H-5 or H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6, 25.7, 26.2, 26.3, 29.4, 31.6 (CH_2), 68.0, 68.4 ($PhOCH_2$), 68.7 [isoquinoline(4)OCH_2], 115.4 (C-2′, C-3′, C-5′, C-6′), 121.3, 126.9 (C-5, C-8), 122.7 (C-3), 127.6, 129.3 (C-6, C-7), 128.5, 129.0 (C-4a, C-8a), 149.7, 150.8 (C-1, C-4), 153.0, 153.4 (C-1′, C-4′).

MS (ESI, +): m/z = 807.4 [M + Na^+], 785.5 [M + H^+], 579.2 [M + H – OC_6H_{13} – Ph – OCH_2]$^+$.

HRMS (ESI, +): m/z [M + H^+] calcd for $C_{50}H_{61}N_2O_6$: 785.5430; found: 785.4504.

4,4′-Bis{4-[4-(octyloxy)phenoxy]butoxy}-1,1′-biisoquinoline (22b)
Purified by chromatography (PE–EtOAc, 1:1) and recrystallization from EtOAc.

Mp 138 °C; R_f = 0.31 (PE–EtOAc, 1:1).

FT-IR (ATR): 2923 (m), 2854 (m), 1505 (s), 1468 (m), 1383 (w), 1301 (m), 1223 (s), 1094 (m), 1036 (m), 824 (m), 772 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.8 Hz, 6 H, CH_3), 1.22–1.42 (m, 20 H, CH_2), 1.70–1.82 [m, 4 H, Ph(4′)OCH_2CH_2], 2.05–2.27 [m, 8 H, Ph(1′)$OCH_2CH_2CH_2$], 3.91 (t, J = 6.6 Hz, 4 H, $PhOCH_2$), 4.08 (t, J = 6.0 Hz, 4 H, $PhOCH_2$), 4.40 [t, J = 5.9 Hz, 4 H, isoquinoline(4)OCH_2], 6.80–6.91 (m, 8 H, H-2′, H-3′, H-5′, H-6′), 7.47 (ddd, J = 8.4, 7.0, 1.3 Hz, 2 H, H-6 or H-7), 7.67 (ddd, J = 8.4, 7.0, 1.3 Hz, 2 H, H-6 or H-7), 7.74 (ddd, J = 8.4, 1.3, 0.8 Hz, 2 H, H-5 or H-8), 8.24 (s, 2 H, H-3), 8.31 (ddd, J = 8.4, 1.3, 0.8 Hz, 2 H, H-5 or H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.1, 26.2, 26.3, 29.3, 29.4, 31.8 (CH_2), 68.0, 68.4 ($PhOCH_2$), 68.7 [isoquinoline(4)OCH_2], 115.4 (C-2′, C-3′, C-5′, C-6′), 121.3, 126.9 (C-5, C-8), 122.7 (C-3), 127.6, 129.3 (C-6, C-7), 128.5, 129.0 (C-4a, C-8a), 149.7, 150.8 (C-1, C-4), 153.1, 153.3 (C-1′, C-4′).

MS (EI, +): m/z (%) = 840.5 (12) [M^+], 741.3 (100) [M – C_7H_{15}]$^+$, 287.0 (12), 277.2 (23), 222.1 (18), 123.0 (45), 110.0 (100), 55.0 (17).

HRMS (ESI, +): m/z [M + H^+] calcd for $C_{54}H_{69}N_2O_6$: 841.5156; found: 841.5143.

4,4′-Bis({6-[4-(hexyloxy)phenoxy]hexyl}oxy)-1,1′-biisoquinoline (22c)
Purified by chromatography (PE–EtOAc, 1:1) and recrystallization from EtOAc.

Mp 84 °C; R_f = 0.30 (PE–EtOAc, 1:1).

