Regioselective Complexation of New Multiple Piperazine/Pyridine Ligands: Differentiation by ^{113}Cd-NMR Spectroscopy

Jari Ratilainen, Karri Airola, Erkki Kolehmainen, and Kari Rissanen*

Department of Chemistry, University of Jyväskylä,
P. O. Box 35, FIN-40351 Jyväskylä, Finland
Fax: (internat.) +358(0)14/602501
E-mail: Rissanen@jykem.jyu.fi

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Eleven novel piperazine containing open-chain ligands **L1**–**L11** were designed to offer symmetrical and asymmetrical complexation sites for metal ions and were synthesized by repetitive synthetic method. The divergent use of aromatic bishalomethyl and mono-*N*-alkylated piperazine compounds as spacers led to a series of long (up to M. W. = 836) oligomeric multidentate *N*-ligands. Due to the lack of solid state methods for structure analysis, an NMR technique using ^{113}Cd nucleus as a probe in solution state was utilised. ^{113}Cd chemical shifts were observed to be dependend on the coordination site and similar coordination sites in different ligands gave characteristically similar ^{113}Cd chemical shifts. As a result ^{113}Cd-NMR spectroscopy proved to be an excellent tool to distinguish between the structures of the different complexation sites on a nearly quantitative level.

Introduction

Piperazine is frequently used as a building block in various ligands due to its ability to act as a metal complexing site via the N atoms[1] or its suitability as a rigid building block for macrocyclic[2] molecules. There exists a lot of experimental data of such small open-chain ligands, where the piperazine nitrogen atoms are coordinated to various metal ions[3]. In macrocyclic ligands piperazine moiety is able to rigidify the molecular skeleton, so that inclusion complex formation with small neutral organic guest molecules can occur[4].

A complexation occurs, when a metal ion is able to adopt the coordination site of the ligand with its coordination sphere[5]. Cd^{2+} ion seems to be ideal for these investigations, because its coordination sphere allows it to bind into the different coordination sites. This kind of coordinative versatility of the Cd^{2+} ion together with its NMR activity makes it an ideal structural probe, which can be used in complexation studies with different ligands. ^{113}Cd nucleus has a nuclear spin of 1/2 and a natural abundance of 12.26% in addition of the 7.6 times bigger receptivity compared to the ^{13}C, which makes it a sensitive and a suitable nucleus for NMR investigations[6]. When all the different coordination sites of the ligand can be saturated selectively by one type of metal ion, it is easy to get high quality structural information of the coordination sites by NMR measurements. These measurements have to be done usually in low temperatures to get rid of or slow down the dynamic chance in the solution state. The only problem for low temperature measurements might be the solubility of the ligand-metal systems, because the temperatures which have to be used will impose limitations for the solvents or solvent mixtures which can be utilised.

Solution and solid state ^{113}Cd-NMR measurements have been earlier used for investigations of covalently bonded metal complexes[7]. Cd^{2+} ion is a suitable nucleus also for studies of Ca^{2+}-ion binding ligands, because it has been found to coordinate similarly to the ligand like Ca^{2+} ion in the solid state[8]. The Cd^{2+} ion has been used as a probe in different NMR investigations[9].

Although there is a lot of information about different piperazine containing ligands, there is no existing literature to such cases where several piperazine moieties have been used in oligomeric open-chain ligands. This paper describes the synthesis and characterization of several new oligomeric ligands, most of them containing from two up to four piperazine units. Based on our earlier discovery on the meso-helicate formation[10] (proved by X-ray diffraction analysis) of similar piperazine containing ligand with two symmetrical coordination sites, we designed a new family of such ligands with symmetrical and asymmetrical coordination sites.

The ligands **L1**–**L11** offer different coordination sites for various transition metal ions. Due to unavailability of single crystals, our attention was focused on the solution state structural analysis using NMR-techniques. After several attempts with different metal ions, Cd^{2+} ion turned out to be a suitable probe and the complexation with the ligands **L1**–**L11** could be followed by ^{113}Cd-NMR spectroscopy in the solution state. These molecules were designed to show selective/sequental complexation of a metal ion into two different coordination sites. In this paper we report the di-

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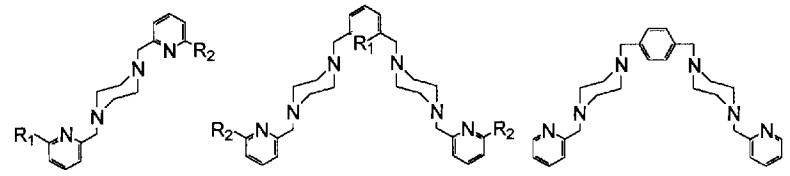
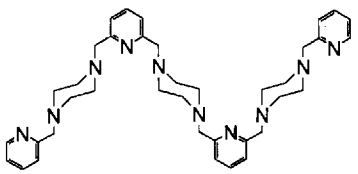
Figure 1. Oligomeric piperazine ligands **L1**–**L11**



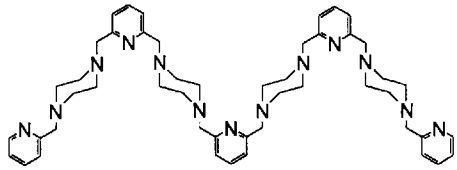
L1: R_1, R_2 = H
L2: R_1, R_2 = CH_2OH
L3: R_1 = H, R_2 = CH_2OH

L4: R_1 = N, R_2 = H
L5: R_1 = CH, R_2 = H
L6: R_1 = N, R_2 = CH_2OH
L7: R_1 = CH, R_2 = CH_2OH

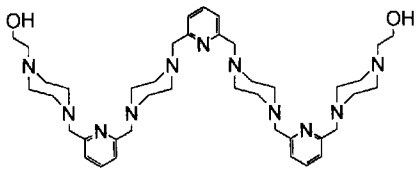
L8



L9



L10



L11

vergent synthesis path for such ligands and the ^{113}Cd-NMR structure analysis of the complexation.

