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Ji-Yeon Lee[a]; Min-Hee Lee[a]; Kyu-Sung Jeong[a]
[a] Department of Chemistry, Center for Bioactive Molecular Hybrids, Yonsei University, Seoul, South Korea

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Synthesis and Binding Properties of Anion Receptors Containing Multiple Hydrogen Bond Donors

JI-YEON LEE, MIN-HEE LEE and KYU-SUNG JEONG*

Department of Chemistry, Center for Bioactive Molecular Hybrids, Yonsei University, Seoul 120-749, South Korea

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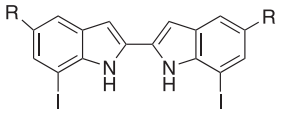
A new biindolyl scaffold, 7,7′-diamino-2,2′-biindolyl, 2 was efficiently synthesized and modified into anion receptors 9 and 10 with extended hydrogen bond donors. The receptor 9 possesses two indole NHs and two amide NHs, while 10 contains two indole NHs and four urea NHs. The receptors 9 and 10 bind oxoanions such as phosphates and carboxylates by multiple hydrogen bonds in DMSO, both of which bind two or three orders of magnitudes higher than does a reference molecule 8 with only two indole NHs. In addition, binding affinities of 10 with a series of dicarboxylates were also investigated, showing the association constants in between 1.6 × 10^5 M^{-1} (malonate) and 8.1 × 10^5 M^{-1} (adipate) in 10% (v/v) MeOH/DMSO at 22 ± 1°C.

Keywords: Anion receptor; Hydrogen bond; Biindolyl; Supramolecular chemistry

INTRODUCTION

Hydrogen bonds play a major role in biotic and abiotic systems including the ordered structures of nucleic acids and proteins, self-assembly of supramolecular aggregates, and selective recognition between receptors and substrates. Owing to appropriate strength, directionality, and convenient manipulation, hydrogen bonds are frequently utilized to construct synthetic receptors that selectively bind a specific guest. Because anions are generally good hydrogen bond acceptors, anion receptors are designed and synthesized by incorporation of multiple hydrogen bond donors in a convergent manner. For this purpose, amido, ureido [1–8] and pyrrolic NHs [9–12] are commonly used, together with the aryl CHs adjacent to hetero atoms, in particular positively charged nitrogen [13].

In recent years, we have demonstrated that biindolyl scaffold **1** can serve as a useful building block for the synthesis of anion receptors [14–17]. The coupling of two biindolyl moieties through rod-like ethynyl linkers yielded macrocycles which contain an internal cavity surrounded by four indole NHs, thus strongly binding halides and oxoanions with high selectivities in acetonitrile [15]. In addition, by sequentially connecting the biindolyl scaffold we also prepared oligoindole foldamers capable of folding into a helical structure when chloride was entrapped in the cavity by forming up to eight hydrogen bonds [14].



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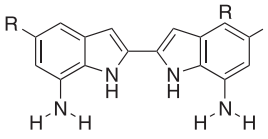

2

We here describe the synthesis of diaminobiindolyl **2** that can be used as a useful scaffold to synthesize anion receptors. The new scaffold **2** with additional diamino groups can be easily modified into anion receptors with multiple hydrogen bond

