Ph.D. Thesis entitled

DEVELOPMENT OF HETEROCYCLIC BASED DERIVATIVES AS ANION RECEPTORS

Submitted by

ANSHU JAIN
(2011RCY7152)

DEPARTMENT OF CHEMISTRY

MALAVIYA NATIONAL INSTITUTE OF TECHNOLOGY JAIPUR

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Ph.D. Thesis entitled

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Submitted in partial fulfilment of the requirements
for the award of the degree of

DOCTOR OF PHILOSOPHY
IN
CHEMISTRY

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DECLARATION

I hereby certify that the work which is being presented in this thesis entitled, **"Development of Heterocyclic based Derivatives as Anion Receptors"** in partial fulfillment of the requirement of the Doctor of Philosophy and submitted to Malaviya National Institute of Technology Jaipur is an authentic record of my own work carried out under the supervision of **Dr. Ragini Gupta**, Associate Professor, Department of Chemistry & Materials Research Centre and **Dr. Madhu Agarwal**, Assistant Professor, Department of Chemical Engineering, Malaviya National Institute of Technology Jaipur. The results contained in this thesis have not been submitted in part or in full, to any other University or Institute for the award of any degree. The content of the thesis has been checked using software, "Turnitin".

Date:

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CERTIFICATE

Ph. D. Viva voice examination of Ms Anshu Jain (ID 2011RCY7152) was held on 15th December 2017. The thesis was examined and approved for the award of Ph. D. degree.

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To my family,

Thank you for encouraging me in all of my pursuits and inspiring me to follow my dreams

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ABSTRACT

Stimulated by the needs of an evolving society, **Chemistry**, like a young discipline, is opening new routes and inventions everyday. The opportunities and challenges associated with these are continuing to attract researchers for new ideas, discovery and useful real world contribution. An illustration of this statement can be provided by **Anion Receptors**; where great relevance of anions in biology and environment has made anion coordination chemistry rise as a new research field. Inspired by the phenomenon of molecular recognition in nature, together with acquired knowledge of chemistry, the design and synthesis of receptors for recognition of anionic species has become thrust area of research. In quest of moieties for designing anion receptor, heterocycles have emerged as efficient candidates with limitless derivatizing potential and inbuilt hydrogen bond donor groups. Pioneer work started with indole moieties and carried forward by other heterocycles, pyrrole and coumarin moieties. However, no receptor for selective detection of anions, especially for fluoride ion in 100% water is reported so far. Thus there exists a vast scope for exploitation of heterocycle derivatives to craft synthetic neutral receptors for selective detection of anionic species.

The present thesis deals with the design, synthesis and characterization of heterocycle based anion receptors. The thesis is divided into seven chapters:

Chapter 1: Prefatory note

Chapter 2: A Review on, “Emergence of Heterocycles as Artificial Neutral Receptors for Naked Eye Recognition and Sensing of Anions”

Chapter 3: Design and synthesis of C_3 symmetric tripodal triazoles. A facile click chemistry approach to anion sensing: Experimental and theoretical aspects

Chapter 4: Synthesis of *N*,*N'*-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides: Unique dipodal molecular clefts containing benzimidazole scaffolds

Chapter 5: Synthesis of rationally designed tri-armed imidazole-indole hybrids 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indoles

Chapter 6: Design and synthesis of 3-{4-[(un)substituted-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-ones

Chapter 7: Design and synthesis of coumarin based receptor, 1-(1-(substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides

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ANNEXURE – I

LIST OF ABBREVIATIONS

S. No.	Abbreviated Form	Extended Form
1	FTIR	Fourier Transform Infrared Spectroscopy
2	NMR	Nuclear Magnetic Resonance
3	HRMS	High Resolution Mass Spectrometry
4	M.P.	Melting Point
5	DMSO	Dimethyl Sulphoxide
6	DMSO-d_6	Deuterated Dimethyl Sulphoxide
7	$CDCl_3$	Deuterated Chloroform
8	CH_3CN	Acetonitrile
9	DCM	Dichloromethane
10	TBA	Tetrabutylammonium Salt
11	TBAF	Tetrabutylammonium Fluoride
12	TLC	Thin Layer Chromatography
13	PEG 400	Polyethylene Glycol 400
14	ESI	Electron Spray Ionisation
15	NaF	Sodium Fluoride
16	B-H Equation	Benesi Hildebrand Equation
17	X^-	Anion
18	δ ppm	Chemical Shift in Parts Per Million
19	υ cm^{-1}	Frequency in wavenumber
20	KBr	Potassium Bromide
21	ICT	Intra Charge Transfer
22	PET	Photoinduced Electron Transfer
23	WHO	World Health Organization
24	BIS	Bureau of Indian Standards

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INTRODUCTION

Anions are an integral part of the natural world, be it in a human body, or in the environment **[1-5]**. Chlorides are found in large quantities as its sodium salt in oceans, while phosphates are found in teeth and bones **[6-7]**. Carbonates are a key component of bio-mineralised rocks **[8]**. Although, anions are often unremarked for their importance, they are critical for maintenance of life and function of environmental processes **[9]**. Ionic recognition is a primal event in biology which drives all fundamental biochemical processes including transport, catalysis, signalling and transcription **[10-11]**.

Iodide plays a vital role in many biological processes, notably thyroid function and neurological activity. The Na^+/I^- symporter (NIS) is a crucial plasma membrane glycoprotein that mediates active I^- transport in thyroid gland, which initiates the thyroid hormone biogenesis. Thyroid hormone is responsible for the regulation of several metabolic activities such as growth and maturation of organ systems. Therefore, iodide content of food products and drinks is often needed as a part of nutritional information. The United States recommended daily allowance of iodide for adults is 150 µg **[12-13]**.

The planar oxy-anion, acetate is the common building block for biosynthesis, for e.g. the fatty acids are produced by connecting C2 units derived from acetate. It also plays specific biochemical functions in the enzymes and antibodies **[14]**.

Chloride ion plays crucial roles in regulation of osmotic pressure, maintenance of pH balance and in activating signal transduction pathways in human body. It also aids in the synthesis of hydrochloric acid in stomach and thus helps in digestion. The desirable limit of chloride concentration in water is 250 mg/L, above which it gives rise to detectable taste **[15-16]**.

Phosphate is one of the important building blocks in biological systems. It plays a significant role in energy production as components of ATP (adenosine triphosphate). It is also a component of DNA and RNA molecules, which carry genetic information. In blood, it acts as a buffer to maintain normal pH. Inorganic phosphate is used in fertilizers in agriculture, from where it reaches waterways. Excessive phosphate (0.1 mg/L) causes eutrophication of aquatic ecosystems **[17].**

Cyanide is widely used in synthesis of resins, synthetic fibers and herbicides. Unfortunately, it is extremely harmful and could be easily absorbed through lungs and skin, which could cause convulsion, loss of consciousness and eventual death **[18].**

Amongst these negatively charged species, fluoride holds paramount place owing to its duplicitous nature **[19-22]**. Fluoride is naturally found in several minerals, (particularly fluorite and fluorapatite), from which it leaches into groundwater **[23]**. It is also present in animals (bone and dental enamel) and in traces in almost all foods **[24]**. It is artificially added, mainly as sodium fluoride and sodium monofluorophosphate, to dental products, such as toothpaste and mouthwash to prevent dental caries **[25]**. The major anthropogenic activity that adds to fluoride in environment is the release of effluent, hydrofluorosilicic acid by the phosphate rock processing in the production of phosphate containing agricultural fertilizers, which is formed by the mixing of silicon tetrafluoride and hydrogen fluoride in the reactor **[26]**. Aluminium smelting industries, which utilizes fluorospar (CaF_2) as flux, too releases fluoride waste in the form sodium fluoride, calcium fluoride, aluminium fluoride and hydrogen fluoride **[27]**. Fluoride is also released in gaseous form by combustion of fluoride containing coal in industries, which during rainfall percolates with rain water and reaches groundwater **[28]**. Due to these activities, over a billion people are forced to drink water containing high levels of fluoride ion **[29]**. Excess of fluoride is well acknowledged as a root cause of skeletal and dental fluorosis **[30]**. It is also stated to cause premature aging of human body, irreversible bone deformation and increased bone fracture **[31]**. It inhibits immune cells to get activated by infection and interferes with hydroxylation of proline to hydroxyproline, which disrupts the synthesis of collagen in bones, tendons and cartilage **[32]**. In the human body, protein preserve their 3D structure *via* hydrogen bonding between adjacent proteins. Fluoride establishes unusual strong bonds with N-H group of amide group and thus disrupts the shape of proteins **[33]**. It also instigates superoxide synthesis in white blood cells and thus demotes their capability to kill pathogens **[34]**. In the light of these facts, World Health Organization (WHO) and Bureau of Indian Standards (BIS) have set the maximum permissible limit of fluoride ion in drinking water as 1.5 ppm **[35]**.

Deleterious health effects of high levels of fluoride ion and strict health regulations by WHO have motivated the scientific community to develop methods to detect fluoride

ion in water **[36]**. The widely used UV-Visible spectroscopic method for the detection of fluoride ion in groundwater sample is colorimetric SPANDNS (sodium 2-(*p*-sulphophenylazo)-l,8-dihydroxy-3,6-naphthalene disulphonate) method, which involves reaction of fluoride ion with a zirconium dye complex. However, this method employs use of toxic reagent, sodium arsenite, which is added into water samples to eliminate the interference by chloride ions, present in drinking water. Another traditional method includes use of ion selective electrode, consisting of fragile lanthanum fluoride electrode. All these methods are lengthy, expensive; require skilled labour and establishment of well-equipped laboratories **[37]**. There is a need to develop a simple and easy method, which detects fluoride ion in aqueous media economically, reliably and quickly.

Development of anion receptors, that can qualitatively or quantitatively respond to, identify, or sense a negatively charge species has emerged as an attractive alternative to expensive and complex methods **[38]**. These systems bind anion and produce a concentration proportional signal, detectable by either naked eye or optical response spectrophotometric methods (UV-Visible or fluorescence) **[39-48].** There are three different approaches usually considered while designing chemosensors; i) binding site - signalling unit, ii) displacement and iii) chemodosimeter approach (**Fig. 1.1) [49]**.

In the first approach, chemosensors are made up of 2 distinct fragments; one carrying the binding site and the other capable of converting binding events into optical signal. The receptor binds the anion and brings about a change in the photophysical properties of chromophoric group attached with it, producing an optical response as the output **[50].**

In the displacement approach, the binding unit and signalling unit remain in the form of coordination complex. The anion displaces the signalling unit and itself coordinates with the receptor's binding site. The free signalling unit gives an optical response **[51].**

Both of the above approaches are reversible in nature, whilst the last, the chemodosimeter approach, is irreversible. Here, anion induces a specific reaction upon binding and generates a naked eye response. This anion induced approach is highly selective and is directly related to anion concentration **[52]**.

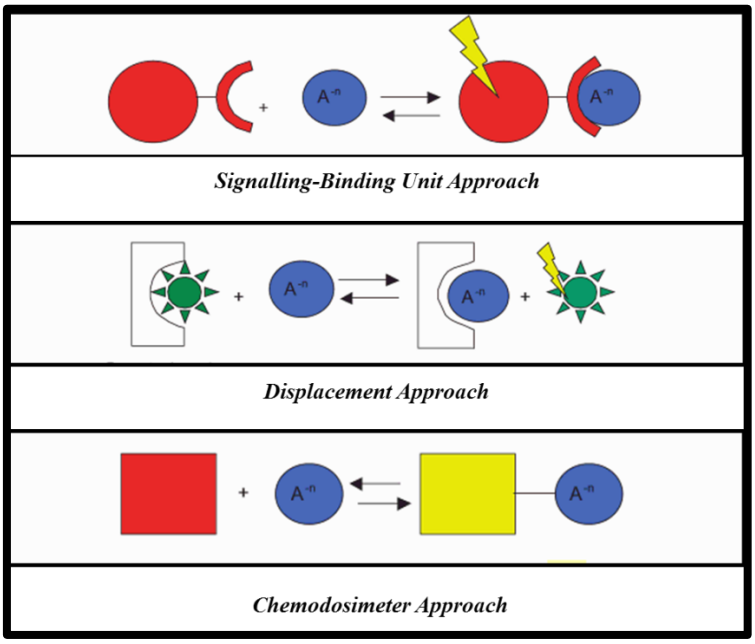


Fig. 1.1: Design approaches for chemosensors

Several design strategies, incorporating above approaches for construction of chemosensors have been attempted *viz*.; Lewis acid, metal-ion coordination, anion – π interactions, cationic receptors were attempted to anion receptors, most of which have been designed for fluoride ion detection **[53-54]**. However, their viability to test fluoride ion under field conditions is restricted to very few examples **[53-54]**. Most of them suffer from interference from related basic ions, acetate and dihydrogen phosphate and inability to function in aqueous media. Recognition studies of these receptors were carried out in aprotic solvents *viz*.; acetonitrile and chloroform, because detecting fluoride ion in water is difficult due to its high hydration enthalpy **[55]**. The synthetic receptor must be able to recognize fluoride ion in presence of high concentration of other anions in aqueous media for its suitability to operate under field conditions. Receptors based on desilylation reaction were found capable to bind fluoride ion in aqueous media, but their slow response restricts their utility for on-site detection **[56]**. There is a need for development of inexpensive, selective and sensitive naked eye fluoride ion receptors, which function in aqueous media for real life detection of fluoride ion.

Researchers have developed synthetic receptors employing heterocyclic moieties *viz.;* indole, coumarin, imidazole, pyrrole to bind anions effectively and selectively **[57-58].** Utilization of heterocyclic moieties served two main purposes, firstly, development of various molecular structures with the limitless derivatizing potential of heterocyclic moieties and secondly, their use also imparts interesting photophysical properties to receptor systems to achieve naked eye sensing **[59-60]**.

In view of the above facts, present research work has been undertaken to develop heterocyclic based receptors for fluoride ion, which is unaffected by the presence of other related basic anions and capable of detecting fluoride ion in aqueous media.

Objectives

1. **To synthesize heterocyclic compounds by using environmentally benign techniques like microwave irradiation, ultrasonication to enhance yield and reduce reaction time.**
2. **Characterization of various synthesized heterocyclic compounds.**
3. **To test synthesized compounds for their anion binding properties, particularly for fluoride ion binding in organic or aqueous media.**
4. **To study their binding ability with other interfering anions.**
5. **To enhance the selectivity of receptors by strategic structural modifications.**

Keeping these objectives in mind and as a part of systematic investigation on design, synthesis and characterization of heterocyclic scaffolds as anion receptors, the present investigation entitled, **"Development of Heterocyclic Based Derivatives as Anion Receptors"** has been undertaken under the joint supervision of Dr. Ragini Gupta, Associate Professor, Department of Chemistry and Dr. Madhu Agarwal, Assistant Professor, Department of Chemical Engineering, Malaviya National Institute of Technology Jaipur. All the newly synthesized receptors have been characterized by FTIR, ^{1}H NMR, ^{13}C NMR and high resolution mass spectrometry (HRMS) techniques. Anion binding studies

have been carried out by IR, UV-Visible, fluorescence, ^{1}H NMR and ^{19}F NMR titrations.

The work carried out can be classified as follows:

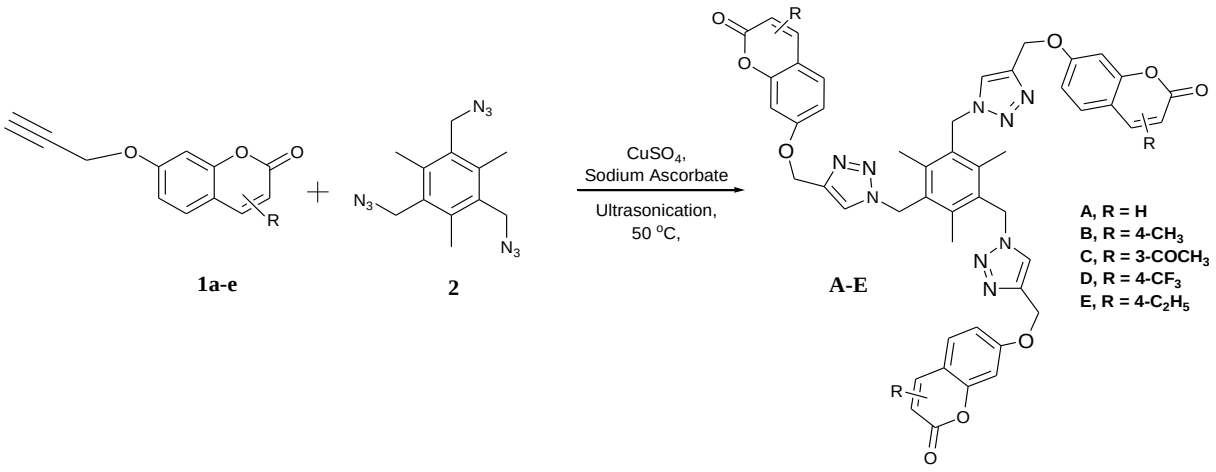
I. Design and synthesis of C_3 symmetric tripodal triazoles *via* click chemistry approach to anion sensing: Experimental and theoretical aspects
II. Synthesis of *N,N′*-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides: Unique dipodal molecular cleft containing benzimidazole scaffolds
III. Synthesis of rationally designed tri-armed imidazole-indole hybrids 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indoles
IV. Design and synthesis of 3-{4-[(un)substituted-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-ones
V. Design and synthesis of coumarin based receptor, 1-(1-(substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides

Series 1 Design and synthesis of C_3 symmetric tripodal triazoles via click chemistry approach to anion sensing: Experimental and theoretical aspects

This chapter is intended to provide an insight to synthesis, characterization and anion binding study of C_3 symmetric tripodal receptors, 7,7',7''-(((((2,4,6-trimethylbenzene-1,3,5-triyl)tris(methylene))tris(1H-1,2,3-triazole-1,4diyl))tris (methylene))tris(oxy)) tris(substituted-2H-chromen-2-ones) **A-E** having hexasubstituted aryl core decorated with an alternate array of coumarin-triazole moieties and methyl groups for fluoride ion recognition (TBA salt) in DMSO.

Selective recognition of anions has attracted a great deal of attention because of their numerous applications in the field of environment, clinical and chemical sciences **[61]**. The creation of an artificial receptor which is preferentially selective towards a specific anion requires the presence of multiple interactions between anion and receptor in a complementary approach **[62]**. The topology of receptor must be organised to complement the size and shape of anion to gain selectivity **[63]**. The tripodal receptors constitute a special class of ionophores which consists of

multiarmed ligands with each arm containing a functional group, capable of binding anion **[64]**. Tripodal molecular platform allows rational control of selectivity by adjusting its rigidity of arms and its cavity size, thus these possess advantage in terms of selectivity over monopodal and even dipodal receptors **[65].** Due to these advantages, design of artificial tripodal receptors is an active thrust area amongst researchers **[66]**.



1a-e **2** **A-E**

Scheme 1.1: Synthesis of 7,7',7''-(((((2,4,6-trimethylbenzene-1,3,5-triyl)tris (methylene))tris(1H-1,2,3-triazole-1,4diyl)) tris(methylene))tris(oxy))tris (substituted-2H-chromen-2-ones) A-E

A new revolution has been generated in anion coordination chemistry for designing molecular scaffolds with the employment of 1,2,3- triazoles produced from 1,3-dipolar cycloaddition between azide and terminal alkyne **[67]**. Studies on macrocyclic triazolophanes **[68]**, aryl triazoles **[69]** and triazole **[70]** containing molecules have shown that C-H---X^- hydrogen bonds are strong enough to play major roles in anion coordination chemistry.

Synthesis

Variously substituted alkynes, (un)substituted-7-prop-2-ynyloxy-chromen-2-one **(1a-e)** and C_3 symmetric azide, 1,3,5-tris-azidomethyl-2,4,6-trimethyl-benzene **(2)** were synthesized using literature methods **[71-72]**. Cu(I) catalyzed Huisgen 1,3-dipolar cycloaddition reaction between C_3 symmetric azide and terminal alkynes have been

successfully carried out to produce 1,2,3- triazoles **A-E** in excellent yields **(Scheme 1.1)**.

All the receptors synthesized were characterized by standard spectroscopic techniques (FTIR, ^{1}H-NMR, ^{19}F NMR, ^{13}C-NMR and HRMS). In the FTIR spectra of receptors, **A-E**, absorption band in the region 3010-3005 cm^{-1} and 2952-2825 cm^{-1} are obtained due to C-H stretching vibration in methyl and aromatic C-H, respectively. Absorption bands at 1710, 1608 and 1443 cm^{-1} may be attributed to C=O, C=C and C=N stretching vibrations, respectively. Besides these, receptor **D** also shows characteristic strong absorption band at 1116 cm^{-1} due to C-F stretching frequency of trifluoromethyl group**.**

The ^{1}H NMR spectra of receptors **A-E** exhibit sharp singlet at δ 8.47 ppm due to presence of triazole C-H proton. A multiplet from δ 6.12 to 7.49 ppm is observed for aromatic protons. Peaks at δ 4.40 and 5.70 ppm may be attributed to methylene protons. All receptors display a singlet at δ 2.48 ppm due to presence of methyl protons. Receptor **B** shows a singlet at δ 1.23 due the presence of substituent, methyl group in coumarin ring. A singlet at δ 2.30 was observed due to $COCH_3$ protons in receptor **C**. ^{1}H NMR spectra of receptor **E** displays a multiplet and triplet at δ 1.80 and 2.30, respectively due to presence of ethyl group in coumarin ring. ^{13}C NMR spectra of receptors **A-E** show characteristic signals at δ 161 (C=O) and 155 ppm (C=N). Signals at δ 62 and δ 49 ppm may be attributed to presence of carbons of methylene and methyl groups. Disappearance of signals at δ 75 ppm due to alkyne carbon CΞC present in compounds **1(a-e)** confirms the formation of receptors **A-E**. Aromatic C=C peaks are observed in region ranging from δ 102 to 152 ppm. The ^{19}F NMR spectrum of receptor **D** show a singlet at δ - 84.20 ppm due to presence of trifluoromethyl group.

Further confirmation was provided by HRMS data which gave an accurate molecular ion peak $[M+H]^{+}$ at m/z 886.8768 **(A)**, 928.9611 **(B)**, 1012.9991 **(C)**, 1090.8737 **(D)** and 971.0389 **(E)** that agrees well with their calculated molecular formula

Anion binding studies

All the receptors synthesized were comprehensively examined for their anion binding properties by UV-Visible, fluorescence, ^{1}H NMR and ^{19}F NMR spectroscopic

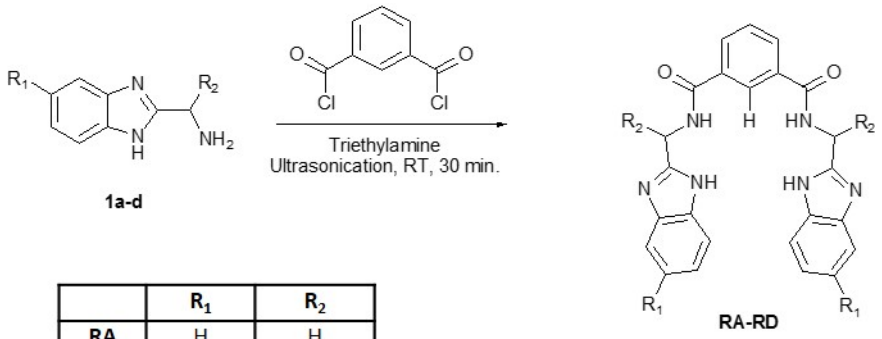
titrations using anions (TBA salts) *viz*.; fluoride, chloride, iodide, bromide, acetate, dihydrogen phosphate and hydrogen sulphate in DMSO. Out of the five derivatives synthesized, only one, receptor **D,** 7,7',7''-(((((2,4,6-trimethylbenzene-1,3,5-triyl)tris(methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy)) tris(4-(trifluoromethyl)-2H-chromen-2-one) (1 x 10^{-5} M) displays selective five-folds fluorescence enhancement with fluoride ion (TBA salt) at 480 nm over other anions in DMSO at a detection limit of 0.5 ppm, lower than WHO recommended level. UV-Visible spectrum of receptor **D** exhibited an absorption band centered at 360 nm and 440 nm. Interestingly, with fluoride anion, peak at 360 nm completely disappeared and absorbance of peak at 440 nm increased. No obvious spectral changes were observed with other anions. Strategical incorporation of trifluoromethyl group in the scaffold of receptor **D** fine tunes the binding ability so that it can bind fluoride ion in the preorganized C_3 symmetric topology formed by flexible arms of tripodal receptor exclusively through C-H--F^- hydrogen binding interactions. This was well supported by fluorescence, UV-Visible, ^{1}H NMR and ^{19}F NMR titrations. ^{1}H NMR titration validates C-H--F^- hydrogen binding interactions *via* downfield shift of C-H peak. ^{19}F NMR titration further supported the C-H--F^- hydrogen binding interactions by the disappearance of signal at δ -102 ppm due to free fluoride ion. The scientific results obtained from Job's plot and mass spectral data indicated that receptor binds fluoride ion in 1:1 stoichiometric ratio.

Series 2 Synthesis of N, N'-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides : Unique dipodal molecular clefts containing benzimidazole scaffolds

Herein, synthesis, characterization and anion binding studies of a series of benzimidazole based dipodal receptors, *N*,*N'*-bis-(5-(un)substituted-1H-benzoimidazol-2-ylalkyl)-isophthalamides **RA-RD** have been described which can selectively bind fluoride ion in aqueous media, with a distinct colour change, detectable by a naked eye.

More and more attention has been focused on the development of colorimetric receptors, because it facilitates detection on-site, without resorting to expensive instrument and hence are low cost **[73-74]**. 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.



	R_1	R_2
RA	H	H
RB	H	CH_3
RC	NO_2	H
RD	NO_2	CH_3

Scheme 1.2: Synthesis of *N,N'*-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides, RA-RD

Keeping this in mind, a series of elegantly designed cleft-like dipodal receptors, *N,N'*-bis-(5-(un)substituted-1H-benzoimidazol-2-ylalkyl)-isophthalamides **RA-RD** have been synthesized to capture fluoride ion in a preorganized cavity, defined by amidic NH, benzimidazole NH and vicinal aromatic hydrogen, which are suitable to form hydrogen binding arrays with fluoride ion **[75]**.

Synthesis

2-Aminoalkyl benzimidazoles **(1a-d)** were prepared according to the literature method **[76],** which then were reacted with *m*-phthaloyl chloride in dichloromethane under ultrasonication in presence of catalytic amount of trimethylamine to yield corresponding title compounds in good yield (**RA-RD**) **(Scheme 1.2)**.

All the synthesized receptors **RA-RD** were characterized by FTIR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data. In the FTIR spectra, receptors **RA-RD** display characteristic broad band in the region 3405-3129 cm^{-1} and an absorption band from 2917-2900 cm^{-1} attributable to N-H stretching vibration of N-H groups and aromatic C-H, respectively. Receptors **RA-RD** show absorption band ranging from 1657-1645

cm^{-1} due to conjugated C=O stretching vibration. Two absorption bands in the region 1525-1515 and 1375-1345 cm^{-1} may be attributed to N-O stretching vibration of nitro groups present in receptors **RC-RD.**

The ^{1}H NMR spectra of receptors **RA-RD** exhibit two sharp singlets in the region δ 8.3-8.5 and δ 11.28-12.2 ppm due to the presence of amidic N-H and imidazole N-H protons, respectively. A multiplet from δ 7.08- 8.07 ppm is assigned to aromatic protons. Aliphatic C-H peaks are observed in the region δ 2.46-2.50 (CH_3) and 4.70-5.29 ppm (CH_2). In the ^{13}C NMR spectrum, peak at δ 185 ppm may be attributed to C=O group. Aromatic carbons are observed in the region δ 112-151 ppm.

Molecular ion peak $[M+H]^+$ obtained at m/z 425.1874 **(RA)**, 453.1989 **(RB)**, 515.1356 **(RC),** 543.1680 **(RD)** are in good agreement with their corresponding molecular formula, which confirms the formation of receptors, *N,N'*-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides, **RA-RD.**

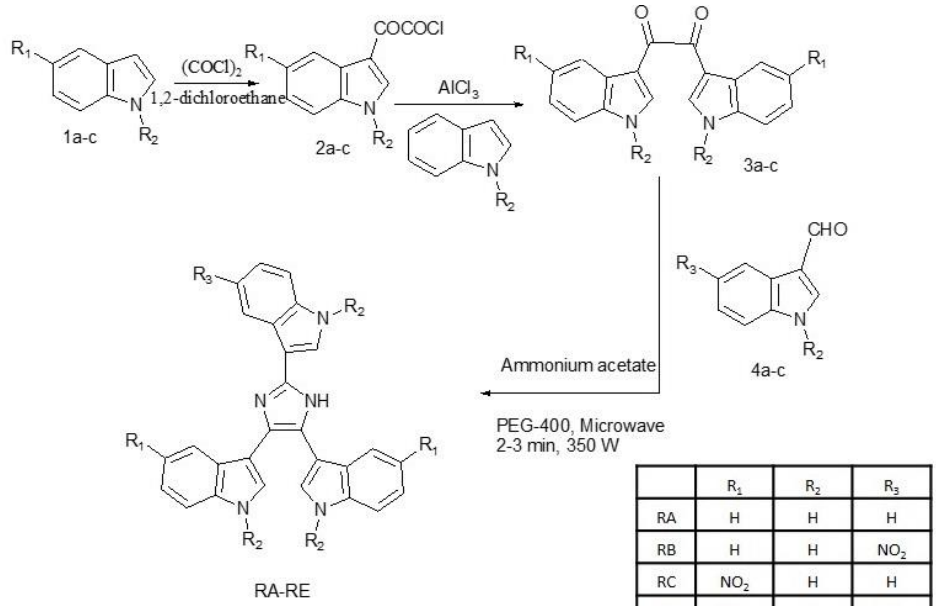
Anion binding studies

The fluoride ion binding studies have been meticulously conducted by naked eye, UV-Visible and ^{1}H NMR spectroscopic techniques in 9:1 DMSO-water. Out of the four derivatives synthesized, receptor **RC** binds fluoride ion exclusively with a minimum detection limit of 1.5 ppm. The sensing event can be demonstrated by change in colour of receptor from yellow to orange. UV-Visible spectrum of receptor **RC** shows a considerable bathochromic shift of 117 nm from 348 to 465 nm upon addition of varying concentrations of fluoride ion (TBA salt). The Job's plot and mass spectroscopic data confirm 1:1 stoichiometric ratio between receptor **RC** and fluoride ion. ^{1}H NMR titration of receptor RC with fluoride ion showed downfield shift of NH (amidic and benzimidazole) and CH proton peaks, which validated the presence of hydrogen binding interactions between receptor **RC** and fluoride ion. ^{19}F NMR titration further supported the binding interaction between receptor **RC** and fluoride ion. The binding constant of receptor RC for fluoride ion was calculated to be 5.59 x 10^3 M^{-1}.

Series 3 Synthesis of rationally designed tri-armed imidazole-indole hybrids, 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indoles

This chapter discusses the design, synthesis and characterization of novel tri-armed imidazole-indole hybrids, 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indoles, to selectively sense fluoride ion without any interference from other anions in 9:1 DMSO-water **(Scheme 1.3)**.

Interesting photophysical properties of heterocycles make them strong contenders for chromophoric unit and further, inbuilt acidic hydrogen bond donor groups (N-H) in several heterocyclic moieties can serve as binding sites for anions **[76]**. Amongst these heterocycles, imidazole N-H is acidic enough to act as an excellent hydrogen bond donor **[77]**. Furthermore, acidity can be modified by suitable insertion of substituents in the ring **[78]**. Given the acknowledged photophysical properties of imidazole and indole, it was anticipated that the introduction of indole rings containing electron withdrawing nitro groups, could fine-tune the binding property of imidazole moiety. In this connection, present series describes simple and easy to synthesize tri-armed imidazole-indole hybrids **(RA-RE),** containing varying number of electron withdrawing group(s) as selective naked eye receptor for fluoride ion sensing in 9:1 DMSO-water **(Scheme 1.3)**. Molecular structures of the receptors are so designed that both heterocyclic units, indole and imidazole have been rationally employed as chromophore and binding unit, respectively.



	R1	R2	R3
RA	H	H	H
RB	H	H	NO_2
RC	NO_2	H	H
RD	NO_2	H	NO_2
RE	NO_2	Boc	NO_2

Scheme 1.3: Synthesis of 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indoles (RA-RE)

Synthesis

1,2-Bis(indolyl)-ethane-1,2-dione derivatives **(3a-c)** were synthesized in stepwise reaction of appropriately substituted indole **(1a-c)** and oxalyl chloride in 1,2-dichloroethane to give compound **2a-c**, which on further treatment with indole derivatives in presence of aluminium(III) chloride afforded compounds **3a-c**. Compounds **3a-c** are microwave irradiated with formyl indole derivatives **(4a-c)** and ammonium acetate in polyethylene glycol (PEG 400) to yield the desired final product 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indole **(RA-RE)** in good yields **(Scheme 1.3)**.

All the compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR and HRMS techniques. The FTIR spectra of receptors **RA-RD** display characteristic broad absorption band due to N-H stretching of imidazolium N-H and indolic N-H in the region 3417-3313 cm^{-1} and 3185-3055 cm^{-1}, respectively. Receptor **RE** exhibits absorption band at 3375 cm^{-1} due to the presence of N-H stretching of only imidazole N-H. The disappearance of strong absorption band at 1610 cm^{-1} due to C=O stretching present in compounds **3a-c** indicate the formation of products. A broad band from 2978-2914 cm^{-1} is attributed to aromatic C-H vibration. Absorption band from 1644-1618 cm^{-1} and 1328-1208 cm^{-1} may be ascribed to C=C and C-N streching vibrations, respectively. Two bands in the region 1550-1515 cm^{-1} and 1390-1350 cm^{-1} are observed due to N-O stretching of nitro group(s) present in receptors **RB-RE**.

The ^{1}H NMR spectra of receptors, **RA-RD** show characteristic sharp singlets due to imidazolium N-H and indole N-H in the region δ 12.10-12.55 ppm and δ 9.7-9.81 ppm, respectively. Receptor **RE** displays a sharp singlet at δ 12.15 ppm due to presence of imidazolium N-H only. A multiplet from δ 7.11-8.28 ppm is observed for aromatic protons. The ^{13}C NMR spectra of receptors **RA-RE** display characteristic peak at δ 139.05 ppm due to presence of C=N in the molecular structure of receptors. The disappearance of peak at δ 185 ppm due to C=O in the spectra of receptors, which was present in compounds **3a-c**, confirms the formation of products. Aromatic carbons are observed in region ranging from δ 112-136 ppm.

Molecular ion peaks at m/z 414.1884 **(RA)**, 459.1427 **(RB)**, 504.1381 **(RC)**, 549.1192 **(RD)** and 849.2776 **(RE)** $[M+H]^+$ in HRMS spectra also confirm the formation of products.

Anion binding studies

The anion binding abilities of receptors **RA-RE** (1×10^{-4} M in DMSO) were carefully investigated by naked eye using anions as their TBA salts in 9:1 DMSO-water. An instant and distinctive colour change from yellow to orange was observed upon addition of TBA salt of fluoride ion into receptor **RD** (1×10^{-4} M in DMSO). It is worthwhile to state that detection limit for fluoride ion detection is found to be 1.5 ppm, which is regarded as the maximum permissible limit for fluoride ion in drinking water. Other anions, when were added to receptor individually, they did not show any colour change. Receptors **RA-RC** was found insensitive to the addition of anions and no change in colour was noticed in their solutions, even at high concentration (1×10^{-3} M) of anions (TBA salts). Another receptor **RE** was found to give similar qualitative colour change with fluoride ion as receptor **RD**. In order to enhance the binding affinity and selectivity, electron withdrawing nitro group(s) was introduced at 5^{th} position of indole rings in molecular skeleton of receptors and it was observed that receptors **RD** and **RE,** containing maximum number of nitro groups, gave promising results in terms of naked eye change in presence of fluoride ion (TBA salt) and were further studied.

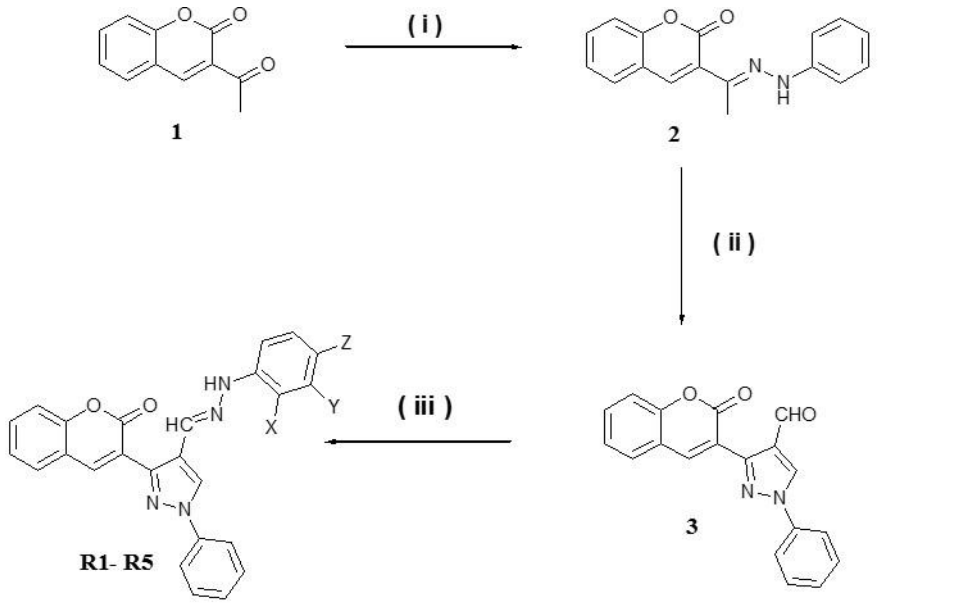
The naked eye colour change of receptor **RD** upon addition of fluoride ion was well supported by a red shift of 80 nm from a wavelength of 330 nm to 410 nm in UV-Visible spectroscopic studies in 9:1 DMSO-water**.** In the ^{1}H NMR spectra of receptor **RD**, the sharp singlet at δ 12.2 ppm, corresponding to imidazole N-H, showed a downfield shift upon addition of fluoride ion and disappeared altogether, when fluoride concentration reached 10 equivalents. Indole N-H at δ 9.8 ppm remains unchanged during titration. ^{1}H NMR titration suggests that sensing process is mainly due to the deprotonation of imidazolium N-H by fluoride ion. This fact is further corroborated by the synthesis of receptor **RE**, where three indolic N-H are protected by di-*tert*-butyl dicarbonate (Boc) and it still gave similar naked eye response to fluoride ion, indicating the participation of only imidazolium N-H in the fluoride ion

sensing process and not by both indolic and imidazolium N-H. The working pH range of receptor **RD** was found to be 6.5-8.0.

Series 4 Design and synthesis of 3-{4-[(un)substituted-phenyl)-hydrazonomethyl] -1-phenyl-1H-pyrazol-3-yl}-chromen-2-ones

This chapter enumerates the synthesis, characterization and anion binding studies of 3-{4-[(un)substituted-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-ones for instantaneous and selective naked eye detection of safe and permissible limits of inorganic fluoride ion in 1:1 DMSO-water.

Colorimetric fluoride ion detection *via* artificial organic receptors have been developed by research groups, most of which can bind only organic fluoride, *i.e.* tetrabutylammonium fluoride (TBAF), which restrict their viability in providing adequate solution to the concerned problem **[79]**. Therefore, it appears prudent to examine if it is possible to develop a receptor with capability of detecting inorganic fluoride ion *via* naked eye, thereby dispensing the use of expensive instruments **[80].**



	X	Y	Z
R1	NO_2	H	NO_2
R2	H	H	H
R3	NO_2	H	H
R4	H	CF_3	H
R5	H	H	H

Scheme 1.4: Synthesis of R1-R5, 3-{4-[(substituted-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one

A series of rationally designed coumarin-pyrazole based scaffolds equipped with N-H and C-H hydrogen bond donors (**R1-R5**) have been designed by condensing coumarin and pyrazole moieties and condensed with (un)substituted phenylhydrazines to yield receptors with acidic N-H and C-H groups for establishing efficient and selective binding with inorganic fluoride ion in 1:1 DMSO-water **[81]**.

Synthesis

Compounds 3-acetyl coumarin **(1)** and 3-[1-(phenylhydrazono)-ethyl]-chromen-2-one **(2)** were prepared by following the procedure of Perekalin *et al.* and Chodankar *et al.*, respectively **(Scheme 1.4) [82-83]**. Sonication of compound **2** with DMF/$POCl_3$ at 80 ^oC yielded formyl 3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde **(3) [84]**, which gave the title compounds as orange coloured products **(R1-R5)** upon microwave irradiation with (un)substituted phenylhydrazine.

The FTIR spectra of receptors **R1-R5** display characteristic broad absorbance band from 3428-3201 cm^{-1} due to N-H stretching vibration. Aromatic C-H stretching vibration is observed in the region of 2941-2841 cm^{-1}. Characteristic sharp absorbance peak at 1721 cm^{-1} is ascribed to C=O stretching vibration. Aromatic C=C stretching vibration is observed at 1567 cm^{-1}. Two absorbance bands centered at 1545 and 1385 cm^{-1}, due to N-O vibration (NO_2), prove the presence of nitro groups in receptors **R1-R3**. A band at 1087 cm^{-1} may be attributed to C-F stretching of CF_3 group present in receptor **R4**.

In the ^1H NMR spectra of receptors **R1-R5**, two sharp singlets at δ 9.10 and 11.59 ppm appeared due to presence of HC=N and N-H protons. A singlet at δ 8.74 ppm is observed due to the presence of pyran-H. A multiplet ranging from δ 7.38-8.43 ppm may be attributed to aromatic protons in molecular structure of receptors. The disappearance of peak at δ 9.97 ppm (pyrazolyl CHO) in the spectra confirms the formation of desired products. The ^{13}C NMR spectra of **R1-R5** display characteristic peak around δ 129 (=C-H) and 155 ppm (C=N). Aromatic carbons are observed in the region from δ 116 – 139 ppm**.** In the ^{19}F NMR spectra of receptor **R4**, a singlet at δ 81 ppm may be attributed to presence of CF_3 group.

Further validation was provided by HRMS data, which gave an accurate molecular ion peak $[M+H]^+$ at m/z 497.1750 **(R1),** 452.1289 **(R2),** 452.1276 **(R3)**, 475.1316

(R4) and 407.1451 **(R5)**, that agreed well with their corresponding calculated molecular weight.

Anion binding studies

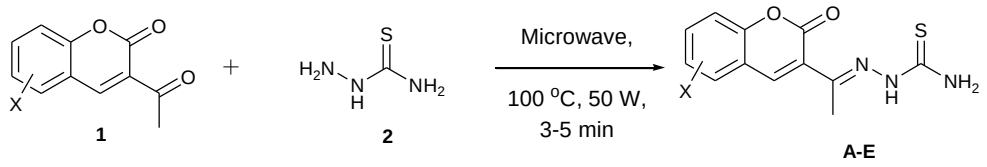
Anion binding studies were investigated for the inorganic fluoride binding in highly competitive media, 1:1 (DMSO-water). Only one, 3-{4-[(2,4-dinitrophenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one (**R1**), of the four coumpounds synthesized, is found to be capable to selectively detect inorganic fluoride *via* naked eye amongst other anionic species in aqueous media at concentration of 0.95 ppm. A distinct visual colour change from yellow to pink was instantly noticed on addition of fluoride, a change that is not observed in presence of any other anions. It is worthwhile to cite that colour intensity increased with increasing fluoride concentration, showing distinct colour changes at 1.5, 3, 5 ppm and above respectively, which proves the feasibility of the receptor solution for knowing the fluoride ion levels semi-quantitatively.

Inclusion of electron withdrawing substituent (nitro group) onto the molecular framework of **R1** polarized the N-H fragment and its H-bond donor tendency increased sufficiently to compete with water molecules and thus **R1** is capable to detect fluoride in competitive solvent with binding constant K, as 1.98×10^4 M^{-1}. Anion binding studies carried out by UV-Visible titration showed peak shift from 410 nm to 495 nm, on addition of sodium fluoride in UV-Visible spectrum, which validated the colour change. Job's plot data confirmed 1:1 stoichiometry between **R1** and fluoride ion. NMR investigation revealed that development of beautiful colour on interaction between fluoride and receptor is attributed to deprotonation of N-H moiety by fluoride ion.

Series 5 Design and synthesis of Coumarin based receptor, 1-(1-(substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides

This chapter deals with synthesis, characterization and anion binding studies of naked eye neutral receptors 1-(1-(substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides **A-E** for semi-quantitative detection of inorganic fluoride ion (sodium salt) in aqueous media.

Inherent photophysical properties of coumarin scaffold makes it undeniably a good choice for synthesis of receptors **[85-86]**. Reported coumarin related receptors detect fluoride ion in organic or organo-aqueous media, which hampers the very purpose of detecting fluoride in drinking water **[87-90]**. Devising chemoreceptors for fluoride in 100 % aqueous media remains a challenging task due to its high hydration enthalpy **[91]**.



1 **2** **A-E**

Receptor A , X = H,
B , X = 6-NO_2,
C, X = 8-OCH_3,
D, X = 7-$N(C_2H_5)_2$,
E, X = 7,8-benzo

Scheme 1.5: Synthesis of receptors 1-(1-(substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides A-E

In our efforts towards developing receptors which are able to bind fluoride ion in aqueous media, receptors 1-(1-(substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides **A-E** were designed by attaching coumarin indicator to thiosemicarbazide moiety containing N-H as binding site. Receptors were judiciously synthesized incorporating both electron-withdrawing and electron-releasing groups at strategic positions to study their impact on visual colour change for fluoride ion detection in aqueous media **[92].**

Synthesis

1-(1-(Substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides **A-E** have been synthesized *via* condensation of 3-acetyl coumarin derivatives **(1a-e)** and thiosemicarbazide **(2)** under microwave irradiation **(Scheme 1.5)**. Compounds were obtained in good to excellent yields.

Structure of receptors **A-E** was established on the basis of standard spectroscopic techniques (FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy). In the IR spectra of receptors, **A-E**, characteristic broad absorbance band from 3457-3260 cm^{-1} is assigned to N-H stretching vibration due to the presence of NH and NH_2 group, which were

absent in the FTIR spectra of compound **1.** Peak at 1719 cm^{-1} may be assigned to C=O stretching frequency. Receptors **A-E** show absorption bands at 1618-1589 and 1596-1496 cm^{-1} due to symmetric and asymmetric C=N stretching vibration. Two absorption bands at 1540 and 1352 cm^{-1} are observed due to N-O stretching of nitro group present in receptor **B.**

The ^{1}H NMR spectra of receptors **A-E** exhibit characteristic sharp singlet in the region δ 9.29-10.45 ppm due to presence of N-H group. A singlet in the region δ 7.9-8.9 ppm is assigned to pyran–H present in coumarin ring. A multiplet from δ 7.3-8.4 ppm is observed for aromatic protons in the molecular structure of receptors. ^{13}C NMR of receptors **A-E** showed characteristic signal around δ 160 ($>C-NH_2$), 165 (-C=N) and δ 178 ppm (C=O). Further verification was provided by HRMS data which gave an accurate molecular ion peak $[M+H]^+$ at m/z 262.0009, 307.0500, 292.0563, 333.1242 and 312.4568 that agrees well with their calculated molecular formula.

Anion binding studies

Amongst easy-to-synthesize receptors **A-E**, receptor **B** showed instant colour change from yellow to pink instantly upon addition of fluoride salt (sodium fluoride) 1 x 10^{-5} M in aqueous media. Interestingly, receptor **B** also gave distinct colour changes perceivable even with naked eye at different fluoride ion (sodium salt) concentrations (*viz*., <1.5, 1.5-5 and >5 ppm) fluoride in water which allows a semi-quantitative data to be generated for fluoride contaminated drinking water**.**

Anion binding properties were examined by UV-Visible spectroscopy and ^{1}H NMR titration. UV-Visible spectrum of receptor B consisted of maxima centred at 358 nm, which upon addition of fluoride ion (sodium salt), decreased gradually and disappeared. A new maxima shifted to longer wavelength at 500 nm, with the appearance of a clear and distinct isobestic point at 405 nm. Stoichiometric ratio was obtained from Job's plot and mass spectrometric analysis, where it was observed that receptor **B** binds fluoride ion in 1:1 stoichiometric ratio. The binding constant of receptor **B** for fluoride ion was found to be 1.38 x 10^{5} M^{-1} from Benesi Hildebrand plot. Insight into receptor-anion binding event was realized by ^{1}H NMR titrations, which proved that deprotonation of NH proton of thiosemicarbazide caused dramatic colour change from yellow to pink.

Analytical applications

Preliminary investigation of receptor **B** with everyday commodity items, toothpaste and mouthwash clearly show visual colour change from yellow to pink, which may be helpful for detecting presence of fluoride ion in these items. Drinking water samples were also collected from Bagru and Sanganer districts of Jaipur city and fluoride ion concentration was determined semi-quatitatively by observing visual colour change with receptor **B**. Quantitative fluoride ion concentration was also determined by the application of calibration curve, obtained from addition of standard sodium fluoride solutions into receptor **B** solution in UV-Visible spectroscopic titration. This method is simple and it has the potential for being developed as a tool for detecting different levels of fluoride in ground water.

Conclusion

The research work presented in this thesis exemplifies the exploitation of wide spectrum of heterocyclic scaffolds for trapping biologically significant anionic species. Novel heterocyclic derivatives, based on triazole, benzimidazole, indole-imidazole hybrids, coumarin have been designed, synthesized and examined for anion binding studies with the range of anions. It was observed that with the employment of heterocycles, judicious placement of substituents and correct orientation of hydrogen bond donor groups, goals of achieving selective and sensitive fluoride ion detection in aqueous media have been achieved to great extent. Gradual progress has been achieved in the development of heterocyclic receptors for fluoride ion detection in the present research work and a shift away from receptor systems that detect fluoride ion only under laboratory conditions to new anion receptors that are capable of detecting fluoride ion under real-world conditions can be noticed.

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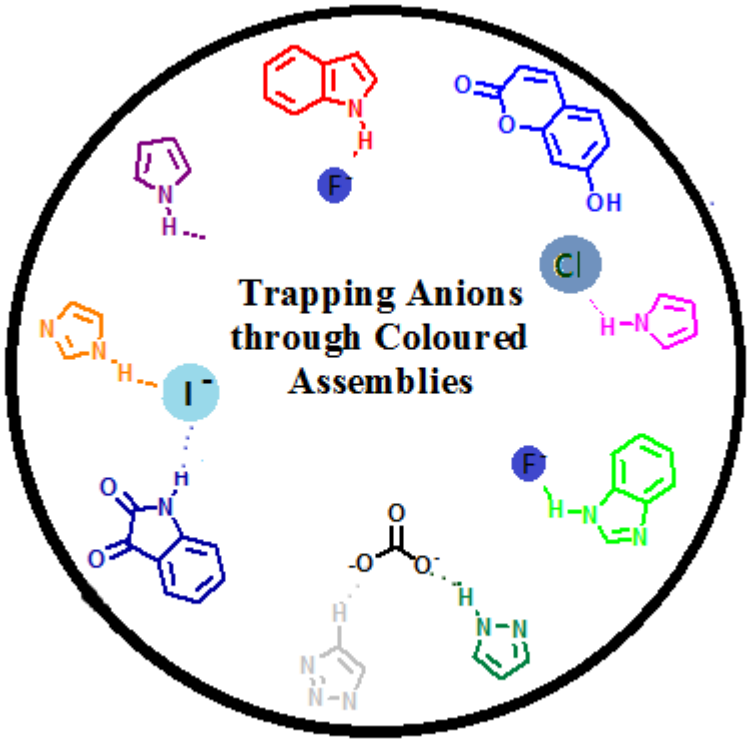
Chapter-2

A Review on "Emergence of Heterocycles as Artificial Neutral Receptors for Naked Eye Recognition and Sensing of Anions"



INTRODUCTION

The fundamental biological processes in nature rely on enzyme-substrate interactions, which are largely regulated by the concentration of anions present in biological world. These anions are carefully perceived and bound by the binding sites of sophisticated proteins **[1].** The sulphate binding protein found in *Salmonella typhimurium* binds sulphate ion to transport it across the cell membrane **[2]**. The enzyme haloalkane dehalogenase in *Xanthobactor autotrophicus* binds chloride ion and becomes active form to initiate catalytic activity **[3]**. This has stimulated chemists to develop synthetic anion receptors which can replicate the anionic recognition found in biological systems **[4-7]**.

Anion receptors are the synthetic molecules that can qualitatively or quantitatively recognize, or sense a negatively charged species. These can be broadly categorized into cationic and neutral receptors **[8].** Cationic anion receptors, which marked the beginning of anion recognition chemistry, are positively charged receptors which establish electrostatic interactions with anions **[9].** Moieties comprising of quaternary ammonium groups, guanidinium, isothiouronium, porphyrins, polyamines, etc. have been largely exploited for the fabrication of cationic receptors to attain effective electrostatic binding with anions **[10-17]**. On the other hand, neutral receptors, containing acidic N-H or O-H hydrogen bond donor groups depend on hydrogen bonding to establish interaction with anions. Larger binding constants could be accomplished with positively charged receptors, but they lack directional and selective nature of hydrogen bonding present in neutral receptors **[18].** Moreover, in cationic anion receptors, associated counter-anion creates competition for the desired anion **[19]**. Therefore, neutral receptors are preferred over cationic receptors **[20]**. Neutral receptors usually incorporate molecules containing urea/thiourea, secondary amide, sulphonamides, *etc.* **[21-24]** which possess acidic N-H, for the formation of hydrogen bond with anions **[25-30]**.

Amongst neutral anion receptors, molecular systems that can recognize and sense anions selectively through visible, electrochemical and optical responses are of special interest **[31-37]**. Color change, which can be observed *via* naked eye, is highly valued as they provide results at-site and thus obviate the use of any expensive spectroscopic instrument and trained personnel **[38-40]**.

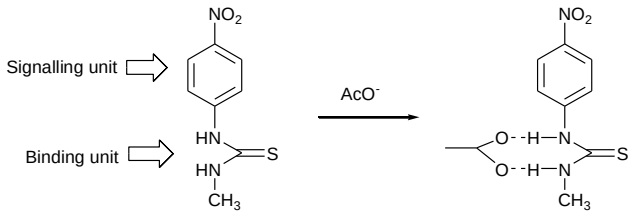
There are three various approaches for devising chemosensors **(Fig. 1.1, 2.1) [41]**:

- **Binding – signalling unit approach,**
- **Displacement approach**
- **Chemodosimeter approach**

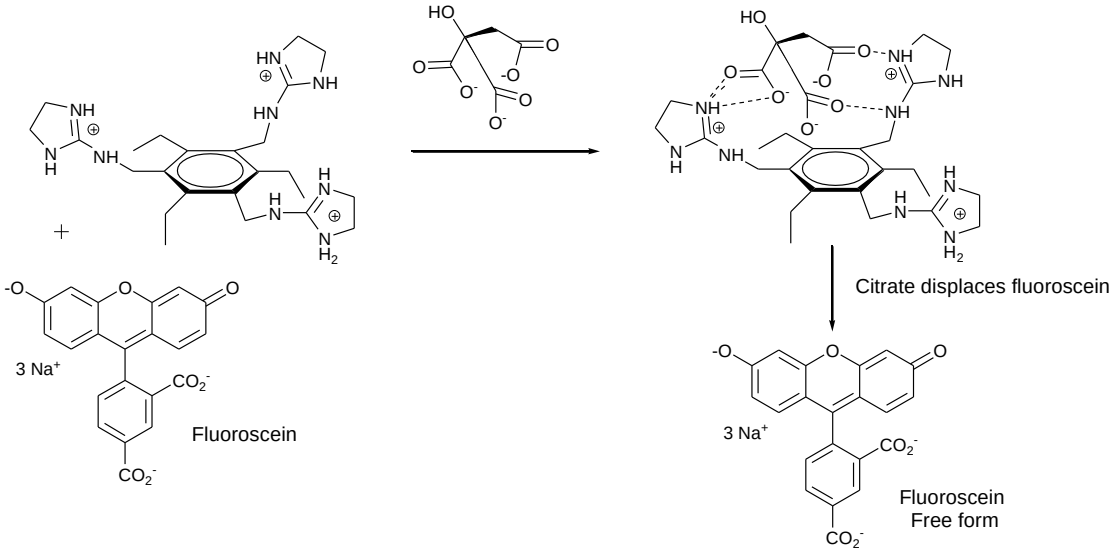
In the first approach, receptor consists of signaling unit which is covalently attached to binding unit. Receptor binds the anion through its binding site, which brings about a change in the photophysical properties of signalling unit attached with it, producing an optical response as the output **[42]**. This approach is mostly exploited for the development of chemosensors. Nitrophenyl group as signalling unit conjugated to binding subunit, thiourea moiety, is a typical example of this approach. Anions such as, acetate and fluoride bind *via* hydrogen bonding interactions to receptor's binding site *i.e.,* thiourea and this binding event induces change in photophysical properties of signalling unit, nitrophenyl, which is observed as a colour change detectable by naked eye **(Fig. 2.1a) [43].**

In the displacement approach, the binding unit and signalling unit remain in a form of coordination complex. When a target anion is added to the solution containing this coordination complex, anion displaces the signalling unit and itself coordinates with the receptor's binding site. The free signalling unit gives optical response either by colour change or by spectroscopic methods **[44]**. Fluorescein as a signalling has been used for the construction of receptor, where 5-carboxy-fluorescein and guanidinium moiety form a coordination complex. When citrate ion is added to this solution, it binds to guanidinium moiety and displaces fluorescein, which comes into its fluorescence behaviour **(Fig. 2.1b) [45]**.

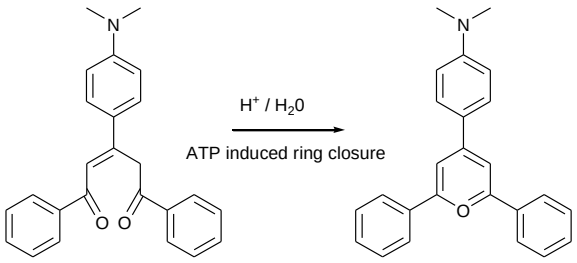
In the chemodosimeter approach, anion triggers a specific reaction upon binding which is responsible for generating a naked eye response. This anion induced approach is highly selective and is directly related to anion concentration **[46]**. For example, receptor containing diarylpent-2-en-1,5-dione backbone detects adenosine triphosphate (ATP) ion with a colour change, detectable by naked eye. The change in colour was due to anion induced cyclization of diarylpent-2-en-1,5-dione moiety to corresponding pyrylium cation **(Fig. 2.1c) [47]**.



(a) Binding - signalling unit approach



(b) Displacement approach



(c) Chemodosimeter approach

Fig. 2.1: Different design approaches for chemosensors

Fluoride, amongst the anionic species, is the most explored individual of the diverse family of anions **[48-57]**. Being the most electronegative atom, it rightfully achieves strong hydrogen bond interactions with an unmatched selectivity **[58]**. It is usually observed that the colorimetric receptors exhibit moderate or even no change in

presence of other anions, however with fluoride; they show dramatic and interesting colour changes. The negative charge brought by fluoride ion modifies the dipole associated to the charge transfer spectrum of receptor system and thus a colour change is obtained **[59]**.

Many reviews have been published on the design, synthesis and application of neutral anion receptors **[60-71]**. The realization that simple organic compounds incorporating heterocycles can detect anions selectively and effectively, has led to the development of chromogenic receptors based on heterocyclic derivatives **[72]**. Elegance in design was achieved by the wise incorporation of other systems, mostly, urea/thiourea, amide, into heterocyclic systems in order to gain more interactions with negatively charged species, **[74-76]**. Recent trend indicates towards the utilization of triazole moiety for the formulation of neutral anion receptors, where the untapped potential of C-H hydrogen bond donor groups has been exploited **[77-80]**. The hydrogen bonding behaviour of triazole C-H could be modulated by inclusion of appropriate substituents and other hydrogen bond donor groups to achieve maximum interactions with anionic species **[81-82]**.

This mini review is not an exhaustive account on heterocyclic derivatives as anion receptors, but summarizes their employment as motifs for naked eye anion receptors **(Fig. 2.2).** Briefly, it also discusses their selectivity, recognition and sensing abilities for anions in organic solvents or in aqueous media covering selective literature references from 2006 to recent development till date. The content of the review has been cateogorized under the following headings:

1. **Naked eye anion receptors based on five membered aromatic ring with one hetero atom**
2. **Naked eye anion receptors based on five membered aromatic ring with two hetero atoms**
3. **Naked eye anion receptors based on five membered aromatic ring with three hetero atoms**
4. **Naked eye anion receptors based on six membered aromatic ring with one hetero atom**
5. **Naked eye anion receptors based on fused systems**

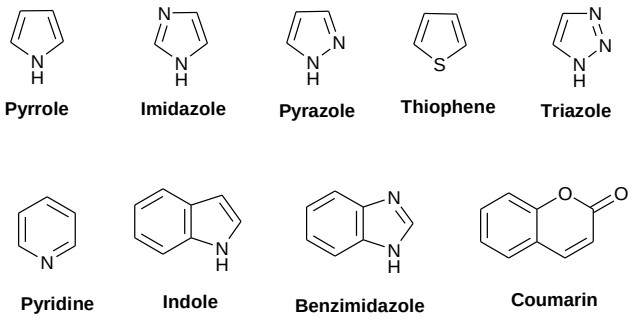


Fig 2.2: **Commonly used heterocyclic moieties for designing anion receptors**

Naked eye anion receptors based on five membered aromatic ring with one hetero atom

The first section of review showcases the development of naked eye anion receptors based on five membered aromatic ring with one hetero atom, *viz.*; pyrrole and thiophene. The anion binding studies of selective receptors based on these scaffolds have been briefly discussed here.

Pyrrole based anion receptors

Pyrrole motif contains acidic N-H, which is capable to trap anions and it can also be covalently attached with other hydrogen bond donor groups to develop multiple binding sites with anions. One such naked eye anion receptor, where pyrrole has been conjugated with thiourea functionalities, has been reported by Gale and coworkers in 2006 **(Fig. 2.3)**. They found that these receptors were capable of establishing binding interactions with anions, fluoride, acetate and benzoate (TBA salt), in DMSO as solvent, with a visual change from yellow to red perceptible to the naked eye. UV-Visible and ^{1}H NMR studies pointed that the interactions of receptors with basic anions lead to deprotonation, which was observed as colour change in receptor solution **[83-84].** However a more efficient colorimetric and fluorescent chemosensor **3a-b**, with pyrrole NH as binding site were designed for fluoride and hydroxide ion (TBA salt) detection by Velmathi *et al.* in 2011 **(Fig. 2.3)**. Receptor **3a-b**, synthesized *via* Schiffs base condensation, became yellow and permanganate coloured in presence of fluoride and hydroxide ions, respectively. Receptor **3b**, functionalized with nitro group as chromogenic signalling unit, exhibited predominant colour change than receptor **3a**. UV-Visible, fluorescence, IR and NMR spectroscopic techniques were

employed to study anion binding properties of receptors and it was observed that deprotonation of pyrrole NH by F^-/OH^- was responsible for drastic colour change **[85]**.

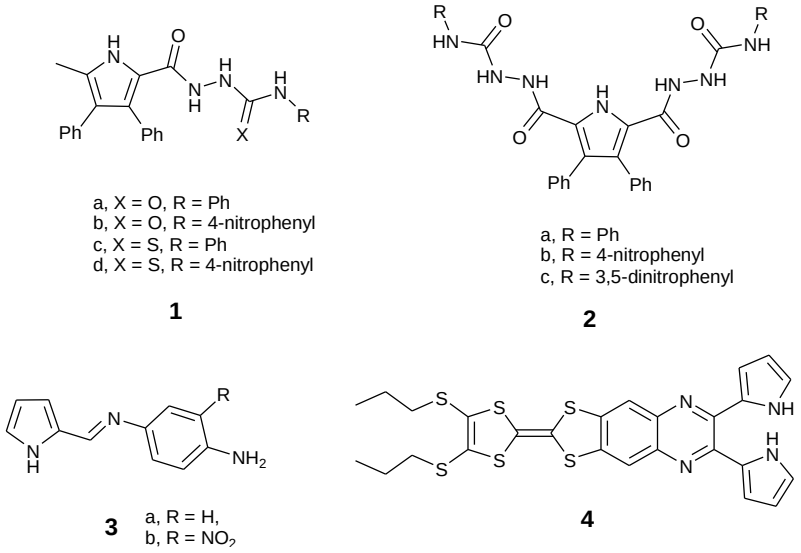


Fig. 2.3: Pyrrole based naked eye receptors 1-4

Another approach was designed by using dipyrrolyl motifs as recognition sites to develop chemosensor **4** for sensing fluoride ion selectively in DCM solution. Tetrathiafulvalene (TTF) moiety was used as redox tag **(Fig. 2.3) [86]**. TTF and its derivatives have been known for their remarkable high π donating ability and redox properties, which enabled receptor **4** to display specific naked eye colour change from orange to pink upon addition of fluoride ion selectively over other anions in DCM solution.

Thiophene based anion receptors

Thiophene scaffolds have been covalently attached with motifs containing hydrogen bond donor groups, mostly urea/thiourea to craft naked eye receptors, where thiophene acts as an efficient π- conjugated bridges for sensing anions *via* colour change. Very few examples taking thiophene have been reported in literature. Thiophene has been conjugated with thiosemicarbazide to yield receptors, **5a-b** and **6a-d** by Sreekanth *et al.* and Santos-Figureroa *et. al*., respectively **[87-88].** Receptors **5a-b** have been characterized for the selective fluoride ion binding in DMSO by means of UV-Visible, fluorescence spectroscopic techniques and crystal X-ray

diffraction methods. Both receptors gave colour change from colourless to yellow upon addition of fluoride ion (TBA salt), preferentially over other anions. It was reported that fluoride ion interacts with thiourea NH groups initially by hydrogen bonding interactions, which was followed by deprotonation of NH in an excess amount of fluoride ion **[87]**. A highly selective and sensitive chemodosimeter for fluoride ion detection in solid as well as in solution was developed by M. Kaur *et al.* They utilizined chemodosimeter approach to design a diketopyrrolopyrrole derivative **6** containing two trimethylsilyl groups **(Fig. 2.4).** Addition of fluoride ion to receptor caused blue shift in absorption and fluorescence spectra. UV-Visible absorption, fluorescence and cyclic voltammetry were employed for exploring anion recognition properties. These studies revealed that there is a triggered cleavage of the Si-C bond in receptor due to the strong affinity of fluoride ion for silicon **[88]**.

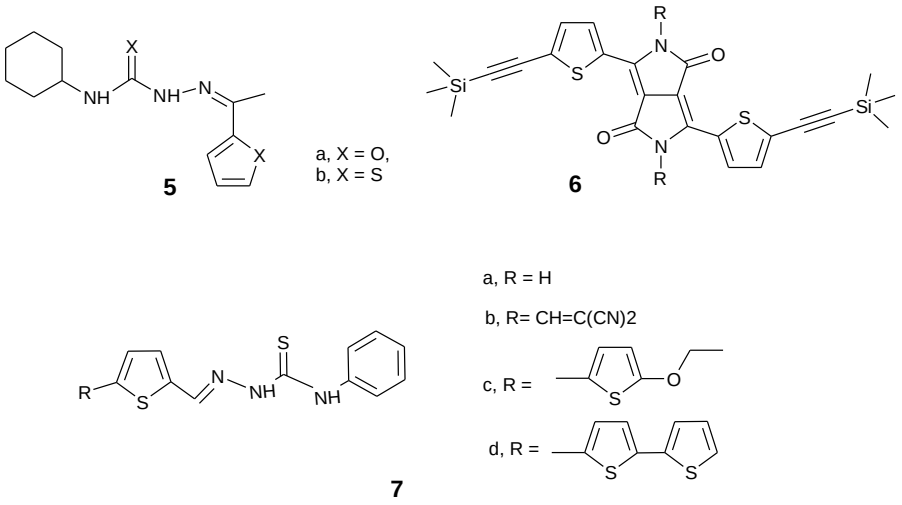


Fig. 2.4: Thiophene based naked eye receptors 5-7

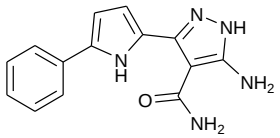
A series of thiosemicarbazones, **7a-d** containing thienyl moiety have been developed for chromogenic detection of anions, F^-, CN^-, CH_3COO^- and $H_2PO_4^-$ in CH_3CN by spectroscopic techniques **(Fig. 2.4).** Sensing abilities were observed in the form of appearance of new red shifted bands upon addition of more basic anions, TBA salts of F^- and CN^- into receptor solution in UV-Visible spectra. While less basic anions, CH_3COO^- and $H_2PO_4^-$ could trigger weak coordination event in only receptors, **b** and **c**, which was visible as small shifts in absorbance bands **[89]**.

Naked eye anion receptors based on five membered aromatic ring with two hetero atoms

In this second section, a series of representative naked eye receptors based on five membered aromatic ring with two hetero atoms *viz.*; pyrazole and imidazole motifs have been described.

Pyrazole based anion receptor

Naked eye receptor, 5-amino-3-(5-phenyl-1H-pyrazole-4-carboxamide, **8 (Fig.2.5)** was synthesized by Yang and Trofimov group and its anion binding study was carried out in both DMSO and water with TBA and sodium salts. Receptor selectively bind fluoride ion over other anions as observed by fluorescence data where emission intensity increased with addition of fluoride about 607 times at wavelength of 424 nm. The deprotonation of pyrazole NH was responsible for sensing of fluoride, as observed in ^{1}H NMR titrations by authors **[90]**.



8

Fig 2.5: Pyrazole based naked eye sensor 8

Imidazole based anion receptors

Imidazole, containing an inbuilt acidic N-H hydrogen bond donor group, is enriched with interesting photophysical properties, which have been exploited to design novel anion receptors in organic as well as aqueous media. One such interesting fluoride ion receoptors, 2,4,5-triphenylimidazole derivatives, **9a-f** have been designed and synthesized by Goswami *et al*. Out of which one derivative, **9a** containing nitro group at *p*-position of 2-phenyl ring with respect to imidazole ring, exhibited colorimetric response to the presence of fluoride ion (TBA salt) from yellow to red in CH_3CN-H_2O (9:1) **(Fig. 2.6)**. Acetate ion (TBA salt) also triggered the same visible response as fluoride ion, but at larger concentration than fluoride ion. Binding capabilities were studied by naked eye colour change observations, UV-Visible, fluorescence, IR and NMR titrations. **[91]**. More elegant design, imidazole bearing rhodamine based

fluoride probe, **10** was reported by G. Sivaraman and D. Chellappa **(Fig. 2.6)**. This probe showed high selective turn- on fluorescence towards fluoride ion (TBA salt) that enabled its naked eye detection. Authors attributed the fluorescent change to the fluoride triggered spirolactum ring opening. The probe was also found non-toxic to cells and thus feasible for fluorescent imaging in living cells (HeLa cells) under physiological conditions **[92].**

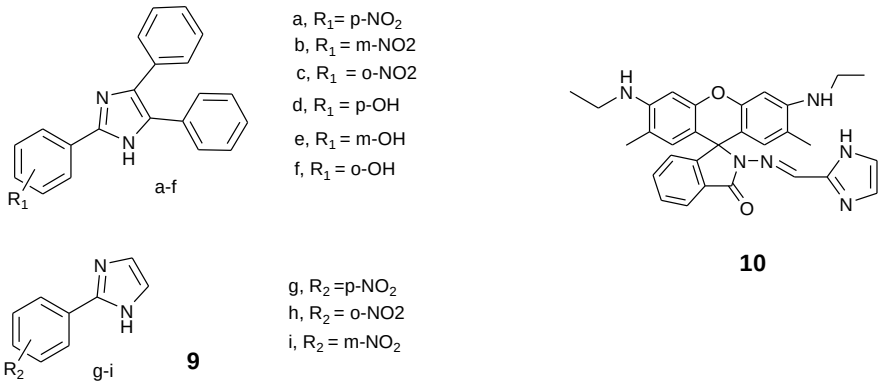


Fig. 2.6: Imidazole based naked eye receptors 9-10

Naked eye anion receptors based on five membered aromatic ring with three hetero atoms

Triazole, a new motif for the development of anion receptors has been included in this section and anion binding studies of receptors reported in literature have been briefly discussed.

Triazole based anion receptors

The advent of Cu(I) catalyzed azide-alkyne click reaction to generate triazole has been instrumental in the development of anion receptors, owing to the modular nature as well as synthetic simplicity and reliability of click reaction **[93]**. It has proven to be an attractive strategy as ligation motif in sensors and thus found numerous applications in coordination and supramolecular chemistry **[94]**. Triazole based ligands have been documented to coordinate transition metal anions **[95]**. In addition, 1,2,3-triazole motif has also been reported to be a versatile anion recognition unit and its several derivatives bind anions through C-H---anion hydrogen bond **[96]**. Most of

the triazole based receptors are fluorescent and found applications in bioimaging due to their bio-compatible nature **[97-98]**, herein only naked eye sensors are discussed.

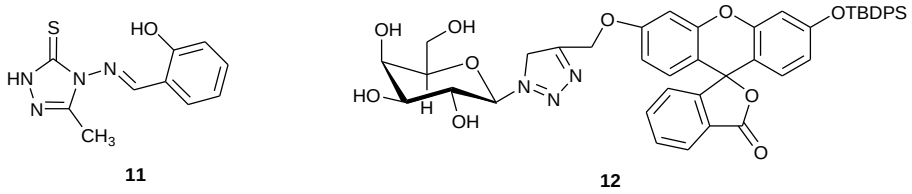


Fig. 2.7 Triazole based naked eye anion receptors 11-12

Triazole based simple colorimetric receptor, 4-salicyclidene amino-3-methyl-1,2,4-triazole-5-thione, **11** has been developed by Sreekanth *et. al*. in 2013. It yielded colour change from colourless to yellow in the presence of fluoride and acetate ions (TBA salts) in DMSO solvent **(Fig. 2.7)**. Fluorescence titrations showed that a positive turn-on fluorescence response was also observed in addition of these anions. ^{1}H NMR titrations of receptor with these anions indicated that receptor binds anions *via* hydrogen bonding interactions through its phenolic OH and amide NH **[99]**. Du and coworkers developed more sensitive and selective fluoride ion receptor, sugar functionalized triazole, **12**, which showed fluorescent as well as naked eye colour change by the mechanism of fluoride induced desilylation reaction**.** Naked eye colour change from colourless to bright yellow was observed in the presence of 1.5 ppm of F^- (TBA^+ or Na^+) at WHO recommended levels of fluoride ion in drinking water. This fluorescent probe could also detect fluoride ion at 0.38 ppm, selectively over other anions and was successfully applied to the imaging of fluoride in HepG2 cells, because of high water solubility and bio-compatibility nature of probe **[100]**.

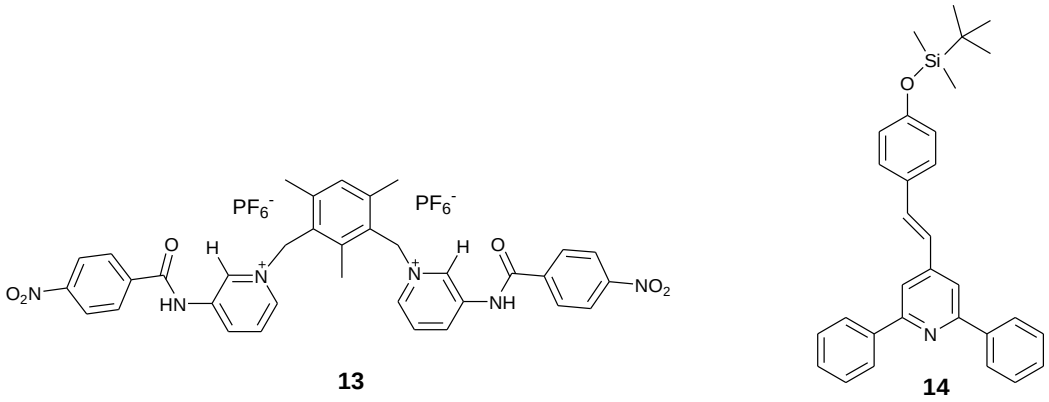
Naked eye anion receptors based on six membered ring with one hetero atom

Pyridine motif has been exploited in literature for developing naked eye anion receptors in this cateogary. The selective literature based on pyridine scaffold as anion receptor has been included in this section.

Pyridine based anion receptors

A pincer shaped amide-pyridinium based receptor, **13** for naked eye sensing acetate ion was prepared by Bao *et al*. in 2012 **(Fig. 2.8)**. Receptor bind acetate ion with visual colour change selectively over fluoride, dihydrogen sulphate, chloride,

bromide, iodide, nitrate and hydrogen sulphate ions (TBA salts). UV-Visible, ^{1}H NMR titrations and molecular simulation was carried out by authors to show that selectivity of receptor for acetate ion was ascribed to the synergistic effects of hydrogen binding, electrostatic interactions and induced fit process. **[101]**. In 2013, a highly selective chromofluorogenic fluoride ion chemodosimeter **14**, based on pyridine derivative functionalized with *tert*-butyldimethylsilyl ether was designed and documented by Elsayed and coworkers. Anion binding studies were investigated by UV-Visible as well as fluorescence titrations. Upon addition of fluoride ion (TBA salt) into receptor solution in water, both visible and fluorescent response was obtained. Hydrolysis of silyl ether moiety by addition of fluoride ion produced a coloured as well as fluorescent emissive phenolate ion in the receptor, which accounted for selective colorimetric and fluorometric behaviour of receptor for fluoride ion **[102]**



13 **14**

Fig. 2.8: Pyridine based receptors, 13-14

Naked eye anion receptors based on fused systems

The last section of this review highlights the development of naked eye anion receptors, based on fused heterocyclic systems, *viz.;* indole, benzimidazole and coumarin, which have been extensively employed to craft anion receptors. Summarized view of the anion binding studies and advancement in the molecular framework from simple to complex have been presented here.

