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Oxaazamacrocycles incorporating quinoline moiety: synthesis and study of their binding properties towards metal cations

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Novel dioxa- and trioxadiazamacrocycles have been synthesized by the Pd(0)-catalyzed amination of 4,6- and 4,7-dichloroquinolines with linear di- and trioxadiamines. Macrocyclization reaction was shown to be more successful for 4,6-dichloroquinoline providing yields of corresponding macrocycles up to 32%. 4,6-Di(2-methoxyethylamino)quinoline was obtained in 88% yield for comparative studies. The synthesis of the macrocycles comprising two 4,7-disubstituted quinoline moieties and two oxadiamine linkers has been accomplished. The binding properties of 4,6-diamino derivatives of quinoline have been studied with 17 metal cations using UV-vis and fluorescence spectroscopy. UV, fluorescence, and NMR spectral data demonstrated the formation of the complexes of different composition depending on the nature of ligand and metal cation. One of the macrocycles (**5c**) was shown to be applicable as a selective fluorescent and colorimetric chemosensor for Cu(II). Macrocyclic ligands **5** clearly showed different behavior in the presence of metal cations compared to the non-cyclic derivative **10**.

Introduction

Design and synthesis of simple and efficient fluorescent chemosensors for metal cations is a flourishing field of modern organic synthesis. Quinoline moiety is one of the most frequently used fluorophores due to its relevant fluorescence properties, possibilities of their modification and enhancement *via* substitution in the heteroaromatic core. Most often quinoline derivatives are used for fluorimetric detection of Zn cations. The simplest 8-hydroxyquinoline, its derivatives and 6-methoxy-8-sulfonamidoquinoline were used almost three decades ago in fluorescent visualizing and assaying the histochemically active Zn(II) in the brain.[1] Further water-soluble groups were introduced in position 6 of the quinoline moiety and it gave possibility to detect Zn(II) in cells.[2,3] Chemosensors contain various ionophore fragments: dipicolylamino group,[4,5] *N,N'*-di(quinolin-2-ylmethyl) substituted diamines and polyamines.[6] Various diamines with *N,N*-di(quinolin-2-ylmethyl)amino groups which act simultaneously as receptor and signaling groups have been reported.[7-10] All these chemosensors provide significant fluorescence enhancement on the coordination with zinc. Some of them were claimed to be quite selective for Zn(II) in the presence of Cd(II), and *vice versa*, some other quinolines with certainly arranged alkoxy and amino substituents and bearing dipicolylamino receptor group were shown to be selective for Cd(II) in the presence of Zn(II).[11,12] *N,N',N''*-tri(quinolin-4-yl)derivative of tris(2-aminoethyl)amine was used as a fluorescent chemosensor for phosphate anions.[13] Quinoline was employed as the exocyclic fluorophore for creating macrocyclic chemosensors. It was combined with 1,4,7-triazacyclononane (TACN) for traditional sensing Zn(II)[14] or for detecting cyanide anion,[15] decoration of 1,4,8,10-tetraazacyclododecane (cyclen) gave a remarkable sensor for Zn(II).[16] The quinoline-bearing cyclen-Gd(III) complex provided zinc-responsive bimodal MRI and fluorescent imaging probe for biological applications,[17] and Zn(II) complex with quinoline-modified cyclen was shown to recognize thymine in DNA bulges.[18] Quinoline moieties were introduced as exocyclic substituents for different purposes also into benzocrown ethers,[19] benzoazacrown ethers,[20] thiaazacrown ethers,[21-23] and tetraazamacrocycles – derivatives of 2,6-disubstituted pyridine.[24] For detecting Cu(II) calix[4]arene and analogous cyclotriveratrylene were modified with quinoline substituents,[25,26] while even tetraphenylporphyrine, itself a powerful fluorophore, was combined with quinoline to form a chemosensor for Ag(I) cations.[27]

On the other hand, rare examples are described in literature where quinolines are incorporated as endocyclic blocks of macrocyclic systems. Macrocyclic oligomers based on 2,8-disubstituted quinolines were synthesized and tested as G-quadruplex ligands,[28] tetraazamacrocycles containing two 2,3-disubstituted quinolines were synthesized and their Cu(II) and Co(II) complexes were tested in binding DNA fragments and inhibiting HCV NS3/4a protease.[29,30] It is to be also mentioned that in spite of the known fluorescent properties of 6-

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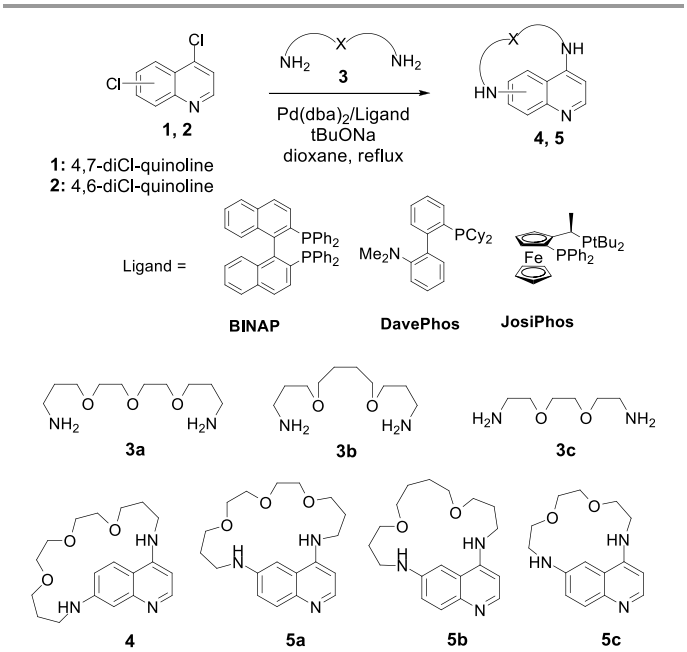
Electronic Supplementary Information (ESI) available: fluorimetric and UV-Vis studies of binding various metal cations by **5a-c** and **10**, fluorimetric and UV-Vis titration studies for **5a**/Cu^{2+}, **5a**/Al^{3+}, **5c**/Cu^{2+}, **10**/Cu^{2+} and **10**/Zn^{2+} systems, ^{1}H NMR studies of the Zn^{2+}/**10** system, ^{1}H and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/x0xx00000x

aminoquinoline, which is used as fluorescent derivatizing agent for chromatographic separation of peptides,[31,32] there is only one reported sophisticated detector comprising this moiety as an antenna in Eu(III)-based fluorescent detector for Zn(II).[33] Thus, in accordance with the literature data mentioned above we decided to synthesize nitrogen- and oxygen-containing macrocycles based on variously disubstituted quinolines and to compare their binding properties towards different metal cations by means of UV-vis and fluorescence spectroscopy.

Results and Discussion

For the synthesis of the target macrocycles we chose the Pd(0)-catalyzed amination reaction which is a powerful and universal tool for creating C(sp^2)-N bonds successfully employed by us previously for the synthesis of various macrocyclic systems containing aromatic and heteroaromatic moieties.[34-36] Pd(0)-catalyzed macrocyclization reactions were carried out using commercially available 4,6-, 4,7- and 4,8-dichloroquinolines under conditions which were established by us previously for the catalytic macrocyclization ($Pd(dba)_2$/BINAP catalytic system, *t*BuONa as base, boiling dioxane as solvent, equimolar amounts of reagents with C = 0.05 M). It was found out that 4,8-dichloroquinoline gave only inseparable mixtures of linear and cyclic oligomers and no target macrocycle could be isolated, probably, due to unfavourable reciprocal position of two reaction centres. Its isomer 4,7-dichloroquinoline (**1**) provided the macrocyclic derivative **4** in the reaction with the trioxadiamine **3a** which possesses the longest chain (Scheme 1).

The yield under standard conditions was low (7%, Table 1, entry 1), thus we tried two other catalytic systems which proved to be also efficient in the Pd(0)-catalyzed macrocyclization reaction. The application of DavePhos and Josiphos ligands allowed to increase the yield of compound **4** to some extent, however, it remained rather low (entries 2, 3). Other oxadiamines with shorter chains did not lead to the formation of corresponding macrocycles.



Scheme 1. Pd-catalyzed synthesis of the macrocycles **4** and **5a-c**.

Table 1. Synthesis of quinoline-based macrocycles **4**, **5a-c**.

