Indole-Based Anion Receptors: Highlights from 2008 to Date

Xiaoping Bao[1,*], Yuhui Zhou[2] and Baoan Song[1,*]

[1]*Center for Research and Development of Fine Chemicals, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang, 550025, PR China*

[2]*Department of Chemistry, Guizhou University, Guiyang 550025, PR China*

Abstract: Indole-based anion receptors are developing rapidly nowadays due to a nearly limitless derivatizing capability of indole functionality. This mini-review summarizes the progress on synthetic anion receptors containing indole functionality from 2008 to date, including the recognition behaviors and sensing properties of these receptors for different anions.

Keywords: Indole group, anion recognition, anion sensing, supramolecular chemistry.

1. INTRODUCTION

Development of anion receptors has been becoming a research focus in the field of supramolecular chemistry because anions play important roles in chemical, biological and environmental systems [1]. Compared with other hydrogen-bond donor groups, indole NH was relatively less studied as recognition unit of anion receptors. The lack of effort on application of indole NH in the area of anion receptor is somewhat surprising as some proteins in biological system employ this group as hydrogen-bond donor to bind sulfate ion [2].

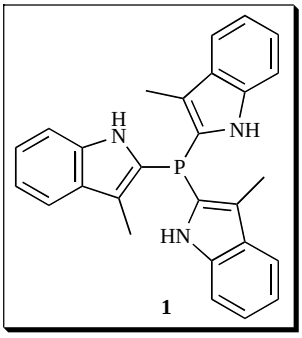
Although possessing a high structural similarity with pyrrole group, indole-based anion receptors sometimes displayed some recognition behaviors obviously different from those based on pyrrole group [3]. Apart from stronger hydrogen-bond donating ability, relatively larger steric hindrance while accessing target anions also contributed to the observed differences for indole-based anion receptors.

This mini-review summarizes the progress on synthetic anion receptors containing indole group from 2008 to date. The content of this article is divided into two parts: anion recognition and anion sensing including colorimetric sensing, fluorescent sensing, and dual sensing using combination of colorimetric and fluorescent responses.

2. ANION RECOGNITION

In 2008, Browning and co-workers developed a C_3-symmetric phosphine with indolyl substituents (compound **1**) as anion receptor [4]. The anion binding properties of compound **1** were studied in CD_2Cl_2 and it was found that compound **1** could selectively bind chloride and acetate ions through the formation of 1:1 complex with the stability constants of 3920 and 2730 M^{-1}, respectively. Although an accurate stability constant for F^- binding could not be obtained, a high affinity for F^- was very evident due to the occurrence of a large downfield shift for indole NH upon addition of F^- in CD_2Cl_2. Moreover, single crystal of binding complex between compound **1** and F^- confirmed that three indole NH of compound **1** worked in concert to bind one F^- *via* three-fold hydrogen-bonding interactions.

Jurczak *et al*. reported three cleft-shaped anion receptors **2–4** deriving from indole-7-amine [5]. Proton NMR titration experiments (in DMSO-d_6 containing 0.5% H_2O) showed that replacement of aniline with indolamine (possessing an additional binding site–indolyl NH) could enhance the binding affinity for the tested anions more than five times, except for compound **2**. Strong intramolecular hydrogen bond and unfavorable ligand preorganization in compound **2** were responsible for the unobvious differences in the stability constants with aniline-substituted analogue.



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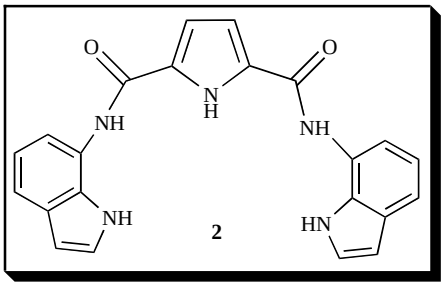

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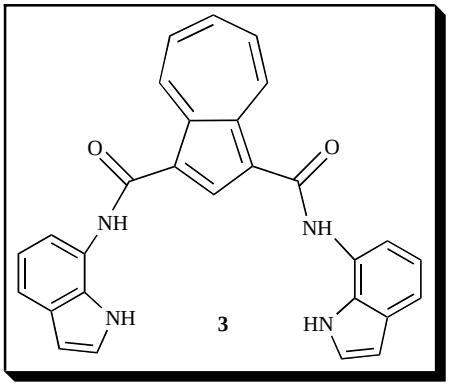

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Ito and co-workers synthesized a series of indolylmethane derivatives **5–9** and studied their anion binding properties by ^{1}H NMR

*Address correspondence to these authors at the Center for Research and Development of Fine Chemicals, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang, 550025, PR China; Tel: +86 851 8292170; Fax: +86 851 3622211; E-mails: baoxp_1980@yahoo.com.cn; songbaoan22@yahoo.com

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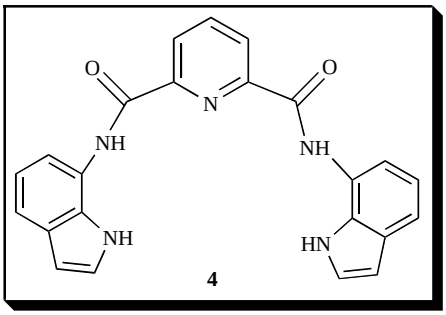


titration method in $CDCl_3$ [6]. The obtained results indicated that compound **5** selectively bound chloride ion (with an association constant of 1200 M^{-1}) over other anions including bromide, iodide, bisulfate and nitrate ions. In contrast, its analogous compounds **6**–**9** did not exhibit a noticeable affinity and selectivity toward all the examined anions.

