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Recognition of anions and monocarboxylic acids by a fluorescent guanidine-based receptor

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A guanidine-based fluorescent receptor has been synthesised to study its binding behaviour towards anions (F^-, Cl^-, Br^-, I^- and AcO^-). The two donor N—H bonds of the receptor do not point in the same direction; rather, one N—H bond is intramolecularly hydrogen-bonded with the carbonyl oxygen atom. The nature of the donor–acceptor (DA) arrangement induces moderate binding properties. The binding behaviour towards monocarboxylic acids (benzoic acid and phenylacetic acid) is also compared. The binding behaviour of receptor **1** towards the F^- anion is higher among the anions studied, whereas in the case of monocarboxylic acid, the binding constant with phenylacetic acid is higher than benzoic acid.

Keywords: molecular recognition; hydrogen bonding; fluorescence sensor; guanidine

The guanidinium group is a versatile moiety in bioactive molecules (*1*). Many synthetic receptors containing a guanidinium moiety have been designed and studied for their recognition pattern for a wide range of anions (*2*). These types of receptors interact strongly with the oxoanions such as carboxylates and phosphates in enzymes (*3*). In the case of synthetic receptors, they are mainly used to recognise different anions. Although the guanidinium moiety is used extensively for recognition purposes, there is not much discussion on its dynamic nature in donor–acceptor (DA) arrays. It is thus a challenging task to use the guanidine moiety for the recognition of anions. It is also interesting to study its binding with a monocarboxylic acid using a receptor containing a single guanidine amide moiety as a part of a dihydroperimidine at the *peri* positions of a naphthalene ring.

To study the recognition behaviour, we have synthesised a fluorescent guanidine-based receptor **1** in which two nitrogen atoms make up the six-membered ring of the naphthalene moiety and the other nitrogen atom is attached to a benzoyl group. This type of benz-fused dihydroperimidine amide has a very interesting DA array. Herein, the binding behaviour of this receptor **1** towards different anions (*4*) and benzoic acid has been discussed. Receptor **1** may exist in three different tautomeric forms in the solution phase (Scheme 1) (*5*). Among these three, forms **I** and **II** may recognise a carboxylic acid moiety (*6*), whereas form **III** may recognise anions or oxoanions.

In fact, both anions as well as benzoic acid bind with the most stable conformation of receptor **1** (form **I**), which is the actual form adopted in the solid state as confirmed by the single-crystal X-ray structure determination (see Supporting Information), although molecular structures in the solid and solution states may also differ. But here the ^{1}H NMR spectrum of the complex also proves the similar arrangement of the DA array, in the solid state (Figure 1). The anions bind with receptor **1** via a single donor N—H site, whereas the monocarboxylic acid interacts via two-point binding modes. The overall binding interaction of receptor **1** is weak towards guests. In the case of monocarboxylic acid, either the ring 'N' or *exo* 'N' acts as the hydrogen bond acceptor towards a hydroxyl group, whereas the N—H of either the N(ring)—H or N(*exo*)—H acts as the hydrogen bond donor towards the carbonyl oxygen (Scheme 2).

The receptor **1** was synthesised by a simple one-pot, two-step procedure (Scheme 3). The yellow-coloured product was isolated and used for the binding studies. The structure of receptor **1** was confirmed by the spectral data[1] (*7*) as well as by the single-crystal X-ray structure determination.[2]

To study the binding behaviour of receptor **1** for anions, we performed ^{1}H NMR studies with an equivalent amount of tetrabutylammonium fluoride in which one N—H_a (δ 10.08 ppm) peak remains unchanged, whereas the other N—H_b (δ 9.09 ppm) peak disappeared. This implies that the N—H_a proton did not interact with the fluoride ion and that proton H_b was deprotonated by the fluoride base (Figure 1) (*8*). From this observation, it is clear that the receptor **1** binds the fluoride ions using only