Results

^{113}Cd-NMR chemical shifts of Cd^{2+} complexes [as $Cd(ClO_4)_2$] of the compounds **L1**–**L6** and **L8**–**L10** were measured in aqueous ethanol solutions at −50°C and are collected in Table 1. Measurements in pure H_2O at the range 0–30°C gave broad spectral lines for the Cd^{2+} complexes with **L1**–**L6** and **L8**–**L10**, thus being impractical for any structural deductions. The Cd^{2+} complexes with **L7** and **L11** were sparingly soluble in the used solvents, and were therefore rejected from the measurement series. The broad lines observed at ambient temperature are due to the ligand exchange which can be frozen at low temperatures as recommended by Granger[11].

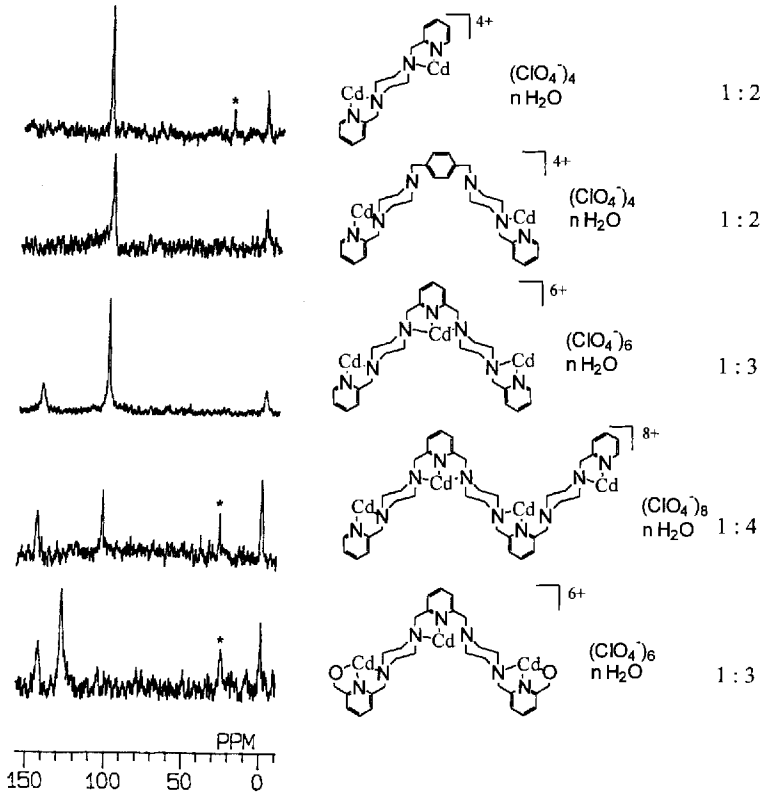
Table 1 shows differently coordinated Cd^{2+} ions and their signals in ^{113}Cd-NMR spectra. According to these results, it is easy to distinguish and assign the different coordination sites. When Cd^{2+} ion is coordinated into two nitrogens, it gives a chemical shift around δ = 100 deshielded from the standard [0.1 M $Cd(ClO_4)_2$ in ethanol]. In ethanol at −50°C 0.1M $Cd(ClO_4)_2$ is δ = 14.5 shielded from that at saturated $Cd(ClO_4)_2$ in D_2O at 30°C. The three nitrogen coordination to the Cd^{2+} ion gives a signal near δ = 144 and two nitrogen and one oxygen coordination between δ = 127 and 138 depending on the structure of the ligand (Figure 2). In addition, the spectra were quantitative, because the amount of certain coordination site has an effect to the size of the measured signals. If we compare the Cd^{2+} complexes of **L4** and **L9**, in case of **L4** the two nitrogen coordination site gave bigger and also sharper signal, whereas in case of **L9** both two and three nitrogen containing coordination sites signals were in the same level. Under these conditions the uncomplexed Cd^{2+} gave signal shifted about 21–27 ppm to the lower field from the standard. This phenomenon is propably caused by the very small amount of water used in dissolving the metal complexes, which tend to precipitate out from the pure ethanol solution. The sharp

Table 1. ^{113}Cd-NMR chemical shifts[a] determined for Cd^{2+} complexes of the ligands **L1**–**L6** and **L8**–**L10**

Ligand-Cd^{2+} (mol ratio)	Coordination site / Number [b]		
	N(pip)-N(pyr)-N(pip)/3	HO-N(pyr)-N(pip)/3	N(pyr)-N(pip)/2
L1 (1:2)			100.4
L2 (1:2)		127.1	
L3 (1:1)		137.0	
L3 (1:2)		137.6	100.0
L4 (1:3)	144.2		101.7
L5 (1:2)			97.1
L6 (1:2)	143.1	127.8	
L6 (1:3)[c]	143.5	128.3	
L8 (1:2)			98.6
L9 (1:4)	144.4		102.6
L10 (1:5)	143.6		102.1

[a] Chemical shifts are in ppm (±0.2 ppm) with the positive direction to the lower shieldings from the reference which is 0.1 M $Cd(ClO_4)_2$ in ethanol in a 5 mm outer diameter NMR tube inserted coaxially inside the 10 mm diameter sample tube. – [b] Includes the number of donors of the ligand (doesn't include the donors of coordinated solvent molecules). – [c] Partially precipitated at −50°C.

