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Mini-Review

A supramolecular optic sensor for selective recognition AMP

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ABSTRACT

Cu-coordinated complex based on 7-membered amide cycle has been designed and synthesized. And its binding ability with nucleotides (AMP, adenosine 5′-monophosphate; ADP, adenosine 5′-diphosphate; ATP, adenosine 5′-triphosphate) has been studied by UV–vis spectrum. Results indicate that the receptor shows the highest binding ability with AMP among studied nucleotides and can selectively and strongly bind nucleotides at neutral medium. The receptor can be used as optical sensor for the detection of AMP.

Contents

Introduction

In recent years, increasing attention in the field of host–guest chemistry has been devoted to the fast development of anion recognition systems [1–5].With the aid of supramolecular chemistry, recognition and sensing of anionic anaylates has recently emerged as a key research field. Detection of nucleotides has paramount importance as they form the fundamental units of all the life forms [6–10]. Of all the nucleosides and nucleotides, the recognition of adenosine 5′-monophosphate (AMP), adenosine 5′-diphosphate (ADP) or adenosine 5′-triphosphate (ATP) is vital[11–15] since nucleotide phosphates such as AMP, ADP or ATP are important for their role in bioenergetics, metabolism, and transfer of genetic information[16,17]. Most known receptors for these nucleotides use complementary hydrogen bonding, but such a recognition in the aqueous medium would be limited due to the interference from hydroxyl groups of the sugar moiety and competitive hydrogen bonding of the solvent [18–20]. Progress in this area would require new strategies for the selective recognition and subsequent signaling of the event under physiological pH conditions.

In previous reported literature, the recognition of adenosine was focused on supramolecular catalysis area at certain pH condition [21,22]. In this paper, we reported the recognition of adenosine in neutral medium. Recently, we synthesized a novel 7-membered receptor 1 (Scheme 1) and reported its anion recognition properties [5]. Later, we found receptor 1 also could interact with AMP, ADP and ATP. Herein, we reported the interaction of receptor 1 with AMP, ADP and ATP which selectively combined with AMP in water solution and signals the event through changes in absorption spectroscopy.

Experimental

Apparatus and reagents

Most of the starting materials were obtained commercially and all reagents, and solvents employed were of analytical grade. AMP, ADP

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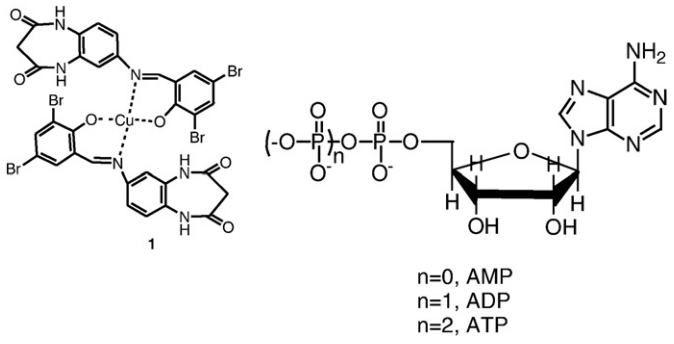


Scheme 1. Chemical structures of receptor **1** and nucleotides.

and ATP were purchased from Sigma-Aldrich Chemical Co., stored in a desiccator under vacuum containing self-indicating silica, and used without any further purification. Dimethyl sulfoxide (DMSO) was distilled in vacuo after dried with CaH_2. C, H and N elemental analysis was made on Vanio-EL. ^{1}H NMR spectrum was recorded on a Varian UNITY Plus-400 MHz Spectrometer. FAB-MS was made on VG ZAB–HS. UV–vis Spectroscopy titrations were made on a Shimadzu UV2450 Spectrophotometer at 298.2 ± 0.2 K. The stability constants K_s were obtained by the non-linear least square calculation method through data fitting.

