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Design and Synthesis of Multidentate Dinucleating Ligands Based on 1,8-Naphthyridine

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Abstract—Several novel multidentate dinucleating ligands based on 1,8-naphthyridine have been synthesized in which the 1,8-naphthyridine moiety serves as a bridging unit. These ligands can link two metal ions like the *syn*, *syn* coordination mode of bridging carboxylate groups encountered in a variety of dimetallic centers in biology. Stable dimetallic complexes with variable metal–metal separations and geometries readily form with the use of these ligands.

Introduction

Two metal ions bridged by one or more carboxylate groups perform a variety of functions in metalloproteins.[1–3] The bridging carboxylate holds the metal ions in close proximity with flexible separations, providing a platform and coordination environment for their synergistic action. In most dinuclear metallohydrolases, the hydrolysis of biologically important substrates such as DNA, RNA and peptides is achieved by cooperation of two metal ions bridged by a carboxylate group.[1,2,4–6] The two metal ions dramatically accelerate the hydrolysis rates of otherwise inert substrates by stabilizing the leaving group and providing a high local concentration of the nucleophilic hydroxide ion. The bridging carboxylate binding mode can facilitate formation of additional water (hydroxide) and substrate bridges, which can also be important for function. The active sites of diiron-containing redox active proteins such as methane monooxygenase (MMO), ribonucleotide reductase (RNR) and hemerythrin (Hr) contain similarly bridged dimetallic centers required to activate O_2.[3,7,8]

Ligands containing carboxylate groups have been used in biomimetic studies, yielding many successful models for dinuclear metal centers in nature.[9–17] Such carboxylate-bridged compounds typically form by self-assembly with additional ligands occupying terminal positions in the coordination spheres of the metal ions. The ability of such a self-assembled system to perform a biomimetic function in solution under various reaction conditions is limited, however. When dissolved in an aqueous solvent such self-assembled dimetallic complexes can dissociate to form mononuclear species.[17] Self-assembled systems also disassemble when the oxidation states of the metals change under redox conditions.[9] An effective way to solve this stability problem is to use multidentate ligands, preferentially with embedded carboxylate bridges. Enhanced stability is expected for dinuclear compounds derived from such ligands.

Extensive efforts to prepare multidentate dinucleating ligands with bridging carboxylate units have been undertaken in our laboratory and elsewhere. Several such ligands have been synthesized, but their ability to afford the desired dimetallic complexes has been modest at best.[18–21] The difficulty arises from the structural features of the bridging carboxylate. The *syn*, *syn* coordination mode is most common for bridging carboxylate groups when they link two metal ions. Since chelating arms can only be introduced from the γ position, as indicated in Fig. 1, large macrocyclic chelating rings cannot be avoided. The unfavorable ring size makes formation of the desired dinuclear compound very difficult. The pendant arms tend to be flexible, a property that also contributes to the instability of the desired dinuclear compounds. In proteins, secondary or tertiary structures such as 4-helix bundles are available to form a binding pocket. The ligands come from side chains, housed in the folded protein, which are well positioned to coordinate the

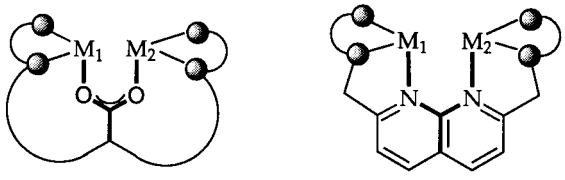

Figure 1. Schematic representation of the bridging modes of carboxylate and 1,8-naphthyridine ligands. Boldface lines in the latter outline the 'masked carboxylate' feature.

Keywords: 1,8-naphthyridine; multidentate dinucleating ligand.
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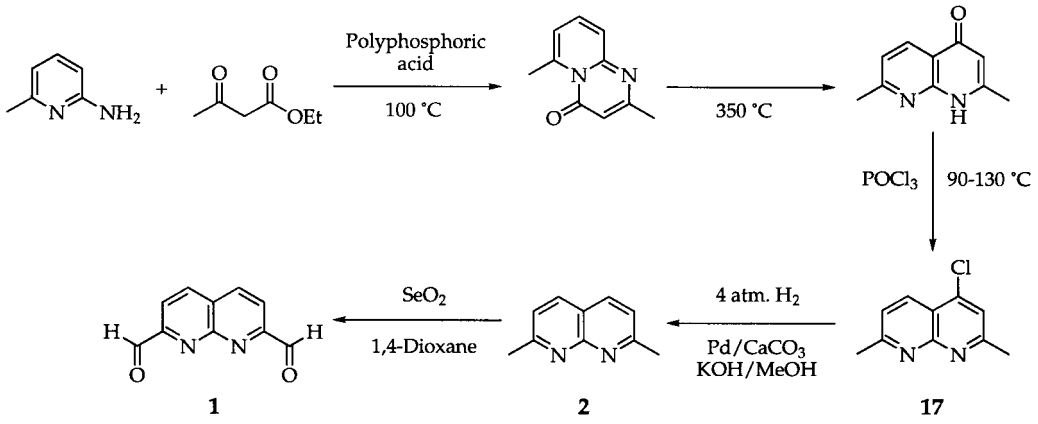


Scheme 1.

metal ions, a feature difficult to achieve with small molecule ligands.

