Structural Studies on Hydrogen-Bonding Receptors for Barbiturate Guests That Use Metal Ions as Allosteric Inhibitors

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Receptor **1** was designed to bind barbiturate substrates through a six-point hydrogen-bonding motif only in the absence of metal allosteric cofactors. It was predicted that the binding of metal ions by bipyridine ligands in **1** would result in a geometric change in the receptor to inhibit substrate recognition. However, receptor **1** showed minimal affinity for the barbiturate guests even in the absence of the metal. Binding studies on model compounds **2**, **3**, **5**, and **6** revealed that the inactivity of **1** is due to an intramolecular hydrogen bond between the N–H donor groups and the nitrogen atoms on the first heterocycle of the bipyridine ligands. This intramolecular hydrogen-bonding was eliminated by altering the position of the tether between the bipyridine ligands and the active site to produce receptor **7**. Consequently, the high affinity exhibited by **7** for the barbiturate substrate (K_a = 2.8±0.7 × 10^3 M^{-1} in 9:1 CD_2Cl_2/CD_3CN) was significantly reduced by the addition of Zn^{II} ions as a negative allosteric co-factor.

Introduction

Nature often uses allostery to reversibly alter molecular structure and consequently regulate dynamic functions such as molecular recognition and catalytic activity. In these complex natural systems, the binding of a co-factor at a location that is not the active site promotes reversible conformational alterations that are transmitted across the molecular structure to the active site, thereby, varying the receptor's affinity for its substrate. Allosteric effects are considered to be positive when the induced conformational changes increase the binding efficacy, and negative when the initial interaction of the cofactor results in a decrease in the binding efficacy.[1,2]

Inspired by these natural systems, chemists are building smaller, synthetically accessible molecules that mimic the behavior of natural receptors. Several artificial receptors, in which the binding ability is regulated through allosteric effects, have been reported.[3−27] In one recent example, Nabeshima and co-workers describe a receptor where the complexation of Fe^{II} by bipyridine ligands tethered to the ends of three polyether chains regulates the receptor's affinity for alkaline-earth metals.[28] This allostery is based on the Fe^{II}-induced rearrangement of the polyether chains to form an ionophoric pseudocryptand.

We have used the complexation of Cu^{I} ions by bipyridine ligands to inhibit molecular recognition in hydrogen-bonded host−guest complexes.[29,30] In our examples, the negative allostery is a direct result of the complexation-induced distortion of the hydrogen-bonding surface responsible for interacting with the substrate. Here we introduce an alternative to distorting a molecular recognition site and describe a receptor in which the binding of a metal ion by bipyridine ligands within the receptor alters the accessibility to and the size of the binding pocket rendering it unsuitable to accommodate the guest species. We have chosen barbiturates as substrates because their wide use as sedatives and anticonvulsants[31,32] make them attractive targets. The reported examples where barbiturates are bound and separated from mixtures of organic compounds and biological solutions are based on hydrogen-bonding networks that are formed within the host−guest complex.[33−38] The ability to control the binding between the molecular recognition partners would enhance a receptor's versatility.

Receptor Design

All of the receptors **1**−**7** are adaptations of the bis(2,6-diaminopyridine) structural motif that has been successfully used to bind barbiturate guests.[39,40] As is illustrated with the first receptor we designed (**1**) in Scheme 1, the host−guest recognition is based on the receptor's triangular-shaped cleft that is lined with two convergent hydrogen bonding donor−acceptor−donor arrays furnishing a complementary binding site for the guest. The isophthoyl linker enforces the correct shape and size of the binding pocket. It also prevents intramolecular hydrogen-bonding

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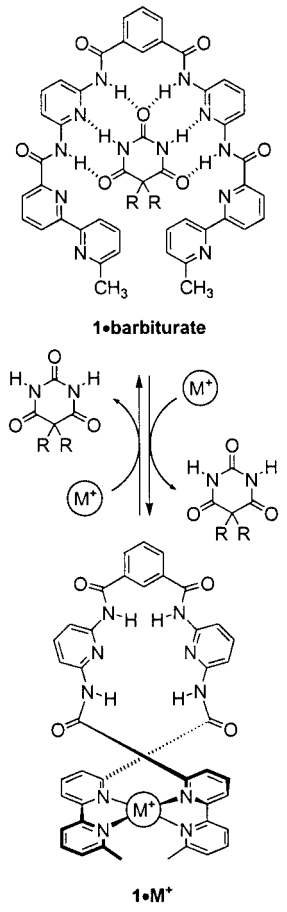


Scheme 1. The allosteric regulation in receptor **1**; the coordination of a metal ion closes the entrance of the hydrogen-bond-lined cleft in receptor **1** and shuts down the binding of barbiturate guests

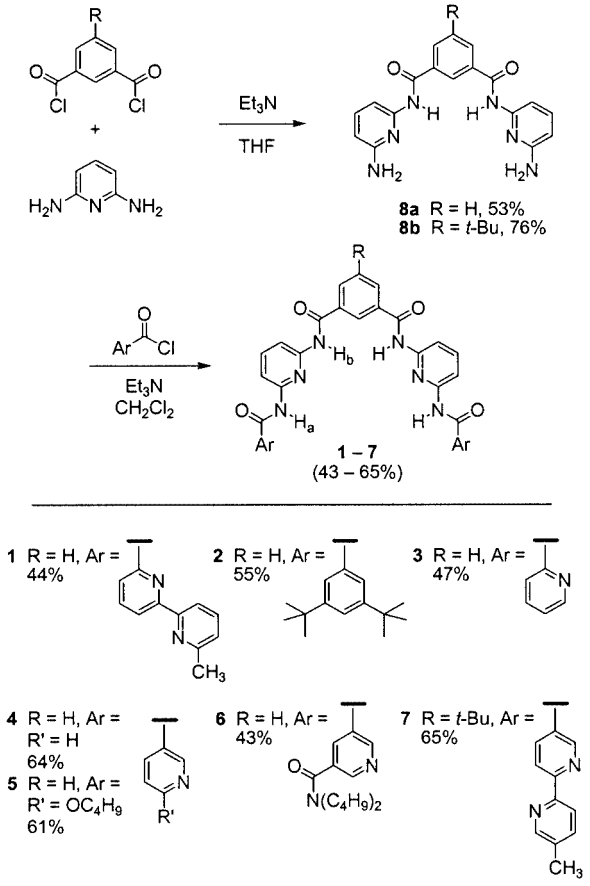
between the two diaminopyridine units, although as will be described later in this report, the presence of other intramolecular hydrogen bonds will be an obstacle.

What makes receptor **1** unique is the two metal-coordinating bipyridine ligands that are flanking the entrance of the recognition cleft. The receptor was designed to respond to the presence of metal ions by undergoing dramatic structural changes when the ligands swing towards each other and chelate the metal. The metal complexation effectively seals the entrance of the cleft and forces the two aminopyridyl groups closer to each other causing a shrinkage in the binding cavity and a distortion of the hydrogen bond surface lining it. These effects render the binding site inaccessible to the guest and unsuitable in size and shape. The binding of the barbiturate by the receptor should be inhibited (negative allostery). Scheme 1 illustrates this concept using receptor **1** which offers the 6,6′-disubstituted 2,2′-bipyridyl allosteric metal-binding site. The allosteric cofactor is a Cu^{I} ion. We have already used this metal-ligand partnership with success.[29,30] In this paper we describe how receptor **1** is, in fact, not capable of binding a barbiturate even in the absence of the metallic cofactor. Several model compounds are used to identify the structural problems with receptor **1**, ultimately leading to the realization of a successful allosteric host (**7** → **7·Zn**).

