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SYNTHESIS OF MACROBI- AND MACROTRICYCLIC COMPOUNDS COMPRISING PYRIMIDYL SUBSTITUTED CYCLEN AND CYCLAM

Sergei M. Kobelev,[1] Alexei D. Averin,[1] Alexei K. Buryak,[2] Franck Denat,[3] Roger Guilard,[3*] and Irina P. Beletskaya[1,2*]

[1]Lomonosov Moscow State University, Department of Chemistry, Leninskie Gory 1-3, Moscow, 119991, Russia
[2]A.N. Frumkin Institute of Physical Chemistry and Electrochemistry, 31 Leniskii prosp., Moscow, 119991, Russia
[3]Institut de Chimie Moléculaire de l'Universite de Bourgogne (ICMUB) UMR CNRS 5260, 9 av. Alain Savary, 21078 Dijon, France

Abstract - The synthesis of novel N^1,N^7-bis(bromobenzyl)cyclens and N^1,N^8-bis(bromobenzyl)cyclams is described. Arylation of these compounds with excess 4,6-dichloropyrimidine and 2-chloropyrimidine gave corresponding tetrasubstituted cyclen and cyclam in good yields. Bis(bromobenzyl)bis(pyrimidyl) substituted cyclens and cyclams were used in the Pd-catalyzed reactions with polyamines to give macrobi- and macrotricycles. The yields of macropolycyclic compounds were shown to be dependent on the nature of starting tetraazamacrocycles and polyamines. In the case of cyclam monopyrimidyl derivatives were also obtained and macropolycyclic compounds were synthesized on their base.

INTRODUCTION

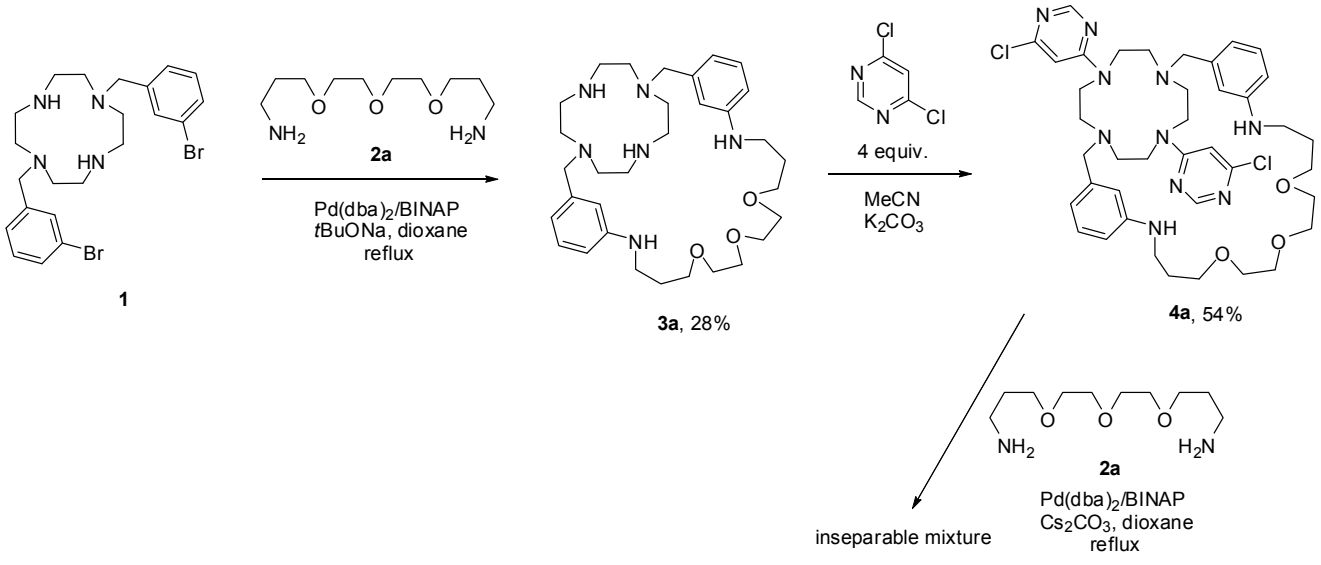
Amino substituted pyrimidines attract a keen interest of chemists first of all due to an extremely broad spectrum of their physiological activity. More specifically, 4,6-diaminopyrimidines were tested as protein kinase inhibitors,[1-4] as inhibitors of kinases of other types: CHK1,[5] lymphocyte-specific tyrosine kinase,[6,7] Janus kinase,[8] VEGFR-2 kinase,[9,10] and also as cannabioid receptor CB1 ligand.[11] In other studies 4,6-diaminopyrimidines were tried for prevention and cure of the metabolism diseases,[12] in the treatment of CNS diseases,[13] their use as 5-HT7 ligands was also investigated.[14]

‡This paper is dedicated to Prof. Dr. Albert Eschenmoser on the occasion of his 85h birthday

To the moment, several macrocycles which include pyrimidine moiety are known. Macrocycles comprising 4,6-diaminopyrimidine[15-17] and 2,4-diaminopyrimidine[18-22] were described in the literature, in some compounds 2,4-diaminopyrimidine fragment constitutes a part of the macrocycle by disubstitution in positions 4 and 5.[23,24] Pyrimidocrown ethers were synthesized on the basis of 4,6-dioxy-, 4,6-dithiopyrimidines,[25] and 2,4-diamino pyrimidines.[26-29] Synthesis and physicochemical investigations of the macrocycles on the basis of 2-thio-4-aminopyrimidines were carried out.[30-35] A number of macrocycles were tested for their medical applications: their antitumor[18,19,22] and antiproliferative[16,20,21] activity was studied, some derivatives were tried as gistamine H4 receptor modulators.[23] All described macrocycles were synthesized using conventional multistep methods.

Earlier we demonstrated that the amination of 2-chloropyrimidine and 2,4-dichloropyrimidine with various linear diamines proceeded smoothly, moreover, the diamination of 2,4-dichloropyrimidine could be carried out under non-catalytic conditions.[36] However, the monoamination of 2,4-dichloropyrimidine turned out not to be selective. The introduction of the symmetrical 4,6-dichloropyrimidine in the diamination process demanded the use of the palladium catalyst, as it has been shown by us quite recently.[37] Using this approach several macrocycles containing 4,6-diaminopyrimidine fragment have been synthesized, thus the application of Buchwald-Hartwig amination[38] extended the family of arene spacers which can be incorporated in the macrocycle using a convenient one-pot procedure. Taking these facts into consideration, we decided to modify various derivatives of tetraazamacrocycles like cyclen and cyclam with 6-chloropyrimidine moieties in order to synthesize novel macrotricyclic compounds.

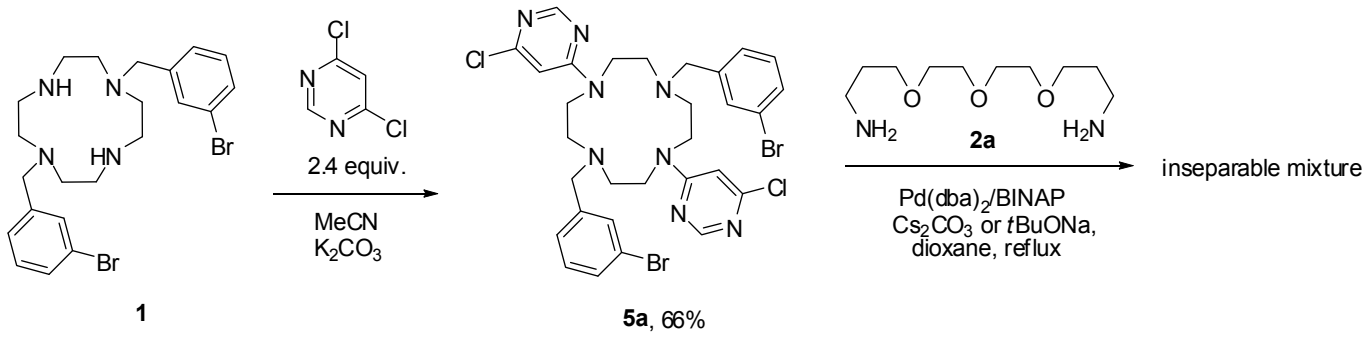
RESULTS AND DISCUSSION



Scheme 1. Modification of macrobicycle **3a** with two 6-chloro-4-pyrimidyl substituents

First of all, we synthesized a macrobicyclic compound containing *trans*-disubstituted cyclen (1,4,7,10-tetraazacyclododecane) and trioxadiamine chain according to a procedure published by us previously[39] (Scheme 1). For this purpose we used N^1,N^7-bis(3-bromobenzyl)cyclen **1** in the Pd-catalyzed reaction with trioxadiamine **2a** and obtained target macrobicycle **3a** in 28% yield. Then it was reacted with 4 equivalents of 4,6-dichloropyrimidine to give *trans*-dipyrimidyl substituted macrobicycle **4a** in 54% yield. Further attempts to introduce this compound in the cyclization with the second molecule of trioxadiamine to obtain macrotricycle of a new type were unsuccessful though 16 mol% $Pd(dba)_2$/BINAP were used according to our method elaborated for the synthesis of 4,6-diamino-based macrocycles,[37] and only inseparable mixture of unidentified products was obtained though no unreacted compound **4a** was detected in the reaction mixture.

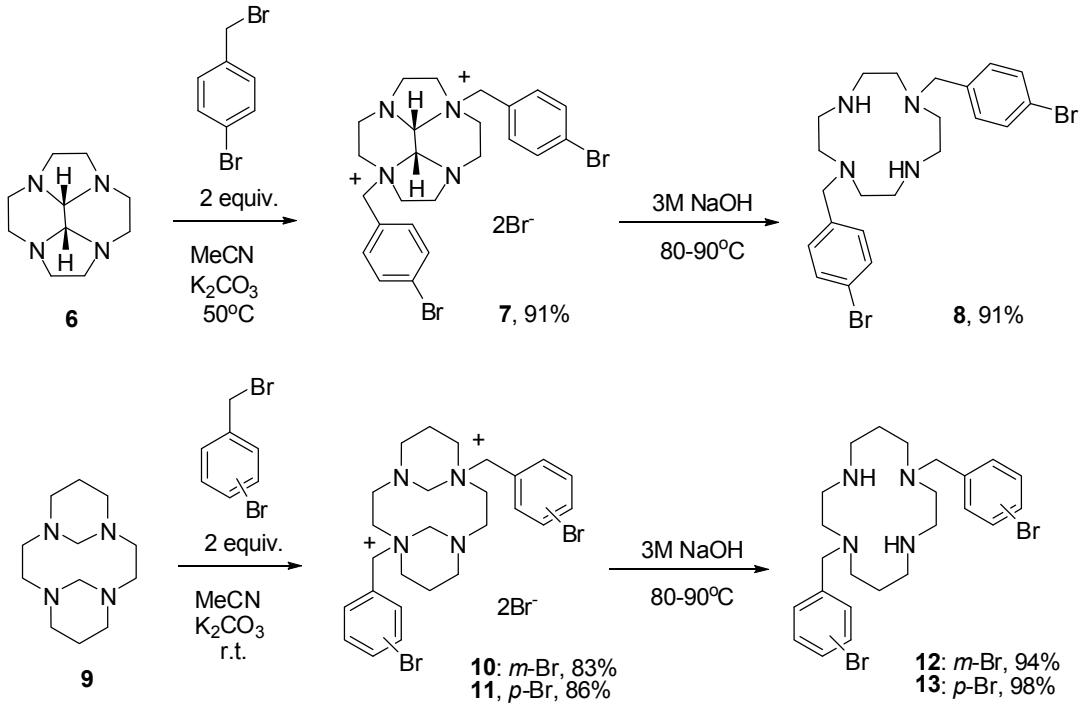
We assumed that possibly the trioxadiamine chain could be an obstacle in the formation of the third macrocycle and tried another approach. N^1,N^7-bis(3-bromobenzyl)cyclen **1** was modified with two 6-chloropyrimidyl substituents (Scheme 2) to give compound **5a** in 66% yield.



Scheme 2. Attempts to use **5a** in macrocyclization reaction

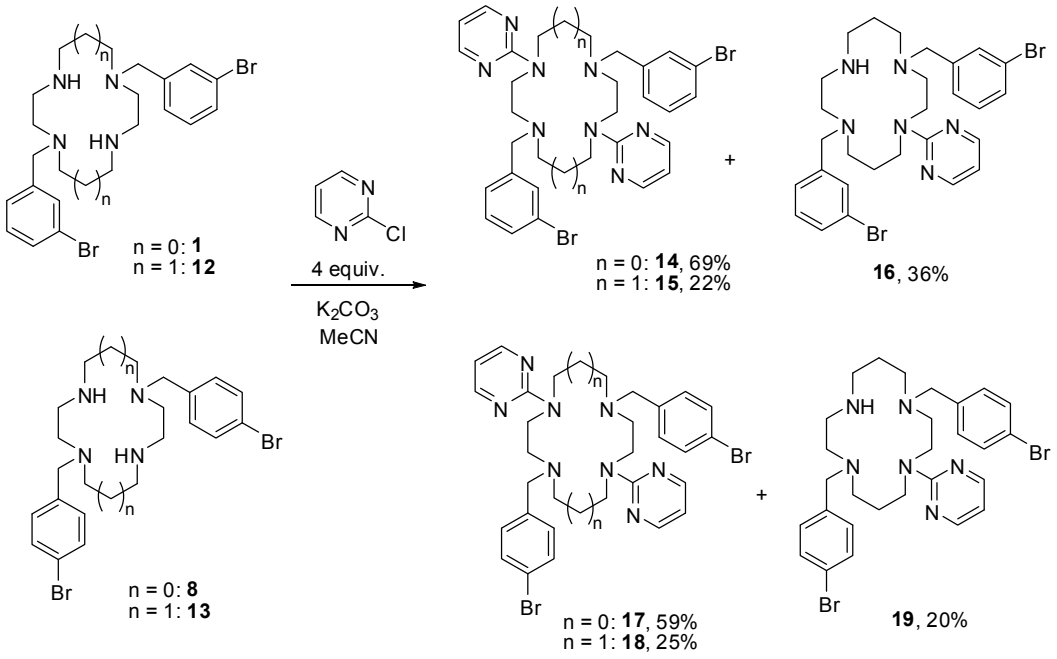
This tetrasubstituted cyclen was reacted with trioxadiamine **2a** using Pd catalysis, but in this case also no cyclization occurred. After failure with Cs_2CO_3 as a base, we tried the use of an excess *t*BuONa in order to substitute chlorine atoms in 6-chloropyrimidyl substituents by *tert*-butoxy groups and simultaneously to carry out the cyclization, but again the reaction gave only an inseparable mixture of unknown compounds. Such unfavorable behavior of the cyclen derivative bearing two pyrimidyl substituents led us to a deeper investigation of the cyclization processes in which pyrimidyl substituted cyclen and cyclam can participate in order to reveal how these substituents affect the cyclization. Moreover, the compounds which combine tetraazamacrocycles with pyrimidine fragment are of interest as host molecules for cations because they bear additional donor nitrogen atoms.