Synthesis

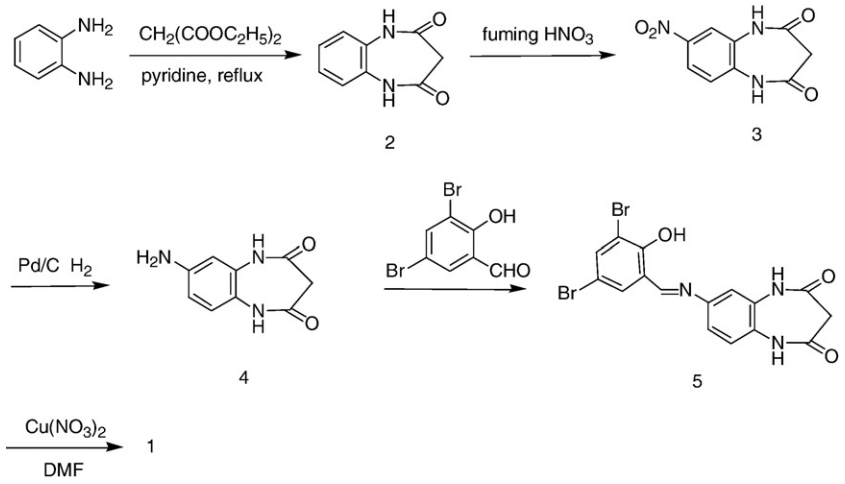
Receptor **1** was synthesized according to the route shown in Scheme 2. Benzo-1,4-diazacycloheptane[2,3-d]-5,7-dione (2) [23] 1,2-phenylenediamine (10.8 g, 0.1 mol), diethyl malonate (16 ml, 0.1 mol) and pyridine (200 ml) were put in a 250 ml three-neck flask. The mixture was refluxed with N_2 for 72 h. After cooling, the mixture was filtrated and the colorless solid obtained. The solid was washed with ethanol and ether sequentially, and dried in vacuum. Yield: 72%. ^{1}H NMR(400 MHz, DMSO-d_6, 298 K) δ = 10.38 (s, 2H, NH), 7.11–7.18 (m, 4H, ph-H), 3.17 (s, 2H, CH_2). Elemental analysis: Calc. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90; Found: C, 61.69; H 4.59; N, 15.96. FAB-MS(*m*/*z*): 177 $(M+H)^+$. (4′-Nitrobenzo)[1′, 2′-d]-1,4-diazacycloheptane[2,3-d]-5,7-dione(3) Benzo-1,4-diazacycloheptane [2,3-d]-5,7-dione (10 mmol, 1.7 g) was dissolved in concentrated H_2SO_4 (43 ml). Fuming HNO_3 (1.1 ml) was added dropwise with stirring at 273 K. After the addition was completed, the mixture was stirred for 2 h and then poured into ca. 200 ml ice-water. The solution was filtered to give a yellow solid, which was washed with distilled water, recrystallized from methanol and dried in vacuum. Yield: 85%.

Table 1
Crystallographic data of **1**.

Compound	**1**
Empirical formula	$C_{44}H_{48}Br_4CuN_{10}O_{10}$
Formula weight	1260.10
Temperature, K	294(2)
System, Space group	Monoclinic, P2(1)/*n*
a, (Å)	12.035(2)
b, (Å)	8.9193(14)
c, (Å)	23.017(4)
α (°)	90
β (°)	94.422(5)
γ (°)	90
V, (Å^3)	2463.4(7)
Z	2
Crystal size, mm^3	0.20 × 0.14 × 0.06
D_{calcd}, Mg m^{-3}	1.699
F (000)	1262
2θ range (°)	1.77–27.46
Reflections collected	20,636
R(int)	0.0619
GOF on F^2	1.020
Data/restraints/parameters	5613/0/326
Final R_1 and wR_2 [$I>2\sigma(I)$]	0.0522, 0.1067
R_1 and wR_2 [all data]	0.0856, 0.1220
Largest diff. Peak hole (e Å^{-3})	0.607 and −0.657
Extinction coefficient	0.0022(4)

^{1}H NMR(400 MHz, DMSO-d_6, 298 K) δ = 10.96 (s, 1H, NH), 10.74 (s, 1H, NH), 8.04, 7.3 (m, 3H, ph-H), 3.3 (s, 2H, CH_2). Elemental analysis: Calc. for $C_9H_7N_3O_4$: C, 48.88; H, 3.19; N, 19.00; Found: C, 48.76; H 3.58; N, 18.61. FAB-MS(*m*/*z*): 222.1 $(M+H)^+$ (4′-aminobenzo)[1′, 2′-d]-1,4-diazacycloheptane[2,3-d]-5,7-dione(4) A slurry of compound (4′-nitrobenzo)[1′,2′-d]-1,4-diazacycloheptane[2,3-d]-5,7-dione (221 mg) and Pd/C (10%, 70 mg) in dry ethanol (200 ml) was maintained under hydrogen with stirring for 12 h. The mixture was filtered through a bed of Celite and then washed twice with ethanol (2 × 20 ml). The solvents were removed under reduced pressure and the yellowish solid dried in vacuum. Yield: 92%. ^{1}H NMR(400 MHz, DMSO-d_6, 298 K) δ = 10.15 (s, 1H, NH), 9.91 (s, 1H, NH), 6.76 (d, 1H, ph-H), 6.38 (m, 1H, ph-H), 6.27 (d, 2H, ph-H), 5.16 (s, 2H, NH_2) 3.08 (s, 2H, CH_2). Elemental analysis: Calc. for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98; Found: C, 56.41; H 4.96; N, 21.87.