Results and Discussion

Synthesis of the Receptors

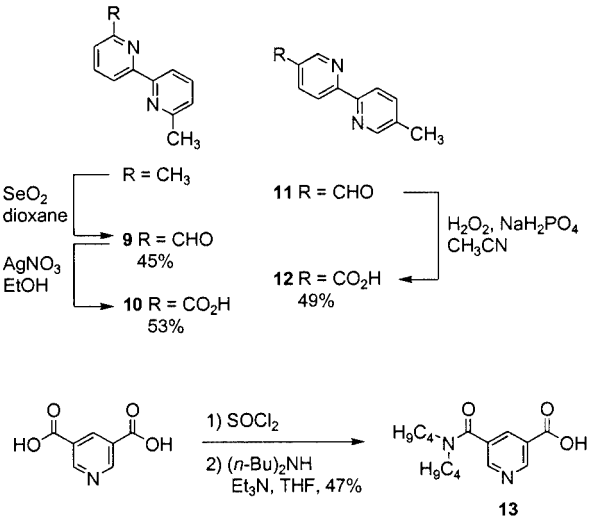
All of the receptors **1**−**7** can be constructed from simple building blocks using procedures adapted from the literature.[39,40] The syntheses begin by preparing the two bis(2,6-diaminopyridine) derivatives **8a** and **8b**, which differ only in the presence of the organic-solubilizing *tert*-butyl group on the central benzene ring. These two isophthalamides are readily prepared by reacting isophthaloyl and 5-*tert*-butylisophthaloyl chloride with an excess of 2,6-diaminopyridine as shown in Scheme 2. Receptors **1**−**7** can then be constructed from either **8a** or **8b** and the acid chloride of the appropriate carboxylic acid.



Scheme 2. Synthesis of receptors **1**−**7**

The isomeric bipyridine carboxylic acids **10** and **12**, required to construct bipyridine receptors **1** and **7**, are synthesized as shown in Scheme 3 by oxidizing the known bipyridine carboxaldehydes **9**[41] and **11**.[42] Commercially available 3,5-di-*tert*-butylbenzoic acid, picolinic acid, and nicotinic acid are used to synthesize receptors **2**, **3**, and **4**, respectively. 6-Butoxynicotinic acid, which is required for the synthesis of receptor **5**, is obtained from 6-bromonic-

otinic acid according to the literature procedures.[43] The *N*,*N*-dibutylaminocarbonyl-substituted nicotinic acid (**13**) is prepared in one step from 3,5-pyridinedicarboxylic acid as is also illustrated in Scheme 3. This modified nicotinic acid can be easily converted into receptor **6** by reacting its acid chloride with the bis(2,6-diaminopyridine) compound **8a**.



Scheme 3. Synthesis of the carbxylic acids required to prepare receptors **1**, **6**, and **7**

The Binding Activity of Receptor 1 Towards Barbiturate Guests

The ability of bipyridine receptor **1** to recognize and bind its barbiturate substrate is readily evaluated using ^{1}H NMR spectroscopy. Because the hydrogen atoms in the hydrogen-bond donors N−H$_a$ and N−H$_b$ (see Scheme 2 for atom assignments) are central to successful guest binding, the changes in the chemical shifts of the signals corresponding to these protons when the guest is added can be monitored. Surprisingly, when a CD_2Cl_2 solution of receptor **1** is treated with aliquot amounts of a solution of 5,5-dibutylbarbiturate in the same solvent, there are insignificant changes in the positions (Δδ less than 0.1 ppm) of the signals corresponding to the N−H$_a$ (Figure 1) and N−H$_b$ (not shown) protons, which appear at 10.35 and 8.83 ppm, respectively before the addition of the substrate (Table 1).

The atypical downfield position of the signal for the N−H$_a$ protons (the signals for these protons in similar systems appear in the range δ = 8.2−8.8 ppm)[39,40,44,45] strongly suggests that these hydrogens are tied up in hydrogen bonds. The fact that the position and shape of the signal at δ = 10.35 ppm do not vary upon diluting the solution argues that any hydrogen-bonding must be intramolecular, most likely between the N−H$_a$ donor and one of the nitrogen atom acceptors of the bipyridine rings. These interactions may lead to the folding of the receptor into a conformation incapable of binding the barbiturate as is shown by the fact that the chemical shifts are unaffected by the presence of the guest species. As a consequence, the titration data do not fit any binding model. Receptor **1** exhibits a very low and uncharacterizable affinity for its barbiturate guest.

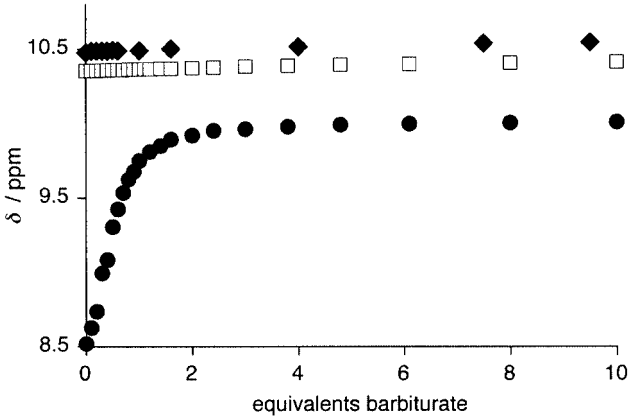


Figure 1. Changes in the chemical shift of the signals corresponding to the N−H$_a$ protons in the ^{1}H NMR spectra of solutions (5 mM in CD_2Cl_2) of receptors **1** (□), **2** (●) and **3** (◆) upon the addition of a solution of 5,5-dibutylbarbiturate (100 mM in CD_2Cl_2)

Table 1. The chemical shifts corresponding to the N−H$_a$ and N−H$_b$ protons in the ^{1}H NMR spectra of receptors **1**, **2**, **3**, **5**, **6**, and **7** before and after the addition of 1 molar equivalent of 5,5-dibutylbarbiturate

Receptor[a]	alone		+ 5,5-dibutylbarbiturate[b]	
	N−H$_a$ (δ/ppm)	N−H$_b$ (δ/ppm)	N−H$_a$ (δ/ppm)	N−H$_b$ (δ/ppm)
1	10.35	8.83	10.36	8.87
2	8.52	8.37	9.75	9.62
3	10.48	8.12	10.49	8.11
5	8.56	8.33	9.74	9.52
6	9.30	9.20	9.84	9.77
7	8.83	8.68	9.55	9.49

[a] 5 mM CD_2Cl_2. [b] 100 mM in CD_2Cl_2.

Unlike receptor **1**, in the absence of the barbiturate guest, the signals corresponding to the N−H$_a$ and N−H$_b$ protons in **2** appear upfield in the ^{1}H NMR spectrum (CD_2Cl_2) at δ = 8.52 and 8.37 ppm, respectively (Table 1). This can be expected of a bis(2,6-diaminopyridine)-based receptor that is free of intramolecular hydrogen bonds. Figure 1 shows the significant downfield changes (Δδ more than 1.5 ppm) in the chemical shift of the N−H$_a$ protons as the solution of the receptor is treated with a solution 5,5-dibutylbarbiturate indicating effective hydrogen-bonding between host and guest. The titration data correlate well with the calculated curve for a 1:1 binding model giving an association constant (K_a) of 8000 M^{-1} in CD_2Cl_2 indicating that the steric bulk imposed by the aromatic substituents at the rim of the binding pocket does not prevent the access of the substrate to receptor **2**. It would be unlikely, therefore, that spatial bulk alone is the reason for receptor **1**′s inability to bind its barbiturate substrate.

