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Benzimidazole scaffold as dipodal molecular cleft for swift and efficient naked eye fluoride ion recognition via preorganized N-H and aromatic C-H in aqueous media

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A series of elegantly designed cleft-like dipodal receptors, N,N'-bis-(5-(un)substituted-1H-benzoimidazol-2-ylalkyl)-isophthal-amides (**RA-RD**) has been synthesized and characterized for colorimetric detection of fluoride ion in 9:1 DMSO-water. The phenyl ring in the molecular framework of receptors is symmetrically armed with two benzimidazole moieties using amide groups as linkers to yield dipodal receptors, with multiple hydrogen bond donor sites for anion sensing. Anion binding studies, conducted qualitatively and spectroscopically in 9:1 DMSO-water, show that the receptor **RC** binds fluoride ion exclusively with a detection limit of 1.5 ppm over other anions. UV-visible spectra of receptor **RC** shows a considerable bathochromic shift of 117 nm from 348 nm to 465 nm upon addition of varying concentrations of fluoride ion (tetrabutylammonium salt). Jobs plot and mass spectroscopic data confirm 1:1 stoichiometric ratio between receptor **RC** and fluoride ion. ^{1}H NMR titration reveals the presence of hydrogen binding interactions between receptor **RC** and fluoride ion responsible for naked eye colour change. ^{19}F NMR titration further supports the binding interaction between receptor **RC** and fluoride ion. The binding constant of receptor **RC** for fluoride ion is calculated to be 5.59×10^{3} M^{-1}.

Keywords: Molecular recognition, Anion recognition, Fluoride ion recognition, Dipodal receptors, Colorimetric receptors Benzimidazoles, Preorganisation

Fluoride ion recognition has materialised as a worthy target of contemporary research in supramolecular chemistry due to its dual nature – being considered essential for prevention of dental caries and at the same time dangerous to human health above the permissible limit[1-8]. Various design concepts and strategies have been thoroughly investigated by the researchers in the field of supramolecular chemistry to develop synthetic host guest complexes[9-11]. The last decade has seen much progress in the field of fluoride detection and is extensively reviewed with the development of receptors claiming efficient and selective ion recognition[12-15]. However, the crescendo of reported anion receptors with various motifs and non-covalent interactions which detect fluoride in apolar media needs a thorough reappraisal[16, 17]. In view of the fact that fluoride possesses high hydration enthalpy and that the receptor has to compete with highly structured water molecules solvation sphere around the spherical ion to bind fluoride, there is a growing need for systems capable of recognizing and binding fluoride in competitive media [18].

The numerous examples of recognizing anions are precisely designed to rely on hydrogen bonding, being inspired by ion-molecule interactions in nature[19]. Hydrogen bonding has an edge over electrostatic force in terms of selectivity and directional nature, which facilitates the design of receptors having ability to discriminate between anions with varied geometries[20]. Molecular cleft has opened a new era in supramolecular chemistry with convergent hydrogen binding sites directed towards centre[21, 22]. The design can be further modulated to allow incorporation of more hydrogen bond donors with the aim of establishing high binding affinity with anion[23, 24]. A multitude of synthetic molecules capable of anion recognition by the formation of hydrogen bonding with anions includes, amide[25], urea/thiourea[26], indole[27], pyrrole[28], guanidinium[29] and benzimidazole[30]. Amongst these, benzimidazoles, constitute an attractive backbone for anion recognition, which itself carries in-built hydrogen bond donor site, providing these scaffolds with additional hydrogen bond donor groups, may potentially lead to multiplication of their interaction with negatively charged species[31]. This moiety has been extensively utilized in the synthesis of cation as well as anion recognition systems that display colorimetric and fluorometric response upon binding with ions[32, 33]

Colour change of receptors, perceivable by the naked eye as an output for detection event, is highly desirable[34]. It facilitates detection of the analyte onsite, without resorting to expensive instrumentation[35]. These are generally constructed on receptor-chromophore binomial, where ion binds at receptor site and chromophore is responsible for

turning binding event into optical signal[36-40]. Bearing this in mind, we have developed a dipodal receptor, **RC**, based on phenyl ring symmetrically armed with benzimidazole moieties through amide bonds, where two benzimidazole N-H, together with two amide NH and aromatic C-H provide five acidic hydrogen bond donor groups as binding sites for fluoride ion. The fluoride ion binding studies have been meticulously conducted by naked eye, UV-visible, ^{1}H NMR and ^{19}F NMR spectroscopic techniques.