N-(2″-hydroxyl-3″,5″-dibromophenyl-methylene-yl)-4′-imino-benzo[1′,2′-d]-1,4-diazacycloheptane[2,3-d]-5,7-dione [HODBrphC=NphDNHexDO](5) (4′-aminobenzo)[1′,2′-d]-1,4-diazacycloheptane [2,3-d]-5,7-dione (1 mmol, 191 mg) and 3,5-dibromo-salicylaldehyde (1 mmol, 278 mg) were suspended in dry ethanol (100 ml). The mixture was heated under reflux for 8 h and the orange-yellow



Scheme 2. Synthesis route for receptor **1**.

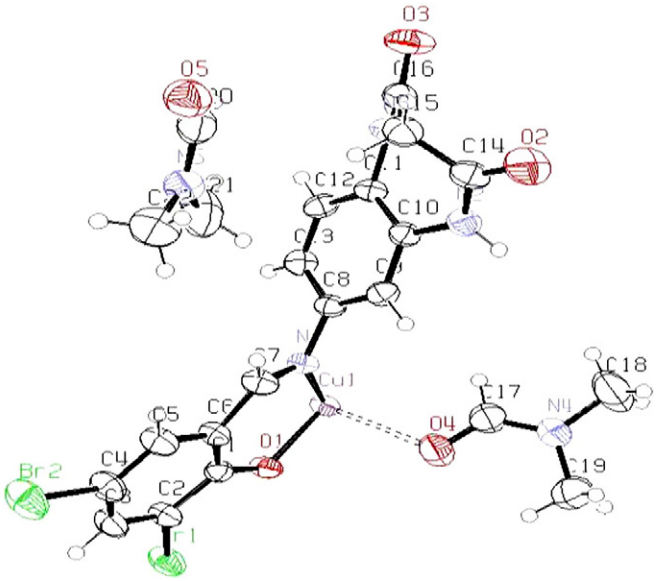


Fig. 1. The crystal structure of **1** and the hydrogen atoms are shown as small circles with arbitrary radii (ellipsoids at 50% probability).

Table 2
Details of intermolecular hydrogen bonds in receptor 1.

Donor–H…Acceptor	N_2–H_2 …O5(b)	N_3–H_3A … O4(a)
D–H Å	0.872	0.943
H…A Å	1.991	1.964
D…A Å	2.855	2.890
D–H … A(°)	170.10	166.98

Symmetry code: a) $-x+1/2, y+1/2, -z+1/2$; and b) $x, y-1, z$.

precipitate was separated by filtration. The solid was washed with diethyl ether and dried under vacuum. Yield: 89%. ^{1}H NMR(400 MHz, DMSO-d_6, 298 K) δ = 14.41 (s, 1H, OH), 10.54 (s, 2H, NH), 8.97 (s, 1H, CH), 7.9 (d, 2H, ph-H), 7.3 (d, 2H, ph-H), 7.2 (m, 1H, ph-H) 3.24 (s, 2H, CH_2). Elemental analysis: Calc. for $C_{16}H_{11}N_3OBr_2 \cdot 2H_2O$: C, 42.04; H, 3.31; N, 9.19; Found: C, 42.35; H 2.88; N, 9.45. Cu(II) [HODBrphC=NphDNHexDO]$_2$ (1) 5 (0.1 mmol) and $Cu(NO_3)_2$ (0.05 mmol) were stirred for 1 h in DMF (20 ml), then stood at room temperature. After a month, the green crystal appeared. Elemental analysis: Calc. for $C_{32}H_{20}N_6O_6Br_4Cu \cdot 5H_2O$: C, 39.72; H, 2.08; N, 8.68; Found: C, 39.22; H 3.55; N, 8.91.

