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Diethyl Malonate-Based Turn-On Chemical Probe for Detecting Hydrazine and Its Bio-Imaging and Environmental Applications With Large Stokes Shift

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Diethyl malonate-based fluorescent probe **NE-N_2H_4** was constructed for monitoring hydrazine (N_2H_4). The novel probe **NE-N_2H_4** exhibits good properties, such as large Stokes shift (about 125 nm), good selectivity, and low cytotoxicity. This sensing probe **NE-N_2H_4** can be operated to detect hydrazine in living HeLa cells. Especially after soaking in probe solution, the thin-layer chromatography (TLC) plate could detect the vapor of hydrazine. Therefore, the probe **NE-N_2H_4** might be used to monitor hydrazine in biosamples and environmental problem.

Keywords: fluorescent probe, hydrazine, Stokes shift, gas detection, cell imaging

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INTRODUCTION

Hydrazine (N_2H_4) and its substituted derivatives are usually applied in the aerospace industry as rocket propellant due to the distinctive properties of flammability and explosion (Serov and Kwak, 2010). This molecule N_2H_4 has also been employed as a catalyst, corrosion inhibitor, and reducing agent in many different fields including pharmaceutical, agricultural, and applied chemical industries (Kean et al., 2006; Khaled, 2006; Rosca and Koper, 2008). Due to its high toxicity, it is also considered as a terrible pollutant to creatures and humans, which could make the lungs, livers, and kidneys cancerous (Garrod et al., 2005). Hence, 10 ppb is the upper line (CDC, 1988). That is why it is important to develop good methods for sensing N_2H_4 in real-time detection and environmental pollution.

In modern times, chromatography–mass spectrometry, titrimetric, and electrochemical methods have been reported for monitoring N_2H_4 (Karimi-Maleh et al., 2014; McAdam et al., 2015). During the past few years, molecular probes have been developed for biological imaging with good properties of high sensitivity, large Stokes shift, good selectivity, good biocompatibility, and real-time detection, etc., which were regarded as the most practical method (Lakowicz, 2006; Li et al., 2014; Tang et al., 2015; Zhou X. et al., 2015).

During the last few decades, a series of turn-on probes were applied to detect N_2H_4 in living biosamples (Cui et al., 2014; Goswami et al., 2014a,b, 2015; Liu et al., 2014, 2019; Qian et al., 2014; Qu et al., 2014; Raju et al., 2014; Sun et al., 2014, 2015; Xiao et al., 2014; Jin et al., 2015; Nandi et al., 2015; Yu et al., 2015; Zhang et al., 2015; Zhou J. et al., 2015; Dai et al., 2016; Reja et al., 2016; Chen et al., 2017; Li et al., 2017, 2018, 2019; Ma et al., 2017; Mahapatra et al., 2017; Jung et al., 2019; Paul et al., 2019; Shi et al., 2019; Xing et al., 2019; Fang et al., 2020; Han et al., 2020; Hou et al., 2020; Vijay and Velmathi, 2020), a few of which were constructed by cleavage of C = C bond

(Sun et al., 2014; Reja et al., 2016; Li et al., 2017, 2018, 2019; Liu et al., 2019; Hou et al., 2020). Many examples were developed by the deprotection group from the fluorescent group (Cui et al., 2014; Goswami et al., 2014a, 2015; Liu et al., 2014; Qian et al., 2014; Qu et al., 2014; Raju et al., 2014; Jin et al., 2015; Sun et al., 2015; Yu et al., 2015; Zhang et al., 2015; Zhou J. et al., 2015; Chen et al., 2017; Ma et al., 2017; Mahapatra et al., 2017; Shi et al., 2019; Xing et al., 2019; Fang et al., 2020; Vijay and Velmathi, 2020). Additionally, the rest of the fluorescent molecules were used to monitor N_2H_4 using the property of special nucleophilicity of N_2H_4 (Goswami et al., 2014b; Xiao et al., 2014; Nandi et al., 2015; Dai et al., 2016; Jung et al., 2019; Paul et al., 2019; Han et al., 2020). That is why it is necessary to construct a powerful molecule for monitoring N_2H_4 by the way of cleavage of C = C bond.

In this report, a novel fluorescent probe, **NE-N_2H_4,** has been constructed to monitor N_2H_4 with improved properties including good selectivity, low cytotoxicity, and large Stokes shift over other analytes by cleavage of C = C bond (**Scheme 1**). The probe **NE-N_2H_4** was applied to imaging N_2H_4 in living HeLa cells. Besides, the probe **NE-N_2H_4** could monitor vapor of N_2H_4 by way of thin-layer chromatography (TLC) plate after soaking in solution of probe **NE-N_2H_4**. Therefore, this novel probe **NE-N_2H_4** could be regarded as a powerful pool for monitoring N_2H_4 in biosystems and environmental pollution.