Gale *et al*. found that 1, 3-diindolylurea (compound **10**) was a selective $H_2PO_4^-$ receptor in aqueous DMSO-d_6 [7]. Compound **10** was proved to bind $H_2PO_4^-$ with a stability constant of 5170 M^{-1} in the medium of DMSO-d_6-10% water, which was nearly nine-fold higher than that of $PhCOO^-$ under the same conditions. While water content was further increased up to 25%, compound **10** still bound $H_2PO_4^-$ with a moderate binding affinity (K_a = 160 M^{-1}). Fig. (**1**) displayed a DFT calculated structure of $H_2PO_4^-$ complex with compound **10**.

The same research group also prepared 1, 3-diindolylthiourea (compound **11**) according to the synthetic route in Scheme **1** [8]. Different with compound **10**, a much lower binding affinity for $H_2PO_4^-$ (K_a = 1630 M^{-1}) was observed in DMSO-d_6-0.5% water along with a loss of selectivity for $H_2PO_4^-$. One possible explanation was that conformational interconversion of thiourea group in

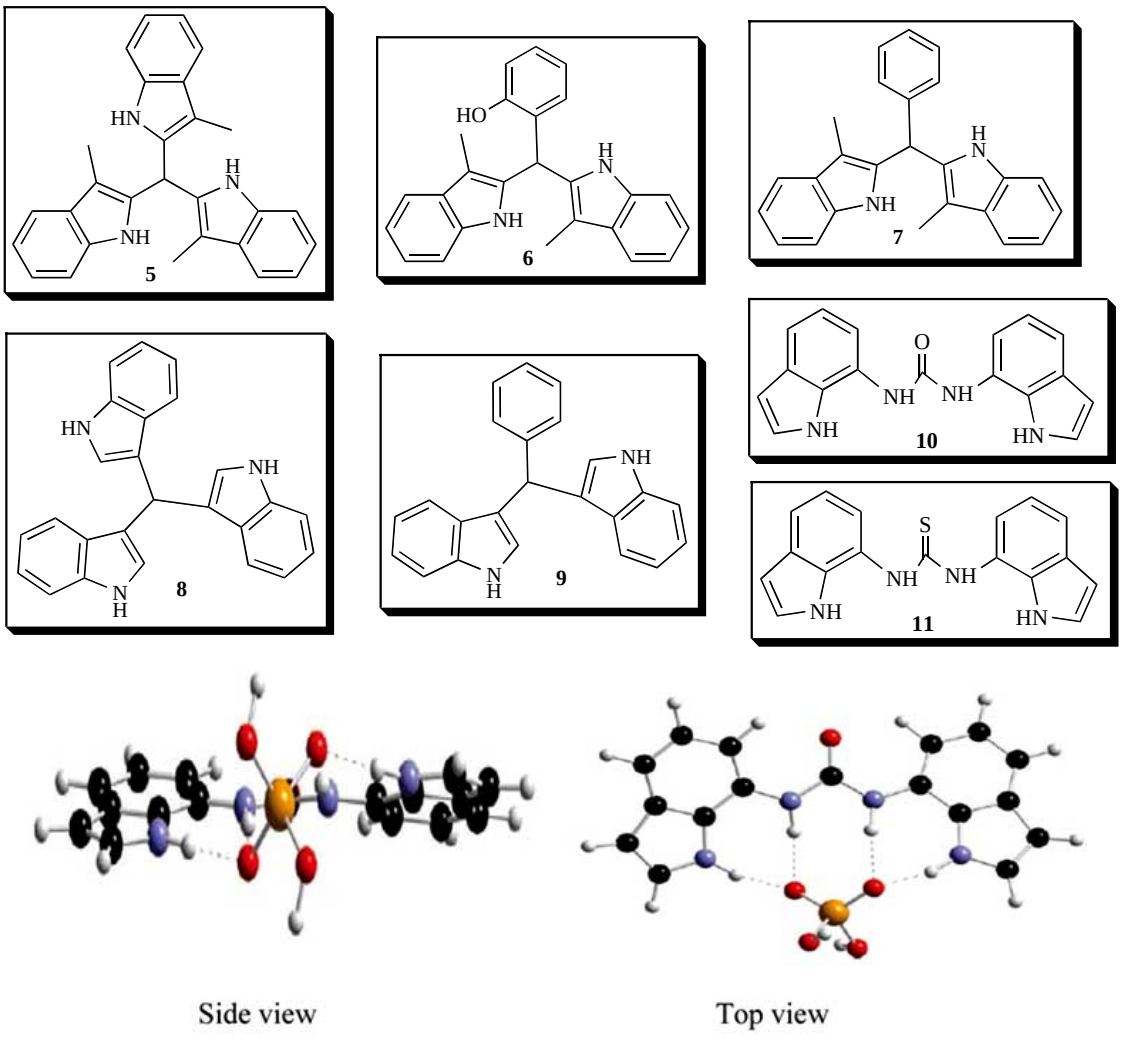
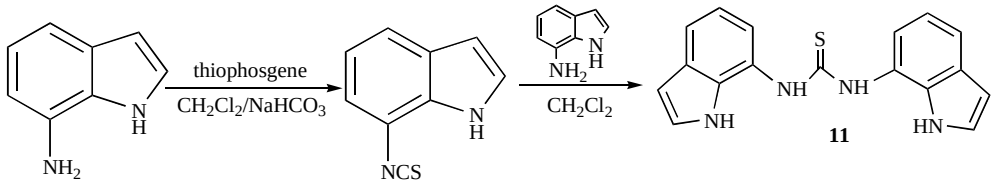


