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Fluorene-based chemodosimeter for "turn-on" sensing of cyanide by hampering ESIPT and live cell imaging†

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A new salicylaldehyde appended fluorene-based chemodosimeter (**FSal**) has been designed by taking consideration of the special nucleophilicity of cyanide ion. **FSal** shows selective affinity towards CN^- over other anions (namely F^-, Br^-, NO_3^-, ClO_4^-, N_3^-, $H_2PO_4^-$, AcO^-, I^-, Cl^-, and NO_2^-) through turn-on fluorescence with a minimum detection limit of 0.06 ppm. The turn-on fluorescence of the **FSal**–CN complex resulting from hampering ESIPT is also supported by DFT and TDDFT calculations. Biological compatibility and live cell imaging of this unique probe have also been explored.

1. Introduction

The cyanide anion (CN^-) is one of the most deadly poisons to mammals,[1,2] although it is extensively used in industrial processes, including heap leaching of gold from ore, metallurgy, and electroplating. It is also used in fibers and the resin industry.[3] Despite safeguards and stringent norms set by different regulatory bodies, the accidental release of cyanide can contaminate drinking water and become a serious threat to the environment.[4] Environmental implications may be caused by some food plants like cassava and also by some Rosaceae such as apricot seeds (and also almonds, apples, cherries, plums, pears *etc.*) which produce cyanogenic glycosides during natural defense mechanisms. The glycosides are hydrolyzed by enzymes upon injury or stress to produce HCN.[5] Furthermore, the release of cyanide into the environment, with potentially dangerous effects, is an added source of concern.[6] In living cells, cyanide binds with the Fe^{3+} in heme units, and affects the oxygen supply. The active site of cytochrome c is inactivated by CN^- and blocks the electron transport chain. As a result, cellular respiration is inhibited.[7] All the above factors demand the development of a receptor for CN^- sensing in aqueous as well as in cellular environments.

Fluorescent chemosensors have many advantages, including high sensitivity, low operational cost, ease of detection and suitability as diagnostic tools for biological concerns.[8–13] There are several methods for the selective detection of CN^-, which include cyanide addition to Zn^{II}-porphyrin,[14] a polymer–Cu^{II}-complex,[15] CdSe quantum dots,[16] and organoboron derivatives.[17] Hydrogen-bonding interactions,[18] luminescent lifetime measurements,[19] and deprotonation techniques[20] have also been adopted for this purpose. However, there is growing interest to develop a chemodosimetric probe for CN^- to circumvent the interference from other anions and this approach is based on an irreversible reaction of the strong nucleophile, CN^-, which has been used in cyanohydrin reactions.[21] The carbonyl centers, which are *ortho* with respect to a hydroxyl group, act as strong electrophiles due to the resonance-assisted hydrogen bonds (RAHBs) introduced by Gilli *et al.*[22] and the nucleophilic addition to the carbonyl centers become very facile.[23]

Keeping the above in perspective, we have designed and synthesized a novel chemodosimetric probe **FSal** (Scheme 1) to detect CN^- based on fluorene as a color reporting group and salicylaldehyde as an electrophile for the employment of an intramolecular hydrogen bond with a phenolic proton. We have also synthesized two model compounds **FBal** and **FMBal** according to Scheme 1 to support the sensing mechanism. To date, various chemosensors[24] which have been reported for CN^-, suffer from several limitations such as a high detection limit, interference of other anions like F^- or AcO^- and high temperature. In this circumstance, it is a challenge for us to fabricate a unique chemodosimetric system which can detect CN^- from an aqueous solution without being affecting by other anions and at levels lower than the permissible level for cyanide (0.2 ppm) in drinking water set by the Environment Protection Agency (EPA).[25] To the best of our knowledge, this is the first

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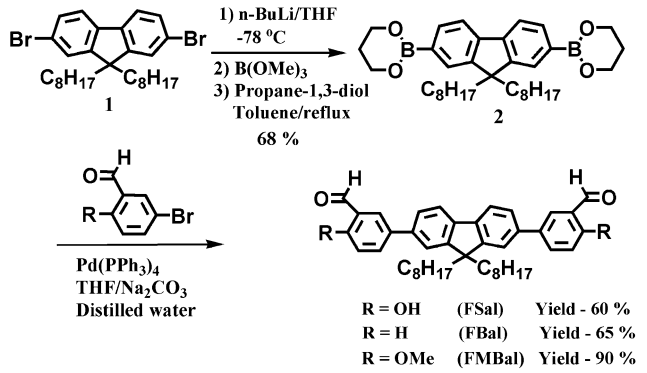
† Electronic supplementary information (ESI) available: Detailed NMR spectra, MALDI-TOF mass spectra for all compounds, UV-Vis spectra, PL spectra, and details of theoretical calculations and biological studies. See DOI: 10.1039/c4tb00388h



