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Preparation of New Bis(8-aminoquinoline) Ligands and Comparison with Bis(8-hydroxyquinoline) Ligands on Their Ability to Chelate Cu^{II} and Zn^{II}

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New bis(8-aminoquinoline) ligands linked on the C2 carbon atom of both quinolines have been prepared. When the linker includes a one-atom amino group, the corresponding compound is an excellent chelator of Cu^{II} ions and forms a mononuclear species with high metal ion selectivity relative to Zn^{II} chelation. This selectivity for Cu^{II} ions was not observed for a bis(8-hydroxyquinoline) analogue. The chelating properties of these ligands are compared to those of the bis(8-aminoquinoline) ligands with different linkers between their N8 nitrogen atoms. The N8-linked bis(8-aminoquinoline) ligands have a higher affinity for Cu^{II} when the linker includes a three-atom unit or when the linker is linked directly through the N8 atom. Other ligands, including that with a dimethylamino linker on C2, are less efficient and seem to chelate Cu^{II} and Zn^{II} with an affinity that is similar to that for dipicolylamine.

Introduction

8-Hydroxyquinoline is an efficient bidentate ligand (L) of metal ions (M) such as Ag^{I}, Cd^{II}, Co^{II}, Cu^{II}, Fe^{III}, Ga^{III}, Lu^{III}, Mn^{II}, Ni^{II}, Pb^{II}, or Zn^{II}, with equilibrium constants K_{LM}, which change with the nature of metal ions, but with values that are always above 10^7 M^{-1} for the ML species.[1–3] This ligand can form stable metal complexes with different ligand-to-metal ratios (L/M = 1, 2, or 3 depending on the metal center). The ligand–metal association constants are also very high for the L_2M and L_3M complexes (log K_{L_2M} or log $K_{L_3M} > 7$ for L_2M and L_3M, respectively). We have recently prepared a new series of bis(8-hydroxyquinoline) ligands with a short aliphatic linker bridging the C2 carbon atom of each entity (α position to the aromatic nitrogen atom) that favor the formation of metal complexes that include two 8-hydroxyquinoline ligands around the metal ion.[4] A noticeable increase in the equilibrium constants was observed for Cu^{II} and Zn^{II}. The constants were 10^4 to 10^6 times higher than for the monomeric 8-hydroxyquinoline ligand. These enhanced chelating properties facilitate the efficient removal of Cu^{II} or Zn^{II} ions of toxic amyloid aggregates under physiological conditions and at low concentrations. Under these diluted conditions, the second affinity constant of monomeric 8-hydroxyquinoline for these metal ions (approximately 10^{11} and 10^7 M^{-1} for Cu^{II} and Zn^{II}, respectively) are indeed too low to form L_2M complexes.

Following our strategy on tuning the metal ion concentrations in amyloid aggregates, we have decided to design new bis(8-aminoquinoline) ligands for selective chelation of Cu^{II} ions over Zn^{II} ions. Indeed, 8-aminoquinoline is, like 8-hydroxyquinoline, able to chelate metal ions, although the corresponding metal complexes are less stable. However an advantage of 8-aminoquinoline arises as a result of its metal selectivity for Cu^{II} ions. The affinity constants for different metals ions are ranked as follows: Cu^{II} (log $K_{LCu^{II}} \approx 6$; log $K_{L_2Cu^{II}} \approx 5$) > Ni^{II} (log $K_{LNi^{II}} \approx 5$; log $K_{L_2Ni^{II}} \approx 3.5$) >> Fe^{III} (log $K_{LFe^{III}} \approx 3$) > Zn^{II}, Co^{II}, Cd^{II} (log $K_{LM} \approx 2.5$) > Ca^{II}, Mg^{II}, Sr^{II} (log $K_{LM} \approx 1.5$).[2,3] In fact, 8-aminoquinoline should be considered as a selective chelator for Cu^{II} ions through the LM and L_2M complexes that can be formed.

Covalently linking two 8-aminoquinolines should increase the affinity for Cu^{II} and favor complexes with two quinoline entities around the metal center under diluted conditions. To favor this dimeric ligand concept, the linker has to be short and in the vicinity of the nitrogen atoms. Two positions can be involved: the C2 position and the N8 amino nitrogen atom (Figure 1). Only a few examples of bis(8-aminoquinoline)s have been described previously and they all have a linker between the amino residues. An example is the tridentate ligand **1** (Figure 2), which is an efficient chelator of Ni^{II},[5] Tl^{I},[5] Pd^{II},[5] Pt^{II},[5,6] and Cu^{II}.[7,8] Interestingly, the formation of a mononuclear Cu^{II} complex of **1** has been evidenced by X-ray diffraction. Ligand **2** is an-

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other example and has been shown to form metal complexes with Ni^{II},[9] Cu^{II},[9] Co,[10] and Fe^{II}.[11] Importantly, the *N*′,*N*′-dimethylated form of **2** and other analogues of **2** including malonamide linkers at the N8 position are also efficient metal chelators.[11,12]

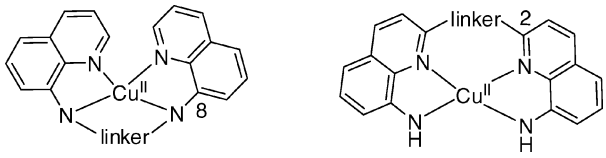


Figure 1. Expected structures for the Cu^{II} complexes with bis(8-aminoquinoline) chelators prepared in the present study.

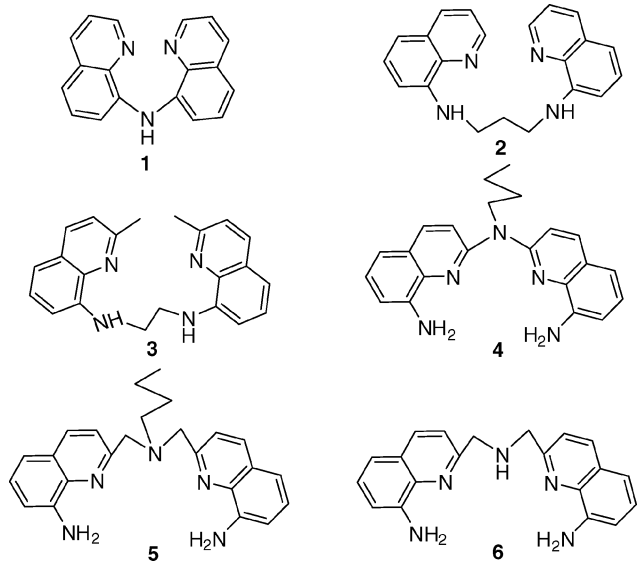


Figure 2. Structures of the bis(8-aminoquinoline) studied.

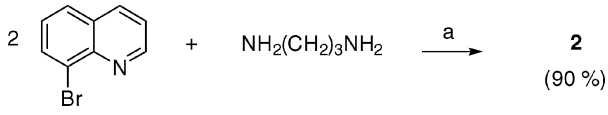
We have synthesized new bis(8-aminoquinoline) ligands in which the quinoline entities are bridged with different linkers attached at their C2 positions (Figure 2). Their capacity to selectively chelate Cu^{II} ions under physiological conditions was compared to that of other ligands bridged at N8, to that of the 8-aminoquinoline monomer, and also to that of dimeric analogues of the 8-hydroxyquinoline series. The selectivity for Cu^{II} ions was compared to that for Zn^{II} ions.

Results and Discussion

Ligands Design and Synthesis

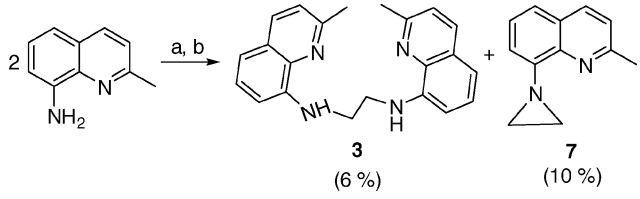
All the bis(8-aminoquinoline) ligands studied are shown in Figure 2. Compound **1** can form a tridentate ligand in which the bis(8-aminoquinoline) can be used as a backbone. It was synthesized by the method of Peters et al.[5] All other ligands prepared have four chelating nitrogen atoms on the quinoline entities. They have been designed in order to be symmetric and thus to simplify the study.