Pyridyl receptors **3**, **4**, and **5** are useful to identify which of the nitrogen heterocycles is responsible for the intramol-

ecular hydrogen-bonding in receptor **1**. ^{1}H NMR spectroscopy studies show that the molecular recognition behavior of 2-pyridyl receptor **3** is similar to that of the bipyridyl receptor **1**. In the absence of any 5,5-dibutylbarbiturate, the signal corresponding to the N−H_a (10.48 ppm in CD_2Cl_2) protons of receptor **3** is shifted downfield similar to that of the bipyridyl receptor **1** (Table 1). The signal, as well as that for the N−H_b protons, also undergoes minimal changes in its chemical shift (Δδ less than 0.1) upon the addition of the barbiturate (Figure 1) indicating little association between the receptor and the barbiturate. At this stage, to conclude that the pyridine directly attached to the bis(2,6-diaminopyridine) scaffold is involved in intramolecular hydrogen-bonding to the N−H_a protons is not unreasonable.

This conclusion can be supported by examining the structure of 2-pyridyl receptor **3** in the crystalline state. X-ray quality crystals of **3** can be grown by slowly evaporating a chloroform solution of the receptor. The crystal structure (Figure 2) reveals the presence of intramolecular hydrogen bonds between the N−H_a protons and the nitrogen atoms on the pyridine rings that are closer to the mouth of the binding pocket. The structure of the receptor in the crystal also adopts a non-productive conformation and the two donor−acceptor−donor hydrogen-bonding surfaces (N1−H, N10, N2−H, and N3−H, N30, N4−H) diverge away from each other. The C1−C9 bond must rotate as much as 173° to regenerate the active hydrogen-bond-lined cleft.

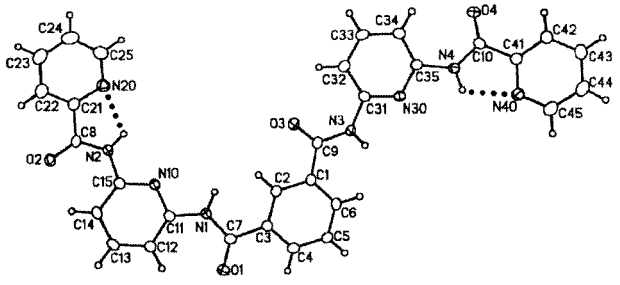


Figure 2. The structure of 2-pyridyl receptor **3** in the crystal showing the intramolecular N2−H···N20 and N4−H···N40 hydrogen bonds (dotted lines); the distances of 2.16 Å for N2−H···N20 and 2.19 Å for N4−H···N40 are well within hydrogen bond allowances; torsional angles are 3.7° for N2−C8−C21−N20 and 8.0° for N4−C10−C41−N40

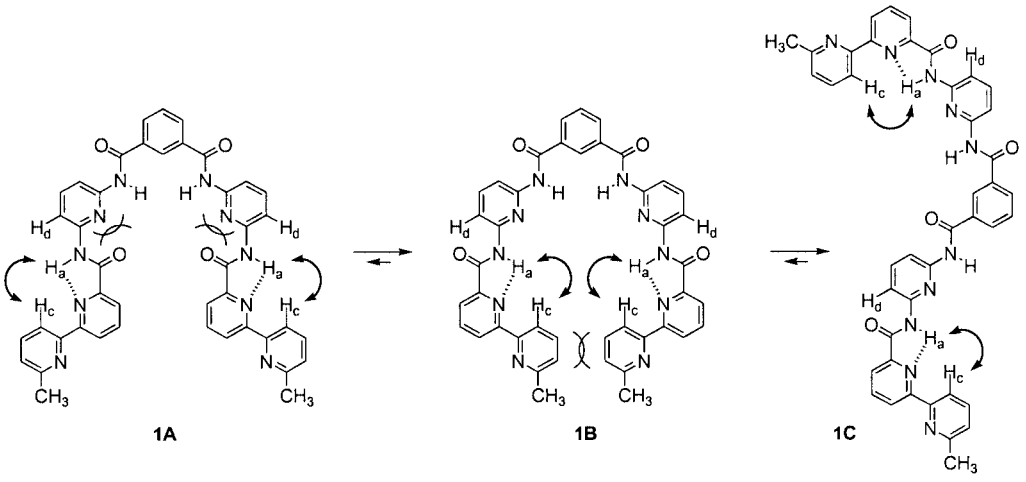
The 3-pyridyl receptor **4** is too insoluble in non-competitive solvents such as $CHCl_3$ and CH_2Cl_2 to estimate the association constants with barbiturate guests, however, the *n*-butoxy groups attached to the pyridine rings in **5** solubilize this receptor enough to investigate its binding behavior. The signal corresponding to the N−H_a protons (8.56 ppm) in the ^{1}H NMR spectrum of receptor **5** (CD_2Cl_2) indicates that these hydrogens are not already involved in hydrogen-bonding, presumably because the hydrogen-bond acceptors reside further from the donors in 3-pyridine **5** than in 2-pyridine **3**. The addition of one molar equivalent of 5,5-dibutylbarbiturate to a CD_2Cl_2 solution of the 3-pyridyl receptor **5**, therefore, results in the downfield shift of the signals corresponding to the N−H_a and N−H_b protons to positions similar to those for the active receptor **2** (Table 1). Because the signals corresponding to N−H_a and N−H_b shift significantly downfield and reach saturation after 1−2 molar equivalents of 5,5-dibutylbarbiturate are added to the active receptor **2**, the activity of any particular receptor can be tested simply by the addition of only one equivalent of the substrate. Complete ^{1}H NMR titrations are only necessary when an estimation of the association constant is absolutely indispensable.

The signals in the ^{1}H NMR spectrum corresponding to the N−H_a and N−H_b protons in 3-pyridyl receptor **6** (CD_2Cl_2) initially appear at δ = 9.30 and 9.20 ppm, respectively (Table 1), which are further downfield than those for receptors **2** and **5** but not as far downfield as those for receptors **1** and **3**. In the case of **6**, the signals shift upfield to δ = 9.04 ppm for N−H_a and to 8.93 ppm for N−H_b when the sample is diluted from 5 mM to 0.3 mM signifying that these protons are involved in intermolecular not intramolecular hydrogen-bonding. This aggregation does not significantly interfere with the binding of barbiturates, and the addition of one molar equivalent of 5,5-dibutylbarbiturate to the 3-pyridyl receptor **6** induces a downfield shifting of the signals for protons N−H_a and N−H_b to δ = 9.84 ppm and 9.77 ppm, respectively (Table 1).

The binding behavior of receptors **1**−**6** suggests that intramolecular hydrogen bonding between the N−H_a protons and the nitrogen atoms of the pyridine rings directly attached to the bis(2,6-diaminopyridine) scaffold (**1** and **3**, for example) is the root of the poor host-guest association. It appears that the pyridine rings further removed from the rim of the binding pocket in bipyridine receptor **1** play little role in the inhibition of the molecular recognition and receptors lacking the intramolecular hydrogen bond (**2**, **5**, and **6**) retain their ability to complex 5,5-dibutylbarbiturate.

Three possible conformations of the bipyridyl receptor **1** are presented in Scheme 4. We propose that the intramolecular hydrogen bonds between the N−H_a donor and the acceptors on the adjacent pyridine rings lock the bottom portion of the receptor into the planar geometry common to all three conformers **1A**, **1B**, and **1C**. This suggestion is strengthened by the existence of an NOE (in CD_2Cl_2) between the N−H_a protons and the C−H_c protons on the outermost pyridine rings as shown by the double-headed arrows in the scheme.