Fig. (1). A DFT calculated structure of $H_2PO_4^-$ complex with compound **10**.



Scheme 1. Synthesis of compound **11**.

solution reduced the binding affinity of compound **11** for $H_2PO_4^-$. Additionally, crystal structure of Cl^- complex with compound **11** clearly showed that four NH groups of compound **11** all participated in hydrogen-bonding interactions with Cl^- with a 1:1 complexation ratio (Fig. **2**).

In 2009, Gale and co-workers also reported the binding behaviors of compound **10** for alkylcarbamate in DMSO-d_6 [9]. Urea NH and indole NH were both involved in hydrogen-bonding interactions with carboxylate group of alkylcarbamate as shown in Fig. (**3**).

Caltagirone *et al*. firstly reported platinum(II)-induced preorganization of compound **12** [10]. Compound **12** displayed the strongest affinity for $H_2PO_4^-$ (K_a = 90 M^{-1} in DMSO-d_6-0.5% water) and no obvious selectivity. However, preorganized compound **12** (i.e., compound **13**) exhibited a significantly higher affinity for anions than compound **12**. Additionally, a distinct selectivity for $H_2PO_4^-$ with the binding constant of 3644 M^{-1} was also found for compound **13**.

Gale's group synthesized four compounds **14**–**17** containing 2-amidoindole (or 7-nitro-2-amidoindole) as binding sites [11]. These compounds displayed moderate affinities toward the examined anions. In most cases, a subtle selectivity for $H_2PO_4^-$ was seen. Additionally, compounds **14**–**17** formed a 1:1 complex with the examined anion, except for compound **17** and $H_2PO_4^-$ (a 1:2 host-guest complex).

Jurczak *et al.* prepared three diamidodiindolylmethane compounds **18**–**20** as anion receptors (Scheme **2**) [12]. The stability constants of these compounds with anions were determined by ^1H NMR titration method in DMSO-d_6 containing different amount of water (0.5%, 5%, 10% and 25%, v/v). Compounds **18**–**20** demonstrated a common preference for more basic $PhCOO^-$ /$H_2PO_4^-$ over Cl^-/Br^- and the formed complexes all indicated a 1:1 stoichiometry. Aliphatic amide **18** bound anions with the largest affinity and the formed complex between compound **18** and $H_2PO_4^-$ was most stable. Even in a highly competitive medium of DMSO-d_6 containing 10% water, an obvious binding affinity was still observed with an association constant of nearly 6000 M^{-1}. Under the same experimental conditions, the association constant of more basic $PhCOO^-$ with compound **18** was less than 600 M^{-1}. Introduction of additional pyrrole NH to compound **20** did not enhance the affinity for

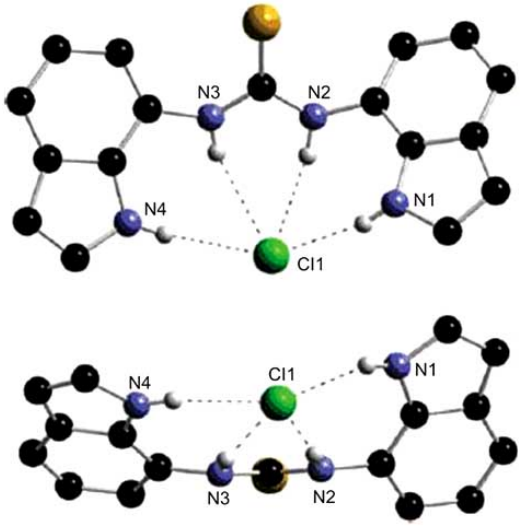


Fig. (2). The X-ray crystal structures of Cl^- complex with compound **11** (top view and side view).