Experimental

All chemicals were purchased from Sigma Aldrich, TCI and Spectrochem Chemicals, India and were used without further purification. All solvents were dried before use. Dimethyl sulphoxide was dried over calcium hydride and distilled.

Melting points were determined in open glass capillaries and are reported uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum Two instrument using KBr pellets. ^{1}H NMR, ^{19}F and ^{13}C NMR were recorded on a Jeol ECS 400 MHz spectrometer using DMSO-d_6 as solvent. TMS was taken as an internal standard and the chemical shifts are reported in δ ppm. Resonance multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Mass spectra were recorded on a Xevo G2-S Q-Tof system (Waters, USA), capable of recording high-resolution mass spectrum (HRMS) in the ESI (electrospray ionization) mode. Elma S 70 H Ultrasonic unit with 37 KHz output frequency was employed for ultrasonication synthesis. UV-visible spectra were recorded on a Perkin Elmer UV-vis NIR spectrophotometer (Lambda 750) in standard 3.5 mL quartz cells with 10 mm path length. The purity of compounds was checked by TLC using silica gel as adsorbent and solvents of increasing polarity as mobile phase.

The receptors were prepared as follows: To *m*-phthaloyl chloride (4 mmol) solution in dichloromethane, was added benzimidazole derivatives (8.1 mmol) with catalytic amount of trimethylamine under ultrasonication irradiation and stirred for 20-30 min at room temperature. The reaction progress was examined by thin film chromatography using solvent system, (8:2) pet ether: ethyl acetate. After completion of reaction, as monitored by TLC, the reaction mixture was poured into a saturated sodium bicarbonate solution, filtered and washed with water (3×50 mL) to afford the desired dipodal products (**RA-RD**).

N,N'-Bis-(1H-benzoimidazol-2-ylmethyl)-isophthal-amide (**RA**): M. pt.: 188 °C. Yield: 88.1%. FTIR (KBr, υ cm^{-1}): 3259 (N-H), 3010 (aliphatic C-H), 1645 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 4.70 (2H, s, CH_2), 7.12-7.47 (m, 11H, aromatic C-H), 8.06 (s, 1H, phenyl C-H), 8.50 (s, 2H, amide N-H), 11.28 (s, 2H, benzimidazole N-H). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 115.17, 122.61, 127.46, 128.92, 129.01, 130.88, 134.51, 138.06, 152.78, 166.49, 166.79, 167.42. MS (ESI) *m/z*: 425.1874 $[M+H]^+$. calcd. for $C_{24}H_{20}N_6O_2$: 424.1648.

N,N'-Bis-[1-(1H-benzoimidazol-2-yl)-ethyl]-isophthal-amide (**RB**): M. pt.: 196 °C. Yield: 87.50%. FTIR (KBr, υ cm^{-1}): 3129 (N-H), 3008 (aliphatic C-H), 1635 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 2.4 (3H, d, CH_3), 4.50 (1H, q, CH), 7.08-7.35 (m, 11H, aromatic C-H), 7.9 (s, 1H, phenyl C-H), 8.3 (s, 2H, amide N-H), 11.37 (s, 2H, benzimidazole N-H). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 54.46, 113.56, 120.12, 125.67, 126.78, 128.26, 129.56, 130.10, 133.75, 145.73, 165.42, 165.98. MS (ESI) *m/z*: 453.1989 $[M+H]^+$. calcd. for $C_{26}H_{24}N_6O_2$: 452.1961.

N,N'-Bis-(5-nitro-1H-benzoimidazol-2-ylmethyl)-isophthalamide (**RC**): M. pt.: 205 °C. Yield: 84.40%. FTIR (KBr, υ cm^{-1}): 3356 (N-H), 3015 (aliphatic C-H), 1678 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 5.29 (2H, s, CH_2), 7.33-7.63 (3H, m, aromatic C-H), 8.15-.8.17 (m, 6H, aromatic C-H), 8.4 (s, 1H, phenyl C-H), 9.87 (s, 2H, amide N-H), 12.2 (s, 2H, benzimidazole N-H). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 57.36, 108.45, 111.89, 114.46, 116.06, 121.65, 124.01, 124.10, 127.62, 128.25, 128.89, 131.70, 134.50, 135.81, 137.24, 143.90, 151.11, 166.15, 185.49. MS (ESI) *m/z*: 515.1356 $[M+H]^+$. calcd. for $C_{24}H_{18}N_8O_6$: 514.1349

