

# New Synthetic Receptors for Molecular Recognition of Anions and Their Practical Applications

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## Anion receptors

Fluoride is beneficial to human health in small quantities; it plays vital roles in preventing dental decay and in treating osteoporosis. In contrast, excess fluoride consumption can cause dental fluorosis or mottled enamel and skeletal fluorosis, a bone disease that is a major problem in India. It has been reported that an excess of fluoride can cause the inhibition of over 100 different enzyme systems. Acute fluoride exposure can cause collagen breakdown, decreased thyroid activity, bone cancer, immune-system disturbance, and anaemia. Recently, fluoride has also been suspected of playing a role in terminal diseases, including those that arise due to damage in the hippocampal area of brain. Despite this knowledge, introduction of fluoride to the environment by excessive usage of fertilizers and industrial wastes continues. Given the balance between positive and negative effects of fluoride, its detection has attained significance.

In addition, the detection of organic anions, such as carboxylate, is also of interest as these play vital roles in numerous metabolic processes, such as the glyoxalate cycle, generation of high-energy phosphate bonds, and in the dicarboxylate cycle for autotrophic carbon dioxide fixation. Among the widespread organic anions, the discrimination of geometric isomeric dicarboxylates, such as *cis/trans* isomers (maleate and fumarate ions), has acquired significance because of the different biological behaviours of these isomers. For example, fumarate is produced during the Krebs cycle, whereas maleate is an inhibitor of the Krebs cycle. Owing to the similar physical and chemical properties, it is difficult to discriminate between isomeric dicarboxylates by using conventional analytical methods. While the discrimination of these geometrical isomeric dicarboxylates has previously been achieved by using a colorimetric/fluorometric detection approach, the receptors employed are complicated organic molecules that require skilled processes and difficult synthetic procedures. Therefore, the development of new 'easy-to-synthesis' receptors for the discrimination of geometrical isomers, such as maleate and fumarate, remains a challenging task that needs to be addressed.


In general, anion receptors are the molecules that can recognize or sense the anions. While instrumental methods, such as anion monitor probes, are available for the detection of anions, they are time consuming and require skilled efforts to operate. In contrast, colorimetric methods of detection are widely employed due to their low cost, instantaneous results, easy/safe to handle format, and their selectivity and sensitivity, which is typically equal to that of instrumental methods. Therefore, designing novel synthetic receptors for the colorimetric detection of anions has attracted considerable attention in the last two decades, and as a result, colorimetric anion receptor chemistry has been studied extensively.


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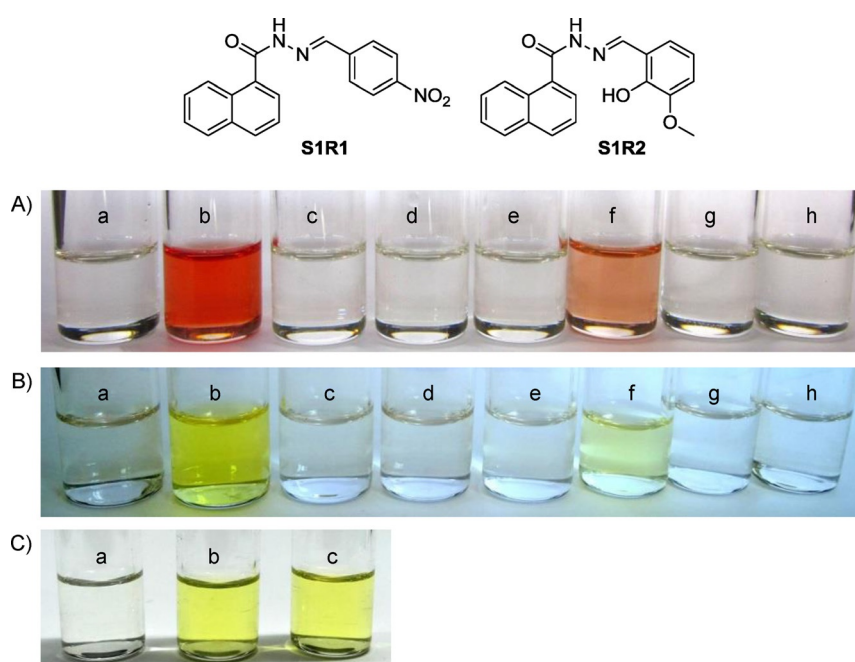
 The full thesis is available as Supporting Information on the WWW under <http://dx.doi.org/10.1002/open.201500119>.