In order to address these problems, we have employed nitrogen analogues of the carboxylate group, 2,3-phthalazine and 1,8-naphthyridine,[22,23] as bridging units for the design of multidentate dinucleating ligands. The 1,8-naphthyridine molecule can coordinate two metal ions in a *syn*, *syn* mode just like a bridging carboxylate group,[23–27] and the 2,7-positions are readily functionalized to install chelating groups. Favorable five-membered rings can be formed, as depicted in Fig. 1. Here we report the synthesis and characterization of nine such ligands.

Results and Discussion

Synthesis of 1,8-naphthyridine-2,7-dicarboxaldehyde (1)

This key precursor molecule was prepared following a published procedure[28] but with certain improvements (Scheme 1). Instead of 2,7-dimethyl-1,8-naphthyridine (**2**),

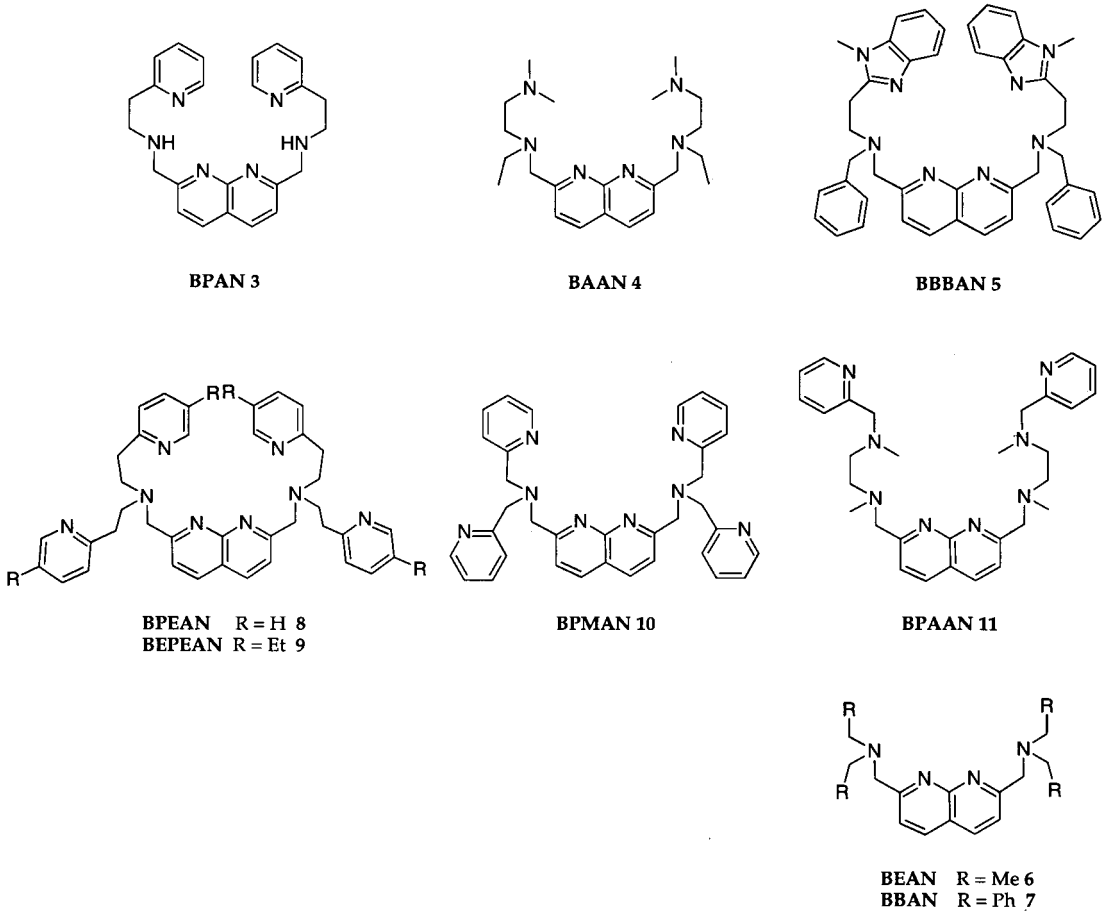
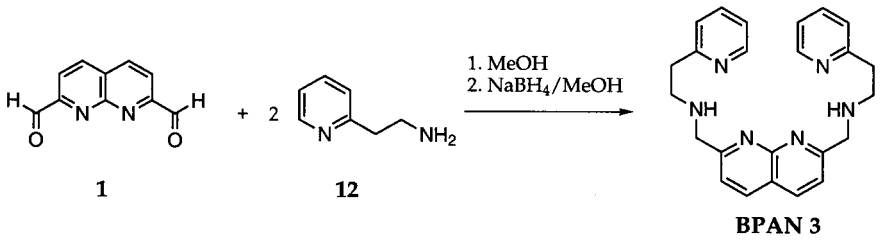


Figure 2. Dinucleating ligands based on 1,8-naphthyridine prepared in this work.