FT-IR (ATR): 2935 (m), 2864 (m), 1509 (s), 1474 (m), 1299 (m), 1229 (s), 1095 (m), 1038 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.9 Hz, 6 H, CH_3), 1.30–1.36 (m, 8 H, CH_2), 1.41–1.48 (m, 4 H, CH_2), 1.62–1.79 (m, 12 H, CH_2), 1.82–1.89 (m, 4 H, CH_2), 2.00–2.07 (m, 4 H, CH_2), 3.90 (t, J = 6.6 Hz, 4 H, $PhOCH_2$), 3.96 (t, J = 6.5 Hz, 4 H, $PhOCH_2$), 4.33 [t, J = 6.3 Hz, 4 H, isoquinoline(4)OCH_2], 6.80–6.85 (m, 8 H, H-2′, H-3′, H-5′, H-6′), 7.47 (ddd, J = 8.4, 7.0, 1.4 Hz, 2 H, H-6 or H-7), 7.66 (ddd, J = 8.4, 7.0, 1.4 Hz, 2 H, H-6 or H-7), 7.74 (ddd, J = 8.4, 1.3, 0.9 Hz, 2 H, H-5 or H-8), 8.23 (s, 2 H, H-3), 8.32 (ddd, J = 8.4, 1.3, 0.9 Hz, 2 H, H-5 or H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6, 25.7, 26.0, 29.3, 29.4, 31.6 (CH_2), 68.5, 68.7 [$PhOCH_2$, isoquinoline(4)OCH_2], 115.4 (C-2′, C-3′, C-5′, C-6′), 121.3, 126.9 (C-5, C-8), 122.8 (C-3), 127.6, 129.3 (C-6, C-7), 128.5, 129.1 (C-4a, C-8a), 149.8, 150.7 (C-1, C-4), 153.1, 153.3 (C-1′, C-4′).

MS (ESI, +): m/z = 1683.0 [2 × MH^+], 841.5 [M + H^+].

HRMS (ESI, +): m/z [M + H^+] calcd for $C_{54}H_{69}N_2O_6$: 841.5156; found: 841.5160.

4,4′-Bis({6-[4-(octyloxy)phenoxy]hexyl}oxy)-1,1′-biisoquinoline (22d)
Purified by chromatography (PE–EtOAc, 2:1).

Mp 94 °C; R_f = 0.32 (PE–EtOAc, 1:2).

FT-IR (ATR): 2929 (m), 2854 (m), 1507 (s), 1472 (m), 1299 (m), 1227 (s), 1173 (m), 1095 (m), 1035 (m), 822 (m), 769 (s), 627 cm^{-1} (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 6 H, CH_3), 1.23–1.48 (m, 20 H, CH_2), 1.59–1.72 (m, 8 H, CH_2), 1.73–1.79 (m, 4 H, CH_2), 1.82–1.90 (m, 4 H, CH_2), 2.00–2.07 (m, 4 H, CH_2), 3.90 (t, *J* = 6.6 Hz, 4 H, $PhOCH_2$), 3.96 (t, *J* = 6.5 Hz, 4 H, $PhOCH_2$), 4.33 [t, *J* = 6.4 Hz, 4 H, isoquinoline(4)OCH_2], 6.81–6.86 (m, 8 H, H-2′, H-3′, H-5′, H-6′), 7.47 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 2 H, H-6 or H-7), 7.67 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 2 H, H-6 or H-7), 7.74 (ddd, *J* = 8.4, 1.3, 0.8 Hz, 2 H, H-5 or H-8), 8.23 (s, 2 H, H-3), 8.32 (ddd, *J* = 8.4, 1.3, 0.8 Hz, 2 H, H-5 or H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 25.9, 26.0, 26.1, 29.3, 29.4, 31.8 (CH_2), 68.5, 68.7 [$PhOCH_2$, isoquinoline(4)OCH_2], 115.4 (C-2′, C-3′, C-5′, C-6′), 121.3, 126.9 (C-5, C-8), 122.7 (C-3), 127.6, 129.3 (C-6, C-7), 128.5, 129.1 (C-4a, C-8a), 149.8, 150.7 (C-1, C-4), 153.1, 153.3 (C-1′, C-4′).

