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SYNTHESIS OF MACROBICYCLES COMPRISING 2,7-DIAMINO-NAPHTHALENE MOIETY VIA PALLADIUM-CATALYZED AMINATION REACTION

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Abstract – An original synthetic approach to bismacroyclic ligands bearing naphthalene moiety was developed. First, the macrocycles comprising 2,7-diaminonaphthalene fragment were reacted with 2,7-dibromonaphthalene, 4,4'-dibromobiphenyl or bromobenzyl bromide affording corresponding *N,N'*-bis(bromoaryl) or *N,N'*-bis(bromobenzyl) substituted macrocycles. Pd-catalyzed macrocyclization of these compounds with a wide range of di- and polyamines led to a series of new macrobicyclic ligands. The yields of the macrobicycles are strongly dependent on the nature of starting compounds, reaching 35% in some cases.

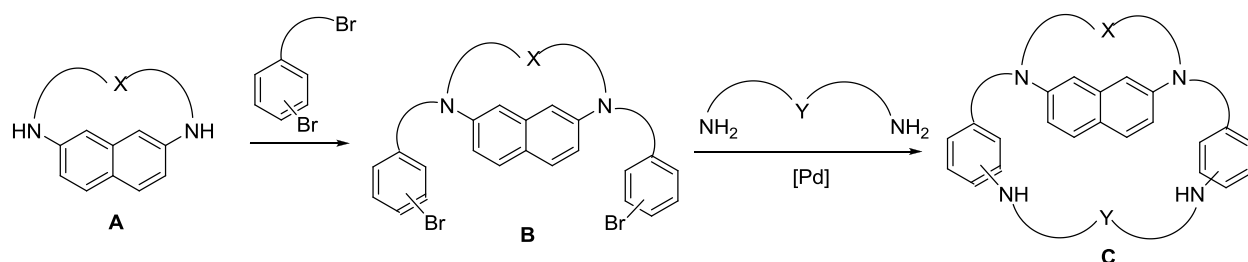
INTRODUCTION

Different fields of coordination chemistry find practical applications in modern technology such as development of chemosensors for environment control, chemotherapeutic or diagnostic agents, treatment

This paper is dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.

of nuclear waste. Thus there is a great demand for the design and synthesis of efficient complexing agents, first of all, able of binding selectively different metal cations. Macrocycles comprising several donor atoms are an important class of compounds possessing valuable coordination properties, and complex architectures have been developed on their basis to finely fit the needs for selective cation binding. Ligand properties could be tuned not only by varying the number and nature of donor groups but also by introducing different non-coordinating structural motifs. Condensed aromatic moieties are of major interest in ligand design for chemosensing and sequestration of toxic and radioactive metal ions. The first macrocyclic compounds involving the naphthalene moiety were described in the literature over 70 years ago.¹ This emissive hydrophobic aromatic system is drawing considerable attention and dozen of works appeared dealing with the synthesis and investigation of azacrown ethers derivatives functionalized by exocyclic naphthalene substituents and macrocycles of different geometry based on naphthalene, which are of the main interest for us. A number of polyoxamacrocycles containing 2,3-, 1,5- and 1,8-disubstituted naphthalene were investigated in binding alkali metals using NMR titration technique,²⁻⁴ macrocycles with larger cavities with two 2,3-disubstituted naphthalene moieties were synthesized,⁴⁻⁶ other substituents were introduced in positions 1 and 4 to modify their coordination properties.^{7,8} A number of works is dedicated to coordination properties of the macrocycles based on 1,1'-binaphthalene fragment including interesting spherands.^{4,9,10} All these monomacrocyclic compounds coordinate alkali metal cations, ammonia and simplest alkylammonium cations, as do more sophisticated polyoxa bismacrocycles,⁴ macrobicycle,¹¹ and macrotricycle.¹² Azamacrocycles involving naphthalene and Schiff bases,¹³ diamides,¹⁴ diimides,¹⁵ lactames¹⁶ were prepared. Naphthalene system can be linked to tetraazamacrocycles¹⁷ or incorporated into calixarene¹⁸ and catenane¹⁹ structures, attached to porphyrins.²⁰ These compounds are of interest for supramolecular chemistry and could be used *e.g.* as organic anions receptors²¹ or molecular rotors.²²

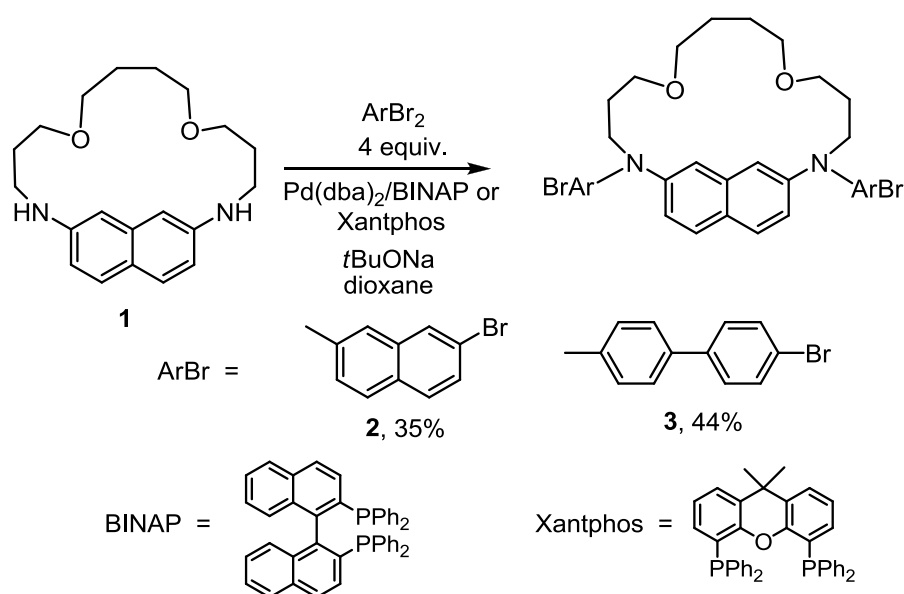
Recently, we have developed an efficient synthesis of polyoxa and polyaza macrocycles of type **A** involving 2,7-diaminonaphthalene moiety.^{23,24} These macrocycles could be used as starting compounds for the synthesis of more sophisticated bismacrocyclic ligands. For example, *N*-functionalization of aromatic amino groups providing dibromides **B** followed by Pd-catalyzed cyclization reaction could be a rational way to new cryptands **C** (Scheme 1). In this work the influence of structural parameters of intermediate compounds on the synthesis of macrobicycles **C** was investigated. The described results clearly demonstrated the interest and limitation of this synthetic approach.



Scheme 1

RESULTS AND DISCUSSION

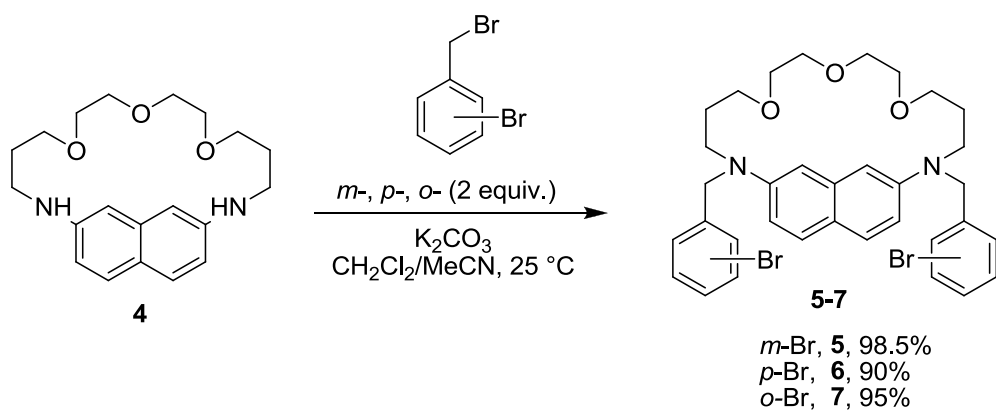
The synthetic approach illustrated on Scheme 1 is based on selective transformations, thus the structure of dihalogenides **B** is a key factor for successful preparation of target macrobicycles. Indeed, the selective substitution of one halogen atom by a macrocyclic diamine **A** is important for the first step. In the second step, the macrocyclization involving substitution of the second resting halogen atoms by another diamine should proceed smoothly. Pd-Catalyzed amination reaction could provide the desirable selectivity for both transformations according to our earlier investigations.²⁵⁻²⁷ Moreover, the difference in the reactivity of alkyl and aryl halogenides could be used to perform a selective first step. Bearing this in mind we have prepared two series of *N,N'*-disubstituted macrocyclic compounds using model dioxa- and trioxadiazamacrocycles **1** and **4** (Scheme 2, 3). The first series of macrocycles was prepared using selective Pd-catalyzed arylation of the macrocycle **1** with aromatic dibromides²⁵ such as 2,7-dibromonaphthalene, and 4,4'-dibromobiphenyl (Scheme 2). These arylating agents were chosen due to the fact that two bromine atoms are located in different aromatic rings what would make the cyclization step easier.



