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A new class of efficient 4-[(nitro substituted-phenyl)-hydrazonomethyl]-1-phenyl-1*H*-pyrazole-3-carboxylate derived colorimetric chemosensor for selective sensing of fluoride and other biologically important anions

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Abstract. A new class of efficient colorimetric chemosensors derived from 4-[(nitro substituted-phenyl)-hydrazonomethyl]-1-phenyl-1*H*-pyrazole-3-carboxylate have been synthesized and characterized. The synthesized receptors exhibit instant color change from yellow to dark purple along with significant bathochromic shifts when interacted with fluoride ions. The UV-Visible and ^{1}H NMR titration experiments revealed that 4-[(4-nitro-phenyl)-hydrazonomethyl]-1-phenyl-1*H*-pyrazole-3-carboxylate derivatives showed selective sensing of fluoride ions in preference to Cl^-, Br^-, I^-, PF_6^-, HSO_4^-, ClO_4^-, CH_3COO^- and $H_2PO_4^-$ ions while 4-[2,4-dinitro-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazole-3-carboxylate derivatives showed sensing of acetate, dihydrogen phosphate ion and fluoride ion in organic media.

Keywords. Pyrazole; receptor; sensor; anions; fluoride ion.

1. Introduction

The selective sensing of anionic species through artificial receptors have gained immense interest in the recent past[1] due to involvement of various anions in biological, chemical, environmental and pathological events of varying complexity.[2] Among the biologically important anions, sensing of fluoride ions is a significant research area[3] because of its functional diversity which is both beneficial and detrimental. For example, it is well-established that fluoride ion plays important role in preventing dental caries and treatment of osteoporosis[4] while excess of fluoride ion causes several adverse effects like fluorosis, kidney disorder, bone and skeletal cancer.[5] Amongst several approaches adopted[6] for the development of fluoride ion receptors, sensing of fluoride through colorimetric neutral receptors seems to be of utmost significance as they require minimum instrumentation and quick response through anion induced color changes of solution.[7] Previous reports on colorimetric sensing of fluoride ions[8] include molecular hosts having precise alignment of optical signaling chromophoric units with suitable anion binding sites such as urea, thiourea, amide and sulfonamides, which can provide one or more H-bond donor sites for selective recognition of anionic species through N–H–X hydrogen bonds.[9] The interaction of anion with receptor triggers a change in photophysical response of the chromophoric unit to allow sensing through visual color changes.[10] The selectivity and colorimetric response of receptors depend on the structure of the hydrogen bond complexes and basicity of anions. Among the anions, fluoride ion, usually forms strong hydrogen bond with a hydrogen bond donor fragment of the artificial receptor at lower concentration, and at higher concentration the interaction would likely stimulate the proton transfer reaction, which depends on the acidity of hydrogen bond donor group of the receptor. The colorimetric sensors based on the deprotonation of the binding moiety by anions are highly sensitive and selective in nature.

Heterocyclic systems like imidazole, pyrrole, naphthyridine, pyrazole *etc.*, belong to an important class of nitrogen containing systems and they are of considerable pharmacological interest in view of their uses as anti-microbial,[11a] anti-cancer,[11b] anti-inflammatory,[11c] anti-tubercular,[11d] anti-parasitic,[11e] anti-pyretic[11f] and anti-fungal[11g] agents. In continuation of our work on anion sensing,[12] it was envisaged that functionalized pyrazole derivative like 4-formyl-3-carboxylate pyrazole might display interesting anion binding and sensing characteristic because of its structural features which involve methine proton of pyrazole and basic hydrogen bond acceptor fragment in condensed heterocyclic system integrated with formyl and ester

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functionality which can be modulated for the construction of effective recognition sites for noncovalent interactions. In this paper, we report the synthesis of pyrazole based molecular receptors for sensing of fluoride ion and other biologically and environmentally important anions. To design the receptors, we introduced hydrazone functionality substituted with electron withdrawing nitro unit which are probably responsible for the changes in color as well as to increase hydrogen bond donor tendency.[12,13] It has been observed that these synthesized receptor molecules (**5a** and **5e**) exhibit significant binding ability for fluoride ions in preference to other anions which include Cl^-, Br^-, I^-, $H_2PO_4^-$, HSO_4^-, CH_3COO^-, ClO_4^- and PF_6^-.