We also believe that conformer **1A** is not favoured due to the electron-pair repulsion between the carbonyl oxygens and the pyridine nitrogens of the two bis(2,6-diaminopyridine)s. This is also highlighted in Scheme 4 and is supported by the absence of an NOE between the N−H_a protons and the C−H_d protons. In order to completely relieve the N···O strain, rotation of the C−N bonds forces the two bipyridine ligands to converge directly above the entrance of the binding pocket as is illustrated by conformer **1B**. Presumably, the entrance of the guest into the binding site is hindered in this conformer. This ligand···ligand steric strain can be

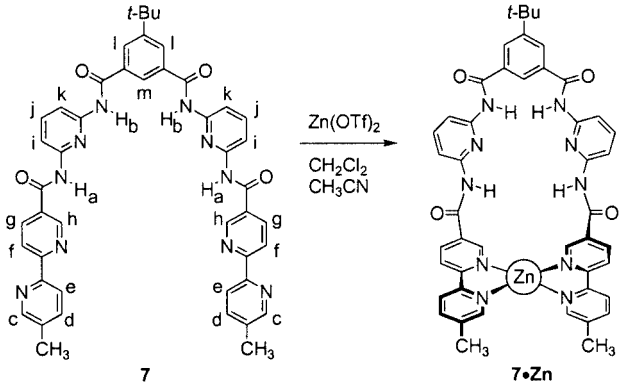


Scheme 4. Three possible conformations of receptor **1**; the NOEs are shown by double-headed arrows and the steric and electronic repulsions are shown by intersecting curves

eliminated by rotation of the C−C bond to form conformer **1C**. This geometry is similar to the one observed in the crystal structure of receptor **3** and can be assumed to be inactive towards binding barbiturate guests as the hydrogen-bonding donor−acceptor−donor surfaces are divergent and the binding pocket is destroyed.

A Successful Bipyridine-Based Receptor 7·Zn

Receptors **5** and **6** are active binders of barbiturates because of the inability of the pyridyl nitrogen to hydrogen bond with N−H_a. The 5,5′-disubstituted bipyridyl receptor **7** should, therefore, also be active (Scheme 2). In this case, bis(2,6-diaminopyridine) **8b** was used to enhance the solubility of the receptor in CH_2Cl_2 and $CHCl_3$. The allosteric regulation using receptor **7** cannot be tested using copper ion as the co-factor because the preparation of **7·Cu** produces uncharacterizable coordination complexes. This is not completely surprising because Cu^I complexes of 5,5′-disubstituted bipyridines are generally less stable than analogous complexes prepared with the 6,6′-disubstituted bipyridines.[46] However, the air stable Zn^{II} complex **7·Zn** can prepared by treating the bipyridyl receptor **7** with one equivalent of zinc triflate in 10% CH_3CN/CH_2Cl_2 (Scheme 5).



Scheme 5. The complexation of zinc ion seals the entrance of the binding cavity in receptor **7**

The ^1H NMR spectrum of coordination complex **7·Zn** exhibits significant changes in the chemical shifts of the signals in the aromatic region due to the chelation of the Zn^{II} ion by the bipyridine ligands of the receptor (Figure 3). The signals corresponding to the aromatic protons of the bipyridine rings (H_d−H_h) shift downfield as would be expected due to the electron-withdrawing effect of the Lewis acid. The exception is the upfield shift of the signal for H_c, which can be attributed to the placement of this proton within the shielding cone of the opposite bipyridine ligand as has been previously observed for similar zinc complexes.[47,48] The upfield shift of the signal corresponding to protons H_i upon the complexation of the metal suggests that they are less deshielded by the carbonyl oxygen of the adjacent amide, which is rotated away from H_i because of the geometric requirements of the metal coordination. We attribute the downfield shift of the signals for protons H_l to restricting the rotation of the adjacent C−C=O single bond, which forces the carbonyl groups to be in close proximity to H_l. Electrospray mass spectrometry also supports the formation of the complex **7·Zn**. A peak at m/z = 1159.1648 corresponding to the mass of $[7 + Zn + 2OTf + H]^+$ and another peak at m/z = 859.2445 which corresponds to $[7+Zn-H]^+$ are both present in the mass spectrum.

The binding ability of bipyridyl receptor **7** and its zinc complex **7·Zn** to the barbiturate substrate can be tested in

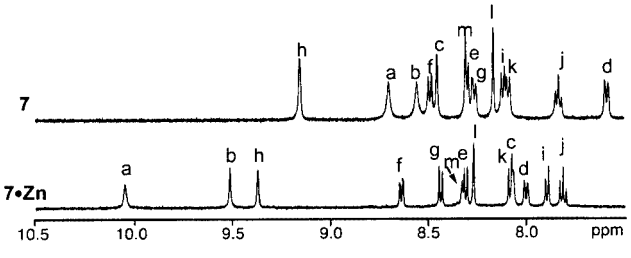


Figure 3. Partial ^1H NMR spectrum (500 MHz, 9:1 CD_2Cl_2/CD_3CN) of the bipyridyl receptor **7** and its zinc complex **7·Zn**. The aromatic peaks are assigned on the structures based on 2-dimensional NMR studies (GCOSY and TROESY) of the two compounds. See Scheme 5 for atom labels

an identical fashion as described previously by monitoring the changes in the chemical shifts of the signals corresponding to the N−H_a and N−H_b protons upon the addition of 5,5-dibutylbarbiturate to a solution of the receptor in CD_2Cl_2. Before the addition of the substrate, the signals appear at δ = 8.83 ppm and 8.68 ppm, respectively (Table 1). The addition of one molar equivalent of 5,5-dibutylbarbiturate shift the signals downfield as was observed for the other active receptors (**2**, **5**, and **6**), indicative of the formation of effective hydrogen-bonding between the receptor and the substrate. ^{1}H NMR titration experiments (2 mM in 9:1 CD_2Cl_2/CD_3CN mixture) estimate the value of K_a to be $2.8\pm0.7 \times 10^3$ M^{-1} when the collected data is fit to a 1:1 binding model (Figure 4).

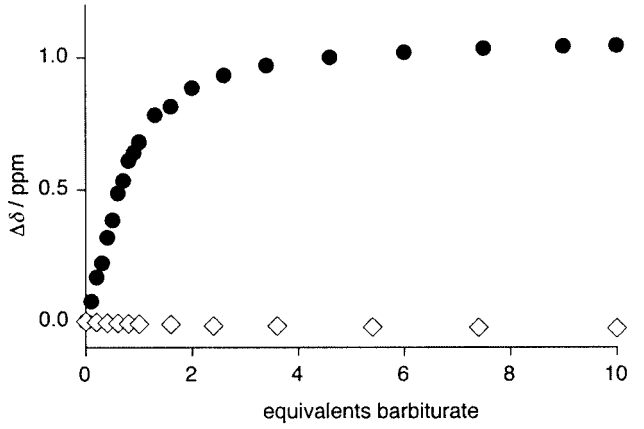


Figure 4. Changes in the chemical shift of the signals corresponding to the N−H_a protons in the ^{1}H NMR spectra of solutions (2 mM in 9:1 CD_2Cl_2/CD_3CN) of receptors **7** (●) and **7·Zn** (◇) upon the addition of a solution of 5,5-dibutylbarbiturate (20 mM in 9:1 CD_2Cl_2/CD_3CN)

The effect that the metal has on the binding ability of bipyridyl receptor **7** to barbiturate guests can be studied by treating a solution (9:1 CD_2Cl_2/CD_3CN) of the complex **7·Zn** with 5,5-dibutylbarbiturate. The addition of the barbiturate to the Zn^{II} complex leads to an insignificant (Δδ less than 0.1 ppm) but observable upfield shift in the signals corresponding to proton N−H_a (Figure 4). This is attributed to the dilution of the receptor solution upon the addition of the substrate solution. This also indicates that there is no association between the receptor and its substrate. Therefore, the metal has prevented the binding of the substrate and rendered the receptor inactive.