To create a representative series of *trans*-dipyrimidyl substituted tetraazamacrocycles for their further investigations in the macrocyclization reactions, besides N^1,N^7-bis(3-bromobenzyl)cyclen **1**, we synthesized previously unknown N^1,N^7-bis(4-bromobenzyl) cyclen **8**, N^1,N^8-bis(3-bromobenzyl)cyclam (1,5,8,11-tetraazacyclotetradecane) **12** and N^1,N^8-bis(4-bromobenzyl)cyclam **13** (Scheme 3). These compounds were obtained starting from *cis*-glyoxal-cyclen **6** or formaldehyde-cyclam **9** according to a procedure described previously.[40, 41] This method has recently become a versatile tool for creating various derivatives of cyclen and cyclam.[42] Intermediate salts **7**, **10** and **11** were isolated in high yields, and treatment of these compounds with 3M solutions of NaOH at 80-90 ^{o}C gave *trans*-bis(bromobenzyl) substituted cyclen and cyclams **8**, **12**, **13** in high yields.



Scheme 3. Synthesis of *trans*-bis(bromobenzyl) substituted cyclen and cyclams **8**, **12** and **13**

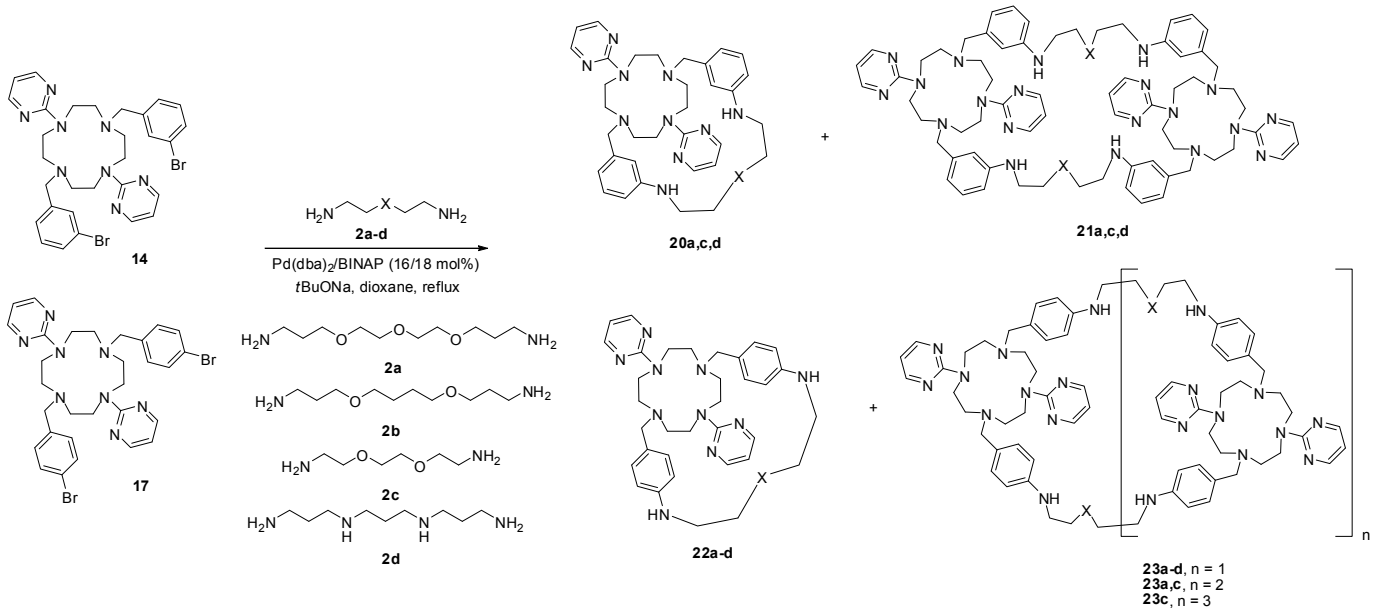
Compounds **1**, **8**, **12** and **13** were modified with 2-pyrimidyl substituents *via* simple reactions with 4-fold excess of 2-chloropyrimidine in boiling acetonitrile in the presence of K_2CO_3 (Scheme 4). The use of the excess of 2-chloropyrimidine was crucial in this case because the use of stoichiometric amounts of the reagents led to low yields of dipyrimidyl derivatives.



Scheme 4. Modification of compounds **1**, **8**, **12** and **13** with 2-pyrimidyl substituents

The reactions of cyclen-based compounds **1** and **8** afforded dipyrimidyl derivatives **14** and **17** in good yields (69% and 59%, respectively), however, derivatives containing cyclam **15** and **18** were obtained in low yields (22% and 25%), though the excess of the arylating reagent was used. Together with the target molecules monopyrimidyl derivatives **16** and **19** were isolated in comparable yields (36% and 20%). The reason for such poor reactivity of the cyclam derivatives may be explained by steric differences between cyclen- and cyclam-containing compounds.

Cyclen derivatives **14** and **17** were used in the Pd-catalyzed amination reactions with equimolar amounts of di- and polyamines **2a-d**, the reactions were run in boiling dioxane (c = 0.02 M), $Pd(dba)_2$/BINAP (16/18 mol%) catalytic system was employed, *t*BuONa was used as a base (Scheme 5). The results of the reactions are collected in Table 1. The reactions with all di- and polyamines provided corresponding macrobicyclic compounds **20** and **22**, the yields being dramatically dependent on the substitution in the benzene ring. While compound **14** with 3-bromobenzyl substituents afforded target macrobicycles **20a**,**c**,**d** in rather good yields (up to 31%, Table 1, entries 1, 2), the reactions of compound **17** with 4-bromobenzyl substituents gave lower yields of macrobicycles **22a-d** (8-19%, entries 4-7). The most interesting feature of this reaction is the formation of great amounts of macrotricyclic compounds **21** and **23** which in fact are cyclic dimers of target molecules. In many cases their yields surpassed those of macrobicycles (entries 3-5, 7). These cryptands of cylindrical shape are undoubtedly very promising for the investigation of their coordination properties. In the reactions of **17** with oxadiamines **2a,c** the formation of cyclic trimers **23a,c** (n=2) and cyclic tetramer **23c** (n=3) was observed.



Scheme 5. Synthesis of macrobi- and macrotricycles **20**-**23**

MALDI-TOF mass spectroscopy was very useful in distinguishing between macrobi- and macropolycycles. ^{1}H NMR spectra were also helpful: in macrobicycles **20** and **22** the signals of pyrimidine protons are shifted downfield by 0.1 ppm as compared to macrotri- and macropolycycles **21** and **23**.

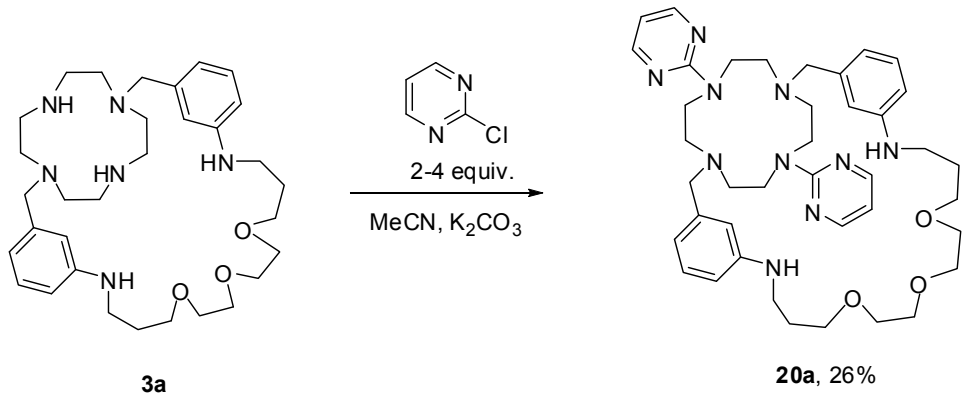
Table 1. Pd-catalyzed amination of dipyrimidyl derivatives of cyclen **14** and **17**.

Entry	Starting compounds	Yields of macrobicycles, %[a)]	Yields of macropolycycles, %[a)]
1	**14** + **2a**	**20a**, 29	**21a**, 14
2	**14** + **2c**	**20c**, 31	**21c**, 17
3	**14** + **2d**	**20d**, 15	**21d**, 17
4	**17** + **2a**	**22a**, 19	**23a** (n=1), 20; **23a** (n=2), 23
5	**17** + **2b**	**22b**, 8	**23b** (n=1), 31
6	**17** + **2c**	**22c**, 16	**23c** (n=1), 3; **23c** (n=2, 3, 4), 4[b)]
7	**17** + **2d**	**22d**, 16	**23d** (n=1), 20

[a)] Yields after column chromatography
[b)] Yield of inseparable mixture of cyclic oligomers

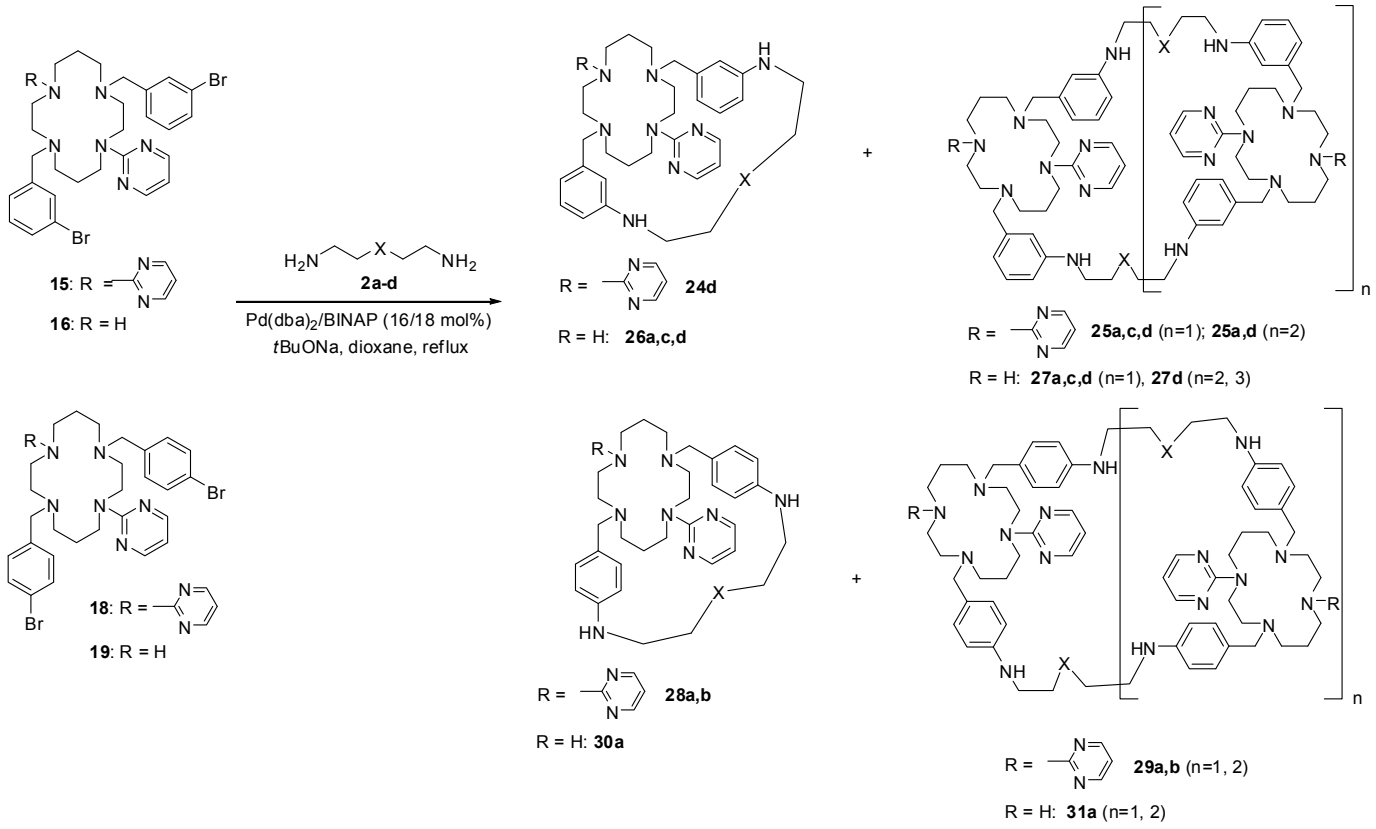
We verified the possibility of obtaining dipyrimidyl substituted macrobicycle **20a** *via* an alternative route, by reacting macrobicycle **3a** with 2-chloropyrimidine (Scheme 6). It proved to be quite successful, and the yield of **20a** was 26%, which is close to that obtained in the macrocyclization reaction (29%, entry 1).

It means that the approach *via* macrocyclization of tetrasubstituted cyclen is quite justified, moreover, it affords the introduction of the polyamine chain with dialkylamino groups in the macrobicycle at the final step, what is obviously impossible in the synthesis according alternative route (2-chloropyrimidine will readily arylate dialkylamino groups of the polyamine chain as well as those of cyclen).



Scheme 6. Modification of macrobicycle **3a** with two 2-pyrimidyl substituents

Next we investigated the behavior of the cyclam derivatives **15**, **16**, **18**, and **19** in the same reactions (Scheme 7, Table 2).