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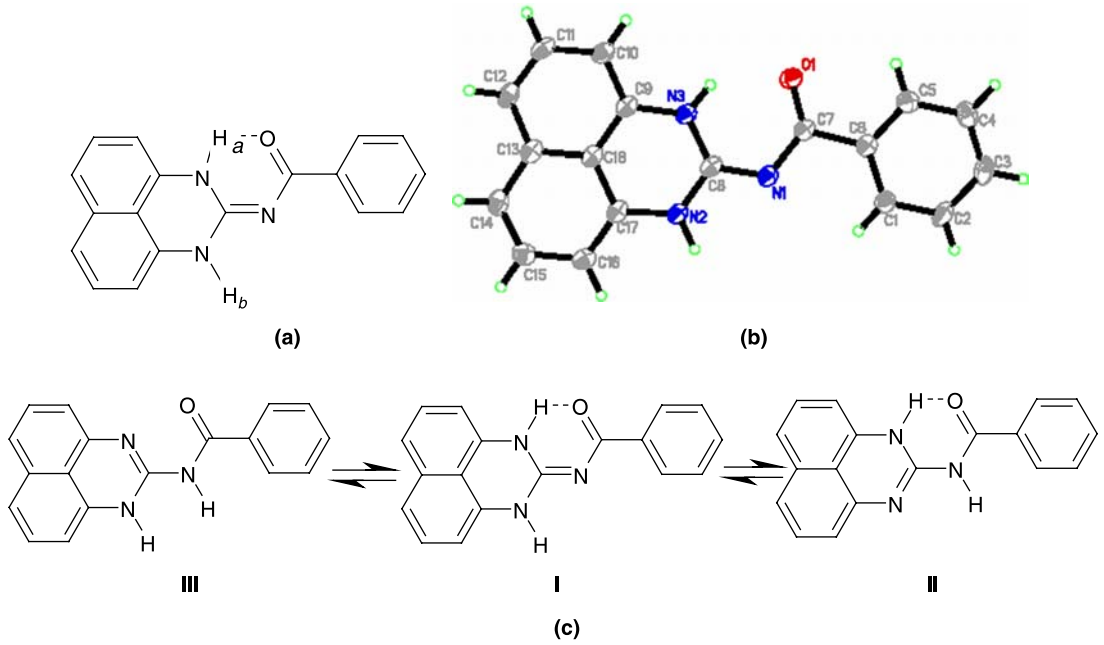


Scheme 1. (a) Receptor **1**, (b) ORTEP diagram of receptor **1** and (c) tautomeric forms of receptor **1**.