N,N'-Bis-[1-(5-nitro-1H-benzoimidazol-2-yl)-ethyl]-isophthalamide (**RD**): M. pt.: 178 °C. Yield: 82.11%. FTIR (KBr, υ cm^{-1}): 3278 (N-H), 3002 (aliphatic C-H), 1657 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 2.56 (3H, s, CH_3), 4.65 (1H, q, CH), 7.13-7.59 (m, 3H, aromatic C-H), 7.9-8.05 (m, 8H, aromatic C-H), 8.2 (s, 1H, phenyl C-H), 8.3 (s, 2H, amide N-H), 11.8 (s, 2H, benzimidazole N-H). ^{13}C NMR DMSO-d_6, 100 MHz, ppm) 54.23, 110.36, 112.45, 113.68, 116.59, 120.48, 122.78, 124.39, 125.54, 126.84, 128.74, 132.58, 134.68, 138.98, 142.74, 165.72, 183.68. MS (ESI) *m/z*: 543.1680 $[M+H]^+$. calcd. for $C_{26}H_{22}N_8O_6$: 542.1662.

Results and discussion

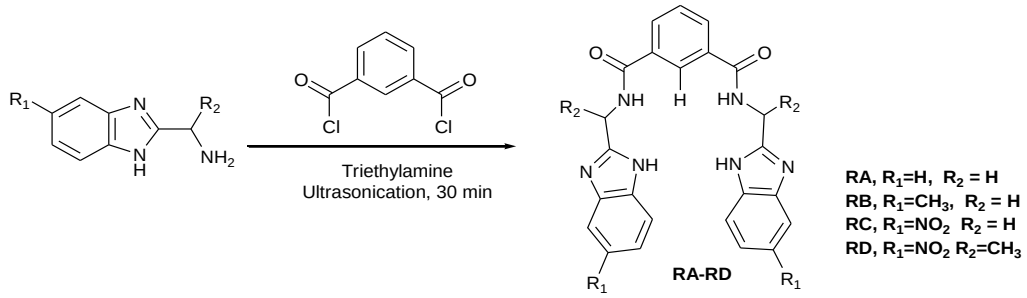
The reaction between benzimidazole derivatives and *m*-phthaloyl chloride in dicloromethane under

ultrasonication in presence of catalytic amount of trimethylamine, resulted in corresponding title compounds (**RA-RD**) (Scheme 1). The crude compounds were obtained in good yield and characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS spectroscopic techniques.

Naked eye colorimetric sensing of receptors was studied with different anions, viz., fluoride, chloride, bromide, iodide, acetate, nitrate, dihydrogen phosphate and hydrogen sulphate (tetrabutyl-ammonium salts). Only receptor **RC** showed dramatic and sudden colour change from pale yellow to orange with fluoride ion at 1.5 ppm concentration. Other anions failed to induce any colour change as shown in Fig. 1. As expected from the basicity of anions, fluoride ion gave a stronger complex than other anions examined.

To corroborate the preliminary naked eye test, receptor **RC** was evaluated as colorimetric receptor by spectrophotometric titration in presence of different anions (TBA salts) in 9:1 DMSO-water using constant receptor concentration and increasing concentration of anions. As shown in Fig. 2, receptor exhibited a strong absorption band at 348 nm, which upon addition of fluoride red shifted to 465 nm. With progressive addition of fluoride salt solution from 1×10^{-5} to 1×10^{-3} *M*, intensity of peak at 348 nm was remarkably reduced, with simultaneous growth of a new peak at 465 nm. A large bathochromic shift of 117 nm can be attributed to hydrogen binding between receptor and fluoride ion. Meanwhile, the colour of solution changed from pale yellow to orange. Amongst other anions, addition of acetate induced some change spectroscopically. The peak at 348 nm reduced, with simultaneous increase in intensity of peak at 550 nm. New peak formation, similar to fluoride ion addition, did not take place (Fig. 3). Similar naked eye change and spectral changes were not observed with other anions. This proves the selectivity of receptor **RC** for fluoride ion qualitatively as well as spectroscopically.

Other receptors **RA**, **RB** and **RD** did not produce any colour change upon addition of any anion. The colour change on addition of **RC**



Synthesis of receptors (**RA-RD**)

Scheme 1

Fig. 1 – Colour changes in the receptor **RC** (1×10^{-5} *M* in DMSO) in presence of 10 equivalents of different anions (as their TBA salts). [A, B, C, D, E, F, G, H and I represent receptor **RC**, **RC**+F^-, **RC**+Cl^-, **RC**+Br^-, **RC**+I^-, **RC**+CH_3COO^-, **RC**+$H_2PO_4^-$, **RC**+HSO_4^- and **RC**+NO_3^- respectively].