2. Experimental

2.1 *General procedure for the synthesis of **4a***

To a cooled and anhydrous dimethylformamide (80 mL), $POCl_3$ (25.5 mL) was added drop wise at 0°C and stirred the reaction mixture for 30 min at same temperature. Phenyl hydrazone (13.5 g, 1 mmol) (**3a**) was added at 0°C. The reaction mixture was stirred at room temperature for 2 h. After completion of reaction as monitored by TLC, the reaction mixture was poured over crushed ice under stirring. Thereafter the mixture was neutralized with 10% $NaHCO_3$ solution which resulted in the formation of white solid. The solid product was filtered under vacuum and dried in air to give a compound **4a**.

2.2 *General procedure for the synthesis of **5a***

To **4a** (1 g, 4.1 mmol) in 20 mL ethanol, 4-nitro phenylhydrazine (0.736 g, 4.8 mmol) was added. The reaction mixture was refluxed for 45 min and then cooled to room temperature. A yellow solid product was filtered off, washed with hot ethanol (3 × 10 mL) and then dried under vacuum to give desired compound **5a** as yellow solid. Selected analytical data for compounds **5a** and **5e** are given below: Compound **5a**: Yield (90%); M.p.: 238°C; IR (KBr), ν_{max} (cm^{-1}): 1605 (C=N), 1704 (C=O). TOF-MS ES+ m/z calcd: 379.37. found: 380.23 (M+1); Anal. Calcd.for $C_{19}H_{17}N_5O_4$: C 60.15, H 4.52, N 18.46, O 16.87%. Found: C 60.08, H 4.36, N 18.35%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (t, 3H, $COOCH_2CH_3$), δ 4.42 (q, 2H, $COOCH_2CH_3$), δ 7.14 (d, 1H, ArH), δ 7.36 (m, 2H, ArH), δ 7.47–7.51 (m, 2H, ArH), δ 7.77 (d, 2H, $ArH_{nitrophenyl}$), δ 8.11 (d, 2H, $ArH_{nitrophenyl}$), δ 8.41(bs, 2H, $CH_{pyrazole}$+$CH_{azomethine}$), 10.45 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 14.2, 60.8, 110.2, 118.47, 120.24, 121.89, 125.20, 126.38, 128.31, 130.44, 138.18, 138.38, 140.92, 152.45, 161.68. Compound **5e**: Yield (88%); M.p.: 234°C; IR (KBr), ν_{max} (cm^{-1}): 1601 (C=N), 1698 (C=O). TOF-MS ES+ m/z calcd: 458.27. found: 459.34 (M+1); Anal. Calcd. for $C_{19}H_{16}BrN_5O_4$: C 49.80, H 3.52, Br 17.44, N 15.28, O 13.97%. Found: C 49.88, H 3.43, N 15.37%; ^{1}HNMR (400 MHz, $CDCl_3$): δ 1.12 (t, 3H, $COOCH_2CH_3$), δ 4.10 (q, 2H, $COOCH_2CH_3$), δ 6.75 (d, 2H, ArH), δ 7.29 (d, 2H, ArH), δ 7.44 (d, 2H, $ArH_{nitrophenyl}$), δ 7.75 (d, 2H, $ArH_{nitrophenyl}$), δ 8.21 (s, 1H, $CH_{azomethine}$), δ 8.24 (s, 1H, $CH_{pyrazole}$), δ 10.55 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 14.7, 63.4, 110.1, 113.7, 118.3, 124.0, 125.1, 126.8, 127.0, 128.1, 132.6, 140.5, 149.8, 150.6, 152.o, 158.7.