Scheme 2.

a mixture of **2** and 4-methoxy-2,7-dimethyl-1,8-naphthyridine was obtained when hydrogenation was performed under 1 atom of H_2 following the previously reported syntheses.[28] The latter compound was isolated and its formula assigned by ^{1}H NMR spectroscopy and high resolution mass spectrometry. This product presumably arises from substitution of the chloride group in 4-chloro-2,7-dimethyl-1,8-naphthyridine by methoxide formed in basic methanol solution. This reaction might be catalyzed by palladium present in the mixture. This observation, although not useful in the present context, may provide a way to functionalize 2,7-dimethyl-1,8-naphthyridine at the 4 position with alkoxide or phenolate groups for future applications. When the hydrogenation reaction was run under 4–6 atmospheres of H_2, the desired compound **2** was obtained as the only product in very high yield (98%).

Ligand design

With the use of 1,8-naphthyridine as the linker, hexadentate ligands BPAN (**3**), BAAN (**4**) and BBBAN (**5**) were designed and synthesized, as depicted in Fig. 2. Dimetallic complexes formed from these ligands are expected to be stabilized by chelation involving multiple nitrogen donor atoms. Several coordination sites remain available that can be filled by external ligands or substrates. This property is important for modeling metallohydrolases, where substrate and water both must bind to the metal ions and be activated. Negatively charged carboxylate groups can be introduced at the available positions in models for nonheme diiron centers. Tetradentate ligands BEAN (**6**) and BBAN (**7**) were also prepared. Up to three carboxylate groups can be incorporated as external ligands to assemble dinuclear metal complexes with the use of these ligands.

Octadentate ligands BPEAN (**8**), BEPEAN (**9**) and BPMAN (**10**) were also synthesized. These molecules can be viewed as two fused tripodal moieties. The corresponding tripodal tris(2-pyridylmethyl)amine (TPA) and tris(2-pyridylethyl)amine (TPEA) ligands have been extensively employed in dinuclear copper and iron chemistry. The first peroxo-bridged dicopper(II) compound was obtained by reacting a mononuclear Cu(I)TPA compound with O_2 at low temperature.[29] In addition, several unique bis-single-oxygen-atom bridged diiron(III) compounds have been obtained with 2 equiv of TPA type ligands.[30,31] High-valence dinuclear Fe(III)Fe(IV) compounds were obtained when treating some of these diiron(III) TPA compounds with H_2O_2 at low temperature.[32,33] The ligand BPAAN (**11**) was also prepared. It derives from the mononuclear ligand *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)-1,2-diaminoethane, and its donating ability is expected to differ owing to the incorporation of four tertiary amines.

By employing 1,8-naphthyridine as the bridging unit, we have constructed new ligands in which the two tripodal units face one another. These dinucleating ligands are expected to afford stable dinuclear metal compounds because of the chelate effect and the favorable chelate ring sizes (five for BPMAN and six for TPEAN and TEPEAN) that arise upon metal ion binding. The 1,8-naphthyridine bridge will restrain the metal–metal distance to a certain extent, a feature that may lead to different chemistry compared to what has been observed previously with the simpler tripodal ligands. Additional coordination sites between the two metal ions are also available, if desired, once the dinuclear complexes are assembled. This feature could facilitate the formation of single-atom and/or peroxo bridges between two metal ions in O_2 activation chemistry.

Synthesis of BPAN

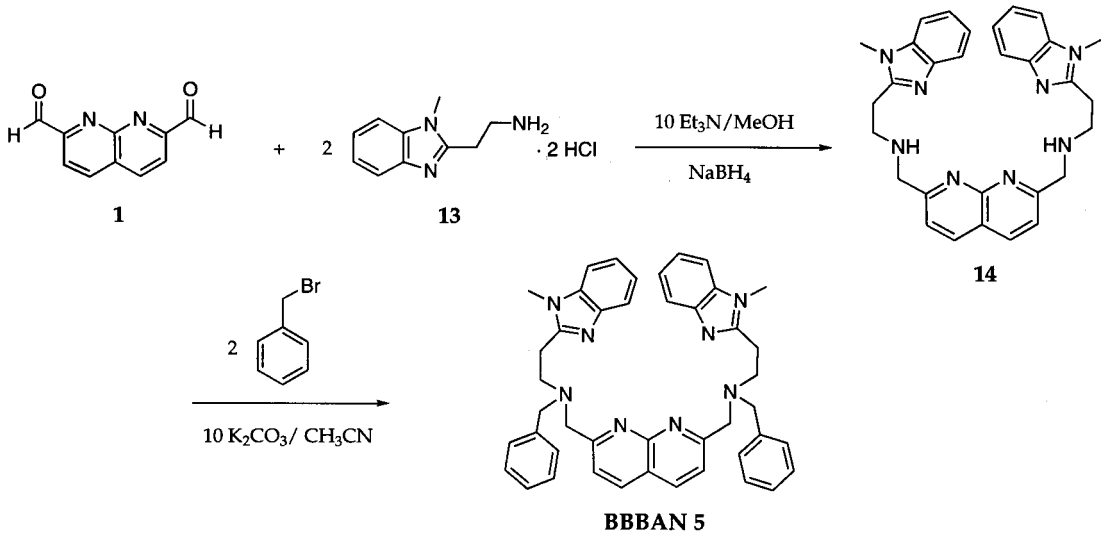
This ligand was prepared by reacting 1,8-naphthyridine-2,7-dicarboxaldehyde with 2-(2-aminoethyl)pyridine (**12**) in methanol. The product was obtained in 70% yield after purification (Scheme 2).

