Turn-on fluorescent probe designed for fluoride ion sensing in aqueous media

Arundhati Roy, Tanmoy Saha, Pinaki Talukdar

PII: S0040-4039(15)01105-3
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.06.086
Reference: TETL 46478

To appear in: *Tetrahedron Letters*

Received Date: 23 May 2015
Revised Date: 25 June 2015
Accepted Date: 26 June 2015

Please cite this article as: Roy, A., Saha, T., Talukdar, P., Turn-on fluorescent probe designed for fluoride ion sensing in aqueous media, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.06.086

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Turn-on Fluorescent Probe Designed for Fluoride Ion Sensing in Aqueous Media

Arundhati Roy[a], Tanmoy Saha[a] and Pinaki Talukdar[*a]

[a] *Department of Chemistry, Dmitri Mendeleev Block, Indian Institute of Science Education and Research, Pune, 411008, India*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Fluoride sensing
Aqueous condition
Off-on probe
Selectivity
Live cell imaging

ABSTRACT

A NBD-based probe for selective detection of fluoride ion in aqueous media is reported. The probe was designed by applying rules for water solubility and membrane permeability. The probe functions through the fluoride mediated cascade reaction which was studied by ^{1}H-NMR, HPLC analysis, UV-vis and fluorescence spectroscopy. The sensing process was marked by the by a color change from colorless to yellow, and an intriguing 120-fold turn-on green fluorescence. Application of the probe for selective detection of fluoride was demonstrated by live-cell imaging.

1. Introduction

Anions play indispensable roles in a wide range of biological and chemical processes.[1] Among biologically relevant anions, fluoride (F^-) is one of the most attractive targets because of its importance in health and environmental issues. It is used extensively in toothpaste, pharmaceutical agents and is added to drinking water owing to their role in prevention in dental caries. It is associated with nerve gases and the refinement of uranium used in nuclear weapon manufacture. But a large intake of fluoride can cause both acute and chronic toxicity in human body as it inhibits the biosynthesis of neurotransmitters in fetuses and can cause diseases such as osteoporosis, fluorosis, urolithiasis or even cancer.[2] As an essential element of human body, the U.S. Public Health Service affirmed the optimal level of consumed fluoride to be 1 mg per day. Considering the widespread use of fluoride in daily life and its implication in biological effects, it is very important to develop highly sensitive, selective molecular probe for detection of F^- ion in chemical as well as in biological systems.

The fluorescent analysis method has gained considerable attention owing to its high sensitivity, operational simplicity and *in vivo* imaging analysis both qualitatively as well as quantitatively.[3] In past decade, a large number of fluorescent probes for F^- sensing have been developed exploiting anion-π interaction,[4] hydrogen bonding,[5] Lewis acid-base interaction[2b,6] and fluoride induced chemical reaction.[7] Hydrogen bonding approach is not effective in aqueous solution owing to the strong tendency of hydration of fluoride ions. The boron-fluoride complexation approach is also not suitable for biological applications because of its instability and cytotoxicity. Moreover, Lewis acidic boron based receptors bind with fluoride ions covalently and cause fluorescence quenching due to intramolecular charge transfer between the boron p_π orbital and electrons from F^- ions.

Fluoride also has very high affinity towards silicon which has been exploited in the development of numerous fluorescent probes for selective detection of the ion. In these probes, F^- mediated desilylation of either alkyne silyl ether are reported to provide ratiometric,[7d,8] *on-off*[9] and *off-on*[10] fluorescence responses. Subsequently, silyl ether deprotection strategies were also applied for developing probes that release fluorophore via cascade reaction mechanisms.[7a,7d,11] Sensing activity either in pure organic solvent or in combined aqueous/organic media is a general concern of most desilylation based probes and probes functioning in aqueous media are rare. Till date, a coumarin based probe **1** by Kim *et. al.*[7e] and a 2-aryl benzothiazole based