2.3 *General procedure for the synthesis of **5b***

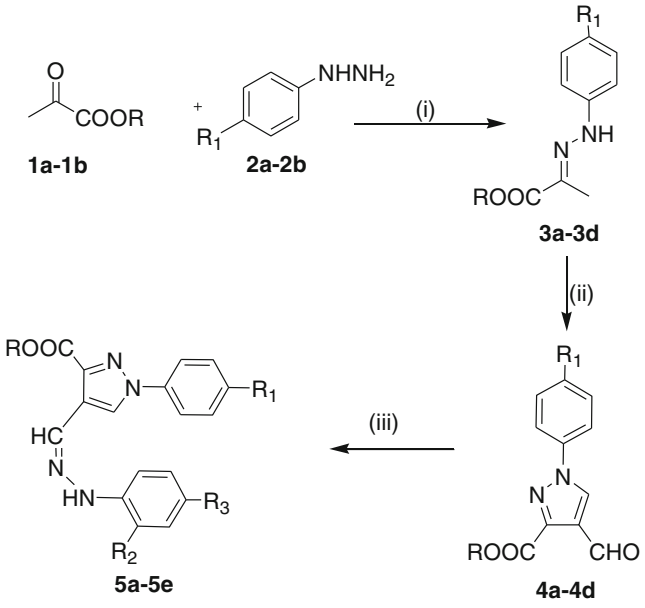
To **4a** (1 g, 4.1 mmol) in 20 mL ethanol, 2,4-dinitro phenylhydrazine (0.972 g, 4.9 mmol) was added. The reaction mixture was refluxed for 45 min and then cooled to room temperature. Orange solid was filtered off, washed with hot ethanol (3 × 10 mL) and then dried under vacuum to give the desired compound **5b** as orange solid. Compound **5b**: Yield (93%); M.p.: 232°C; IR (KBr), ν_{max} (cm^{-1}): 1598 (C=N), 1712 (C=O). TOF-MS ES+ m/z calcd: 424.11 found: 425.22 (M+1); Anal. Calcd.for $C_{19}H_{16}N_6O_6$: C 53.77, H 3.80, N 19.80, O 22.62%. Found: C 53.63, H 3.74, N 19.69%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (t, 3H, $COOCH_2CH_3$), δ 4.45 (q, 2H, $COOCH_2CH_3$), δ 7.31 (d, 2H, ArH), δ 7.73 (d, 2H, ArH), δ 7.82 (m, 1H, ArH), δ 8.10 (m, 1H, ArH_{DNP}), δ 8.29 (m, 1H, ArH_{DNP}), δ 8.67 (s, 1H, $CH_{Pyrazole}$), δ 8.93 (s, 1H, $CH_{azomethine}$), δ 9.04 (m, 1H, ArH_{DNP}), δ 11.58 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 14.4, 61.5, 103.3, 113.7, 114.6, 119.8, 124.2, 127.0, 128.7, 130.3, 138.9, 142.5, 147.31, 161.8. Compound **5c**: Yield (95%); M.p.; 235°C; IR (KBr), ν_{max}(cm^{-1}): 1609 (C=N), 1720 (C=O). TOF-MS ES+ m/z calcd: 438.39 found:.461.22 (M+Na); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, 3H, $COOCH_2CH_3$), δ 2.19 (s, 3H, CH_3), δ 4.31 (q, 2H, $COOCH_2CH_3$), δ 7.37-7.46 (m, 4H, ArH), δ 8.04 (m, 2H, ArH_{DNP}), δ 8.76-8.79 (m, 2H, $CH_{Pyrazole}$+$CH_{azomethine}$), δ 8.99 (s, 1H, ArH_{DNP}), δ 11.78 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$): 14.4, 17.9, 61.7, 116.5, 119.9, 123.6, 126.3, 126.9, 129.9, 130.8, 131.5, 134.0, 138.2, 138.9, 141.2, 142.0, 144.9, 161.3.

3. Results and Discussion

In our effort to prepare receptor molecules (**5a**–**5e**), first we prepared 4-formyl-1-substituted phenyl-1*H*-pyrazole-3-carboxylate derivatives (**4a**–**4d**) in 90-95%

yield *via* two step synthetic protocol. In the first step, alkyl-2-oxopropanoate (**1a**–**1b**) reacted with substituted phenyl hydrazine (**2a**–**2b**) in presence of trifluroacetic acid in water at room temperature for 5–15 minutes to give **3a**–**3d** in more than 90% yield. Compound **3a-3d** was then reacted with DMF-$POCl_3$ at 0°C to provide **4a**–**4d** in more than 92% yield.[14] Reaction of **4a**–**4d** with various phenyl hydrazine reagents afforded the receptor **5a**–**5e** in 88–95% yield as depicted in Scheme 1.

Receptor compounds (**5a–5e**) were characterized by elemental and spectroscopic analysis. For instance, ^{1}H NMR spectrum of **5a** showed a triplet and quartet at δ 1.44 and δ 4.45 for CH_3 and CH_2 protons of ester group, respectively. The azo-methine proton and aromatic proton of pyrazole unit appeared as a non-exchangeable singlet at δ 8.43 and δ 8.44, respectively. The individual assignments of the aromatic proton of pyrazole and azo-methine protons were confirmed by comparison of their spectra with those of precursor compounds. A singlet of NH protons appeared at δ 10.45 which disappeared on deuteration with D_2O. Similarly, other synthesized compounds were characterized by various spectroscopic techniques.



