Highly selective fluorescence turn-on determination of fluoride ions via chromogenic aggregation of a silyloxy-functionalized salicylaldehyde azine

Yun-Hui Zhao, Yubo Li, Yunfei Long, Zhihua Zhou, Zilong Tang, Keqin Deng, Shaowei Zhang

PII: S0040-4039(17)30245-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.02.066
Reference: TETL 48677

To appear in: *Tetrahedron Letters*

Received Date: 14 January 2017
Revised Date: 16 February 2017
Accepted Date: 21 February 2017

Please cite this article as: Zhao, Y-H., Li, Y., Long, Y., Zhou, Z., Tang, Z., Deng, K., Zhang, S., Highly selective fluorescence turn-on determination of fluoride ions via chromogenic aggregation of a silyloxy-functionalized salicylaldehyde azine, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.02.066

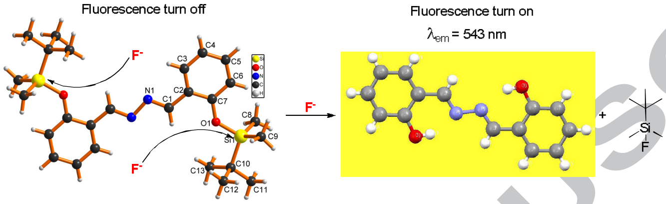
Graphical Abstract

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

Highly selective fluorescence turn-on determination of fluoride ions via chromogenic aggregation of a silyloxy-functionalized salicylaldehyde azine

Leave this area blank for abstract info.

Yun-Hui Zhao*, Yubo Li, Yunfei Long, Zhihua Zhou*, Zilong Tang* , Keqin Deng, Shaowei Zhang



Tetrahedron Letters
journal homepage: www.elsevier.com

Highly selective fluorescence turn-on determination of fluoride ions via chromogenic aggregation of a silyloxy-functionalized salicylaldehyde azine

Yun-Hui Zhao*, Yubo Li, Yunfei Long, Zhihua Zhou*, Zilong Tang* , Keqin Deng, Shaowei Zhang

School of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Xiangtan, Hunan, 411201, China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
fluorescent chemsensor
fluoride ion determination
salicylaldehyde azine
aggregation-induced emission
TBS-protected salicylaldehyde azine

ABSTRACT

A novel fluorescent chemsensor TBS-protected salicylaldehyde azine (TSAA) for fluoride ion was developed based on aggregation-induced emission (AIE). The probe TSAA was prepared by the reaction of salicylaldehyde azine (SAA) with *tert*-butyldimethylsilyl chloride (TBS-Cl) *via* an unusual synthetic methodology and shows only non-emission. Upon treatment with fluoride in aqueous MeCN solution, the TBS protective group of probe TSAA was removed readily and the fluorescence of the probe was switched on, which resulted in a new fluorescence peak around 543 nm. The fluorescent intensity at 543 nm increases linearly with fluoride ion concentration in the range 1–50 μmol L^{-1}. This proposed probe shows excellent selectivity toward fluoride ion over other common anions and cations.

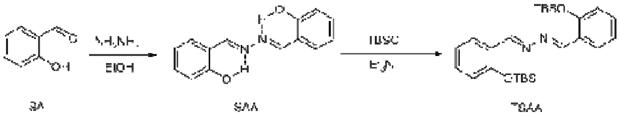
Developing new fluorescent anion sensors and probes is an emerging research area of great importance due to the important roles and potential applications in biological, environmental and supramolecular sciences. Fluoride ion (F^-), the smallest anion, is of special biological significance in preventing from dental cares and in treatment of osteoporosis. [1] Whereas trace fluoride is regarded as an essential ingredient in toothpaste and is essential for body growth. [2] However, a higher concentration of fluoride ion can lead to fluorosis, which cause serious toxic to the biological tissue even to many serious neurodegenerative diseases. [3] For example, in molecular and cell biology system, an exceeded intake of NaF can affect a number of essential cell-signaling components and influence normal cellular metabolism. [4] Moreover, a high level of F^- could also lead to ecological damage and result in dental or skeletal fluorosis, even nephrotoxic changes and urolithiasis in humans. [5] For above reasons, tremendous effort has been devoted to the development of highly selective and sensitive methodology for detection of fluorides, especially for NaF in aqueous solution.

