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REVIEW

Recent Progress in Fluorescent Formaldehyde Detection Using Small Molecule Probes

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Abstract
Formaldehyde (FA, a typical reactive carbonyl species) is a well-known environmental pollutant and a disease-related biomarker, making its sensitive and selective detection significant. Fluorescent probes have been explored for FA perception in environment, intracellular media and in vivo. In this review, we majorly conclude the recently represented fluorescence FA analysis based on small molecule probes. The general FA sensing mechanisms are first introduced. Regarding the FA detection in various environments, sensing tactics and performances are discussed in order of natural environment, living cells and in vivo. In the end, this review discusses the challenges and future trends of FA detection based on fluorescent probes.

Keywords Formaldehyde · Small molecule probe · Fluorescence detection · Environmental monitoring · Intracellular analysis · In vivo imaging

1 Introduction

Aldehydes with reactive carbonyl are essential to produce plastics, detergents, and indoor decorative materials, etc. As an example, formaldehyde (FA, the simplest aldehyde) has been widely used as raw materials in chemical and construction industry [1]. Notably, FA shows high toxicity and carcinogenic effects due to its high reactivity [2, 3], has been defined as the third-largest indoor chemical pollutant by the World Health Organization, and generates from various sources, including food preservatives, industrial activities, and even indoor finish. And thus, the release of FA from these materials attracts extensive concerns. In addition, previous reports indicated that FA can affect some biological transformation processes through participating tricarboxylic acid cycle [4], making biological FA level an important index that reflects the health condition and its abnormality, which may lead to several diseases, such as Alzheimer's disease, aging, cardiovascular disease, and cancers [5]. Therefore, the exploration of facile and sensitive detection methods for FA quantification is significant to evaluate environmental safety and health level.

So far, lots of FA detection methods have been developed based on electrophoresis, gas chromatography, high-performance liquid chromatography, colorimetry, and fluorimetry [2, 6–8]. Among them, fluorescence-based FA detection methods have attracted growing attention due to the high sensitivity and strong interference rejection [9]. To achieve sensitive FA perception, various inorganic nanomaterial and organic small molecule-based fluorimetric probes were reported by nucleophilic and redox reactions [10, 11]. Nanomaterial-based fluorescent probes usually utilize redox reactions, e.g., silver-mirror reaction [12–14]. In comparison to nanomaterial-based probes, small molecule-based chemodosimeters generally respond to FA via nucleophilic reactions and exhibit several advantages including good uniformity, satisfying specificity, and versatile reaction mechanisms [15]. In addition, small molecule-based fluorescent probes possess outstanding selectivity and interference rejection, and have been widely used as optical reporters and imaging tools in last few decades [16–19]. In view of these characters, numbers of small molecule-based fluorescent probes have been exploited for gaseous and aqueous FA detection by

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fluorescence "turn-on" and "ratiometric" strategies. As the growing research interest on FA detection, a summary of very recent works is meaningful for the junior researchers to understand the sensing and design principle of FA sensors.

Despite of the contribution of few excellent reviews on reactive carbonyl species detection [9, 10, 20], summaries focusing on FA analysis are still rare. Most of them only present probes by amino-FA condensation and subsequent reactions. In this review, we aim to summarize the recent advances in fluorescent FA detection using small molecule-based probes in 2016–2021. The general FA detection mechanisms are briefly introduced according to the responsive groups and chemical reaction pathways at first. Then, recent advances of FA detection in environmental, biological and vegetal samples are presented with two aspects: turn-on/off and ratiometric fluorescence variations. The sensing principles of analyte-induced fluorescence changes are discussed. Regarding to the page limit, only few examples are introduced in detail. In the end, this review concludes the current challenges and prospects of small molecule-based probes for FA detection in environmental and bioanalytical applications.

2 Summary of FA Sensing Mechanisms

As mentioned above, small molecule-based probes are able to detect FA through nucleophilic reactions due to the high reactivity of carbonyl [9]. Most responsive groups used in designing probes are amino groups, including primary amine and hydrazine. With different molecular structures, the resulted Schiff-bases undergo diverse pathways and yield various products. Recently, a few new systems have also been explored for FA sensing. Based on responsive group and reaction pathway, the sensing principles can be divided into four categories: primary amine-FA condensation, hydrazine-FA condensation, aza-Cope rearrangement, and other mechanisms.

2.1 Primary Amine-FA Condensation

The formation of Schiff-base (–C=N–) by primary amine-FA condensation is spontaneous and specific, and much effort has been devoted to the development of FA probes based on this mechanism. The lone pair electrons make primary amine strong electron donor, which spontaneously attacks the carbonyl group and forms formimine (typical Schiff-base) [21]. The distinct electron and/or charge transfer characteristics between primary amine and formimine alternate the photophysical pathway of linked fluorophore, thus affect the fluorescence behaviors. Additionally, such a condensation is revisable. In general, the produced formimine possesses free $–N=CH_2$ end group and its rotation turns the fluorescence off by increasing non-irradiative possibility [22]. For example, Song et al. [23] reported a BOD-NH_2 probe detecting FA by fluorescence turn-off strategy (Fig. 1a). Similarly, Wen et al. [24] proposed a diaminomaleonitrile derivate for fluorescence turn off sensing of FA. However, if the rotation of $–N=CH_2$ end group is restricted, fluorescence turn-on approach is also possible for FA sensing based on this reaction. As referred in Chen's report [25], the amino terminated tetraphenylethene emitter is applicable of fluorescence turn-on sensing of FA. In their work, the amino terminated tetraphenylethene emitter was non-emissive in PBS/DMSO mixture due to the good solubility. While the addition of FA leads to the formation of $–N=CH_2$ end group, which diminishes the solubility and causes the aggregation of emitter. As is known, tetraphenylethene is a typical AIEgen and displays strong emission in aggregation state. As a result, the introduction of FA results in dramatic fluorescence increment (Fig. 1b). The formimine possesses strong nucleophilic activity and may produce other products by nucleophilic addition. As an example, FA-caused intra-heterocyclization of dopamine has also been used for fluorescence FA detection [26]. The formed formimine attacks the carbon (5' position) and leads to the formation of new heterocycle product, which emits yellow fluorescence.

2.2 Hydrazine-FA Condensation

Hydrazine with linked bi-amino groups also exhibits high reactivity toward FA through condensation reaction. Different to primary amine, the strong photo-induced electron transfer (PET) effect of hydrazine usually quenches the fluorescence of nearby fluorophores [27]. The formed methylenehydrazine ($–NH–N=CH_2$) largely inhibits the PET effect

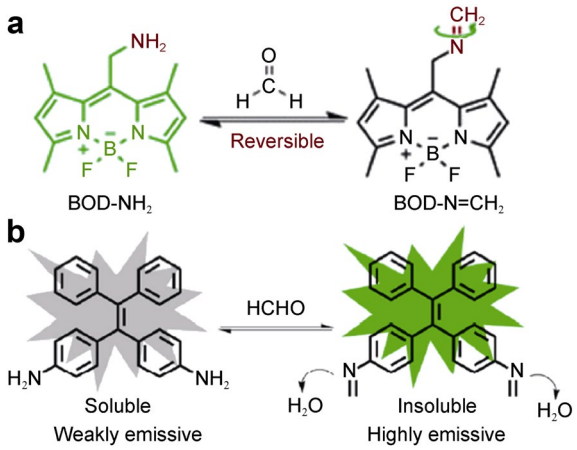

Fig. 1 **a** Schematic representation of fluorescence turn off FA detection with BOD-NH_2 probe. Reprinted with permission from ref. [23]. Copyright 2018, Royal Society of Chemistry. **b** Illustration of AIEgen–mediated fluorescence turn-on mechanism for FA detection. Reprinted with permission from ref. [25]. Copyright 2018, American Chemical Society

and recovers the fluorescence. In this case, hydrazine-linked fluorescent probes generally show fluorescence turn-on character toward FA. For instance, Tang et al. [28] reported a naphthylamide-hydrazine based fluorescence probe (Na-FA) for turn-on FA sensing. The fluorescence of Na-FA is suppressed by hydrazine via PET, subsequent addition of FA changes hydrazine into –NH–N=CH_2 group and destroys the PET processes, which turns the fluorescence on (Fig. 2a). Similarly, pyridine-linked naphthalimide has also been applied for FA detection by Nasirian et al. [29], which shows strong two-photon emission character. In comparison to turn-off strategy, hydrazine-mediated turn-on approach provides higher sensitivity due to the low background. In addition to sole fluorescence turn-on tactics, fluorescence resonance energy transfer (FRET) routes have also been reported by introducing extra donors. That is, the FRET process between donor and acceptor is first blocked because of fluorescence inhibition by hydrazine, while the addition of FA breaks up PET and turns the FRET on. Consequently, ratiometric fluorescence variation is observed. As an example, using coumarin as the donor and naphthylamide-hydrazine as the acceptor, Yuan et al. [30] reported a FRET turn-on method for FA detection (Fig. 2b). As is known, the intrinsic built-in correction character of ratiometric systems enables more sensitive detection. The FRET-based FA detection approach allows FA perception in sub-nanomolar level.