Comp. No.	R	R_1	R_2	R_3
5a	Et	H	H	NO_2
5b	Et	H	NO_2	NO_2
5c	Et	CH_3	NO_2	NO_2
5d	Me	H	NO_2	NO_2
5e	Et	Br	H	NO_2

Scheme 1. Synthesis of receptors **5a–5e**. Reagents and conditions: (i) TFA, H_2O, room temperature, 15 min; (ii) DMF-$POCl_3$, 0°C, 2.5–3 h; (iii) substituted phenyl hydrazine derivative, ethanol, reflux, 1–2 h.

The anion binding characteristics of receptors **5a–5e** with various anions were examined spectrophotometrically and visual colorimetric observation in DMSO-CH_3CN (1.0 : 9.0 v/v). It was observed that receptor **5a** showed an instant change in color from yellow to dark purple with fluoride ion while no change in color was observed with other anions such as Cl^-, Br^-, I^-, HSO_4^-, ClO_4^-, PF_6^-, CH_3COO^- and $H_2PO_4^-$ in form of their tetrabutylammonium salts as depicted in Figure 1a. On the other hand, it was observed that receptor **5b** gave a noticeable color change not only with fluoride ion but also with dihydrogen phosphate and acetate anions (Figure 1b) under similar experimental conditions.

The anion binding ability of receptors **5a-5e** was also examined by UV-Visible spectroscopy in DMSO-CH_3CN (1.0 : 9.0 v/v) at pH 7.7. The receptor **5a** showed an absorption peak at 402 nm that could be ascribed to the absorption maximum for the hydrazone unit present in the receptor molecule. The binding characteristics receptor **5a** with various anions was studied by using their tetrabutylammonium salt of F^-, Cl^-, Br^-, I^-, HSO_4^-, ClO_4^-, PF_6^-, CH_3COO^- and $H_2PO_4^-$ in DMSO-CH_3CN (1.0 : 9.0 v/v). It was observed that receptor **5a** selectively recognizes fluoride ion from a mixture of various anions. For example, when 2.2×10^{-5} M solution of receptor **5a** was treated with tetrabutyl ammonium fluoride, it showed a bathochromic shift ($\Delta\lambda_{max}$) of 155 nm in its UV-Visible spectrum with the appearance of a new absorption peak at 557 nm

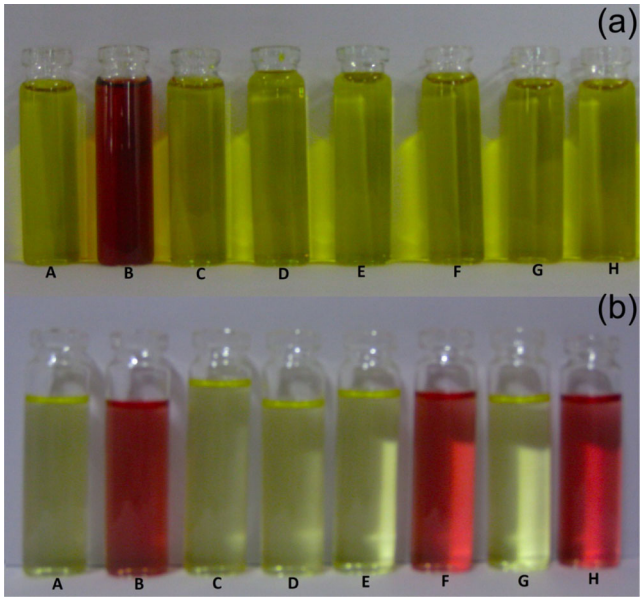


Figure 1. Selectivity of **5a** for fluoride ion over other anions. Color changes of **5a** (a) and **5b** (b) in (22 μM) in DMSO: CH_3CN (1.0 : 9.0 v/v) with the addition of TBA anions (5×10^{-3} M): A = Receptor, B = F^-, C = Cl^-, D = Br^-, E = I^-, F = CH_3COO^-, G = HSO_4^-, H = $H_2PO_4^-$.