Ligand **2** contains a trimethylene linker between the two 8-amino groups – this length appears to be the best, by molecular modelling studies, for the chelation of Cu^{II} by the four nitrogen atoms of the molecule. Ligand **2** was obtained by *N*-arylation between 1,3-diaminopropane and 8-bromoquinoline (Scheme 1). Interestingly, this method allows a significant increase in the synthesis yield relative to previously proposed preparations of **2**.[9,12a]



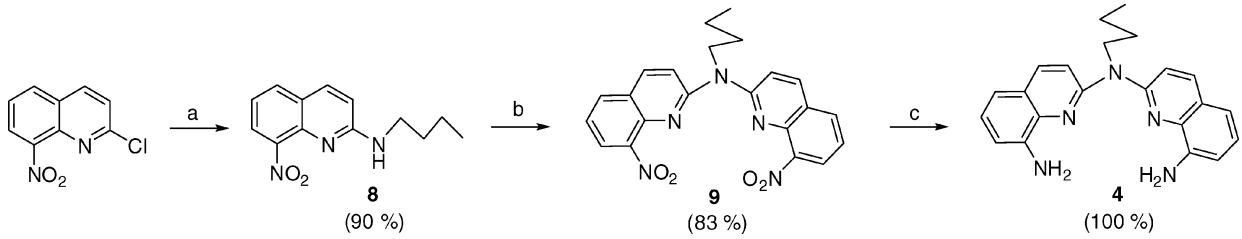
Scheme 1. Synthesis of compound **2**. (a) $Pd_2(dba)_3$, *rac*-binap, NaO*t*Bu, toluene, reflux.

Despite several attempts, we were unable to prepare bis(8-aminoquinoline) derivatives with a short alkyl bridge on C2, even with methods previously used to prepare bis(8-hydroxyquinoline) ligands. In these attempts, 8-amino-, 8-nitro-, or 8-*N*-ethylcarbamate derivatives were used by the method of Yamamoto et al. (for a methylene linker)[13] or by homocoupling of 2-methylquinoline derivatives (for an ethylene linker).[4] Ligand **3** was obtained under these conditions and results from nucleophilic substitution of 1,2-dibromoethane by 8-aminoquinaldine (Scheme 2). Compound **3** was included in the analysis to study the influence of an ethylene linker on the N8 position for metal chelation. The efficiency of this synthesis strategy was, however, very poor relative to that of other methods described to obtain the ethylene linker between the 8-amino residues.[11,14] In addition, the intermolecular reaction forming **3** appears to be in competition with an intramolecular disubstitution reaction to form the aziridine derivative **7**.



Scheme 2. Synthesis of compound **3**. (a) LDA, THF, –90 °C; (b) $Br(CH_2)_2Br$, THF, –90° to room temperature.

Successful couplings on C2 were obtained for linkers that include a nitrogen atom. Ligand **4** results from double *N*-arylation of aminobutane by 2-chloro-8-nitroquinoline followed by reduction of the nitro functions (Scheme 3). Importantly, X-ray analysis of single crystals of the 2-chloro-8-nitroquinoline precursor allows the unambiguous confirmation of the position of the substituents (Figure 3). Ligand **5** is an analogue of **4**, with a longer linker. It was obtained by two successive reductive aminations of 8-(*tert*-butoxycarbonylamino)-2-quinolinecarboxaldehyde by aminobutanol, followed by acidic hydrolysis of the Boc protective groups (Scheme 4). When compared to ligand **4**, compound **5** shows a potential new site for chelation, namely



Scheme 3. Synthesis of compound **4**. (a) $BuNH_2$, reflux; (b) 2-chloro-8-nitroquinoline, $Pd_2(dba)_3$, *rac*-binap, NaO*t*Bu, toluene, reflux; (c) H_2, Pd/C, AcOEt, room temperature.

the amino function at the junction bridge that is separated from N1 of the quinoline by a two-carbon residue. Ligand **6** was prepared to provide an analogue of compound **5** with a secondary amine in this position. It was obtained in two steps by reductive amination between ammonia and the same aldehyde-quinoline precursor used for the synthesis of **5**, followed by deprotection. Importantly, minor modifications of the synthesis protocol led to the preparation of trimer **14**.

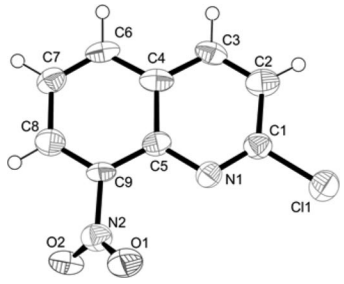
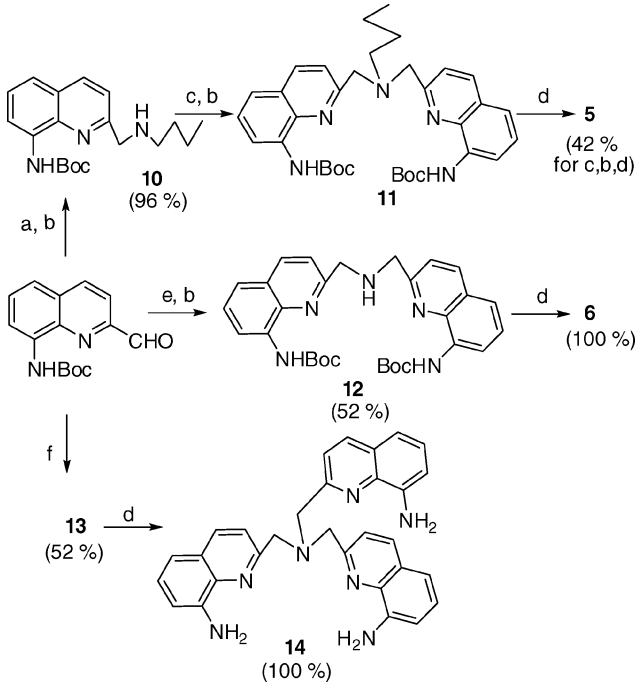
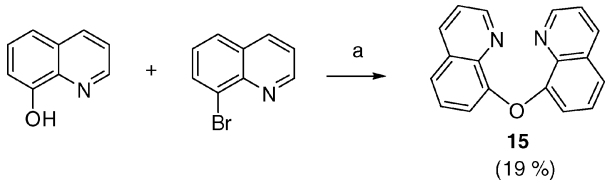


Figure 3. ORTEP drawing of 2-chloro-8-nitroquinoline.



Scheme 4. Synthesis of compounds **5**, **6** and **14**. (a) $BuNH_2$, $Cl(CH_2)_2Cl$, room temperature; (b) $(AcO)_3BHNa$, room temperature; (c) 8-(*tert*-butoxycarbonylamino)-2-quinolinecarboxaldehyde, $Cl(CH_2)_2Cl$, room temperature; (d) TFA, CH_2Cl_2, room temperature; (e) NH_3, $Cl(CH_2)_2Cl$, room temperature; (f) NH_3, $(AcO)_3BHNa$, $Cl(CH_2)_2Cl$, room temperature.

Compound **15** is an analogue of ligand **1** and is useful to study the influence of the heteroatom on the 8-position for metal ion chelation. Compound **15** was obtained by nucleophilic substitution of 8-bromoquinoline by the phenolate form of 8-hydroxyquinoline, activated by copper salts (Scheme 5),[15] although Masao et al. previously proposed another method for the preparation of **15**.[16]



Scheme 5. Synthesis of compound **15**. (a) Cs_2CO_3, $CuCl_2$, DMF, reflux.

Copper(II) Chelation

The stoichiometry of the complexes made with these different ligands and Cu^{II} was determined by metal titration. Experiments were performed in a saline buffer at pH 7.4, under the same conditions used previously for the bis(8-hydroxyquinoline) ligands, for the purposes of comparison.[4]

For all the bis(8-aminoquinoline) with the exception of **3**, the UV/Vis spectra showed the evolution of the peaks for the free ligand as aliquots of $CuCl_2$ were added, until stabilization is observed after the addition of one equivalent of the copper ion. The observation of isosbestic points is in accordance with the formation of only one type of metal complex. These results correlate with the ability of the bis(8-aminoquinoline) ligands to form only one type of Cu^{II} complex in a 1:1 metal/ligand ratio. This M/L ratio is confirmed by mass spectrometry. Importantly, the trimeric ligand **14** gives similar results (see Experimental Section).