*Corresponding author . E-mail: ksjeong@yonsei.ac.kr

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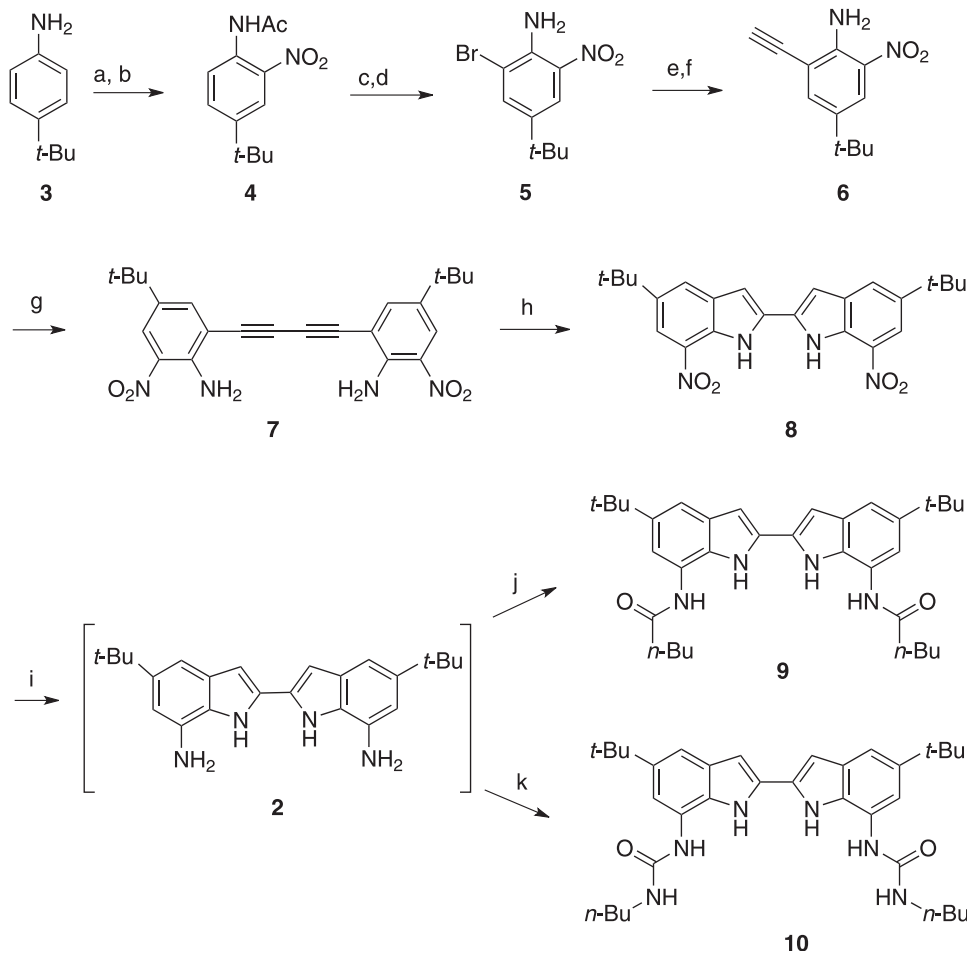
donors, as demonstrated in **9** and **10** containing four and six hydrogen bond donors, respectively [18–20]. The receptors **9** and **10** bind phosphates and carboxylates by hydrogen-bonding interactions and the association constants increase with increasing hydrogen bond donors, **8** (two NHs) < **9**(four NHs) < **10** (six NHs). In addition, the binding properties between **10** and a series of dicarboxylates are also investigated.

RESULTS AND DISCUSSION

The synthesis of diaminobiindolyl **2** and receptors **9** and **10** are outlined in Scheme 1. 4-(*tert*-Butyl)aniline (**3**) was subjected to acetylation (Ac_2O, 94%) followed by nitration (H_2SO_4/HNO_3, 76%) to give 4-(*tert*-butyl)-2-nitroacetanilide (**4**). After deacetylation (KOH/H_2O-EtOH, 81%), **4** was reacted with bromine to provide 2-bromo-4-(*tert*-butyl)-6-nitroaniline (**5**) in 82% yield. The Pd/CuI catalyzed Sonogashira coupling [21] of **5** with trimethylsilyl(TMS)-ethyne (86% yield), followed by deprotection of the TMS group under a basic condition (K_2CO_3/MeOH, 98% yield), gave compound **6**. The oxidative homocoupling ($Cu(OAc)_2 \cdot H_2O$/pyridine 85% yield) [14–17,22,23], then indolization (CuI/DMF, 63% yield) [14–17,24,25] of **6** yielded 3,3′-di-*tert*-butyl-7,7′-dinitro-2,2′-biindolyl (**7**). Then, **7** was reduced in the presence of Raney Ni to give a new building block, 3,3′-di-*tert*-butyl-7,7′-diamino-2,2′-biindolyl (**2**). Without further purification due to poor solubility, **2** was directly coupled with pentanoyl chloride and butane-1-isocyanate to give receptors **9** and **10**, respectively.