while no significant shift in absorption maximum at 402 nm was observed with other anionic species (Cl^-, Br^-, I^-, HSO_4^-, ClO_4^-, PF_6^-, CH_3COO^- and $H_2PO_4^-$) in similar experimental conditions (Figure 2a). These behavior of **5a** could be explained by the formation of more stabilized excited state of **5a** by interaction with fluoride as compared to other anions.[12,13]

Further, it was observed that on gradual addition of a standard solution of tetrabutylammonium fluoride (5×10^{-3} M), the intensity of absorption peak at 402 nm progressively decreased with simultaneous increase in the intensity of absorption peak at 557 nm in UV-Visible spectrum. Critical analysis of UV-Visible titration data indicated that the limiting value of the absorption maximum at 557 nm was reached at three equivalent of fluoride ion instead of one equivalent (Figure 2b) and the receptor can detect fluoride ion in μM range. These observations can be accounted by the hypothesis that initial addition of one equivalent of fluoride ion establishes a hydrogen bond interaction with NH proton of the receptor, and further addition of fluoride ion triggers deprotonation of NH proton,[15] which results in bathochromic shift in absorption maximum. The change in color occurs possibly through efficient charge transfer from donor to acceptor substituents.

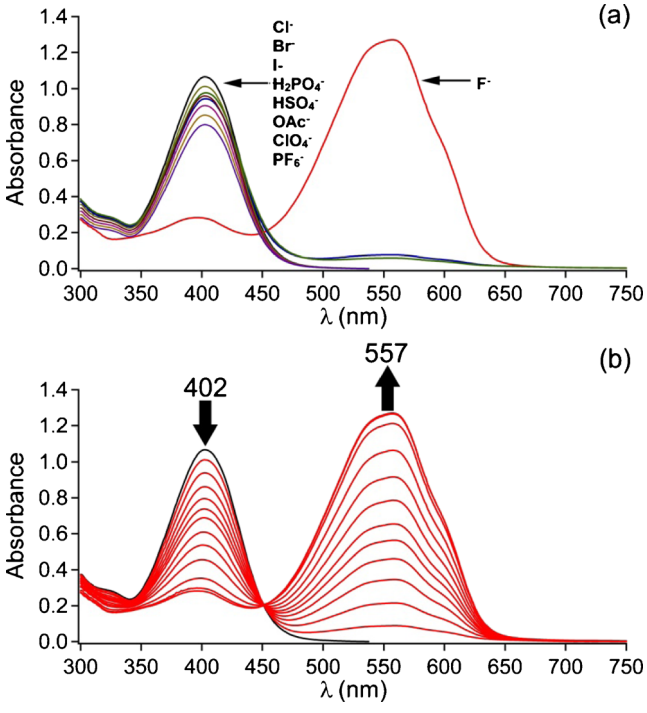


Figure 2. (a) Absorption spectra of **5a** (2.2×10^{-5} M, path length of the cuvette 1 cm) upon addition of F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, HSO_4^-, CH_3COO^-, ClO_4^- and PF_6^- ions (tetrabutyammonium salt) (5×10^{-3} M) in DMSO-CH_3CN (1.0 : 9.0 v/v) (b) UV-Visible titration of **5a** with 0 to 3 equiv. of F^-.

The binding affinity of synthesized receptor **5a** towards fluoride ion was again examined by ^{1}H NMR titration experiments in $CDCl_3$. The ^{1}H NMR spectrum of **5a** on gradual addition of tetrabutylammonium fluoride (Figure 3) indicated that addition of fluoride ions a broadening of hydrazone NH signal and a downfield shift in methine proton of pyrazole and aromatic proton of phenyl unit (attached to pyrazole moiety) was observed whereas an unexpected upfield shift in aromatic proton of nitrophenyl moiety was observed. Analysis of the ^{1}H NMR titration spectra indicated that addition of increasing equivalent of F^- ions to **5a** results in a broadening of hydrazone NH signals at δ 10.45 which completely disappeared after the addition of two equivalents of fluoride ions with appearance of a broad signal at 16 ppm in ^{1}H NMR spectrum that could be ascribed to the formation of stable bifluoride [HF_2^-].[16] However, addition of fluoride ions more than two equivalents to the solution of **5a** resulted in upfield chemical shift in aromatic proton at δ 8.11 of the nitro phenyl units while downfield chemical shift in methine proton of pyrazole at δ 8.41 and aromatic proton of phenyl unit at δ 7.14 which reached its limiting value on addition of three equivalents of fluoride ion. These experimental observations indicate that initial one equivalent of fluoride ion interact through hydrogen bonds with the NH protons of hydrazone subunits of receptor **5a** whereas addition beyond one equivalent of fluoride results in the deprotonation of the NH protons to induce an upfield shift of the aromatic proton of nitrophenyl unit due