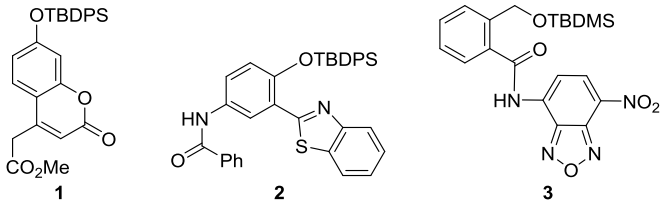
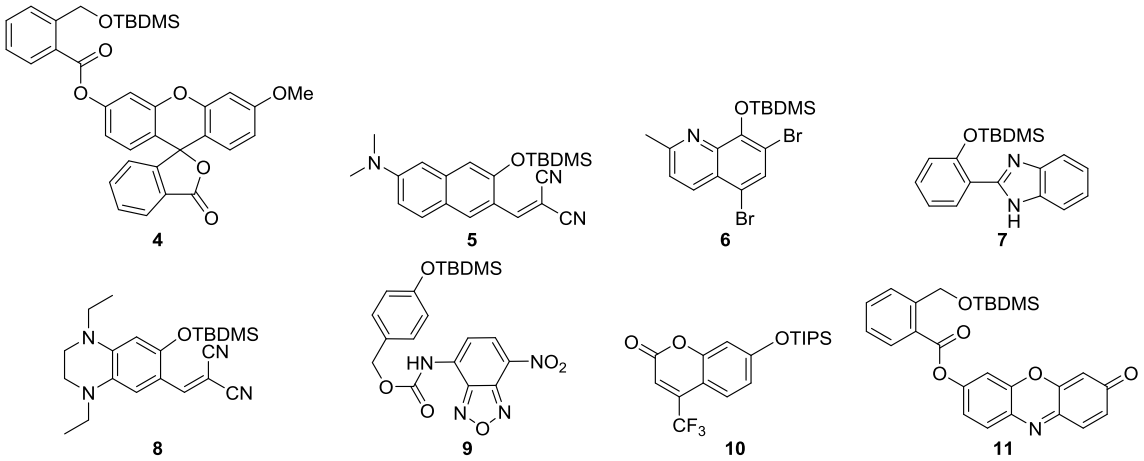


Figure 1. Structures of reported fluorescent F^- probes **1**-**2** working in aqueous media and proposed cascade reaction based probe **3** for sensing F^- ion in aqueous media.

∗ Corresponding author. Tel.: +91-20-25908098; fax: +91-20-25865315; e-mail: ptalukdar@iiserpune.ac.in

Table 1. Structures of desilylation based fluorescent F^- probes **1-11** and prediction of their solubility and membrane permeability properties.



Entry	Probe	clogS [a]	clogP [a]	Sensing media	Reference
1	**2**	-7.85	8.63	H_2O (2 mM CTAB)	12
2	**4**	-6.96	8.12	DMSO	11c
3	**5**	-6.32	5.56	HEPES buffer (10 mM in H_2O, pH 7.4) / CH_3CN (8:2)	7a
4	**6**	-6.09	6.44	THF	10
5	**7**	-5.70	5.52	DMF / H_2O (8:2)	13
6	**8**	-5.49	4.87	HEPES buffer (10 mM in H_2O, pH 7.4) / CH_3CN (7:3)	11b
7	**9**	-5.42	4.63	EtOH/H_2O (9:1)	11d
8	**1**	-5.13	5.17	HEPES buffer (10 mM in H_2O, pH 7.4)	7e
9	**10**	-4.87	4.75	CH_3CN	14
10	**11**	-4.60	5.15	THF/H_2O (95:5)	11e
11	**3**	-3.84	4.17	H_2O (0.5 mM CTAB)	Present work

[a] Values were estimated using *OSIRIS Property Explorer* program.

probe **2** by Rui Hu *et. al.*[12] were reported for sensing fluoride ion in aqueous media (Figure. 1).

Therefore a new endeavour was initiated to address the issue and to design a new probe working under aqueous conditions. Our recent studies on cascade reaction based fluorescent F^- probes[11c,11e] suggest faster response during sensing when compared to many reported probes.[7c-e] In the present study, we present the first desilylation mediated cascade reaction based probe **3**, rationally designed to sense F^- ion in aqueous media.

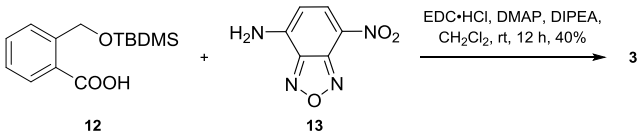
2. Addressing water solubility and membrane permeability

In drug discovery and development, solubility and membrane permeability[15] are two crucial parameters routinely addressed during the design of new molecules. A theoretical analysis of various drug molecules using *OSIRIS Property Explorer*[16] suggests that more than 80% of the drugs on the market have a clogS value greater than -4 (solubility measured in mol L^{-1}). Lipinski rule of five[17] is another important guideline to predict solubility and membrane permeability of a molecule. According to the rule, clogP value of a molecule determines its lipophilicity, and a value less than 5 is crucial for better membrane permeability. It is believed that inefficiency of major fluoride probes comes from the less solubility. Most of the fluoride sensing chemodosimeters is attached with hydrophobic silyl protecting group which leads to the less aqueous solubility. But the aqueous solubility of a probe is essential for its ability to react with a water soluble analyte. Hence, a perfect balance in lypophilicity is required in order to address water solubility for detecting water soluble analytes, and cell permeability to ensure the bio-applicable probe.