X-ray crystallography

A green crystal of 1 with dimensions of 0.20 × 0.14 × 0.06 mm was mounted on a glass fiber. X-ray single-crystal diffraction data were collected on a Rigaku Saturn CCD area detector at 294(2) K with Mo–Ka radiation (λ = 0.71073 Å) .The structure was solved by direct methods and refined on F^2 by full-matrix least squares methods with SHELXL-97 [24]. More details of the crystallographic determination are given in Table 1.

Results and discussion

Receptor **1** was obtained by the reaction of 5 and $Cu(NO_3)_2$ in N,N-dimethylformamide (DMF). The crystals of receptor **1** suitable for X-ray crystal analysis has been obtained and the structure has been confirmed (Fig. 1, the deposition number is CCDC 621069). The overall coordination environment of the Cu(II) atom involves two receptor 1 and two DMF molecules. Four of the Cu1–O1, Cu1–O1A, Cu1–N1, Cu1–N1A bonds are relatively longer (bond lengths 1.913 Å, 1.914 Å, 2.033 Å and 2.033 Å), and they constitute a plane quadrangular geometry around the Cu(II) atom (O1–Cu1–O1A, 180°, O1–Cu1–N1, 90.7°, O1–Cu1–N1A, 89.3°, O1A–Cu1–N1, 89.3°, O1A–Cu1–N1A, 90.7°, N1–Cu1–N1A, 180°); the other two Cu–O4, Cu–O4A contacts are significantly shorter (bond lengths 1.653 Å and 1.653 Å), completing a distorted octahedron as the overall geometry around the Cu(II) atom. The NH of amide forms hydrogen bonds with oxygen atoms of DMF molecules that are derived from two resources: one is coordinated DMF (O4), the other is uncoordinated DMF (O5) (Table 2). The overall crystal structure features chain type with DMF molecules by hydrogen bonds along the b axis (Fig. 2).

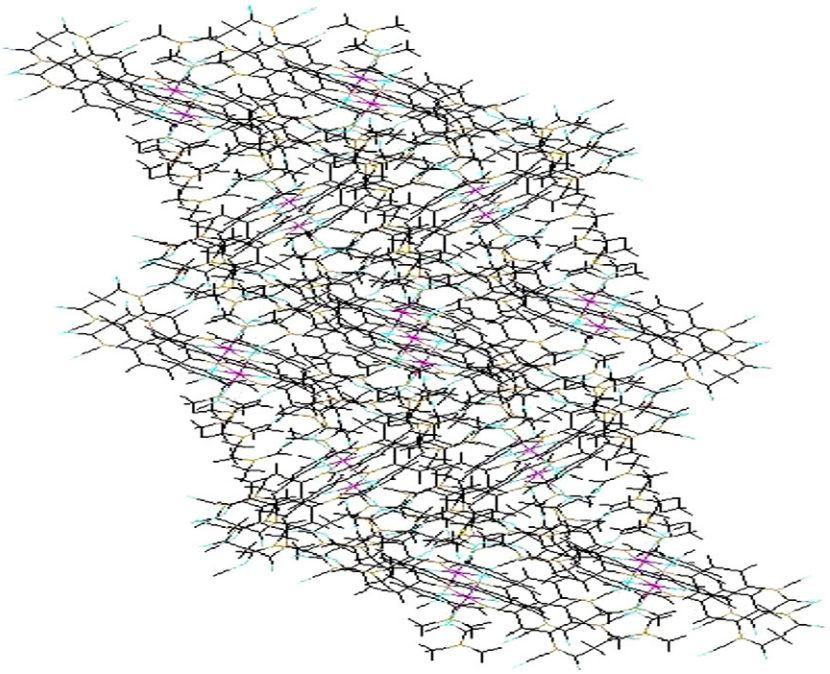


Fig. 2. View of the three-dimensional structure of **1** along the *b* axis.

The interactions of **1** with AMP, ADP and ATP were investigated through UV–vis spectral titrations in DMSO/H_2O (9:1) by the addition of AMP, ADP and ATP to the solution of **1**. Fig. 3 is the interacted absorption spectrum of receptor **1** with nucleotides. With the addition of AMP, the absorbance band at about 325 nm increases gradually. At the same time, the intensity of absorbance band at about 413 nm decreases gradually. In addition, there appears one clear isosbestic point at about 355 nm. This shows that at this point a stable concentration of the complex is formed in the solution with a certain stoichiometric ratio between **1** and AMP. Similarly, the new absorption band develops at 420 nm with the addition of ADP and there appears one stoichiometric ratio at about 370 nm. The addition of ATP also induces similar spectral change of receptor **1**, compared with AMP. The above results show that receptor **1** interacts with AMP, ADP and ATP. Curve fitting of the interaction between the receptor and AMP, ADP and ATP according to Eq. (1) is shown in Fig. 4. The high correlation indicates that receptor binds ribonucleotides at 1:1.