Scheme 1 Synthesis of the fluorene-based probe, **FSal**, and two model compounds, **FBal** and **FMBal**.

report where a salicylaldehyde appended fluorene-based chemodosimeter has been used for the detection of CN^- from water with high selectivity and a low detection limit (0.06 ppm). Again, this novel probe is biocompatible which is an added advantage for live cell applications.

2. Experimental

2.1 Materials

2,7-Dibromo-9,9-dioctylfluorene, 3-bromobenzaldehyde, *n*-BuLi, tri-methylborate, 5-bromosalicylaldehyde, 1,3-propanediol, $Pd(PPh_3)_4$, and tetrabutylammonium cyanide (TBACN) were from Sigma-Aldrich Co. Ltd. and the rest were from Merck India Pvt. Ltd. All the reagents were used without further purification, and all the experiments were performed at room temperature (25 °C). All the solvents used for the synthesis were from Merck India Pvt. Ltd. and were used after distillation under N_2. For spectral detection, the HPLC grade CH_3CN solvent was used, whereas deionized water (obtained from the Millipore Milli-Q system, 18 MΩ) was used to prepare the salt solutions.

2.2 Characterization

All the compounds were characterized by ^{1}H-NMR, ^{13}C-NMR and matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) techniques. The NMR spectra were acquired on 300 and 500 MHz Bruker DPX spectrometers using $CDCl_3$ as the solvent and TMS as the standard reference at room temperature, with the chemical shift given in parts per million. UV-Vis spectra of all the samples were recorded with a Hewlett–Packard UV-Vis spectrophotometer (model 8453). Photoluminescence studies of solutions were recorded with a Horiba Jobin Yvon Fluoromax 3 spectrometer at an excitation wavelength of 360 nm. MALDI-TOF was carried out with a Bruker Daltonics FLEX-PC using dithranol as a matrix.

2.3 Preparation of test solution, absorption and emission measurements

For spectroscopic measurements, the **FSal**, **FBal** and **FMBal** solutions (5 μM) were prepared in CH_3CN separately. The stock solutions of the anions (2 mM) as their potassium salt (only cyanide as tetrabutylammonium salt) were prepared in deionized water. The experiments were done by taking 2 mL probe solution followed by addition of an aqueous solution of different anions. After addition of the anion solution, the resulting solution was shaken well and its spectra were recorded after 5 min. For emission spectra, measurement slits were 5/5.

2.4 Synthesis

9,9-Dioctylfluorene-2,7-bis(trimethylene boronates) (2). Into a solution of 2,7-dibromo-9,9-dioctylfluorene **1** (2 g, 3.6 mmol) in anhydrous THF (30 mL), *n*-BuLi (1.6 M in hexane, 6.7 mL, 10.8 mmol) was added dropwise at −78 °C. The reaction mixture was stirred for 2 h prior to the addition of trimethyl borate (4 mL, 36 mmol) in one portion. The mixture was warmed to room temperature, stirred overnight and was poured into crushed ice containing HCl (2 M) while stirring. The mixture was extracted with ether and the combined extracts were evaporated to give a yellowish liquid (diboronic acid). Then the mixture was refluxed with 1,3-propanediol (0.63 mL, 8.71 mmol) in 40 mL toluene for 10 h. After the workup, the crude product was purified by column chromatography (with silica gel and petroleum ether–ethyl acetate (4 : 1) as the eluent) to afford a yellowish liquid (1.36 g, 68% yield). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.78–7.62 (m, 4H), 7.32 (m, 2H), 4.20 (t, 8H), 2.10 (m, 4H), 1.99 (m, 4H), 1.27–1.03 (m, 20H), 0.84 (t, 6H), 0.60 (m, 4H). ^{13}C-NMR (300 MHz, $CDCl_3$): δ (ppm) 150.4, 143.6, 132.6, 127.7, 127.3, 120.9, 62.7, 55.0, 40.6, 31.9, 30.1, 29.8, 29.3, 27.5, 23.8, 22.7, 14.2. Elemental analysis for $C_{35}H_{52}B_2O_4$ (%) calculated: C 75.28, H 9.39; found: C 75.55, H 9.30. MALDI-TOF (*m*/*z*): calculated: 558.4, found: 558.3.