Therefore theoretical analysis were done for eleven different desilylation based fluorescent F^- probes **1-3** (Figure 1) and **4-11** (Table 1) to correlate their clogS and clogP values to the use of F^- ion sensing media. For these molecules clogS and clogP values were determined from the *OSIRIS Property Explorer* program (Table 1) and presented in the increasing order of clogS values. Surprisingly, for probe **2** which was reported to function in H_2O (2 mM CTAB) media, provided clogS and clogP values of -7.85 and 8.63, respectively. But for other molecules, the estimated order of clogS was **4** < **5** < **6** < **7** < **8** < **9** < **1** < **10** < **11** < **3**. For these molecules, clogP values were in the order **4** > **6** > **5** > **7** > **1** > **11** > **8** > **10** > 9 > **3**. For probe **1**, clogS = -5.13 and clogP = 5.17 values were good enough to correlate to HEPES buffer (10 mM in H_2O, pH 7.4) as the sensing media. For the new probe **3**, clogS = -3.84 and clogP = 4.17 were estimated. These values predict good water solubility and membrane permeability of the probe and therefore prophecy its activity in the aqueous media.

3. Results and Discussion

Encouraged by the noticeable prediction of clogS and clogP value for probe **3**, synthesis of the probe was carried out from acid **12** which was prepared by using reported protocol.[11c] Reaction of **12** with 4-amino-7-nitrobenzofurazan (NBD-NH_2) **13** under EDC•HCl/DMAP coupling conditions in the presence of DIPEA provided **3** with 40% yield (Scheme 1).



Scheme 1. Synthesis of probe **3**.

In order to prove the fluoride mediated cascade reaction mechanism, ^{1}H-NMR titration spectroscopic experiments were carried out. In these experiments, varied proportions (0, 200 and 400 equiv) of tetra-n-butylammonium fluoride (TBAF) were added to solutions of probe **3** in CD_3OD (4 mg in 0.7 mL). For pure probe **3**, characteristic aromatic proton signals at δ = 7.4,

7.5, 7.7, 8.6 and 8.7 ppm were observed in the ^{1}H-NMR spectrum (Figure 2, red trace). ^{1}H-NMR spectra of pure NBD-NH_2 **13** (Figure 2, pink trace) and phthalide **14** (Figure 2, brown trace) were also recorded. ^{1}H-NMR spectrum recorded after treating **3** with TBAF (200 equiv) in CD_3OD at room temperature for 10 minutes, indicated partial disappearance of signals corresponding to **3** and appearance of new signals corresponding to NBD-NH_2 **13** at δ = 6.4 and 8.4 ppm (Figure 2, green trace). Formation of phthalide **14** was also confirmed by appearance of signal at δ = 7.4, 7.6 and 7.8 ppm. ^{1}H-NMR spectrum recorded for the reaction mixture of **3** and TBAF (400 equiv) in CD_3OD indicated complete disappearance of signals corresponding to probe **3** and new sets of signals corresponding to **13** and **14** were present (Figure 2, blue trace). We also observed disappearance of TBDMS group and appearance of TBDMSi-F (Figure S17 and Figure S18).

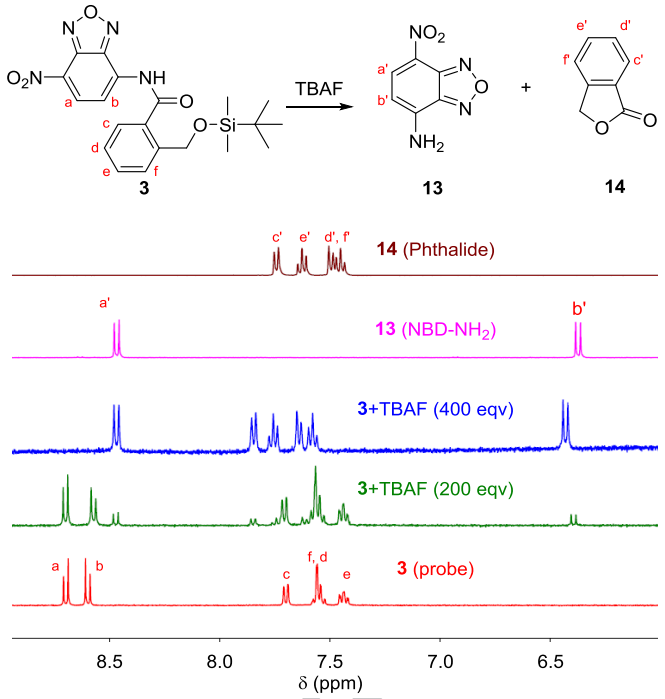


Figure 2. Zoom of ^{1}H-NMR spectra of probe **3** (4.0 mg) upon addition of TBAF (0 – 400 equiv) in CD_3OD (0.7 mL) at room temperature after 10 min. ^{1}H-NMR spectra of pure NBD-NH_2 **13** and phthalide **14** are also presented.