Indole based anion receptors

Indole, biindole and indolocarbazole moieties have swiftly evolved as a new class of anion receptors **[103]**. These scaffolds contain acidic NH, which can be exploited to

trap negatively charged species or these can be connected to urea/thiourea and amide to create hybrid systems for the creation of novel sensors **[104-105]**. A simple example of an indole based receptor is indole conjugated with phenylhydrazine ring **[106]**. Receptor **15** bound AcO^- (TBA salt) with good selectivity over other anions in DMSO, giving a naked eye response from orange to purple. ^1H NMR titration experiments of receptor with acetate indicated hydrogen bonding between receptor's NH and structurally related acetate ion (AcO^-). Similar receptor **16** was reported soon after by Lin *et al.* by coupling 2,3-dikedoine isatin with 4-nitrophenylhydrazine **[107]**. It showed naked eye response for acetate ion (TBA salt) with similar mechanism (from yellow to blue). Another similar receptor **17** based on indole-3-aldehyde as signaling unit and 2, 4-diphenylhydrazine as binding unit was synthesized by the same group. It displayed colorimetric sensing for acetate, fluoride and dihydrogen phosphate ions (TBA salts) **[108]**. Anion binding studies were conducted by UV-Visible and ^1H NMR titrations, which proved that hydrogen binding, followed by deprotonation of phenyl hydrazine N-H was responsible for naked eye detection of anions in above receptor, **17.** However, detection could be realized only in organic solvent, DMSO for these receptors **(Fig. 2.9).**

Indole conjugated bisthiocarbonohydrazones and biscarbonohydrazones **18 (a-e)** were synthesized by Ghosh *et. al*. in good yields by condensation of indole aldehydes and 1,3-diaminothiourea/ 1,3-diaminourea **[109]**. Receptors **18 (a-e)** were capable to selectively sense fluoride ions (TBA salt) over other anions along with an absorbance at NIR region in acetonitrile and dimethyl formamide 9.6:0.4 (v/v) as media. Conjugation and planarity of receptor is attributed for the huge shift from 342 nm to peaks at 522, 572 and 936 nm. A peak in NIR region at 936 nm provides sensing of anion useful in the case where interference from endogenous chromophores is possible. Similar receptor **19,** containing indoline-2,3-dione and 1,3-diaminothiourea subunits have been designed and synthesized by Lin *et al.* for visual detection of acetate ion (TBA salt) in dry DMSO. Anion binding studies were conducted by UV-Visible and ^1H NMR titration experiments, which shows that receptor binds acetate ion *via* hydrogen bonding by two acidic thiourea NH of the receptor **(Fig. 2.9) [110]**.

A series of compounds containing indole and pyrazole moieties, **20 (a-d)** have been synthesized and characterized for anion binding by Ghosh *et al*. in 2012 **(Fig. 2.9)**

[111]. Receptor **20a** showed a large red shift of 335 nm of absorption band upon addition of fluoride ion in DMSO solvent in UV-Visible spectrum and NMR titration proved that deprotonation of indole NH was responsible for this change. Receptor **20c** showed colorimetric response towards fluoride and cyanide ions (TBA salts). Non selective hydrogen bonding interaction was found for fluoride, cyanide, acetate, dihydrogen phosphate and benzoate with receptor **20b**. No colorimetric response was exhibited by receptor **20d**.

Receptor **21** was synthesized and anion recognition properties were investigated by naked eye colour change and UV-Visible, ^{1}H NMR and DFT calculations by Bao and Song *et al.* **[112].** They found receptor to be sensitive and selective towards cyanide ion (TBA salt) in CH_3CN-DMSO medium by the virtue of formation of manifold hydrogen bonding interactions of cyanide ion with phenolic OH, indole NH and amide NH **(Fig. 2.9)**.

Isatin as signaling unit was coupled with acyl-thiourea derivatives to yield receptors **22 (a-c)** with different groups on same molecular framework by Shao *et al.* **(Fig. 2.9).** Anion binding strength of these receptors were checked with different anions using UV–vis spectroscopy and ^{1}H NMR titrations in DMSO and DMSO-d_6, respectively. Receptor **22a** exhibited high affinity for acetate ion (TBA salt) over fluoride due to multiple hydrogen binding interactions with acetate ion. Receptor **22b** did not bind any anion because of lack of binding unit. Receptor **22c** functionalized with strong electron withdrawing units showed naked eye colour change for fluoride due to deprotonation of receptor in DMSO **[113]**. A similar receptor, indole hydrazine based colorimetric and absorption ratiometric anion sensor **23**, has been reported by Bao *et al.* which detects fluoride, acetate and dihydrogen phosphate ions over other anions by naked eye colour change **(Fig. 2.9)**. Anion binding studies were conducted by UV-Visible and ^{1}H NMR spectroscopic techniques, which proved that excess of anion caused deprotonation of indole and hydrazine N-H **[114]**.

Artificial receptors for amino acids are quite limited. Wang *et. al.* reported the Bis(indolyl)methanes as pH responsive receptor **24** for sensing aspartate and glutamate, the two important neurotransmitters, with detection limits as 0.80 ppm and 1,12 ppm respectively, in water containing medium based on the proton transfer

signaling mode **[115]**. Protonation of receptor in the presence of acid modulated its internal charge transfer state which gave rise to color change **(Fig. 2.9)**.

A colorimetric receptor **25** was synthesized by incorporating azobenzene chromophore to 5th position of indole to yield biindole-diazo conjugate by Jeong *et al*. **(Fig. 2.9).** Cyanide ion induced naked eye colour change in receptor from yellow to reddish orange, while less intense visual change was observed upon addition of other anions, fluoride, acetate and dihydrogen phosphate. Colour change was further proved by UV-Visible titration in 10% v/v DMSO-CH_3CN, where absorbance at 480 nm increased, in addition to maxima at 350 nm, upon coordination of anions with receptor **[116]**.

Advancement in design of receptors was attempted by Wang *et al*. by synthesizing two indole based dipodal **26 (a-b)** and one tripodal **26c** chemosensors for selective recognizing ions in semi-aqueous media (1:1) CH_3CN-H_2O **(Fig. 2.10)** Receptor **26a** could detect CN^- ion (TBA salt), with colour change from deep red to yellow, whereas receptor **26b** showed naked eye colour change from colourless to pink with HSO_4^-. Receptor **26c** could detect both CN^- and HSO_4^- with instant colour change from yellow to orange red upon addition of HSO_4^- and cyanide turned the receptor colourless. UV-Visible, fluorescence and ^{1}H NMR spectroscopic titrations results indicated that hydrogen bonding interactions between indole N-H and ions were responsible for naked eye detection **[117]**. Similar type of receptor **27** was prepared by Yan's group for fluoride and acetate sensing in DMSO **(Fig. 2.10) [118]**.

Multiple hydrogen bonding interactions have been incorporated in indolocarbazole based chemosensor **28** by utilizing catechol O-H, along with indole N-H **(Fig. 2.10)** It showed naked eye colour change from light violet to purple in presence of fluoride ion (TBA salt) in aqueous acetonitrile solution (4:1 v/v). Slight change in colour was also observed by addition of acetate. ^{1}H NMR titration revealed that excess of fluoride and acetate ions induced deprotonation of catechol OH, which resulted in colour change **[119].**

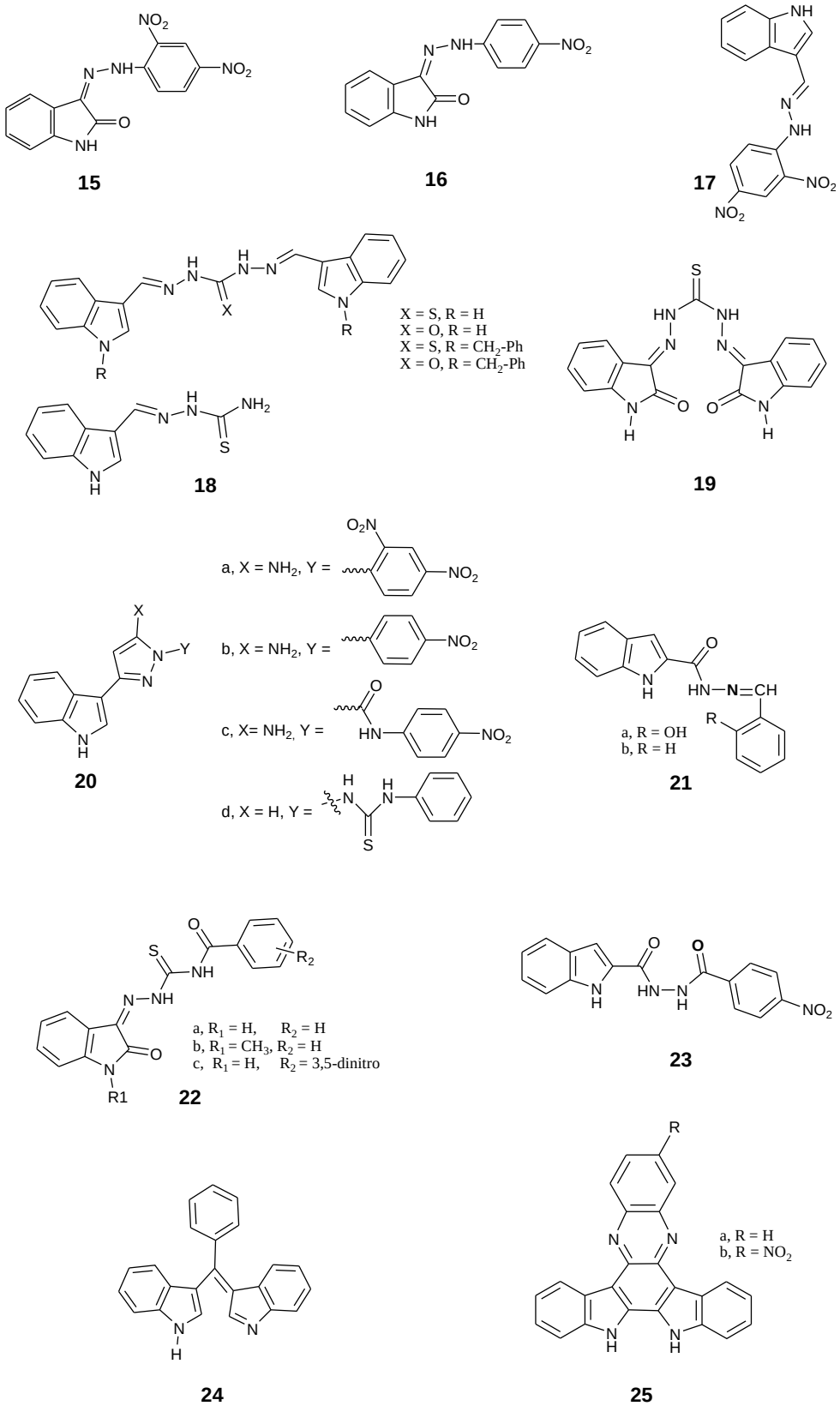


Fig. 2.9: Indole based receptors 15-25

Multiple binding interactions have also been achieved in colorimetric receptors **29 a-b** based on indole moieties, synthesized by Liu *et. al.* for selective recognition of fluoride ion in both pure and aqueous DMSO **(Fig. 2.10)**. The colour of receptor **29a** turned from deep yellow to henna and receptor **29 b** changed its colour from yellow to reddish orange upon addition of fluoride ion (TBA salt). Visual detection is attributed to hydrogen bonding interactions between indole N-H and fluoride ion as demonstrated by UV-Visible and ^{1}H NMR titrations **[120]**.

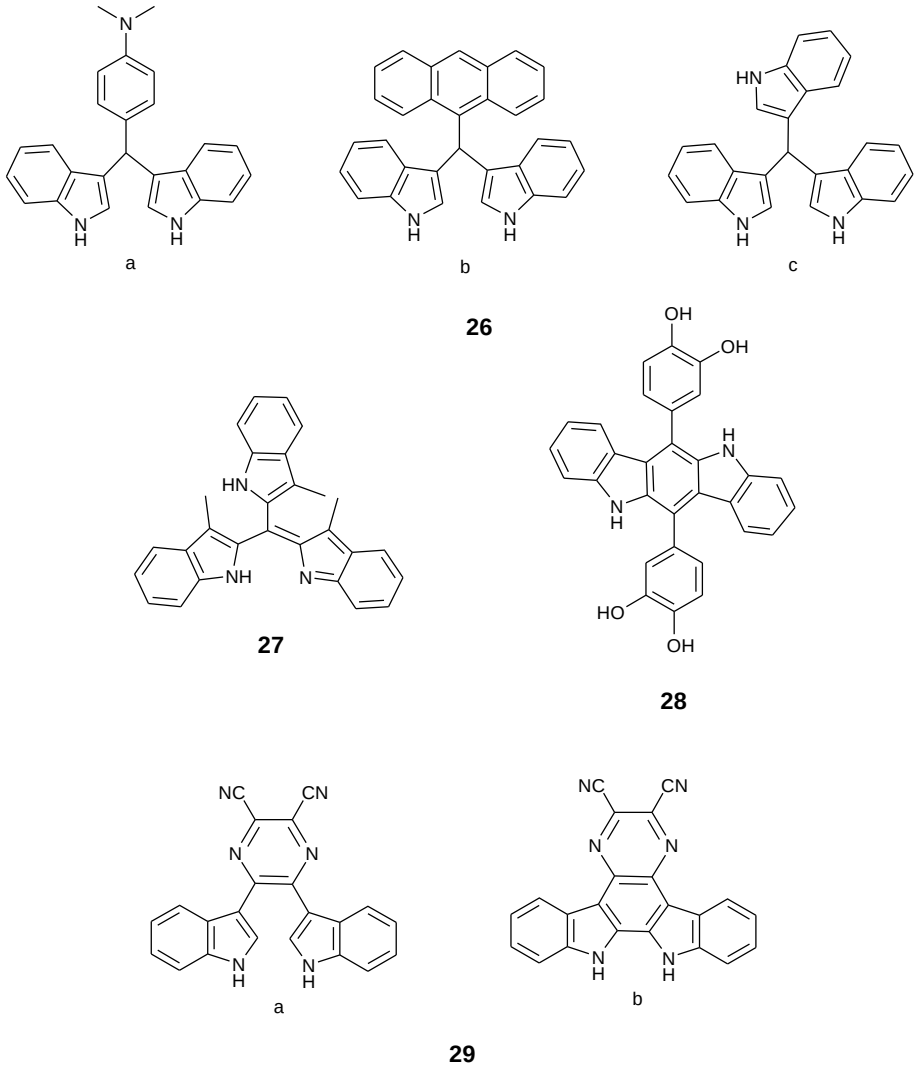


Fig. 2.10: **Indole based anion receptors, 26-29**

Benzimidazole based anion receptors

Benzimidazole has evolved as a new class of anion receptors with intrinsic NH playing the role of binding anion **[121-122]**. Lin *et al.* synthesized two neutral fluorescent anion receptors, **30** based on benzimidazole moieties *N*,*N*'-di-[2'-(benzimidazoyl-2'-)methylene-]-1,10-phenanthroline-2,9-diamide and *N*,*N*'-di-[2'-(benzimidazoyl-2'-)ethyl-]-1,10-phenanthroline-2,9-diamide **(Fig. 2.11)**, exhibiting two dissimilar fluorescence response to anions fluoride/acetate and chloride. In process of anion binding, fluorescence quenching was observed in case of fluoride and acetate, while chloride was reported to show florescence enhancement. PET for fluorescence quenching and anion induced conformational restriction for fluorescence enhancement was accounted for these two different luminescent behaviors **[123]**.

Two interesting metal centred luminescent europiumIII, tris(dibenzoylmethane) $Eu(dbm)_3$, centered with 2-indole-3-yl-imidazo[4-5-f]-1,10-phenanothroline, **31a** and 2-(2-nitrophenyl)-imidazo[4,5-f]-1,10-phenanthroline **31b** complexes **(Fig. 2.11)** were synthesized as anion receptors by Wang *et al.* These receptors were demonstrated for detecting fluoride and hydrogen diphosphte ions with a colour change. Receptor **31a** produced intense colour change from yellow to green in the presence of 0.5 equivalents $H_2PO_4^-$ and 5 equivalents F^- ions, while receptor **31b**, with red emission, could recognize 0.5 equivalents $H_2PO_4^-$ and 5 equivalents F^- by quenching its colour. Spectral studies for anion binding tendencies showed the synergic effects of hydrogen binding interactions and competitive coordinative interactions between ligand and anions, responsible for colour change **[124]**.

A simple cyanide anion naked eye sensor with naphthol and an imine group was synthesized from hydroxyl naphthol and 2-amino benzimidazole, **32 (Fig. 2.11)**. ^1H NMR, FTIR and mass spectral analysis indicated towards the formation of Michael-type adduct under optimum conditions of pH and temperature in aqueous solution. Convenient test strips were also developed, exhibiting the good selectivity as in solution **[125]**. Two colourimetric and fluorometric receptors, **33 a-b** were designed by introducing naphthalene ring to imidazo-anthraquinone system in order to modulate binding properties of imidazole core by Raposo *et al.* **(Fig. 2.11)**. Addition of F^-, CN^- and OH^- induced colour change in receptors' solutions in acetonitrile from yellow to pink, while fluorescence emission of receptor **33a** was switched on and

fluorescence emission of receptor **33b** was quenched. Addition of excess of fluoride caused deprotonation of NH proton of imidazole, which is fluorescent and could be used for sensing metal ions, Cu^{+2}, Pd^{+2} and Hg^{+2} **[126]**.

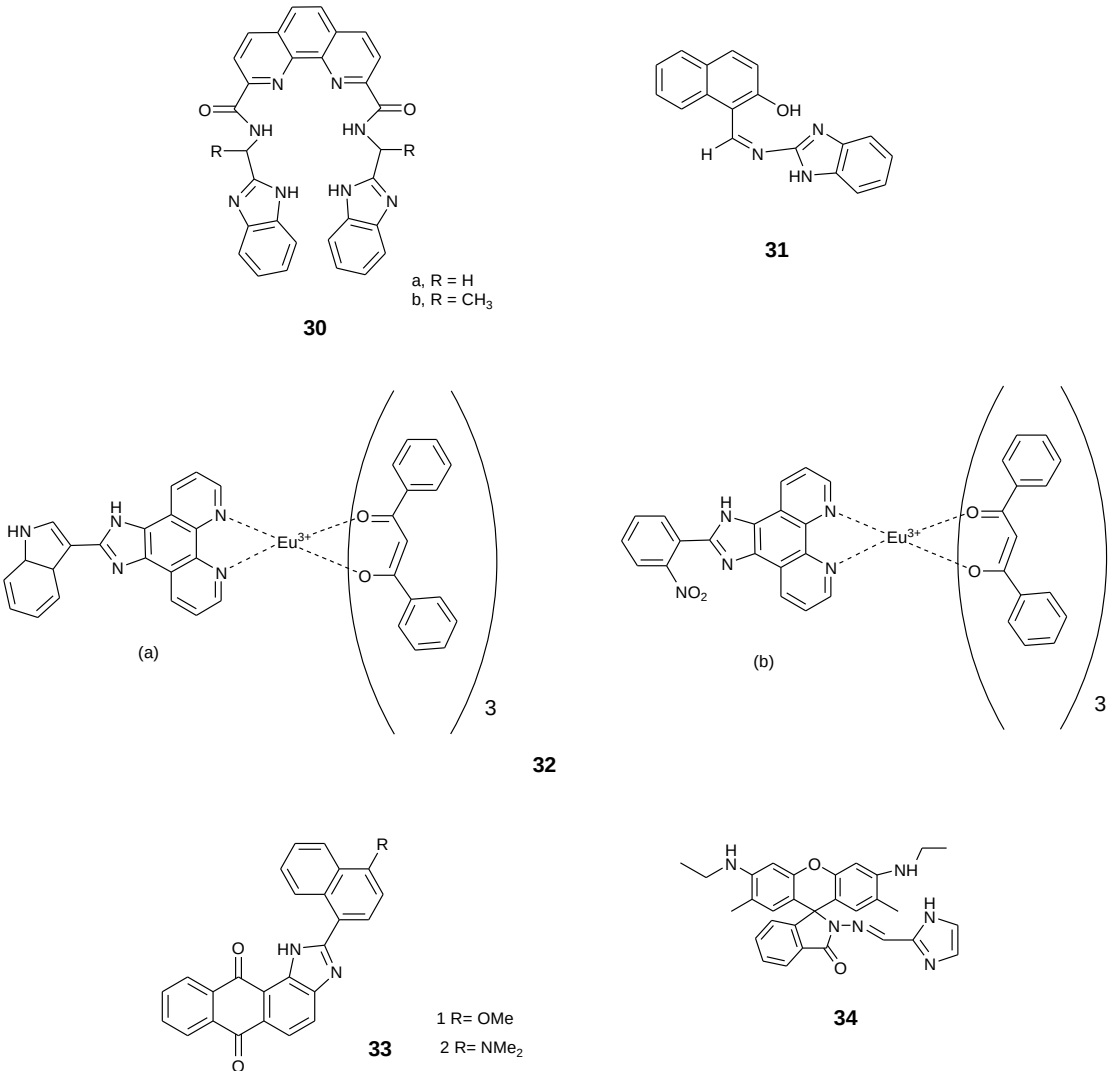
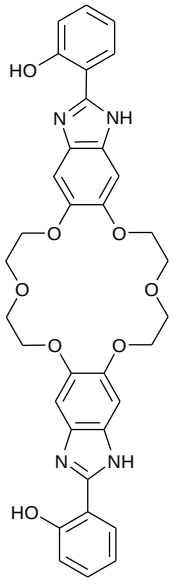


Fig. 2.11: Benzimidazole based anion receptors 30-34

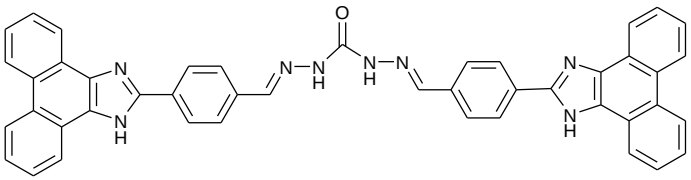
Chemodosimeter approach was used to develop a rhodamine-imidazole based chemosensor, **34** by Chellappa *et al.* in 2013 for colorimetric and fluorescent detection of fluoride ion **[127].** Fluoride ion binding to imidazole N-H triggered spirolactum ring opening, which was observed as fluorescent enhancement by authors. This event was proved by ^{1}H NMR titrations. Colour of receptor changed from colourless to pink colour upon addition of fluoride ion, while no such naked eye colour change was seen by authors with any other anions. Another fluorescent naked eye fluoride ion receptor, based on 2-(4,5-dihydro-1H-imidazol-2-yl)-phenol and

crown ether moieties, **35** has been described for detecting fluoride ion in living cells **(Fig. 2.12) [128].** Receptor could sense fluoride ion with fluorescent naked eye colour change from cyan to blue, observable under UV light. The fluoride ion sensing process was studied by UV-Visible and fluorescent titrations by authors. Receptor was found be cell permeable and could be applied to trace fluoride ion during development of living organism.

Carbonohydrazone bridged Schiff base of phenanthroline-imidazole, **36 (Fig. 2.12)** was synthesized as chemosensor to detect fluoride in DMSO *via* colour change from colourless to light yellow to brownish red. In addition to colorimetric response, it showed 50 nm red shift in fluorescence emission, upon addition of fluoride. Experimental studies proved that deprotonation of imidazole N-H and urea N-H is responsible for optical response. To rationalize the optical response further, density functional and time dependent theory calculations were conducted. Test strips were also prepared by dipping the filter paper into DMSO solution of receptor **[129].**



35



36

Fig. 2.12: Benzimidazole based anion receptors 35-36

Coumarin based anion receptors

Coumarin derivatives have been comprehensively investigated for electronic and photonic applications such as fluorescence probes and charge transfer agents owing to their characteristic photochemical characteristics, reasonable stability, good solubility

and their relative ease of synthesis **[130-140]**. Shao and coworkers documented colorimetric receptor **37** based on coumarin moiety as chromogenic and fluorescent unit and urea as anion binding site **(Fig. 2.13)**. It exhibited high selectivity for acetate ion over fluoride and dihydrogen phosphate due to multiple hydrogen binding interaction in DMSO **[141]**. Shao reported analogue of above receptor, coumarin derivative, **38** in 2011, which in the presence of acetate ion, exhibited "turn-on" fluorescence; resulting from binding induced conformational restriction. Colorimetric response for fluoride, acetate and dihydrogen phosphate was also observed from yellow to red **(Fig. 2.13) [142]**.

Among biologically important anions, fluoride is particularly useful, due to its role in dental health **[143-152]**. The biggest bottleneck in naked eye detection of fluoride is interference by acetate and other anion of comparative basicity **[153-155]**. In 2010, coumarin based phenylhydrazone receptor **39 (Fig. 2.13)** was synthesized and reported by Upadhyay *et al.* that selectively detected fluoride over acetate in DMSO solution. Addition of 1 eq of fluoride to receptor solution (5×10^{-5} M) produced change from yellow to red, while similar addition of acetate ion produced faint pink color. Receptor differentiated the two anions not only visually, but in the terms of wavelength maxima by a margin of 30 nm which is a rare observation in UV spectrum **[156]**. Another fluoride ion selective receptor based on coumarin 7-(diethylamino)-2-oxo-2H-chromene-3-carbaldehyde **40** has been reported, which bound fluoride *via* hydrogen bonding in acetonitrile **(Fig. 2.13) [157]**.

Receptor **41**, containing two coumarin-urea units attached by a flexible diethylenetriamine fragment has been designed and developed by Fusi and Zappia as off-on fluoride ion fluorosensor in both DMSO as well as CH_3CN solvents **(Fig. 2.13)**. Fluorescence emission of receptor in visible range was demonstrated to be quenched by the presence of acetate, chloride and pyrophosphate ions, while fluoride ion enhanced the emission, which proved the selectivity of receptor for fluoride ion **[158]**. Another fluorescent receptor **42** for cyanide ion with coumarin as signal unit and salicyaldehyde functionality as recognition unit has been synthesized by Kim and Hong group **(Fig. 2.13)**. It showed a higher selectivity for cyanide ion over other anionic species in water in fluorescence spectroscopic titration; where emission intensity of receptor at wavelength 450 nm was increased to about 190 fold. The

affinity of receptor for cyanide was ascribed to the nucleophilicity of cyanide ion **[159]**.

Receptors for iodide ion sensing are scarcely reported. One such receptor bearing phenylhydrazone-coumarin moieties, **43** was rationally designed for chemosensing acetate ion as well as fluorescence turn-on probe for iodide ion **(Fig.2.13).** It produced drastic naked eye colour change from yellow to purple upon addition of acetate ion, with red shift in wavelength from 411 to 573 nm in UV-Visible spectra. Exploiting novel strategy based on the redox reaction between Cu^{2+} and iodide, which is a notorious fluorescence quencher due to heavy atom effect, receptor has been developed as fluorescence amplifier probe for iodide **[160]**.

Coumarin as signaling unit and acetamido thiophene ring as hydrogen donor, colorimetric and fluorometric coumarin thiophene based chemosensor, **44** for cyanide, fluoride and acetate was developed by Dede and Seferoglu *et al*., which showed naked eye colour change from light yellow to dark yellow as well as emission quenching in fluorescence spectrum **(Fig. 2.13)**. Other anions failed to induce any spectral changes. Anion binding properties carried out with spectrophotometric and ^{1}H NMR techniques showed that receptor exhibited more affinity towards cynide ion **[161]**.

A ratiometric fluorescent probe **45**, 2-(7-diethylamino-2-oxo-2H-1-benzopyran-3-yl)-7-hydroxyl-1-benzopyrylium **(Fig. 2.13)**, was constructed by hybridizing coumarin and benzopyrylium moieties for sensing sulphite ion. Nucleophilic addition of sulphite to electronically positive benzopyrylium moiety alters the π conjugation of receptor and thus ratiometric sensing is realized. A fluorescent emission peak centered at 640 nm blue shifted to 485 nm upon addition of sulphite ion. Preliminary study conducted by authors showed that receptor is cell permeable and can be used for detecting cellular sulphite **[162].** Another turn-on fluorescent and colorimetric sensor, **46** based on oxidized bis(coumarin)methane, **(Fig. 2.14)** was synthesized for fluoride ion detection in organic media, acetonitrile. Authors found that biscoumarin containing oxidizable H atom was unstable and spontaneously oxidize to conjugated product, however conjugated product can act as colour reporting group as well as binding affinity group containing acidic H donor moiety. Receptor exhibited absorbance band at 261 and 319 nm in UV-Visible spectra. Upon addition of fluoride

ion, a new absorbance band at 349 nm appeared, which was accompanied by naked eye colour change of receptor solution from colourless to yellow **[163]**.

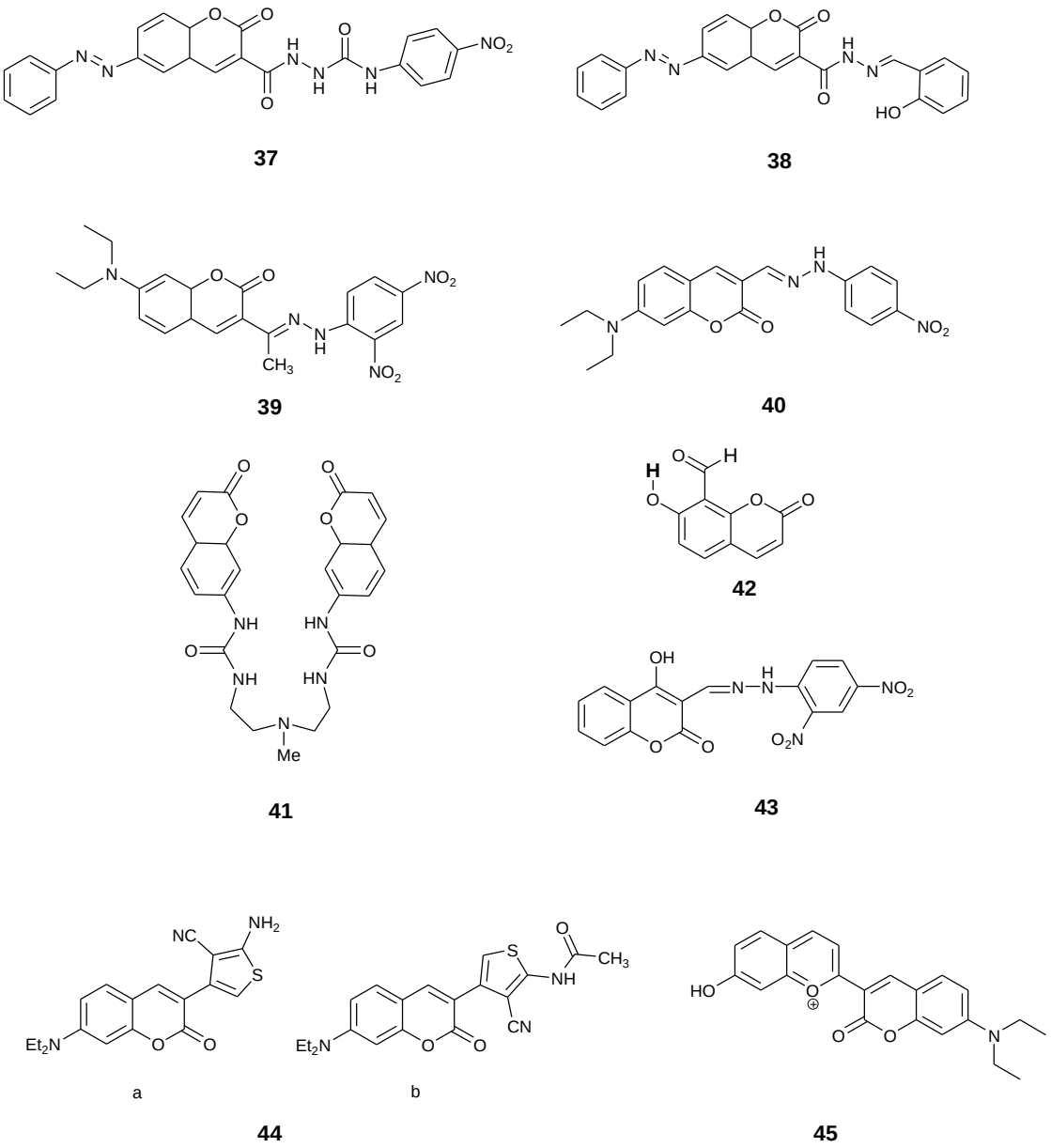


Fig. 2.13: Coumarin based colorimetric anion receptors 37-45

A chromogenic chemosensor, **47**, (2-(3-nitro-2-oxo-2H-chromen-4-ylamino)-3-aminomaleonitrile) was synthesized and documented for the detection of Al^{3+} and F^- by Kim *et al.* **[164]**. The fluoride recognition property of receptor was studied by UV-

Visible titrations, in which absorption bands at 338 and 441 nm disappeared, with simultaneous appearance of absorbance band at 510 nm. In the ^{1}H NMR spectrum of receptor, peaks at 9.96 and 8.07 ppm due to NH and NH_2 disappeared upon addition of 1 equivalent of fluoride ion (TBA salt). Authors concluded that colorimetric response was obtained due to the decrease in the intramolecular charge transfer band by a deprotonation process.

Mishra and coworkers developed a coumarin-thiazole based molecular scaffold, **48** which demonstrated fluorescence quenching upon interaction with Cu^{2+} ion, while remaining silent towards anions **[165]**. When this **48**- Cu^{2+} ensemble was tested for detection of anions, only fluoride ion enabled copper displacement as CuF_2 and led to fluorescent enhancement. Authors claimed that this naked eye sensitive "*On-Off-On*" sensing behavior of probe could mimic the function of sequential logic circuit at molecular level. Limit of detection was found to be 1.60 ppb and 2.12 ppb for Cu^{2+} and F^- ions, respectively.

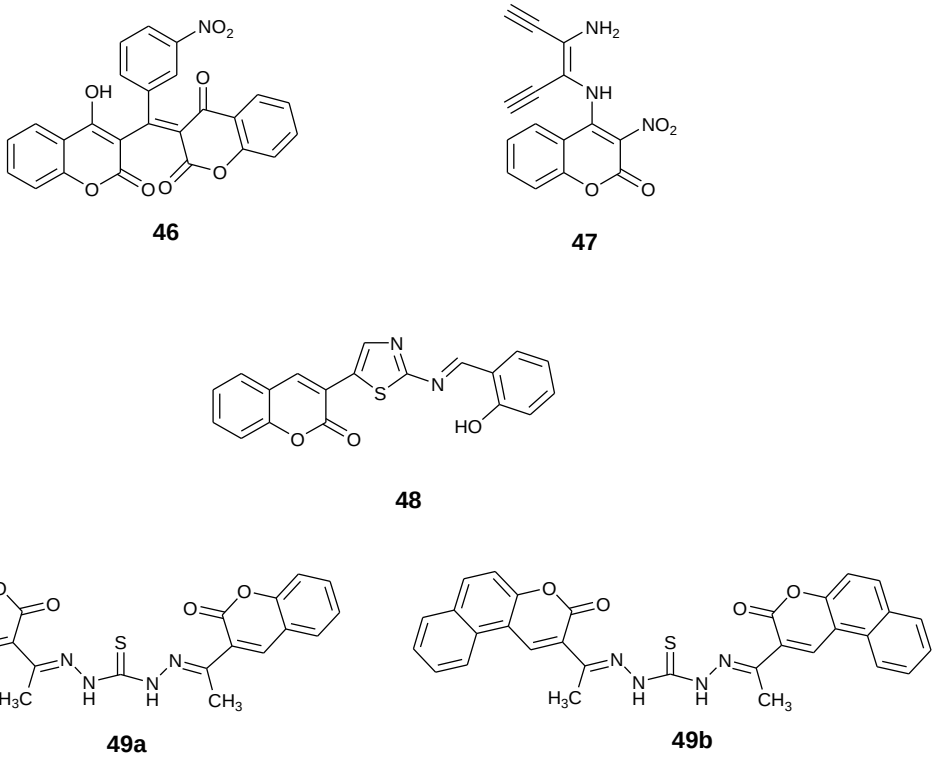


Fig. 2.14: Coumarin based chemosensor 46-49

Coumarin thiocarbonohydrazone receptors **49a-b** have been designed, synthesized and investigated for selective detection of fluoride ions in 2016 **[166]**. Receptor **49a** showed colour change from colourless to pink and 20-fold fluorescent enhancement upon addition of fluoride ion. Receptor **49b** displayed colour change from colourless to deep red and 5-folds fluorescence enhancement upon interaction with fluoride ion. This observation was attributed to deprotonation of NH proton, upon interaction with fluoride ion.

CONCLUSION

Anions have emerged as a valuable target for recognition and sensing due to major roles played by them in biological, environmental, medical and chemical industries. Several moieties have been synthesized to capture anions in this direction. Quest for advancement in the molecular structures for development of inexpensive and convenient method led to the exploration of heterocyclic moieties for binding anions. Exploitation of these moieties has served many purposes. A wide library of molecular structures can be created with the limitless derivatizing potential of heterocyclic moieties. Moreover, their use also imparted interesting photophysical properties to receptor systems to achieve naked eye sensing. Further, the heterocyclic scaffolds containing inbuilt acidic NH has been proven to possess potential to capture anions. The incorporation of other hydrogen bonding moieties, urea/thiourea and amide have been attempted to multiply interactions and it has been observed that wise placement of these moieties with heterocyclic units has generated elegant receptor systems.

The review sums up the heterocyclic derivatives as naked eye receptors documented so far, rely on signaling-binding unit approach, which exhibited colour changes on deprotonation by highly basic anions. Naked eye sensing is commendable with respect to real-life application. The remarkable progress has been achieved in developing heterocyclic derivatives as naked eye receptors. However, the key issues appeared are interference amongst similar basic anions and inability of receptor to function in aqueous media, which are essential for receptor to work in real life conditions.

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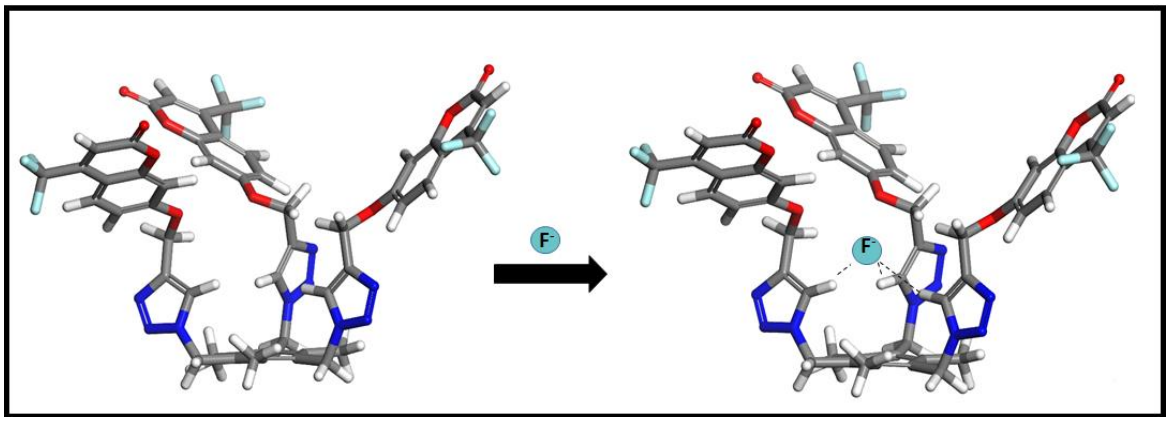
Chapter-3

Design and synthesis of C_3 symmetric tripodal triazoles: A facile click chemistry approach to anion sensing



Highlights:

- Receptor D, equipped with electron withdrawing trifluoromethyl group, binds fluoride ion in an effective C_3 symmetric topology exclusively by hydrogen bonding.
- Selective receptor for fluoride ion at a detection limit of 0.5 ppm, lower than WHO recommended level.
- Five fold fluorescence enhancement upon addition of fluoride ion in DMSO.
- Computational study supported the 3-up conformation of receptor, forming a cavity, where it fits fluoride ion by C-H--F^- hydrogen bonding interactions.

INTRODUCTION

The development of receptors that can detect fluoride ion selectively and exclusively has attracted a considerable attention because of their potential application in many areas ranging from environmental monitoring, medical diagnosis to industrial purposes **[1-3]**. As an essential micronutrient of body, fluoride ion is useful in dental care and osteoporosis **[4]**. The US Public Health Service stated the optimal level of fluoride to be 1 mg per day **[5]**. However, excessive and unnecessary ingestion of fluoride ion by using fluoridated water and dental products is toxic to biological tissues and causes abdominal pain, nausea, coma, dental or skeletal fluorosis, gastric disorders and nephrotoxic changes **[6-8]**. This has inspired the chemists to design and develop new binding motifs which can mimic the efficiency of anion binding based biological processes and are capable of recognizing fluoride ion selectively by the employment of non-covalent interactions **[9-14]**.

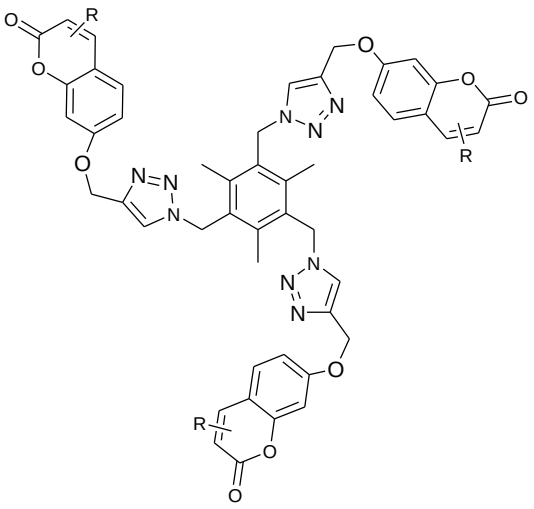
The creation of an artificial receptor which is preferentially selective towards fluoride ion requires the presence of multiple interactions between anion and receptor in a complementary approach **[15-16]**. The topology of receptor must be organised to complement the size and shape of the anion to gain selectivity **[17]**. Tripodal receptors constitute a special class of ionophores which consist of multiarmed ligands with each arm containing a functional group, capable of binding anion **[18]**. Tripodal molecular platform allows rational control of selectivity by adjusting its rigidity of arms and its cavity size, thus these possess advantage in terms of selectivity over monopodal and even dipodal receptors **[19]**. Due to these advantages, design of artificial tripodal receptors is an active thrust area amongst researchers **[20]**.

Molecular receptors have been designed containing different combinations of N-H and/or O-H hydrogen bond donor moieties *viz.*, pyrrole **[21]**, indole **[22]**, imidazole **[23]**, benzimidazole **[24]**, urea **[25]**, thiourea **[26]** and amides **[27]** which coordinate and bind fluoride ion through hydrogen binding interactions. The inherent magnitude of N-H and O-H bond's dipole moment is a significant contributing factor to hydrogen bond donor strength **[28-29]**, whereas, owing to lower electronegativity of carbon atom, C-H hydrogen bond donor as a site for anion binding is scarce **[30]**. In 1,2,3-triazoles, the electronegativity of sp^2 carbon of triazole ring is enhanced by three nitrogen atoms nested together on one side of ring, which imparts necessary

polarization to C-H bond, making it suitable to act as hydrogen bond donor group **[31]**. Studies on macrocyclic triazolophanes **[32]**, and triazole **[33]** containing molecules have shown that C-H---X^- hydrogen bonds are strong enough to play major roles in anion coordination chemistry.

In view of above facts, we have synthesized C_3 symmetric tripodal receptors **A-E** for selective recognition of fluoride ion *via* clicking variously substituted coumarin alkyne with tripodal azide **(Fig. 3.1)**. These receptors are crafted on a hexasubstituted aryl core with alternate three methyl arms and three coumarin-triazole arms. These rationally designed coumarin-triazole arms, protruding upwards from aryl core, form a "3-up" or cone shape to fit spherical fluoride ion in it. Anion binding studies have been meticulously done by UV-Visible, fluorescence, ^{1}H NMR and ^{19}F NMR titrations, which indicated that only receptor **D** having trifluoromethyl group in coumarin scaffold shows binding interaction with fluoride ion. Computational study conducted under density functional theory also validated the experimental results.

The following type of compounds have been prepared and characterized by FTIR, ^{1}H NMR, ^{13}C NMR and HRMS data **(Fig. 3.1)**



A-E

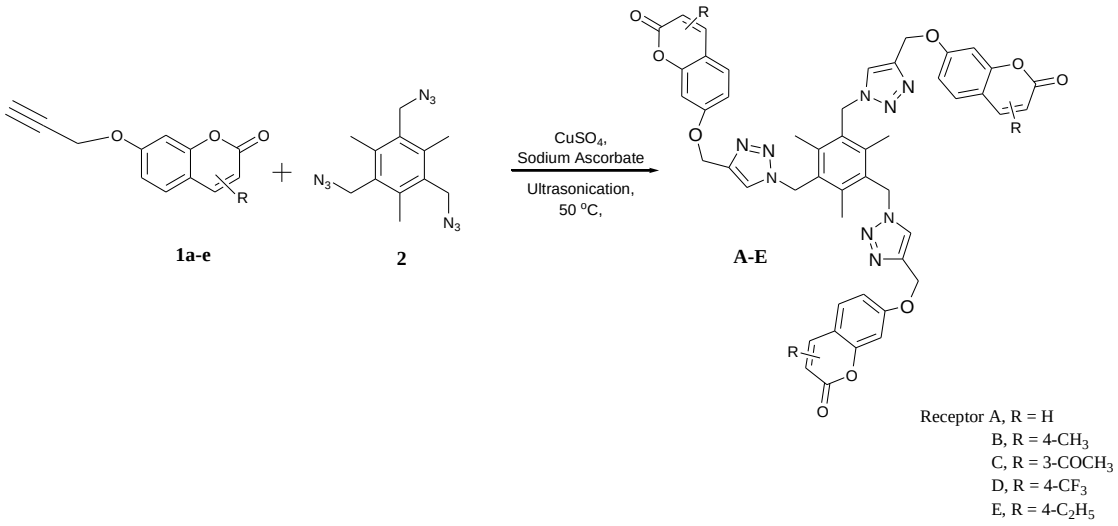
Receptor A, R = H
B, R = 4-CH_3
C, R = 3-$COCH_3$
D, R = 4-CF_3
E, R = 4-C_2H_5

Fig. 3.1: Molecular representation of receptors A-E

RESULTS AND DISCUSSION

Tripodal receptors have been designed on a hexasubstituted aryl core with coumarin-triazole (CT) moieties as its three arms, with the rational to enhance hydrogen donor groups and increase the affinity of receptor towards anionic species. These three arms protrude upwards from the core, which form a cone shape cavity, inside which three C-H hydrogen donor groups come in proximity.

Variuosly substituted alkynes, **(**un)substituted-7-prop-2-ynyloxy-chromen-2-one **(1a-e)** and C_3 symmetric azide, 1,3,5-tris-azidomethyl-2,4,6-trimethyl-benzene **(2)** were synthesized using literature methods **[34-35]**, which upon Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition reaction gave desired products, 1,2,3- Triazoles **A-E (Scheme 3.1)**.



Scheme 3.1: Synthesis of compounds A-E

All the receptors synthesized were characterized by standard spectroscopic techniques (FTIR, ^{1}H-NMR, ^{19}F NMR, ^{13}C-NMR and HRMS). In the FTIR spectra of receptors, **A-E**, broad absorption band in the region 3010-3005 cm^{-1} and 2952-2825 cm^{-1} are obtained due to C-H stretching vibration in methyl and aromatic C-H, respectively. The disappearance of absorption band at 3313 and 2100 cm^{-1} due to ΞC-H and CΞC stretching vibrations, present in compounds **1(a-e)** indicates towards the possible formation of receptors **A-E**. Absorption bands at 1710, 1608 and 1443 cm^{-1} may be attributed to C=O, C=C and C=N stretching vibrations, respectively. Besides these,

receptor **D** also shows characteristic strong absorption band at 1116 cm^{-1} due to C-F stretching frequency of trifluoromethyl group **(Table 3.2, Fig. 3.2)**.

The ^{1}H NMR spectra of receptors **A-E** exhibit sharp singlet at δ 8.47 ppm due to presence of three triazole C-H protons. A multiplet from δ 6.12 to 7.49 ppm is observed for aromatic protons. Peaks at δ 4.40 and 5.70 ppm may be attributed to methylene protons. All receptors display a singlet at δ 2.48 ppm due to presence of methyl protons. Receptor **B** shows a singlet at δ 1.23 due the presence of a methyl group in coumarin ring. A singlet at δ 2.30 was observed due to $COCH_3$ protons in receptor **C**. The ^{1}H NMR spectrum of receptor E displays a multiplet and triplet at δ 1.80 and 2.30, respectively due to presence of ethyl group in coumarin ring. The ^{13}C NMR spectra of receptors **A-E** show characteristic peaks at δ 161 (C=O) and 155 ppm (C=N). The ^{19}F NMR spectrum of receptor **D** show a singlet at δ - 84.20 ppm due to presence of trifluoromethyl group. **(Table 3.2, Fig. 3.3-3.4).**

Further confirmation was provided by HRMS data which gave an accurate molecular ion peak $[M+H]^{+}$ at m/z 886.8768, 928.9611, 1012.9991, 1090.8737 and 971.0389 that agrees well with their calculated molecular formula **(Table 3.2, Fig. 3.5)**.

The names and m.p.'s of all the synthesized receptors **(A-E)** are given in **Table-3.1**. The IR, ^{1}H NMR and mass spectral data of all synthesized compounds are shown in **Table-3.2.**

The IR, ^{1}H NMR, ^{13}C NMR and mass spectrum of receptor **D** are given in **Fig. 3.2, 3.3, 3.4** and **3.5,** respectively.

Table-3.1: Names and m.p.'s of 7',7''-(((((2,4,6-trimethylbenzene-1,3,5-triyl)tris (methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy)) tris(substituted-2H-chromen-2-ones) A-E

Compd No.	Name	M.P. (^{o}C)
A	7,7',7"-(((((2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(2H-chromen-2-one)	212-214
B	7,7',7"-(((((2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(4-(methyl)-2H-chromen-2-one)	198-200
C	7,7',7"-(((((2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(3-(acetyl)-2H-chromen-2-one)	187-189
D	7,7',7"-(((((2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(4-(trifluoromethyl)-2H-chromen-2-one)	215-217
E	7,7',7"-(((((2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(4-(ethyl)-2H-chromen-2-one)	189-191

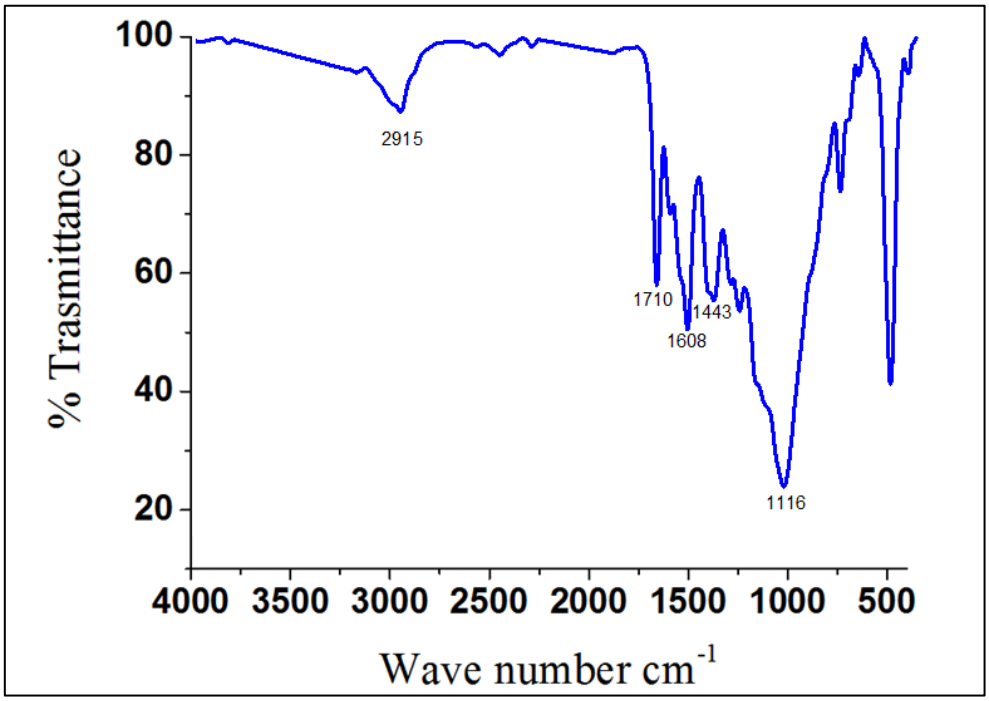


Fig. 3.2: FTIR spectrum receptor D

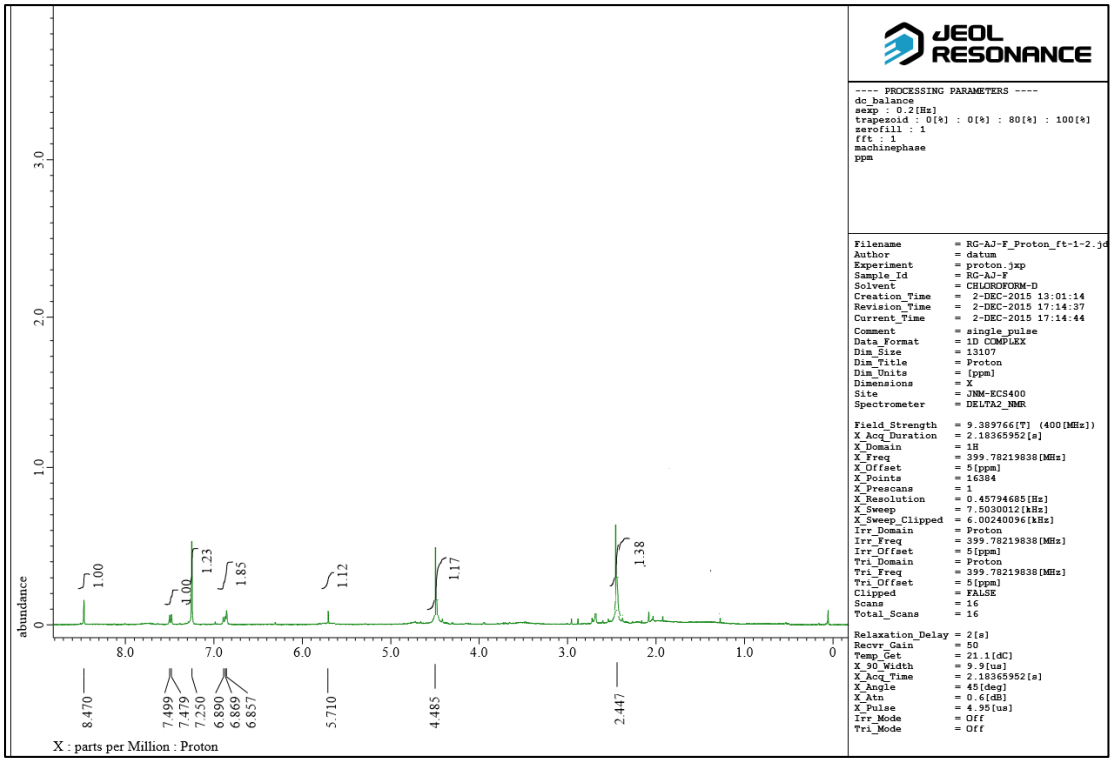


Fig. 3.3: ^{1}H NMR spectrum of receptor D

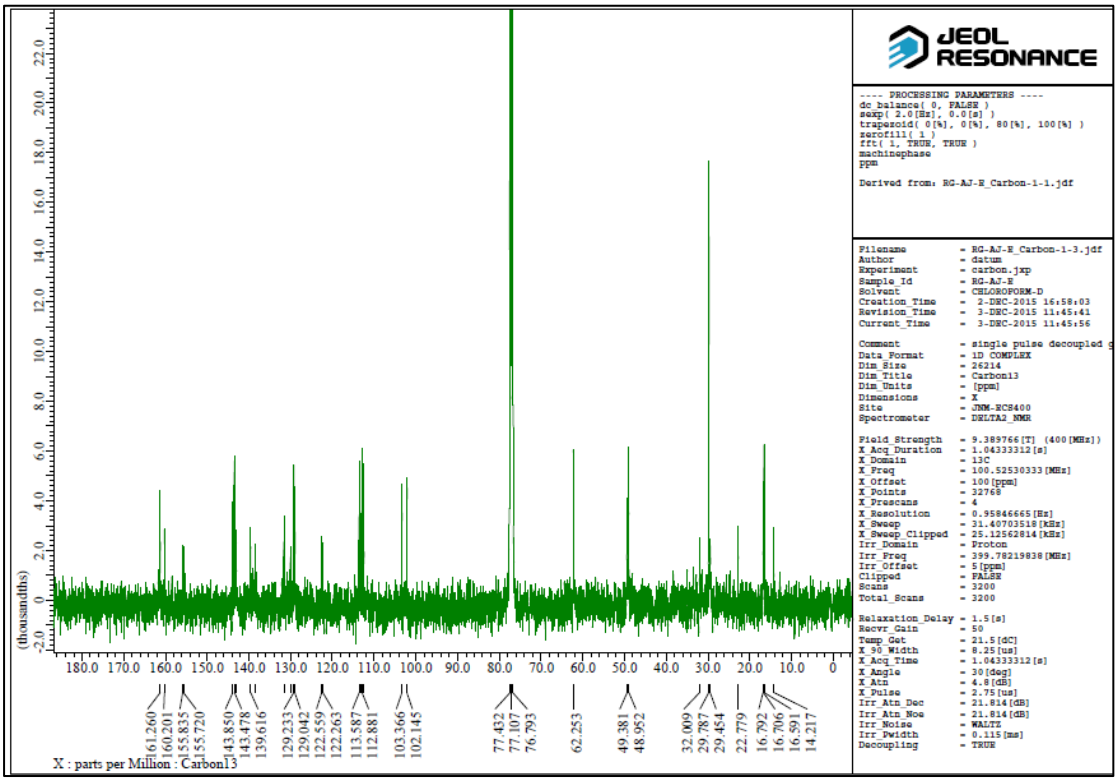


Fig. 3.4: ^{13}C NMR spectrum of receptor D

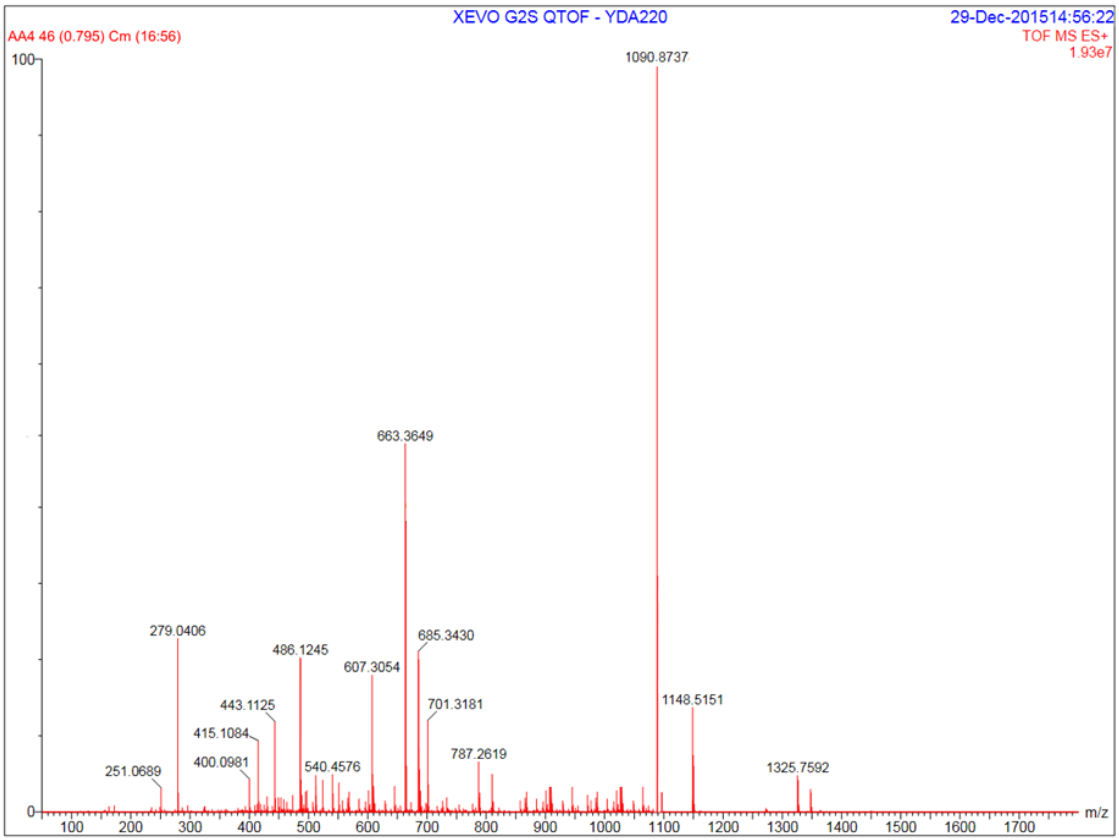


Fig. 3.5: ESI-mass spectrum of receptor D

Table-3.2: Spectral data of 7',7''-(((((2,4,6-trimethylbenzene-1,3,5-triyl)tris (methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(substituted-2H-chromen-2-ones) A-E

Compd No.	**FTIR** (KBr, cm^{-1})	**^{1}H NMR** ($CDCl_3$, 500 MHz, δ ppm)	**^{13}C NMR** ($CDCl_3$, 100 MHz, δ ppm)	**HRMS** $[M+H]^+$
A	3010 (Ar-H), 2921 (Ali-H), 1705 (C=O), 1620 (C=N), 1430 (N=N), 1058 (C-O)	2.48 (s, 9H, $-CH_3$), 4.30 (s, 6H, NCH_2), 5.69 (s, 6H, OCH_2), 6.23-6.88 (m, 15H, Ar-H, pyran-H), 7.62 (s, 3H, triazole C-H)	19.04, 48.34, 62.92, 101.20, 102.80, 112.34, 114.14, 122.19, 131.23, 138.49, 155.40, 162.92	886.8768 Calculated for $C_{48}H_{39}N_9O_9$: 885.8782.
B	3005 (Ar-H), 2934 (Ali-H), 1715 (C=O), 1645 (C=N), 1443 (N=N), 1063 (C-O)	1.23 (s, 9H, $-CH_3$), 2.60 (s, 9H, $-CH_3$), 4.38 (s, 6H, NCH_2), 5.69 (s, 6H, OCH_2), 6.11-6.9 (m, 12H, Ar-H, pyran -H), 7.47 (s, 3H, triazole C-H)	29.75, 49.44, 62.16, 102.10, 103.40, 111.48, 113.44, 125.79, 130.94, 131.63, 138.59, 139.38, 152.84, 155.1, 162.12	928.9611 Calculated for $C_{51}H_{45}N_9O_9$: 927.9579
C	3008 (Ar-H), 2890 (Ali-H), 1705 (C=O), 1615 (C=N), 1423 (N=N), 1069 (C-O)	2.30 (s, 9H, $-COCH_3$), 2.47 (s, 9H, $-CH_3$), 4.38 (s, 6H, $-NCH_2$), 5.68 (s, 6H, $-OCH_2$), 6.12-6.91 (m, 12H, Ar-H, pyran -H), 7.48 (s, 3H, triazole C-H)	62.26, 102.15, 105.26, 112.36, 114.14, 125.75, 129.32, 130.94, 138.58, 152.37, 161.16	1012.9991 Calculated for $C_{54}H_{45}N_9O_{12}$: 1011.9882
D	3010 (Ar-H), 2948 (Ali-H), 1710 (C=O), 1608 (C=N), 1429 (N=N), 1116 (C-F), 1074 (C-O)	2.08 (s, 9H, $-CH_3$), 4.48 (s, 6H, $-NCH_2$), 5.71 (s, 6H, $-OCH_2$), 6.84-7.49 (m, 12H, Ar-H, pyran -H), 8.47 (s, 3H, triazole C-H)	62.26, 102.15, 105.26, 112.36, 114.14, 125.75, 129.32, 130.94, 138.58, 152.37, 155.15, 161.16	1090.8737 Calculated for $C_{51}H_{36}F_9N_9O_9$: 1089.8721
E	3013 (Ar-H), 2825 (Ali-H), 1685 (C=N), 1495 (N=N), 1082 (C-O)	1.80 (m, 6H, $-CH_2$), 2.30 (t, 9H, $-CH_3$), 2.60 (s, 9H, $-CH_3$), 4.78 (s, 6H, $-NCH_2$), 5.69 (s, 6H, $-OCH_2$), 6.21-6.88 (m, 12H, Ar-H, pyran-H), 7.62 (s, 3H, triazole C-H)	49.00, 101.18, 104.86, 114.52, 124.72, 127.42, 132.10, 138.24, 154.56, 160.46	971.0389 Calculated for $C_{54}H_{51}N_9O_9$:970.0376

Anion binding studies

Anion binding studies of receptors **A-E** (1×10^{-4} M) were conducted by UV-Visible, fluorescence, ^{1}H NMR and ^{19}F NMR spectroscopic titrations to gain insight into anion-receptor interactions at room temperature with different anions *viz.*; fluoride, chloride, bromide, iodide, acetate, nitrate and dihydrogen phosphate as tetrabutylammonium salts (TBA).

UV-Visible titrations

UV-Visible spectra of receptors **A-E** (1×10^{-5} M in DMSO) were recorded upon addition of different anions. Receptors **A-C** and **E** failed to exhibit any spectral change even at high anion concentration (10^{-3} M). Only receptor **D** was found capable of exhibiting spectral change in presence of fluoride ion and therefore its fluoride binding property was examined further.

UV-Visible spectra of receptor **D** (1×10^{-5} M in DMSO) exhibited absorption band centred at 360 nm and 455 nm. Interestingly, upon addition of fluoride anion (TBA salt, 1×10^{-4} M), band at 360 nm completely disappeared and band at 455 nm blue shifted by 15 nm to form a new band at 440 nm, which indicated association between receptor **D** and fluoride ion. No obvious spectral changes were observed with other anions **(Fig. 3.6)**, which proves selectivity of receptor for fluoride ion. This implies that incorporation of electron withdrawing group, trifluoromethyl group boosted the binding affinity of receptor **D** for fluoride ion, while electron releasing groups have decreased the binding abilities in other receptors. Similar finding has also been reported by other research group **[36]**.

To evaluate the effect of concentration of fluoride ion on UV-Visible spectrum, the UV-Visible titration was carried out with increasing concentration of fluoride ion from 1×10^{-5} M to 1×10^{-4} M in DMSO **(Fig. 3.6b)**. Upon addition of fluoride ion, intensity of new band at 440 nm increases with increasing concentration of fluoride ion. An isosbestic point at 375 nm was observed, which clearly shows the formation of stable complex between receptor and fluoride ion. The results of these spectral changes could be rationalized on the basis of hydrogen bond interactions between fluoride anion and **D.**

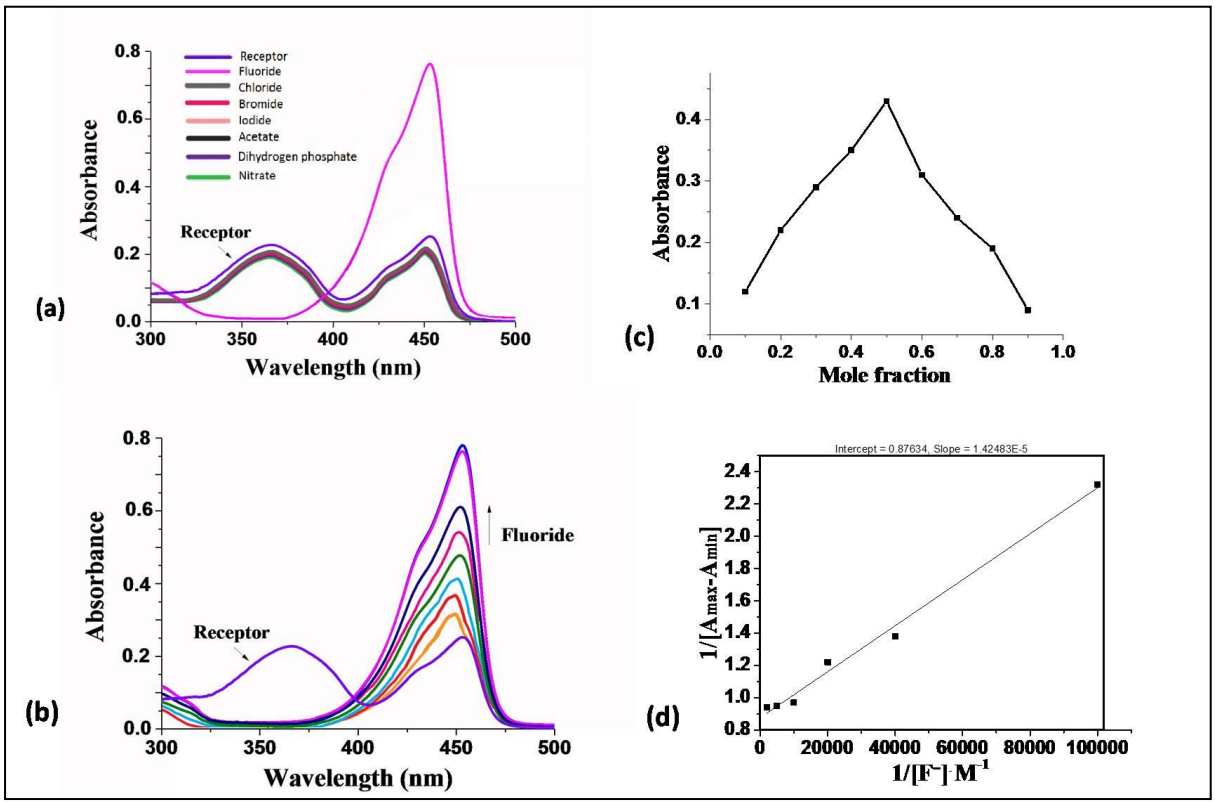


Fig. 3.6: (a) UV-Visible spectra of receptor D (1×10^{-5} M in DMSO) on titration with different ion (TBA salt, 1×10^{-4} M in DMSO) (b) UV-Visible spectra of receptor D (1×10^{-5} M in DMSO) on titration with fluoride ion (TBA salt) from 1×10^{-5} to 1×10^{-4} M in DMSO (c) Jobs Plot with receptor D (1×10^{-2} M in DMSO) and fluoride (TBA salt) 1×10^{-2} M in DMSO (d) Fitting curve of Benesi Hildebrand equation

Stoichiometric ratio of the complexes formed between fluoride ion and receptor was determined using continuous variation method (Job's Plot) **[37]**, where the initial concentration of both receptor and fluoride ion salt were kept same (1×10^{-4} M in DMSO). The molar fraction of fluoride/ (receptor + fluoride) was continuously varied. At the molar fraction of 0.50, the absorbance reached its maxima in UV-Visible spectra, revealing that receptor forms 1:1 complex with fluoride ion **(Fig. 3.6)**. It was also proved by mass spectra of receptor **D** with fluoride ion (TBA salt), which exhibited a peak at 1109.8847 [Calcd for Receptor **D** + F^- +H^+: 1109.8621] **(Fig. 3.7).**

The binding constant of receptor **D** with fluoride was evaluated by Benesi Hildebrand plot **[38]**. The binding constant K, calculated from the graph **(Fig. 3.6)** was found to be 6.1 x 10^4 M^{-1}.

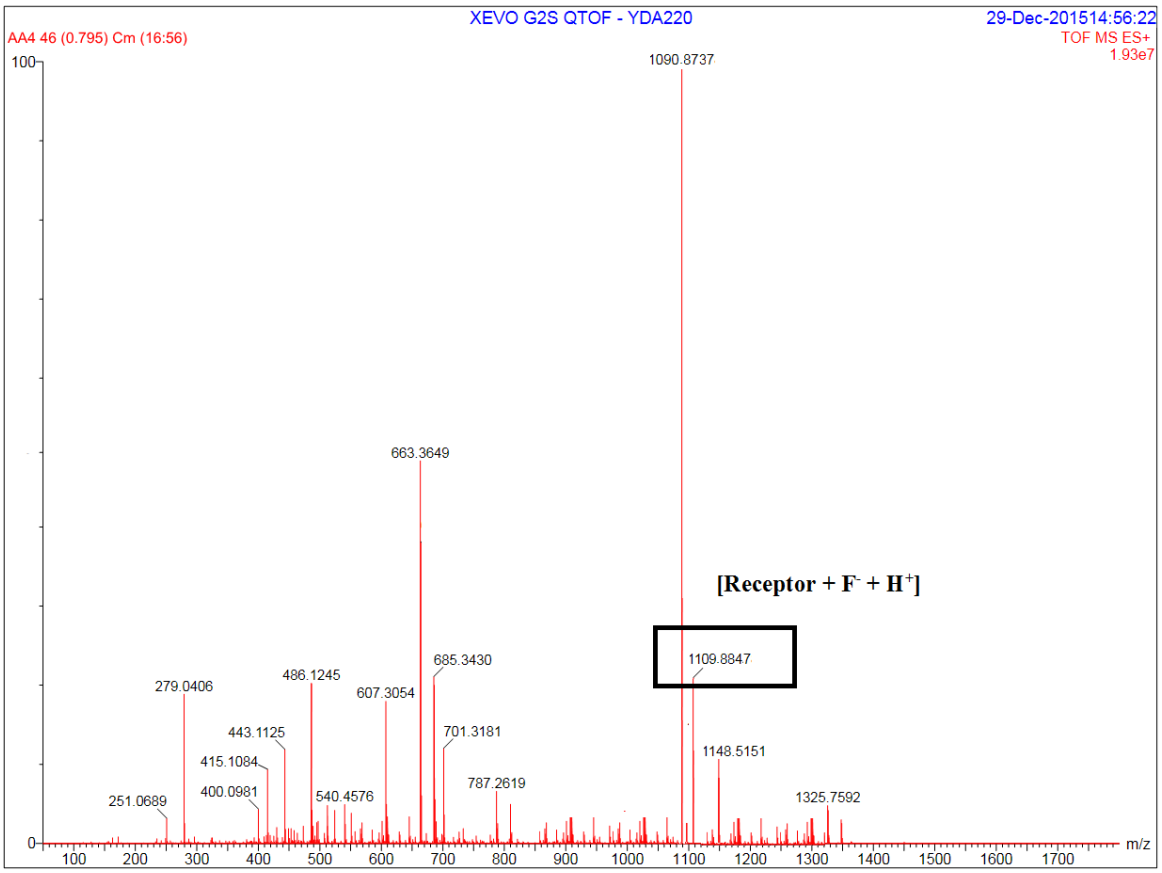


Fig. 3.7: ESI mass spectrum of receptor D- fluoride ion complex

Fluorescence titration experiment

To corroborate well with the results obtained by UV-Visible titrations, the fluorescence titration was carried out with anions as TBA salts. Receptor **D** (1×10^{-5} M in DMSO) exhibited fluorescence emission at 480 nm, when excited at 340 nm. Quantitative investigation was conducted by adding 10 receptor equivalents of each anion salt into receptor **D** solution. Five fold fluorescence enhancement was witnessed only with fluoride ion **(Fig. 3.8)**, while other anions did not bring about any appreciable change. It was established that receptor **D** can selectively bind fluoride over other anions.

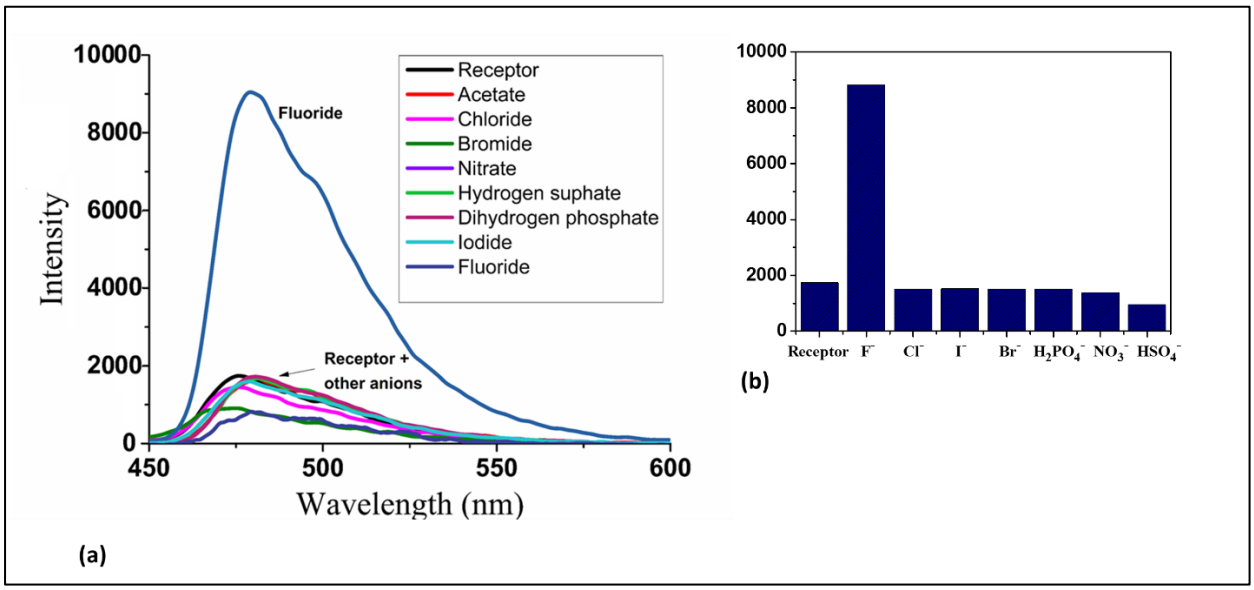


Fig. 3.8: (a) Fluorescence spectra of receptor D (1×10^{-5} M in DMSO) with different anions (TBA salt, 1×10^{-4} M in DMSO) (b) Comparative fluorescence behaviour of receptor D (1×10^{-5} M in DMSO) upon addition of anions (TBA salts)

Comprehensive fluoride ion binding study was performed by preparing different solutions of varying concentration of fluoride anion salt from 1×10^{-6} to 1×10^{-4} M in DMSO. Detailed study with fluoride revealed that on gradual addition of fluoride from 1 to 10 receptor equivalents, intensity of receptor peak at 480 nm increased from 1800 to 9000, which suggested binding interaction between receptor and fluoride ion **(Fig. 3.9)**. The enhancement of fluorescence intensity may be due to increase in rigidity of receptor's structure upon fluoride complexation. Free receptor could rotate freely, but after binding with fluoride ion, the rotation of receptor was markedly restricted **[39]**.

The anti-interference study of receptor D for fluoride ion was carried out by adding 1×10^{-4} M of fluoride ion (TBA salt) with each anion (1×10^{-3} M in DMSO). It is specially noted that the addition of other anions enhanced the fluorescence intensity in the similar manner as fluoride ion alone, which indicated that the presence of other anions does not interfere with the fluorescence enhancement of receptor by fluoride ion as shown in **Fig. 3.10**. These results clearly imply that the receptor **D** shows a high selectivity towards fluoride ion in presence of other interfering anions.