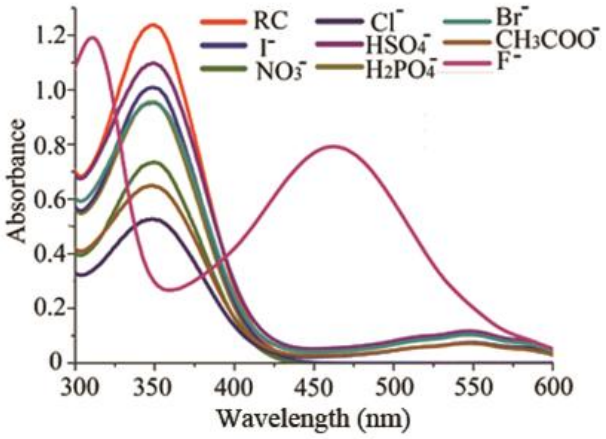


Fig. 2 – Changes in absorbance of receptor **RC** (1×10^{-5} *M* in DMSO) with different anions (TBA salts, 1×10^{-3} *M*) in 9:1 DMSO: water.

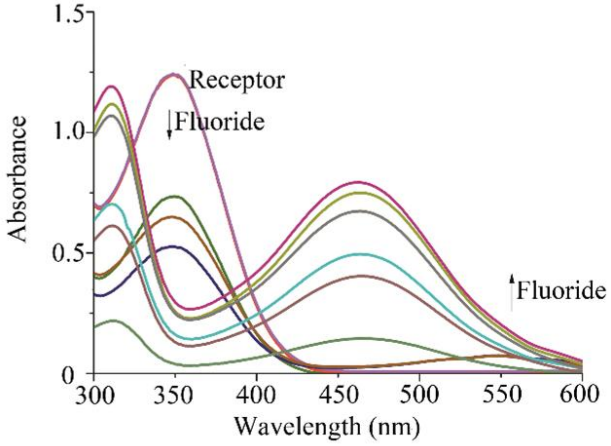


Fig. 3 – UV-visible spectra of receptor **RC** (1×10^{-5} *M* in DMSO) with fluoride ion (TBA salt) from 1×10^{-5} to 1×10^{-3} M in 9:1 DMSO: water.

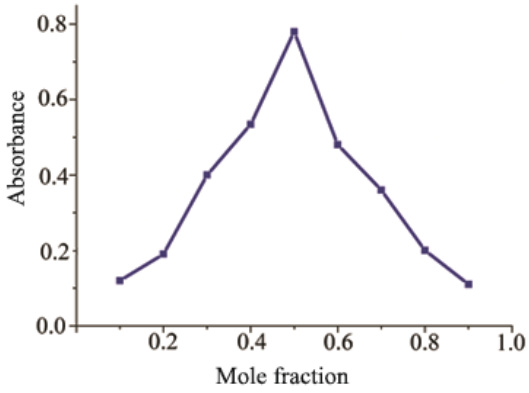


Fig. 4 – Jobs plot with receptor **RC** (1×10^{-2} *M* in DMSO) and fluoride ion (TBA salt) 1×10^{-2} *M* in 9:1 DMSO-water.

may be attributed to the presence of electron withdrawing nitro groups in its structure.

Stoichiometric ratio of the complexes formed between fluoride ion and receptor was determined using continuous variation method, where the concentrations of both receptor **RC** and fluoride ion salt were kept the same (1×10^{-4} *M* in DMSO). The molar fraction of fluoride/ (receptor+fluoride) was varied. It was observed that absorbance maxima was reached at the molar fraction of 0.50 at wavelength 465 nm, indicating that the receptor forms 1:1 complex with fluoride ion (Fig. 4). Further proof of 1:1 stoichiometry of receptor **RC** and fluoride ion is obtained from the mass spectra of receptor RC complex with fluoride ion ($RC+F^-+H^+$ = 534.1456, calculated: 534.1411) (Fig. 5). The experimental isotopic distribution pattern matches exactly with the theoretical pattern for receptor RC-fluoride ion complex (Supplementary data, Fig. S1). The change in absorbance at 465 nm for receptor was plotted against fluoride concentration (Supplementary data, Fig. S2). The binding constant of **RC** with fluoride was evaluated by Benesi Hildbrand equation[41], $1/A\text{-}A_{min} = 1/(\Delta A_{max} + (1/K\ [F^-])(1/\Delta A_{max})$. Here, $\Delta A_{max} = A_{max} - A_{min}$, where, A_{min}, A, A_{max} are the absorptions of receptor **RC** considered in the absence of F^-, at an intermediate, and at a concentration of complete binding, respectively. K is the binding constant, $[F^-]$ is concentration of F^-. From the plot of $1/(A-A_{min})$ against $[F^-]$ for receptor **RC**, the value of K (+10%) was calculated from the ratio of intercept/slope. Binding constant K, calculated from the graph (Fig. 6) was found to be $5.59\times10^3\ M^{-1}$.

