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*Theranostics*

Review

# Fluorescent Sensing of Fluoride in Cellular System

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## Abstract

Fluoride ions have the important roles in a lot of physiological activities related with biological and medical system, such as water fluoridation, caries treatment, and bone disease treatment. Great efforts have been made to develop new methods and strategies for F⁻ detection in the past decades. Traditional methods for the detection of F⁻ including ion chromatography, ion-selective electrodes, and spectroscopic techniques have the limitations in the biomedicine research. The fluorescent probes for F⁻ are very promising that overcome some drawbacks of traditional fluoride detection methods. These probes exhibit high selectivity, high sensitivity as well as quick response to the detection of fluoride anions. The review commences with a brief description of photophysical mechanisms for fluorescent probes for fluoride, including photo induced electron transfer (PET), intramolecular charge transfer (ICT), fluorescence resonance energy transfer (FRET), and excited-state intramolecular proton transfer (ESIPT). Followed by a discussion about common dyes for fluorescent fluoride probes, such as anthracene, naphalimide, pyrene, BODIPY, fluorescein, rhodamine, resorufin, coumarin, cyanine, and near-infrared (NIR) dyes. We divide the fluorescent probes for fluoride in cellular application systems into nine groups, for example, type of hydrogen bonds, type of cleavage of Si-O bonds, type of Si-O bond cleavage and cylization reactions, etc. We also review the recent reported carriers in the delivery of fluorescent fluoride probes. Seventy-four typical fluorescent fluoride probes are listed and compared in detail, including quantum yield, reaction medium, excitation and emission wavelengths, linear detection range, selectivity for F⁻, mechanism, and analytical applications. Finally, we discuss the future challenges of the application of fluorescent fluoride probes in cellular system and *in vivo*. We wish that more and more excellent fluorescent fluoride probes will be developed and applied in the biomedicine field in the future.

Key words: fluoride; fluorescent probes; fluorophores; cell, *in vivo*.

## Introduction

Fluoride ion (F⁻) is widely found in biological systems and the external environment. Proper amount of fluoride may protect teeth from caries and enhance mineral deposition in bone [1]. The American Dental Association (ADA) recommends a fluoride concentration of 0.6~1.2 mg/L in bottled water. But high concentration of F⁻ has been demonstrated to be toxic and causing acute or chronic diseases. Over the years, over exposure to fluoride has been related to the occurrence of several types of pathologies in hu-

mans, such as dental fluorosis, skeleton fluorosis, osteoporosis, metabolic dysfunctions, and cancer [2]. Dental fluorosis appears as unnoticeable, tiny white streaks in the enamel of the tooth in mild forms, and discoloration or brown markings in severe forms, which are permanent or even darken over time. Skeletal fluorosis causes severe pains in joints accompanied with stiffness, which may eventually end with paralysis or the disabled problems. Besides, fluoride can cause neurotoxicity in both laboratory animals and human [3, 4]. The double-side effects of fluoride make it very important to monitor the fluoride concentration *in vitro* and *in vivo*.

Great efforts have been made to monitor fluoride ions by traditional analytical methods. Ion chromatography, a technique that exploits ion exchange activity to separate ions and polar molecules based on their charge differences, has been used to measure fluoride in mulberry leaves, soil, toothpaste, and other substances. However, chromatographic methods are time consuming and require costly instruments [5]. Another widely used method employs ion-selective electrodes (ISE), which shows a linear relationship for the specific ionic activity within a certain ion concentration range, as electrochemical sensors. The difficulties of ISE include electrode drift, time consumption for equilibration and dissolution of the lanthanum fluoride membrane crystal [6]. Most traditional spectroscopic techniques, which study interactions between matter and radiated energy [7], have similar detection ranges down to the microgram level (Additional file 1: **Supplementary Table 1**).

The above fluoride detecting methods cannot be employed for biosensing, especially for the *in vivo* application. In the past decades, fluorescent probes have been broadly studied in biomedicine as promising chemically sensing and analyzing methods that can take the place of traditional analytical methods to some extent. Fluorescent probes make it possible to locate some specific molecules or ions and image them by fluorescence, and transduce the nanoscopic biochemical processes into optical signals. They have become the essential tools in chemistry, medicine, and biochemistry fields [8].

As overdose fluoride may affect multi-tissues in human body, it is important to monitor the trafficking of fluoride in the body, then we will know which tissues or cells easily being targeted by fluoride and avoid the tissue specific toxicity. The advances in fluorescent probes make it possible to simultaneously monitor fluoride ions, in particular, sense and visualize fluoride inside live cells. In this review, we will introduce the general mechanisms for reaction, fluorescent dyes, types and carriers of fluorescent fluoride probes being applied in biosystems. We also analyze the challenges in the future trends of fluorescent fluoride probes in cellular system.

## Photophysical Mechanisms for Fluorescent Probes for Fluoride

Effective fluorescent fluoride probes must meet stringent requirements. They should respond selectively and sensitively to fluoride ions in a complex system that exploits effective fluorescence transduction mechanisms. In general, the mechanisms of fluorescence transduction involves manipulation of electron transfer on binding of the analyte by the probes, including photoinduced electron transfer (PET) [9], intramolecular charge transfer (ICT) [10], fluorescence resonance energy transfer (FRET) [11], excited-state intramolecular proton transfer (ESIPT) [12] and so on.

PET can be pictorially elucidated by molecular orbital theory, during which processes the fluorescence intensity will be decreased, known as "quenching" of the fluorescence [13]. For PET probes, a short aliphatic spacer usually separates the receptor and fluorophore consisting fluorophore-spacer-receptor constructs [14] (**Fig. 1**). ICT happens from an electron donor to an electron acceptor, conjugated without spacer, and the dipole moment is increased during the process. ICT causes significant shifts in the absorption and emission bands, which reflects the strength of the Donor-Accepter interaction (**Fig. 2**). The difference between PET and ICT probes is the way of fluorescence response in recognition processes. PET's quenching effect does not cause the specific spectral shifts. In contrast, ICT probes display ratiometric measurements with clear fluorescence band shifts in the binding processes.