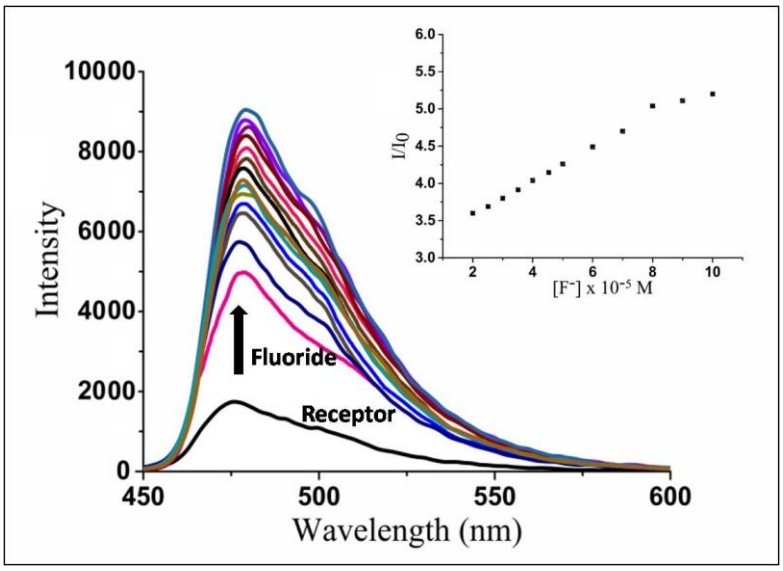


Fig. 3.9: Fluorescence spectra of receptor D (1×10^{-5} M in DMSO) with fluoride ion (TBA salt, 1×10^{-6} to 1×10^{-4} M in DMSO) (Inset) Change in fluorescence intensity at 480 nm wavelength upon addition of fluoride ion (TBA salt, 1×10^{-6} to 1×10^{-4} M in DMSO)

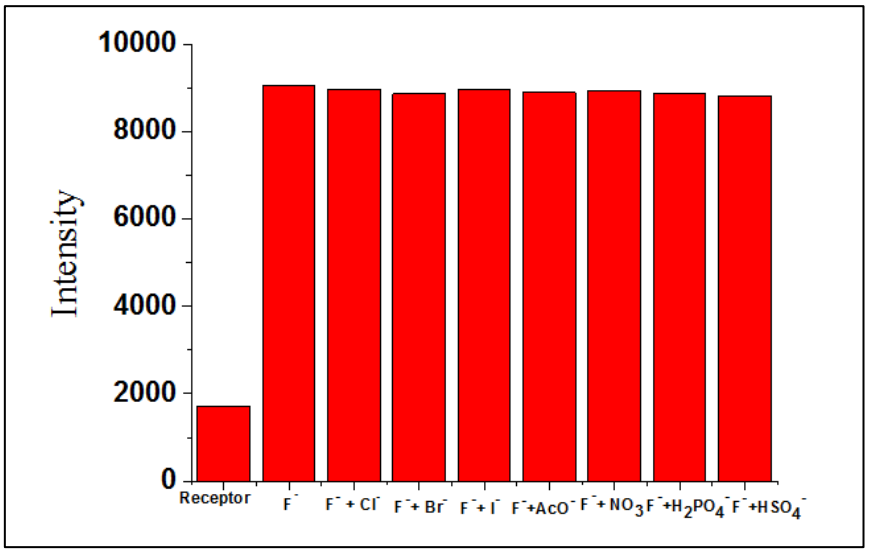


Fig. 3.10: Variation of fluorescence intensity of receptor D (1×10^{-5} M in DMSO) in the presence of fluoride ion (1×10^{-4} M in DMSO) with coexisting competitive anions (1×10^{-3} M in DMSO)

Calculation of detection limit

The calibration curve of receptor **D** was plotted between fluorescence intensity and fluoride ion concentration (1×10^{-5} M to 1×10^{-4} M in DMSO) **(Fig. 3.11)**, which

showed a linear dependence of emission intensity with fluoride ion concentration (R^2 = 0.98). The detection limit (DL) of receptor **D** for fluoride ion was determined from the following equation **[40]**:

DL = 3 x Sbl / S,

Where Sbl is the standard deviation of y-axis; S = slope of the calibration curve.

The detection limit calculated is 2.6 x 10^{-5} M or 0.5 ppm, which proves the sensitivity of receptor towards fluoride ion.

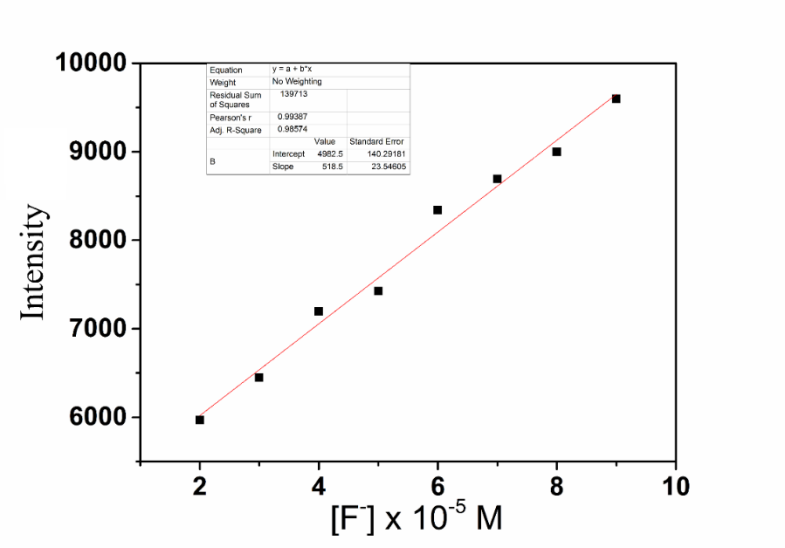


Fig. 3.11: Calibration curve of receptor D (1 × 10^{-5} M in DMSO) against increasing concentration of fluoride ion (1 × 10^{-5} M to 1 × 10^{-4} M in DMSO)

^{1}H NMR studies

In order to obtain an insight into fluoride binding event, the interaction of receptor **D** with fluoride was explored with ^{1}H-NMR titration, performed using DMSO-d_6 solvent. Titration was carried out by adding calculated amount of TBAF (2.5, 5, 7.5 and 10 receptor equivalents in DMSO-d_6) into receptor **D** (1 × 10^{-2} M in DMSO-d_6). C-H peak of triazole appeared at δ 8.47 ppm, which upon addition of 2.5 receptor equivalents of fluoride ion, shifted downfield by 0.19 ppm. Further at higher concentration (10 equivalents) peak shifted downfield by 0.5 ppm, with simultaneous decrease in intensity **(Fig. 3.12)**. The downfield shifting of peak corresponding to C-H protons indicates towards hydrogen binding interactions between receptor and

fluoride ion. Thus receptor binds fluoride ion in a cavity formed by its three functionalized arms in a close proximity, as depicted in **Scheme 3.2**.

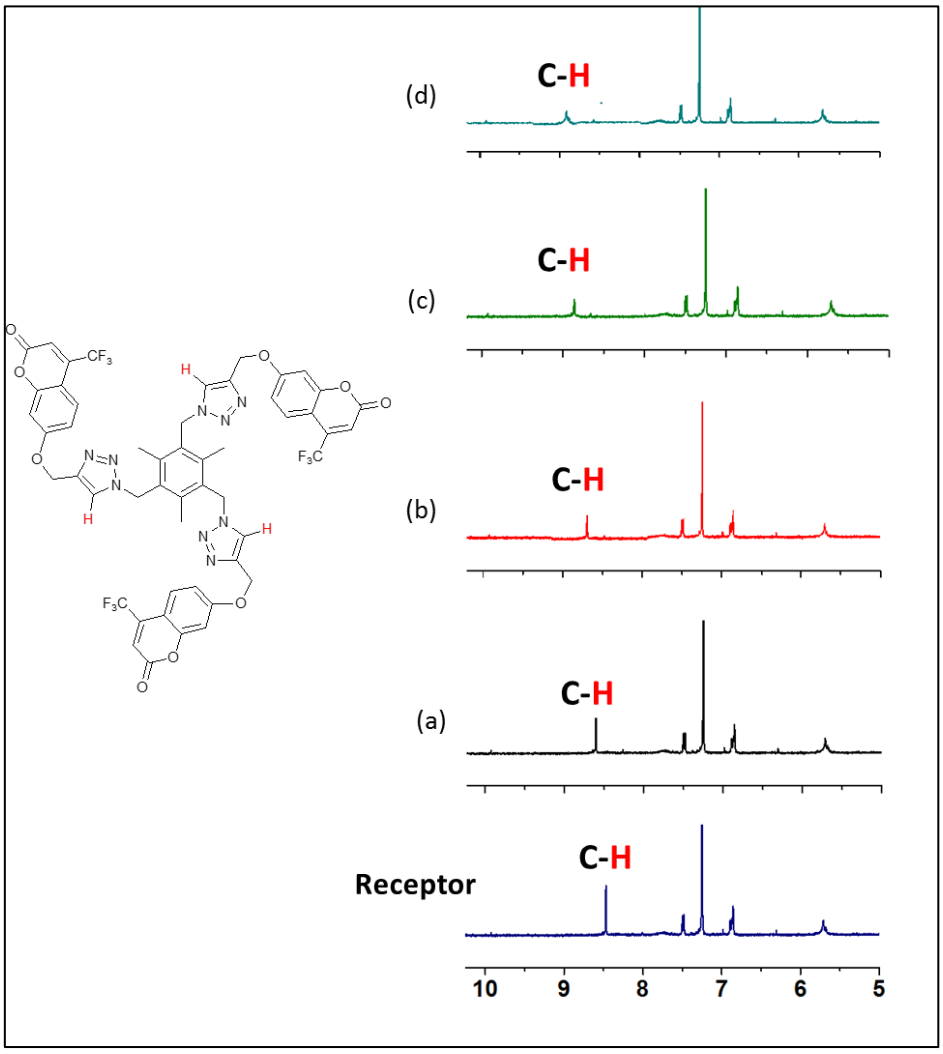


Fig. 3.12: Partial ^{1}H NMR (400 MHz) spectra of receptor D in DMSO-d_6 (1×10^{-2} M) in the presence of (a) 2.5 (b) 5 and (c) 7.5 and (d) 10 equivalents of TBAF in DMSO-d_6

^{19}F NMR titration

The interaction between receptor **D** and fluoride ion was also investigated using ^{19}F NMR titration. The ^{19}F NMR spectrum 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. Receptor **D** displayed a singlet at δ -84.20 ppm due to trifluoromethyl group in the molecular structure. Upon addition of 1 equivalent of receptor **D**, peak at -102 ppm shifted upfield by δ 2.98 ppm and intensity of peak decreased and finally, peak due to F^- ion

disappeared to a large extent, which indicates the existence of binding interaction between receptor and fluoride ion **(Fig. 3.13) [41].**

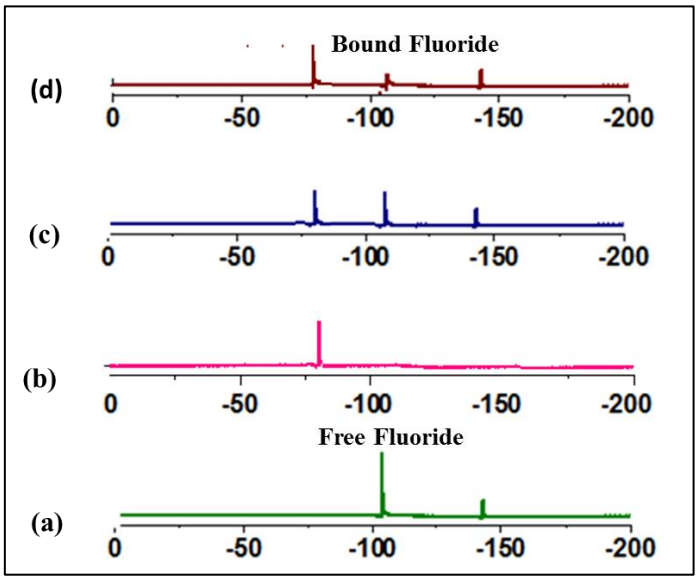
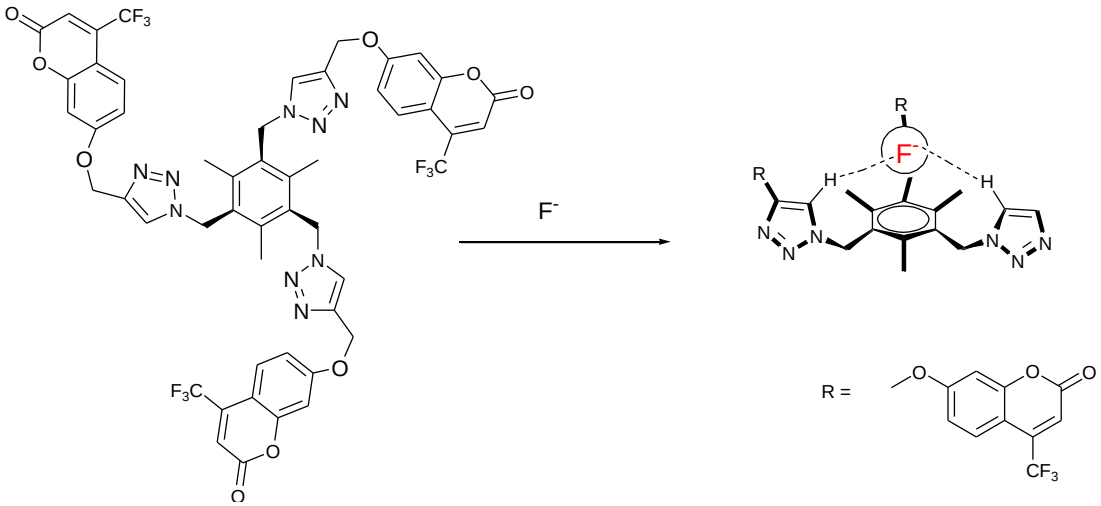


Fig. 3.13. Partial ^{19}F NMR spectra of (a) TBAF.3H_2O (1 x 10^{-2} M) in DMSO-d_6 (b) receptor D (1 x 10^{-2} M) in DMSO-d_6(c) TBAF.3H_2O + 0.5 equivalent receptor D in DMSO-d_6 (d) TBAF.3H_2O + 1 equivalent receptor D in DMSO-d_6



Scheme 3.2: Plausible mechanism of binding interactions between receptor D and fluoride ion

Computational Study

The experimental results have been thoroughly confirmed on the basis of theoretical investigation using Materials Studio DMoL^3 (version 8.0). The receptor and its adduct

with fluoride ion were optimized at the level PWD DND 4.4 basis set. The highest occupied model (HOMO), the lowest unoccupied model (LUMO) and the energy gap ($\Delta E_{HOMO-LUMO}$) have also been investigated at the same level of theory. Graphics were obtained using Materials Studio visualizer **[42-43]**.

The three arm of receptor can arrange in two possible conformations around an aryl core to bind fluoride ion, firstly, a less symmetric conformation (2-up), in which only two arms orient in one direction and prefers to binds fluoride ion by two of the three arms. Second, C_3 symmetric conformation, in which, all three arms direct in same orientation around an aryl core (3-up), giving rise to a cavity and uses all three arms of the tripod to bind fluoride ion **(Fig. 3.14)**. It was found that 3-up (C_3 symmetric conformation) is more stable by 21 kcal/mol than 2-up conformation of the receptor and receptor-fluoride adduct exits predominantly in 3-up conformation. The DFT optimized structure of C_3 symmetric receptor shows that fluoride ion resides low down within the cavity formed by three arms and is hydrogen bonded to the three triazole C-H protons, as anticipated **(Fig. 3.14)**. The hydrogen bonding distance C-H$^{\cdots}$F^{-} in optimized geometry ion was found as 2.7 Å, which is comparable to the reported experimental values observed in the fluoride complexes **[44-45].** The total energy of receptor-fluoride complex (-111631.388 eV) is found lower than the total energy of receptor (-108926.67 eV) alone in solvent, DMSO, which suggests formation of stable complex between receptor and fluoride ion **[46].**

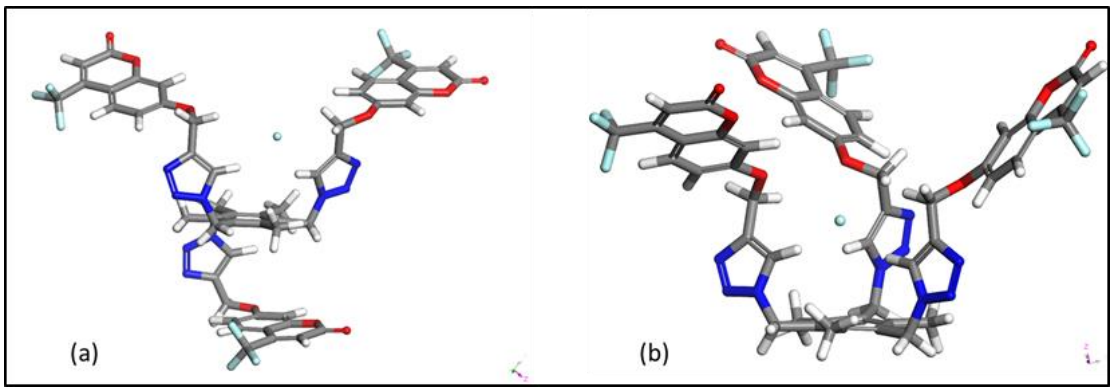


Fig. 3.14: Optimized structures of tripodal receptor (a) 2-up (b) 3-up conformations

The optimized structures of free receptor **D** and receptor-fluoride ion complex with the distribution of their HOMO and LUMO levels are represented in **Fig. 3.15**. The energy difference between HOMO and LUMO were calculated for receptor and

receptor-fluoride ion complex and obtained as 2.705 eV and 1.802 eV, respectively. A significant decrease in band gap by 0.903 eV confirms the presence of intramolecular charge transfer transitions during fluoride ion binding process **[47]**.

Further evidence of hydrogen bonding interaction was provided by triazole C-H bond length. The optimized structure of free receptor showed C-H bond length as 0.92 Å. After fluoride ion binding optimization, it was calculated as 0.934 Å. This observed bond elongation points towards hydrogen abstraction by fluoride ion **[48]**.

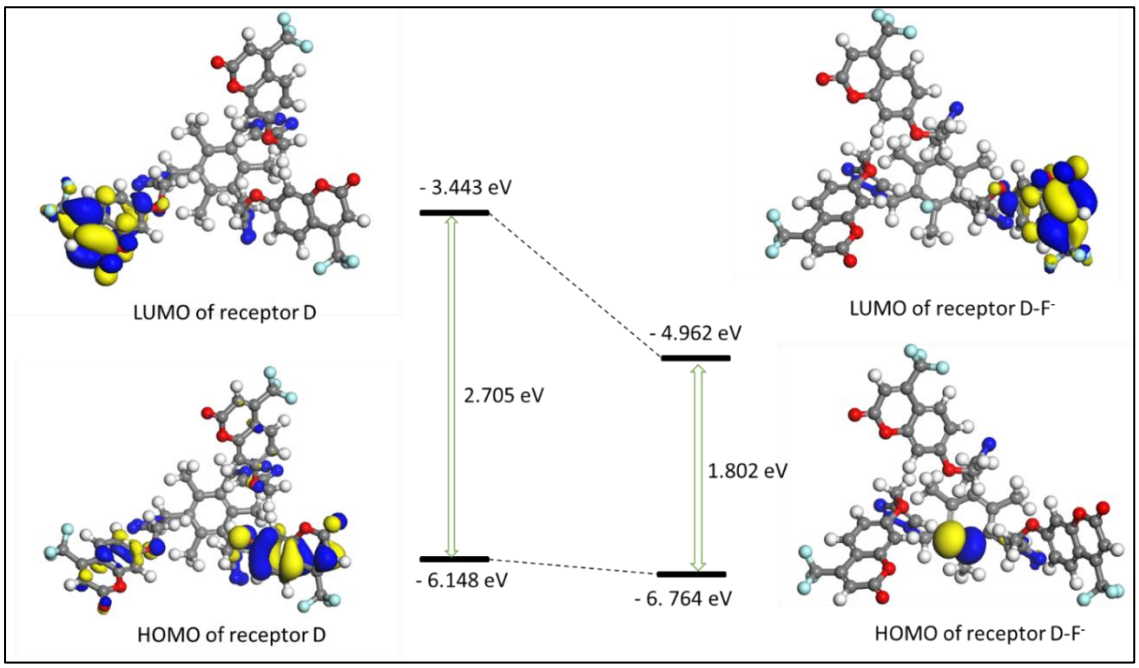


Fig 3.15: **HOMO and LUMO energy levels and the interfacial plots of the orbitals for free receptor D and receptor D-fluoride complex**

Conclusion

Receptor for selective fluoride ion detection has been rationally designed by incorporating coumarin rings into preorganised benzene based tripodal receptors with arms comprising triazole C-H hydrogen bond donor groups. The three arms of receptor orient in same direction bringing the coumarin-triazole arms into close proximity with each other to form a cavity, where it binds fluoride ion *via* hydrogen bonding interaction with C-H protons.

EXPERIMENTAL

1. All chemicals were purchased from commercial sources and were used as received. All solvents were dried before use. Dimethyl sulfoxide was dried over calcium hydride and distilled.
2. Melting points were determined in open glass capillaries and are reported uncorrected.
3. FTIR spectra were recorded on a Perkin Elmer Spectrum Two spectrophotometer and Bruker ALPHA FTIR with platinum ATR using pressed KBr discs in the region of 400 – 4000 cm^{-1}.
4. ^{1}H and ^{13}C NMR were recorded on a Jeol ECS 400 MHz spectrophotometer 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). Trifluoroacetic acid (TFA) was used as external standard for ^{19}F NMR spectra.
5. Mass spectra were recorded on a Xevo G2-S Q-Tof spectrometer (Waters, USA), capable of recording high-resolution mass spectrum (HRMS) in the ESI (Electrospray Ionization) mode.
6. CEM Discover monomode microwave reactor with magnetron frequency of 2455 MHz was used for microwave reaction.
7. Ultrasonication synthesis was performed using Elma S 70 H Ultrasonic bath (Specification: 37 KHz output frequency and 30-80 ^{o}C temperature).
8. UV-Visible spectra were recorded on a Perkin Elmer UV Vis NIR spectrophotometer Lambda 750 and Shimadzu UV-1800 UV-Vis spectrophotometer in standard 3.5 mL quartz cells with 10 mm path length, respectively.
9. Fluorescence spectra were recorded on a Perkin Elmer LS 55 fluorescence spectrophotometer in standard 3.5 ml volume and 10 mm path length quartz cuvettes.
10. The purity of all the synthesized compounds was checked by TLC using silica gel as adsorbent and solvents of increasing polarity as mobile phase.
11. All titration experiments were carried out at room temperature. The stock solutions of compounds were prepared in dry UV-grade DMSO and stored in dry atmosphere. The stock solutions of tetrabutylammonium salts and sodium

salts of fluoride, chloride, iodide, bromide, acetate, nitrate, dihydrogen phosphate and hydrogen sulphate ions with concentration 1×10^{-2} M were also prepared in dry DMSO and distilled water, respectively. For the anion recognition experiments, anion salts were used after proper dilution of stock solutions.

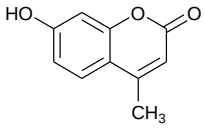
12. ^{1}H NMR titration experiments were performed at room temperature. Anion salt solutions were prepared using tetrabutylammonium salts in DMSO-d_6.
13. Stoichiometric ratio of the complexes formed between fluoride ion and receptor is determined by employment of continuous variation method, where the concentration of both receptor and anion salt are kept same. The molar fraction of anion/ (receptor + anion) is continuously varied. A molar fraction at which the absorbance reaches its maxima in UV-Visible spectra shows the stoichiometric ratio of the complex formed between receptor and anion.
14. The binding constant of receptor with anion is evaluated by Benesi Hildebrand equation

$$1/A\text{-}Amin = 1/ (Amax + (1/K [X^{-}]) (1/\Delta Amax).$$

Here, $\Delta Amax = Amax - Amin$, where, Amin, A, Amax are the absorptions of receptor considered in the absence of X^{-}, at an intermediate, and at a concentration of complete binding. K is binding constant, $[X^{-}]$ is concentration of X^{-}. From the plot of $1/ (A - Amin)$ against $[X^{-}]$ for receptor, the value of K (±10%) is calculated from the ratio of intercept/slope.

15. Fluoride ion concentration was determined by Thermo Scientific Orion Star A214 Fluoride Ion Selective Electrode.
16. The computational calculations were carried out under density functional theory using Materials Studio DMoL^{3} (version 8.0). The geometries optimization has been performed at the level PWD DND 4.4 basis set in DMSO as solvent. Graphics were obtained using Materials Studio visualizer.

Preparation of substituted-7-hydroxycoumarin (I)



Ib

Compound **1** was synthesized by Pechmann reaction following a reported procedure **[49]**. Concentrated sulfuric acid (20 ml) was added to 100 ml round bottom flask and cooled to 0 °C. Resorcinol (0.001 mol, 0.110g) and ethylacetoacetate (0.0015 mol, 0.18 ml) were added to concentrated sulfuric acid under constant stirring for 30 min. The reaction mixture was stirred for overnight at room temperature and reaction progress was monitored using thin layer chromatography (hexane). After completion of reaction, as observed by TLC, reaction mixture was poured into ice water. The precipitate was filtered and white solid product, thus obtained, was recrystallized in ethanol. The synthesized compound was characterized by FTIR, ^{1}H NMR and HRMS spectroscopic techniques.

M.P. (^{o}C)	190-192 ^{o}C (Lit **[49]** 190-192 ^{o}C]
Yield (%)	71 % (Lit **[49]** 72 %]
IR (KBr) ν_{max} cm^{-1}	3412 (O-H), 3010 (C-H), 1676 (C=O), 1610 (C=C)
^{1}H NMR ($CDCl_3$) δ ppm	1.34 (s, 3H, CH_3), 6.38 (s, 1H, Ar-H), 6.55 (dd, 1H, Ar-H), 7.15 (dd, 1H, Ar-H), 7.22 (s, 1H, Ar-H), 7.35 (s, 1H, pyran-H)
Mass [M+H]$^{+}$	177.1666 (Calcd for $C_{10}H_8O_3$: 176.1687)

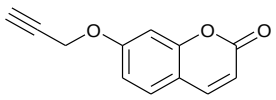
Other substituted-7-hydroxycoumarin (**Ib-e**) derivatives were prepared by following similar procedure and are listed in **Table-3.3**

Table 3.3: Physical characteristics of substituted-7-hydroxycoumarin (Ib-e)

S.No.	X	Mol. Formula	Mol. Weight	Yield (%)	M. P. (°C)
Ib	4-CH_3	$C_{10}H_8O_3$	176.1687	71	190-192
Ic	4-C_2H_5	$C_{11}H_{10}O_3$	190.1953	69	145-147
Id	4-CF_3	$C_{10}H_5F_3O_3$	230.1401	87	178-180
Ie	3-$COCH_3$	$C_{11}H_8O_4$	204.1788	77	120-122

Preparation of (un)substituted-7-Prop-2-ynyloxy-chromen-2-one (1a-e)

7-Prop-2-ynyloxy-chromen-2-one (1a)



1a

7-Prop-2-ynyloxy-chromen-2-one **(1a)** was prepared by following reported method of Luo *et al.* **[34]**. To a solution of 7-hydroxycoumarin (0.01mol, 1.77 g) in dry acetone, propargyl bromide (0.01 mol, 0.75 ml) and anhydrous potassium carbonate (0.01 mol, 1.38 g) were added. The resultant mixture was irradiated under ultrasonic radiation at 50 ^oC. The reaction progress was checked by TLC using hexane as mobile phase. After completion of reaction as observed by TLC after 3-4 hours, the residue was treated with water (15 ml) and extracted with ethyl acetate mixture. The combined organic phases were washed with water, dried over anhydrous sodium sulphate and evaporated in vacuum. The crude product was purified by crystallization from 9:1 hexane: ethyl acetate mixture and characterized by FTIR, ^1H NMR and HRMS.

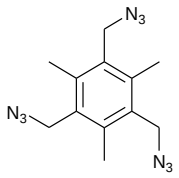
M.P. (^oC)	198-200 ^oC (Lit **[34]** 200-202 ^oC]
Yield (%)	89 % (Lit **[34]** 88 %]
IR (KBr) ν_{max} cm^{-1}	3313 (ΞC-H), 2100 (CΞC), 1696 (C=O)
^1H NMR ($CDCl_3$) δ ppm	3.5 (s, 1H, ΞC-H), 4.56 (s, 2H, CH_2), 6.45 (s, 1H, Ar-H), 6.65 (dd, 1H, Ar-H), 7.10 (dd, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 7.41 (s, 1H, pyran-H)
Mass $[M+H]^+$	200.1945 (Calcd for $C_{12}H_8O_3$: 200.1901)

Other derivatives, **1b-e** were synthesized using similar procedure and physical data of all derivatives are listed in **Table 3.4.**

Table 3.4: Physical characteristics of (un)substituted-7-Prop-2-ynyloxy-chromen-2-one (1a-e)

S.No.	X	Mol. Formula	Mol. Weight	Yield (%)	Melting point (°C)
1a	H	$C_{12}H_8O_3$	200.1901	89	198-200
1b	4-CH_3	$C_{13}H_{10}O_3$	214.2167	88	201-203
1c	4-C_2H_5	$C_{14}H_{12}O_3$	228.2433	87	181-184
1d	4-CF_3	$C_{13}H_7F_3O_3$	268.1881	85	195-196
1e	3-$COCH_3$	$C_{14}H_{10}O_4$	242.2268	84	175-177

Preparation of 1,3,5-tris-azidomethyl-2,4,6-trimethyl-benzene (2)



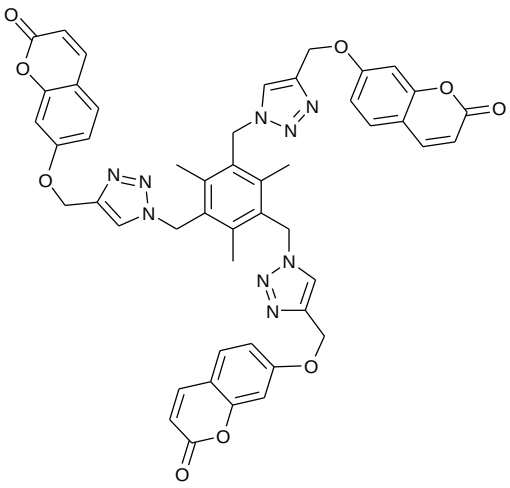
2

1,3,5-tris-azidomethyl-2,4,6-trimethyl-benzene **(2)** was prepared by following a reported literature method **[35].** To a solution of 1,3,5-tris-bromomethyl-2,4,6-trimethyl-benzene (0.001 mol, 0.398g) in dry DMF (5ml), was added sodium azide (0.0043 mol, 0.2814 g) portion wise over 20 minutes. The mixture was then heated at 70 ^oC for overnight. The reaction progress was checked by TLC using 9:1 hexane-ethyl acetate as mobile phase. After completion of reaction, as observed by TLC, the resulting solution was cooled to room temperature and poured into crushed ice. The precipitated solid was filtered off and recrystallized by ethanol to give pure product as white crystalline solid. The pure product, thus obtained was characterized by FTIR, ^1H NMR and high resolution mass spectral data.

M.P. (^{o}C)	165 ^{o}C (Lit **[35]** 164 ^{o}C]
Yield (%)	70% (Lit **[35]** 71 %]
IR (KBr) ν_{max} cm^{-1}	3008 (Ali C-H), 2980 (Ar C-H), 2100 (-N_3),
^{1}H NMR ($CDCl_3$) δ ppm	δ 2.25 (s, 9H), 4.49 (s, 6H)
Mass $[M+H]^+$	286.3456 $[M+H]^+$ Calculated for $C_{12}H_{15}N_9$: 285.3390

Preparation of 7',7''-(((((2,4,6-Trimethylbenzene-1,3,5-triyl)tris (methylene)) tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(substituted-2H-chromen-2-ones) A-E

7',7''-(((((2,4,6-Trimethylbenzene-1,3,5-triyl)tris (methylene)) tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(2H-chromen-2-ones) A



A

In a round bottom flask, 3,5-tris-azidomethyl-2,4,6-trimethylbenzene **(2)** (1.1 mmol; 0.313 g) and alkyne derivative (**1a)** (3 mmol, 0.6 g) were dissolved in *t*-butanol (15 ml) with continuous stirring at room temperature. Water (20 ml), copper sulphate (0.01 mmol, 0.03 g) and sodium ascorbate (0.02 mmol, 0.04 g) were then added and sonicated in an ultrasonic bath at 50 ^{o}C. The progress of reaction was followed by TLC using pet ether (60-80 ^{o}C): ethyl acetate (8:2) as the mobile phase. After the completion of the reaction, as observed by TLC, after 4 hours, the product was extracted with ethyl acetate, washed well with brine solution and dried over sodium

sulphate to furnish an orange coloured solution, which was then concentrated under vacuum. It was then purified by column chromatography using silica gel as stationary phase and pet ether (60-80 ^{o}C): ethyl acetate (9:1) as the mobile phase.

M.P. (^{o}C)	212-214 ^{o}C
Yield (%)	71 %
IR (KBr) ν_{max} **cm**$^{-1}$	2921 (=C-H), 1708 (C=C), 1620 (C=N), 1430 (N=N), 1058 (C-O)
^{1}H NMR ($CDCl_3$) δ ppm	δ 2.48 (s, 9H, -CH_3), 4.30 (s, 6H, -CH_2), 5.69 (s, 6H, -CH_2), 6.23-6.88 (m, 15H, Ar-H), 7.62 (s, 3H, C-H)
Mass [M+H]$^{+}$ m/z	886.8768 $[M+H]^{+}$ Calculated for $C_{48}H_{39}N_9O_9$: 885.8782.

Other derivatives have been synthesized by following similar method. The physical data of receptors A-E are tabulated in **Table 3.5.**

Table 3.5: Physical data of synthesized receptors (A-E)

S. No.	X	Mol. Formula	Mol. Weight	Yield (%)	Melting point (°C)
A	H	$C_{48}H_{39}N_9O_9$	885.8782.	71	212
B	4-CH_3	$C_{51}H_{45}N_9O_9$	927.9579	69	198
C	4-C_2H_5	$C_{54}H_{45}N_9O_{12}$	1011.9882	64	187
D	4-CF_3	$C_{51}H_{36}F_9N_9O_9$	1089.8721	67	215
E	3-$COCH_3$	$C_{54}H_{51}N_9O_9$	970.0376	61	189

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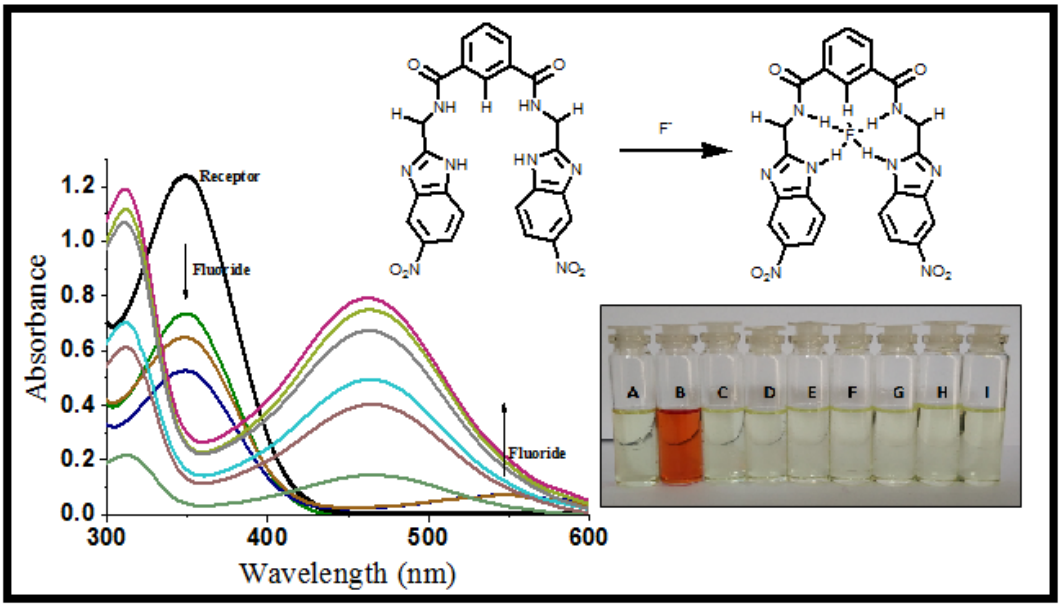
Chapter-4

Synthesis of *N, N'*-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides : Unique dipodal molecular clefts containing benzimidazole scaffolds



Highlights:

- Intricate design of dipodal hosts based on phenyl ring symmetrically armed with benzimidazole moieties through amide bonds for hydrogen binding with guest fluoride ion
- Preorganized rigid cavity containing N-H and aromatic C-H protons for selective and efficient fluoride ion capture

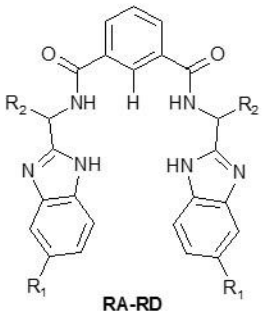
INTRODUCTION

The development of receptors for fluoride ion recognition has materialized as a worthy focus of current research due to duplicious nature of fluoride ion, being considered essential for dental health and at the same time hazardous to human health above maximum permissible limit prescribed by WHO **[1-5]**. Last decade has seen much advancement in the field of fluoride ion recognition and sensing evinced by increasing number of chronicles describing development of new and interesting receptors claiming efficient and selective ion recognition **[6-10]**. However, the crescendo of documented receptors with various motifs which detect fluoride ion in organic solvents needs a comprehensive revision **[11]**. The very fact that fluoride ion possesses high hydration enthalpy and that the receptor has to compete with solvation sphere of water molecules around the spherical ion to bind fluoride ion, there lies a challenge ahead to develop molecular systems capable of recognizing and binding fluoride ion in competitive media **[12-13].**

The numerous reports of anion receptors are designed to rely on hydrogen bonding, being inspired by nature **[14].** Hydrogen bonding has an edge over electrostatic force in terms of selectivity and directional nature, which facilitates the design of receptors having ability to distinguish between anions with varied geometries **[15].** Design can be modulated to allow incorporation of more hydrogen bond donors with the aim to establish high binding affinity with anion **[16-17].** The molecular cleft approach has opened a new era in supramolecular chemistry with multiple hydrogen bonding sites directed towards centre **[18-19]**. A variety of synthetic molecules capable of anion recognition by the formation of hydrogen bonding with anions includes, amide **[20]**, urea/thiourea **[21]**, indole **[22]**, pyrrole **[23]**, guanidinium **[24]** and benzimidazole, which can be combined judiciously to develop molecular clefts **[25]**. Benzimidazole, amongst these, constitute a fascinating backbone for anion recognition, which themselves carry in-built hydrogen bond donor sites. These scaffolds can be decorated with additional hydrogen bond donors to multiply their interaction with anionic species **[26]**. This moiety has been coupled with other motifs and has been extensively utilized in synthesis of cation as well as anion recognition systems that display colorimetric and fluorometric response upon binding with ions **[27-28]**.

Colour change of receptors, perceivable by naked eye as an output for detection event is highly appreciated **[29]**. It facilitates detection of analyte on-site without resorting to expensive instrument **[30]**. These are generally constructed on receptor-chromophore binomial, where ion binds at receptor site and chromophore is responsible for turning binding event into an optical signal **[31]**. Bearing this in mind, we have developed dipodal receptors *N,N'*-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides, **RA-RD (Fig. 4.1)**, for naked eye fluoride ion detection in 9:1 DMSO-water. The phenyl ring in the molecular structure of receptors is symmetrically armed with a benzimidazole moiety using amide groups as linker to yield dipodal receptors, **RA-RD (Fig. 4.1),** varying in substituents, with multiple hydrogen bond donor sites to bind fluoride ion in its cleft. It has been observed that electron withdrawing group at precise location increases the acidity of hydrogen binding groups **[32]**. In this connection, receptor **RC**, equipped with electron withdrawing nitro group at a strategic location, was synthesized, which binds fluoride ion exclusively by the formation of hydrogen binding, with a detection limit of 1.5 ppm, over other anions. Anion binding studies were done by visual detection, UV-Visible, ^{1}H NMR, ^{19}F NMR titrations and mass spectral data.

The following type of compounds have been prepared and characterized by FTIR, ^{1}H NMR, ^{13}C NMR and HRMS data **(Fig. 4.1):**



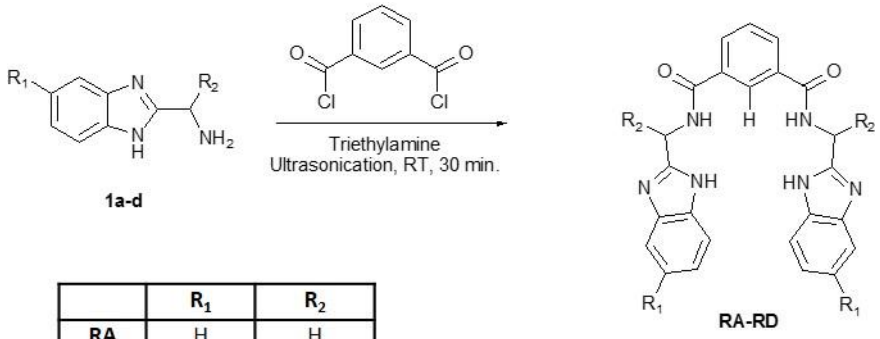
RA-RD

	R_1	R_2
RA	H	H
RB	H	CH_3
RC	NO_2	H
RD	NO_2	CH_3

Fig. 4.1: Molecular representation of *N,N'*-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides, RA-RD

RESULTS AND DISCUSSION

2-Aminoalkyl benzimidazole **(1a-d)** were prepared by following the literature method of Creson and Day *et al.* **[33],** which then were reacted with *m*-phthaloyl chloride in dichloromethane under ultrasonication in presence of catalytic amount of trimethylamine to yield corresponding title compounds in good yield (**RA-RD**) **(Scheme 4.1)**, **(Table 4.4).**



	R_1	R_2
RA	H	H
RB	H	CH_3
RC	NO_2	H
RD	NO_2	CH_3

Scheme 4.1. **Synthesis of *N,N'*-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides, RA-RD**

All the synthesized receptors **RA-RD** were characterized by FTIR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data. In the FTIR spectra, receptors **RA-RD** display characteristic broad band in the region 3405-3129 cm^{-1} and an absorption band from 2917-2900 cm^{-1} may be attributed to N-H stretching vibration of N-H groups (D_2O exchangeable) and aromatic C-H, respectively. Receptors **RA-RD** show absorption band ranging from 1657-1645 cm^{-1} due to conjugated C=O stretching vibration. Two absorption bands in the region 1525-1515 and 1375-1345 cm^{-1} may be attributed to N-O stretching vibration of nitro groups present in receptors **RC-RD (Fig. 4.2, Table 4.2).**

^{1}H NMR spectra of receptors **RA-RD** exhibit two sharp singlets in the region δ 8.3-8.5 and δ 11.28-12.2 ppm due to the presence of amidic N-H and imidazole N-H protons, respectively. A multiplet from δ 7.08-8.07 ppm is assigned to aromatic protons. Aliphatic C-H peaks are observed in the region δ 2.46-2.50 (CH_3) and 4.70-

5.29 ppm (CH_2). In the ^{13}C NMR spectra, peak at δ 185 ppm may be attributed to C=O group. Aromatic carbons are observed in the region δ 112-151 ppm **(Fig. 4.3-4.4, Table 4.2)**

Molecular ion peak $[M+H]^+$ obtained at m/z 425.1874 **(RA)**, 453.1989 **(RB)**, 515.1356 **(RC),** 543.1680 **(RD)** are in good agreement with their corresponding molecular formula, which confirms the formation of products, N,N'-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides, **RA-RD (Fig. 4.5, Table 4.2).**

Physical and spectral data (FTIR, ^1H NMR, ^{13}C NMR and mass) of all synthesized receptors **(RA-RD)** are tabulated in **Table 4.1.** and **4.2** respectively.

The IR, ^1H NMR, ^{13}C NMR and mass spectra of receptor **RC** are given in **Fig. 4.2, 4.3, 4.4 and 4.5,** respectively.

Table 4.1: Physical data of *N,N'*-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides RA-RD

Compd No.	Name	M.P. (^oC)
RA	*N,N'*-Bis-(1H-benzoimidazol-2-ylmethyl)-isophthalamide	188
RB	*N,N'*-Bis-[1-(1H-benzoimidazol-2-yl)-ethyl]-isophthalamide	196
RC	*N,N'*-Bis-(5-nitro-1H-benzoimidazol-2-ylmethyl)-isophthalamide	205
RD	*N,N'*-Bis-[1-(5-nitro-1H-benzoimidazol-2-yl)-ethyl]-isophthalamide	178

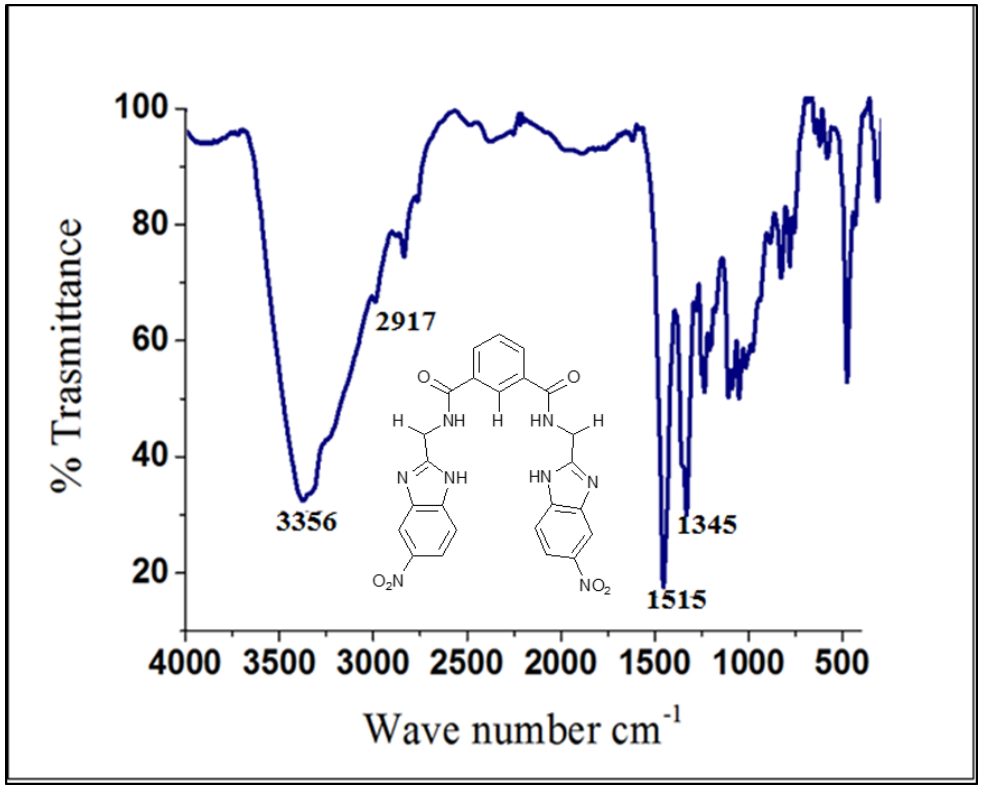


Fig. 4.2: FTIR spectrum of *N,N′*-bis-(5-nitro-1H-benzoimidazol-2-ylmethyl)-isophthalamide, RC

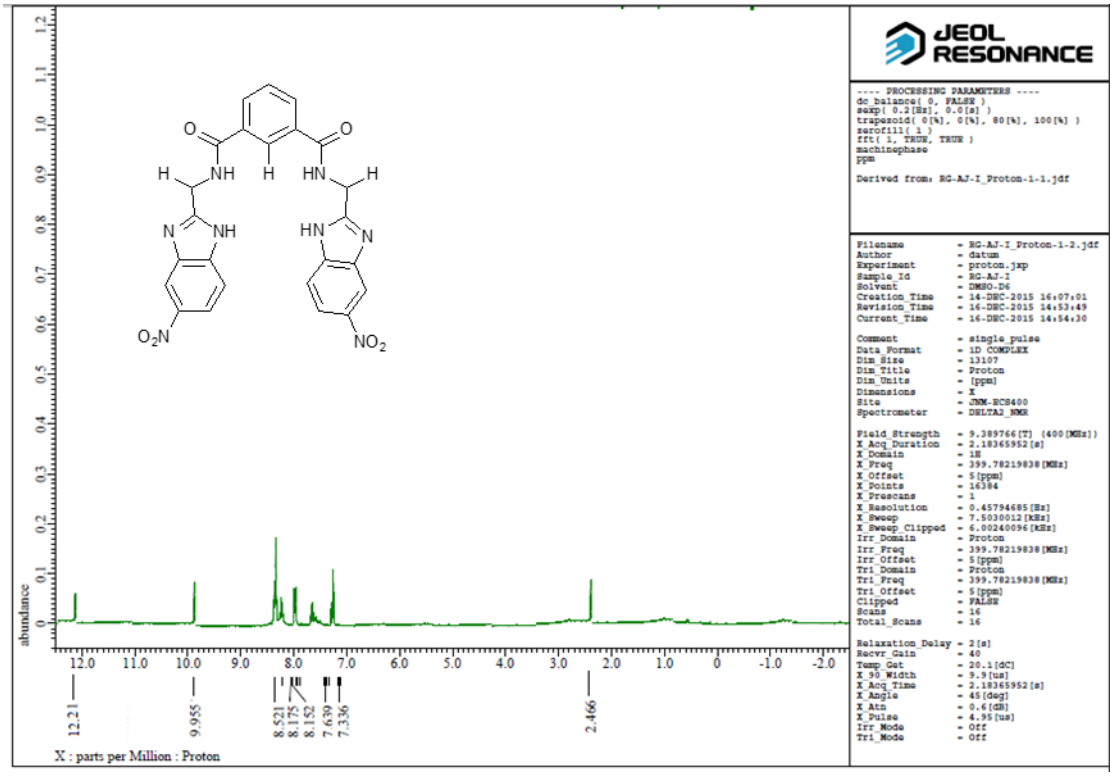


Fig. 4.3: ^{1}H NMR spectrum of *N,N′*-bis-(5-nitro-1H-benzoimidazol-2-ylmethyl)-isophthalamide, RC

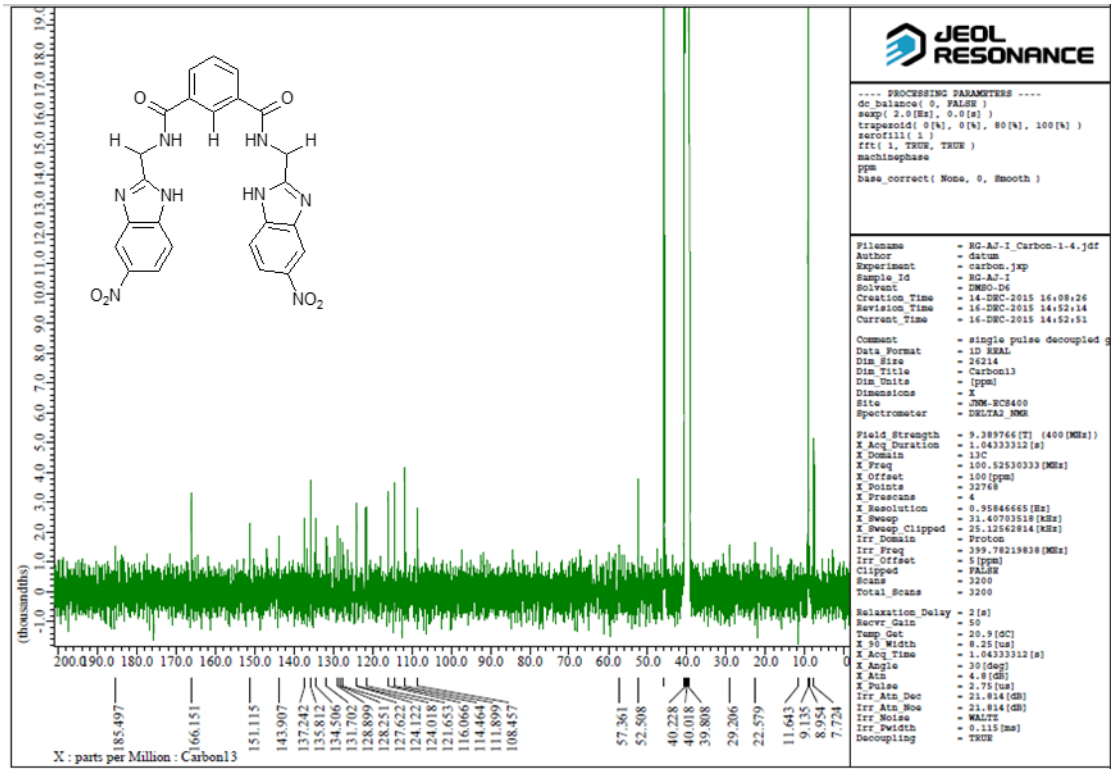


Fig. 4.4: ^{13}C NMR spectrum of *N,N′*-bis-(5-nitro-1H-benzoimidazol-2-ylmethyl)-isophthalamide, RC

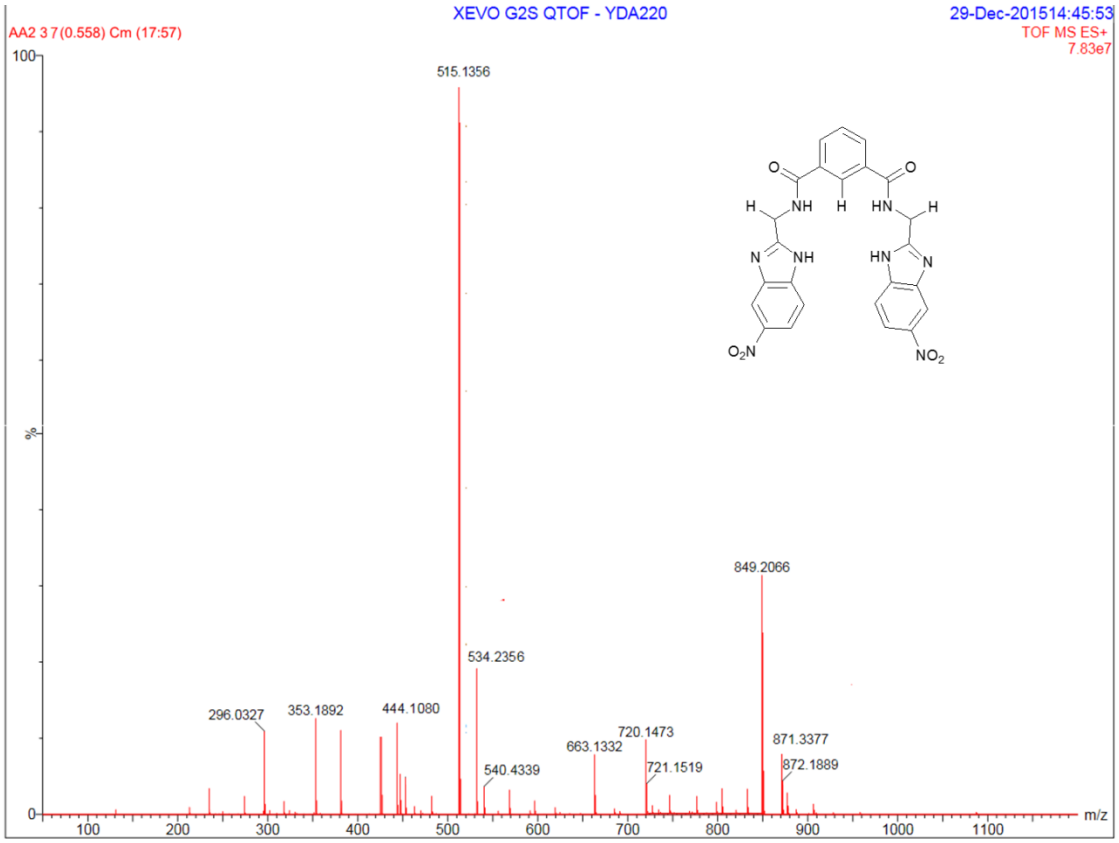


Fig. 4.5: ESI mass spectrum of *N,N′*-bis-(5-nitro-1H-benzoimidazol-2-ylmethyl)-isophthalamide, RC

Table 4.2: Spectral data of receptors *N,N'*-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides, RA-RD

Compd No.	FTIR (KBr, υ cm^{-1})	^{1}H NMR (DMSO-d_6, 400 MHz, δppm)	^{13}C NMR (DMSO-d_6, 100 MHz, δppm)	MS (ESI) m/z $[M+H]^+$
RA	3405 (N-H), 2017 (C-H), 1645 (C=O)	4.70 (2H, s, CH_2), 7.12-7.47 (m, 11H, Ar-H), 8.06 (s, 1H, phenyl C-H), 8.50 (s, 2H, amidic N-H), 11.28 (s, 2H, benzimidazole N-H)	115.17, 122.61, 127.46, 128.92, 129.01, 130.88, 134.51, 138.06, 152.78, 166.49, 166.79, 167.42, 183.78	425.1874 (obsd.) calcd. for $C_{24}H_{20}N_6O_2$: 424.1648
RB	3129 (N-H), 2910 (C-H), 1635 (C=O)	2.4 (3H, d, CH_3), 4.65 (2H, q, CH_2), 7.08-7.35 (m, 11H, Ar-H), 7.9 (s, 1H, phenyl C-H), 8.3 (s, 2H, amidic N-H), 11.37 (s, 2H, benzimidazole N-H)	54.46, 113.56, 120.12, 125.67, 126.78, 128.26, 129.56, 130.10, 133.75, 145.73, 165.42, 165.98, 182.34	453.1989 (obsd.) calcd. for $C_{26}H_{24}N_6O_2$: 452.1961.
RC	3356 (N-H), 2917 (C-H), 1678 (C=O), 1515, 1345 (N-O)	2.45 (2H, s, CH_2), 7.33-7.63 (3H, m, Ar-H), 8.15-.8.17 (m, 6H, Ar C-H), 8.5 (s, 1H, phenyl C-H), 9.95 (s, 2H, amidic N-H), 12.2 (s, 2H, benzimidazole N-H)	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	515.1356 (obsd.) calcd. for $C_{24}H_{18}N_8O_6$: 514.1349
RD	3278 (N-H), 2905 (C-H), 1657 (C=O), 1525, 1375 (N-O)	2.56 (3H, d, CH_3), 4.70 (2H, q, CH_2), 7.13-7.59 (m, 3H, aromatic C-H), 7.9-8.05 (m, 8H, Ar-H), 8.2 (s, 1H, phenyl C-H), 8.3 (s, 2H, amidic N-H), 11.8 (s, 2H, benzimidazole N-H)	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	543.1680 (obsd.) calcd. for $C_{26}H_{22}N_8O_6$: 542.1662.

Anion binding studies

The synthesized receptors, *N,N'*-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides, **RA-RD** were carefully examined for their anion binding tendencies with anions *viz.;* fluoride, chloride, bromide, iodide, acetate, nitrate, dihydrogen phosphate and hydrogen sulphate as their TBA salts by naked eye colour change experiment, UV-Visible, ^{1}H NMR, ^{19}F NMR titrations and mass spectral data.

Naked eye experiment

The anion binding studies of receptors **RA-RD** (1×10^{-5} M in DMSO) were tested with different anions (1 to 10 receptor equivalents) as their TBA salts in 9:1 DMSO-water (**Fig. 4.6)**. A dramatic and sudden colour change from pale yellow to orange was observed upon addition of fluoride ion (1.5 ppm) into receptor **RC** solution in DMSO. Other anions failed to induce any colour change in receptor solution. It is worthy to mention that receptor **RC** could detect fluoride ion at a WHO recommended fluoride ion levels. Other receptors **RA, RB** and **RD** did not produce any colour change upon addition of any anion, even at high concentration (1×10^{-3} M). This led to conclude that judicious incorporation of electro withdrawing nitro group at the 5th position of benzimidazole rings boosted the binding affinity of receptor **RC** for fluoride ion, which was absent in other receptors. Since, only receptor **RC** was found capable of producing colour change in presence of fluoride ion, it was further studied for fluoride ion binding quantitatively by UV-Visible, ^{1}H NMR and ^{19}F NMR titrations.

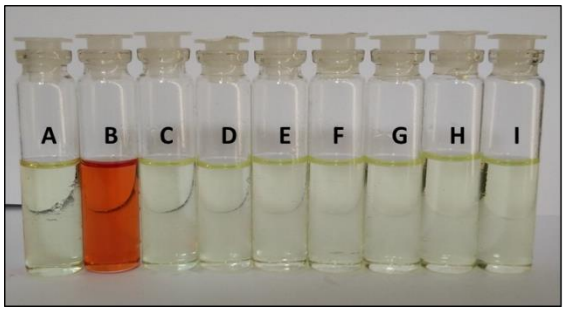


Fig. 4.6: Colour changes in the receptor RC (1×10^{-5} M in DMSO) in presence of 10 equivalents of different anions (TBA salts) where A, B, C, D, E, F, G, H and I represent receptor RC, RC + F^-, RC + Cl^-, RC + Br^-, RC + I^-, RC + CH_3COO^-, RC + $H_2PO_4^-$, RC + HSO_4^- and RC + NO_3^- ions respectively

UV-Visible titration experiment

To corroborate the preliminary naked eye test, receptor **RC** (1×10^{-5} M in DMSO) was evaluated as colorimetric receptor by spectrophotometric titration in presence of different anions (TBA salts, 10 receptor equivalents) in 9:1 DMSO-water. Receptor **RC** exhibited a strong absorption band at 348 nm **(Fig. 4.7).** Addition of different anions as their TBA salts into receptor RC solution produced no change in maxima at 348 nm. On the other hand, maxima at wavelength 348 nm shifted to 465 nm, upon addition of fluoride ion. It was therefore concluded that only receptor bound fluoride ion selectively over other anions, qualitatively as well as quantitatively.

The receptor **RC** and fluoride ion interaction was further investigated by UV-Visible titration, carried out with gradual addition of varying fluoride ion concentration from 1×10^{-5} to 1×10^{-3} M. With progressive addition of fluoride salt solution, intensity of absorption band at 348 nm remarkably reduced, with simultaneous growth of new peak at 465 nm. A large bathochromic shift of 117 nm can be attributed to formation of hydrogen binding interactions between receptor and fluoride ion **(Fig. 4.8)**. The change in absorbance at wavelength 465 nm upon addition of increasing concentration of fluoride ion into receptor RC solution is depicted in **Fig 4.9**.

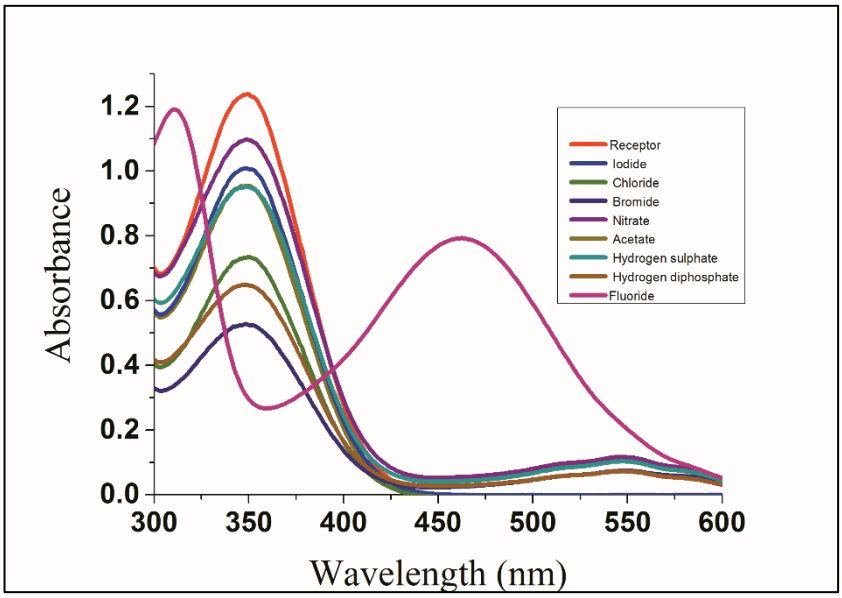


Fig. 4.7: Changes in absorbance of receptor RC (1×10^{-5} M in DMSO) with different anions (TBA salts, 1×10^{-3} M) in 9:1 DMSO: water

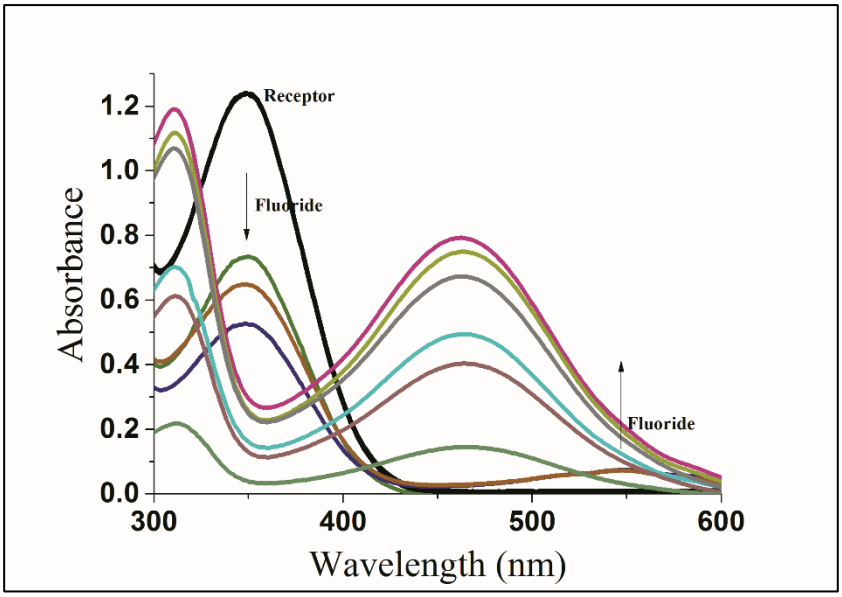


Fig. 4.8: UV-Visible spectra of receptor RC (1×10^{-5} M in DMSO) with fluoride ion (TBA salt) from 1×10^{-5} to 1×10^{-3}M in 9:1 DMSO: water

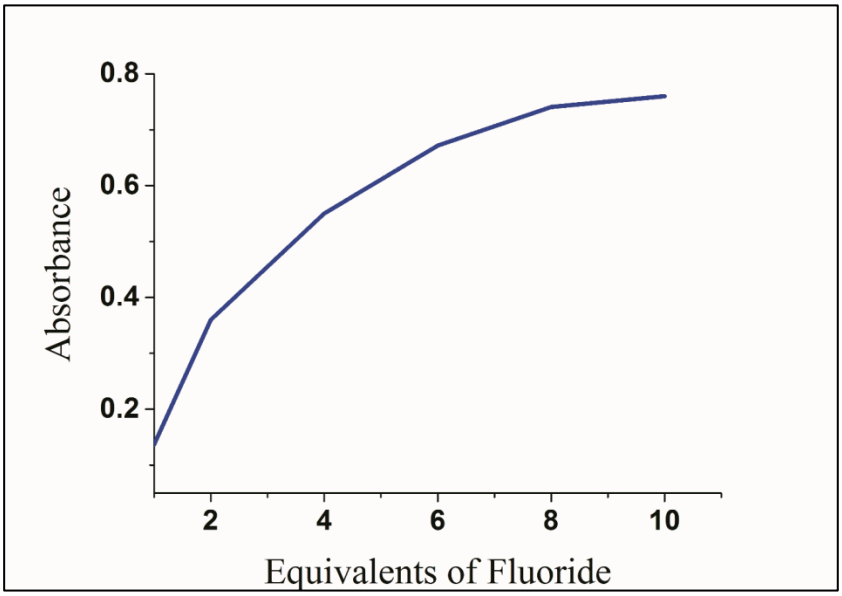


Fig. 4.9: Changes in absorbance at 410 nm of receptor C (1×10^{-5} M in DMSO) with increase in fluoride ion concentration (1×10^{-5} to 1×10^{-3} M in 9:1 DMSO-water)

Stoichiometric ratio of 1:1 was found between fluorde ion and receptor by continuous variation method **(Fig. 4.10).** It was further verified by mass spectra of receptor RC

complex with fluoride ion (**RC** + F^- + H^+ = 534.1456, calcd: 534.1411) **(Fig. 4.11) [34]**.

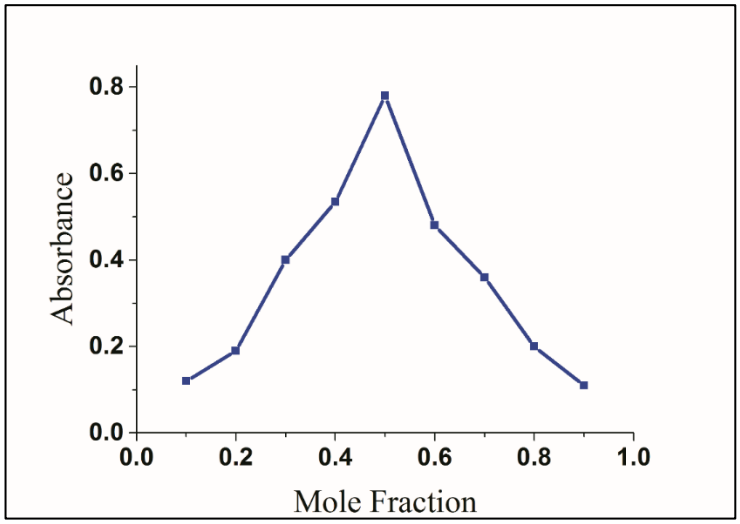


Fig. 4.10: Jobs Plot with receptor RC (1 ×10^{-2} M in DMSO) and Fluoride (TBA salt) 1 ×10^{-2} in 9:1 DMSO-water

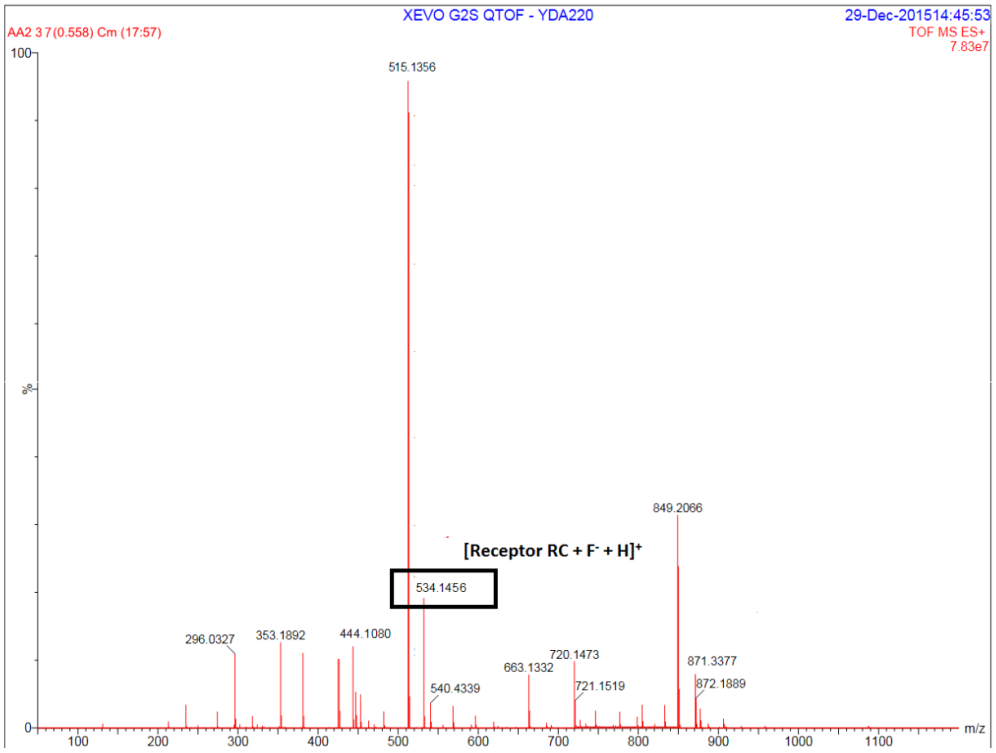


Fig. 4.11: ESI mass spectrum of fluoride ion complex with receptor RC

The binding constant of **RC** with fluoride was evaluated by B-H plot and was found to be 5.59 × 10^3 M^{-1} **(Fig. 4.12) [35].**

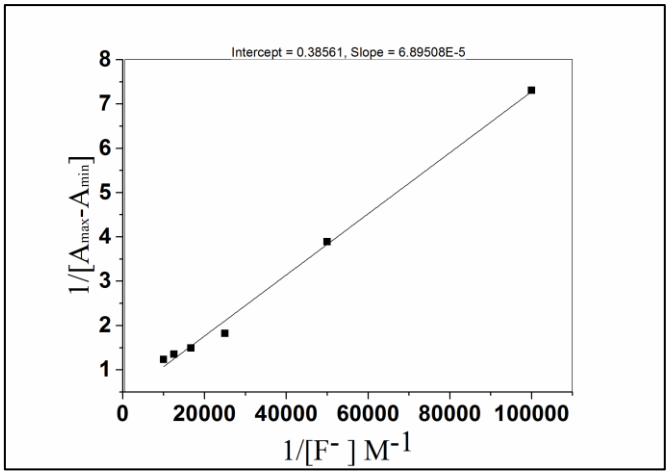


Fig. 4.12: Fitting curve of Benesi Hildebrand equation

^{1}H NMR titration experiment

Further, to shed light on the nature of interaction between receptor and fluoride ion, ^{1}H NMR titration was carried out. Fluoride ion in the form of its TBA salt of varying concentrations (2.5, 5, 7.5 and 10 equivalents) was added sequentially to receptor **RC** solution in DMSO-d_6 (1 ×10^{-2} M). Benzimidazole N-H, amide N-H and phenyl C-H appear at δ 12.23, 9.87 and 8.5 ppm, respectively. After addition of 2 equivalents of fluoride ion solution, 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 5 and 10 equivalents of fluoride ion **(Fig. 4.13)**. These results corroborated that a complex has been formed between receptor and fluoride ion *via* hydrogen bonding.

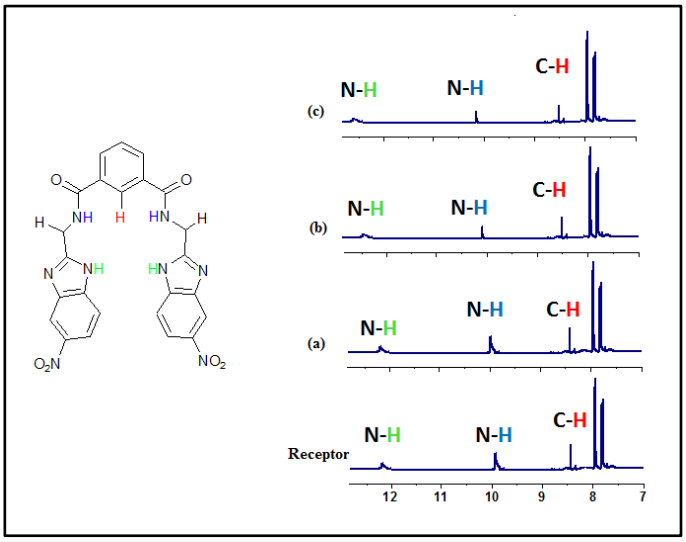


Fig. 4.13: Partial ^{1}H NMR (400 MHz) spectra of receptor RC in DMSO-d_6 (1 ×10^{-2} M) in the presence of (a) 2 (b) 5and (c) 10 equivalents of TBAF in DMSO-d_6

^{19}F NMR titration experiment

The ^{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**, peak at δ -102 ppm shifted upfield by δ 3.71 ppm and intensity of peak decreased and finally, peak due to F^- ion disappeared to a large extent, which indicates the existence of binding interaction between receptor and fluoride ion **[36] (Fig. 4.14).**

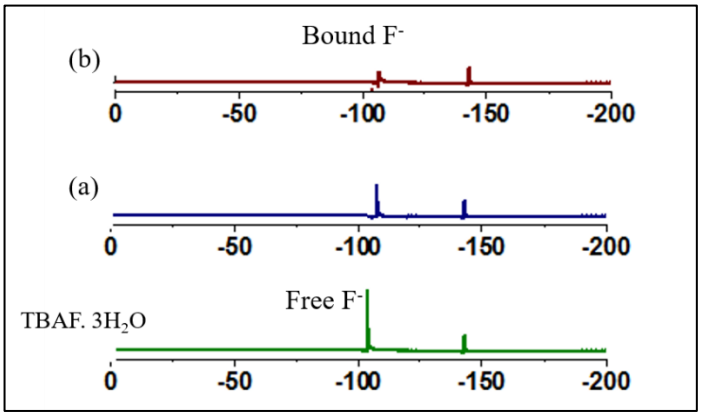
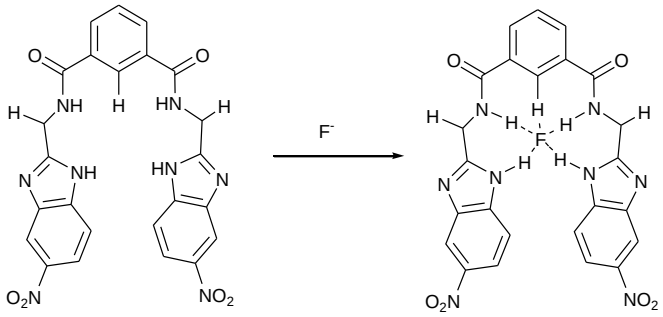


Fig 4.14: ^{19}F NMR spectra of TBAF (1×10^{-2} M) in DMSO-d_6, in presence of (a) 0.5 and (b) 1 equivalents of receptor RC in DMSO

The plausible mode of binding between receptor and F^- is depicted in **Scheme 4.2.**



Scheme 4.2. Plausible binding mode between receptor RC and fluoride ion

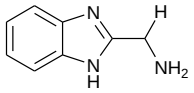
CONCLUSION

Neutral benzimidazole based naked eye receptor has been fabricated to detect fluoride ion at WHO recommended level of 1.5 ppm in aqueous solution. Receptor **RC** binds fluoride by establishing multiple hydrogen bonding interactions. Sensing process can be corroborated by the visible colour change from yellow to orange.

EXPERIMENTAL

Preparation of 2-aminoalkylbenzimidazoles (1a-d)

2-Aminomethylbenzimidazole, 1a



1a

It was prepared by following the reported method of Creson and Day *et al*. **[34]**. o-Phenylene diamine (0.05 mol, 5.4 g) and glycin (0.075 mol, 5.6 g) were dissolved in 100 ml HCl (6 mol L^{-1}) and the reaction mixture was ultrasonicated at room temperture. The progress of reaction was evaluated by TLC using 9:1 pet ether (60-80 ^{o}C)- ethyl acetate as mobile phase. After 30 minutes, on completion of reaction, as observed by TLC, the reaction mixture was cooled at 4 ^{o}C for overnight. Pink solid obtained was filtered and recrystallized from ethanol to yield pure solid. The pure product, thus obtained was characterized by FTIR, ^{1}H NMR and mass spectroscopic techniques.