Synthesis of BBBAN

1-Methyl-2-(2-aminoethyl)benzimidazole (**13**), prepared as the dihydrochloride salt according to a known procedure.[34] Treatment of this compound with 1,8-naphthyridine-2,7-dicarboxaldehyde under reductive amination conditions afforded 2,7-bis(2-(2-(1-methyl)benzimidazolylethyl)aminomethyl)-1,8-naphthyridine (**14**) in 35% yield. The presence of excess of Et_3N is crucial for obtaining a good yield in this reaction. The final ligand BBBAN was obtained in 50% yield by reacting the above product with benzyl bromide, as shown in Scheme 3.

Reductive amination of secondary amines with 1,8-naphthyridine-2,7-dicarboxaldehyde

Ligands BPEAN, BEPEAN BPMAN, BPAAN, BAAN, BEAN and BBAN were prepared by reductive amination of 1,8-naphthyridine-2,7-dicarboxaldehyde with the corresponding secondary amines, as illustrated in Scheme 4. A general procedure using $NaBH(OAc)_3$ as the reductant for the coupling of secondary amines with carboxaldehydes was reported previously and found to be most effective in the syntheses listed here.[35] The final products were purified by flash chromatography and obtaining yields ranging from 30–65% (Experimental).



Scheme 3.

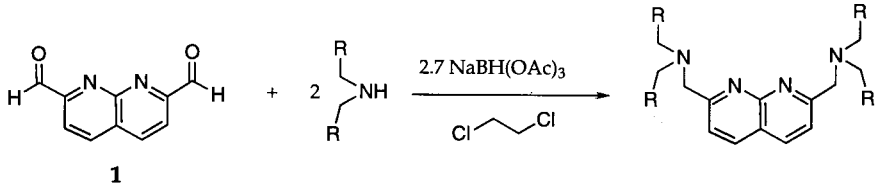
Synthesis of *N*,*N*′-dimethyl-*N*-(2-pyridylmethyl)ethylene-1,2-diamine (15)

Compound **15** is the precursor amine for the synthesis of ligand BPAAN in a reductive amination reaction with 1,8-naphthyridine-2,7-dicarboxaldehyde. This secondary amine was prepared by heating *N*,*N*′-dimethylethylenediamine (**16**) with 2-picolyl chloride hydrochloride, as shown in Scheme 5. Excess *N*,*N*′-dimethylethylenediamine and the solvent were removed and the final product was obtained in 71% yield as a liquid following flash chromatography.

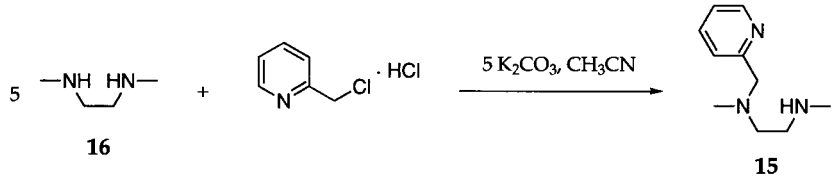
Formation of dinuclear complexes

A variety of dinuclear zinc(II), copper(I), copper(II), nickel(II), manganese(II), cobalt(II) and iron(II) complexes have been prepared from the ligands listed in Fig. 2.[23,36–38] Some general features of these dinuclear complexes are presented here, the details of which will be described elsewhere. In general, these dinuclear complexes show enhanced stability compared to the simple self-assembled molecules. For example, the dinuclear zinc(II) complex is stable in aqueous media and was employed in phosphate ester hydrolysis studies.[23] The dinuclear cores of dicopper and diiron complexes remain unchanged when the oxidation states of the metal ions were varied, as indicated by reversible redox waves observed in cyclic voltammetric studies.[36,38]

A noteworthy feature in the structures of these complexes is the variability in metal–metal distances supported by the 1,8-naphthyridine bridging unit in these ligands. Carboxylate groups afford a variety of metal–metal separations (2.5–4.5 Å). This flexibility may be one important reason why carboxylate groups serve as bridging units in biological dimetallic cores that perform diverse functions. A similarly wide range of metal–metal distances (2.5–4.0 Å) has thus far emerged in our studies of dinuclear complexes prepared from the 1,8-naphthyridine-based multidentate ligands listed in Fig. 2. The metal ions can move out of 1,8-naphthyridine plane to lengthen their separation while remaining bound to both bridging nitrogen atoms. The chelating nitrogen atoms built out from the 2 and 7 positions of 1,8-naphthyridine restrain such in-plane movement of the metal ions. Instead, the out-of-ligand-plane motion occurs to adjust the metal–metal distance in the 1,8-naphthyridine-bridged dinuclear complexes. Thus, flexible separations



Scheme 4.