The binding property of **9** with dihydrogen phosphate was first investigated in DMSO-d_6 by the ^{1}H NMR spectroscopy (Fig. 1). When tetrabutylammonium dihydrogen phosphate (approximately 2 equiv) was added, two NH signals were significantly downfield shifted from 10.91 to 13.32 ppm for indole NHs and from 9.61 to 11.19 ppm for amide NHs, indicative of hydrogen bond formation. In addition, the signals for the aromatic CH^b and CH^c, were slightly upfield shifted by $\Delta\delta = 0.1-0.2$ ppm, while the CH^a



SCHEME 1 Reagents and conditions: (a) $(CH_3CO)_2O$, CH_2Cl_2, room temperature, 40 min, 94%; (b) H_2SO_4, HNO_3,$CHCl_3$, room temperature, 30 min, 76%; (c) KOH, H_2O/EtOH, room temperature, 5 h, 81%; (d) Br_2, CH_2Cl_2, room temperature, 19 h, 82%; (e) trimethylsilylethyne, $Pd(PPh_3)Cl_2$, CuI, Et_3N, THF, 84–87°C, 24 h, 86%; (f) K_2CO_3, MeOH, room temperature, 15 min, 98%; (g) $Cu(OAc)_2H_2O$, pyridine, room temperature, 16 h, 85%; (h) CuI, DMF, 144–146°C, 3 h, 63%; (i) Raney Ni, EtOAc, H_2, room temperature, 11 h; (j) $CH_3(CH_2)_3COCl$, pyridine, N_2, room temperature, 50 min, 55% for two steps; (k) $CH_3(CH_2)_3NCO$, THF, reflux, 4 h, 69% for two steps.

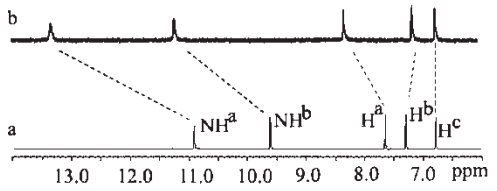
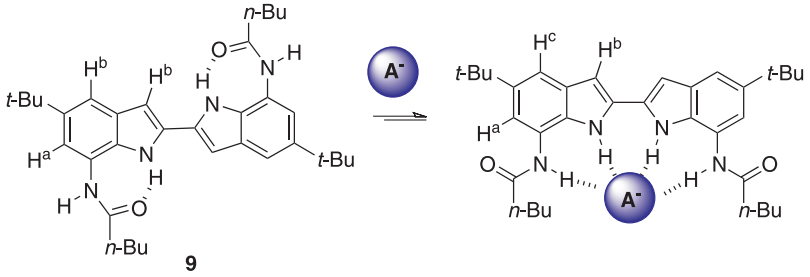


FIGURE 1 Partial ^{1}H NMR spectra (400 MHz, DMSO-d_6, 25°C) of (a) **9** (0.7 mM), (b) **9** in the presence of $H_2PO_4^-$ N^+Bu_4 (~2 equiv).

intramolecular hydrogen bonds with indole NHs. In the presence of dihydrogen phosphate, however, intermolecular hydrogen bond formation of both amide and indole NHs force the carbonyl group to rotate close to the CH^a proton, which induces a downfield shift of the CH^a signal possibly due to deshielding effect of the C═O double bonds and/or intramolecular $CH^a\cdots O{=}C$ hydrogen bond. It should be mentioned that, according to the computer



SCHEME 2 Plausible structures of receptor **9** and its complex with an anion.

signal was downfield shifted from 7.65 to 8.30 ppm. The upfield shifts of the CH^b and CH^c are attributed to the formation of the NH (indole and amide)$\cdots^-O_2P(OH)_2$ hydrogen bonds which leads to increasing polarization of the NH bond. On the other hand, the downfield shift of the CH^a signal possibly results from the conformational change of the carbonyl group. That is, the carbonyl group of **9** is inward directed to form