Scheme 2

A careful choice of the ligand was needed for the successful catalytic reaction of the sterically hindered macrocycle **1** with the dihalides **2**, **3**. Moreover, to obtain the target products in good yields, an excess of the dihalides was employed to prevent undesirable oligomerization reactions. While the reaction of **1** with 4 equiv. of 2,7-dibromonaphthalene proceeded equally smoothly with BINAP and Xantphos, the reaction with 4,4'-dibromobiphenyl worked only with BINAP. After optimization of the reaction conditions we obtained two *N,N'*-bis(bromoaryl) substituted macrocycles **2** and **3** in 35 and 44% yields, respectively. An attempt to employ 3,3'-dibromobiphenyl for *N,N'*-difunctionalization of the macrocycle **1** was unsuccessful as this reaction afforded only a monoarylated compound and oligomers according to the ^1H NMR and MALDI-TOF analysis of the reaction mixture.

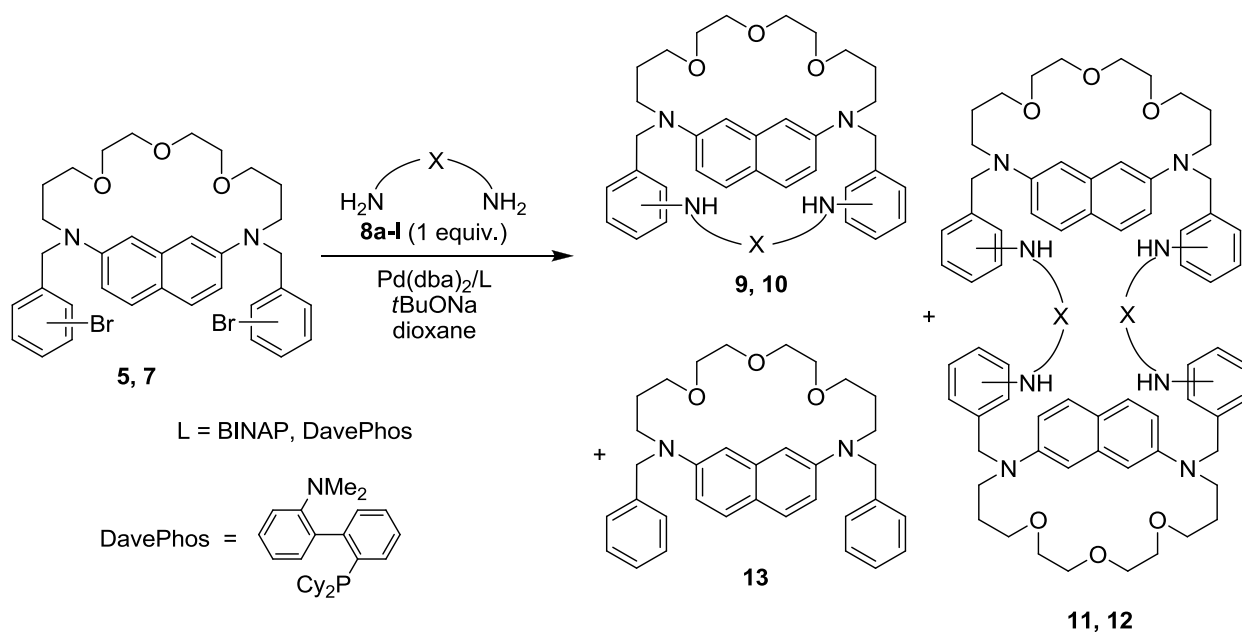
The second series of *N,N'*-bis(bromobenzyl) derivatives **5-7** was obtained starting from the macrocycle **4** and isomeric bromobenzyl bromides in the presence of K_2CO_3 as a base (Scheme 3).



Scheme 3

Next, we investigated the macrocyclization reaction using various di- and polyamines **8a-l** and the halogen-substituted macrocycles **2**, **3**, **5-7** in the presence of Pd catalyst according to our procedure for selective *N,N'*-diarylation of linear polyamines.^{26,27} All our attempts to obtain macrobicycles from dibromoaryl derivatives **2**, **3** using the most long-chain trioxadiazamine **8g** were unsuccessful though a full conversion of starting compounds was observed. Probably, the distance between the two bromine atoms in these rigid structures is too long to provide the desirable macrocyclization.

In contrast, the macrocyclization reaction proceeds easily when dibromide **5** reacted with di- and polyamines **8** including diazacrown ethers **8h,i** and adamantanediamines **8j-l** (Scheme 4, Table 1).



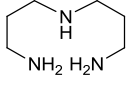
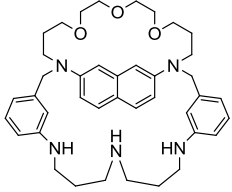
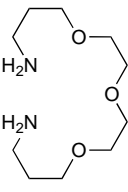
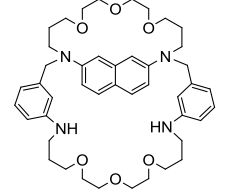
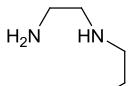
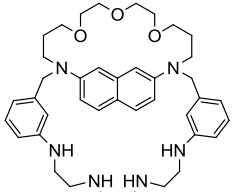
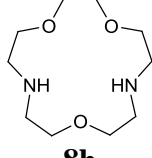
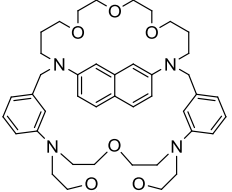
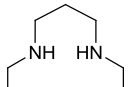
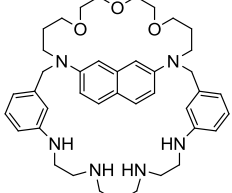
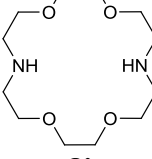
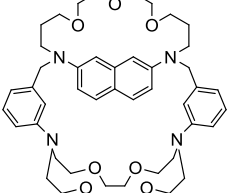
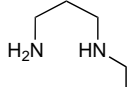
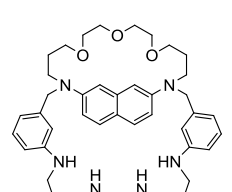
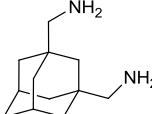
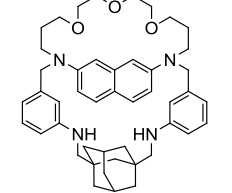
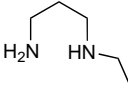
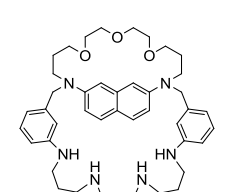
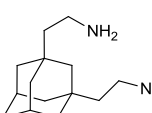
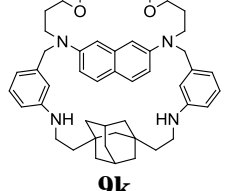
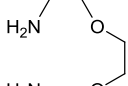
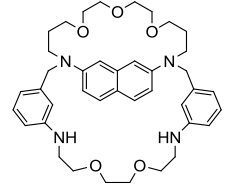
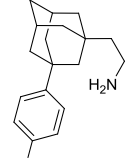
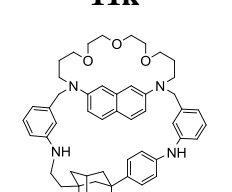
Scheme 4

The reactions were conducted using equimolar amounts of the reagents in boiling dioxane ($C = 0.02 \text{ M}$) with $t\text{BuONa}$ as a base. In the majority of experiments we applied $\text{Pd}(\text{dba})_2/\text{BINAP}$ (8/9 mol%) catalytic system. However, $\text{Pd}(\text{dba})_2/\text{DavePhos}$ (16/18 mol%) was used to carry out macrocyclization with 1,3-bis(aminomethyl)adamantane **8j** and diazacrown ethers **8h,i** in accordance with our previous investigations of the arylation of adamantanediamines.²⁸⁻³⁰

As shown in **Table 1**, a wide range of linear di- and polyamines afforded the target macrobicycles **9a-l** in quite good yields which attained 33-35% in some cases (entries 6, 7). The ^1H NMR and MALDI-TOF analysis of the reaction mixtures indicated that a complete conversion of starting dibromides **5-7** was achieved in all investigated reactions but side products (macrotricyclic cyclodimers **11** and other oligomers) were obtained along with the target compounds. The macrobicycles **9a-l** were isolated by column chromatography and were characterized using conventional methods, ^1H , ^{13}C NMR spectroscopy, MALDI-TOF and HRMS mass-spectrometry.

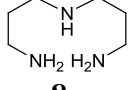
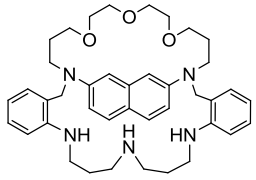
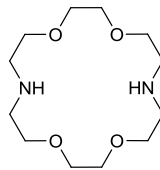
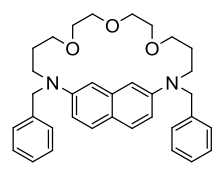
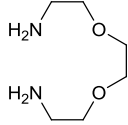
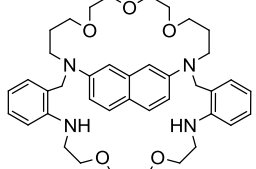
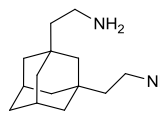
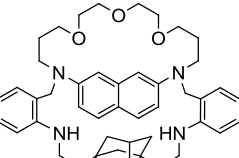
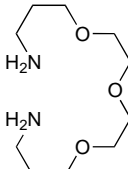
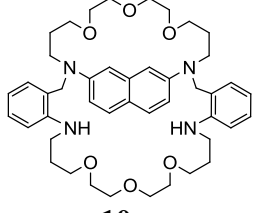
It is to be noted that the ^1H NMR spectra are useful for structural characterization of macrobicycles **9a,b,f,h-l** bearing a short or conformationally rigid spacer linking benzyl moieties. The chemical shifts of diastereotopic PhCH_2N protons are significantly different from one another due to hindered rotation, thus these protons are easily distinguishable from the corresponding signals of the side products. Moreover, some proton resonances of the short spacers are upfield shifted, probably due to their location in the cone-shape shielding zone of the naphthalene ring. The most pronounced upfield shifts are observed for the adamantane-containing macrobicycles.