Many methods have been developed to detect fluoride ion including fluoride ion selective electrodes (ISE), [6] ion chromatography, [7] spectrophotometry, [8] HPLC [9] and fluorimetry [10]. Fluorescent chemosensors, however, are becoming an important detection method for fluoride ion for many reasons: high sensitivity and selectivity, low cost, easy detection, and especially suitability as a diagnostic tool for biological concern. [11] Most of fluorescent fluoride screening methodology have concentrated on receptors that differentiate F^- from other anions, such as chloride, bromide, carbonate or nitrate and convert the binding into an optical signal. However, there are some limitations associate with existing sensing methods. For example, “turn-on” fluorescent anion chemosensors for selective fluoride detection often require complicated synthetic procedures. [12] In addition, the fluorescence spectra of some probes can only be observed in organic solvent and are non-emissive in aqueous solution, which greatly limits their analytical application in environmental detection. Therefore, easy to synthesis and higher sensitivity “turn-on” fluorescent probe for fluoride are still appealing.

Most reported fluorophores such as fluorescein or rhodamine dyes show much weaker emission in aggregate or solid states compared to that in solutions because of concentration- or aggregation-caused quenching effect, [13] which makes fluoride determination challenging. Aggregation-induced emission (AIE) phenomenons, which reported by Tang *et al.* in the past decade, are an emerging class of molecules displaying strong fluorescence in their aggregate or solid states. [14] The novel and sensitive fluorescence ‘turn-on’ feature of the AIE fluorophores makes them potential building blocks in fabrication of chemical sensors, anion sensors, as well as a probe for detection fluoride. [15] However, research work for the sensing of anions by the AIE effect, especially for the ratiometric detection of fluoride in aqueous solution, is very rare. [16]

TBS is a common protecting group for alcohols and phenols.[17] In addition, it can be easily deprotected by fluoride ion. The extraordinary affinity of fluoride to silicon has been claimed as the “driving force” of the reaction between silyl ethers and fluoride ion. [18] Based on this particular affinity, a few novel and sensitive methodologies have been developed to determine the fluoride. [19] Kim and Swager developed a fluoride-sensing approach based on the fluoride ion-triggered formation of highly fluorescent coumarin. [20] Akkaya synthesized bodipy derivatives with silyl-protected phenolic functionalities, and detected fluoride concentrations both in solution and in a poly(methylmethacrylate) matrix. [21] Yang reported a new approach for fluoride sensing based on modulation of the excited-state intramolecular proton transfer (ESIPT) process of 2-(2'-hydroxyphenyl)benzimidazole (HPBI). [22] Li found that silyl-appended spiropyran dye could be used for rapid and sensitive colorimetric detection of fluoride ions. [23]

Herein, we combine the AIE effect of SAA and the extraordinary affinity of fluoride to silicon to develope a novel fluorogenic probe TSAA (Scheme 1), for the selective determination of fluoride ion in aqueous MeCN solution. The new chemosensor could selectively and ratiometric detect fluoride in aqueous solution.