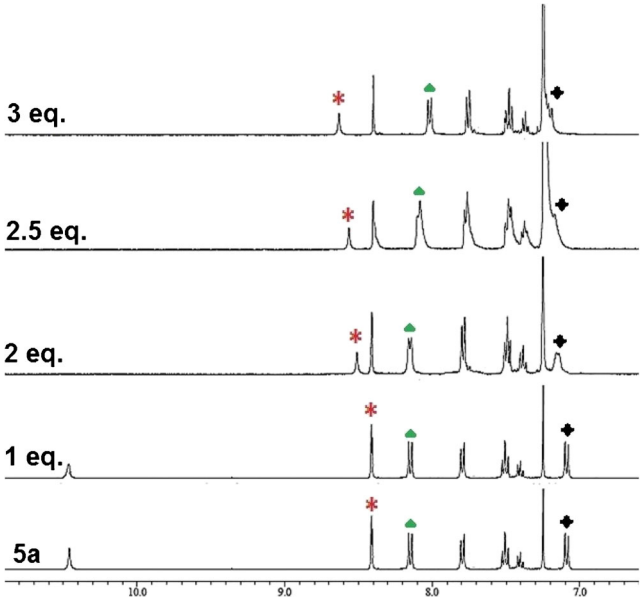
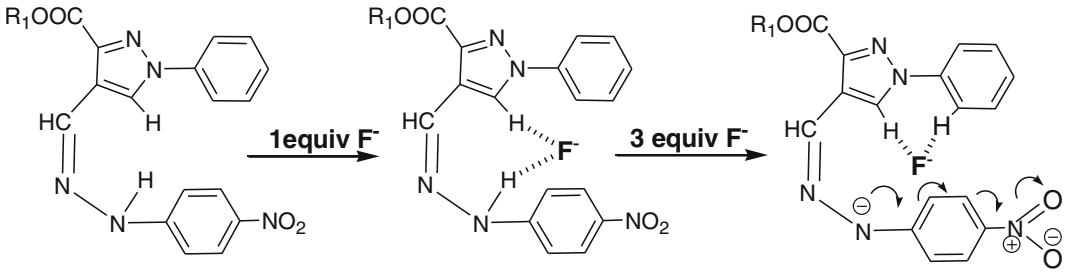


Figure 3. Partial ^{1}H NMR (400 MHz, $CDCl_3$) spectra of **5a** (15 mM) upon addition of various equiv. of TBAF (45 mM). Numbers at left side indicate the equivalent amount of F^- added (* = $ArH_{pyrazole}$, ♣ = $ArH_{nitrophenyl}$, ✤ = ArH).



Scheme 2. A proposed binding mode and deprotonation of **5a** with fluoride ion.

Table 1. Shift in absorption peak (λ_{max}) for receptors **5a–e** with the fluoride ion[a].

Receptor (L)	λ_{max}/nm (L)[a]	λ_{max}/nm (L+F$^-$)	$\Delta\lambda_{max}$/nm
5a	402	557	155
5b	386	492	106
5c	385	493	108
5d	385	492	107
5e	401	556	155

[a] Absorption spectra were taken at a concentration of 22 μM in DMSO-CH_3CN (1.0: 9.0 v/v) solution.

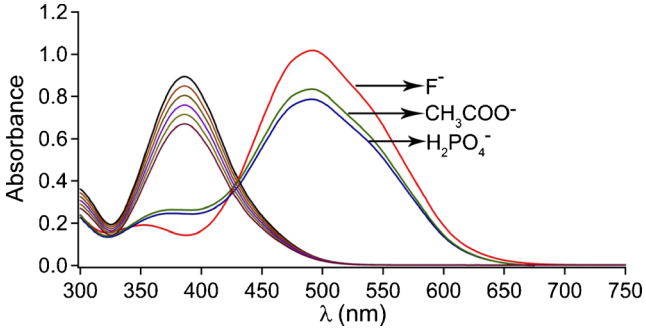
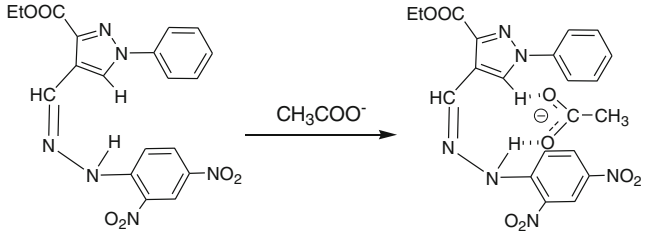