Conclusion

Receptor **1** exhibits low affinity for barbiturates and is, therefore, unsuitable to be used as an allosteric receptor. The binding studies on the control models (**2**−**6**) reveals that this inactivity is due to the intramolecular hydrogen bond between N−H_a and the nitrogen atom of the bipyridine ligands. The alteration in the connectivity of the bipyridine ligands (the allosteric site) to the active site of the receptor produced an active receptor **7** that binds to the barbiturate substrate with an association constant $K_a = 2.8\pm0.7 \times 10^3$ M^{-1} in 9:1 CD_2Cl_2/CD_3CN. This activity of receptor **7** is inhibited by the complexation of Zn^{II} ions to the bipyridine ligands which leads to the reduction of the size of the receptor's binding-pocket. Consequently, the design of an allosteric receptor demands a considerable attention not only to the organization of the active and allosteric sites but even more to the mode of connectivity between the two sites. Such a connection should preserve the independent binding abilities of the two sites (in the absence of the co-factor), yet, still be able to communicate the regulating information from the allosteric site to the binding site upon binding of the co-factor.

Experimental Section

General Remarks: All solvents for synthesis were purchased from Caledon Laboratories Limited. CH_2Cl_2 was distilled from calcium hydride before use. All other solvents were used as received. Solvents used for NMR analysis (Cambridge Isotope Laboratories) were used as received. Column chromatography was performed using silica gel 60 (230−400 mesh) from Silicycle Inc. All reagents and starting materials were purchased from Aldrich or Acros Organics. *N*,*N*′-Bis(6-aminopyridin-2-yl)isophthalamide (**8a**),[39] 6-butoxynicotinic acid,[43] 6,6′-dimethyl-2,2′-bipyridine,[49,50] and 5′-methyl-2,2′-bipyridine-5-carbaldehyde (**11**)[42] were prepared as described in the literature.

^{1}H NMR characterizations were performed on a Varian Inova-300 instrument, working at 299.96 MHz, or on a Varian−Inova 500 instrument, working at 499.92 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane using the residual solvent peak as a reference standard. Coupling constants (*J*) are reported in Hertz (Hz). ^{13}C NMR characterizations were performed on a Bruker-300 instrument, working at 74.99 MHz or a Varian Inova-500 instrument, working at 125.29 MHz. FT-IR measurements were performed using a Nicolet Magna-IR 750. Mass spectrometry measurements were performed a Kratos MS-50 with an electron impact source or by positive mode electrospray ionization on a Micromass ZabSpec Hybrid Sector-TOF. The liquid carrier was infused into the electrospray source by means of a Harvard syringe pump at a flow rate of 10 μL/minute. The sample solution, in the same solvent, was introduced via a 1 μL-loop-injector. Pre-purified nitrogen was used as a spray pneumatic aid and filtered air as the bath gas, heated at ca. 80 °C. For low resolution, the mass spectra were acquired by magnet scan at a rate of 5 seconds/decade at ca. 1000 resolution. For exact mass measurements, the spectra were obtained by voltage scan over a narrow mass range at ca. 10000 resolution. Data acquisition and processing was achieved by using the OPUS software package on a Digital Alpha station with VMS operating system.

***N*,*N*′-Bis(6-aminopyridin-2-yl)-5-*tert*-butylisophthalamide (8b):** A solution of 5-*tert*-butylisophthalic acid (1.00 g, 4.5 mmol) in $SOCl_2$ (15 mL) was heated at reflux overnight under argon. The mixture was cooled to room temperature and the excess thionyl chloride was removed under reduced pressure. The oily residue was vacuum dried for 5 h, dissolved in CH_2Cl_2 (40 mL), and added dropwise to a solution of 2,6-diaminopyridine (2.50 g, 22.9 mmol) and triethylamine (0.76 g, 7.6 mmol) in CH_2Cl_2 (20 mL) at room temperature. After the mixture was stirred for 3 h, the solvent was evaporated and the residue was treated with water (50 mL). The precipitate

that formed was collected by vacuum filtration, washed with 20% aqueous EtOH (200 mL), and vacuum dried. Recrystallization from EtOH/water afforded the product (1.31 g, 76%) as a white solid. M.p. 152−154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9 H), 4.35 (s, 4 H), 6.30 (d, *J* = 8 Hz, 2 H), 7.49 (t, *J* = 8 Hz, 2 H), 7.70 (d, *J* = 8 Hz, 2 H), 8.10 (d, *J* = 2 Hz, 2 H), 8.17 (t, *J* = 2 Hz, 1 H), 8.44 (s, 2 H) ppm. ^{13}C NMR (75.6 MHz, $CDCl_3$): δ = 31.3, 35.1, 103.7, 104.1, 122.5, 128.1, 135.0, 140.3, 149.9, 153.3, 157.2, 164.9 ppm. FT-IR (cast): $\tilde{\nu}$ = 3450, 3369, 3295, 3030, 2965, 1689, 1659, 1614, 1577, 1526, 1450, 1347, 1327, 1293, 1250, 1230, 1164, 1151, 791, 752, 614, 576 cm^{-1}. HRMS (ES): *m*/*z* calcd. for $C_{16}H_{15}N_2O_4$ $[M]^+$ = 404.1960, found = 404.1955.

6′-Methyl-2,2′-bipyridine-6-carbaldehyde (9):[41] We have used a different procedure to prepare this known compound. A solution of 6,6′-dimethyl-2,2′-bipyridine (1.00 g, 5.4 mmol) in dioxane (25 mL) was treated with SeO_2 (0.70 g, 6.3 mmol) and heated at reflux for 24 h. The reaction mixture was filtered while hot through Celite and the filtrate was concentrated under reduced pressure to afford a yellow solid. This solid was dissolved in ethyl acetate (100 mL) and extracted with 0.3 M aqueous $Na_2S_2O_5$ (3 × 30 mL). The combined aqueous layers were treated with Na_2CO_3 until a pH value of 10 was attained and then extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to afford the product (0.47 g, 45%) as a beige solid. M.p. 140−142 °C (ref.[41] 135−136 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3 H), 7.20 (d, *J* = 8 Hz, 1 H), 7.74 (t, *J* = 8 Hz, 1 H), 7.95−7.97 (m, 2 H), 8.33 (d, *J* = 6 Hz, 1 H), 8.66 (dd, J_1 = 6, J_2 = 2 Hz, 1 H), 10.14 (s, 1 H) ppm.