Scheme 5.

between the two metal ions and different binding geometries can be accommodated.

Summary and Conclusions

Dinucleating ligands using arene or alkyl linkers have been prepared and studied previously.[39–42] Self-assembly is still required for such ligands to form dinuclear compounds. Tetranuclear complexes can form with two such ligands and an equilibrium between dinuclear and tetranuclear compounds is often observed. More preorganized dinucleating ligands have been synthesized for hydrolysis studies. Acceleration of hydrolytic reactions of phosphate ester groups has been observed, but structural information is limited.[43–45] The lack of bridging units in these ligands also leaves room for further improvement. Phenoxo- or alkoxo-bridged dinucleating multidentate ligands have been extensively employed to construct stable models for the active site dinuclear cores of many metalloproteins. Successful results were obtained in generating several peroxo-bridged diiron(III) compounds to model diiron-containing O_2 activation proteins.[46,47] Dinuclear compounds have also been prepared to model dinuclear metallohydrolases using similar ligands.[48,49] Although very effective in forming dinuclear compounds, these ligands give phenoxide or alkoxide bridges that are very different from that of the carboxylate group presented in nature. The formation of additional single-atom bridges between two metal ions is difficult to achieve.

In the present work, we employ 1,8-naphthyridine, a masked carboxylate group, as the bridging unit. Effective chelating ligands were readily constructed by functionalizing the 2 and 7 positions of 1,8-naphthyridine, allowing the exact bridging geometry of carboxylate groups in natural systems to be mimicked. A variety of different chelating units previously encountered in mononuclear ligands were incorporated into the dinucleating system following the general procedure described here. Stable dinuclear complexes with different metal ions and binding geometries have been prepared by using these ligands. A range of metal–metal distances occurs (2.5–4.0 Å) similar to that of carboxylate-bridged dinuclear centers. These ligands offer new opportunities for further exploration of the chemistry of dimetallic cores.

Experimental

General procedures and methods

All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. ^{1}H NMR spectra were taken on a Bruker WM-250 spectrometer or a Varian Mercury 300 spectrometer. All spectra were referenced according to a residual solvent peak as an internal standard (chloroform-d_1, δ=7.27; DMSO-d_6, δ=2.50). Fourier-transform infrared spectra were recorded on a Bio-Rad FTS135 instrument. Samples were prepared as either KBr pellets or Nujol™ mulls. Fast atom bombardment (FAB) mass spectrometry was performed in the MIT Department of Chemistry Instrumentation Facility with the use of *m*-nitrobenzyl alcohol as the matrix. 1,8-Naphthyridine-2,7-dicarboxaldehyde (**1**) was prepared according to a modified literature procedure.[28] The compounds bis[2-(2-pyridyl)ethyl]amine,[50] bis{2-[2-(5-ethyl)-pyridyl]ethyl}amine,[39] bis[(2-pyridyl)methyl]amine[50] and 1-methyl-2-(2-aminoethyl)benzimidazole dihydrochloride[34] were prepared by following literature procedures and the purity of these compounds were checked by ^{1}H NMR spectroscopy.

2,7-Dimethyl-1,8-naphthyridine (2). A portion of 4-chloro-2,7-dimethyl-1,8-naphthyridine (10.5 g, 54.5 mmol, **17**) was dissolved in methanol (200 mL). After addition of KOH (7.8 g) the mixture was hydrogenated under 4 atm of H_2 with stirring for 5 h over 5% palladium on calcium carbonate (3 g). The catalyst was filtered off after the reaction and the filtrate was evaporated. The remaining residue was dissolved in dichloromethane (150 mL) and washed with water (100 mL). The organic portion was dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure to give the product **2** as a pale yellow solid (8.5 g, 98%), mp 193–194°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.79 (s, 6H), 7.32 (d, J=9.5 Hz, 2H), 8.02 (d, J=9.5 Hz, 4H). When hydrogenation was performed under 1 atm of H_2 as suggested in the literature,[28] a mixture of **2** and 4-methoxy-2,7-dimethyl-1,8-naphthyridine was obtained in a 3:5 ratio, judging by the integration of the corresponding peaks in ^{1}H NMR spectrum of the mixture, after stirring for 12 h. The product 4-methoxo-2,7-dimethyl-1,8-naphthyridine was purified by flash chromatography (silica, 1:1/ethyl acetate/dichloromethane) as a white solid, mp 148–149°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.73 (s, 3H), 2.75 (s, 3H), 4.02 (s, 3H), 6.64 (s, 1H), 7.24 (d, J=4.0 Hz, 1H), 8.34 (d, J=4.0 Hz, 1H). HRMS (+FAB): Calcd for M^+, 189.1028; Found, 189.1031.