Isobestic points are also observed in the spectra of compound **3**, but stabilization is only reached after the addition of 1.7 equiv. $CuCl_2$. A complex with only one copper ion per ligand is observed by mass spectrometry. It can be proposed that M/L = 1:1 is the ratio of the Cu^{II} complex of **3** but the affinity constant of **3** for Cu^{II} is weak. Therefore, at a ligand concentration of 15 μM, which was used for the

titration experiments, for 1 equiv. $CuCl_2$ added one part of the ligand does not chelate Cu^{II} ion, and the buffer or the solvent are in competition with **3** to chelate the copper ion. This fact probably reflects that the ethylene linker between both amino functions is too short for good coordination of Cu^{II}, in accordance to our observation from molecular modelling studies. It appears that the linker has to be propylene for easy complexation (as for **2**, for which an efficient Cu^{II} chelation is observed).

The affinity of poly(8-aminoquinoline) ligands (with the exception of **3**) for Cu^{II} was estimated, under the same buffered saline conditions (pH 7.4), through competitive chelation experiments with different chelators with known affinity constants for Cu^{II}. Their apparent affinity values (K_{app}) at pH 7.4 were calculated to facilitate comparison.[17] Experiments involved one equivalent (15 μM) of studied ligand, competitor, and $CuCl_2$, except in the case of ethylenediamine (eda), which shows similar affinity constants for (eda)Cu and $(eda)_2Cu$. In this last case, one and two equivalents of eda per ligand studied were tested. The percentage of the bis(8-aminoquinoline)Cu complex formed was determined from the UV/Vis spectra of the competitive chelation mixtures. A value <50% reflects an affinity for Cu^{II} lower than that of the competitor, 50% is observed if both ligands have same affinity for Cu^{II}, and values >50% indicate that the poly(8-aminoquinoline) ligand has a greater affinity for Cu^{II} than the competitor; Table 1 summarizes the results obtained. The relative order of the affinity for Cu^{II} at pH 7.4 of the different ligands is as follows: **3** < **6** ≈ **5** ≈ eda ($\log K_{app(LCu)}$ = 7.8) < **14** < hida ($\log K_{app(LCu)}$ = 10.5) < **4** ≈ dien ($\log K_{app(LCu)}$ = 11.8) < edda ($\log K_{app(LCu)}$ = 13.9) < **2** < edta ($\log K_{app(LCu)}$ = 15.9) ≤ **1**.

The affinity of ligand **3** for Cu^{II} was estimated to be lower than the other ligand affinities from previous titration experiments. More precise values for the affinity constants were determined for **1** and **2** in the case of competition with edta by a method previously used to analyze bis(8-hydroxyquinoline) under the same conditions.[4]

Table 2 summarizes the results obtained for the affinity constants of the poly(8-aminoquinoline) ligands for Cu^{II}. A comparison with 8-aminoquinoline monomer shows that the linkage of two monomers leads to a great increase in the affinity for Cu^{II}. Better affinities are obtained for a linkage between the N8 nitrogen atom, as in the tridentate ligand **1**, which is the most efficient, but a propyl linker, as in **2**, also enables good chelation of Cu^{II}. For a linker through

Table 1. Percentage of the poly(8-aminoquinoline)Cu^{II} complex observed by UV/Vis during competition with different chelators.[a]

	eda		nta	hida	dien	edda	edta
$\log K_1$ ($\log K_{1app}$)	10.5 (7.8)		12.7 (10.45)	11.8 (10.5)	15.9 (11.8)	16.2 (13.9)	18.8 (15.9)
$\log K_2$	9.1		4.7	4.0	5.0		
	eda/L = 1	eda/L = 2					
% **1**-Cu^{II}	–	–	–	–	–	–	55
% **2**-Cu^{II}	–	–	–	–	–	65	25
% **4**-Cu^{II}	–	–	–	70	50	30	–
% **5**-Cu^{II}	≈ 70	≈50	≈ 0	–	–	0	0
% **6**-Cu^{II}	>50	<50	≈ 0	–	–	0	0
% **14**-Cu^{II}	≈ 90	≈ 90	≈ 25	–	–	0	0

[a] Experiments were performed at pH 7.4 with 15 μM of $CuCl_2$, 15 μM of the ligand studied, and 15 μM of the competitor. 30 μM of eda was also tested (eda/L = 2). K_1 and K_2 are the affinity constants for the LM and L_2M species, respectively.[2] K_{1app} is the value of K_1 at pH 7.4.[17]

Table 2. Complexes observed (by UV/vis and/or mass spectrometry) and affinity constants of the poly(8-aminoquinoline) ligands for Cu^{II} and Zn^{II}.

Ligand	Observed complex (L/Cu^{II} ratio)	$\log K_{app}(Cu^{II})$	Observed complex (L/Zn^{II} ratio)	$\log K_{app}(Zn^{II})$ (equiv. $ZnCl_2$ for stable UV spectra)
1	LCu^{II} (1:1)	16.0 ± 1[a]	LZn^{II} (1:1) {MS}	≈ 6[b] (100)
2	LCu^{II} (1:1)	14.7 ± 1[a]	unmetallated {MS}	–(200)
3	LCu^{II} {MS}	–[c]	unmetallated {MS}	–(1000)
4	LCu^{II} (1:1)	≈12	unmetallated {MS}	–(1000)
5	LCu^{II} (1:1)	≈7.8	LZn^{II} (1:1) {MS}	≈ 6.3[b] (3)
6	LCu^{II} (1:1)	<7.8	LZn^{II} (1:1) {MS}	< 6.3[b] (15)
14	LCu^{II} (1:1)	7.8 < $\log K_{app}$ < 10.5	LZn^{II} (1:1)	> 6.3[b] (1)
8-NH_2Quinoline[d]	LCu^{II}	6.1 ($\log K_{app}$ 6.1)	LZn^{II}	2.4 ($\log K_{app}$ 2.4)
	L_2Cu^{II}	4.7		
8-OHQuinoline[d]	LCu^{II}	12.0 ($\log K_{app}$ 9.8)	LZn^{II}	8.5 ($\log K_{app}$ 6.3)
	L_2Cu^{II}	11.0	L_2Zn^{II}	7.3
15	unmetallated	–	unmetallated	–
16	1:1	16.0 ± 1[a]	1:1	12.8 ± 1[a]
Di-2-picolylamine[d]	LCu^{II}	9.3 ($\log K_{app}$ 9.1)	LZn^{II}	7.6 ($\log K_{app}$ 7.4)
	L_2Cu^{II}	4.4	L_2Zn^{II}	4.4

[a] Determined as in ref.[4] [b] Estimated by comparison with the values obtained during $ZnCl_2$ titration with 1,10-phenanthroline and 2,2′-bipyridine. [c] Stabilization at 1.7 equiv. $CuCl_2$. [d] From ref.[3]

the C2 carbon, high Cu^{II} chelation is only observed for ligand **4**, which has the shortest linker with a one-atom unit. Importantly, this one-atom link on C2 corresponds to the linker length that gives the best results for the bis(8-hydroxyquinoline) series.[4] Ligand **16** can be considered as the analogue of **4** in the 8-hydroxyquinoline series (Figure 4). Its affinity for Cu^{II} was determined under the same conditions and is higher than that of **4** (log $K_{LCu^{II}}$ 16 and 12 for **16** and **4**, respectively, at pH 7.4). This result reflects the better affinity of the 8-hydroxyquinoline entity for Cu^{II} relative to 8-aminoquinoline. In fact, relative to the monomers, the linkage by an amino group at C2 leads to an increase in the affinity of approximately 10^6 times for the 8-amino and 8-hydroxy series, as observed by comparison of the affinity values of **4** with 8-aminoquinoline and of **16** with 8-hydroxyquinoline, respectively, at pH 7.4.

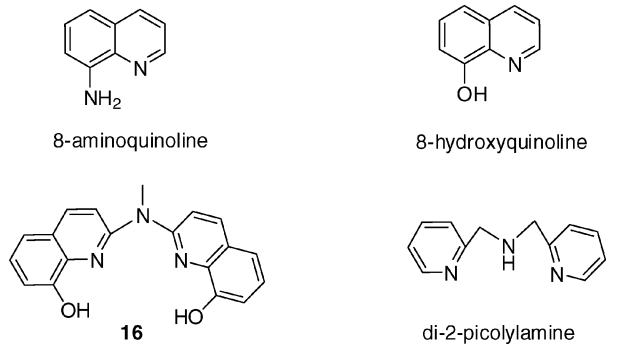


Figure 4. Structures of the principal ligands used to discuss the affinity of the bis(8-aminoquinoline) ligands for Cu^{II} and Zn^{II}.