EXPERIMENT

Synthesis of Probe NE-N_2H_4

Here, 6-hydroxy-2-naphthaldehyde (1.0 mmol, 172.0 mg) and diethyl malonate (1.2 mmol, 192.2 mg) were added to EtOH (5.0 ml). Then, piperidine (1.2 mmol, 102.2 mg) was added to the above solution. After reacting at 25°C for 12 h, distilled H_2O (10.0 ml) was added to the above reaction, which was extracted with dichloromethane (DCM) (50 ml) 3 times. All the extracts were washed with saturated aqueous sodium chloride solution and dried over $MgSO_4$. The solid residue was dealt with flash column chromatography. The probe **NE-N_2H_4** was obtained (83% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (s, 1H), 7.81 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.40 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 7.09–7.04 (m, 2H), 4.41 (dd, J_1 = 6.8, J_2 = 14.0, 2H), 4.33 (dd, J_1 = 7.2, J_2 = 14.0, 2H), 1.37–1.32 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.5, 164.5, 155.3, 142.7,

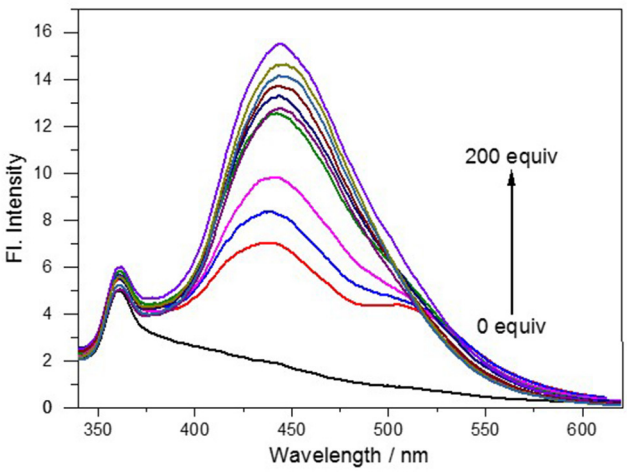
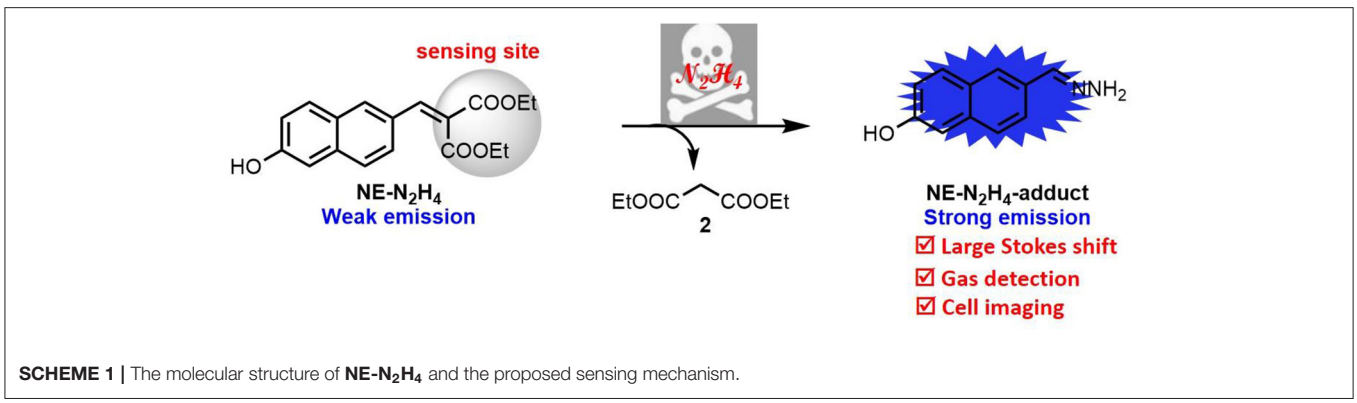
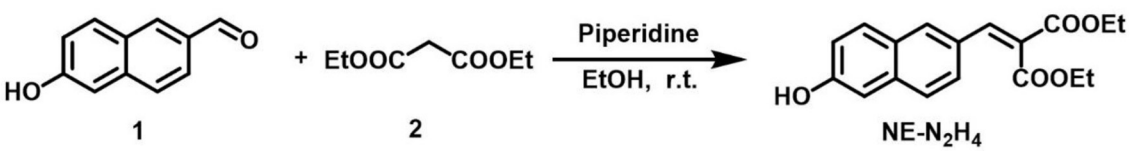


FIGURE 1 | Fluorescence spectra of NE-N_2H_4 (10 μM) in pH 7.4 phosphate buffered saline (PBS)/dimethyl sulfoxide (DMSO0 (v/v = 1/1) in the absence or presence of N_2H_4.