Table 1. The synthesis of macrobicyclic compounds **9a-l** from *N,N'*-bis(3-bromobenzyl) substituted macrocycle **5**.^{a)}

Entry	Polyamine	Product	Yield (%)	Entry	Polyamine	Product	Yield (%)
1	 8a	 9a	25	7	 8g	 9g	35
2	 8b	 9b	20	8 ^{b)}	 8h	 9h	16
3	 8c	 9c	20	9 ^{b)}	 8i	 9i	10
4	 8d	 9d	14	10 ^{b)}	 8j	 9j	17
5	 8e	 9e	19	11	 8k	 9k	20
6	 8f	 9f	33	12	 8l	 9l	8
							23

^{a)} Pd(dba)₂/BINAP (8/9 mol%), equimolar amounts of the reagents in boiling dioxane (C = 0.02 M);^{b)} Pd(dba)₂/DavePhos (16/18 mol%).

Table 2. The synthesis of macrobicyclic compounds **10a,f,g,k** from *N,N'*-bis(2-bromobenzyl) substituted macrocycle **5**.^{a)}

Entry	Polyamine	Product	Yield (%)	Entry	Polyamine	Product	Yield (%)
1	 8a	 10a	19	4 ^{b)}	 8i	 13	46
2	 8f	 10f	18	5	 8k	 10k	7
3	 8g	 10g	27				

^{a)} Pd(dba)₂/BINAP (8/9 mol%), equimolar amounts of the reagents in boiling dioxane (C = 0.02 M);

^{b)} Pd(dba)₂/DavePhos (16/18 mol%).

The results presented in **Table 1** indicated that there is no clear dependence of the macrobicycles yields on the chain length of polyamines what implies that the two *m*-bromobenzyl substituents are easily adjusted to structural parameters of polyamines by rotation of these groups. This conformation flexibility of dibromide **5** allows the successful macrocyclization reaction for rigid adamantane-containing diamines **8j-l** (entries 10-12). It is important to note that diazacrown ethers with secondary amino groups are also suitable reagents with the studied reaction and afford original macrotricyclic ligands **9h,i** (entries 8, 9). Surprisingly, an attempt to prepare macrobicycles using bis(4-bromobenzyl) derivative **6** was unsuccessful even when a long-chain trioxadiazine **8g** was used for macrocyclization. According to NMR and MALDI-TOF analysis, the target macrobicyclic compound was observed in the crude reaction mixtures but only in small amounts. However, all our attempts to isolate these compounds in pure form by column chromatography failed.

On the other hand, *ortho*-isomer **7** turned to be suitable for the macrocyclization (Scheme 4) and we managed to obtain macrobicycles **10** using different diamines (**Table 2**). The reactions of this isomer with linear polyamines **8a,f,g** led to corresponding macrobicycles **10a,f,g** in 18-27% yields (entries 1-3). The most sterically demanding macrocyclization between dibromide **7** and diazacrown ether **8i** gave only compound **13** resulting from the reduction of both bromine atoms (entry 4) while the macrocyclization with another rigid amine, *i.e.* adamantanediamine **8k**, resulted in a low yield of the bicyclic compound (entry 5). Thus, the cyclization reaction of this dibromide with diamines is significantly restricted by the nature of the diamine spacer.

To conclude, we have developed an interesting synthetic approach to sophisticated macrobicyclic ligands *via* Pd-catalyzed macrocyclization reaction. The structure of *N,N'*-difunctionalized intermediate **B** is the key parameter and should be carefully optimized. In favourable cases, the desirable macrobicycles could be obtained in good yields. The cavity size and the donor atoms of these macrobicyclic ligands can be varied according to the nature of starting compounds. Interesting macrotricyclic ligands combining diazacrown and more rigid oxamacrocyclic moieties could also be prepared using this approach.

EXPERIMENTAL

All chemicals were purchased from Aldrich and Acros companies and used without further purification. 4,4'-Dibromobiphenyl, polyamines **8a-i**, BINAP, DavePhos were purchased from Aldrich Co and used without purification. 2,7-Dibromonaphthalene was synthesized following a known method.³¹ Adamantane-containing diamines **8j,l** were provided by Professor G.M. Butov from the Volzhskii Polytechnical Institute, and diamine **8k** was provided by Professor B.S. Orlinson from the Volgograd State Technical University. Pd(dba)₂ was synthesized according to a procedure described.³² Macrocycles **1** and **4** were synthesized using a procedure described earlier.²³ Commercial dioxane was distilled over NaOH and sodium under argon, acetonitrile was distilled over P₂O₅, dichloromethane and methanol were distilled prior to use. Column chromatography was carried out using silica gel (40-60 mkm) purchased from Fluka. ¹H and ¹³C NMR spectra were registered in CDCl₃ using Bruker Avance 400 spectrometer at 400 and 100.6 MHz respectively. Chemical shift values δ are given in ppm and coupling constants *J* in Hz. MALDI-TOF spectra were recorded with Bruker Ultraflex and Bruker Autoflex II spectrometers using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards. ESI-TOF spectra were registered using Bruker microQ-TOF spectrometer.

Typical procedure for the Pd-catalyzed amination reactions.

A two-neck flask (25 mL) flushed with dry argon, equipped with a magnetic stirrer and condenser was charged with aryl halide, Pd(dba)₂ (8-16 mol%), BINAP or Xantphos (9-18 mol%), and absolute dioxane.

The mixture was stirred for 2 min, then appropriate polyamine **8** was added followed by sodium *tert*-butoxide. The reaction mixture was refluxed for 6-30 h, after cooling to room temperature the residue was filtered off, dioxane evaporated *in vacuo*, and the residue was analyzed by NMR spectroscopy. Column chromatography was carried out using a sequence of eluents: petroleum ether-CH₂Cl₂ 10:1-1:4, CH₂Cl₂ in the case of compounds **2** and **3** and CH₂Cl₂, CH₂Cl₂ CH₂Cl₂-MeOH 200:1 – 3:1, CH₂Cl₂-MeOH-NH₃aq 100:20:1 – 10:4:1 in the case of compounds **13-17**.

2,15-Bis-(7-bromonaphth-2-yl)-6,11-dioxa-2,15-diazatricyclo[14.5.3.0^{19,23}]tetracos-1(21),16(24),17,19,22-pentaene (2) was synthesized according to two procedures: a) from macrocycle **1** (82 mg, 0.25 mmol), 2,7-dibromonaphthalene (286 mg, 1 mmol) in the presence of Pd(dba)₂ (12 mg, 8 mol%), Xantphos(13 mg, 9 mol%), sodium *tert*-butoxide (72 mg, 0.75 mmol) in 2.5 mL dioxane, reflux time 20 h; b) from the same amounts of starting compounds in the presence of Pd(dba)₂ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%). Reaction mixtures were combined and chromatographed on silica gel. Eluent petroleum ether – CH₂Cl₂ 1:4, yellow solid. Yield 130 mg (35%). ¹H NMR (CDCl₃): δ 1.91 (bs, 4H), 2.03 (quintet, ³J = 5.0 Hz, 4H), 3.55 (t, ³J = 5.3 Hz, 4H), 3.56 (bs, 4H), 4.22 (t, ³J = 6.6 Hz, 4H), 7.04 (dd, ³J = 8.5 Hz, ⁴J = 1.8 Hz, 2H), 7.33-7.36 (m, 4H), 7.41 (dd, ³J = 8.7 Hz, ⁴J = 1.8 Hz, 2H), 7.49 (d, ³J = 8.8 Hz, 2H), 7.60 (d, ³J = 8.6 Hz, 2H), 7.68 (d, ³J = 8.6 Hz, 2H), 7.72 (s, 2H), 7.85 (s, 2H). ¹³C NMR (CDCl₃): δ 27.2 (2CH₂), 27.4 (2CH₂), 49.2 (2CH₂), 67.1 (2CH₂), 70.7 (2CH₂), 115.0 (2CH), 115.8 (2CH), 120.2 (2CH), 120.4 (2C), 123.6 (2CH), 125.1 (1C), 127.1 (2CH), 127.6 (2C), 127.8 (2CH), 128.6 (4CH), 129.1 (2CH), 135.7 (2C), 136.6 (1C), 145.1 (2C), 146.9 (2C). HRMS (MALDI-TOF) *m/z* calcd for C₄₀H₃₉Br₂N₂O₂ [M+H]⁺ 737.1378, found 737.1324.