The Cu^{II} titration by ligand **15** was also investigated as **15** can be considered as the analogue of the tridentate ligand **1** in the 8-oxygenated series. No metallation was observed, which reflects the absolute necessity of the amino function at position 8 of **1** to explain its high capacity for Cu^{II} chelation.

Zinc(II) Chelation

The Zn^{II} titration was performed under the same conditions. Isobestic points reflecting the formation of a single species are observed in UV/Vis spectra, but more than 1 equiv. $ZnCl_2$ per bis(8-aminoquinoline) was necessary to obtain stabilization of the titration. This reflects the weak affinity of these ligands for Zn^{II} (Table 2). The ligands **3** and **4** chelate Zn^{II} more weakly, and to a less extent, **2**. Interestingly, these three ligands appear to be unmetallated by mass spectrometry. In the cases of **2** and **4**, where a good affinity for Cu^{II} was previously observed, it can be proposed that both ligands are highly selective of Cu^{II} relative to Zn^{II}.

Other poly(8-aminoquinoline) ligands show the LZn species by mass spectrometry performed in the presence of 1 equiv. $ZnCl_2$ per ligand. We attempted to evaluate their affinity for this metal ion. In the titration of $ZnCl_2$ with 2,2′-bipyridine (log $K_{app(LZn^{II})} \approx 5$),[3,17] stabilization is achieved with 20 and 250 equiv. $ZnCl_2$ in CH_3OH/buffer (1:1) and DMSO/buffer (8:2), respectively. Stabilization is achieved with 3 and 50 equiv. $ZnCl_2$ in CH_3OH/buffer (1:1) and DMSO/buffer (8:2), respectively, for a similar experiment with 1,10-phenanthroline (log $K_{app(LZn^{II})} = 6.3$).[3,17] In the DMSO/buffer (8:2) mixture, stabilization is observed with 100 equiv. in titration with **1**. Therefore the logarithm of its affinity constant for Zn^{II} is between 5 and 6.3, which is clearly less than that for Cu^{II}. The same argument allows us to propose values of log $K_{app(\mathbf{14}\text{–}Zn^{II})} > 6.3$, log $K_{app(\mathbf{5}\text{–}Zn^{II})} \approx 6.3$, and log $K_{app(\mathbf{6}\text{–}Zn^{II})} \approx 5$ for **14**, **5**, and **6** when analyzed in the CH_3OH/buffer (1:1) mixture.

Bis(8-aminoquinoline) ligands **5** and **6** appear to be poorly selective for Cu^{II} relative to Zn^{II} (Table 2). Their affinities for Cu^{II} seem also moderate when compared to **1**, **3**, and, more appropriately, to **4**, which has a linker at the same position, i.e. between C2 of both 8-aminoquinolines. In fact, the observed affinity is closer to that observed with di-2-picolylamine (Figure 4) in which the two pyridine groups are bridged with the same linker that is used in ligand **6**.[2,3] The amino group of the linker participates in metal chelation in Cu^{II} or Zn^{II} complexes of di-2-picolylamine.[18,19] Ligands **5** and **6** could behave in a similar manner; the aniline parts of the ligands are not involved in the chelation. The fact that the linker of **6** includes a secondary amine, in contrast to a tertiary amine in **5**, could explain the small difference observed in its affinity for Cu^{II} and Zn^{II} when **6** was compared to **5**; a secondary amine is less favorable for chelation.

The incorporation of a third quinoline entity, as in **14**, has no favorable effect on the selectivity of the studied metal ions; however, its affinity for Cu^{II} is higher than that of **5** and **6**, but not as high as those observed for **1**, **2**, or **4**. Interestingly, incorporation of a third quinoline entity also results in an increase in the affinity for Zn^{II}, since, under the conditions used here, 1 equiv. $ZnCl_2$ is sufficient to obtain 100% of the metal complex with the trimer **14**. The same behavior was not observed with the bis(aminoquinoline) ligands.

Importantly, the bis(8-hydroxyquinoline) **16** shows a high affinity for Zn^{II}. In fact, both log $K_{LCu^{II}}$ and log $K_{LZn^{II}}$ for compound **16** are high and of the same factor as those previously observed for other bis(8-hydroxyquinoline) ligands.[4] This ability to efficiently chelate Zn^{II} is a major difference when this ligand is compared to the ligands **1**, **2**, and **4** of the bis(8-aminoquinolinequinoline) series. Ligands **1**, **2** and **4**, as for the 8-aminoquinoline parent monomers, chelate Cu^{II} efficiently and not Zn^{II}, whereas **16** chelates both metal ions, as for 8-hydroxyquinoline (the parent monomer of **16**). Therefore, the metal selectivity observed in the monomers is retained in these bis(quinoline) ligands.

Crystal Structure of Copper(II) Complex of Ligand 4

As ligand **4** is new and shows interesting selective chelation of Cu^{II} relative to Zn^{II}, we were determined to investigate the structure of the Cu^{II} complexes of **4**. Ligand **4** was metallated with 1 equiv. $CuCl_2$ in CH_3OH, and single crys-

tals of monomeric complex **17** were obtained by slow evaporation of the solvent. The crystals were analyzed by X-ray diffraction. Figure 5 summarizes the results obtained. The complex is five-coordinate with a distorted square-pyramidal configuration and a coordination sphere in which all the pyridine and primary amino nitrogen atoms of the ligand are coordinated. These atoms occupy the equatorial plane, and the Cu^{II} complex includes a chlorido ligand as a fifth axial ligand. Interestingly, a similar geometry was previously observed for Cu^{II} complexes of bis(8-hydroxyquinoline), which involved, as for **4**, a one-atom linker between both C2 positions of the quinoline entities.[4]

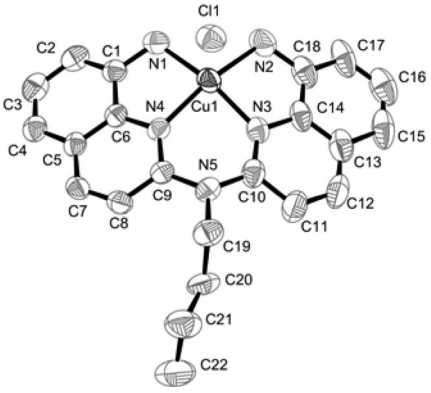


Figure 5. ORTEP drawing of complex **17**. Selected bonds lengths [Å] and angles [°]: N1–C1 1.437(7), N2–C18 1.441(8), Cu–N1 2.000(4), Cu–N2 2.026(4), Cu–N3 1.958(5), Cu–N4 1.970(4), Cu–Cl 2.5096(15), N1–Cu–N2 96.82(19), N1–Cu–N3 162.14(19), N1–Cu–N4 84.53(16), N1–Cu–Cl 97.85(13), N2–Cu–N3 84.99(19), N2–Cu–N4 162.63(19), N2–Cu–Cl 96.47(16), N3–Cu–N4 88.56(16), N3–Cu–Cl 99.60(13), N4–Cu–Cl 100.51(12), C9–N5–C10 125.9(4), C9–N5–C19 117.1(4), C10–N5–C19 116.9(4).

Conclusions

New bis(8-aminoquinoline) ligands linked at the C2 position of both quinoline moieties have been prepared. When the linker includes a one-atom amino group (compound **4**), the ligands are excellent chelators of Cu^{II} and form mononuclear species with a high selectivity relative to Zn^{II}. These chelating properties were compared to those of the bis(8-aminoquinoline) ligands that contain a linker between their N8 nitrogen atoms. These latter ligands have high affinities for Cu^{II} when the linker includes three-atom units (compound **2**) or when the linker is linked directly through the N8 atom (compound **1**). Other ligands, including that with a dimethylamino linker on C2, were less efficient and seemed to chelate Cu^{II} and Zn^{II} with an affinity that is similar to that for dipicolylamine. The precise determination of the affinity constants of the promising ligand **4** for Cu^{II}, the analysis of the redox properties of the copper complexes, and the study of ligand selectivity against other metal ions need now to be investigated.