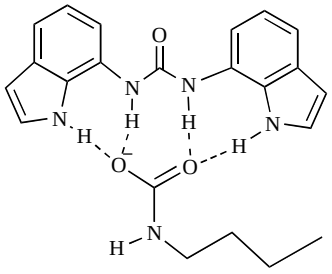
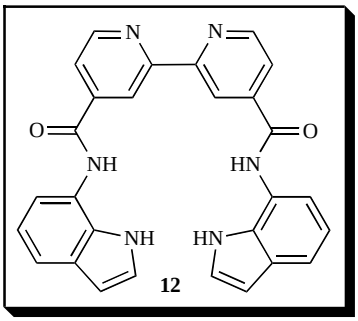
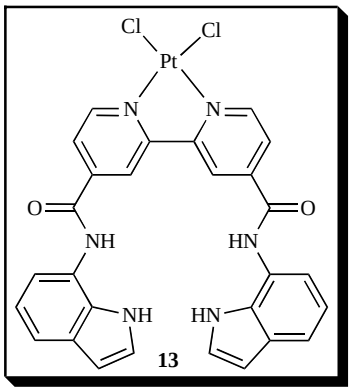
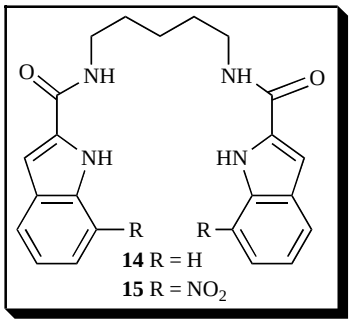
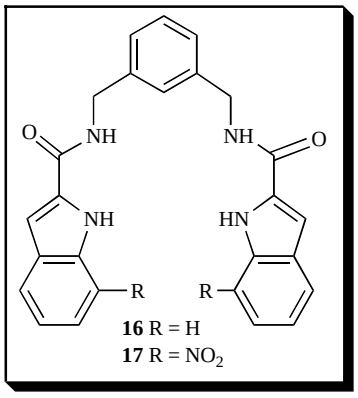


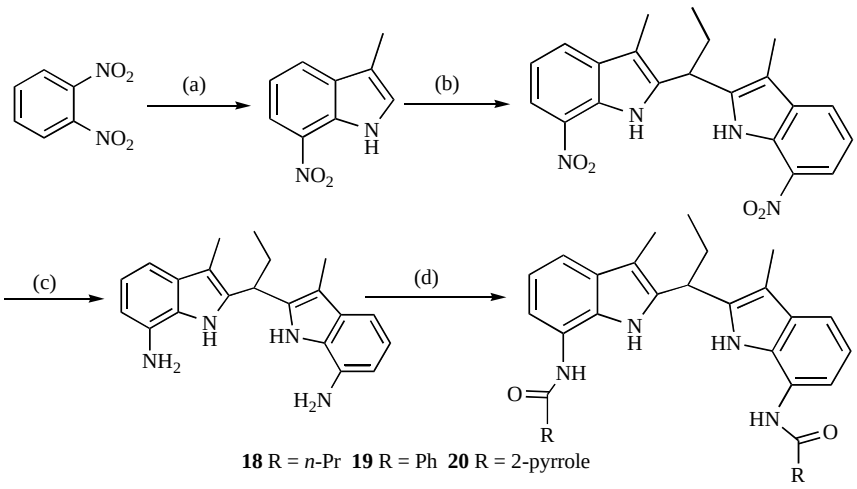
Fig. (3). Proposed interaction mode between compound **10** and *n*-butylcarbamate.











Scheme 2. Synthetic route of compounds **18-20**. (**a**) $CH_3CH=CHMgBr$; (**b**) C_2H_5CHO, HCl; (**c**) H_2, Pd/C; (**d**) RCOCl.

anions. In compound **20**, unfavorable preorganization effect and long distance of pyrrole NH from "binding center" were responsible for the above phenomena.

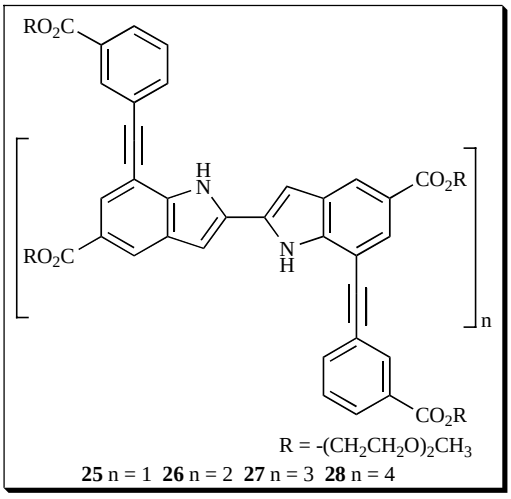
Gale and co-workers reported the synthesis of four 2,7-disubstituted indole-based anion receptors **21–24** and studied anion-induced conformational changes of these compounds by the NOE experiments [13]. Compounds **21–24** exhibited conformational preorganization in acetone solution, where *anti-anti* conformer was predominant. The above receptors were stabilized by intramolecular hydrogen bonds in the *anti-anti* conformer. Anion-triggered chemical shift changes showed that binding of halides (Cl^- and Br^-) took place mainly at indole NH. Nitrate ion established hydrogen-bonding interactions mainly through urea/thiourea NH groups in compounds **22/23**, and AcO^- was strongly bound involving in all hydrogen-bond donors. The formed hydrogen-bonding complex predominantly adopted a *syn-syn* conformation so that all NH protons were spatially close in order to cooperatively participate in hydrogen-bonding interactions with anions. It is noteworthy that addition of NO_3^- to the solution of compounds **21–24** did not cause any conformational changes.