2.3 Aza-Cope Rearrangement

Aza-Cope rearrangement is one of the important and fundamental reactions that produce C–C and C–N bonds under mild condition, and has been widely used in asymmetric catalysis [31, 32]. In this reaction, butylene amine (usually called as homoallylamine) reacts with FA to form butylene imine. The following rearrangement reaction leads to the retroflexion of cationic butylene imine-contained molecular structure and the hydrolysis of cationic imine in turn, which yields end aldehyde group [33]. Convention of butylene imine to aldehyde group changes the electron interaction affinity to the connected fluorophores, and results in ratiometric fluorescence variation [34, 35]. Such a reaction is first applied for FA detection by Chang et al. [36].

Using homoallylamine functionalized quinoline derivative as the probe, Li et al. [37] proposed a ratiometric FA detection system. The probe emits green fluorescence (485 nm) and becomes yellow emissive (570 nm) after FA stimulation (Fig. 3a). With introducing thiophen and carbazol into emission center, Gu et al. [38] reported a probe for dual-channel FA sensing. The addition of FA turned homoallylamine into aldehyde, which induced the change of fluorescence emission maxima from 393 to 542 nm and variation of absorption maxima from 300 to 400 nm. As a result, both colorimetric and fluorescence ratiometric FA sensing were realized (Fig. 3b). Additionally, fluorescence turn-on FA sensing with aza-Cope rearrangement is also feasible. For example, Yang et al. [39] displayed the FA-enhanced emission of benzoxadiazole-based probe. With the modification of different electron-withdrawing and electron-donating groups, they achieved the preparation of FA probe with negligible fluorescence via intramolecular charge transfer (ICT) effect. The FA-probe reaction destroyed the ICT process and boosted the fluorescence.

With cascade reactions, several sensing systems were also presented with the trigger of aza-Cope rearrangement. As referred in Zhang's report [40], a FA-reactive lysine analogue was site-specifically incorporated into the critical site

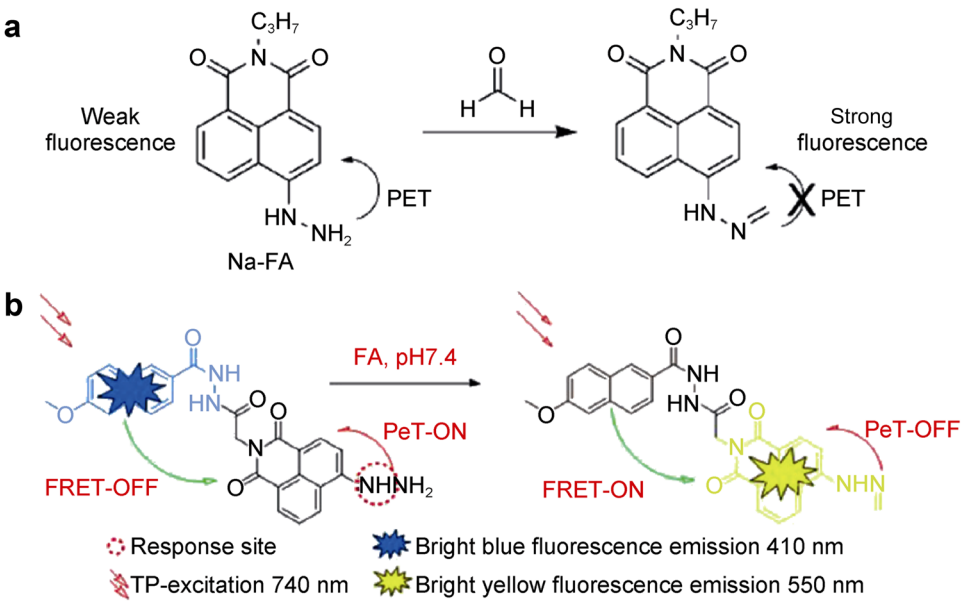

Fig. 2 **a** Design of the two-photon fluorescent Na-FA probe. Reprinted with permission from ref. [28]. Copyright 2016, Wiley–VCH. **b** Response mechanism of two-photon FRET-based ratiometric fluorescent sensor toward FA. Reprinted with permission from ref. [30]. Copyright 2020, Elsevier

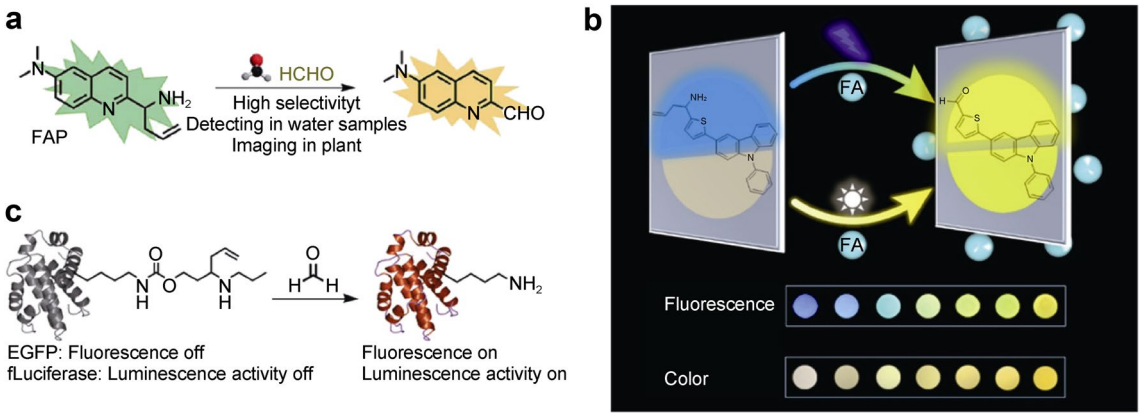

Fig. 3 **a** Schematic illustration of FAP-based ratiometric FA sensing mechanism. Reprinted with permission from ref. [37]. Copyright 2017, Royal Society of Chemistry. **b** Diagrammatic representation of dual-channel FA sensing. Reprinted with permission from ref. [38]. Copyright 2020, Elsevier. **c** Illustration of PrAK-mediated FA sensing. Reprinted with permission from ref. [40]. Copyright 2020, Wiley–VCH

of green fluorescent protein first, the FA-induced 2-aza-Cope rearrangement generated aldehyde, which subsequently attacked the amide carbon and left free amino group (Fig. 3c). The regeneration of free amino group distinctly enhances the fluorescence of green fluorescent protein and can be applied for FA monitoring. Du et al. [41] found that the reactivity of such a cascade reaction is highly dependent on the N-substitution group of homoallylamine, and conducted systematic study on this issue. The optimal 2-aza-Cope reactivity to FA was found to be N-p-methoxybenzyl substitution over other 24 groups, which showed 20-folds fluorescence enhancement after adding FA.

2.4 Other Mechanisms

All above three mechanisms are dependent on amino-aldehyde condensation reaction and the formation of imine. However, a few probes react with FA through other pathways. For instance, Lin's group [42] explored a benzopyrylium-based responsive unit that recognizes sulfite and FA. The Michael addition reaction between sulfite and benzopyrylium closes the fluorescence, and the addition of FA leads to the exfoliation of sulfite and recovery of fluorescence (Fig. 4a). This mechanism, however, provides the reversible response toward sulfite and FA, which is totally different from those of amino-aldehyde condensation reactions. Through involving benzopyrylium unit into the conjugation plane, Wang et al. [43] achieved near-infrared FA sensing with ratiometric characters. Based on this mechanism, Tan et al. [44] reported a FRET probe by linking naphthalimide and xanthene. The xanthene shows reactivity toward sulfite and FA, similar to that of benzopyrylium. The proposed FREP probe is capable of FA sensing with a LOD of 7.48 nmol/L. In addition, FA-stimulated ring opening of N-phenylsuccinimide has also been explored for FA detection. According to Bi's work [45], the formed carbinolamine is trend to attack N-phenylsuccinimide, which opens the azacyclo structure and changes the fluorescence character (Fig. 4b).