9,9-Dioctylfluorene-2,7-bis-(5-salicylaldehyde) (FSal). 9,9-Dioctylfluorene-2,7-bis(trimethylene boronate) (**2**) (0.558 g, 1.0 mmol), 5-bromosalicylaldehyde (0.4 g, 2.0 mmol) and $Pd(PPh_3)_4$ (0.008 g) were added to a mixture of 15 mL THF and aqueous 2 M Na_2CO_3 (7 mL) under a nitrogen atmosphere. The mixture was vigorously stirred at 90 °C for 24 h. After the mixture was cooled to room temperature, it was poured into 100 mL deionized water. The aqueous layer was extracted with dichloromethane three times. The combined organic layers were washed with water and dried over sodium sulfate. After vacuum evaporation of the solvent, the residue was purified by column chromatography (with silica gel and DCM–petroleum ether as the eluent) to give a yellowish liquid (0.378 g, 60% yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 11.03 (s, 2H), 10.03 (s, 2H), 7.87–7.77 (m, 6H), 7.56–7.51 (m, 4H), 7.13–7.10 (d, 2H), 2.08–2.02 (m, 4H), 1.33–0.71 (m, 30H). ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) 196.8, 161.0, 152.0, 140.1, 138.4, 136.0, 133.9, 131.9, 125.7, 121.0, 120.9, 120.4, 118.2, 55.5, 40.6, 32.0, 30.0, 29.8, 29.5, 23.9, 22.8, 14.2. Elemental analysis calculated (%) for $C_{43}H_{50}O_4$: C 81.90, H 7.93; found: C 81.63, H 8.05. MALDI-TOF (*m*/*z*): calculated: 630.8, found: 630.4.

9,9-Dioctylfluorene-2,7-bis-(3-bromobenzaldehyde) (FBal). 9,9-Dioctylfluorene-2,7-bis(trimethylene boronate) (**2**) (0.279 g, 0.5 mmol), 3-bromobenzaldehyde (0.185 g, 1.0 mmol) and $Pd(PPh_3)_4$ (0.006 g) were added to a mixture of 10 mL THF and aqueous 2 M Na_2CO_3 (4 mL) under a nitrogen atmosphere. The

mixture was vigorously stirred at 90 °C for 24 h. After the mixture was cooled to room temperature, it was poured into 100 mL deionized water. The aqueous layer was extracted with dichloromethane three times. The combined organic layers were washed with water and dried over sodium sulfate. After vacuum evaporation of the solvent, the residue was purified by column chromatography (with silica gel and DCM–petroleum ether as the eluent) to give a yellowish liquid (0.194 g, 65% yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 10.13 (s, 2H), 8.19 (s, 2H), 7.96–7.94 (d, 2H), 7.89–7.81 (dd, 4H), 7.67–7.61 (m, 6H), 2.09–2.05 (m, 4H), 1.33–0.70 (m, 30H). ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) 192.5, 152.1, 142.6, 140.6, 138.8, 137.0, 133.2, 129.6, 128.8, 128.1, 126.3, 121.5, 120.5, 55.6, 40.4, 32.0, 30.3, 29.8, 29.4, 23.9, 22.7, 14.1. Elemental analysis for $C_{43}H_{50}O_2$ (%) calculated: C 86.24, H 8.42; found: C 85.81, H 8.47. MALDI-TOF (m/z): calculated: 598.8, found: 598.4.

9,9-Dioctylfluorene-2,7-bis-(5-bromo-2 methoxybenzaldehyde) (FMBal). Powdered K_2CO_3 (0.066 g, 0.48 mmol, 3 equiv.) was added to a solution of 9,9-dioctylfluorene-2,7-bis-(5-salicylaldehyde) (0.1 g, 0.16 mmol) in dry DMF (4 mL) under N_2 and the mixture was stirred at room temperature for 15 min. MeI (0.068 g, 0.48 mmol, 3 equiv.) was added dropwise and the reaction mixture was stirred at room temperature for 12 hours. It was then quenched with water (50 mL) and the solution was extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with water, and brine, dried over sodium sulfate and concentrated. The residue was purified by column chromatography (with silica gel, EtOAc–petroleum ether as the eluent) to give a white solid (0.094 g, 90% yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 10.55 (s, 2H), 8.16–8.15 (d, 2H), 7.90–7.86 (dd, 2H), 7.77–7.47 (d, 2H), 7.58–7.53 (m, 4H), 7.12–7.09 (d, 2H), 4.00 (s, 6H), 2.06–2.01 (m, 4H), 1.25–0.75 (m, 30H). ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) 190.0, 161.3, 151.9, 140.1, 138.5, 134.6, 134.4, 126.8, 125.7, 125.0, 121.0, 120.2, 112.2, 56.0, 55.5, 40.5, 31.8, 30.1, 29.8, 29.3, 23.9, 22.7, 14.1. Elemental analysis for $C_{45}H_{54}O_4$ (%) calculated: C 82.03, H 8.26; found: C 81.67, H 7.94. MALDI-TOF (m/z): calculated: 658.9, found: 658.4.