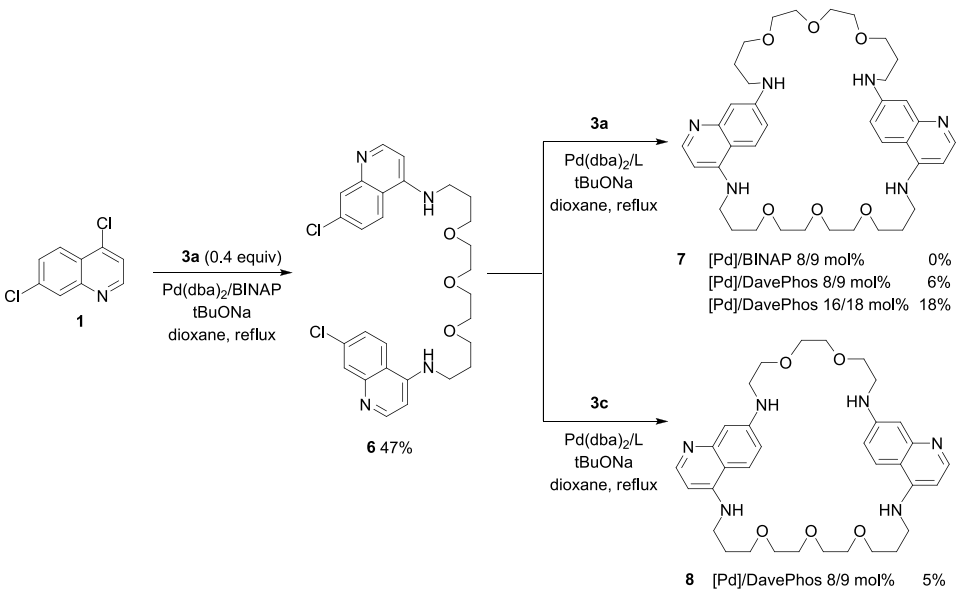
Entry	Arylhalide/Diamine	Ligand	Product	Yield, %
1	**1**/**3a**	BINAP	**4**	7
2	**1**/**3a**	DavePhos	**4**	11
3	**1**/**3a**	JosiPhos	**4**	11
4	**2**/**3a**	DavePhos	**5a**	30
5	**2**/**3b**	DavePhos	**5b**	28
6	**2**/**3c**	DavePhos	**5c**	32

Much better results were obtained with 4,6-dichloroquinoline (**2**). The reactions were carried out using $Pd(dba)_2$/DavePhos catalytic system as it provided a better result with 4,7-dichloroquinoline, and corresponding oxadiazamacrocycles **5a-c** were isolated in comparable yields 28-32% after column chromatography (entries 4-6). It should be noted that in all cases the full conversion of starting compounds was observed, however, at least two thirds of the amination products were complex and inseparable mixtures of linear and cyclic oligomers.

Macrocyclic compounds **4**, **5a-c** were analyzed by ^1H and ^{13}C NMR spectroscopy which clearly demonstrated the unsymmetrical character of oxadiamine chain with distinct difference in the chemical shifts of the protons in two CH_2NH fragments (Figure 1). Protons close to position 4 of the quinoline moiety were shifted downfield by 0.1-0.2 ppm (CH_2 group) and 1.3-2.5 ppm (NH protons) as compared to the corresponding protons close to position 7 or 6. With an increase in the macrocycle size in compounds **5a-c** the difference between chemical shifts of NH protons increases, and their absolute chemical shifts also move downfield. Also the chemical shifts of the aromatic protons differ substantially suggesting different orientation of the nitrogen lone pairs which results in different mesomeric donor effects (*e.g.*, chemical shifts of H^7 protons in **5a,b** and **5c**) as well as a difference in the distances between aromatic protons and electronegative oxygen atoms of the oxadiamine chains which governs negative inductive effects through the space (*e.g.*, chemical shifts of H^5 protons in **5a,b** and **5c**; see also our previous observations for macrocycles in refs.[37-39]).

Taking into consideration a substantial difference in the reactivity of two chlorine atoms in positions 4 and 7, we decided to synthesize macrocycles with larger cavities comprising two quinoline and two oxadiamine fragments. For this purpose at first *N,N'*-di(7-chloroquinolin-4-yl) derivative of trioxadiamine **6** was synthesized by reacting 2.5 equiv. of 4,7-dichloroquinoline with trioxadiamine under less diluted conditions (Scheme 2).

The resulting compound, isolated in 47% yield, was then introduced in the Pd(0)-catalzyed macrocyclization reaction



Scheme 2. Two-step synthesis of macrocycles **7** and **8**

with the second molecule of trioxadiamine **3a**. With BINAP ligand only complex mixture of oligomers was obtained, while with DavePhos ligand corresponding macrocycle **7** was obtained. Its yield could be increased to 18% by the application of greater amount of catalyst (16 mol%). We also showed the possibility to synthesize another macrocycle **8** with two different oxadiamine linkers (Scheme 2). Compounds **7** and **8** feature symmetrical oxadiamine chains evidenced by their NMR spectra. The composition of these molecules as well as of previously described macrocycles **4** and **5** was supported by the MALDI-TOF mass spectra.

In view of further investigations of spectroscopic properties (UV, fluorescent and NMR) and binding abilities of the macrocyclic diaminoquinoline derivatives we synthesized a linear derivative, 4,6-di(2-methoxyethylamino)quinoline (**10**). Compound **10** possesses two NCH_2CH_2O fragments and can be compared with its macrocyclic analogue **5c** for elucidation of the role of macrocycle in coordination with metal cations. The reaction was run using an excess of (2-methoxy)ethylamine (**9**) and provided the target compound in excellent 88% yield (Scheme 3).

Comparing ^{1}H NMR spectrum of compound **10** with those of macrocycles **5** (Figure 1) one easily notes substantially upfield-shifted NH protons (by 1-1.5 ppm averagely), while the difference in the chemical shifts of the aromatic protons is the biggest for compounds **10** and **5c** which contains the shortest dioxadiamine chain, and minimal for compounds **10** and **5a** containing the longest trioxadiamine chain, which obviously provides less conformational strain.

The next part of our work is dedicated to the spectroscopic studies of macrocyclic (**5a-c**) and non-cyclic (**10**) derivatives,

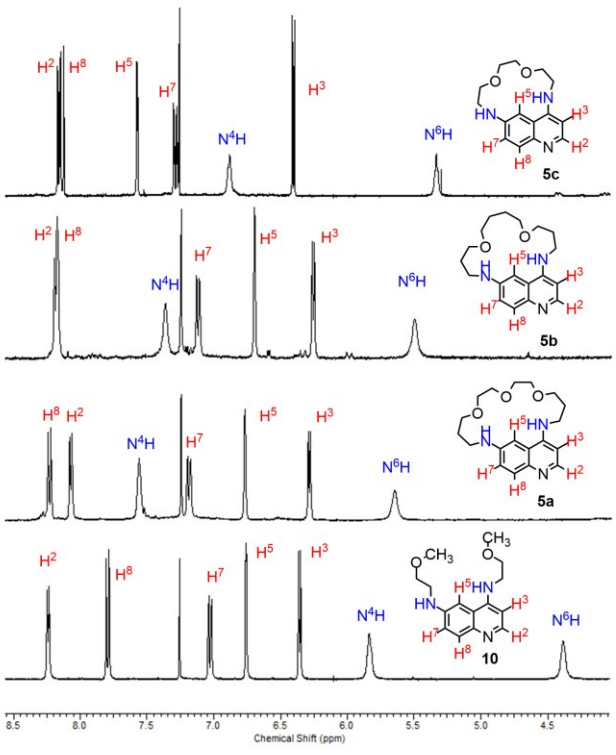
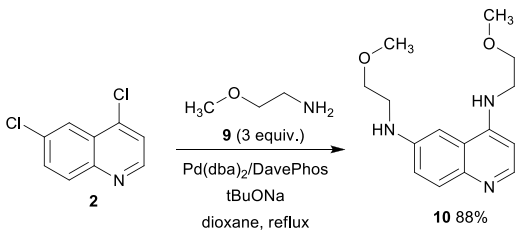


Figure 1. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of **5a**, **5b**, **5c** and **10**: the influence of the cycle size on the chemical shifts of aromatic and NH protons.



Scheme 3. Synthesis of 4,6-di(2-methoxyethylamino)quinoline (**10**).