3 Environmental and Biological FA Analysis

As mentioned above, the World Health Organization labels FA as the third-largest indoor chemical pollutant, which is also known as an essential volatile organic compound. In consideration of its distinct influence in various fields including environment, biological process, and plant growth, detection of FA is thus a significant issue that benefits the deep understanding of its biological function and the monitoring of environmental quality. The highly reactive character of FA enables the development of diverse fluorescence probes for its sensitive detection by various chemical reactions. Accordingly, lots of small molecule-based fluorescence sensing systems for FA detection have been constructed toward three aspects: environmental analysis, living cell imaging, tissue and in vivo visualization.

3.1 Environmental FA Analysis

Since FA can release from various materials, its environmental contamination causes wide attention because exogenous FA can enter organisms through contact, drinking water, breathing, or eating. In consideration of the low molecular weight and melting point, FA generally exists at gaseous state. In addition, it also shows strong adsorption ability, making the existence on material surface or inner space possible. In this part, the FA detection examples in air, solutions

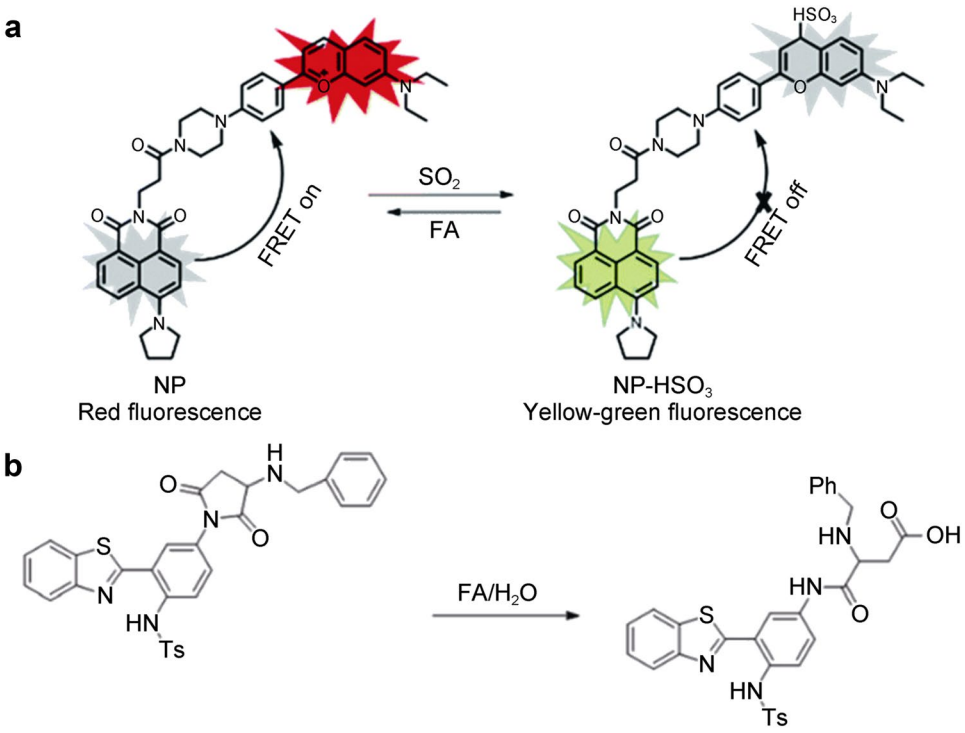

Fig. 4 **a** Schematic representation of reversible sulfite and FA sensing with benzopyrylium-based responsive unit. Reprinted with permission from ref. [42]. Copyright 2019, Royal Society of Chemistry. **b** Diagram of FA-induced ring-opening of azacyclo probe. Reprinted with permission from ref. [45]. Copyright 2021, Royal Society of Chemistry

and leather products are briefly introduced. Although the rotation of formed –N=CH_2 group can cause fluorescence quenching and is able to indicate FA concentration, this way shows low sensitivity due to the high background. And most of proposed probes reported FA with turn-on or ratiometric fluorescence variations.

The hydrazine substituted 4-chloro-7-nitro-1,2,3-benzoxadiazole (denoted as FAP) was reported for the turn-on FA sensing in air [46]. As indicated above, hydrazine can quench the fluorescence through PET mechanism, and formation of methylenehydrazine blocks PET process and turns the fluorescence on. This probe enables FA detection with a LOD of 0.89 μg/L. Using 4-nitrobenzyl homoallylamine terminated tetraphenylethene (TPE-FA) as the probe, Zhao et al. [47] realized fluorescence turn-on and portable detection of gaseous FA. In their work, the FA-induced aza-Cope rearrangement excised 4-nitrobenzyl and destroyed the corresponding PET process (Fig. 5a). As a result, enhanced fluorescence with increasing FA concentrations was observed. They also fabricated a portable solid FA

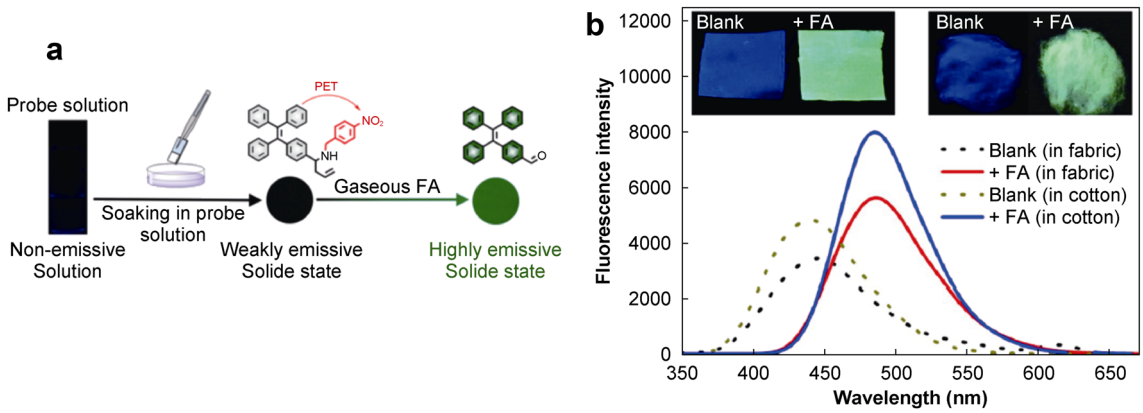

Fig. 5 **a** Scheme of preparation of TPE-FA loaded FA test plate and fluorescence response to gaseous FA. Reprinted with permission from ref. [47]. Copyright 2018, American Chemical Society. **b** The fluorescence spectra of the TF-FA loaded fabric and cotton test substrates in the absence and presence of FA, excited at 305 nm. Inset images are the corresponding photographs of fabric (left) and cotton (right) test substrates in the absence and presence of FA. Reprinted with permission from ref. [53]. Copyright 2019, Elsevier

sensor by direct loading of TPE-FA onto high performance thin-layer chromatography silica gel plate. And the proposed sensor allows FA sensing as low as 0.036 mg/m^3. Through the introduction of squaraine-hydrazine adducts, Liu et al. [48] proposed a fast response probe toward aqueous FA sensing. The addition of FA resulted in visible increment of absorbance at 650 nm, leading to the colorimetric change of solution within 1 second providing a convenient "mix-and-detect" platform.

The FA detection with fluorescence turn-on tactic was also applied in leather products inspection by Wang et al. [49] using a 2-(2-aminoethoxy)-ethanol modified naphthalimide-hydrazine (FAP-1) probe. The 2-(2-aminoethoxy)-ethanol modification is critical to increase the solubility of naphthalimide-hydrazine, which authorizes aqueous FA analysis. This FAP-1 probe permited the FA detection in aqueous media down to 0.76 μmol/L. And the detected FA in leather products was calculated to be 33.7 mg/kg, which was more accurate than standard colorimetric assay utilizing 2,4-dinitrophenylhydrazine and acetylacetone as chemical derivatizing agents. With similar design, FA detection in milk samples was also achieved [50].