Figure 2. ^{113}Cd-NMR spectra of Cd^{2+} complexes of compounds **L1**, **L4**, **L6**, **L8** and **L9** measured in dilute ethanol or aqueous ethanol at −50 °C (* marks uncomplexed Cd^{2+})



signals were recorded below −30 °C, which made the use of pure water as a solvent impossible. The water in the samples affected to the frequencies of the uncomplexed Cd^{2+} ions, and there seems to be a small dependence between the amount of water and the chemical shift of the Cd^{2+} coordinated to two nitrogens. The three nitrogen coordination site was not affected by water, because the variation in the chemical shifts is only 0.9 ppm. The two nitrogen and one oxygen containing coordination site with Cd^{2+} ion gave the signals at δ = 127.1 (**L2**), 128.3 (**L6**) and 137.0 (**L3**). This difference comes primarily from the different constitution of the ligands than from the solvent effect, because larger amount of water was needed to dissolve the three $Cd(ClO_4)_2$ equivalent containing Cd^{2+} complex with **L6** than 1 : 1 Cd^{2+} complex with **L3** or 2 : 1 Cd^{2+} complex with **L2**. Further, by adding the second equivalent of $Cd(ClO_4)_2$ into the **L3** sample, the uncomplexed Cd^{2+} ion gave the signal at δ = 21.3, while it was located at δ = 25.4 in **L6**.

The Cd^{2+} ions showed an interestingly selectivity with ligand **L3** (Figure 3). In the 1 : 1 complex the only peak, which was seen in the spectrum was at δ = 137.0. After adding the second equivalent of the $Cd(ClO_4)_2$ to the sample, an other signal arose at δ = 100.0, which indicated the occupation of the two nitrogen containing coordination site. In the Cd^{2+} complexes of **L6** this kind of selectivity was not as clear as above. There was only a minor change between the spectra of 1 : 2 and 1 : 3 mixtures of **L6** and $Cd(ClO_4)_2$. This indicates that the Cd^{2+} ion is not able to predominantly bind into one of the two different three coordination sites. According to these measurements at different molar ratios it is clear, that the Cd^{2+} ions favour the three coordination site in **L3**, while in **L6** such a selectivity is not observed. Additionally, in the measurement conditions used the Cd^{2+} ion concenctration had no clear effect to the chemical shifts of complexed Cd^{2+} ions. This suggests that the ^{113}Cd-NMR chemical shifts are characteristic to the different coordinating sites, and can thus be used for differentiation of the complexation sites and properties of different ligands.

Discussion

Aromatic mono- and bishalomethyl molecules can *N*-alkylate piperazine easily in the presence of suitable base[12]. Application of divergent, step-by-step synthetic strategy, allows the construction of extended oligomeric piperazine ligands. The most easiest way is to *N*-alkylate the both equivalently reactive nitrogen atoms, but for a selective oligomerization of the molecular chain, mono-*N*-alkylated asymmetric building blocks are needed. The purification of the products in mono-*N*-alkylation reactions was possible without time consuming chromatographic methods by using the physical properties of the free piperazine. When four mole equivalent or more of piperazine was used compared to the other starting compound in *N*-alkylation reaction conditions, almost pure mono-*N*-alkylated piperazine derivatives were obtained and purified simply just by sublimating out the free piperazine *in vacuo*.

Figure 3. Concentration effect in ^{113}Cd-NMR measurements (* marks uncomplexed Cd^{2+})