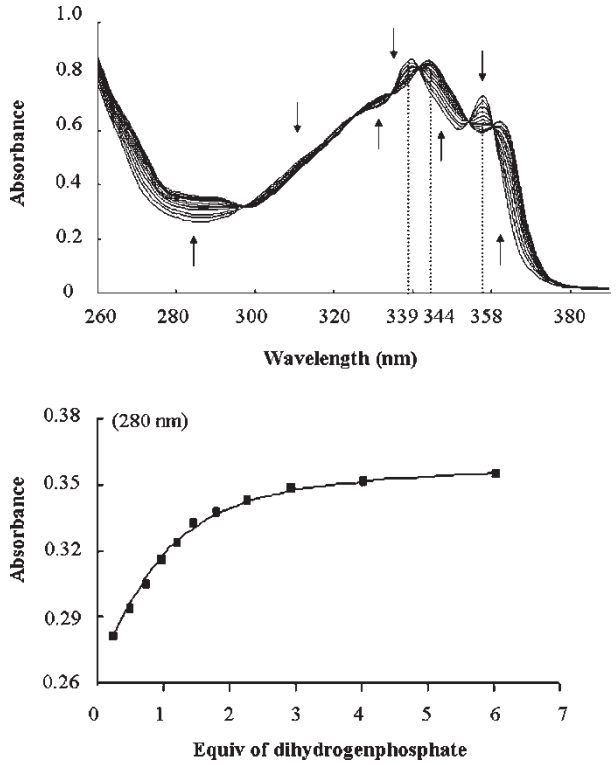


FIGURE 2 UV-visible absorption spectral changes of **9** (2.0×10^{-5} M) upon addition of $H_2PO_4^-$ N^+Bu_4 in DMSO and the experimental (dark square) and theoretical (solid line) saturation curve at 280 nm.

modeling [26], the biindolyl unit in **9** exists in a transoid conformation to minimize dipole–dipole repulsion but it adopts a cisoid conformation in the presence of an anion, forming simultaneous multiple hydrogen bonds with both indole and amide NHs (Scheme 2).

The binding properties of receptors toward oxoanions were revealed by the UV-visible titrations in dimethyl sulfoxide (DMSO, containing 0.1–0.2% of water) at 22 ± 1°C. As a representative example, the absorption spectrum of **9** (2.0×10^{-5} M) was gradually changed when dihydrogen phosphate was added up to 12×10^{-5} M (Fig. 2). Several isosbetic points (297, 334, 341, 354, and 360 nm) are clearly seen, reflecting that **9** and its complex exist in equilibrium. The association constant (K_a) were determined by non-linear squares fitting analysis of the titration curve [27], and are averaged ones obtained at least two different wavelengths. The titration experiments were all duplicated and errors in the magnitudes of the association constants are within 20%.

The association constants are summarized in Table I and depend on the number of hydrogen bond donors of the receptor. For example, the association constants of **9** are 4.3×10^4 M^{-1} and

TABLE I Association constants (K_a, M^{-1}) between receptors **8**, **9**, and **10** and anions in DMSO (containing 0.1–0.2% water) at 22 ± 1°C

	K_a (M^{-1})		
Anion†	**8**	**9**	**10**
AcO^-	40 ± 8	$(4.3 \pm 0.3) \times 10^4$	$(7.5 \pm 0.4) \times 10^4$
$H_2PO_4^-$	56 ± 3	$(1.4 \pm 0.1) \times 10^5$	$(3.9 \pm 0.1) \times 10^5$
$HP_2O_7^{3-}$	Nd‡	$(5.2 \pm 0.3) \times 10^5$	$>5 \times 10^6$

† Anions were used as tetrabutylammonium salts. ‡ Not determined.

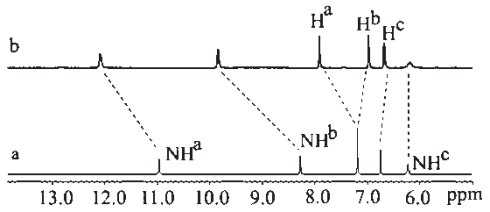


FIGURE 3 Partial ^{1}H NMR spectra (400 MHz, DMSO-d_6, 25°C) of (a) **10** (1.8 mM), (b) **10** in the presence of $H_2PO_4^-$ N^+Bu_4 (1.1 equiv).

$1.4 \times 10^5\,M^{-1}$ for acetate and dihydrogen phosphate, respectively. For comparison, a reference molecule **8** having two indole NH donors comparison showed the association constants of 40 (acetate) and $56\,M^{-1}$ (dihydrogen phosphate) under the same conditions. In addition, the receptor **10** ($K_a > 5 \times 10^6\,M^{-1}$) having six NH donors showed much stronger binding affinity toward pyrophosphate than **9** ($K_a = 5.2 \times 10^5\,M^{-1}$). On the other hand, the association constant of **10** toward acetate and dihydrogen phosphate were found to be only two to three times higher than those of **9**. This observation implies that the additional NH donors in **10** are not effectively participated in the binding of acetate and dihydrogen phosphate, as proved by the ^{1}H NMR spectroscopy (Fig. 3). When tetrabutylammonium dihydrogen phosphate (1.1 equiv) was added to a DMSO-d_6 solution (2 mM) of **10**, the signals for the indole NH^a and the urea NH^b are considerably downfield shifted by $\Delta\delta = 1.24$ ppm and 1.65 ppm, while that of the urea NH^c was negligibly changed.