As is known, ratiometric sensing systems with built-in correction characters provide high sensitivity and accuracy. And many works on the development of ratiometric fluorescence probes have been reported. The aza-Cope rearrangement mechanism is often used in the design of ratiometric FA probes. For example, using 2-(2-hydroxyphenyl)benzothiazole as the emitter, Zhou et al. [51] reported a HBT-FA probe for ratiometric FA sensing based on aza-Cope rearrangement reaction. The change of end homoallylamine into aldehyde altered the conjugation of emitter, which caused red-shift of emission maxima from 462 to 541 nm. The fluorescence intensity ratio (F_{541}/F_{462}) was utilized for quantifying aqueous FA in the concentration range of 0–30 mmol/L with 3 h reaction time. The LOD was determined to be 0.041 mmol/L. The simple paper or film-based gaseous analysis causes wide research interest. By loading HBT-FA into filter paper strips, FA gas-induced fluorescence color change from 37% FA solution was observed under UV light irradiation [52].

By exploring triphenylamine as the fluorophore and homoallylamine as the responsive motif, Zhai et al. [53] proposed a TP-FA probe for achieving ratiometric FA sensing. As the same in Zhou's work [51], FA-induced formation of benzaldehyde increased the length of π-conjugation and led to red-shift of emission maxima from 422 nm to 488 nm, allowed FA sensing in aqueous media with LOD of 51 μmol/L through 1 h reaction. The TP-FA also shows AIE character, making it possible to gaseous FA detection in solid state. Zhai et al. [53] also prepared fabric and cotton test substrates by simple TP-FA solution soakage. As shown in Fig. 5b, the fabric and cotton test substrates exhibit strong blue emission, while they emits intense green light after FA stimulation. The visible fluorescence color change demonstrated the practical application of TP-FA soaked fabric and cotton test substrates in gaseous FA perception. Interestingly, this probe only responses to FA, and other aldehydes including cetaldehyde, propylaldehyde, butyraldehyde, and isobutyraldehyde don't cause any comparable fluorescence variation.

These two ratiometric probes show long response time and high LODs that may hinder the sensitive FA detection. The long response time may be attributed to the intrinsic multistep pathway. To realize accurate and sensitive FA analysis, Chen et al. [54] explored an anthracene carboximide-based fluorescent probe for ratiometric FA sensing with hydrazine-FA condensation. The hydrazine group coupled probe emited red fluorescence at 600 nm, while FA-mediated generation of methylenehydrazine yielded green emission at 530 nm. This probe detected aqueous FA in 5 min reaction and showed good linearity toward FA concentration from 0 to 60 μmol/L. The LOD was calculated to be 120 nmol/L.

3.2 Intracellular FA Detection and Imaging

It is reported that FA is also a normal metabolite of living cells, and can induce DNA damage through forming mono-adduct [55]. Thus, the intracellular FA abnormality may cause diseases and its detection and imaging is very important to monitor the biological status. In comparison to aqueous or gaseous FA sensing, intracellular FA analysis requires good solubility and low toxicity of probes. In other words, insoluble and toxic small molecules are not favorable in intracellular detection and imaging. To avoid this condition, hydrophilic and biocompatible functional groups are usually decorated into probe backbone in typical assays. For example, Yuan et al. [56] developed a butanoic acid functionalized naphthalimide hydrazine (NID) probe for fluorescence turn-on FA sensing in MCF-7 cancer cells. The NID pretreated MCF-7 cells showed increased fluorescence upon incubation with FA, and negligible fluorescence was observed in control group without addition of FA. Similarly, using N, N-dimethyl ethylamine terminated naphthalimide hydrazine (NaFP) as the probe, Gu et al. [57] achieved turn-on aqueous FA detection with a LOD of 65 nmol/L ($S/N = 3$). And imaging of FA in HeLa cells was realized with NaFP probe. Through hydrazide functionalization, Bi et al. [58] proposed a sensitive MPAB probe for FA sensing. The addition of FA boosted the fluorescence of probe with 18.9-folds increment and the LOD was determined to be 20 nmol/L. This probe endows the perception of endogenous FA in living SMMC-7721 cells.

Except hydrazine-FA condensation, aza-Cope rearrangement has also been utilized to design imaging probe for FA.

For instance, Xu et al. [59] developed AENO probe for turn-on FA detection based on homoallylamine-modified naphthol. The end homoallylamine with electron donating capability blocks the ICT process and thus the AENO displays ignorable emission. However, the introduction of FA changes homoallylamine into aldehyde, a typical electron-withdrawing group. As a result, the ICT process from phenol to generated aldehyde occurs, which shows bright emission. Due to the multistep reaction nature, the fluorescence response of AENO probe toward FA is complete over 150 min. In view of the long reaction time, the AENO probe is able to image intracellular FA after 3 h incubation with exogenous FA. With UV light irradiation, this probe is also applicable for ratiometric FA sensing [60]. The elimination of homoallylamine not only alters the electron state of probe, but also changes the spatial structure of molecule. The homoallylamine modified pyrene probe has been explored to detect FA via aza-Cope rearrangement-regulated excimer formation [61]. Without addition of FA, the homoallylamine with large steric effect inhibits the formation of pyrene excimer, thus only weak emission is observed. However, the addition of FA induces the generation of aldehyde, which eliminates the steric effect and promotes the formation of pyrene excimer. Therefore, strong ultramarine emission around 470 nm after FA introduction appears. With such a character, this probe allows FA imaging in human esophageal carcinoma line HEK293T cells after exogenous FA incubation.

For intracellular analysis, selective target recognition in special organelles/locations is very important to illustrate the endogenous process and distribution. It is generally accepted that liposome-like cell membrane consists of phospholipide backbone and lots of functional proteins. Active groups that can bind to the phospholipide and/or surface protein will facilitate the adsorption and penetration of probes. To achieve FA visualization on cell membrane, Sheng et al. [62] developed a fluorescent probe Mem-FA based on dodecyl chain functionalized naphthalimide hydrazine derivative. The hydrophobic interaction between dodecyl chain and phospholipide benefits the cell membrane anchorage of probe. The sensing mechanism is dependent on typical hydrazine-FA condensation-induced PET block and fluorescence turn-on. With cell membrane targeting affinity and selective FA response character, Mem-FA has been applied for fluorescent FA imaging in live HeLa cells. As shown in Fig. 6a, the control cells show negligible emission after Mem-FA incubation, while they display strong green fluorescence on cell membrane after the addition of exogenetic FA. In addition, the membrane fluorescence of $NaHSO_3$-treated HeLa cells is ignorable even with exogenetic FA, demonstrating the fluorescence response originates from FA stimulation. Moreover, this probe can detect endogenous FA by tetrahydrofolate (Tet) driven one-carbon cycle. Taken together, the proposed Mem-FA probe is applicable of exogenetic and endogenous FA sensing on cell membrane.

The overexpressed asialoglycoprotein receptor on the surface of hepatocytes cell membrane indicates the possibility of specific FA detection in hepatoma cells using β-D-galactose as the targeting group. In view this principle, Zhou et al. [63] reported a β-D-galactose linked naphthalimide hydrazine derivative for turn-on intracellular FA imaging in HepG-2 cells. To illustrate the recognition capability, cervical cancer cell (HeLa) and normal cell (L929) with low asialoglycoprotein receptor expression were tested as control groups. Negligible fluorescence was observed in HeLa and L929 cells. In contrast, bright emission in HepG-2 cells appeared (Fig. 6b). The good specificity indicates the feasibility of FA imaging HepG-2 cells and diagnosis of hepatoma cells.