A further proof of the mechanism was provided from HPLC analysis. HPLC chromatograms recorded in the gradient method using acetonitrile and H_2O eluent (for details information see SI) displayed signal at t_R = 14.5, 13.5 and 37.0 min for pure NBD-NH_2 **13** (Figure 3, green trace), Phthalide **14** (Figure 3, pink trace) and **3** (Figure 3, black trace), respectively. Probe **3** (10 μM) was separately treated with 100 and 300 equiv of TBAF in MeOH at room temperature for 5 min. HPLC analysis of these samples confirmed consumption of **3** and formation of amine **13** and phthalide **14** (Figure 3, red and blue traces for 100 and 300 equiv, respectively). We have also carried out thin layer chromatographic (TLC) analysis of the reaction mixture. The reaction of **3** with TBAF clearly confirms the formation of **14** and **13** (Figure S7).

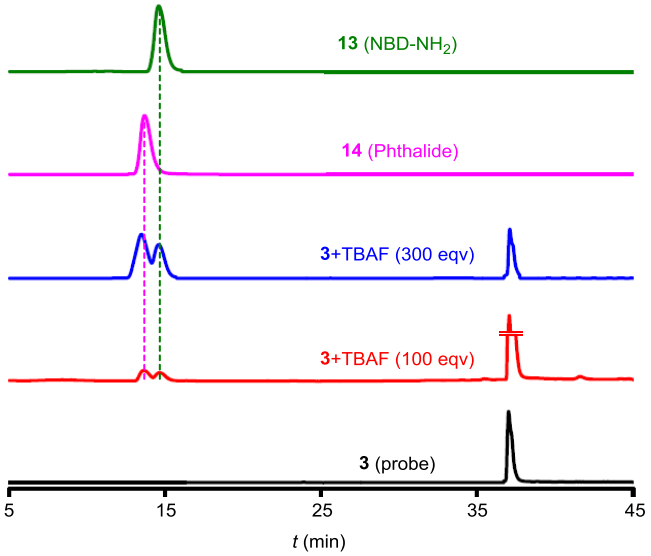


Figure 3. HPLC chromatograms of probe **3** (10 μM) upon reaction with TBAF (100 and 300 equiv) recorded in a gradient solvent system of CH_3CN and H_2O. Chromatograms of pure **3**, Phthalide **14** and NBD-NH_2 **13** are also presented.

The probe **3** was soluble in water and its photophysical properties were studied in the aqueous media (0.5 mM CTAB *i.e.* Cetrimonium bromide). Compound **3** displayed an absorption maxima centered at λ_{max} = 400 nm (Figure 4, black trace) with molar extinction coefficient, ε = 10120 M^{-1} cm^{-1}. On the other hand, NBD-NH_2 **13** displayed an absorption band with λ_{max} = 460 nm with ε = 18840 M^{-1} cm^{-1} (Figure. S3). When TBAF (15 mM) was added to the solution of the probe **3** (10 μM) and the reaction was monitored with time upto 60 min, decrease in absorbance at λ = 278 nm, 400 nm and a subsequent enhancement in absorbance at 460 nm were observed. Therefore, solubility and F^- sensing data of **3** in water corroborates to its estimated logS and clogP values.

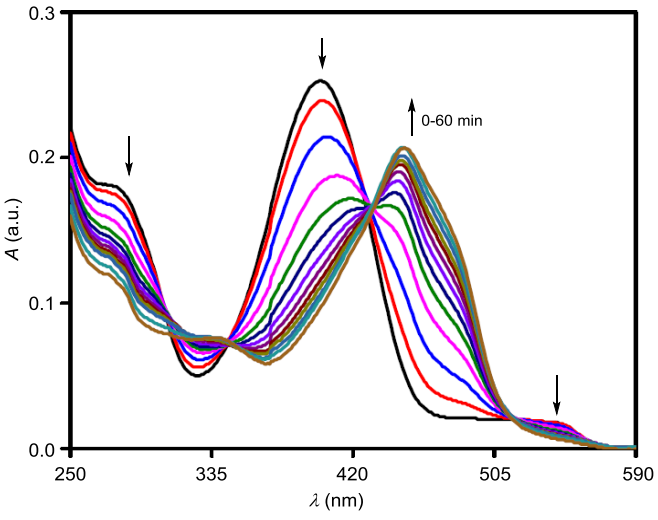


Figure 4. Changes of absorbance of probe **3** (10 μM) with time (0 – 60 min) towards TBAF (15 mM) in water (0.5 mM CTAB).