MS (ESI, +): *m*/*z* = 919.6 [M + Na^+], 897.6 [M + H^+].

HRMS (ESI, +): *m*/*z* [M + H^+] calcd for $C_{58}H_{76}N_2O_6$: 897.5782; found: 897.5771.

1-(4-Bromobutoxy)-4-(hexyloxy)benzene (18a)

The general procedure described for **8**, **9** and **14**, was used with 4-hexyloxyphenol (750 mg, 3.44 mmol) and 1,4-dibromobutane (0.99 mL, 1.78 g, 8.26 mmol) to obtain **18a**.

Yield: 857 mg (76%); colorless solid; mp 45 °C; R_f = 0.18 (PE–EtOAc, 100:1).

FT-IR (ATR): 2935 (m), 2871 (m), 1508 (s), 1473 (m), 1394 (m), 1277 (m), 1226 (s), 1114 (m), 1044 (m), 1029 (s), 827 (vs), 770 (s), 653 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.32–1.42 (m, 6 H, CH_2), 1.69–1.80 [m, 2 H, Ph(4)OCH_2CH_2], 1.86–1.97 (m, 2 H, H-2′), 2.00–2.12 (m, 2 H, H-3′), 3.49 (t, *J* = 6.6 Hz, 2 H, H-4′), 3.90 [t, *J* = 6.2 Hz, 2 H, Ph(4)OCH_2], 3.94 (t, *J* = 6.7 Hz, 2 H, H-1′), 6.77–6.86 (m, 4 H, H-2, H-3, H-5, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6, 25.7, 31.6 (CH_2), 28.0 [Ph(4)OCH_2CH_2], 29.4 (C-2′), 29.5 (C-3′), 33.6 (C-4′), 67.4 (C-1′), 68.7 [Ph(4)OCH_2], 115.4 (C-2, C-3, C-5, C-6), 152.9, 153.4 (C-1, C-4).

MS (EI, +): *m*/*z* (%) = 328.1 (28) [M + $^{79}Br]^+$, 135 (64) [$BrC_4H_8^+$], 110 (100), 55 (56), 43 (32).

HRMS (EI, +): *m*/*z* [M^+] calcd for $C_{16}H_{25}BrO_2$: 328.1038; found: 328.1025.

1-(4-Bromobutoxy)-4-(octyloxy)benzene (18b)

The general procedure described for **8**, **9** and **14** was used with 4-octyloxyphenol (750 mg, 3.37 mmol) and 1,4-dibromobutane (0.97 mL, 1.75 g, 8.09 mmol) to obtain **18b**.

Yield: 877 mg (73%); colorless solid; mp 52 °C; R_f = 0.16 (PE–EtOAc, 100:1).

FT-IR (ATR): 2920 (m), 1508 (s), 1473 (m), 1226 (s), 1044 (m), 1028 (s), 826 (vs), 769 (m), 653 cm^{-1} (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.23–1.48 (m, 10 H, CH_2), 1.71–1.79 (m, 2 H, CH_2), 1.88–1.95 (m, 2 H, CH_2), 2.02–2.10 (m, 2 H, CH_2), 3.48 (t, *J* = 6.6 Hz, 2 H, CH_2Br), 3.90 (t, *J* = 6.6 Hz, 2 H, OCH_2), 3.94 (t, *J* = 6.1 Hz, 2 H, OCH_2), 6.78–6.85 (m, 4 H, H-2, H-3, H-5, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 4.1 (CH_3), 22.7, 26.1, 28.0, 29.3, 29.4, 29.5, 31.8, 33.5 (CH_2), 67.5, 68.7 (OCH_2), 115.4 (C-2, C-3, C-5, C-6), 152.9, 153.3 (C-1, C-4).

MS (EI, +): *m*/*z* (%) = 356.1 (100) [M + $^{79}Br]^+$, 135.0 (70) [$BrC_4H_8]^+$, 110.0 (78).

HRMS (ESI, +): *m*/*z* [M + H^+] calcd for $C_{18}H_{30}BrO_2$: 357.1429; found: 357.1425.