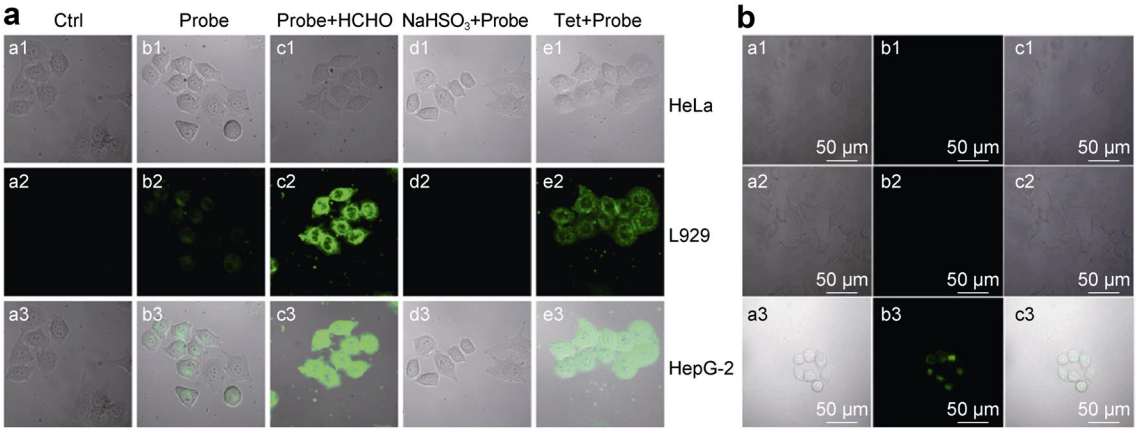

Fig. 6 **a** Bright-field, fluorescence and merge imaging of live HeLa cells with Mem-FA probe upon various treatments. Reprinted with permission from ref. [62]. Copyright 2021, Royal Society of Chemistry. **b** Confocal fluorescence imaging of HeLa (a1–a3), L929 (b1–b2) and HepG-2 (c1–c2) cells incubated with 5 μmol/L NFP-G. Reprinted with permission from ref. [63]. Copyright 2021, Elsevier

3.3 FA Visualization In Tissue and In Vivo

The detection and imaging of biological FA in tissue and in vivo is essential for health status judgement and disease diagnosis. Many works focusing on this aspect were reported. Different from cell imaging assays, thick tissues and organs with large absorbance lead to short fluorescence imaging depth of field. On the other hand, short wavelength light irradiation also causes visible phototoxicity to them. To realize effective fluorescence imaging in tissue and in vivo, probes with two-photon emission characters were developed [64]. The near-infrared excitation enables deep fluorescence imaging and weakens the phototoxicity.

For example, Lin's group [28, 65, 66] found that naphthalimide-based fluorophores exhibit strong two-photon emission. Upon two-photon excitation, the naphthalimide hydrazine probe shows 900-folds fluorescence enhancement after FA stimulation, which is much higher than that with one-photon model (325-folds). With such a high sensitivity of two-photon fluorescence, they applied the probe for liver and tumor tissue slice imaging. As shown in Fig. 7a, the distribution of endogenous FA in liver organs is depicted with two-photon imaging technique. The accumulation of FA majorly focuses on 20–40 μm depth, and FA existence below 10 μm and more than 50 μm is not observed. The FA distribution in tumor tissue slice, however, generally concentrates during 10–30 μm depth [66]. Besides, quinoline derivatives have also been reported with two-photon emission [67]. The homoallylamine functionalization first quenches the fluorescence, and subsequent FA exposure turns on the fluorescence. In addition to turn-on strategy, naphthaldehyde-based two-photon probe has been explored for ratiomtric FA sensing with homoallylamine modification [68]. The probe which shows blue emission at 438 nm and emits green light (533 nm) after FA stimulation is applied for two-photon imaging of endogenous formaldehyde levels in different mouse organ tissues with 760 nm excitation. As manifested in Fig. 7b, FA exists in all mouse organ tissues, and its levels in liver and brain are higher than that in kidney and colon.

Recent reports reveal that the FA generation and metastasis in acidic lysosomes largely affect its biological roles, thus the investigation of lysosomal FA in acidic microenvironment is also important beyond neutral condition. It is reported that amino-FA condensation reaction is also pH dependent. To merit this demand, Liu et al. [69] reported

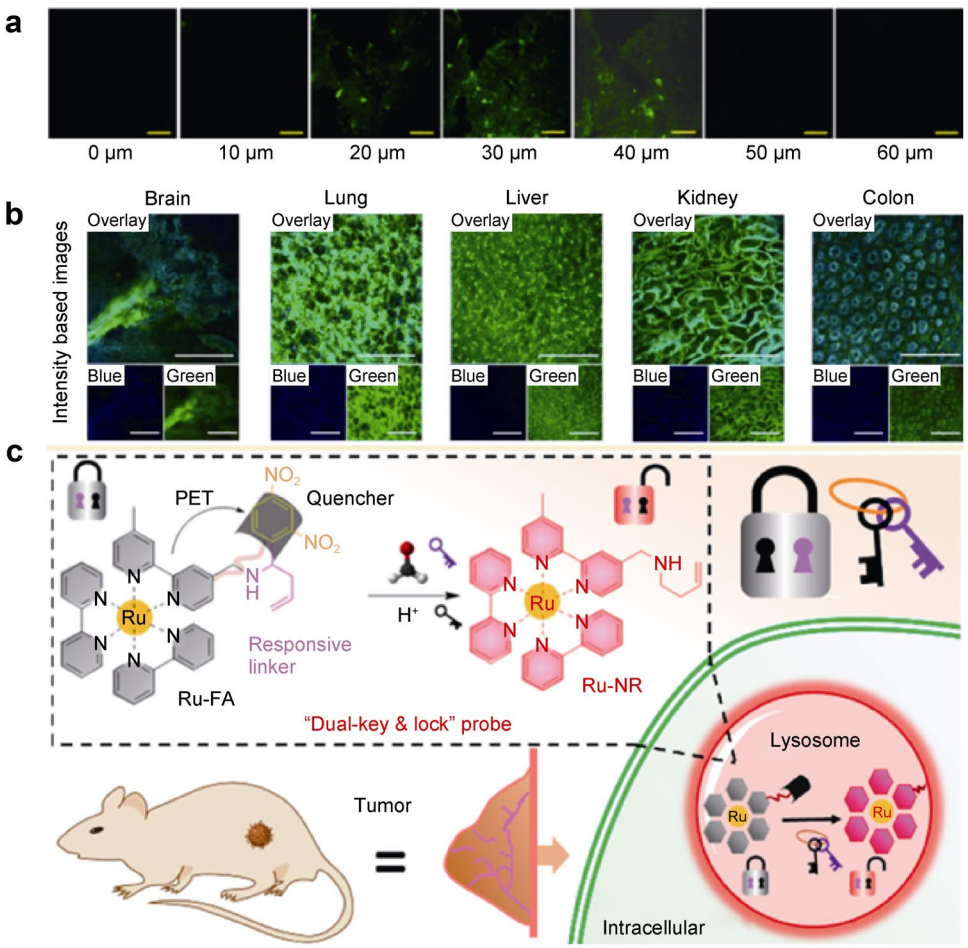

Fig. 7 **a** Fluorescence images of liver slides incubated with probe (10 mm) for 1 h. Excitation was at 880 nm by femtosecond laser, and the emission collection was from 500–550 nm. Scale bar: 50 mm. Labels from 0–60 mm indicate scanning depths of the tissue slices. Reprinted with permission from ref. [28]. Copyright 2016, Wiley–VCH. **b** Ratiometric imaging of FA in different mouse organ tissues. Reprinted with permission from ref. [68]. Copyright 2017, American Chemical Society. **c** Schematic illustration of "dual-key and lock" Ru-FA probe for lysosomal FA sensing. Reprinted with permission from ref. [69]. Copyright 2019, American Chemical Society

a ruthenium(II) complex probe (Ru-FA) for lysosomal FA sensing in cells and tumors based on "dual-key-and-lock" strategy. That is, 2,4-dinitrobenzene quenches the emission of Ru(II) emitter through PET mechanism, and FA-induced aza-Cope rearrangement in acidic condition facilitates the elimination of homoallylamine-2,4-dinitrobenzene and recovery of emission (Fig. 7c). However, without the assistance of acid, this probe doesn't show visible emission even with FA stimulation.

The FA pollution in plants affects their growth and development, and may lead to dramatic decrease of productivity and quality. Therefore, mapping the distribution of FA in plants is also an important issue for monitoring of plants health and contamination. As reported in previous works, toxic pollutants primary exist in root tip of plants. Toward this goal, few probes have been applied for FA imaging in plant root tip tissues. The strongly emissive *N*,*N*-dimethylquinolin-6-amine has been widely used as the chromophore because of its excellent photophysical properties. With homoallylamine modification, the resulted FAP probe showed visible fluorimetric changes within 5 min and became equilibrium after 150 min reaction [37]. To verify the practical application of FA imaging in plant, *Arabidopsis thaliana* root tip tissues were used. As shown in Fig. 8a, the root tip tissues display strong green emission and weak red emission after FAP probe incubation. In contrast, the addition of exogenous FA weakens the green emission and results in strong red emission. Such a distinct fluorescence change proves that FAP probe can detect FA in living plants. In addition, Wu et al. [70] developed a BT-1 probe for endogenous FA imaging based N-heterocyclic derivatives. The probe utilizes primary amine-FA condensation reaction, which alters the electron transfer and turns on the blue fluorescence. As displayed in Fig. 8b, *Arabidopsis thaliana* root tip tissues show enhanced fluorescence only after exogenous FA incubation. These reports demonstrate that small molecule probes are capable of FA sensing in air, solution, cell, and in vivo.