Next, binding properties between **10** and a series of dicarboxylates were examined. Unlike acetate and dihydrogen phosphate, when bis(tetrabutylammonium) dicarboxylates were added, all of the three NH signals were largely downfield shifted by more than 2 ppm as a result of strong hydrogen bonds (Fig. 4). For example, the NH^a, NH^b, and NH^c signals in the presence of succinate were shifted from 10.98 ppm, 8.29 ppm, and 6.25 ppm to 12.26 ppm, 10.41 ppm, and 8.25 ppm in DMSO, respectively. The association constants of **10** with dicarboxylates were

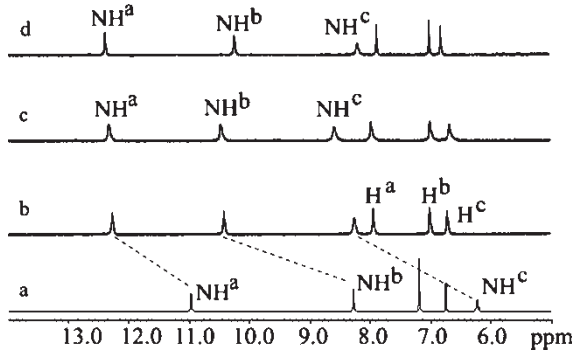


FIGURE 4 Partial ^{1}H NMR spectra (400 MHz, DMSO-d_6, 25°C) of **10** in the presence of bis tetrabutylammonium dicarboxylates (~ 5 equiv) (a) none, (b) succinate, (c) glutarate, and (d) adipate.

TABLE II Association constants (K_a, M^{-1}) between **10** and dicarboxylates in 10% (v/v) MeOH/ DMSO at 22 ± 1°C

Anion	K_a (M^{-1})
Malonate	$(1.6 \pm 0.2) \times 10^5$
Succinate	$(2.5 \pm 0.5) \times 10^5$
Glutarates	$(4.7 \pm 0.8) \times 10^5$
Adipate	$(8.1 \pm 0.6) \times 10^5$
Citrate	$(3.6 \pm 0.8) \times 10^5$

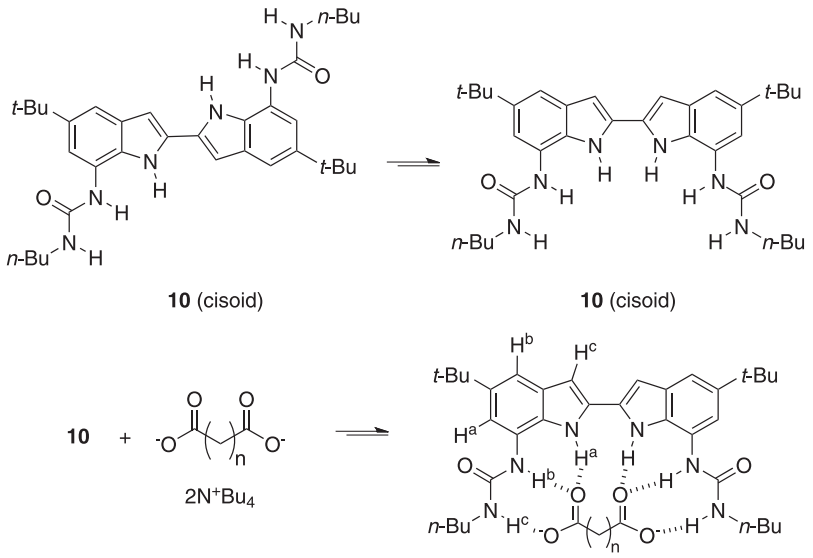
found to be too high ($K_a > 10^6\,M^{-1}$) in DMSO, and therefore were determined in a more hydrogen bond-competitive medium 10% v/v MeOH/DMSO.

As summarized in Table II, the association constants are in the range of $1.6 \times 10^5\,M^{-1}$ for malonate to $8.1 \times 10^5\,M^{-1}$ for adipate. The 1:1 stoichiometry of the complex was confirmed by the continuous variation method (Job plot) [28,29]. The binding selectivity between dicarboxylates is low, possibly because the conformational flexibility of **10** (Scheme 3). In a transoid conformation, two hydrogen bonding sides are far away but become closer by adopting a cisoid conformation upon binding an anion. The distance between two hydrogen bonding sides depends on the degree of the bond rotation in between two indole rings, which in turn depends on the chain length of dicarboxylates. Consequently, the binding affinities of the dicarboxylates studied here are all strong but the selectivities are low.