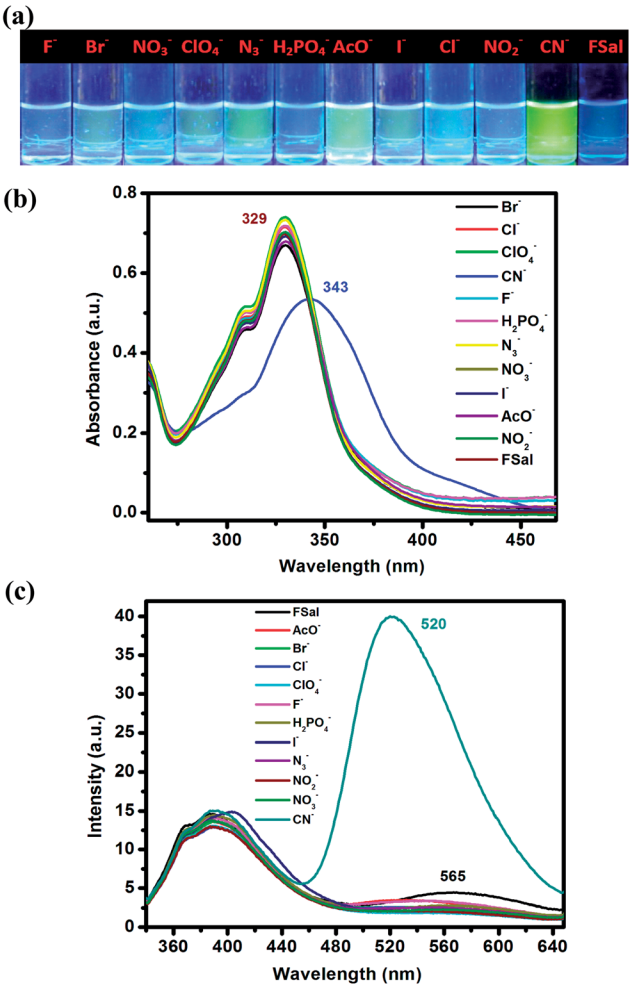


Fig. 1 (a) The fluorogenic response of **FSal** (5 μM in CH_3CN) with 26 equiv. of CN^- and 50 equiv. of other anions in H_2O. (b) The absorption spectra of **FSal** (5 μM in CH_3CN) upon addition of 5 equiv. of CN^- and 10 equiv. of other anions in H_2O. (c) The emission spectra of **FSal** (5 mM in CH_3CN) upon addition of CN^- (26 equiv.) and an excess of other anions (50 equiv.) in H_2O. Excitation at 329 nm (slit 5/5).

3. Results and discussion

Starting from 2,7-dibromo-9,9-dioctylfluorene, followed by boronate ester formation and subsequent reaction with the aldehyde compounds, we have synthesized a fluorene-based salicylaldehyde containing probe (**FSal**) and two model compounds (**FBal** and **FMBal**) according to Scheme 1. All compounds are soluble in all common organic solvents like CH_3CN, DMSO, chloroform, tetrahydrofuran, methanol *etc.* **FSal** shows an absorption maximum at 329 nm (π–π^*) along with a shoulder at 308 nm and an emission maximum at 380 nm (λ_{ex} = 329 nm), along with a low intensity broad peak from 520–640 nm in the CH_3CN solvent (Fig. 1b and c). The ability of **FSal** to complex with other anions (F^-, Br^-, NO_3^-, ClO_4^-, N_3^-, $H_2PO_4^-$, AcO^-, I^-, Cl^-, NO_2^-) has been explored with the help of UV-Vis absorption and emission spectrometry. Upon addition of only 5 equivalents of CN^-, the absorption peak of **FSal** (5 μM) shows a red shift of 14 nm (Fig. 1b) with a decrease in intensity, whereas the addition of other anions (in excess at 10 equiv.) does not affect the absorption maximum. However, a low intensity broad peak is prominent in the 400–450 nm region after addition of CN^- to **FSal** and a visible colour change (from colourless to yellow; Fig. S13 in the ESI†) is observed, indicating the formation of a **FSal**–CN complex.