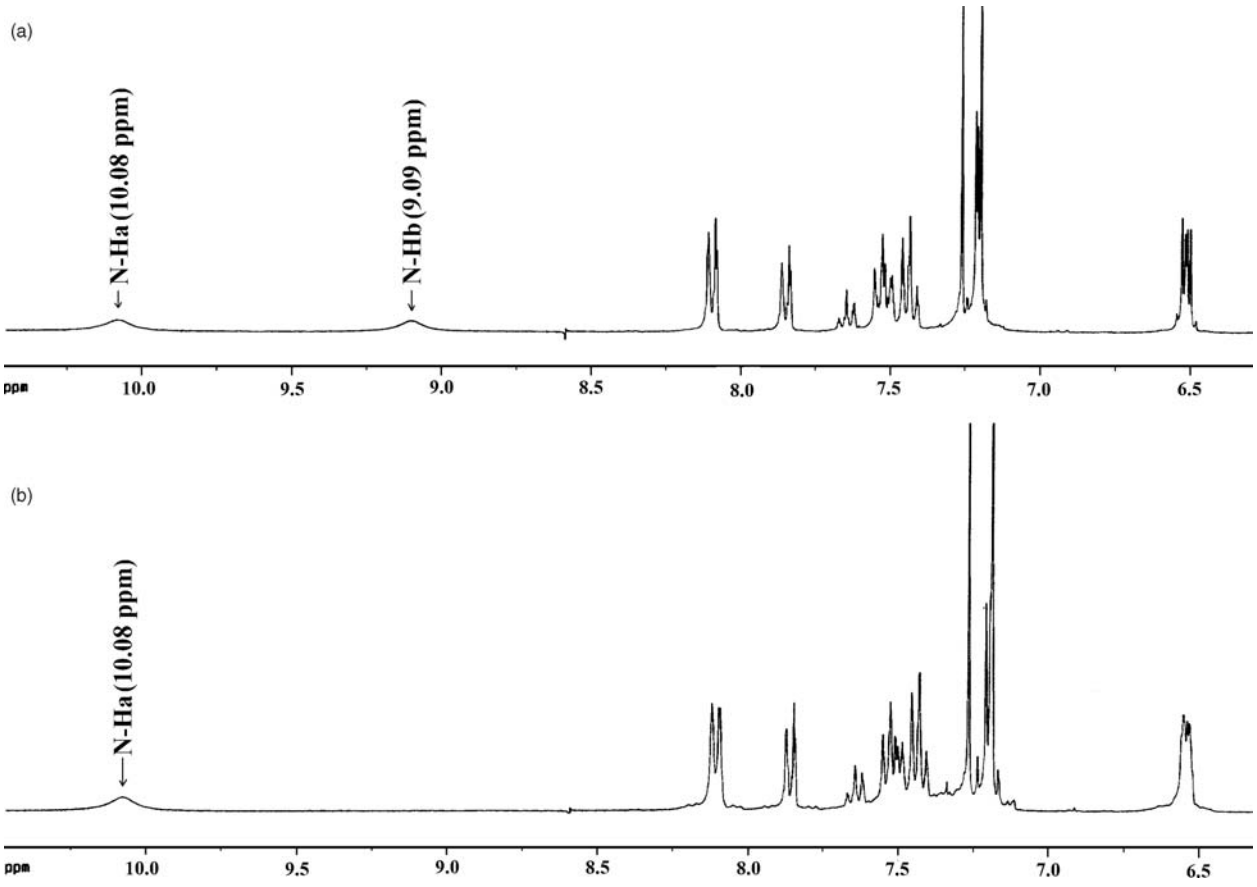
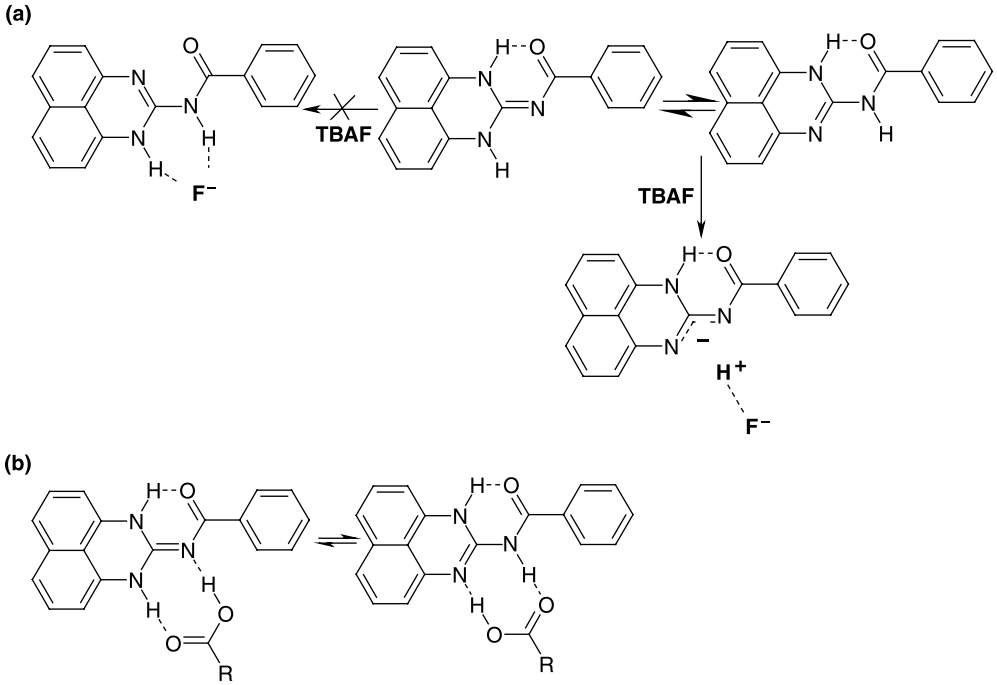


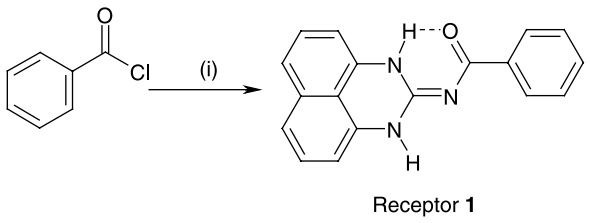
Figure 1. Partial ^{1}H NMR spectra (300 MHz, $CDCl_3$) of (a) receptor **1** (3 mM) and (b) an equivalent amount of tetrabutylammonium fluoride.