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## Schiff bases as fluoride ion receptors

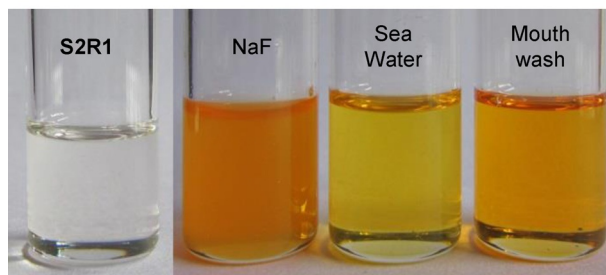
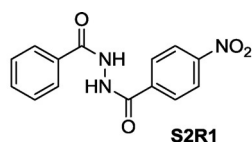
A receptor based on the Schiff base 1-naphthohydrazide was synthesised for the selective detection of fluoride ions. (*E*)-*N'*-(4-Nitrobenzylidene)-1-naphthohydrazide (**S1R1**) was found to be selective towards fluoride ions over other anions in organic media (Figure 1A). The presence of a carbonyl group in the receptor makes the proton of the binding site more acidic, and therefore, the receptor can become deprotonate with addition of a basic anion such as fluoride, giving rise to an observable colour change. The mechanism involved in the colour change was determined to be deprotonation of acidic proton followed by stabilization of the complex through an intramolecular charge-transfer (ICT) transition, as evidenced by the formation of an HF<sub>2</sub> peak in <sup>1</sup>H NMR titration. However, the acidic proton is easily solvated even with trace amounts of water, and because of this, **S1R1** is unable to detect fluoride in organo-aqueous media. An alternative receptor, (*E*)-*N'*-(2-hydroxy-3-methoxybenzylidene)-1-naphthohydrazide (**S1R2**) with a hydroxy functionality containing a highly base-labile hydroxy group, was synthesised that detects basic fluoride ions via a deprotonation mechanism, not only in organic solutions (Figure 1B) but also in organo-aqueous media (Figure 1C). In organo-aqueous solution, addition of the basic fluoride ion leads to deprotonation of base-labile hydroxy proton, giving rise to a colour change that allows colorimetric detection.



**Figure 1.** Change in colour of A) **S1R1** and B) **S1R2**: a) free receptor, b) F<sup>-</sup>, c) Cl<sup>-</sup>, d) Br<sup>-</sup>, e) I<sup>-</sup>, f) AcO<sup>-</sup>, g) HSO<sub>4</sub><sup>-</sup> and h) H<sub>2</sub>PO<sub>4</sub><sup>-</sup> ions; C) Colour change of **S1R2** in MeCN/H<sub>2</sub>O (9:1) after adding F<sup>-</sup> ions: a) free receptor, b) **S1R2** + NaF (3 equiv) and c) **S1R2** + TBAF (3 equiv). Reproduced with permission from Ref. [3]. Copyright © 2014 Elsevier B.V.

## Detection of inorganic fluoride ion in aqueous media

New receptors were designed and synthesized for the colorimetric detection of fluoride ion based on the benzohydrazide scaffold. *N'*-Benzoyl-4-nitrobenzohydrazide (**S2R1**) was found to be highly selective towards fluoride ion over other anions. This receptor was able to detect inorganic fluoride, such as NaF, in aqueous solution (Figure 2). The presence of two carbonyl groups in the receptor makes the NH proton highly acidic; therefore, these receptors are capable of competing with water molecules to bind fluoride ions. In the presence of NaF, **S2R1** in aqueous solutions underwent a significant colour change from colourless to yellow with  $\Delta\lambda_{\text{max}}$  of 149 nm. The mechanism involved in the colour change was determined to be deprotonation, formation of imidic acid intermediate, followed by stabilization of complex through ICT. This was confirmed by <sup>1</sup>H NMR titrations, where the formation of the imidic acid tautomer was observed. In addition, **S2R1** successfully detected fluoride ions in sea water and commercially available mouth wash (Figure 2), and the amount of fluoride present in the samples could be quantified using UV/vis spectroscopy.