4 Conclusion and Perspective

In this review, we have provided an overview on the recent advances of fluorescence-based in vitro and in vivo FA detection using small molecule probes. To facilitate the understanding for junior researchers, the sensing mechanisms are comprehensively summarized. As shown in Table 1, the characteristics of recently released representative FA fluorescent probes are listed. Most of these probes show rapid and selective response toward FA over other species by converting the detection events into fluorescence. With further molecular structure optimization, some ratiometric probes allow FA detection down to nmol/L level. Besides, the mapping of endogenous FA in vivo endows deep understanding of its actual biological functions.

Despite the successful development of sensitive and selective small molecule-based detection systems for FA analysis in vitro and in vivo, some issues regard this research direction still exist. For chemodosimeter-based FA assays, several drawbacks still need to be overcome in future. Here, we'd like to share our viewpoints of challenges focusing on fluorimetric sensing performances of FA probes.

(1) Portable FA analysis with high sensitivity. Although the aqueous FA sensing is usually achieved with μmol/L and even nmol/L (μg/m^3) sensitivity, the gaseous sensing with portable devices with low LODs is still rare. According to the indoor air standard by World Health Organization, the maximum FA concentration is 0.08 mg/m^3. However, the LODs of gaseous FA sensing are generally at the level of 0.20 to 2.00 mg/m^3. The high LODs might hinder its practical application in air quality monitoring. A possible reason for low gaseous FA detection sensitivity is ascribed to the slow reaction rate. The development of simple and effective

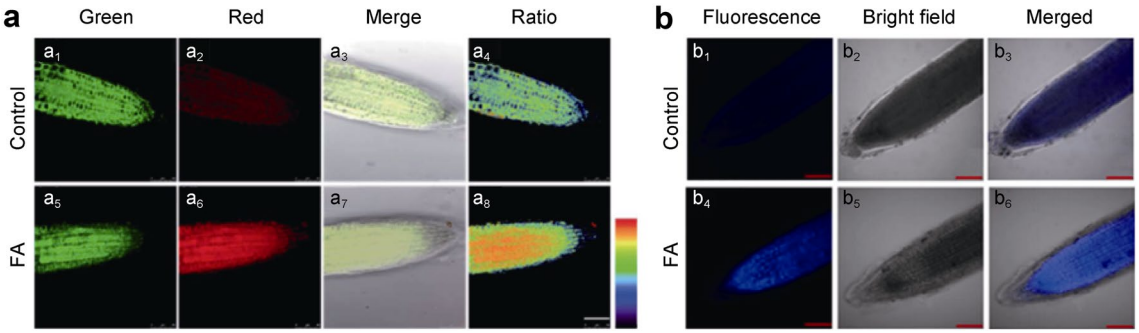

Fig. 8 **a** Confocal microscopy images of *Arabidopsis thaliana* root tip tissues after FAP incubation without (up) and with (bottom) exogenous FA stimulation. Reprinted with permission from ref. [37]. Copyright 2017, Royal Society of Chemistry. **b** Confocal microscopy images of *Arabidopsis thaliana* root tip tissues after BT-1 incubation without (up) and with (bottom) exogenous FA stimulation. Reprinted with permission from ref. [70]. Copyright 2018, Elsevier

Table 1 A summary of recently published fluorescent probes for environmental and biological FA analysis

Probe	Strategy	LOD	Linear range	Application	Reference
FAP	Hydrazine-FA	0.89 μg/L	0.015–0.8 mg/L	Gaseous FA	[46]
TPE-FA	Aza-Cope	0.036 mg/m^3	0–1.6 mg/m^3	Gaseous FA	[47]
SQOH-hydrazine	Hydrazine-FA	60 μmol/L	0–36 mmol/L	Beer	[48]
FAP-1	Hydrazine-FA	0.76 μmol/L	0–60 mg/kg	Leather	[49]
NaP	Hydrazine-FA	1.62×10^{-6} mol/L	0–200 μmol/L	Milk	[50]
HBT-FA	Aza-Cope	4.1×10^{-4} mol/L	0–30 mmol/L	Gaseous FA	[51]
TP-FA	Aza-Cope	5.1×10^{-5} mol/L	0–5.6 mmol/L	Gaseous FA	[53]
Anthracene carboximide	Hydrazine-FA	120 nmol/L	0–60 μmol/L	Gaseous FA	[54]
NID	Hydrazine-FA	0.36 μmol/L	0–100 μmol/L	MCF-7 cells	[56]
NaFP	Hydrazine-FA	65 nmol/L	0–300 μmol/L	HeLa cells	[57]
MPAB	Hydrazine-FA	20 nmol/L	0–30 μmol/L	SMMC-7721 cells	[58]
AENO	Aza-Cope	0.57 μmol/L	0–1.0 mmol/L	HeLa cells	[59]
RFFP	Aza-Cope	1.87×10^{-5} mol/L	0–3.0 mmol/L	HeLa cells	[60]
B1	Aza-Cope	0.107 μmol/L	0 -10 μmol/L	HEK293T	[61]
Mem-FA	Aza-Cope	214 nmol/L	0–300 μmol/L	HeLa cells	[62]
NFP-A	Hydrazine-FA	0.18 μmol/L	0–30 μmol/L/0–15 μmol/L	HepG-2 cells	[63]
PFM	Hydrazine-FA	10 μmol/L	0–200 μmol/L	Neurovascular cells	[64]
Na-FA	Hydrazine-FA	7.1×10^{-7} mol/L	0–200 μmol/L	Liver tissue	[65]
X-FA	Hydrazine-FA	0.78 μmol/L	0–100 μmol/L	Tumour slices	[66]
FATP-1	Aza-Cope	0.3 μmol/L	0–2 mmol/L	Brains tissue	[67]
Probe 1	Aza-Cope	10 μmol/L	200–400 μmol/L	Organ tissue	[68]
Ru-FA	2-aza-Cope	19.8 nmol/L	0–60 μmol/L	Lysosomes	[69]
BT-1	Primary amine-FA	2 μmol/L	0–10 mol/L	Arabidopsis thaliana	[70]

probes to percept FA in short time might be an interesting research direction.

(2) Selective FA perception over other aldehydes. The summarized probes in this review detect FA via chemical interaction toward reactive carbonyl, which generates new species and varied fluorescence signals. It should be noticed that all aldehydes possess reactive carbonyl and similar reaction activity. Regarding this situation, the proposed probes almost present reactivity toward diverse aldehydes. Despite that few examples show the differentiation capability of FA from propylaldehyde and butyraldehyde [53, 54], distinguishing FA from acetaldehyde is still a challenge [71]. To solve this problem, probes with designed molecular structure that regulates steric effect might be possible for specific FA detection.

(3) Multiple aldehydes analysis. Despite of the containing of reactive carbonyl, aldehyde with different molecular structures exhibits diverse chemical reactivity and biological influences. As reported, FA shows strong toxicity and has been recognized as a known human carcinogen. Acetaldehyde, however, is a natural fermentation product in alcoholic beverages and its effect is related to the alcohol intake. In addition, the acute toxicities of various aldehydes are different. As a result, the efficient discrimination of various aldehydes with a simple strategy is appealing. Unfortunately, the proposed probes at present only allow the detection of one or two aldehydes. It is well-known that "chemical nose" technique combining different signal collectors is a good candidate for multi-targets analysis [72–74]. This drawback might be overcome through multidimensional analysis with the integration of "chemical nose" technique and data process tools.

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Declarations

Conflict of interest The authors declare no competing financial interest.

References

1. Birlouez-Aragon I, Morales F, Fogliano V, Pain JP. The health and technological implications of a better control of neoformed contaminants by the food industry. Pathol Biol. 2010;58(3):232–8.