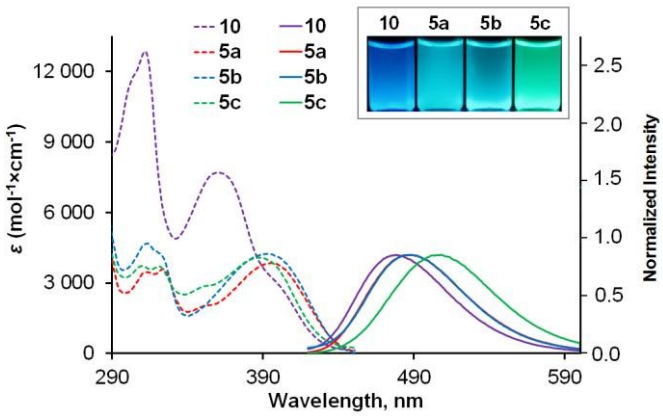


Figure 2. Absorbtion (dashed lines) and normalized luminescence (solid lines) spectra of the compounds **5a**, **5b**, **5c** and **10** in acetonitrile solution. Inset: visible emission of the solutions of compounds in acetonitrile.

Table 2. Photophysical properties of the compounds **5a**, **5b**, **5c** and **10**.

Compound	λ_{abs}, nm	λ_{ex}, (nm)	λ_{em}, nm	Φ^a
5a	312, 324, 397	397	488	0.57
5b	312, 322, 395	395	488	0.56
5c	311, 321, 387	385	507	0.52
10	312, 360	390[b]	478	0.63

[a] quantum yields of fluorescence were determined using 9,10-dichloro-antracene in acetonitrile (0.64) as a standard[40]

[b] maximum in excitation spectrum (λ_{em} = 478 nm)

the dependence of their UV-vis and fluorescent spectra on the presence of different metal cations.

Absorption and emission maxima as well as quantum yields are summarized in Table 2. It is known that the fluorescence of various aminoquinolines proceeds via intramolecular charge transfer (ICT)[41,42] due to the presence of electron donor and electron acceptor sites in these molecules. Figure 2 shows that three macrocycles possess enough similar absorption spectra while the UV spectrum of compound **10** notably differs from them. Compound **5c** possesses the most bathochromic emission maximum (507 nm), two other macrocycles have almost the same emission spectra (λem = 488 nm), and compound **10** emits at 478 nm. Compounds **5a-c** and **10** exhibit high quantum yields (0.52-0.63) what corresponds to the literature data for 3-aminoquinolines[43,44], though for other amino substituted quinolines data on quantum yields are almost absent. In our case we may also suppose that additional stabilization of excited state can be provided by the intramolecular hydrogen bonds in oxadaimine chains.[41,44,45]

The influence of 17 metal cations (Li(I), Na(I), K(I), Mg(II), Ca(II), Ba(II), Al(III), Mn(II), Fe(II), Co(II), Ni(II), Zn(II), Cu(II), Ag(I), Cd(II), Pb(II), Hg(II)) on the spectroscopic properties of compounds **5a-c** and **10** were studied in acetonitrile by a gradual addition of 1, 2, 3, and 4 equiv. of corresponding perchlorates. Spectral curves presented on the Figure 3 correspond to 4 equiv. of metal cations added.

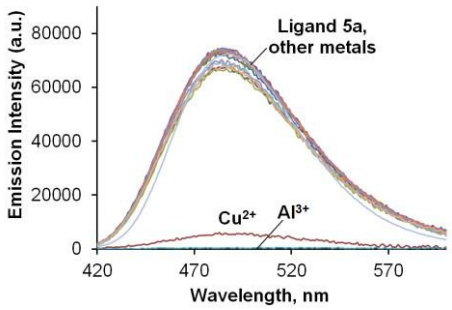


Figure 3. Luminescence spectra of **5a** ([**5a**] = 26 μM, MeCN, λ_{ex} = 395 nm) before and after addition of 4 equiv. of metal perchlorates.

Special investigations showed that further addition of salts did not lead to notable changes in UV-vis and fluorescence spectra in all cases studied.

With macrocycle **5a** the addition of the majority of cations did not significantly alter UV and fluorescence spectra, but Cu(II) reduced fluorescence intensity 15 times, and Al(III) quenched it almost totally (Fig. 3). The same cations led to strong changes in UV spectra as well (Fig. S2). We carried out fluorimetric (Figs. S3, S4) and spectrophotometric (Fig. 4) titrations of the macrocycle **5a** with $Cu(ClO_4)_2$ and established the successive formation of two complexes, Cu(**5a**)$_2$ and Cu(**5a**). Their stoichiometry and stability constants (Table 3, entry 1) were obtained from non-linear regression analysis by Specfit program[46]. The coordination of the copper cation proceeds probably at the nitrogen atom at position 6 because alternative coordination to two other nitrogen atoms would lead to enhancement of the emission instead of quenching.[41] The adjacent oxygen atom also participates in the copper coordination in Cu(**5a**)$_2$ complex. As for Cu(**5a**) complex, one may suppose the coordination of one nitrogen and two oxygen atoms of the trioxadiamine chain, the fourth coordination place may be occupied by acetonitrile molecule.

Fluorimetric titration of the same ligand with $Al(ClO_4)_3$ (Figs. S7 and S8) revealed the formation of the resulting complex of ML_2 type. Spectrophotometric titration (Fig. 5) supports the formation of the complex with metal-to-ligand ratio 1:2, non-linear regression analysis of the titration curves and calculations evidenced the formation of only the complex with

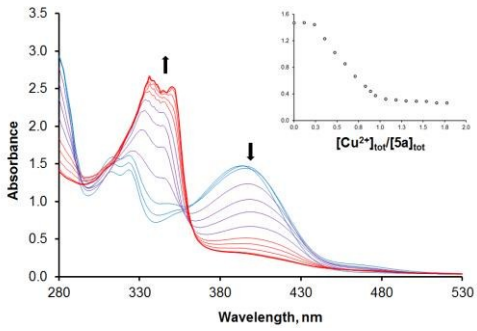


Figure 4. Evolution of UV–vis spectrum of **5a** (394 μM solution in CH_3CN) upon addition of $Cu(ClO_4)_2$ (0 - 1.3 equiv.). Inset: changes of absorbance at 395 nm plotted against $[Cu(ClO_4)_2]/[\mathbf{5a}]_{tot}$.

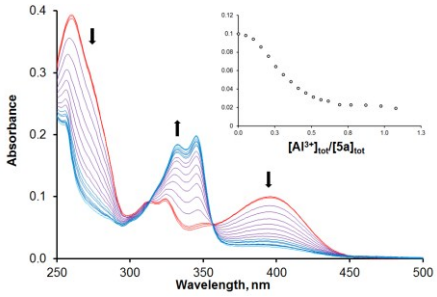


Figure 5. Evolution of UV–vis spectrum of **5a** (26 μM solution in CH_3CN) upon addition of $Al(ClO_4)_3$ (0 - 1.1 equiv.). Inset: changes of absorbance at 395 nm plotted against $[Al(ClO_4)_3]/[\mathbf{5a}]_{tot}$.

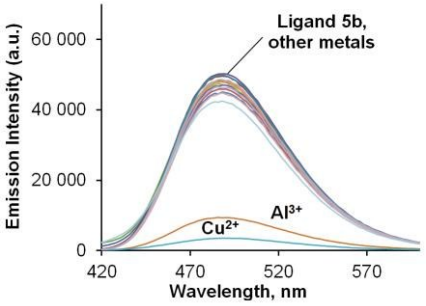


Figure 6. Luminescence spectra of **5b** ([**5b**] = 24 μM, MeCN, λ_{ex} = 395 nm) before and after addition of 4 equiv. of metal perchlorates.

2:1 ligand to metal stoichiometry. The stability constants of $Al(\mathbf{5a})_2$ were calculated from UV and fluorimetric titrations as lgβ = 11.15±0.07 and 11.85±0.05, respectively. The difference in the binding Cu(II) and Al(III) can be explained by a stronger affinity of the aluminium cation to oxygen atoms, its higher coordination number and absence of tendency to form complexes with acetonitrile molecule.

Investigations of the ligand **5b** possessing two oxygen atoms in the cycle showed that again only Cu(II) and Al(III) led to fluorescence quenching (Fig. 6) and caused notable changes in the UV spectra (Fig. S12). However, in this case Al(III) diminished the fluorescence intensity only 6 times, compared to almost full quenching of **5a** emission by this cation. One may assume that the difference in the structure of oxadiamine chains in **5a** and **5b** causes this fact.