M.P. (^{o}C)	261-263 ^{o}C (Lit **[34]** M. P. 262-264 ^{o}C)
Yield (%)	92 % (Lit **[34]** Yield 91 %)
IR (KBr) ν_{max} cm^{-1}	3260 (N-H), 1620 (C=C), 1609 (C=N)
^{1}H NMR ($CDCl_3$) δ ppm	1.7 (s, 3H, CH_3), 3.25 (s, 1H, NH_2), 6.5-7.5 (4H, m, Ar-H), 7.8 (s, 1H, imidazole N-H)
Mass $[M+H]^+$	148.1809 $[M+H]^+$(Calcd for $C_8H_9N_3$: 147.1700)

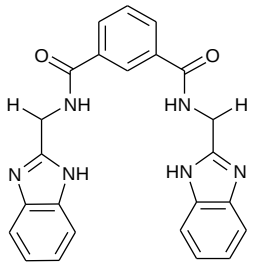
All other derivatives were prepared similarly. Physical and analytical data of synthesized compounds are given in **Table 4.3.**

Table 4.3: Physical data of 2-aminoalkylbenzimidazole derivatives, 1a-d

S. No.	R_1	R_2	Mol. Formula	Mol. Weight	Yield %	M. P. (^{o}C)
1a	H	H	$C_8H_9N_3$	147.17	81	263
1b	H	CH_3	$C_9H_{11}N_3$	161.20	76	135
1c	NO_2	H	$C_8H_8N_4O_2$	192.17	74	188
1d	NO_2	CH_3	$C_9H_{10}N_4O_2$	206.20	71	194

Preparation of *N,N'*-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides,RA-RD

***N,N'*-Bis-(1H-benzoimidazol-2-ylmethyl)-isophthalamide(RA)**



RA

To *m*-phthaloyl chloride (0.004 mol, 0.812 g) solution in dichloromethane, was added 2-aminomethylbenzimidazole (0.008 mol, 1.176 g) with catalytic amount of trimethylamine, under ultrasonication irradiation and stirred at room temperature. The reaction progress was examined by thin film chromatography using solvent system (8:2) pet ether (60-80 ^{o}C):ethyl acetate. After completion of reaction, as monitored by TLC, the reaction mixture was poured into saturated sodium bicarbonate solution, filtered and washed with water (3x50 ml) to afford desired dipodal product, **RA**, which was purified by coloumn chromatography (9:1 pet ether (60-80 ^{o}C) :ethyl acetate). The pure title compound was characterized by FTIR, ^{1}H NMR, ^{19}C NMR and mass spectroscopic techniques.

M.P.(^{o}C)	188 ^{o}C
Yield (%)	88 %
IR (KBr) ν_{max} cm^{-1}	3405 (N-H), 1645 (C=O)
^{1}H NMR (DMSO-d_6) δ ppm	4.70 (2H, 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) δ 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.
Mass m/z [M+H]$^{+}$	425.1874 [M+H]$^{+}$. calcd. for$C_{24}H_{20}N_6O_2$: 424.1648.

All other receptors, **RB-RD** were prepared similarly. Physical and analytical data of synthesized compounds are given in **Table 4.4.**

Table 4.4: Physical data of N,N'-bis-(5-substituted-1H-benzoimidazol-2-yl-alkyl)-isophthalamides,RA-RD

CompdNo.	**R_1**	**R_2**	**Mol. Formula**	**Mol. Weight**	**Yield %**	**Time (min)**
RA	H	H	$C_{24}H_{20}N_6O_2$	424.1648	88.1	20
RB	H	CH_3	$C_{26}H_{24}N_6O_2$	452.1961	87.5	25
RC	NO_2	H	$C_{24}H_{18}N_8O_6$	514.1349	84.40	20
RD	NO_2	CH_3	$C_{26}H_{22}N_8O_6$	542.1662	82.11	30

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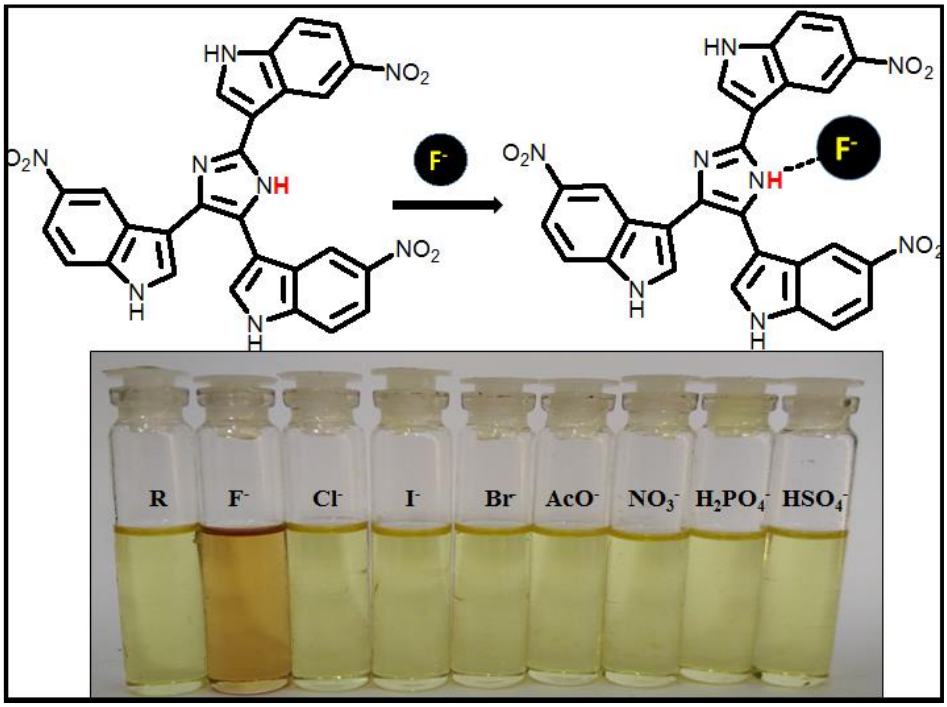
Chapter 5

Synthesis of rationally designed tri-armed imidazole-indole hybrids 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indole



Highlights:

- Novel tri-armed imidazole-indole hybrids, with judicious placement of nitro groups to selectively bind fluoride ion sensing at 1.5 ppm concentration in 9:1 DMSO-water
- Naked eye detection of fluoride ion without any interference from other anions

INTRODUCTION

Anion complexation chemistry has evolved as a significant multidisciplinary research area across environment, chemistry and biology, considering the important roles played by the anions in daily life **[1-6]**. From spherical fluoride ion to tetrahedral sulphate and phosphate ions, anions find their importance everywhere in nature and thus demand continuous research **[7-8].** Drawing inspiration from nature, together with acquired knowledge of chemistry, researchers are imaginatively manipulating the chemical moieties to craft the diverse array of receptors for the selective recognition of desired anion **[9-10]**. Till date, multitude of approaches have been tried with various functionalities *viz.,* tailoring the acidity of N-H group for deprotonation to occur **[11]**, anion-π interactions **[12]** and hydrophobic effects **[13-14]**, etc. to achieve selective binding with anions for effective hydrogen bonding

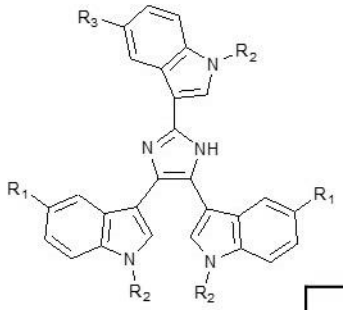
Amongst the ubiquitous anions, fluoride anion recognition has acquired a considerable attention of scientific community because it is one of the trace element required in the formation of teeth and bones in humans **[15-18]**. However, excessive intake of fluoride ion through drinking water is well documented to cause dental fluorosis, bone diseases and lesions of thyroid and liver **[19-20]**. This proves that beneficial and injurious effects of fluoride ion intake is concentration dependant. The maximum permissible limit of fluoride ion in drinking water is 1.5 ppm, according to World Health Organization (WHO) standard **[21]**. Available method to quantitatively detect the concentration of fluoride in drinking water is by the use of lanthanum fluoride based membrane electrode, which is time consuming, expensive and requires skilful handling, since the electrode is quite fragile **[22-23]**. To overcome these obstacles, development of a simple and robust procedure using anion receptor is essential, which can determine the fluoride ion at environmentally significant levels. In view of this requirement, colorimetric receptors have attracted considerable attention by providing easy detection of analyte *via* naked eye under visible light **[24-25]**.

A review of literature reveals that, so far, molecules containing functional groups *viz.,* urea/thiourea **[26-28],** secondary amide **[29-30]** and thiosemicarbazide **[31-32]** have been employed to effectively and selectively bind fluoride ion through the formation of hydrogen bond with N-H units of these groups. Covalent attachment of these

molecules with appropriate signalling unit, such as, nitrophenyl, azo dye etc. yields the complete receptor, which can convert anion-receptor binding event into either colour or fluorescence change as an output **[33-34]**. Heterocycles, which have recently been introduced as anion receptors, can act as both chromophore and binding units **[35-36].** Interesting photophysical properties of heterocycles make them strong contenders for chromophoric unit and further, inbuilt acidic hydrogen bond donor groups (N-H) in several heterocyclic moieties can serve as binding sites for anions **[37]**. Amongst these heterocycles, imidazole N-H is acidic enough to act as an excellent hydrogen bond donor **[38]**. Moreover, acidity can be tailored by suitable insertion of substituents in the ring and it has been reported to be annulated with another imidazole, benzene, anthraquinone, naphthalene and naphthalimide units for enhancing NH acidity, rendering it fit to effectively bind fluoride ion by several research groups **[39-42]**. Recently, quinone-ferrocene systems bridged by imidazole moiety and quinone-imidazole system have been reported by Elango *et al*., which exhibited naked eye response towards fluoride and cyanide ions in aqueous media at neutral pH **[43-44]**. Although an appreciable number of receptors are known for fluoride ion, their applicability to real life applications is restricted to very few and most of these reported receptors, usually urea/thiourea based, exhibit multi-anion sensitivity **[45-46]**. Further, there exists a challenge to develop receptor for detecting fluoride ion in competitive media, owing to its high hydration enthalpy (-505 kJ/mol) **[47-48]**.

Given the known photophysical properties of imidazole and indole **[49-50]**, it was envisaged that the introduction of indole rings containing electron withdrawing nitro groups, could fine-tune the binding property of imidazole moiety. In this connection, we report structurally simple and easy to synthesize tri-armed imidazole-indole hybrids, 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indole **(RA-RE),** containing varying number of electron withdrawing group(s) as selective naked eye receptor for fluoride ion sensing in 9:1 DMSO-water **(Fig. 5.1)**.

The following type of compounds have been synthesized **(RA-RE) (Fig. 5.1)** and characterized by FTIR, ^{1}H NMR, ^{13}C NMR and HRMS spectroscopic studies:



RA-RE

	R_1	R_2	R_3
RA	H	H	H
RB	H	H	NO_2
RC	NO_2	H	H
RD	NO_2	H	NO_2
RE	NO_2	Boc	NO_2

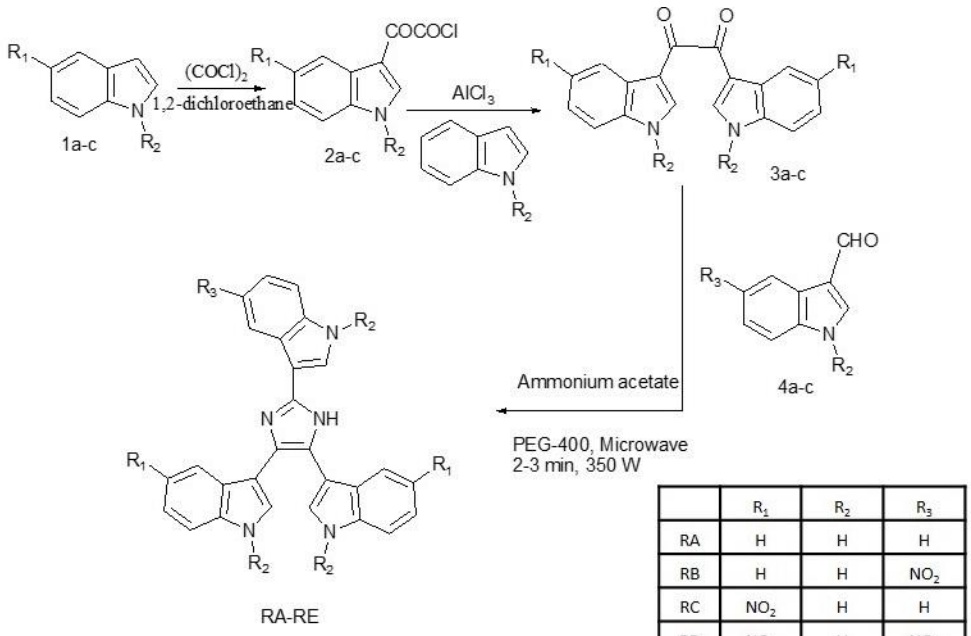
Fig. 5.1: **Molecular representation of 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indole (RA-RE)**

RESULTS AND DISCUSSION

Receptors **RA-RE (Fig.5.1)** have been synthesized by environmentally friendly protocol. 1,2-Bis(indolyl)-ethane-1,2-dione derivatives **(3a-c)** were prepared in stepwise reaction of appropriately substituted indole **(1a-c)** and oxalyl chloride in dichloroethane to give compound **2a-c**, which on further treatment with indole derivatives in presence of aluminium chloride afforded compounds **3a-c**. Compounds **3a-c** are irradiated with formyl indole derivatives **(4a-c)** and ammonium acetate in polyethylene glycol (PEG 400) at 300 W and 180^{o}C in microwave to yield desired final product 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indole **(RA-RE)** in good yields **(Scheme 5.1)**. Compared with the traditional method, this protocol offers several advantages like excellent yields, shorter reaction times, minimal environmental effects and clean reaction.

All the compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic techniques. FTIR of receptors **RA-RD (Fig. 5.1)** show characteristic broad absorption band due to N-H stretching of imidazolium N-H and indolic N-H in the region 3417-3313 cm^{-1} and 3185-3055 cm^{-1} respectively. Receptor **RE** shows absorption band at 3375 cm^{-1} due to N-H stretching of only imidazole N-H. The disappearance of strong absorption band at 1610 cm^{-1} due to C=O stretching present in compounds **3a-c (Scheme 5.1)** indicate the formation of products. A broad band

from 2978-2914 cm^{-1} is assigned to aromatic C-H vibration. Absorption band from 1644-1618 cm^{-1} and 1328-1208 cm^{-1} may be attributed to C=C and C-N streching vibrations, respectively. Two bands in the region 1550-1515 cm^{-1} and 1390-1350 cm^{-1} are observed due to N-O stretching of nitro group(s) present in receptors **RB-RE (Table 5.2, Fig. 5.2).**



	R_1	R_2	R_3
RA	H	H	H
RB	H	H	NO_2
RC	NO_2	H	H
RD	NO_2	H	NO_2
RE	NO_2	Boc	NO_2

Scheme 5.1: Synthesis of 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indoles (RA-RE)

^{1}H NMR spectra of receptors, **RA-RD** exhibit characteristic sharp singlets due to imidazolium N-H and indole N-H in the region δ 12.10-12.55 ppm and δ 9.7-9.81 ppm, respectively. Receptor **RE** displays a sharp singlet at δ 12.15 ppm due to presence of imidazolium N-H only. A multiplet from δ 7.11-8.28 ppm is observed for aromatic protons. ^{13}C NMR spectra of receptors **RA-RE** display characteristic peak at δ 139.05 ppm due to presence of C=N in the molecular structure of receptors. The disappearance of peak at δ 185 ppm due to C=O in the spectra of receptors, which was present in compounds **3a-c**, confirms the formation of products. Aromatic carbons are observed in region ranging from δ 112-136 ppm **(Table 5.2, Fig. 5.3-5.4)**

Peaks at m/z 414.1884 **(RA)**, 459.1427 **(RB)**, 504.1381 **(RC)**, 549.1192 **(RD)** and 849.2776 **(RE)** $[M+H]^+$ in HRMS spectra also confirm the formation of products **(Table 5.2, Fig. 5.5)**.

The names and m.p.'s of all the synthesized compounds **(RA-RE)** are given in **Table-5.1** The IR, ^{1}H NMR and mass spectral data of all synthesized compounds are shown in **Table-5.2.**

The IR, ^{1}H NMR, ^{13}C NMR and mass spectrum of receptor **RD** are given in **Fig. 5.3, 5.4, 5.5** and **5.6,** respectively.

Table-5.1: Names and m.p.'s of 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indole (RA-RE)

Compd No.	Name	M.P. (^{o}C)
RA	3-[2,5-(1H-indol-3-yl)-1H-imidazol-4-yl]-1H-indole	164
RB	3-[2,5-(1H-indol-3-yl)-1H-imidazol-4-yl]-5 nitro-1H-indole	124
RC	3-[5-(5-nitro-1H-indol-3-yl)-2-(1H-indoly-3-yl)-1H-imidazol-4-yl]-5 nitro-1H-indole	211
RD	3-[2,5-(5-nitro-1H-indol-2-yl)-1H-imidazol-4-yl]-5 nitro-1H-indole	222
RE	3-[2,5-(5-nitro-tert butyl-1H-indol-2-yl)-1H-imidazol-4-yl]-5 nitro-tert butyl-1H-indole	194

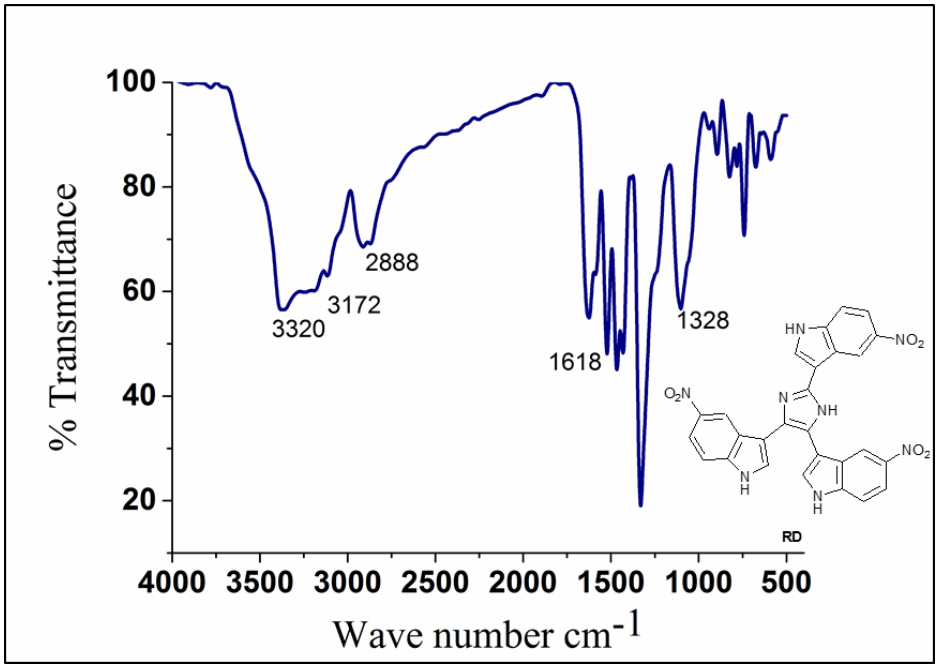


Fig. 5.2: FTIR spectrum of 3-[2,5-(5-nitro-1H-indol-2-yl)-1H-imidazol-4-yl]-5 nitro-1H-indole, RD

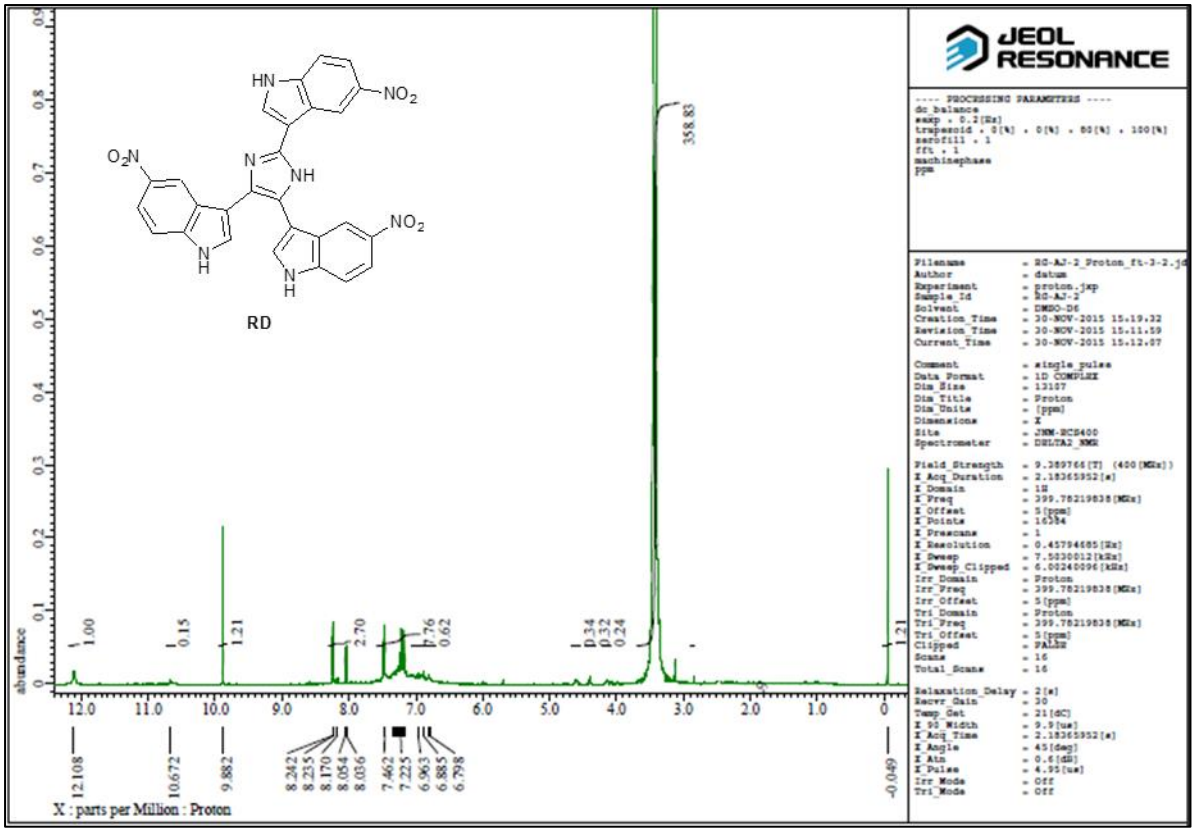


Fig. 5.3: ^{1}H NMR spectrum of 3-[2,5-(5-nitro-1H-indol-2-yl)-1H-imidazol-4-yl]-5 nitro-1H-indole, RD

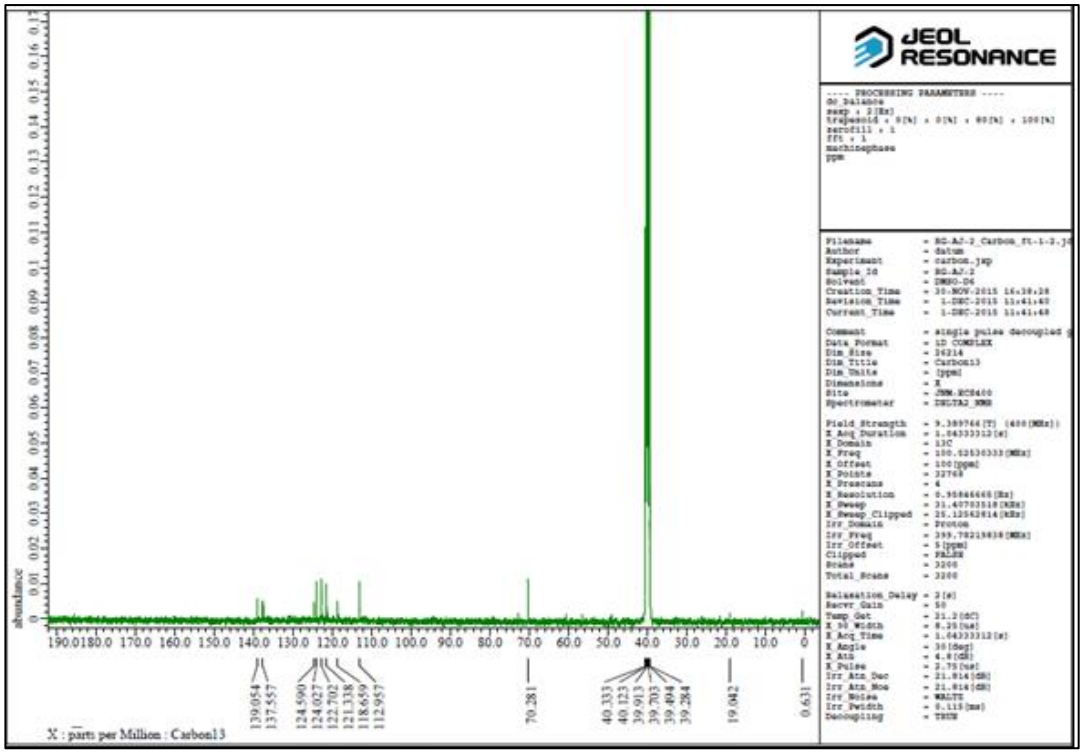


Fig.5.4: ^{13}C NMR spectrum of 3-[2,5-(5-nitro-1H-indol-2-yl)-1H-imidazol-4-yl]-5 nitro-1H-indole, RD

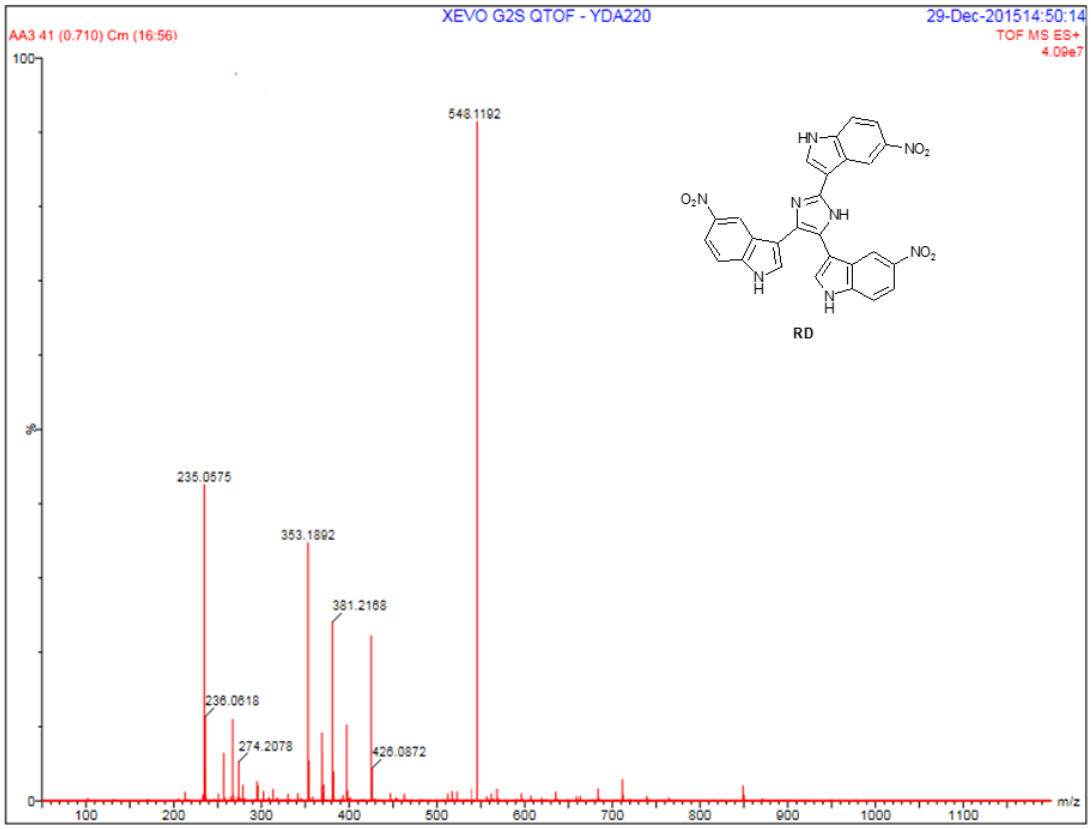


Fig.5.5: ESI Mass spectrum of 3-[2,5-(5-nitro-1H-indol-2-yl)-1H-imidazol-4-yl]-5 nitro-1H-indole, RD

Table-5.2: Spectral data for 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indole (RA-RE)

Compd No.	FTIR(KBr, $\upsilon_{max}cm^{-1}$)	^{1}H NMR (DMSO-d_6, 500 MHz, δppm)	^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm)	HRMS $[M+H]^+$
RA	3406 (Imidazole N-H), 3170 (Indole N-H), 2924 (=C-H), 1644 (C=C), 1234 (C-N)	7.11-7.99 (m, 15H, Ar-H), 9.23 (s, 3H, indole N-H), 12.10 (s, 1H, imidazole N-H)	112.23, 117.95, 120.61, 122.95, 123.29, 123.89, 136.84, 137.30	414.1884 (obsd) Cacd for $C_{27}H_{19}N_5$: 413.1840
RB	3313 (Imidazole N-H), 3055 (Indole N-H), 2914 (=C-H), 1635 (C=C), 1550, 1319 (N-O), 1208 (C-N).	7.20-8.28 (m, 14H, Ar-H), 9.33 (s, 3H, indole N-H), 12.15 (s, 1H, imidazole N-H)	111.33, 118.91, 121.41, 122.95, 124.19, 124.79, 137.84, 138.30	459.1427 (obsd) Calcd for $C_{27}H_{18}N_6O_2$: 458.1491.
RC	3417 (Imidazole N-H), 3185 (Indole N-H), 2978 (=C-H), 1616 (C=C), 1550, 1306 (N-O), 1199 (C-N)	7.59-8.17 (m, 13H, Ar-H), 9.91 (s, 3H, indole N-H), 12.22 (s, 1H, imidazole N-H)	49.12, 51.77, 112.61, 121.59, 123.09, 127.57, 129.10, 130.13, 132.47, 136.11	504.1381 (obsd) Calcd for $C_{27}H_{17}N_7O_4$: 503.1342
RD	3320 (Imidazole N-H), 3172 (Indole N-H), 2888 (=C-H), 1618 (C=C), 1521, 1360 (N-O), 1328 (C-N).	7.22-8.23 (m, 12H, Ar-H), 9.88 (s, 3H, indole N-H), 12.10 (s, 1H, imidazole N-H)	70.28, 112.95, 118.65, 121.33, 122.70, 124.02, 124.59, 137.55, 139.05	549.1192 (obsd) Calcd for $C_{27}H_{16}N_8O_6$: 548.1193
RE	3375 (Imidazole N-H), 2975 (=C-H), 1647 (ester C=O), 1515, 1350 (N-O), 1283 (C=N)	1.65 (s, 9H, CH_3), 7.33-8.17 (m, 12H, Ar-H), 12.15 (s, 1H, imidazole N-H)	30.34, 71.20, 111.98, 118.46, 120.65, 122.33, 124.82, 138.65	849.2776 (obsd) Calcd for $C_{42}H_{40}N_8O_{12}$: 848.2766.

Anion binding studies

The synthesized receptors **RA-RE** were studied for their anion binding tendencies by naked eye, UV-Visible and NMR spectroscopic techniques using different anions as their tetrabutylammonium salts (TBA) *viz.*, fluoride, acetate, chloride, bromide, iodide, dihydrogen phosphate, hydrogen sulphate and nitrate in competitive media, 9:1 DMSO-water.

Naked eye sensing experiment

The anion binding abilities of receptors **RA-RE** (1×10^{-4} M in DMSO) were carefully investigated by naked eye using anions as their TBA salts in 9:1 DMSO-water. An instant and distinctive colour change from yellow to orange was observed upon addition of TBA salt of fluoride ion into receptor **RD** (1×10^{-4} M in DMSO) **(Fig 5.6(a))**. It is worthy to mention that detection limit for fluoride ion is found to be 1.5 ppm, which is regarded as the maximum permissible limit for fluoride in drinking water. Other anions, when were added to receptor individually, they did not show any colour change **(Fig. 5.6(a)).** However, when 1 equivalent of fluoride ion (TBA salt) was added to these solutions, an instantaneous change in colour was noticed in receptor **RD** (1×10^{-4} M in DMSO) **(Fig. 5.6(b))**, similar to colour change induced by fluoride ion alone. It establishes that receptor **RD** can selectively bind fluoride ion irrespective of the presence of other anions. Receptors **RA-RC** were found insensitive to the addition of anions and no change in colour was noticed in their solutions, even at high concentration (1×10^{-3} M) of anions (TBA salts). Another receptor **RE** was found to give similar qualitative colour change with fluoride ion as receptor **RD**. In order to enhance the binding affinity and selectivity, electron withdrawing nitro group(s) was introduced at 5^{th} position of indole rings in molecular framework of receptors and it was observed that receptors **RD** and **RE,** containing maximum number of nitro groups, gave promising results in terms of naked eye change in presence of fluoride ion (TBA salt) and were further studied.

Fig. 5.6: (a) Colour changes in the receptor RD (1×10^{-4} M in DMSO), in presence of 1equivalent of different anions (TBA salts) in 9:1 DMSO-water, where A, B, C, D, E, F, G and H represent F^-, Cl^-, Br^-, I^-, CH_3COO^-, $H_2PO_4^-$, HSO_4^- and NO_3^- ions, respectively. (b) Colour changes in the receptor RD (1×10^{-4} M in DMSO), in presence of 1equivalent each of fluoride and different anions (TBA salts) in 9:1 DMSO-water, where A, B, C, D, E, F, G and H are receptor and, $F^- + Cl^-$, $F^- + Br^-$, $F^- + I^-$, $F^- + CH_3COO^-$, $F^- + H_2PO_4^-$, $F^- + HSO_4^-$ and $F^- + NO_3^-$, respectively

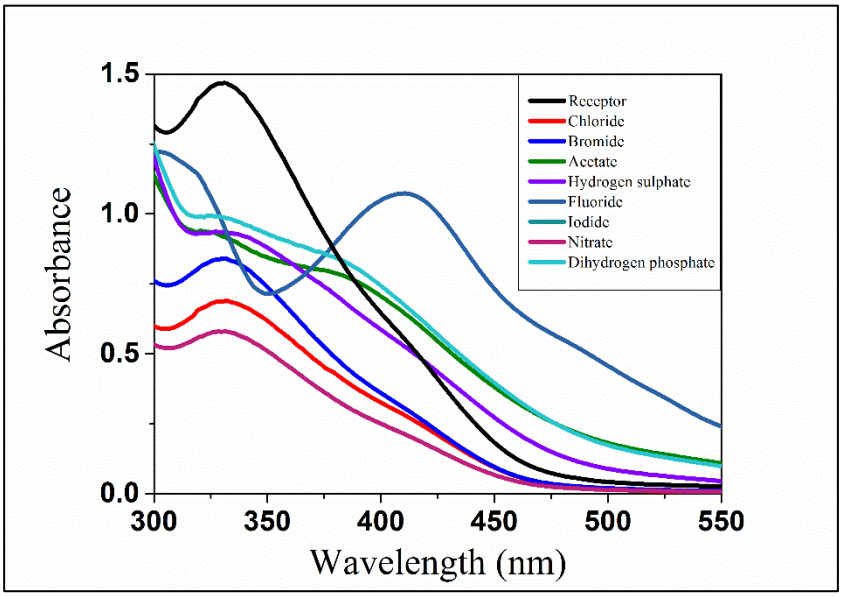


Fig. 5.7: UV-Visible spectra of receptor RD (1×10^{-4} M in DMSO) upon addition of different anions (TBA salts, 1×10^{-4} M) in 9:1 DMSO-water

UV-Visible titration experiment

Further investigation on anion affinity studies of receptor **RD** were performed using UV-Visible spectrophotometry to corroborate the initial qualitative studies. Receptor **RD** reveals maxima at 330 nm in UV-Visible spectra. Different anions, (TBA salts), when were added into the solution of receptor **RD** in DMSO, produces no change in maxima of receptor **(Fig. 5.7)**. On the other hand, when fluoride was added, peak at 330 nm disappeared and a new peak at 410 nm appeared. The red shift of 80 nm established that the binding interaction took place between fluoride ion and receptor. The results obtained established the selective and sensitive nature of receptor for fluoride spectroscopically. To ascertain the receptor-fluoride ion interaction, UV-Visible titration experiment was carried out with incremental addition of fluoride to receptor solution. Upon titration with fluoride with concentration varying from 1×10^{-5} to 1×10^{-3} M, peak at 330 nm decreased and absorbance of new peak at 410 nm increased **(Fig. 5.7-5.8)**. These observations led to deduce that the formation of hydrogen bonding interaction between fluoride ion and receptor may be responsible for the large bathochromic shift in the maxima of receptor **[51]**. For more information on the binding process, ^{1}H NMR titration was carried out.

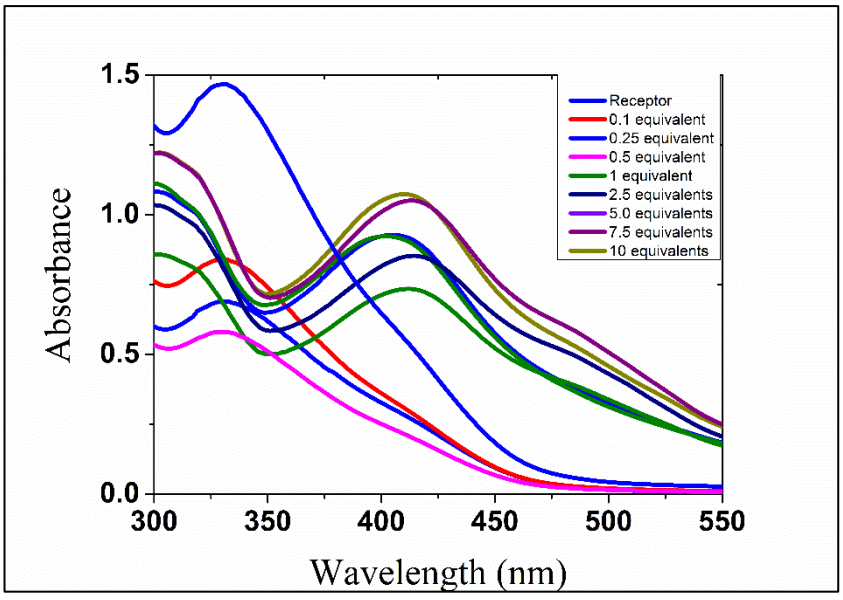


Fig. 5.7: UV-Visible spectra of receptor RD (1×10^{-4} M in DMSO) upon addition from 0.1 to 10 equivalents of fluoride ion (TBA salt) in 9:1 DMSO-water

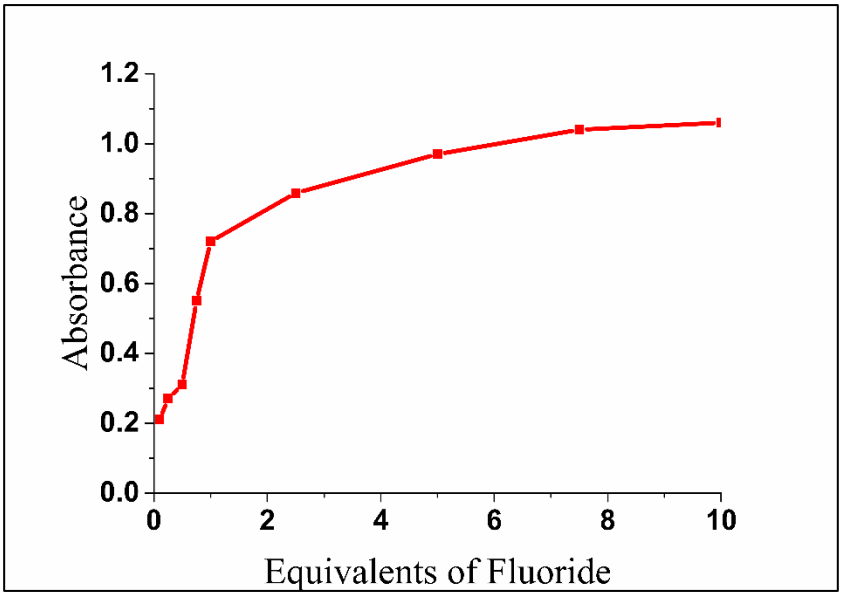


Fig. 5.8: Changes in absorbance at 410 nm of receptor RD (1×10^{-4} M in DMSO) with increase in fluoride ion concentration (1×10^{-5} to 1×10^{-3} M in 9:1 DMSO-water)

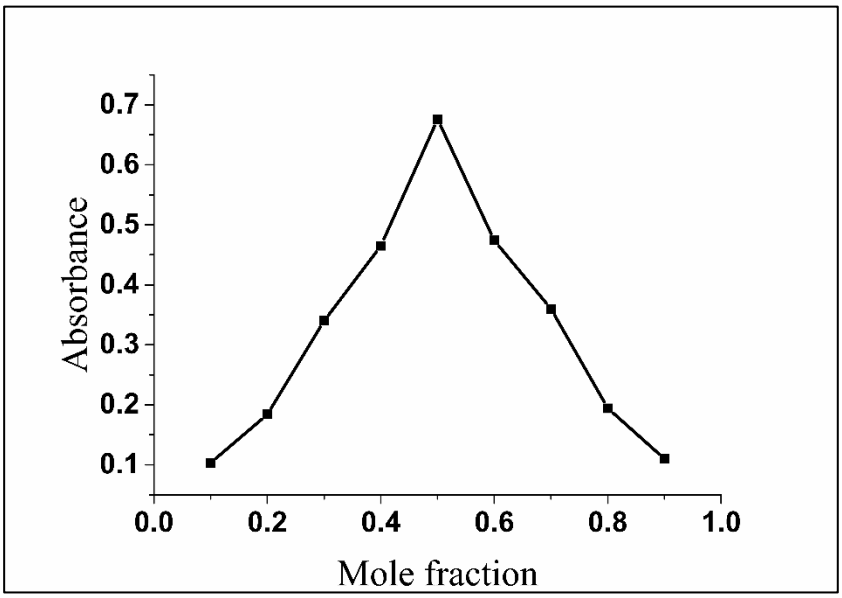


Fig. 5.9: Job's Plot with receptor RD (1×10^{-4} M in DMSO) and fluoride ion (TBA salt) 1×10^{-4} in 9:1 DMSO-water

Continuous variation method (Job's plot) was employed for the determination of stoichiometric ratio of the complex formed between fluoride ion and receptor **RD**,

where the concentration of both receptor and fluoride ion salt were kept constant (1×10^{-4} M in DMSO) **[52]**. The molar fraction of fluoride/ (receptor + fluoride) is continuously varied. At the molar fraction of 0.50, the absorbance reaches its maxima, revealing that receptor forms 1:1 complex with fluoride ion **(Fig. 5.9).** It was also proved by mass spectrum of receptor **RD** with fluoride ion (TBA salt), which exhibited a peak at m/z 568.0351 [Calculated for receptor **RD** + F^- +H^+: 568.1092] **(Fig. 5.10)**

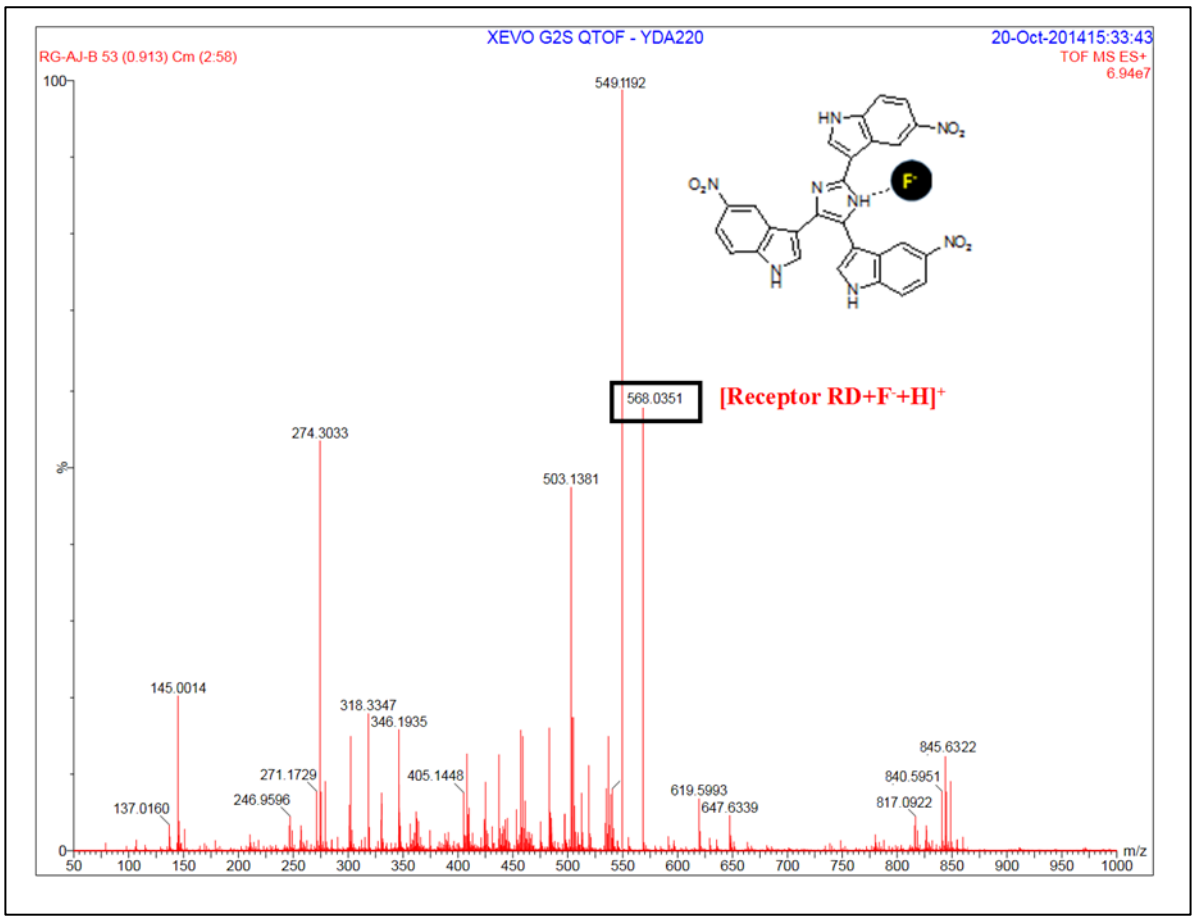


Fig. 5.10: ESI-mass spectrum of complex of receptor RD with fluoride ion

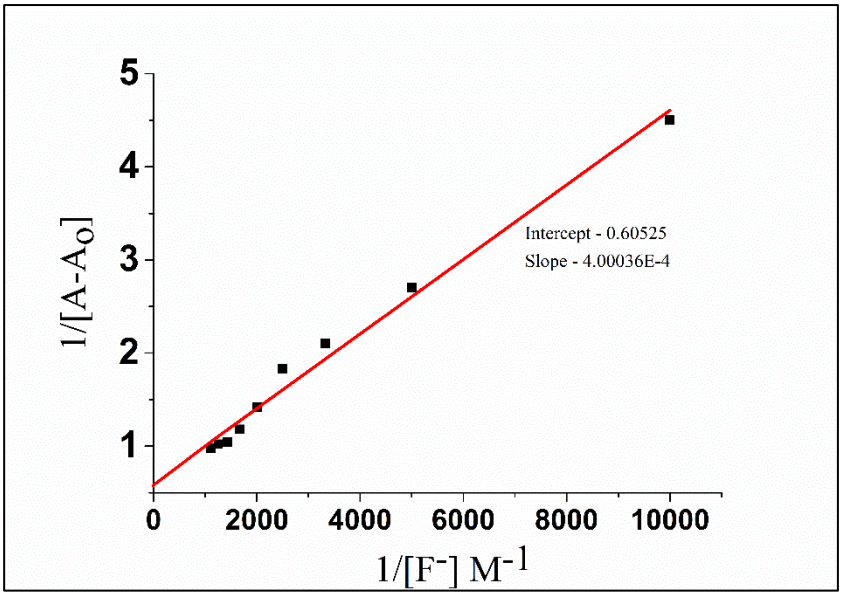


Fig. 5.11: Fitting curve of Benesi Hildebrand equation of receptor RD with fluoride ion

The binding constant of receptor **RD** with fluoride is evaluated by Benesi Hildebrand plot **[53].** The binding constant K, calculated from the graph **(Fig. 5.11)** was found to be $0.15 \times 10^4\ M^{-1}$.

^{1}H NMR titration experiment

The foregoing result of UV-Visible spectroscopic titration indicates towards the formation of binding interaction between receptor **RD** and fluoride ion. In order to affirm the mechanism of sensing event, ^{1}H NMR titration was carried out. Receptor **RD** solution is prepared in DMSO-d_6 (1×10^{-2} M) and fluoride ion in the form of its TBA salt of varying concentrations (2.5, 5, 7.5 and 10 equivalents) were added sequentially **(Fig. 5.12).** It was observed in the ^{1}H NMR spectrum of receptor **RD**, the sharp singlet at δ 12.2 ppm, corresponding to imidazole N-H, showed a downfield shift upon addition of fluoride ion and intensity of peak decreased as the concentration of fluoride ion increased. The peak disappeared altogether, when fluoride concentration reached 10 equivalents. Indole N-H at δ 9.8 ppm remains unchanged during titration. It is evident that interaction between receptor and fluoride ion initiated by hydrogen bonding, as depicted by downfield shift of imidazolium N-H proton in initial stage. Later, the excess addition of fluoride ion triggered the deprotonation of imidazolium N-H proton, witnessed by the disappearance of N-H peak and appearance of peak corresponding to HF_2^- ion at 16.1 ppm **[54]**.

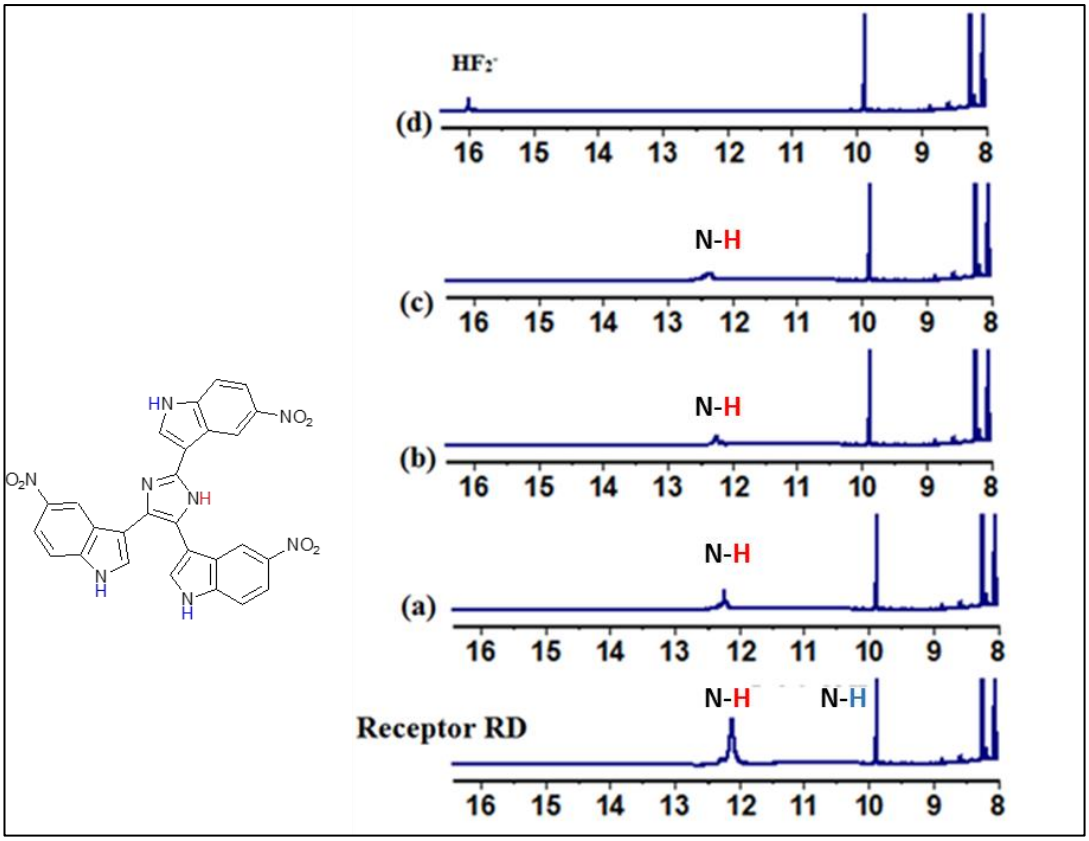
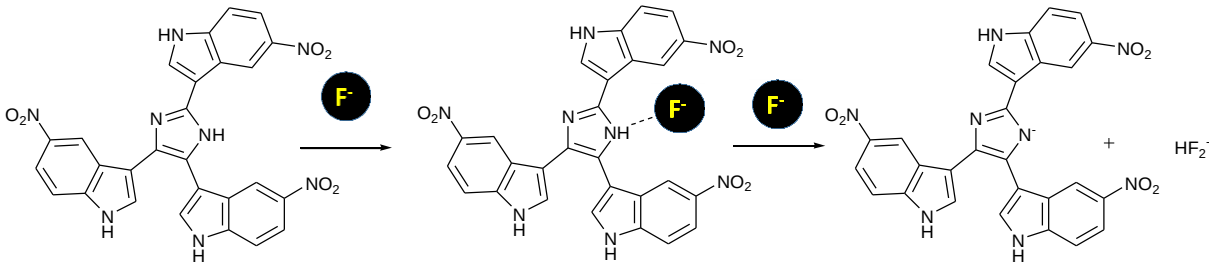


Fig. 5.12: Partial ^{1}H NMR (400 MHz) spectra of receptor RD in DMSO-d_6 (1×10^{-2} M) in the presence of (a) 2.5, (b) 5, (c) 7.5 and (d) 10 equivalents of TBAF in DMSO-d_6

Further evidence of participation of only imidazolium N-H was provided by the synthesis of compound **RE**, where three indole NH are protected by di-*tert*-butyl dicarbonate (Boc). It exhibited naked eye colour change from yellow to orange in presence of fluoride ion similar to receptor **RD**, which proves that three indole NH are not involved in binding process.

On the basis of above studies, the plausible mechanism of binding between **RD** and fluoride ion is depicted in **Scheme 5.2**.



Scheme 5.2: Plausible mechanism of binding between receptor RD and fluoride ion

The pH effect on RD-F^- interaction

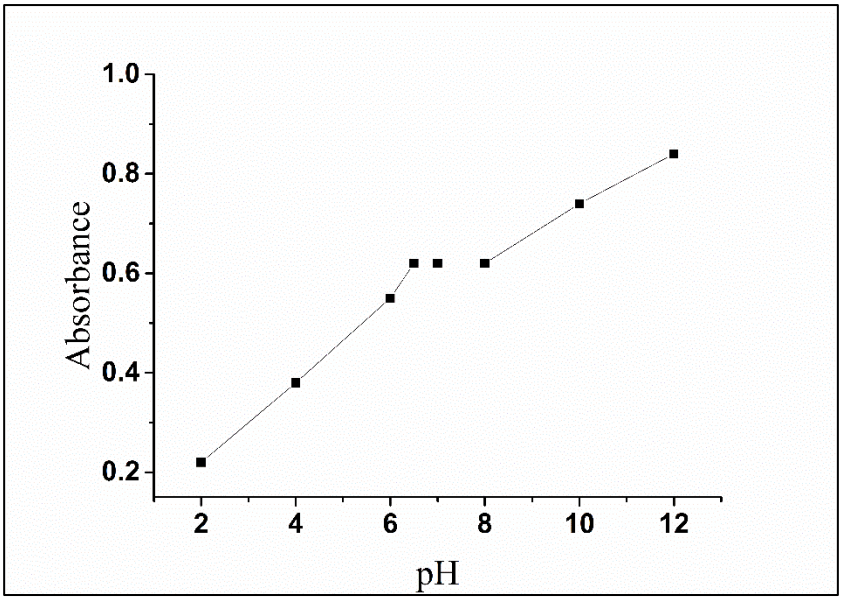


Fig. 5.13: Changes in absorbance of receptor RD (1×10^{-4} M in DMSO) and fluoride ion (1×10^{-4} M in 9:1 DMSO-water) with varying pH (2-12)

To investigate the effect of pH on receptor RD-F^- binding affinity, changes in the intensity of the absorbance band at 410 nm were observed over a pH range 2-12 **(Fig. 5.13).** The working pH range was found to be 6.5-8.0, where the intensity of absorbance remains constant. Below pH 6.5, intensity of absorbance band at 410 nm decreased rapidly. This is probably due to protonation of fluoride ion, to form weakly ionized hydrofluoric acid, which decreases the affinity of fluoride ion to bind receptor

binding site, N-H. Above pH 8.0, intensity of this absorption peak at 410 nm increased, which can be attributed to increased availability of deprotonated receptor to establish stronger hydrogen binding interactions with fluoride ion.

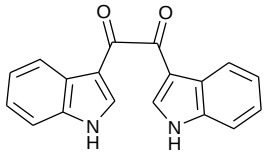
CONCLUSION

A structurally simple and easy to synthesize imidazole-indole based receptor **RD** has been synthesized for easy and robust detection of inorganic fluoride in 9:1 DMSO-water. It senses fluoride ion at 1.5 ppm (WHO recommended level) with colour change from yellow to orange, perceivable by naked eye. Detection of fluoride ion in aqueous media makes the receptor suitable for practical applications.

EXPERIMENTAL

Preparation of 1,2-bis(5-substituted-3-indolyl)ethane-1,2-dione,3a-b

1,2-Bis(3-indolyl)ethane-1,2-dione, 3a



3a

1,2-Bis(3-indolyl)ethanedione **(3a)** was prepared by following a literature method **[55]**. To a stirred suspension of indole (0.005 mol, 0.585 g) **1a**, in dichloroethane (20 ml), oxalyl chloride (0.005 mol, 0.45 ml) was slowly added at 0 $^{\circ}$C, after which the reaction mixture was stirred for further 20 minutes at room temperature to give a crystalline deposit of 3-indoyl glyoxalyl chloride **(2a)**. Aluminium(III) chloride, (0.022 mol, 3 g) in a mixture of dichloroethane (5 ml) and heptane (3 ml) was then slowly added to the above reaction mixture in portions over a period of 3-5 minutes. Then, a solution of indole (0.005 mol, 0.585 g) in dichloroethane (5 ml) was added dropwise and the mixture was stirred until the reaction was complete, as monitored by thin layer chromatography (ethyl acetate). It was poured into ice-water (100 ml), extracted with ethyl acetate, dried over sodium sulphate and concentrated under reduced pressure. The residue so obtained was recrystallized from ethanol to afford brown crystals and was characterized by FTIR, ^{1}H NMR and mass spectral data.

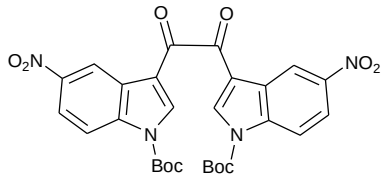
M.P.(^{o}C)	275-278 ^{o}C (Lit **[55]** M.P. 274-276 ^{o}C)
Yield (%)	88 % (Lit **[55]** Yield 75.6 %)
IR (KBr) ν_{max} cm^{-1}	3410 (N-H), 2980 (=C-H), 1610 (C=O)
^{1}H NMR (DMSO d_6) δ ppm	7.32 (m, 4H, Ar-H), 7.57 (m, 2H, Ar-H), 8.28 (m, 2H, Ar-H), 12.26 (s, 2H, NH)
Mass [M+H]$^{+}$	289.3042 [M+H]$^{+}$Calcd. for $C_{18}H_{12}N_2O_2$: 288.3001

Compound, **3b** was prepared similarly. Physical data of synthesized compounds are given in **Table 5.3**

Table 5.3: Physical data of 1,2-bis(5-substituted-3-indolyl)ethanedione derivatives 3a-b

S. No.	X	Mol. Formula	Mol. Wt	Yield %	M.P. (^{o}C)
1	H	$C_{18}H_{12}N_2O_2$	288.3001	88	275-278
2	NO_2	$C_{18}H_{10}N_4O_6$	378.0110	81	250-252

Preparation of Boc-protected 1,2-bis-(5-nitro-1H-indol-3-yl)-ethane-1,2-dione (3c)

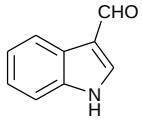


3c

The title compound was prepared by following literature method **[56]**. To the solution of 1,2-bis-(5-nitro-1H-indol-3-yl)-ethane-1,2-dione (0.001 mol, 0.378 g) in THF was added aqueous sodium bicarbonate (0.336 g in 10 ml of water) with constant stirring at 0 ^{o}C. Boc anhydride (0.0024 mol, 0.52 g) was then added dropwise after 10 minutes and reaction was stirred for 24 hours. The progress of reaction was monitored by TLC. After completion of reaction, as indicated by TLC (ethyl acetate), product was extracted by dichloromethane, washed with citric acid and brine solution and dried over sodium sulphate. Pale yellow coloured solid was obtained by concentrating the above solution under reduced pressure and was recryatallized by absolute ethanol. Pure compound was characterized by FTIR, ^{1}H NMR and mass spectral data.

M.P.(^{o}C)	212 ^{o}C (Lit **[56]** M.P. 211^{o}C)
Yield (%)	74 % (Lit **[56]** Yield 75.6 %)
IR (KBr) ν_{max} cm^{-1}	2995 (=C-H), 1690 (ester C=O), 1635 (C=O), 1245 (C-N)
^{1}H NMR (DMSO-d_6) δ ppm	δ1.62 (s, 9H, CH_3), 7.1-7.8 (m, 8H, Ar-H)
Mass [M+H]$^{+}$	579.5280[M+H]$^{+}$ (Calcd for $C_{28}H_{26}N_4O_{10}$: 578.5312)

Preparation of indole-3-carbaldehyde (4a-b)



4a

It was prepared by following the method of Joshi *et al.* **[57]**. Phosphorus oxychloride (0.06 mol, 5.5 ml) was added slowly with continuous stirring into *N*,*N*-dimethyl formamide (30 ml) at 10-15 °C. To the resultant solution, indole (0.05 mol, 10.55 g) was added in portions with stirring at 40-50 °C. The solution was further stirred for 45 minutes and then poured into water (100 ml). Sodium hydroxide solution (2N, 100 ml) was then added and the mixture was heated on a water bath for an hour. It was cooled, filtered and dried. The compound thus obtained was recrystallized from absoluteethanol and was characterized by FTIR, ^{1}H NMR and mass spectral data.

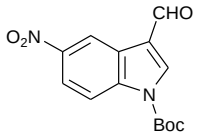
M.P. (^{o}C)	193-196 ^{o}C (Lit **[57]** M.P. 194-196 ^{o}C)
Yield (%)	86 % (Lit **[57]**Yield 81 %)
IR (KBr) ν_{max} cm^{-1}	3220-3100 (N-H), 3025 (=C-H), 1620 (C=O)
^{1}H NMR ($CDCl_3$) δ ppm	δ 7.2 (m, 2H, Ar-H), 7.4 (m, 2H, Ar-H), 8.5 (s, 1H, -HC=O), 8.9 (s, 1H, N-H)
Mass [M+H]$^{+}$	146.1612 [M+H]$^{+}$(C_9H_7NO: 145.1580)

5-nitro-indole-3-carbaldehyde **(4b)** has been prepared in a similar manner and is listed in **Table-5.4**

Table 5.4: Physical data of (un)substituted indole-3-carbaldehydes (4a-b)

Compd No.	X	Mol. Formula	Mol. Wt	Yield %	M.P. (^{o}C)
4a	H	C_9H_7NO	145.16	86	193-196
4b	NO_2	$C_9H_6N_2O_3$	189.15	78	300

Preparation of 3-formyl-5-nitro-indole-1-carboxylic acid tert-butyl ester (4c)



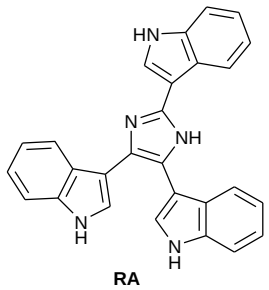
4c

To the solution of 5-nitro-1H-indole-3-carbaldehyde (0.001 mol, 0.189 g) in THF (5 ml) was added aqueous sodium bicarbonate (0.336 g in 10 ml of water) with constant stirring at 0 ^{o}C. Boc anhydride (0.0024 mol, 0.52 g) was then added dropwise after 10 minutes and reaction was stirred for 24 hours. The progress of reaction was monitored by TLC (8:2 pet ether-ethyl acetate). After completion of reaction, product was extracted by dichloromethane, washed with citric acid and brine solution and dried over sodium sulphate. Pale yellow coloured solid was obtained by concentrating the above solution under reduced pressure and was recrystallized by ethanol to obtain desired title compound. Pure compound was characterized by FTIR, ^{1}H NMR and mass spectral data **[56].**

M.P.(^{o}C)	198 ^{o}C (Lit **[56]** M.P. 199 ^{o}C)
Yield (%)	91 % (Lit **[56]** Yield 90 %)
IR (KBr) ν_{max} cm^{-1}	3044 (=C-H), 1695 (ester C=O), 1630 (C=O)
^{1}H NMR ($CDCl_3$) δ ppm	δ 1.63 (s, 9H, CH_3), 7.2-7.4 (m, 3H, Ar-H), 7.7 (s, 1H, Ar-H)
Mass [M+H]$^{+}$	291.2746 [M+H]$^{+}$**(**$C_{14}H_{14}N_2O_5$: 290.2714)

Preparation of 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indole (RA-RE)

3-[2,5-(1H-indol-3-yl)-1H-imidazol-4-yl]-1H-indole, RA



RA

A mixture of 1,2-bis(indolyl)-ethane-1,2-dione (0.001 mol, 0.288 g), indole aldehyde (0.001 mol, 0.145 g) and ammonium acetate (0.004 mol, 0.30 g) in polyethylene glycol (2 ml) was irradiated at 180 °C and 350 W power. The progress of reaction was monitored by TLC in 9:1 (ethyl acetate: methanol). After completion of reaction, as observed by TLC after 5 minutes, the reaction mixture was cooled to room temperature and poured into 100 ml ice water. The separated solid was filtered and washed with water to yield brown solid, which was purified by column chromatography (ethyl acetate) to yield desired title product.

M.P. (^{o}C)	164 ^{o}C
Yield (%)	89.10 %
IR (KBr) ν_{max} cm^{-1}	3406 (Imidazole N-H), 3170 (Indole N-H), 2924 (=C-H), 1644 (C=C), 1234 (C-N)
^{1}H NMR(DMSO-*d*$_6$, 500 MHz, ppm)	δ7.11-7.99 (m, 15H, Ar-H), 9.23 (s, 3H, indole N-H), 12.10 (s, 1H, imidazole N-H)
^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm)	112.23, 117.95, 120.61, 122.95, 123.29, 123.89, 136.84, 137.30.
Mass[M+H]$^{+}$	414.1884 $[M+H]^{+}$ Calculated for $C_{27}H_{19}N_5$: 413.1840.

All other receptors, **RB-RE** were prepared similarly. Physical data of synthesized compounds are given in **Table 5.5.**

Table 5.5: Physical data of of 3-[2,5-{(un)substituted-1H-indol-3-yl}-1H-imidazol-4-yl]-(un)substituted-1H-indole derivatives (RA-RE)

Compd No.	R_1	R_2	R_3	Mol. Formula	Mol. Weight	Yield %	Time (min.)
RA	H	H	H	$C_{27}H_{19}N_5$	412.1840	89	5
RB	H	H	NO_2	$C_{27}H_{18}N_6O_2$	458.1491	88	6
RC	NO_2	H	H	$C_{27}H_{17}N_7O_4$	503.1342	85	5
RD	NO_2	H	NO_2	$C_{27}H_{16}N_8O_6$	548.1193	87	8
RE	NO_2	Boc	NO_2	$C_{42}H_{40}N_8O_{12}$	848.2766	85	6

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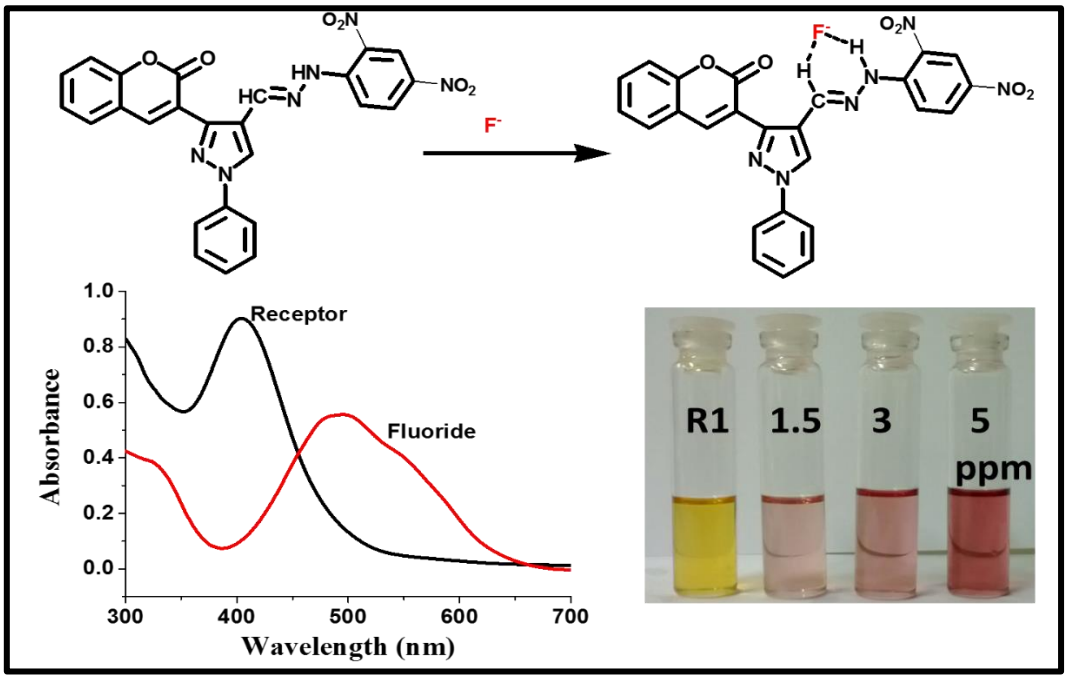
Chapter-6

Design and synthesis of 3-{4-[(un)substituted-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}- chromen-2-ones



Highlights:

- Instantaneous and selective bare eye detection of safe and permissible limits of inorganic fluoride ion (0.95 ppm) in 1:1 DMSO-water
- Perceivable colour grading at 1.5, 3 and 5 ppm of fluoride ion levels for semi-quantitative detection

INTRODUCTION

The design and synthesis of chemosensors for fluoride ion detection has been fascinating the researchers over the past decade because of the significant health and environmental consequences of fluoride ion levels **[1-5]**. Fluoridated drinking water, toothpaste, mouthwash and food items constitute the major sources that contribute to fluoride ion intake by human body **[6]**. Though, necessary in small amounts for prevention of dental caries, regular intake of excess fluoride ion is reported to cause several chronic diseases such as nausea **[7-8]**, skeletal and dental fluorosis **[9-10]**, hyperglycemia **[11]**, coma **12]** and osteomalecia **[13]**. This dubious nature of fluoride ion has arisen a mounting interest in chemists to develop routes for fast, easy and inexpensive detection of fluoride ion in water both qualitatively as well as quantitatively **[14]**. Traditional procedures for fluoride ion detection using ion meter or spectroscopic techniques are expensive, time consuming and require skillful personnel **[15]**. On the other hand, naked eye receptor is simple, easy to use and well suited for instantaneous on-site analysis **[16-17]**. Colorimetric fluoride ion receptors have been developed, most of which can bind only organic fluoride, *i.e.* tetrabutylammonium fluoride (TBAF), which restricts their viability in providing adequate solution to the concerned problem **[18-20]**. Therefore, it appears prudent to examine if it is possible to develop a receptor with capability of detecting inorganic fluoride ion *via* naked eye, thereby dispensing the use of expensive instruments.

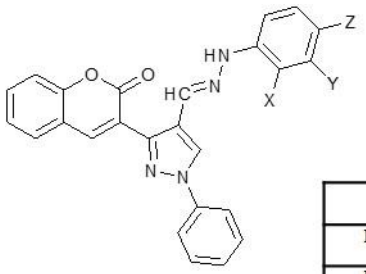
Chemosensors are usually assembled on receptor-chromophore binomial, wherein anion binds at receptor site and chromophore is responsible for turning this event into an optical signal or visual colour change **[21-22]**. Heterocyclic compounds containing conjugated π bonds associated with them, are excellent candidates as signalling unit due to interesting photophysical properties **[23]**. These signalling units are covalently attached to binding units, containing acidic N-H, to construct colorimetric anion receptors **[24]**. Acidity of N-H groups can be fine-tuned by suitable insertion of electron withdrawing groups, which increases the binding capabilities of receptor with anions **[25]**. When anion interact with such receptors, it establishes hydrogen bonding interactions with N-H group of receptors initially, followed by deprotonation of N-H, which triggers an extended conjugation or π-delocalisation and alters the dipole associated to the charge-transfer transition or in other words, stabilizes the excited

state of chromophoric group. This is ultimately observed as vivid colour change as output **[26]**. Design of receptors can be further reformed by the incorporation of more hydrogen bond donors with the aim to establish high binding affinity with anion **[27]**. Introducing acidic C-H group(s) along with N-H groups in the structure of receptor enhances the strength of interactions with anion. Triazole C-H, aromatic C-H and imine C-H can fruitfully serve this purpose **[28-30]**.

Selective detection of fluoride ion over other anions in competitive media necessitates the fine-tuning of the acidity of protons by suitable placement of electron withdrawing substituents **[31]**. Another problem with receptors is their inability to function in aqueous media since acidity of water molecules is higher than that of protons of receptor involved in binding **[32]**. To realize this act, researchers have attempted to incorporate moieties *viz.*, urea/thiourea **[33-34]**, pyrrole **[35-36]**, indole **[37-38]**, imidazole **[39]** *etc*., having acidic N-H group that can form hydrogen bond with fluoride ion effectively and give a discernible colour change **[40]**. Unfortunately, in most of these cases, receptors cannot distinguish between fluoride ion and related basic anions, acetate and hydrogen diphosphate due to competitive interactions **[41-42]**.

Scanty reports of heterocycles as selective naked eye inorganic fluoride ion receptors in aqueous media **[43-44]** motivated us to develop a new fluoride ion receptor **R1-R5 (Fig 6.1)** which could provide a distinctive solution to mitigate the above said problems. Literature survey revealed that coumarin unit has been condensed with thiazole moiety to construct chromophoric units **[45-46]**. Pyrazole too has been explored as anion receptor **[47]**. However, no report of coumarin-pyrazole as chromophoric unit has been reported so far, this encouraged us to explore its utility in construction of anion receptors. Further, these compounds are easy to prepare and stable. Receptors 3-{4-[(un)substituted-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-ones**, R1-R5** have been variously substituted with electron withdrawing groups, nitro and trifluoromethyl groups, at differing positions to study their influence on fluoride binding properties **(Fig 6.1)**. Out of the five derivatives synthesized, receptor **R1** detects inorganic fluoride ion (NaF) in competitive media,1:1 DMSO-water, *via* naked eye colour change from yellow to pink, which can serve as useful aid for practical purpose.

The following type of compounds have been synthesized and characterized by standard spectroscopic techniques (FTIR, ^{1}H NMR, ^{13}C NMR and HRMS) **(Fig 6.1):**



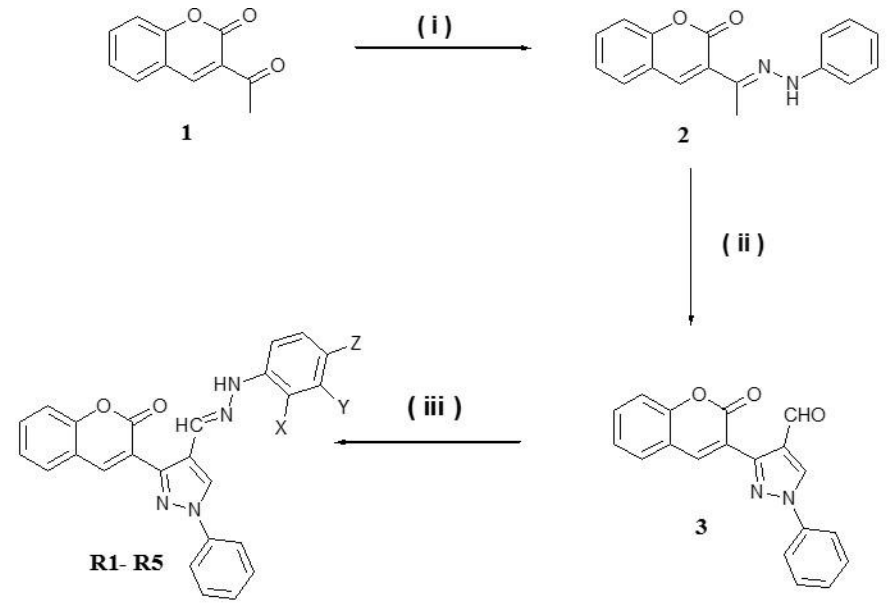
R1-R5

	X	Y	Z
R1	NO_2	H	NO_2
R2	H	H	H
R3	NO_2	H	H
R4	H	CF_3	H
R5	H	H	H

Fig. 6.1: Molecular representation of receptors, 3-{4-[(un)substituted-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-ones (R1-R5)

RESULTS AND DISCUSSION

In general, receptors are crafted through binding unit- signaling unit approach **[48]**. Accordingly, heterocyclic moieties, coumarin and pyrazole have been combined together to form a colorimetric signaling unit and further, condensed with (un)substituted phenylhydrazines to yield imine bond with acidic N-H and C-H hydrogen bond donor groups as a binding unit for fluoride ion **(Scheme 6.1)**. Variously substituted receptors with electron withdrawing groups at differing positions, **R1-R5**, were prepared to have a rational idea about their effects on the anion binding capabilities.



(i) Phenylhydrazine, microwave, 100 W, 80 °C
(ii) DMF-$POCl_3$, ultrasonication, 80 °C
(iii) (un)substituted phenylhydrazine, microwave, 100 W, 80 °C

	X	Y	Z
R1	NO_2	H	NO_2
R2	H	H	H
R3	NO_2	H	H
R4	H	CF_3	H
R5	H	H	H

Scheme 6.1: Synthesis of 3-{4-[(un)substituted-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-ones (R1-R5)

Compounds 3-acetyl coumarin **(1)** and 3-[1-(phenylhydrazono)-ethyl]-chromen-2-one **(2)** were prepared by following the procedure of Perekalin *et al.* and Chodankar *et al.*, respectively **(Scheme 6.1) [49-50]**. Sonication of compound **2** with DMF/$POCl_3$ at 80 ^oC yielded formyl 3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde **(3) [51]**, which gave the title compounds as orange coloured products **(R1-R5)** upon microwave irradiation with (un)substituted phenylhydrazine.

FTIR spectra of receptors **R1-R5 (Fig. 6.2)** show characteristic broad absorbance band from 3428-3201 cm^{-1} due to N-H stretching vibration. =C-H Stretching vibration is observed in the regionof 2941-2841 cm^{-1}. Characteristic sharp absorbance peak at 1721 cm^{-1} is assigned to C=O stretching vibration. Aromatic C=C stretching vibration is observed at 1567 cm^{-1}. Two absorbance bands centered at 1545 and 1385 cm^{-1}, due to N-O vibration (NO_2), show the presence of nitro groups in receptors **R1-R3**. A

peak at 1087 cm^{-1} may be attributed to C-F stretching of CF_3 group present in receptor **R4 (Table 6.2, Fig. 6.2).**

In the ^1H NMR spectra of receptors **R1-R5**, two sharp singlets at δ 9.10 and 11.59 ppm appeared due to presence of HC=N and N-H protons. A singlet at δ 8.74 ppm is observed due to the presence of pyran-H. A multiplet ranging from δ 7.38-8.43 ppm may be attributed to aromatic protonsin molecular structure of receptors. The disappearance of peak at δ 9.97 ppm (pyrazolyl CHO) in the spectra confirms the formation of desired products. ^{13}C NMR spectra of **R1-R5** display characteristic peak around δ 129 (=C-H) and 155 ppm (C=N). Aromatic carbons are observed in the region from δ116 – 139 ppm **(Table 6.2, Fig. 6.3-6.4).** In ^{19}F NMR spectra of receptor **R4**, a singlet at δ -81 ppm may be attributed to presence of CF_3 group.