6′-Methyl-2,2′-bipyridine-6-carboxylic Acid (10): A rapidly stirred suspension of aldehyde **9** (0.50 g, 2.5 mmol) in EtOH (20 mL) was treated with a solution of silver nitrate (0.45 g, 2.6 mmol) in water (4.5 mL). A 1 M NaOH solution (11.1 mL) was added dropwise over a period of 20 min. The resulting black mixture was stirred for 24 h at room temperature. The mixture was filtered through Celite and the filtrate was washed with CH_2Cl_2 (2 × 10 mL) to remove any unchanged starting material. The pH of the water layer was adjusted to 3.5 by the addition of a 1:1 mixture of 4 N HCl and acetic acid. The resulting solution was extracted with $CHCl_3$ (5 × 20 mL) and the combined organic layers were dried with Na_2SO_4 and filtered. Concentration of the filtrate under reduced pressure afforded the product (0.29 g, 53%) as a pale yellow solid, which was carried on without further purification. M.p. 189−190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3 H), 7.26 (d, *J* = 8 Hz, 1 H), 7.76 (t, *J* = 8 Hz, 1 H), 8.06 (t, *J* = 8 Hz, 1 H), 8.11 (t, *J* = 8 Hz, 1 H), 8.22 (d, *J* = 8 Hz, 1 H), 8.68 (d, *J* = 8 Hz, 1 H) ppm. ^{13}C NMR (125.3 MHz, [D$_6$]DMSO): δ = 25.1, 118.8, 124.1, 124.7, 125.4, 138.3, 139.3, 149.2, 154.5, 156.1, 158.4, 166.7 ppm. FT-IR (microscope): $\tilde{\nu}$ = 2998, 2919, 2616, 2566, 1769, 1704, 1584, 1474, 1447, 1416, 1323, 1261, 1155, 805, 770, 724, 634 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{12}H_{10}N_2O_2$ $[M]^+$ = 214.0742, found = 214.0746.

5′-Methyl-2,2′-bipyridine-5-carboxylic Acid (12): A mixture of 5′-methyl-2,2′-bipyridine-5-carbaldehyde (**11**)[42] (0.40 g, 2.0 mmol), 35% aqueous solution of H_2O_2 (0.5 mL) and acetonitrile (10 mL) was treated with NaH_2PO_4 (0.10 mg, 0.8 mmol) dissolved in water (2 mL). The mixture was stirred in a water bath cooled to 5−10 °C and then treated with an aqueous solution (10 mL) of $NaClO_2$ (0.50 g, 5.52 mmol) dropwise over a period of 1 h while maintaining the temperature of the reaction at less than 10 °C. After stirring for another 2 h at 5−10 °C, a small amount of Na_2SO_3 (0.10 mg) was added to destroy the unchanged HOCl and H_2O_2. The resulting mixture was cooled in an ice bath and treated with 10% HCl solution until a pH of 3.5 was obtained. The deposited beige solid (0.21 g, 49%) was filtered off, washed with water (10 mL) and vacuum dried. This product was carried on without further purification. M.p. > 300 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 2.37 (s, 3 H), 7.80 (dd, J_1 = 8, J_2 = 2.0 Hz, 1 H), 8.35 (d, *J* = 8 Hz, 1 H), 8.38 (dd, J_1 = 8, J_2 = 2 Hz, 1 H), 8.47 (d, *J* = 8 Hz, 1 H), 8.56 (d, *J* = 2 Hz, 1 H), 9.13 (d, *J* = 2 Hz, 1 H), 10.31 (br. s, 1 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 17.9, 119.9, 120.8, 126.3, 134.6, 137.6, 138.1, 149.9, 150.1, 151.8, 158.5, 166.2 ppm. FT-IR (microscope): $\tilde{\nu}$ = 3060, 2921, 2473, 1703, 1594, 1557, 1469, 1369, 1265, 1143, 1053, 1033, 839, 788, 766, 744, 714, 659 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{12}H_{10}N_2O_2$ $[M]^+$ = 214.0742, found = 214.0741.

5-[(Dibutylamino)carbonyl]nicotinic Acid (13): A solution of 3,5-pyridinedicarboxylic acid (1.00 g, 6.0 mmol) in dry CH_2Cl_2 (25 mL) was treated with $SOCl_2$ (10 mL) and heated at reflux overnight under argon. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was dried under vacuum for 5 h to remove traces of $SOCl_2$. The resulting residue was dissolved in dry THF (25 mL) and treated dropwise with a solution of dibutylamine (0.77 g, 6.0 mmol) and triethylamine (0.60 g, 6.0 mmol) in THF (20 mL). The mixture was stirred overnight at room temperature under argon. An aqueous solution of 10% NaOH (3 mL) was added and the mixture was stirred for an additional 30 min. The solvent was removed under reduced pressure, the residue was treated with water (20 mL), washed with CH_2Cl_2 (3 × 10 mL), and treated with 10% HCl solution until a pH of 3 was attained. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure to afford the product (0.78 g, 47%) as a beige solid, which was used without further purification. M.p. 158−160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7 Hz, 3 H), 0.97 (t, *J* = 7 Hz, 3 H), 1.16 (br. m, 2 H), 1.41 (br. m, 2 H), 1.52 (br. m, 2 H), 1.66 (br. m, 2 H), 3.18 (t, *J* = 7 Hz, 2 H), 3.52 (t, *J* = 7 Hz, 2 H), 8.38 (t, *J* = 2 Hz, 1 H), 8.84 (d, *J* = 2 Hz, 1 H), 9.30 (d, *J* = 2 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.7, 14.0, 19.9, 20.4, 29.7, 31.0, 45.3, 49.2, 126.0, 133.0, 136.3, 150.6, 151.0, 167.1, 167.8 ppm. FT-IR (cast): $\tilde{\nu}$ = 2957, 2930, 2872, 1632, 1594, 1458, 1310, 1281, 1230, 1197, 1153, 1113, 1102, 747 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{15}H_{22}N_2O_3$ $[M]^+$ = 278.1630, found = 278.1635.

Bipyridine Receptor 1: A solution of 6′-methyl-2,2′-bipyridine-6-carboxylic acid **10** (46 mg, 0.2 mmol) in $SOCl_2$ (15 mL) was heated at reflux for 4 h under argon. The $SOCl_2$ was removed under reduced pressure and the residue was vacuum dried for 5 h. The solid residue was dissolved in THF (20 mL) and treated dropwise with a solution of *N*,*N*′-bis(6-aminopyridin-2-yl)isophthalamide (**8a**) (38 mg, 0.1 mmol) and triethylamine (0.22 g, 0.2 mmol) in THF (20 mL) at room temperature under argon. The mixture was stirred overnight at room temperature, washed with water (3 × 10 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to afford a yellow residue. Purification by flash chromatography (alumina, 1% to 10% gradient of MeOH in $CHCl_3$) followed by recrystallized from ethanol/water afforded the product (36 mg, 44%) as a white solid. M.p. > 300 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.58 (s, 6 H), 7.12 (d, *J* = 8 Hz, 2 H), 7.64−7.72 (m, 3 H), 7.85 (t, *J* = 8 Hz, 2 H), 7.98 (t, *J* = 5 Hz, 2 H), 8.13−8.27 (m, 10 H), 8.53 (s, 1 H), 8.58 (d, *J* = 7 Hz, 2 H), 8.74 (s, 2 H), 10.34 (s, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.5, 110.1, 118.0, 122.4, 123.9, 124.4, 125.4, 129.7, 131.4, 134.7, 137.4, 138.5, 141.1, 148.3, 149.4, 149.9, 150.1 162.5, 164.5, 175.6, 176.2 ppm. FT-IR (cast): $\tilde{\nu}$ = 3346, 1692, 1583, 1507, 1447,

1391, 1301, 1243, 1156, 1074, 994, 797, 758, 712, 634 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{42}H_{33}N_{10}O_4$ $[M + H]^+$ = 741.2686, found = 741.2685.