1-[(6-Bromohexyl)oxy]-4-(hexyloxy)benzene (18c)

The general procedure described for **8**, **9** and **14** was used with 4-hexyloxyphenol (750 mg, 3.44 mmol) and 1,6-dibromohexane (1.27 mL, 2.01 g, 8.26 mmol) to obtain **18c**.

Yield: 824 mg (67%); colorless solid; mp 51 °C; R_f = 0.26 (PE–EtOAc, 100:1).

FT-IR (ATR): 2935 (m), 1508 (s), 1474 (m), 1226 (s), 1031 (s), 825 (vs), 769 (s), 725 (m), 645 (m), 533 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.27–1.57 (m, 10 H, CH_2), 1.69–1.82 (m, 4 H, CH_2), 1.83–1.95 (m, 2 H, CH_2), 3.42 (t, *J* = 6.8 Hz, 2 H, CH_2Br), 3.90 (t, *J* = 6.6 Hz, 2 H, OCH_2), 3.91 (t, *J* = 6.5 Hz, 2 H, OCH_2), 6.80–6.83 (m, 4 H, H-2, H-3, H-5, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6, 25.3, 25.7, 27.9, 29.2, 29.4, 31.6, 32.7, 33.8 (CH_2), 68.3, 68.6 (OCH_2), 115.4 (C-2, C-3, C-5, C-6), 153.1, 153.3 (C-1, C-4).

MS (EI, +): *m*/*z* (%) = 358.1 (72) [M + $^{81}Br]^+$, 110.0 (100).

HRMS (ESI, +): *m*/*z* [M + Na^+] calcd for $C_{18}H_{29}BrNaO_2$: 379.1249; found: 379.1230.

1-[(6-Bromohexyl)oxy]-4-(octyloxy)benzene (18d)

The general procedure described for **8**, **9** and **14** was used with 4-octyloxyphenol (250 mg, 1.12 mmol) and 1,6-dibromohexane (0.41 mL, 656 mg, 2.69 mmol) to obtain **18d**.

Yield: 332 mg (77%); colorless solid; mp 57 °C; R_f = 0.34 (PE–EtOAc, 100:1).

FT-IR (ATR): 2935 (m), 2857 (m), 1508 (s), 1474 (m), 1229 (s), 1030 (s), 1008 (m), 997 (m), 826 (s), 770 (m), 645 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.24–1.54 (m, 14 H, CH_2), 1.69–1.82 (m, 4 H, CH_2), 1.83–1.93 (m, 2 H, CH_2), 3.42 (t, *J* = 6.8 Hz, 2 H, CH_2Br), 3.89 (t, *J* = 6.4 Hz, 2 H, OCH_2), 3.90 (t, *J* = 6.4 Hz, 2 H, OCH_2), 6.80–6.83 (m, 4 H, H-2, H-3, H-5, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 25.3, 26.1, 27.9, 29.2, 29.4, 31.8, 32.7, 33.8 (CH_2), 68.3, 68.6 (OCH_2), 115.4 (C-2, C-3, C-5, C-6), 153.1, 153.3 (C-1, C-4).

GC-MS (EI): *m*/*z* (%) = 386 (56) [M + $^{81}Br]^+$, 384 (100) [M^+], 383 (12), 377 (16).

HRMS (ESI, +): *m*/*z* [M + Na^+] calcd for $C_{20}H_{33}BrNaO_2$: 407.1562; found: 407.1546.

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(16) Application of the catalyst system $NiCl_2 \cdot 6H_2O/Zn/PPh_3$ to 4-ethoxy-1-bromoisoquinoline yielded only 38% of the desired 1,1′-biisoquinoline **22a**, whereas no product was formed with $NiBr_2(PPh_3)_2/Zn/Et_4NI$. As the latter system catalyzed the reaction with 4-ethoxy-1-chloroisoquinoline, the experiments were carried out with chloroisoquinolines **20** in the presence of nickel chloride as the catalyst.