Scheme 7. Synthesis of macrobi- and macrotricycles **24-31**

Table 2. Pd-catalyzed amination of dipyrimidyl derivatives of cyclam **15**, **16**, **18**, and **19**

Entry	Starting compounds	Yields of macrobicycles, %[a)]	Yields of macropolycycles, %[a)]
1	**15** + **2a**	**24a**, 0	**25a** (n=1), 13; **25a** (n=2), 10
2	**15** + **2c**	**24c**, 0	**25c** (n=1), 16
3	**15** + **2d**	**24d**, 29	**25d** (n=1), 9, **25d** (n=2), 6
4	**16** + **2a**	**26a**, 30	**27a** (n=1), 7
5	**16** + **2c**	**26c**, 29	**27c** (n=1), 8
6	**16** + **2d**	**26d**, 24	**27d** (n=1), 29; **27d** (n=1, 2, 3), 12[b)]
7	**18** + **2a**	**28a**, 6	**29a** (n=1), 19; **29a** (n=2), 13
8	**18** + **2b**	**28b**, 5	**29b** (n=1), 14; **29b** (n=2), 12
9	**19** + **2a**	**30a**, 30	**31a** (n=1), 6; **31a** (n=2), 4

[a)] Yields after column chromatography
[b)] Yield of inseparable mixture of cyclic oligomers

To our surprise, compound **15** did not form expected macrobicycles with tri- and dioxadiamines **2a**,**c** but rather gave only macrotricyclic cyclodimers **25a**,**c** (Table 2, entries 1, 2). Only with tetraamine **2d** the cryptand **24d** was obtained in 29% yield (entry 3). When using monopyrimidyl derivative **16**, macrobicyclic cryptands **26a**,**c**,**d** were synthesized in normal yields (entries 4-6), and corresponding macrotricycles **27a**,**c**,**d** were as well isolated in all cases. One may suppose that the formation of only cyclodimers in the reactions with dipyrimidyl derivative **15** could occur due to steric hindrances caused by the presence of two pyrimidyl substituents. Cyclic trimers were obtained in the reactions of **15** with trioxadiamine **2a** and tetraamine **2d**. The reaction with trioxadiamine **2a** carried out with bis(4-bromobenzyl) derivatives of cyclam **18**, **19** demonstrated that in these cases *p*-bromo substituted species reacted more reluctantly than their *m*-bromo substituted isomers (entries 7, 8), the same observation was made for cyclen derivatives earlier. The yields of target macrobicycles **28a,b** were low (5-6%), but the yields of cyclic dimers and trimers were substantially higher (12-19%). However, here dipyrimidyl derivative **18**, contrary to its isomer **15**, did give macrobicycles **29a**,**b** with tri- and dioxadiamines **2a**,**b**, possibly due to more favorable geometry provided by *para* position of bromine substituents. The use of a less sterically hindered monopyrimidyl compound **19** gave rise to 30% yield of the corresponding macrobicycle **30a** (entry 9). It is to be noted that almost in all macrocyclization reactions the formation of quite substantial amounts of presumably linear oligomers was noted, but as these compounds were isolated only as complex mixtures and their composition could not be established neither by NMR nor by MALDI mass spectroscopy, their yields cannot be accurately evaluated.

CONCLUSION

The following conclusions can be drawn from the experimental data described above. While the substitution of the first chlorine atom for amino group in 4,6-dichloropyrimidine proceeds readily without catalyst, the substitution of the second chlorine atom is problematic. Though it is possible to obtain macrocycles by a one-pot intramolecular diamination reaction from 4,6-dichloropyrimidine, as it was described by us earlier,[37] macrocyclization reaction did not occur in the case of bis(chloropyrimidyl) substituted tetraazamacrocycles. However, the substitution of remaining two nitrogen atoms in *trans*-bis(bromobenzyl) derivatives of cyclen and cyclam with 2-pyrimidyl groups provided interesting substrates for the synthesis of macrobi- and macrotricycles *via* Pd-catalyzed amination reactions. The reactions of N^1,N^7-bis(bromobenzyl)cyclen with 2-chloropyrimidine turned out to be more successful than those of N^1,N^8-bis(bromobenzyl)cyclam which provided almost equal amounts of di- and monopyrimidyl derivatives. The reactions of dipirymidyl derivatives of cyclen generally gave better yields of macrobicyclic compounds than those of cyclam derivatives, the latter provided only macrotricyclic cryptands in several cases, however, monopyrimidyl derivatives of cyclam gave reasonable yields of macrobicycles. It is clear that pyrimidyl substituents govern seriously the course of the macrocyclization reactions, and the combination of the type of initial tetraazamacrocycle, number of pyrimidine moieties, and the nature of polyamine influences the yields of macrobi- and macrotricycles. Macropolycyclic molecules synthesized in the course of the present investigation will surely find applications as host molecules, and such investigations are underway now.

EXPERIMENTAL

All chemicals were purchased from Aldrich and Acros companies and used without further purification. *Cis*-glyoxal-cyclen **6** and formaldehyde-cyclam **9** were provided by CheMatech Co. $Pd(dba)_2$ was synthesized according to a procedure described.[43] N^1,N^7-bis(3-bromobenzyl)cyclen (**1**) and macrocycle **3a** were synthesized according to a described method.[39] Commercial dioxane was distilled over NaOH and sodium under argon, acetonitrile was distilled over P_2O_5, dichlromethane and methanol were distilled prior to use. Column chromatography was carried out using silica gel (40-60 mkm) purchased from Fluka. ^{1}H and ^{13}C NMR spectra were registered in $CDCl_3$ 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 spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards.

(8b*R*,8c*R*)-2a,6a-Bis(4-bromobenzyl)decahydro-4a,8a-diaza-2a,6a-diazoniacyclopenta[*fg*]acenaphthylene dibromide (7). *Cis*-glyoxal-cyclen **6** (9 mmol, 1.74 g) was dissolved in dry acetonitrile (27 mL),

p-bromobenzylbromide (18 mmol, 4.5 g) was added, and the reaction mixture was stirred at 50 °C for 72 h. After cooling to room temperature the solution was filtered off, the residue was washed with acetonitrile (2x15 mL) and dried *in vacuo* to give compound **7** as white crystalline powder. Yield 5.71 g (91%). ^{1}H NMR (DMSO-d_6): δ 2.93 (q, J = 8.3 Hz, 2H), 3.40-3.47 (m, 4H), 3.59-3.72 (m, 4H), 4.22 (td, J = 11.3 Hz, 3.6 Hz, 2H), 4.84 (d, J = 13.4 Hz, 2H), 4.87 (s, 2H), 5.01 (d, J = 13.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 4H), 7.79 (d, J = 8.4 Hz, 4H), 4 protons are hidden by CHD_2 multiplet. ^{13}C NMR (DMSO-d_6): δ 42.2 (2C), 46.6 (2C), 55.4 (2C), 58.9 (2C), 60.2 (2C), 76.4 (2C), 124.6 (2C), 126.6 (2C), 132.4 (4C), 134.8 (4C).

1,7-Bis(4-bromobenzyl)-1,4,7,10-tetraazacyclododecane (8). Compound **7** (8.19 mmol, 5.71 g) was treated with KOH (143 mmol, 8g) in 50 mL water at 80-90 °C under stirring for 72 h. The reaction mixture was extracted with CH_2Cl_2 (2x30 mL), organic fractions were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give compound **8** as slightly beige crystalline powder. Yield 3.79 g (91%), mp 135-136 °C. ^{1}H NMR ($CDCl_3$): δ 2.38 (bs, 2H), 2.45-2.58 (m, 8H), 2.58-2.68 (m, 8H), 3.52 (s, 4H), 7.17 (d, J = 8.2 Hz, 4H), 7.45 (d, J = 8.4 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 45.0 (4C), 51.8 (4C), 59.2 (2C), 121.1 (2C), 130.6 (4C) 131.5 (4C), 138.1 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{22}H_{31}Br_2N_4$ $[M+H]^+$ 509.0915, found 509.0924.

1,8-Bis(3-bromobenzyl)-1,4,8,11-tetraazacyclotetradecane (12). Formaldehyde-cyclam **9** (17.9 mmol, 4 g) was dissolved in dry acetonitrile (120 mL), *m*-bromobenzylbromide (35.8 mmol, 8.93 g) was added, and the reaction mixture was stirred at room temperature for 24 h. Then the solution was filtered off, the residue was washed with acetonitrile (20 mL) and dried *in vacuo* to give 1,8-bis(3-bromobenzyl)-4,11-diaza-1,8-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane dibromide (**10**) as white crystalline powder practically insoluble in common solvents for NMR spectroscopy (D_2O, DMSO-d_6, CD_3OD). Yield 10.7 g (83%). Then it was treated with NaOH (750 mmol, 30g) in 40 mL water at 80-90 °C under stirring for 24 h. The reaction mixture was extracted with CH_2Cl_2 (2x30 mL), organic fractions were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give compound **12** as slightly beige crystalline powder. Yield 7.48 g (94%), mp 73-75 °C. ^{1}H NMR ($CDCl_3$): δ 1.82 (quintet, J = 5.0 Hz, 4H), 2.48 (t, J = 5.5 Hz, 4H), 2.58-2.63 (m, 4H), 2.70 (t, J = 5.2 Hz, 4H), 2.72-2.76 (m, 4H), 2.96 (bs, 2H), 3.64 (s, 4H), 7.10 (t, J = 7.7 Hz, 2H), 7.18 (d, J = 7.6 Hz, 2H), 7.29 (d, J = 7.7 Hz, 2H), 7.41 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 25.7 (2C), 47.4 (2C), 49.8 (2C), 52.3 (2C), 53.9 (2C), 57.5 (2C), 122.4 (2C), 127.9 (2C), 129.6 (2C), 130.0 (2C), 131.6 (2C), 140.4 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{24}H_{35}Br_2N_4$ $[M+H]^+$ 537.1228, found 537.1199.

1,8-Bis(4-bromobenzyl)-1,4,8,11-tetraazacyclotetradecane (13). Formaldehyde-cyclam **9** (17.4 mmol, 3.9 g) was dissolved in dry acetonitrile (120 mL), *p*-bromobenzylbromide (34.8 mmol, 8.7 g) was added, and the reaction mixture was stirred at room temperature for 24 h. Then the solution was filtered off, the residue was washed with acetonitrile (20 mL) and dried *in vacuo* to give 1,8-bis(4-bromobenzyl)-4,11-diaza-1,8-diazoniatricyclo[9.3.1.$1^{4,8}$]hexadecane (**11**) white crystalline powder practically insoluble in common solvents for NMR spectroscopy (D_2O, DMSO-d_6, CD_3OD). Yield 10.8 g (86%). Then it was treated with NaOH (750 mmol, 30g) in 40 mL water at 80-90 °C under stirring for 24 h. The reaction mixture was extracted with CH_2Cl_2 (2x30 mL), organic fractions were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give compound **13** as slightly yellow crystalline powder. Yield 7.86 g (98%), mp 134-135 °C. ^{1}H NMR ($CDCl_3$): δ 1.83 (quintet, J = 5.2 Hz, 4H), 2.50 (t, J = 5.5 Hz, 4H), 2.56-2.60 (m, 4H), 2.68-2.75 (m, 8H), 3.62 (s, 4H), 7.16 (d, J = 8.2 Hz, 4H), 7.40 (d, J = 8.2 Hz, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.8 (2C), 47.5 (2C), 49.7 (2C), 52.2 (2C), 53.8 (2C), 57.9 (2C), 121.0 (2C), 130.7 (4C) 131.6 (4C), 138.2 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{24}H_{35}Br_2N_4$ $[M+H]^+$ 537.1228, found 537.1253.

1,7-Bis(3-bromobenzyl)-4,10-dipyrimidin-2-yl-1,4,7,10-tetraazacyclododecane (14). N^1,N^7-Bis(3-bromobenzyl)cyclen (**1**) (0.25 mmol, 128 mg) was treated with 2-chloropyrimidine (1 mmol, 115 mg) in dry acetonitrile (5 mL) under reflux, in the presence of K_2CO_3 (138 mg) for 8 h. After cooling to room temperature the reaction mixture was filtered off, the residue was washed with 10 mL CH_2Cl_2, combined organic fractions were evaporated *in vacuo* and chromatographed on silica gel. Eluent CH_2Cl_2-MeOH 100:1-50:1. Yield 116 mg (69%). Pale-yellow crystalline powder, mp 90-92 °C. ^{1}H NMR ($CDCl_3$): δ 2.80 (t, J = 4.6 Hz, 8H), 3.66 (s, 4H), 3.71 (t, J = 4.6 Hz, 8H), 6.30 (t, J = 4.8 Hz, 2H), 6.96 (t, J = 7.7 Hz, 2H), 7.07 (d, J = 7.6 Hz, 2H), 7.21 (d, 7.8 Hz, 2H), 7.35 (s, 2H), 8.08 (d, J = 4.8 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 46.9 (4C), 54.1 (4C), 59.4 (2C), 108.9 (2C), 122.0 (2C), 127.7 (2C), 129.3 (2C), 129.6 (2C), 132.2 (2C), 141.8 (2C), 157.1 (4C), 161.6 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{30}H_{35}Br_2N_8$ $[M+H]^+$ 665.1351, found 665.1320.

1,8-Bis(3-bromobenzyl)-4,11-dipyrimidin-2-yl-1,4,8,11-tetraazacyclotetradecane (15). N^1,N^8-Bis(3-bromobenzyl)cyclam (**12**) (1 mmol, 538 mg) was treated with 2-chloropyrimidine (4 mmol, 458 mg) in dry acetonitrile (15 mL) under reflux, in the presence of K_2CO_3 (552 mg) for 18 h. After cooling to room temperature the reaction mixture was filtered off, the residue was washed with 15 mL CH_2Cl_2, combined organic fractions were evaporated *in vacuo* and chromatographed on silica gel. Eluent CH_2Cl_2-MeOH 100:1. Yield 153 mg (22%). Pale-yellow crystalline powder, mp 169-170 °C. ^{1}H NMR ($CDCl_3$): δ 1.89

(quintet, *J* = 6.9 Hz, 4H), 2.54 (t, *J* = 6.1 Hz, 4H), 2.75 (t, *J* = 6.2 Hz, 4H), 3.59 (s, 4H), 3.73 (t, *J* = 6.2 Hz, 4H), 3.79 (t, *J* = 7.7 Hz, 4H), 6.38 (t, *J* = 4.7 Hz, 2H), 7.08 (t, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.46 (s, 2H), 8.21 (d, *J* = 4.7 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 26.0 (2C), 47.0 (2C), 47.6 (2C), 51.9 (2C), 52.4 (2C), 60.0 (2C), 109.0 (2C), 122.2 (2C), 127.6 (2C), 129.6 (2C), 129.8 (2C), 132.0 (2C), 141.9 (2C), 157.5 (4C), 161.5 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{32}H_{39}Br_2N_8$ $[M+H]^+$ 693.1664, found 693.1627.