2. Casset A, Marchand C, Le Calvé S, Mirabel P, de Blay F. Human exposure chamber for known formaldehyde levels: generation and validation. Indoor Built Environ. 2005;14(2):173–82.
3. Reingruber H, Pontel LB. Formaldehyde metabolism and its impact on human health. Curr Opin Toxicol. 2018;9:28–34.
4. Burgos-Barragan G, Wit N, Meiser J, Dingler FA, Pietzke M, Mulderrig L, Pontel LB, Rosado IV, Brewer TF, Cordell RL, Monks PS, Chang CJ, Vazquez A, Patel KJ. Mammals divert endogenous genotoxic formaldehyde into one-carbon metabolism. Nature. 2017;548(7669):549–54.
5. Whiteman DC, Wilson LF. The fractions of cancer attributable to modifiable factors: a global review. Cancer Epidemiol. 2016;44:203–21.
6. Jiang X, Li C, Chi Y, Yan J. TG-FTIR study on urea-formaldehyde resin residue during pyrolysis and combustion. J Hazard Mater. 2010;173(1–3):205–10.
7. Duan H, Deng W, Gan Z, Li D, Li D. SERS-based chip for discrimination of formaldehyde and acetaldehyde in aqueous solution using silver reduction. Microchim Acta. 2019;186(3):175–86.
8. Yuan ZC, Hu B. Mass spectrometry-based human breath analysis: towards COVID-19 diagnosis and research. J Anal Test. 2021;5(4):287–97.
9. Tang Y, Ma Y, Yin J, Lin W. Strategies for designing organic fluorescent probes for biological imaging of reactive carbonyl species. Chem Soc Rev. 2019;48(15):4036–48.
10. Li HY, Zhao SN, Zang SQ, Li J. Functional metal-organic frameworks as effective sensors of gases and volatile compounds. Chem Soc Rev. 2020;49(17):6364–401.
11. Xu Z, Chen J, Hu LL, Tan Y, Liu SH, Yin J. Recent advances in formaldehyde-responsive fluorescent probes. Chin Chem Lett. 2017;28(10):1935–42.
12. Li HJ, Sun X, Xue F, Ou N, Sun BW, Qian DJ, Chen M, Wang D, Yang J, Wang X. Redox induced fluorescence on–off switching based on nitrogen enriched graphene quantum dots for formaldehyde detection and bioimaging. ACS Sustain Chem Eng. 2018;6(2):1708–16.
13. Nandi S, Sharma E, Trivedi V, Biswas S. Metal-organic framework showing selective and sensitive detection of exogenous and endogenous formaldehyde. Inorg Chem. 2018;57(24):15149–57.
14. Burris AJ, Tran K, Cheng Q. Tunable enhancement of a graphene/polyaniline/poly(ethylene oxide) composite electrospun nanofiber gas sensor. J Anal Test. 2017;1(2):12–22.
15. Liu X, Li N, Li M, Chen H, Zhang N, Wang Y, Zheng K. Recent progress in fluorescent probes for detection of carbonyl species: Formaldehyde, carbon monoxide and phosgene. Coord Chem Rev. 2020;404:213109.
16. Cheng D, Xu W, Gong X, Yuan L, Zhang XB. Design strategy of fluorescent probes for live drug-induced acute liver injury imaging. Acc Chem Res. 2021;54(2):403–15.
17. Jiang WL, Wang WX, Mao GJ, Yan L, Du Y, Li Y, Li CY. Construction of nir and ratiometric fluorescent probe for monitoring carbon monoxide under oxidative stress in zebrafish. Anal Chem. 2021;93(4):2510–8.
18. She ZP, Wang WX, Jiang WL, Wang ZQ, Mao GJ, Fei J, Li Y, Li CY. Accurate fluorescence diagnosis of cancer based on sequential detection of hydrogen sulfide and pH. Anal Chem. 2021;93(34):11826–35.
19. Li K, Ren TB, Huan S, Yuan L, Zhang XB. Progress and perspective of solid-state organic fluorophores for biomedical applications. J Am Chem Soc. 2021;143(50):21143–60.
20. Bruemmer KJ, Brewer TF, Chang CJ. Fluorescent probes for imaging formaldehyde in biological systems. Curr Opin Chem Biol. 2017;39(17):17–23.
21. Liu X, Manzur C, Novoa N, Celedón S, Carrillo D, Hamon JR. Multidentate unsymmetrically-substituted Schiff bases and their metal complexes: Synthesis, functional materials properties, and applications to catalysis. Coord Chem Rev. 2018;357:144–72.
22. Song H, Rajendiran S, Kim N, Jeong SK, Koo E, Park G, Thangadurai TD, Yoon S. A tailor designed fluorescent 'turn-on' sensor of formaldehyde based on the BODIPY motif. Tetrahedron Lett. 2012;53(37):4913–6.
23. Song X, Han X, Yu F, Zhang J, Chen L, Lv C. A reversible fluorescent probe based on C=N isomerization for the selective detection of formaldehyde in living cells and in vivo. Analyst. 2018;143(2):429–39.
24. Wen X, Yan L, Fan Z. One-step construction of a novel AIE probe based on diaminomaleonitrile and its application in double-detection of hypochlorites and formaldehyde gas. New J Chem. 2021;45(18):8155–65.
25. Chen W, Han J, Wang X, Liu X, Liu F, Wang F, Yu RQ, Jiang JH. Aggregation-induced emission-based fluorescence probe for fast and sensitive imaging of formaldehyde in living cells. ACS Omega. 2018;3(10):14417–22.
26. Martínez-Aquino C, Costero AM, Gil S, Gaviña P. A new environmentally-friendly colorimetric probe for formaldehyde gas detection under real conditions. Molecules. 2018;23(10):2646–54.
27. Li P, Zhang D, Zhang Y, Lu W, Wang W, Chen T. Ultrafast and efficient detection of formaldehyde in aqueous solutions using chitosan-based fluorescent polymers. ACS Sens. 2018;3(11):2394–401.
28. Tang Y, Kong X, Xu A, Dong B, Lin W. Development of a two-photon fluorescent probe for imaging of endogenous formaldehyde in living tissues. Angew Chem Int Ed. 2016;55(10):3356–9.
29. Nasirian A, Tikum AF, Fortibui MM, Lee S, Kim J. Napthalimide-based fluorescent probe for selective and sensitive sensing of formaldehyde and biological applications. Dyes Pigm. 2021;188:109156.
30. Yuan G, Ding H, Peng L, Zhou L, Lin Q. A novel fluorescent probe for ratiometric detection of formaldehyde in real food samples, living tissues and zebrafish. Food Chem. 2020;331:127221.
31. Wei L, Wang CJ. Recent advances in catalytic asymmetric aza-Cope rearrangement. Chem Commun. 2021;57(81):10469–83.
32. Rueping M, Antonchick AP. Catalytic asymmetric aminoallylation of aldehydes: a catalytic enantioselective Aza-Cope rearrangement. Angew Chem Int Ed. 2008;47(52):10090–3.
33. Fiedler D, Bergman RG, Raymond KN. Supramolecular catalysis of a unimolecular transformation: Aza-Cope rearrangement within a self-assembled host. Angew Chem Int Ed. 2004;43(48):6748–51.
34. Brewer TF, Burgos-Barragan G, Wit N, Patel KJ, Chang CJ. A 2-aza-Cope reactivity-based platform for ratiometric fluorescence imaging of formaldehyde in living cells. Chem Sci. 2017;8(5):4073–81.
35. Mc Cormack MP, Shalumova T, Tanski JM, Waters SP. Development of a 2-Aza-Cope-[3+2] dipolar cycloaddition strategy for the synthesis of quaternary proline scaffolds. Org Lett. 2010;12(17):3906–9.
36. Brewer TF, Chang CJ. An Aza-Cope reactivity-based fluorescent probe for imaging formaldehyde in living cells. J Am Chem Soc. 2015;137(34):10886.
37. Li Z, Xu Y, Zhu H, Qian Y. Imaging of formaldehyde in plants with a ratiometric fluorescent probe. Chem Sci. 2017;8(8):5616–21.
38. Gu J, Li X, Zhou G, Liu W, Gao J, Wang Q. A novel self-calibrating strategy for real time monitoring of formaldehyde both in solution and solid phase. J Hazard Mater. 2020;386:121883.
39. Yang X, He L, Xu K, Yang Y, Lin W. The development of an ICT-based formaldehyde-responsive fluorescence turn-on probe with a high signal-to-noise ratio. New J Chem. 2018;42(15):12361–4.
40. Zhang Y, Du Y, Li M, Zhang D, Xiang Z, Peng T. Activity-based genetically encoded fluorescent and luminescent probes for detecting formaldehyde in living cells. Angew Chem Int Ed. 2020;59(38):16352–6.