Scheme 2. Mode of binding of receptor **1** to (a) a fluoride ion and (b) the carboxylic acid moiety of a monocarboxylic acid.

one donor site through form **I** or **II**. A similar observation was found in the case of ^{1}H NMR studies with an equivalent amount of benzoic acid. In this case, the N—H_a peak also remained unchanged, whereas the chemical shift of N—H_b was very small ($\Delta\delta = 0.02$ ppm) with respect to our recently reported pyridine amide-based receptors (*9*). The binding behaviour with anions and benzoic acid, determined by both UV–vis and fluorescence titration methods (Table 1), is comparable.

The binding behaviour of receptor **1** was studied by UV–vis and fluorescence titrations. In both cases, the binding patterns were almost similar. The UV–vis titrations were carried out with receptor **1** (1.017×10^{-4} M) in $CHCl_3$ solution. The solutions of guest substrates were also prepared in *ca.* 1×10^{-3} M order in $CHCl_3$. Upon addition of the guest solutions, the absorbance ($\lambda_{max} = 282$ nm) decreased gradually (Figure 2, inset). The binding constants for all the anions,



Scheme 3. Reagents and conditions: (i) (a) NH_4SCN, dry acetone, reflux, 20 min; (b) 1,8-naphthalene diamine, dry acetone, reflux, 3 h, 54%.

benzoic acid and phenylacetic acid with receptor **1** were calculated by plotting $1/\Delta I$ versus $1/[G]$ (Table 1) (*10*).

Fluorescence titrations were also performed in $CHCl_3$. The emission spectra of receptor **1** (1.017×10^{-4} M) appear as double humps ($\lambda_{max} = 400$ and 417 nm) with almost equal intensity. These two humps gradually merged during titration upon addition of the increasing amount of guest substrates (F^- and AcO^-) in $CHCl_3$ (see Supporting Information). The receptor **1** also behaves as a possible sensor towards different monocarboxylic acids (*10*). The enhancement of emission intensity of receptor **1** in the case of F^- and AcO^- is much higher than other anions as well as monocarboxylic acids. In these cases, the receptor **1** strongly binds to the F^- and AcO^- ions through the N—H proton. In all the cases, the fluorescence intensity gradually increases upon continuous addition of the guest solution but through a slight initial decrease in intensity. Although the nature of the emission spectra with other anions and monocarboxylic acids is similar, their enhancement of emission intensity is very weak. The nature of emission spectra is partially governed by the basicity of anions. Among all the anions, the enhancement of emission intensity is the weakest in the case of I^-. The nature of the emission spectra with monocarboxylic acids was almost similar to the anions, where regular enhancement of the intensity was observed. The emission intensity of receptor **1** was enhanced more in the case of phenylacetic acid than benzoic acid. Thus, in all the cases, except for F^- and AcO^-, the host–guest interactions occurred through hydrogen bonding in a neutral

Table 1. Association constants [$K_a(M^{-1})$][a] and free energy changes [ΔG(kcal/mol)] at 25°C for receptor **1** and guests in a 1:1 mode of interaction as determined by the UV–vis and fluorescence titration methods in $CHCl_3$.

	Method			
	UV[b]		Fluorescence[c]	
Guest	K_a	ΔG	K_a	ΔG
F^-	1.24×10^3	−4.22	1.73×10^3	−4.41
Cl^-	6.79×10^2	−3.86	9.17×10^2	−4.04
Br^-	4.73×10^2	−3.65	8.41×10^2	−3.99
I^-	3.93×10^2	−3.54	1.08×10^3	−4.14
AcO^-	1.11×10^3	−4.15	4.05×10^2	−3.56
Benzoic acid	1.61×10^2	−3.01	6.20×10^2	−3.81
Phenylacetic acid	1.03×10^3	−4.11	9.54×10^2	−4.06

[a] All the errors are ± 20%.
[b] For receptor **1**: $\lambda_{max} = 282$ nm.
[c] For receptor **1**: λ_{max}(ex) = 282 nm, λ_{max}(em) = 416 nm, emission slit width = 15.0 nm, excitation slit width = 10.0 nm, scan rate = 400 nm/min.

environment. But in the case of F^- and AcO^-, the host–guest interactions occurred in a partial ionic environment. This also inferred a higher association constant (Table 1) with F^-, determined by both UV and fluorescence titration methods as well as the ^1H NMR spectra of a 1:1 complex of receptor **1** with tetrabutylammonium fluoride (Figure 1). These results also reflect the nature of the binding constant values (Table 1), which were determined by plotting $I_0/I_0 - I$ versus $1/[G]$ from the fluorescence titrations (Figure 3) (*11*).