The addition of Cu(II) ions to a solution of macrocycle **5c** quenched the emission, while Al(III) cations diminished it only by 35% (Fig. 7b,c). Addition of other 15 cations did not cause notable changes in the fluorescence spectra. As only Cu(II) was found to profoundly quench the emission, the experiments with competitive addition of copper and other cations were carried out (Fig. S17). They revealed that the presence of all other 16 cations taken in equimolar amounts did not interfere the detection of Cu(II) by fluorescence spectroscopy. The same was true for the UV spectra (Fig. 7a) depicting cross-selectivity of Cu(II) and other cations (Fig. S17), and this selectivity makes the ligand **5c** a good candidate for further investigations as a fluorescent and colorimetric sensor for Cu(II). There are several recently developed fluorimetric chemosensors for copper,[47-51] however, there is only one macrocyclic sensor based on thiacalix[4]crown ether with two pyrene fluorophores which proved to be the most sensitive.[52] It should be also noted that there a plenty of colorimetric detectors of copper ions were reported,[53-60] though some of them are indeed not chemosensors but rather molecular probes as they sense also other cations like Hg(II) or Fe(III).

The fluorimetric titration of the macrocycle **5c** with $Cu(ClO_4)_2$ clearly showed the formation of the complex with 1:1 metal-to-ligand stoichiometry (Figs. S18, S19). Spectrophotometric titration (Fig. 8) also demonstrated the presence of Cu(**5c**) complex with excess Cu(II), but it also suggested that the complex of ML_2 type is present in the solution. This was firmly

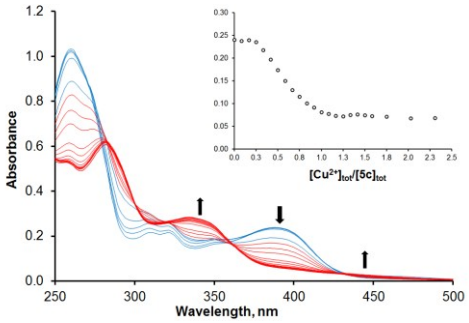


Figure 8. Evolution of UV–vis spectrum of **5c** (60 μM solution in CH_3CN) upon addition of $Cu(ClO_4)_2$ (0 - 2.3 equiv.). Inset: changes of absorbance at 385 nm plotted against $[Cu(ClO_4)_2]/[\mathbf{5c}]_{tot}$.

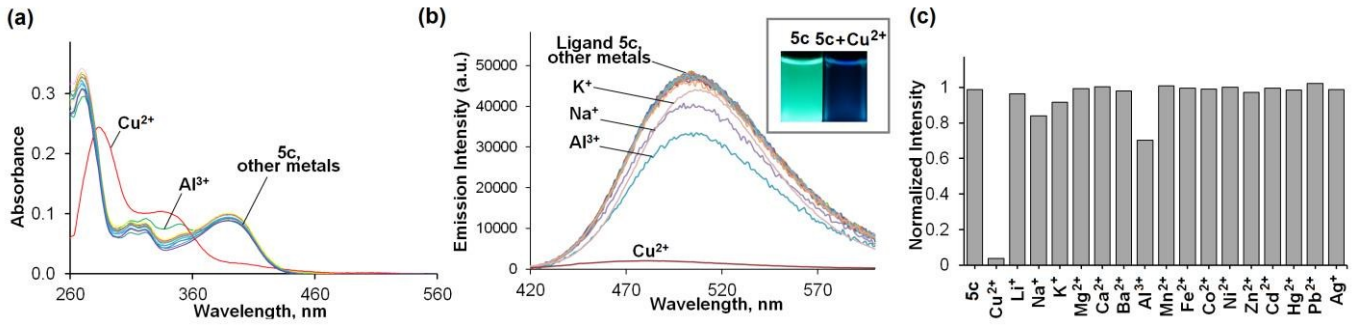


Figure 7. (a) UV–vis spectra of **5c** ([**5c**] = 24 μM, MeCN) before and after the addition of 4 equiv. of metal perchlorates. (b) Fluorescence spectra of **5c** ([**5c**] = 24 μM, MeCN, λ_{ex} = 385 nm) before and after addition of 4 equiv. of metal perchlorates. Inset: visual emission changes upon addition of Cu(II) ions. (c) Normalized fluorescence intensity of studied solutions at 507 nm (λ_{ex} = 385 nm).

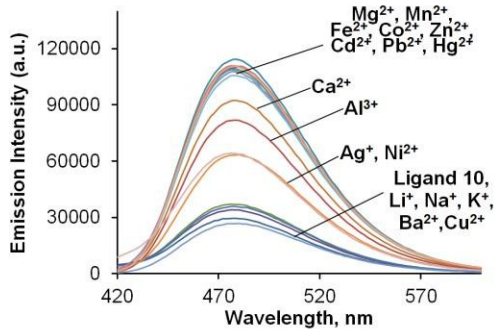


Figure 9. Fluorescence spectra of **10** ([**10**] = 20 μM, MeCN, λ_{ex} = 390 nm) before and after addition of 4 equiv. of metal perchlorates.

supported by the fitting of both titration curves using non-linear regression analysis by Specfit program[46]. Stability constants for both complexes were calculated (Table 3, entry 2). Taking into consideration titration data, the binding mode of copper cation to the ligand **5c** seems to be similar to that described above for the ligand **5a**.

The addition of various metal salts to the solution of the non-cyclic ligand **10** led to different changes in the emission spectra (Fig. 9), providing mainly enhancement of the fluorescence. It is interesting that in the presence of 4 equiv. of Cu(II) emission notably did not change while with 4 equiv. of Al(III) it increased 3 times, and 4 equiv. of Mg(II), Mn(II), Fe(II), Co(II), Zn(II), Cd(II), Pb(II) and Hg(II) led to 4-fold enhancements of the emission.

The UV spectra also changed substantially in the presence of all these metals, however, the changes were different for Cu(II) and Al(III) on one hand, and for the rest of metals, on the other (Fig. S24). Further we shall discuss the reasons for such behavior.

Fluorimetric titration of the ligand **10** with $Cu(ClO_4)_2$ (Fig. 10) at first led to a 3-fold increase in the emission upon addition of 0.5 equiv. of the metal (formation of ML_2 complex), and then the intensity of the fluorescence steadily decreased suggesting the formation of the ML complex. This supposition is supported by the spectrophotometric titration (Fig. 11) which demonstrated the presence of the first isosbestic point up to 0.4 equiv. of Cu(II) added, and the second isosbestic point which is clearly observed after 0.6 equiv. of Cu(II). This fact evidences the presence of three particles in equilibrium at *ca*

Table 3. Calculated stability constants of the complexes of **5a**, **5c** and **10** with Cu(II) ions[a]

Ligand	Complex	lgβ (UV-vis)	lgβ (Fluorescence)
5a	$Cu(\mathbf{5a})_2$	10.5±0.3	11.7±0.5
	Cu(**5a**)	6.3±0.3	7.0±0.3
5c	$Cu(\mathbf{5c})_2$	14.5±0.2	14.5±0.3
	Cu(**5c**)	8.4±0.2	8.0±0.2
10	$Cu(\mathbf{10})_2$	11.7±0.2	11.3±0.2
	Cu(**10**)	6.4±0.1	6.1±0.1

[a] Constants were calculated using Specfit program[46]

0.5 equiv. of Cu(II) – free ligand, ML_2 and ML complexes. The stoichiometry of the complexes and their stability constants (Table 3, entry 3) were calculated using non-linear regression analysis by Specfit program[46].

Complexes of **5a** and **10** with Cu(II) possess similar stability while the complexes of **5c** with Cu(II) is notably more stable (see Table 3). We suppose that it is due to a more rigid structure of the macrocycle **5c** which contains the shortest oxadiamine chain. Lesser number of oxygen atoms in **5c** compared to **5a** leads to a lower stability of its complex with Al(III) and weaker response of the quinoline signaling unit to coordination with this cation. This makes the ligand **5c** the most selective towards copper cations.