2,15-Bis-(4'-bromobiphenyl-4-yl)-6,11-dioxa-2,15-diazatricyclo[14.5.3.0^{19,23}]tetracos-1(21),16(24),17,19,22-pentaene (3) was synthesized from macrocycle **1** (115 mg, 0.35 mmol), 4,4'-dibromobiphenyl (437 mg, 1.4 mmol) in the presence of Pd(dba)₂ (32 mg, 16 mol%), BINAP (39 mg, 18 mol%), sodium *tert*-butoxide (100 mg, 1.05 mmol) in 3.5 mL dioxane, reflux time 20 h. Eluent petroleum ether – CH₂Cl₂ 1:2-1:4 and CH₂Cl₂ – MeOH, 200:1, beige crystalline powder, m.p. 108-110°C. Yield 126 mg (44%). ¹H NMR (CDCl₃): δ 1.89 (bs, 4H), 2.00 (quintet, ³J = 5.0 Hz, 4H), 3.52-3.57 (m, 8H), 4.14 (t, ³J = 6.6 Hz, 4H), 7.05 (dd, ³J = 8.7 Hz, ⁴J = 1.8 Hz, 2H), 7.20 (m, AA'MM'-biph, 4H), 7.46 (m, AA'MM'-biph, 4H), 7.48 (d, ³J = 8.0 Hz, 2H), 7.50 (m, AA'MM'-biph, 4H), 7.55 (m, AA'MM'-biph, 4H), 7.62 (bs, 2H). ¹³C NMR (CDCl₃): δ 27.2 (2CH₂), 27.5 (2CH₂), 49.0 (2CH₂), 67.2 (2CH₂), 70.7 (2CH₂), 113.8 (2CH), 119.7 (2CH), 120.2 (1C), 120.7 (2C), 122.5 (4CH), 127.5 (4CH), 127.7 (2CH), 128.1 (4CH), 131.8 (4CH), 132.9 (2C), 136.7 (1C), 139.6 (2C), 146.4 (2C), 146.9 (2C). HRMS (MALDI-TOF) *m/z* calcd for C₄₄H₄₃Br₂N₂O₂ [M+H]⁺ 789.1691, found 789.1735.

2,16-Bis(3-bromobenzyl)-6,9,12-trioxa-2,16-diazatricyclo[15.5.3.0^{20,24}]pentacosa-1(22),17(25),18,20,23-pentaene (5) was synthesized from the macrocycle **4** (500 mg, 1.35 mmol), *m*-bromobenzyl bromide (675 mg, 2.7 mmol), in the presence of K₂CO₃ (785 mg, 5.7 mmol) in 15 mL MeCN and 2 mL CH₂Cl₂, by stirring for 48 h at rt. The reaction mixture was diluted with 50 mL CH₂Cl₂, the residue was filtered off, the organic solvents were evaporated *in vacuo*, and the target compound **5** was obtained as a pale-yellow glassy solid. Yield 910 mg (98.5%). ¹H NMR (CDCl₃): δ 1.98 (quintet, ³*J* = 5.5 Hz, 4H), 3.56 (t, ³*J* = 5.1 Hz, 4H), 3.64–3.70 (m, 8H), 3.87–3.91 (m, 4H), 4.60 (s, 4H), 6.59 (dd, ³*J* = 9.0 Hz, ⁴*J* = 2.1 Hz, 2H), 7.10 (d, ⁴*J* = 2.1 Hz, 2H), 7.13–7.21 (m, 4H), 7.36 (d, ³*J* = 6.6 Hz, 2H), 7.38–7.42 (m, 4H). ¹³C NMR (CDCl₃): δ 26.7 (2CH₂), 48.3 (2CH₂), 53.3 (2CH₂), 68.5 (2CH₂), 71.0 (2CH₂), 71.4 (2CH₂), 103.8 (2CH), 111.6 (2CH), 119.9 (1C), 122.7 (2C), 125.1 (2CH), 128.5 (2CH), 129.4 (2CH), 129.9 (2CH), 130.1 (2CH), 136.8 (1C), 142.2 (2C), 146.6 (2C). HRMS (MALDI-TOF) *m/z* calcd for C₃₄H₃₉N₂Br₂O₃ [M+H]⁺ 681.1327, found 681.1322.

2,16-Bis(4-bromobenzyl)-6,9,12-trioxa-2,16-diazatricyclo[15.5.3.0^{20,24}]pentacosa-1(22),17(25),18,20,23-pentaene (6) was synthesized from the macrocycle **4** (317 mg, 0.92 mmol), *p*-bromobenzyl bromide (504 mg, 2 mmol), in the presence of K₂CO₃ (550 mg, 4 mmol) in 10 mL MeCN and 1 mL CH₂Cl₂, by stirring for 48 h at rt. The reaction mixture was diluted with 40 mL CH₂Cl₂, the residue was filtered off, the organic solvents were evaporated *in vacuo*, and the target compound **6** was obtained as a pale-yellow glassy solid. Yield 560 mg (90%). ¹H NMR (CDCl₃): δ 1.96 (quintet, ³*J* = 4.5 Hz, 4H), 3.55 (t, ³*J* = 5.0 Hz, 4H), 3.61–3.68 (m, 8H), 3.85–3.89 (m, 4H), 4.56 (s, 4H), 6.58 (dd, ³*J* = 8.8 Hz, ⁴*J* = 2.3 Hz, 2H), 7.08 (d, ⁴*J* = 2.3 Hz, 2H), 7.11 (m, AA'MM'-Ph, 4H), 7.37 (d, ³*J* = 8.8 Hz, 2H), 7.39 (m, AA'MM'-Ph, ³*J* = 8.2 Hz, 4H). ¹³C NMR (CDCl₃): δ 26.5 (2CH₂, Δ*v*_{1/2} = 20 Hz), 48.0 (2CH₂, Δ*v*_{1/2} = 20 Hz), 52.8 (2CH₂, Δ*v*_{1/2} = 20 Hz), 68.2 (2CH₂, Δ*v*_{1/2} = 15 Hz), 70.5 (2CH₂, Δ*v*_{1/2} = 15 Hz), 71.0 (2CH₂), 103.5 (2CH, Δ*v*_{1/2} = 15 Hz), 111.2 (2CH, Δ*v*_{1/2} = 20 Hz), 119.6 (1C), 120.1 (2C, Δ*v*_{1/2} = 15 Hz), 127.9 (4CH, Δ*v*_{1/2} = 15 Hz), 128.1 (2CH, Δ*v*_{1/2} = 15 Hz), 131.2 (4CH), 136.6 (1C, Δ*v*_{1/2} = 15 Hz), 138.2 (2C, Δ*v*_{1/2} = 20 Hz), 146.2 (2C, Δ*v*_{1/2} = 15 Hz). HRMS (MALDI-TOF) *m/z* calcd for C₃₄H₃₉N₂Br₂O₃ [M+H]⁺ 681.1327, found 681.1356.

2,16-Bis(2-bromobenzyl)-6,9,12-trioxa-2,16-diazatricyclo[15.5.3.0^{20,24}]pentacosa-1(22),17(25),18,20,23-pentaene (7) was synthesized from the macrocycle **4** (140 mg, 0.38 mmol), *o*-bromobenzyl bromide (207 mg, 0.84 mmol), in the presence of K₂CO₃ (254 mg, 1.8 mmol) in 5 mL MeCN and 1 mL CH₂Cl₂, by stirring for 48 h at rt. The reaction mixture was diluted with 40 mL CH₂Cl₂, the residue was filtered off, the organic solvents were evaporated *in vacuo*, and the target compound **7** was obtained as a pale-yellow glassy solid. Yield 245 mg (95%). ¹H NMR (CDCl₃): δ 2.08–2.15 (m, 4H), 3.66 (t, ³*J* = 5.0 Hz, 4H),

3.75–3.82 (m, 8H), 3.97–4.01 (m, 4H), 4.70 (s, 4H), 6.55 (d, $^3J = 8.8$ Hz, 2H), 7.15–7.20 (m, 2H), 7.22–7.26 (m, 6H), 7.44 (d, $^3J = 8.8$ Hz, 2H), 7.65 (d, $^3J = 7.7$ Hz, 2H). ^{13}C NMR (CDCl_3): δ 26.9 (2CH₂), 48.4 (2CH₂), 54.3 (2CH₂), 68.5 (2CH₂), 70.9 (2CH₂), 71.4 (2CH₂), 103.2 (2CH), 111.2 (2CH), 119.7 (1C), 122.6 (2C), 127.4 (2CH), 128.0 (2CH), 128.2 (2CH), 128.4 (2CH), 132.6 (2CH), 136.8 (1C), 137.6 (2C), 146.4 (2C). HRMS (MALDI-TOF) m/z calcd for C₃₄H₃₉N₂Br₂O₃ [M+H]⁺ 681.1327, found 681.1302.

Macrobicycle 9a was synthesized from compound **5** (136 mg, 0.2 mmol), triamine **8a** (26 mg, 0.2 mmol) in the presence of Pd(dba)₂ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium *tert*-butoxide (58 mg, 0.6 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 5:1, pale-yellow glassy compound. Yield 32 mg (25%). ^1H NMR (CDCl_3): δ 1.93 (bs, 4H), 2.02 (bs, 4H), 2.83–2.89 (m, 4H), 3.04–3.12 (m, 4H), 3.49–3.90 (m, 16H), 4.34 (d, $^2J = 18.0$ Hz, 2H), 4.68 (bs, 2H), 4.80 (d, $^2J = 18.0$ Hz, 2H), 6.17 (bs, 2H), 6.24 (d, $^3J = 8.3$ Hz, 2H), 6.43 (d, $^3J = 8.8$ Hz, 2H), 6.54 (d, $^3J = 7.5$ Hz, 2H), 7.01–7.07 (m, 4H), 7.18 (d, $^3J = 9.0$ Hz, 2H), NH proton of dialkylamino group was not assigned. ^{13}C NMR (CDCl_3): δ 25.9 (2CH₂), 27.4 (2CH₂), 40.7 (2CH₂), 45.9 (2CH₂), 49.7 (2CH₂), 53.7 (2CH₂), 68.7 (2CH₂), 70.9 (2CH₂), 71.1 (2CH₂), 103.1 (2CH), 108.3 (2CH), 111.8 (2CH), 112.3 (2CH), 114.4 (2CH), 119.1 (1C), 127.8 (2CH), 129.4 (2CH), 137.0 (1C), 140.2 (2C), 146.3 (2C), 147.9 (2C). HRMS (MALDI-TOF) m/z calcd for C₄₀H₅₄N₅O₃ [M+H]⁺ 652.4227, found 652.4208.