**Figure 2.** Change in colour of **S2R1** upon addition of NaF (3 equiv), seawater and commercial mouthwash in aqueous media.

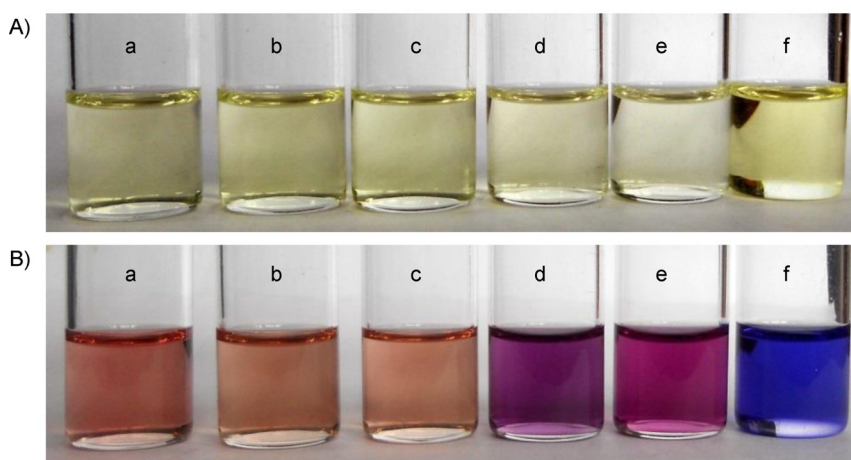
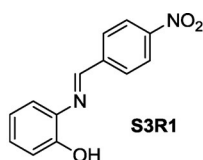
### Solvatochromic fluoride ion receptor and its molecular switch application

(*E*)-2-[(4-Nitrobenzylidene)amino]phenol (**S3R1**) was designed and synthesised for colorimetric detection of fluoride ions. In DMSO, the colour of the **S3R1** solution changed from pale yellow to blue upon addition fluoride ions. Furthermore, this receptor showed unique solvatochromic properties, displaying different colouration in different solvents only when fluoride ions were present due to the introduction of charge separation in the receptor (Figure 3).

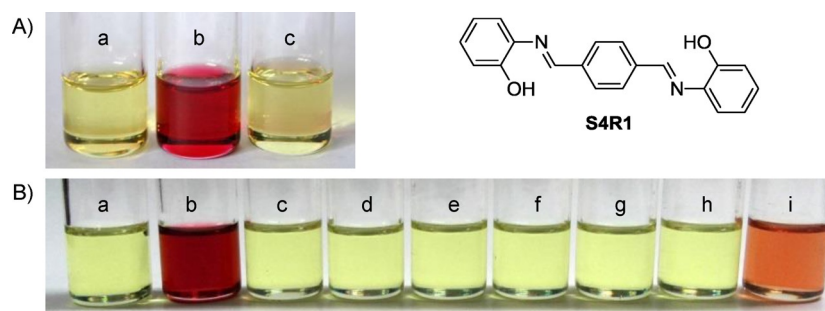
This property was applied to determine the percentage composition of binary solvent mixtures. **S3R1** was able to detect  $\text{Cu}^{2+}$  ions colorimetrically, where it exhibited a colour change from pale yellow to orange–red. Using this dual detection property, the receptor was subjected to molecular logic-gate applications wherein it showed on–off switching operations where the receptor gave output signals corresponding to the INHIBIT circuit with input signals.

### Colorimetric discrimination of isomeric dicarboxylate anions

A series of new receptors were synthesised to demonstrate geometrical isomeric discrimination of dicarboxylate anions, in particular, maleate and fumarate ions. Among these receptors, 2,2'-(1*E*,1'*E*)-[1,4-



**Figure 3.** Solvatochromism in **S3R1** in different solvents upon adding  $\text{F}^-$  ions. A) **S3R1** alone and B) **S3R1** +  $\text{F}^-$  ions (2 equiv): a) 1,4-dioxane, b) THF, c)  $\text{CH}_2\text{Cl}_2$ , d) acetone, e) MeCN and f) DMSO.