2,7-Bis[2-(2-pyridylethyl)aminomethyl]-1,8-naphthyridine (BPAN, 3). To a solution of 1,8-naphthyridine-2,7-dicarboxaldehyde (1.6 g, 8.6 mmol) in methanol (100 mL) was added 2-(2-aminoethyl)pyridine (2.2 mL, 18.1 mmol, **12**). The solution was allowed to stir for 3 h. The methanol solvent was evaporated by heating to 40°C under reduced pressure. Formation of the bis(imine) was confirmed by ^{1}H NMR spectroscopy ($CDCl_3$, 300 MHz) δ 3.27 (t, J=8.5 Hz, 2H), 4.19 (t, J=8.5 Hz, 2H), 7.10–7.15 (m, 2H), 7.17 (d, J=12.0 Hz, 2H), 7.55–7.62 (m, 2H), 8.22 (d, J=10.0 Hz, 2H), 8.27 (d, J=10.0 Hz, 2H), 8.54 (s, 1H), 8.57 (d, J=5.0 Hz, 2H). The solid residue was redissolved in methanol (100 mL). To this solution was added $NaBH_4$ (650 mg, 17.2 mmol) and the reaction was allowed to stir overnight. The reaction was quenched by addition of 6 M HCl to adjust the pH to 2. Brine (100 mL) was added and the pH of the solution was adjusted to ~11 with 30% aqueous NaOH solution. Methanol was removed under reduced pressure. The aqueous solution was extracted with CH_2Cl_2 (2×100 mL). The CH_2Cl_2 extracts were combined and dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure. The residue was purified by flash chromatography (silica, 95:5/acetonitrile/30% ammonium hydroxide in water) as a brown oil (2.5 g, 73%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.06 (d, J=6.0 Hz, 2H), 3.12 (d, J=6.0 Hz, 2H), 4.19 (s, 4H), 7.19 (d, J=8.2 Hz, 2H), 7.08–7.13 (m, 2H), 7.53 (d, J=8.2 Hz, 2H), 7.55–7.62 (m, 2H), 8.11

(d, J=8.0 Hz, 2H), 8.52 (d, J=5.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.7, 49.3, 55.8, 120.5, 121.2, 121.3, 123.3, 136.4, 137.1, 149.3, 155.3, 160.1, 164.1. HRMS (+FAB): Calcd for M^+, 1399.2297; Found, 1399.2301.

2,7-Bis{2-[2-(1-methyl)benzimidazolylethyl]-*N*-benzyl-aminomethyl}-1,8-naphthyridine (BBBAN, 5). To a solution of 1,8-naphthyridine-2,7-dicarboxaldehyde (340 mg, 1.83 mmol) in methanol (50 mL) was added 1-methyl-2-(2-aminoethyl)benzimidazole dihydrochloride (906 mg, 3.65 mmol, **13**) and triethylamine (1.85 g, 18.3 mmol). The solution was allowed to stir for 5 h. To this solution was added $NaBH_4$ (285 mg, 7.5 mmol) and the reaction was allowed to stir overnight. The reaction was quenched by addition of 6 M HCl to adjust the pH to 2. Brine (100 mL) was added and the pH of the solution was adjusted to ~11 with 30% aqueous NaOH solution. Methanol was removed under reduced pressure. The aqueous solution was extracted with CH_2Cl_2 (2×100 mL). The CH_2Cl_2 extracts were combined and dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure. The product 2,7-bis{2-[2-(1-methyl)benzimidazolylethyl]aminomethyl}-1,8-naphthyridine (**14**) was purified by flash chromatography (silica, 94:6/acetonitrile/30% ammonium hydroxide in water) as a light pink solid (2.5 g, 73%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.18 (t, J=7.0 Hz, 4H), 3.34 (t, J=7.0 Hz, 4H), 3.73 (s, 6H), 4.29 (s, 4H), 7.24–7.30 (m, 6H), 7.59 (d, J=8.3 Hz, 2H), 7.71–7.75 (m, 2H), 8.12 (d, J=8.3 Hz, 2H). To a solution of **14** (300 mg, 0.6 mmol) in acetonitrile (30 mL) was added benzyl bromide (203 mg, 1.2 mmol) and anhydrous K_2CO_3 (830 mg, 6.0 mmol). The solution was allowed to stir overnight. The solvent was removed under reduced pressure. The residue was extracted with 40 mL of methylene chloride and washed with 1 M aqueous Na_2CO_3 solution (2×50 mL). The organic portion was dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure. The residue was purified by flash chromatography (silica, 19:1/acetonitrile/30% ammonium hydroxide in water) as a light yellow solid (200 mg, 49%), mp 65.5–67.0°C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.97–3.05 (m, 8H), 3.27 (s, 6H), 3.66 (s, 4H), 3.99 (s, 4H) 7.05–7.18 (m, 16H), 7.54 (d, J=8.5 Hz, 2H), 7.58–7.61 (m, 2H), 7.79 (d, J=8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.6, 29.5, 51.5, 58.8, 60.4, 108.8, 118.8, 120.4, 121.6, 121.8, 126.9, 128.1, 128.3, 128.6, 135.6, 136.6, 138.9, 142.3, 153.2, 154.5, 164.0. HRMS (+FAB): Calcd for $(M+H)^+$, 685.3767; Found, 685.3760.