Macrobicycle 9b was synthesized from compound **5** (136 mg, 0.2 mmol), tetraamine **8b** (29 mg, 0.2 mmol) in the presence of Pd(dba)₂ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium *tert*-butoxide (58 mg, 0.6 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 3:1, pale-yellow glassy compound. Yield 27 mg (20%). ^1H NMR (CDCl_3): δ 1.93 (bs, 2H), 2.04 (bs, 2H), 2.19 (bs, 2H), 2.34 (bs, 2H), 2.45 (bs, 4H), 3.15 (bs, 4H), 3.51 (t, $^3J = 7.4$ Hz, 4H), 3.54–3.70 (m, 8H), 3.81–3.89 (m, 4H), 4.32 (d, $^2J = 17.6$ Hz, 2H), 4.50 (bs, 2H), 4.85 (d, $^2J = 17.6$ Hz, 2H), 6.31 (bs, 2H), 6.41 (d, $^3J = 7.8$ Hz, 2H), 6.54 (d, $^3J = 8.6$ Hz, 2H), 6.60 (d, $^3J = 7.6$ Hz, 2H), 7.03 (bs, 2H), 7.07 (t, $^3J = 7.8$ Hz, 2H), 7.21 (d, $^3J = 8.8$ Hz, 2H), two NH protons of dialkylamino groups were not assigned. ^{13}C NMR (CDCl_3): δ 27.4 (2CH₂), 41.2 (2CH₂), 45.8 (2CH₂), 46.6 (2CH₂), 49.3 (2CH₂), 53.4 (2CH₂), 68.7 (2CH₂), 70.9 (2CH₂), 71.2 (2CH₂), 103.8 (2CH), 109.3 (2CH), 111.8 (2CH), 112.5 (2CH), 115.7 (2CH), 119.2 (1C), 127.8 (2CH), 129.5 (2CH), 137.1 (1C), 140.4 (2C), 146.5 (2C), 147.4 (2C). HRMS (MALDI-TOF) m/z calcd for C₄₀H₅₅N₆O₃ [M+H]⁺ 667.4335, found 667.4320.

Macrobicycle 9c was synthesized from compound **5** (136 mg, 0.2 mmol), tetraamine **8c** (32 mg, 0.2 mmol) in the presence of Pd(dba)₂ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium *tert*-butoxide (58 mg, 0.6 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH-NH₃aq 100:20:1, pale-yellow

glassy compound. Yield 27 mg (20%). ^1H NMR (CDCl_3): δ 1.49 (bs, 2H), 1.97 (bs, 4H), 2.46 (t, $^3J = 7.0$ Hz, 4H), 2.64 (bs, 4H), 3.05 (t, $^3J = 5.2$ Hz, 4H), 3.40–3.72 (m, 12H), 3.86 (s, 4H), 4.03 (bs, 2H), 4.33 (bs, 2H), 4.88 (bs, 2H), 6.36 (bs, 2H), 6.40 (dd, $^3J = 7.8$ Hz, $^4J = 1.9$ Hz, 2H), 6.58 (d, $^3J = 7.7$ Hz, 2H), 6.82 (dd, $^3J = 9.1$ Hz, $^4J = 2.4$ Hz, 2H), 7.07 (d, $^3J = 2.4$ Hz, 2H), 7.14 (t, $^3J = 7.7$ Hz, 2H), 7.34 (d, $^3J = 8.8$ Hz, 2H), two NH protons of dialkylamino groups were not assigned. ^{13}C NMR (CDCl_3): δ 27.4 (2CH₂), 30.3 (1CH₂), 43.1 (2CH₂), 47.7 (2CH₂), 48.3 (2CH₂), 49.0 (2CH₂), 53.1 (2CH₂), 68.8 (2CH₂), 70.9 (2CH₂), 71.3 (2CH₂), 103.0 (2CH), 109.8 (2CH), 111.3 (2CH), 111.5 (2CH), 115.4 (2CH), 119.5 (1C), 128.2 (2CH), 129.4 (2CH), 140.3 (1C), 142.6 (2C), 146.6 (2C), 148.6 (2C). HRMS (MALDI-TOF) m/z calcd for C₄₁H₅₇N₆O₃ [M+H]⁺ 681.4492, found 681.4464.

Macrobicycle 9d was synthesized from compound **5** (136 mg, 0.2 mmol), tetraamine **8d** (35 mg, 0.2 mmol) in the presence of Pd(dba)₂ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium *tert*-butoxide (58 mg, 0.6 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH-NH₃aq 100:20:1, pale-yellow glassy compound. Yield 20 mg (14%). ^1H NMR (CDCl_3): δ 1.59 (quintet, $^3J = 6.4$ Hz, 4H), 1.95–2.01 (m, 4H), 2.44 (s, 4H), 2.47 (t, $^3J = 6.8$ Hz, 4H), 3.03 (t, $^3J = 6.4$ Hz, 4H), 3.55 (t, $^3J = 4.9$ Hz, 4H), 3.62–3.69 (m, 8H), 3.84–3.88 (m, 4H), 4.59 c (4H), 6.38–6.42 (m, 4H), 6.57 (d, $^3J = 7.6$ Hz, 2H), 6.64 (dd, $^3J = 9.0$ Hz, $^4J = 2.3$ Hz, 2H), 7.05 (d, $^4J = 2.3$ Hz, 2H), 7.13 (t, $^3J = 8.0$ Hz, 2H), 7.35 (d, $^3J = 9.0$ Hz, 2H), NH protons were not assigned. ^{13}C NMR (CDCl_3): δ 27.1 (2CH₂), 28.9 (2CH₂), 42.6 (2CH₂), 47.9 (2CH₂), 48.6 (2CH₂), 48.7 (2CH₂), 53.1 (2CH₂), 68.8 (2CH₂), 70.9 (2CH₂), 71.3 (2CH₂), 102.8 (2CH), 110.3 (2CH), 110.9 (2CH), 111.3 (2CH), 115.2 (2CH), 119.5 (1C), 128.2 (2CH), 129.3 (2CH), 137.2 (1C), 140.4 (2C), 146.8 (2C), 148.6 (2C). HRMS (MALDI-TOF) m/z calcd for C₄₂H₅₉N₆O₃ [M+H]⁺ 695.4648, found 695.4673.

Macrobicycle 9e was synthesized from compound **5** (225 mg, 0.33 mmol), tetraamine **8e** (62 mg, 0.33 mmol) in the presence of Pd(dba)₂ (15 mg, 8 mol%), BINAP (17 mg, 9 mol%), sodium *tert*-butoxide (96 mg, 1 mmol) in 17 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH-NH₃aq 100:20:2-100:20:3, pale-yellow glassy compound. Yield 43 mg (19%). ^1H NMR (CDCl_3): δ 1.54 (quintet, $^3J = 6.2$ Hz, 2H), 1.61 (quintet, $^3J = 6.6$ Hz, 4H), 1.95–2.02 (m, 4H), 2.51–2.58 (m, 8H), 3.03 (t, $^3J = 6.3$ Hz, 4H), 3.55 (t, $^3J = 4.9$ Hz, 4H), 3.63–3.69 (m, 8H), 3.84–3.88 (m, 4H), 4.58 (s, 4H), 6.37 (bs, 2H), 6.40 (d, $^3J = 8.1$ Hz, 2H), 6.58 (d, $^3J = 7.6$ Hz, 2H), 6.62 (dd, $^3J = 9.0$ Hz, $^4J = 2.1$ Hz, 2H), 7.04 (d, $^4J = 2.1$ Hz, 2H), 7.14 (t, $^3J = 7.7$ Hz, 2H), 7.33 (d, $^3J = 9.0$ Hz, 2H), NH protons were not assigned. ^{13}C NMR (CDCl_3): δ 27.0 (2CH₂), 29.3 (3CH₂), 42.3 (2CH₂), 47.7 (2CH₂), 48.3 (2CH₂), 48.7 (2CH₂), 53.3 (2CH₂), 68.8 (2CH₂), 70.9 (2CH₂), 71.3 (2CH₂), 102.9 (2CH), 110.2 (2CH), 110.9 (2CH), 111.4 (2CH), 115.3 (2CH), 119.4 (1C), 128.2 (2CH), 129.3 (2CH), 137.1 (1C), 140.4 (2C), 146.8 (2C), 148.8 (2C). HRMS (MALDI-TOF) m/z

calcd for $C_{43}H_{61}N_6O_3$ $[M+H]^+$ 709.9829, found 709.9790.