FRET is the interaction between donor and acceptor which results in a transfer of excitation energy. The whole process can be influenced by several factors, including the distance between donor and acceptor, the spectrum overlaps between the donor and acceptor, the dipole moment of the molecules and so on [15, 16] (**Fig. 3**). ESIPT commonly happens in the molecules with a five- or a six-membered ring which undergoes tautomerization process accompanied with emission changes. ESIPT chromophores can avoid self-absorption, or the inner filter effect, and improve the fluorescence analysis [17] (**Fig. 4**).
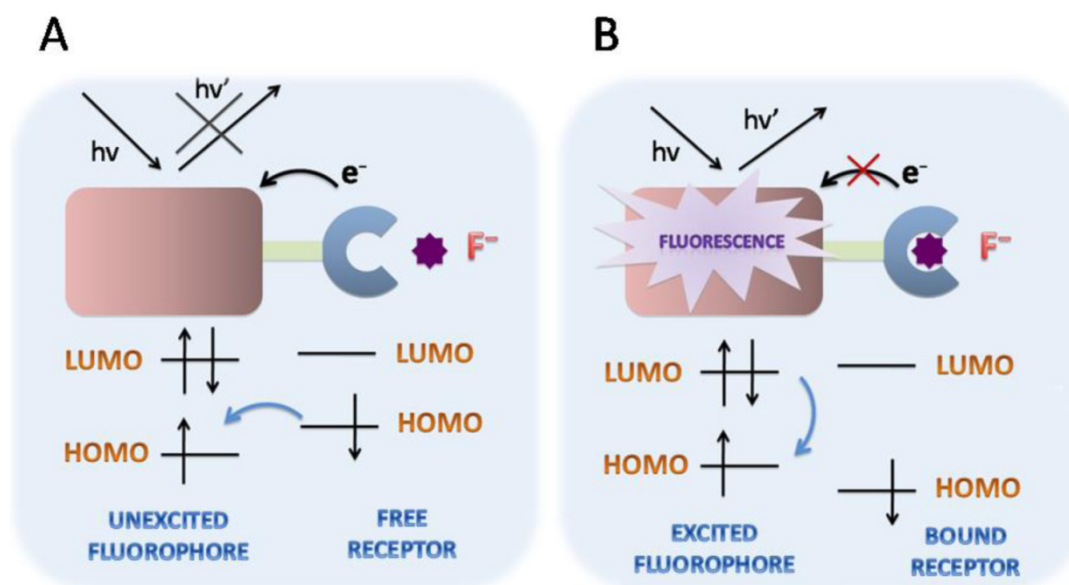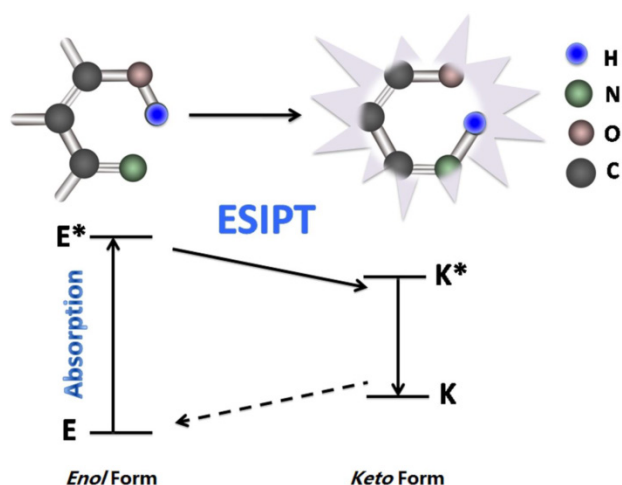
**Figure 1.** Schematic PET mechanisms for fluorescent fluoride probes. A. PET fluorescent fluoride probes is consisted of fluorophore-spacer-receptor constructs, for a short aliphatic spacer separates the fluorophore and receptor. Besides, a relatively high-energy electron pair without bonding is required in the receptors. After excitation, an electron of HOMO is promoted to LUMO, in which a rapid intramolecular electron transfer occurs between the HOMO of receptor and the LUMO of excited fluorophore in the unbound state. The quenching effect of the probe is in the fluorescence "off" state. B. However, the bounded receptor caused electron pair coordinating to F-, making the HOMO of receptor even become lower than that of the fluorophore. The perturbed receptor redox potential slowed down or even switched off the PET process, then causing fluorescence"turned on". HOMO (highest occupied molecular orbital); LUMO (lowest unoccupied molecular orbital).
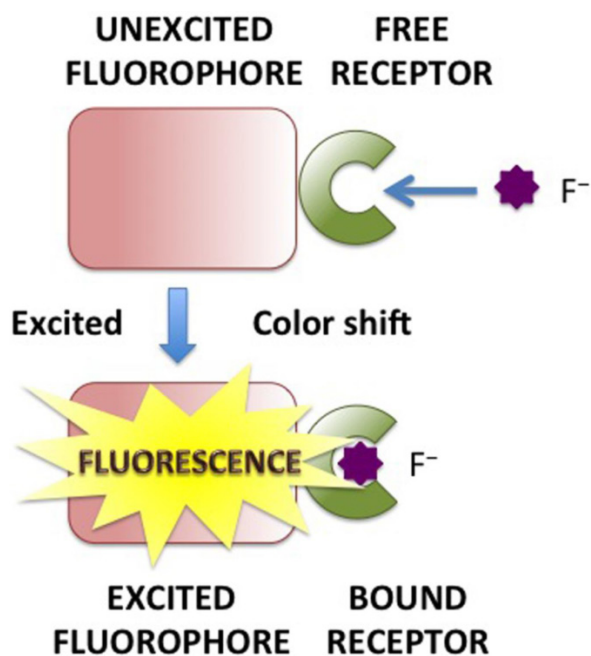


**Figure 2.** Schematic ICT mechanisms in designing fluorescent fluoride probes. The fluorophore possessing an electron-donating group is directly connected to an electron-withdrawing group without spacer. During the recognition processes, the electron density in the fluorophore is affected by the coordination between the recognition group and fluoride, resulting in the color changes of fluorescence emission. ICT causes significant shifts in the absorption and fluorescence emission bands.
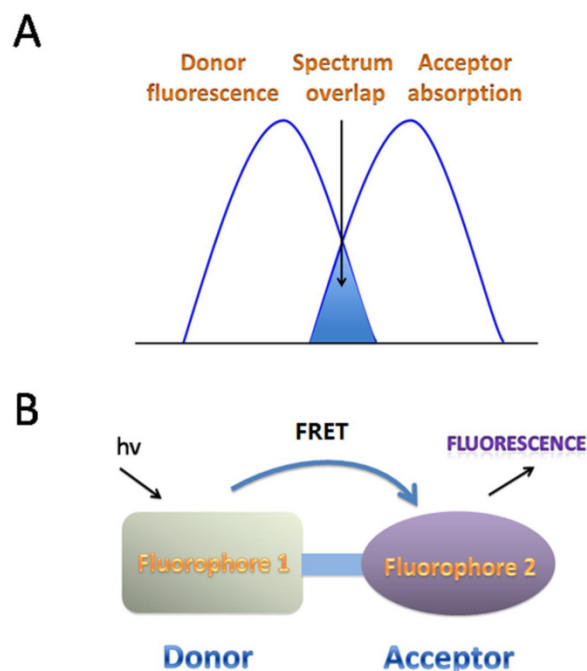


**Figure 3.** FRET mechanisms for fluorescent fluoride probes. A. Schematic representation of the interaction of two different fluorophores. The extent of spectral overlap between the emission spectrum of fluorophore 1 (Donor) and the absorption spectrum of fluorophore 2 (Acceptor) is required to allow for FRET to occur. B. FRET happens with an energy transfers from the excited fluorophore 1 (Donor) to the longer-wavelength fluorophore 2 (Acceptor) (D* + A→D + A*), which is coupled in resonance, causing light emission from the acceptor, accompanied with a loss of emission from the donor.

**Figure 4.** Schematic mechanism of ESIPT for fluorescent fluoride probes. ESIPT is based on the large Stokes' shift. The unexcited molecules usually exist as an enol (E) form in which the intramolecular hydrogen-bond is formed. Upon photo excitation it undergoes an extremely fast tautomerization process into a keto form (E*→K*). Then an ESIPT process occurs and the intramolecular hydrogen-bond stabilizes the keto form. Both radiative decay and the deactivation channel lead to excited keto (K*) form to the ground state keto (K) forms. Since the ESIPT is much faster than radiative decay, the fluorescence observed for the ESIPT chromophores is very often. Moreover, the significant differences in absorbing (E*) and emitting (K*) feature are apt to generate a large Stokes' shifted fluorescence, which is desirable because the self-absorption can be avoided, improving the fluorescence analysis.