To explain the colorimetric response of **FSal**, we have performed density functional theory (DFT) calculations on **FSal** and its product, **FSal**–CN.[26] Geometry optimization was carried out at the B3LYP/6-31 G(d) level[27] and optimized geometries were considered for single-point time dependent DFT (TD-DFT) calculations at the B3LYP/TZVP level.[28] The lowest energy geometries of **FSal** and **FSal**–CN, corresponding to a H transfer from phenolic oxygen to formyl oxygen, are shown in Fig. 2a and b. This proton transfer has also been validated by ^{1}H NMR studies (Fig. 3). ^{1}H NMR titrations were performed in $CDCl_3$, with 0.016 mmol of **FSal** dissolved in 0.5 mL of $CDCl_3$. TBACN was dissolved in $CDCl_3$ and added to the NMR tube *via* a syringe, followed by shaking for 5 minutes. The results revealed

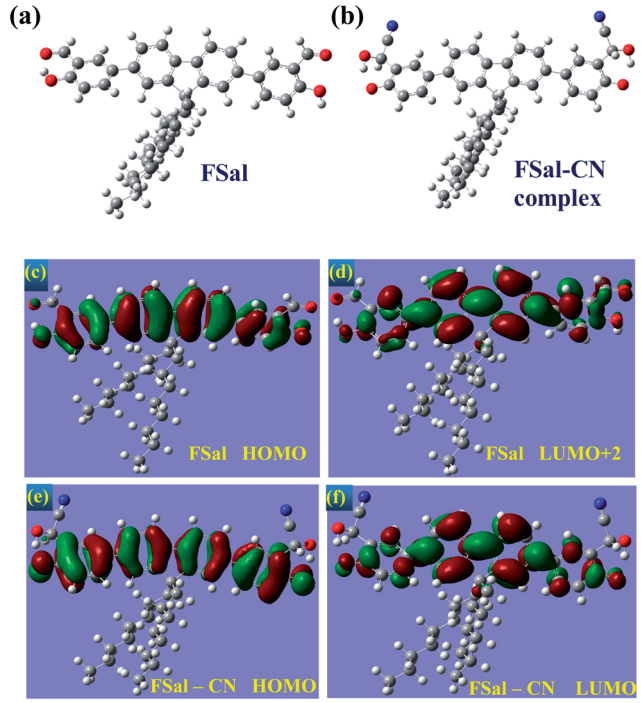


Fig. 2 (a and b) The optimized geometry of **FSal** and the **FSal**–CN complex. The HOMO and LUMO diagrams of **FSal** (c and d) and **FSal**–CN (e and f).

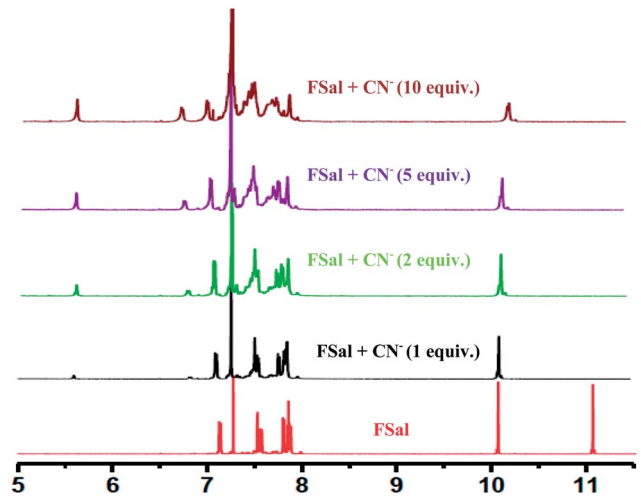


Fig. 3 The partial ^{1}H NMR spectra of **FSal** in the presence of different concentrations of CN^- ions in $CDCl_3$.

that after the addition of CN^- to **FSal**, the aldehyde proton is shifted upfield (from $\delta = 10.03$ ppm to $\delta = 5.6$ ppm) in $CDCl_3$ at room temperature, indicating the formation of cyanohydrin due to the nucleophilic attack of CN^- on the formyl group of **FSal**. As a result, a negative charge has moved to the phenolic oxygen to generate a partial quinonoid structure in which the negative charge is delocalized over the conjugated system.