Macrobicyclic 9f was synthesized from compound **5** (119 mg, 0.18 mmol), dioxadiazine **8f** (26 mg, 0.18 mmol) in the presence of $Pd(dba)_2$ (8 mg, 8 mol%), BINAP (10 mg, 9 mol%), sodium *tert*-butoxide (50 mg, 0.54 mmol) in 5 mL dioxane. Reflux time 24 h. Eluent CH_2Cl_2 -MeOH 50:1, pale-yellow glassy compound. Yield 48 mg (33%). 1H NMR ($CDCl_3$): δ 1.87–1.98 (m, 2H), 2.01–2.11 (m, 2H), 3.08–3.14 (m, 8H), 3.27–3.40 (m, 4H), 3.47–3.53 (m, 4H), 3.57–3.74 (m, 8H), 3.82–3.92 (m, 4H), 4.31 (d, $^2J = 17.5$ Hz, 2H), 4.93 (d, $^2J = 17.5$ Hz, 2H), 6.36 (bs, 2H), 6.43 (d, $^3J = 7.8$ Hz, 2H), 6.56–6.64 (m, 4H), 7.04 (bs, 2H), 7.13 (t, $^3J = 7.7$ Hz, 2H), 7.33 (d, $^3J = 8.6$ Hz, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 27.5 (2CH₂), 43.2 (2CH₂), 48.9 (2CH₂), 53.0 (2CH₂), 68.6 (2CH₂), 69.2 (2CH₂), 70.3 (2CH₂), 71.0 (2CH₂), 71.4 (2CH₂), 103.3 (2CH), 110.8 (2CH), 111.4 (2CH), 111.6 (2CH), 115.8 (2CH), 119.6 (1C), 128.1 (2CH), 129.2 (2CH), 137.3 (1C), 140.4 (2C), 146.5 (2C), 148.2 (2C). HRMS (MALDI-TOF) m/z calcd for $C_{40}H_{53}N_4O_5$ $[M+H]^+$ 669.4016, found 669.4085.

Macrobicyclic 9g was synthesized from compound **5** (68 mg, 0.10 mmol), trioxadiazine **8g** (22 mg, 0.10 mmol) in the presence of $Pd(dba)_2$ (4.5 mg, 8 mol%), BINAP (5.5 mg, 9 mol%), sodium *tert*-butoxide (28 mg, 0.30 mmol) in 5 mL dioxane. Reflux time 24 h. Eluent CH_2Cl_2 -MeOH 50:1, pale-yellow glassy compound. Yield 30 mg (35%). 1H NMR ($CDCl_3$): δ 1.94–2.01 (m, 8H), 3.12 (t, $^3J = 6.1$ Hz, 4H), 3.24 (bs, 4H), 3.30–3.33 (m, 4H), 3.38 (t, $^3J = 5.6$ Hz, 4H), 3.54 (t, $^3J = 4.9$ Hz, 4H), 3.60–3.70 (m, 8H), 3.84–3.88 (m, 4H), 4.57 (s, 4H), 6.41–6.49 (m, 4H), 6.59 (d, $^3J = 7.6$ Hz, 2H), 6.64 (d, $^3J = 8.0$ Hz, 2H), 7.02 (bs, 2H), 7.15 (t, $^3J = 7.7$ Hz, 2H), 7.35 (d, $^3J = 8.6$ Hz, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 26.9 (2CH₂), 28.6 (2CH₂), 42.4 (2CH₂), 48.4 (2CH₂), 53.4 (2CH₂), 68.7 (2CH₂), 69.9 (2CH₂), 70.2 (2CH₂), 70.3 (2CH₂), 71.0 (2CH₂), 71.4 (2CH₂), 103.2 (2CH), 110.3 (2CH), 111.4 (2CH), 111.6 (2CH), 115.5 (2CH), 119.7 (1C), 128.3 (2CH), 129.4 (2CH), 137.2 (1C), 140.5 (2C), 147.0 (2C), 148.7 (2C). HRMS (MALDI-TOF) m/z calcd for $C_{44}H_{61}N_4O_6$ $[M+H]^+$ 741.4591, found 741.4622.

Macrotricyclic 9h was synthesized from compound **5** (225 mg, 0.33 mmol), diazacrown ether **8h** (72 mg, 0.33 mmol) in the presence of $Pd(dba)_2$ (30 mg, 16 mol%), DavePhos (23 mg, 18 mol%), sodium *tert*-butoxide (96 mg, 1 mmol) in 13 mL dioxane. Reflux time 24 h. Eluent CH_2Cl_2 -MeOH 100:1, pale-yellow glassy compound. Yield 38 mg (16%). 1H NMR ($CDCl_3$): δ 2.01 (quintet, $^3J = 6.0$ Hz, 4H), 2.46–2.60 (m, 4H), 3.02 (ddd, $^2J = 13.8$ Hz, $^3J = 6.5$ Hz, $^3J = 4.2$, 2H), 3.29–3.36 (m, 2H), 3.41–3.48 (m, 2H), 3.49–3.62 (m, 16H), 3.64–3.70 (m, 4H), 3.84 (dt, $^2J = 14.8$ Hz, $^3J = 7.5$ Hz, 2H), 3.91 (t, $^3J = 4.2$ Hz, 4H), 4.32 (d, $^2J = 17.5$ Hz, 2H), 5.01 (d, $^2J = 17.5$ Hz, 2H), 6.27 (bs, 2H), 6.36 (d, $^3J = 8.3$ Hz, 2H), 6.55 (d, $^3J = 7.5$ Hz, 2H), 6.58 (d, $^3J = 9.1$ Hz, 2H), 7.08 (bs, 2H), 7.13 (t, $^3J = 7.8$ Hz, 2H), 7.29 (d, $^3J = 9.0$ Hz, 2H). ^{13}C

NMR (CDCl₃): δ 28.2 (2CH₂), 49.5 (2CH₂), 51.2 (2CH₂), 51.7 (2CH₂), 53.7 (2CH₂), 68.1 (2CH₂), 68.5 (2CH₂), 70.9 (2CH₂), 71.1 (2CH₂), 71.2 (2CH₂), 71.4 (2CH₂), 104.7 (2CH), 108.8 (2CH), 110.7 (2CH), 112.5 (2CH), 113.9 (2CH), 119.8 (1C), 127.9 (2CH), 129.2 (2CH), 137.3 (1C), 139.7 (2C), 146.2 (2C), 147.6 (2C). HRMS (ESI-TOF) m/z calcd for C₄₄H₅₉N₄O₆ [M+H]⁺ 739.4434, found 739.4429.

Macrotricyclic 9i was synthesized from compound **5** (225 mg, 0.33 mmol), diazacrown ether **8i** (86 mg, 0.33 mmol) in the presence of Pd(dba)₂ (30 mg, 16 mol%), DavePhos (23 mg, 18 mol%), sodium *tert*-butoxide (96 mg, 1 mmol) in 13 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 50:1, pale-yellow glassy compound. Yield 27 mg (10%). ¹H NMR (CDCl₃): δ 1.85–1.98 (m, 4H), 3.25–3.55 (m, 24H), 3.56–3.70 (m, 8H), 3.81–3.91 (m, 8H), 4.29 (d, ² J = 17.1 Hz, 2H), 5.01 (d, ² J = 17.1 Hz, 2H), 6.37 (bs, 2H), 6.42 (d, ³ J = 8.4 Hz, 2H), 6.54 (d, ³ J = 7.3 Hz, 2H), 6.73 (d, ³ J = 8.9 Hz, 2H), 7.05 (bs, 2H), 7.12 (t, ³ J = 7.8 Hz, 2H), 7.33 (d, ³ J = 9.0 Hz, 2H). ¹³C NMR (CDCl₃): δ 27.9 (2CH₂), 49.0 (2CH₂), 50.1 (4CH₂), 54.3 (2CH₂), 68.7 (2CH₂), 69.0 (4CH₂), 70.5 (4CH₂), 70.9 (2CH₂), 71.3 (2CH₂), 105.2 (2CH), 110.2 (2CH), 110.9 (2CH), 112.9 (2CH), 114.5 (2CH), 120.1 (1C), 128.1 (2CH), 129.0 (2CH), 137.0 (1C), 140.0 (2C), 146.9 (2C), 148.5 (2C). HRMS (ESI-TOF) m/z calcd for C₄₆H₆₃N₄O₇ [M+H]⁺ 783.4696, found 783.4691.