It has been already stated above that the UV spectrum of compound **10** is quite different from those of macrocyclic molecules **5a-c**. Interestingly, the addition of majority of metal cations except Cu(II) and Al(III) led to the spectra very similar to those of the complexes of these metals with macrocycles **5a-c**. All these facts may be explained by the changes in the electron donor properties of nitrogen atoms caused by the coordination to these cations. It should be mentioned that the distance between amino groups in positions 4 and 6 is too large to allow their simultaneous binding copper cation. We suppose a difference in the coordination mode in the case of the non-cyclic ligand **10** and macrocyclic ligands **5a-c**. In compound **10** the metal at first coordinates to the nitrogen atom in position 4 or to the quinoline nitrogen what enhances the ICT by weakening the electron density of the heterocyclic site of the molecule. The formation of the complexes with 1:1 stoichiometry engages the coordination of the nitrogen atom in position 6 what prohibits ICT and leads to fluorescence quenching. In the case of the macrocyclic ligands **5a-c**, which possess a more rigid structure and oxygen atoms in the chain,

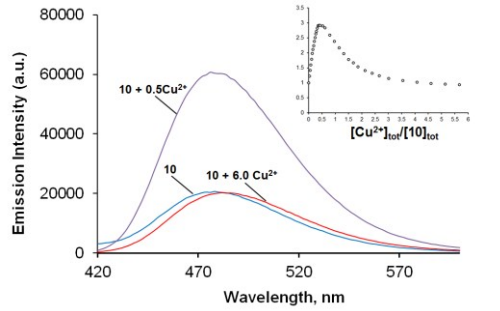


Figure 10. Evolution of fluorescence spectrum of **10** (9 μM solution in CH_3CN) upon addition of $Cu(ClO_4)_2$ (0, 0.5 and 6.0 equiv.) (λ_{ex} = 390 nm). Inset: changes of emission intensities at 478 nm plotted against $[Cu(ClO_4)_2]/[\mathbf{10}]_{tot}$.

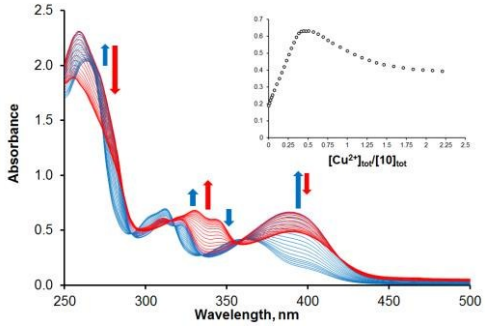


Figure 11. Evolution of UV–vis spectrum of **10** (54 μM solution in CH_3CN) upon addition of $Cu(ClO_4)_2$ (0-0.5 equiv. - blue, 0.5-2 equiv. - red). Inset: changes of absorbance at 390 nm plotted against $[Cu(ClO_4)_2]/[\mathbf{10}]_{tot}$.

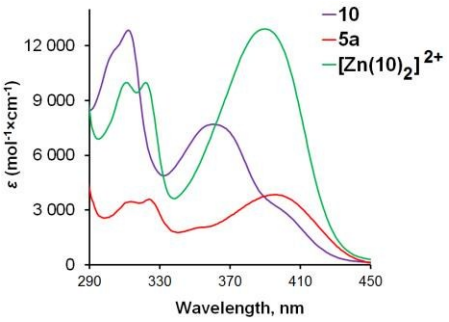


Figure 12. Comparison of the absorption spectra of the macrocycle **5a**, the ligand **10** and Zn(**10**)$_2$(ClO$_4$)$_2$ complex.

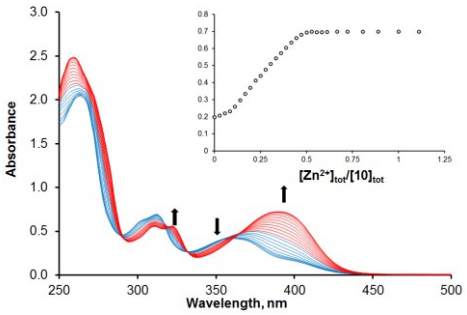


Figure 13. Evolution of UV–vis spectrum of **10** (54 μM solution in CH_3CN) upon addition of $Zn(ClO_4)_2$ (0 - 0.6 equiv.). Inset: changes of absorbance at 390 nm plotted against $[Zn(ClO_4)_2]/[\mathbf{10}]_{tot}$.

metal cations binding is provided by the amino group in the position 6 in both CuL_2 and CuL complexes what causes fluorescence quenching. The nitrogen atom at position 4 in macrocyclic ligands weakly conjugates with the heteroaromatic ring which is supported by a likelihood of the UV spectra of free compounds **5a-c** and complexes M(**10**)$_2$ (Fig. 12). In macrocycles the coordination involves the nitrogen atom at position 6 what results in the fluorescence quenching according to ICT mechanism (see a plausible scheme in Supporting Information). Though it is known that Cu(II) often quenches the fluorescence being a paramagnetic ion, we nevertheless suppose that our considerations of ICT mechanism also have grounds because with the ligand **10** the emission enhancement was observed on the addition of 0.5 equiv. Cu(II) ions.

To prove our supposition about the mode of cation binding and its influence on the fluorescence of ligand **10,** we carried out fluorimetric, spectrophotometric and NMR titrations of this ligand with $Zn(ClO_4)_2$. The changes in the emission (Fig. S29, S30) and absorbtion (Fig. 13) spectra clearly showed the formation of the complex with metal-to-ligand ratio 1:2. Spectrophotometric titration (Fig. 13) also gave evidence for the formation of the intermediate complex, presumably of ML_4 type, due to the first isosbestic point corresponding to 0-0.2 equiv. of Zn(II) and the second one corresponding to 0.3-0.6 equiv. of Zn(II). These observations are in a good agreement with the data obtained from NMR titration of **10** with $Zn(ClO_4)_2$ in CD_3CN (Figs. S33-S36). In the beginning of titration chemical shifts move upfield or downfield and after addition of 0.25 equiv. of Zn(II) they begin to move in the opposite direction. The formation of ML_4 complex suggests initial coordination at the quinoline nitrogen, and downfield bias of the chemical shifts of H^2 and H^8 quinoline protons upon the addition of 0.1 and 0.2 equiv. of zinc perchlorate is in agreement with this supposition. In the final complex, in comparison with the free ligand **10**, we observe profound downfield biases of the chemical shifts of both NH protons (from 4.89 to 5.32 ppm and from 6.08 to 7.35 ppm), methylene protons in corresponding CH_2N groups are shifted downfield by 0.17 and 0.03 ppm, protons H^3 and H^7 of the quinoline moiety are also shifted downfield by 0.24 and 0.20 ppm, respectively, while chemical shift of H^2 proton is biased upfield by 0.12 ppm. These changes in the chemical shifts are in a good agreement with the supposed coordination of Zn(II) to both 2-methoxyethylamino moieties which causes the increase in the fluorescence intensity. The podand attached to position 4 of the quinoline core seems to form a more stable complex with zinc cation. The stoichiometry of the complexes of **10** with Zn(II) was supported by the data obtained from non-linear regression analysis of by Specfit program[46]; their stability constants turned to be much higher than those calculated for relative copper complexes and were found to be lgβ = 20.0±0.4 for Zn(**10**)$_4$ and lgβ = 11.9±0.2 for Zn(**10**)$_2$. The data discussed above are in the agreement with our supposition about coordination of the metals to ligand **10**.

Conclusions

To sum up, we elaborated the synthesis of quinoline-containing oxaazamacrocycles using Pd(0)-catalyzed amination reaction and demonstrated that macrocyclization of 4,6-dichloroquinoline occurred easier than that of isomeric 4,7-dichloroquinoline. 4,6-Di(2-methoxyethylamino)quinoline was synthesized also *via* Pd(0)-catalyzed amination for comparison with macrocyclic compounds **5a-c**. UV and fluorescent spectra of the macrocycles comprising 4,6-diaminoquinoline moiety and different oxadiamine chains were investigated in acetonitrile in the presence of 17 metal cations; Cu(II) and in some cases Al(III) were found to quench fluorescence. Non-cyclic derivative **10** was found to be responsive for the majority of metals by the enhancement of fluorescence and significant changes in UV spectra. The formation of CuL_2 and CuL complexes was established for **5a**, **5c** and **10** ligands by fluorimetric and spectrophotometric titrations. It was found out that in the case of macrocyclic ligands **5a** and **5c** the binding of the metal cations proceeds in a different way compared to acyclic ligand **10**. This fact was proved by different changes in UV-vis and fluorescent spectra in the case of Cu binding with **5a,c** and **10** ligands and by the additional UV, fluorescent and NMR experiments elucidating binding Zn cations with the ligand **10**. Additional experiments with the macrocycle **5c** to establish cross-selectivity of Cu(II) sensing in the presence of 16 other metals has shown that it can be developed as fluorescent and colorimetric chemosensor for copper cations.