Based on the outcome from UV-visible studies, fluorescence spectroscopic experiments were carried out to demonstrate the fluoride sensing properties of **3** in aqueous media. At first, temporal response of the probe **3** towards fluoride ion was determined. Upon addition of TBAF (15 mM) to the **3** (10 μM) in

water (containing 0.5 mM CTAB), the fluorescence emission band centered at λ = 553 nm (λ_{ex} = 460 nm) displayed gradual enhancement in intensity and saturation complete reaction was observed within 60 min of addition (Figure 5A). A succeeding fluorescence kinetics experiment was carried out to determine the rate (k) of the reaction under pseudo first order conditions (Figure 5B). Monitoring of fluorescence intensity at λ = 553 nm (λ_{ex} = 460 nm), provided pseudo first order rate constant k = 0.0008268 s^{-1} and $t_{1/2}$ = 13.97 min. The response of the probe **3** (10 μM) towards TBAF (15 mM) was also determined in organic solvent, e.g. THF (Figure S5 and S6) at room temperature and a faster saturation (within 30 minutes) of fluorescence intensity was observed under these conditions.

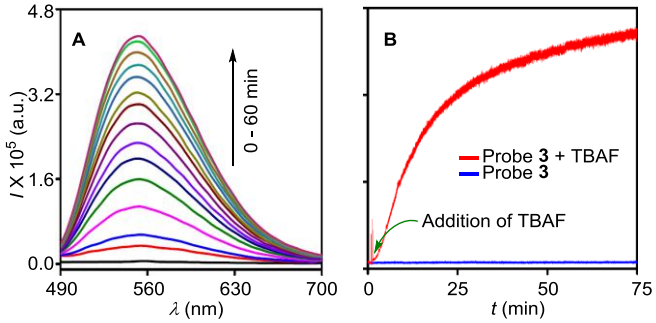


Figure 5. Fluorescence spectra (λ_{ex} = 460 nm) of probe **3** (10 μM) at 0 – 60 min upon addition of 0.5 mM TBAF (A). Fluorescence kinetics profile of probe **3** (10 μM) at λ = 553 nm (λ_{ex} = 460 nm) towards 15 mM TBAF (B).

Quantitative *off-on* response of the probe **3** (10 μM) towards fluoride was then evaluated by fluorometric titration with increasing concentration of the TBAF (0 – 16 mM) in water (Figure. 6A). Probe **3** was non fluorescent when excited at λ = 460 nm and quantum yield, Φ_F = 0.016 (standard: N-methyl NBD nitrobenzofurazan) amine in acetonitrile, Φ_F = 0.38). The variation of fluoride ion concentration (0 – 16 mM) provided a stepwise enhancement of fluorescence intensity up to 14 mM concentration of TBAF. The addition of TBAF (14 mM) to the probe **3** resulted strong fluorescence centered at λ_{em} = 553 nm with Φ_F = 0.89. These data ensured 120- and 56-fold enhancements in fluorescence intensity and quantum yield, respectively, during the sensing of fluoride ion by probe **3**. When fluorescence intensities at λ = 553 nm were plotted against respective fluoride ion concentration, a linear relationship (Figure 3B) was observed up to 5 mM of TBAF (regression factor, R = 0.9759). From the linear region of the plot, a limit of detection (*LOD*) = 24.5 μM (*i.e.* 0.46 ppm) which is well below of 4 ppm, the allowed concentration level in drinking water set by USEPA. Thus, the probe **3** is a promising indicator for detection of F^- ion in environmental and biological systems because the ion is toxic at higher concentration (0.1 mM for drinking water standard and 3 mM for biological systems).

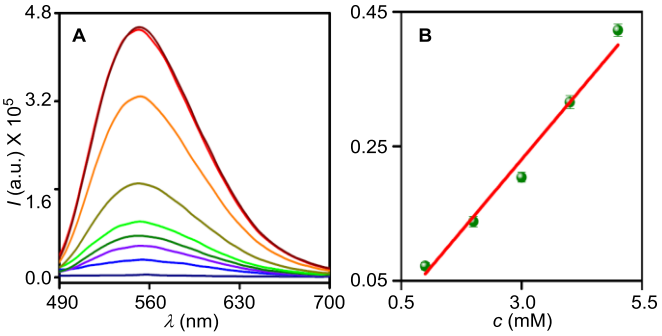


Figure 6. Fluorescence spectra of the probe **3** (10 μM in water containing 0.5 mM CTAB) in the presence of increasing concentration of TBAF (0, 2, 4, 6, 8, 10, 12, 14, 16 mM) with λ_{ex} = 460 nm (A). Linear relationship between the I_{553} and C_{TBAF} of the probe **3** (1 □ 5 mM) (B).