Scheme 1 Synthesis of probe TSAA

SAA was synthesized according to the method reported by Xiang and Tong.[24] TSAA can't be prepared by conventional synthetic method. Initially, SAA and excessive amounts of TBS-Cl were added into anhydrous THF under the presence of imdazole. However, both mono-silyl and di-silyl were formed as a inseparable mixture. Di-silyl compound also can't be obtained as single product in other solvent or under other reaction conditions. After a series of screenings, triethylamine (TEA) was used as a base and solvent to provide the single target product. This phenonmenon maybe caused by the strong intramolecular hydrogen-bond (Scheme 1). TSAA has some special features in molecular design compared to most conventional AIE fluorophores: (1) two salicylaldimine units are connected by a rotatable N-N single bond rather than C-C bond; (2) intramolecular hydrogen bonds of salicylaldimine moieties and stacking of molecules in aggregate state inhibit the free intramolecular rotation resulted in the reduced attenuation of non-radioactive energy to trigger the fluorescence "turn on". [24] This probe TSAA shows a drastic change in UV-vis absorption and fluorescence emission under the presence of fluoride over other anions in CH_3CN/H_2O (90:10, v/v). Because of the high affinity of fluoride for silicon, TBS group was easily deprotected by fluoride (Figure 1).

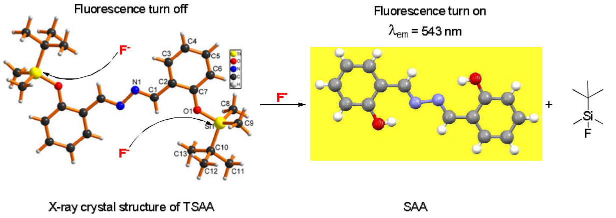


Fig. 1 TSAA transformed to SAA in the presence of fluoride ion

A single crystal of TSAA (CCDC 1511881) is obtained by slow evaporation of its MeCN solution, which enables further confirmation of its molecular structure by crystallographic analysis (Tables S1). The crystal is nearly non-emissive and the image of a square crystal is given in figure 1.

SAA is a strong yellow fluorescent dye with maximal emission at 543 nm upon excitation at 354 nm (Figure 2a). It can be observed that TSAA was a no fluorescent compound in contrast to its parent molecule, SAA. The silylation of the hydroxy group of SAA effectively quenches its fluorescence emission. Dual spectroscopic changes are caused by release of SAA through a fluoride-induced Si-O bond cleavage (Figure 2a, b).

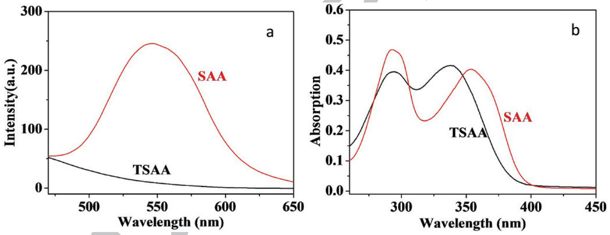


Fig. 2 (a) Fluorescence spectra of 10 μmol L^{-1} SAA and TSAA in 90% (v/v) MeCN–H_2O solution; (b) absorption spectra of 10 μmol L^{-1} SAA and TSAA in 90% (v/v) MeCN–H_2O solution.

TSAA is stable under ambient conditions, and is soluble in common organic solvents, but insoluble in water. Figure S3 of the Supporting Information showed the UV−vis absorption spectra of free TSAA in different organic solvents, and one could see that the free TSAA was colorless with a strong absorption band at around 334 nm in either the polar or the nonpolar organic solvent except DMF and DMSO, but no obvious absorption could be observed in the longer wavelength, reflecting that TSAA mainly existed as the silyl protected form.

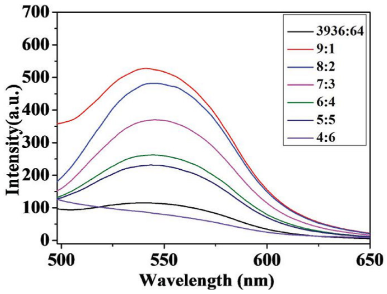


Fig. 3 Effect of MeCN concentration (V_{MeCN}/V_{water} = 3936/64, 9/1, 8/2, 7/3, 6/4, 5/5, 4/6) on fluorescence intensity of TSAA (10 μmol L^{-1}) in the presence of fluoride ion