Experimental

Materials and methods

Unless otherwise noted, all chemicals and starting materials were obtained commercially from Acros and Aldrich-Sigma Co. and used without further purification. ^{1}H and ^{13}C NMR spectra were registered with Bruker Avance-400 spectrometer in $CDCl_3$ or CD_3CN, using the residual signals of $CHCl_3$ or CHD_2CN as internal standards. Mass-spectra MALDI-TOF of positive ions were recorded with Bruker Daltonics Autoflex II device using 1,8,9-trihydroxyanthracene (dithranol) as matrix and polyethyleneglycols as internal standards. Accurate mass measurements (HRMS ESI) were performed with a Thermo Scientific Orbitrap Elite high-field orbitrap hybrid mass spectrometer. Preparative column chromatography was carried out using silica gel 40/60 from Merck Co. Commercially available compounds were used without special purification. Dioxane was distilled successively over NaOH and sodium under argon, CH_2Cl_2 and CH_3CN were distilled over CaH_2, MeOH was used freshly distilled. $Pd(dba)_2$ was synthesized according to a known method and used without recrystallization[61].

Synthesis of macrocyclic ligands 4 and 5

General method for the Pd(0)-catalyzed synthesis of macrocyclic ligands based on quinoline. A two-neck flask equipped with a magnetic stirrer and reflux condenser, flushed with dry argon, was charged with 4,7-dichloroquinoline (**1**) or 4,6-dichloroquinoline (**2**), (0.2-0.3 mmol), $Pd(dba)_2$ (8 mol%), phosphine ligand (9 mol%), and absolute dioxane (4-6 ml), after stirring for 2 min diamine **3a-c** (0.2-0.3 mmol) and *t*BuONa (0.6-0.75 mmol) were added, and the reaction mixture was refluxed for 24 h. After cooling down to ambient temperature the reaction mixture was diluted with CH_2Cl_2, the solution was filtered and evaporated *in vacuo*, and the residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2–MeOH (gradient from 100:1 to 3:1 v/v) and CH_2Cl_2–MeOH–NH_3(aq) (gradient from100:20:1 to 10:4:1 v/v).

1,2,3,4,6,7,9,10,12,13,14,15-Dodecahydro-19,16-methenopyrido [4,3-*l*][1,4,7,11,17]trioxa-diazacycloicosine (4) was synthesized from compound **1** (50 mg, 0.25 mmol), trioxadiamine **3a** (55 mg, 0.25 mmol), in the presence of $Pd(dba)_2$ (12 mg, 8 mol%), DavePhos (9 mg, 9 mol%) and *t*BuONa (72 mg, 0.75 mmol). Eluent CH_2Cl_2 – MeOH – NH_3(aq) 100:20:3. Yield 9 mg (11%), yellow glassy compound. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.75 (quintet, ^3J = 4.6, 2H, $CH_2C\underline{H}_2CH_2$), 2.10 (quintet, ^3J = 4.1 Hz, 2H, $CH_2C\underline{H}_2CH_2$), 3.18 (t, ^3J = 5.7 Hz, 2H, $C\underline{H}_2$NQuin), 3.26 (t, ^3J = 5.1 Hz, 2H), 3.41 (q, ^3J = 4.7 Hz, 2H, CH_2NQ), 3.52-3.57 (m, 2H, CH_2O), 3.65-3.70 (m, 4H, CH_2O), 3.75-3.80 м (4H, CH_2O), 4.37 (broad s, 1H, NHQuin), 6.11 (d, ^3J = 4.9 Hz, 1H, H3(Q)), 6.87 (broad s , 1H, NHQ), 7.08 (broad s, 1H, H8(Q)), 7.38 (d, ^3J = 9.3 Hz, 1H, H6(Q)), 7.74 (d, ^3J = 9.3 Hz, 1H, H5(Q)), 8.25 (d, ^3J = 4.9 Hz, 1H, H2(Q)). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9 (1C, $CH_2\underline{C}H_2CH_2$), 32.1 (1C, $CH_2\underline{C}H_2CH_2$), 38.8 (1C, CH_2NQ), 43.9 (1C, CH_2NQ), 66.8 (1C, CH_2O), 69.5 (1C, CH_2O), 70.4 (1C, CH_2O), 71.0 (1C, CH_2O), 71.1 (1C, CH_2O), 72.7 (1C, CH_2O), 95.2 (1C, CH(Q)), 111.0 (1C, CH(Q)), 112.6 (1C, CH(Q)), 122.4 (1C, CH(Q)), 147.9 (1C, CH(Q)) (4 quaternary carbon atoms were not unambiguously assigned because of low concentration and broadening of the signals). HRMS (MALDI, dithranol, PEG-300) m/z calcd. for $C_{19}H_{28}N_3O_3$ $(M+H)^+$ 346.2131; found 346.2095.

1,2,3,4,6,7,9,10,12,13,14,15-Dodecahydro-16,18-ethenopyrido[4, 3-*l*][1,4,7,11,16]trioxadiaza-cyclononadecine (5a) was synthesized from 4,6-dichloroquinoline (**2**) (50 mg, 0.25 mmol), trioxadiamine **3a** (55 mg, 0.25 mmol), in the presence of $Pd(dba)_2$ (12 mg, 8 mol%), DavePhos (9 mg, 9 mol%) and *t*BuONa (72 mg, 0.75 mmol). Eluent CH_2Cl_2 – MeOH 5:1. Yield 26 mg (30%), yellow glassy compound. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94 (quintet, ^3J = 5.4 Hz, 2H, $CH_2C\underline{H}_2CH_2$), 2.12 (quintet, ^3J = 5.0 Hz, 2H, $CH_2C\underline{H}_2CH_2$), 3.38 (broad s, 2H), 3.57 (q, ^3J = 5.0 Hz, 2H, CH_2NQ), 3.61-3.65 (m, 2H, CH_2O), 3.67-3.72 (m, 6H, CH_2O), 3.82 (broad s, 4H, CH_2O), 5.68 (broad s, 1H, NH), 6.30 (d, ^3J = 6.7 Hz, 1H, H3(Q)), 6.78 (broad s, 1H, H5(Q)), 7.22 (dd, ^3J = 9.2 Hz, ^4J = 1.9 Hz, 1H, H7(Q)), 7.56 (broad s, 1H, NH), 8.08 (d, ^3J = 6.7 Hz, 1H, H2(Q)), 8.24 (d, ^3J = 9.2 Hz, 1H, H8(Q)). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.4 (1C, $CH_2\underline{C}H_2CH_2$), 27.8 (1C, $CH_2\underline{C}H_2CH_2$), 43.1 (1C, CH_2NQ), 43.8 (1C, CH_2NQ), 69.7 (1C, CH_2O), 70.5 (1C, CH_2O), 70.7 (1C, CH_2O), 70.8 (2C, CH_2O), 72.1 (1C, CH_2O), 95.5 (1C, C3(Q) or C7(Q)), 98.8 (1C, C7(Q) or C3(Q)), 118.6 (1C, C10(Q)), 120.2 (1C, CH(Q)), 122.9 (1C, CH(Q)), 130.5 (1C, C(Q)), 137.5 (1C, C2(Q)), 148.3 (1C, C(Q)), 152.8 (1C, C(Q)). HRMS (MALDI, dithranol, PEG-300) m/z calcd. for $C_{19}H_{28}N_3O_3$ $(M+H)^+$ 346.2131; found 346.2165. HRMS (ESI) m/z calcd. for $C_{19}H_{28}N_3O_3$ $(M+H)^+$ 346.21307; found 346.21298.