41. Du Y, Zhang Y, Huang M, Wang S, Wang J, Liao K, Wu X, Zhou Q, Zhang X, Wu YD, Peng T. Systematic investigation of the aza-Cope reaction for fluorescence imaging of formaldehyde in vitro and in vivo. Chem Sci. 2021;12(41):13857–69.
42. Ma Y, Gao W, Zhu L, Zhao Y, Lin W. Development of a unique reversible fluorescent probe for tracking endogenous sulfur dioxide and formaldehyde fluctuation in vivo. Chem Commun. 2019;55(75):11263–6.
43. Wang M, Liu Q, Sun X, Zheng S, Ma Y, Wang Y, Yan M, Lu Z, Fan C, Lin W. Ratiometric and reversible detection of endogenous SO_2 and HCHO in living cells and mice by a near-infrared and dual-emission fluorescent probe. Sens Actuators B. 2021;335:129649.
44. Tan L, Ding H, Chanmungkalakul S, Peng L, Yuan G, Yang Q, Liu X, Zhou L. A smart TP-FRET-based ratiometric fluorescent sensor for bisulfite/formaldehyde detection and its imaging application. Sens Actuators B. 2021;345:130331.
45. Bi A, Liu M, Huang S, Zheng F, Ding J, Wu J, Tang G, Zeng W. Construction and theoretical insights into the ESIPT fluorescent probe for imaging formaldehyde in vitro and in vivo. Chem Commun. 2021;57(28):3496–9.
46. Ge H, Liu G, Yin R, Sun Z, Chen H, Yu L, Su P, Sun M, Alamry KA, Marwani HM, Wang S. An aldimine condensation reaction based fluorescence enhancement probe for detection of gaseous formaldehyde. Microchem J. 2020;156:104793.
47. Zhao X, Ji C, Ma L, Wu Z, Cheng W, Yin M. An aggregation-induced emission-based "turn-on" fluorescent probe for facile detection of gaseous formaldehyde. ACS Sens. 2018;3(10):2112–7.
48. Liu T, Yang L, Zhang J, Liu K, Ding L, Peng H, Belfield KD, Fang Y. Squaraine-hydrazine adducts for fast and colorimetric detection of aldehydes in aqueous media. Sens Actuators B. 2019;292:88–93.
49. Wang Y, Sun X, Han Q, James TD, Wang X. Highly sensitive and selective water-soluble fluorescent probe for the detection of formaldehyde in leather products. Dyes Pigm. 2021;188:109175.
50. Xin F, Tian Y, Jing J, Zhang X. A two-photon fluorescent probe for imaging of endogenous formaldehyde in HeLa cells and quantitative detection of basal formaldehyde in milk samples. Anal Methods. 2019;11(23):2969–75.
51. Zhou Y, Yan J, Zhang N, Li D, Xiao S, Zheng K. A ratiometric fluorescent probe for formaldehyde in aqueous solution, serum and air using Aza-Cope reaction. Sens Actuators B. 2018;258:156–62.
52. Taihong Liu RM, Haonan P, Jing L, Liping D, Yu F. Adlayer chemistry on film-based fluorescent gas sensors. Acta Phys-Chim Sin. 2020;36(10):1908025.
53. Zhai B, Zhang Y, Hu Z, He J, Liu J, Gao C, Li W. A ratiometric fluorescent probe for the detection of formaldehyde in aqueous solution and air via Aza-Cope reaction. Dyes Pigm. 2019;171:107743.
54. Chen J, Chen K, Han B, Xue Y, Chen W, Gao Z, Hou X. A novel single-fluorophore-based ratiometric fluorescent probe for detection of formaldehyde in air. Tetrahedron. 2020;76(50):131681.
55. Yu R, Lai Y, Hartwell HJ, Moeller BC, Doyle-Eisele M, Kracko D, Bodnar WM, Starr TB, Swenberg JA. Formation, accumulation, and hydrolysis of endogenous and exogenous formaldehyde-induced DNA damage. Toxicol Sci. 2015;146(1):170–82.
56. Yuan W, Zhong X, Han Q, Jiang Y, Shen J, Wang B. A novel formaldehyde fluorescent probe based on 1, 8-naphthalimide derivative and its application in living cell. J Photochem Photobiol A. 2020;400:112701.
57. Gu L, Tang Y, Lin W. A new highly selective fluorescence probe for the imaging of endogenous formaldehyde in living cells. Tetrahedron. 2021;78:131808.
58. Bi A, Gao T, Cao X, Dong J, Liu M, Ding N, Liao W, Zeng W. A novel naphthalimide-based probe for ultrafast, highly selective and sensitive detection of formaldehyde. Sens Actuators B. 2018;255:3292–7.
59. Xu J, Zhang Y, Zeng L, Liu J, Kinsella JM, Sheng R. A simple naphthalene-based fluorescent probe for high selective detection of formaldehyde in toffees and HeLa cells via aza-Cope reaction. Talanta. 2016;160:645–52.
60. He L, Yang X, Liu Y, Kong X, Lin W. A ratiometric fluorescent formaldehyde probe for bioimaging applications. Chem Commun. 2016;52(21):4029–32.
61. Zhang D, Liu D, Li M, Yang Y, Wang Y, Yin H, Liu J, Jia B, Wu X. A simple pyrene-based fluorescent probe for highly selective detection of formaldehyde and its application in live-cell imaging. Anal Chim Acta. 2018;1033:180–4.
62. Sheng W, Zhang X, Yu M, Jin M, Li N, Sun C, Wang L, Xia Q, Li X, Zhang Y, Zhu B, Liu K. A novel cell membrane-targeting fluorescent probe for imaging endogenous/exogenous formaldehyde in live cells and zebrafish. Analyst. 2021;146(24):7554–62.
63. Zhou L, Cui J, Yu Z, Zou D, Zhang W, Qian J. A β-d-galactose-guided fluorescent probe for selectively bioimaging endogenous formaldehyde in living HepG-2 cells. Sens Actuators B. 2021;332:129494.
64. Liang XG, Chen B, Shao LX, Cheng J, Huang MZ, Chen Y, Hu YZ, Han YF, Han F, Li X. A fluorogenic probe for ultrafast and reversible detection of formaldehyde in neurovascular tissues. Theranostics. 2017;7(8):2305–13.
65. Tang Y, Zhao Y, Lin W. Preparation of robust fluorescent probes for tracking endogenous formaldehyde in living cells and mouse tissue slices. Nat Protoc. 2020;15(10):3499–526.
66. Lee YH, Tang Y, Verwilst P, Lin W, Kim JS. A biotin-guided formaldehyde sensor selectively detecting endogenous concentrations in cancerous cells and tissues. Chem Commun. 2016;52(75):11247–50.
67. Chen J, Shao C, Wang X, Gu J, Zhu HL, Qian Y. Imaging of formaldehyde fluxes in epileptic brains with a two-photon fluorescence probe. Chem Commun. 2020;56(27):3871–4.
68. Singha S, Jun YW, Bae J, Ahn KH. Ratiometric imaging of tissue by two-photon microscopy: observation of a high level of formaldehyde around mouse intestinal crypts. Anal Chem. 2017;89(6):3724–31.
69. Liu C, Zhang R, Zhang W, Liu J, Wang YL, Du Z, Song B, Xu ZP, Yuan J. A "dual-key-and-lock" ruthenium complex probe for lysosomal formaldehyde in cancer cells and tumors. J Am Chem Soc. 2019;141(21):8462–72.
70. Wu Y, Zheng Z, Wen J, Li H, Sun S, Xu Y. Imaging of formaldehyde in live cells and plants utilizing small molecular probes with large stokes shifts. Sens Actuators B. 2018;260:937–44.
71. Cao Y, Teng Z, Zhang J, Cao T, Qian J, Wang J, Qin W, Guo H. A fluorescent probe for distinguish detection of formaldehyde and acetaldehyde. Sens Actuators B. 2020;320:128354.
72. Sun Y, Lu F, Yang H, Ding C, Yuan Z, Lu C. Fluorescent sensor array for separation-free dopamine analogue discrimination *via* polyethyleneimine-mediated self-polymerization reaction. Nanoscale. 2019;11(27):12889–97.
73. Yang H, Lu F, Sun Y, Yuan Z, Lu C. Fluorescent gold nanocluster-based sensor array for nitrophenol isomer discrimination *via* an integration of host–guest interaction and inner filter effect. Anal Chem. 2018;90(21):12846–53.
74. Yuan Z, Du Y, Tseng YT, Peng M, Cai N, He Y, Chang HT, Yeung ES. Fluorescent gold nanodots based sensor array for proteins discrimination. Anal Chem. 2015;87(8):4253–9.