Nonaqueous reaction media was unfavorable for the removal of silyl protecting group due to the poor solubility of fluoride ion in organic solvents. Therefor, we tuned the reaction conditions to the MeCN-H_2O cosolvent mixtures. Furthermore, the effect of MeCN concentration on fluorescence intensity of the reaction system was studied, and the results are shown in Fig. 3. It showed that fluorescence intensity remains almost unchanged when MeCN concentration is in the range 0–50%, and increases dramatically when the concentration of MeCN is above 60%. However, the fluorescence intensity was sharply decreased in

99% MeCN-H_2O solution because of the poor solubility of F^-. To facilitate the real sample analysis, 90% MeCN-H_2O solution was selected as the reaction media in the following experiment.

The effect of the reaction time on fluorescence intensity of this system was studied and the results are shown in Fig. 4. It can be seen that fluorescence intensity increased gradually with increasing the reaction time, and the complete cleavage of TBS group from the probe required about 2h under the optimized reaction conditions. And the sensitivity of the present method has almost no remarkable change with increasing the incubation time. A 30-min reaction time was selected as a compromise of sensitivity and analytical frequency. Previous reports showed that fluoride ion recognition process usually needed a few hours in aqueous solution to complete the detection process due to the low solubility of probe.

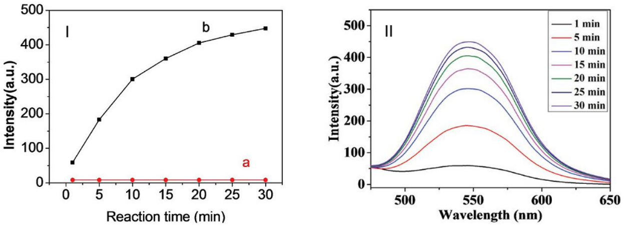


Fig. 4 (I) Reaction-time profile of TSAA (10 μmol L^{-1}) in the absence *a* and presence *b* of fluoride ion (2.0 μmol L^{-1}). (II) The fluorescence intensity were continuously monitored at time intervals.

To demonstrate the applicability of the proposed approach for quantitative detection of F^-, we measured the fluorescence spectra of TSAA containing F^- at varied concentrations under the optimized experimental conditions. As shown in Fig. 5, the TSAA exhibited non-emission in the absence of F^-; however, with the addition of F^-, the emission around 543 nm gradually increased. The fluorescence intensity was plotted as a function of the fluoride concentration, and a typical calibration graph was obtained. The fluorescence intensity (I) is linear with fluoride concentration (*c*) in the range 1–50 μmol L^{-1} with a correlation coefficient of R = 0.998 (n = 6). The linear regression equation was determined to be $I = 5.73c$ [μmol L^{-1}]+24.83 (n=6, R = 0.998). The detection limit was determined from three times the standard deviation of the blank signal as 0.81 μmol L^{-1}. The relative standard deviation (n = 6) was 1.7% for 10 μmol L^{-1} of fluoride ion.

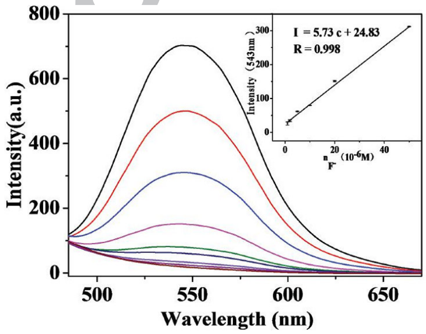


Fig. 5 Fluorescent emission changes (λ_{ex} = 543 nm) of TSAA (10μmol L^{-1}) in the presence of increasing amounts of F^- in 90% MeCN-H_2O (v/v) solution. The signal changes with increases in F^- concentrations (0, 1, 2, 5, 10, 20, 50, 100, 200 μM). Fluorescent emission enhancement (I) of TSAA at 543 nm as a function of the concentrations of F^-. The magnitudes of the error bars were calculated from the uncertainty given by three independent measurements.