Selectivity of the probe **3** was evaluated in the next stage because; the specificity of the probe towards fluoride ion even under competing environment of other analytes is desired for its applications in environmental and biological sciences. Selectivity of the probe towards fluoride in the competing environment of these potentially interfering analytes was also evaluated under similar conditions. In each case, probe **3** (10 μM) was treated with 15 mM of other possibly interfering analytes (Br^-, I^-, Cl^-, ClO_4^-, PF_6^-, NO_3^-, HSO_4^-, OAc^-, SO_4^{2-}, H_2O_2, Na_2S, Cys and GSH) in water (0.5 mM CTAB) at room temperature for 60 min and fluorescence intensity was monitored at λ = 553 nm (λ_{ex} = 460 nm). No significant fluorescent intensity was observed in the presence of applied analytes indicating the inertness of the probe towards these species (Figure 7A, front row, violet bars). However the treatment of TBAF (15 mM) resulted about 120-fold fluorescent intensity enhancement (Figure 7A, back row, blue bar). The addition of TBAF (15 mM) to cuvettes containing probe **3** and a competing analyte provided fluorescence enhancement (Figure 7A, back row, red bars) similar to the addition of the anion to pure probe **3** in water (0.5 mM CTAB). Thus, probe **3** possesses high selectivity towards fluoride with equal efficiency in the presence of other competing unions. Response of **3** towards F^- ion under ambient light was marked by

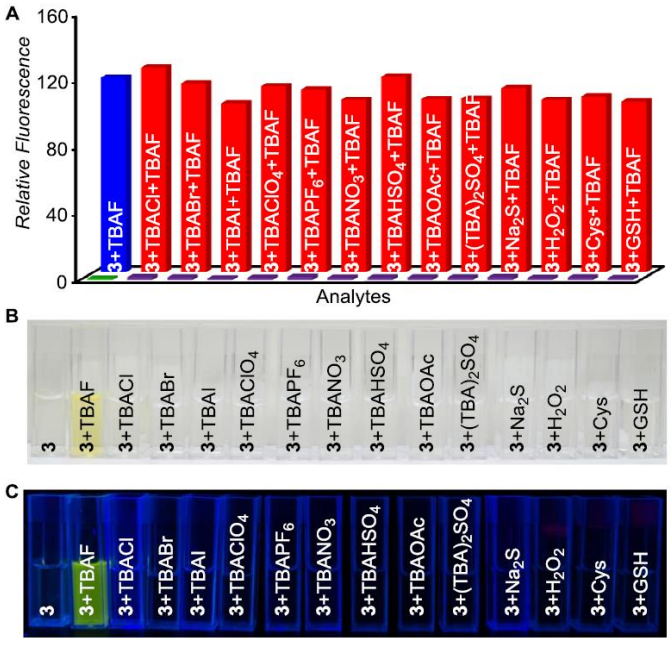


Figure 7. Relative fluorescence intensity at λ = 553 nm (λ_{ex} = 460 nm) for **3** (10 μM) in water (0.5 mM CTAB) toward F^- (15 mM) and various other analytes (either of TBABr, TBAI, TBACl, $TBAClO_4$, $TBAPF_6$, $TBANO_3$, $TBAHSO_4$, TBAOAc, $(TBA)_2SO_4$, Na_2S, H_2O_2, Cys and GSH) in the absence and presence of various analytes (15 mM each) (A). Each data was recorded after 1 h of the addition of an analyte. Color codes: ■ = **3**, ■ = **3**+TBAF, ■ = **3**+analyte (either of TBABr, TBAI, TBACl, $TBAClO_4$, $TBAPF_6$, $TBANO_3$, $TBAHSO_4$, TBAOAc, $(TBA)_2SO_4$, Na_2S, H_2O_2, Cys and GSH) and ■ = **3**+analyte+TBAF. Photographs taken under ambient light (B) and handheld UV-lamp (C) in the absence and presence of various analytes.

the visible change from colorless to yellow demonstrating the expediency of the probe as a "naked eye" indicator for F^- ion in water (Figure 7B).The probe was inert to other analytes and no change in color was observed for any of these analytes. The fluorescence turn-*on* response upon sensing of F^- ion was also confirmed by the appearance of green fluorescence of the reaction mixture when cuvette images were taken under handheld UV-lamp (λ_{ex} = 365 nm) (Figure 7C). These results confirmed that the probe **3** is highly selective towards F^- ion.

Application of probe **3** was demonstrated by live cell fluorescence imaging technique using HeLa cells. When cells were incubated with only probe **3** (10 μM in 1:100 DMSO-DMEM v/v, pH = 7.4) at 37 ^oC for 1h, no significant fluorescence was observed (Figure 8 B-C). On the other hand, when cells pre-treated with 2 mM F^- (1:1000 DMSO-DMEM v/v, pH = 7.4) for 30 min and then incubated with the probe **3** (10 μM in 1:100 DMSO-DMEM v/v, pH = 7.4) for 30 min showed strong fluorescence inside these cells (Figure 8 E-F). These fluorescence images demonstrate the permeation of probe **3** through the living cell membranes and its ability of sensing intracellular F^- ions.