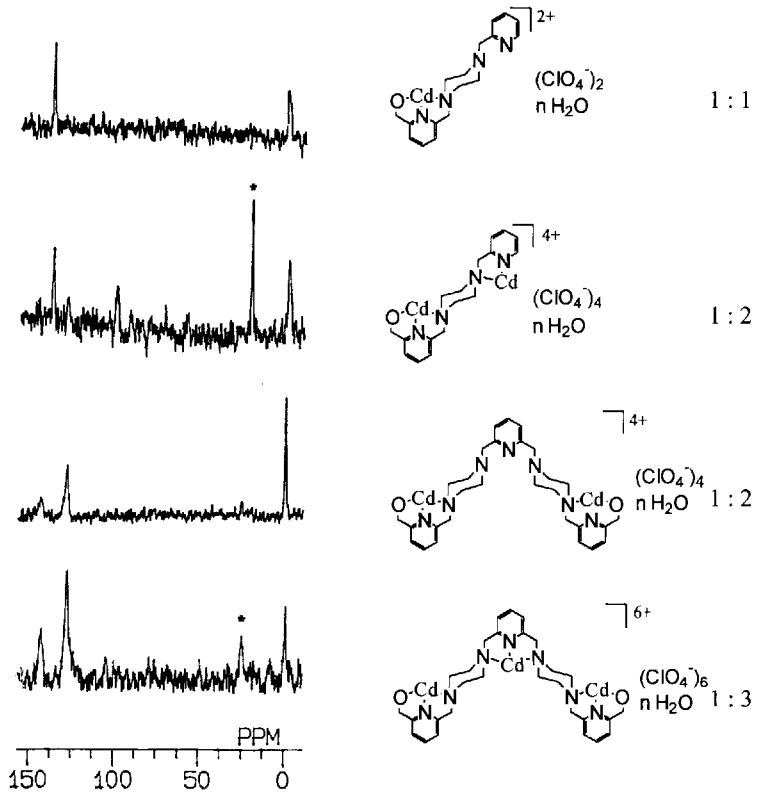
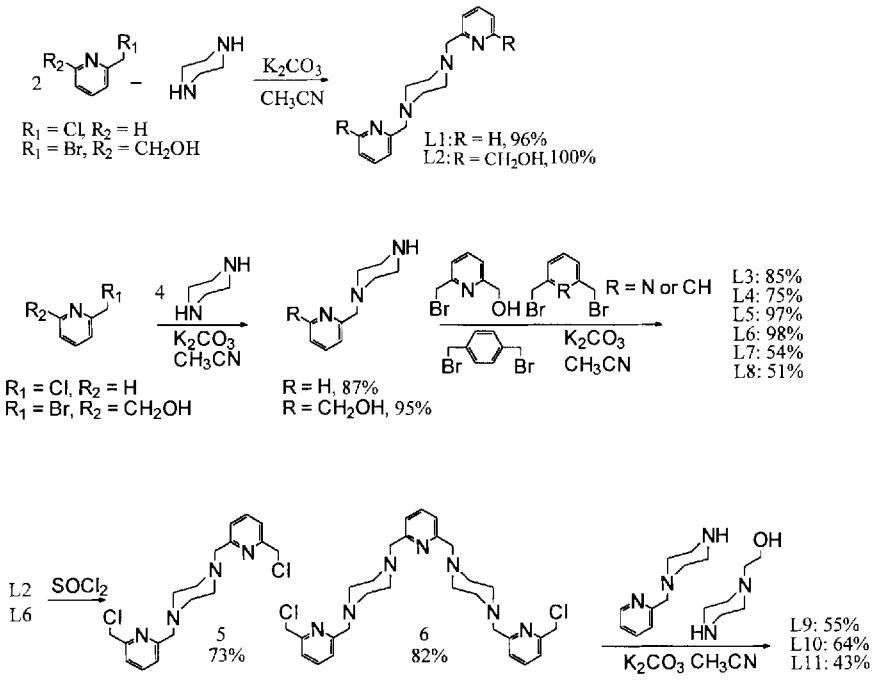


Figure 4. Divergent synthesis of the oligomeric open-chain ligands



Independent on the size of the molecule, ^{1}H- and ^{13}C-NMR spectra of the ligands are very similar and simple. Nevertheless, it is easy to observe from the ^{1}H-NMR spectra when the *N*-alkylation reaction is complete, because the *N*-alkylated methylene protons are about 1 ppm shielded when compared to the corresponding halomethylene protons.

Open-chain piperazine ligands complex easily various metal ions. Depending on the coordination sphere of the metal ion and on the structure of the ligand, the com-

plexation can be structure selective, *viz.* the structure of the piperazine unit may be either in *chair* or *boat* conformation[13]. The number of complexing sites increase when the number of coordination subunits is increased, resulting a ligand capable of complexing several, maybe even different, metal ions. Based on our earlier observation on the dinuclear *meso*-helicate formation[10] of a simple, but oligomeric open-chain piperazine ligand and Co^{2+} ions, we started to survey a NMR method for structural analysis of similar piperazine containing oligomeric ligands with symmetrical or asymmetrical coordination sites. According to the X-ray studies[10], as well as ^{113}Cd-NMR measurements, we are confident that the overall structures of the metal complexes are quite similar both in the solid and solution state, which convinces us that also NMR method can be used for structural analysis of multinuclear metal complexes in the solution state. However, the X-ray proof of the structure of the dinuclear metal complex[10] with oligomeric open-chain ligand in the solid state was an important starting point for the use of the NMR method for the solution state structure analysis of multinuclear metal complexes forming ligands. Without any single crystal structure results, the flexibility of the oligomeric open-chain ligands might have rendered the specific determinations of the structures of multinuclear metal complexes in the solution state.

In summary, we have presented in this paper a synthesis of novel oligomeric ligands, which offer symmetrical or asymmetrical coordination sites for metal ions. It was possible to increase the length of the ligands selectively by divergent synthetic method.

^{113}Cd-NMR spectroscopy offers very convenient tool for study of complexation of metal ions into different electron donors containing ligands. Cd^{2+} ion has an ability to adopt different coordination geometries, which makes its use possible for structure analysis of complexes of various ligands by NMR spectroscopy in the solution state. This method may prove to be valuable in the structure analysis of poorly crystallizable metal-ligand systems, such as nitrogen containing dendrimers, which are known to form multinuclear complexes with metal ions[14]. The only restriction might be the solubility of the complexes, but even at low concentrations it is possible to reach reliable structural verification.