SCHEME 1 | The molecular structure of **NE-N_2H_4** and the proposed sensing mechanism.



SCHEME 2 | Synthesis of the fluorescent probe NE-N_2H_4.

135.6, 131.2, 130.7, 128.3, 128.0, 127.0, 125.9, 124.4, 118.8, 109.5, 61.9, 61.7, 14.2, 14.0; high-resolution mass spectrometry (HRMS) [electrospray ionization (ESI)] m/z calcd for $C_{18}H_{18}O_5$ $(M+H)^+$: 315.1230; found 315.1228.

Vapor Gas Detection

TLC plates were soaked in the probe **NE-N_2H_4** solution [0.1 mM, in dimethylsulfoxide (DMSO)]. After the **NE-N_2H_4** probe-loaded TLC plates were dried over air-blast drying box, the plates were put onto a series of flasks with different concentrations of N_2H_4 for 10 min. Then, the color of probe-loaded TLC plates was observed under UV light of 365 nm.

Cell Imaging

HeLa cells were grown in modified Eagle's medium (MEM) replenished with 10% fetal bovine serum (FBS) with the atmosphere of 5% CO_2 and 95% air at 37°C for 24 h. The HeLa cells were washed with phosphate buffered saline (PBS) three times when used. HeLa cells were treated with **NE-N_2H_4** (20.0 μM) for 30 min, then with N_2H_4 (200.0 μM) for 30 min at 37°C. The ideal fluorescence images were acquired with a Nikon A1MP confocal microscopy with the equipment of a CCD camera.

RESULTS AND DISCUSSION

Design and Synthesis of Probe NE-N_2H_4

As we all know, aldehyde group was easily reacted with nucleophile to construct C=C bond. Therefore, the simple compound of 6-hydroxy-2-naphthaldehyde was modified simply as the fluorescent group. The turn-on probe **NE-N_2H_4** was developed by modifying a novel recognition site of diethyl malonate with functional aldehyde group in **Scheme 2**. The structure of the **NE-N_2H_4** was characterized by ^1H, ^{13}C NMR, and HRMS (**Supplementary Figures 8–10**).

The Spectral Property of Probe NE-N_2H_4

This developed probe **NE-N_2H_4** was applied to measure spectral properties with the addition of N_2H_4 including absorption spectroscopy and fluorescence spectroscopy. The probe **NE-N_2H_4** exhibited no fluorescence under excitation at 320 nm without addition of N_2H_4 (**Supplementary Figure 1**, **Figure 1**). In contrary, strong fluorescence emission appeared at 445 nm after adding N_2H_4 to the solution of **NE-N_2H_4,** with a quantum yield of 0.35. When the addition of N_2H_4 was up to 200 equivalent, the fluorescence enhancement emerged to the high point (**Figure 1**). Therefore, the probe **NE-N_2H_4** was easy to respond to N_2H_4, which was suitable for sensing N_2H_4 as a powerful pool with a large Stokes shift. The pH effect of PBS buffer was examined in **Supplementary Figure 2**. The fluorescent intensity increased from acid to basic rapidly. The