1,2,3,4,6,7,8,9,11,12,13,14-Dodecahydro-15,17-ethenopyrido[4,3-*f*][1,14,5,10]dioxadiaza-cyclooctadecine (5b) was synthesized from 4,6-dichloroquinoline (**2**) (50 mg, 0.25 mmol), dioxadiamine **3b** (51 mg, 0.25 mmol), in the presence of $Pd(dba)_2$ (12 mg, 8 mol%), DavePhos (9 mg, 9 mol%) and *t*BuONa (72 mg, 0.75 mmol). Eluent CH_2Cl_2 – MeOH 10:1. Yield 22 mg (27%), yellow glassy compound. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67 (quintet, ^3J = 5.1 Hz, 2H, $CH_2C\underline{H}_2CH_2$), 1.96-2.00 (m, 4H, $CH_2C\underline{H}_2CH_2$), 2.09 (quintet, ^3J = 4.8 Hz, 2H, $CH_2C\underline{H}_2CH_2$), 3.37 (t, ^3J = 5.7 Hz, 2H), 3.50-3.54 (m, 4H), 3.57 (t, ^3J = 7.5 Hz, 2H), 3.69 (t, ^3J = 4.8 Hz, 2H, CH_2O), 3.81 (t, ^3J = 4.8 Hz, 2H, CH_2O), 5.52 (broad s, 1H, NHQuin), 6.27 (d, ^3J = 6.6 Hz, 1H, H3(Q)), 6.71 (d, ^4J = 2.3 Hz, 1H, H5(Q)), 7.15 (dd, ^3J = 9.2 Hz, ^4J = 2.3 Hz, 1H, H7(Q)), 7.38 (broad s, 1H, NHQuin), 8.17 (d, ^3J = 6.6 Hz, 1H, H2(Q)), 8.20 (d, ^3J = 9.2 Hz, 1H, H8(Q)). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.0 (1C, $CH_2\underline{C}H_2CH_2CH_2$), 27.8 (1C, $CH_2CH_2\underline{C}H_2CH_2$), 28.4 (1C, $CH_2\underline{C}H_2CH_2$), 28.9 (1C, $CH_2\underline{C}H_2CH_2$), 44.0 (1C, CH_2NQ), 44.4 (1C, CH_2NQ), 70.9 (1C, CH_2O), 72.0 (1C, CH_2O), 72.1 (2C, CH_2O), 95.7 (1C, C3(Q) or C7(Q)), 99.9 (1C, C7(Q) or C3(Q)), 118.5 (1C, C10(Q)), 118.9 (1C, CH(Q)), 125.1 (1C, CH(Q)), 133.1 (1C, C(Q)), 140.2 (1C, C2(Q)), 147.6 (1C, C(Q), 151.7 (1C, C(Q)). HRMS (MALDI, dithranol, PEG-300) m/z calcd. for $C_{19}H_{28}N_3O_2$ $(M+H)^+$ 330.2182; found 330.2157.

1,2,3,5,6,8,9,10-Octahydro-11,13-ethenopyrido[4,3-*h*][1,4,7,12]di-oxadiazacyclotetradecine (5c) was synthesized from 4,6-dichloroquinoline (**2**) (50 mg, 0.25 mmol), dioxadiamine **3c** (37 mg, 0.25 mmol), in the presence of $Pd(dba)_2$ (12 mg, 8 mol%), DavePhos (9 mg, 9 mol%) and *t*BuONa (72 mg, 0.75 mmol). Eluent CH_2Cl_2 – MeOH 5:1. Yield 29 mg (32%), green-yellow glassy compound. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.53 (q, ^3J = 5.1 Hz, 2H, CH_2NQ), 3.60 (q, ^3J = 4.6 Hz, 2H, CH_2NQ), 3.63-3.66 (m, 2H, CH_2O), 3.73 (t , ^3J = 4.2 Hz, 2H, CH_2O), 3.82-3.85 (m, 2H, CH_2O), 3.89 (t ,^3J = 5.3 Hz, 2H, CH_2O), 5.33 (broad s, 1H, NH), 6.41 (d ,^3J = 6.3 Hz, 1H, H3(Q)), 6.89 (broad s, 1H, NH), 7.31 (dd, ^3J = 9.1 Hz, ^4J = 2.4 Hz, 1H, H7(Q)), 7.57 (d, ^4J = 2.4 Hz, 1H, H5(Q)), 8.14 (d, ^3J = 9.1 Hz, 1H, H8(Q)), 8.17 (d, ^3J = 6.3 Hz, 1H, H2(Q)). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.3 (1C, CH_2NQ), 45.8

(1C, CH_2NQ), 68.4 (1C, CH_2O), 69.9 (1C, CH_2O), 72.2 (1C, CH_2O), 73.2 (1C, CH_2O), 96.9 (1C, C3(Q)) or C7(Q)), 98.2 (1C, C7(Q) or C3(Q)), 119.2 (1C, C10(Q)), 122.1 (1C, CH(Q)), 124.0 (1C, CH(Q)), 131.0 (1C, C(Q)), 137.9 (1C, C2(Q)), 147.6 (1C, C(Q)), 153.4 (1C, C(Q)). HRMS (MALDI, dithranol, PEG-200+PEG-300) m/z calcd. for $C_{15}H_{20}N_3O_2$ $(M+H)^+$ 274.1556; found 274.1520. HRMS (ESI) m/z calcd. for $C_{15}H_{20}N_3O_2$ $(M+H)^+$ 274.15555; found 274.15518.

Synthesis of macrocycles 7 and 8

***N,N'*-(3,3'-(2,2'-oxibis(ethan-2,1-diyl)bis(oxy))bis(propane-3,1-diyl))bis(7-chloroquinoline-4-amine) (6).** A two-neck flask equipped with a magnetic stirrer and reflux condenser, flushed with dry argon, was charged with compound 4,7-dichloroquinoline (**1**) (124 mg, 0.63 mmol), $Pd(dba)_2$ (6 mg, 4 mol%), BINAP (7 mg, 4.5 mol%), and absolute dioxane (2.5 ml), after stirring for 2 min trioxadiamine **3a** (55 mg, 0.25 mmol) and *t*BuONa (72 mg, 0.75 mmol) were added, and the reaction mixture was refluxed for 24 h. After cooling down to ambient temperature the reaction mixture was diluted with CH_2Cl_2, the solution filtered and evaporated *in vacuo*, and the residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2 and CH_2Cl_2–MeOH (gradient from 100:1 to 3:1 v/v). Eluent CH_2Cl_2 – MeOH 10:1. Yield 64 mg (47%), beige solid, m.p.=106°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.93 (quintet, ^3J = 5.4 Hz, 4H, $CH_2C\underline{H}_2CH_2$), 3.33 (q, ^3J = 5.1 Hz, 4H, CH_2NQ), 3.54-3.60 (m, 8H, CH_2O), 3.65-3.70 (m, 4H, CH_2O), 6.25 (broad s, 2H, NH), 6.31 (d, ^3J = 5.3 Hz, 2H, H3(Q)), 7.28 (d, ^3J = 9.0 Hz, 2H, H6(Q)), 7.75 (d, ^3J = 9.0 Hz, 2H, H5(Q)), 7.89 (s, 2H, H8(Q)), 8.44 (d, ^3J = 5.3 Hz, 2H, H2(Q)). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1 (2C, $CH_2\underline{C}H_2CH_2$), 42.1 (2C, CH_2NHQ), 70.3 (2C, CH_2O), 70.4 (2C, CH_2O), 70.5 (2C, CH_2O), 98.5 (2C, C3(Q)), 117.2 (2C, C10(Q)), 121.9 (2C, CH(Q)), 125.0 (2C, CH(Q)), 127.9 (2C, CH(Q)), 134.8 (2C, C7(Q)), 148.5 (2C, C4(Q)), 150.3 (2C, C9(Q)), 151.4 (2C, C2(Q)). HRMS (MALDI, dithranol, PEG-600) m/z calcd. for $C_{28}H_{33}Cl_2N_4O_3$ $(M+H)^+$ 543.1930; found 543.1876.

General method for the Pd(0)-catalyzed synthesis of macrocycles 7 and 8. A two-neck flask equipped with a magnetic stirrer and reflux condenser, flushed with dry argon, was charged with compound **6**, (0.2 mmol), $Pd(dba)_2$ (8-16 mol%), phosphine ligand (9-18 mol%), and absolute dioxane (4 ml), after stirring for 2 min diamine (0.2 mmol) and *t*BuONa (0.6 mmol) were added, and the reaction mixture was refluxed for 24 h. After cooling down to ambient temperature the reaction mixture was diluted with CH_2Cl_2, the solution filtered and evaporated *in vacuo*, and the residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2–MeOH (gradient from 100:1 to 3:1 v/v) and CH_2Cl_2–MeOH–NH_3(aq) (gradient from100:20:1 to 10:4:1 v/v).