Further, to shed light on the nature of interaction between receptor and fluoride ion, ^{1}H NMR titrations were carried out. Fluoride ion in the form of its TBA salt of varying concentrations (2.5, 5, 7.5 and 10 equiv.) was added sequentially to receptor **RC** solution in DMSO-d_6 (1×10^{-2} *M*). Peaks for benzimidazole N-H, amide N-H and phenyl C-H appear at δ 12.23, 9.87 and 8.4 respectively. It was noticed that after addition of 2 equivalents of fluoride ion solution, the signals shifted downfield by δ 0.1, 0.05 and 0.03 ppm respectively, with simultaneous decrease in intensities. Downfield shifting was further observed upon addition of five and ten equivalents of fluoride ion (Fig. 7). These results corroborate the formation of a complex between the receptor and the fluoride ion via hydrogen bonding. No evidence of deprotonation was found. The plausible mode of binding between receptor and fluoride is depicted in Scheme 2.

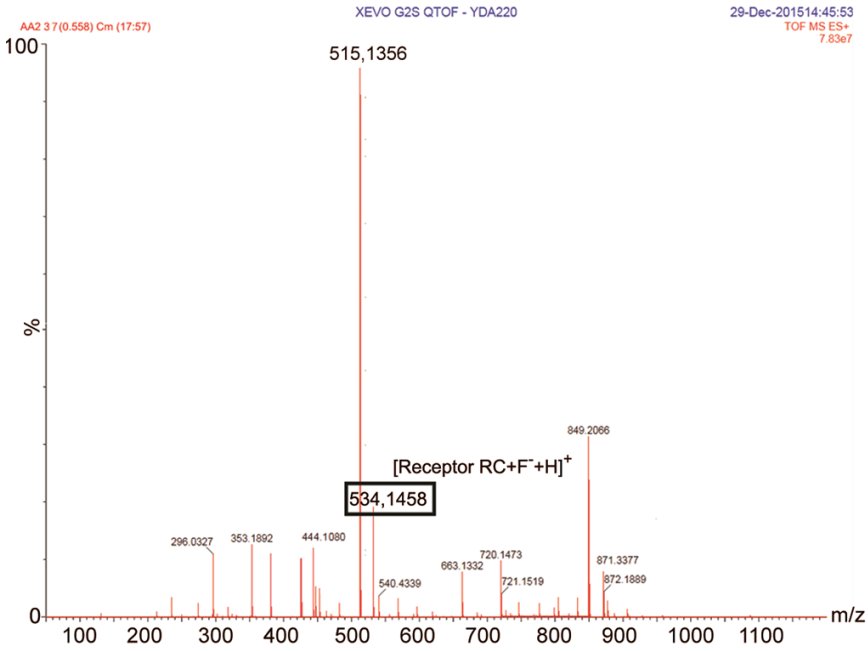


Fig. 5 – ESI mass spectra of fluoride ion complex of receptor **RC**.