Recently, Chetia and Iyer (*12*) reported benzimidazole-based receptors for the sensing of anions, where the two N—H bonds are directed inwards and bind with the spherical anions. In this case, selectivity towards F^- was observed, whereas in the present perimidine-based system both F^- and AcO^- show higher interactions. The binding constant values for the receptor **1** containing a single donor site as well as reported two donor sites are comparable (*8, 12*).

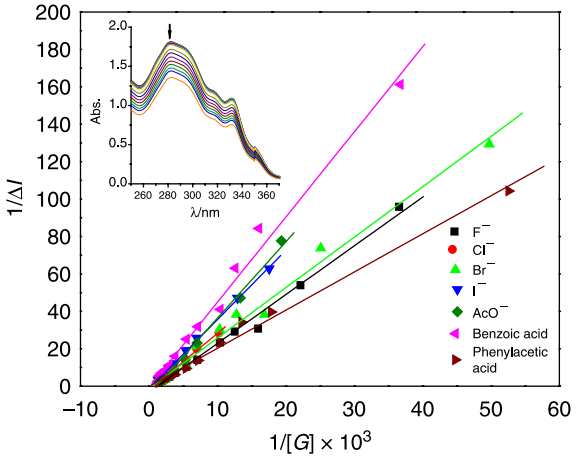


Figure 2. Binding constant curves calculated by the UV–vis method of receptor **1** with various anions (inset: UV–vis titration spectra with F^-) and monocarboxylic acids in $CHCl_3$.

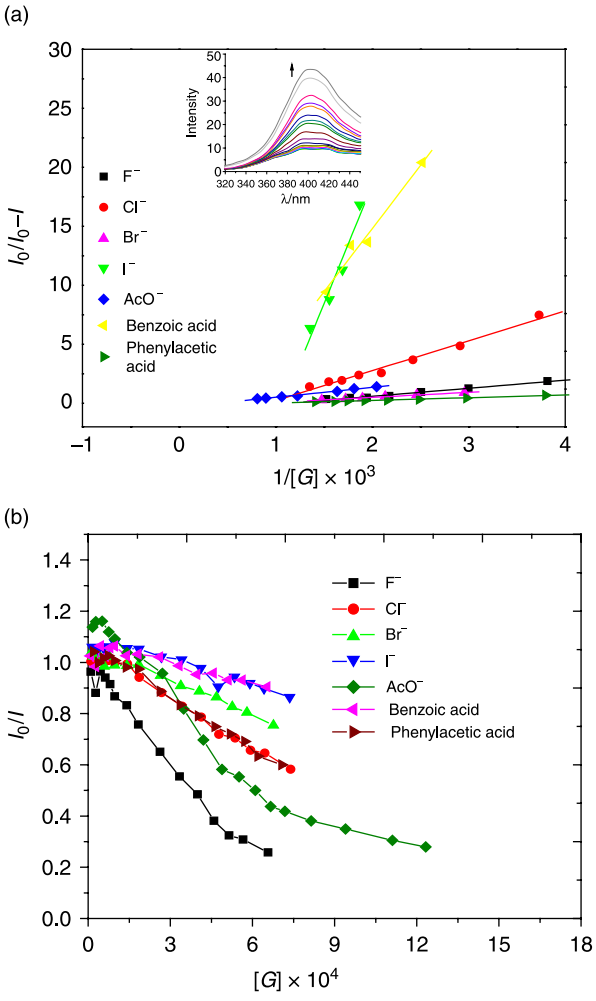


Figure 3. (a) Binding constant calculation curves of receptor **1** with anions and monocarboxylic acids (inset: fluorescence titration spectra with AcO^-) and (b) Stern–Volmer plots determined by fluorescence titration methods.

The association constants of the guests with receptor **1** show the overall binding behaviour. Among the anions, the association constant for F^- is higher with respect to the other anions due to the influence of equilibrium between the receptor and its deprotonated form during interaction with these anions; however, all the other anions bind with the receptor via a single-point hydrogen bonding interaction. The binding constant with monocarboxylic acids is also comparable due to the two-point interactions with the *exo* imide 'N' and the ring N—H of the receptor.