2,7-Bis{bis[2-(2-pyridyl)ethyl]aminomethyl}-1,8-naphthyridine (BPEAN, 8). To a solution of 1,8-naphthyridine-2,7-dicarboxaldehyde (0.60 g, 3.22 mmol) in dichloroethane (100 mL) was added bis[2-(2-pyridyl)ethyl]amine (1.47 g, 6.45 mmol) and sodium triacetoxyborohydride (1.84 g, 8.70 mmol). The solution was allowed to stir for 12 h under Ar. The reaction was quenched by addition of 1 M aqueous NH_4OH (150 mL), and the product was extracted with CH_2Cl_2 (2×100 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure. The residue was purified by flash chromatography (silica, 92:3:5/CH_2Cl_2/MeOH/Et_3N) as a brown oil (1.0 g, 51%). The oil solidified to a brown semisolid after extensive drying under vacuum. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.88–3.00 (m, 16H), 4.00 (s, 4H), 6.94–7.02 (m, 8H), 7.24 (d, J=8.2 Hz, 2H), 7.40–7.46 (m, 4H), 7.81 (d, J=8.2 Hz, 2H), 8.39 (d, J=5.0 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.3, 54.6, 61.3, 120.5, 121.1, 121.2, 123.5, 136.1, 136.5, 149.1, 154.8, 160.5, 164.7. HRMS (+FAB): Calcd for $(M+H)^+$, 609.3454; Found, 609.3450.

2,7-Bis{bis[2-(2-(5-ethyl)pyridyl)ethyl]aminomethyl}-1,8-naphthyridine (BEPEAN, 9). The same procedure as described for the preparation of ligand BPEAN was followed except that 1,8-naphthyridine-2,7-dicarboxaldehyde (0.50 g, 2.69 mmol), bis{2-[2-(5-ethyl)pyridyl]ethyl}-amine (1.55 g, 5.47 mmol) and sodium triacetoxyborohydride (1.60 g, 7.56 mmol) were used. The final product was purified by flash chromatography (silica, 70:20:10/CH_3CN/CH_2Cl_2/30% NH_4OH in water) as a brown oil (0.74 g, 38%). The oil solidified to a brown semisolid after extensive drying under vacuum. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, J=7.2 Hz, 12H), 2.58 (q, J=7.2 Hz, 8H), 2.93–3.01 (m, 16H), 4.06 (s, 4H), 6.95 (d, J=8.0 Hz, 4H), 7.32 (dd, J=8.0 Hz, J'=2.0 Hz, 4H), 7.36 (d, J=8.5 Hz, 2H), 7.87 (d, J=8.5 Hz, 2H), 8.29 (d, J=2.0 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.7, 25.9, 35.9, 54.7, 61.3, 120.4, 121.3, 123.0, 135.5, 136.4, 136.4, 148.7, 154.9, 157.8, 164.9. HRMS (+FAB): Calcd for $(M+H)^+$, 721.4706; Found, 721.4693.

2,7-Bis[bis(2-pyridylmethyl)aminomethyl]-1,8-naphthyridine (BPMAN, 10). The same procedure as described for the preparation of ligand BPEAN was followed except that 1,8-naphthyridine-2,7-dicarboxaldehyde (0.40 g, 2.15 mmol), bis(2-pyridylmethyl)amine (0.90 g, 4.51 mmol) and sodium triacetoxyborohydride (1.18 g, 5.59 mmol) were used. The final product was purified by recrystallization from CH_3CN as a light yellow solid (0.44 g, 37%), mp 171–173°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.91 (s, 8H), 4.09 (s, 4H), 7.11–7.15 (m, 4H), 7.54–7.67 (m, 8H), 7.86 (d, J=8.0 Hz, 2H), 8.11 (d, J=8.0 Hz, 2H), 8.53 (d, J=4.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 60.6, 60.9, 120.7, 121.8, 122.2, 123.3, 136.5, 137.0, 149.2, 155.0, 159.2, 164.0. HRMS (+FAB): Calcd for $(M+H)^+$, 553.2828; Found, 553.2838.

2,7-Bis(*N*,*N*-diethyl-aminomethyl)-1,8-naphthyridine (BEAN, 6). The same procedure as described for the preparation of ligand BPEAN was followed except that 1,8-naphthyridine-2,7-dicarboxaldehyde (350 mg, 1.88 mmol), diethylamine (275 mg, 3.76 mmol) and sodium triacetoxyborohydride (1.07 g, 5.08 mmol) were used. The final product was purified by flash chromatography (silica, 9:1/CH_3CN/30% NH_4OH in water) and obtained as a brown oil after removing the solvents (300 mg, 53%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.03 (t, J=7.2 Hz, 12H), 2.59 (q, J=7.2 Hz, 8H), 3.91 (s, 4H), 7.75 (d, J=8.3 Hz, 2H), 8.07 (d, J=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3, 47.9, 60.5, 120.4, 121.5, 136.6, 155.0, 165.3. HRMS (+FAB): Calcd for $(M+H)^+$, 301.2392; Found, 301.2399.