The selectivity of the probe TSAA herein has been determined by examining the changes in the fluorescence spectra of probe TSAA caused by other anions, such as Cl^-, Br^-, IO_3^-, IO_4^-, NO_3^-, NO_2^-, Ac^-, CO_3^{2-}, SO_4^{2-}, SO_3^{2-} were investigated. After the addition 1.0 equiv. of each of these anions for 30min, the fluorescence spectra of solution TSAA were measured and shown in Fig. 6a. It can be observed that only fluoride gave dramatic changes in fluorescence spectra, while other anions did not cause obvious changes under identical conditions. The fluorescence peak at 543 nm accompanied with remarkable color response from colorless to yellow was found only in TSAA holding F^- solution, and no other anions caused observable color changes, which indicated that the probe TSAA could selectively signal F^- due to the highly special affinity between fluorine and silicon.

The effective applications of the probe caused by cations, such as Ag^+, Ba^{2+}, Ca^{2+}, Li^+, Mg^{2+}, NH_4^+, Ni^{2+}, Zn^{2+} were also studied. After the addition 1 equiv. of each of these anions for 30min, the fluorescence spectra of solution TSAA were measured. Fig. 6b showed that the addition of these cations did not result in any changes in the fluorescence spectrum. Other fluoride were tested under the same condtions. As can be seen in figure S5, CaF_2, MgF_2 and AlF_3 did not result in either new emission wavelengths or enhancement in fluorescence intensity.

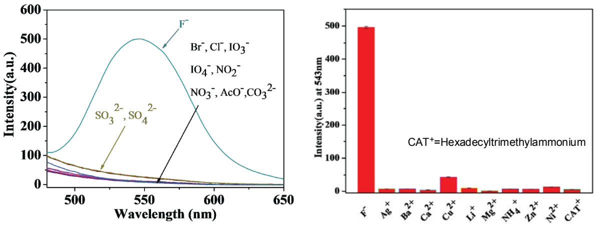


Fig. 6 Fluorescent emission changes (λ_{ex} = 543 nm) of TSAA (10 μmol L^{-1}) upon addition of various (a) anions and (b) cations (10 μmol L^{-1}) in 90% MeCN-H_2O solution

To gain further insight of the reaction, we used ^{1}H NMR spectra to monitor the process of F- detection with TSAA in $CDCl_3$ and CD_3OD before and after the addition of F^-. As shown in Fig. 7, TSAA exhibited one sharp peak around 9.0 ppm, corresponding to the signals of the N=CH (salicylaldehyde hydrazone). There was no change in the ^{1}H NMR spectrum of TSAA under the UV light for 2h in the absence of fluoride ion, which indicated the probe was stable in $CDCl_3$-CD_3OD cosolvent in the absence of fluoride. Nevertheless, when probe was reacted with fluoride ion in 50% $CDCl_3$-CD_3OD mixture at 60 °C for 20 h, the signal of the N=CH was gradually disappeared and 0.3 ppm upfield shift, while a new peak at around 8.7 ppm emerged. This phenomenon maybe caused by the intramolecular hydrogen bond. The signal of the N=CH disappeared completely after heating for 96 h. The peak of OH was not emerged maybe due to the existence of CD_3OD. And the slow reaction process was resulted by the trace solubility of fluoride ion in the $CDCl_3$-CD_3OD mixture. The chemical shifts of TBS were also moved slightly. Therefore, the result strongly supported the formation of SAA from TSAA (Figure S4), including the removal of the TBS and the recovery of the hydroxyl group, by attack of fluoride.