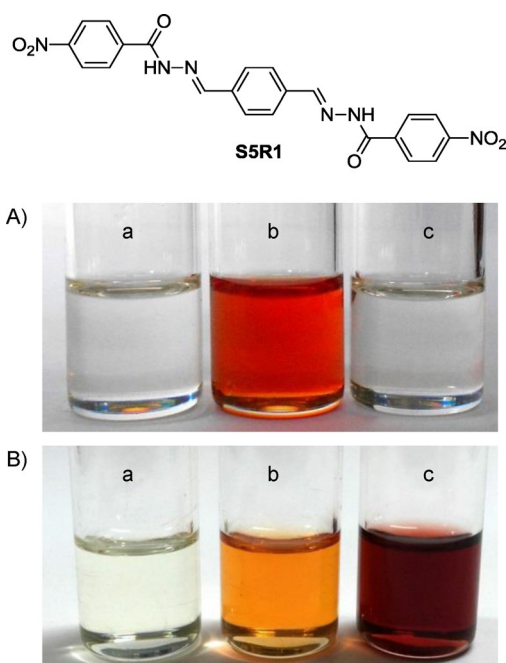
**Figure 4.** Change in colour of **S4R1** upon addition of A) dicarboxylates: a) free receptor, b) **S4R1** + maleate and c) **S4R1** + fumarate; and B) other anions: a) free receptor, b)  $F^-$ , c)  $Cl^-$ , d)  $Br^-$ , e)  $I^-$ , f)  $NO_3^-$ , g)  $HSO_4^-$ , h)  $H_2PO_4^-$  and i)  $AcO^-$ .

phenylenebis(methanylylidene))bis(azanylylidene))diphenol (**S4R1**) exhibited a prominent colour change from pale yellow to reddish pink only with the addition of maleate ions (Figure 4A). The colour change arises due to a bathochromic shift of 133 nm in the UV-vis spectrum. This shift occurs because of the formation of a charge-transfer complex between the receptors and maleate ion. The maleate ion binds to the receptor through hydrogen bonding, as confirmed by  $^1H$  NMR titrations. The selectivity of the receptors for the maleate ion and the notable colour change can be correlated with the change in receptor orientation upon binding with the maleate ion. In addition, these receptors were shown to detect fluoride ions in a colorimetric manner by a colour change from pale yellow to blood red (Figure 4B). This colorimetric detection was made possible by the intermolecular proton-transfer interaction, established between the phenolic oxygen and the fluoride ions, which further lead to intramolecular charge transfer between maleate ions and the receptors.

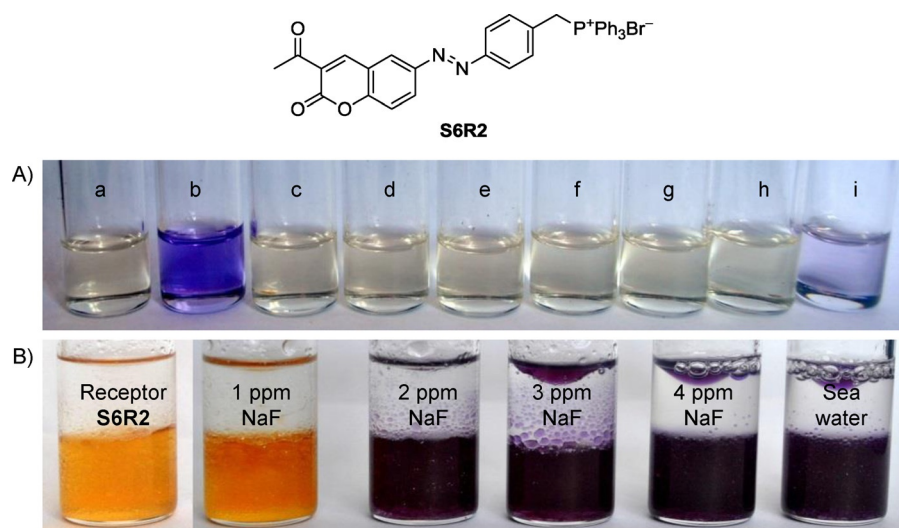
#### Discrimination of maleate over fumarate and ratiometric fluoride ion detection