Macrobicyclic 9j was synthesized from compound **5** (225 mg, 0.33 mmol), diamine **8j** (63 mg, 0.33 mmol) in the presence of Pd(dba)₂ (30 mg, 16 mol%), DavePhos (23 mg, 18 mol%), sodium *tert*-butoxide (96 mg, 1 mmol) in 13 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 100:1, pale-yellow glassy compound. Yield 41 mg (17%). ¹H NMR (CDCl₃): δ -0.42 (d, J = 12.0 Hz, 1H), 0.13 (d, J = 2.0 Hz, 1H), 0.54 (d, J = 11.6 Hz, 1H), 0.63 (d, J = 11.5 Hz, 1H), 0.90–0.95 (m, 4H), 1.21 ym. (s, 2H), 1.56 (d, J = 11.6 Hz, 2H), 1.89 (bs, 2H), 1.92–2.00 (m, 4H), 2.41 (d, J = 14.7 Hz, 2H), 2.73 (d, J = 14.7 Hz, 2H), 3.52–3.83 (m, 10H), 3.86–3.93 (m, 4H), 3.98 (ddd, ³ J = 11.3 Hz, ³ J = 6.6 Hz, ³ J = 2.7 Hz, 2H), 4.30 (d, ² J = 18.1 Hz, 2H), 5.05 (d, ² J = 18.1 Hz, 2H), 6.31 (bs, 2H), 6.32 (d, ³ J = 7.0 Hz, 2H), 6.49 (d, ³ J = 7.5 Hz, 2H), 6.58 (dd, ³ J = 9.1 Hz, ⁴ J = 2.1 Hz, 2H), 7.05 (t, ³ J = 8.0 Hz, 2H), 7.11 (d, ⁴ J = 2.1 Hz, 2H), 7.26 (d, ³ J = 9.1 Hz, 2H), NH protons were not assigned. ¹³C NMR (CDCl₃): δ 28.1 (2CH₂, 1CH), 28.4 (1CH), 35.0 (2C), 36.0 (1CH₂), 38.7 (2CH₂), 39.4 (2CH₂), 44.7 (1CH₂), 49.4 (2CH₂), 52.4 (2CH₂), 55.0 (2CH₂), 68.6 (2CH₂), 71.2 (2CH₂), 71.6 (2CH₂), 102.6 (2CH), 108.0 (2CH), 111.1 (2CH), 111.5 (2CH), 113.7 (2CH), 119.3 (1C), 128.2 (2CH), 129.0 (2CH), 137.5 (1C), 140.2 (2C), 146.4 (2C), 149.3 (2C). HRMS (ESI-TOF) m/z calcd for C₄₆H₅₉N₄O₃ [M+H]⁺ 715.4587, found 715.4582.

Macrobicyclic 9k was synthesized from compound **5** (136 mg, 0.2 mmol), diamine **8k** (45 mg, 0.2 mmol) in the presence of Pd(dba)₂ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium *tert*-butoxide (58 mg, 0.6

mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 200:1, pale-yellow glassy compound. Yield 30 mg (20%). ¹H NMR (CDCl₃): δ 0.13 (d, *J* = 12.2 Hz, 1H), 0.53 (d, *J* = 12.2 Hz, 1H), 0.74 (d, *J* = 11.6 Hz, 2H), 0.80 (dd, ³*J* = 12.8 Hz, ³*J* = 6.3 Hz, 2H), 0.90 (td, ³*J* = 12.9 Hz, ³*J* = 3.3 Hz, 2H), 1.10 (d, ³*J* = 11.9 Hz, 2H), 1.47 (d, ³*J* = 12.0 Hz, 2H), 1.51 (s, 2H), 1.56 (d, ³*J* = 12.0 Hz, 2H), 1.92 (bs, 3H), 2.05 (bs, 1H), 2.13–2.23 (m, 2H), 2.93 (td, ³*J* = 12.8 Hz, ³*J* = 6.1 Hz, 2H), 3.08 (td, ³*J* = 14.3 Hz, ³*J* = 3.2 Hz, 2H), 3.50–3.60 (m, 4H), 3.62–3.71 (m, 4H), 3.75–3.80 (m, 2H), 3.84–3.97 (m, 6H), 4.44 (d, ²*J* = 17.8 Hz, 2H), 4.72 (d, ²*J* = 17.8 Hz, 2H), 6.37 (d, ³*J* = 8.0 Hz, 2H), 6.41–6.46 (m, 4H), 6.66 (d, ³*J* = 7.5 Hz, 2H), 7.03 (d, ⁴*J* = 1.9 Hz, 2H), 7.10 (t, ³*J* = 7.7 Hz, 2H), 7.28 (d, ³*J* = 9.0 Hz, 2H), NH protons were not assigned. ¹³C NMR (CDCl₃): δ 27.3 (2CH₂), 28.7 (2CH), 28.8 (2CH), 32.2 (2C), 36.4 (1CH), 38.0 (2CH₂), 39.9 (2CH₂), 40.1 (2CH₂), 42.2 (2CH₂), 49.4 (2CH₂), 51.6 (1CH₂), 53.7 (2CH₂), 68.7 (2CH₂), 71.6 (2CH₂), 103.2 (2CH), 106.8 (2CH), 111.6 (2CH), 112.6 (2CH), 113.8 (2CH), 119.7 (1C), 128.0 (2CH), 129.2 (2CH), 136.8 (1C), 140.7 (2C), 146.5 (2C), 148.4 (2C). HRMS (ESI-TOF) *m/z* calcd for C₄₈H₆₃N₄O₃ [M+H]⁺ 743.4900, found 743.4864.

Cyclic dimer 11k was obtained as the second product in the synthesis of the macrobicyclic compound **9k**. Eluent CH₂Cl₂-MeOH 100:1, pale-yellow glassy compound. Yield 12 mg (8%). ¹H NMR (CDCl₃): δ 1.18–1.62 (m, 32H), 1.90–2.02 (m, 12H), 2.93–2.97 (m, 8H), 3.53 (t, ³*J* = 4.6 Hz, 8H), 3.60–3.67 (m, 16H), 3.83–3.88 (m, 8H), 4.52 (s, 8H), 6.39–6.43 (m, 8H), 6.56 (d, ³*J* = 7.2 Hz, 4H), 6.62 (dd, ³*J* = 8.7 Hz, ⁴*J* = 2.0 Hz, 4H), 7.03 (bs, 4H), 7.09 (t, ³*J* = 7.6 Hz, 4H), 7.32 (d, ³*J* = 9.0 Hz, 4H), NH protons were not assigned. ¹³C NMR (CDCl₃): δ 26.8 (4CH₂), 28.8 (4CH), 32.4 (4C), 36.4 (2CH₂), 38.4 (4CH₂), 41.8 (8CH₂), 43.5 (4CH₂), 47.6 (2CH₂), 48.4 (4CH₂), 53.7 (4CH₂), 68.7 (4CH₂), 71.0 (4CH₂), 71.4 (4CH₂), 103.3 (4CH), 110.2 (4CH), 111.2 (4CH), 111.7 (4CH), 115.0 (4CH), 119.7 (2C), 128.3 (4CH), 129.3 (4CH), 137.0 (2C), 140.7 (4C), 147.0 (4C), 148.7 (4C). MS (MALDI-TOF) *m/z* calcd for C₉₆H₁₂₅N₈O₆ [M+H]⁺ 1485.97, found 1486.92.

Macrobicyclic compound 9l was synthesized from compound **5** (225 mg, 0.33 mmol), diamine **8l** (87 mg, 0.33 mmol) in the presence of Pd(dba)₂ (15 mg, 8 mol%), BINAP (17 mg, 9 mol%), sodium *tert*-butoxide (96 mg, 1 mmol) in 17 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 200:1, pale-yellow glassy compound. Yield 60 mg (23%). ¹H NMR (CDCl₃): δ 1.34–1.38 (m, 2H), 1.45–1.80 (m, 12H), 1.86–2.05 (m, 4H), 2.15 (bs, 2H), 2.96–3.00 (m, 2H), 3.42–3.75 (m, 12H), 3.82–3.87 (m, 4H), 4.56 (s, 2H), 4.59 (s, 2H), 4.64 (bs, 1H), 5.66 (bs, 1H), 6.45 (d, ³*J* = 8.0 Hz, 1H), 6.57–6.65 (m, 3H), 6.70 (m, AA'MM', 2H), 6.78–6.82 (m, 2H), 6.99 (bs, 1H), 7.03 (bs, 1H), 7.09–7.16 (m, 4H), 7.21–7.25 (m, 2H), 7.42 (m, AA'MM', 2H). ¹³C NMR (CDCl₃): δ 26.5 (1CH₂), 27.7 (1CH₂), 29.2 (2CH), 32.8 (1C), 36.1 (1CH₂), 38.1 (1CH₂), 41.8 (bs, 2CH₂), 42.6 ym. (2CH₂), 43.2 (1CH₂), 47.5 (1CH₂), 48.3 (1C), 48.5 (1CH₂), 48.8

(1CH₂), 53.4 (1CH₂), 54.0 (1CH₂), 68.6 (1CH₂), 68.8 (1CH₂) 71.0 (2CH₂), 71.1 (1CH₂), 71.5 (1CH₂), 103.1 (1CH), 103.3 (1CH), 108.3 (1CH), 111.2 (1CH), 111.4 (1CH), 113.3 (1CH), 113.4 (1CH), 115.1 (1CH), 116.0 (1CH), 117.4 (2CH), 118.1 (1CH), 119.8 (1C), 125.2 (2CH), 128.1 (1CH), 128.5 (1CH), 128.9 (1CH), 129.5 (1CH), 139.9 (1C), 140.4 (1C), 141.6 (1C), 143.2 (1C), 143.8 (1C), 146.4 (1), 147.1 (1C), 148.8 (1C), one quaternary carbon atom was not assigned. HRMS (MALDI-TOF) m/z calcd for C₅₂H₆₃N₄O₃ [M+H]⁺ 791.4900, found 791.4950.