Di-*tert*-butylphenyl Receptor 2: A solution of 3,5-di-*tert*-butylbenzoic acid (50 mg, 0.2 mmol) in oxalyl chloride (15 mL) was heated at reflux for 4 h under argon. The oxalyl chloride was removed under reduced pressure and the residue was vacuum dried for 5 h. The solid obtained was dissolved in THF (30 mL) and treated dropwise with a solution of *N*,*N*′-bis(6-aminopyridin-2-yl)isophthalamide (**8a**) (38 mg, 0.1 mmol) and triethylamine (0.22 g, 0.2 mmol) in THF (20 mL) at room temperature under argon. After stirring the mixture overnight at room temperature, the solvent was evaporated to afford a yellow residue, which was purified by flash chromatography (alumina, 1% MeOH in $CHCl_3$) to afford the product (48 mg, 55%) as a white solid. M.p. > 180 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 36 H), 7.60−7.65 (m, 6 H), 7.72 (d, *J* = 1 Hz, 2 H), 7.82 (t, *J* = 8 Hz, 2 H), 8.08 (d, *J* = 8 Hz, 2 H), 8.09 (dd, J_1 = 8, J_2 = 2 Hz, 2 H), 8.15 (d, *J* = 8 Hz, 2 H), 8.35 (s, 2 H), 8.48 (s, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 31.5, 35.12, 109.8, 110.3, 121.4, 125.9, 126.7, 129.6, 130.8, 133.7, 134.9, 141.1, 149.4, 150.1, 151.8, 164.3, 166.6 ppm. FT-IR (cast): ṽ = 3421, 3285, 3015, 2963, 2905, 2868, 1680, 1584, 1506, 1478, 1449, 1393, 1363, 1307, 1242, 1158, 1136, 898, 885, 800, 756, 704, 666, 596, 543 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{48}H_{56}N_6NaO_4$ $[M + Na]^+$ = 803.4261, found = 803.4261.

General Procedure for the Preparation of Receptors 3, 4, 5, and 6: A solution of the corresponding carboxylic acid (1.2 mmol) in $SOCl_2$ (15 mL) was heated at reflux for 4 h under argon. The excess $SOCl_2$ was removed under reduced pressure and the residue was dried under vacuum for 5 h. The solid obtained was dissolved in CH_2Cl_2 (20 mL) and treated dropwise with a solution of *N*,*N*′-bis(6-aminopyridin-2-yl)isophthalamide (**8a**) (175 mg, 0.5 mmol) and triethylamine (100 mg, 1.0 mmol) in THF (20 mL) at room temperature under argon. After the mixture was stirred overnight, the solvent was evaporated under reduced pressure. The residue was treated with water (20 mL) and the precipitate that formed was filtered off, washed with water (10 mL), and vacuum dried. The product was purified by chromatography over alumina using a gradient of 1% to 10% MeOH in $CHCl_3$ as the eluent.

Pyridine Receptor 3: The carboxylic acid was picolinic acid (0.14 g, 1.2 mmol) and the product (0.13 g, 47%) was collected as a beige solid. M.p. > 270 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50−7.46 (m, 2 H), 7.67 (t, *J* = 8 Hz, 1 H), 7.94 (m, 6 H), 8.17−8.13 (m, 6 H), 8.30 (d, *J* = 8 Hz, 2 H), 8.57 (s, 1 H), 8.63 (d, *J* = 5 Hz, 2 H), 8.72 (br. s, 2 H), 10.41 (s, 2 H) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 108.6, 110.2, 122.2, 124.5, 127.1, 127.6, 128.4, 131.6, 138.6, 141.0, 148.6, 149.0, 150.8, 161.7, 165.2, 175.7 ppm. FT-IR (microscope): ṽ = 3330, 1089, 1053, 1680, 1667, 1589, 1514, 1482, 1449, 1393, 1307, 1245, 1229, 1155, 1090, 1076, 999, 800, 748, 714, 691, 613, 590 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{30}H_{22}N_8NaO_4$ $[M + Na]^+$ = 581.1662, found = 581.1664.

Pyridine Receptor 4: The carboxylic acid was nicotinic acid (0.14 g, 1.2 mmol) and the product (0.18 g, 64%) was collected as a white solid. M.p. 192−194 °C. ^1H NMR (300 MHz, [D_6]DMSO): δ = 7.55 (m, 2 H), 7.69 (t, *J* = 8 Hz, 1 H), 7.89 (m, 2 H), 7.93 (s, 2 H), 7.95 (d, *J* = 4 Hz, 2 H), 8.20, (dd, J_1 = 8, J_2 = 2 Hz, 2 H), 8.33 (dt, J_1 = 8, J_2 = 2 Hz, 2 H), 8.58 (br. s, 1 H), 8.77 (m, 2 H), 9.12 (d, *J* = 2 Hz, 2 H), 10.60 (s, 2 H), 10.77 (s, 2 H) ppm. ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 111.4, 111.6, 123.4, 127.3, 128.9, 129.8, 131.4, 134.1, 135.6, 140.2, 148.8, 150.2, 150.4, 152.4, 164.6, 165.2 ppm. FT-IR (microscope): ṽ = 3428, 3319, 3233, 3042, 1667, 1590, 1524, 1477, 1444, 1391, 1304, 1239, 1160, 1028, 805, 733, 715 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{30}H_{22}N_8NaO_4$ $[M + Na]^+$ = 581.1662, found = 581.1656.

Pyridine Receptor 5: The carboxylic acid was 6-butoxynicotinic acid[43] (0.23 g, 1.2 mmol) and the product (0.21 g, 61%) was collected as a white solid. M.p. 244−246 °C. ^1H NMR (500 MHz, CD_2Cl_2): δ = 0.97 (t, *J* = 7 Hz, 6 H), 1.50−1.45 (m, 4 H), 1.79−1.73 (m, 4 H), 4.36 (t, *J* = 7 Hz, 4 H), 6.81 (d, *J* = 8 Hz, 2 H), 7.67 (t, *J* = 8 Hz, 1 H), 7.82 (t, *J* = 8 Hz, 2 H), 8.13−8.06 (m, 8 H), 8.33 (s, 2 H), 8.48 (s, 1 H), 8.56 (s, 2 H), 8.72 (s, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.9, 19.3, 31.0, 66.7, 110.1, 110.5, 111.3, 122.9, 125.8, 129.7, 131.0, 134.8, 137.7, 141.1, 147.2, 149.5, 149.8, 163.9, 164.4, 166.6 ppm. FT-IR (cast): ṽ = 3315, 2957, 1677, 1600, 1514, 1487, 1446, 1398, 1369, 1293, 1241, 797 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{38}H_{39}N_8O_6$ $[M + H]^+$ = 703.2993, found = 703.2984.