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Experimental Section

General: All chemicals and solvents were reagent grade and used as received. 2-Bromomethyl-6-hydroxymethylpyridine (**3**) was prepared according to a published procedure[15]. – ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AM250 ASPECT 3000, a Jeol JNM GSX 270 and a Bruker DRX500 FT NMR spectrometer. All chemical shifts are relative to the internal tetramethylsilane. – Mass spectra were run on a Jeol JMS-300 and VG AutoSpec HRMS spectrometer. – Melting points (uncorrected) were measured with Gallenkamp GWB and Electrothermal IA9200 devices.

^{113}Cd NMR: Samples for ^{113}Cd-NMR measurements were prepared by dissolving the appropriate amounts of the ligands **L1**–**L11** (20 mg) and $Cd(ClO_4)_2$ in absolute ethanol. Water was added into the samples until the possible precipitates were dissolved. ^{113}Cd-NMR spectra were recorded on a Jeol JNM GSX 270 FT NMR spectrometer operating at 59.93 MHz at −50°C without any field or frequence lock. The pulse angle was determined and the tunable 10 mm broad-band probehead was adjusted and shimmed by using saturated $Cd(ClO_4)_2$ solution in D_2O at 30°C. The chemical shift scale was fixed to the signal of the sample of 0.1 M $Cd(ClO_4)_2$ in ethanol in a 5 mm outer diameter NMR tube inserted coaxially inside the 10 mm diameter sample tube. The acquisition parameters were as follows: (1) spectral width 50000 Hz; (2) pulse delay 10 s; (3) acquisition time 0.33 s; (4) data points 32000; (5) pulse width 13.5 μs (45° pulse); (6) collected number of scans 500. A continuous bilevel proton decoupling was used during the acquisition. The effect of the relaxation of the Cd-nucleus to the signal-to-signal ratio was checked by measuring one of the samples (**L4**) with 5 s pulse delay utilising Bruker Avance DRX 500 NMR spectrometer. No effect was seen and this indicates that the 10 s pulse delay is long enough and the areas of the signals give information of the number of the complexation sites, and the spectra are quantitative.

2-(Chloromethyl)pyridine (**1**): Thionyl chloride (40 ml) was stirred and cooled in an ice bath and 2-(hydroxymethyl)pyridine (45.8 mmol) was added in portions over 1 h. The resulting solution was heated at reflux for 4 h, thionyl chloride was removed in vacuo, and the residue was washed with light petroleum ether (b.p. 40–60°C). The crude **1** hydrochloride was dissolved in 50 ml of water and neutralized with aqueous $NaHCO_3$ solution. Extraction of the aqueous phase with CH_2Cl_2 (4 × 40 ml), followed by drying with Na_2SO_4 and evaporation, resulted in 5.4 g (92%) of colorless oil. – ^{1}H NMR ($CDCl_3$): δ = 4.64 (s, 2H, CH_2Cl), 7.21 (m, 1H, H_{Ar}), 7.44 (d, 1H, H_{Ar}), 7.66 (m, 1H, H_{Ar}), 8.55 (d, 1H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 46.7, 122.8, 123.0, 137.1, 149.4, 156.6. – MS (EI); *m/z*: 127 [M^+].

N-(2-Pyridylmethyl)piperazine (**2**): Into a stirred mixture of piperazine (81.3 mmol) and K_2CO_3 (2 g) in CH_3CN (100 ml) was added a solution of **1** (16.2 mmol) in CH_3CN (30 ml). The resulting mixture was refluxed for 4 h and the inorganic residue was filtered off. Evaporation of the solvent, followed by sublimation of the free piperazine in vacuum, resulted in **2** as a reddish thick oil. yield 2.5 g (87%). – ^{1}H NMR ($CDCl_3$): δ = 1.71 (s, 1H, N*H*), 2.41 (bs, 4H, NCH_2CH_2NH), 2.85 (t, 4H, NCH_2CH_2NH), 3.58 (s, 2H, NCH_2Ar), 7.10 (m, 1H, H_{Ar}), 7.35 (d, 1H, H_{Ar}), 7.58 (m, 1H, H_{Ar}), 8.49 (d, 1H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 46.6, 55.2, 65.9, 122.7, 123.9, 137.0, 149.9, 159.1. – MS (EI); *m/z*: 177 [M^+].

N-[6-(2-Hydroxymethyl)pyridylmethyl]piperazine (**4**): Prepared according to the procedure for **2**. 2-Bromomethyl-6-hydroxymethylpyridine (**3**) was used instead of 2-chloromethylpyridine (**1**). Yield 2.67 g (95%). – ^{1}H NMR ($CDCl_3$): δ = 2.44 (ls, 4H, NCH_2CH_2NH), 2.86 (t, 4H, NCH_2CH_2NH), 3.62 (s, 2H, NCH_2Ar), 4.70 (s, 2H, CH_2OH), 7.11 (d, 1H, H_{Ar}), 7.30 (d, 1H, H_{Ar}), 7.62 (t, 1H, H_{Ar}). – ^{13}C-NMR ($CDCl_3$): δ = 46.3, 54.9, 64.8, 65.3, 119.4, 122.1, 137.6, 157.8, 160.1. – MS (EI); *m/z*: 201 [M^+].