Experimental Section

General: 8-(*tert*-Butoxycarbonylamino)-2-quinolinecarboxaldehyde and 8-aminoquinaldine were synthesized as described previously.[20] 2,2′-Bipyridine, diethylenetriamine (dien), ethylenediamine-*N*,*N*′-diacetic acid (edda), ethylenediamine (eda), ethylenediaminetetraacetic acid (edta), *N*-(2-*h*ydroethyl)iminodiacetic acid (hida), nitrilotriacetic acid (nta) and 1,10-phenanthroline were from Aldrich. *N*-Methyl-2,2′-iminobis(8-quinolinol) (**16**) was from Fluka. THF was distilled from benzophenone and sodium. Other commercially available reagents and solvents were purchased from standard chemical suppliers and used without further purification. Chromatography was performed on silica gel. NMR spectra were recorded on Bruker spectrometers at 250 or 300 MHz. Mass spectra were performed in positive mode. UV/Vis spectra were recorded on a Perkin–Elmer Lambda 35 spectrophotometer. The given UV/Vis characteristics of the metal complexes corresponded to values observed at the saturation of the metal titration, i.e. with the number of equivalents of metal ion allowing the formation of 100% of metal complex. 1 equiv. of $CuCl_2$ per ligand was used except for **2** (1.7 equiv. $CuCl_2$). Table 2 gives the number of equivalents used in the case of $ZnCl_2$.

X-ray Analysis: Data collection were collected at 180 K on an Oxford Diffraction Xcalibur diffractometer (for 2-chloro-8-nitroquinoline) or a Bruker Kappa APEX II diffractometer (for **17**), by using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) and equipped with a Cooler Device (an Oxford Instrument Cooler Device for the Xcalibur and an Oxford Cryosystem Cryostream for the Kappa APEX). The structures have been solved by direct methods by using SIR92[21] and refined by means of least-squares procedures on F^2 with the aid of the program SHELXL97,[22] which is included in the software package WinGX version 1.63.[23] The atomic scattering factors were taken from the International Tables for X-ray Crystallography.[24] The hydrogen atoms were geometrically placed and refined by using a riding model. All non-hydrogen atoms were anisotropically refined, and in the last cycles of refinement, a weighting scheme was used, where the weighting was calculated from the following formula: $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$. Drawings of molecules were carried out with the program ORTEP32 with 50% probability displacement ellipsoids for the non-hydrogen atoms.[25] The crystal data for the determined structures are given in Table 3. In the case of **17**, it was not possible to resolve diffuse electron-density residuals (enclosed solvent molecules). Treatment with the SQUEEZE facility from PLATON led to a smooth refinement.[26] Since a few low order reflections are missing from the data set, some data will be underestimated. Thus, the values given for $D_{calcd.}$, $F(000)$, and the molecular weight are only valid for the ordered part of the structure. CCDC-691635 (**17**) and -691636 (2-chloro-8-nitroquinoline) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Bis(8-quinolinyl)amine (**1**): This compound was synthesized as described previously.[5] UV/Vis [DMSO/tris·HCl 20 mM pH 7.4, NaCl 150 mM (8:2, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 268 (43700), 341 (5100), 399 nm (16900). **1**–Cu^{II}Cl: UV/Vis [DMSO/tris·HCl 20 mM pH = 7.4, NaCl 150 mM (8:2, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 287 (40700), 368 (3300), 486 nm (14100). MS (DCI {Desorption Chemical Ionization}, NH_3): *m*/*z* = 369 $[LCuCl]^+$. **1**–Zn^{II}Cl: UV/Vis (CH_3OH): λ_{max} (ε, $M^{-1}cm^{-1}$) = 288 (31800), 299 (27900), 369 (3400), 490 nm (13200). MS (DCI, NH_3): *m*/*z* = 370 $[LZnCl]^+$.

***N*,*N*′-Di-8-quinolinyl-1,3-propanediamine (2):** A suspension of tris(dibenzylideneacetone)dipalladium(0) (55 mg, 0.06 mmol) and *rac*-2,2′-bis(diphenylphosphanyl) 1,1′,binaphthalene (75 mg, 0.12 mmol) in toluene (6 mL) was stirred under argon for 5 min at room temperature. 8-Bromoquinoline (500 mg, 314 μL,

Table 3. Details of crystallographic measurements and refinements.

	2-Chloro-8-nitroquinoline	**17**
Formula	$C_9H_5ClN_2O_2$	$C_{22}H_{22}ClN_5Cu$
M_w	208.60	455.44
T [K]	180	180
Crystal system	orthorhombic	monoclinic
Space group	*Pca*21	*C*12/*c*1
a [Å]	18.090(4)	14.4031(5)
b [Å]	3.7781(7)	23.1045(4)
c [Å]	12.581(2)	14.1703(7)
β [°]	90	105.244(2)
V [Å^3]	859.9(3)	4549.4(3)
Z	4	8
$\rho_{calcd.}$ [g cm^{-3}]	1.611	1.330
μ [mm^{-1}]	0.413	1.094
F(000)	424	1880
Crystal size [mm]	0.25 × 0.125 × 0.025	0.22 × 0.15 × 0.08
θ range [°]	2.77–25.66	1.71–24.55
Collected/independent reflections	7517/1636	30210/3761
Reflections with [$F^2>4\sigma(F^2)$]	1636	3761
R_{int}	0.2353	0.0534
Parameters	128	263
GOF on F^2	0.855	0.993
$R_1[F^2>4\sigma(F^2)]/wR2$	0.0629/0.1442	0.0605/0.1830
$\Delta\rho_{max}/\Delta\rho_{min}$ [e Å^3]	0.275/–0.311	0.552/–0.751

2.40 mmol), 1,3-diaminopropane (89 mg, 100 μL, 1.20 mmol), toluene (6 mL), and sodium *tertio*-butanolate (323 mg, 3.36 mmol) were then added, which resulted in a red solution. The solution was stirred at 100 °C for 3 d. After cooling down, the solution was filtered through Celite and extracted with CH_2Cl_2, and the solvents were evaporated. The crude product was purified by chromatography (CH_2Cl_2, 0–5% CH_3OH). The product was dissolved in CH_2Cl_2 and precipitated at 4 °C by addition of HCl (4 equiv., from 1 M solution in ethyl ether). The precipitate was dissolved in H_2O, and the solution was alkalinized to pH 10 with aqueous ammonia. The product was extracted with CH_2Cl_2, and the solvent was evaporated to give **2** as a brown powder (355 mg, 90%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.70 (dd, J = 1.5, 4.0 Hz, 2 H), 8.06 (dd, J = 1.5, 8.0 Hz, 2 H), 7.37 (m, 4 H), 7.05 (dd, J = 0.5, 8.0 Hz, 2 H), 6.71 (dd, J = 0.5, 8.0 Hz, 2 H), 6.24 (br. t, J = 5.0 Hz, 2 H), 3.55 (m, 4 H), 2.27 (quint, J = 7.0 Hz, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.8, 144.8, 138.3, 136.0, 128.7, 127.8, 121.4, 113.8, 104.7, 41.3, 29.0 ppm. UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, M^{-1}cm^{-1}) = 255 (44400), 360 nm (6200). MS (DCI, NH_3): m/z = 329 [M + H]$^+$. HRMS (ESI): calcd. for $C_{21}H_{21}N_4$ 329.1766; found 329.1739. $C_{21}H_{20}N_4$·0.05CH_2Cl_2 (332.66): calcd. C 76.01, H 6.08, N 16.84; found C 75.93, H 6.06, N 16.57. **2**–Cu^{II}: UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, M^{-1}cm^{-1}) = 230 (55700), 303 (11800), 315 (10400), 360 nm (1100, sh.). MS (ESI): m/z = 390 [LCu – H]$^+$. **2**–Zn^{II}: UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4; NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, M^{-1}cm^{-1}) = 232 (55400), 300 (9600), 314 (9200), 364 nm (700, sh.).