1,8-Bis(3-bromobenzyl)-4-pyrimidin-2-yl-1,4,8,11-tetraazacyclotetradecane (16) was obtained as the second product in the synthesis of compound **15**. Eluent CH_2Cl_2-MeOH 25:1. Yield 219 mg (36%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.64 (quintet, *J* = 6.2 Hz, 2H), 1.78 (quintet, *J* = 5.0 Hz, 2H), 2.35 (bs, 1H), 2.44 (t, *J* = 4.9 Hz, 2H), 2.59 (bs, 4H), 2.63 (t, *J* = 5.0 Hz, 2H), 2.68 (t, *J* = 5.7 Hz, 2H), 2.73 (t, *J* = 5.2 Hz, 2H), 3.41 (s, 2H), 3.55 (t, *J* = 5.4 Hz, 2H), 3.56 (s, 2H), 3.66 (t, *J* = 7.6 Hz, 2H), 6.26 (t, *J* = 4.8 Hz, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.30 (s, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.55 (s, 1H), 8.08 (d, *J* = 4.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 26.0, 26.8, 45.8, 45.9, 47.4, 47.5, 50.9, 51.2, 52.8, 53.8, 57.8, 59.9, 108.5, 121.5, 122.4, 127.3, 127.5, 129.2, 129.4, 129.8, 130.1, 131.7, 132.1, 141.9, 142.0, 157.2 (2C), 160.8. HRMS (MALDI-TOF) *m/z* calcd for $C_{28}H_{37}Br_2N_6$ $[M+H]^+$ 615.1446, found 615.1418.

1,7-Bis(4-bromobenzyl)-4,10-dipyrimidin-2-yl-1,4,7,10-tetraazacyclododecane (17). N^1,N^7-Bis(4-bromobenzyl)cyclen (**8**) (2 mmol, 1.02 mg) was treated with 2-chloropyrimidine (8 mmol, 916 mg) in dry acetonitrile (30 mL) under reflux, in the presence of K_2CO_3 (1.1 g) for 16 h. After cooling to room temperature the reaction mixture was filtered off, the residue was washed with 20 mL CH_2Cl_2, combined organic fractions were evaporated *in vacuo* and chromatographed on silica gel. Eluent CH_2Cl_2-MeOH 100:1-50:1. Yield 786 mg (69%). Pale-beige crystalline powder, mp 154-156 °C. ^{1}H NMR ($CDCl_3$): δ 2.76 (t, *J* = 4.4 Hz, 8H), 3.62 (s, 4H), 3.68 (t, *J* = 4.4 Hz, 8H), 6.31 (t, *J* = 4.7 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 4H), 7.20 (d, *J* = 8.2 Hz, 4H), 8.05 (d, *J* = 4.7 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 46.7 (4C), 54.1 (4C), 59.3 (2C), 108.9 (2C), 120.3 (2C), 130.8 (8C), 138.3 (2C), 157.0 (4C), 161.5 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{30}H_{35}Br_2N_8$ $[M+H]^+$ 665.1351, found 665.1382.

1,8-Bis(4-bromobenzyl)-4,11-dipyrimidin-2-yl-1,4,8,11-tetraazacyclotetradecane (18). N^1,N^8-Bis(4-bromobenzyl)cyclam (**13**) (2 mmol, 1.076 g) was treated with 2-chloropyrimidine (4 mmol, 916 mg) in dry acetonitrile (30 mL) under reflux, in the presence of K_2CO_3 (1.01 g) for 16 h. After cooling to room temperature the reaction mixture was filtered off, the residue was washed with 20 mL CH_2Cl_2, combined

organic fractions were evaporated *in vacuo* and chromatographed on silica gel. Eluent CH_2Cl_2-MeOH 50:1. Yield 345 mg (25%). Pale-beige crystalline powder, mp 184-186 °C. ^{1}H NMR ($CDCl_3$): δ 1.86 (quintet, *J* = 6.7 Hz, 4H), 2.52 (t, *J* = 6.1 Hz, 4H), 2.74 (t, *J* = 6.0 Hz, 4H), 3.54 (s, 4H), 3.71 (t, *J* = 6.0 Hz, 4H), 3.79 (t, *J* = 7.6 Hz, 4H), 6.38 (t, *J* = 4.7 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 4H), 7.32 (d, *J* = 8.2 Hz, 4H), 8.18 (d, *J* = 4.7 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 26.0 (2C), 46.9 (2C), 47.5 (2C), 52.0 (2C), 52.5 (2C), 60.0 (2C), 109.0 (2C), 120.5 (2C), 130.7 (4C), 131.0 (4C), 138.5 (2C), 157.4 (4C), 161.3 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{32}H_{39}Br_2N_8$ $[M+H]^+$ 693.1664, found 693.1690.

1,8-Bis(4-bromobenzyl)-4-pyrimidin-2-yl-1,4,8,11-tetraazacyclotetradecane (19) was obtained as the second product in the synthesis of compound **18**. Eluent CH_2Cl_2-MeOH 10:1. Yield 253 mg (20%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.60 (bs, 2H), 1.79 (bs, 2H), 2.36 (bs, 2H), 2.52-2.63 (m, 8H), 2.76 (bs, 2H), 3.34 (s, 2H), 3.50 (bs, 2H), 3.51 (s, 2H), 3.58 (t, *J* = 6.6 Hz, 2H), 6.27 (t, *J* = 4.4 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 8.04 (d, *J* = 4.4 Hz, 2H), NH proton was not assigned. ^{13}C NMR ($CDCl_3$): δ 25.9, 26.2, 45.9, 46.1, 47.1, 47.4, 50.7, 51.1, 52.5, 53.1, 57.7, 59.5, 108.7, 120.3, 121.0, 130.6, 130.8 (2C), 131.2, 137.7, 137.8, 157.2 (2C), 160.8. HRMS (MALDI-TOF) *m/z* calcd for $C_{28}H_{37}Br_2N_6$ $[M+H]^+$ 615.1446, found 615.1429.

Typical procedure for the synthesis of macrobicycles **20a,c,d**, **22a-d**, **24d, 26a,c,d**, **28a,b**, **30a** and macropolycycles **21a,c,d**, **23a-d**, **26a,c,d**, **27a,c,d**, **29a,b**, **31a**.

A two-neck flask (15 mL) flushed with dry argon, equipped with a magnetic stirrer and condenser was charged with cyclen or cyclam derivatives **14-19** (**1**) (0.1 - 0.22 mmol), $Pd(dba)_2$ (16 mol%), BINAP (18 mol%), absolute dioxane was added to make 0.02 M concentration of the starting compounds. The mixture was stirred for 2 min, then appropriate amine **2a-d** (0.1 - 0.22 mmol) was added followed by sodium *tert*-butoxide (0.3 – 0.66 mmol). The reaction mixture was refluxed for 24-30 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: CH_2Cl_2, CH_2Cl_2-MeOH 50:1 – 3:1, CH_2Cl_2-MeOH-NH_3aq 100:20:1 – 10:4:1.

32,37-Dipyrimidin-2-yl-12,15,18-trioxa-1,8,22,29,32,37-hexaazatetracyclo[27.5.5.1^{3,7}.1^{23,27}]hentetra-conta-3(41),4,6,23(40),24,26-hexaene (20a) was synthesized from compound **14** (0.12 mmol, 78 mg), trioxadiamine **2a** (0.12 mmol, 26 mg), in the presence of $Pd(dba)_2$ (11 mg), BINAP (13 mg), *t*BuONa (35 mg), in dioxane (5 mL). Eluent CH_2Cl_2-MeOH 10:1. Yield 25 mg (29%), pale-yellow crystalline powder, mp 134-135 °C. ^{1}H NMR ($CDCl_3$): δ 1.77 (bs, 4H), 3.10 (bs, 4H), 3.28 (bs, 4H), 3.38 (bs, 4H), 3.56 (t, *J*

= 5.3Hz, 4H), 3.59-3.63 (m, 8H), 3.66-3.70 (m, 4H), 3.80 (bs, 4H), 3.89 (bs, 4H), 6.44 (bs, 4H), 6.48 (bs, 4H), 7.00 (bs, 2H), 8.18 (bs, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 28.8 (2C), 41.2 (2C), 47.2 (bs, 4C), 53.0 (4C), 59.2 (2C), 69.5 (2C), 70.0 (2C), 70.5 (2C), 110.8 (2C), 112.1 (bs, 2C), 115.3 (bs, 2C), 118.6 (2C), 129.1 (2C), 149.0 (2C), 157.4 (4C), 162.0 (2C), two aromatic quaternary carbon atoms were not assigned. HRMS (MALDI-TOF) *m/z* calcd for $C_{40}H_{57}N_{10}O_3$ $[M+H]^+$ 725.4615, found 725.4589.

32,66,71,78-Tetrapyrimidin-2-yl-12,15,18,46,49,52-hexaoxa-1,8,22,29,32,35,42,56,63,66,71,78-dodecaazaheptacyclo[61.5.5.5^{29,35}.1^{3,7}.1^{23,27}.1^{37,41}.1^{57,61}]dooctaconta-3(82),4,6,23(81),24,26,37(75),38,40,57(74),58,60-dodecaene (21a) was obtained as the second product in the synthesis of macrobicycle **20a**. Eluent CH_2Cl_2-MeOH 3:1. Yield 12 mg (14%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.84 (bs, 8H), 3.13 (t, *J* = 5.4 Hz, 8H), 3.23 (bs, 16H), 3.50-3.70 (m, 32H), 3.85 (bs, 16H), 4.37 (bs, 4H), 6.39 (t, *J* = 4.8 Hz, 4H), 6.42-6.51 (m, 12H), 7.02 (t, *J* = 7.7 Hz, 4H), 8.11 (d, *J* = 4.8 Hz, 8H). HRMS (MALDI-TOF) *m/z* calcd for $C_{80}H_{113}N_{20}O_6$ $[M+H]^+$ 1449.9152, found 1449.9107.

27,32-Dipyrimidin-2-yl-11,14-dioxa-1,8,17,24,27,32-hexaazatetracyclo[22.5.5.1^{3,7}.1^{18,22}]hexatriaconta-3(36),4,6,18(35),19,21-hexaene (20c) was synthesized from compound **14** (0.17 mmol, 114 mg), dioxadiamine **2c** (0.17 mmol, 25 mg), in the presence of $Pd(dba)_2$ (16 mg), BINAP (19 mg), *t*BuONa (50 mg), in dioxane (7 mL). Eluent CH_2Cl_2-MeOH 10:1. Yield 34 mg (31%), pale-yellow crystalline powder, mp 167-168 °C. ^{1}H NMR ($CDCl_3$): δ 3.08 (bs, 4H), 3.20-3.45 (m, 8H), 3.68 (s, 4H), 3.71 (bs, 8H), 3.60-4.05 (m, 8H), 4.20 (bs, 2H), 6.35 (bs, 2H), 6.41-6.48 (m, 4H), 6.58 (s, 2H), 6.91 (bs, 2H), 8.28 (bs, 4H). ^{13}C NMR ($CDCl_3$): δ 43.4 (2C), 45.1 (bs, 4C), 53.1 (bs, 4C), 57.0 (bs, 2C), 69.1 (bs, 2C), 70.1 (2C), 111.0 (2C), 112.2 (2C), 116.1 (2C), 118.7 (2C), 129.6 (2C), 148.9 (2C), 157.6 (4C), 162.0 (2C), two aromatic quaternary carbon atoms were not assigned. HRMS (MALDI-TOF) *m/z* calcd for $C_{36}H_{49}N_{10}O_2$ $[M+H]^+$ 653.4040, found 653.4006.

27,56,61,68-Tetrapyrimidin-2-yl-11,14,40,43-tetraoxa-1,8,17,24,27,30,37,46,53,56,61,68-dodecaazaheptacyclo[51.5.5.5^{24,30}.1^{3,7}.1^{18,22}.1^{32,36}.1^{47,51}]doheptaconta-3(72),4,6,18(71),19,21,32(65),33,35,47(64),48,50-dodecaene (21c) was obtained as the second product in the synthesis of macrobicycle **20c**. Eluent CH_2Cl_2-MeOH 3:1. Yield 19 mg (17%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 3.00-3.27 (m, 16H), 3.24 (bs, 8H), 3.63 (s, 8H), 3.68 (bs, 16H), 3.86 (bs, 16H), 4.46 (bs, 4H), 6.39-6.51 (m, 12H), 6.63 (s, 4H), 6.99 (bs, 4H), 8.08 (bs, 8H). ^{13}C NMR ($CDCl_3$): δ 43.4 (4C), 46.1 (bs, 8C), 52.6 (bs, 8C), 56.7 (bs, 4C), 69.6 (4C), 70.1 (4C), 110.8 (4C), 113.0 (bs, 4C), 116.8 (bs, 4C), 120.2 (bs, 4C), 129.1 (4C),

148.6 (4C), 157.4 (8C), 161.5 (4C), for aromatic quaternary carbon atoms were not assigned. HRMS (MALDI-TOF) *m/z* calcd for $C_{72}H_{97}N_{20}O_4$ $[M+H]^+$ 1305.8002, found 1304.7953.

30,35-Dipyrimidin-2-yl-1,8,12,16,20,27,30,35-octaazatetracyclo[25.5.5.1^{3,7}.1^{21,25}]nonatriaconta-3(39),4,6,21(38),22,24-hexaene (20d) was synthesized from compound **14** (0.14 mmol, 94 mg), tetraamine **2d** (0.14 mmol, 26 mg), in the presence of $Pd(dba)_2$ (13 mg), BINAP (16 mg), *t*BuONa (40 mg), in dioxane (6 mL). Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3. Yield 15 mg (15%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.72 (quintet, *J* = 6.3 Hz, 6H), 2.71 (t, *J* = 6.5 Hz, 4H), 2.73 (t, *J* = 6.5 Hz, 4H), 2.79 (bs, 4H), 2.91 (bs, 4H), 3.08 (t, *J* = 6.3 Hz, 4H), 3.63 (s, 4H), 3.74 (t, *J* = 4.5 Hz, 8H), 6.35 (t, *J* = 4.8 Hz, 2H), 6.39 (d, *J* = 7.7 Hz, 2H), 6.57 (d, *J* = 7.1 Hz, 2H), 6.64 (s, 2H), 7.00 (t, *J* = 7.7 Hz, 2H), 8.16 (d, *J* = 4.8 Hz, 4H), NH protons were not assigned. HRMS (MALDI-TOF) *m/z* calcd for $C_{39}H_{57}N_{12}$ $[M+H]^+$ 693.4829, found 693.4860.

30,62,67,74-Tetrapyrimidin-2-yl-1,8,12,16,20,27,30,33,40,44,48,52,59,62,67,74-hexadecaazaheptacyclo-[57.5.5.5^{27,33}.1^{3,7}.1^{21,25}.1^{35,39}.1^{53,57}]octaheptaconta-3(78),4,6,21(77),22,24,35(71),36,38,53(70),54,56-dodecaene (21d) was obtained as the second product in the synthesis of macrobicycle **20d**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:25:5. Yield 17 mg (17%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.64-1.76 (m, 12H), 2.67 (bs, 16H), 2.79 (bs, 16H), 3.02 (bs, 8H), 3.60 (s, 8H), 3.74 (bs, 16H), 6.26 (t, *J* = 3.7 Hz, 4H), 6.33 (d, *J* = 7.6 Hz, 4H), 6.42 (s, 4H), 6.51 (d, *J* = 7.1 Hz, 4H), 6.92 (t, *J* = 7.5 Hz, 4H), 8.07 (d, *J* = 3.7 Hz, 8H), NH protons were not assigned. HRMS (MALDI-TOF) *m/z* calcd for $C_{78}H_{113}N_{24}$ $[M+H]^+$ 1385.9580, found 1385.9644.