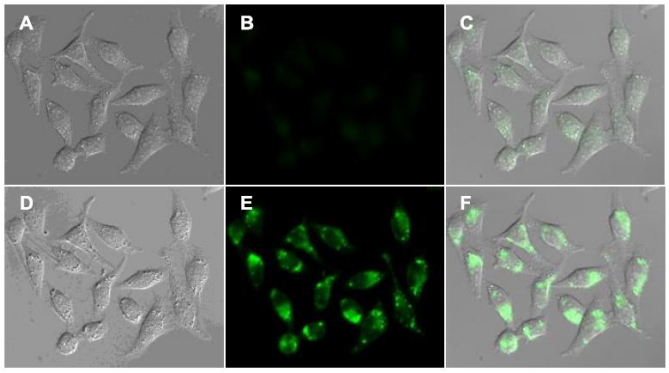


Figure 8. Cell images of HeLa cell: differential interference contrast (DIC) (A), fluorescence (B), and overlay (C), image of HeLa cell incubated with probe **3** (10 μM) for 1 h. (D − F) are the respective DIC, fluorescence and overlay image of HeLa cell first incubated with incubation with NaF (2 mM) for 30 min followed by probe **3** (10 μM) for 30 min.

4. Conclusions

In summary, we have presented the design, synthesis, and properties of a colorimetric and fluorometric probe for detection of F^- in aqueous media. The probe displayed a 120-fold enhancement in fluorescence intensity and a fluorescence quantum yield enhancement of 56-fold upon addition of F^-. The probe exhibits high sensitivity and selectivity toward fluoride over other interfering anions. The detection limit of the probe was found to be 24.5 μM (*i.e.* 0.46 ppm) which is comparable with the reported *LOD* values so far. A change in color from colorless to yellow and non-fluorescent to green fluorescence prove the significance of the probe in "naked-eye" detection of F^- in water. The cell permeability and ability of the probe to detect F^- in live cell was also confirmed by live cell imaging.

Acknowledgments

We acknowledge IISER Pune and DST-SERB (Grant No. SR/S1/OC-65/2012) for financial supports. A.R. and T.S. thank University Grand Commission (UGC) for research fellowships.

Supplementary Material

Supplementary material (complete experimental procedures, and spectral data for new compound and details of photophysical characterization data for probe **3**) associated with this article can be found, in the online version, at