***N,N′*-Bis(2-methyl-8-quinolinyl)-1,2-ethanediamine (3):** To a solution of 8-aminoquinaldine (0.50 g, 3.16 mmol) in dry THF (5 mL), under argon at –90 °C, was added, over a period of 30 min, a solution of lithium diisopropylamine·THF (4.2 mL, 6.33 mmol, 1.5 M in cyclohexane) and dry THF (7.5 mL). After stirring for 30 min at –90 °C, 1,2-dibromoethane (0.55 mL, 6.33 mmol) was added dropwise, the temperature was then increased to room temperature, and the mixture was stirred for 15 h. Water (6 mL) was added, and, after stirring for 90 min, THF was evaporated. The aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (75 mL) and H_2O (75 mL). The solvent was evaporated, and the crude product was purified by chromatography (CH_2Cl_2, 0–100% ethyl acetate). The product was dissolved in CH_2Cl_2 (1 mL) and precipitated with hexane (6 mL) to give, after filtration, washing with hexane, and drying, **3** as a white powder (34 mg, 6%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.5 Hz, 2 H), 7.33 (m, 2 H), 7.24 (d, J = 8.5 Hz, 2 H), 7.03 (d, J = 8.0 Hz, 2 H), 6.78 (d, J = 7.5 Hz, 2 H), 6.45 (br. s, 2 H), 3.75 (m, 4 H), 2.68 (s, 6 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.7, 144.1, 137.5, 136.2, 126.8, 126.7, 122.2, 114.0, 105.0, 42.8, 25.0 ppm. UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, M^{-1}cm^{-1}) = 254 (44200), 341 nm (6000). MS (DCI, NH_3): m/z = 343 [M + H]$^+$. $C_{22}H_{22}N_4$·0.3CH_2Cl_2 (367.62): calcd. C 72.80, H 6.19, N 15.23; found C 72.41, H 6.02, N 14.87. **3**–Cu^{II}: UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, M^{-1}cm^{-1}) = 235 (44400), 255 nm (23800, sh.). MS (ESI): m/z = 405 [LCu]$^+$. **3**–Zn^{II}: UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, M^{-1}cm^{-1}) = 236 (43900), 304 (8700), 316 nm (8000).

8-(1-Aziridinyl)-2-methylquinoline (9): This compound was obtained during the synthesis of **3** after a column chromatography on silica gel, as a brown powder (58 mg, 10%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.5 Hz, 1 H), 7.40–7.30 (m, 3 H), 7.12 (dd, J = 1.5, 7.0 Hz, 1 H), 2.79 (s, 3 H), 2.32 (s, 4 H) ppm. MS (DCI, NH_3): m/z = 185 [M + H]$^+$.

2-Chloro-8-nitroquinoline: Was synthesized as described previously.[27] More precise NMR spectroscopic data than previously published are given, and other unpublished characterizations are added. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.5 Hz, 1 H), 8.10 (dd, J = 1.5, 7.5 Hz, 1 H), 8.05 (dd, J = 1.5, 8.0 Hz, 1 H), 7.65 (m, 1 H), 7.55 (d, J = 8.5 Hz, 1 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 153.5, 147.1, 138.9, 138.8, 131.9, 127.6, 125.8, 125.0, 124.5 ppm. MS (DCI, NH_3): m/z = 209 [M + H]$^+$, 226 [M + NH_4]$^+$, 243 [M + N_2H_7]$^+$. $C_9H_5ClN_2O_2$ (208.60): calcd. C 51.82, H 2.42, N 13.43; found C 51.76, H 2.37, N 13.24. Recrystallization from $CDCl_3$ provided single crystals suitable for analysis by X-ray diffraction, which allowed the confirmation of the position of the chlorido ligand.

***N*-Butyl-8-nitro-2-quinolinamine (8):** A suspension of 2-chloro-8-nitroquinoline (200 mg, 0.96 mmol) in *n*-butylamine (9.5 mL) was heated to reflux for 15 h. The yellow solution obtained was concentrated under vacuum. The crude product was dissolved in CH_3OH and poured in diethyl ether (3 mL) and then centrifuged. The supernatant was concentrated to give **8** as a yellow oil (210 mg, 90%). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.83 (dd, J = 1.5, 7.5 Hz, 1 H), 7.77 (d, J = 9.0 Hz, 1 H), 7.69 (dd, J = 1.5, 8.0 Hz, 1 H), 7.14 (m, 1 H), 6.67 (d, J = 9.0 Hz, 1 H), 5.07 (br. s, 1 H), 3.47 (m, 2 H), 1.60 (m, 2 H), 1.39 (m, 2 H), 0.93 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 157.8, 145.6, 140.2, 136.7, 131.5, 124.7, 124.1, 119.7, 113.3, 41.3, 31.5, 20.2, 13.8 ppm. MS (DCI, NH_3): m/z = 246 $[M + H]^+$. $C_{13}H_{15}N_3O_2$ (245.28): calcd. C 63.66, H 6.16, N 17.13; found C 63.33, H 6.21, N 16.64.

***N*-Butyl-2,2′-iminobis(8-nitroquinoline)** (**9**): To a solution of **8** (229 mg, 0.94 mmol) in dry toluene (5 mL) under argon were added tris(dibenzylideneacetone)dipalladium(0) (17 mg, 19.0 μmol) and *rac*-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene (23 mg, 37 μmol). The red solution was stirred for 5 min, after which 2-chloro-8-nitroquinoline (292 mg, 1.40 mmol) and sodium *tert*-butoxide (105 mg, 1.09 mmol) were successively added. The temperature of the reaction medium was gradually raised to 100 °C with stirring. The mixture was allowed to react overnight at this temperature. A second portion of each reagent was then added: tris(dibenzylideneacetone)dipalladium(0) (8 mg), *rac*-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene (10 mg), and sodium *tert*-butoxide (26 mg). The mixture was heated at 100 °C with stirring until TLC analysis showed disappearance of the starting material. The reaction was quenched by addition of 33% ammonium hydroxide (8 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (CH_2Cl_2/hexane, 8:2) to give **9** as a yellow powder (322 mg, 83%). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.14 (d, J = 9.0 Hz, 2 H), 7.99 (dd, J = 1.5, 7.5 Hz, 2 H), 7.93 (dd, J = 1.5, 8.0 Hz, 2 H), 7.73 (d, J = 9.0 Hz, 2 H), 7.43 (m, 2 H), 4.45 (t, J = 7.5 Hz, 2 H), 1.83 (m, 2 H), 1.47 (m, 2 H), 0.98 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 156.2, 146.4, 138.7, 137.0, 131.5, 126.2, 124.2, 122.8, 117.3, 48.9, 30.4, 20.3, 13.9 ppm. UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 210 (91400), 226 (53500, sh.), 270 (42100), 294 (26700, sh.), 383 nm (28400). MS (DCI, NH_3): m/z = 418 $[M + H]^+$. $C_{22}H_{19}N_5O_4$ (417.42): calcd. C 63.30, H 4.59, N 16.78; found C 63.18, H 4.49, N 16.39.

***N*-Butyl-2,2′-iminobis(8-quinolinamine) (4):** To a solution of **9** (230 mg, 0.55 mmol) in ethyl acetate (35 mL) was added palladium (50 mg, 10%) on charcoal. The flask was then loaded with H_2 (1 bar) and stirred for 4 h at room temperature. The mixture was filtered through Celite, and the solvent was then evaporated. The crude product was dissolved in CH_2Cl_2 and precipitated with 4 volumes of hexane. The supernatant was collected by filtration to give, after evaporation of the solvent, **4** as a brown powder (197 mg; quantitative yield). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.90 (d, J = 9.0 Hz, 2 H), 7.32 (d, J = 9.0 Hz, 2 H), 7.20 (m, 2 H), 7.10 (dd, J = 1.0, 8.0 Hz, 2 H), 6.93 (dd, J = 1.0, 7.5 Hz, 2 H), 4.60 (s, 4 H), 4.48 (t, J = 7.5 Hz, 2 H), 1.88 (m, 2 H), 1.47 (m, 2 H), 0.97 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 154.1, 142.1, 137.2, 137.0, 125.3, 125.0, 116.3, 116.1, 111.3, 48.9, 30.6, 20.7, 14.1 ppm. UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 211 (53400, sh.), 302 (40300), 367 (20000), 382 nm (14600, sh.). MS (DCI, NH_3): m/z = 358 $[M + H]^+$. HRMS (ESI): calcd. for $C_{22}H_{24}N_5$ 358.2032; found 358.2023. **4**–Cu^{II}: UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 211 (65400), 235 (33800, sh.), 275 (37000), 302 (5900, sh.), 329 (17900), 352 (19000), 366 nm (20900). MS (ESI): m/z = 419 $[LCu - H]^+$. **4**–Zn^{II}: UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 213 (47000), 234 (24800), 274 (25600), 303 (10900, sh.), 330 (11600), 348 (12300), 363 nm (13100).