The TD-DFT calculation for **FSal** also indicates that the peak at 329 nm is due to a π–π^* transition (Fig. 2c and d, HOMO–LUMO+2 at 338 nm with an oscillator strength $f = 1.45$) and after addition of CN^- to **FSal**, the low intensity broad peak appears in the 400–450 nm region, which is for the charge-transfer band from the negatively charged quinone part to the fluorene moiety (Fig. 2e and f). This transition, calculated at 410 nm with an oscillator strength $f = 1.51$, corresponds to the HOMO–LUMO transition (Tables ST1 and ST2 in the ESI†).

The fluorescence response of **FSal** (5 μM in CH_3CN) was studied with the addition of different anions (CN^- 26 equiv. and an excess of other anions at 50 equiv. in H_2O). The emission maximum of **FSal** is shifted to 520 nm after the addition of CN^- with a 9 fold increase in intensity, whereas the addition of other anions does not lead to any significant changes (Fig. 1c). Due to excited state intramolecular proton transfer (ESIPT), which opens routes for nonradiative deactivation, **FSal** is a weak emitter in acetonitrile.[29] After the addition of CN^-, the formyl group of **FSal** generates a cyanoalkoxide anion (deprotonated cyanohydrine) that exchanges the phenolic proton. This process hampers the ESIPT and results in a strong emission.[29] ESIPT is a photoinduced procedure in which a proton jumps across the intramolecular hydrogen bond (IMHB) from a proton donor group to a proton acceptor group, and was first described by Weller.[30] The sensing mechanism for **FSal** with CN^- is shown in (Fig. 4a). To test the sensing mechanism through ESIPT, two model compounds have been synthesized (**FBal** and **FMBal**). As **FBal** has no phenolic-OH group and **FMBal** has a methyl protected phenolic-OH group, the possibility of ESIPT is minimized

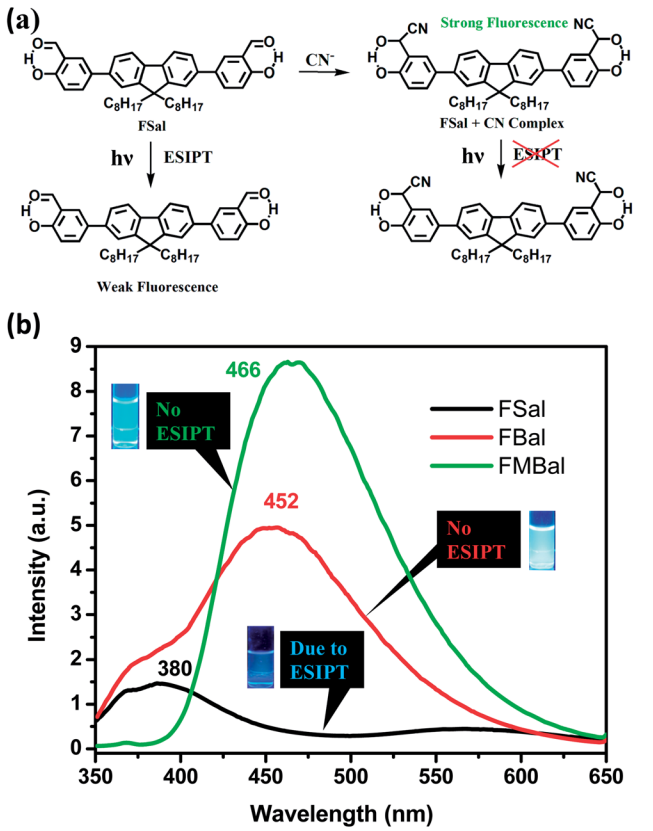


Fig. 4 (a) A scheme of the sensing mechanism of **FSal** for CN^-. (b) Representative emission spectra of three probes (5 μM in CH_3CN).

(Fig. 4b). **FBal** and **FMBal** produce absorbance maxima at 327 and 330 nm and emission maxima at 452 and 466 nm (Fig. S14–S18†) respectively. Even under UV irradiation (λ_{ex} = 365 nm), the solutions of these two moieties show strong emission.