References and Notes

1. (a) Martínez-Máñez, R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419-4476; (b) Duke, R. M.; Veale, E. B.; Pfeffer, F. M.; Kruger, P. E.; Gunnlaugsson, T. *Chem. Soc. Rev.* **2010**, *39*, 3936-3953; (c) Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79-128; (d) Hudson, Z. M.; Wang, S. *Acc. Chem. Res.* **2009**, *42*, 1584-1596.
2. (a) Ayoob, S.; Gupta, A. K. *Critical Reviews in Crit. Rev. Env. Sci. Technol.* **2006**, *36*, 433-487; (b) Wade, C. R.; Broomsgrove, A. E. J.; Aldridge, S.; Gabbaï, F. P. *Chem. Rev.* **2010**, *110*, 3958-3984; (c) Cametti, M.; Rissanen, K. *Chem. Commun.* **2009**, 2809-2829; (d) Zhou, Y.; Zhang, J. F.; Yoon, J. *Chem. Rev.* **2014**, *114*, 5511-5571.
3. (a) Krishnamachari, K. A. *Prog Food Nutr Sci.* **1986**, *10*, 279-314; (b) Schäferling, M.; Wolfbeis, O. S. *Chem. Eur. J.* **2007**, *13*, 4342-4349; (c) Maity, D.; Manna, A. K.; Karthigeyan, D.; Kundu, T. K.; Pati, S. K.; Govindaraju, T. *Chem. Eur. J.* **2011**, *17*, 11152-11161.
4. (a) Guha, S.; Saha, S. *J. Am. Chem. Soc.* **2010**, *132*, 17674-17677; (b) Guha, S.; Goodson, F. S.; Corson, L. J.; Saha, S. *J. Am. Chem. Soc.* **2012**, *134*, 13679-13691.
5. (a) Swinburne, A. N.; Paterson, M. J.; Beeby, A.; Steed, J. W. *Chem. Eur. J.* **2010**, *16*, 2714-2718; (b) Veale, E. B.; Tocci, G. M.; Pfeffer, F. M.; Kruger, P. E.; Gunnlaugsson, T. *Org. Biomol. Chem.* **2009**, *7*, 3447-3454.
6. Keymeulen, F.; De Bernardin, P.; Giannicchi, I.; Galantini, L.; Bartik, K.; Dalla Cort, A. *Org. Biomol. Chem.* **2015**, *13*, 2437-2443.
7. (a) Kim, D.; Singha, S.; Wang, T.; Seo, E.; Lee, J. H.; Lee, S.-J.; Kim, K. H.; Ahn, K. H. *Chem. Commun.* **2012**, *48*, 10243-10245; (b) Zheng, F.; Zeng, F.; Yu, C.; Hou, X.; Wu, S. *Chem. Eur. J.* **2013**, *19*, 936-942; (c) Zhu, B.; Yuan, F.; Li, R.; Li, Y.; Wei, Q.; Ma, Z.; Du, B.; Zhang, X. *Chem. Commun.* **2011**, *47*, 7098-7100; (d) J Zhang, J. F.; Lim, C. S.; Bhuniya, S.; Cho, B. R.; Kim, J. S. *Org. Lett.* **2011**, *13*, 1190-1193; (e) Kim, S. Y.; Park, J.; Koh, M.; Park, S. B.; Hong, J.-I. *Chem. Commun.* **2009**, 4735-4737; (f) Buckland, D.; Bhosale, S. V.; Langford, S. J. *Tetrahedron Lett.* **2011**, *52*, 1990-1992; (g) Kim, S. Y.; Hong, J.-I. *Org. Lett* **2007**, *9*, 3109-3112.
8. (a) Fu, L.; Jiang, F.-L.; Fortin, D.; Harvey, P. D.; Liu, Y. *Chem. Commun.* **2011**, *47*, 5503-5505; (b) Cao, J.; Zhao, C.; Feng, P.; Zhang, Y.; Zhu, W. *RSC Adv.* **2012**, *2*, 418-420.
9. Bozdemir, O. A.; Sozmen, F.; Buyukcakir, O.; Guliyev, R.; Cakmak, Y.; Akkaya, E. U. *Org. Lett.* **2010**, *12*, 1400-1403.
10. Bao, Y.; Liu, B.; Wang, H.; Tian, J.; Bai, R. *Chem. Commun.* **2011**, *47*, 3957-3959.
11. (a) Dong, M.; Peng, Y.; Dong, Y.-M.; Tang, N.; Wang, Y.-W. *Org. Lett.* **2011**, *14*, 130-133; (b) Hou, P.; Chen, S.; Wang, H.; Wang, J.; Voitchovsky, K.; Song, X. *Chem. Commun.* **2014**, *50*, 320-322; (c) Roy, A.; Kand, D.; Saha, T.; Talukdar, P. *Chem. Commun.* **2014**, *50*, 5510-5513; (d) Roy, A.; Datar, A.; Kand, D.; Saha, T.; Talukdar, P. *Org. Biomol. Chem.* **2014**, *12*, 2143-2149; (e) Roy, A.; Kand, D.; Saha, T.; Talukdar, P. *RSC Adv.* **2014**, *4*, 33890-33897.
12. Hu, R.; Feng, J.; Hu, D.; Wang, S.; Li, S.; Li, Y.; Yang, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 4915-4918.
13. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **2001**, *46*, 3-26.
14. Sander T. *OSIRIS Property Explorer Applet.* Accessed May 25, 2014, from http://www.openmolecules.org/propertyexplorer/applet.html.

15. (a) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Drug Delivery Rev.* **1997**, *23*, 3-25; (b) P Leeson, P. *Nature* **2012**, *481*, 455-456.
16. Yang, X.-F.; Qi, H.; Wang, L.; Su, Z.; Wang, G. *Talanta* **2009**, *80*, 92-97.
17. Sokkalingam, P.; Lee, C.-H. *J. Org. Chem.* **2011**, *76*, 3820-3828.

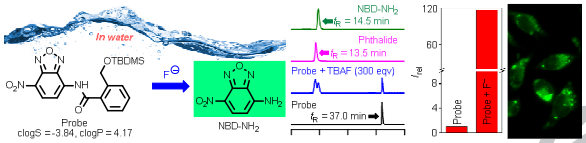
vGraphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Turn-on Fluorescent Probe Designed for Fluoride Ion Sensing in Aqueous Media

Arundhati Roy,[a] Tanmoy Saha[a] and Pinaki Talukdar*[a]

Leave this area blank for abstract info.



Highlights

1. The first rationally designed for F^- ion detection in the aqueous media.
2. Establishment of the sensing mechanism by ^{1}H-NMR titration, TLC and HPLC analysis.
3. Rapid response towards F^- ion with $t_{1/2}$ = 13.9 min and pseudo first order rate constant k = 0.0008268 s^{-1}.
4. 120-Fold turn-on green fluorescence.
5. Cell permeability and intracellular F^- ion detection by live-cell imaging.