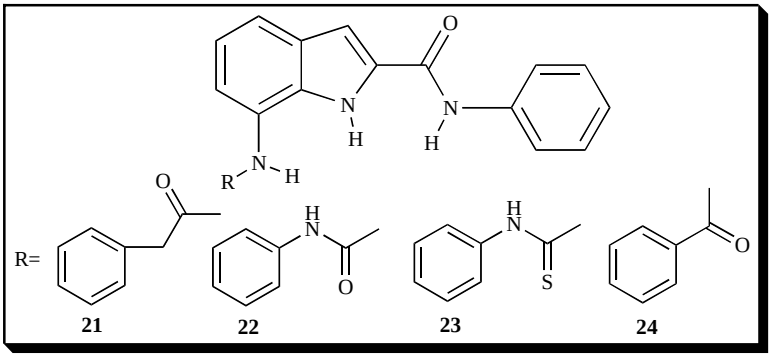
3. ANION SENSING

In order to design more elegant chemosensors, huge efforts have been paid to the development of anion receptors that possess the capability of binding specific anions and translating the binding event into measurable optical signal changes.

3.1. Anion Fluorescent Sensors

Fluorescence detection has a high sensitivity and selectivity, which makes anion fluorescent sensors develop very rapidly. In 2008, Jeong *et al*. reported the synthesis and anion binding properties of four oligoindole foldamers **25–28** [14]. These compounds' folding and recognition properties were studied by ^1H NMR and fluorescence titration spectra. Compounds **25–28** had a strong fluorescence in the absence of anion. Shorter oligoindoles **25–26** did not show noticeable changes in the emission spetrum upon addition of Cl^-, however, significant changes were found for longer oligoindoles **27** and **28** upon addition of Cl^- (Fig. **4**). Obvious hypochromic effect and drastic bathochromic shift of the emission band proved the formation of helical folding. The affinities of compounds **25–28** toward Cl^- strongly relied on the chain length (from less than 1 M^{-1} for **25** to 2.9×10^5 M^{-1} for **28**).





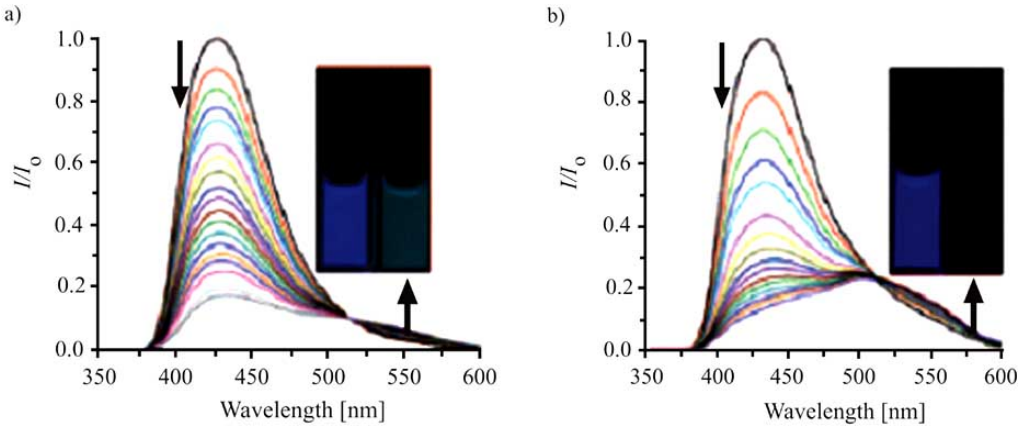


Fig. (4). Fluorescence spectral changes of **27** (left) and **28** (right) upon addition of Cl^- in 20% (v/v) $MeOH/CH_2Cl_2$ at 24 ± 1°C.

Compared with fluorescence quenching, chemosensors based on fluorescence enhancement are highly desirable in the practical applications as they can improve the sensitivity of fluorescence detection. Very recently, Bao and co-workers studied the recognition and sensing properties of N-salicyloyltryptamine (compound **29**) by UV-vis, fluorescence and ^1H NMR titration spectra [15]. Compound **29** could selectively bind biologically important F^- and AcO^- concomitant with obvious changes in the absorption and emission spectra. Interestingly, addition of F^- to DMSO solution of compound **29** caused a remarkable enhancement and a notable blueshift in its emission spectra (Fig. **5**). Based on the results of ^1H NMR and fluorescence titration experiments, a possible binding model was proposed (Scheme **3**). As far as fluorescence enhancement is concerned, an increase in receptor rigidity after complexation of F^- makes nonradiative decay from the excited state less possible, thereby leading to the observed fluorescence enhancement of compound **29**.