Stability constants of receptor **1** for ribonucleotides are calculated according to the Eq. (1), 1:1 host-guest complexation [25–28].

$$X = X_0 + 0.5\Delta\varepsilon\left\{c_H + c_G + 1/K_s - \left[(c_H + c_G + 1/K_s)^2 - 4c_H c_G\right]^{1/2}\right\} \quad (1)$$

where c_G and c_H are the concentration of guest and host, respectively. X is the intensity of absorbance at certain concentration of host and guest. X_0 is the intensity of absorbance of host when the anion isn't added. K_s is the affinity constant of host-guest complexation. $\Delta\varepsilon$ is the

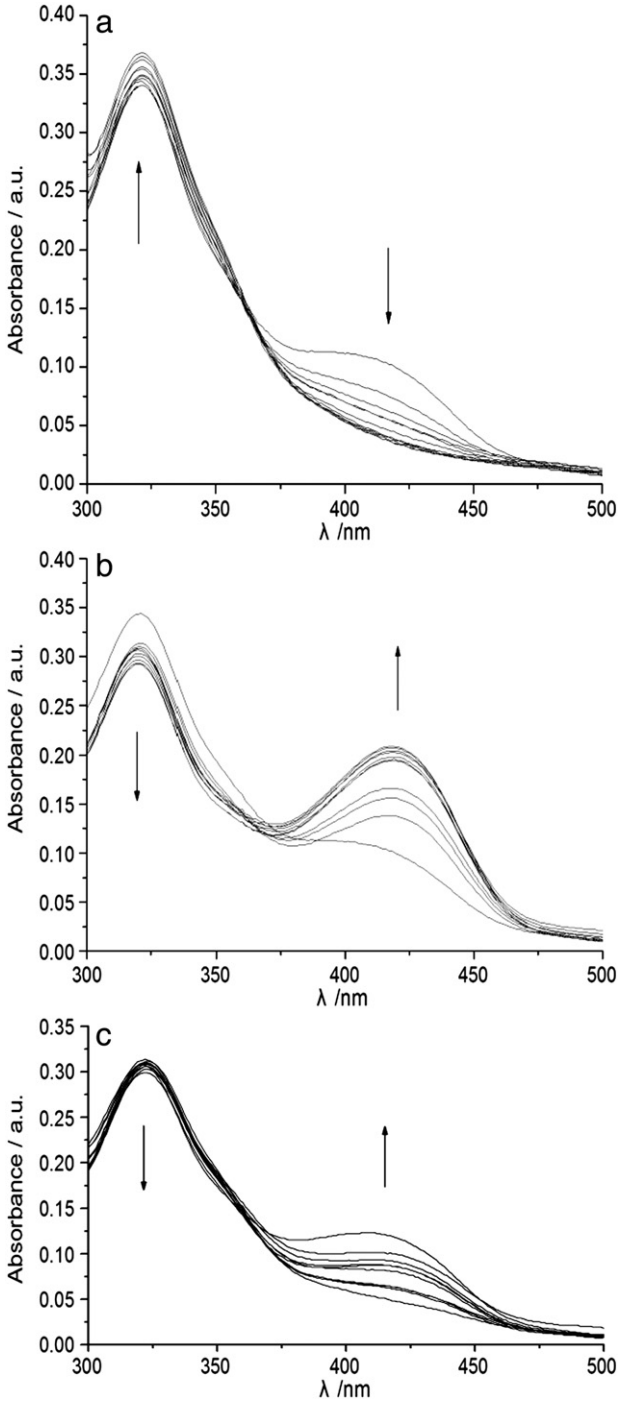


Fig. 3. UV–vis spectral changes of receptor **1** (2.0×10^{-5} mol·L^{-1}) upon the addition of AMP (a), ADP(b) and ATP(c), the concentration of nucleotides is from 0 to 160×10^{-5} mol·L^{-1}. Arrows indicate the direction of increasing ribonucleotides adenosine concentration.