Macrobicycle 10a was synthesized from compound **7** (112 mg, 0.16 mmol), triamine **8a** (21 mg, 0.16 mmol) in the presence of Pd(dba)₂ (7.5 mg, 8 mol%), BINAP (9 mg, 9 mol%), sodium *tert*-butoxide (48 mg, 0.5 mmol) in 8 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 10:1, pale-yellow glassy compound. Yield 20 mg (19%). ¹H NMR (CDCl₃): δ 1.31–1.37 (m, 4H), 1.71–1.78 (m, 4H), 2.69–2.75 (m, 4H), 3.30 (ddd, ²*J* = 14.7 Hz, ³*J* = 10.2 Hz, ³*J* = 5.1 Hz, 2H), 3.34–3.58 (m, 14H), 3.66–3.70 (m, 4H), 4.06 (d, ³*J* = 14.7 Hz, 2H), 5.02 (d, ²*J* = 14.7 Hz, 2H), 6.53 (d, ³*J* = 8.0 Hz, 2H), 6.67 (t, ³*J* = 7.3 Hz, 2H), 7.03 (d, ⁴*J* = 2.0 Hz, 2H), 7.11 (d, ³*J* = 7.3 Hz, 2H), 7.14–7.21 (m, 4H), 7.61 (d, ³*J* = 9.0 Hz, 2H), NH protons were not assigned. ¹³C NMR (CDCl₃): δ 25.8 (2CH₂), 30.0 (2CH₂), 42.0 (2CH₂), 45.2 (2CH₂), 48.6 (2CH₂), 51.4 (2CH₂), 68.9 (2CH₂), 70.7 (2CH₂), 71.0 (2CH₂), 106.1 (2CH), 110.2 (2CH), 111.4 (2CH), 116.4 (2CH), 120.4 (1C), 123.0 (2C), 127.4 (2CH), 128.6 (2CH), 128.8 (2CH), 130.3 (2CH), 137.5 (1C), 146.1 (2C). HRMS (MALDI-TOF) m/z calcd for C₄₀H₅₄N₅O₃ [M+H]⁺ 652.4226, found 652.4260.

Macrobicycle 10f was synthesized from compound **7** (133 mg, 0.19 mmol), dioxadiazine **8f** (28 mg, 0.19 mmol) in the presence of Pd(dba)₂ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium *tert*-butoxide (55 mg, 0.57 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 100:1, pale-yellow glassy compound. Yield 24 mg (18%). ¹H NMR (CDCl₃): δ 1.67–1.74 (m, 4H), 2.79 (dt, ³*J* = 10.4 Hz, ³*J* = 5.7 Hz, 2H), 3.00 (dd, ³*J* = 10.4 Hz, ³*J* = 5.7 Hz, 2H), 3.05–3.23 (m, 8H), 3.32–3.51 (m, 8H), 3.55–3.68 (m, 4H), 3.71 (t, ³*J* = 4.4 Hz, 4H), 4.09 (d, ²*J* = 13.8 Hz, 2H), 4.89 (bs, 2H), 4.93 (d, ²*J* = 13.8 Hz, 2H), 6.57 (d, ³*J* = 8.0 Hz, 2H), 6.69 (t, ³*J* = 7.3 Hz, 2H), 7.11–7.18 (m, 6H), 7.20 (t, ³*J* = 7.8 Hz, 2H), 7.60 (d, ³*J* = 8.7 Hz, 2H). ¹³C NMR (CDCl₃): δ 25.9 (2CH₂), 43.3 (2CH₂), 45.7 (2CH₂), 52.4 (2CH₂), 68.4 (2CH₂), 69.3 (2CH₂), 69.8 (2CH₂), 70.7 (2CH₂), 71.1 (2CH₂), 108.9 (2CH), 110.3 (2CH), 113.0 (2CH), 116.5 (2CH), 120.9 (1C), 122.7 (2C), 128.2 (2CH), 128.5 (2CH), 130.3 (2CH), 136.9 (1C), 146.9 (2C), 148.1 (2C). HRMS (MALDI-TOF) m/z calcd for C₄₀H₅₃N₄O₅ [M+H]⁺ 669.4016, found 669.4042.

Macrobicycle 10g was synthesized from compound **7** (112 mg, 0.16 mmol), trioxadiazine **8g** (35 mg, 0.16 mmol) in the presence of Pd(dba)₂ (7.5 mg, 8 mol%), BINAP (9 mg, 9 mol%), sodium *tert*-butoxide

(48 mg, 0.5 mmol) in 8 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 100:1, pale-yellow glassy compound. Yield 33 mg (27%). ¹H NMR (CDCl₃): δ 1.76 (quintet, ³J = 6.1 Hz, 4H), 1.78–1.83 (m, 4H), 3.08–3.17 (m, 12H), 3.29 (t, ³J = 6.4 Hz, 4H), 3.39–3.46 (m, 8H), 3.54–3.58 (m, 4H), 3.74–3.78 (m, 4H), 4.47 (s, 4H), 4.81 (bs, 2H), 6.82 (d, ³J = 8.1 Hz, 2H), 6.88 (t, ³J = 7.3 Hz, 2H), 7.11–7.17 (m, 6H), 7.21 (t, ³J = 7.7 Hz, 2H), 7.57 (d, ³J = 8.7 Hz, 2H). ¹³C NMR (CDCl₃): δ 25.2 (2CH₂), 28.6 (2CH₂), 40.6 (2CH₂), 45.3 (2CH₂), 52.9 (2CH₂), 68.8 (2CH₂), 69.3 (2CH₂), 69.8 (2CH₂), 70.0 (2CH₂), 70.7 (2CH₂), 71.1 (2CH₂), 107.4 (2CH), 109.8 (2CH), 113.2 (2CH), 116.3 (2CH), 121.4 (1C), 122.0 (2C), 128.5 (2CH), 128.7 (2CH), 129.7 (2CH), 136.9 (1C), 147.0 (2C), 147.7 (2C). HRMS (MALDI-TOF) *m/z* calcd for C₄₄H₆₁N₄O₆ [M+H]⁺ 741.4653, found 741.4653.

2,16-Bis(bromobenzyl)-6,9,12-trioxa-2,16-diazatricyclo[15.5.3.0^{20,24}]pentacosa-1(22),17(25),18,20,23-pentaene (13) was obtained instead of the cyclization product from compound **7** (133 mg, 0.19 mmol), diazacrown ether **8i** (49 mg, 0.19 mmol) in the presence of Pd(dba)₂ (17.5 mg, 16 mol%), BINAP (13.5 mg, 18 mol%), sodium *tert*-butoxide (55 mg, 0.57 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 200:1, pale-yellow glassy compound. Yield 46 mg (46%). ¹H NMR (CDCl₃): δ 1.95–2.02 (m, 4H), 3.56 (t, ³J = 5.1 Hz, 4H), 3.65–3.70 (m, 8H), 3.88–3.92 (m, 4H), 4.64 (s, 4H), 6.65 (dd, ³J = 8.8 Hz, ⁴J = 2.1 Hz, 2H), 7.09 (d, ⁴J = 2.1 Hz, 2H), 7.21–7.32 (m, 10H), 7.38 (d, ³J = 9.0 Hz, 2H). ¹³C NMR (CDCl₃): δ 26.8 (2CH₂), 48.3 (2CH₂), 53.7 (2CH₂), 68.7 (2CH₂), 71.0 (2CH₂), 71.5 (2CH₂), 103.6 (2CH), 111.7 (2CH), 119.7 (1C), 126.5 (4CH), 126.7 (2CH), 128.4 (2CH), 128.5 (4CH), 137.0 (1C), 139.5 (2C), 147.0 (2C). HRMS (MALDI-TOF) *m/z* calcd for C₃₄H₄₁N₂O₃ [M+H]⁺ 525.3117, found 525.3078.

Macrobicycle 10k was synthesized from compound **7** (133 mg, 0.19 mmol), diamine **8k** (42 mg, 0.19 mmol) in the presence of Pd(dba)₂ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium *tert*-butoxide (55 mg, 0.57 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 200:1, pale-yellow glassy compound. Yield 10 mg (7%). ¹H NMR (CDCl₃): δ 0.32 (d, *J* = 12.0 Hz, 1H), 0.50 (d, *J* = 12.0 Hz, 1H), 0.56 (d, *J* = 11.3 Hz, 2H), 0.86–1.99 (m, 18H), 2.86–2.94 (m, 4H), 3.29–3.59 (m, 12H), 3.64–3.68 (m, 4H), 4.11 (d, ²J = 14.3 Hz, 2H), 4.99 (d, ²J = 14.3 Hz, 2H), 6.54 (d, ³J = 8.0 Hz, 2H), 6.66 (t, ³J = 7.3 Hz, 2H), 6.99 (bs, 2H), 7.13 (t, ³J = 7.1 Hz, 2H), 7.19 (d, ³J = 7.7 Hz, 2H), 7.21 (d, ³J = 7.6 Hz, 2H), 7.62 (d, ³J = 9.0 Hz, 2H), NH protons were not assigned. ¹³C NMR (CDCl₃): δ 25.7 (2CH₂), 28.9 (2CH), 32.7 (2C), 35.8 (1CH₂), 38.1 (2CH₂), 39.4 (2CH₂), 41.3 (2CH₂), 43.1 (2CH₂), 44.7 (2CH₂), 48.3 (1CH₂), 51.4 (2CH₂), 68.6 (2CH₂), 70.6 (2CH₂), 71.1 (2CH₂), 106.9 (2CH), 110.1 (2CH), 112.0 (2CH), 115.9 (2CH), 120.9 (1C), 122.6 (2C), 128.5 (2CH), 128.7 (2CH), 130.4 (2CH), 137.6 (1C), 146.4 (2C), 148.1 (2C). HRMS (MALDI-TOF) *m/z* calcd for C₄₈H₆₃N₄O₃ [M+H]⁺ 743.4900, found 743.4947.

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