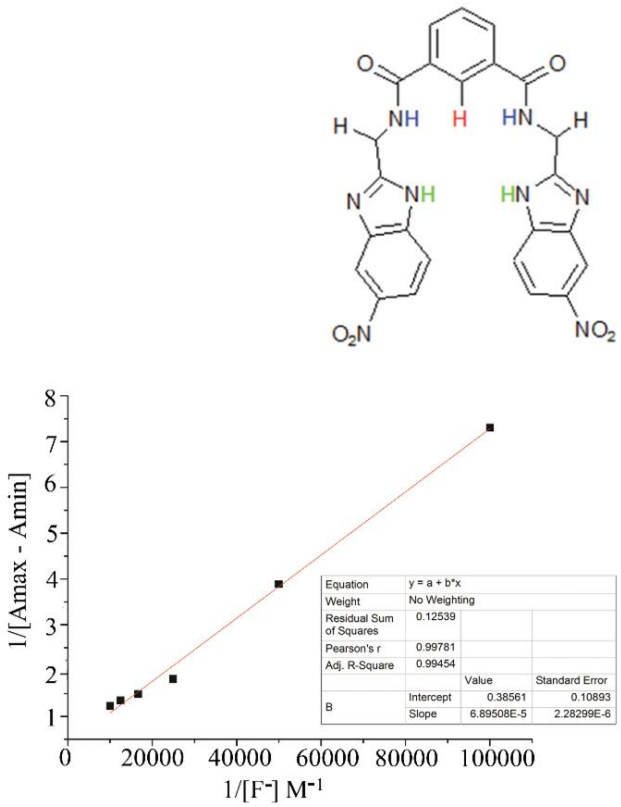


Fig. 6 – Fitting curve of Benesi Hildbrand equation.

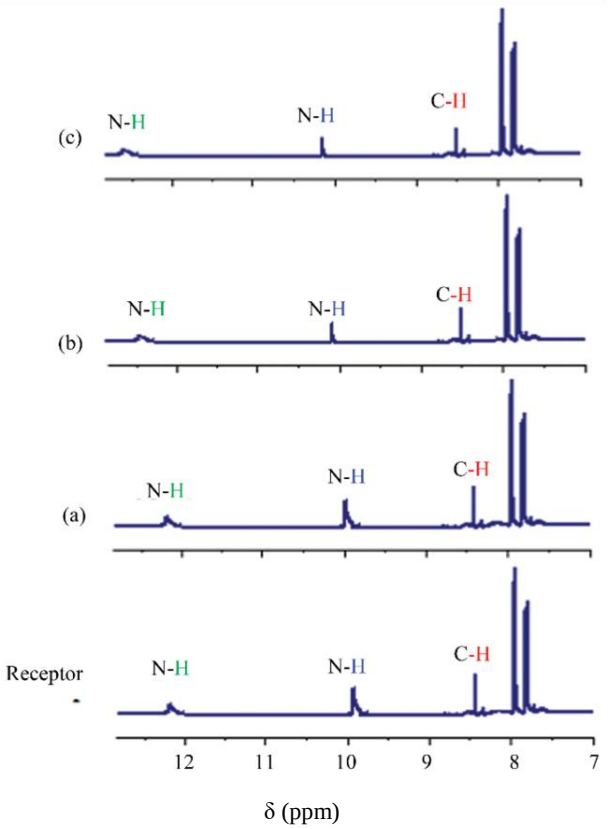
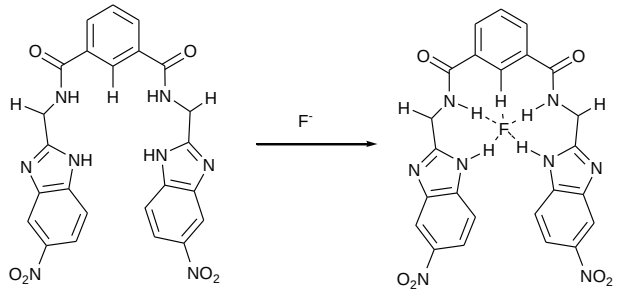


Fig. 7 – Partial ^{1}H NMR (400 MHz) spectra of receptor **RC** in DMSO-d_6 (1×10^{-2} *M*) in the presence of (a) 2, (b) 5, and, (c) 10 equivalents of TBAF in DMSO-d_6.



Plausible binding mode between receptor **RC** and fluoride ion

Scheme 2

The interaction between receptor **RC** and fluoride ion was also investigated using ^{19}F NMR titration. ^{19}F NMR spectra of TBAF in DMSO-*d*6 revealed a singlet at δ –102 ppm due to F^- ion and a weak doublet at δ -142 ppm due to HF_2^- ion. Upon addition of 1 equivalent of receptor RC, the peak at –102 ppm shifted upfield by δ 3.71 ppm and intensity of peak decreased and finally, the peak due to F^- ion disappeared to a large extent, which indicates the existence of binding interaction between receptor and fluoride ion[42] (Supplementary data, Fig. S3).

In conclusion, a neutral colorimetric receptor based upon benzimidazole scaffold has been fabricated to detect fluoride in aqueous solution. The receptor binds fluoride by virtue of multiple hydrogen bonding interactions with the anion. The sensing process can be substantiated by the visible colour change from yellow to orange.

Supplementary data

Supplementary data associated with this article are available in the electronic form at http://www.niscair.res.in/jinfo/ijca/IJCA_56A(05)513-518_SupplData.pdf.

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