N,N'-Bis(2-pyridylmethyl)piperazine (**L1**): Into a stirred mixture of piperazine (5.8 mmol) and K_2CO_3 (2 g) in CH_3CN (20 ml) was added a solution of **1** (11.6 mmol) in CH_3CN (20 ml). The mixture was refluxed for 4 h and the inorganic residue was filtered off. Evaporation of the solvent gave 1.5 g (96%) of yellow solid, m.p. 92–94°C. – ^{1}H NMR ($CDCl_3$): δ = 2.53 (bs, 8H, $N(CH_2CH_2)_2N$), 3.63 (s, 4H, NCH_2Ar), 7.11 (m, 2H, H_{Ar}), 7.35 (d, 2H, H_{Ar}), 7.60

(t, 2H, H_{Ar}), 8.50 (d, 2H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 53.8, 65.2, 122.6, 123.9, 137.0, 149.9, 159.1. – HRMS; *m/z*: (M^+, $C_{16}H_{20}N_4$) calcd. 268.1680; found 268.1678.

N,N'-Bis[6-(2-hydroxymethyl)pyridylmethyl]piperazine (**L2**): Into a stirred mixture of piperazine (2.67 mmol) and K_2CO_3 (2 g) in CH_3CN (30 ml) was added slowly a solution of **3** (5.3 mmol) in CH_3CN (30 ml) at room temperature. The mixture was refluxed for 4 h and the inorganic residue was filtered off. Evaporation of the solvent gave 0.88 g (100%) of thick oil. – ^{1}H NMR ($CDCl_3$): δ = 2.59 [bs, 8H, N(CH_2CH_2)N], 3.70 (s, 4H, NCH_2Ar), 4.71 (s, 4H, CH_2OH), 7.09 (d, 2H, H_{Ar}), 7.32 (d, 2H, H_{Ar}), 7.63 (t, 2H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 53.8, 64.6, 64.8, 119.4, 122.4, 137.8, 158.0, 158.9. – HRMS; *m/z*: (M^+, $C_{18}H_{24}N_4O_2$) calcd. 328.1877; found 328.1883.

N-[6-(2-Hydroxymethyl)pyridylmethyl]-N'-(2-pyridylmethyl)piperazine (**L3**): Into a stirred mixture of **2** (4.2 mmol) and K_2CO_3 (2 g) in CH_3CN (25 ml) was added slowly a solution of **3** (4.2 mmol) in CH_3CN (25 ml) at room temp. The mixture was refluxed for 4 h and the inorganic residue was filtered off. The solvent was evaporated and the residue was dissolved in hot petroleum ether (b.p. 60–95°C) and filtered. Evaporation of the ether gave 1.0 g (85%) of **L3** as a reddish thick oil. – ^{1}H NMR ($CDCl_3$): δ = 2.53 [s, 8H, N(CH_2CH_2)$_2$N], 3.62 (s, 2H, NCH_2Ar), 3.64 (s, 2H, NCH_2Ar), 4.69 (s, 2H, CH_2OH), 7.12 (m, 2H, H_{Ar}), 7.28 (d, 1H, H_{Ar}), 7.35 (d, 1H, H_{Ar}), 7.60 (m, 2H, H_{Ar}), 8.49 (d, 1H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 53.8, 53.9, 64.6, 64.9, 65.2, 119.3, 122.3, 122.7, 123.9, 137.0, 137.7, 149.9, 158.1, 159.0, 159.1. – HRMS; *m/z*: (M^+, $C_{17}H_{22}N_4O$) calcd. 298.1785; found 298.1783.

2,6-Bis-[(N'-(2-pyridylmethyl)]-N-(piperazidylmethyl)pyridine (**L4**): Into a stirred mixture of *N*-(2-pyridylmethyl)piperazine (**2**) (6.9 mmol) and K_2CO_3 (3 g) in CH_3CN (30 ml) was added a solution of 2,6-bisbromomethylpyridine (**7**) (3.1 mmol) in CH_3CN (30 ml). The resulting mixture was refluxed for 4 h and the inorganic residue was filtered off. The solvent was evaporated and the residue was washed with cold CH_3CN. Yield 1.07 g (75%) of yellowish solid, m.p. 138–140°C. – ^{1}H NMR ($CDCl_3$): δ = 2.54 [s, 16H, N(CH_2CH_2)$_2$N], 3.64 (s, 8H, NCH_2Ar), 7.14 (m, 2H, H_{Ar}), 7.26 (d, 2H, H_{Ar}), 7.37 (d, 2H, H_{Ar}), 7.59 (m, 3H, H_{Ar}), 8.52 (d, 2H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 53.9, 54.0, 65.1, 65.3, 121.9, 122.7, 123.9, 137.0, 137.3, 149.9, 158.7, 159.2. – HRMS; *m/z*: (M^+, $C_{27}H_{35}N_7$) calcd. 457.2954; found 457.2968.