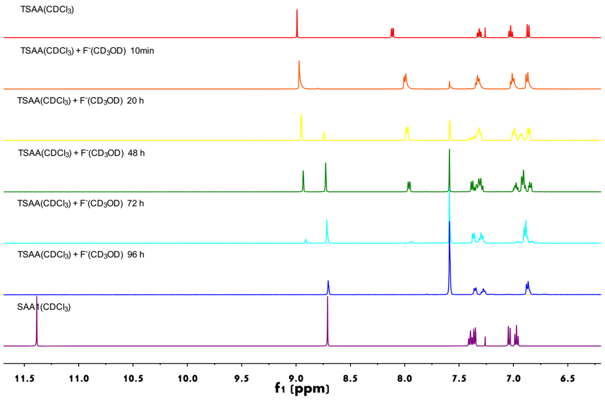


Fig. 7 The changes of ^{1}H Chemical shift (ppm) under the presence of fluoride with increasing of reaction time

In this study, a novel fluorescent chemsensor TSAA was synthesized and demonstrated as a fluorescent probe for the sensitive and selective detection of fluoride ions with significant enhancement of fluorescence intensity. The signal transduction occurs via a fluoride-triggered Si-O bond cleavage that results in the formation of an intramolecular hydrogen bond imine compound SAA. The probe TSAA features a ratiometric fluorescent response to fluoride with a marked emission enhancement and shows high selectivity for fluoride over other anions and cations. It has the relatively wide linear ranges and low detection limit for fluoride detection in an MeCN-H_2O solution. This simple and sensitive F^- detection has the potential to be a general detection method for fluoride ion in an aqueous environment.

Acknowledgments

The generous financial support from the National Natural Science Foundation of China (Nos. 21372070 and 21471052), the Hunan Provincial Education Department Scientific Research Fund (No. 14k035) are gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at

References and notes

[1] (a) Farley, J. R.; Wergedal, J. E.; Baylink, D. J. *Science* **1983**, *222*, 330; (b) Kleerekoper, M. *Endocrinol. Metab. Clin. North Am.* **1998**, *27*, 441; (c) Lennon, M. A. *Bull. W.H.O.* **2006**, *84*, 759.

[2] Horowitz, H. S. *J. Public Health Dent.* **2003**, *63*, 3.

[3] Kirk, K. L. Biochemistry of the Elemental Halogens and Inorganic Halides, *Plenum Press*, *New York*, **1991**, 58.

[4] Barbier, O.; Arreola-Mendoza, L.; Del Razo, L. M. *Chem.-Biol. Interact.* **2010**, *188*, 319.

[5] (a)Bowman-James, K. *Acc. Chem. Res.* **2005**, *38*, 671; (b) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465; (c) Weatherall, J. A. Pharmacology of Fluorides. In Handbook of Experimental Pharmacology XX/1; *Springer-Verlag: Berlin, Part 1*, **1969**, 141; (d) Cittanova, M. L.; Lelongt, B.; Verpont, M. C. *Anesthesiology,* **1996**, *84*, 428; (e) Singh, P. P.; Barjatiya, M. K.; Dhing, S.; Bhatnagar, R.; Kothari, S. *Dhar, V. Urol. Res.* **2001**, *29*, 238.

[6] (a) Capka, V.; Bowers, C. P.; Narvesen, J. N.; Rossi, R. E.; *Talanta* **2004**, *64*, 869; (b) Ruiz-Payan, A.; Ortiz, M.; Duarte-Gardea, M. *Microchem. J.* **2005**, *1*, 19; (c) Hutchinson, J. P.; Evenhuis, C. J.; Johns, C.; Kazarian, A. A.; Breadmore, M. C.; Macka, M.; Hilder, E. F.; Guijt, R. M.; Dicinoski, G. W.; Haddad, P. R. *Anal. Chem.* **2007**, *79*, 7005.

[7] (a) Kalyakina, O. P.; Dolgonosov, A. M. *J. Anal. Chem.* **2003**, *58*, 951; (b) Thangavel, S.; Dash, K.; Dhavile, S. M.; Chaurasia, S. C.; Mukherjee, T. *J. Chromatogr. A* **2005**, *1074*, 229.