## Common Dyes for Fluoride Fluorescent Probes

A suitable fluorophore platform is quite important for fluorescent fluoride probes, and may affect their biological applications and efficiency. The reported dyes for fluorescent fluoride probes include anthracene, naphalimide, pyrene, BODIPY, fluorescein, rhodamine, resorufin, coumarin and cyanine (**Fig.5**). Near-infrared (NIR) dyes are paid more and more attentions during the recent years. All the molecular formulas of the mentioned fluorescent fluoride probes are listed in supplementary figures (Additional file 1: **Supplementary Figure 1, 2, 3, 4**).

### Anthracene Dyes

Anthracene consists of three fused benzene rings, and its emission spectrum peaks at 400~450 nm under ultraviolet light. Since Kim and Yoon reported a fluorescent PET fluoride probe based on a bi-surea-anthracene derivative [18], more PET probes
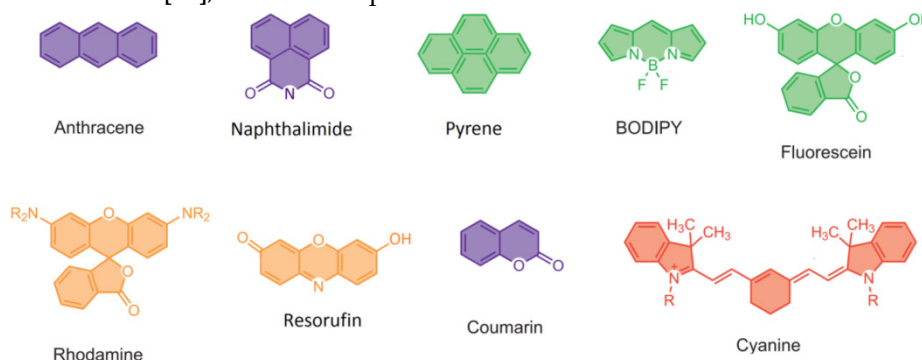
have been designed based on urea-anthracene derivatives and hydrogen-bond theory is mostly used among them. The metal-free organic dyes linked to anthracene-containing π-conjugations have also been used for the probe design [19]. *Probe 1* was based on anthracene-9,10-dicarbaldehyde bis-*p*-nitrophenylhydrazone and its fluoride detection limit was $2 \times 10^{-6}$ M [20]. The bond between *Probe 1* and $F^-$ was recognized as light red to dark brown by naked eye inspection and underwent the intensity changes around 482 nm and 672 nm, respectively.

### Naphthalimide Dyes

1,8-Naphthalimide probes containing electron donor and acceptor moieties are the typical ICT fluorophores, and are ideal for the construction of colorimetric and ratiometric fluorescence probes. 1,8-Naphthalimide has an excitation wavelength of 420 nm and is highly desirable for sensing in competitive media. Its derivatives have high stability, quantum yield and convenient functionalization at 4-position site and are broadly applied in fluorescent probes [21]. In an earlier report, Emma *et al.* demonstrated the use of the 1,8-Naphthalimide in PET probes for anions and the deprotonation could also occur in competition, or in conjunction, with such hydrogen bond [22]. Later, the method was modified either on the aromatic "naphthalene" moiety itself, or at the "N-imide site", which makes it to incorporate with different functional groups and structural motifs possible [23, 24]. Additionally, 1,8-Naphthalimide-derived fluorescent fluoride probes can be used to image live cells by two-photon spectroscopy. Zhang *et al.* synthesized a colorimetric and ratiometric fluorescent *Probe 2* that employed 4-amino-1,8-naphthalimide as reporter for $F^-$ [25]. Upon addition of 120 μM $F^-$, *Probe 2* showed a 49 nm red-shift in the emission band from blue to green in $CH_3CN$, which was based on the fact that $F^-$ can promote the cleavage of Si-O bond with the release of the green fluorescent 4-amino-1,8-naphthalimide.



**Figure 5.** Molecular formulas of common dyes of fluorescent probes for fluoride.

## Pyrene Dyes

Pyrene is consisting of four fused benzene rings in a polycyclic aromatic hydrocarbon structure. Pyrene moiety exhibits intramolecular excimer due to strong π-π interaction between two fluorophore units and excimer emission is changed in the presence of guest ions. Its fluorescence emission spectrum is around 490~520 nm and very sensitive to solvent polarity. The molecules with pyrene have several advantages over other fluorophores, such as the magnitude of the emission intensity ratios between the monomers and the excimers, relatively long lifetimes and the high fluorescence quantum yields [26]. The pyrene excimer transformation mechanism was exploited in fluorescent fluoride *Probes 3* and *4*. It has two pyrene moieties, which were linked by flexible -O-Si-Si-O- or -O-Si-O- chains [27]. The intracellular pyrene monomer luminescence could be clearly observed within HeLa cells over the short wavelength range 410~440 nm.

## BODIPY Dyes

Boron-dipyrromethene (BODIPY) dyes have high absorption coefficients, high fluorescence quantum efficiencies, high affinities with silicon, and exceptional stability. Although Treibs and Kreuzer have reported BODIPY-set as early as 1968 [28], it is till the mid 1990s that the application of BODIPY-based dyes in fluorescent probes was fully achieved. Compared to the cyanine dyes and NIR-active fluorophores, the BODIPY dyes have the shorter wavelength emission maxima and smaller extinction coefficients. Liu *et al.* have realized the direct conversion of BODIPY based fluorescent probes may promote [$^{18}$F] fluorination of the BODIPY dye emitting in the NIR region in nude mice bearing human U87MG glioblastoma tumors [29]. The application of PET mechanism in BODIPY fluorescent probes has also been reported by other research groups. For example, a BODIPY *Probe 5* was synthesized with alkynyl groups as electron donating groups [30]. Because of the high affinity between Si and F$^-$, the alkynyl groups underwent catalyzed deprotection and electron transfer then occurred in the system. Addition of F$^-$ to *Probe 5* in $CH_2Cl_2$ resulted in ratiometric changes around 571nm/551nm and 584nm/564nm, respectively. BODIPY based *Probe 6* contained two dimesitylboryl ($Mes_2B$) moieties. It showed intense absorption at λ = 576 nm and a highly efficient orange-red emission at λ = 602 nm in the presence of F$^-$. The reaction processes accompanied with a visually detectable color change from pink to blue [31].

## Fluorescein Dyes

The fluorescein dye with spirolactam structure is non-fluorescent. The ring-opening processes of the spirolactam results in the open form and a strong fluorescence color change [32]. The fluorescence of fluorescein is very intense and its peak excitation and peak emission occurs at 494 nm and 521 nm, respectively. Due to relatively large visible-range extinction coefficients, high stability against light and high fluorescence quantum yield, it is a widely applied platform in fluorescent sensing for reactive oxygen species and metal cations. Swamy and his colleagues synthesized a fluorescein derivative that bore a boronic acid group as binding site. This probe showed an F$^-$-induced emission "off-on" type fluorescence enhancement because the coordination of F$^-$ with the ligand groups changed the PET reaction from the amine nitrogen to the photo excited fluorescein moiety [33]. The fluorophore of *Probe 7* is a fluorescein moiety which had a better solubility in water. Its *tert*-butyldimethylsilyl (TBDMS)/*tert*-butyldiphenylsilyl (TBDPS) group functioned as a fluoride reactive subunit [34]. Upon the addition of F$^-$, *Probe 7* penetrated the cellular membrane of HeLa cells and sensitively detected F$^-$. The detection limit was 18 μM in HEPES-THF.