3.2. Anion Colorimetric Sensors

Colorimetric sensors need not resort to any equipment to qualitatively determine target analytes (color changes are seen by naked

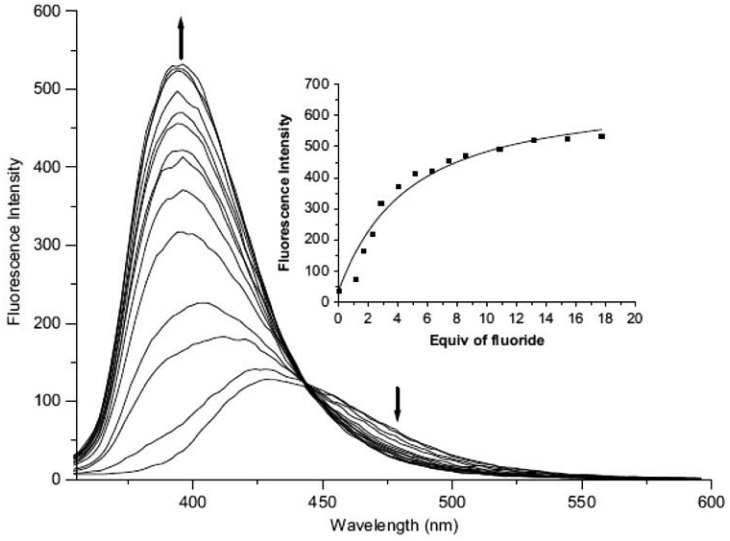
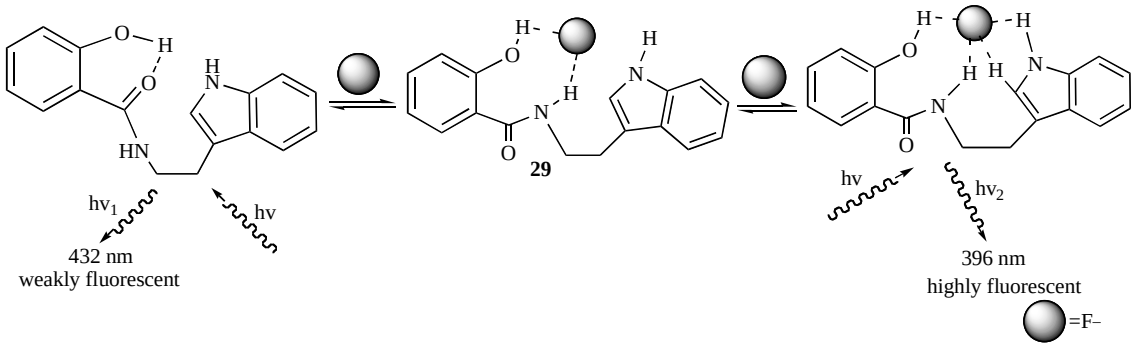


Fig. (5). The fluorescence spectral changes of compound **29** (2.0×10^{-5} M) in DMSO upon addition of F^- (λ_{ex} = 310 nm). The inset was nonlinear curve fitting of the fluorescence intensity at 396 nm against the amount of the added F^-.



Scheme 3. The possible binding process between compound **29** and F^-.

eyes) and therefore possess lots of advantages over other kinds of sensors.

In 2008, Lin *et al.* reported a phenylhydrazone-based indole derivative (compound **30**) as colorimetric sensor for AcO^- [16]. Compound **30** bound AcO^- with a good selectivity in DMSO and an obvious color change from orange to purple was observed after addition of AcO^- (Fig. **6**). Proton NMR titration experiments indicated that indole NH and tautomeric OH cooperatively bound structurally complementary AcO^-. Soon after this report, this group also synthesized an analogous compound **31** [17]. Compound **31** likewise displayed a preferable binding for AcO^-, however, a color change from yellow to blue was seen in this case (Fig. **7**).

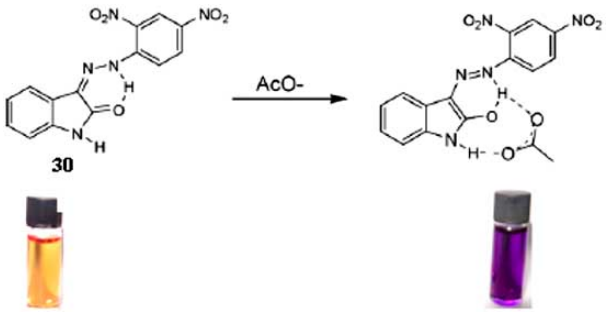


Fig. (6). Color changes of compound **30** (3×10^{-5} M) upon addition of 10.0 equiv of AcO^- in DMSO.

Fig. (7). Color change of compound **31** (2×10^{-5} M) upon addition of 10.0 equiv of AcO^- in DMSO.