30,35-Dipyrimidin-2-yl-11,14,17-trioxa-1,7,21,27,30,35-hexaazatetracyclo[25.5.5.2^{3,6}.2^{22,25}]hentetraconta-3,5,22,24,38,40-hexaene (22a) was synthesized from compound **17** (0.15 mmol, 100 mg), trioxadiamine **2a** (0.15 mmol, 33 mg), in the presence of $Pd(dba)_2$ (14 mg), BINAP (17 mg), *t*BuONa (44 mg), in dioxane (7.5 mL). Eluent CH_2Cl_2-MeOH 10:1 – 3:1. Yield 21 mg (19%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.87 (quintet, *J* = 5.8 H, 4H), 2.67-2.82 (m, 4H), 2.84 (t, *J* = 4.7 Hz, 4H), 3.23 (t, *J* = 6.1 Hz, 4H), 3.55 (s, 4H), 3.59-3.72 (m, 20H), 6.37 (t, *J* = 4.7 Hz, 2H), 6.51 (d, *J* = 8.2 Hz, 4H), 7.15 (d, *J* = 8.2 Hz, 4H), 8.19 (d, *J* = 5.7 H, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 29.1 (2C), 42.4 (2C), 48.1 (4C), 53.7 (4C), 60.0 (2C), 70.1 (2C), 70.2 (2C), 70.7 (2C), 109.0 (2C), 112.3 (4C), 127.7 (2C), 130.6 (4C), 148.0 (2C), 157.2 (4C), 162.0 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{40}H_{57}N_{10}O_3$ $[M+H]^+$ 725.4615, found 725.4651.

30,63,68,77-Tetrapyrimidin-2-yl-11,14,17,43,46,50-hexaoxa-1,7,21,27,30,33,39,54,60,63,68,77-dodecaazaheptacyclo[58.5.5.5^{27,33}.2^{3,6}.2^{22,25}.2^{35,38}.2^{55,58}]trioctaconta-3,5,22,24,35,37,55,57,71,73,80,82-dodecaene (23a, n=1) was obtained as the second product in the synthesis of macrobicycle **22a**. Eluent CH_2Cl_2-MeOH 3:1. Yield 22 mg (20%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.86 (quintet, *J* = 5.8 Hz, 8H), 2.79 (bs, 8H), 2.88 (bs, 8H), 3.15 (t, *J* = 6.8 Hz, 8H), 3.53-3.76 (m, 48H), 6.26 (t, *J* = 4.7 Hz, 4H), 6.44 (d, *J* = 8.1 Hz, 8H), 7.03 (d, *J* = 8.1 Hz, 8H), 8.07 (d, *J* = 4.7 Hz, 8H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 29.0 (4C), 41.7 (4C), 47.1 (8C), 54.1 (8C), 59.7 (4C), 69.7 (4C), 70.2 (4C), 70.6 (4C), 108.6 (4C), 112.2 (8C), 127.6 (4C), 130.5 (8C), 147.4 (4C), 157.1 (8C), 161.6 (4C). HRMS (MALDI-TOF) *m/z* calcd for $C_{80}H_{113}N_{20}O_6$ $[M+H]^+$ 1449.9152, found 1449.9208.

Cyclic trimer (23a, n=2) was was obtained as the third product in the synthesis of macrobicycle **22a**. Eluent CH_2Cl_2-MeOH 3:1. Yield 26 mg (23%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.83 (quintet, *J* = 5.8 Hz, 12H), 2.77 (bs, 24H), 3.13 (t, *J* = 6.3 Hz, 12H), 3.52-3.60 (m, 36H), 3.62-3.66 (m, 12H), 3.71 (bs, 24H), 6.27 (t, *J* = 4.5 Hz, 6H), 6.38 (d, *J* = 8.1 Hz, 12H), 6.95 (d, *J* = 8.1 Hz, 12H), 8.10 (d, *J* = 4.5 Hz, 12H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 29.1 (6C), 41.7 (6C), 46.4 (12C), 53.8 (12C), 59.3 (6C), 69.7 (6C), 70.2 (6C), 70.6 (6C), 108.6 (6C), 112.2 (12C), 127.6 (6C), 130.3 (12C), 147.2 (6C), 57.1 (12C), 161.6 (6C). MS (MALDI-TOF) *m/z* calcd for $C_{120}H_{169}N_{30}O_9$ $[M+H]^+$ 2174.37, found 2174.45.

29,34-Dipyrimidin-2-yl-11,16-dioxa-1,7,20,26,29,34-hexaazatetracyclo[24.5.5.2^{3,6}.2^{21,24}]tetraconta-3,5,21,23,37,39-hexaene (22b) was synthesized from compound **17** (0.15 mmol, 100 mg), dioxadiamine **2b** (0.15 mmol, 31 mg), in the presence of $Pd(dba)_2$ (14 mg), BINAP (17 mg), *t*BuONa (44 mg), in dioxane (7.5 mL). Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:1. Yield 9 mg (8%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.70 (bs, 4H), 1.87 (quintet, *J* = 5.7 Hz, 4H), 2.90 (bs, 8H), 3.21 (t, *J* = 5.4 Hz, 4H), 3.45 (bs, 4H), 3.56 (t, *J* = 5.3 Hz, 4H), 3.58 (bs, 4H), 3.67 (bs, 8H), 6.37 (t, *J* = 4.4 Hz, 2H), 6.49 (bs, 4H), 7.14 (bs, 4H), 8.18 (d, *J* = 4.4 Hz, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 26.9 (2C), 29.4 (2C), 42.8 (2C), 48.0 (bs, 4C), 53.4 (bs, 4C), 59.6 (bs, 2C), 70.1 (2C), 71.1 (2C), 109.2 (2C), 112.3 (4C), 130.7 (4C), 147.8 (2C), 157.2 (4C), 162.0 (2C), two quaternary aromatic carbons were not assigned. HRMS (MALDI-TOF) *m/z* calcd for $C_{40}H_{57}N_{10}O_2$ $[M+H]^+$ 709.4666, found 709.4644.

29,60,65,74-Tetrapyrimidin-2-yl-11,16,42,47-tetraoxa-1,7,20,26,29,32,38,51,57,60,65,74-dodecaazaheptacyclo[55.5.5.5^{26,32}.2^{3,6}.2^{21,24}.2^{34,37}.2^{52,55}]octaconta-3,5,21,23,34,36,52,54,68,70,77,79-dodecaene (23b, n=1) was obtained as the second product in the synthesis of macrobicycle **22b**. Eluent CH_2Cl_2-

MeOH- NH_3aq 100:20:2. Yield 33 mg (31%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.66 (bs, 8H), 1.83 (quintet, *J* = 5.8 Hz, 8H), 2.77 (bs, 16H), 3.14 (t, *J* = 6.5 Hz, 8H), 3.41-3.46 (m, 8H), 3.51 (t, *J* = 5.7 Hz, 8H), 3.57 (bs, 8H), 3.72 (bs, 16H), 6.27 (t, *J* = 4.5 Hz, 4H), 6.38 (d, *J* = 8.0 Hz, 8H), 6.96 (d, *J* = 8.0 Hz, 8H), 8.10 (d, *J* = 4.5 Hz, 8H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 26.5 (4C), 29.4 (4C), 42.0 (4C), 46.5 (8C), 53.8 (8C), 59.3 (4C), 69.4 (4C), 70.8 (4C), 108.6 (4C), 112.2 (8C), 127.3 (4C), 130.3 (8C), 147.2 (4C), 157.1 (8C), 161.6 (4C). HRMS (MALDI-TOF) *m/z* calcd for $C_{80}H_{113}N_{20}O_4$ $[M+H]^+$ 1417.9254, found 1417.9197.

25,30-Dipyrimidin-2-yl-10,13-dioxa-1,7,16,22,25,30-hexaazatetracyclo[20.5.5.2^{3,6}.2^{17,20}]hexatriaconta-3,5,17,19,33,35-hexaene (22c) was synthesized from compound **17** (0.15 mmol, 100 mg), dioxadiamine **2c** (0.15 mmol, 22 mg), in the presence of $Pd(dba)_2$ (14 mg), BINAP (17 mg), *t*BuONa (44 mg), in dioxane (7.5 mL). Eluent CH_2Cl_2-MeOH 3:1. Yield 16 mg (16%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 2.95 (bs, 4H), 3.20 (t, *J* = 5.0 Hz, 4H), 3.30 (bs, 4H), 3.47 (bs, 4H), 3.63 (bs, 4H), 3.66 (s, 4H), 3.71 (t, *J* = 5.0 Hz, 4H), 3.92 (bs, 4H), 6.31 (bs, 4H), 6.44 (t, *J* = 4.6 Hz, 2H), 7.11 (bs, 4H), 8.18 (d, *J* = 4.6 Hz, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 43.5 (2C), 48.6 (bs, 4C), 51.4 (bs, 4C), 58.7 (bs, 2C), 69.5 (2C), 70.1 (2C), 110.1 (2C), 112.4 (4C), 127.7 (2C), 131.8 (4C), 147.6 (2C), 157.1 (4C), 162.0 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{36}H_{49}N_{10}O_2$ $[M+H]^+$ 653.4040, found 653.4081.

25,52,57,66-Tetrapyrimidin-2-yl-10,13,37,40-tetraoxa-1,7,16,22,25,28,34,43,49,52,57,66-dodecaazaheptacyclo[47.5.5.5^{22,28}.2^{3,6}.2^{17,20}.2^{30,33}.2^{44,47}]doheptaconta-3,5,17,19,30,32,44,46,60,62,69,71-dodecaene (23c, n=1) was obtained as the second product in the synthesis of macrobicycle **22b**. Eluent CH_2Cl_2-MeOH- NH_3aq 100:20:1. Yield 3 mg (3%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 2.85 (bs, 16H), 3.23 (bs, 8H), 3.64 (s, 8H), 3.67 (s, 8H), 3.68-3.82 (m, 24H), 6.31 (t, *J* = 4.7 Hz, 4H), 6.42 (d, *J* = 8.1 Hz, 8H), 7.04 (d, *J* = 8.1 Hz, 8H), 8.07 (d, *J* = 4.7 Hz, 8H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 43.6 (4C), 46.3 (8C), 53.4 (8C), 58.9 (4C), 69.7 (4C), 70.2 (4C), 108.9 (4C), 112.7 (8C), 131.4 (8C), 157.2 (8C), aromatic quaternary carbons were not assigned. HRMS (MALDI-TOF) *m/z* calcd for $C_{72}H_{97}N_{20}O_4$ $[M+H]^+$ 1305.8002, found 1304.7962.

Cyclic trimer 23c (n=2) and cyclic tertramer 23c (n=3) were obtained as a separate fraction in the synthesis of macrobicycle **22c**. Eluent CH_2Cl_2-MeOH- NH_3aq 100:20:2. Yield 41 mg (41%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 2.79 (bs, 8(n+1)H), 3.22 (t, *J* = 4.4 Hz, 4(n+1)H), 3.60 (bs, 4(n+1)H), 3.63 (s, 4(n+1)H), 3.66 (t, *J* = 4.4 Hz, 4(n+1)H), 3.71 (bs, 8(n+1)H), 6.28 (t, *J* = 4.6 Hz, 2(n+1)H), 6.41 (d,

J = 7.9 Hz, 4(n+1)H), 6.97 (d, *J* = 7.9 Hz, 4(n+1)H), 8.09 (d, *J* = 4.6 Hz, 4(n+1)H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 43.6 (2(n+1)C), 46.5 (4(n+1)C), 53.7 (bs, 4(n+1)C), 59.2 (bs, 2(n+1)C), 69.6 (2(n+1)C), 70.2 (2(n+1)C), 108.7 (2(n+1)C), 112.6 (4(n+1)C), 127.6 (2(n+1)C), 130.4 (4(n+1)C), 146.9 (2(n+1)C), 157.2 (4(n+1)C), 161,6 (2(n+1)C). MS (MALDI-TOF) *m/z* calcd for $C_{108}H_{145}N_{30}O_6$ $[M+H]^+$ 1958.20, found 1958.15 (**23c** (n=2)); calcd for $C_{144}H_{193}N_{40}O_8$ $[M+H]^+$ 2610.59, found 2610.48 (**23c** (n=3).

28,33-Dipyrimidin-2-yl-1,7,11,15,19,25,28,33-octaazatetracyclo[23.5.5.2^{3,6}.2^{20,23}]nonatriaconta-3,5,20,22,36,38-hexaene (22d) was synthesized from compound **17** (0.15 mmol, 100 mg), tetraamine **2d** (0.15 mmol, 28 mg), in the presence of $Pd(dba)_2$ (14 mg), BINAP (17 mg), *t*BuONa (44 mg), in dioxane (7.5 mL). Eluent CH_2Cl_2-MeOH- NH_3aq 100:20:3. Yield 17 mg (16%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.72-1.82 (m, 6H), 2.76 (t, *J* = 6.4 Hz, 4H), 2.77 (t, *J* = 6.5 Hz, 4H), 2.84 (t, *J* = 4.7 Hz, 8H), 3.18 (t, *J* = 6.1 Hz, 4H), 3.53 (s, 4H), 3.66 (t, *J* = 4.7 Hz, 8H), 6.37 (t, *J* = 4.8 Hz, 2H), 6.49 (d, *J* = 8.2 Hz, 4H), 7.18 (d, *J* = 8.2 Hz, 4H), 8.18 (d, *J* = 4.7 Hz, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 28.4 (2C), 29.8 (1C), 43.5 (2C), 48.3 (2C), 48.4 (4C), 48.5 (2C), 53.9 (4C), 59.9 (2C), 109.1 (2C), 112.4 (4C), 127.6 (2C), 130.5 (4C), 147.6 (2C), 157.2 (4C), 162.0 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{39}H_{57}N_{12}$ $[M+H]^+$ 693.4829, found 693.4788.