## Rhodamine dyes

Rhodamine dyes, belonging to the xanthene class of dyes, generally have high molar absorptivities in the visible region. They show high brightness, good photostability, and the ability to modulate dye's substitution. Rhodamine has different derivatives, and the fluorescence emission spectrum and excitation wavelength of simplest rhodamine are 496 nm and 517 nm, respectively. Several fluorinated rhodamine derivatives have been synthesized [35]. Sivaraman and Chellappa have reported a rhodamine fluoride probe with high selectivity and colorimetric fluorescence. Fluoride triggered spirolactam ring opening processes caused the fluorescent changes, which was based on the density functional theory calculations and $^1$HNMR titrations. It could image the intracellular fluoride in HeLa cells [36].

## Resorufin Dyes

Resorufin exhibits maximal emission at 585 nm and excitation at 550 nm, respectively. It can be exploited as a signaling fluorophore group in cellular system without any damage. The fluorescence emission may be quenched by the alkylation of the 7-hydroxy group in resorufin. The fluoride-induced Si-O bond cleavage may cause the release of resorufin, resulting in dual spectroscopic changes. *Probe 8* was a dual chromogenic and fluorescent probe. Upon the

addition of fluoride, it showed an obvious change by UV-Vis observation. It released resorufin through substitution by F- at the silicon center [37]. 3000 equiv of F- induced 200-fold enhanced fluorescence intensity at 589 nm in $CH_3CN/H_2O$.

## Coumarin Dyes

Coumarin is one of fragrant organic chemical compounds. It belongs to a classic type of "push-pull" dyes. Upon excitation, an ICT process occurs from the electron donor to the acceptor. Coumarin can be rendered nonfluorescent by caging with trialkylsilyloxy moieties. With the addition of F-, the caging groups are removed and a "turn-on" fluorescence emission was induced which involved the reactive "turn on" fluorescence. Based on DHBC (double hydrophilic block copolymer), *Probe 9* was a "turn-on" fluorescent reactive probe for F- with high sensitivity and selectivity [38]. F- induced cyclization produced temperature-sensitive fluorescent coumarin moieties. The unimers and micellar nanoparticles were very sensitive and selective to F- with the detection limits of 0.065 ppm ( diblockunimers ) and 0.05 ppm( micelles ), respectively. Its drawbacks were that the sensing process was based on the intensity changes of only one single emission band, which made it difficult to calculate concentrations.

## Cyanine Dyes

Cyanine dyes contain two connected nitrogen centers by a polymethine bridge. They have odd number of carbons in the molecule. Cyanine dyes have many merits such as the large extinction coefficients, strong fluorescence, moderate-to-high fluorescence quantum yields and easily tunable maximum of absorption and emission by varying both the length of the polymethine bridge and the heterocyclic structure [39]. Cyanine has different derivatives, and some of them are promising to be NIR region fluorescent probes. *Probe 10* was based on 1-ethyl-4-(*p-tert*-bytyldimethylsilane ether styryl) quinolinnium iodide, one of cyanine derivatives [40]. Under optimized conditions, absorbance at 600 nm has a linear relationship with $1.0\times10^{-7}$ ~$1.0\times10^{-4}$ M fluoride.

## NIR dyes

The absorption and emission bands of the above mentioned dyes are within the ultraviolet-visible (UV-Vis) light range (**Fig. 6**). It is difficult to use them targeting fluoride in living animals. The limited tissue penetration and auto-fluorescence interference problems usually result in low signal-to-noise ratio. Recent years, researchers have paid more attention to the NIR fluorescent probes which have absorption and emission peaks between 650~900 nm *in vivo* bioimaging. These probes have less photo-damage to cells or tissues, deeper tissue penetration, and less cross with auto-fluorescence background [41].

*Probe 11* was an earlier NIR "turn-on" fluorescence probe for fluoride with a dicyanomethylene-4H-chromene moiety. It had several features including high off/on ratio responses as well as high selectivity to fluoride [42]. This probe showed a significant "turn-on" fluorescence response at 718 nm proportional to fluoride from 0.01 to 2 mM and its detection limit was $8.5\times10^{-8}$ M. *Probe 12* was based on 1,2,3,3-tetramethyl-3H-indolium iodide and 2-(4-formylphenyl) phenanthroimidazole [43]. The fluoride induced deprotonation of N-H on the imidazole moiety attributed to its unique emission in the NIR region and excitation in the visible light region.
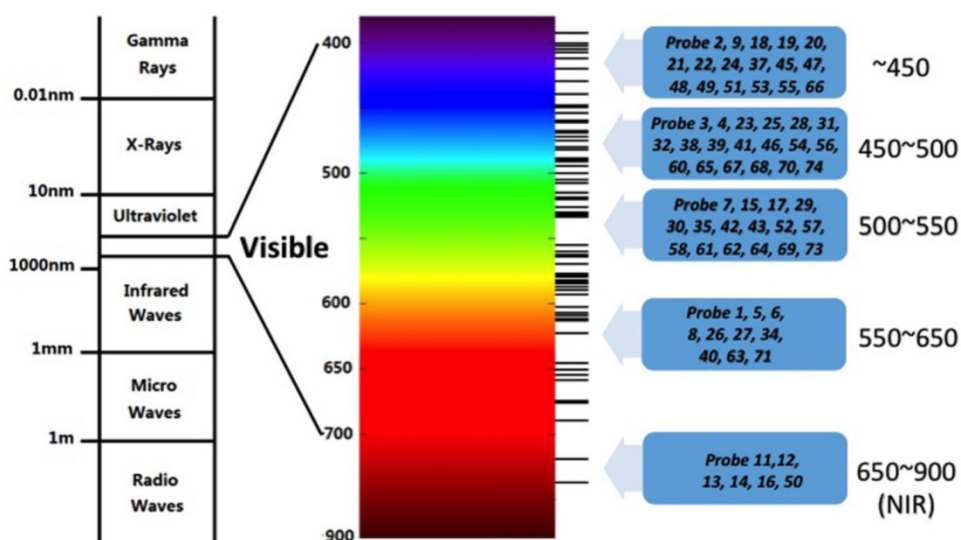


**Figure 6.** Spectrum distribution of *Probe1~Probe 74*.

Other representing NIR fluoride probes are *Probe 13* to *Probe 16*. The selectivity of *Probe 13* towards F- was related with the decreasing HOMO-LUMO gap upon stepwise judicious substitutions over ethylacetoacetate [44]. *Probe 14* exploited the extraordinary affinity of F- for Si, and displayed an obvious color change accompanied with a distinct NIR fluorescence upon F- within 30 s [45]. A fully aromatic D-π-A-π-D-type molecule 3,6-*bis*[4-(4-(diphenylamino)-phenyl)phenyl]-N-octyl-1,4-diketo-pyrrolo [3,4-c]pyrrole (TDP) operated as one- and two-photon probe selectively for F- in *Probe 15* [46]. But the fluoride induced ratiometric changes in emission spectra upon two-photon were higher than in one-photon excitation. TDP may sense fluoride anions under longer excitation wavelength and lower input laser power.