[2-(Butylamino)methyl]-*N*-Boc-8-quinolinamine (10): 1-Butylamine (80 μL, 0.80 mmol) was added to a solution of 8-(*tert*-butoxycarbonylamino)-2-quinolinecarboxaldehyde (100 mg, 0.36 mmol) in dichloroethane (5.0 mL) under argon, and the mixture was stirred for 1 h at room temperature. $(CH_3COO)_3BHNa$ (200 mg, 0.94 mmol) was then added, and the mixture was stirred for 40 h at room temperature. Aqueous saturated $NaHCO_3$ (20 mL) was added, and the product was extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were pooled and dried (Na_2SO_4), and the solvent was evaporated to give **10** as a yellow oil (117 mg, 96%). ^1H NMR (250 MHz, $CDCl_3$): δ = 9.00 (br. s, 1 H), 8.39 (br. d, J = 7.0 Hz, 1 H), 8.08 (d, J = 8.5 Hz, 1 H), 7.46 (dd, J = 8.5 and 7.0 Hz, 1 H), 7.41 (dd, J = 2.0, 8.5 Hz, 1 H), 7.39 (dd, J = 1.5, 8.5 Hz, 1 H), 4.10 (s, 1 H), 2.73 (t, J = 7.5 Hz, 2 H), 2.13 (br. s, 1 H), 1.59 (s, 9 H), 1.56 (m, 2 H), 1.40 (m, 2 H), 0.94 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 162.0, 157.2, 152.8, 136.8, 134.7, 127.0, 126.8, 120.8, 120.0, 114.7, 80.4, 54.6, 48.9, 31.7, 28.4, 20.4, 14.0 ppm. MS (DCI, NH_3): m/z = 330 $[M + H]^+$.

2,2′-[(Butylimino)dimethanediyl]bis(*N*-Boc-8-quinolinamine) (**11**): A solution of **10** (39 mg, 0.12 mmol) and 8-(*tert*-butoxycarbonylamino)-2-quinolinecarboxaldehyde (36 mg, 0.13 mmol) in 1,2-dichloroethane (2.5 mL) was stirred for 30 min at room temperature. $(CH_3COO)_3BHNa$ (35 mg, 0.16 mmol) was added. The mixture was stirred for 20 h at room temperature, after which the solvent was evaporated. CH_2Cl_2 (10 mL) and aqueous saturated $NaHCO_3$ (10 mL) were added, and the organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were pooled and dried (Na_2SO_4), and the solvent was evaporated to give **11** as a pale yellow powder, which was characterized by ^1H NMR spectroscopy before being introduced in the next step without further purification. ^1H NMR (250 MHz, $CDCl_3$): δ = 9.02 (br. s, 2 H), 8.38 (br. d, J = 7.5 Hz, 2 H), 8.09 (d, J = 8.5 Hz, 2 H), 7.72 (d, J = 8.5 Hz, 2 H), 7.46 (dd, J = 7.5, 8.0 Hz, 2 H), 7.38 (dd, J = 1.5, 8.0 Hz 2 H), 3.99 (s, 4 H), 2.62 (t, J = 7.0 Hz, 2 H), 1.62 (m, 2 H), 1.59 (s, 18 H), 1.34 (m, 2 H), 0.87 (t, J = 7.5 Hz, 3 H) ppm.

2,2′-[(Butylimino)dimethanediyl]bis(8-quinolinamine) (**5**): Compound **11** obtained in the previous step was dissolved in CH_2Cl_2 (0.5 mL) and trifluoroacetic acid (0.5 mL). The mixture was stirred for 45 min at room temperature, and the solvents were evaporated. The product was dissolved in CH_2Cl_2 (5 mL), washed with saturated aqueous $NaHCO_3$ (2 × 5 mL), and dried (Na_2SO_4), after which the solvent was evaporated. The crude product was purified by chromatography (hexane, 20–50% ethyl acetate) to give **5** as an orange oil (20 mg, 42% for two steps). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.5 Hz, 2 H), 7.65 (d, J = 8.5 Hz, 2 H), 7.28 (dd, J = 7.5, 8.5 Hz, 2 H), 7.12 (dd, J = 1.0, 8.5 Hz, 2 H), 6.90 (dd, J = 1.0, 7.5 Hz, 2 H), 4.98 (br. s, 4 H), 3.97 (s, 4 H), 2.60 (t, J = 7.0 Hz, 2 H), 1.60 (tt, J = 7.0, 7.5 Hz, 2 H), 1.32 (qt, J = 7.5, 8.0 Hz, 2 H), 0.85 (t, J = 8.0 Hz, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 143.7, 137.4, 136.2, 127.7, 126.8, 126.7, 121.3, 115.8, 110.0, 60.9, 54.3, 29.4, 20.5, 13.9 ppm. UV/Vis [CH_3OH /tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ nm (ε, $M^{-1}cm^{-1}$) = 253 (55400), 339 nm (6200). MS (DCI, NH_3): m/z = 386 $[M + H]^+$. HRMS (ESI): calcd. for $C_{24}H_{28}N_5$ 386.2345; found 386.2321. **5**–Cu^{II}: UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1,

v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 236 (53200), 253 nm (32000, sh.) MS (ESI): *m/z* = 447 [LCu – H]$^+$. **5**–Zn^{II}: UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 236 (59800), 306 (12600), 318 nm (12000). MS (ESI): *m/z* = 484 [LZnCl]$^+$.

2,2′-(Iminodimethanediyl)bis(*N*-Boc-8-quinolinamine) (12): To a solution of 8-(*tert*-butoxycarbonylamino)-2-quinolinecarboxaldehyde (300 mg, 1.10 mmol) in 1,2-dichloroethane (15 mL) was added NH_3 (1.75 mmol, 0.25 mL of a solution 7 M in CH_3OH), and the mixture was stirred for 30 min at room temperature. $(CH_3COO)_3$BHNa (432 mg, 2.04 mmol) was added, and the mixture was stirred for 15 h at room temperature. The solvent was then evaporated. The crude product was purified by chromatography (100% ethyl acetate) to give **12** as a pale yellow powder (150 mg, 52%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.98 (br. s, 2 H), 8.41 (br. d, *J* = 7.0 Hz, 2 H), 8.10 (d, *J* = 8.5 Hz, 2 H), 7.53 (d, *J* = 8.5 Hz, 2 H), 7.48 (dd, *J* = 7.5, 8.0 Hz, 2 H), 7.40 (dd, *J* = 1.5, 8.0 Hz, 2 H), 4.25 (s, 4 H), 2.21 (br. s, 1 H), 1.53 (s, 18 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.7, 152.9, 137.4, 136.8, 134.8, 127.1, 126.9, 120.9, 120.0, 114.7, 80.4, 54.9, 28.3 ppm. MS (DCI, NH_3): *m/z* = 530 [M + H]$^+$. $C_{30}H_{35}N_5O_4$·0.25$C_4H_8O_2$ (551.66): calcd. C 67.16, H 6.77, N 12.71; found C 67.59, H 7.10, N 12.23.

2,2′-(Iminodimethanediyl)bis(8-quinolinamine) (6): A solution of **12** (100 mg, 0.19 mmol) in CH_2Cl_2 (2.5 mL) and trifluoroacetic acid (2.5 mL) was stirred for 45 min at room temperature, after which the solvents were evaporated. Ethyl ether (10 mL) was added, and the solvent was evaporated again. The product was dissolved in CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ (2 × 40 mL), and dried (Na_2SO_4), and the solvent was evaporated to give **6** as a light brown powder (62 mg, quantitative yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.5 Hz, 2 H), 7.40 (d, *J* = 8.5 Hz, 2 H), 7.29 (dd, *J* = 8.0, 8.0 Hz, 2 H), 7.13 (dd, *J* = 1.0, 8.0 Hz, 2 H), 6.91 (br. d, *J* = 8.0 Hz, 2 H), 5.01 (br. s, 4 H), 4.22 (s, 4 H), 2.60 , (br. s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.0, 143.6, 137.6, 136.4, 127.7, 126.8, 120.8, 115.9, 110.2, 54.9 ppm. UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 252 (40300), 336 nm (4500). MS (DCI, NH_3): *m/z* = 330 [M + H]$^+$. $C_{20}H_{19}N_5$·0.1CH_2Cl_2 (337.89): calcd. C 71.45, H 5.73, N 20.73; found C 71.95, H 6.00, N 20.21. **6**–Cu^{II}: UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 234 (40300), 252 nm (27000, sh.). MS (ESI): *m/z* = 391 [LCu – H]$^+$. **6**–Zn^{II}: UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 236 (40000), 304 (5900), 320 nm (5800). MS (ESI): *m/z* = 392 [LZn^{II} – H]$^+$.