In conclusion, we have demonstrated that diaminobiindolyl **2** is a useful building block to synthesize receptors **9** and **10** with extended hydrogen bond donors. The receptors strongly bind oxyanions by hydrogen-bonding interactions in a highly polar medium, and the binding affinities were proven to strongly depend on the number of hydrogen bond donors of receptors. The conformation of the receptor can be controlled from transoid to cisoid by anion binding, which is an important feature for the construction of molecular machines responsible to an external stimulation [30,31].

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. ^{1}H and ^{13}C NMR spectra were acquired using Bruker DPX-400 and chemical shifts were reported in ppm downfield relative to the residual protonated solvent peaks ($CHCl_3$: 7.26 ppm for ^{1}H NMR spectrum, 77 ppm for ^{13}C NMR spectrum). Infrared spectra were recorded on a Nicollet Impact 360 FT-IR spectrometer. UV-visible absorption spectra were recorded using a HP 8453 UV-Visible spectrophotometer. All reagents were used as received, and solvents were used either as purchased or purified by standard methods.



SCHEME 3 Two possible conformations of **10** and a suggested structure of its complex with dicarboxylates.

4-*tert*-Butyl-2-nitroacetanilide (**4**): Acetic anhydride (19 mL, 0.2 mol) was added to 4-*tert*-butylaniline (**3**) (25 g, 0.17 mol) in CH_2Cl_2 (120 mL) and the solution was stirred at room temperature for 40 min. Then, saturated $NaHCO_3$ solution was carefully added and the solution was stirred for additional 30 min. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and concentrated to give essentially pure 4-*tert*-butylacetanilide as a white solid (30 g, 94%). Mp 160–161°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.83 (s, 1H; NH), 7.47 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.4$ Hz, 2H), 2.01 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.6, 145.8, 137.3, 125.8, 119.4, 34.5, 31.8, 24.5. IR (KBr) ν 3567(NH), 1667(C═O) cm^{-1}.

To a solution of 4-*tert*-butylacetanilide (30 g, 0.16 mol) in $CHCl_3$ (350 mL) were added sulfuric acid (26 mL, 0.49 mol) and nitric acid (21 mL, 0.45 mol). The solution was stirred at room temperature for 30 min and washed sequentially with H_2O, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/hexane 4:1) to give **4** as a light yellow solid (28 g, 76%). Mp 95°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H; NH), 7.83 (d, $J = 2.0$ Hz, 1H), 7.74 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.52 (d, $J = 8.4$ Hz, 1H), 2.04 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.5, 148.1, 142.4, 130.9, 128.7, 125.3, 121.0, 34.4, 30.7, 23.3. IR (KBr) ν 3342 (NH), 1704 (C═O), 1516 and 1340 (NO_2) cm^{-1}.

2-Bromo-4-*tert*-butyl-6-nitroaniline (**5**): To a solution of **4** (20 g, 0.09 mol) in ethanol (200 mL) was added an aqueous solution (30 mL) containing KOH (24 g, 0.43 mol). The mixture was stirred at room temperature for 5 h. After concentration, the residue was dissolved in EtOAC and washed with water and brine. The solution was dried over anhydrous $MgSO_4$ and concentrated, and the residue was purified by column chromatography (silica gel, CH_2Cl_2/hexane 3:1) to give 4-*tert*-butyl-6-nitroaniline as an orange solid (13 g, 81%). Mp 99°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, $J = 2.0$ Hz, 1H), 7.52 (dd, $J = 8.8$, 2.0 Hz, 1H), 7.30 (s, 2H), 6.97 (d, $J = 8.8$ Hz, 1H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.0, 138.6, 134.7, 130.0, 120.6, 119.9, 34.2, 31.2. IR (KBr) ν 3477 (NH_2), 1516 and 1340 (NO_2) cm^{-1}.