Some NIR fluoride probes have been used in cell culture system. *Probe 16* had a B-Se bond linking a BODIPY dye with benzotrifluoride [47]. After incubated with 1.0 μM F- for 1 h, human hepatoma cells (HepG$_2$) showed an increase in the intracellular fluorescence intensity with 1.0 μM BODIPY-Se.

## Types of Fluorescent Fluoride Probes in biosystems

### Type of Hydrogen-Bond

The majority of the existing fluorescent fluoride probes are based on the hydrogen bond between NH group and F-. As the smallest and the most electronegative element, fluorine has unique chemical properties and is able to form strong hydrogen-bond with other hydrogen-bearing functional groups, such as NH group (**Fig. 7A**). The acidic NH groups of hydrogen-bond donor, such as urea, thiourea, and amide, may function as fluoride binding site. Fluoride can in turn deprotonate the acidic amidic NH groups to block the charge separation and modify the charge dispersion, then a quenching effect is achieved following the PET mechanisms. According to the report, the pK$_a$ of HF may be 1.5 [48]. Most of hydrogen-bond type fluoride probes were based on PET mechanisms.

On the basis of hydrogen-bond, a series of fluorescent fluoride *Probes 17~27* have been designed. *Probes 17* and *18* were based on salicylaldehyde-based colorimetric and fluorescent [49], while *Probes 19~22* were based on anthraimidazoledione *via* an ICT process [50]. In order to improve the selectivity and sensitivity, the connecting between polyphenylacetylene and naphthalimide unit in the side chain was used to design the polymer *Probes 23* [51]. By the visible detection, *Probes 23* could detect 10 μM~100 μM fluoride. Other hydrogen-bond type fluoride probes include *Probes 24~26* in which naphthalimide

derivatives were chosen as chromogenic and fluorogenic signaling subunit [52-54].

Despite their high sensitivity and selectivity, hydrogen-bond probes have certain limitations for biosensing because of the high solvability of fluoride in water. The hydration free energy of fluoride is around *ca*.100~110 kcal /mol, close to the energy in a C-H covalent bond [55]. Most reported hydrogen-bonding fluoride probes work only in organic solvents, and their biological applications are inhibited in water.

Fewer hydrogen-bond type fluoride probes were reported in cell biology study. A phenolic OH group was employed to design *Probe 27* [56] as the color-reporting unit through F⋯H-O interactions. It possessed good membrane permeability and accumulated in lysosomes of cells because the fluorescence intensity of *Probe 27* could be enhanced in protein containing acidic environments, thus it might be a promising lysosome marking reagent.
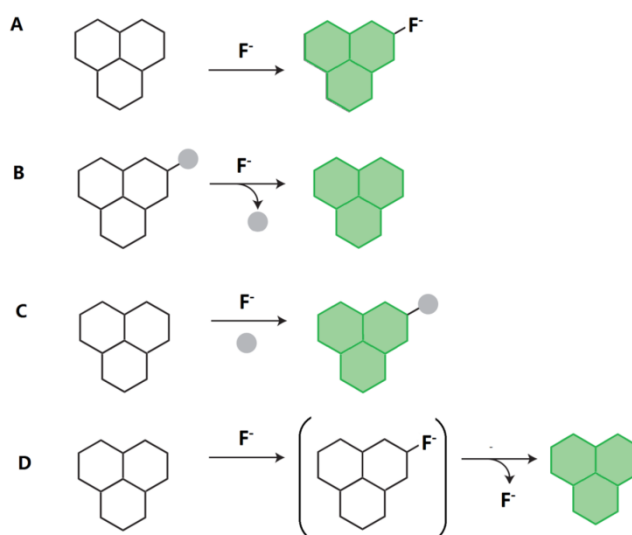


**Figure 7.** Representative mechanism for fluorescent fluoride probes. A. Binding site-signaling subunit approach (hydrogen-bond and organoboron compounds); B. Bond-cleavage reactions (cleavage of Si-O bonds, cleavage of Si-O bonds and cylization reactions, and cleavage of Si-C bonds); C. Organic addition and metal-ligand substitution approach (nucleophilic addition reaction and metal-mediated fluorescent fluoride probes); D. Tandem reaction cascades to unmask a fluorogenic scaffold (intramolecular hydrogen transfer reaction). The green "polyaromatic" shape is used to represent a generic fluorophore.

### Type of Cleavage of Si-O Bonds

Fluoride may easily remove silyl ether because of the high affinity between fluoride and silicon (**Fig. 7B**), thus some fluorescent fluoride probes are developed based on fluoride-mediated desilylation such as *Probes 28~34*. However, the requirements of long reaction time and organic solvent in the reaction systems restrict the utility in biosystem. Recent years, many of them have been modified for the application in cellular research. For example, Lee *et al.* designed a

new coumarin-based *Probe 28* which was based on the electron "push-pull" effect and it exhibited a red shift to 500 nm in emission intensity in aqueous media within 10 min [57].

TBDMS and TBDPS groups are the most widely used moieties for *in vivo* fluorescent fluoride probes. TBDPS moiety may be used in place of TBDMS to inhibit the accessibility of water molecules to the silicon atom. Both TBDMS and TBDPS have been used in fluoride-mediated desilylation and sugar-functionalized fluorescent fluoride *Probe 29* [58]. *Probe 29* was based on the silylation at the phenolic hydroxyl group by TBDMS, and exhibited the properties of fast reactivity, high selectivity, and non-cytotoxicity in aqueous media. The whole reaction required only 5 min and the detection range was 0.1 to 1 mM in PBS. It showed no toxicity to human carcinoma cell lines at 50 mM and 100 mM by MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide) assay. The sugar residue in *Probe 30* improved both water solubility and biocompatibility. In fully aqueous and cellular systems, the probe showed better colorimetric, sensitivity and selectivity toward $F^-$, and presented good imaging of $F^-$ in HepG2 cells [59].

TBMCA (TBDMS-7- hydroxycoumarin-4-acetic acid methyl ester) and its bulkier lipophilic TBDPS analog (TBPCA) were designed to reduce cleavage of the silicon group by water in *Probe 31* [60]. TBPCA had a high selectivity toward $F^-$ against other anions. In A549 human lung epithelial cells, TBPCA fluorescence displayed an intracellular fluoride concentration of $1.86 \times 10^{-2}$ pmol. *Probe 32* was consisted of an non-toxic ICT structure and a lipophilic TBDPS moiety [61]. The probe showed a higher selectivity toward $F^-$ than other anions with a reaction range from 0.5 to 28 mM and a detection limit of 0.08 mM. When it was used to detect RAW 264.7 macrophage cells treated with 3 mM NaF, the significant intracellular fluorescence was observed. Another probe with good cell permeability and intracellular imaging was *Probe 33* which contained the relatively hydrophilic TCF (2-dicyanomethylene-3-cyano-4,5,5-trimethyl-2,5-dihydrofuran) and TBDPS [62]. In addition, *Probe 33* could be used to detect $F^-$ quantitatively by the ratiometric absorption and "turn-on" fluorescence spectroscopy methods with a detection limit of 0.07 mM.