2,7-Bis(*N*,*N*-dibenzyl-aminomethyl)-1,8-naphthyridine (BBAN, 7). The same procedure as described for the preparation of ligand BPEAN was followed except that 1,8-naphthyridine-2,7-dicarboxaldehyde (275 mg, 1.48 mmol), dibenzylamine (600 mg, 2.96 mmol) and sodium

triacetoxyborohydride (0.86 g, 4.06 mmol) were used. The final product was purified by recrystallization from CH_3CN as a light yellow solid (270 mg, 33%), mp 167–169°C. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.65 (s, 8H), 3.96 (s, 4H), 7.20–7.44 (m, 20H), 7.83 (d, J=8.4 Hz, 2H), 8.10 (d, J=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 58.7, 60.7, 120.6, 121.6, 127.1, 128.4, 128.9, 136.9, 139.4, 154.9, 164.6. HRMS (+FAB): Calcd for $(M+H)^+$, 549.3018; Found, 549.3031.

2,7-Bis[2-(*N*,*N*-dimethyl-amino)ethyl-*N*′-ethyl-amino-methyl]-1,8-naphthyridine (BAAN, 4). The same procedure as described for the preparation of ligand BPEAN was followed except that 1,8-naphthyridine-2,7-dicarboxaldehyde (400 mg, 2.15 mmol), *N*,*N*-dimethyl-*N*-ethylethylenediamine (500 mg, 4.30 mmol) and sodium triacetoxyborohydride (1.23 g, 5.81 mmol) were used. The final product was purified by flash chromatography (silica, 9:1/CH_3CN/30% NH_4OH in water) as a brown oil (495 mg, 60%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, J=7.1 Hz, 6H), 2.16 (s, 12H), 2.41 (t, 6.5 Hz, 4H), 2.06–2.72 (m, 8H), 3.93 (s, 4H), 7.73 (d, J=8.4 Hz, 2H), 8.05 (d, J=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1, 46.0, 48.8, 52.2, 57.8, 61.3, 120.5, 121.4, 136.6, 154.9, 165.1. HRMS (+FAB): Calcd for $(M+H)^+$, 386.3158; Found, 386.3148.

2,7-Bis{2-[*N*-methyl-*N*-(2-pyridylmethyl)-amino]ethyl-*N*′-methyl-amino-methyl}-1,8-naphthyridine (BPAAN, 11). To a solution of *N*,*N*′-dimethylethylenediamine (8.82 g, 0.10 mol, **16**) in acetonitrile (200 mL) was added 2-picolyl chloride hydrochloride (3.28 g, 0.02 mol) and anhydrous K_2CO_3 (13.8 g, 0.1 mol). The solution was heated to 60°C and allowed to stir at this temperature under an Ar atmosphere. After 24 h, the excess *N*,*N*′-dimethylethylenediamine and the solvent acetonitrile were removed under reduced pressure. The remaining yellow liquid was dissolved in 100 mL of methylene chloride and washed with saturated aqueous Na_2CO_3 (2×100 mL). The organic portion was collected and dried over anhydrous $MgSO_4$. Volatiles were removed under reduced pressure. The product *N*,*N*′-dimethyl-*N*-(2-pyridylmethyl)-1,2-diaminoethane (**15**) was purified by flash chromatography (silica, 9:1/CH_3CN/30% NH_4OH in water) as a light yellow liquid (2.55 g, 71%). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 1H), 2.27 (s, 3H), 2.42 (s, 3H), 2.59 (d, J=6.0 Hz, 2H), 2.70 (d, J=6.0 Hz, 2H), 3.67 (s, 2H), 7.13–7.17 (m, 1H), 7.40 (d, J=7.8 Hz, 1H), 7.62–7.68 (m, 1H), 8.52–8.54 (m, 1H). HRMS (+FAB): Calcd for $(M+H)^+$, 179.1422; Found, 179.1419. The same procedure as described for the preparation of ligand BPEAN was followed except that 1,8-naphthyridine-2,7-dicarboxaldehyde (380 mg, 2.04 mmol), **15** (732 mg, 4.08 mmol) and sodium triacetoxyborohydride (1.15 g, 5.40 mmol) were used. The final product BPAAN was purified by flash chromatography (silica, 9:1/CH_3CN/30% NH_4OH in water) as a brown oil (685 mg, 65%). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.20 (s, 6H), 2.22 (s, 6H), 2.61 (s, 8H), 3.62 (s, 4H), 3.84 (s, 4H), 7.02–7.07 (m, 2H) 7.32 (d, J=7.8 Hz, 2H), 7.50–7.55 (m, 2H), 7.66 (d, J=8.4 Hz, 2H), 8.01 (d, J=8.4 Hz, 2H), 8.41–8.44 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.9, 43.2, 55.6, 55.7, 64.1, 64.9, 120.5, 121.5, 121.9, 123.0, 136.3, 136.7, 148.9, 154.8, 159.0, 164.0. HRMS (+FAB): Calcd for $(M+H)^+$, 512.3376; Found, 512.3384.

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