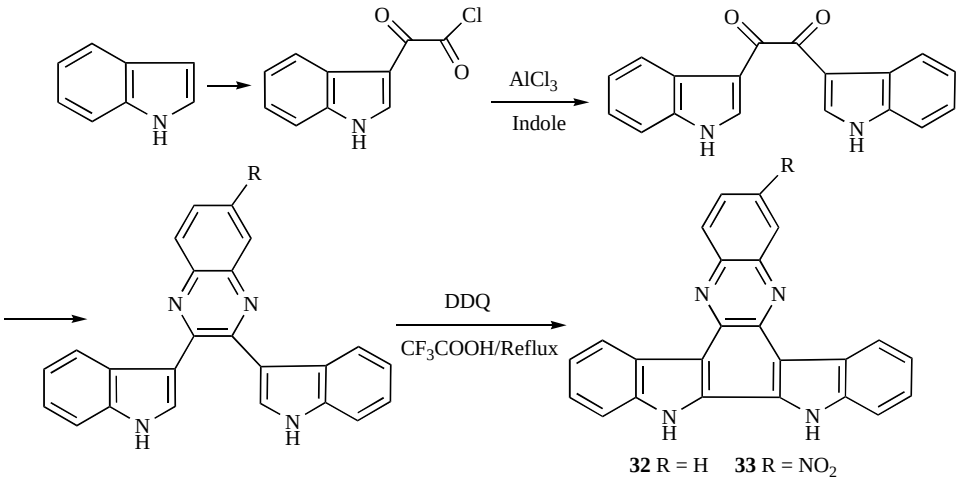
3.3. Dual Optical Sensors

Dual optical sensors can simultaneously demonstrate colorimetric and fluorescent responses for target analyte, which make them attract growing attentions from supramolecular chemists in recent years.

In 2008, Yan's group reported the synthesis (Scheme **4**) and anion recognition properties of two indolo-carbazole-quinoxaline compounds (**32** and **33**) [18]. Both compounds had a highly flat rigid structure along with a large π system and showed a selective binding for F^- and AcO^- over other anions. Interestingly, addition of F^- or AcO^- could trigger a significant bathochromic shift in the UV-vis spectrum of compound **33** in DMSO along with a visible color change from bright yellow to gray. In contrast, for compound **32**, colorimetric sensing was realized only in the case of F^-. Cooperative utilization of two compounds provided a simple way for distinguishing F^- from AcO^- by the naked-eye observation. Significant fluorescence quenching of compound **32** as well as no shift in the emission peak were observed upon addition of AcO^- (Fig. **8**). Fluoride and dihydrogenphosphate ions also caused similar changes. Fluorescence quenching also occurred after addition of the above-mentioned three anions to DMSO solution of compound **33**.

In 2009, Shiraishi *et al*. synthesized an indole-azadiene conjugate (compound **34**) through one-step condensation reaction and studied its binding properties toward various anions [19]. Compound **34** showed a highly selective recognition for fluoride ion over other nine anions, along with a significant color change from colorless to yellow and an appearance of green fluorescence. ^1H NMR analysis and *ab initio* calculation proved that fluoride-induced UV-vis and fluorometric response (Fig. **9**) of compound **34** were driven simply by hydrogen-bonding interaction instead of deprotonation effect. Additionally, the same group also prepared a BODIPY-indole conjugate (compound **35**) as a highly selective chemosensor for fluoride ion [20]. Compound **35** bound F^- in a 1:1 stoichiometry in CH_3CN through a H-bonding interaction from indolic NH, eventually resulting to a drastic color change from blue to green and significant quenching of orange fluorescence (Fig. **10**).

In the same year, Chow and co-workers synthesized two disubstituted maleimide dyes (compounds **36** and **37**) with two symmetrical NH binding sites, which exhibited a distinct color change and fluorescence quenching after interaction with F^-, CN^- and $H_2PO_4^-$ in CH_2Cl_2 [21]. For compounds **36** and **37**, hydrogen-bonding interactions played a key role in the formation of binding complex with $H_2PO_4^-$.



Scheme 4. Synthesis of compounds **32** and **33**.

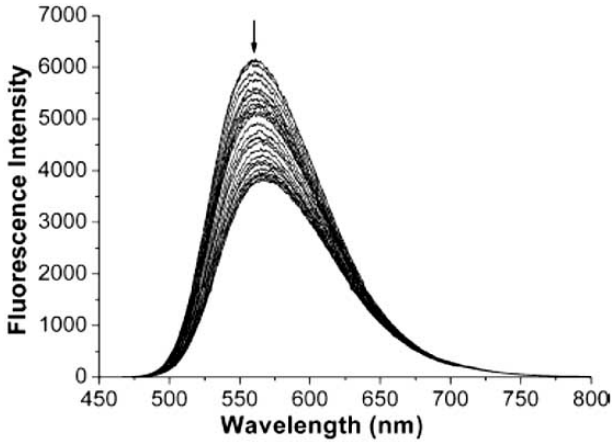


Fig. (8). Fluorescence quenching of compound **32** (1.5×10^{-5} M) upon titration with AcO^- in DMSO.