28,58,63,72-Tetrapyrimidin-2-yl-1,7,11,15,19,25,28,31,37,41,45,49,55,58,63,72-hexadecaazaheptacyclo[53.5.5.5^{25,31}.2^{3,6}.2^{20,23}.2^{33,36}.2^{50,53}]octaheptaconta-3,5,20,22,33,35,50,52,66,68,75,77-dodecaene (23d, n=1) was obtained as the second product in the synthesis of macrobicycle **22d**. Eluent CH_2Cl_2-MeOH- NH_3aq 100:35:6. Yield 21 mg (20%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.66-1.80 (m, 12H), 2.65-2.79 (m, 32H), 3.08 (t, *J* = 6.1 Hz, 8H), 3.55 (s, 8H), 3.70 (bs, 16H), 6.26 (t, *J* = 4.5 Hz, 4H), 6.39 (d, *J* = 8.0 Hz, 8H), 6.96 (d, *J* = 8.0 Hz, 8H), 8.09 (d, *J* = 4.5 Hz, 8H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 28.7 (4C), 29.8 (2C), 42.9 (4C), 46.5 (8C), 48.7 (8C), 53.9 (8C), 59.4 (4C), 108.6 (4C), 112.3 (8C), 127.4 (4C), 130.3 (8C), 147.2 (4C), 157.2 (8C), 161.6 (4C). HRMS (MALDI-TOF) *m/z* calcd for $C_{78}H_{113}N_{24}$ $[M+H]^+$ 1385.9580, found 1385.9537.

32,67,73,81-Tetrapyrimidin-2-yl-12,15,18,47,50,53-hexaoxa-1,8,22,29,32,36,43,57,64,67,73,81-dodecaazaheptacyclo[62.6.6.6^{29,36}.1^{3,7}.1^{23,27}.1^{38,42}.1^{58,62}]hexaoctaconta-3(86),4,6,23(85),24,26,38(78),39,41,58(77),59,61-dodecaene (25a, n=1) was synthesized from compound **15** (0.1 mmol, 69 mg), trioxadiamine **2a** (0.1 mmol, 22 mg), in the presence of $Pd(dba)_2$ (8 mg), BINAP (10 mg), *t*BuONa (30 mg), in dioxane (5 mL). Eluent CH_2Cl_2-MeOH 10:1. Yield 8 mg (13%), pale-yellow crystalline powder,

mp 112-113 °C. ^{1}H NMR ($CDCl_3$): δ 1.78-1.94 (m, 16H), 2.52 (bs, 8H), 2.75 (bs, 8H), 3.17 (t, *J* = 5.8 Hz, 8H), 3.49-3.60 (m, 24H), 3.63 (s, 8H), 3.77 (bs, 16H), 6.34 (t, *J* = 4.3 Hz, 4H), 6.41 (bs, 4H), 6.55 (bs, 4H), 6.59 (d, *J* = 8.1 Hz, 4H), 7.01 (t, *J* = 7.8 Hz, 4H), 8.18 (d, *J* = 4.3 Hz, 8H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.6 (4C), 29.2 (4C), 41.6 (4C), 46.7 (bs, 4C), 47.2 (bs, 4C), 51.7 (bs, 4C), 51.9 (4C), 60.4 (4C), 69.6 (4C), 70.2 (4C), 70.6 (4C), 108.9 (4C), 111.1 (4C), 113.4 (4C), 117.9 (4C), 128.8 (4C), 148.4 (4C), 157.4 (8C), 161.5 (4C), four quaternary aromatic carbon atoms were not assigned. HRMS (MALDI-TOF) *m/z* calcd for $C_{84}H_{121}N_{20}O_6$ $[M+H]^+$ 1505.9778, found 1505.9721.

Cyclic trimer (25a, n=2) was obtained as the second product in the synthesis of macrotricycle **25a** (n=1). Eluent CH_2Cl_2-MeOH 10:3. Yield 8 mg (10%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.85 (quintet, *J* = 5.8 Hz, 12H), 1.89 (bs, 12H), 2.54 (bs, 12H), 2.79 (bs, 12H), 3.17 (t, *J* = 6.0 Hz, 12H), 3.46-3.61 (m, 36H), 3.63 (s, 12H), 3.76 (bs, 24H), 6.36 (t, *J* = 4.5 Hz, 6H), 6.43 (d, *J* = 6.8 Hz, 6H), 6.58 (s, 6H), 6.64 (d, *J* = 7.1 Hz, 6H), 7.03 (t, *J* = 7.6 Hz, 6H), 8.19 (t, *J* = 4.5 Hz, 12H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.6 (6C), 29.1 (6C), 41.6 (6C), 46.7 (bs, 12C), 51.6 (bs, 12C), 60.3 (6C), 69.6 (6C), 70.2 (6C), 70.5 (6C), 109.0 (6C), 111.2 (6C), 113.4 (6C), 117.9 (6C), 128.7 (6C), 148.4 (6C), 157.4 (12C), 161.5 (6C), six quaternary aromatic carbon atoms were not assigned. MS (MALDI-TOF) *m/z* calcd for $C_{126}H_{181}N_{30}O_9$ $[M+H]^+$ 2258.46, found 2258.34.

27,57,63,71-Tetrapyrimidin-2-yl-11,14,41,44-tetraoxa-1,8,17,24,27,31,38,47,54,57,63,71-dodecaaza-heptacyclo[52.6.6.6^{24,31}.1^{3,7}.1^{18,22}.1^{33,37}.1^{48,52}]hexaheptaconta-3(76),4,6,18(75),19,21,33(68),34,36, 48(67),49,51-dodecaene (25c, n=1) was synthesized from compound **15** (0.1 mmol, 69 mg), dioxadiamine **2c** (0.1 mmol, 15 mg), in the presence of $Pd(dba)_2$ (8 mg), BINAP (10 mg), *t*BuONa (30 mg), in dioxane (5 mL). Eluent CH_2Cl_2-MeOH 10:1. Yield 11 mg (16%), pale-yellow crystalline powder, mp 132-134 °C. ^{1}H NMR ($CDCl_3$): δ 1.87 (bs, 8H), 2.51 (bs, 8H), 2.73 (bs, 8H), 3.21 (t, *J* = 5.0 Hz, 8H), 3.51 (bs, 8H), 3.55 (s, 8H), 3.60 (s, 8H), 3.72 (t, *J* = 6.9 Hz, 8H), 3.77 (bs, 8H), 6.34 (t, *J* = 4.7 Hz, 4H), 6.41 (d, *J* = 7.6 Hz, 4H), 6.60 (d, *J* = 7.9 Hz, 4H), 6.62 (s, 4H), 7.00 (t, *J* = 7.6 Hz, 4H), 8.19 (d, *J* = 4.7 Hz, 8H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.7 (4C), 43.4 (4C), 47.0 (4C), 47.2 (4C), 51.8 (4C), 52.1 (4C), 60.5 (4C), 69.6 (4C), 70.1 (4C), 108.8 (4C), 111.5 (4C), 113.5 (4C), 118.3 (4C), 128.8 (4C), 140.5 (4C), 148.1 (4C), 157.4 (8C), 161.5 (4C). HRMS (MALDI-TOF) *m/z* calcd for $C_{76}H_{105}N_{20}O_4$ $[M+H]^+$ 1361.8628, found 1361.8586.

29,35-Dipyrimidin-2-yl-1,7,11,15,19,26,29,35-octaazatetracyclo[24.6.6.2^{3,6}.1^{20,24}]hentetraconta-3,5,20(39),21,23,40-hexaene (24d) was synthesized from compound **15** (0.22 mmol, 153 mg), tetraamine

2d (0.22 mmol, 42 mg), in the presence of $Pd(dba)_2$ (20 mg), BINAP (25 mg), *t*BuONa (64 mg), in dioxane (11 mL). Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:2-100:20:3. Yield 46 mg (29%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.72 (quintet, *J* = 5.8 Hz, 6H), 1.87 (bs, 4H), 2.52 (bs, 4H), 2.67-2.75 (m, 12H), 3.04 (t, *J* = 6.2 Hz, 4H), 3.48 (bs, 4H), 3.67 (bs, 4H), 3.82 (bs, 4H), 4.00 (bs, 2H), 6.33 (t, *J* = 4.7 Hz, 2H), 6.38 (d, *J* = 7.8 Hz, 2H), 6.60 (d, *J* = 7.9 Hz, 2H), 6.62 (s, 2H), 6.98 (t, *J* = 7.5 Hz, 2H), 8.17 (d, *J* = 4.7 Hz, 4H), two NH protons of dialkylamino groups were not assigned. ^{13}C NMR ($CDCl_3$): δ 26.1 (2C), 28.8 (3C), 43.0 (2C), 46.9 (2C), 47.3 (2C), 48.4 (2C), 48.8 (2C), 52.7 (2C), 54.2 (2C), 60.8 (2C), 108.7 (2C), 111.0 (2C), 113.2 (2C), 117.8 (2C), 128.7 (2C), 141.0 (2C), 148.6 (2C), 157.3 (4C), 161.6 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{41}H_{61}N_{12}$ $[M+H]^+$ 721.5142, found 721.5167.

30,63,69,77-Tetrapyrimidin-2-yl-1,8,12,16,20,27,30,34,41,45,49,53,60,63,69,77-hexadecaazaheptacyclo[58.6.6.6^{27,34}.1^{3,7}.1^{21,25}.1^{36,40}.1^{54,58}]dooctaconta-3(82),4,6,21(81),22,24,36(74),37,39,54(73),55,57-dodecaene (25d, n=1) was obtained as the second product in the synthesis of macrobicycle **24d**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3-100:35:6. Yield 15 mg (9%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.66 (quintet, *J* = 6.5 Hz, 4H), 1.72 (quintet, *J* = 5.7 Hz, 8H), 2.50 (bs, 8H), 2.60-2.76 (m, 24H), 3.08 (t, *J* = 5.6 Hz, 8H), 3.51 (bs, 8H), 3.54 (s, 8H), 3.68-3.86 (m, 16H), 6.34 (t, *J* = 4.0 Hz, 4H), 6.39 (d, *J* = 7.6 Hz, 4H), 6.55 (d, *J* = 7.8 Hz, 4H), 6.59 (s, 4H), 7.00 (t, *J* = 7.7 Hz, 4H), 8.18 (d, *J* = 4.0 Hz, 8H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.9 (4C), 29.3 (4C), 29.7 (2C), 42.6 (4C), 46.9 (4C), 47.4 (4C), 48.1 (4C), 48.5 (4C), 51.9 (4C), 52.2 (4C), 60.6 (4C), 108.8 (4C), 111.0 (4C), 113.1 (4C), 117.9 (4C), 128.8 (4C), 140.5 (4C), 148.4 (4C), 157.4 (8C), 161.6 (4C). HRMS (MALDI-TOF) *m/z* calcd for $C_{82}H_{121}N_{24}$ $[M+H]^+$ 1442.0206, found 1442.0269.

Cyclic trimer (25d, n=2) and cyclic tetramer (25d, n=3) were obtained as a separate fraction in the synthesis of macrobicycle **24d**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:35:6. Yield 9 mg (6%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.66 (quintet, *J* = 7.0 Hz, 2(n+1)H), 1.73 (bs, 4(n+1)H), 1.86 (bs, 4(n+1)H), 2.50 (bs, 4(n+1)H), 2.60-2.78 (m, 12(n+1)H), 3.10 (bs, 4(n+1)H), 3.54 (s, 4(n+1)H), 3.71-3.84 (m, 8(n+1)H), 6.34 (bs, 2(n+1)H), 6.40 (d, *J* = 7.1 Hz, 2(n+1)H), 6.54 (s, 2(n+1)H), 6.61 (d, *J* = 7.2 Hz, 2(n+1)H), 7.02 (t, *J* = 7.4 Hz, 2(n+1)H), 8.18 (d, *J* = 4.1 Hz, 4(n+1)H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.7 (2(n+1)C), 29.5 (2(n+1)C), 30.2 ((n+1)C), 42.7 (2(n+1)C), 46.8 (2(n+1)C), 47.3 (2(n+1)C), 48.3 (2(n+1)C), 48.4 (2(n+1)C), 51.8 (2(n+1)C), 51.9 (2(n+1)C), 60.6 (2(n+1)C), 108.8 (2(n+1)C), 111.0 (2(n+1)C), 113.3 (2(n+1)C), 117.8 (2(n+1)C), 128.8 (2(n+1)C), 140.5 (2(n+1)C), 148.8 (2(n+1)C), 157.4 (4(n+1)C), 161.5 (2(n+1)C). MS (MALDI-TOF) *m/z* calcd for $C_{123}H_{181}N_{36}$ $[M+H]^+$ 2162.53, found 2162.41 (**25d** (n=2)); calcd for $C_{164}H_{241}N_{48}$ $[M+H]^+$ 2883.03, found 2882.86 (**25d** (n=3).

37-Pyrimidin-2-yl-11,14,17-trioxa-1,7,21,28,31,37-hexaazatetracyclo[26.6.6.2^{3,6}.1^{22,26}]tritetraconta-3,5,22(41),23,25,42-hexaene (26a) was synthesized from compound **16** (0.18 mmol, 111 mg), trioxadiamine **2a** (0.18 mmol, 40 mg), in the presence of $Pd(dba)_2$ (17 mg), BINAP (20 mg), *t*BuONa (52 mg), in dioxane (7 mL). Eluent CH_2Cl_2-MeOH 10:1-3:1. Yield 37 mg (30%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.78 (quintet, *J* = 6.1 Hz, 2H), 1.84 (quintet, *J* = 6.0 Hz, 4H), 2.05 (bs, 2H), 2.48 (t, *J* = 5.2 Hz, 2H), 2.68 (bs, 2H), 2.77 (bs, 2H), 2.86 (bs, 2H), 2.95 (bs, 2H), 3.00 (bs, 2H), 3.12 (t, *J* = 6.3 Hz, 2H), 3.19 (t, *J* = 6.3 Hz, 2H), 3.48 (s, 2H), 3.52 (s, 2H), 3.53-3.60 (m, 8H), 3.62-3.66 (m, 4H), 3.70 (bs, 2H), 3.93 (bs, 2H), 6.43 (t, *J* = 4.9 Hz, 1H), 6.46 (d, *J* = 8.2 Hz, 2H), 6.49 (d, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 7.3 Hz, 1H), 6.59 (s, 1H), 6.78 (s, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 8.1 Hz, 1H), 8.24 (d, *J* = 4.9 Hz, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 23.6, 25.7, 28.9, 29.0, 41.4 (2C), 43.8, 46.1, 46.4, 49.4, 50.1, 51.6, 52.7, 53.8, 58.6, 60.3, 69.4, 69.5, 70.1, 70.2, 70.6 (2C), 109.1, 110.7, 110.9, 114.4, 114.9, 117.7, 118.1, 129.1 (2C), 137.9 (2C), 149.0, 149.2, 157.6 (2C), 161.6. HRMS (MALDI-TOF) *m/z* calcd for $C_{38}H_{59}N_8O_3$ $[M+H]^+$ 675.4710, found 675.4729.