To a solution of 4-*tert*-butyl-6-nitroaniline (16 g, 0.08 mol) in CH_2Cl_2 (300 mL) at 0°C was added dropwise a solution of Br_2 (11 mL, 2.5 equiv) in CH_2Cl_2 (60 mL). The solution was stirred at room temperature for 19 h and washed sequentially with 1 N NaOH aqueous solution, saturated $Na_2S_2O_3{\cdot}5H_2O$ solution, and brine. The organic layer was dried over $MgSO_4$ and concentrated, and the residue was purified by column chromatography (silica gel, CH_2Cl_2/hexane 2:1) to give **5** as a brown solid (18 g, 82%). Mp 61°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, $J = 2.4$ Hz, 1H), 7.92 (d, $J = 2.4$ Hz, 1H), 7.04 (s, 2H; NH), 1.25 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 140.2, 138.4, 136.8, 130.9, 120.6, 111.2, 33.3, 30.1. IR (thin film) ν 3493 (NH_2), 1499 and 1344 (NO_2) cm^{-1}.

2-Ethynyl-4-*tert*-butyl-6-nitroaniline (**6**): **5** (3.4 g, 0.01 mol), $Pd(PPh_3)Cl_2$ (0.13 g, 0.18 mmol) and CuI (0.07 g, 0.36 mmol) were placed in a Schlenk flask. The flask was degassed under high vacuum and back-filled with nitrogen, which process was repeated three times. Degassed tetrahydrofuran (15 mL), triethylamine (60 mL) and trimethylsilylethyne (2.5 mL, 1.5 equiv) were sequentially added, and the resulting solution was stirred under nitrogen at 84–87°C for 24 h. After cooled to room temperature, the mixture was filtered through celite and concentrated. The residue was dissolved CH_2Cl_2,

and washed with saturated $NaHCO_3$ (40 mL) and brine (40 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/hexane 3:1) to give a TMS-protected precursor as a yellow solid (3.0 g, 86%). Mp 69°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, $J = 2.4$ Hz, 1H), 7.70 (d, $J = 2.4$ Hz, 1H), 6.92 (s, 2H; NH), 1.25 (s, 9H), 0.28 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 144.2, 138.6, 137.5, 131.4, 122.9, 111.9, 103.0, 100.1, 34.3, 31.2, 0.48. IR (thin film) ν 3489 (NH_2), 2149 (C≡C), 1520 and 1352 (NO_2) cm^{-1}.

The TMS-protected precursor (3.0 g, 0.01 mol) was dissolved in MeOH (40 mL) containing K_2CO_3 (0.28 g, 2.0 mmol). The solution was stirred at room temperature for 15 min. K_2CO_3 was filtered and the solution was concentrated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/hexane 3:1) to give **6** as an oily liquid (2.1 g, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, $J = 2.4$ Hz, 1H), 7.73 (d, $J = 2.4$ Hz, 1H), 7.04 (s, 2H; NH), 4.71 (s, C(sp)-H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 144.5, 138.4, 137.8, 131.2, 122.8, 111.4, 88.8, 79.1, 34.2, 31.1. IR (thin film) ν 3489 (NH_2), 3281 (C≡C−H), 2100 (C≡C), 1516 and 1348 (NO_2) cm^{-1}.

Compound **7**: **6** (2.1 g, 9.8 mmol) was dissolved in pyridine (40 mL) and $Cu(OAc)_2$. H_2O (2.0 g, 9.8 mmol) was added. The mixture was stirred at room temperature for 16 h, then filtered through celite. After concentration, the residue was dissolved in $CHCl_3$ (40 mL), washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/hexane 2:1) to give **7** as an orange solid (1.8 g, 85%). Mp 235–236°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, $J = 2.4$ Hz, 2H), 7.86 (d, $J = 2.4$ Hz, 2H), 7.31 (s, 4H; NH), 1.27 (s, 18H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.4, 138.7, 131.6, 124.2, 110.1, 81.0, 79.5, 34.3, 31.1. IR (KBr) ν 3473 (NH_2), 2137 (C≡C), 1511 and 1348 (NO_2) cm^{-1}.

Compound **8**: **7** (1.6 g, 3.6 mmol) was dissolved in DMF (40 mL) containing CuI (1.4 g, 7.2 mmol) and was stirred at 144–146°C for 3 h. After it cooled down to room temperature, the mixture was filtered through celite and concentrated. The residue was dissolved in EtOAc, and the solution was washed with saturated $NaHCO_3$ (50 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/hexane 2:1) to give **8** as an orange solid (0.99 g, 63%). Mp 287–288°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 2H; NH), 8.26 (d, $J = 1.6$ Hz, 2H), 8.02 (d, $J = 1.6$ Hz, 2H), 7.00 (d, $J = 2.5$ Hz, 2H), 1.45 (s, 18H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 143.4, 133.6, 132.9, 132.8, 128.5, 125.7, 116.9, 103.5, 35.0, 31.9. IR (KBr) ν 3416 (NH), 1511 and 1348 (NO_2) cm^{-1}. HRMS-FAB (m/z) $[M]^+$ calcd for $C_{24}H_{26}N_4O_4$ 434.1954; found 434.1954. Anal. Calcd for $C_{24}H_{26}N_4O_4$: C, 66.34; H, 6.03; N, 12.89. Found: C, 66.47; H, 6.06; N 13.00.