Further validation was provided by HRMS data, which gave an accurate molecular ion peak $[M+H]^+$ at m/z 497.1750 **(R1),** 452.1289 **(R2),**452.1276 **(R3)**, 475.1316 **(R4)** and 407.1451 **(R5)**, that agreed well with their corresponding calculated molecular weight (**Table 6.2, Fig. 6.5**).

Physical and spectral data (FTIR, ^1H NMR, ^{13}C NMR and mass) of all the synthesized compounds **(R1-R5)** are tabulated in **Table 6.1** and**6.2,** respectively.

The IR, ^1H NMR, ^{13}C NMR and mass spectra of receptor **R1** are given in **Fig. 6.2, 6.3, 6.4 and 6.5,** respectively.

Table 6.1: Physical data of 3-{4-[(un)substituted-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-ones (R1-R5)

Compd. No.	Name	M.P. (^oC)
R1	3-{4-[(2,4-Dinitro-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one	198
R2	3-{4-[(4-Nitro-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one	253
R3	3-{4-[(2-Nitro-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one	210
R4	3-{1-Phenyl-4-[(3-trifluoromethyl-phenyl)hydrazonomethyl]-1H-pyrazol-3-yl}-chromen-2-one	234
R5	3-[1-Phenyl-4-(phenylhydrazonomethyl)-1H-pyrazol-3-yl]-chromen-2-one	188

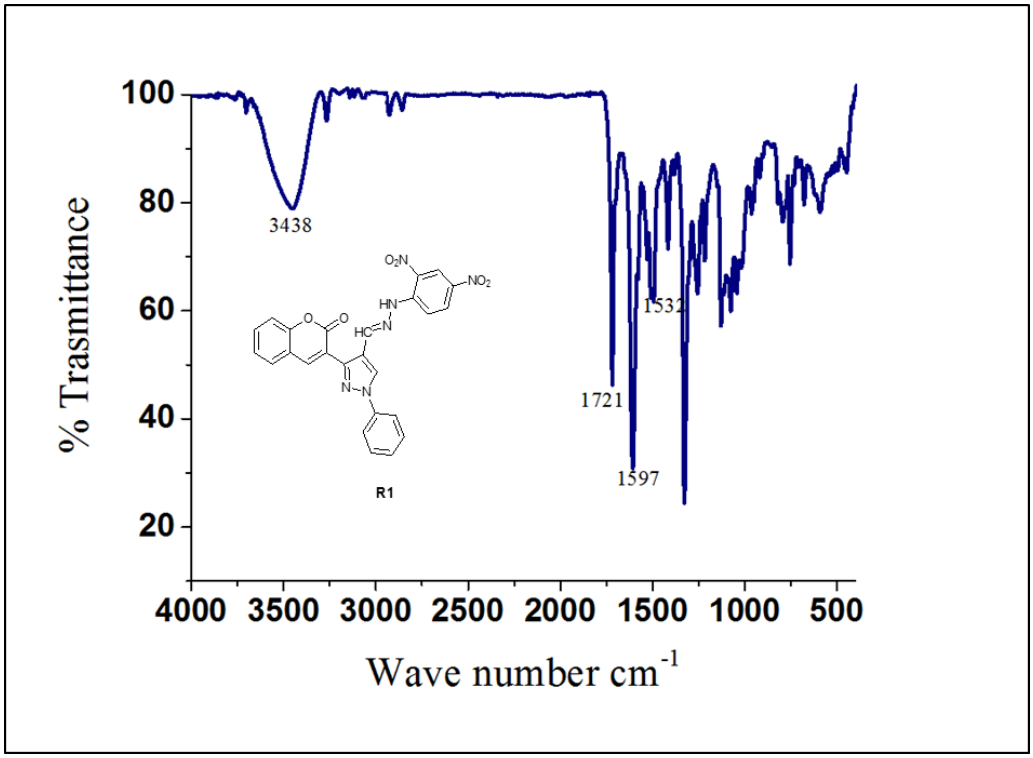


Fig. 6.2: FTIR spectrum of 3-{4-[(2,4-dinitro-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one (R1)

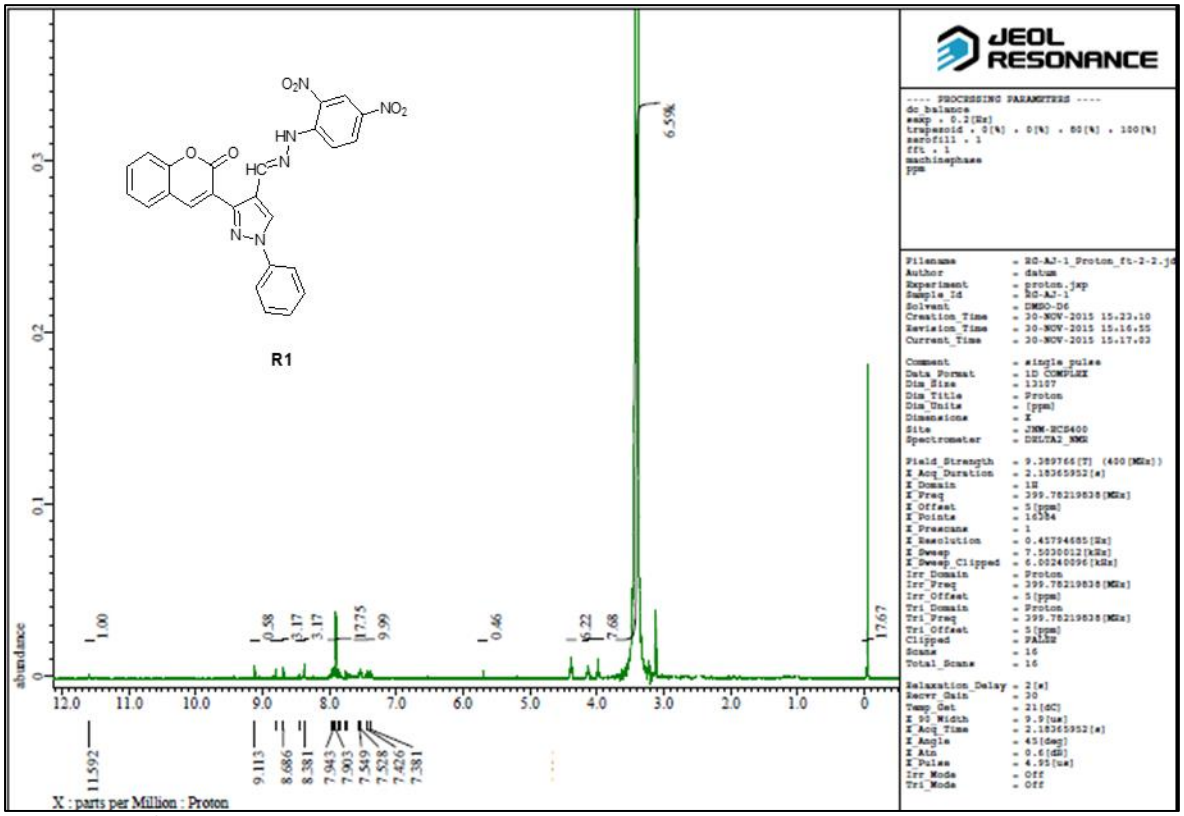


Fig. 6.3: ^{1}H NMR spectrum of 3-{4-[(2,4-Dinitro-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one (R1)

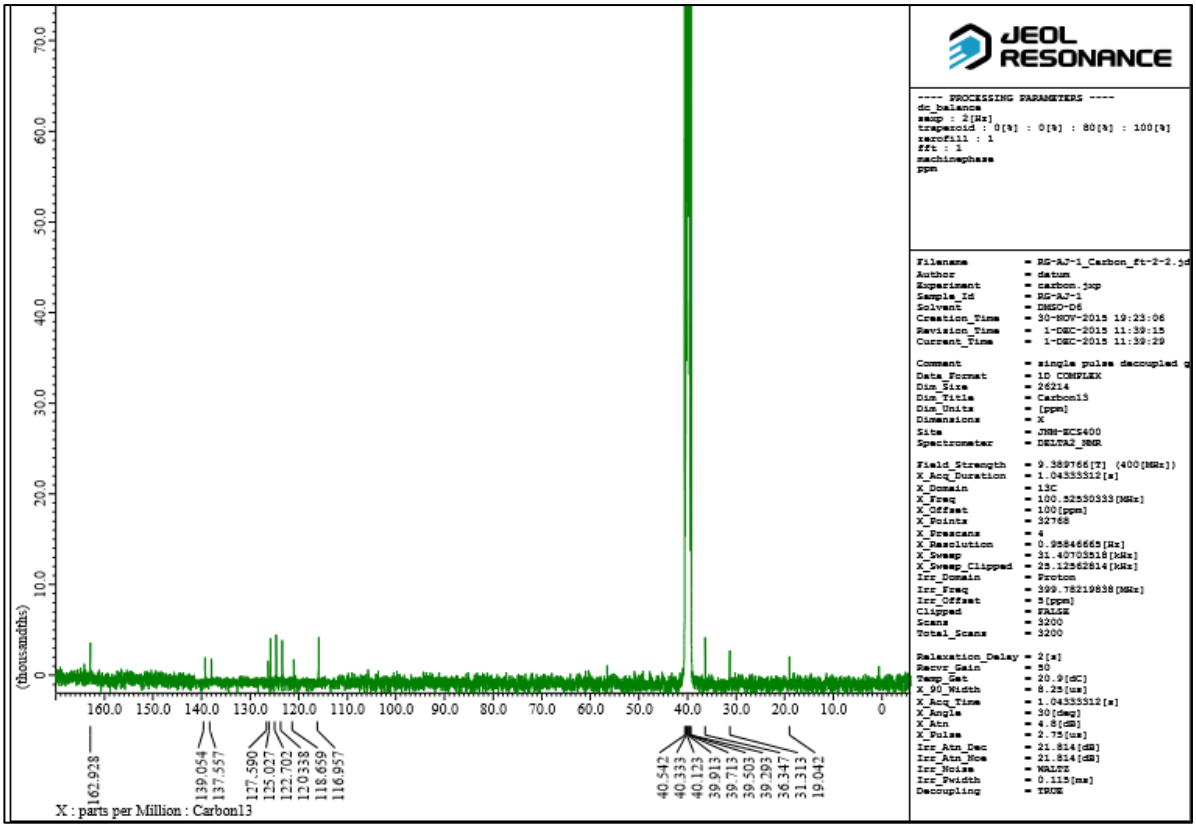


Fig. 6.4: ^{13}C NMR spectrum of 3-{4-[(2,4-Dinitro-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one (R1)

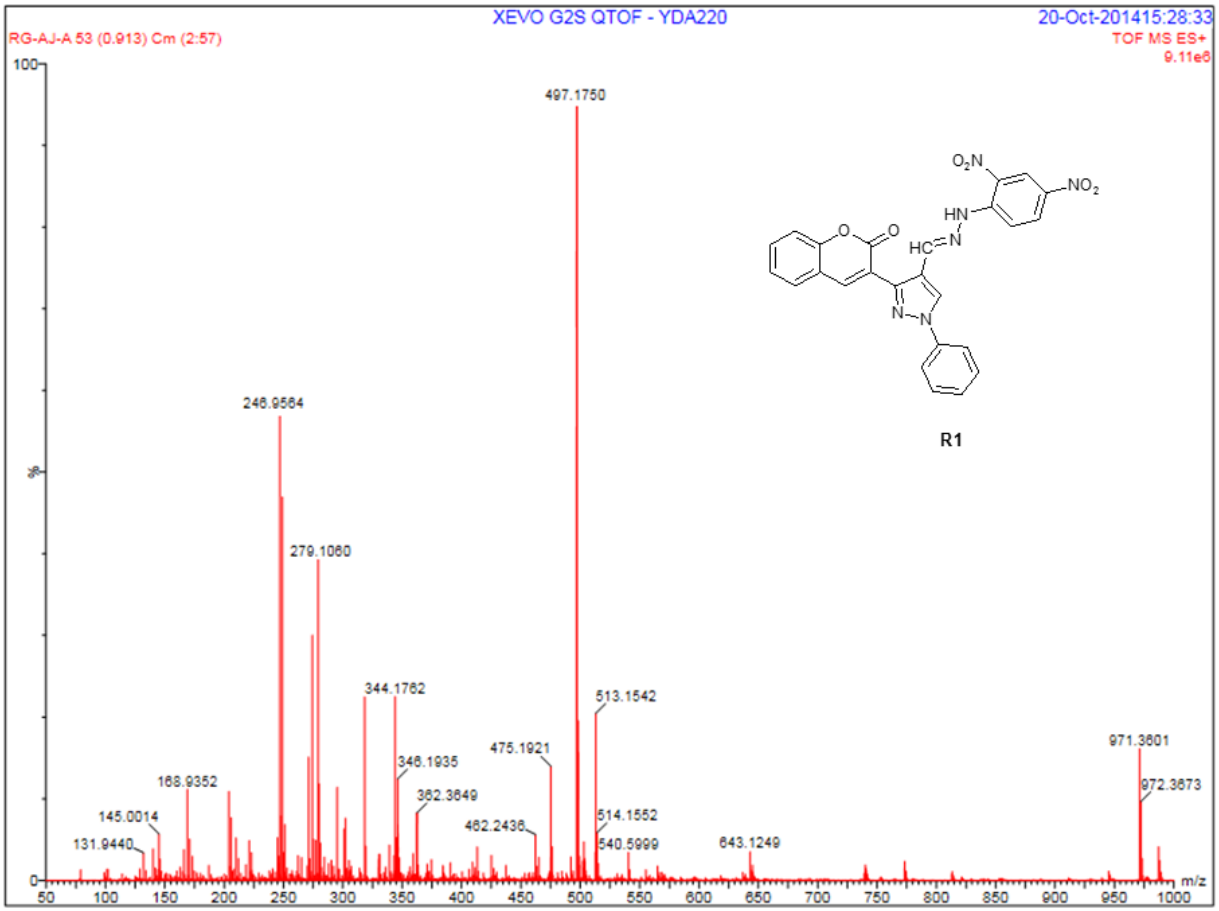


Fig. 6.5: ESI mass spectrum of 3-{4-[(2,4-Dinitro-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one (R1)

Table 6.2: Spectral data of 3-{4-[(un)substituted-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-ones (R1-R5)

Compd No.	FTIR (KBr, υ cm^{-1})	^{1}H NMR (DMSO-d_6, 400 MHz, δppm)	^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm)	MS (ESI) m/z $[M+H]^+$
R1	3438 (N-H), 2941 (=C-H), 1721 (C=O), 1532 (C=N)	7.38-7.9 (m, 12H, Ar-H), 8.38(s, 1H, pyran C-H),8.68(s, 1H, pyrazolyl C-H), 9.11 (s, 1H, -CH=N),11.59 (s, 1H, N-H)	116.95, 119.65, 119.40, 120.17, 122.16, 125.32, 127.35, 127.74, 129.33, 130.37, 131.71, 137.77, 139.56, 155.87, 162.92	497.1750 (obsd) calcd. for $C_{25}H_{16}N_6O_6$: 496.1741
R2	3445 (N-H), 2900 (=C-H), 1726 (C=O), 1529 (C=N)	7.03-7.97 (m, 13H, Ar-H), 8.94 (s, 1H, pyran C-H), 9.38 (s, 1H, pyrazolyl C-H), 9.84 (s, 1H, -CH=N), 11.11 (s, 1H, N-H)	114.54, 118.91, 121.15, 123.44, 126.54, 127.11, 129.33, 131.67, 133.34, 138.86, 143.14, 145.28, 146.36, 153.97, 159.54.	452.1289 (obsd) calcd. for $C_{25}H_{17}N_5O_4$: 451.1281
R3	3335 (N-H), 2890 (=C-H), 1716 (C=O), 1524 (C=N)	7.03-7.97 (m, 13H, Ar-H), 8.42 (s, 1H, pyran C-H), 9.24 (s, 1H, pyrazolyl C-H), 9.88 (s, 1H, -CH=N), 10.23 (s, 1H, N-H)	112.38, 116.78, 120.84, 121.46, 125.44, 126.33, 128.29, 130.67, 134.86, 141.28, 144.26, 146.97, 152.88, 155.32	452.1276 (obsd) calcd. for $C_{25}H_{17}N_5O_4$: 451.1281
R4	3288 (N-H), 2811 (=C-H), 1705 (C=O), 1553 (C=N)	7.03-8.32 (m, 13H, Ar-H), 8.88 (s, 1H, pyran H), 9.24(s, 1H, pyrazolyl C-H), , 9.89 (s, 1H, -CH=N), 10.44 (s, 1H, N-H)	115.71, 118.40, 121.17, 123.16, 126.35, 128.33, 131.37, 132.77, 139.56, 143.19, 145.69, 146.36, 153.97, 159.54	475.1316 (obsd) calcd. for $C_{26}H_{17}F_3N_4O_2$: 474.1304
R5	3201 (N-H), 2899 (=C-H), 1719 (C=O), 1524 (C=N)	7.33-7.88 (m, 15H, Ar-H), 8.17 (s, 1H, pyran H), 8.36 (s, 1H, pyrazolyl C-H), 8.88 (s, 1H, -CH=N), 10.27 (s, 1H, N-H)	112.18, 116.01, 121.14, 124.46, 127.75, 128.64, 131.57, 134.77, 136.36, 142.19, 144.63	407.1451 (obsd) calcd. for $C_{25}H_{18}N_4O_2$: 406.1430

Anion binding studies

The synthesized receptors **R1-R5** were comprehensively studied for their anion binding proficiencies by naked eye**,** UV-Visible, FTIR and ^{1}H NMR titrations and mass spectral data.

Qualitative naked eye detection experiment

Initially, colorimetric experiments of all the receptors (1×10^{-5} M in DMSO) were conducted with different anions *viz*., fluoride, chloride, bromide, iodide, nitrate, hydrogen sulfate, dihydrogen phosphate and acetate, in the form of their sodium salts (1×10^{-4} M in 1:1 DMSO-water). It was observed that only receptor **R1** was capable of exhibiting a strong and immediate colour change from yellow to pink, which was easily detectable by naked eye selectively for only fluoride ion at minimum concentration of 0.95 ppm **(Fig. 6.6)**. Other anions did not produce any perceptible change in colour, even at higher concentrations (1×10^{-3} M). This implies either there is weak or no coordination between anion and receptor. It was further observed that increasing fluoride ion concentration led to intensification of colour from light pink (0.95-1.5 ppm) to pink (1.6-3ppm) and it gets stabilized to dark pink at higher concentration (5 ppm).

Receptors, **R2** to **R5** were tested with different anions for any visual change, but no naked eye change was brought by any anion, even at higher concentrations, 1×10^{-3} M, indicating that no anion-receptor coordination took place, which could cause change in colour. Therefore, anion binding studies of receptor **R1** was further investigated quantitatively.

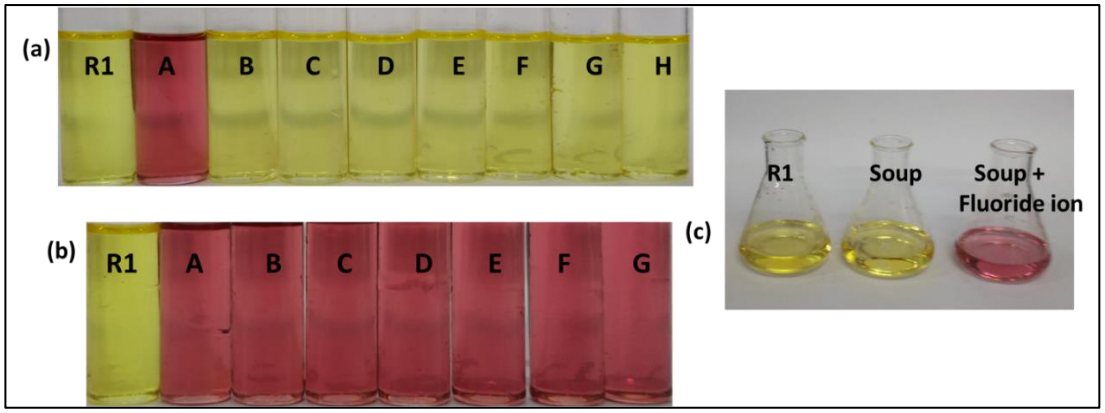


Fig. 6.6: (a) Colour changes in the receptor R1 (1×10^{-5} M in DMSO) in presence of 10 equivalents of different anions (sodium salts) (b) Colour changes in the receptor R1 (1×10^{-5} M in DMSO) in presence of 10 equivalents of fluoride and different anions (sodium salts) where A, B, C, D, E, F and G are Cl^-, Br^-, I^-, CH_3COO^-, $H_2PO_4^-$, HSO_4^- and NO_3^- respectively. (c) Colour change in the receptor R1 (1×10^{-5} M in DMSO) in the soup prepared (sodium salts of all above anions except F^-, at concentration 1×10^{-2} M in 1:1 DMSO-water)

Interference studies

Sensitivity and selectivity are the two most important parameters thatdescribe a receptor precisely. A soup of all anions, except fluoride ion, was prepared by adding their respective sodium salts in 1:1 DMSO-water to mimic the natural groundwater condition. Receptor **R1** solution, in equal volume, was thenadded to it **(Fig. 6.6(c))**. No colour change could be observed, but when a solution of fluoride ion was added to the solution of soup and receptor, immediate colour change from yellow to pink was observed. These qualitative interference studies showed that receptor **R1** is capable of producing naked eye response only in the presence of fluoride ion, irrespective of the presence of any other anions.

UV-Visible titration experiment

In the UV-Visible spectrum of receptor **R1**, characteristic maxima at 410 nm was observed in absence of external analyte, which red shifted by 80 nm upon addition of fluoride ion (10 receptor equivalents) in 1:1 DMSO-water. On the other hand, no change in absorption peak could be noticed in presence of other sodium salts of

anions, chloride, bromide, iodide, nitrate, hydrogen sulfate, dihydrogen phosphate and acetate (10 receptor equivalents) **(Fig. 6.7).** Further, when the UV-Visible spectra of receptor **R1** was recorded with increasing concentration of fluoride ions (1 to 100 equivalents), the peak centered at 410 nm decreased with concurrent increase in absorbance of red-shifted peak at 490 nm **(Fig. 6.8a-b)**. Finally, it was observed that fluoride ion concentration of 5 ppm and above, peak at 410 nm completely disappeared **(Fig. 6.8a)**. The large red shift observed in the maxima of receptor indicates towards formation of possible hydrogen binding interactions between receptor and fluoride ion. Further information on deprotonation can be obtained by ^{1}H NMR titrations only. An isobestic point at 400 nm was observed which indicates the formation of fixed binding ratio between receptor **R1** and fluoride ion.

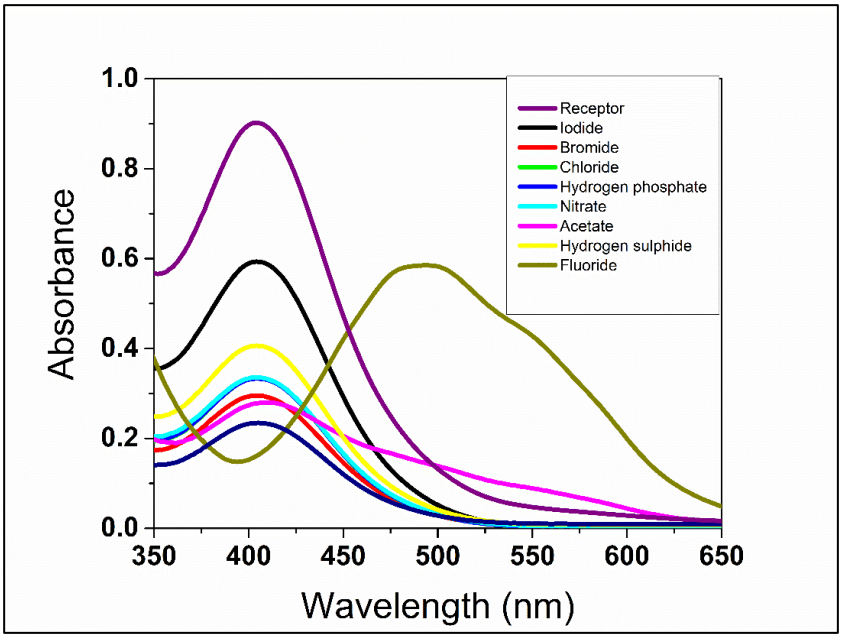


Fig. 6.7: Changes in absorbance of receptor R1 (1×10^{-5} M in DMSO) with different anions (sodium salts, 1×10^{-4} M) in 1:1 DMSO: water

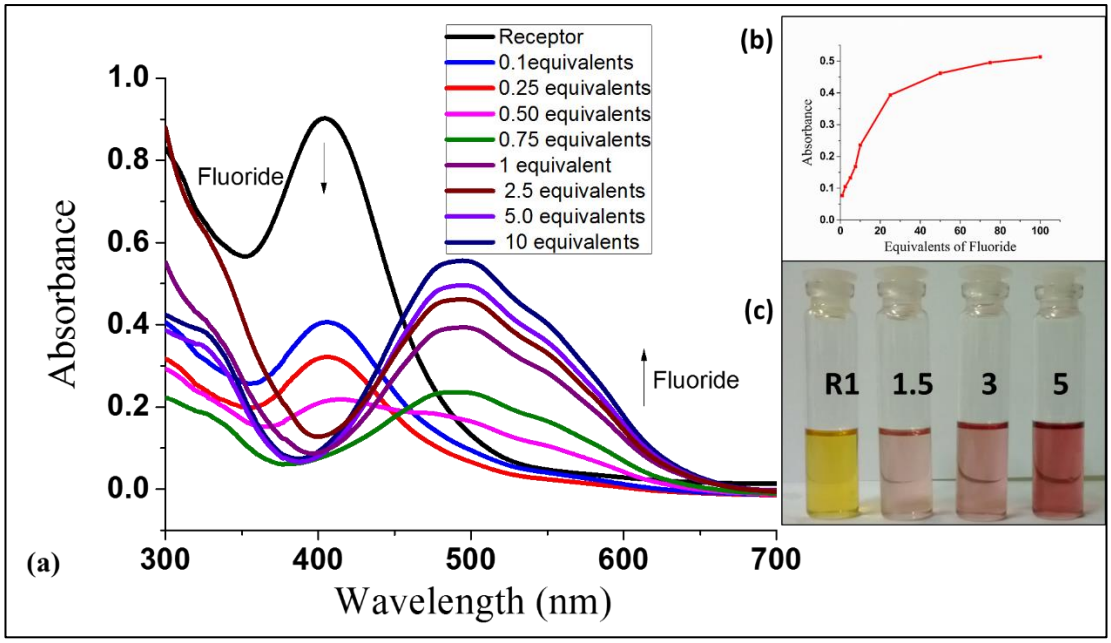


Fig. 6.8: (a) UV-Visible spectra of receptor R1 (10^{-5} M in DMSO) with fluoride ion (sodium salt) from 10^{-5} to 10^{-3} M in 1:1 DMSO: water (b)Changes in absorbance at 495 nm of receptor R1 (1×10^{-5} M in DMSO) with increase in fluoride ion concentration (1×10^{-5} to 1×10^{-3} M in 1:1 DMSO-water) (c) Colour changes in receptor R1 (10^{-5} M in DMSO)with increasing concentration of sodium fluoride in 1:1 DMSO: water (1.5, 3 and 5 ppm respectively)

Stoichiometric ratio of the complexes formed between fluoride ion and receptor was determined by employment of continuous variation method (Job's plot) **[52]**, which revealed that receptor forms 1:1 complex with fluoride ion **(Fig. 6.9).** It was also proved by mass spectra of receptor **R1** with fluoride ion, which exhibited a peak at 516.2689 [Calculated for Receptor **R1** + F^- +H^+: 516.2050] **(Fig. 6.10).** The binding constant K of **R1** with fluoride was calculated as 1.98×10^4 M^{-1} from B-H plot **(Fig. 6.11) [53]**.

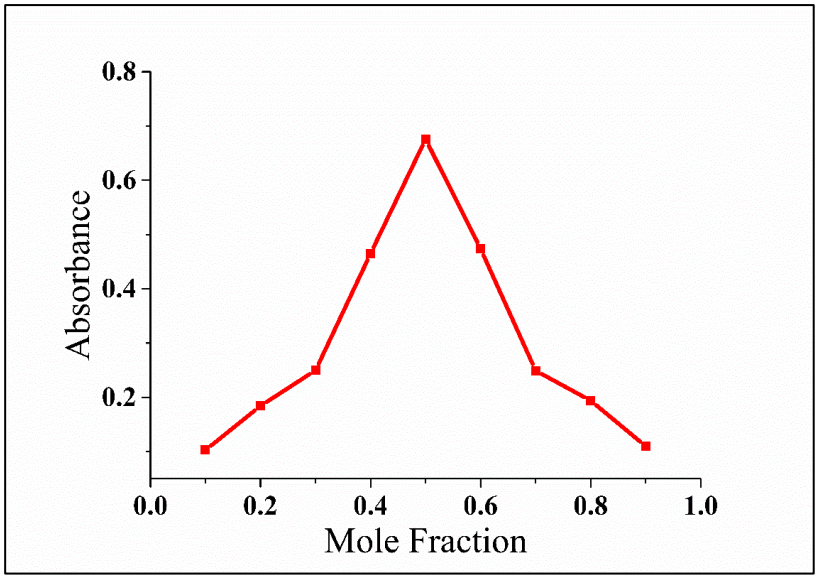


Fig. 6.9: Job's Plot with receptor R1 (1×10^{-4} M in DMSO) and fluoride (sodium salts) 1×10^{-4} M in 1:1 DMSO-water

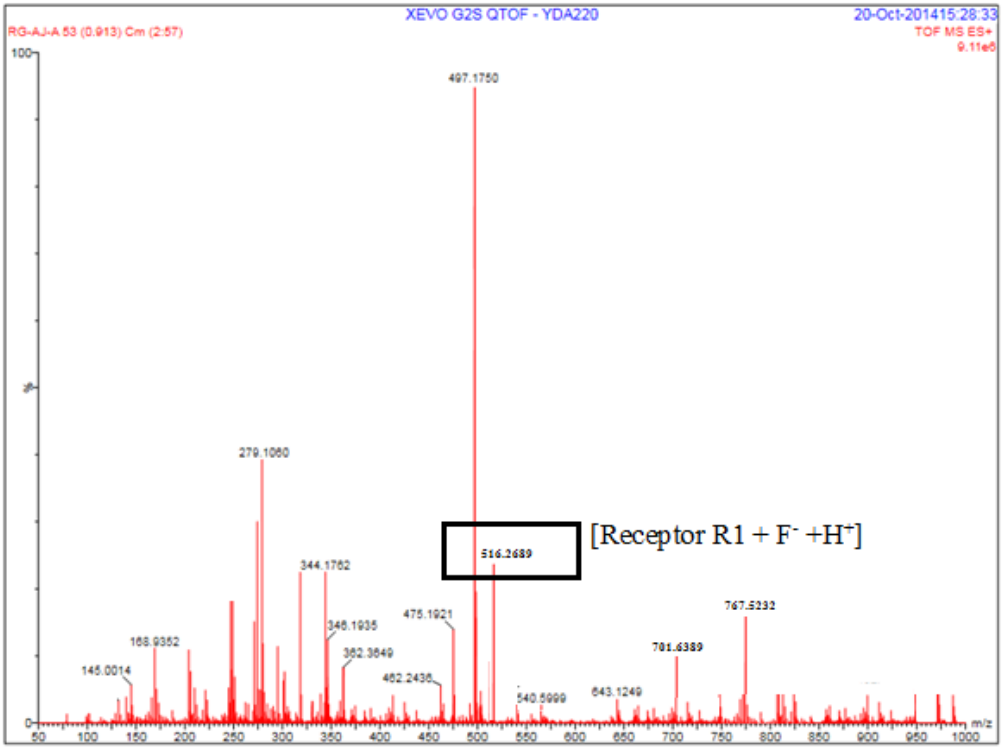


Fig. 6.10: ESI-Mass spectrum of fluoride ion complex of receptor R1

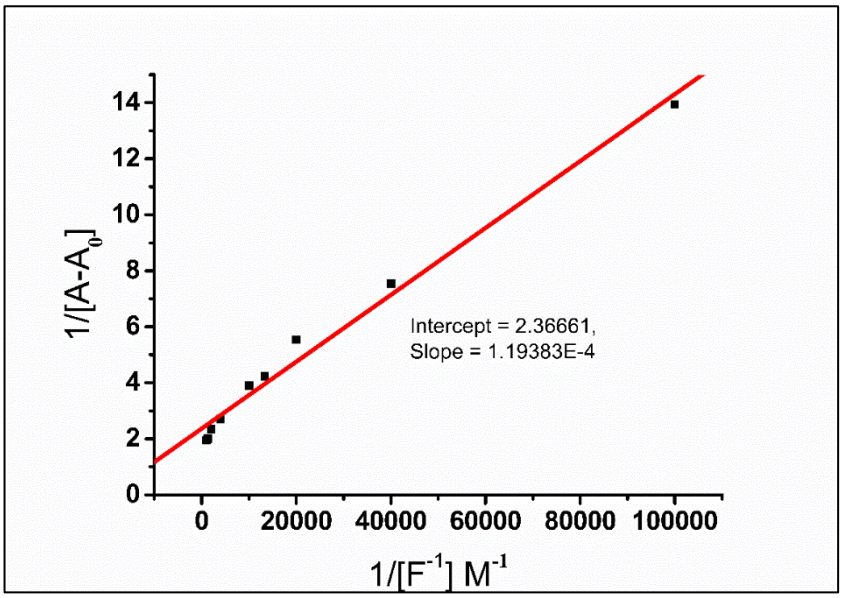


Fig. 6.11: Linear fitting curve of B-H plot of receptor R1 with fluoride ion

FTIR anion binding study

IR anion binding study of receptor **R1** with fluoride ion has been investigated using KBr discs. In the FTIR spectrum of **R1**, N-H and C-H absorption bands appeared at 3438 and 2941 cm^{-1}, respectively. These absorption bands broadened with the addition of fluoride salt and exhibited an intense band in the region 2880-3430 cm^{-1}. The broadening of peaks indicated towards the formation of hydrogen bonding between N-H and C-H of **R1** with fluoride ion. Further disappearance of N-H absorbance band indicate towards possible deprotonation **(Fig. 6.12)**.

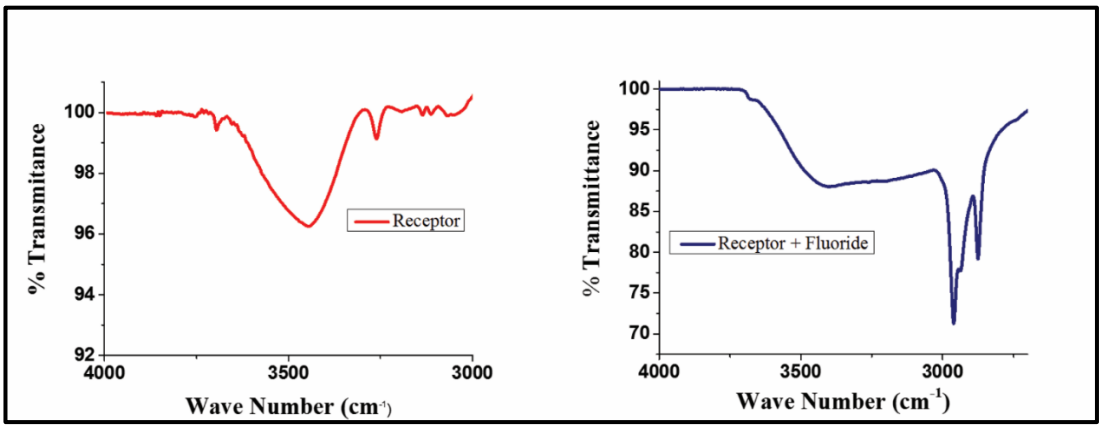


Fig. 6.12: (a) FTIR spectrum of receptor R1. (b) FTIR spectrum of receptor R1 in presence of 1 equivalent of fluoride ion

^{1}H NMR titration experiment

Insight of anion-receptor binding site and nature of interaction could be realized by ^{1}H NMR titration. For ^{1}H-NMR titration, receptor **R1** solution (DMSO-d_6, 10^{-2} M) was taken and fluoride ion (tetrabutylammonium salt in DMSO-d_6) at different concentration (2.5, 5 and 10 equivalents) were mixed together. Initially N-H (H_a) and C-H absorption peaks (H_b) appeared at δ 11.59 ppm and 9.10 ppm, respectively, which upon addition of 2.5 equivalents of fluoride ion, shifted downfield by 0.11 and 0.05 ppm, respectively with simultaneous decrease in their intensities. Further downfield shifting of H_a and H_b was observed upon addition of 5 equivalents of fluoride and finally proton, H_a was deprotonated (absence of peak) in presence of 10 equivalents of fluoride, substantiating the process of colour change **(Fig. 6.13)**. Careful examination of ^{1}H NMR titration results showed the involvement of two types of interactions between receptor **R1** and fluoride ion, *viz*., hydrogen bonding and deprotonation. Initial addition of fluoride induced the formation of hydrogen bonding between receptor and fluoride, whereas its further addition of the same led to deprotonation of N-H. C-H hydrogen donor group acted as an auxillary binding site with N-H proton. The proposed mechanism is depicted in **Scheme 6.2**.

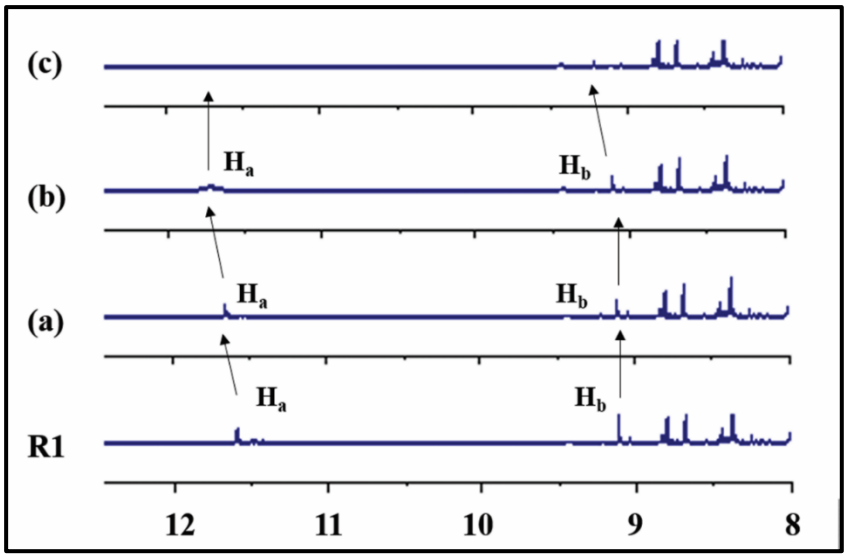
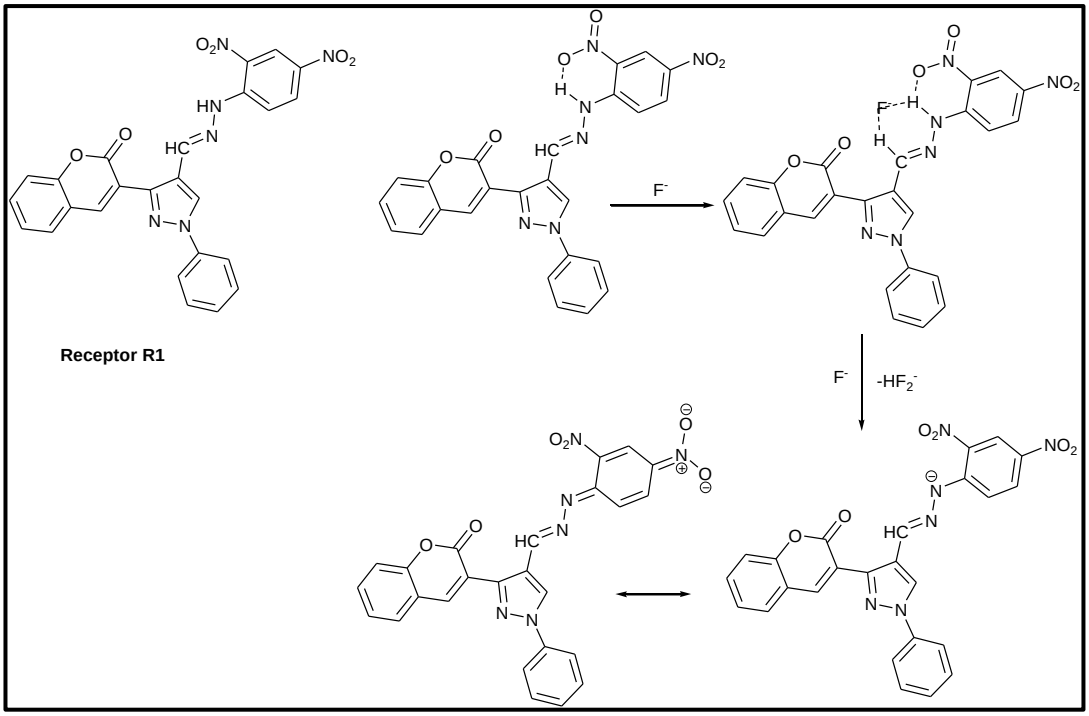


Fig. 6.13: Partial ^{1}H NMR (400 MHz) spectra of R1 in DMSO-d_6 (1 x 10^{-2} M) in the presence of (a) 2.5, (b) 5, and (c) 10 equivalents of TBAF in DMSO-d_6



Scheme 6.2. **Proposed mechanism of binding between R1 and fluoride ion**

As discussed earlier, receptors, **R2** to **R5** yielded no naked eye change in presence of any anion, even at higher concentrations, 1×10^{-3} M. Spectroscopically too, no evidence of any receptor-ion interaction was observed. It is therefore concluded that strategic substitution of electron withdrawing groups at 2 and 4 position has yielded the variation in fluoride ion binding abilities. Two nitro groups have enhanced the acidity of hydrogen bond donor groups in the structure of receptor **R1** and made it capable enough to detect fluoride ion *via* naked eye. Moreover, insertion of electron withdrawing substituent (nitro groups) onto the molecular framework of **R1** polarized the N-H fragment and its H-bond donor tendency increased sufficiently to compete with water molecules and thus **R1** is capable to detect fluoride ion in competitive solvent. Receptor **R2-R4**, although have electron withdrawing groups, could not show any detectable response towards any anion. This could be attributed to the fact that in addition to electron withdrawing group at 4-position in **R1**, there is also an additional electron withdrawing group at ortho position which assists the hydrogen bond donor capacity of NH and CH by forming six membered ring as shown in **Scheme 6.2**. No anion triggered colour change in receptor **R5**, which is seemingly obvious in absence of any electron withdrawing groups in its structure. Above observations leads to the

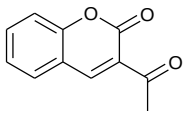
conclusion that on increasing the number of nitro groups, acidity and recognition properties of N-H group with fluoride ion increases. Similar observation was reported by Shang *et. al*. also **[54].**

CONCLUSION

We have described an unprecedented colorimetric receptor **R1** synthesized by an environment sustainable route capable of binding inorganic fluoride ion selectively and sensitively in aqueous media with its rationally placed N-H and C-H groups. Naked eye recognition of fluoride ion makes receptor suitable for on-site analysis. By the plethora of qualitative and quantitative studies, we have been able to demonstrate that receptor **R1** can serve as an aid to detect inorganic fluoride ion semi-quantitatively in natural water samples without suffering from any interference by other anions.

EXPERIMENTAL

Preparation of 3-acetyl coumarin (1)

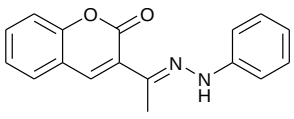


1

3-Acetylcoumarin was prepared according to the procedure reported previously **[49]**. A mixture of salicyaldehyde (0.01 mol, 1.1 ml) and ethylacetoacetate (0.01 mol, 1.3 ml) was taken in a round bottom flask and stirred in the presence of piperidine (0.1 ml) as a catalyst. The progress of reaction was checked on precoated silica thin layer chromatographic sheets (pet ether and ethyl acetate (8:2)). On completion of reaction, as observed by the disappearance of spots of reactants in TLC after 30 minutes, reaction mixture was cooled and was then purified by column chromatography using pet ether and ethyl acetate (9:1) as mobile phase. Pure compound was obtained as pale yellow coloured solid and characterized by ^{1}H NMR, IR and mass spectral data.

M.P. (^{o}C)	121 ^{o}C (Lit **[49]** M.P. 122 ^{o}C)
Yield (%)	96%(Lit **[49]** Yield 95%)
IR (KBr) ν_{max} cm^{-1}	2980 (C-H), 1723 (pyrone C=O), 1686 (acetyl C=O), 1297, 1259 (C-O)
^{1}H NMR ($CDCl_3$) δ ppm	δ 2.68 (s, CH_3), 7.32 (s, 2H), 7.63 (s, 2H), 8.46 (s, pyran H)
Mass [M+H]$^{+}$	189.1768[M+H]$^{+}$ (Calcd for $C_{11}H_8O_3$:188.1794)

Preparation of 3-[1-(Phenylhydrazono)-ethyl]-chromen-2-one(2)



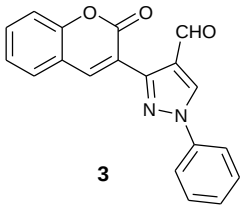
2

3-[1-(Phenylhydrazono)-ethyl]-chromen-2-one (**2)** was synthesized by following theprocedure of Chodankar *et al.* **[50]**. 3-Acetyl coumarin **(1)** (0.02 mol, 3.76 g) and phenylhydrazine (0.02mol, 2.16 g) were subjected to microwave irradiation in neat

condition for 3 minutes at 80 ^{o}C and 100W power. The progress of the reaction was followed by thin layer chromatography with pet ether: ethyl acetate (8:2) as mobile phase. After completion of reaction, as observed by TLC, the compound was cooled to room temperature and was then purified by column chromatography with pet ether: ethyl acetate (9:1) as mobile phase. Pure compounds were obtained as orange colour solidswhich was then characterized by ^{1}H NMR, IR and mass spectroscopic techniques.

M.P.(^{o}C)	187 ^{o}C (Lit **[50]** M.P. 186-188 ^{o}C)
Yield (%)	93 %(Lit **[50]** Yield 92 %)
IR (KBr) ν_{max} cm^{-1}	3315-3418 cm^{-1} (N-H), 2921 (=C-H), 1744 cm^{-1} (C=O), 1295, 1245 (C-O)
^{1}H NMR (DMSO-d_6) δ ppm	δ 2.22 (s, 3H, -CH_3), 6.77-7.85 (m, 8H, Ar-H), 8.29 (s, 1 H, pyran H), 9.42 (s, 1H, -NH)
Mass m/z [M+H]$^{+}$	279.3072[M+H]$^{+}$ (Calcd. for $C_{17}H_{14}N_2O_2$: 278.3053)

Preparation of 3-(2-Oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (3)



3

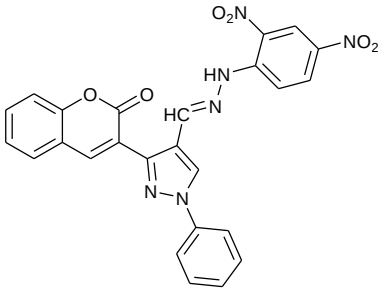
Title compound **(3)** was prepared according to literature method **[51]**. Vilsmeier reagent was prepared from N, N- dimethyl formamide (10 ml) and phosphorous oxychloride (0.015 mol, 1.35 ml) at room temperature with constant stirring as described in literature. Then, phenylhydrazone derivative, **2** (0.015 mol, 4.17g) was added portionwise in it at 0-5 ^{o}C with constant stirring. After complete addition, the reaction mixture was ultrasonicated for 20 minutes at 80 ^{o}C. The progress of reaction was checked by thin film chromatography with pet ether: ethyl acetate (7:3) as solvent system. The reaction mixture was cooled, poured into ice-cold water and sodium

bicarbonate solution was then added to it till pH 8 was obtained. The product so obtained was filtered, washed with water (50 × 2 ml) and dried**.** Pure compounds were obtained as orange solid after recrystallization from ethanol and was then characterized by FTIR, ^{1}H NMR and mass spectroscopic techniques.

M.P.(^{o}C)	212-214^{o}C (Lit **[51]** M.P. 213-215^{o}C)
Yield (%)	91%(Lit **[51]** Yield 78 %)
IR (KBr) ν_{max} cm^{-1}	2989 (=C-H), 1764 cm^{-1} (-CO of coumarin ring), 1722 cm^{-1} (CO of aldehyde group), 1616 (C=N), 1288, 1246 (C-O)
^{1}H NMR (DMSO-d_6) δ ppm	δ 7.41-8.00 (m, 8H, Ar-H), 8.46 (s, 1H, pyran-H), 9.27 (s, 1H, C-H), 9.97 (s, 1H, -CHO)
Mass m/z [M+H]$^{+}$	317.3078 [M+H]$^{+}$(Calcd for $C_{19}H_{12}N_2O_3$: 316.3102)

Preparation of 3-{4-[(un)substituted-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-ones (R1-R5)

3-{4-[(2,4-Dinitro-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one (R1)



R1

Conventional methodology

3-(2-Oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde **(3)** (0.005 mol, 1.58 g) and 2,4-dinitrophenylhydrazine (0.005 mol, 0.99 g) were taken in a round bottom flask and refluxed in absolute ethanol (10 ml). Reaction progress was monitored by thin film chromatography, where disappearance of spots of reactants

after 25 minutes indicated the completion of reaction. The reaction mixture, was then filtered, washed with cold diethyl ether. Desired title compound **R1** was obtained as orange solid by purification with column chromatography (6:4, pet ether: ethyl acetate).

Using microwave irradiation

Equimolar amount (5 mmol) of **3** and 2,4-dinitrophenylhydrazine were irradiated under neat condition by microwaves for 5-8 minutes at 100 ^{o}C using 150 W power. The reaction progress was checked by thin layer chromatography using solvent pet ether and ethyl acetate (1:1). The product so obtained, were washed with cold diethyl ether and purified by column chromatography (6:4, pet ether: ethyl acetate) to afford the desired title receptor **R1.**

M.P. (^{o}C)	198-200 ^{o}C
Yield (%)	84 %
IR (KBr) ν_{max} cm^{-1}	3438 (N-H), 2941 (=C-H), 1721 (C=O), 1532 (C=N)
^{1}H NMR (DMSO-d_6) δ ppm	δ 7.38-8.43 (m, 12H, Ar-H), 8.74 (s, 1H, pyran C-H), 9.10 (s, 1H, -CH=N), 11.59 (s, 1H, N-H)
^{13}C NMR (DMSO-d_6) δ ppm	116.71, 119.01, 119.40, 120.17, 122.16, 125.32, 127.35, 127.74, 129.33, 130.37, 131.71, 132.77, 139.56, 143.19, 145.69, 148.78, 155.87, 162.92
Mass m/z [M+H]$^{+}$	497.1750 [M+H]$^{+}$ (calcd. for $C_{25}H_{16}N_6O_6$: 496.1741)

All other receptors, **R2-R5** were prepared similarly. Physical and analytical data of synthesized compounds are given in **Table 6.3.**

Table 6.3: Physical data of 3-{4-[(un)substituted-phenyl)hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-ones (R1-R5)

Compd No.	X	Y	Z	Mol. Formula	Mol. Wt.	Yield %		Time (min)	
						(a)	(b)	(a)	(b)
R1	NO_2	H	NO_2	$C_{25}H_{16}N_6O_6$	496	71	84	35	6
R2	H	H	H	$C_{25}H_{17}N_5O_4$	451	64	82.7	40	8
R3	NO_2	H	H	$C_{25}H_{17}N_5O_4$	451	67	84	35	7
R4	H	CF_3	H	$C_{26}H_{17}F_3N_4O_3$	474	68	83.6	45	6
R5	H	H	H	$C_{25}H_{18}N_4O_2$	406	73	86.4	30	5

(a) - Conventional method
(b) - Using microwave irradiation

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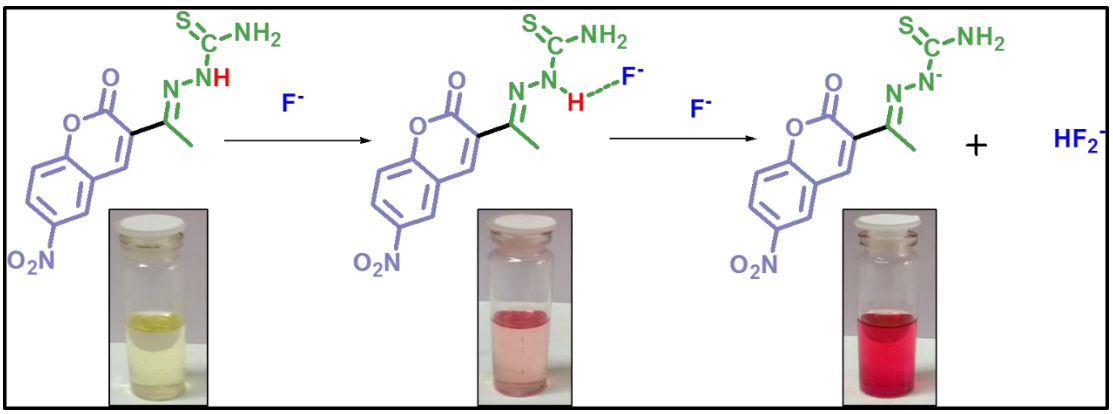
Chapter-7

Design and synthesis of coumarin based receptors, 1-(1-(substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides



Highlights:

- Instantaneous visual detection of inorganic fluoride ion in water from 0.19 - 5 ppm concentration
- Semi-quantitative assessment of fluoride ion in drinking water from 0.19-1.5 ppm,1.5 – 5 ppm, 5 ppm and above by discernible colour gradation
- Bare eye detection of fluoride ion in toothpaste and mouthwash is possible for real life applications

INTRODUCTION

Myriads of anions play several important roles in biological, chemical, clinical and environmental processes **[1]**. They are ubiquitous and play crucial role as cofactors and enzyme substrates in biological systems **[2]**. Further, processes like cell proliferation, cell migration, and cell volume homeostasis involve anion channels **[3]**. On the other hand, certain anions such as fluoride, phosphate, nitrate and cyanide are documented as pollutants **[4]**. Amongst these anionic species, fluoride is of paramount interest due to its two-faced nature **[5]**. Prevention of dental caries and osteoporosis by fluoride ion intake is widely advertised resulting in sporadic water fluoridation and addition of fluoride to commercial dental products **[6]**. Although helpful in lower doses, at higher concentrations, it proves to be highly toxic to human body, since that it is easily absorbed, but is excreted slowly from the body **[7]**. Needless to say that its overexposure causes dental and skeletal fluorosis, nephrotoxicity in humans and animals and is reported to be responsible for inhibition of certain enzymatic functions **[8]**. WHO guidelines have set 1.5 ppm as permissible limit for fluoride in drinking water and EPA, USA has listed maximum contaminated level of fluoride as 4 ppm **[9]**. Ground water, in many parts of the world, notably Africa, China and India, contain high levels of fluoride, much greater than the permissible limit, yet people are forced to consume it, since it is the only source of drinking water **[10]**.

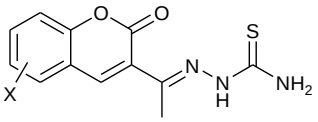
Stimulated by public health concerns by such alarming high levels of fluoride in water, the design and synthesis of receptors for fluoride ion detection is fast becoming a fertile field of research **[11]**. Amongst them, colorimetric receptors that can recognize and sense anions selectively through visible colour change perceptible by naked eye are of particular interest since it obviates the requirement of any spectroscopic instrument **[12-15]**. A significant number of chemosensors for fluoride ion have been developed; but their utility to test in drinking water under field conditions is restricted to very few chemosensors because of strong solvation of both binding site and fluoride ion in aqueous media **[16-17]**. Several strategies like Lewis acid or metal – ion coordination, anion – π interactions and cationic receptors have been explored to accomplish detection of fluoride ion in aqueous media **[18-20]**, but have failed because they detect fluoride ion of only organic origin, *i.e.*, in tetrabutylammonium fluoride (TBAF). Chemodosimeter approach based on

desilylation reaction was found to operate in aqueous media; but the slow response, time limits its on-site applicability **[21]**. Neutral receptors comprising of moieties *viz.*, pyrroles, indoles, indolocarbazoles, imidazoles and benzimidazoles covalently attached with binding functionalities *i.e.*, amides and urea/thioureas have been documented for fluoride ion recognition and sensing **[22-35]**. Coordination of acidic protons of these moieties with fluoride ion induces either colour or fluorescence changes **[36].** Recognition studies of most of these receptors were carried out in aprotic media *i.e.*, acetonitrile and chloroform, to avoid competition of solvent (water/ alcohol) **[37-39]**. Further, most of the receptors are limited to detection of tetrabutylammonium fluoride (TBAF), which is far away from use in real life applications **[40]**. Attempts have been made by Khanmohammadi *et al.* and Trivedi *et al.* to detect sodium fluoride in recent years **[41-42]**. For practical considerations, anion binding in 100% aqueous media is essential. Fluoride is the most challenging anion to detect in aqueous solvent because of its high hydration enthalpy. A considerable number of receptors effective in aqueous conditions have been reported but they suffer from complications like longer detection time for the colour change to appear, while turn off fluorescent receptors lack the sensitivity **[43]**. There is a need to develop simple, easy to synthesize, inexpensive receptor suitable for practical purposes.

Coumarin derivatives have been extensively investigated for electronic and photonic applications such as fluorescence probes, charge transfer agents and solar energy collectors due to their inherent photochemical characteristics, reasonable stability, and relative ease of synthesis **[44-45]**. Receptors capable of sensing fluoride in organic solvent based on coumarin scaffold have been reported, but they exhibited fluoride binding properties in organic solvents **[46-47]**. Fluoride ion detection in aqueous media with coumarin scaffold is scarcely reported **[48]**.

In our efforts towards study of fluoride ion binding in aqueous media, we herein report receptors 1-(1-((un)substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides **A-E (Fig. 7.1)**, designed with coumarin scaffold as chromophoric group and thiosemicarbazide N-H as binding site. Our aim was to synthesize naked eye receptors for fluoride ion detection, so five receptors were designed containing both electron-withdrawing and electron-releasing groups, which could visually detect fluoride ion in the form of their inorganic sodium salts. Real life applications of

receptor **B** have also been discussed with commodity items of daily use i.e., toothpaste and mouthwash. Fluoride ion concentration in drinking water samples has also been investigated, which may be helpful for detecting different levels of fluoride ion in ground water, especially suitable for rural areas, where the literacy rate is low.



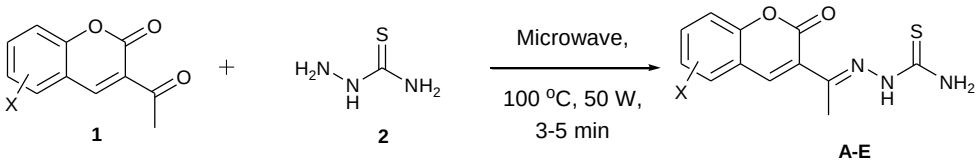
A-E

Receptor A , X = H,
B , X = 6-NO_2,
C, X = 8-OCH_3,
D, X = 7-$N(C_2H_5)_2$,
E, X = 7,8-benzo

Fig. 7.1: Molecular representation of receptors, 1-(1-((un)substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides (A-E)

RESULTS AND DISCUSSION

Diversely substituted 3-acetyl coumarins **(1a-e)** were synthesized by following reported method of Perekalin *et al*. **[49]**, which were then condensed with thiosemicarbazide under microwave irradiation to yield desired receptors 1-(1-(substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides**(A-E)** in almost quantitative yield **(Scheme 7.1)**.



1 **2** **A-E**

Receptor A , X = H,
B , X = 6-NO_2,
C, X = 8-OCH_3,
D, X = 7-$N(C_2H_5)_2$,
E, X = 7,8-benzo

Scheme-7.1: Synthesis of 1-(1-((un)substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides(A-E)

Structure of receptors **A-E** was established on the basis of standard spectroscopic techniques (FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy). In the IR spectra of

receptors **A-E**, characteristic broad absorbance band from 3457-3260 $cm^{-1}$is assigned to N-H stretching vibration due to the presence of NH and NH_2 group, which were absent in IR spectra of compound **1 (Scheme 7.1)**. Peak at 1719 cm^{-1} may be attributed to C=O stretching frequency. Receptors **A-E** show absorption bands at 1618-1589 and 1596-1496 cm^{-1} due to symmetric and asymmetric C=N stretching vibration. Two absorption bands at 1540 and 1352 cm^{-1} are observed due to N-O stretching of nitro group present in receptor **B.** The C=S stretching frequency has been observed at 1011 cm^{-1} **(Table 7.2, Fig. 7.2)**.

^{1}H NMR spectra of receptors **A-E** display characteristic sharp singlet in the region δ 9.29-10.45 ppm due to N-H group, which was absent in 3-acetylcoumarins **(1)**. A singlet in the region δ 7.9-8.9 ppm is assigned to pyran–H present in coumarin ring. A multiplet from δ 7.3-8.4 ppm is observed for aromatic protons in the molecular structure of receptors. ^{13}C NMR of receptors **A-E** showed characteristic peak around δ 160 (>C-NH_2), 165 (-C=N) and δ 178 ppm (C=O). Aromatic C=C peaks are observed in region ranging from δ 114 to 144 ppm. **(Table 7.2, Fig. 7.3-7.4).**

Further confirmation was provided by HRMS data which gave an accurate molecular ion peak $[M+H]^+$ at m/z 262.0009, 307.0500, 292.0563, 333.1242 and 312.4568 that agrees well with their calculated molecular formula **(Table 7.2, Fig. 7.5)**.

The names and m.p.'s of all the receptors synthesized **(A-E)** are given in **Table-7.1.** The IR, ^{1}H NMR and HRMS data of all synthesized compounds are shown in **Table-7.2.**

The IR, ^{1}H NMR, ^{13}C NMR and mass spectra of receptor **B** are given in **Fig.-7.2, 7.3, 7.4** and **7.5,** respectively.

Table-7.1: Names and m.p.'s of 1-(1-((un)substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides (A-E)

Compd No.	Name	M.P. (^{o}C)
A	1-(1-(2-Oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide	220-222
B	1-(1-(6-Nitro-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide	235-235
C	1-(1-(8-Methoxy-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide	202-205
D	1-(1-(7-Diethylamino-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide	142-144
E	1-(1-(7,8-Benzo[h]-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide	242-245

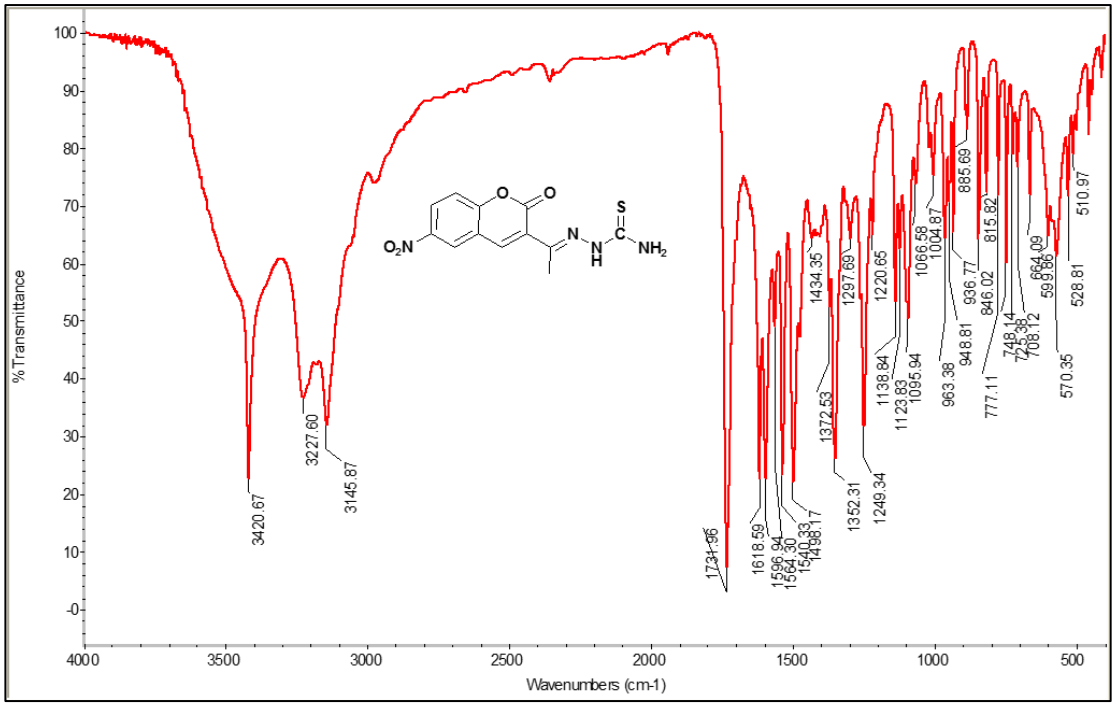


Fig. 7.2: FTIR spectrum of 1-(1-(6-Nitro-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide (B)

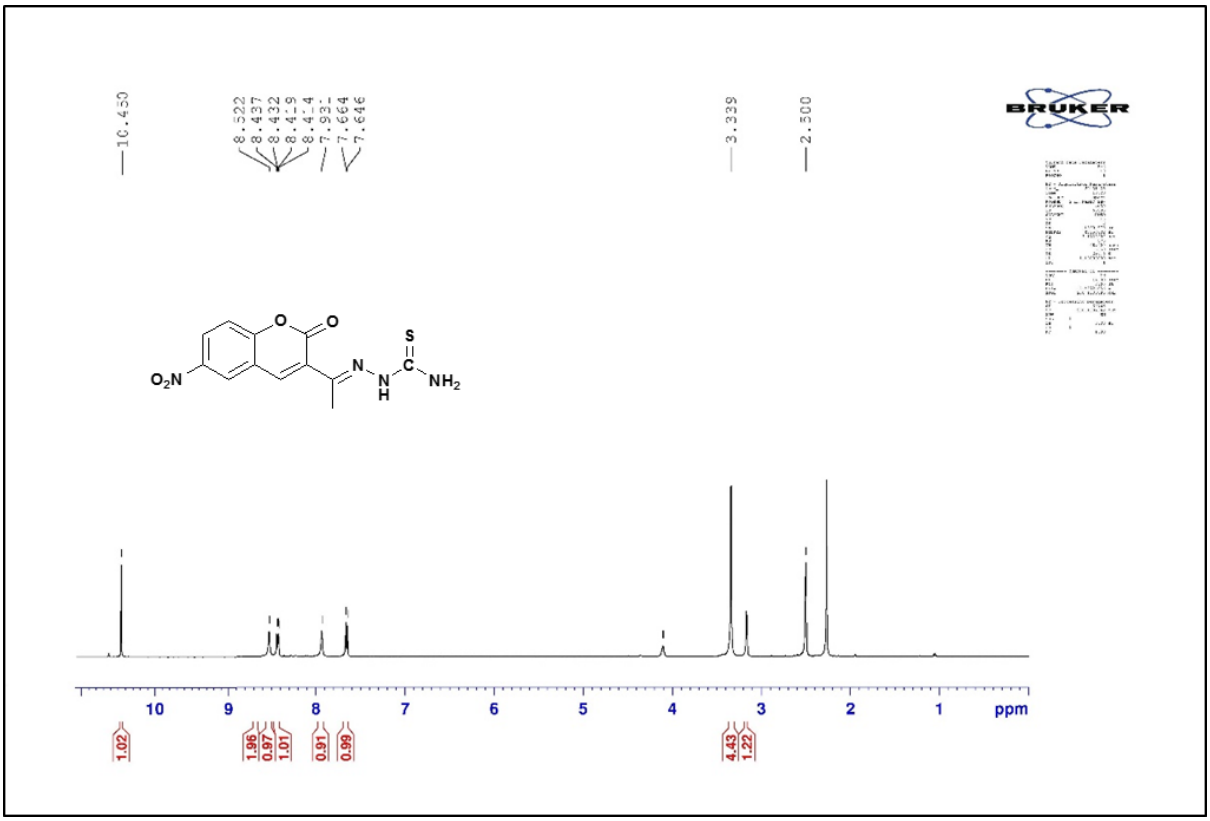


Fig. 7.3: ^{1}H NMR spectrum of 1-(1-(6-Nitro-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide (B)

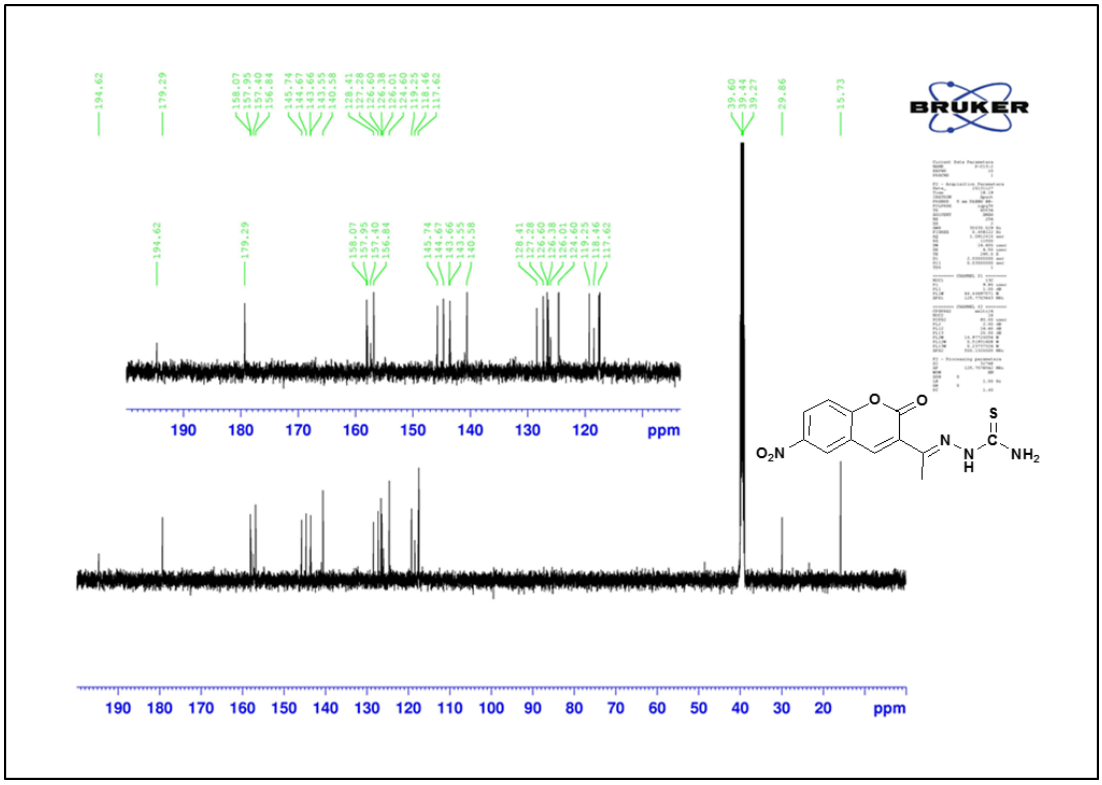


Fig. 7.4: ^{13}C NMR spectrum of 1-(1-(6-Nitro-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide (B)

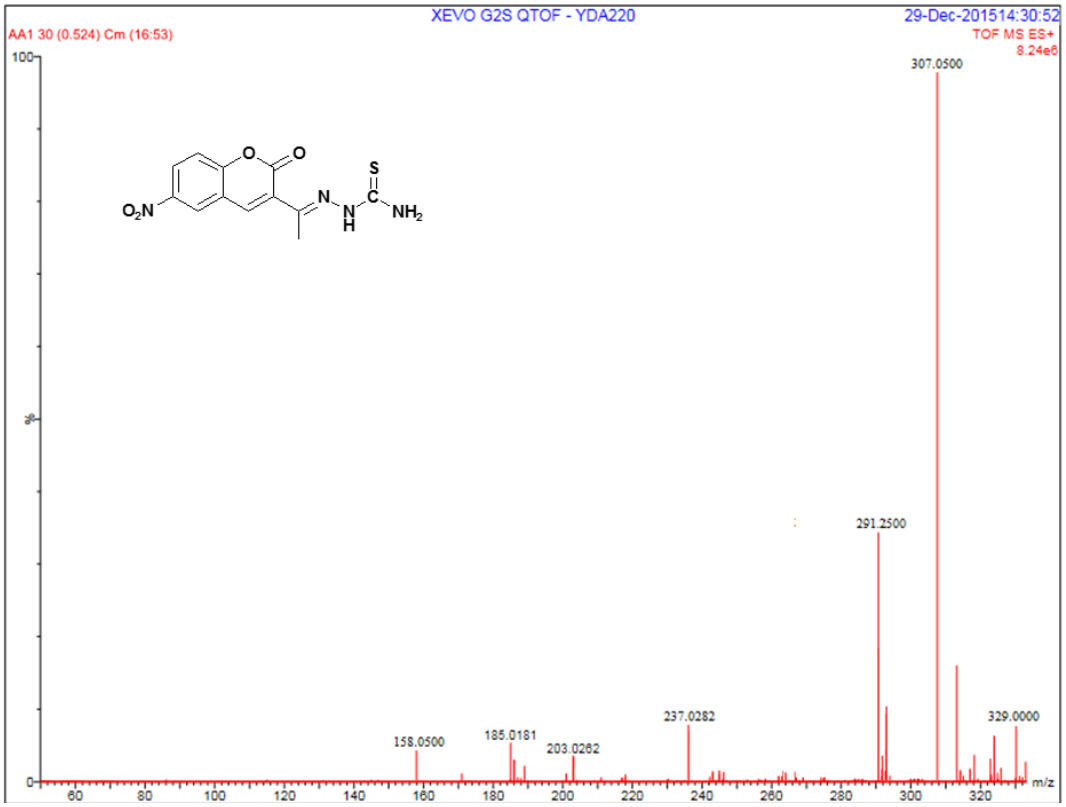


Fig. 7.5: ESI mass spectrum of 1-(1-(6-Nitro-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide (B)

Table-7.2: Spectral data of 1-(1-((un)substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides(A-E)

Compd No.	**FTIR**(KBr, $\upsilon_{max}cm^{-1}$)	**^{1}H NMR** (DMSO-d_6, 500 MHz, δppm)	**^{13}C NMR** (DMSO-d_6, 100 MHz, δppm)	**HRMS** $[M+H]^+$
A	3388, 3236, 3149 (N-H, NH_2), 3040 (aliphatic C-H), 1719 (C=O), 1604 (C=N), 1496 (asym. C=N), 1115, 1073 (C-O), 1011, 762 (C=S)	2.25 (s, 3H, H_3C-C=N), 3.34 (s, 2H, NH_2), 7.42-7.96 (m, 4H, Ar H), 8.4 (s, 1H, pyran H), 10.45 (s, 1H, NH)	38.50, 114.97, 117.93, 124.79, 128.11, 131.38, 140.99, 144.96, 152.36, 158.12, 178.23	262.0009 (obsd), calcd for $C_{12}H_{11}N_3O_2S$: 261.057
B	3420, 3227, 3145 (N-H, NH_2), 1731 (C=O), 1618 (C=N), 1596 (asym. C=N), 1540, 1352 (N-O), 1123, 1095 (C-O), 1066, 777 (C=S)	2.50 (s, 3H, H_3C-C=N), 3.33 (s, 2H, NH_2), 7.64 (d, 1H, Ar H), 7.93 (s, 1H, Ar H), 8.41 (d, 1H, Ar H), 8.66 (s, 1H, pyran H), 10.45 (s, 1H, NH)	39.44, 117.62, 124.60, 126.38, 128.41, 140.58, 143.66, 157.40, 158.07, 179.29, 194.62.	307.0500 (obsd), calcd for $C_{12}H_{10}N_4O_4S$: 306.0423
C	3405, 3299, 3178 (N-H, NH_2), 1724 (C=O), 1614 (C=N), 1570 (asym. C=N), 1137, 1096 (C-O), 1077, 759 (C=S)	2.49 (s, 3H, H_3C-C=N), 3.41 (s, 2H, NH_2), 3.91 (s, 3H, OCH_3), 7.30 (m, 3H, Ar H), 7.96 (s, pyran H) 9.29 (s, 1H, NH)	39.40, 56.01, 114.41, 119.38, 124.58, 125.77, 142.08, 145.83, 158.74, 179.13	292.0562 (obsd), calcd for $C_{13}H_{13}N_3O_3S$: 291.0678
D	3406, 3260, 3159 (N-H, NH_2), 1714 (C=O), 1600 (C=N), 1562 (asym. C=N), 1117, 1086, (C-O), 757 (C=S)	2.48 (s, 3H, H_3C-C=N),2.49 (t, 6H), 3.86 (2H, NH_2), 4.83 (q, 4H), 7.92 (2H, m, Ar H), 8.99 (pyran H), 9.83 (s, 1H, NH)	30.09, 39.45, 44.35, 95.73, 107.41, 114.91, 132.37, 147.59, 152.89, 158.21, 159.83, 194.15	333.1242 (obsd), calcd for $C_{16}H_{20}N_4O_2S$: 332.1307
E	3457, 3343, 3209 (N-H, NH_2), 1716 (C=O), 1589 (C=N), 1507 (asym. C=N), 1237, 1096 (C-O), 1041, 767 (C=S)	2.49 (s, 3H, H_3C-C=N), 3.34 (s, 2H, NH_2), 7.42 (2H, Ar H), 7.64 (s, 1H, Ar H), 7.76 (s, 1H, Ar H), 7.96 (s, 1H, pyran H), 8.45 (s, 1H, NH)	39.14, 48.23, 112.75, 116.05, 122.63, 124.67, 125.87, 127.94, 128.47, 129.59, 133.39, 137.35, 146.03	312.4568 (obsd), calcd for $C_{16}H_{13}N_3O_2S$: 311.078

Anion binding studies

All the synthesized receptors **A-E** were thoroughly examined for their anion binding capabilities by qualitative (naked eye detection) as well as quantitative (UV-Visible, and ^{1}H NMR titrations) and mass spectral analysis of receptor and fluoride ion complex.

Naked eye sensing experiment

Initially, colour changes in receptor solutions **A-E** (1×10^{-5} M in 9:1 DMSO-water) were assessed by adding 1 to 100 equivalents of different anion (sodium salts) *viz.*, fluoride, acetate, chloride, bromide, iodide, dihydrogen phosphate, hydrogen sulphate and nitrate ions into it **(Fig.7.6).** An instant colour change from pale yellow to pink was observed with receptor **B** upon addition of fluoride ion (sodium salt) at 0.19 ppm, while no obvious colour change could be observed with other anions. Receptor **A** gave colorimetric response with fluoride at a higher concentration (1×10^{-3} M), below this concentration, no discernible visual colour change by naked eye was observed, which limits its practical utility. Receptors **C-E** failed to show any colour change even at high fluoride concentration (1×10^{-3} M) or with any other anion salt. For practical utility of receptors, they should be capable to bind inorganic fluoride (sodium fluoride being commonly found salt) in aqueous media as well as give a quick visual response at permissible limits of fluoride ion in drinking water. Only receptor **B** was found suitable for this purpose and was further explored for its viability as a bare eye receptor for fluoride ion detection. While, receptors **C** to **E** were found insensitive to the addition of salts of different anions even at higher concentrations (1×10^{-3} M), which may be due to decrease in acidity of NH proton by presence of electron releasing groups.