31,72-Dipyrimidin-2-yl-11,14,17,46,49,52-hexaoxa-1,7,21,28,31,35,42,56,63,66,72,80-dodecaazaheptacyclo[61.6.6.6^{28,35}.2^{3,6}.1^{22,26}.1^{37,41}.1^{57,61}]hexaoctaconta-3,5,22(84),23,25,37(77),38,40,57(76),58,60,85-dodecaene (27a, n=1) was obtained as the second product in the synthesis of macrobicycle **26a**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:1. Yield 8 mg (7%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.68 (bs, 4H), 1.75 (bs, 4H), 1.83 (quintet, *J* = 5.8 Hz, 8H), 2.44 (bs, 4H), 2.62 (bs, 16H), 2.72 (bs, 4H), 3.10 (t, *J* = 6.3 Hz, 4H), 3.17 (t, *J* = 6.1 Hz, 4H), 3.42 (s, 4H), 3.49-3.60 (m, 20H), 3.63 (bs, 12H), 3.70 (bs, 4H), 6.29 (t, *J* = 4.6 Hz, 2H), 6.40-6.65 (m, 12H), 6.89 (t, *J* = 7.5 Hz, 2H), 7.07 (t, *J* = 7.7 Hz, 2H), 8.11 (d, *J* = 4.6 Hz, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.7 (2C), 26.6 (2C), 29.1 (2C), 29.3 (2C), 41.4 (2C), 41.6 (2C), 45.8 (2C), 46.9 (2C), 47.0 (2C), 47.4 (2C), 51.0 (4C), 52.9 (2C), 53.5 (2C), 59.0 (2C), 60.5 (2C), 69.6 (4C), 70.2 (4C), 70.6 (4C), 108.4 (2C), 110.4 (2C), 111.4 (2C), 113.4 (2C), 113.6 (2C), 117.5 (2C), 118.0 (2C), 128.7 (2C), 129.0 (2C), 140.0 (2C), 140.1 (2C), 148.1 (2C), 148.5 (2C), 157.3 (4C), 161.0 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{76}H_{117}N_{16}O_6$ $[M+H]^+$ 1349.9342, found 1349.9301.

32-Pyrimidin-2-yl-10,13-dioxa-1,7,16,23,26,32-hexaazatetracyclo[21.6.6.2^{3,6}.1^{17,21}]octatriaconta-3,5,17(36),18,20,37-hexaene (26c) was synthesized from compound **16** (0.17 mmol, 103 mg), dioxadiamine **2c** (0.17 mmol, 25 mg), in the presence of $Pd(dba)_2$ (16 mg), BINAP (19 mg), *t*BuONa (52 mg), in dioxane (7 mL). Eluent CH_2Cl_2-MeOH 10:1-3:1. Yield 30 mg (29%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.92 (quintet, *J* = 5.2 Hz, 4H), 2.49 (bs, 4H), 2.77 (bs, 8H), 3.20 (t, *J* = 5.0 Hz, 2H),

3.38 (t, *J* = 5.5 Hz, 2H), 3.49 (bs, 4H), 3.68 (bs, 10H), 3.83 (t, *J* = 4.9 Hz, 2H), 6.43-6.53 (m, 5H), 6.61 (bs, 1H), 7.03 (bs, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 8.26 (d, *J* = 4.8 Hz, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 22.8, 26.2, 43.8, 44.1, 45.8 (2C), 48.9, 50.4, 51.0, 51.4, 53.4, 54.3, 59.6 (2C), 69.1, 69.6, 70.2, 70.3, 109.6, 111.0, 111.1, 115.9, 116.8, 118.2, 118.7, 129.2, 129.3, 135.8, 136.6, 148.9, 149.4, 157.7 (2C), 161.6. HRMS (MALDI-TOF) *m/z* calcd for $C_{34}H_{51}N_8O_2$ $[M+H]^+$ 603.4135, found 603.4112.

26,62-Dipyrimidin-2-yl-10,13,40,43-tetraoxa-1,7,16,23,26,30,37,46,53,56,62,70-dodecaazaheptacyclo[51.6.6.6^{23,30}.2^{3,6}.1^{17,21}.1^{32,36}.1^{47,51}]hexaheptaconta-3,5,17(74),18,20,32(67),33,35,47(66),48,50,75-dodecaene (27c, n=1) was obtained as the second product in the synthesis of macrobicycle **26c**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:2. Yield 8 mg (8%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.67 (bs, 4H), 1.75 (bs, 4H), 2.43 (bs, 4H), 2.62 (bs, 16H), 2.72 (bs, 4H), 3.20 (t, *J* = 4.6 Hz, 4H), 3.26 (bs, 4H), 3.41 (s, 4H), 3.48-3.72 (m, 28H), 6.36 (t, *J* = 4.8 Hz, 2H), 6.44-6.59 (m, 8H), 6.61 (d, *J* = 7.5 Hz, 4H), 6.92 (t, *J* = 7.7 Hz, 2H), 7.05 (t, *J* = 7.8 Hz, 2H), 8.21 (d, *J* = 4.8 Hz, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.7 (2C), 26.5 (2C), 43.4 (4C), 45.8 (2C), 46.4 (2C), 46.9 (2C), 47.4 (2C), 51.0 (2C), 51.7 (2C), 52.9 (2C), 53.4 (2C), 59.0 (2C), 60.3 (2C), 69.6 (2C), 69.7 (2C), 70.2 (4C), 108.4 (2C), 110.9 (2C), 111.7 (2C), 113.8 (2C), 114.1 (2C), 118.1 (2C), 128.7 (2C), 129.1 (2C), 140.0 (4C), 147.8 (2C), 148.2 (2C), 157.5 (4C), 161.1 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{68}H_{101}N_{16}O_4$ $[M+H]^+$ 1205.8192, found 1205.8134.

35-Pyrimidin-2-yl-1,7,11,15,19,26,29,35-octaazatetracyclo[24.6.6.2^{3,6}.1^{20,24}]hentetraconta-3,5,20(39),21,23,40-hexaene (26d) was synthesized from compound **16** (0.15 mmol, 93 mg), tetraamine **2d** (0.15 mmol, 28 mg), in the presence of $Pd(dba)_2$ (14 mg), BINAP (17 mg), *t*BuONa (44 mg), in dioxane (7.5 mL). Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3. Yield 23 mg (24%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.62-1.80 (m, 10H), 2.43 (bs, 2H), 2.52-2.80 (m, 18H), 3.04 (t, *J* = 6.5 Hz, 2H), 3.10 (t, *J* = 6.1 Hz, 2H), 3.49 (s, 2H), 3.53 (s, 2H), 3.78 (bs, 4H), 6.30 (t, *J* = 4.8 Hz, 1H), 6.40-6.67 (m, 6H), 7.05 (t, *J* = 7.1 Hz, 2H), 8.17 (d, *J* = 4.8 Hz, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 24.9, 27.2, 28.6, 29.0, 29.7, 42.6, 43.0, 45.2, 45.7, 45.9, 48.0, 48.2, 48.4, 49.3 (2C), 51.2, 52.9, 53.2, 54.0, 60.1, 60.7, 108.5, 110.6, 111.2, 113.6, 113.9, 117.8, 118.2, 128.9, 129.0, 140.1, 140.2, 148.7, 148.8, 157.4 (2C), 161.3. HRMS (MALDI-TOF) *m/z* calcd for $C_{37}H_{59}N_{10}$ $[M+H]^+$ 643.4924, found 643.4892.

29,68-Dipyrimidin-2-yl-1,7,11,15,19,26,29,33,40,44,48,52,59,62,68,76-hexadecaazaheptacyclo[57.6.6.6^{26,33}.2^{3,6}.1^{20,24}.1^{35,39}.1^{53,57}]dooctaconta-3,5,20(80),21,23,35(73),36,38,53(72),54,56,81

dodecaene (27d, n=1) was obtained as the second product in the synthesis of macrobicycle **26d**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:35:6. Yield 28 mg (29%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.62-1.80 (m, 20H), 2.43 (bs, 4H), 2.52-2.80 (m, 36H), 3.05 (t, *J* = 5.9 Hz, 4H), 3.09 (t, *J* = 6.0 Hz, 4H), 3.42 (s, 4H), 3.53 (s, 4H), 3.62 (bs, 4H), 3.70 (bs, 4H), 6.27 (bs, 2H), 6.43 (d, *J* = 5.8 Hz, 4H), 6.56 (d, *J* = 7.6 Hz, 4H), 6.63 (bs, 4H), 6.89 (t, *J* = 7.5 Hz, 2H), 7.04 (t, *J* = 7.7 Hz, 2H), 8.10 (bs, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.8 (2C), 26.9 (2C), 29.4 (4C), 30.2 (2C), 52.7 (2C), 42.8 (2C), 45.4 (2C), 45.7 (2C), 45.8 (2C), 48.3 (2C), 48.5 (4C), 49.1 (4C), 51.1 (2C), 52.8 (2C), 53.0 (2C), 54.1 (2C), 60.2 (2C), 60.6 (2C), 108.4 (2C), 110.5 (2C), 111.3 (2C), 111.4 (2C), 113.5 (2C), 117.8 (2C), 118.2 (2C), 128.7 (2C), 128.9 (2C), 140.2 (4C), 148.7 (4C), 157.3 (4C), 161.1 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{74}H_{117}N_{20}$ $[M+H]^+$ 1285.9770, found 1285.9722.

Cyclic trimer (27d, n=2) and cyclic tetramer (27d, n=3) were obtained as a separate fraction in the synthesis of macrobicycle **26d**. Eluent CH_2Cl_2-MeOH-NH_3aq 10:4:1. Yield 12 mg (12%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.68 (bs, 4(n+1)H), 1.75 (bs, 6(n+1)H), 2.44 (bs 2(n+1)H), 2.62 (bs, 10(n+1)H), 2.66 (bs 4(n+1)H), 2.70 (bs, 4(n+1)H), 3.06 (bs, 2(n+1)H), 3.13 (bs, 2(n+1)H), 3.43 (s, 2(n+1)H), 3.53 (s, 2(n+1)H), 3.63 (bs, 2(n+1)H), 3.71 (bs, 2(n+1)H), 6.27 (bs, (n+1)H), 6.44 (bs, 2(n+1)H), 6.55 (d, *J* = 7.6 Hz, 2(n+1)H), 6.64 (d, *J* = 6.8 Hz, 2(n+1)H), 6.90 (t, *J* = 6.1 Hz, (n+1)H), 7.06 (t, *J* = 7.1 Hz, (n+1)H), 8.11 (bs, 2(n+1)H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.8 ((n+1)C), 26.9 ((n+1)C), 29.4 ((n+1)C), 29.7 (2(n+1)C), 42.6 ((n+1)C), 42.8 ((n+1)C), 45.9 (2(n+1)C), 47.6 ((n+1)C), 48.2-48.5 (m, 5(n+1)C), 51.1 (2(n+1)C), 53.0 ((n+1)C), 53.8 ((n+1)C), 59.1 ((n+1)C), 60.6 ((n+1)C), 108.4 ((n+1)C), 110.5 ((n+1)C), 111.5 ((n+1)C), 113.5 ((n+1)C), 113.6 ((n+1)C), 117.7 ((n+1)C), 118.1 ((n+1)C), 128.7 ((n+1)C), 129.0 ((n+1)C), 140.2 (2(n+1)C), 148.6 (2(n+1)C), 157.3 (2(n+1)C), 161.0 ((n+1)C). MS (MALDI-TOF) *m/z* calcd for $C_{111}H_{175}N_{30}$ $[M+H]^+$ 1928.46, found 1928.52 (**27d** (n=2)); calcd for $C_{148}H_{233}N_{40}$ $[M+H]^+$ 2570.95, found 2570.81 (**27d** (n=3).

30,36-Dipyrimidin-2-yl-11,14,17-trioxa-1,7,21,27,30,36-hexaazatetracyclo[25.6.6.2^{3,6}.2^{22,25}]tritetraconta-3,5,22,24,40,42-hexaene (28a) was synthesized from compound **18** (0.15 mmol, 104 mg), trioxadiamine **2a** (0.15 mmol, 33 mg), in the presence of $Pd(dba)_2$ (14 mg), BINAP (17 mg), *t*BuONa (44 mg), in dioxane (7.5 mL). Eluent CH_2Cl_2-MeOH 10:1. Yield 7 mg (6%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.78-1.90 (m, 8H), 2.45-2.56 (m, 4H), 2.74 (bs, 4H), 3.18 (t, *J* = 5.1 Hz, 4H), 3.55-3.67 (m, 16H), 3.76 (bs, 8H), 6.34 (t, *J* = 4.8 Hz, 2H), 6.46 (d, *J* = 8.2 Hz, 4H), 7.07 (d, *J* = 8.2 Hz, 4H), 8.20 (d, *J* = 4.8 Hz, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.8 (2C), 29.2 (2C), 41.8 (2C), 46.8 (2C), 47.3 (2C), 51.9 (2C), 53.4 (2C), 59.9 (2C), 69.7 (2C), 70.2 (2C), 70.6 (2C), 108.8 (2C), 112.3

(4C), 128.0 (2C), 130.2 (4C), 148.9 (2C), 157.4 (4C), 161.5 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{42}H_{61}N_{10}O_3$ $[M+H]^+$ 753.4928, found 753.4950.

30,63,69,79-Tetrapyrimidin-2-yl-11,14,17,44,47,50-hexaoxa-1,7,21,27,30,34,40,54,60,63,69,79-dodecaazaheptacyclo[58.6.6.6^{27,34}.2^{3,6}.2^{22,25}.2^{36,39}.2^{55,58}]hexaoctaconta-3,5,22,24,36,38,55,57,73,75,83,85-dodecaene (29a, n=1) was obtained as the second product in the synthesis of macrobicycle **28a**. Eluent CH_2Cl_2-MeOH 10:1-3:1. Yield 22 mg (19%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.75-1.91 (m, 16H), 2.43-2.58 (m, 8H), 2.73 (bs, 8H), 3.16 (bs, 8H), 3.42-3.67 (m, 32H), 3.76 (bs, 16H), 6.34 (t, *J* = 4.6 Hz, 4H), 6.48 (d, *J* = 8.1 Hz, 8H), 7.08 (d, *J* = 8.1 Hz, 8H), 8.17 (d, *J* =4.6 Hz, 8H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.6 (4C), 29.1 (4C), 41.8 (4C), 46.8 (4C), 47.4 (4C), 51.5 (4C), 51.6 (4C), 59.8 (4C), 69.7 (4C), 70.2 (4C), 70.6 (4C), 108.7 (4C), 112.3 (8C), 128.0 (4C), 130.1 (8C), 147.4 (4C), 157.4 (8C), 161.4 (4C). HRMS (MALDI-TOF) *m/z* calcd for $C_{84}H_{121}N_{20}O_6$ $[M+H]^+$ 1505.9778, found 1505.9834.