From this study, it can be concluded that the simple dihydroperimidine-based fluorescent receptor **1** can recognise both anions and monocarboxylic acids by single-point and two-point hydrogen bonding interactions, respectively, and the values of their binding constants are close to one another. Receptor **1** may be considered as a new fluorescent chemosensor for a wide range of guest substrates. The nature of the receptor towards the anions is also very important for studying the selectivity for F^- and AcO^-. Another structural feature is that the two donor sites of the guest substrate are not involved in the recognition of anions due to strong intramolecular hydrogen bonding as confirmed by the spectral changes in the ^{1}H NMR and also by the single-crystal X-ray structure of receptor **1**.

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Notes

1. Spectral data of receptor **1** [*N-(1H,3H-perimidin-2-ylidene)-benzamide*]: To an ammonium thiocyanate (152 mg, 2 mmol) solution in dry acetone (20 ml), benzoyl chloride (0.25 ml, 2.1 mmol) was added dropwise at room temperature. This mixture was refluxed for 20 min and cooled down to room temperature. Now, 1,8-naphthalene diamine (316 mg, 2 mmol) in dry acetone (10 ml) was added dropwise and the whole mixture was again refluxed for another 3 h. The solvent was distilled off and the residue dried under vacuum. This mixture was washed with water and extracted with $CHCl_3$ (25 ml × 4). The $CHCl_3$ solution was dried over anhydrous Na_2SO_4 and evaporated out under reduced pressure to obtain a deep brown crude solid. The crude was purified by column chromatography using silica gel (100–200 mesh) and 15% EtOAc in petroleum ether (boiling range 60–80°C) as the eluent to afford a yellow solid compound (receptor **1**, 310 mg, 54%). Mp. 226–227°C. FT-IR (CH_2Cl_2): 3197, 2923, 2852, 1670, 1622, 1458, 1360, 1268 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 10.08 (bs, 1H), 9.09 (bs, 1H), 8.09 (d, 2H, $J = 7.8$ Hz), 7.85 (d, 1H, $J = 7.2$ Hz), 7.64 (t, 1H, $J = 7.4$ Hz), 7.55–7.49 (m, 2H), 7.43 (t, 1H, $J = 7.0$ Hz), 7.20 (d, 2H, $J = 4.1$ Hz), 6.51 (d, 2H, $J = 5.0$ Hz). ^{1}H NMR ($CDCl_3$, 300 MHz) [Complex with TBAF (1 eq.)]: δ (ppm): 10.08 (bs, 1H), 8.09 (d, 2H, $J = 7.5$ Hz), 7.85 (d, 1H, $J = 8.4$ Hz), 7.64 (t, 1H, $J = 7.4$ Hz), 7.55–7.48 (m, 2H), 7.40 (t, 1H, $J = 7.4$ Hz), 7.20 (d, 2H, $J = 4.1$ Hz), 6.54 (dd, 2H, $J = 5.7$ Hz), 3.35 (t, 8H, $J = 8.4$ Hz), 1.65 (m, 8H), 1.46 (m, 8H), 0.99 (t, 12H, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm): 177.04, 153.47, 135.93, 135.24, 132.34, 129.41, 129.08, 128.57, 128.51, 127.85, 120.33, 110.95. Mass (ESI): *m/z* (%): 288.0 [$M + H^+$, 100], 289 [$M + 2H^+$, 29], 130 (14), 105.1 (32). Anal. calcd for $C_{18}H_{13}N_3O$; C, 75.25; H, 4.56; N, 14.62. Found: C, 75.20; H, 4.62; N, 14.65.
2. Single crystals of receptor **1** were grown by slow evaporation at room temperature from chloroform solution. Crystal data (CCDC No. 672282): $C_{18}H_{13}N_3O$, $M = 287.31$, Monoclinic, Space group = *C*2/*c* (No. 15); $a = 23.0876(11)$; $b = 8.7890(4)$; $c = 13.8108(9)$ Å, $\beta = 106.315(5)°$; $V = 2689.6(3)$ Å^3, $Z = 8$, $D_c = 1.419$ g cm^{-3}, $R_1 = 0.0577$, $wR_2 = 0.1807$.

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