The selectivity of **FSal** has been further demonstrated by observing a visual greenish yellow fluorescent color only for CN^- (Fig. 1a) under a 365 nm UV lamp. However, **FBal** and **FMBal** have no affinity towards CN^- (Fig. S19 in the ESI†). Competitive fluorescence studies were performed in order to elucidate the effectiveness of **FSal** under harsh conditions. The fluorescence spectra of **FSal** (5 μM, in CH_3CN) were recorded after addition of the CN^- anion (25 equiv. in H_2O) in the presence of an excess of other anions (100 equiv. in H_2O, Fig. S20 in the ESI†). A representative bar plot (Fig. 5a), showing the fluorescence response of individual anions (red bars) as well as the selective sensing of cyanide by **FSal** in the presence of an excess of other anions (green bars), reveals the retention of the activity of **FSal** in different environments.

A titration experiment was carried out by taking **FSal** (5 μM in CH_3CN) with gradual addition of an aqueous solution of CN^- (Fig. 5b). The intensity of the peak at 520 nm gradually increases up to 26 equiv. of CN^-. A plot of I/I_0 (where I is the intensity at 520 nm for the **FSal**–CN complex and I_0 is the intensity of **FSal** at 565 nm) against [CN^-] reveals that the curve is linearly fitted from 0 to 5 equiv. of CN^- (Fig. 5c), from which we estimate a detection limit of 0.06 ppm.[31] This limit of detection is much lower than the limit (0.2 ppm) set by the EPA for drinking water. From the Job's plot[32] (Fig. 5d) the binding ratio of **FSal** and CN^- is found to be 1 : 2.

To demonstrate the application of CN^- sensing in cells, we first tested whether this sensor (**FSal**) possessed any cytotoxicity. To elucidate this possibility, the cytotoxicity of **FSal** was performed using a MTT assay[33] for SH-SY5Y neuronal cells (Fig. 6a) with a wide range of **FSal** concentrations. Details of the experiments are given in the ESI.† **FSal** does not show any significant cytotoxicity in SH-SY5Y cells. To further demonstrate the CN^- sensing potential of this novel sensor in cells, internalization of **FSal** was investigated by incubating it with cells. After washing, the cells were treated with CN^-. After CN^- treatment (3 mM), as shown in (Fig. 6c), a successful response is found to CN^- in the