A dual-channel *Probe 34* for $F^-$ has been developed and synthesized from 4-hydroxy-1,8-Naphthalimide and *t*-butyldiphenylsilyl derivative [63]. The probe could quantitatively determine $F^-$ both in water and organic media. In $CH_3CN/H_2O$, the probe may detect fluoride with a concentration of 0.35 mg/L, lower than EPA's (United States Environmental Protection Agency) requirements, which is 1.0 to 4.0 mg/L of fluoride in drinking water. *Probe 34* could also be used to detect intracellular fluoride of A549 cells.

## Type of Si-O Bond Cleavage and Cylization Reactions

*Probe 35* was synthesized *via* the cleaved Si-O bond of FTBS (di-*tert*-butyldimethylsilyl ether). The deprotection of TBS produced a fluorescein spirocycle-opened species in the presence of fluoride [64]. The fluorescence intensity had a linear relationship with fluoride between 0.1~2.0 µM and its limit of detection was 0.041 µM. Kim and Swager constructed several coumarin derivatives *Probe 36~39* with various electrondonating groups as ratiometric probes for $F^-$ [65]. Amplification of a "turn-on" conjugated polymer is achieved by FRET mechanisms and the chromophore was linked to the polymer. Comparing with *Probe 39*, *Probe 37* was a small-molecule-based counterpart. Over the same time and with all the same other conditions, *Probe 39* was more sensitive, and required a higher $F^-$ concentration for the fluorescence transformation.

## Type of Cleavage of Si−C Bonds

It is well known that the cleavage of Si-C is much easier than Si-O bond and fluoride ions may trigger the cleavage reaction of the Si-C bond in $-C \equiv C-SiMe_3$ and generate terminal acetylenes. Such cleavage of Si-C bonds with the addition of fluoride has been used to design fluorescent fluoride probes (**Fig. 7B**). Fluoride ions could break the Si-C bond in $-C \equiv C-SiMe_3$ within 5 min and readily reach equilibrium in a BOIDPY-derivative *Probe 40* with a detection limit of 67.4 nM [66]. *Probe 41* was developed with core-substituted naphthalene diimide (cNDI)-based receptors for sensing of $F^-$ [67]. Upon addition of $F^-$ in $CH_2Cl_2$, the cleavage resulted in the remove of the TMS group. The desilylation of the TMS moieties switched on the chromophore emission, and the color was immediately changed from yellow to dark brown.

## Type of Organoboron Compounds

As a Lewis base, $F^-$ can strongly interact with boron and cause specific acid base interactions. There is unique LUMO in boron compounds bearing three identical π-conjugated groups, and π-conjugation is divergently extended through the vacant π-orbital of the boron atom. In the interaction between $F^-$ and boron, B-O bonds are broken. The extended π-conjugation of the organoboron derivative is interrupted, and an obvious change occurs in their fluorescent properties (**Fig. 7A**).

There are many reports about fluoride probes based on B-F interactions, such as *Probe 42* to *Probe*

*49*. ***Probe 42*** containing a boric acid structure displayed a binding constant of $9.2 \times 10^{10}$ M$^{-3}$ and exhibited "turn-on" type fluorescence enhancement by the blocking of PET mechanism [33]. When the intramolecular charge transfer happened between electrons from F$^-$ and the boron π-orbital, Lewis acidic boron-based probes covalently bond with F$^-$, causing the fluorescence quenching. Other defects include poor sensing of F$^-$ in aqueous media, cytotoxicity and instability. All these block their biological applications. Many borane-containing asymmetric bidentate probes have been tried to enhance the binding affinity with F$^-$ in aqueous solution and increase the ability of capturing F$^-$ from water. ***Probe 43*** was noteworthy due to its heteronuclear bidentate Lewis acid [68]. The 1,8-naphthalenediyl backbone promoted fluoride anion chelation, and enforced the proximity of the two Lewis acidic sites. Thus ***Probe 43*** featured with a high binding constant ($2.3 \times 10^4$ M$^{-1}$) in a THF/water (90/10, v/v) mixture. Coulombic effects featured to increase anion affinity, and the strong negative inductive effect could be exerted by cationic substituents in ***Probe 44*** [69]. The imidazolium group strongly interacted with F$^-$ through a (C-H)$^+$···F$^-$-type ionic hydrogen-bond. ***Probe 45*** consisting of a boronic acid and an imidazolium moiety, could sense fluoride ranging from 0 to 1.3 mM in CH$_3$CN/water (95/5, v/v, HEPES buffer) solution [70]. ***Probe 46*** with a naphthalimide fluorophore at the axial position also belonged to B-O bond fluoride probes [71].

With polychromophoric systems, many borane-BODIPY dyads ***Probe 47~49*** were synthesized. Their two functionalities could be replaced at two positions of phenyl spacer (position 1 and position 3) [72]. The two fluorescent chromophores were remarkably close due to the unique "V" shape structure. The relative direction of the BMes$_2$ and BODIPY units is the major factor to control fluorescent emission. Thus, they could effectively function as sensitive and selective fluorescent probes for fluoride ions. The binding constants were $1.4 \times 10^5$ M$^{-1}$, $1.0 \times 10^5$ M$^{-1}$ and $2.2 \times 10^5$ M$^{-1}$, respectively. The selectivity toward F$^-$ was quite remarkable against other interfering species such as CN$^-$ [72].

### Type of Nucleophilic Addition Reaction

In the fluoride probes based on the nucleophilic addition reaction, fluoride may react with electron-deficient fluorophores, resulting in the disappearance of the double bond and creation of two new single in the compound (**Fig. 7C**).

A FRET cassette-type ***Probe 50*** contained two naphthalimide donors and a squaraine acceptor. During its FRET process, the spectral overlap was removed by the decompositions of acceptor chromophore [73]. Its detection limit of fluoride was 0.2 mM in acetonitrile by naked eye observation and ratiometric fluorescence analysis. Another example was ***Probe 51***, in which fluoride reacted with maleimide as fluorochrome, which could discriminate F$^-$ from other halogenide anions [74]. The polymerization of maleimide moiety was initiated by the reaction between fluoride and C=C double bond. The fluorescence intensity was dramatically increased in 10-fold within 20 minutes and the probe had a detection limit of 50 mM fluoride.

### Type of Intramolecular Hydrogen Transfer Reaction

The proton transfer process mechanism has contributed to the design of fluorescent fluoride probes for many years (**Fig. 7D**). The phenolic OH protons were transferred to F$^-$ and produced a spiro-cycle-opened emissive anionic species, causing the strong fluorescence enhancement at 514 nm in ***Probe 52***. [75]. Bhalla *et al.* firstly reported to exploit a cyclization of terphenyl to triphenylene in absence of any oxidizing reagent mechanism to develop fluorescent probe for F$^-$ [76]. The addition of F$^-$ deprotected OTBS groups of terphenyl derivative in ***Probe 53*** and led to the formation of triphenylene by an irreversible cyclization. The probe showed a detection limit of $2 \times 10^{-6}$ M fluoride. F$^-$ could induce intramolecular cyclization of pyridinium. The charged pyridinium ring and aminophenyl moiety are the two main units of the quenching effect during the PET process in ***Probe 54*** [77]. ***Probe 54*** in CH$_3$CN solution exhibited weak fluorescence in the absence of fluoride. The fluoride detection limit of ***Probe 54*** was $2.72 \times 10^{-6}$ M by fluorescence titration. Based on anion-catalyzed intramolecular hydrogen transfer, pyrazolopyridine was used as a fluorescent as well as chromogenic probe for F$^-$ detection in ***Probe 55*** [78].