1,3-Bis[(N'-(2-pyridylmethyl)]-N-(piperazidylmethyl)benzene (**L5**): Prepared according to the procedure for **L4**. 1,3-*Bis*(bromomethyl)benzene (**8**) was used instead of 2,6-*bis*(bromomethyl)pyridine (**7**). The residue was dissolved in hot light petroleum ether (b.p. 60–90°C) and the unsolvable matter was separated. Evaporation of the ether gave 1.18 g (97%) of thick oil, which solidified extremely slowly, m.p. 99–102°C. – ^{1}H NMR ($CDCl_3$): δ = 2.50 [bs, 16H, N(CH_2CH_2)$_2$N], 3.48 (s, 4H, NCH_2Ar), 3.64 (s, 4H, NCH_2Ar), 7.17 (m, 6H, H_{Ar}), 7.36 (d, 2H, H_{Ar}), 7.61 (t, 2H, H_{Ar}), 8.52 (d, 2H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 53.7, 53.9, 63.6, 65.2, 122.6, 123.8, 128.6, 130.7, 136.9, 138.5, 149.8, 159.1. – HRMS; *m/z*: (M^+, $C_{28}H_{36}N_6$) calcd. 456.3001; found 456.3004.

1,4-Bis[(N'-(2-pyridylmethyl)]-N-(piperazidylmethyl)benzene (**L8**): Prepared according to the procedure for **L4**. 1,4-*Bis*(bromomethyl)benzene (**9**) was used instead of 2,6-*bis*(bromomethyl)pyridine (**7**). After filtering the inorganic matter off, the residue was cooled in refrigerator and the precipitate was separated and washed with cold CH_3CN. Yield 0.64 g (51%) of yellow solid, m.p. 153–155°C. – ^{1}H NMR ($CDCl_3$): δ = 2.50 [bs, 16H, N(CH_2CH_2)$_2$N], 3.47 (s, 4H, NCH_2Ar), 3.64 (s, 4H, NCH_2Ar), 7.14 (m, 2H, H_{Ar}), 7.28 (s, 4H, H_{Ar}), 7.36 (d, 2H, H_{Ar}), 7.61 (m, 2H, H_{Ar}), 8.53 (d, 2H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 53.7, 53.9, 63.5, 65.3, 122.6, 123.9, 129.8, 137.0, 137.5, 149.9, 159.2. – HRMS; *m/z*: (M^-, $C_{28}H_{36}N_6$) calcd. 456.3001; found 456.2991.

2,6-Bis{N-[N'-(2-hydroxymethyl-6-pyridylmethyl)]piperazidylmethyl}pyridine (**L6**): Into a stirred mixture of **4** (4.8 mmol) and K_2CO_3 (3 g) in CH_3CN (25 ml) was added slowly a solution of 2,6-*bis*(bromomethyl)pyridine (**7**) (2.4 mmol) in CH_3CN (20 ml) at room temp. The mixture was refluxed for 4 h and the inorganic residue was filtered off. Evaporation of the solvent gave 1.20 g (98%) of a brownish solid, m.p. 100–102°C. – ^{1}H NMR ($CDCl_3$): δ = 2.55 [bs, 16H, N(CH_2CH_2)$_2$N], 3.65 (s, 4H, NCH_2Ar), 3.67 (s, 4H, NCH_2Ar), 4.71 (s, 4H, CH_2OH), 7.08 (d, 2H, H_{Ar}), 7.28 (m, 4H, H_{Ar}), 7.60 (m, 3H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 53.8, 64.7, 64.8, 65.0, 119.4, 122.0, 122.3, 137.3, 137.7, 158.1, 158.6, 159.2. – HRMS; *m/z*: (M^+, $C_{29}H_{39}N_7O_2$) calcd. 517.3165; found 517.3164.

2,6-Bis{N-[N'-(2-hydroxymethyl-6-pyridylmethyl)]piperazidylmethyl}benzene (**L7**): Prepared according to the procedure for **L6**. 1,3-*Bis*(bromomethyl)benzene (**8**) was used instead of 2,6-*bis*(bromomethyl)pyridine (**7**). The product was eluted with methanol through a short aluminium oxide column. Yield 0.40 g (54%) of a brownish thick oil. – ^{1}H NMR ($CDCl_3$): δ = 2.48 [bs, 16H, N(CH_2CH_2)$_2$N], 3.49 (s, 4H, NCH_2Ar), 3.66 (s, 4H, NCH_2Ar), 4.70 (s, 4H, CH_2OH), 7.08 (d, 2H, H_{Ar}), 7.24 (m, 6H, H_{Ar}), 7.61 (t, 2H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 53.6, 53.8, 63.5, 64.7, 64.8, 119.4, 122.3, 128.7, 130.8, 137.7, 138.4, 158.0, 159.3. – HRMS; *m/z*: (M^+, $C_{30}H_{40}N_6O_2$) calcd. 516.3213; found 516.3217.

N,N'-Bis[6-(2-chloromethyl)pyridylmethyl]piperazine (**5**): **L2** (2.6 mmol) was dissolved in thionyl chloride (50 ml) and the resulting solution was heated at reflux for 4 h. Thionyl chloride was removed in vacuo, and the residue was washed with light petroleum ether (b.p. 40–60°C). The crude hydrochloride was dissolved in 50 ml of water and neutralized with aqueous $NaHCO_3$ solution. Extraction of the aqueous phase with CH_2Cl_2 (4 × 40 ml), followed by drying with Na_2SO_4 and evaporation, resulted in 0.69 g (73%) of yellowish solid. – ^{1}H NMR ($CDCl_3$): δ = 2.61 [bs, 8H, N(CH_2CH_2)N], 3.70 (s, 4H, NCH_2Ar), 4.64 (s, 4H, CH_2Cl), 7.36 (t, 4H, H_{Ar}), 7.68 (t, 2H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 47.5, 53.8, 64.8, 121.8, 123.2, 138.1, 156.7.