(*N',N''E,N',N''E*)-*N',N''*-[1,4-Phenylenebis(methanylylidene))bis(4-nitrobenzohydrazide) (**S5R1**) was synthesised for the colorimetric discrimination of maleate over fumarate ions. **S5R1**, with a benzohydrazide functional group as a binding site, exhibited a significant colour change from colourless to orange–red only in the presence of maleate ions, whereas **S5R1** in the presence of fumarate ions failed to exhibit any colour change (Figure 5A). The colour change arises due to the formation of an intermolecular hydrogen-bond complex between the maleate ion and the receptor, as confirmed by  $^1H$  NMR titrations. In contrast, a receptor that does not contain carbonyl groups has restricted flexibility and steric hindrance, and therefore does not show any response either with maleate ions or with fumarate ions.

**S5R1** was examined for colorimetric detection of fluoride ions wherein the change in colour was observed along with the concentration of fluoride ions. **S5R1** displayed a colour change from colourless to orange upon adding one equivalent of fluoride ions. Further, at higher concentrations of fluoride ions, the orange colour transformed to blood red (Figure 5B). This ob-



**Figure 5.** A) Change in colour of **S5R1** upon addition of dicarboxylates: a) free receptor, b) maleate and c) fumarate. B) Colour change of **S5R1** upon addition of  $F^-$  ions: a) free receptor, b) **S5R1** +  $F^-$  (1 equiv) and c) **S5R1** +  $F^-$  (4 equiv).



**Figure 6.** A) Change in colour of **S6R2**: a) free receptor, b)  $F^-$ , c)  $Cl^-$ , d)  $Br^-$ , e)  $I^-$ , f)  $NO_3^-$ , g)  $HSO_4^-$ , h)  $H_2PO_4^-$  and i)  $AcO^-$ . B) Extraction process of  $F^-$  ions from aqueous solutions and sea water using a solution of **S6R2** in  $CH_2Cl_2$ . Reproduced with permission from Ref. [5]. Copyright © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

servation was attributed to the formation of a hydrogen-bonded complex at lower concentrations of the fluoride ions and at higher concentrations of the deprotonation of receptor.

#### Extraction of fluoride ions from sea water

New receptors with an active methylene group as the binding site were designed and synthesised for the selective detection of fluoride ions. ((*E*)-{4-[(3-Acetyl-2-oxo-2*H*-chromen-6-yl)diazenyl]benzyl}triphenylphosphonium bromide (**S6R2**) displayed a colour change from pale yellow to dark blue (Figure 6A) along with a significant bathochromic shift of 256 nm upon addition of fluoride ions. The colour change and bathochromic shift are caused by charge-transfer transitions. The receptors showed very good sensitivity by displaying colour change even in the presence of 0.2 ppm fluoride ions in organic media. In addition, these receptors were able to extract the fluoride ions from aqueous media to organic solutions, which resulted in a colour change. The practical application of these receptors was evaluated by extracting fluoride ions from sea water. Though **S6R1** failed to extract fluoride ions from sea water, **S6R2** extracted fluoride ions from sea water with 99% efficiency (Figure 6B). In addition, **S6R2** was able to quantify the amount of fluoride ions present in the sea water, and the level was found to be 1.4 ppm, which is in good agreement with earlier reports.

**Keywords:** anion receptors · charge transfer · colorimetric detection · extraction · solvatochromism

#### Publications arising from this work:

- Madhuprasad, A. N. Shetty, D. R. Trivedi, *RSC Adv.* **2012**, 2, 10499–10504.
- Madhuprasad, N. Swathi, J. R. Manjunatha, U. K. Das, A. N. Shetty, D. R. Trivedi, *New J. Chem.* **2014**, 38, 1484–1492.
- M. Kigga, D. R. Trivedi, *J. Fluorine Chem.* **2014**, 160, 1–7.
- Madhuprasad, D. R. Trivedi, *Anal. Methods* **2014**, 6, 3817–3825.
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