There are also some biological applications of fluoride probes based on proton transfer processes. ***Probe 56*** was used to detect intracellular fluoride in PC3 prostate tumor-initiating cells and HeLa cells [79]. ***Probe 56*** exhibited the lower cytotoxicity, better water solubility and membrane permeability. Its fluoride detection limit was 8.54 mM.

### Type of Metal-mediated Fluorescent Probes

The metal-mediated strategies for fluorescent sensing for F$^-$ have been conducted in many ways. The cleavage reactions are driven by the specific metal ions, varying from hydrolysis, desulfurization to deprotection. The metal induced reaction could release weakly bounded dyes and generate fluorescent signals (**Fig. 7C**).

***Probe 57*** was an example of Al(III) ion mediated

fluoride probe in which fluoride enabled coordination between two Alizarin Red S molecules and a central Al(III) ion without interference from other common anions [80]. The binary complex *Probe 57* showed sensitive changes to F- ranging from $5\times10^{-6}$ to $3\times10^{-4}$ M. Im *et al.* developed a $Cu^{2+}$ mediated *Probe 58* in which TPEN-$Cu^{2+}$ complex was used to mask sulfide ions [81]. Some reports indicated that -COOH could substitute Zr-EDTA to form ternary complexes, such as $Zr(H_2O)_2EDTA$, causing fluorescent color changes from yellow to blue in *Probe 59*. Fluoride ions ($1.5\times10^{-5}$ to $1.5\times10^{-4}$ M) may shift the blue to orange red [82, 83]. A ligand exchange between 3-hydroxy-2′-flavone (FS) bound and Zr-EDTA occurred in *Probe 60* consisting of Zr-EDTA and FS [84]. Comparing with -COOH to coordinate to Zr(IV), fluoride has a stronger affinity. Fluoride (0.10 to 10 mM) quenched the strong fluorescence of (Zr(CDs-COO)$_2$EDTA) and formed non-fluorescent complex $Zr(F)_2EDTA$ in *Probe 61* [85]. Duan's group has reported continuous research on Ru mediated fluoride probes [86, 87]. The photoactive Ru-bipy moiety in *Probe 62* enhanced the affinity of fluoride and provided a PET fluorogenic signaling channel [86]. *Probe 63* is based on the PET mechanism involving a Ru-bipy fluorophore and a 2,4-dinitrophenylhydrazone [87].

### Type of Bifunctional Fluorescent Probes

As opposed to fluorescent fluoride probes for a single ion, bifunctional probes may independently identify two ions with different spectral responses. The two-stage process is the key by which the probe reacts with the first ion easily visualized by fluorescence changes, and the second ion triggers recognition as a relay host. Bifunctional probes can differentiate and detect analytes with distinct spectroscopic responses by overcoming difficulties such as cross-talk and a large invasive effect.

*Probe 64* was designed according to the anion-to-cation relay recognition concept, wherein F- and Cu (II) ions were sensed by the two-stage process unprecedentedly via a fluorescence "off-on-off" mechanism [88]. The "turn-on" effect was triggered by the cyclization reaction between fluoride and Si, whilst the quenching "turn-off" effect was caused by Cu(II). Similarly, *Probe 65* used the anion relay recognition concept and proved the highly selective for F- and CN-, based on a unique triple output modes, including fluorescence intensity, color, and absorption band [89]. The fluoride detection limit was 1.86 µM with a significant linear fluorescence response to F- (5.0 to 45.0 µM). Among another bifunctional fluorescent *Probe 66* [90], the 1,3-alternate calix[4]-crown-5 platform selectively bounded potas-

sium ions, and the triarylboranes showed enhanced size selectivity toward F-. The alkynyl groups acted as efficient conduits for electron communication, and relayed strong ICT from oxygen to boron [91]. The compound showed the high selectivity and sensitivity for F- in $CH_2Cl_2$.

The biological biofunctional fluoride probes have also been explored in recent years. The colorimetric and fluorescence response toward $Fe^{3+}$ and F- was studied in *Probe 67* [92]. Fluoride could reverse the *Probe 67*-Fe complex formation via the chelation process. MTT assay showed that the HeLa cells' viability was nearly 80% after being treated with 60 mM *Probe 67* for 24h. The probe had a good cellular permeability and could sense both $Fe^{3+}$ and F- inside cells. *Probe 68* was developed to sense F- and $Zn^{2+}$ at the same time in a living organism [93]. *Probe 68* was cellular permeable and could be used in fluoride toxicity or bioactivity research in cells.

## Carriers of Fluoride Probes

### Polymers

Polymer-based fluoride probes display several important advantages, such as amplified signal. The binding efficiency and selectivity to fluoride can be increased by carrying polymer chains with various recognition elements [94]. The following polymers have been used in fluorescent fluoride probes, double hydrophilic block copolymer (DHBC), diketopyrrolopyrrole (DPP), *etc*.

A coil-rod-coil triblock copolymer, P(MMA-*co*-NBDAE)-*b*-PF-*b*-P(MMA-*co*-NBDAE) was assembled as micellar nanoparticles in *Probe 69* [95]. When the micellar concentration was around 0.1 g/L in $C_3H_6O$ at room temperature ( 25°C ), *Probe 69* could detect 4.78 µM F- and was also with a visible color change as well as a colorimetric change. In order to control molecular weight of the polymer and its distribution, reversible addition-fragmentation chain transfer polymerization (RAFT) is generally used [96, 97]. Recently, Tian *et al.* used RAFT polymerization technique to develop several fluoride polymer probes [98, 99]. The probe with a higher the molecular weight was more sensitive to F-.

Recently, more researches focus on the way for designing the bioimaging materials with effective sensing capability for fluoride ions and potential high biocompatibility. Hua's group reported a series of fluorescent fluoride probes incorporating Diketopyrrolopyrrole (DPP) core and different electron donor or acceptor moieties [100-102]. By strong deprotonated interaction, fluoride ion might function as a quencher to interrupt electronic energy transfer process, and *Probe 71* afforded a fluorescence quenching

rate of approximately 95%. It was fabricated into polymeric nanoparticle (diameter of 100~200 nm) for living cell imaging in KB cells. The fluorescent signals were increased gradually with the endocytosis progress. *Probe 71* showed a lower cytotoxicity by using a standard MTT assay.

### Supramoleculer Gel

Low-molecular-weight organogelators (LMOGs) can be self-assembled into entangled 3D networks. The weak noncovalent interactions, including π–π interaction, hydrogen-bond, and van der Waals forces in the molecules, usually contribute to the formation of LMOGs [103, 104]. Fluoride might function as one of trigger factors to produce distinct changes in the physical and structural properties [105, 106].

The LOMG fluoride probes have the limited ability to detect fluoride ions because they rely on the auxiliary gelating moieties. The sensitivity toward highly polar $F^-$ could be lowered by van der Waals interaction. Fluorophores can directly interact with $F^-$ and integrate into LMOGs. The sensitivity toward fluoride could be achieved by responding to the minimized structural modifications in wholly π-conjugated LMOGs, such as *Probe* 72. It was one of the wholly π-conjugated organic gelators with entangled nanoribbon structures [107]. Fluoride deprotonated the salicylidene aniline moiety, and produced a reversible gel-to-sol transition with the obvious UV-Vis and fluorescence changes.