2,6-Bis{N-[N'-(2-chloromethyl-6-pyridylmethyl)]piperazidylmethyl}pyridine (**6**): **L6** (1.5 mmol) was dissolved in thionyl chloride (30 ml) and the resulting solution was heated at reflux for 4 h. Thionyl chloride was removed in vacuo, and the residue was washed with light petroleum ether (b.p. 40–60°C). The crude hydrochloride was dissolved in 50 ml of water and neutralized with aqueous $NaHCO_3$ solution. Extraction of the aqueous phase with CH_2Cl_2 (4 ± 30 ml), followed by drying with Na_2SO_4 and evaporation, resulted in 0.70 g (82%) of brown solid. – ^{1}H NMR ($CDCl_3$): δ = 2.56 [bs, 16H, N(CH_2CH_2)$_2$N], 3.66 (s, 8H, NCH_2Ar), 4.63 (s, 4H, CH_2Cl), 7.32 (m, 6H, H_{Ar}), 7.62 (m, 3H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 47.5, 53.8, 53.9, 64.9, 65.0, 121.7, 122.1, 123.1, 137.4, 138.1, 156.7, 158.5, 159.1.

N,N'-Bis(2-(6-{N-[N'-(2-pyridylmethyl)piperazidyl]}methyl)pyridylmethyl)piperazine (**L9**): Into a stirred mixture of *N*-(2-pyridylmethyl)piperazine (**2**) (1.7 mmol) and K_2CO_3 (1 g) in CH_3CN (30 ml) was added slowly a solution of **5** (0.85 mmol) in CH_3CN (30 ml) at room temp. The mixture was refluxed for 4 h and the inorganic residue was filtered off and washed with small amount of $CHCl_3$. Evaporation of the solvents gave 0.3 g (55%) yellow solid, m.p. 168–171°C. – ^{1}H NMR ($CDCl_3$): δ = 2.54 [bs, 24H, N(CH_2CH_2)$_2$N], 3.63 (s, 12H, NCH_2Ar), 7.08 (m, 2H, H_{Ar}), 7.26 (d, 4H, H_{Ar}), 7.35 (d, 2H, H_{Ar}), 7.55 (m, 4H, H_{Ar}), 8.42 (d, 2H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 52.0, 63.2, 63.4, 120.5, 121.1,

122.3, 135.4, 135.7, 148.3. – HRMS; *m/z*: (M^+, $C_{38}H_{50}N_{10}$) calcd. 646.4220; found 646.4217.

2,6-Bis(N-(N'-(6-(2-{N-[N'-(2-pyridylmethyl)piperazidylmethyl]}pyridylmethyl))piperazidylmethyl))pyridine (**L10**): Prepared according to the procedure for **L9**. The *bis*(chloromethyl) compound **6** was used instead of **5**. Evaporation of the solvents gave 0.32 g (64%) of black solid, m.p. 180–182°C. – ^{1}H NMR ($CDCl_3$): δ = 2.55 [bs, 32H, $N(CH_2CH_2)_2N$], 3.65 (s, 16H, NCH_2Ar), 7.13 (m, 2H, H_{Ar}), 7.26 (d, 4H, H_{Ar}), 7.37 (d, 4H, H_{Ar}), 7.59 (m, 5H, H_{Ar}), 8.52 (d, 2H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 53.8, 53.9, 65.1, 65.2, 122.0, 122.7, 123.9, 137.0, 137.3, 149.9, 158.6, 159.2. – HRMS; *m/z*: (M^+, $C_{49}H_{65}N_{13}$) calcd. 835.5486; found 835.5485.

2,6-Bis(N-(N'-(6-(2-{N-[N'-(2-hydroxyethyl)piperazidylmethyl]}pyridylmethyl))piperazidylmethyl))pyridine (**L11**): Prepared according to the procedure for **L10**. *N*-(2-hydroxyethyl)piperazine (**10**) was used instead of *N*-(2-pyridylmethyl)piperazine (**2**). Evaporation of the solvents gave 0.15 g (43%) of black solid, m.p. 167–169°C. – ^{1}H NMR ($CDCl_3$): δ = 2.54 [bs, 36H, $N(CH_2CH_2)_2NCH_2CH_2OH$], 3.59 (t, 4H, NCH_2CH_2OH), 3.64 (s, 12H, NCH_2Ar), 7.26 (m, 6H, H_{Ar}), 7.58 (t, 3H, H_{Ar}). – ^{13}C NMR ($CDCl_3$): δ = 53.5, 53.7, 53.8, 58.3, 59.9, 64.9, 65.0, 121.9, 122.0, 137.3, 158.4, 158.6, 158.7. – HRMS; *m/z*: (M^+, $C_{41}H_{63}N_{11}O_2$) calcd. 741.5166; found 741.5167.

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