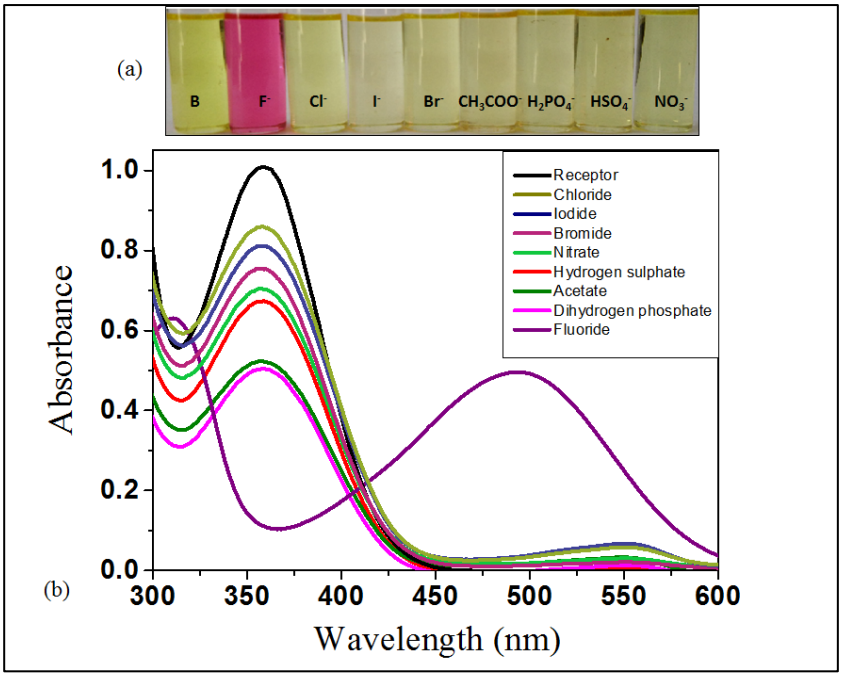


Fig. 7.6: (a) Colour changes of receptor B (1×10^{-5} M in 9:1 DMSO:water) with 10 equivalents of sodium salts of different anions (b) Changes in absorbance of receptor B (1×10^{-5} M in 9:1 DMSO:water) with different anions (sodium salts, 1×10^{-4} M) in distilled water

UV-Visible titration experiment

To validate these initial qualitative studies, detailed anion binding studies of receptor **B** were conducted using UV-Visible and NMR spectrophotometer. For UV-Visible experiments, the receptor Bsolution (1×10^{-5} M in 9:1 DMSO-water) was prepared and sodium salts of different anions (100 equivalents) were added into it. Free receptor **B** gave a maxima at 358 nm, which shifted to 500 nm upon addition of fluoride solution (1×10^{-3} M sodium salt in distilled water). Other anions induced no spectral response **(Fig.7.6)**.

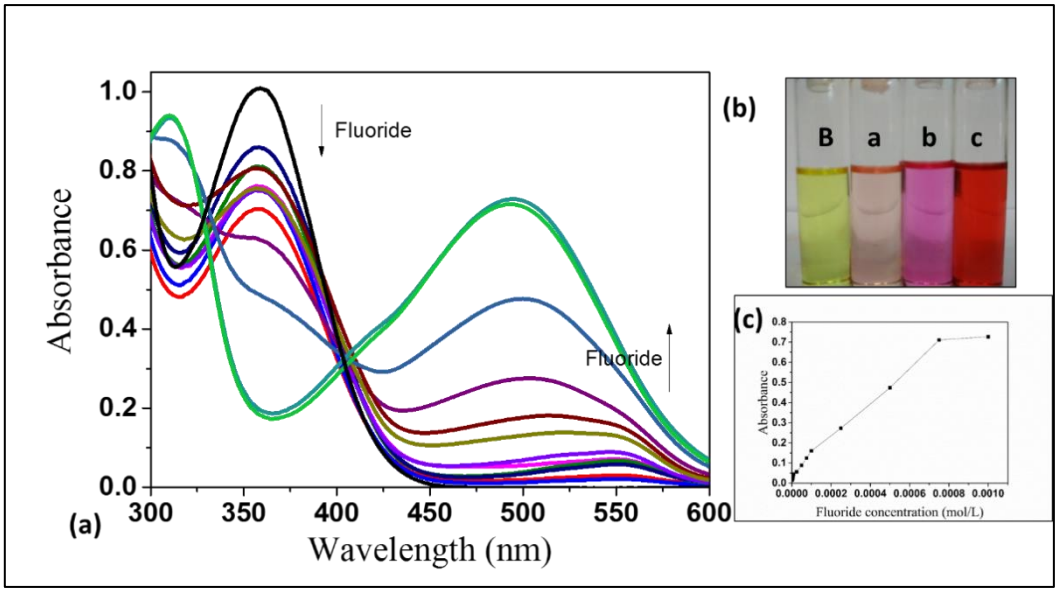


Fig. 7.7: (a) UV-Visible spectra of receptor B (1×10^{-5} M in 9:1 DMSO: water) with fluorideion (sodium salt) from 5×10^{-6} to 1×10^{-3} M in distilled water. (b) The colour changes of receptor B (1×10^{-5} M in 9:1 DMSO: water) (B) with NaF in distilled water at 0.19 ppm, (b) 1.5 ppm (c) and 5 ppm. (c) Changes in absorbance at 500 nm of receptor B (1×10^{-5} M in 9:1 DMSO:water) with increase in fluoride ion concentration (5×10^{-6} to 1×10^{-3} M)

In order to further evaluate the binding characteristics of receptor **B** with fluoride ion, sodium salt of varying fluoride ion concentrations (5×10^{-6} to 1×10^{-3} M)were added into receptor **B** solution (1×10^{-5} M in 9:1 DMSO-water). On titration with fluoride ion, absorbance at 358 nm decreased with the simultaneous formation of a new band at 500 nm, indicating towards possible binding between receptor and fluoride ion. Addition of fluoride ion from 0.5 to 100 equivalents into receptor solution caused the increase in the intensity of new band at 500 nm **(Fig. 7.7).** The bathochromic shift witnessed was probably due to the formation of hydrogen bond between anion and receptor N-H proton. With higher concentration of fluoride ion, pink colour changed to red, indicating towards the possibility of deprotonation of N-H caused at higher concentration of fluoride ion **[50]**. An isobestic point at 405 nm was observed which indicates the formation of fixed binding ratio between receptor **B** and fluoride ion.**Fig.7.8** shows absorbance wavelength ratiometric plot of receptor based on $A_{500\ nm}/ A_{358nm.}$

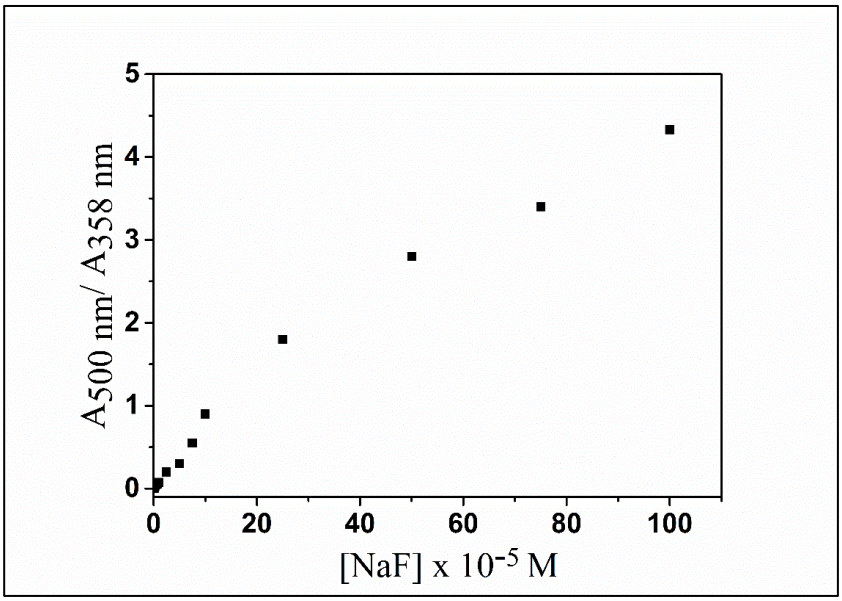


Fig. 7.8: Wavelength ratiometric plot based on $A_{500\ nm}/ A_{358nm}$ as a function of added fluoride concentration from 5 $\times 10^{-6}$ to 1×10^{-3} M

Stoichiometry was determined by the Job's plot of receptor **B** with fluoride ion, where it was observed that receptor B binds fluoride ion in 1:1 stoichiometry ratio**[51](Fig. 7.9),** which wasalsoproved by mass spectra of receptor **B** with fluoride ion (sodium salt), which exhibited a peak at 326.1872 [receptor B + F^- +H^+, calcd 326.0487] **(Fig.7.10).**

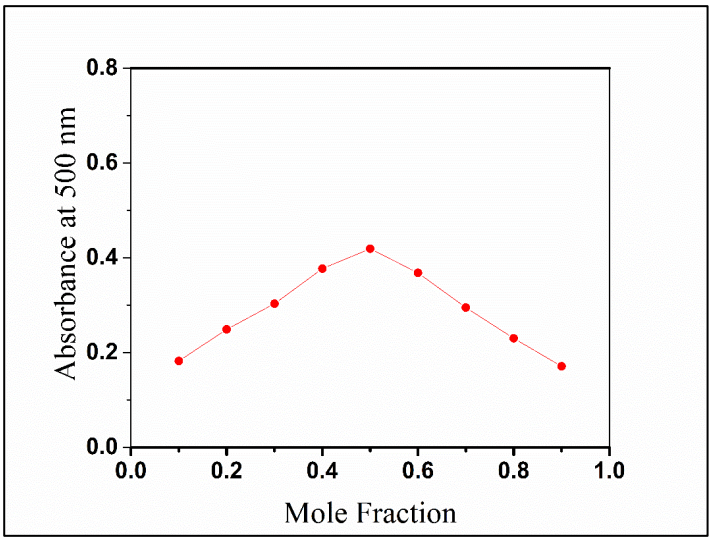


Fig.7.9: Job's Plot with receptor B 1×10^{-4} M in 9:1 DMSO-water and fluoride ion (sodium salt) 1×10^{-4}M in water

Another noteworthy feature of the receptor **B**, apart from the capability to sense fluoride ion in aqueous media, is the naked eye detection of fluoride ion at different levels by exhibiting colour gradation from light pink (0.19-1.5 ppm) to pink (1.5 – 5 ppm), pink to red (5 ppm and above). In this manner, receptor **B** is capable of not only detecting the mere presence of fluoride ion in water, but also gives an idea about the levels of fluoride ion in water.

Detection limit calculation

Visual method was employed for calculation of detection limit in Nesseler's tube. Receptor **B** can visually detect minimum concentration of 0.19 ppm of fluoride ion, below which no naked eye response was obtained. It was also calculated from calibration plot (0.19 ppm) (**Fig.7.**) [**52]**

LOD = 3 x (Standard deviation/ Slope of the calibration curve)

where, LOD is limit of detection; Standard deviation calculated = 0.00687

Slope of the calibration curve = 0.01876

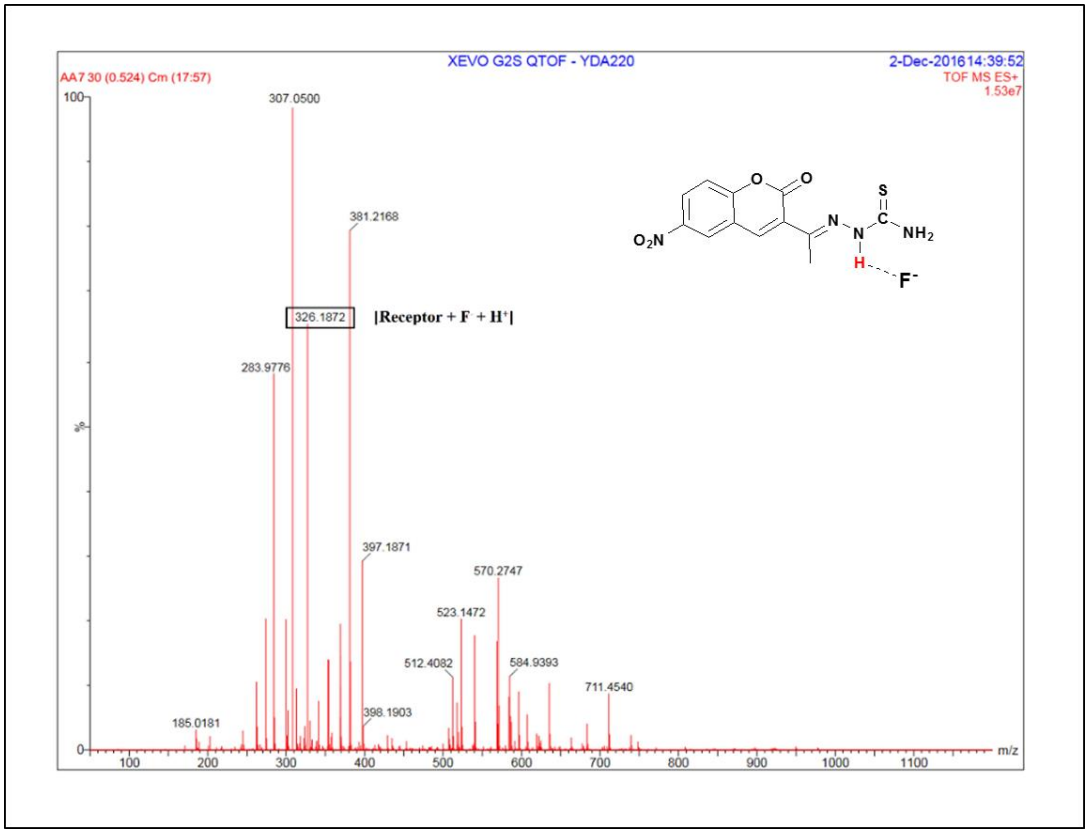


Fig. 7.10: ESI-Mass spectrum of fluoride complex of receptor B

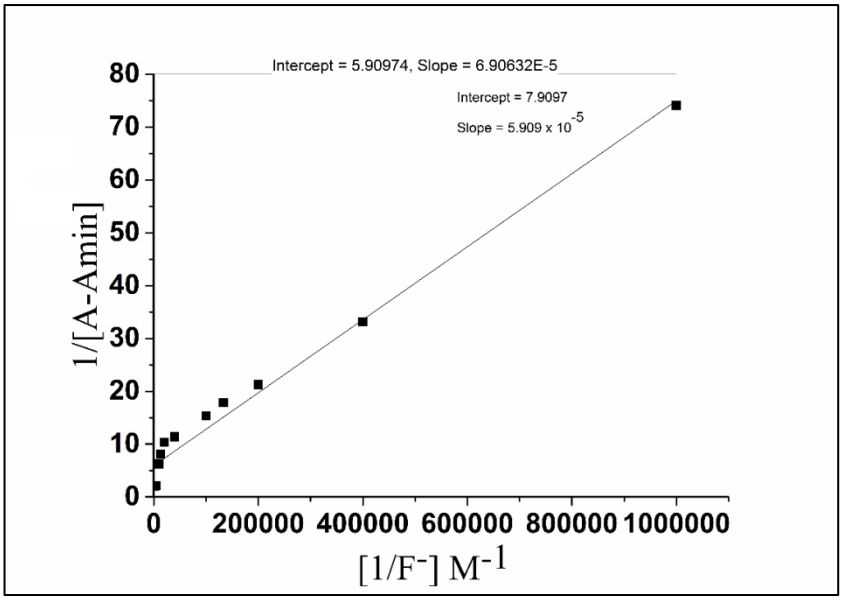


Fig. 7.11: Fitting curve of Benesi-Hildebrand Plot of receptor B with fluoride ion

The binding constant, K of receptor **B** with fluoride was evaluated by Benesi Hildebrand plot and calculated from the ratio of intercept/slope. Binding constant K **(Fig.7.11)** was found to be 1.38×10^5 M^{-1}, indicating high affinity of receptor **B** towards fluoride ion. **[53].**

^{1}H NMR titration experiment

Insight into receptor-fluoride ion interaction could be realized by ^{1}H-NMR titration. For ^{1}H-NMR titration, receptor **B** solution was prepared in DMSO-d_6 (10^{-2} M) and fluoride ion (TBA) was added at different concentrations (1,2,4,6,8 and 10 equivalents prepared in DMSO-d_6) **(Fig.7.12).** Addition of 1 to 8 equivalents of fluoride ion resulted in the downfield shift of the NH proton. Upon addition of 10 equivalents of fluoride ion into receptor, the peak disappeared completely, with simultaneous appearance of bifluoride ion peak at 16.1 ppm. This data indicates receptor interacts with fluoride ion *via* NH proton of thiosemicarbazide moiety primarily by hydrogen bonding, whereas further addition of fluoride ion caused the deprotonation of NH proton.

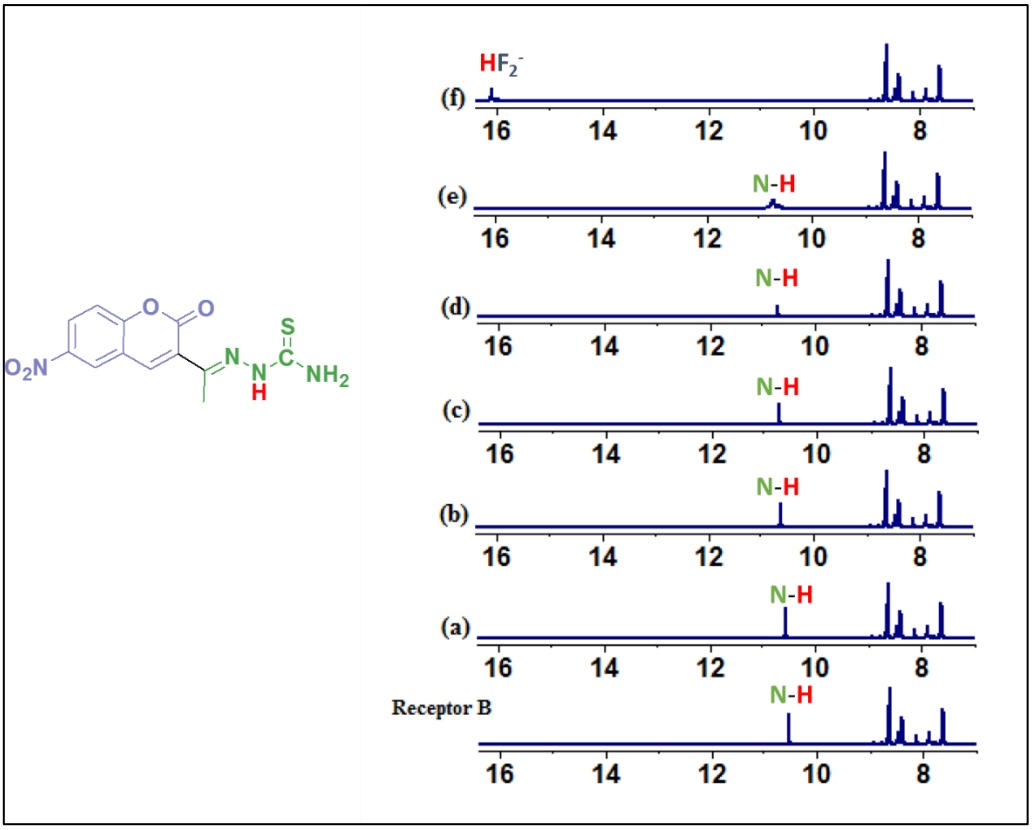
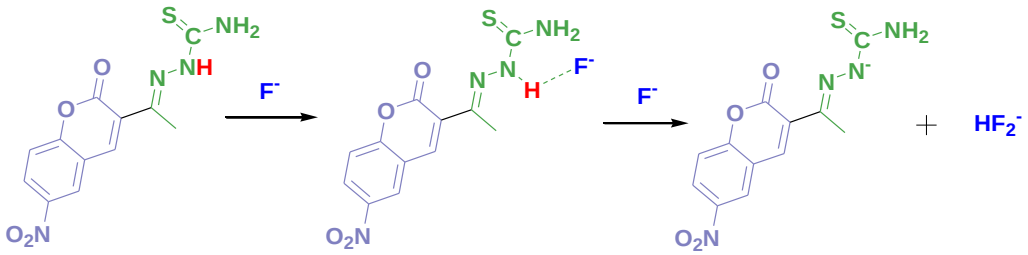


Fig. 7.12:Partial ^{1}H NMR spectra of receptor B in DMSO-d_6(10^{-2} M) in the presence of (a) 1, (b) 2, (c) 4, (d) 6, (e) 8 and (f) 10 equivalents of TBAF in DMSO-d_6

The proposed mechanism is shown in **Scheme 2**.



Scheme 7.2:Proposed binding mechanism of receptor B with fluoride ion

pH effect on receptor B-F^- interactions

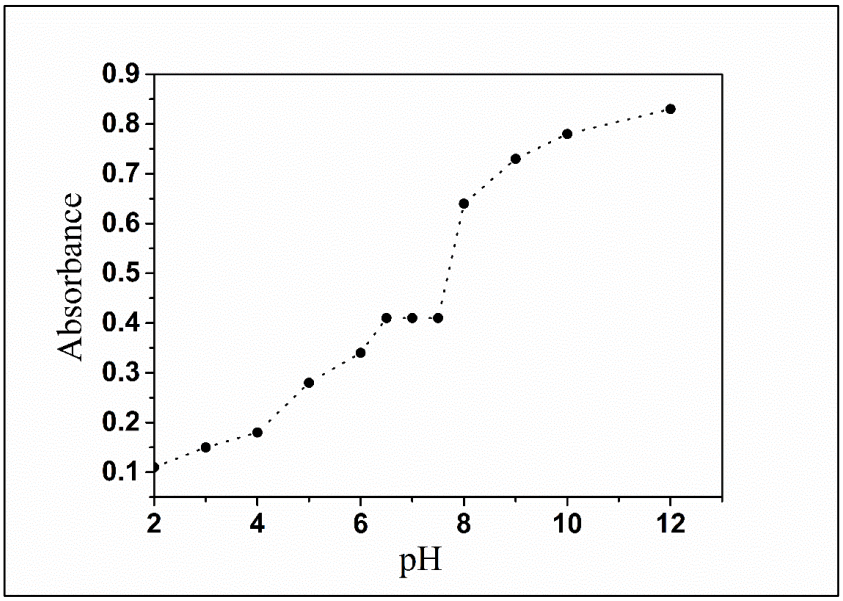


Fig. 7.13: Absorbance changes of receptor B at 500 nm with respect to various pH of solution (2-12) containing 2 ×10^{-4} M NaF

The effect of pH on receptor-fluoride ion binding affinity was investigated by observing the changes in the intensity of the absorbance band at 500 nm, which is characteristic for the formation of receptor-F^- complex, over a pH range 2-12 (**Fig. 7.13**). The working pH range was found to be 6.5-7.5, where the intensity of absorbance remains constant. Below pH 6.5, intensity of absorbance band at 500 nm decreased rapidly. This is probably due to protonation of fluoride ion, to form weakly ionized hydrofluoric acid, which decreases the affinity of fluoride ion to bind receptor binding sites, N-H. Above pH 7.5, intensity of this absorption band increased, which can be ascribed to increased availability of deprotonated receptor to establish stronger hydrogen binding interactions with fluoride ion. These type of pH dependency has also been reported earlier for other colorimetric fluoride receptors **[47, 54]**.

Analytical application

Different brands of toothpaste and mouthwash nowadays contain fluoride as sodium salt to prevent dental caries, which in most of the cases exceeds the permissible limit. Toothpaste is known to contain approximately 1000 ppm of fluoride salt, while it is not even listed in contents of mouthwash. One of the popular brand of toothpaste

(India) was taken for checking the fluoride levels in it and solution containing 5 mg/l of it was prepared in distilled water, while1ml of mouthwash is diluted with 100 ml of distilled water. Receptor **B** solution was prepared as 1 x 10^{-5} M in 9:1, DMSO-water. Absorbance and the colour changes were recorded with receptor **B** alone and with toothpaste and mouthwash solutions **(Fig.7.14).**

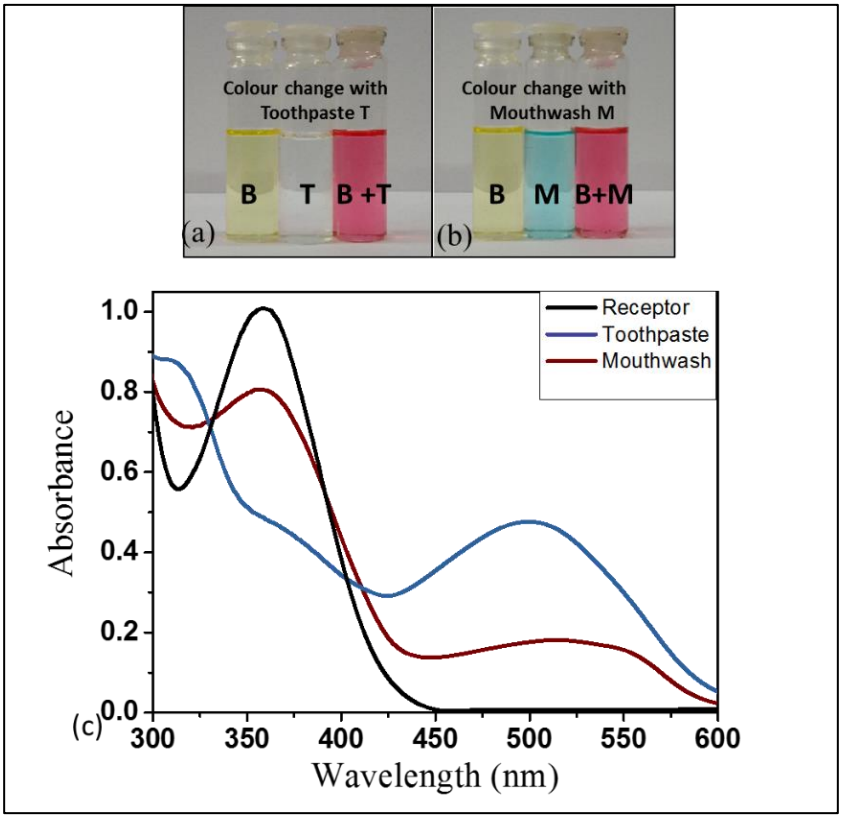


Fig. 7.14: (a) Colour Changes (B+T) of Receptor (B) with toothpaste solution (T) in distilled water. (b) Colour Changes (B+M) of receptor (B) with mouthwash solution (M) in distilled water. (c) UV visible changes in the spectra of receptor (1×10^{-5} M in 9:1 DMSO-water) with addition of toothpaste and mouthwash

Visual change in colour from yellow to pink of receptor **B** solution was instantly observed in both cases and was further proved by observing a red shift in wavelength from 358 nm to 500 nm in UV-Visible spectra. Quantitatively, fluoride ion was estimated in toothpaste and mouthwash solutions by the application of calibration curve, obtained from a plot of absorbance of receptor **B** and various NaF concentrations at 500 nm **(Fig. 7.15).** The value obtained from the plot for toothpaste solution (approx. 5 ppm) is 4.86 ppm, which is in good agreement with the reported

value. For mouthwash, fluoride ion concentration was found to be 190.8 ppm, when the value obtained from the graph (1.90) was multiplied by dilution factor (100) which is in agreement with reported value **[47]**. Colour intensities of receptor **B** with toothpaste and mouthwash solution appeared same, because receptor **B** provides same intensity of colour for fluoride levels in the range of 1.5 – 5 ppm.

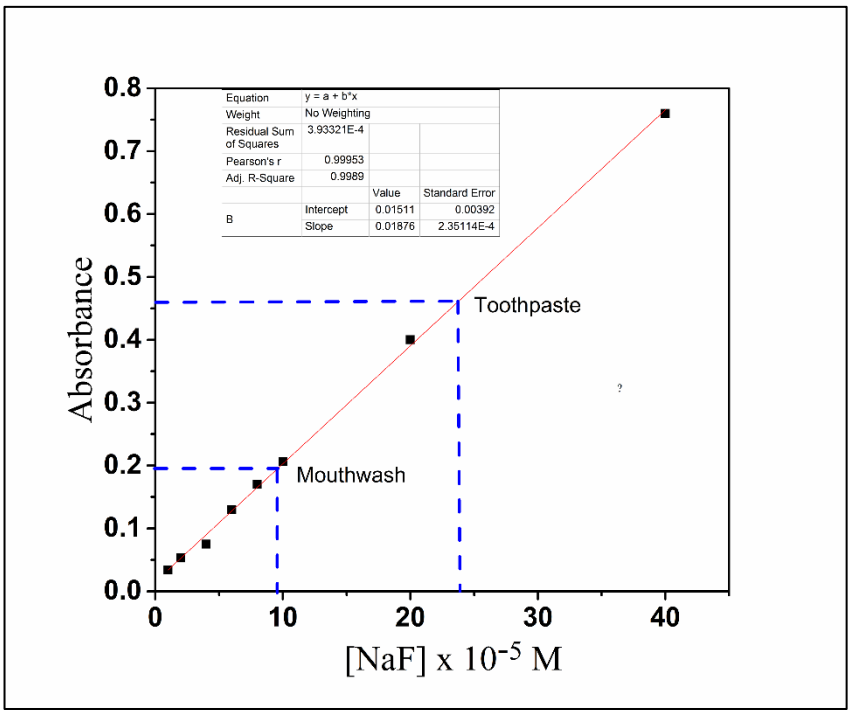


Fig. 7.15: Calibration curve for the determination of the concentration of fluoride ion in toothpaste and mouthwash

To assess the utility of receptor B for practical real life applications, tap and groundwater samples (containing different fluoride ion concentration) from Sanganer and Bagru district, Rajasthan, India were collected and their fluoride ion concentration was determined by ion meter. Naked eye colour changes for the same water samples were then observed by addition of receptor **B** in them. Gradation in colour was clearly noticed with variation in fluoride ion concentration. To corroborate the observed results, UV-Visible spectral study was also conducted, which showed red shift in wavelength at 350 nm to 500 nm and increase in absorbance of new band at 500 nm with increase in fluoride ion concentration **(Fig.7.16 and Fig. 7.17)**.

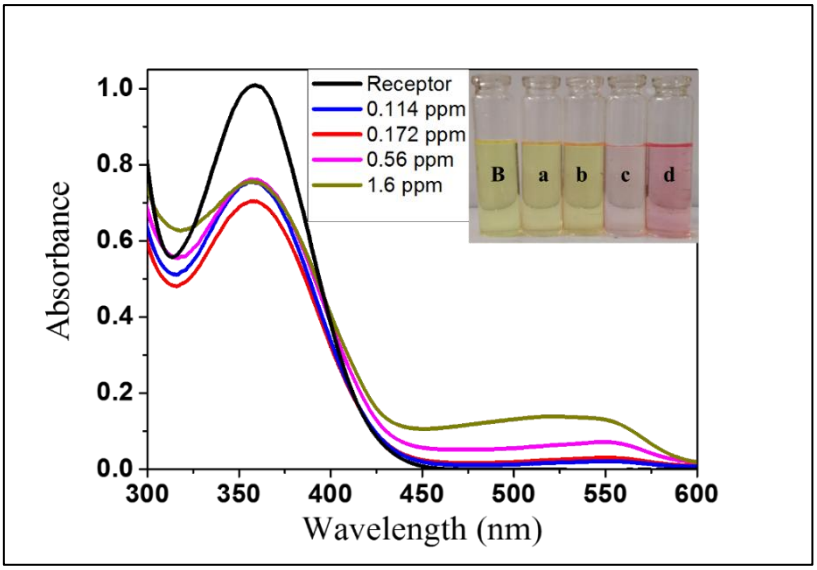


Fig. 7.16: UV-Visible changes in the spectra of receptor B (1 x 10^{-5} M in 9:1 DMSO-water) with addition of water samples collected from Bagru district. Inset showing colour changes of receptor B (1 x 10^{-5} M in 9:1 DMSO-water) with water samples containing fluoride concentration as, a) 0.172, b) 0.11, c) 0.56 and d) 1.6 ppm

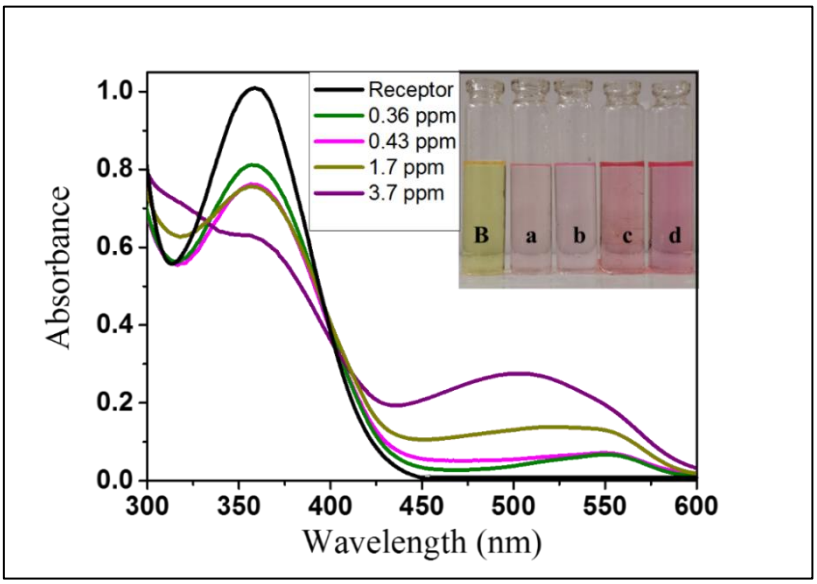


Fig. 7.17: UV-Visible changes in the spectra of receptor B (1 x 10^{-5} M in 9:1 DMSO-water) with addition of water samples collected from Sanganer district. Inset showing colour changes of receptor B (1 x 10^{-5} M in 9:1 DMSO-water) with water samples containing fluoride concentration as, a) 0.36, b) 0.43, c) 1.7 and d) 3.7 ppm

The fluoride ion concentration in various water samples were obtained using calibration graph, which had been plotted between absorbance taken at 500 nm wavelength and standard NaF solutions (**Fig.7.14**). Then, these values were plotted against fluoride ion concentration values obtained by the Fluoride ion selective electrode (F-ISE) **(Table 7.3)** (**Fig.7.18**). The graph obtained shows that values obtained by receptor B were in good agreement with standard method, fluoride ion standard electrode (F-ISE).

Table 7.3: Determination of fluoride ion in the water samples with proposed method and Fluoride Ion Selective Electrode

Drinking water samples	Fluoride ion concentration measured by Receptor B (ppm)	Fluoride ion concentration measured by F-ISE (ppm)
1	0.3	0.34
2	0.57	0.61
3	0.35	0.38
4	0.598	0.63
5	0.5	0.53
6	0.667	0.7
7	1.27	1.4
8	1.041	1.07
9	1.39	1.6
10	1.022	1.09
11	3.2	3.6
12	1.9	1.93

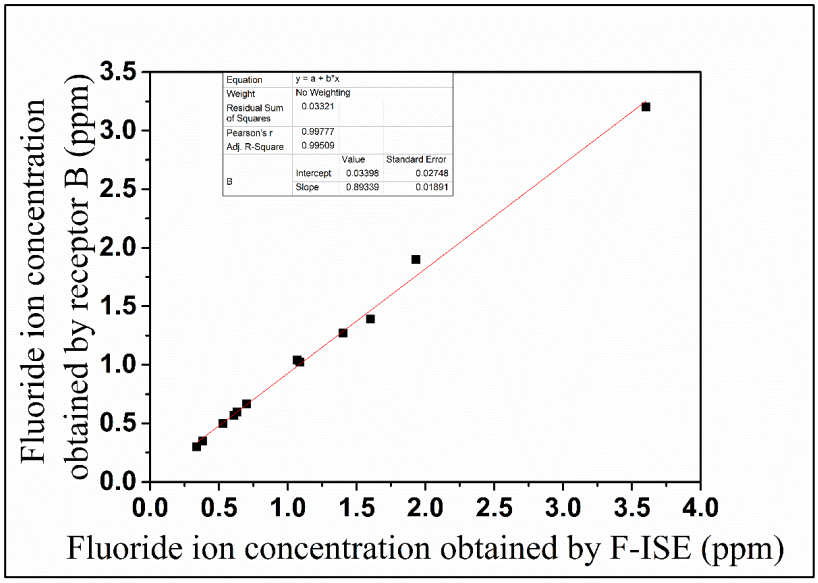


Fig. 7.18: Comparison of fluoride ion concentration obtained by receptor B using UV-Visible spectrophotometer and F-ISE (Fluoride Ion Selective Electrode)

Spike and recovery

The proposed receptor **B** was applied to determine of fluoride ion in drinking water samples collected from Sanganer and Bagru districts of Jaipur city, in order to test the validity of the method. Recovery tests were used to examine the reliability and accuracy of the method. Known concentration of sodium fluoride were spiked into the water sample and fluoride ion content was determined at optimum conditions. Sample was spiked in triplicate and the average was calculated with relative standard deviation (RDS). The fluoride content of different samples and recoveries of added analyte were calculated by the application of calibration curve (**Fig.7.14**) and the results showed that it is possible to determine the fluoride concentration in real sample solutions using receptor B (**Table 7.4**). The recovered fluoride concentration versus spiked fluoride concentration graph has been plotted, from which actual concentration can be calculated (**Fig.7.19**) **[55].**

Table 7.4. Calculation of recovery percentage in drinking water sample after spiking with known concentration of fluoride ion

Fluoride concentration in Drinking water sample- 0.36 ppm (5 ml)	Spiked fluoride concentration (ppm) (5 ml)	Final Concentration after spiking (ppm) (10 ml)	Obtained fluoride concentration (ppm) (10 ml)	RSD % (n=3)	Recovery %
	1	0.68	0.61	2.3	88
	2	1.18	1.059	1.7	89.8
	3	1.68	1.518	2.1	90.4
	4	2.18	1.95	1.9	89.6

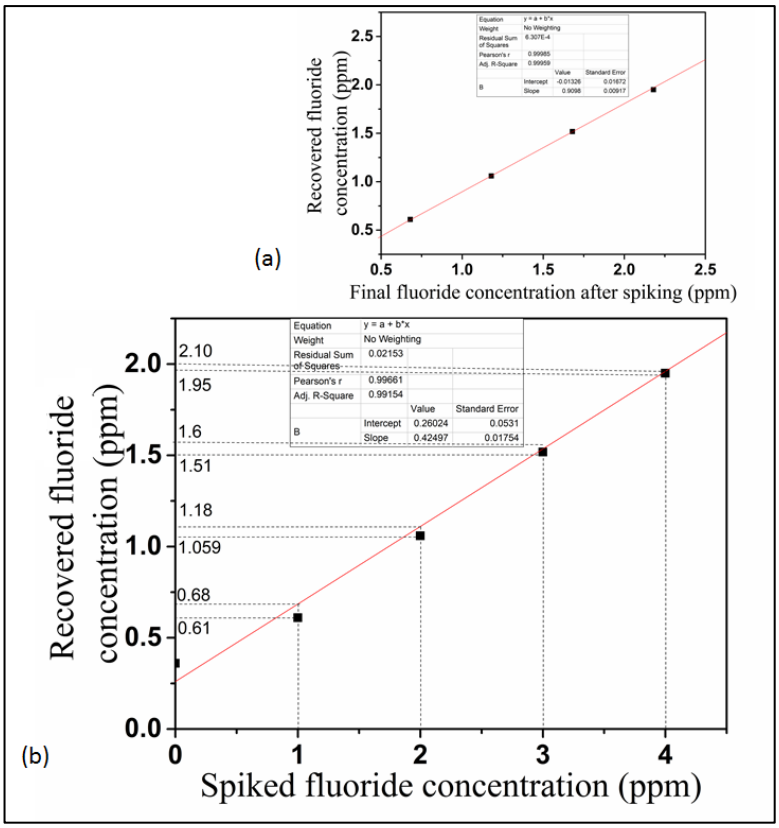


Fig. 7.19: (a) Graph plotted between final fluoride concentration after spiking (ppm) and recovered fluoride concentration (ppm) (b) Graph plotted between spiked fluoride concentration (ppm) and recovered fluoride concentration (ppm)

Interference from metal ions

Receptors, containing thiosemcarbazide moiety, have been documented to bind metal ions, especially, Hg^{+2} and Cu^{+2} through free NH_2 and sulphur atom **[56-57]**. Therefore interference study was conducted to check the possibility of binding of receptor **B** with these metal ions. UV-Visible spectroscopic study was carried out with receptor B solution ($1x10^{-5}$ M in 9:1 DMSO-water), fluoride (1×10^{-5} M as sodium salt in water), Hg^{+2} and Cu^{+2} (1×10^{-5} M as nitrate salts in water). It was observed that no spectral change was observed when these metal ions were added to receptor B solution, indicating absence of any interaction between receptor B and metal ions (**Fig. 7.20).**

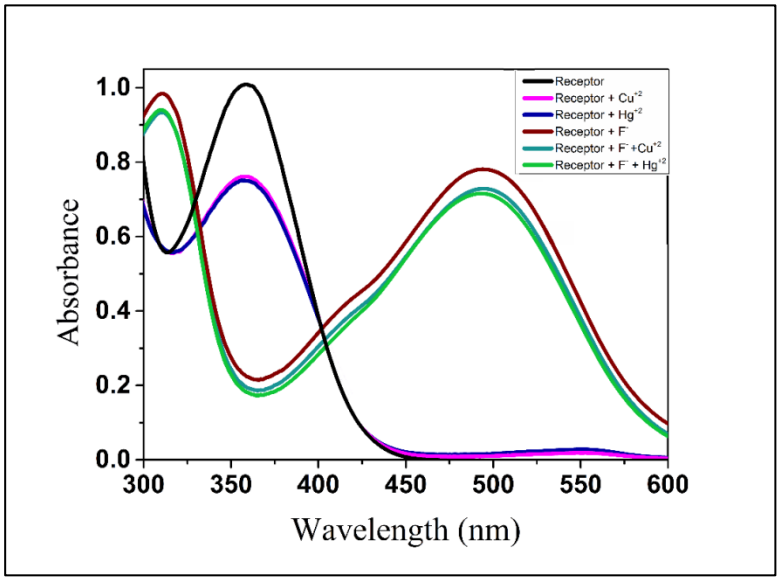


Fig. 7.20: Changes in absorbance of receptor B (1×10^{-5} M in 9:1 DMSO-water) upon addition of fluoride ion (1×10^{-5} M as sodium salt in water) in presence of Hg^{+2} and Cu^{+2} (1×10^{-5} M as nitrate salts in water)

CONCLUSION

Herein, we have described a simple, easy to synthesize receptor **B** which can detect fluoride selectively over other anions in aqueous media colorimetrically with high value of binding constant. Detection limit was found as low as 0.19 ppm. It gives distinct colour change below 1.5 ppm, 1.5 – 5 ppm and 5 ppm and above. This is particularly helpful in places like Rajasthan, India, where there are some remote places with more than 14 ppm of fluoride in ground water and literacy rate is low. Naked eye detection of fluoride ion levels in commodity items of daily use *i.e.*, toothpaste and mouthwash with receptor **B** is also possible.

EXPERIMENTAL

Preparation of (un)substituted-3-acetylcoumarins (1a-e)

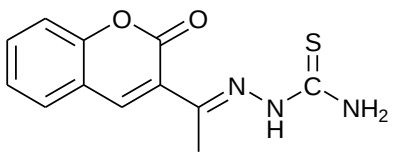
3-Acetylcoumarin **(1a**) other substituted 3-acetylcoumarin were prepared according to literature method as described in Chapter- 6 and their physical characteristics are listed in **Table-7.5.**

Table 7.5: Physical characteristics of substituted 3-acetylcoumarins

S. No.	X	Mol. Formula	Mol. Weight	Yield (%)	M. P. (°C)
1a	H	$C_{11}H_8O_3$	188	96	121
1b	8-OCH_3	$C_{12}H_{10}O_4$	218.21	91	174-176
1c	6-NO_2	$C_{11}H_7O_5N$	233.17	86	192-194
1d	7-$N(C_2H_5)_2$	$C_{15}H_{17}NO_3$	259.30	89	162-163
1e	7,8-Benzo	$C_{15}H_{12}O_3$	238.24	92	168-170

Preparation of 1-(1-((un)substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides(A-E)

1-(1-(2-Oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide (A)



A

Conventional methodology

A mixture of 3-acetylcoumarin **1a** (0.001 mol, 0.188 g) and thiosemicarbazide (0.001 mol, 0.091 g) were taken in a round bottom flask and refluxed in 5 ml of absolute ethanol. The progress of reaction was monitored by thin layer chromatography (pet

ether (60-80 ^{o}C): ethyl acetate: 8:2). On the completion of reaction, as observed by the disappearance of spots of reactants in thin layer chromatography, after 30 minutes, reaction mixture was cooled to room temperature and filtered. Further purification was done by column chromatography (pet ether: ethyl acetate: 8:2) and desired title compound **A** was obtained as yellow solid.

Using microwave irradiation

Equimolar amounts (0.001 mol) of 3-acetylcoumarin (0.188 g) and thiosemicarbazide (0.091g) were irradiated by microwaves at 100 ^{o}C using 50 W power for about 3 minutes under solvent free conditions. The reaction progress was checked by TLC using pet ether (60-80 ^{o}C): ethyl acetate: 8:2 as mobile phase. After the completion of the reaction, the product so formed was cooled to room temperature and purified by column chromatography (pet ether: ethyl acetate: 8:2), whereby pure desired compound was obtained as yellow solid.

M.P. (^{o}C)	121 ^{o}C
Yield (%)	96%
IR (KBr) ν_{max} cm^{-1}	3388, 3236, 3149 (N-H, NH_2), 3040 (aliphatic C-H), 1719 (C=O), 1604 (C=N), 1496 (asym. C=N), 1115, 1073 (C-O), 1011, 762 (C=S)
^{1}H NMR(DMSO-d_6, 500 MHz, δ ppm)	2.25 (s, 3H, H_3C-C=N), 3.34 (s, 2H, NH_2), 7.42-7.96 (m, 4H, Ar H), 8.4 (s, 1H, pyran H), 10.45 (s, 1H, NH).
^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm)	38.50, 114.97, 117.93, 124.79, 128.11, 131.38, 140.99, 144.96, 152.36, 158.12, 178.23
Mass [M+H]$^{+}$	262.0009 $[M+H]^{+}$ (calcd for $C_{12}H_{11}N_3O_2S$: 261.057)

All other receptors, **B-E** were prepared similarly. Physical data of synthesized compounds are given in **Table 7.6.**

Table 7.6: Physical data of 1-(1-(substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazides (A-E)

Compd No.	X	Mol. Formula	Mol. Weight	Yield %		Time (min)	
				(a)	(b)	(a)	(b)
A	H	$C_{12}H_{11}N_3O_2S$	261	86.28	93.27	30	3
B	6-NO_2	$C_{12}H_{10}N_4O_4S$	306	80.30	88.01	35	5
C	8-OCH_3	$C_{12}H_{10}N_4O_4S$	306	80.30	88.01	35	5
D	7-$N(C_2H_5)_2$	$C_{16}H_{13}N_3O_2S$	311	75.15	84.21	35	4
E	7,8-benzo	$C_{13}H_{13}N_3O_3S$	291	76.67	84.44	25	5

(a) – Conventional method
(b) – Using microwave irradiation

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Chapter~ 8: Conclusions and Scope for Future Work

Conclusions and scope of the future work

The work presented in this thesis has enriched the exploration in the field of fluoride ion sensing with the development of novel neutral receptors for robust detection of fluoride ion both in organic as well as aqueous media by exploiting the photophysical properties of wide spectrum of hetetocyclic derivatives.

Novel heterocyclic derivatives have been formulated, synthesized and investigated for anion binding studies with the range of biologically significant anions. We have reported unique C_3 symmetric tripodal receptors, 7,7',7''-(((((2,4,6-trimethylbenzene-1,3,5-triyl)tris(methylene)) tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy)) tris(substituted-2H-chromen-2-ones) which can specifically capture fluoride ion in the cavity formed by its three arms in close proximity. Multiple C-H hydrogen bond donor groups have been employed to establish interactions with fluoride ion, which is validated by spectroscopic studies as well as computational calculations, carried out under density functional theory.

Neutral colorimetric receptor based upon benzimidazole scaffold, N,N'-bis-(5-(un)substituted-1H-benzoimidazol-2-ylalkyl)-isophthalamides have been designed to detect fluoride in aqueous solution, which binds fluoride ion by virtue of multiple hydrogen bonding interactions with fluoride ion. Tri-armed indole-imidazole hybrids have been synthesized for easy and quick detection of inorganic fluoride in 9:1 DMSO-water. It senses fluoride ion at 1.5 ppm (WHO recommended level) with colour change from yellow to orange, perceivable by naked eye.

We have demonstrated a series of coumarin-pyrazole based scaffolds, 3-{4-[(un)substituted-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-ones, as colorimetric naked eye receptors, capable of binding inorganic fluoride ion selectively and sensitively in aqueous media with its rationally placed N-H and C-H groups. Efforts were made to devise a reliable, inexpensive and easy to use for fluoride naked eye detection in water by the synthesis of receptor, 1-(1-(6-nitro-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide. It could sense fluoride selectively over other anions at a detection limit of 0.19 ppm in aqueous media with high value of binding constant. It gives distinct colour change below 1.5 ppm, 1.5 – 5 ppm and 5 ppm and above. Receptor synthesized can serve as an aid to detect

inorganic fluoride ion semi-quantitatively in natural water samples without suffering from any interference by other anions. This is particularly helpful in remote places with more than 14 ppm of fluoride in ground water to get an idea of fluoride ion levels semiquantitatively.

The present research work fulfills the aims and objectives outlined in chapter-1. It also offers different possibilities for future work. There lies a scope for the development of receptor, which is 100% water soluble. Moreover, test strips can be made, which can to sense trace quantities of anions such as fluoride and provide instant and convenient results on-site. This area of research could also provide number of applications, including in organocatalysis, in separating mixtures of anions in industrial or radioactive waste, in synthesis of optode membranes and molecular logic gates.

APPENDIX- I

LIST OF NEW SYNTHESIZED COMPOUNDS

Chapter – 3		
S. No.	**Compd No.**	**Name of Synthesized Compounds**
1	**A**	7,7',7''-(((((2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(2H-chromen-2-one)
2	**B**	7,7',7''-(((((2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(4-(methyl)-2H-chromen-2-one)
3	**C**	7,7',7''-(((((2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(3-(acetyl)-2H-chromen-2-one)
4	**D**	7,7',7''-(((((2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(4-(trifluoromethyl)-2H-chromen-2-one)
5	**E**	7,7',7''-(((((2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene))tris(1H-1,2,3-triazole-1,4-diyl))tris(methylene))tris(oxy))tris(4-(ethyl)-2H-chromen-2-one)
Chapter – 4		
6	**RA**	N,N'-Bis-(1H-benzoimidazol-2-ylmethyl)-isophthalamide
7	**RB**	N,N'-Bis-[1-(1H-benzoimidazol-2-yl)-ethyl]-isophthalamide
8	**RC**	N,N'-Bis-(5-nitro-1H-benzoimidazol-2-ylmethyl)-isophthalamide
9	**RD**	N,N'-Bis-[1-(5-nitro-1H-benzoimidazol-2-yl)-ethyl]-isophthalamide
Chapter – 5		
10	**RA**	3-[2,5-(1H-indol-3-yl)-1H-imidazol-4-yl]-1H-indole
11	**RB**	3-[2,5-(1H-indol-3-yl)-1H-imidazol-4-yl]-5 nitro-1H-indole
12	**RC**	3-[5-(5-Nitro-1H-indol-3-yl)-2-(1H-indoly-3-yl)-1H-imidazol-4-

		yl]-5 nitro-1H-indole
13	**RD**	3-[2,5-(5-Nitro-1H-indol-2-yl)-1H-imidazol-4-yl]-5 nitro-1H-indole
14	**RE**	3-[2,5-(5-Nitro-tert butyl-1H-indol-2-yl)-1H-imidazol-4-yl]-5 nitro-tert butyl-1H-indole
Chapter – 6		
15	**R1**	3-{4-[(2,4-Dinitro-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one
16	**R2**	3-{4-[(4-Nitro-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one
17	**R3**	3-{1-Phenyl-4-[(3-trifluoromethyl-phenyl)-hydrazonomethyl]-1H-pyrazol-3-yl}-chromen-2-one
18	**R4**	3-[1-Phenyl-4-(phenyl-hydrazonomethyl)-1H-pyrazol-3-yl]-chromen-2-one
19	**R5**	3-{4-[(2,4-Dinitro-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one
Chapter – 7		
20	**A**	1-(1-(2-Oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide
21	**B**	1-(1-(6-Nitro-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide
22	**C**	1-(1-(8-Methoxy-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide
23	**D**	1-(1-(7-Diethylamino-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide
24	**E**	1-(1-(7,8-Benzo[h]-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide

APPENDIX-II

LIST OF PUBLICATIONS/ABSTRACT

PAPERS

1. Ragini Gupta, **Anshu Jain** and Bindu Vashney. Synthesis of 5,6-dihydropyran-2-one derivatives under coupled ultrasonication and phase transfer catalysed in situ generated ketenes with chalcones. Journal of Indian Chemical Society. 2014, 91(8), 1533-1538.
2. **Anshu Jain,** Ragini Gupta and Madhu Agarwal. Instantaneous and selective bare eye detection of inorganic fluoride ion by coumarin-pyrazole based receptors. Journal of Heterocyclic Chemistry, 2017, 54(5), 2808-2816.
3. **Anshu Jain,** Ragini Gupta and Madhu Agarwal. Coumarin based receptor for naked eye detection of inorganic fluoride ion in aqueous media. Analytical Chemistry Letters, 2017, 7(2), 170-187.
4. **Anshu Jain,** Ragini Gupta and Madhu Agarwal. Rational tri-armed imidazole-indole hybrids as naked eye receptor for fluoride ion sensing. Synthetic Communications, 2017, 47(14), 1307-1318.
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6. **Anshu Jain,** Ragini Gupta, Yachana Jain, Mitlesh Kumari and Madhu Agarwal. Recent trends in coumarin based neutral receptors for naked eye sensing of anions. Chemistry and Biology Interface, 2017, 7(2), 102-115.
7. **Anshu Jain,** Yachana Jain**,** Ragini Gupta and Madhu Agarwal. New Journal of Chemistry, Communicated.

Publications in Conferences:

1. Ragini Gupta, **Anshu Jain** and Madhu Agarwal. Bare Eye Detection of Inorganic Fluoride in Water via Coumarin Scaffold as Anion Receptor;, National Conference on Frontiers in Chemistry, 13th- 14th March, 2015, PP- 47.
2. Ragini Gupta, **Anshu Jain**, Madhu Agarwal. Novel Indole based colorimetric anion receptor for fluoride ion.. Indian Science Congress, Kolkata, Jan 2013, P-242
3. Ragini Gupta, **Anshu Jain**. Indole Based Anion Receptor. International Workshop on Chemistry for a Sustainable Future, Jaipur, 10-12th Dec 2012 P-52
4. Ragini Gupta, Bhawana Saraswat, Yogita Madan, **Anshu Jain**. Mechanochemistry: Greening Organic Synthesis.. P-53, International Workshop on Chemistry for a Sustainable Future, Jaipur, 10-12th Dec 2012
5. **Anshu Jain,** Yachna Jain, Mitlesh Kumari, Ragini Gupta. Development of magnetically separable and recyclable citrate ornamented nanoparticles as efficient catalyst for synthesis of benzimidazole derivative under ultrasonic irradiation**.** International Conference on, "Frontiers at the Chemistry – Allied Sciences Interface, 25th- 26th April, 2016, organized by Centre of Advanced Studies, Department of Chemistry, University of Rajasthan, Jaipur.
6. Mitlesh Kumari, **Anshu Jain**, Yachana Jain, Ragini Gupta. Lemon Juice Modified Nano Magnetically Separable Catalyst For The Efficient Synthesis of Biologically Important Antipyrine Schiffs Base Under Ultrasonication. International Conference on, "Frontiers at the Chemistry – Allied Sciences Interface, 25th- 26th April, 2016, organized by Centre of Advanced Studies, Department of Chemistry, University of Rajasthan, Jaipur.
7. Yachana Jain, Mitlesh Kumari, Anshu Jain, **Ragini Gupta**. Click chemistry approach for the synthesis of heterobioconjugates in water using cyclodextrin as a phase transfer catalyst under ultrasonication. International Conference on, "Frontiers at the Chemistry – Allied Sciences Interface, 25th- 26th April, 2016, organized by Centre of Advanced Studies, Department of Chemistry, University of Rajasthan, Jaipur.

BRIEF BIODATA OF AUTHOR

Ms Anshu Jain was born in Jaipur, Rajasthan in 1987. She has graduated in Science (Biotechnology, Botany and Chemistry) from International College of Girls, affiliated to University of Rajasthan, Jaipur (2006-2009). She has pursued her Master's degree in Chemistry from Malaviya National Institute of Technology, Jaipur during 2009-2011. After completing master's degree, she cleared CSIR-JRF and registered herself in CSIR for fellowship. She joined the research group of Dr. Ragini Gupta, Associate Professor, Malaviya National Institute of Technology, Jaipur on Dec, 2011 and started her research work on "Development of Heterocyclic based Derivatives as Anion Receptor".

She has presented her research work in various national and international conferences. She also has six publications (research articles and review) in international and national journals of repute in the area of Chemistry.

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Coumarin Based Receptor for Naked Eye Detection of Inorganic Fluoride Ion in Aqueous Media

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Abstract: In this communication, we wish to report the design, synthesis and real life applications of coumarin based "naked eye" artificial receptor for fluoride ion detection in aqueous media. Amongst easy-to-synthesize 1-(1-(substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide (receptors A-E), receptor B exhibited remarkable colour change from yellow to pink instantly upon addition of fluoride salt (sodium fluoride) 1 x 10^{-5} M (0.19 ppm), in aqueous media. Interestingly, receptor B also gave distinct and discernible colour changes perceivable even with naked eye at different fluoride ion (sodium salt) concentrations (*viz*., <1.5, 1.5-5 and >5 ppm) fluoride in water which allows a semi-quantitative data to be generated for fluoride contaminated drinking water. Preliminary investigation with everyday commodity items like toothpaste and mouthwash clearly show visual colour change, which may be helpful for detecting presence of fluoride in these items. This method is so simple that it has the potential for being developed as a tool for detecting different levels of fluoride in ground water, especially suitable for rural areas, where the literacy rate is low. The working pH range of receptor B was found to be 6.5-7.5. The binding constant of receptor for fluoride ion was found to be 1.38 x 10^5 M^{-1}.

Key words: Naked eye detection, colorimetric receptor, inorganic fluoride, aqueous media, coumarin, sodium fluoride, coumarin thiosemicarbazone.

Introduction

Myriads of anions play several crucial roles in biological, clinical, chemical and environmental processes [1]. Anions are omniprevalent and play significant role as cofactors and enzyme substrates in biological systems [2]. Further, processes like cell proliferation, cell migration and cell volume homeostasis involve anion channels [3]. On the other hand, certain anions such as fluoride, phosphate, nitrate and cyanide are documented as pollutants [4].

Amongst these anionic species, fluoride is of paramount interest due to its two-faced nature [5]. Prevention of dental caries and osteoporosis by fluoride is widely advertised resulting in sporadic water fluoridation and addition of fluoride ion (sodium salt) to commercial dental products [6]. Although helpful in lower doses, at higher concentrations, it proves to be highly toxic to human body, since that it is easily absorbed, but is excreted slowly from the body [7]. Needless to say that its

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overexposure causes dental and skeletal fluorosis, nephrotoxicity in humans and animals and is reported to be responsible for inhibition of certain enzymatic functions [8]. World Health Organisation guidelines have set 1.5 ppm as permissible limit for fluoride in drinking water and Environmental Protection Agency, USA has listed maximum contaminated level of fluoride as 4 ppm. Ground water, in many parts of the world, notably Africa, China and India, contain high levels of fluoride, much greater than the permissible limit, yet people are forced to consume it, since it is the only source of drinking water [9]. Other pollutants present in water and surrounding environment include metal ions such as lead, mercury, copper, chromium, etc. Stimulated by public health concerns for such high levels of toxic metals, Gupta *et. al*. have developed many potentiometric sensors for lead(II), mercury(II), nickel(II), copper(II) and aluminium(III) ions, which offered high selectivity, lower detection limit and fast response time [10-20]. Various turn-on fluorescent chemosensors for detection of aluminium(III) and zinc(II) have also been developed by the same research group, which detect these ions by naked eye under UV lamp [21-23]. Similarly, the design and synthesis of receptors for colorimetric receptors that can recognize and sense anions selectively through visible colour change perceivable by naked eye are of particular interest since it obviates the requirement of any spectroscopic instrument and the necessity of any skilled personnel to detect them [24-28]. A significant number of chemosensors for fluoride ion have been developed; but their utility to test in drinking water under field conditions is restricted to very few chemosensors because of strong solvation of both binding site and fluoride ion in aqueous media [29-30]. Several strategies like Lewis acid or metal-ion coordination, anion-π interactions and cationic receptors have been explored to accomplish detection of fluoride in aqueous media [31], but have failed because they detect fluoride ion of only organic origin, *i.e.*, in tetrabutylammonium fluoride (TBAF). Chemodosimeter approach based on desilylation reaction was found to operate in aqueous media; but the slow response time limits its on-site applicability [32]. Thus, neutral receptor with directional hydrogen bonding moieties having chromophoric scaffolds decorated with binding functionalities *i.e*. amides, guanidinium, immidazolium derivatives and urea/thioureas capable of converting the binding event at molecular level into macroscopic event have been developed [33-38]. Pyrroles, indoles, biindoles, indolocarba-zoles, imidazoles and benzimidazoles have also been identified as potential candidates for anion recognition and sensing [39-40]. Coordination of acidic protons of these moieties with fluoride induces colour or fluorescence changes [41]. However, their performance in a competitive solvent like water needs to be overcome, since most of them work in either organic or 9:1 organo-aqueous solutions which hinders the purpose of fluoride detection in drinking water.

Coumarin derivatives have been extensively investigated for electronic and photonic applications such as fluorescence probes, charge transfer agents, solar energy collectors and non-linear optical properties due to their inherent photochemical characteristics, reasonable stability, and in relative ease of synthesis [42], but anion sensors derived from coumarins have been scarcely reported [42-43]. Shao *et. al.* and Ghosh *et. al*. have reported various coumarin based fluoride sensors, but they all exhibited fluoride binding properties only in organic solvents [44-45]. Anion detection in aqueous media has been reported by Lee *et. al*. with coumarin scaffold *via* chemodosimeter approach [46]. To the best of our knowledge, no reports are available using coumarin based derivatives for naked eye detection of fluoride in aqueous media.

A perusal of literature reveals that recognition studies of receptors reported are limited to detection of tetrabutylammonium fluoride (TBAF) and were carried out in aprotic media *i.e*., DMSO, acetonitrile and chloroform, to avoid competition of solvent (water/ alcohol) as a hydrogen bonding donor. Attempts have been made by Khanmohammadi *et. al.* and Trivedi *et. al.* to detect sodium fluoride in recent years [47-48]. For practical considerations, anion binding in aqueous media is essential. Fluoride is the most challenging anion to detect in aqueous media because of its high hydration enthalpy. A considerable number of receptors effective in aqueous conditions have been reported but they suffer from complications like longer detection time for the colour change to

appear, while turn off fluorescent receptors lacked the sensitivity. Thus, there is a need to develop simple, easy to synthesize, inexpensive receptor which can overcome these shortcomings and is suitable for practical purposes. So, herein we report coumarin based naked eye receptors A-E for fluoride ion detection in aqueous media, based on hydrogen binding and deprotonation mechanism. These results entail the higher capability of receptor to compete with water for anion binding, a necessary thing for practical purpose. Real life applications of receptor B are also discussed with commodity items of daily use i.e., toothpaste and mouthwash.

Experimental

Materials and methods

All reagents were purchased from Sigma Aldrich, India and were used without further purification. Melting points were determined in open glass capillaries and are reported uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum. Two spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz at the Department of Chemistry, Indian Institute of Technology, Roorkee using DMSO-d_6 as a 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 spectrometer (Waters, USA), capable of recording high-resolution mass spectrum (HRMS) in the ESI (Electrospray Ionization) mode. CEM discover mono mode microwave reactor with magnetron frequency of 2455 MHz was used for microwave reactions. 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. Visualization was accomplished by UV light or iodine adsorption.

Synthetic procedure

Variously substituted 3-acetyl coumarins were synthesized according to the reported method [49].

General procedure for the synthesis of receptors, 1-(1-(substituted-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide (A-E)

Equimolar amounts (0.001 mol) of substituted acetyl coumarins and thiosemicarbazide (0.091 g) were irradiated using microwave at 100°C and 50 W power for about 3 minutes under solvent free conditions. The products so formed were purified by column chromatography (pet ether: ethyl acetate: 8:2) and pure compounds were obtained as yellow solids.

Spectroscopic data for receptor A, 1-(1-(2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide

Yield: 95.27 %. m p 220°C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm) δ 2.25 (s, 3H, H_3C-C=N), 3.34 (s, 2H, NH_2), 7.42 (m, 2H, Ar H), 7.64 (s, 1H, Ar H), 7.76 (s, 1H, Ar H), 7.96 (s, 1H, pyran H), 10.45 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz, ppm) 38.50, 114.97, 117.93, 124.79, 128.11, 131.38, 140.99, 144.96, 152.36, 158.12, 178.23. FTIR (KBr, cm^{-1}) 3388, 3236, 3149 (N-H, NH_2), 1719 (C=O), 1604 (C=N), 1496 (asym. C=N), 1115, 1073 (C-O), 1011, 762 (C=S). MS (ESI) m/z=262.0009 $[M+H]^+$, calculated for $C_{12}H_{11}N_3O_2S$: 261.057.

Spectroscopic data for receptor B, 1-(1-(6-nitro-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide

Yield: 94.01%, m p 235°C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 2.50 (s, 3H, H_3C-C=N), 3.33 (s, 2H, NH_2), 7.64 (d, 1H, Ar H), 7.93 (s, 1H, Ar H), 8.41 (d, 1H, Ar H), 8.66 (s, 1H, pyran H), 10.45 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz, ppm): 39.44, 117.62, 124.60, 126.38, 128.41, 140.58, 143.66, 157.40, 158.07, 179.29, 194.62. FTIR (KBr, cm^{-1}): 3420, 3227, 3145 (N-H, NH_2), 1731 (C=O), 1618 (C=N), 1596 (asym. C=N), 1540, 1352 (N-O), 1123, 1095 (C-O), 1066, 777 (C=S). MS (ESI) m/z = 307.0500 $[M+H]^+$, calculated for $C_{12}H_{10}N_4O_4S$: 306.0423.

Spectroscopic data for receptor C, 1-(1-(8-methoxy-2-oxo-2*H*-hromen-3-yl)-ethylidene)-thiosemicarbazide

Yield: 93.31 %, m p 202°C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 2.49 (s, 3H, H_3C-C=N),

3.41 (s, 2H, NH_2), 3.91 (s, 3H, OCH_3), 7.30 (m, 3H, Ar H), 7.96 (s, 1H, pyran H) 10.44 (s, 1H, NH) ^{13}C NMR (DMSO-d_6, 125 MHz, ppm): 39.40, 56.01, 114.41, 119.38, 124.58, 125.77, 142.08, 145.83, 158.74, 179.13. FTIR (KBr, cm^{-1}): 3405, 3299, 3178 (N-H, NH_2), 1724 (C=O), 1614 (C=N), 1570 (asym. C=N), 1137, 1096 (C-O), 1077, 759 (C=S), MS (ESI) m/z = 292.0562 $[M+H]^+$, calculated for $C_{13}H_{13}N_3O_3S$: 291.0678.

Spectroscopic data for receptor D, 1-(1-(7-diethylamino-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide

Yield: 93.21%, m p 142°C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 2.48 (s, 3H, H_3C-C=N), 2.49 (t, 6H, CH_3), 3.86 (2H, NH_2), 4.83 (q, 4H, CH_2), 7.92 (s, 1H, Ar H), 8.15 (2H, m, Ar H), 8.99 (s, 1H, pyran H), 9.83 (s, 1H, NH) ^{13}C NMR (DMSO-d_6, 125 MHz, ppm): 30.09, 39.45, 44.35, 95.73, 107.41, 114.91, 132.37, 147.59, 152.89, 158.21, 159.83, 194.15. FTIR (KBr, cm^{-1}): 3406, 3260, 3159 (N-H, NH_2), 1714 (C=O), 1600 (C=N), 1562 (asym. C=N), 1117, 1086, (C-O), 1017, 757 (C=S). MS (ESI) m/z = 333.1242 $[M+H]^+$, calculated for $C_{16}H_{20}N_4O_2S$: 332.1307.

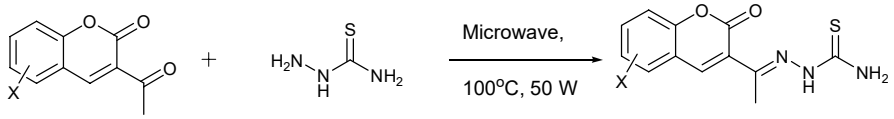
Spectroscopic data for receptor E, 1-(1-(7,8-benzo[h]-2-oxo-2*H*-chromen-3-yl)-ethylidene)-thiosemicarbazide

Yield: 93.20 %, m p 242°C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 2.49 (s, 3H, H_3C-C=N), 3.34 (s, 2H, NH_2), 7.65 (m, 2H, Ar H), 8.06 (d, 2H, Ar H), 8.17 (s, 1H, Ar H), 8.21 (d, 1H, Ar H), 8.32 (s, 1H, pyran H), 9.29 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz, ppm): 39.14, 48.23, 112.75, 116.05, 122.63, 124.67, 125.87, 127.94, 128.47, 129.59, 133.39, 137.35, 146.03. FTIR (KBr, cm^{-1}): 3457, 3343, 3209 (N-H, NH_2), 1716 (C=O), 1589 (C=N), 1507 (asym. C=N), 1237, 1096 (C-O), 1041, 767 (C=S). MS (ESI) m/z = 312.4568 $[M+H]^+$ $[M+H]^+$, $C_{16}H_{13}N_3O_2S$: 311.078.

Results and discussion

Diversely substituted 3-acetyl coumarins were synthesized using reported method [49] which were then condensed with thiosemicarbazide without any solvent under microwave irradiation to yield desired receptors (A-E) in almost quantitative yield, which were then characterized by standard spectroscopic techniques (Scheme 1). This green protocol, in contrast to conventional method of heating, proved fruitful in terms of reduced pollution, clean and mild conditions, reduced time, high atom economy, lower cost and ease of purification.

The receptors were designed with coumarin scaffold as chromophoric unit and thiosemicarbazide N-H as binding site. Our aim was to synthesize naked eye receptors for fluoride ion detection, so five receptors were designed containing both electron-withdrawing and electron-releasing groups, which could visually detect anions in the form of their inorganic sodium salts. Initially, colour changes in receptor solutions A-E ($1x10^{-5}$ M in 9:1 DMSO-water) were examined by adding 1 to 100 equivalents of different anion salts *viz.*, fluoride, acetate, chloride, bromide, iodide, dihydrogen phosphate, hydrogen sulphate and nitrate into it. (Figure 1) An instant colour change from pale yellow to pink was observed with receptor A and B upon addition of fluoride ion (sodium salt), while no obvious colour change could be observed with other anions, suggesting no anion-receptor coordination takes place. Receptors



Receptor A , X = H,
B , X = 6-NO_2,
C, X = 8-OCH_3,
D, X = 7-$N(C_2H_5)_2$,
E, X = 7,8-benzo

Scheme 1. Synthesis of 1-(1-(substituted-2-oxo-2*H*-chromen-3-yl) -ethylidene)-thiosemicarbazide (A-E)

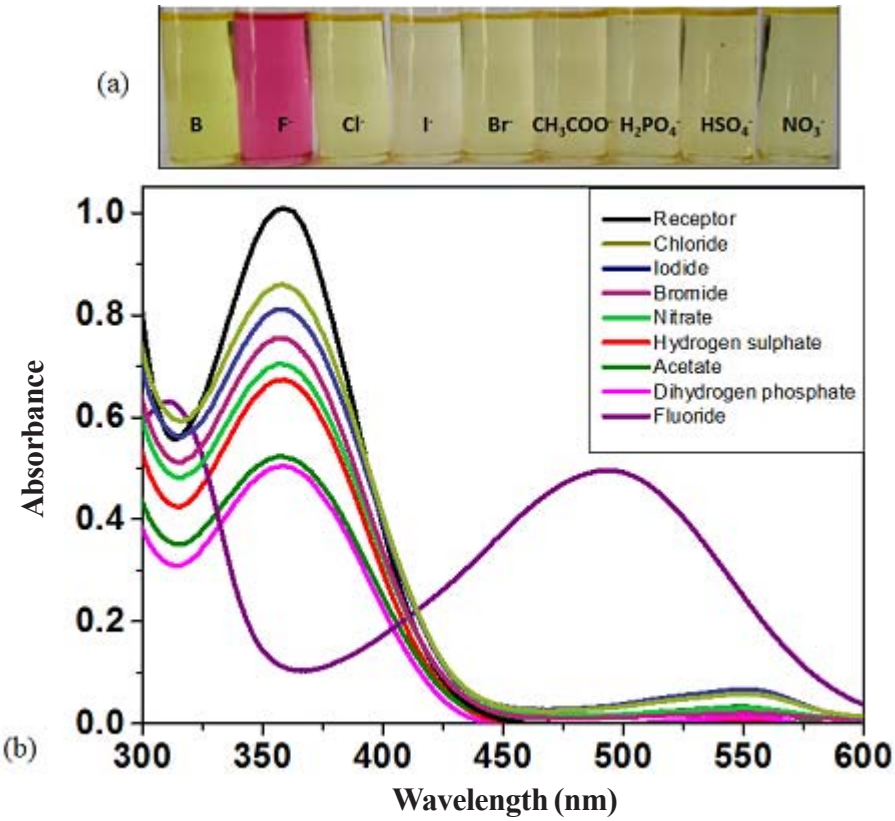


Fig. 1. (a) Colour changes of receptor **B** (1×10^{-5} M in 9:1 DMSO:water) with 10 equivalents of sodium salts of different anions (b) Changes in absorbance of receptor **B** (1×10^{-5} M in 9:1 DMSO:water) with different anions (sodium salts, 1×10^{-4} M) in distilled water

C-E failed to show any colour change even at high fluoride concentration (10^{-3} M) or with any other anion salt. Receptor A gave colorimetric response with fluoride at 2 ppm, below this concentration, no discernible visual colour change by naked eye was observed, which limits it's practical utility. An instant colour change from pale yellow to pink was witnessed with receptor B, upon addition of 1 equiv. of fluoride ($1x10^{-5}$ M, 0.19 ppm).

For practical utility of receptors, they should be capable to bind inorganic fluoride (sodium fluoride being commonly found salt) in aqueous media as well as give a quick visual response at permissible limits of fluoride ion in drinking water. Only receptor B was found suitable for this purpose and was further studied. While, receptors C to E were found insensitive to the addition of salts of different anions even at higher concentrations ($1x10^{-3}$ M), which may be due to decrease in acidity of NH proton by electron releasing groups. While in receptor B, acidity of N-H increased due to presence of electron withdrawing group, nitro group at coumarin ring.

To validate these initial qualitative studies, detailed anion binding studies of receptor B were conducted using UV-visible and NMR spectrophotometer. For UV-visible experiments, the receptor B solution ($1x10^{-5}$ M in 9:1 DMSO-water) was prepared and sodium salts of different anions (100 equivalents) were added into it. Free receptor B gave a maxima at 358 nm, which shifted to 500 nm upon addition of fluoride solution (sodium salt in distilled water). Other anions induced no spectral response (Figure 1). In order to further evaluate the binding characteristics of receptor B with fluoride ion, sodium salt of varying fluoride ion concentration (5×10^{-6} to $1x10^{-3}$ M) was added into receptor B solution ($1x10^{-5}$ M in 9:1 DMSO-water). On titration with fluoride ion, absorbance at 358 nm decreased with the simultaneous formation of a new band at 500 nm,

indicating towards possible binding between receptor B and fluoride ion. Simultaneously, colour of receptor also changed from yellow to pink. Addition of fluoride ion from 0.5 to 100 equivalents into receptor solution caused the increase in the intensity of new band at 500 nm (Figure 2). The bathochromic shift witnessed was probably due to the formation of hydrogen bond between anion and receptor N-H proton. With higher concentration of fluoride ion, pink colour changed to red, indicating towards the possibility of deprotonation of N-H caused at higher concentration of fluoride ion [50]. An isobestic point at 405 nm was observed which indicates the interaction between receptor B and fluoride ion. 1:1 Stoichiometry was determined by the Jobs plot of receptor B with fluoride (Figure 3). 1:1 Stoichiometry was also proved by mass spectra of receptor B with fluoride ion (sodium salt), which exhibited a peak at 326.1872 [receptor B + F^- +H^+, calculated 326.0487] (Figure 6). Figure 4 depicts change in absorbance with increase in concentration of fluoride ion (5 x 10^{-6} to 1 x 10^{-3} M). Figure 5 shows absorbance wavelength ratiometric plot of receptor based on $A_{500\ nm}$/ A_{358nm} as a function of added fluoride ion concentration from 5 x 10^{-6} to 1 x 10^{-3} M.

Another noteworthy feature of the receptor B, apart from the capability to sense fluoride ion in aqueous media, is the naked eye detection of fluoride ion at different levels. Receptor exhibits colour gradation from light pink (0.19-1.5 ppm) to pink (1.5-5 ppm), pink to red (5 ppm and above). In this manner, receptor B is capable of not only detecting the mere presence of fluoride ion in water, but also gives an idea about the levels of fluoride ion in water.