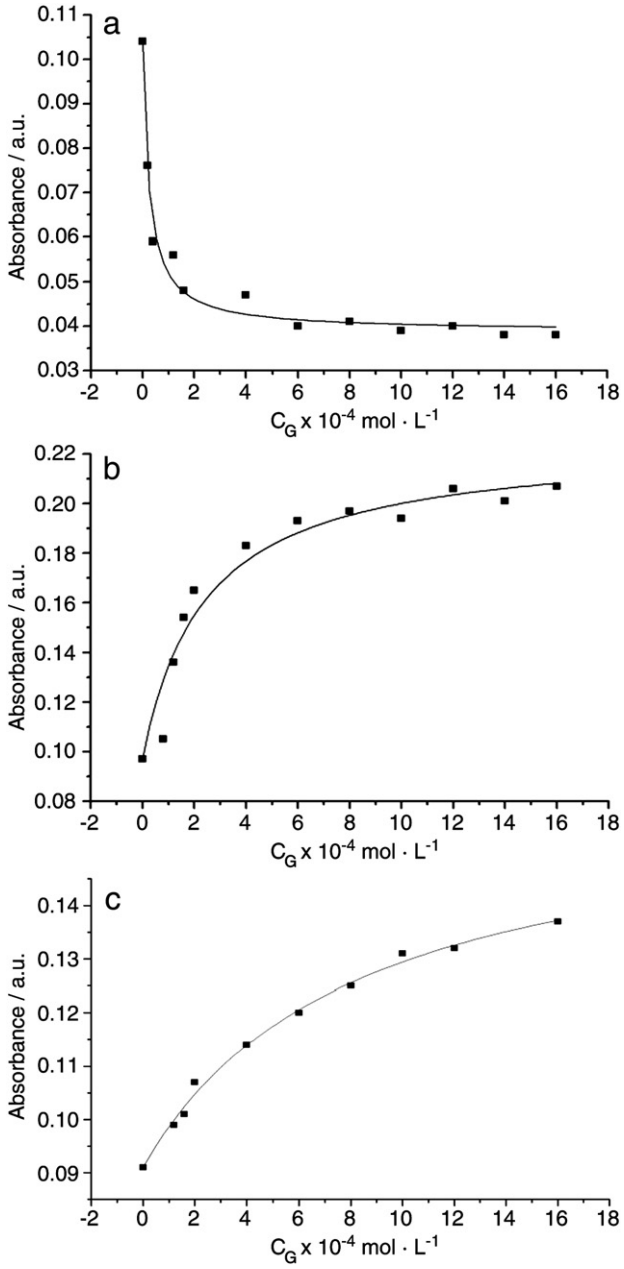


Fig. 4. Curve fitting of the interaction between receptor and AMP(a), ADP(b) and ATP(c).

Table 3
The stability constant of receptor **1** with nucleotides.

Nucleotides	K_s ($mol^{-1}L$)
AMP	$39{,}754 \pm 5637$
ADP	4141 ± 924
ATP	1227 ± 130

change in molar extinction coefficient. The stability constant of receptor **1** with nucleotides were determined by non-linear least square method according to UV–vis titration data and listed in Table 3. Obviously, the binding ability of nucleotides with receptor **1** is in the order: AMP>ADP>ATP, which is due to the shorter chain of AMP which is matched well with receptor **1**, the stronger binding ability. The binding ability of AMP with receptor **1** is the strongest among studied nucleotides. According to the crystal structure of receptor **1**, nucleotides may interact with receptor **1** by electrostatic interaction (Cu^{2+}—O^-), which Cu^{2+} is from receptor and O^- is from phosphate of nucleotides. In addition, adenine of nucleotides forms π–π staking with 7-membered amide cycle of receptor **1**. Therefore, the binding ability of nucleotides with receptor 1 is influenced by the chain length of nucleotides. According to stability constant, AMP, the shortest chain among studied nucleotides, stack well with receptor **1**.

Conclusion

In conclusion, we demonstrated a highly sensitive and selective absorption assay for AMP through beneficial properties of the receptor **1** and the UV–vis indicator. The uniqueness of this assay is that it successfully discriminates AMP from ADP, ATP and other nucleotides through the visual change in absorption intensity. Studies are in progress to evaluate the selectivity of the receptor **1** toward other biologically important analytes.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.inoche.2010.04.006.

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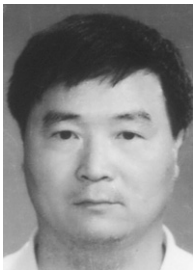

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