Pyridine Receptor 6: The carboxylic acid was 5-[(dibutylamino)carbonyl]nicotinic acid (**13**) (0.33 g, 1.2 mmol) and the product (0.19 g, 43%) was collected as a yellow solid. M.p. 140−142 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 7 Hz, 6 H), 0.91 (t, *J* = 8 Hz, 6 H), 1.12 (br. m, 4 H), 1.32 (br. m, 4 H), 1.47 (br. m, 4 H), 1.56 (br. m, 4 H), 3.16 (br. t, 4 H), 3.41 (br. t, 4 H), 7.64 (t, *J* = 8 Hz, 1 H), 7.79 (t, *J* = 8 Hz, 2 H), 8.01 (d, *J* = 8 Hz, 2 H), 8.13 (d, *J* = 8 Hz, 2 H), 8.19 (dd, J_1 = 8, J_2 = 2 Hz, 2 H), 8.27 (t, *J* = 2 Hz, 2 H), 8.61 (s, 1 H), 8.84 (d, *J* = 2 Hz, 2 H), 8.95 (br. s, 2 H), 9.06 (br. s, 2 H), 9.13 (d, *J* = 2 Hz, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.5, 12.8, 19.7, 20.2, 29.5, 30.8, 44.9, 49.0, 110.9, 111.1, 125.1, 129.3, 129.7, 131.8, 132.7, 134.1, 134.4, 140.7, 149.0, 149.6, 149.9, 150.6, 163.6, 165.2, 167.9 ppm. FT-IR (cast): ṽ = 3266, 2958, 2931, 2872, 1680, 1620, 1587, 1515, 1446, 1299, 1241, 1158, 1109, 1026, 799, 751, 584 cm^{-1}. HRMS (EI): *m*/*z* calcd. for $C_{48}H_{56}N_{10}NaO_6$ $[M + Na]^+$ = 891.4282, found = 891.4292.

Bipyridine Receptor 7: A solution of 5′-methyl-2,2′-bipyridine-5-carboxylic acid (**12**) (0.26 g, 1.2 mmol) in $SOCl_2$ (15 mL) was heated at reflux for 4 h under argon. The excess $SOCl_2$ was removed under reduced pressure and the residue was vacuum dried for 5 h. The solid obtained was dissolved in CH_2Cl_2 (20 mL) and treated dropwise with a solution of *N*,*N*′-bis(6-aminopyridin-2-yl)-5-*tert*-butylisophthalamide (**8b**) (0.20 g, 0.5 mmol) and triethylamine (0.10 g, 1.0 mmol) in CH_2Cl_2 (20 mL) at room temperature under argon. After the mixture was stirred overnight, it was washed with water (3 × 10 mL), dried with anhydrous Na_2SO_4, and filtered. Concentration of the filtrate under reduced pressure afforded a beige residue. Purification by flash chromatography (alumina, 1% to 10% MeOH in $CHCl_3$) afforded the product (0.26 g, 65%) as a white solid. M.p. >190 °C (dec.). ^1H NMR (500 MHz, CD_2Cl_2): δ = 1.43 (s, 9 H), 2.38 (s, 6 H), 8.12 (d, *J* = 8 Hz, 2 H), 8.17 (d, *J* = 8 Hz, 2 H), 7.63 (d, *J* = 9 Hz, 2 H), 7.86 (t, *J* = 8 Hz, 2 H), 8.28 (s, 2 H), 8.29 (d, *J* = 6 Hz, 2 H), 8.34 (d, *J* = 9 Hz, H_e), 8.48 (s, 1 H), 8.51 (s, 2 H), 8.53 (d, *J* = 6 Hz, 2 H), 8.62 (br. s, 2 H), 8.71 (br. s, 2 H), 9.17 (s, 2 H) ppm. ^{13}C NMR (125.3 MHz, $CDCl_3$): δ = 29.8, 31.3, 35.3, 110.3, 120.6, 121.3, 122.3, 128.7, 128.9, 134.2, 134.6, 136.3, 136.4, 137.6, 140.9, 147.9, 149.3, 149.5, 149.6, 151.7, 158.5, 162.3, 163.4, 164.8 ppm. FT-IR (cast): ṽ = 3288, 2964, 1682, 1588, 1513, 1447, 1396, 1298, 1241, 1158, 1128, 1028, 896, 838, 798, 744, 651 cm^{-1}. HRMS (ES): *m*/*z* calcd. for $C_{46}H_{41}N_{10}O_4$ $[M + H]^+$ = 797.3312, found = 797.3312.

Zinc Complex 7·Zn: A solution of bipyridine receptor **7** (5 mg, $6.3 \cdot 10^{-3}$ mmol) in CH_2Cl_2 (5 mL) was treated with a solution of $Zn(OTf)_2$ (2.3 mg, 6.3×10^{-3} mmol) in CH_3CN (1 mL). The mixture was stirred for 15 min at room temperature under argon. The

solvent was evaporated under reduced pressure and the residue treated with CH_2Cl_2 (1 mL). The deposited white solid (7.3 mg, 100%) was collected by filtration and vacuum dried. ^1H NMR (500 MHz, 10% CD_3CN in CD_2Cl_2): δ = 1.40 (s, 9 H), 2.36 (s, 6 H), 7.82 (t, *J* = 8 Hz, 2 H), 7.90 (d, *J* = 8 Hz, 2 H), 8.01 (d, *J* = 8 Hz, 2 H), 8.07 (s, 2 H), 8.09 (d, *J* = 8 Hz, 2 H), 8.27 (s, 2 H), 8.31 (d, *J* = 8 Hz, 2 H), 8.33 (s, 1 H), 8.45 (d, *J* = 8 Hz, 2 H), 8.65 (d, *J* = 8 Hz, 2 H), 9.38 (s, 2 H), 9.52 (s, 2 H), 10.50 (s, 2 H) ppm. ^{13}C NMR (125.7 MHz, 10% CD_3CN in CD_2Cl_2): δ = 18.4, 31.0, 35.2, 109.7, 110.4, 122.2, 122.6, 122.9, 129.5, 134.3, 134.7, 139.1, 140.8, 141.8, 142.1, 146.1, 147.5, 148.5, 149.9, 150.8, 151.6, 153.6, 163.6, 165.0 ppm. FT-IR (cast): $\tilde{\nu}$ = 3270, 2963, 1681, 1586, 1522, 1477, 1449, 1390, 1245, 1161, 1031, 901, 840, 799, 737, 639 cm^{-1}. HRMS (ES): *m/z* calcd. for $C_{46}H_{39}N_{10}O_4Zn$ $[M - H]^+$ = 859.2447, found = 859.2445, calcd. for $C_{48}H_{41}F_6N_{10}O_{10}S_2Zn$ $[M + 2OTf + H]^+$ = 1159.1644, found = 1159.1648.

General Procedure to Measure Association Constants Using ^1H NMR Titration Experiments: A solution of the receptor (500−600 μL, 2−5 mM in CD_2Cl_2 or 9:1 CD_2Cl_2/CD_3CN) was transferred to an NMR tube fitted with a rubber septum to minimize the evaporation of the solvent. Aliquot amounts of a solution of 5,5-dibutylbarbiturate (20−100 mM in the same solvent) were added to the NMR tube through the rubber septum via a syringe. The number of additions varied between 15 and 20 with an increase in the amount of substrate solution added until a total of 10 molar equivalents of the guest was attained. The chemical shifts of the signals corresponding to the $N-H_a$ protons were monitored and the collected data were analyzed using a non-linear least square regression program to fit the data to a theoretical model for the binding process. The program used was kindly provided by Dr. Christopher A. Hunter (Department of Chemistry, University of Sheffield, UK).

X-ray Crystal Data for 3: $C_{30}H_{22}N_8O_4$, molecular weight = 558.56, crystal dimensions = 0.34 × 0.18 × 0.06 mm, monoclinic, space group $P2_{1/c}$ (No. 14), *a* = 11.4591(11), *b* = 17.3834(17), *c* = 13.5351(13) Å, β = 101.9892(19), *V* = 2637.4(4) $Å^3$, *T* = −80 °C, *Z* = 4, μ = 0.098 mm^{-1}, 15018 reflections measured, 5394 unique, $R_1[F_o^2 \geq 2\sigma(F_o^2)] = 0.0772$, wR_2 $[F_o^2 \geq -3\sigma(F_o^2)] = 0.2051$ (all data).

CCDC-224144 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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