Efficacy of receptor B for real world application largely depends on the selectivity and the sensitivity of receptor for the anion. The selectivity of receptor towards fluoride ion over other anions was examined by treating the receptor B with 1 equivalent fluoride ion in presence of 1 equivalent of chloride, bromide, iodide, dihydrogen phosphate, hydrogen sulphate and nitrate ions (sodium salt). As witnessed with bare eyes, no difference

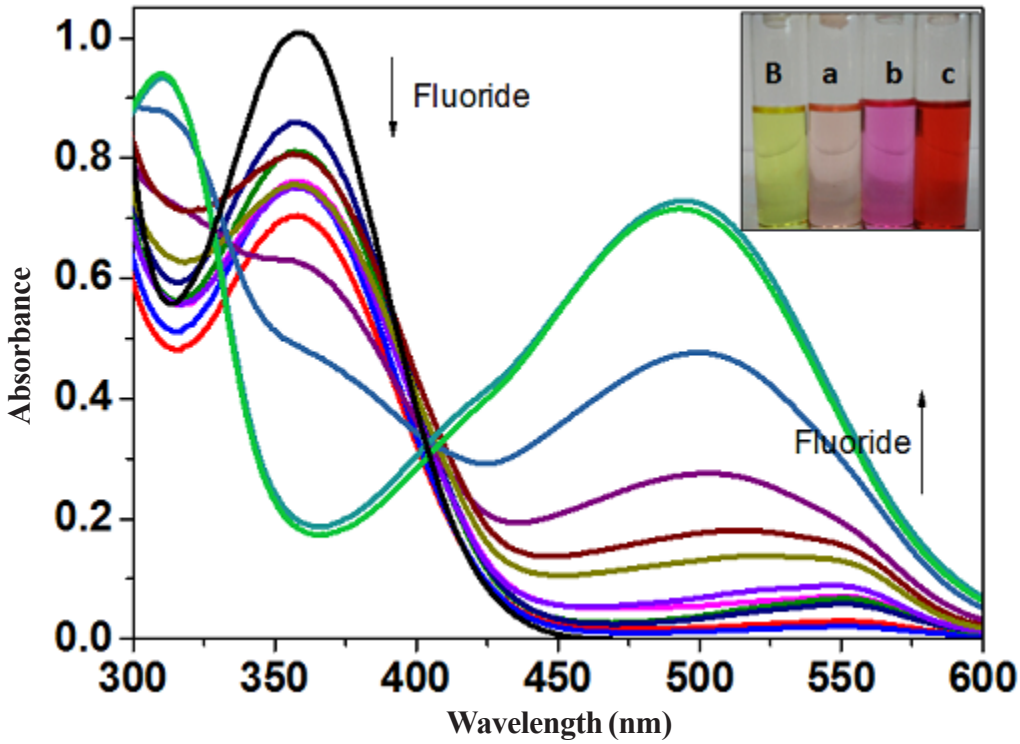


Fig. 2. (a) Colour changes of receptor **B** (1×10^{-5} M in 9:1 DMSO:water) with 10 equivalents of sodium salts of different anions (b) Changes in absorbance of receptor **B** (1×10^{-5} M in 9:1 DMSO:water) with different anions (sodium salts, 1×10^{-4} M) in distilled water

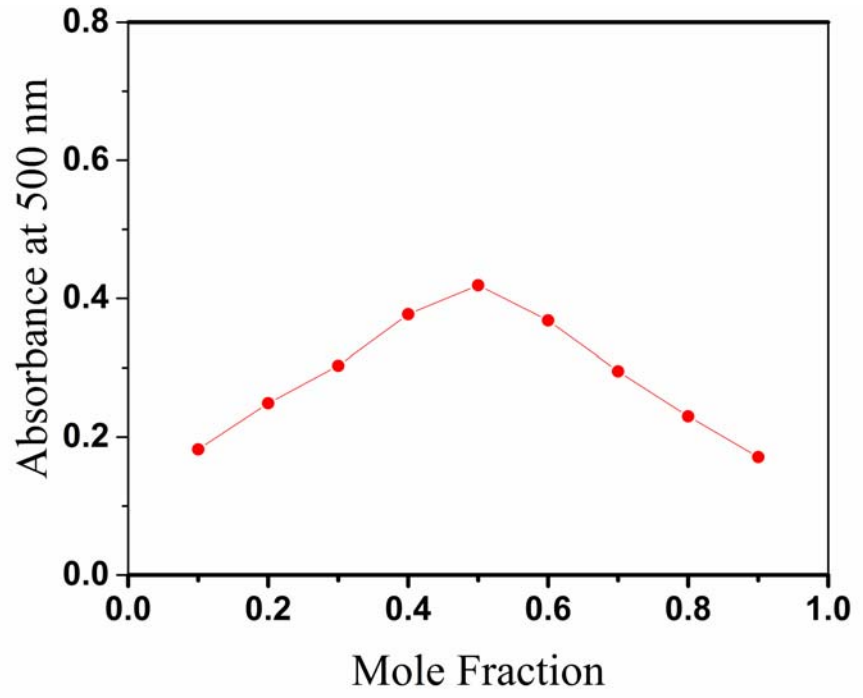


Fig. 3. Jobs Plot with receptor **B** 1×10^{-4} M in 9:1 DMSO-water and fluoride ion (sodium salt) 1×10^{-4}M in water

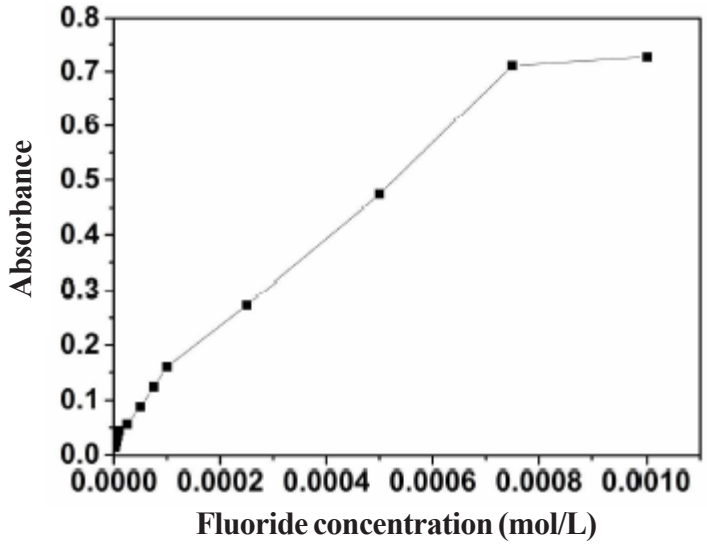


Fig. 4. Changes in absorbance at 500 nm of receptor **B** (1 x 10^{-5} M in 9:1 DMSO:water) with increase in fluoride ion concentration (5 x 10^{-6} to 1 x 10^{-3} M)

in colour appeared. This proved the selective nature of receptor B to detect fluoride ion in presence of other competing anions. Moreover, significant shift as observed earlier in the absorption band upon addition of fluoride in UV-visible spectrum of receptor with different anions validated the selectivity of receptor for fluoride (Figure 1). Detection of fluoride ion at 0.19 ppm proved the sensitivity of receptor B for fluoride ion. Detection limit was calculated from calibration plot (3 x standard deviation/slope of curve), where standard deviation calculated and slope of curve are 0.00687 and 0.01876, respectively (Figure 11) [51,52]

The binding constant of receptor B with fluoride was evaluated by Benesi Hildbrand equation [53]

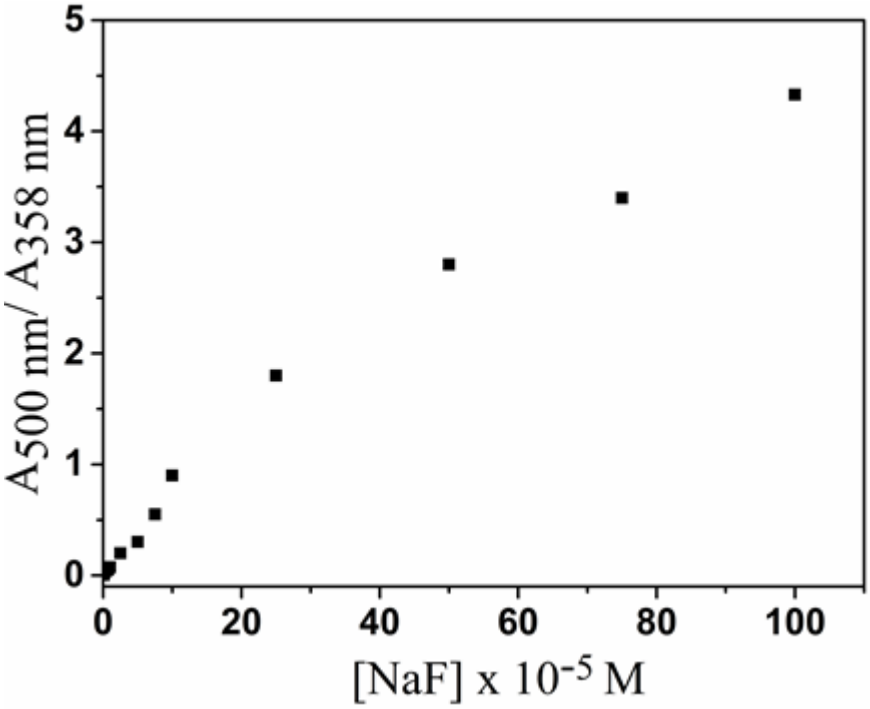


Fig. 5. Wavelength ratiometric plot based on $A_{500\ nm}/ A_{358nm}$ as a function of added fluoride concentration from 5×10^{-6} to 1×10^{-3} M

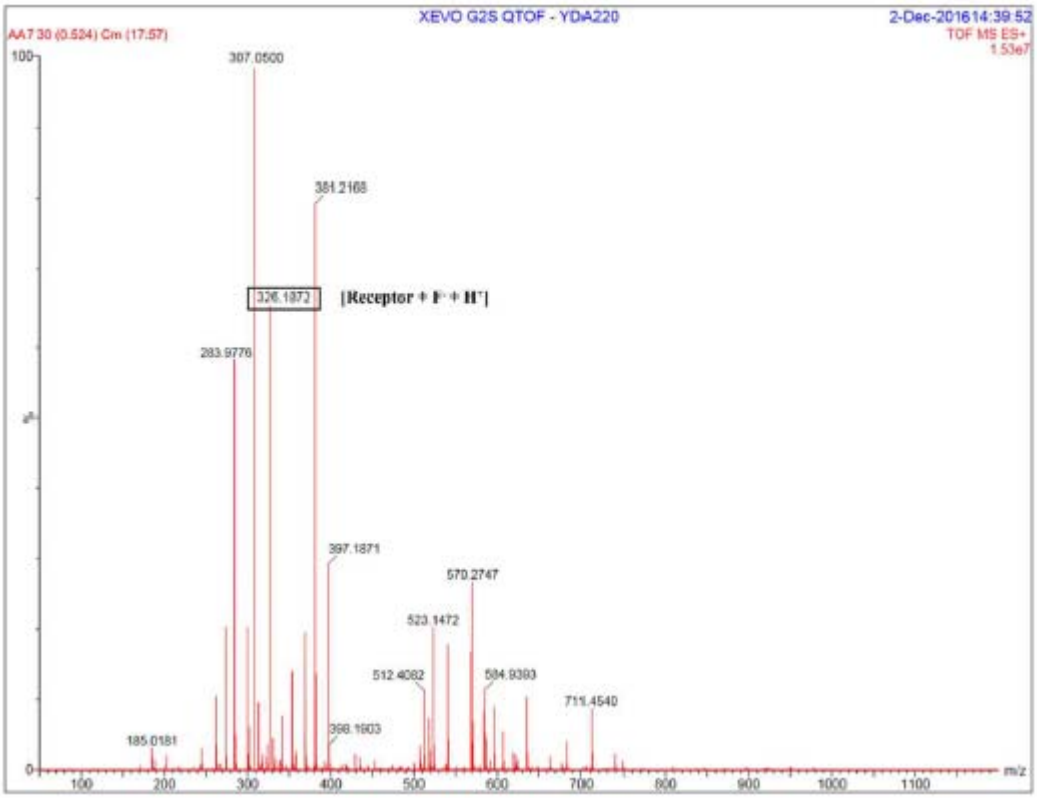


Fig. 6. ESI-Mass spectrum of fluoride complex of receptor **B**

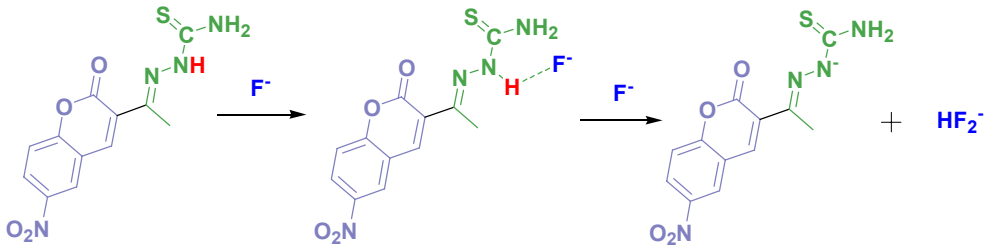
1/A-Amin = 1/(Amax+ (1/K [F"])(1/ΔAmax).

Here, ΔAmax = Amax-Amin, where, Amin, A, Amax are the absorptions of receptor B considered in the absence of F^-, at an intermediate, and at a concentration of complete binding. K is the binding constant, [F^-] is concentration of F". From the plot of 1/ (A–Amin) against [F^-] for receptor-B, the value of K (+10 %) was calculated from the ratio of intercept/slope. Binding constant K, calculated from the graph (Figure 7) was found to be 1.38 x 10^5 M^{-1}, indicating high affinity of receptor B towards fluoride ion.

For ^{1}H-NMR titration, receptor B solution was prepared in DMSO-d_6 (10^{-2} M) and fluoride ion (Tetrabutylammonium fluoride salt) was added at different concentrations (1,2,4,6,8 and 10 equivalents) (Figure 8) ^{1}H-NMR titration of receptor B upon addition of 1 to 8 equivalents of fluoride ion resulted in the downshield shift of the NH proton. At 10 equivalents of fluoride, the peak disappeared completely, with simultaneous appearance of bifluoride ion peak at 16.1 ppm. This data indicates that there is interaction of anion and receptor primarily by hydrogen bonding *via* NH proton of thiosemicarbazide moiety, then deprotonation event took place when excess of TBAF was added. The proposed mechanism is shown in Scheme 2.

pH effect on receptor B-F^- interactions

The effect of pH on receptor-fluoride ion binding affinity was investigated by observing the changes in the intensity of the absorbance band at 500 nm, which is characteristic for the forma-



Scheme 2. Proposed binding mechanism of receptor B with fluoride ion

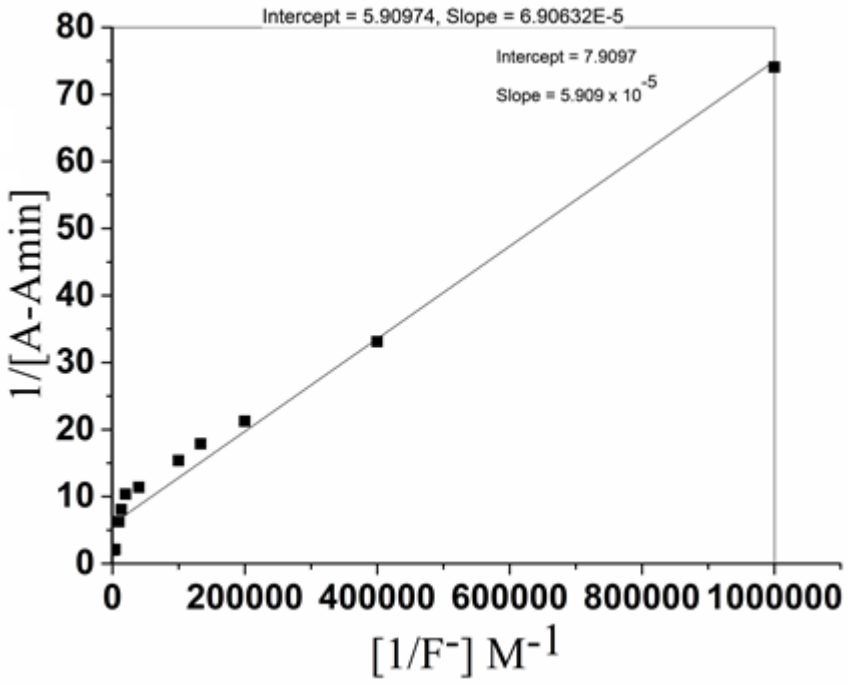


Fig. 7. Fitting curve of Benesi-Hildbrand Plot of receptor **B** with fluoride ion

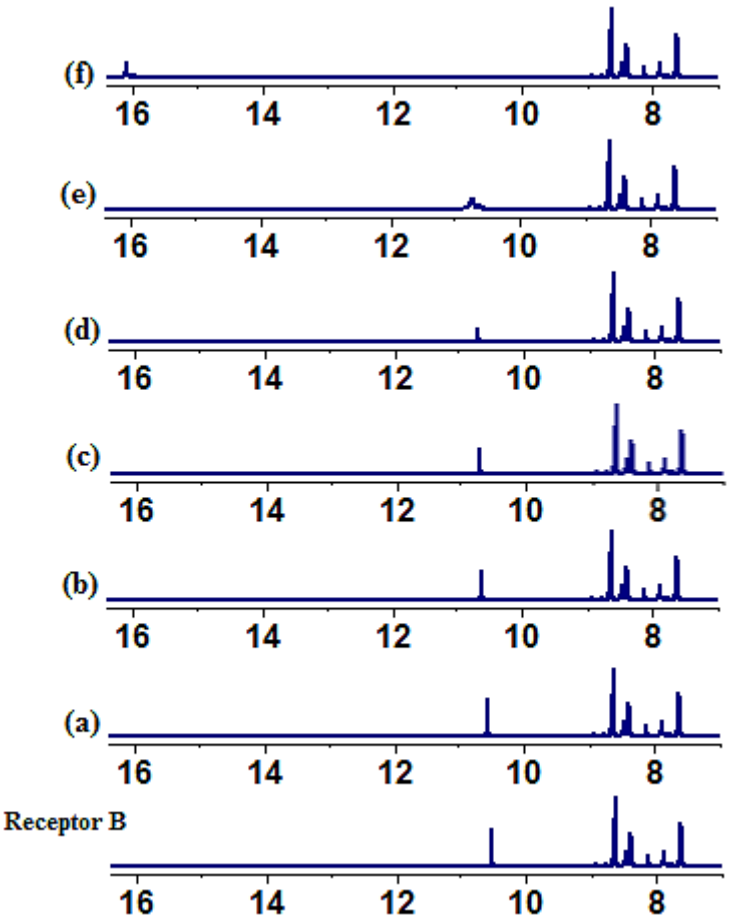


Fig. 8. Partial ^{1}H NMR spectra of receptor **B** in DMSO-d_6 (10^{-2} M) in the presence of (a) 1, (b) 2, (c) 4, (d) 6, (e) 8 and (f) 10 equivalents of TBAF in DMSO-d_6

tion of receptor-F^- complex, over a pH range 2-12 (Figure 9). The working pH range was found to be 6.5-7.5, where the intensity of absorbance remains constant. Below pH 6.5, intensity of absorbance band at 500 nm decreased rapidly. This is probably due to protonation of fluoride ion, to form weakly ionized hydrofluoric acid, which decreases the affinity of fluoride ion to bind receptor binding sites, N-H. Above pH 7.5, intensity of this absorption band increased, which can be attributed to increased availability of deprotonated fluoride ion to establish stronger hydrogen binding interactions with receptor's binding site, N-H. These type of pH dependency has also been reported earlier for other colorimetric fluoride receptors [47, 54].

Analytical application

Toothpastes and mouthwash nowadays have fluoride as sodium salt to prevent dental caries, which in most of the cases exceeds the permissible limit. Toothpaste is known to contain approximately 1000 ppm of fluoride salt, while it is not even listed in contents of mouthwash. The popular brand of toothpaste (India) has been taken and solution of 5 mg/l of it was prepared in distilled water, while 1ml of mouthwash is diluted with 100 ml of distilled water. Receptor B solution was prepared as $1x10^{-5}$ M in 9:1, DMSO-water. Absorbance and the colour changes were recorded with receptor B and toothpaste solution and mouthwash solution (Figure 10). Visual change in colour from yellow to pink was instantly observed in both cases and was further proved by red shift in wavelength from 358 nm to 500 nm in UV-visible spectra upon addition of toothpaste and mouthwash solutions. Quantitatively, fluoride ion was estimated in toothpaste and mouthwash solutions by the application

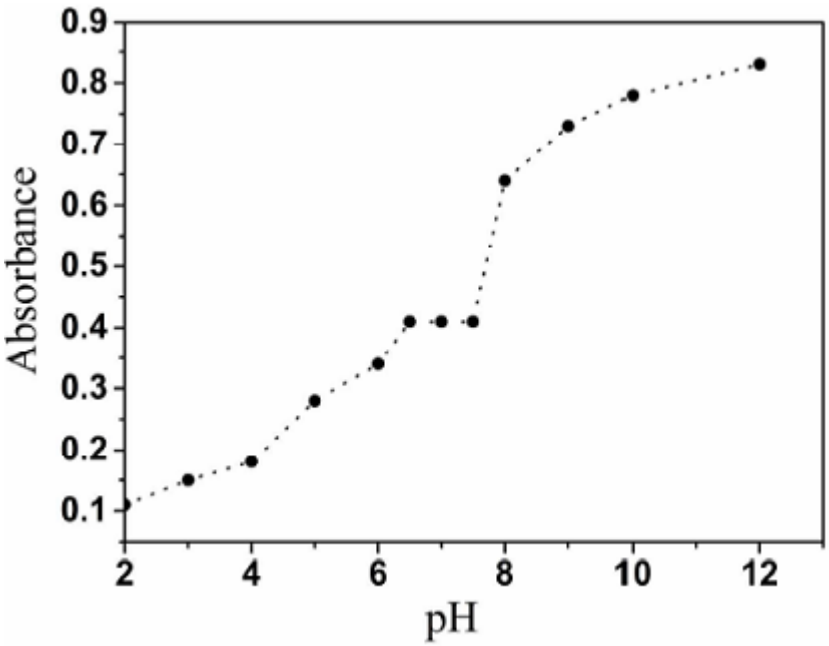


Fig. 9. Absorbance changes of receptor **B** at 500 nm with respect to various pH of solution (2-12) containing 2 x 10^{-4} M NaF

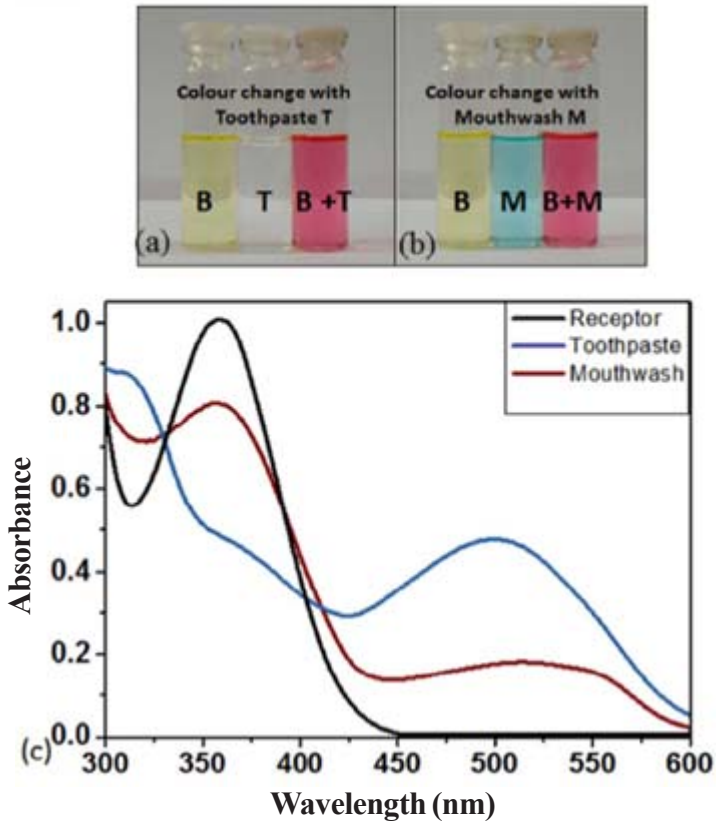


Fig. 10. (a) Colour Changes (B+T) of Receptor **(B)** with toothpaste solution (T) in distilled water. (b) Colour Changes (B+M) of receptor **(B)** with mouthwash solution (M) in distilled water. (c) UV visible changes in the spectra of receptor (1 x 10^{-5} M in 9:1 DMSO-water) with addition of toothpaste and mouthwash

of calibration curve, obtained from a plot of absorbance of receptor B and various NaF concentrations at 500 nm (Figure 11). The value obtained from the plot for toothpaste solution (approx. 5 ppm) is 4.86 ppm, which is in good agreement with the reported value. For mouthwash, fluoride ion concentration was found to be 190.8 ppm, when the value obtained from the graph (1.90) was multiplied by dilution factor (100) [47]. Colour intensities of receptor B with toothpaste and mouthwash appeared same, because receptor B provides same intensity of colour for fluoride levels in the range of 1.5 - 5 ppm.

For real life analysis, tap and groundwater samples (containing different fluoride concentration) from Sanganer and Bagaru district, Rajasthan, India were collected and their fluoride concentration was determined by ion meter. Naked eye colour changes were then observed for the same water samples by addition of receptor B. Gradation in colour was clearly noticed with variation in fluoride ion concentration. To corroborate the observed results, spectral study was also conducted, which showed red shift in wavelength at 350 nm to 500 nm and increase in absorbance of new band at 500 nm with increase in fluoride ion concentration (Figure 12 and Figure 13).

Spike and recovery

The proposed receptor B was applied to determine of fluoride ion in drinking water samples collected from Sanganer and Bagaru districts of Jaipur city, in order to test the validity of the method. Recovery tests were used to examine the reliability and accuracy of the method. Known concentration of sodium fluoride were spiked into the water samples and fluoride ion content was determined at optimum conditions. Sample was spiked in triplicate and the average was calculated with relative standard deviation (RDS). The fluoride content of different samples and recoveries of added analyte were calculated by the application of calibration curve (Figure 11) and the results showed that it is possible to determine the fluoride concentration in real sample solutions using receptor B (Table 1). The recovered fluoride concentration versus spiked fluoride concentration graph has been plotted, from which actual concentration can be calculated (Figure 14).

The fluoride concentration calculated for various water samples by receptor B using UV-visible spectrophotometer were plotted with those obtained by the Fluoride ion selective electrode (F-ISE) (Table 2) (Figure 15). The graph obtained shows that values obtained by receptor B were in

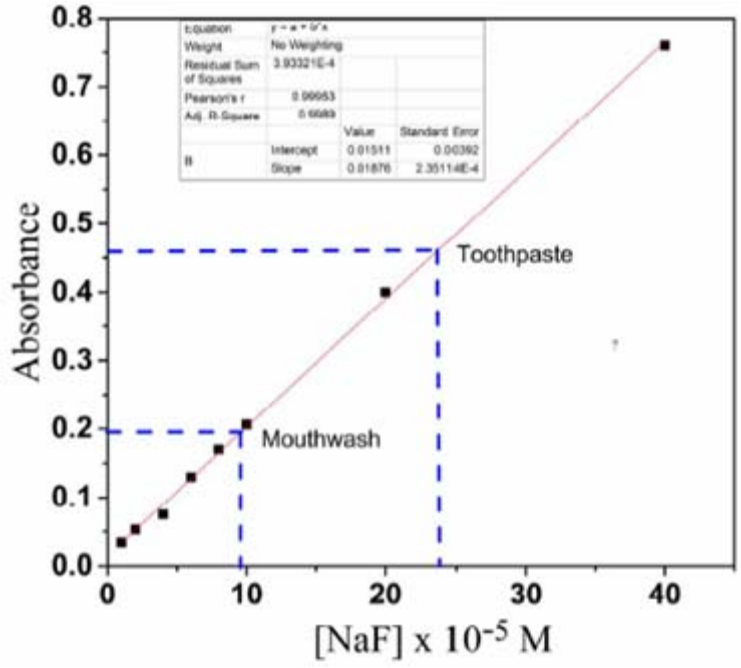


Fig. 11. Calibration curve for the determination of the concentration of fluoride ion in toothpaste and mouthwash

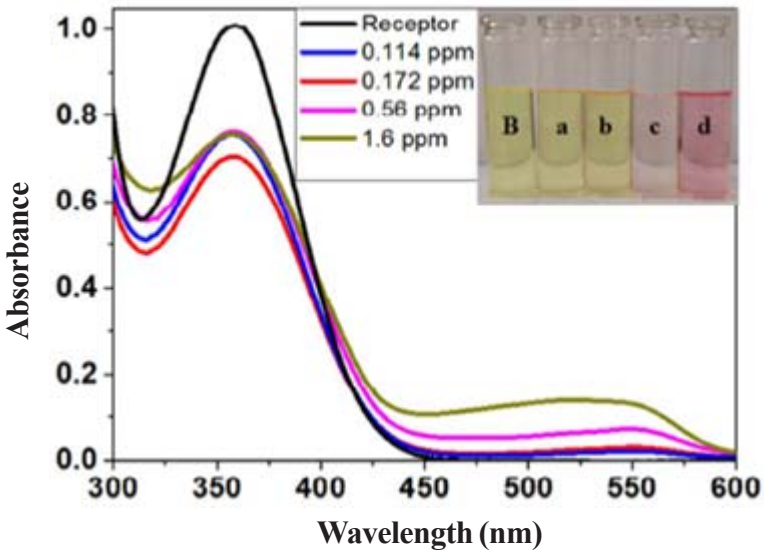


Fig. 12. UV-visible changes in the spectra of receptor **B** (1 x 10^{-5} M in 9:1 DMSO-water) with addition of water samples collected from Bagru district. Inset showing colour changes of receptor **B** (1 x 10^{-5} M in 9:1 DMSO-water) with water samples containing fluoride concentration as, a) 0.172, b) 0.11, c) 0.56 and d) 1.6 ppm

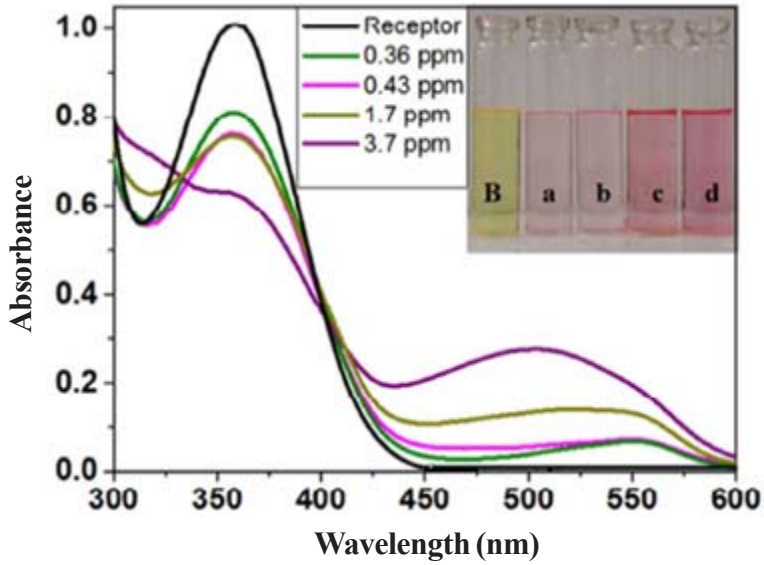


Fig. 13. UV-visible changes in the spectra of receptor **B** (1 x 10^{-5} M in 9:1 DMSO-water) with addition of water samples collected from Sanganer district. Inset showing colour changes of receptor **B** (1 x 10^{-5} M in 9:1 DMSO-water) with water samples containing fluoride concentration as, a) 0.36, b) 0.43, c) 1.7 and d) 3.7 ppm

good agreement with standard method, fluoride ion standard electrode (F-ISE).

Conclusion

We have described a simple, easy to synthesize receptor which can detect fluoride selectively over other anions in aqueous media colorimetrically with high value of binding constant. Detection limit was found as low as 0.19 ppm. Deprotonation of N-H of thiosemicarbazone accounted for this colour change as confirmed by proton NMR. It gives distinct colour change below 1.5 ppm, 1.5 - 5 ppm and 5 ppm and above. This is particularly helpful in places like Rajasthan, India, where there are

Table 1. Calculation of recovery percentage in drinking water sample after spiking with known concentration of fluoride ion

	Spiked fluoride concentration (ppm) (5 ml)	Final Concentration after spiking (ppm) (10 ml)	Obtained fluoride concentration (ppm) (10 ml)	RSD % (n=3)	Recovery %
Drinking	1	0.68	0.61	2.3	88.0
water	2	1.18	1.059	1.7	89.8
sample	3	1.68	1.518	2.1	90.4
0.36 ppm (5 ml)	4	2.18	1.95	1.9	89.6

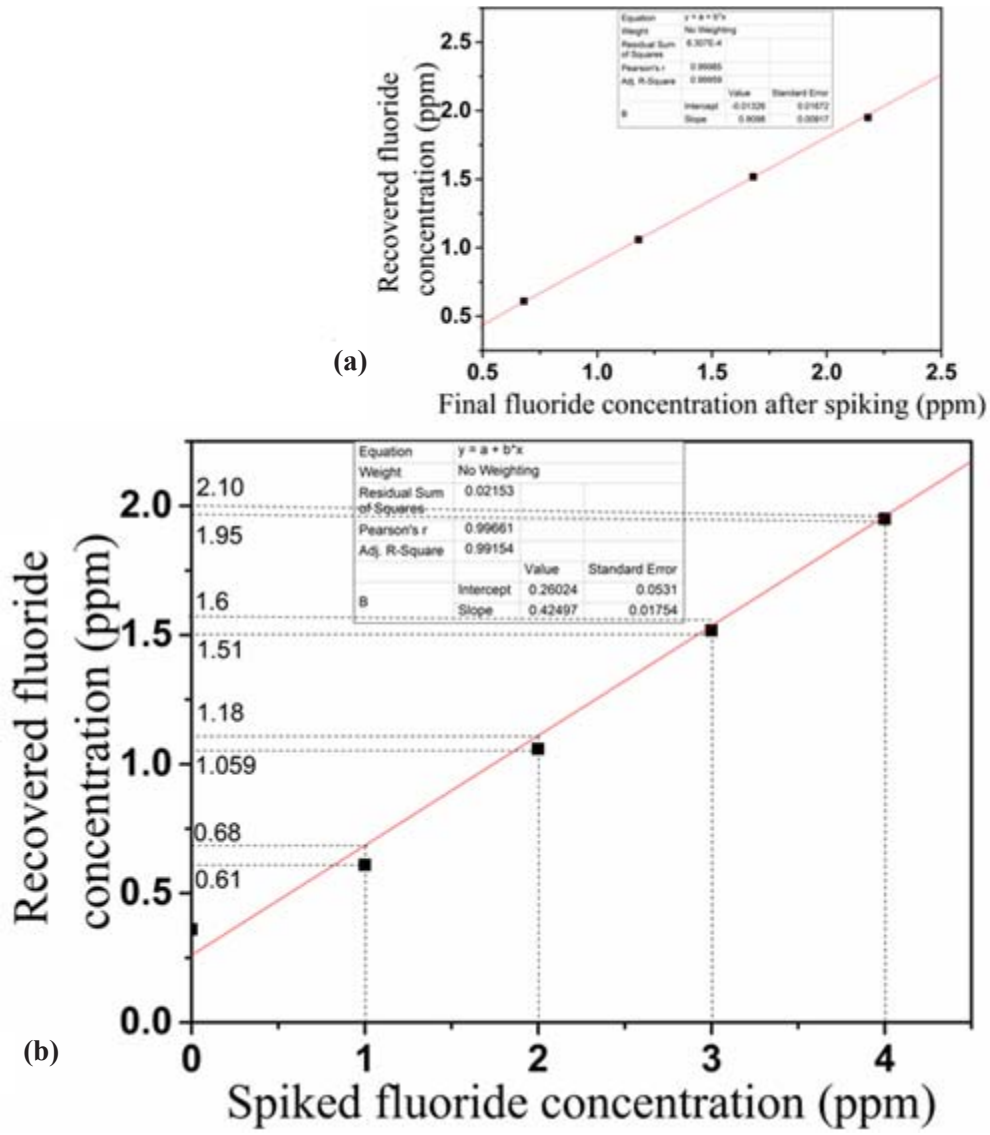


Fig. 14. (a) Graph plotted between final fluoride concentration after spiking (ppm) and recovered fluoride concentration (ppm) (b) Graph plotted between spiked fluoride concentration (ppm) and recovered fluoride concentration (ppm)

Table 2. Determination of fluoride ion in the water samples with proposed method and Fluoride Ion Selective Electrode

Drinking water samples	Fluoride ion concentration measured by receptor B (ppm)	Fluoride ion concentration measured by F-ISE (ppm)
1	0.3	0.34
2	0.57	0.61
3	0.35	0.38
4	0.598	0.63
5	0.5	0.53
6	0.667	0.7
7	1.27	1.4
8	1.041	1.07
9	1.39	1.6
10	1.022	1.09
11	3.2	3.6
12	1.9	1.93

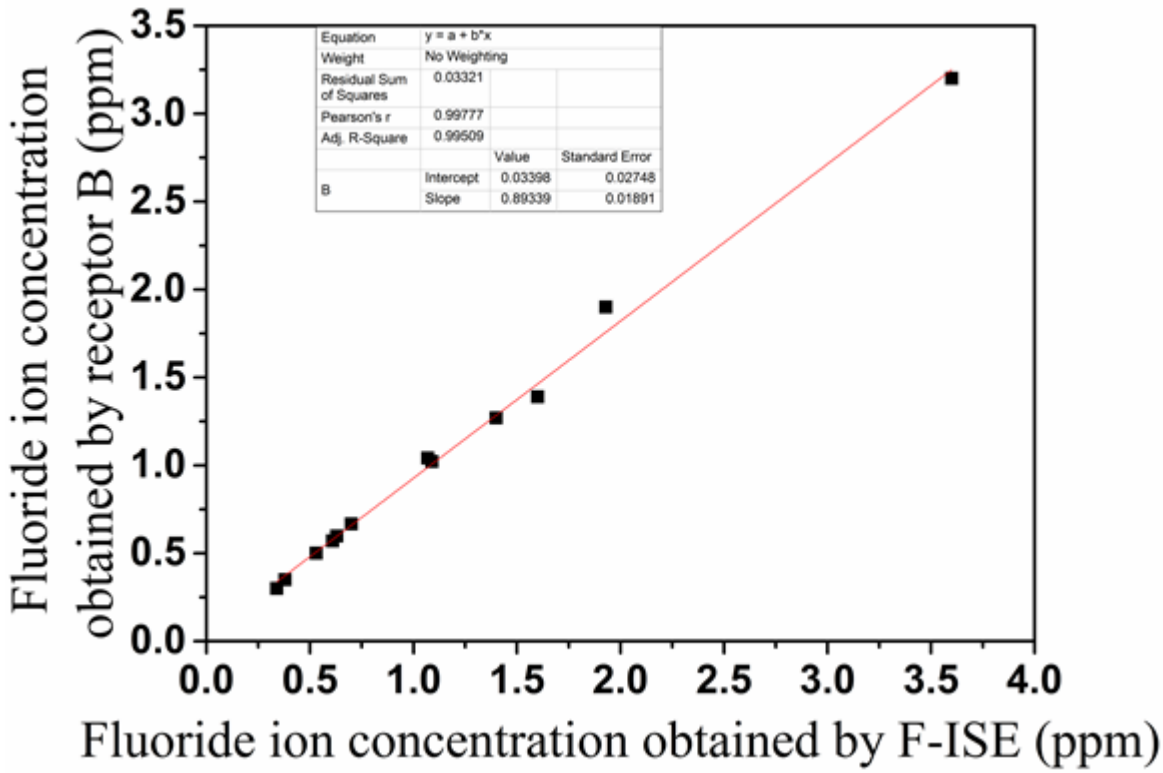


Fig. 15. Comparison of fluoride ion concentration obtained by receptor **B** using UV-visible spectrophotometer and F-ISE (Fluoride Ion Selective Electrode)

some remote places with more than 14 ppm of fluoride in ground water. Further work is underway for developing test strips. In near future, we hope to develop more sensitive method for fluoride detection.

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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

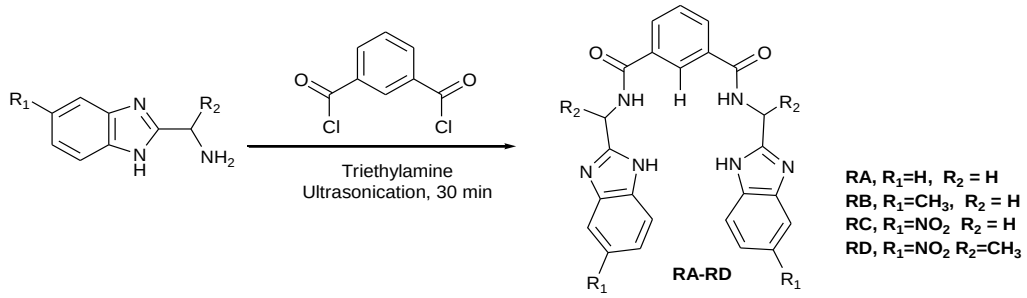
The reaction between benzimidazole derivatives and *m*-phthaloyl chloride in dicloromethane under

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].

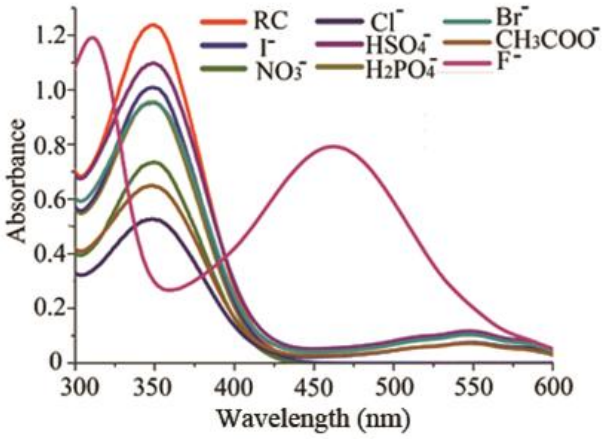


Fig. 2 – Changes in absorbance of receptor **RC** (1×10^{-5} *M* in DMSO) with different anions (TBA salts, 1×10^{-3} *M*) in 9:1 DMSO: water.

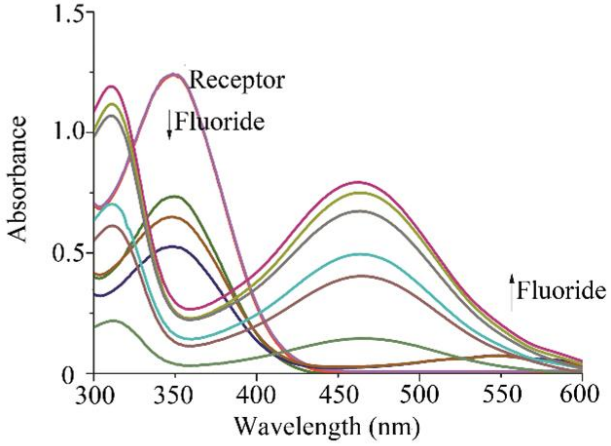


Fig. 3 – UV-visible spectra of receptor **RC** (1×10^{-5} *M* in DMSO) with fluoride ion (TBA salt) from 1×10^{-5} to 1×10^{-3} M in 9:1 DMSO: water.

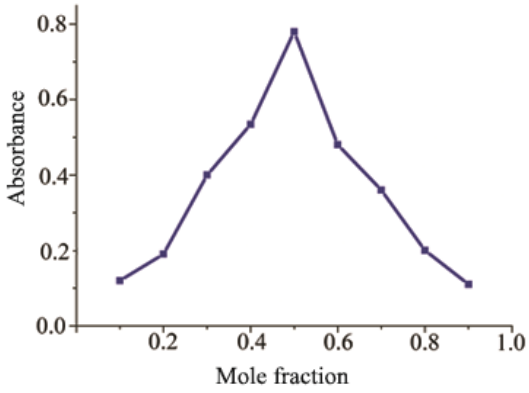


Fig. 4 – Jobs plot with receptor **RC** (1×10^{-2} *M* in DMSO) and fluoride ion (TBA salt) 1×10^{-2} *M* in 9:1 DMSO-water.

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.

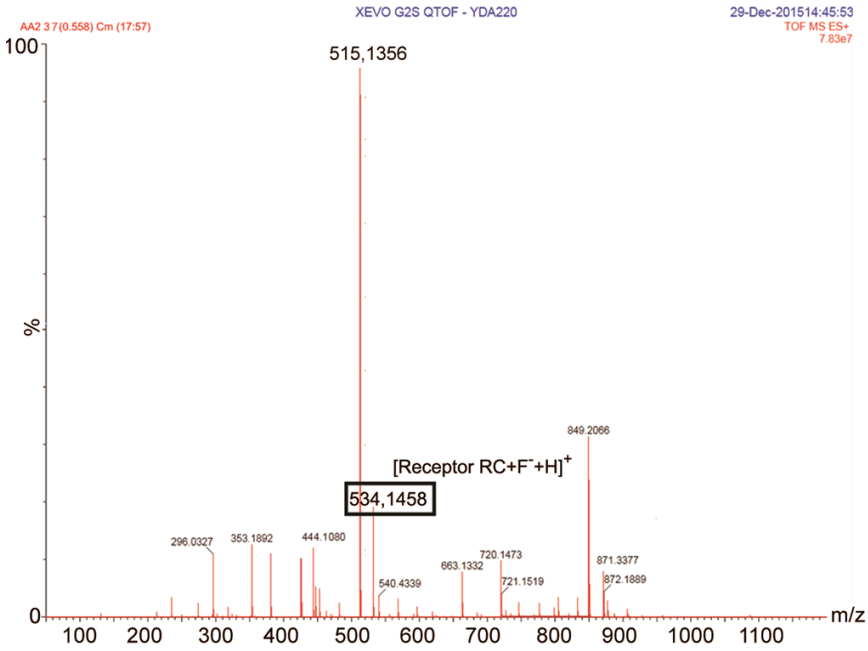


Fig. 5 – ESI mass spectra of fluoride ion complex of receptor **RC**.

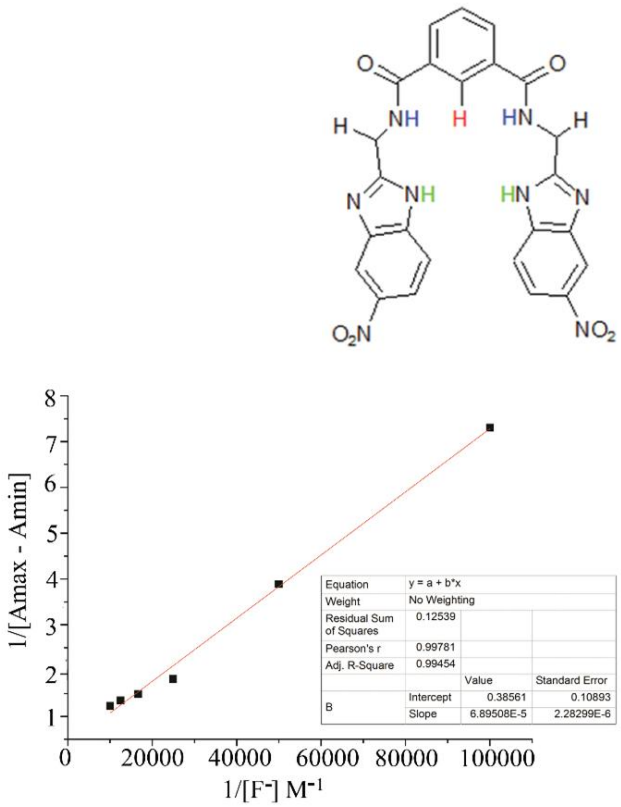


Fig. 6 – Fitting curve of Benesi Hildbrand equation.

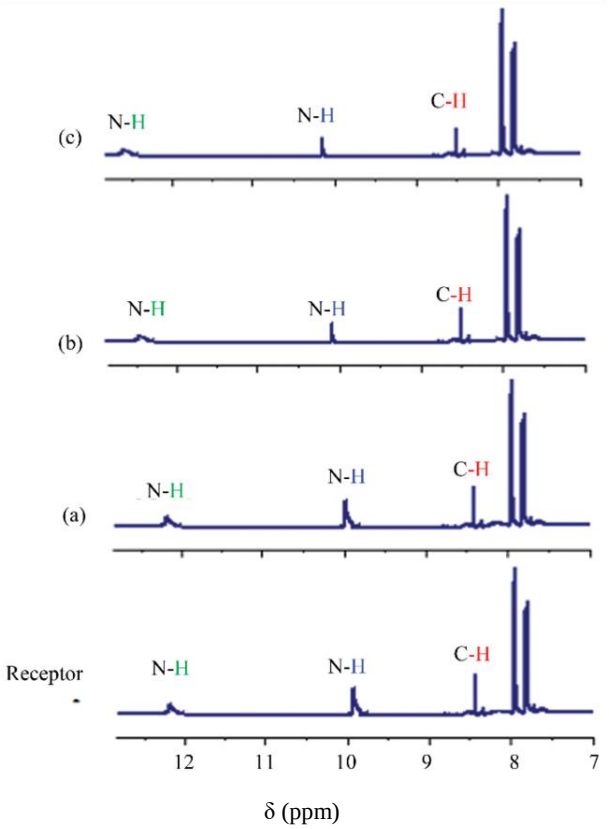
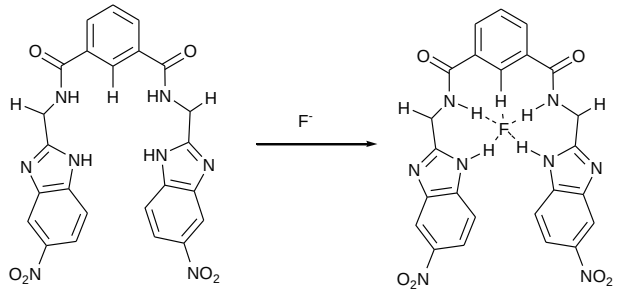


Fig. 7 – Partial ^{1}H NMR (400 MHz) spectra of receptor **RC** in DMSO-d_6 (1×10^{-2} *M*) in the presence of (a) 2, (b) 5, and, (c) 10 equivalents of TBAF in DMSO-d_6.



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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Instantaneous and Selective Bare Eye Detection of Inorganic Fluoride Ion by Coumarin–Pyrazole-Based Receptors

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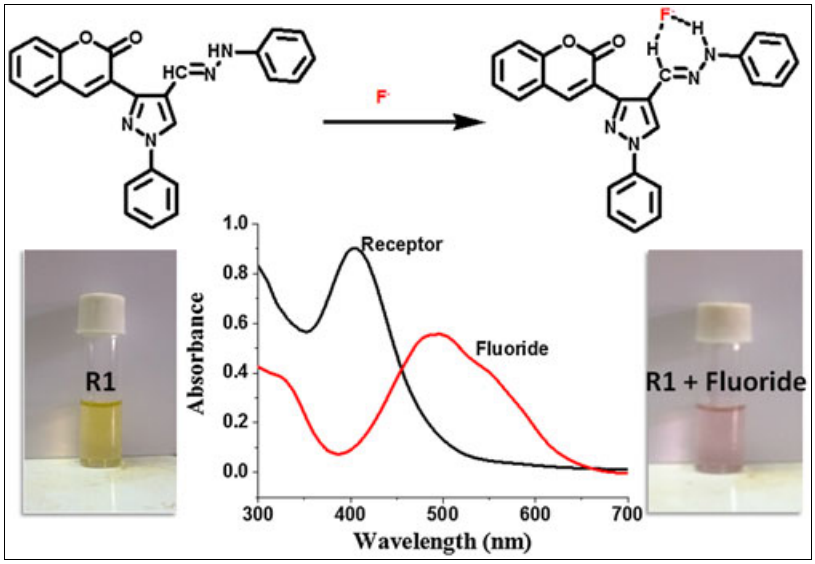


A series of rationally designed coumarin–pyrazole-based scaffolds, equipped with N—H and C—H hydrogen bond donors (**R1**–**R5**) and containing various electron-withdrawing groups at key positions, are synthesized and characterized in order to investigate their inorganic fluoride binding properties in highly competitive media (1:1 DMSO–water). Only one, 3-{4-[(2,4-dinitrophenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one (**R1**), of the five compounds synthesized, is found to be capable to selectively detect inorganic fluoride *via* naked eye amongst other anionic species in aqueous media. Qualitative and spectroscopic studies exhibit that receptor **R1** has the potential of showing instantaneous change of color from yellow to pink upon addition of sodium fluoride (0.95 ppm) in aqueous media, at concentration lower than that recommended by World Health Organization (1 ppm). Intensity of color increases with increasing fluoride concentration till 5 ppm, beyond which intensity of color change becomes saturated. This has established the applicability of this receptor for assessment of the level of fluoride in water. Anion binding studies carried out by UV–visible titration portrayed substantial bathochromic peak shift from 410 to 495 nm, upon addition of varying concentrations of aqueous sodium fluoride solution, which has validated the color change. Jobs plot data confirmed 1:1 stoichiometry between **R1** and fluoride ion. ^{1}H-NMR investigation reveals that the deprotonation of N—H hydrogen donor group of receptor **R1** and its interaction with fluoride ion is responsible for the observed color change.

INTRODUCTION

The design and synthesis of chemosensors for fluoride are fast captivating the researchers over the past decade because of the significant health and environmental implications of fluoride levels [1–5]. Minerals containing fluoride, in Earth's crust, release fluoride into ground water, while other sources contributing to fluoride intake by human body are the fluoridated toothpaste, mouthwash, and food items [6]. Although necessary in limited amount for dental health, regular intake of excess fluoride causes several chronic diseases such as nausea [7,8], skeletal and dental fluorosis [9,10], hyperglycemia [11], coma [12], and osteomalecia [13]. This evokes a mounting interest in chemists to develop procedures for instantaneous, easy, and inexpensive detection of fluoride ion in water both qualitatively as well as quantitatively [14]. Conventional methods for fluoride ion detection using ion meter or spectroscopic techniques are expensive, time consuming, and require skillful personnel [15].

Naked eye receptors, on the other hand, are simple, easy to use, and well suited for instantaneous on-site analysis [16,17]. Colorimetric fluoride detection *via* artificial organic receptors have been developed by research groups, most of which can bind only organic fluoride, i.e. tetrabutyl ammonium fluoride ($TBAF^-$), which limits their feasibility in providing adequate solution to the concerned problem [18–20]. Therefore, it appears prudent to examine if it is possible to develop a receptor with capability of detecting inorganic fluoride ion *via* naked eye, thereby dispensing the use of expensive instruments.

Chemosensors are generally constructed on receptor-chromophore binomial, wherein anion binds at receptor site, and chromophore is responsible for turning this event into an optical signal or visual color change [21]. Chrompophoric unit consists of a system of conjugated bonds that brings down the energy gap between HOMO and LUMO to visible region [22]. Heterocyclic compounds are excellent candidates as signaling unit due to interesting photophysical properties [23]. These signaling units are covalently conjugated to binding units, containing acidic N—H, to develop colorimetric anion receptors [24]. Acidity of N—H groups can be fine-tuned by appropriate insertion of electron-withdrawing groups, which increases the binding tendencies of receptor with anions [25]. When anion interacts with such receptors, it establishes hydrogen bonding interactions with N—H group of receptors initially, followed by deprotonation of N—H. Deprotonation triggers an extended conjugation or π-delocalization and alters the dipole associated to the charge-transfer transition or, in other words, stabilizes the excited state of chromophore group. This ultimately observed as vivid color change as output [26]. Design of receptors can be further modulated by the incorporation of more hydrogen bond donors with the aim to establish high binding affinity with anion [27]. Introducing acidic C—H groups along with N—H groups in the structure of receptor enhances the strength of interactions with anion. Triazole C—H, aromatic C—H, and imine C—H can fruitfully serve this purpose [28–30].

Selective detection of fluoride ion over other anions in competitive media necessitates the fine-tuning of the acidity of protons by suitable placement of electron-withdrawing substituents [7]. Another problem with receptors is their inability to function in aqueous media because acidity of water molecules is higher than that of protons of receptor involved in binding [31]. To achieve this feat, researchers have attempted to incorporate moieties *viz.*, urea/thiourea [23,32], pyrrole [33,34], indole [33,35], imidazole [36], etc., having acidic N—H group that can form hydrogen bond with fluoride ion and give a visible color change. Fluoride effectively binds the acidic protons *via* hydrogen bonding, owing to its small size and high charge density, thus imparting highly conjugated intramolecular charge transfer which gives a discernible color change [37]. Unfortunately, in most of these cases, receptors cannot distinguish between fluoride and related basic anions, acetate and dihydrogen phosphate due to competitive interactions [38,39].

Our group is engaged in synthesis of biologically significant heterocyclic derivatives [40–42] and scanty reports of heterocycles as selective naked eye fluoride receptors [43–45] motivated us to develop a new fluoride ion receptor **R1** which could provide a distinctive solution to mitigate the above said problems. Literature survey revealed that coumarin unit has been condensed with thiazole moiety to construct chromophoric units [46,47]. Pyrazole too has been explored as anion receptor [48]. However, no report of coumarin–pyrazole as chromophoric unit has been reported so far, this encouraged us to explore its utility in construction of anion receptors. Further, these compounds are easy to prepare and stable. Receptor **R1**, synthesized for this purpose has been comprehensively examined for its binding abilities with fluoride ion *via* N—H and aliphatic C—H hydrogen bond donor groups by qualitative naked eye detection and spectroscopic techniques (UV, FTIR, and ^{1}H-NMR).

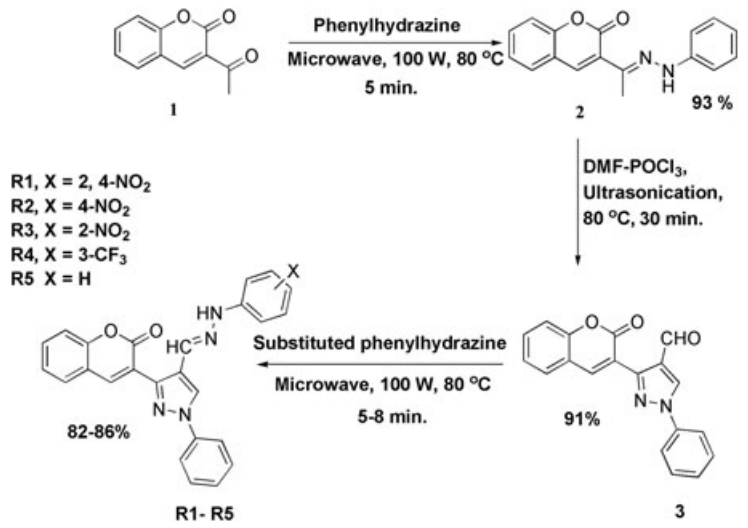
RESULTS AND DISCUSSION

In general, receptors are crafted through binding unit-signaling unit approach [49]. Accordingly, heterocyclic moieties, coumarin and pyrazole, have been combined together to form a colorimetric signaling unit and further condensed with (un)substituted phenylhydrazines to yield imine bond with acidic N—H and C—H hydrogen bond donor groups as a binding unit for fluoride ion binding (Scheme 1). Variously substituted receptors with electron-withdrawing groups at differing positions, **R1**–**R5**, were prepared to study their effects on the anion binding capabilities.

Compounds **1** and **2** were prepared by following methods reported elsewhere [50,51]. Sonication of compound **2** yielded formyl pyrazolyl coumarin **3** [52], which gave the desired receptors as orange-colored products (**R1**–**R5**) upon microwave irradiation with (un) substituted phenylhydrazine. Spectral data obtained by ^{1}H-NMR, ^{13}C-NMR, FTIR, and mass spectroscopy are found to be in good agreement with the proposed structures of receptors, **R1**–**R5**.

Initially, colorimetric experiments of all the receptors (10^{-5} M in DMSO) are conducted with different anions, viz., fluoride, chloride, bromide, iodide, nitrate, hydrogen sulfate, dihydrogen phosphate, and acetate, in the form of their sodium salts (10^{-4} M in 1:1 DMSO–water). It is

Scheme 1. Synthesis of receptors **R1–R5.**



observed that only receptor **R1** is able to exhibit a strong and immediate change in color from yellow to pink; this change in color as detectable by naked eye is seen to have occurred selectively for fluoride ion at minimum concentration of 0.95 ppm (Fig. 1). Other anions have not produced any perceptible change in color, even at higher concentrations (10^{-3} M). This implies either there is weaker or there has not been any coordination between anion and receptor. It is further seen that increasing fluoride concentration leads to intensification of color from light pink (0.95–1.5 ppm) to pink (1.6–3 ppm), and it gets stabilized at higher concentration (5 ppm), where dark pink is seen. The distinguishable color changes with gradual increase in fluoride ion concentration envisage the determination of fluoride levels semi-quantitatively without the use of any spectroscopic tool.

Sensitivity and selectivity are the two important parameters to describe receptor precisely. An advantage of this receptor **R1** is that it can selectively bind fluoride ion even in the presence of other anions. When other anions are added to receptor individually, they do not show any color change. Instantaneous change in color is noticed upon addition of fluoride ion (Fig. 1). Second, a soup of all anions, except fluoride, have been prepared by adding their respective sodium salts (10^{-2} M) in 1:1 DMSO–water to mimic the natural condition. Receptor **R1** solution, in equal volume, has been added to the above soup. No color change could be observed, but, when fluoride ion is added to the solution of soup and receptor, instantaneous color change from yellow to pink was immediately observed. These qualitative interference studies showed that receptor **R1** is capable of producing

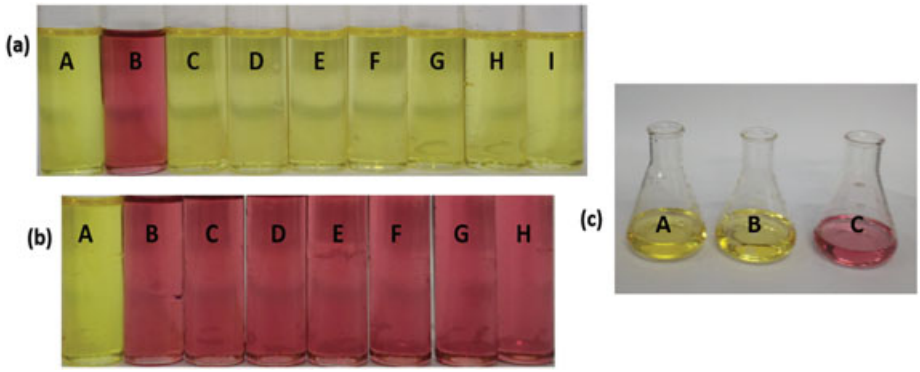


Figure 1. (a) Color changes in the receptor **R1** (10^{-5} M in DMSO) in the presence of 10 equivalents of different anions (sodium salts) where A, B, C, D, E, F, G, H, and I represent receptor **R1**, **R1** + F^-, **R1** + Cl^-, **R1** + Br^-, **R1** + I^-, **R1** + $CH3COO^-$, **R1** + $H2PO4^-$, **R1** + $HSO4^-$, and **R1** + $NO3^-$, respectively. (b) Color changes in the receptor **R1** (10^{-5} M in DMSO) in the presence of 10 equivalents of fluoride and different anions (sodium salts) where A, B, C, D, E, F, G, and H are receptor **R1**, **R1** + F^- + Cl^-, **R1** + F^- + Br^-, **R1** + F^- + I^-, **R1** + F^- + $CH3COO^-$, **R1** + F^- + $H2PO4^-$, **R1** + F^- + $HSO4^-$, and **R1** + F^- + $NO3^-$, respectively. (c) Color change in the receptor **R1** (10^{-5} M in DMSO) in the soup (sodium salts of all above anions except F^-, at concentration 10^{-2} M in 1:1 DMSO–water) prepared, where A, B, and C represent receptor **R1**, **R1** + soup, and **R1**+ soup + F^-, respectively. [Color figure can be viewed at wileyonlinelibrary.com]

naked eye response only in the presence of fluoride, irrespective of the presence of any other anions.

Quantitatively, anion-receptor binding studies have been carried by UV–visible, FTIR, and ^{1}H-NMR titrations. In the absence of external analyte, UV–visible spectrum of receptor **R1** is characterized by maxima at 410 nm. The anion sensing potential of receptor is vigilantly studied by following the spectral changes upon addition of different anion salts, fluoride, chloride, bromide, iodide, nitrate, hydrogen sulfate, dihydrogen phosphate, and acetate (10 equivalents). On addition of fluoride, a considerable red shift of 80 nm was observed in absorption peak of receptor **R1**. On the other hand, no change in absorption peak could be noticed in the presence of other anions (Fig. 2). Further, when the increased concentration of fluoride ions (1 to 100 equivalents) is introduced, peak centered at 410 nm is seen to have decreased with concurrent increase in absorbance of red-shifted peak at 490 nm. Finally, at higher concentration of fluoride (5 ppm and above), peak at 410 nm completely disappears (Fig. 3). The large bathochromic shift of 80 nm in peaks indicates that spectral changes may be detectable by bare eyes.

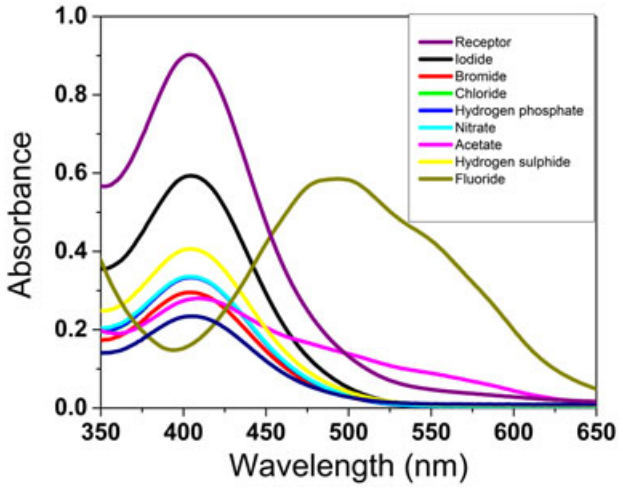


Figure 2. Changes in absorbance of receptor **R1** (10^{-5} M in DMSO) with different anions (sodium salts, 10^{-4} M) in 1:1 DMSO:water. [Color figure can be viewed at wileyonlinelibrary.com]

Stoichiometric ratio of the complexes formed between fluoride ion and receptor is determined by employment of continuous variation method, where the concentration of both receptor **R1** and fluoride ion salt is kept constant (10^{-4} M in DMSO). The molar fraction of fluoride/(receptor + fluoride) is continuously varied. At a molar fraction of 0.50, the absorbance reaches its maxima, revealing that receptor forms 1:1 complex with fluoride ion (Fig. 4). Figure 5 depicts change in UV–visible absorbance of receptor **R1** at 490-nm wavelength upon addition of increasing concentration of fluoride ion (10^{-5} to 10^{-3} M) in the form of sodium fluoride in 1:1 DMSO–water.

The binding constant of **R1** with fluoride is evaluated by Benesi Hildbrand equation [53].

$$1/\text{A-Amin} = 1/(\text{Amax} + (1/\text{K}\,[\text{F}^-])\,(1/\,\Delta\text{Amax}).$$

Here, ΔAmax = Amax − Amin, where, Amin, A, and Amax are the absorptions of Receptor **R1** considered in the absence of F^-, at an intermediate, and at a concentration of complete concentration. K is binding constant, and $[F^-]$ is concentration of F^-. From the plot of 1 / (A − Amin) against $[F^-]$ for **R1**, the value of K (+10%) is calculated from the ratio of intercept/slope. Binding constant K, calculated from the graph (Fig. 6) is found to be 1.98×10^4 M^{-1}.

Infrared anion binding study of receptor **R1** with fluoride has been investigated using KBr discs. In the FTIR spectra of **R1**, N—H and C—H absorption bands

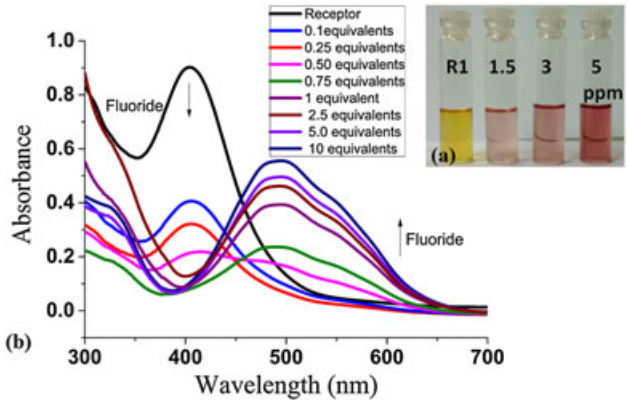


Figure 3. (a) Color changes in receptor **R1** (10^{-5} M in DMSO) with increasing concentration of sodium fluoride in 1:1 DMSO:water (1.5, 3, and 5 ppm, respectively) (b) UV–visible spectra of receptor **R1** (10^{-5} M in DMSO) with fluoride (sodium salt) from 10^{-5} to 10^{-3} M in 1:1 DMSO:water. [Color figure can be viewed at wileyonlinelibrary.com]

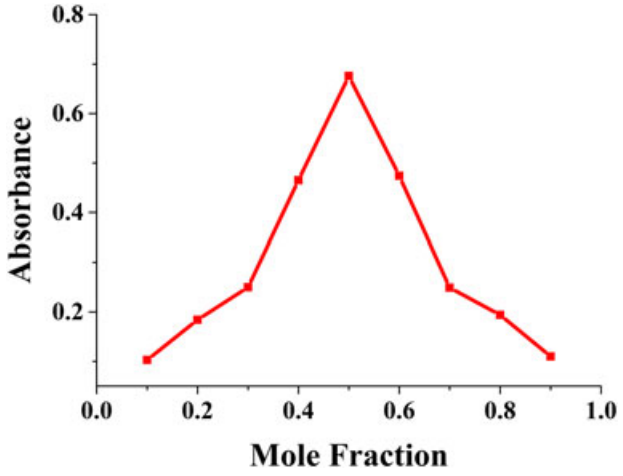


Figure 4. Jobs Plot with receptor **R1** (10^{-4} M in DMSO) and fluoride (sodium salts) 10^{-4} M in 1:1 DMSO–water. [Color figure can be viewed at wileyonlinelibrary.com]

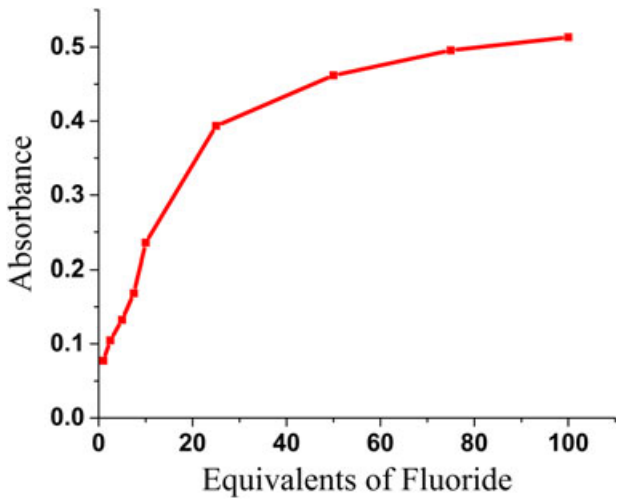


Figure 5. Changes in absorbance at wavelength 490 nm of receptor **R1** (10^{-5} M in DMSO) with increase in fluoride ion concentration (10^{-5} to 10^{-3} M in 1:1 DMSO–water). [Color figure can be viewed at wileyonlinelibrary.com]

appear at 3438 and 2941 cm^{-1}. These absorption bands seem to broaden with the addition of fluoride salt and exhibit an intense band in the region 2880–3430 cm^{-1}. The broadening of peaks indicates towards the formation of hydrogen bonding between N—H and C—H of **R1** with fluoride ion (Fig. 7).

Insight of anion-receptor binding site and nature of interaction could be realized by ^{1}H-NMR titration. For ^{1}H-NMR titration, receptor **R1** solution (DMSO-d_6, 10^{-2} M) was taken, and fluoride ions (tetrabutylammonium salt in DMSO-d_6) at different concentrations (2.5, 5, and 10 equivalents) were mixed together. Initially N—H (H_a) and C—H absorption peaks

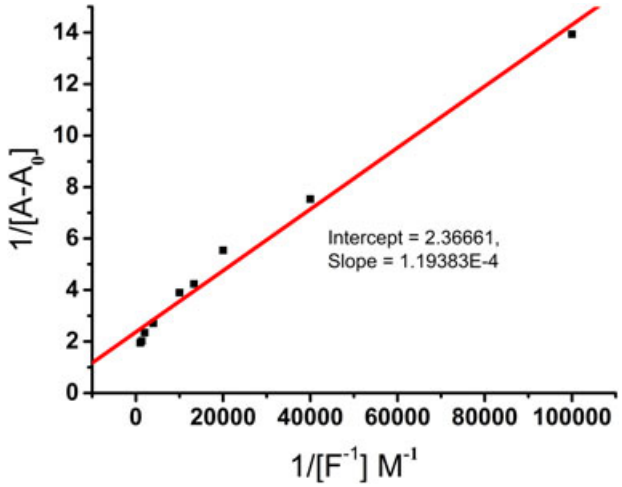


Figure 6. Fitting curve of Benesi–Hildbrand plot. [Color figure can be viewed at wileyonlinelibrary.com]

(H_b) appear at δ 11.59 and 9.11 ppm, respectively, which upon addition of 2.5 equivalents of fluoride ion, shifted downfield by 0.11 and 0.05 ppm, respectively, with simultaneous decrease in their intensities. Further downfield shifting of H_a and H_b is observed on addition of 5 equivalents of fluoride, and, finally, proton H_a is deprotonated (absence of peak) in the presence of 10 equivalents of fluoride, substantiating the process of color change (Fig. 8).

Careful examination of ^{1}H-NMR titration results shows the involvement of two types of interactions between receptor **R1** and fluoride ion, *viz*., hydrogen bonding and deprotonation. Initial addition of fluoride induces the formation of hydrogen bonding between receptor and fluoride, whereas further addition of the same leads to deprotonation of N—H. C—H hydrogen donor group acts as an auxillary binding site with N—H proton. The proposed mechanism is depicted in Scheme 2. Receptor **R1** binds fluoride ion by N—H and C—H hydrogen bond donor groups through hydrogen bonding, initially, with the formation of a six-membered ring. Excess of fluoride ion causes deprotonation of N—H group and induces π-delocalization (internal charge transfer), which is ultimately observed as naked eye color change.

Receptors **R2** to **R5** were tested with different anions for any visual change, but no naked eye change is brought by any anion, even at higher concentrations, 10^{-3} M, signifying towards either no or weak anion-receptor coordination took place which could cause change in color. Spectroscopically, too, no evidence of any receptor-ion interaction is observed. It is therefore concluded that strategic substitution of electron-withdrawing groups at 2 and 4 position has yielded the variation in fluoride ion binding abilities. Two nitro groups have enhanced the acidity of hydrogen bond

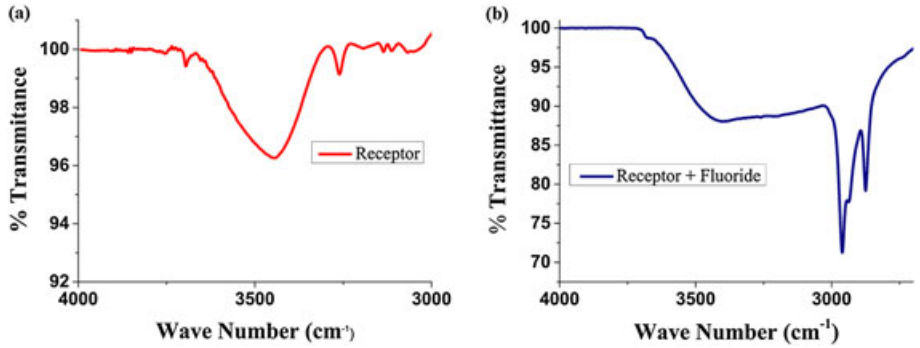


Figure 7. (a) FTIR spectra of receptor **R1**. (b) FTIR spectra of receptor **R1** in the presence of 1 equivalent of fluoride ion. [Color figure can be viewed at wileyonlinelibrary.com]

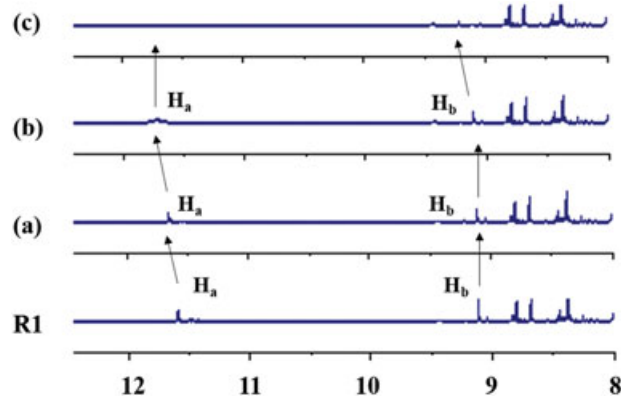
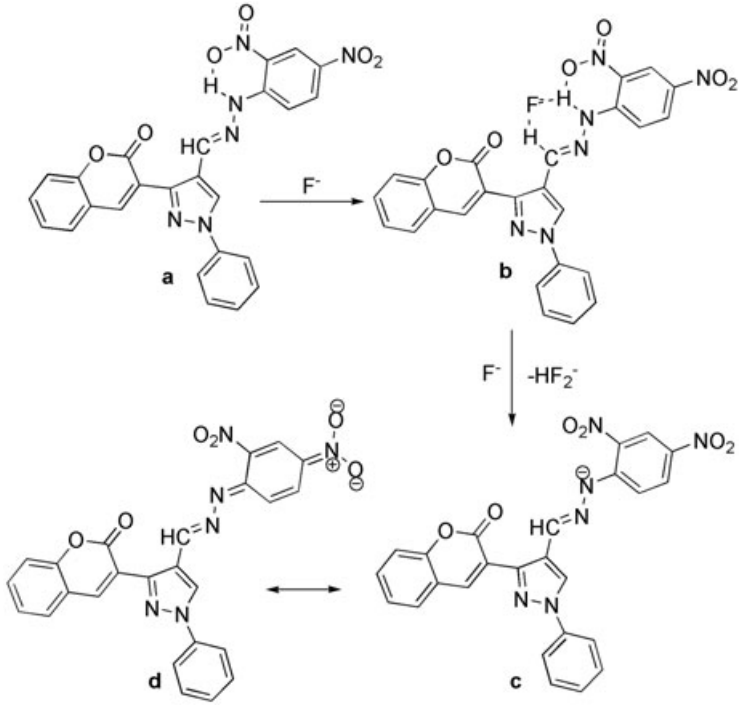


Figure 8. Partial ^{1}H NMR (400 MHz) spectra of **R1** in DMSO-*d6* (10^{-2} M) in the presence of (a) 2.5, (b) 5, and (c) 10 equivalents of TBAF in DMSO-*d6*. [Color figure can be viewed at wileyonlinelibrary.com]

donor groups in the structure of receptor **R1** and made it capable enough to detect fluoride ion via naked eye. Moreover, insertion of electron-withdrawing substituent (nitro groups) onto the molecular framework of **R1** polarized the N—H fragment and its H-bond donor tendency increased sufficiently to compete with water molecules, and thus **R1** is capable to detect fluoride in competitive solvent. Receptors **R2–R4**, although having electron-withdrawing groups, could not show any detectable response towards any anion. This could be attributed to the fact that in addition to electron-withdrawing group at 4-position in **R1**, there is also an additional electron-withdrawing group at ortho position, which assists the hydrogen bond donor capacity of NH and CH by forming a six-membered ring as shown in

Scheme 2. Proposed mechanism of binding between **R1** and fluoride ion.