Figure 4. Absorption spectra of **5b** (2.2×10^{-5} M, path length of the cuvette 1 cm) upon addition of F$^-$, Cl$^-$, Br$^-$, I$^-$, $H_2PO_4^-$, HSO_4^-, CH_3COO^-, ClO_4^- and PF_6^- ions (tetrabutyammonium salt) (5×10^{-3} M) in DMSO-CH_3CN (1.0 : 9.0 v/v).



Scheme 3. A proposed binding mode of **5b** with acetate ion.

to through-bond propagation of electron density. The downfield shift of methine proton and aromatic proton of the phenyl unit on addition of three equivalents of fluoride ion in $CDCl_3$ indicated that both the methine and aromatic protons of phenyl unit participate in the formation of cooperative hydrogen bonds with anionic guest (Scheme 2).[17]

Similar experiments were performed with **5b**, **5c** and **5d**. It was observed that these receptors exhibited bathochromic shifts of lower magnitude as compared to **5a** and **5e** in the UV-Visible spectrum with fluoride ions (Table 1), possibly due to the extended conjugation present in **5a** and **5e**. Additionally, it was interesting to observe that receptors **5b**, **5c** and **5d** showed bathochromic shifts of similar magnitude in their λ_{max} values on addition of tetrabutylammoniumdihydrogen phosphate and acetate ions as shown in Figure 4. The additional binding ability of receptors **5b** and **5d** for dihydrogen phosphate and acetate ions can possibly be ascribed to the comparatively more acidic nature of the NH protons due to the presence of two electron withdrawing nitro substituents. The UV-Visible titration experiments of receptor **5b** with F$^-$ ion indicated that intensity of absorption at 386 nm progressively decreased with gradual appearance of a new peak at 492 nm along with a color change from yellow to purple which reached a saturation point on addition of three equivalents of fluoride ions (Figure S1, see Supplementary Information).

Similarly, the titration profiles of **5b** with CH_3COO^- and $H_2PO_4^-$ ion was further studied from UV-visible spectrum in DMSO-CH_3CN (1.0 : 9.0 v/v). A bathochromic shift ($\Delta\lambda_{max}$) of 105 nm in its UV-Visible spectrum was observed with the appearance of a new absorption peak at 491 nm which reached the limiting values on addition of two equivalents of the respective anions (Figures S2 and S3). These observations suggest that the F$^-$ ion interact with **5b** in a similar manner as that of **5a**, while the CH_3COO^- and $H_2PO_4^-$ ions interact with **5b** exclusively through hydrogen bonding (Scheme 3). The receptors **5e** and **5d** showed similar behavior in the colorimetric and UV-Visible experiments as that of **5a** and **5b**, respectively, thereby suggesting that the aromatic proton of the phenyl unit

(attached to pyrazole) (in **5a** and **5b**) when replaced by methyl and bromine (in **5c** and **5e**), respectively, do not affect the binding mode of anions.

4. Conclusions

In conclusion, a new class of efficient colorimetric chemosensors derived from 4-[(nitro substituted-phenyl)-hydrazonomethyl]-1-phenyl-1*H*-pyrazole-3-carboxylate (**5a**–**5e**) have been synthesized and characterized. The synthesized receptors exhibit significant bathochromic shifts when interacted with fluoride ions along with prominent color change. The UV-Visible and ^{1}H NMR titration experiments revealed that receptor **5a** and **5e** showed selective sensing of fluoride ions *via* hydrogen bond interaction in preference to Cl^-, Br^-, I^-, HSO_4^-, ClO_4^-, PF_6^-, CH_3COO^- and $H_2PO_4^-$ ions whereas receptors **5b**, **5c** and **5d** showed sensing of acetate and dihydrogenphosphate ions along with fluoride ion in organic media.

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