Cyclic trimer (29a, n=2) was obtained as the third product in the synthesis of macrobicycle **28a**. Eluent CH_2Cl_2-MeOH 3:1. Yield 15 mg (13%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.75-1.91 (m, 24H), 2.43-2.58 (m, 12H), 2.73 (bs, 12H), 3.16 (bs, 12H), 3.42-3.67(m, 48H), 3.76 (bs, 24H), 6.34 (t, *J* = 4.6 Hz, 6H), 6.48 (d, *J* = 8.1 Hz, 12H), 7.08 (d, *J* = 8.1 Hz, 12H), 8.19 (d, *J* =4.6 Hz, 12H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.8 (6C), 29.1 (6C), 41.8 (6C), 46.8 (6C), 47.4 (6C), 51.5 (6C), 51.6 (6C), 59.9 (6C), 69.7 (6C), 70.2 (6C), 70.6 (6C), 108.7 (6C), 112.3 (12C), 128.0 (6C), 130.1 (12C), 147.4 (6C), 157.4 (12C), 161.4 (6C). MS (MALDI-TOF) *m/z* calcd for $C_{126}H_{181}N_{30}O_9$ $[M+H]^+$ 2258.46, found 2258.37.

29,35-Dipyrimidin-2-yl-11,16-dioxa-1,7,20,26,29,35-hexaazatetracyclo[24.6.6.2^{3,6}.2^{21,24}]dotetraconta-3,5,21,23,39,41-hexaene (28b) was synthesized from compound **18** (0.15 mmol, 104 mg), dioxadiamine **2b** (0.15 mmol, 31 mg), in the presence of $Pd(dba)_2$ (14 mg), BINAP (17 mg), *t*BuONa (44 mg), in dioxane (7.5 mL). Eluent CH_2Cl_2-MeOH 10:1. Yield 6 mg (5%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.64-1.68 (m, 4H), 1.81-1.90 (m, 8H), 2.50 (bs, 4H), 2.74 (bs, 4H), 3.16 (t, *J* = 6.3 Hz, 4H), 3.40-3.45 (m, 4H), 3.52 (t, *J* = 5.6 Hz, 4H), 3.52 (s, 4H), 3.67-3.80 (m, 8H), 6.34 (t, *J* = 4.7 Hz, 2H), 6.46 (d, *J* = 8.1 Hz, 4H), 7.08 (d, *J* = 8.1 Hz, 4H), 8.19 (d, *J* = 4.7 Hz, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.6 (2C), 26.5 (2C), 29.4 (2C), 42.0 (2C), 46.8 (2C), 47.2 (2C), 51.5 (2C), 52.2 (2C), 59.7 (2C), 69.4 (2C), 70.8 (2C), 108.8 (2C), 112.3 (4C), 127.4 (2C), 130.3 (4C), 147.5 (2C), 157.4 (4C), 161.5 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{42}H_{61}N_{10}O_2$ $[M+H]^+$ 737.4979, found 737.4960.

29,61,67,77-Tetrapyrimidin-2-yl-11,16,43,48-tetraoxa-1,7,20,26,29,33,39,52,58,61,67,77-dodecaaza-heptacyclo[56.6.6.6^{26,33}.2^{3,6}.2^{21,24}.2^{35,38}.2^{53,56}]tetraoctaconta-3,5,21,23,35,37,53,55,71,73,81,83-dodecaene (29b, n=1) was obtained as the second product in the synthesis of macrobicycle **28b**. Eluent CH_2Cl_2-MeOH 3:1. Yield 15 mg (14%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.66 (bs, 8H), 1.86 (bs, 16H), 2.51 (bs, 8H), 2.76 (bs, 8H), 3.17 (bs, 8H), 3.44 (bs, 8H), 3.48-3.60 (m, 16H), 3.68-3.80 (m, 16H), 6.35 (t, *J* = 4.1 Hz, 4H), 6.48 (d, *J* = 7.5 Hz, 8H), 7.09 (d, *J* = 7.5 Hz, 8H), 8.20 (d, *J* = 4.1 Hz, 8H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.6 (4C), 26.5 (4C), 29.4 (4C), 42.0 (4C), 46.8 (4C), 47.2 (4C), 51.5 (4C), 51.7 (4C), 59.7 (4C), 69.4 (4C), 70.8 (4C), 108.8 (4C), 112.3 (8C), 127.4 (4C), 130.3 (8C), 147.5 (4C), 157.4 (8C), 161.5 (4C). HRMS (MALDI-TOF) *m/z* calcd for $C_{84}H_{121}N_{20}O_4$ $[M+H]^+$ 1473.9880, found 1473.9843.

Cyclic trimer (29b, n=2) was obtained as the third product in the synthesis of macrobicycle **28b**. Eluent CH_2Cl_2-MeOH 3:1. Yield 13 mg (12%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.66 (bs, 12H), 1.86 (bs, 24H), 2.51 (bs, 12H), 2.76 (bs, 12H), 3.17 (bs, 12H), 3.44 (bs, 12H), 3.48-3.60 (m, 24H), 3.68-3.80 (m, 24H), 6.34 (t, *J* = 4.1 Hz, 6H), 6.48 (d, *J* = 7.5 Hz, 12H), 7.09 (d, *J* = 7.5 Hz, 12H), 8.18 (d, *J* = 4.1 Hz, 12H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.7 (6C), 26.6 (6C), 29.4 (6C), 42.1 (6C), 46.8 (6C), 47.5 (6C), 51.5 (6C), 51.6 (6C), 59.9 (6C), 69.4 (6C), 70.8 (6C), 108.7 (6C), 112.3 (12C), 127.5 (6C), 130.1 (12C), 147.4 (6C), 157.4 (12C), 161.5 (6C). MS (MALDI-TOF) *m/z* calcd for $C_{126}H_{181}N_{30}O_6$ $[M+H]^+$ 2210.48, found 2210.59.

30-Pyrimidin-2-yl-11,14,17-trioxa-1,7,21,27,30,36-hexaazatetracyclo[25.6.6.2^{3,6}.2^{22,25}]tritetraconta-3,5,22,24,40,42-hexaene (30a) was synthesized from compound **19** (0.17 mmol, 105 mg), trioxadiamine **2a** (0.17 mmol, 37 mg), in the presence of $Pd(dba)_2$ (16 mg), BINAP (19 mg), *t*BuONa (50 mg), in dioxane (8.5 mL). Eluent CH_2Cl_2-MeOH 10:1-3:1. Yield 35 mg (30%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.76 (bs, 2H), 1.83 (quintet, *J* = 6.0 Hz, 4H), 1.96 (bs, 2H), 2.50-2.58 (m, 4H), 2.72 (bs, 2H), 2.79 (bs, 2H), 2.91 (bs, 4H), 3.19 (t, *J* = 5.9 Hz, 2H), 3.20 (t, *J* = 6.2 Hz, 2H), 3.44 (s, 2H), 3.45 (s, 2H), 3.56 (t, *J* = 5.1 Hz, 4H), 3.56-3.60 (m, 4H), 3.61-3.65 (4H), 3.74 (bs, 2H), 3.87 (bs, 2H), 6.39 (t, *J* = 4.8 Hz, 1H), 6.50 (d, *J* = 8.1 Hz, 2H), 6.53 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 8.22 (d, *J* = 4.8 Hz, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 23.7 (1C), 25.6 (1C), 29.1 (2C), 41.9 (2C), 44.5 (1C), 46.0 (1C), 47.1 (1C), 49.2 (1C), 52.0 (1C), 52.1 (1C), 53.0 (1C), 53.7 (1C), 60.0 (2C), 69.7 (2C), 70.2 (2C), 70.5 (2C), 109.0 (1C), 112.6 (4C), 127.6 (2C), 130.4 (2C), 130.9 (2C), 148.0 (2C), 157.6 (2C), 161.6 (1C). HRMS (MALDI-TOF) *m/z* calcd for $C_{38}H_{59}N_8O_3$ $[M+H]^+$ 675.4710, found 675.4737.

30,69-Dipyrimidin-2-yl-11,14,17,44,47,50-hexaoxa-1,7,21,27,30,34,40,54,60,63,69,79-dodecaaza-heptacyclo[58.6.6.6^{27,34}.2^{3,6}.2^{22,25}.2^{36,39}.2^{55,58}]hexaoctaconta-3,5,22,24,36,38,55,57,73,75,83,85-dodecaene (31a, n=1) was obtained as the second product in the synthesis of macrobicycle **30a**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:1. Yield 7 mg (6%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.66 (bs 4H), 1.77 (bs, 4H), 1.84 (quintet, *J* = 5.9 Hz, 8H), 2.43 (bs, 4H), 2.60-2.75 (m, 20H), 3.12 (bs, 4H), 3.19 (bs, 4H), 3.42 (s, 4H), 3.45 (s, 4H), 3.50-3.72 (m, 32H), 6.31 (2H, *J* = 4.7 Hz, 2H), 6.39 (d, *J* = 8.1 Hz, 4H), 6.52 (d, *J* = 8.0 Hz, 4H), 6.99 (d, *J* = 8.1 Hz, 4H), 7.05 (d, *J* = 8.0 Hz, 4H), 8.14 d (*J* = 4.7 Hz, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.6 (2C), 26.4 (2C), 29.2 (4C), 41.8 (4C), 46.0 (4C), 46.8 (2C), 47.5 (2C), 50.8 (2C), 52.0 (2C), 52.5 (2C), 54.0 (2C), 58.9 (2C), 59.9 (2C), 69.5 (2C), 69.6 (2C), 70.2 (4C), 70.6 (4C), 108.3 (2C), 112.3 (4C), 112.5 (4C), 126.7 (2C), 127.1 (2C), 129.9 (4C), 130.1 (4C), 147.3 (2C), 147.5 (2C), 157.2 (4C), 161.1 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{76}H_{117}N_{16}O_6$ $[M+H]^+$ 1349.9342, found 1348.9390.

Cyclic trimer (31a, n=2) was obtained as the third product in the synthesis of macrobicycle **30a**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:1. Yield 5 mg (4%), pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.66 (bs, 6H), 1.77 (bs, 6H), 1.83 (bs, 12H), 2.42 (bs, 6H), 2.55-2.68 (m, 24H), 2.72 (bs, 6H), 3.11 (t, *J* = 5.7 Hz, 6H), 3.18 (bs 6H), 3.38 (s, 6H), 3.52 (s, 6H), 3.53-3.80 (m, 48H), 6.26 (bs, 3H), 6.35 (d, *J* = 7.8 Hz, 6H), 6.52 (d, *J* = 7.3 Hz, 6H), 6.97 (d, *J* = 7.8 Hz, 6H), 7.06 (d, *J* = 7.3 Hz, 6H), 8.12 (bs, 6H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.7 (3C), 26.5 (3C), 29.1 (6C), 41.7 (6C), 45.9 (6C), 46.9 (3C), 47.5 (3C), 50.7 (3C), 51.3 (3C), 52.4 (3C), 52.8 (3C), 58.3 (3C), 59.4 (3C), 69.7 (6C), 70.2 (6C), 70.6 (6C), 108.3 (3C), 112.2 (6C), 112.4 (6C), 127.0 (3C), 127.1 (3C), 129.9 (6C), 130.3 (6C), 147.1 (3C), 147.6 (3C), 157.2 (6C), 161.0 (3C). MS (MALDI-TOF) *m/z* calcd for $C_{114}H_{175}N_{24}O_9$ $[M+H]^+$ 2024.40, found 2024.31.

Additional information (synthesis of compounds 4a and 5a)

32,37-Bis(6-chloropyrimidin-4-yl)-12,15,18-trioxa-1,8,22,29,32,37-hexaazatetracyclo-[27.5.5.1^{3,7}.1^{23,27}]hentetraconta-3(41),4,6,23(40),24,26-hexaene (4a).

A flask flushed with argon was charged with macrobicycle **3a** (93 mg, 0.16 mmol), 2,4-dichloropyrimidine (95 mg, 0.64 mmol), dry acetonitrile (2 mL) and K_2CO_3 (84 mg). The reaction mixture was stirred at room temperature for 24 h, filtered, the residue was washed with CH_2Cl_2 (5 mL), combined organic fractions were evaporated *in vacuo* and chromatographed on silica gel. Eluent CH_2Cl_2-MeOH 20:1. Yield 63 mg (54%). Pale-yellow glassy solid. ^{1}H NMR ($CDCl_3$): δ 1.82 (quintet, *J* = 6.0 Hz,

4H), 2.87 (bs, 8H), 3.10 (bs, 4H), 3.47-3.64 (m, 20H), 3.66-3.71 (m, 4H), 6.35 (s, 2H), 6.42 (s, 2H), 6.43 (d, J = 7.8 Hz, 2H), 6.51 (d, J = 7.2 Hz, 2H), 7.02 (t, J = 7.5 Hz, 2H), 8.16 (s, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 29.1 (2C), 41.7 (2C), 48.7 (4C), 53.2 (4C), 60.5 (2C), 69.7 (2C), 70.2 (2C), 70.5 (2C), 101.9 (2C), 112.1 (2C), 112.8 (2C), 118.0 (2C), 129.0 (2C), 139.2 (2C), 148.6 (2C), 157.5 (2C), 159.0 (2C), 162.7 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{40}H_{55}Cl_2N_{10}O_3$ $[M+H]^+$ 793.3835, found 793.3876.

1,7-Bis(3-bromobenzyl)-4,10-bis(6-chloropyrimidin-4-yl)-1,4,7,10-tetraazacyclododecane (5a). A flask flushed with argon was charged with N^1,N^7-bis(3-bromobenzyl)cyclen (**1**) (0.25 mmol, 128 mg), 2,4-dichloropyrimidine (89 mg, 0.6 mmol), dry acetonitrile (2.5 mL) and K_2CO_3 (138 mg). The reaction mixture was stirred at room temperature for 24 h, filtered, the residue was washed with CH_2Cl_2 (5 mL), combined organic fractions were evaporated *in vacuo* to dryness. Yield 121 mg (66%). Pale-beige crystals, mp 186-187 °C. ^{1}H NMR ($CDCl_3$): δ 2.80 (bs, 8H), 3.57 (bs, 8H), 3.68 (s, 4H), 6.27 (s, 2H), 7.08 (bs, 4H), 7.32 (bs, 4H), 8.14 (s, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 47.9 (4C), 53.5 (4C), 59.3 (2C), 101.6 (2C), 122.5 (2C), 127.6 (2C), 129.9 (2C), 130.5 (2C), 132.1 (2C), 140.5 (2C), 157.7 (2C), 159.5 (2C), 162.6 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{30}H_{33}Br_2Cl_2N_8$ $[M+H]^+$ 733.0572, found 733.0549.

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