Scheme 2. No anion triggered color change in receptor **R5**, which is seemingly obvious in absence of any electron-withdrawing groups in its structure. Above observations lead to the conclusion that on increasing the number of nitro groups, acidity and recognition properties of N—H group with fluoride ion increase. Similar observation was reported by Shang *et al.* also [54].

CONCLUSION

We have described an unprecedented colorimetric receptor **R1** synthesized by environment sustainable route capable of binding inorganic fluoride selectively and sensitively in aqueous media with its rationally placed N—H and C—H groups. Naked eye recognition of fluoride ion makes receptor suitable for on-site analysis. By the plethora of qualitative and quantitative studies, we have been able to demonstrate that receptor **R1** can serve as an aid to detect inorganic fluoride semi-quantitatively in real samples without suffering from any interference by other anions.

EXPERIMENTAL

General procedure. All chemicals were purchased from commercial sources and were used as received. 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. Fourier transform infrared spectra were recorded on a Perkin Elmer Spectrum Two spectrophotometer using pressed KBr discs in the region of 400–4000 cm^{-1}. ^{1}H-NMR and ^{13}C-NMR were recorded on a Jeol ECS 400-MHz spectrophotometer using DMSO-d_6 as solvent. Tetramethylsilane 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 spectrometer (Waters, USA), capable of recording high-resolution mass spectrum (HRMS) in the electrospray ionization (ESI) modes. CEM discover mono mode microwave reactor with magnetron frequency of 2455 MHz was used for microwave reaction. Ultrasonication synthesis was performed using Elma S 70 H Ultrasonic sonication with 37-KHz output frequency. Ultraviolet–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 all compounds was checked by TLC using silica gel as adsorbent and solvents of increasing polarity as mobile phase.

General procedure for the Vilsmeier formylation reaction of 2. Vilsmeier reagent was prepared from *N,N*-dimethyl formamide (10 mL) and phosphorous oxychloride (1.35 mL) at room temperature with constant stirring as described in literature [52]. Then, phenylhydrazone derivative, **2** (15 mmol), was added portionwise in it at 0–5°C with constant stirring. After complete addition, the reaction mixture was ultrasonicated for 20 min at 80°C. The progress of reaction was checked by thin film chromatography with pet ether:ethyl acetate (7:3) as solvent. The reaction mixture was cooled, poured into ice-cold water, and neutralized with sodium bicarbonate solution to pH 8. The product so obtained was filtered, washed with water (50 × 2 mL), and dried. Vilsmeir formylation carried out by ultrasonic irradiation completed in less time and gave higher yield than conventional stirring method. This protocol proved efficient in terms of less reaction time in comparison to 2.5 to 3 h reported in conventional method [52].

General procedure for the reaction of substituted phenyl hydrazine with compounds 3. Equimolar amount (5 mmol) of **3** and substituted phenylhydrazine were irradiated under microwave for 5–8 min at 100°C and 150-W power. The reaction progress was checked by thin layer chromatography using solvent pet ether and ethyl acetate (1:1). Compounds obtained were washed with cold diethyl ether and purified by column chromatography (pet ether:ethyl acetate) to afford the desired title receptors **R1**–**R5.**

3-{4-[(2,4-Dinitro-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one (R1). Orange solid, yield 84%, mp 198°C. FTIR (KBr, υ cm^{-1}): 3438 (N—H), 2941 (=C—H), 1721 (C=O), 1532 (C=N). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 7.38–7.9 (m, 12H, Ar—H), 8.38(s, 1H, pyran C—H), 8.68 (s, 1H, pyrazolyl C—H), 9.11 (s, 1H, —CH=N), 11.59 (s, 1H, N—H). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 116.71, 119.01, 119.40, 120.17, 122.16, 125.32, 127.35, 127.74, 129.33, 130.37, 131.71, 132.77, 139.56, 143.19, 145.69, 148.78, 155.87, 162.92. MS (ESI) *m/z*: 497.1750 $[M + H]^+$ calcd. for $C_{25}H_{16}N_6O_6$: 496.1741.

3-{4-[(4-Nitro-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one (R2). Yellow solid, yield 82.7%, mp 253°C. FTIR (KBr, υ cm^{-1}): 3445 (N—H), 2900 (=C—H), 1726 (C=O), 1529 (C=N). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 7.03–7.97 (m, 13H, Ar—H), 8.94 (s, 1H, pyran C—H), 9.38 (s, 1H, pyrazolyl C—H), 9.84 (s, 1H, —CH=N), 11.11 (s, 1H, N—H). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 114.54, 118.91, 121.15, 123.44, 126.54, 127.11, 129.33, 131.67, 133.34, 138.86, 143.14, 145.28, 146.36, 153.97, 156.84. MS (ESI) *m/z*: 452.1289 $[M + H]^+$ calcd. for $C_{25}H_{17}N_5O_4$: 451.1281.

3-{4-[(2-Nitro-phenyl)-hydrazonomethyl]-1-phenyl-1H-pyrazol-3-yl}-chromen-2-one (R3). Yellow solid, yield 84%, mp 210°C. FTIR (KBr, υ cm^{-1}): 3335 (N—H), 2890

(═C—H), 1716 (C═O), 1524 (C═N). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 7.03–7.97 (m, 13H, Ar—H), 8.42 (s, 1H, pyran C—H), 9.24 (s, 1H, pyrazolyl C—H), 9.88 (s, 1H, —CH═N), 10.23 (s, 1H, N—H). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 112.38, 116.78, 120.84, 121.46, 125.44, 126.33, 128.29, 130.67, 134.86, 141.28, 144.26, 146.97, 152.88, 155.32. MS (ESI) *m/z*: 452.1276 $[M + H]^+$ calcd. for $C_{25}H_{17}N_5O_4$: 451.1281.

3-{1-Phenyl-4-[(3-trifluoromethyl-phenyl)-hydrazonomethyl]-1H-pyrazol-3-yl}-chromen-2-one (R4). Yellow solid, yield 83.6%, mp 234°C. FTIR (KBr, υ cm^{-1}): 3288 (N—H), 2811 (═C—H), 1705 (C═O), 1553 (C═N). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 7.03–8.32 (m, 13H, Ar—H), 8.88 (s, 1H, pyran H), 9.24 (s, 1H, pyrazolyl C—H), 9.89 (s, 1H, —CH═N), 10.44 (s, 1H, N—H). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 115.71, 118.40, 121.17, 123.16, 126.35, 128.33, 131.37, 132.77, 139.56, 143.19, 145.69, 146.36, 153.97, 159.54. MS (ESI) *m/z*: 475.1316 $[M + H]^+$. calcd. for $C_{26}H_{17}F_3N_4O_2$: 474.1304.

3-[1-Phenyl-4-(phenyl-hydrazonomethyl)-1H-pyrazol-3-yl]-chromen-2-one (R5). Yellow solid, yield 86.4%, mp 188°C. FTIR (KBr, υ cm^{-1}): 3201 (N—H), 2899 (═C—H), 1719 (C═O), 1524 (C═N). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm) δ 7.33–7.88 (m, 15H, Ar—H), 8.17 (s, 1H, pyran H), 8.36 (s, 1H, pyrazolyl C—H), 8.88 (s, 1H, —CH═N), 10.27 (s, 1H, N—H). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 112.18, 116.01, 121.14, 124.46, 127.75, 128.64, 131.57, 134.77, 136.36, 142.19, 144.63. MS (ESI) *m/z*: 407.1451 $[M + H]^+$ calcd. for $C_{25}H_{18}N_4O_2$: 406.1430.

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Recent trends in coumarin based neutral synthetic receptors for naked eye sensing of anions

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Abstract: Coumarin moiety is increasingly employed for the construction of artificial neutral receptors and sensors for effectively binding anions of various sizes and geometries. A lion's share of these receptors have been documented and developed for the detection of highly basic fluoride ion because of its deleterious effects. This review showcases the development of coumarin as artificial neutral receptors for binding and sensing anions by colour change detectable by naked eye, which are useful for at-site analysis without resorting to expensive instruments, covering literature references from the year 2010 till date.

Keywords: Anion receptor, naked eye receptor, heterocycle, hydrogen binding, coumarin derivatives

Introduction

Nature's fundamental biological processes involving receptor-guest interactions or enzyme-substrate are regulated *via* ions' concentration; wherein anions are selectively detected and complexed through the intricate binding sites of proteins [1]. Most widely found are the two basic pyrrole containing macrocycles, haeme protein and porphyrin, which bind Fe^{+2} and Mg^{+2} ions for conducting vital functions in human body and plants [2]. This has encouraged the innovation in chemical sensor technology and development of abiotic host molecular systems capable of imitating the ionic recognition found in biological systems [3-7].

Anion receptors can be broadly categorized into cationic and neutral receptors [8]. Cationic anion receptors are positively charged receptors which establishes electrostatic interactions with anions. These receptors marked the beginning of anion recognition chemistry, with the earliest artificial receptor being reported in 1968 which was a macrocyclic compound consisting of two bridgehead ammonium units, capable

of encapsulating halide ions [9]. Moieties, guanidinium, quaternary ammonium groups, isothiouronium, polyamines, porphyrins etc. have been largely employed for the formulation of cationic receptors to achieve electrostatic binding with anions [10-17]. Although, larger binding constants could be achieved with positively charged receptors, they lack directional and selective nature of hydrogen bonding. Moreover, associated counter-anion with charged hosts creates competition for desired anion.

In contrast to this, neutral receptors rely on hydrogen bonding, which possess higher degree of directionality and strength than columbic forces and is arguably the most common forces utilized in crafting anion receptors [18-20]. Urea/thiourea, secondary amide, sulphonamides [21-24] possess acidic N-H, which can build hydrogen bond with negatively charged species and thus have found their use in creating anion receptors. Moreover these moieties offer several advantages which enabled their extensive exploitation in composing putative anion receptors. Synthetic accessibility of urea and thiourea has enabled their incorporation in a wide variety of putative anion receptors [25-29]. They possess two acidic hydrogen bonds and have been extensively utilized for developing receptors for binding carboxylates and phosphates [30].

Anions play several significant roles in biological as well as in environment, this demands continuous research for the development of techniques to quantify them [31-34]. Amongst them, host molecules that can recognize and sense anions selectively through visible, electrochemical and optical responses are of particular interest [35-37]. Color change, which can be detected *via* naked eye is highly appreciated being a low cost and does not require any spectroscopic instrument and requisite in terms of practical purpose [38-40]. There are three popular approaches for designing chemosensors (**Figure 1**) [41]:

- **Binding – signalling unit approach,**
- **Displacement approach**
- **Chemodosimeter approach**

In the first approach, receptor consists of chromophoric units, covalently attached to binding unit [42]. Receptor binds the anion and brings about a change in the photophysical properties of chromophore attached with an optical response as the output.

Chromophoric groups become coloured by absorbing light in visible region (400-700 nm). These consist of a system of conjugated bonds that brings down the energy gap between HOMO and LUMO to visible region. Appropriate anchoring of electron donor and acceptor groups to this system generates a charge transfer band, corresponding to transition of electrons from donor to acceptor group *via* conjugated system, upon excitation with light [43].

In the displacement approach, binding and signalling units form a coordination complex. In solution, anion displaces the signalling unit from the complex, which comes into its non-coordinated spectroscopic behaviour [44].

Both of the above approaches are reversible in nature, while the last, the chemodosimeter approach, is irreversible in nature [45]. Here, anion induces a specific reaction on binding and generates a naked eye response. This anion induced approach is highly selective and is directly related to anion concentration

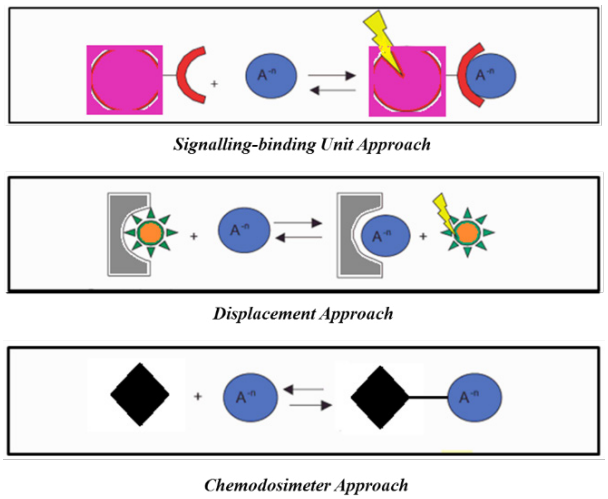


Figure 1 Design approaches for chemosensors [46]

Various non-covalent interactions, mainly coulombic [47-48], anion- pi interactions [49], metal based [50] have been exploited for trapping anions. A large share of receptors utilizes polarized N-H that behaves as hydrogen bond donor to bind anions [51-54]. The acidity of these protons can be modulated by electronic and substituents effects [55]. Insertion of electron withdrawing groups such as nitro, trifluoromethyl groups etc. onto the framework of molecular structures of receptors has enhanced the binding capabilities which has often been accompanied by visible colour change in case of deprotonation [56]. Fluoride, amongst the anionic species, is undoubtly the most investigated individual of the vast family of anions [57]. Being the most electronegative atom, it rightfully establishes the strongest hydrogen bond interactions with an unmatched selectivity [58]. It is well noted observation that the colorimetric receptors show moderate or slight changes in presence of other anions, however with fluoride, receptors exhibit drastic colour changes. Beautiful and interesting colour changes with fluoride have been reported usually with anion receptors capable of donating one or more hydrogen bonds. The negative charge brought by the anion modifies the dipole associated to the charge transfer spectrum and thus a colour change is obtained. [59].

Coumarin, with the structure of benzo-α-pyrones has been extensively investigated for electronic and photonic applications such as fluorescence probes, charge transfer agents, solar energy collectors and non linear optical properties due to their inherent photochemical characteristics, reasonable stability, good solubility and their relative ease of synthesis [60-61]. A great number of receptors for metal ions have been developed in recent years, however anion sensors derived from coumarins are scarcely reported [62-70]. This review comprehensively describes the employment of coumarin and sensing abilities for anions in organic solvents or in aqueous media covering literature references from 2010 to recent development till date.

Naked eye coumarin based anion receptors

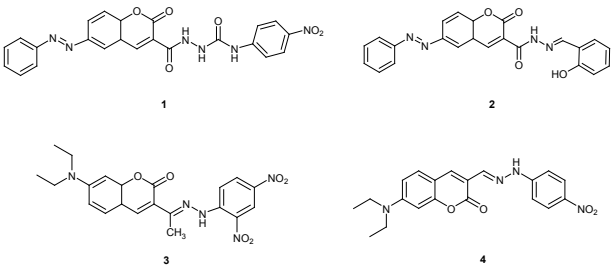


Figure 2 Coumarin based naked eye receptors, **1-4**

Shao *et. al.* reported colorimetric and fluorescent receptor **1** based on coumarin moiety as chromogenic and fluorescent unit and urea as anion binding site. It exhibited high selectivity for acetate ion over fluoride and dihydrogen phosphate due to multiple hydrogen binding interaction in DMSO. Fluorescent spectrum of receptor with acetate ion showed hypsochromic shift with significant increase in florescence intensity. The fluorescence in emission spectrum was observed due to anion induced conformation restriction [71]. Shao in 2011,

reported analogue of above, a coumarinschiffs base derivative **2**, which in the presence of acetate ion, exhibited "turn-on" fluorescence; resulting from binding induced conformational restriction. Colorimetric response for fluoride, acetate and dihydrogen phosphate was observed from yellow to red (**Figure 2**) [72].

Among the entire range of biologically important anions, fluoride is particularly useful, owing to its role in preventing dental caries and treatment of osteoporosis [73-82]. The biggest bottleneck in naked eye detection of fluoride is interference by acetate and other anion of comparative basicity [83-85]. In 2010, Coumarin based phenylhydrazone receptor **3** was synthesized and reported by Upadhyay *et. al.* that selectively detected fluoride over acetate in DMSO solution. Addition of 1 eq of fluoride to receptor solution (5×10^{-5}M) produced change from yellow to red, while similar addition of acetate ion produced faint pink color. Receptor differentiated the two anions not only visually, but in the terms of maxima by a margin of 30 nm which is a rare observation in UV spectrum (**Figure 2**) [86].

Liu *et. al.* reported fluoride receptor based on coumarin7-(diethylamino)-2-oxo-2H-chromene-3-carbaldehyde **4**, which bound fluoride *via* hydrogen bonding in acetonitrile. The receptor exhibited a large red shift of 145 nm along with change in the colour from yellow to blue upon addition of fluoride ion in acetonitrile and without interference of other anions such as Cl^-, Br^-, I^-, NO_3^-, $H_2PO_4^-$, HSO_4^-, and AcO^-. The ^{1}H NMR spectrum titration established that F^- first formed a hydrogen bonding interaction with receptor **4** and then, excess of fluoride induced deprotonation (**Figure 2**) [87].

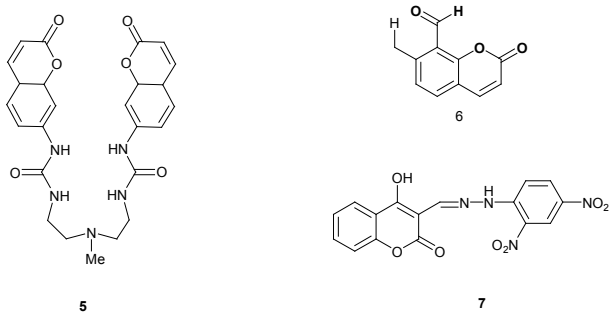
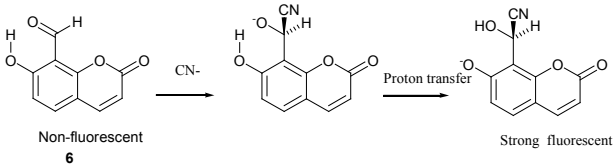


Figure 3 Coumarin based naked eye receptors, **5-7**

An off-on fluoride ion fluorosensor, 1,11-bis(4-methylcoumarin-7-yl)-6-methyl-1,3,6,9,11-pentaazaundeca-2,10-dione **5**, containing two coumarin-urea units attached by a flexible diethylenetriamine fragment has been designed and developed by Fusi and Zappia. Anion binding tendencies was investigated in both DMSO as well as CH_3CN solvents. Fluorescence emission of receptor in visible range (400 nm) was demonstrated to be quenched by the presence of acetate, chloride and pyrophosphate ions, while fluoride ion enhanced the emission, which proved the selectivity of receptor for fluoride ion (**Figure 3**) [88].

A fluorescent chemodosimeter **6** for cyanide ion with coumarin as signal unit and salicyaldehyde functionality as recognition unit has been synthesized by Kim and Hong group. It showed a higher selectivity for cyanide ion over other anions in water as demonstrated in fluorescence spectroscopy titration; wherein emission intensity of dosimeter at λ = 450 nm was enhanced to about 190 folds on addition of cyanide. The affinity and selectivity of chemodosimeter for cyanide was due to the nucleophilicity of cyanide as indicated by ^{1}H-NMR titration where aldehyde proton shifted upfield due to formation of cynohydrin, from δ 10.1 to 6.1 ppm (**Scheme 1**). In-vivo selectivity was also examined with living cells at pH 7.4 by using fluorescence microplate reader where only cyanide treated P19 cells showed enhancement

in fluorescent intensity in living cells (**Figure 3**) [89].



Scheme 1 Fluorescentchemodosimeter for selective detection of cyanide in water

Receptors bearing phenylhydrazone-coumarin moieties, **7** was rationally designed for chemosensing acetate ion as well as fluorescence turn-on probe for iodide ion**.** It produced dramatic colour change from yellow to purple upon addition of acetate ion, with bathochromic shift from 411 to 573 nm in UV-visible spectra. Exploiting novel strategy based on the redox reaction between Cu^{+2} and iodide, which is a notorious fluorescence quencher due to heavy atom effect, receptor has been developed as fluorescence amplifier probe for iodide (**Figure 3**) [90].

Coumarin as signaling unit and acetamidothiophene ring as hydrogen donor, colorimetric and fluorimetriccoumarinthiophene based chemosensor, **8** for cyanide, fluoride and acetate was developed by Dede and Seferoglu *et. al*., which showed naked eye colour change from light yellow to dark yellow as well as emission quenching in fluorescence spectrum. Other anions failed to induce any spectral changes. Anion binding properties carried out with spectrophotometric and H NMR techniques showed that receptor exhibited more affinity towards cynide ion (**Figure 4**) [91].

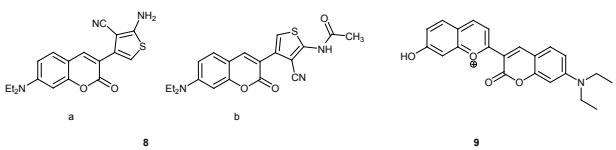


Figure 4 Coumarin based naked eye receptors, **8-9**

2-(7-diethylamino-2-oxo-2H-1-benzopyran-3-yl)-7-hydroxyl-1- benzopyrylium, a ratiometric fluorescent probe, **9** constructed by hybridizing coumarin and benzopyrylium moieties for sensing sulphite ion. Nucleophilic addition of sulphite to electronically positive benzopyrylium moiety alters the π conjugation of receptor and thus ratiomatric sensing is realized. A fluorescent emission peak centered at 640 nm blue shifted to 485 nm upon addition of sulphite ion. Preliminary study conducted by authors showed that receptor is cell permeable and can be used for detecting cellular sulphite (**Figure 4**)[92].

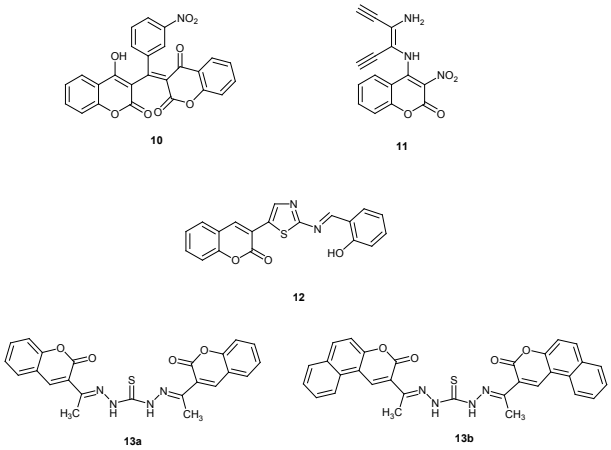
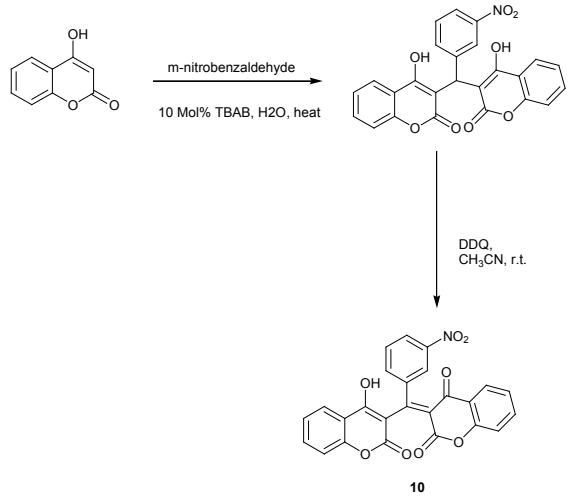


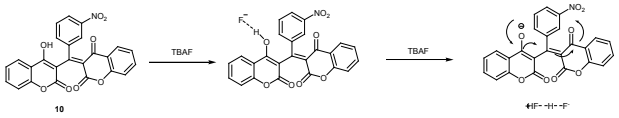
Figure 5 Coumarin based naked eye receptors, **10-13**

Mahapatra *et. al.* designed and synthesized turn-on fluorescent and colorimetric sensor, **10** based on oxidized bis(coumarin)methane, 3,3'-(3-nitrophenylmethylene)-bis-(4-hydroxycoumarin) (**Figure 5**) for fluoride ion detection in organic media, acetonitrile (Scheme 2). Authors found that biscoumarin containing oxidizable H atom, was unstable and spontaneously oxidize to conjugated product. The conjugated product can act as colour reporting group as well as binding affinity group containing acidic H donor moiety. They conducted anion binding studies by UV-visible, fluorescence and NMR titrations to show selective nature of receptor towards fluoride ion

over other anionic species. Receptor exhibited absorbance band at 261 and 319 nm in UV-visible spectra. Upon addition of fluoride ion, a new absorbance band at 349 nm appeared, which was accompanied by naked eye colour change of receptor solution from colourless to yellow. Authors found that no other anions could trigger similar naked eye and spectral change upon addition to receptor solution. The stoichiometry between receptor and fluoride ion was found to be 1:2 from Jobs plot. Fluorescence enhancement was observed at 394 nm, when excited at 287 nm, upon addition of fluoride ion into receptor solution in acetonitrile. ^{1}H NMR spectra of receptor showed peak at 9.5 ppm due to O-H proton, which shifted downfield and disappeared at 1.5 equivalents of fluoride ion. Fluoride ion established hydrogen bonding with receptor initially, followed by proton transfer, which gave rise to drastic colour change (**Scheme 3**) [93].



Scheme 2 Synthesis of 3,3'-(3-nitrophenylmethylene)-bis-(4-hydroxycoumarin), **10**



Scheme 3 Proposed binding mechanism of receptor **10**

A new chromogenic multifunctional chemosensor, **11**, (2-(3-nitro-2-oxo-2H-chromen-4-ylamino)-3-aminomaleonitrile) was synthesized and documented for the detection of Al^{3+} and F^- by Kim *et. al.*(**Figure 5**) [94]. Receptor was synthesized in a single step by coupling 2,3-diaminomaleonitrile with 4-chloro-3-nitrocoumarin in methanol.The preferential selectivity of receptor as fluoride ion naked eye receptor has been studied by authors in presence of various competing anions, chloride, bromide, iodide, acetate, benzoate, dihydrogen phosphate and cyanide, where no interference was observed. The fluoride recognition property of receptor was studied by UV-visible titrations, in which absorption bands at 338 and 441 nm disappeared, with simultaneous appearance of absorbance band at 510 nm.1:1 stoichiometry between receptor and fluoride ion was proved by Jobs plot and ESI mass spectroscopy. In ^{1}H NMR spectra of receptor, peaks at 9.96 and 8.07 ppm due to NH and NH_2 disappeared upon addition of 1 equivalent of fluoride ion (TBA salt). Authors concluded that colorimetric response was obtained due to the decrease in the intramolecular charge transfer band by a deprotonation process.

Mishra and coworkers synthesized coumarin-thiazole based molecular scaffolds, out of which probe **12** exhibited fluorescence quenching on interaction with Cu^{+2} ion, while remaining silent towards anions(**Figure 5**) [95]. When this **12**- Cu^{+2} ensemble was tested for detection of anions, only fluoride ion enabled copper displacement as CuF_2 and led to fluorescent enhancement. Authors reported that this naked eye sensitive "*On-Off-On*" sensing behavior of probe could mimic the function of sequential logic circuit at molecular level. Paper strips have been developed by dipping the pieces of small cellolose paper into receptor solution and were then dried. They showed the analytical application of probe by detecting Cu^{+2}/F^- ions on paper strips and real contaminated water

samples.Paper strips changed its colour from fluorescent blue-green to deep blue (under UV light at 365 nm) upon addition of Cu^{+2} ions. Interestingly, when this strip was dipped into the solution of fluoride ion, the naked-eye sensitive color of the paper strip was regained from a deep blue to a fluorescent blue-green (under UV light at 365 nm). Limit of detection was found to be 1.60 ppb and 2.12 ppb for Cu^{+2} and F^- ions, respectively.

Two thiocarbonohydrazone receptors functionalized with coumarin derivatives, **13a-b** have been designed, synthesized and investigated for selective detection of fluoride ions by Sahu*et. al.* in 2016(**Figure 5**) [96]. Receptor **13a** displayed distinct colour change from colourless to pink and 20-fold fluorescent enhancement upon addition of fluoride ion. Receptor **13b** exhibited colour change from colourless to deep red and 5-folds fluorescence enhancement upon interaction with fluoride ion. Receptor **13a** and **b** showed absorption band at 342 and 379 nm, which decreased in intensity with simultaneous appearance of new bands at 546 and 542, respectively on interaction with fluoride ion. At lower concentrations of fluoride ion, 1:1 stoichiometry was observed, while at higher concentration, 1:2 binding was seen between receptor and fluoride ion. Authors provided insight into the nature of interaction by NMR titrations. Receptor **13a** demonstrated broadening and subsequent collapse of two NH signals at 9.76 and 10.41 ppm to a single broad peak at 10.17 ppm, which disappeared on addition of excess of fluoride ion (5 equivalents). This observation could be ascribed to initial hydrogen bonding formation, followed by deprotonation. Characteristic triplet at 16 ppm corresponding to the formation of HF_2^- ion through deprotonation was observed by authors.

Yeap*et. al.* synthesized chalcone based probe, **14**, containing coumarin and naphthol at both ends *via* aldol condensation [97] (**Scheme 4**). Receptor, with coumarin unit as signalling unit and naphthol as binding unit, displayed high selectivity and sensitivity towards fluoride ion in acetonitrile. Authors studied anion binding properties by fluorescence spectroscopic titrations at excitation wavelength of 420 nm. Receptor exhibited an emission band at 524 nm, which upon addition of fluoride ion, showed enhancement in fluorescence intensity. Authors ascribed this interaction to internal charge transfer developed by deprotonation of OH from naphthol unit and formation of HF_2^- complex (**Scheme 5**).

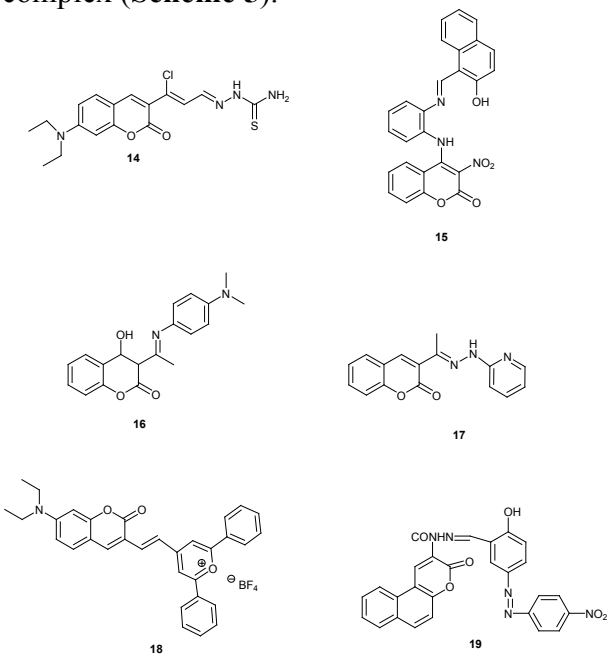
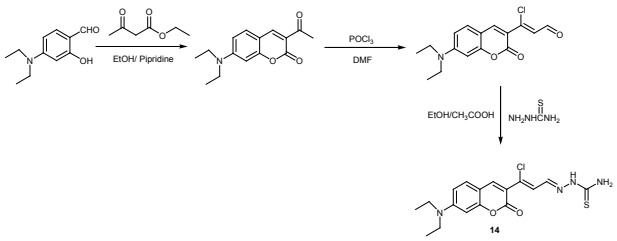
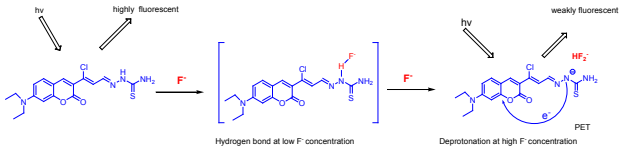


Figure 6 Coumarin based naked eye receptors, **14-19**

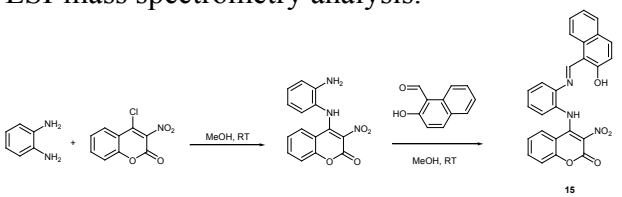


Scheme 4 Chalcone based probe, **14**

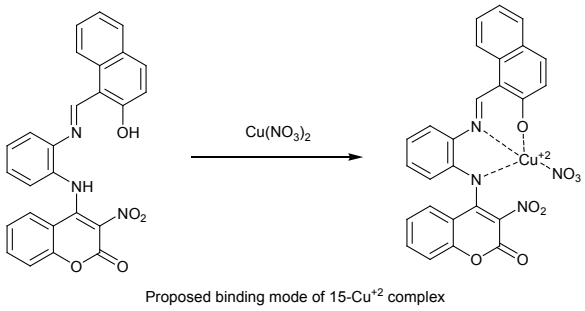


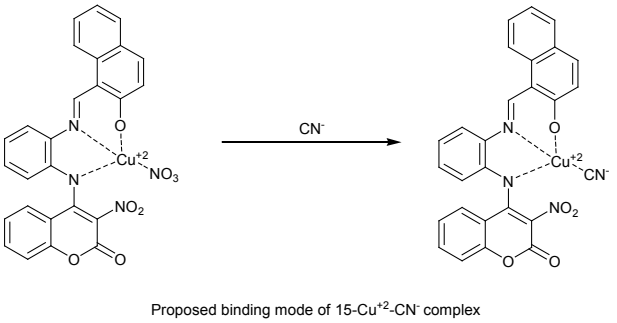
Scheme 5 Proposed binding model of 14 with fluoride ion

Kim *et. al.* designed assymetric coumarin-conjugated naphthol based chemosensor, **15** for sequential sensing of Cu^{+2} and CN^- ions in aqueous media (**Figure 6**) [98]. Chemosensor, (*E*)-4-((2-((2-hydroxynaphthalen-1-yl) methylene)amino)phenylamino)- 3-nitro-2H-chromen-2-one, was synthesized by coupling of 4-((2-aminophenyl)amino)-3-nitro- 2H-chromen-2-one and 2-hydroxy-1-naphthaldehyde with a 58% yield in absolute methanol (**Scheme 6**). Receptor exhibited naked eye colour change from orange to yellow in presence of Cu^{+2} ion. The receptor- Cu^{+2} could sense cyanide ion *via* naked eye colour change (**Scheme 7**) and in-depth UV-visible study was carried out by authors, where other anions, OAc^-, F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, N_3^- and SCN^- demonstrated almost no change in both UV-visible spectra and color of receptor- Cu^{+2} under the identical conditions. 1:1 stoichiometry between receptor-Cu^{+2} and CN^- was observed from Jobs plot and ESI-mass spectrometry analysis.



Scheme 6 Synthesis of chemosensor, (*E*)-4-((2-((2-hydroxynaphthalen-1-yl)methylene)amino) phenylamino)- 3-nitro-2H-chromen-2-one, **15**



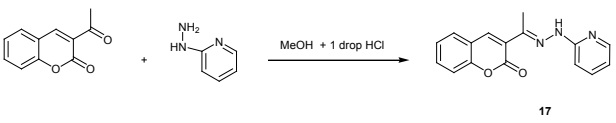


Scheme 7 Proposed binding mechanism of receptor **15**

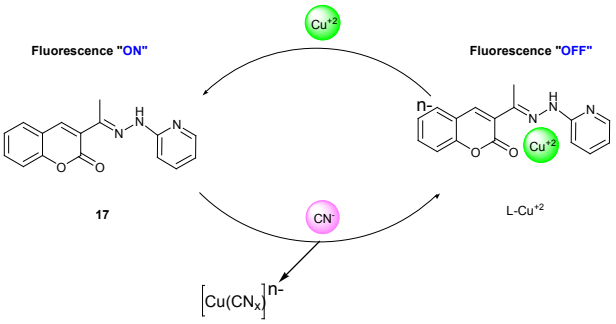
Mondal *et. al.* developed coumarin based fluorescent turn-on chemosensor, **16** for HSO_4^- ions by economically cheap method involving Schiff base condensation of 3-acetyl-4-hydroxycoumarin and N,N'-dimethyl-p-phenylenediamine in 1:1 molar ratio in methanolic medium [99]. UV-visible spectra of receptor revealed absorbance bands at 321 and 369 nm. Upon gradual addition of HSO_4^- ions, absorbance band at 321 red shifted to 330 nm and band at 369 nm disappeared resulting in two distinct isosbestic points at 307 nm and 357 nm. Other anionic species could not trigger any spectral response upon addition. In the absence of external analyte, emission spectrum of receptor displayed weak band at 422 nm, when excited at 370 nm. Fluorescence intensity increased 17 folds and emission maxima blue shifted by 46 nm to yield new maxima centred at 376 nm. Jobs plot indicated 1:1 stoichiometry between receptor and HSO_4^-. This receptor also

showed fluorescence turn-on behaviour towards Zn^{+2} ions.

Mukherjee *et. al*. documented coumarin based luminescent chemosensor, **17** for Cu^{+2} and CN^- ions in 2016 [100]. Receptor was prepared in a single step 1:1 condensation of 2- hydrazinopyridine with 3-acetylcoumarin (**Scheme 8**) and characterized by ^1H NMR, ^{13}C NMR, FTIR and Mass spectroscopic studies. Receptor worked for selective fluorescent recognition of Cu^{+2} inMeOH/H_2O (4:1, v/v at pH = 7.2 aqueous solution) medium with 1:1 binding stoichiometry. The in-situ Cu^{+2} complex thus prepared, showed high selectivity towards CN^-*via* Cu^{+2} displacement approach with detection limit in the micro molar range (Scheme 9).

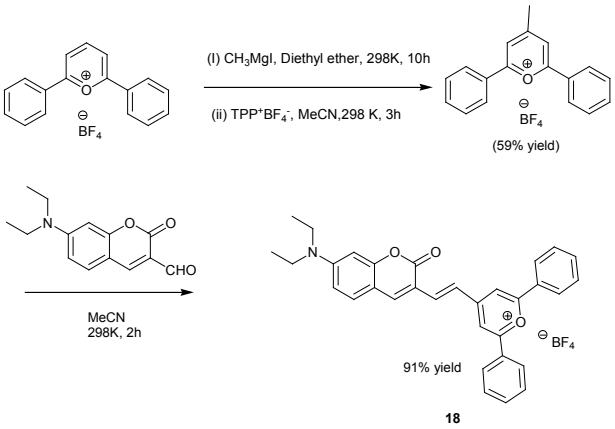


Scheme 8 Synthesis of coumarin based luminescent chemosensor, **17**

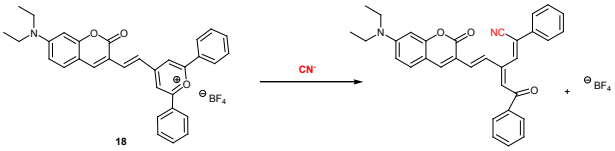


Scheme 9 Proposed binding model for fluorescence response of **17**-Cu^{+2} with fluoride ion

A pyrylium–coumarin dyad, **18** was synthesized and reported by Shiraishi *et. al*. in 2016 for ratiometric colorimetric sensing of cyanide ion in aqueous media (9:1 acetonitrile-water) (**Scheme 10**) [101]. Receptor displayed long-wavelength absorption band at 643 nm in UV-visible spectrum due to the strong intramolecular charge transfer (ICT) from the diethylaminocoumarin to pyrylium moiety. Addition of cyanide ion into receptor solution triggered ring cleavage within 8 minutes, which suppressed the ICT phenomenon (Scheme 11). This resulted in the appearance of new band at 472 nm assigned to π to π* transition of the diethylaminocoumarin moiety itself, with decrease in intensity of band at 643 nm. Limit of detection of receptor for cyanide ion was found as low as 8 μM by authors.



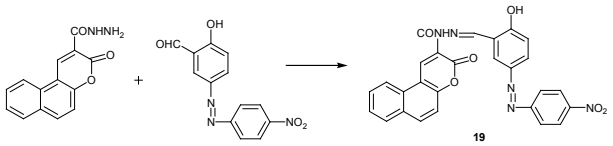
Scheme 10. Synthesis of pyrylium–coumarin dyad, **18**



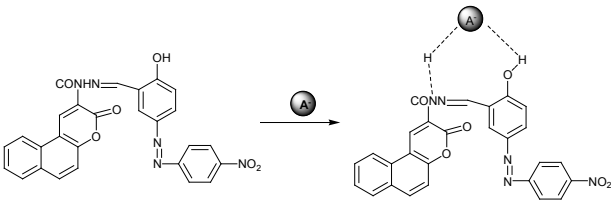
Scheme 11 Proposed mechanism of nucleophilic addition to receptor **18**

Zhao *et. al.* synthesized coumarin based receptor, **19** by using phenprocoumon containing acyl hydrazine and p-nitro azo salicyladehyde(**Scheme 12**) [102]. Authors designed receptor with nitro moiety as signaling group and phenolic hydroxyl moiety as anion binding site. They carried out anion recognition properties in the presence of OAc^-, F^-, OH^-, Cl^-, Br^-, I^- and $H_2PO_4^-$. Addition of OAc^-, F^-, OH^- and $H_2PO_4^-$ in DMSO into the receptor solution caused change in colour of

receptor from yellow to blue. In UV-visible spectrum, receptor displayed absorbance band at 383 nm, which upon addition of OAc^-, F^-, OH^- and $H_2PO_4^-$ showed a red shift in maxima and a new absorbance band centred at 598 nm was formed. An isobestic point at 439 nm was observed by authors indicative of formation of fixed stoichiometry between receptor and anion. Selectivity of receptor for anions followed order: $OAc^- > F^- > OH^- > H_2PO_4^-$, which authors attributed to guest basicity and shape complementarity between host and anionic guests (**Scheme 13**). Fluorescence emission spectrum of receptor displayed two weak emission bands at 413 and 663 nm. Upon addition of these anions, intensity of band at 413 nm increased and intensity of band at 663 nm decreased and gradually disappeared. Authors concluded that addition of these anions elicited visible decrease in fluorescence intensity due to quenching PET process from –OH or –NH group to $–NO_2$ group.



Scheme 12 Synthesis of coumarin based receptor **19**



Scheme. 13 Proposed binding model of **19** with anions

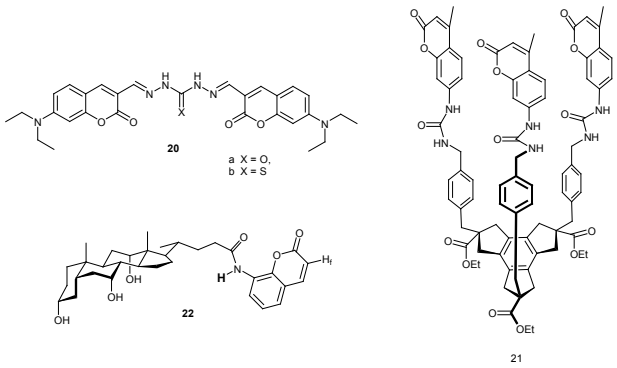
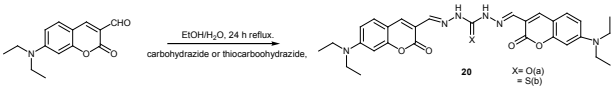


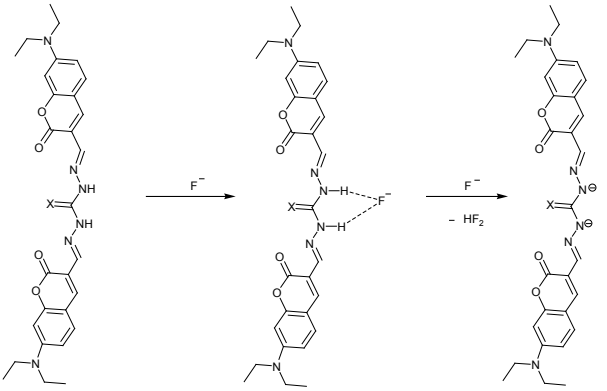
Figure 7 Coumarin based naked eye receptors, **20-22**

Coumarinthiocarbohydrazone (**20a**) and coumarincarbohydrazone(**20b**) were developed and reported by Singh *et. al* in 2016 for fluoride ion detection in CH_3CN/DMSO media(**Scheme 14**) [103]. Receptor **20a** exhibited specific selectivity and sensitivity for fluoride ion over other anions *via* naked eye colour change and fluorescence ON-OFF-ON fluorescence response. Authors carried out UV-visible spectroscopic titrations in CH_3CN containing 0.25 % DMSO. Receptor **20a** showed absorption band at 448 nm, corroponding to n-π* transition and at 278 nm, corresponding to π-π* transition. Receptor **20b** showed absorbance bands at 446 and 275 nm. Fluoride ion produced light brown colour in both receptors, while other anionic species failed to induce any response. In UV-visible spectra of receptor a, addition of fluoride ion induced decrease in intensity of 448 nm and maxima shifted slightly towards longer wavelength. Fluorescence spectra of receptor **20a** consisted of emission maxima centred at 516 nm, when excited at 450 nm. Addition of fluoride ion caused quenching in emission intensity by 70% (switched off). Authors attributed the quenching phenomenon to the formation of hydrogen bonding between receptor and fluoride ion. Further addition of fluoride ion, emission band slightly blue shifted by 20 nm and intensity of new band increased (switched on), which occurred due to formation

of deprotonation species (**Scheme 15**). Detection limit was found to be 9.2 μM.In case of receptor **20b**, fluorescence intensity decreased by only 18% upon addition of fluoride ion. Both receptors established 1:1 stoichiometric ratio with fluoride ion, as observed by authors from Jobs plot.



Scheme 14 Synthesis of Coumarinthiocarbohydrazone, **20a** and coumarincarbohydrazone, **20b**



Scheme 15 Proposed binding mechanism of receptor **20** with fluoride ion

Choi and coworkers developed C_3V-symmetric tris(coumarin-urea) anion receptor, **21** from trindane based tripodal scaffold for detection of $H_2PO_4^-$ and F^- ions (**Figure 7**) [104]. Receptor with urea group as recognition unit and coumarin as signaling unit naked-eye detectable turn-on fluorescence selectively in the presence of $H_2PO_4^-$ and F^- ions in CH_3CN. The colourless solution of receptor displayed maxima at 332 nm, which was red shifted by 5 nm, upon addition of anions, to form a new band at 337 nm. Addition of anions resulted in red shift of emission maxima of receptor into visible region 415 nm, naked eye detectable under UV lamp (365 nm). ^{1}H NMR titration experiments indicated towards the formation of a hydrogen bonded 1:1 caviplex receptor-$H_2PO_4^-$, whereas F^- ion, being more basic anion, induced the deprotonation of urea-NH protons.

Neutral cholic acid-coumarin conjugate, **22** was synthesized and reported by Li *et. al*. in 2015 for anion recognition by cooperative coumarin C-H and adjoining amide N-H fragments (**Figure 7, 8**) [105]. Receptor was synthesized by reaction ofmonomers cholic acid and 7-amino-coumarin with N-hydroxybenzotriazole (HOBt), *o*-benzotriazol-1-yl-tetramethyluronium hexafluorophosphate (HBTU) and N,N'-diisopropylethylamine (DIEA) in dry DMF at room temperature in a yield of 78%. UV-visible spectra of receptor consisted of absorption band centred at 345 nm, which decresed slightly in intensity upon addition of anions ($H_2PO_4^-$, F^-, Cl^-, Br^-), with red shift in band towards 356 nm. Fluorescence emission spectra of receptor showed maxima at 380-510 nm upon excitation at wavelength 345 nm. Addition of $H_2PO_4^-$ resulted in enhanced fluorescence emission at 452 nm. Authors claimed that excellent biocompatibility of receptor makes it an efficient and non-destructive probe for anion detection in living cells.

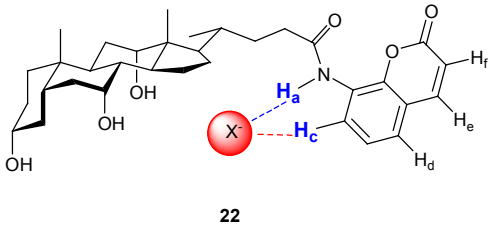


Figure 8 Binding modelcholic acid-coumarin conjugate, **21**with anions

Conclusion

The review sums up the coumarin derivatives as naked eye receptors documented so far, rely on signaling-binding unit approach, which exhibited colour changes on deprotonation by highly basic anions. Naked eye sensing is commendable with respect to real-life application. The remarkable progress has been

achieved in developing coumarin derivatives as naked eye receptors. Use of coumarin also imparted interesting photophysical properties to receptor systems to achieve naked eye sensing.The incorporation of hydrogen binding moieties, urea/thiourea and amide have been attempted to create hybrids. However, the key issues appeared are interference amongst related basic anions and receptor functioning in aqueous media, which are pre-requisites for practical purpose. It remains a challenge to develop receptors in 100% aqueous media i.e. water.

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Rationally designed tri-armed imidazole-indole hybrids as naked eye receptors for fluoride ion sensing

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Rationally designed tri-armed imidazole-indole hybrids as naked eye receptors for fluoride ion sensing

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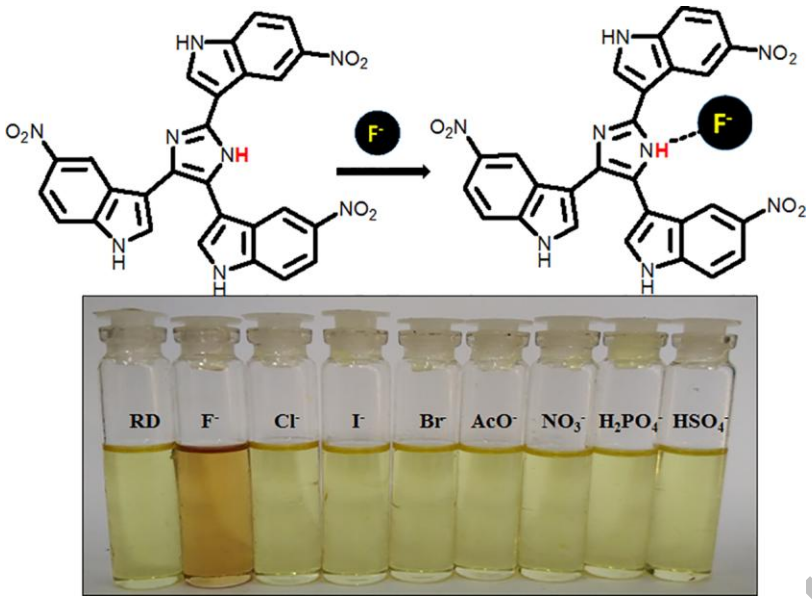
Abstract

The present communication describes the design, synthesis and characterization of unique tri-armed imidazole-indole hybrids **RA**-**RE** for naked eye detection of fluoride ion in 9:1 DMSO-water at concentration level of 1.5 ppm, which is recommended permissible limit of fluoride ion. Molecular structures of the receptors are so fabricated that both heterocyclic units, *viz.*, indole and imidazole have been rationally employed as chromophore and binding unit, respectively. Strategical introduction of nitro group(s) at the 5th position of indole ring remarkably enhances the binding ability of receptor **RD** making it highly selective towards fluoride ion (tetrabutylammonium salt) over other typical anionic species. The sensing event can be visualized by naked eyes swiftly with colour change. This observation is well corroborated by a red shift of 80 nm in UV-visible spectroscopic studies. A peak at 16.1 ppm due to HF_2^- in ^1H NMR titration validates the deprotonation of imidazolium N-H by fluoride ion.

GRAPHICAL ABSTRACT



KEYWORDS: colorimetric sensing, fluoride receptor, imidazole, indole, naked eye sensing

INTRODUCTION

Anion complexation chemistry has evolved as a stimulating multidisciplinary research area across chemistry, environment and biology, considering the importance of anion-molecule interactions in the areas of medicine, materials development, physiology, synthetic chemistry and analyte sensing [1]. From spherical fluoride ion to tetrahedral sulphate and phosphate ions, anions find their importance everywhere in nature, with involvement in vital functions and thus demand continuous research [2]. Drawing inspiration from nature, together with acquired knowledge of chemistry, researchers are artistically manipulating the chemical moieties to craft the diverse array of receptors for the selective recognition of desired anion [3]. Till date, multitude of approaches have been attempted with various functionalities to achieve selective binding with anions, most

commonly being preorganization of N-H and O-H moieties for effective hydrogen bonding [4], tailoring the acidity of N-H group for deprotonation to occur [5], anion-π interactions [6] and hydrophobic effects [7], etc.

Amongst the ubiquitous anions, fluoride anion recognition has captured a substantial attention of scientific community because it is one of the trace element required in the formation of teeth and bones in humans [8]. However, it is well documented that excessive intake of fluoride ion through drinking water causes dental fluorosis, bone diseases and lesions of thyroid and liver [9]. This proves that beneficial and injurious effects of fluoride ion intake is concentration dependant, which has been set as 1.5 ppm in drinking water by World Health Organization (WHO) [10]. Available conventional method to quantitatively ascertain the concentration of fluoride in drinking water by lanthanum fluoride based membrane electrode is time consuming and requires skilful handling, since the electrode is quite fragile and expensive [11]. To overcome these obstacles, development of a simple and robust procedure for the fabrication of anion receptor is essential, which can detect analyte *via* naked eye and give semi quantitative information about safe/ unsafe fluoride levels. In view of this requirement, colorimetric receptors provide easy detection of analyte *via* naked eye under visible light [12].

A review of literature reveals the employment of molecules containing functional groups, urea/thiourea [13], secondary amide [14] and thiosemicarbazide [15] to effectively and selectively bind fluoride ion through the formation of hydrogen bond with N-H units of these groups. Covalent attachment of these molecules with appropriate signalling unit,

such as, nitrophenyl, azo dye etc. yields the complete receptor, which can convert anion-receptor binding event into either colour or fluorescence change as an output [16]. Heterocycles, which have recently been introduced as anion receptors, can act as both chromophore and binding units [17]. Interesting photophysical properties of heterocycles make them strong contenders for chromophoric unit and further, inbuilt acidic hydrogen bond donor groups (N-H) in several heterocyclic moieties can serve as binding sites for anions [18]. Amongst these heterocycles, imidazole N-H is acidic enough to act as an excellent hydrogen bond donor [19]. Moreover, acidity can be tailored by proper insertion of electron withdrawing substituents in the ring at critical positions and it can be annulated with another imidazole, benzene, anthraquinone, naphthalene and naphthalimide units for enhancing its NH acidity, rendering it fit to effectively bind fluoride ion by several research groups [20]. Recently, quinone-ferrocene systems bridged by imidazole moiety and quinone-imidazole system have been reported by Elango *et. al*., which exhibited naked eye response towards fluoride and cyanide ions in aqueous media at neutral pH [21]. Although an appreciable number of receptors are known for fluoride ion detection, their applicability to real life applications is restricted to very few since most of them are urea/thiourea based, which exhibit multi-anion sensitivity and lack selectivity [22]. Further, there exists a challenge to develop receptor for detecting fluoride ion in competitive media, owing to its high hydration enthalpy (-505 KJ/mol) [23].

Taking into perpective all this scenario [24], it was envisaged that the introduction of electron withdrawing nitro group at 5^{th} position of indole ring could fine-tune the binding

property of imidazole moiety and serve as selective naked eye receptor for fluoride ion sensing. To the best of our knowledge, this system has not been documented earlier.

RESULTS AND DISCUSSION

Compounds **RA-RE** have been synthesized by environment friendly protocol (**Scheme 1**). 1,2-bis(indolyl)-ethane-1,2-dione derivatives **(3a-c)** were prepared in stepwise reaction of appropriately substituted indole **(1a-c)** and oxalyl chloride in dichloroethane to give compound **2a-c**, which on further treatment with indole derivatives in presence of aluminium chloride afforded compounds **3a-c**. Compounds **3a-c** are irradiated with formyl indole derivatives **(4a-c)** and ammonium acetate in polyethylene glycol (PEG 400) at 300 W and 180^{o} C in microwave to yield desired final product **RA-RE** in good yields. Compared with the traditional method, this protocol offers several advantages like excellent yields, shorter reaction times, minimal environmental effects and clean reaction. Reaction proceeds without the addition of acid or base catalyst.

All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, FTIR and mass spectroscopy. FTIR of receptors **RA-RD** show characteristic broad absorption band due to N-H stretching of imidazolium N-H and indolic N-H in the region 3417-3313 cm^{-1} and 3185-3055 cm^{-1} respectively. Receptor **RE** shows absorption band at 3375 cm^{-1} due to N-H stretching of only imidazole N-H. A broad peak from 2978-2914 cm^{-1} is assigned to aromatic C-H vibration. Absorption band from 1644-1618 cm^{-1} and 1328-1208 cm^{-1} have been assigned to C=C and C-N streching vibrations. Two bands in the region 1550-1515 cm^{-1} and 1390-1350 cm^{-1} are observed due to N-O stretching in nitro group(s)

present in receptors **RB-RE**. ^{1}H NMR spectra of receptors, **RA-RD** exhibit characteristic sharp singlets due to imidazolium N-H and indole N-H in the region δ 12.10-12.55 and δ 9.7-9.81 ppm, respectively. Receptor **RE** displays a sharp singlet at δ 12.15 ppm due to imidazolium N-H. A multiplet from δ 7.11-8.28 ppm is observed for aromatic protons. Peaks at m/z 414, 549, 459, 504 and 849 $[M+H]^+$ in the mass spectra of **RA-RE**, also confirm the formation of products.

Colorimetric Sensing, Interference Studies And UV-Visible Titration Experiment

The anion recognition proficiencies of receptors **RA-RE** (10^{-4} M in DMSO) were vigilantly probed by naked eye, UV-visible and NMR spectroscopic techniques using different anions as their tetrabutylammonium salts (TBA) *viz.*, fluoride, acetate, chloride, bromide, iodide, dihydrogen phosphate, hydrogen sulphate and nitrate in competitive media, 9:1 DMSO-water. Receptors **RA-RC** were found insensitive to the addition of anions and no change in colour was noticed in their solutions, even at high concentration (10^{-3} M) of anions (TBA salts). On the other hand, an instant and distinctive colour change from yellow to orange was observed on addition of TBA salt of fluoride ion into receptor **RD** (10^{-4} M in DMSO) (**Fig 1(a)).** It is worthy to mention that detection limit for fluoride ion detection is found to be 1.5 ppm, which is regarded as the maximum permissible limit for fluoride in drinking water. Other anions, when were added to receptor individually, they did not show any colour change **(Fig. 1(a))**. However, when 1 equivalent of fluoride ion (TBA salt) was added to these solutions, an instantaneous change in colour was noticed in receptor **RD** (10^{-4} M in DMSO) **(Fig. 1(b))**, similar to colour change induced by fluoride ion alone. It establishes that receptor **RD** can

selectively bind fluoride ion irrespective of the presence of other anions. Another receptor **RE** was found to give similar qualitative colour change with fluoride ion as receptor **RD**. In order to enhance the binding affinity and selectivity, electron withdrawing nitro group(s) was introduced at 5^{th} position of indole rings in molecular framework of receptors and it was observed that receptors **RD** and **RE** gave promising results in terms of naked eye change in presence of fluoride ion (TBA salt).

Further investigation on anion affinity studies of receptor **RD** is performed using UV-visible spectrophotometer to corroborate the initial qualitative studies. Receptor **RD** reveals a maxima at 330 nm in UV-visible spectra. Different anions, acetate, chloride, bromide, iodide, dihydrogen phosphate, hydrogen sulphate and nitrate (TBA salts), when added into the solution of receptor **RD** in DMSO, produces no change in spectrum of receptor **(Fig. 2)**. On the other hand, when fluoride is added, peak at 330 nm disappears and a new peak at 410 nm appears. The red shift of 80 nm establishes that the binding event takes place between fluoride ion and receptor. The results obtained establishes the selective and sensitive nature of receptor for fluoride spectroscopically. To ascertain the receptor-fluoride ion interaction, UV-visible titration experiment was carried out with incremental addition of fluoride to receptor solution. On titration with fluoride from 10^{-5} M to 10^{-3} M, peak at 330 nm decreases and absorbance of new peak at 410 nm increases **(Fig. 3)**. From the results obtained, the formation of hydrogen bonding interaction between fluoride ion and receptor is expected to be responsible for the large bathochromic shift in the maxima of receptor [25]. However, more information on the binding process can be obtained by ^{1}H NMR titration only.

Determination of binding constant

Continuous variation method is employed for the determination of stoichiometric ratio of the complex formed between fluoride ion and receptor **RD**, where the concentration of both receptor and fluoride ion salt are kept constant (10^{-4} M in DMSO). The molar fraction of fluoride/ (receptor + fluoride) is continuously varied. At the molar fraction of 0.50, the absorbance reaches its maxima, revealing that receptor forms 1:1 complex with fluoride ion **(Fig. 4)**. 1:1 Stoichiometry was also proved by mass spectra of receptor **RD** with fluoride ion (TBA salt), which exhibited a peak at m/z 568.0351 [Receptor **RD** + F^- +H^+] **(Fig. 5). Figure 6** depicts the change in absorbance at wavelength 410 nm upon gradual addition of fluoride ion (10^{-5} to 10^{-3} M) into receptor RD solution (10^{-4} M in DMSO).

The binding constant of receptor **RD** with fluoride is evaluated by Benesi Hildbrand equation [26]

$1/A\text{-}Amin = 1/(\Delta Amax + (1/K[F^-])(1/\Delta Amax)$.

Here, $\Delta Amax = Amax - Amin$, where, Amin, A, Amax are the absorptions of receptor **RD** considered in the absence of F^-, at an intermediate, and at a concentration of complete concentration. K is binding constant, $[F^-]$ is concentration of F^-. From the plot of $1/ (A-Amin)$ against $[F^-]$ for receptor **RD**, the value of K (+10%) was calculated from the ratio of intercept/slope. Binding constant K, calculated from the graph **(Fig. 7)** is found to be $0.15 \times 10^4\ M^{-1}$.

^{1}H NMR Titration Experiment

The foregoing result of UV-visible spectroscopic titration indicates towards the formation of binding interaction between receptor **RD** and fluoride ion. In order to affirm the mechanism of sensing event, ^{1}H NMR titration is carried out. Receptor **RD** solution is prepared in DMSO-d_6 (10^{-2} M) and fluoride ion in the form of its TBA salt of varying concentrations (2.5, 5, 7.5 and 10 equivalents) has been added sequentially **(Fig. 8)**. It is observed in the ^{1}H NMR spectra of receptor **RD**, the sharp singlet at δ 12.2 ppm, corresponding to imidazole N-H, shows a downfield shift upon addition of fluoride ion and intensity of peak decreases as the concentration of fluoride ion increases, which disappears altogether, when fluoride concentration reaches 10 equivalents. Indole N-H at δ 9.8 ppm remains unchanged during titration. It is evident that interaction between receptor and fluoride ion initiates by hydrogen bonding, as depicted by downfield shift of imidazolium N-H proton in initial stage. Later, excess addition of fluoride ion triggers the deprotonation process, witnessed by the disappearance of N-H peak and appearance of peak corresponding to HF_2^- ion at 16.1 ppm [27]

Further evidence is provided by the synthesis of compound **RE**, where three indole NH are protected by di-tert-butyl dicarbonate (Boc). It exhibits naked eye colour change from yellow to orange in presence of fluoride ion similar to receptor **RD**, which proves that three indole NH are not involved in binding process.

On the basis of above studies, the plausible mechanism of binding between **RD** and fluoride ion is depicted in **Scheme 2.**

The plethora of anion binding studies conducted has shown that the introduction of nitro group at the 5th position of the indole ring enhances the binding ability of receptor **RD** (10^{-4} M in DMSO) towards fluoride ion (1.5 ppm)**.** Further, it gave a visible colour change from yellow to orange upon addition of fluoride ion into the solution of receptor **RD** in DMSO. This phenomenon may be explained by the fact that nitro groups are electron withdrawing in nature and their insertion onto the molecular framework of receptor **RD** increased the acidity of imidazole N-H, which can establish hydrogen binding interactions with highly basic fluoride ion. This event was followed by deprotonation of N-H, which was evident in ^{1}H NMR titration, where a new peak at 16.1 ppm appeared due to HF_2^- ion. Deprotonation triggers an extended conjugation or π-delocalisation and alters the dipole associated to the charge-transfer transition or in other words, stabilizes the excited state of chromophoric group [28]. This ultimately is observed as a vivid colour change as output. Similar findings have been documented by other research groups too [6, 29].

Ph Effect On RD-F$^-$ Interaction

To investigate the effect of pH on receptor RD-F$^-$ binding affinity, changes in the intensity of the absorbance band at 410 nm were observed over a pH range 2-12 **(Fig. 9).** The working pH range was found to be 6.5-8.0, where the intensity of absorbance remains constant. Below pH 6.5, intensity of absorbance band at 410 nm decreased rapidly. This is probably due to protonation of fluoride ion, to form weakly ionized hydrofluoric acid, which decreases the affinity of fluoride ion to bind receptor binding site, N-H. Above pH 8.0, intensity of this absorption band increased, which can be

attributed to increased availability of deprotonated fluoride ion to establish stronger hydrogen binding interactions with receptor's binding site, N-H.

CONCLUSIONS

Structurally simple and easy to synthesize imidazole-indole based receptor **RD** has been synthesized for easy and robust detection of inorganic fluoride in 9:1 DMSO-water. It senses fluoride at 1.5 ppm with colour change from yellow to orange, perceivable by naked eye. Detection of fluoride in aqueous media makes the receptor suitable for practical applications.

EXPERIMENTAL

All chemicals were purchased from Sigma Aldrich, TCI and Spectrochem Chemicals, India and were used without further purification. Starting substrates, 3-formylindoles were prepared by following literature [30].

Melting points were determined in open glass capillaries and are reported uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Jeol ECS 400 MHz spectrophotometer 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). FTIR spectra were recorded on a Perkin Elmer Spectrum Two spectrophotometer using pressed KBr discs in the region of 400 – 4000 cm^{-1}. Mass spectra were recorded on a Xevo G2-S Q-Tof spectrometer (Waters, USA), capable of recording high-resolution mass spectrum (HRMS) in the ESI (Electrospray

Ionization) modes. CEM discover mono mode microwave reactor with magnetron frequency of 2455 MHz was used for microwave reaction. Ultrasonication synthesis was performed using Elma S 70 H Ultrasonicator with 37 KHz output frequency. UV-visible spectra was recorded on a Perkin Elmer Lambda 750 UV-Vis NIR spectrophotometer in standard 3.5 mL quartz cells with 10 mm path length. The purity of all compounds was checked by TLC using silica gel as adsorbent and solvents of increasing polarity as mobile phase.

Synthesis Of Receptors 3-[2,5-{(Un)Substituted-1H-Indol-3-Yl}-1H-Imidazol-4-Yl]-(Un)Substituted-1H-Indole (RA-RE)

A mixture of 1,2-bis(substituted-indolyl)-ethane-1,2-dione (3a-c) (1mmol), indole aldehyde (4a-c) (1mmol) and ammonium acetate (4 mmol) in polyethylene glycol (2 ml) was irradiated at 180 $^{\circ}$C and 350 W power for 8-10 minutes. The progress of reaction was monitored by thin film chromatography 4:1 (ethyl acetate: methanol). The reaction mixture was cooled to room temperature and poured on 100 ml ice water. The separated solid was filtered and washed with water to yield brown solid as desired title product.

3-[2,5-(1H-indol-3-yl)-1H-imidazol-4-yl]-1H-indole (**RA**): Brown solid, yield: 89.10 %, m.p.: 164 ^{o}C. FTIR (KBr, υ cm^{-1}): 3406 (Imidazole N-H), 3170 (Indole N-H), 2924 (=C-H), 1644 (C=C), 1234 (C-N). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ (ppm) 7.38-7.94 (m, 15H, Ar-H), 9.23 (s, 3H, indole N-H), 12.10 (s, 1H, imidazole N-H). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 104.48, 105.55, 112.35, 117.811, 129.80, 133.46, 142.06, 147.98. MS (ESI) m/z: 414.1884 $[M+H]^{+}$ Calculated for $C_{27}H_{19}N_5$: 413.1840.

SUPPLEMENTARY MATERIAL

Experimental details and ^{1}H NMR, ^{13}C NMR and mass spectral data for this article can be accessed on the publisher's website.

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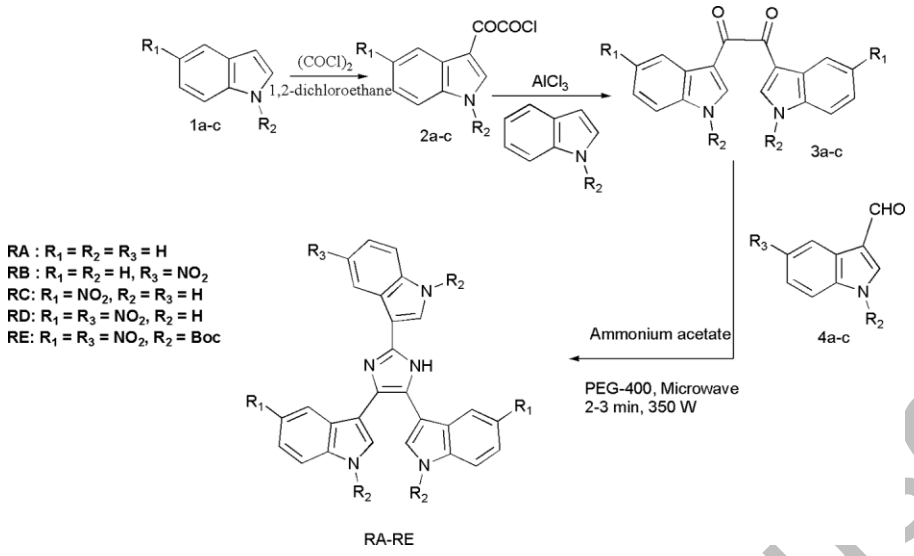
Scheme 1.



Scheme 2.

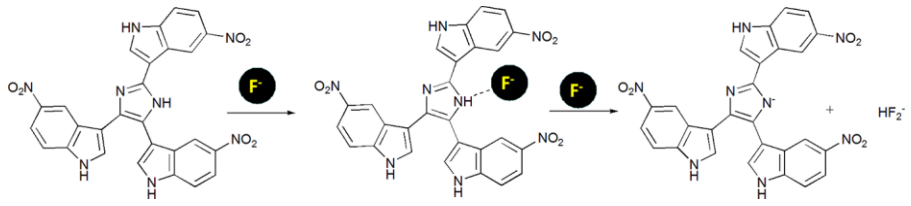


Figure 1. (a) Colour changes in the receptor RD (10-4 M in DMSO), in presence of 1equivalent of different anions (TBA salts) in 9:1 DMSO-water, where A, B, C, D, E, F and G represent F-, Cl-, Br-, I-, CH3COO-, H2PO4-, HSO4- and NO3- ions, respectively. (b) Colour changes in the receptor RD (10-4 M in DMSO), in presence of 1equivalent each of fluoride and different anions (TBA salts) in 9:1 DMSO-water, where A, B, C, D, E, F, G and H are receptor and, F- + Cl-, F- + Br-, F- + I-, F- + CH3COO-, F- + H2PO4-, F- + HSO4- and F- + NO3-, respectively

Figure 2. UV-visible spectra of receptor RD (10-4 M in DMSO) upon addition of different anions (TBA salts, 10-4 M) in 9:1 DMSO-water

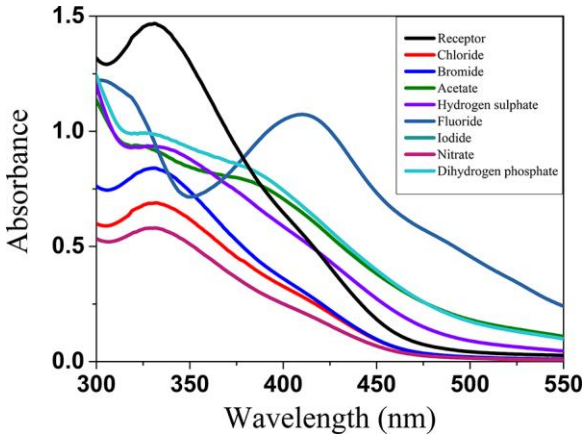


Figure 3. UV-visible spectra of receptor RD (10-4 M in DMSO) upon addition from 0.1 to 10 equivalents of fluoride ion (TBA salt) in 9:1 DMSO-water

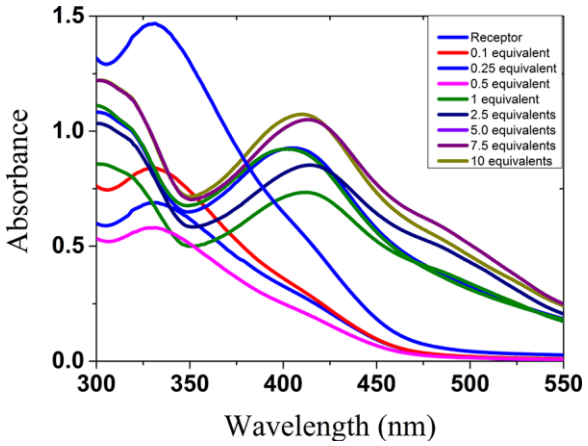


Figure 4. Jobs Plot with receptor RD (10-4 M in DMSO) and fluoride ion (TBA salt) 10-4 in 9:1 DMSO-water

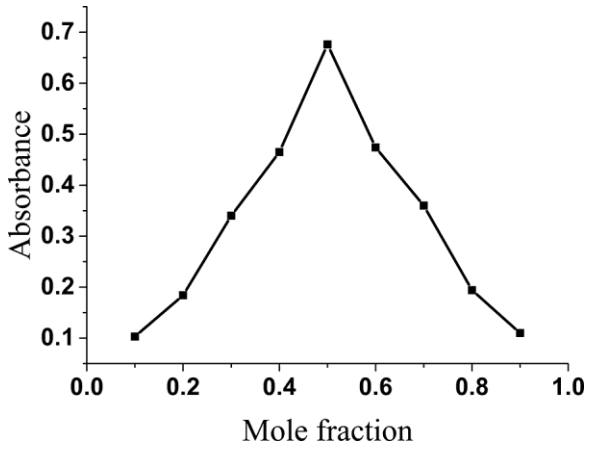


Figure 5. ESI-mass spectrum of complex of fluoride ion and receptor RD

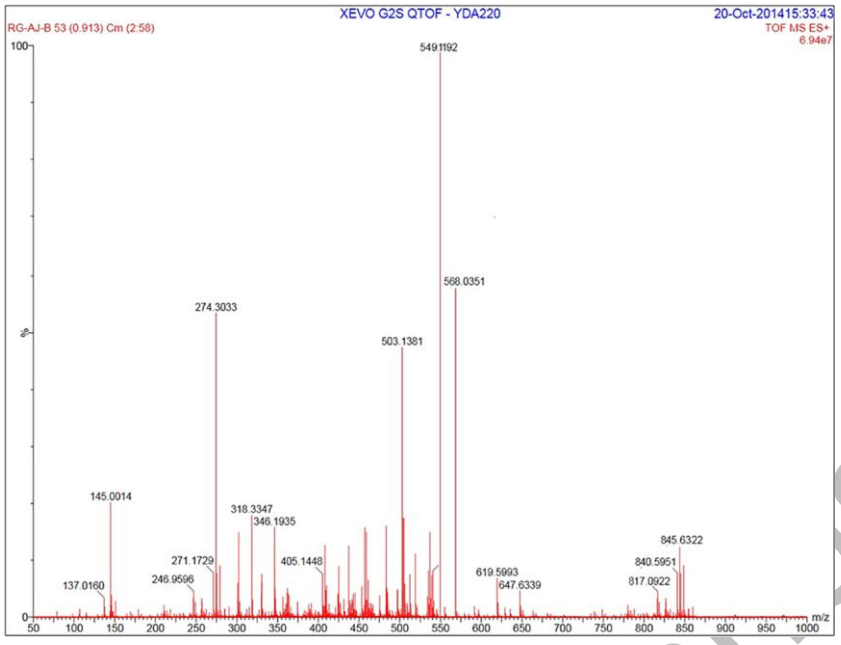


Figure 6. Changes in absorbance at 410 nm of receptor RD (10-4 M in DMSO) with increase in fluoride ion concentration (10-5 to 10-3 M in 9:1 DMSO-water)

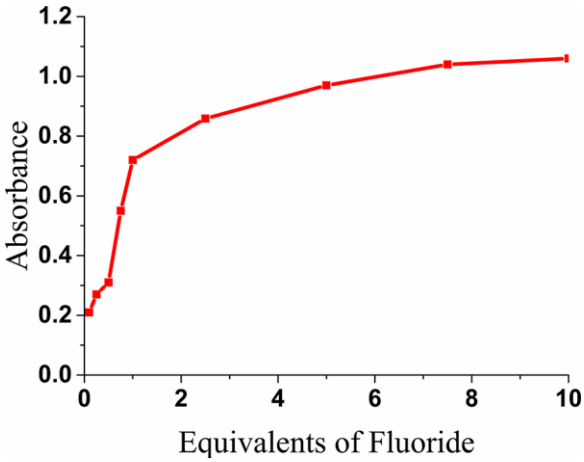


Figure 7. Fitting curve of Benesi Hildbrand equation

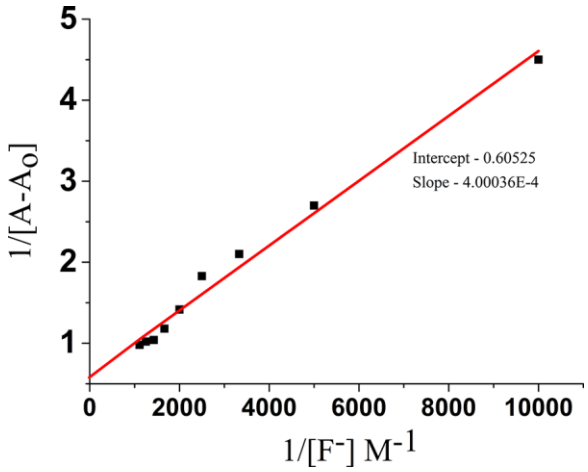


Figure 8. Partial 1H NMR (400 MHz) spectra of receptor RD in DMSO-d6 (10-2 M) in the presence of (a) 2.5, (b) 5, (c) 7.5 and (d) 10 equivalents of TBAF in DMSO-d6

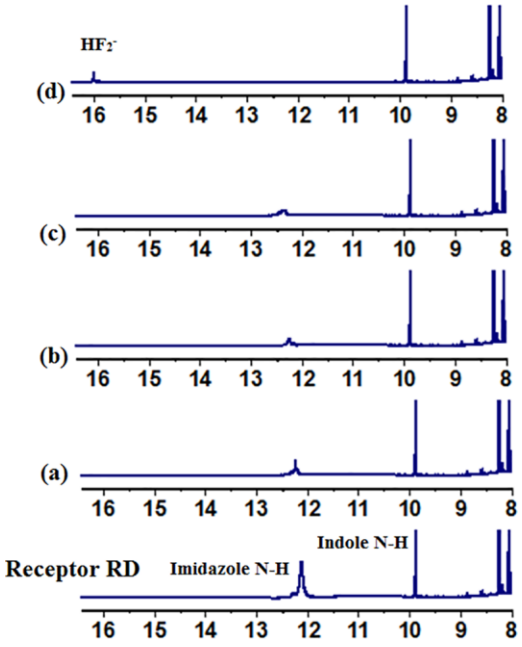


Figure 9. Changes in absorbance of receptor RD (10-4 M in DMSO) and fluoride ion (10-4 M in 9:1 DMSO-water) with varying pH (2-12)