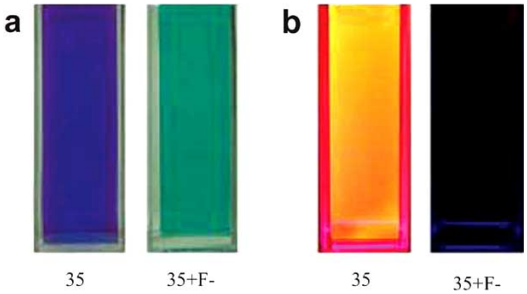


Fig. (10). Change in color (**a**) and fluorescence color (**b**) of a MeCN solution containing compound **35** upon addition of F^-.

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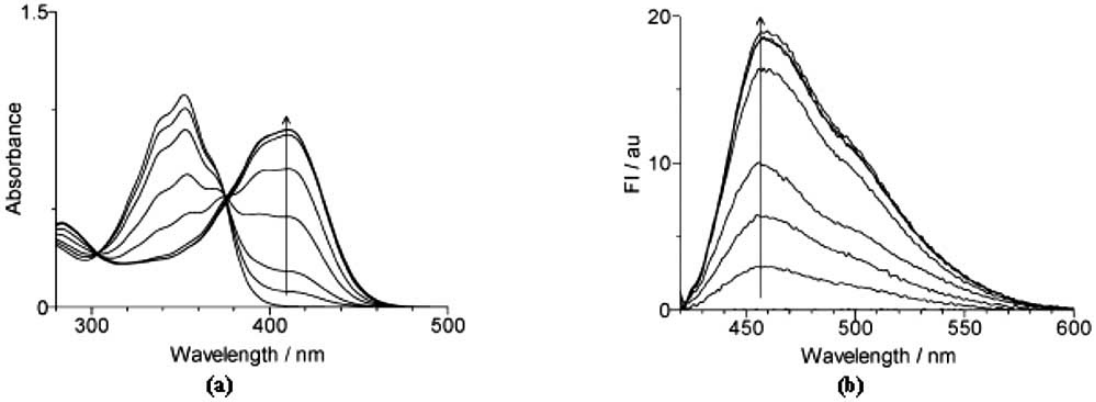
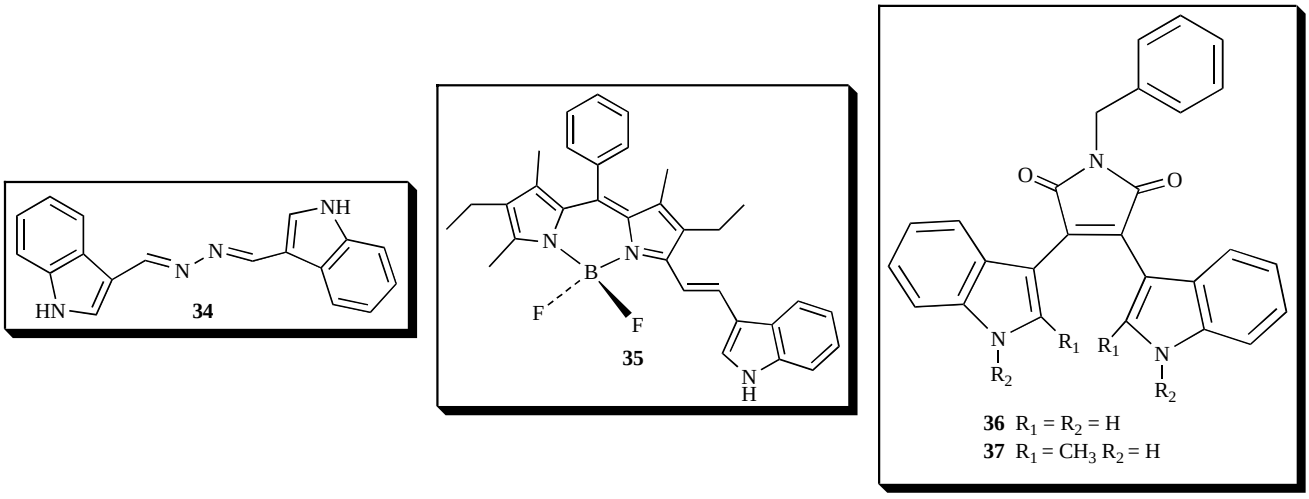


Fig. (9). Absorption titration (**a**) and fluorescence titration (**b**) of compound **34** (25 μM) with F^- (as a n-Bu_4N^+ salt) in DMSO.



4. CONCLUSIONS

In the last nearly two and a half years, indole group had been increasingly employed in the construction of various anion receptors and sensors. Some of anion receptors containing indole NH exhibited high affinities and selectivities toward specific anions, even in a highly competitive aqueous environment. More elaborate and practical chemosensors based on indole NH will be bound to appear in the future, which can effectively recognize and sense specific anions in a 100% aqueous solution.

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