8,9,10,11,13,14,16,17,19,20,21,22,30,31,32,33,35,36,38,39,41,42,43,44-tetracosahydro-7,4:23,26-dimethenodipyrido[3,4-*i*$_1$:4',3'-*l*][1,4,7,21,24,27,11,17,31,37]hexaoxatetraaza-cyclotetracontine (7) was synthesized from compound **6** (109 mg, 0.2 mmol), trioxadiamine **3a** (44 mg, 0.2 mmol), in the presence of $Pd(dba)_2$ (18 mg, 16 mol%), DavePhos (14 mg, 18 mol%) and *t*BuONa (58 mg, 0.6 mmol). Eluent CH_2Cl_2 – MeOH – NH_3(aq) 20:6:1. Yield 25 mg (18%), light-yellow glassy compound. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85 (quintet, ^3J = 5.8 Hz, 4H $CH_2C\underline{H}_2CH_2$), 1.91 (quintet, ^3J = 5.6 Hz, 4H, $CH_2C\underline{H}_2CH_2$), 3.26 (q, ^3J = 5.3 Hz, 4H, CH_2NQ), 3.34 (q, ^3J = 5.0 Hz, 4H, CH_2NQ), 3.45-3.72 (m, 24H, CH_2O), 4.61 (broad s, 2H, NH), 5.95 (broad s, 2H, NH), 6.15 (d, ^3J = 5.6 Hz, 2H, H3(Q)), 6.65 (d, ^3J = 9.0 Hz, 2H, H6(Q)), 6.85 (s, 2H, H8(Q)), 7.50 (d, ^3J = 9.0 Hz, 2H, H5(Q)), 8.27 (d, ^3J = 5.6 Hz, 2H, H2(Q)). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.4 (2C, $CH_2\underline{C}H_2CH_2$), 28.6 (2C, $CH_2\underline{C}H_2CH_2$), 41.5 (2C, CH_2NQ), 41.6 (2C, CH_2NQ), 69.7 (2C, CH_2O), 70.1 (4C, CH_2O), 70.4 (2C, CH_2O), 70.5 (4C, CH_2O), 96.1 (2C, C3(Q)), 104.9 (2C, C6(Q)), 110.7 (2C, C10(Q)), 115.8 (2C, C8(Q)), 121.0 (2C, C5(Q)), 149.3 (2C, C2(Q)), 150.0 (2C, C(Q)), 150.1 (2C, C(Q)), 150.5 (2C, C(Q)). HRMS (MALDI, dithranol, PEG-600) m/z calcd. for $C_{38}H_{55}N_6O_6$ $(M+H)^+$ 691.4183; found 691.4140.

5,6,7,8,10,11,13,14,16,17,18,19,28,29,31,32,35,36-octadecahydro-27*H*,34*H*-26,23:37,1-dimethenodipyrido[3,4-*d*$_1$:4',3'-*l*][1,4,7,20,23,11,17,26,32]pentaoxatetraazacyclopentatriacontine (8) was synthesized from compound **6** (109 mg, 0.2 mmol), trioxadiamine **3a** (30 mg, 0.2 mmol), in the presence of $Pd(dba)_2$ (9 mg, 8 mol%), DavePhos (7 mg, 9 mol%) and *t*BuONa (58 mg, 0.6 mmol). Eluent CH_2Cl_2 – MeOH – NH_3(aq) 20:6:1. Yield 6 mg (5%), light-yellow glassy compound. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96 (quintet, ^3J = 5.7 Hz, 4H, $CH_2C\underline{H}_2CH_2$), 3.30 (q, ^3J = 4.8 Hz, 4H, CH_2N), 3.48 (broad s, 4H, CH_2N), 3.60 (t, 4H, ^3J = 5.3 Hz, CH_2O), 3.60-3.64 (m, 4H, CH_2O), 3.68 (s, 4H, CH_2O), 3.67-3.71 (m, 4H, CH_2O), 3.74 (t, 4H, ^3J = 4.8 Hz, CH_2O), 4.65 (broad s, 2H, NH), 6.22 (d, ^3J = 5.8 Hz, 2H H3(Q)), 6.57 (dd, ^3J = 9.0 Hz, ^4J = 2.3 Hz, 2H, H6(Q)), 6.76 (broad s, 2H, H8(Q)), 7.42 (d, ^3J = 9.0 Hz, 2H, H5(Q)), 8.20 (d, ^3J = 5.8 Hz, 2H, H2(Q)) (two NH protons were not unambiguously assigned). HRMS (MALDI, dithranol, PEG-300) m/z calcd. for $C_{34}H_{47}N_6O_5$ $(M+H)^+$ 619.3608; found 619.3559.

Synthesis of N^4,N^6-bis(2-methoxyethyl)quinoline-4,6-diamine (10).

A two-neck flask equipped with a magnetic stirrer and reflux condenser, flushed with dry argon, was charged with compound 4,6-dichloroquinoline (2) (50 mg, 0.25 mmol), $Pd(dba)_2$ (12 mg, 8 mol%), DavePhos (9 mg, 4.5 mol%), and absolute dioxane (2.5 ml), after stirring for 2 min amine 9 (57 mg, 0.75 mmol) and *t*BuONa (72 mg, 0.75 mmol) were added, and the reaction mixture was refluxed for 24 h. After cooling down to ambient temperature the reaction mixture was diluted with CH_2Cl_2, the solution filtered and evaporated *in vacuo*, and the residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2 and CH_2Cl_2–MeOH (gradient from 100:1 to 3:1 v/v). Eluent CH_2Cl_2 – MeOH 10:1. Yield 60 mg (88%), green-yellow glassy compound. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.36 (m, 2H, CH_2NQ), 3.39 (s, 3H, CH_3O), 3.41 (s, 3H, CH_3O), 3.50 (q, ^3J = 5.2 Hz, 2H, CH_2NQ), 3.63 (t, ^3J = 5.2 Hz, 2H, CH_2O), 3.72 (t , ^3J = 5.3 Hz, 2H, CH_2O), 4.38 (broad s, 1H, NH), 5.83 (broad s, 1H, NH), 6.41 (d ,^3J = 5.5 Hz, 1H, H3(Q)), 6.76 (d, ^4J = 2.3 Hz, 1H, H5(Q)), 7.02 (dd, ^3J = 9.0 Hz, ^4J = 2.3 Hz, 1H, H7(Q)), 7.80 (d, ^3J = 9.0 Hz, 1H, H8(Q)), 8.25 (d, ^3J = 5.5 Hz, 1H, H2(Q)). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.8 (1C, CH_2NQ), 43.5 (1C, CH_2NQ), 58.7 (1C, CH_3O), 58.8 (1C, CH_3O), 70.3 (1C, CH_2O), 70.7 (1C, CH_2O), 97.3 (1C, C3(Q)) or C7(Q)), 98.7 (1C, C7(Q) or C3(Q)), 119.9 (1C, C10(Q)), 120.8 (1C, CH(Q)), 128.8 (1C, CH(Q)), 140.2 (1C, C(Q)), 144.9 (1C, C2(Q)), 145.7 (1C, C(Q)), 149.4 (1C, C(Q)). HRMS (MALDI, dithranol, PEG-200+PEG-300) m/z calcd. for $C_{15}H_{22}N_3O_2$ $(M+H)^+$ 276.1712; found 276.1653. HRMS (ESI) m/z calcd. for $C_{15}H_{22}N_3O_2$ $(M+H)^+$ 276.17120; found 276.17087.

Studies of binding metal ions

UV-vis spectra were registered with Agilent Cary 60 device in CH_3CN (for HPLC, Merck) at room temperature. Fluorescence spectra were

obtained with Horiba Jobin Yvon Fluoromax-2 apparatus in CH_3CN at room temperature, all spectra were corrected. Luminescence quantum yields of compounds were determined relative to 9,10-dichloroantracene according to a standard procedure.[62] Aliquots of metal salts solutions were added manually with a Hamilton syringe. All metal salts used were perchlorates of general $M(ClO_4)n•xH_2O$ formula. The spectra of complexes and stability constants were calculated using nonlinear regression analysis by Specfit/32 program[46].

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Nitrogen- and oxygen-containing macrocycles with endocyclic quinoline moiety synthesized *via* Pd(0)-catalyzed amination were found to be perspective fluorescent chemosensors for Cu(II).