2,2′,2′′-(Nitrilotrimethanediyl)tri(*N*-Boc-8-quinolinamine) (13): To a solution of 8-(*tert*-butoxycarbonylamino)-2-quinolinecarboxaldehyde (50 mg, 0.18 mmol) in 1,2-dichloroethane (2.5 mL) was added NH_3 (0.21 mmol, 30 μL of a solution 7 M in CH_3OH), and the mixture was stirred for 5 min at room temperature. $(CH_3COO)_3$BHNa (72 mg, 0.34 mmol) was then added. The mixture was stirred for 15 h at room temperature, after which the solvent was evaporated. CH_2Cl_2 (10 mL) and aqueous saturated $NaHCO_3$ (10 mL) were added, and the organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were pooled and dried (Na_2SO_4), and the solvent was evaporated. The crude product was purified by chromatography (100% CH_2Cl_2) to give **13** as a pale yellow powder (25 mg, 52%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.03 (s, 3 H), 8.39 (br. d, *J* = 7.5 Hz, 3 H), 8.11 (d, *J* = 8.5 Hz, 3 H), 7.75 (d, *J* = 8.5 Hz, 3 H), 7.47 (dd, *J* = 7.5, 8.0 Hz, 3 H), 7.38 (dd, *J* = 1.5, 8.0 Hz, 3 H), 4.10 (s, 6 H), 1.59 (s, 27 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 157.8, 152.9, 137.3, 136.7, 134.9, 127.1, 127.0, 121.4, 119.9, 114.6, 80.5, 61.0, 28.4 ppm. MS (DCI, NH_3): *m/z* = 786 [M + H]$^+$.

2,2′,2′′-(Nitrilotrimethanediyl)tri(8-quinolinamine) (14): A solution of **13** (10 mg, 0.013 mmol) in CH_2Cl_2 (0.5 mL) and trifluoroacetic acid (0.5 mL) was stirred for 45 min at room temperature. The solvents were then evaporated. Ethyl ether (5 mL) was added, and the solvent was evaporated again. The product was dissolved in CH_2Cl_2 (15 mL), washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), and dried (Na_2SO_4), and the solvent was evaporated to give **14** as a light brown powder (6 mg, quantitative yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.5 Hz, 3 H), 7.67 (br. d, *J* = 8.5 Hz, 3 H), 7.29 (dd, *J* = 7.0, 8.0 Hz, 3 H), 7.12 (dd, *J* = 1.0, 8.5 Hz, 3 H), 6.90 (br. d, *J* = 7.0 Hz, 3 H), 4.99 (br. s, 6 H), 4.08 (br. s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 143.8, 137.5, 136.3, 127.8, 126.9, 121.4, 115.8, 110.1, 60.7 ppm. UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 254 (65900), 324 nm (9100). MS (DCI, NH_3): *m/z* = 486 [M + H]$^+$. HRMS (ESI): calcd. for $C_{30}H_{28}N_7$ 486.2406; found 486.2401. **14**–Cu^{II}: UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 237 (65400), 254 nm (46900, sh.). MS (ESI): *m/z* = 547 [LCu – H]$^+$. **14**–Zn^{II}: UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 236 (71900), 306 nm (15000). MS (ESI): *m/z* = 548 [LZn –H]$^+$.

8,8′-Oxydiquinoline (15): To a solution of 8-hydroxyquinoline (71 mg, 0.49 mmol) in dry DMF (2.0 mL) under argon was added cesium carbonate (156 mg, 0.48 mmol), 8-bromoquinoline (32 μL, 50 mg, 0.24 mmol), and $CuCl_2$·$2H_2O$ (4.1 mg, 0.024 mmol). The mixture was then heated to reflux for 72 h. After cooling the mixture, CH_2Cl_2 (5 mL) and an aqueous solution of Na_2-edta (5 mL, 0.12 M) were added. The organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with an edta solution (5 mL, 0.12 M in H_2O) and water. The solvent was evaporated, and the crude product was purified by chromatography (toluene/50–100% ethyl acetate, then 100% CH_3OH). The solvent was evaporated to give **15** as a white powder (13 mg, 19%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.95 (dd, *J* = 1.5, 4.0 Hz, 2 H), 8.21 (dd, *J* = 1.5, 8.5 Hz, 2 H), 7.61 (dd, *J* = 1.0, 8.0 Hz, 2 H), 7.46 (dd, *J* = 8.5, 4.0 Hz 2 H), 7.42 (dd, *J* = 7.5, 8.0 Hz, 2 H), 7.14 (dd, *J* = 1.0, 7.5 Hz, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.8, 150.2, 141.1, 135.9, 129.9, 126.6, 123.0, 121.8, 117.0 ppm. UV/Vis [CH_3OH/tris·HCl 20 mM pH 7.4, NaCl 150 mM (1:1, v/v)]: λ_{max} (ε, $M^{-1}cm^{-1}$) = 232 (53300), 240 (42900), 2994 (9400), 327 nm (5800, sh.). MS (DCI, NH_3): *m/z* = 273 [M + H]$^+$. HRMS (ESI): calcd. for $C_{18}H_{13}N_2O$ 273.1028; found 273.1011.

Determination of the Metal/Ligand Stoichiometry: UV/Vis absorption spectra and spectrophotometric titrations were performed in the presence of 20 mM tris·HCl pH 7.4 buffer, 150 mM NaCl. An organic solvent (CH_3OH or DMSO) was added goods that the ligands and metal complexes were soluble at the concentrations used in these experiments. To a 15-μM solution of ligand were added aliquots of concentrated solutions of $CuCl_2$ or $ZnCl_2$, in order to induce negligible volume variations. After these additions, changes in UV/Vis absorption spectra were immediately observed and were constant after two additions as a result of a fast complexation process. Tested metal/ligand ratios were from 0 to 10 for $CuCl_2$ and from 0 to 10^5 for $ZnCl_2$.

Preparation of Metal Complexes for Mass Spectrometry Characterization: Solutions of ligands (1 mM) in CH_3OH were metallated in the presence of one equivalent of metal ion ($CuCl_2$ or $ZnCl_2$) over 1 h at room temperature. The solvent was then evaporated.

Estimation of the Metal-to-Ligand Affinity Constants: When the ligand studied formed only the LM species, and stabilization occurred after one equivalent of the metal salt was added. Solutions (15 μM) of the studied ligand (L_s), competitor chelator (L_c), and metal ion (M) in 1:1:1 ratio were analyzed spectrophotometrically at 20 °C to determine the concentration of L_s, ML_s, L_c, or ML_c species at equilibrium. Experiments were performed in 20 mM tris·HCl pH 7.4, 150 mM NaCl buffer where an organic solvent (CH_3OH or DMSO) was added so that of the ligands and metal complexes were soluble at the concentrations used. The initial concentration was *C*. The metal is completely chelated in the experiments, and $[ML_s] + [ML_c] = C = [ML_s] + [L_s] = [ML_c] + [L_c]$. At equilibrium, $[ML_s] = x\%$ of *C*, then $[L_s] = (1 - x)\%$ of *C*, $[ML_c] = (1 - x)\%$ of *C* and $[L_c] = x\%$ of *C*. Concentrations of L_s and ML_s were calculated for different wavelengths that correspond to the parts of the UV/Vis spectra in which the L_c and ML_c species do not absorb. This was done by using the corresponding values ε of L_s and ML_s at these wavelengths. When only one species, L_s or ML_s, absorbs, $[ML_s]$ or $[L_s]$ was calculated directly from the Beer–Lambert law (controls were performed, which show that the ligands and the complexes follow this law). For parts of the spectra in which both L_s and ML_s absorb, the percentage of ML_s in the mixture is: $ML_s\ (\%) = (A_{obs} - A_{L_s(15\,\mu M)})/(A_{ML_s(15\,\mu M)} - A_{L_s(15\,\mu M)}) = x\%$, where A_{obs} is the observed absorbance and A_{L_s} and A_{ML_s} are the absorbance for $C = 15\,\mu M$ of L_s and ML_s, respectively, at the studied wavelength. The estimated values were confirmed by comparison with UV/Vis spectra obtained in the same solvent for 15 μM of L_s in the presence of the percentage of metal salt corresponding to the calculated percentage of ML_s. When good competition with edta was observed, the affinity constants were estimated as described previously.[4] In the other cases, they were estimated as proposed in the Results and Discussion part of the present manuscript.

Single Crystals of the Copper(II) Complex of Ligand 4 (17): To a solution of **4** (11.1 mg, 0.031 mmol) in CH_3OH (2.0 mL) was added $CuCl_2·2H_2O$ (5.4 mg, 0.031 mmol) dissolved in CH_3OH (0.103 mL). A blue solution formed. Slow evaporation of the solvent at room temperature gave **17** as dark blue needles suitable for X-ray analysis.

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