[8] (a) Li, H. B.; Xu, X. R. *Talanta* **1999**, *48*, 57; (b) Themelis, D. G.; Tzanavaras, P. D. *Anal. Chim. Acta* **2001**, *429*, 111.

[9] Xu, X. R.; Li, H. B.; Gu, J. D.; Peng, K. J. *Chromatographia* **2004**, *59*, 745.

[10] (a) Nishimoto, J.; Yamada, T.; Tabata, M. *Anal. Chim. Acta* **2001**, *428*, 201; (b) 21 Garrido, M.; Lista, A. G.; Palomeque, M.; Band, B. S. F. *Talanta* **2002**, *58*, 849.

[11] (a) Badugu, R.; Lakowicz, J. R.; Geddes, C. D. *Sens. Actuators B* **2005**, *104*, 103; (b) 23 Cho, E. J.; Moon, J. W.; Ko, S. W.; Lee, J. Y.; Kim, S. K.; Yoon, J.; Nam, K. C. *J. Am. Chem. Soc.* **2003**, *125*, 12376; (c) 24 Zhou, G.; Cheng, Y.; Wang, L.; Jing, X.; Wang, F. Macromolecules **2005**, *38*, 2148.

[12] (a) Jiang, X.; Vieweger, M. C.; Bollinger, J. C.; Dragnea, B.; Lee, D. *Org. Lett.* **2007**, *9*, 3579; (b) Cao, J.; Zhao, C.; Feng, P.; Zhang, Y.; Zhu, W. *RSC Advances* **2012**, *2*, 418.

[13] Thomas III, S. W.; Joly, G. D.; Swager, T. M. *Chem. Rev.* **2007**, *107*, 1339.

[14] Hong, Y.; Lam, J. W. Y.; Tang, B. Z. *Chem. Soc. Rev.* **2011**, *40*, 5361.

[15] Zhang, L.; Hu, W.; Yu, L.; Wang, Y. *Chem. Commun.* **2015**, *51*, 4298.

[16] (a) Turan, I. S.; Cakmak, F. P.; Sozmen, F. *Tetrahedron Lett.* **2014**, *55*, 456; (b) Bineci, M.; Bağlan, M.; Atılgan, S. *Sens. Actuators B* **2016**, *222*, 315; (c) Jiang, G.; Liu, X.; Wu, Y.; Wang, J.; Dong, X.; Zhang, G.; Li, Y.; Fan, X. *RSC Adv.* **2016**, *6*, 59400.

[17] (a) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549; (b) Ranu, B. C.; Jana, U.; Majee, A. *Tetrahedron Lett.* **1999**, *40,* 1985; (c) Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. *Chem. Rev.* **2004**, *104*, 199.

[18] Yang, X. *Spectrochimica Acta Part A* **2007**, *67*, 321.

[19] Kim, S. Y.; Hong, J. I. *Org. Lett.* **2007**, *9*, 3109.

[20] Kim, T.-H.; Swager, T. M. *Angew. Chem. Int.* **2003**, *42*, 4803.

[21] Bozdemir, O. A.; Sozmen, F.; Buyukcakir, O.; Guliyev, R.; Cakmak, Y.; Akkaya, E. U. *Org. Lett.* **2010**, *12*, 1400.

[22] Yang, X.; Qi, H.; Wang, L.; Su, Z.; Wang, G. *Talanta* **2009**, *80*, 92.

[23] Li, Y.; Duan, Y.; Zheng, J.; Li, J.; Zhao, W.; Yang, S.; Yang, R. *Anal. Chem.* **2013**, *85*, 11456.

[24] Tang, W.; Xiang, Y.; Tong, A. *J. Org. Chem.* **2009**, *74*, 2163.

1. Highly sensitive and selective methodology for detection of fluoride ions
2. A fluorescence ‘turn-on’ probe under the presence fluoride ions
3. A ratiometric detection of fluoride in aqueous solution