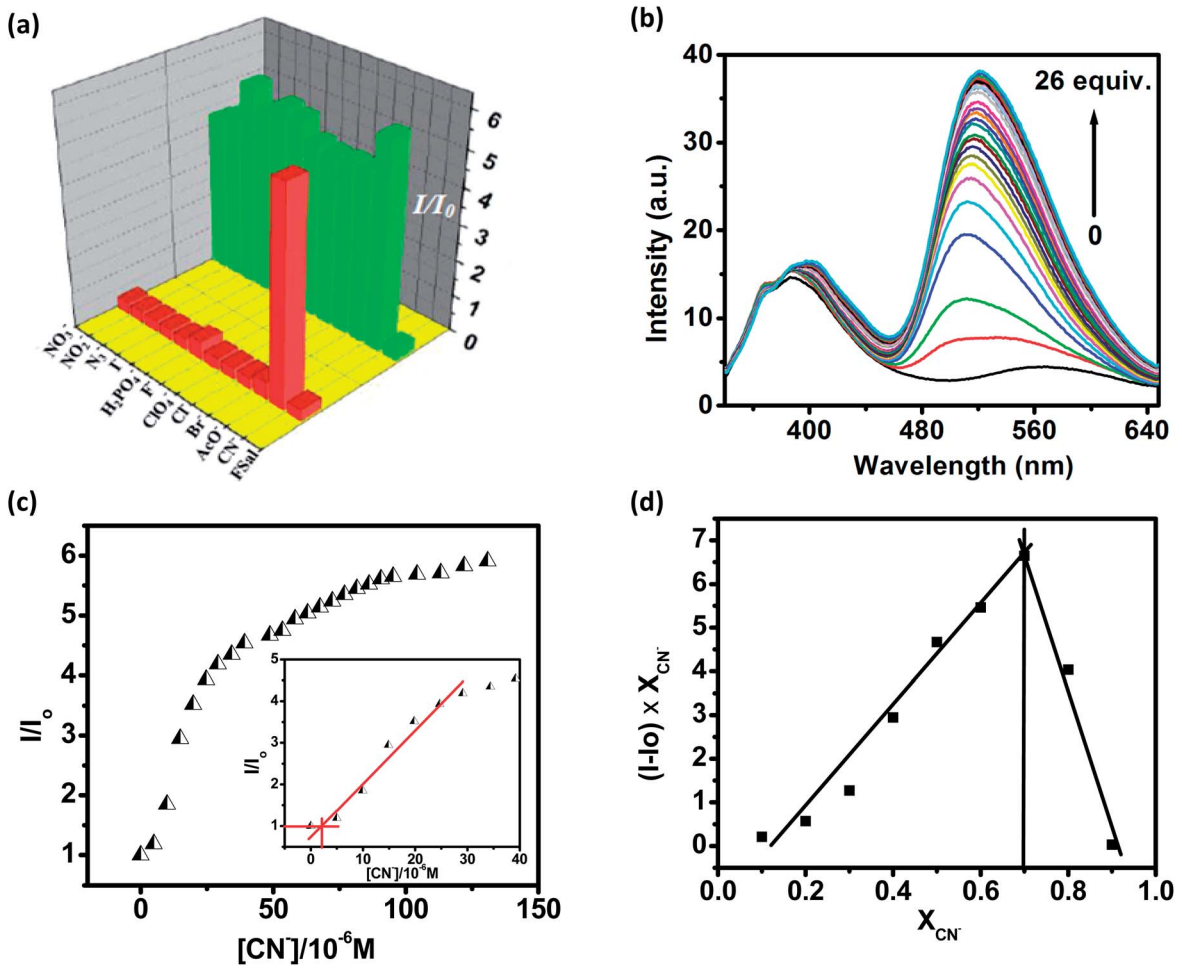


Fig. 5 (a) A bar plot of the fluorescence response for individual anions (red bars) and the selectivity response towards CN^- in the presence of an excess of other anions (100 equiv.) (green bars). (b) The fluorescence titration profile of **FSal** (5 μM in CH_3CN) with CN^- (0–26 equiv.) in H_2O. (c) A plot of I/I_0 *vs.* the [CN^-] fluorescence titration spectra. Inset: an extension of (c) for cyanide concentrations at 0–8 equiv. (d) A Job's plot for the stoichiometry determination of **FSal** to CN^- indicating a 1 : 2 ratio of **FSal** to CN^-, observed from the emission spectra.

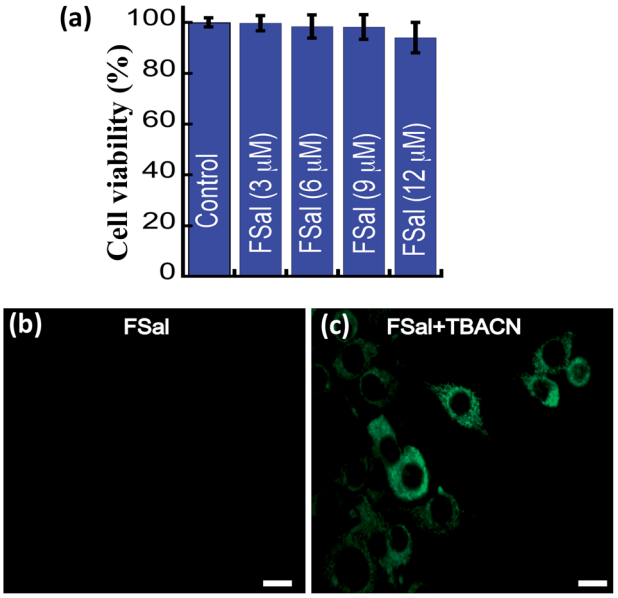


Fig. 6 (a) A MTT assay for **FSal**. (b) Fluorescence imaging of SH-SY5Y neuronal cells which were incubated with **FSal** (12 μM) and (c) SH-SY5Y cells after treatment with 3 mM tetrabutylammonium cyanide.

cytoplasm of SH-SY5Y neuronal cells. The data indicate that our sensor (**FSal**) can detect the CN^- that accumulated inside the cells.

Conclusion

In summary, we have designed and synthesized a salicylaldehyde-appended fluorene-based chemodosimeter (**FSal**) which has been recognized as a CN^- sensor with high selectivity and a very low detection limit (0.06 ppm which is much below the permissible level (0.2 ppm) of drinking water) for the first time. TD-DFT calculations support the proposed mechanism. Our designed probe is biocompatible and *in vitro* cell imaging with SH-SY5Y neuronal cells has been explored. Our designed probe **FSal** is nontoxic and *in vitro* cell imaging provides a good response after the addition of CN^-. Hence, it can be employed for real-life applications. Therefore, our compound will cover a wide range of chemical and biological applications.

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