Diaminobiindolyl **2**: **8** (1.4 g, 0.32 mmol) was dissolved in EtOAC (200 mL) containing Raney Ni (1 spoon). The flask was degassed and back-filled with H_2, and was stirred at room temperature with H_2 balloon for 11 h. The mixture was filtered through celite which was repeatedly washed with THF. The solvent was removed to give 2 (1.1 g containing some impurities) as a dark gray solid, which was directly used for next reactions due to the limited solubility.

Receptor **9**: Valeroyl chloride (0.4 mL, 3.1 mmol) was added to a solution of crude **2** (0.23 g, 0.61 mmol) in anhydrous pyridine (10 mL) under N_2 at 0°C. The mixture was stirred at room temperature for 50 min and concentrated. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ and brine. Some of the solvent was removed and then hexane was added to precipitate **9** as an off-white solid (0.2 g, 55% for two-steps). Mp 298–299°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 2H; NH), 9.64 (s, 2H; NH), 7.68 (s, 2H), 7.31 (s, 2H), 6.81 (s, 2H), 2.50 (m, 4H), 1.68 (m, 4H), 1.42 (m, 4H), 1.33 (s, 18H), 0.95 (t, $J = 7.4$ Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.9, 142.9, 131.5, 130.1, 127.6, 123.6, 112.9, 112.4, 99.7, 36.6, 34.9, 32.3, 27.8, 22.5, 14.4. IR (KBr) ν 3273 (NH), 1642 (C═O) cm^{-1}. HRMS-TOF (m/z) $[M + Na]^+$ calcd for $C_{34}H_{46}N_4O_2$ 565.3519; found 565.3515. Anal. Calcd for $C_{34}H_{46}N_4O_2$: C, 75.24; H, 8.54; N, 10.32. Found: C, 75.38; H, 8.49; N 10.14.

Receptor **10**: Isocyanate (0.37 mL, 3.3 mmol) was added to a solution of crude **2** (0.25 g, 0.67 mmol) in THF (80 mL) under N_2. The solution was refluxed for 4 h and then cooled down to room temperature. The solution was concentrated and the residue was washed with EtOAc and acetone to give an off-white solid (0.29 g, 69% for two-steps). Mp 309–310°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 2H; NH), 8.28 (s, 2H; NH), 7.20 (s, 4H), 6.75 (d, $J = 2.0$ Hz, 2H), 6.23 (t, $J = 5.9$ Hz, 2H; NH), 3.16 (m, 4H), 1.47 (m, 4H), 1.36 (m, 4H), 1.31 (s, 18H), 0.91 (t, $J = 7.3$ Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.4, 143.0, 131.5, 130.5, 127.6, 124.8, 111.6, 110.9, 99.6, 34.8, 32.5, 32.3, 20.2, 14.3. IR (KBr) ν 3514 (NH), 1761 (C═O) cm^{-1}. HRMS-FAB (m/z) $[M]^+$ calcd for $C_{34}H_{48}N_6O_2$ 572.3839; found 572.3845.

Titrations: The experiments were conducted using UV-visible spectroscopy and were all duplicated at 22 ± 1°C. A solution of a receptor (2.0×10^{-5} M) in DMSO or in 10% v/v MeOH/DMSO was first prepared. Using this solution as a solvent, a stock solution of an anion was prepared. A 2.0 mL of the receptor solution was transferred to a UV cell (3 mL), and an initial spectrum was taken. Small portions of the anion solution (5 μL initially and then 10–50 μL) were added to the solution, and the spectrum was recorded after each addition and 12–15 data points were obtained. The association constants (K_a) were

determined by nonlinear curve fitting of the titration curves, plotting the absorbance at two or three wavelengths against the equivalent of the anion added. All of the titration curves were well fitted to the expression of a 1:1 binding isotherm.

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