*Probe 73* was based on low-molecular-weight gel consisting of an anthracene chromophore [108]. With the addition of fluoride ions, TBAF promoted gelation of *Probe 73* and accompanied a remarkable fluorescence enhancement. Hydrogel *Probe 74* contained a water-insoluble silylated fluorescent dye, BTBPA (N-(3-(benzo[d]thiazol-2-yl)-4-(tert-butyldiphenylsilyl oxy)phenyl)acetamide), and selectively traced $F^-$ within 15s at different pH levels [109]. The hydrogel makes the use of other water-insoluble fluorescent probes possible, which also widens their utility, and avoids adding organic solvents to water-organic solvent composites, thus minimizes negative effects and enhances the accuracy of the results.

All the information about the spectroscopic and analytical parameters of the fluorescent fluoride probes (*Probe 1* to *Probe 74*) is listed in Additional file 1: **Supplementary Table 2**.

## Challenges in the future biosensor of fluoride

Overdose fluoride may have toxic effects, including influencing cellular signaling pathways, inducing apoptosis and inhibiting function of ion channels [110, 111]. Besides, fluoride might inhibit the functions of G-protein activator and Ser/Thr phosphatase and affect other important cell signaling [112]. The essential effects of fluoride on the cellular physiological and biological functions urge us to face critical challenges in the applications of fluorescent probes *in vivo* or in the cellular culture system. An ideal fluorescent probe for biosensing fluoride should possess good aqueous solubility, high sensitivity and selectivity, good chemical and photochemical stability, long excitation and emission wavelengths, low background interference, low or no toxicity, and facile synthetic access [113]. Besides these basic characteristics, here we will only emphasize the following features.

### Suitable fluorescent dyes of fluoride probes in living cells or *in vivo*

The classical fluorescent probes for fluoride usually have the apparent optical signal changes to realize naked-eye detection [114, 115], or optical response with a huge ratiometric value (>200 nm) to provide more precise built-in correction with minimized environmental effects [116]. As for the applications in the cellular system, the fluorescent fluoride probes should be exhibiting long wavelength absorption and emission bands, sufficient solubility in water, and good cell membrane permeability [65]. The fluorescent fluoride probes rely much on the instruments which are used to observe the fluoride changes within cells, such as fluorescent microscope, flow cytometer, confocal laser scanning microscope (CLSM), two-photon excitation microscopy analysis. Thus the dyes should match the excitation and emission spectrum of the related detecting instruments. In order to locate the distribution of fluoride, other fluorescent molecules have to be used to label nucleus, endosome, lysosome, or certain proteins. So the dyes in the fluorescent fluoride probes should not react with those fluorescent molecules in a cross-link manner.

With the increasing use of small animal molecular imaging system, more challenges are put forward to fluoride probes and other biomarkers. As we know, small animal models have a great advantage in disease studies that cannot be performed in humans. How to use the molecular imaging technologies as well as imaging instruments to display fluoride *in vivo*? A recent exciting fluorescent fluoride probe *in vivo* was reported by Kyo Han Ahn's group. They developed a coumarin derivative for the detection of $F^-$ in cells as well as in live zebrafish by one-photon or two-photon microscopy [117]. On the other hand, cellular and tissue imaging in NIR wavelengths between 650 and 900 nm is advantageous for *in vivo* imaging [118, 119]. Compared to visible light, NIR dyes are paid more attention due to their lower photo

damage, fluorescence background, intense photon penetration through deep tissues and light scattering properties. NIR dyes bring light on the effective imaging in deep tissues, which distinguishes NIR-fluoride from other biological chromophores or components, such as water, lipids and hemoglobin. Thus NIR fluorescence imaging for fluoride in cells and small animals might be a future trend. NIR fluoride fluorophores may make it possible to investigate physiological processes within the context of a living organism, and provides the in-time and in-place picture of fluorosis diseases. When NIR fluoride probes are administrated *in vivo*, one of the essential questions is how to keep the efficient delivery and activation of the probe in the tissue of interest.

### Suitable carriers for the delivery of fluoride probes

Fluoride ion is highly solvated in water and loses its basicity due to hydration. It has a similar hydration free energy with C-H covalent bond, which is calculated to be of *ca*.100~110 kcal/mol. Although some fluoride probes have high sensitivity and selectivity, the delivery of them *in vivo* or in living cells still remains some problems. For example, hydrogen-bond probes have certain limitations for biosensing fluoride, and some of them work only in organic solvents, and the detection of fluoride ions is inhibited by water [120].

Carriers or scaffolds for the delivery of fluoride probes *in vivo* are going to be a future trend. Polymers, gel particles or other nanoparticles/materials will draw more attention in the future to design fluoride probes. Polymer based fluoride probes have some advantages comparing to other small organic compounds. They may increase or amplify the fluoride signals by increasing both the binding efficiency and recognition selectivity for specific analytes. Unimers and micellar nanoparticles have been reported to be very sensitive and selective in $F^-$ fluorescence measurements. They also show biocompatibility and water dispersibility, as well as the capability of integration with featured temperature-sensing functions. Their drawbacks are that the sensing process is based on the intensity changes of a single emission band, which makes it difficult to calculate concentrations. Some fluoride-responsive LMOGs have excellent sensitivity, for example, after the minimized structural modifications the wholly π-conjugated LMOGs can show highly sensitive fluoride responses. In addition, the integration of fluorophores-$F^-$ into LMOGs can improve the sensitivity further.

### Sensitivity of fluorescent probes for $F^-$ in living cells and *in vivo*

The sensitivity is quite important for detecting intracellular fluoride. Right now the researches on the dynamic function or trafficking of fluoride within cells are delayed due to the limited fluorescent fluoride probes. An ideal fluorescent fluoride probe should be good for monitoring dynamic molecular events, and imaging biological processes of fluoride ions with high precision both in time and in space. However, few fluoride probes match this goal. Unlike other ions (such as $Ca^{2+}$), we know little about the concentration of intracellular fluoride ions, either in cytoplasm or in specific cellular organelles.

Another challenge is the tissue specific blockage which may affect the penetrating of fluoride probes. As we know, tooth and bone tissues are easily targeted by fluoride, whilst these tissues have highly mineralized components, which may block the *in vivo* sensing of fluoride by the fluorescent probes. Tooth and bone tissues also have high background of auto-fluorescence, which is the major interfering factor for the fluorescent probes. On the other hand, fluoride has different combination forms in the live cells and in tooth/bone tissues. The free status of fluoride ions within cells, or fluorapatite in tooth and bone puts forward the questions for the classical or traditional design ways for the fluoride probes, especially challenging their sensitivity for the future *in vivo* applications.

## Conclusions

In this review, we have provided an overview of the developments in the area of fluorescent fluoride probes. The traditional measurement methods for $F^-$ are convenient for *in vitro* samples and are applicable over a wider fluoride detection range. The newly developed fluorescent probes can be exploited for the fluoride detection in living cells or *in vivo*, applying this reaction-based approach to pre-clinical and clinical diagnostics, or other applications. The fluorescent fluoride probes for the cellular or *in vivo* applications might be a promising trend in $F^-$ detection in the future. We envisage that, in future, the field of fluoride recognition and sensing will continue to expand.

## Supplementary Material

Additional File 1:
Supplementary Figures 1-4. Supplementary Tables 1-2.
http://www.thno.org/v05p0173s1.pdf

## Acknowledgments

## Conflicts of interest

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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