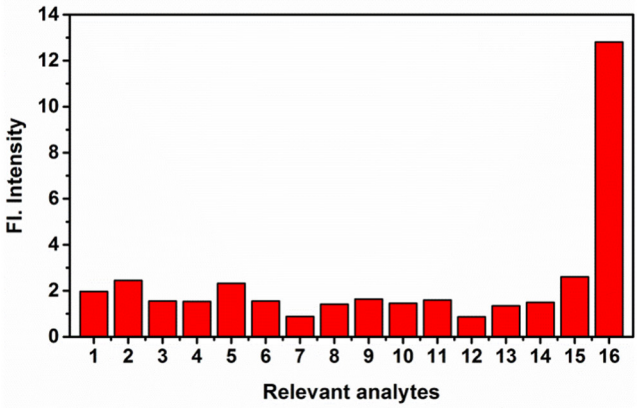


FIGURE 3 | The fluorescence intensity of **NE-N_2H_4** (10 μM) in the presence of various analytes (10 equiv) in phosphate buffered saline (PBS) buffer [pH 7.4 PBS/dimethylsulfoxide (DMSO) (v/v = 1/1)]. 1: None; 2: SO_3^{2-}; 3: NO_2^-; 4: NO_3^-; 5: I^-; 6: Br^-; 7: Fe^{2+}; 8: H_2O_2; 9: NO; 10: Li^+; 11: Zn^{2+}; 12: Ni^{2+}; 13: Cys; 14: GSH; 15: S^{2-}; 16: N_2H_4.

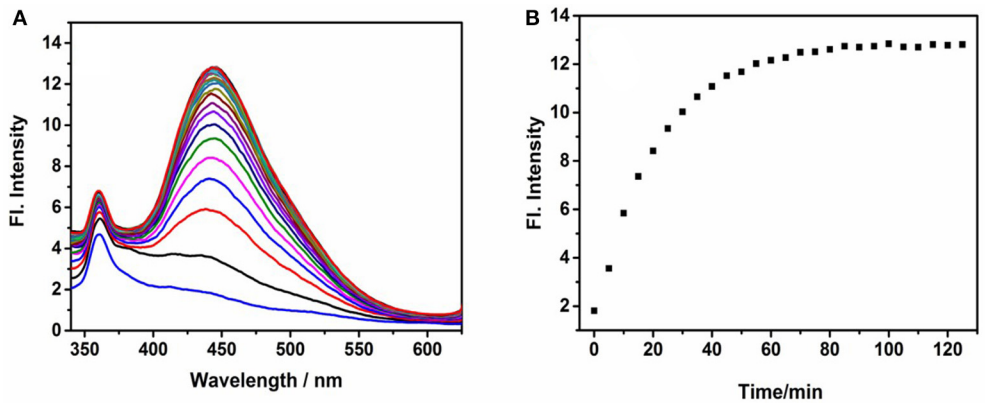


FIGURE 2 | Fluorescence spectra of NE-N_2H_4 (10 μM) in pH 7.4 phosphate buffered saline (PBS)/dimethylsulfoxide (DMSO) (v/v = 1/1) in the absence or presence of N_2H_4 (10 equiv). **(A,B)** were depicted in Response Rate and Selectivity of Probe NE-N_2H_4.

main reason is that the nucleophilic substitution to the probe **NE-N_2H_4** reacted easily in alkaline conditions.

Mechanism

The sensing mechanism was examined by adding N_2H_4 to the solution of probe **NE-N_2H_4**. The reaction solution was detected by HRMS. When probe **NE-N_2H_4** (20 μM) was treated with N_2H_4 (200 μM), a peak at m/z 187.0879 emerged in HRMS spectrum in accordance with the predicted **NE-N_2H_4-adduct** (**Supplementary Figure 4**). The **NE-N_2H_4-adduct** was constructed in one step easily characterized by ^{1}H NMR and HRMS (**Supplementary Figures 5, 6**). Additionally, the absorption spectra of **NE-N_2H_4** (10 μM) in absence or presence of N_2H_4 (10 equiv) and the synthetic **NE-N_2H_4-adduct** in pH 7.4 PBS/DMSO (v/v = 1/1) were listed in **Supplementary Figure 3**, which is consistent with the proposed mechanism (**Scheme 1**).

Response Rate and Selectivity of Probe NE-N_2H_4

The time course of probe **NE-N_2H_4** was measured after the addition of N_2H_4 (10 equiv) (**Figures 2A,B**). Notably, the fluorescence enhancement was increased obviously as time goes on. That is to say, the sensing probe **NE-N_2H_4** could be fit for imaging N_2H_4 in living cells. Another important factor is selectivity research of **NE-N_2H_4** compared to other interfering species. It is very crucial whether the sensing molecule **NE-N_2H_4** is suitable for cell imaging in the biosystem. The selectivity research was performed in **Figure 3** over other competitive molecules. We find that fluorescence intensity showed almost no change after adding N_2H_4, when the solution of probe **NE-N_2H_4** was added with other competitive molecules including SO_3^{2-}, NO_2^-, NO_3^-, I^-, Br^-, Fe^{2+}, H_2O_2, NO, Li^+, Zn^{2+}, Ni^{2+}, Cys, GSH, S^{2-}, and N_2H_4. In conclusion, the sensing probe **NE-N_2H_4**

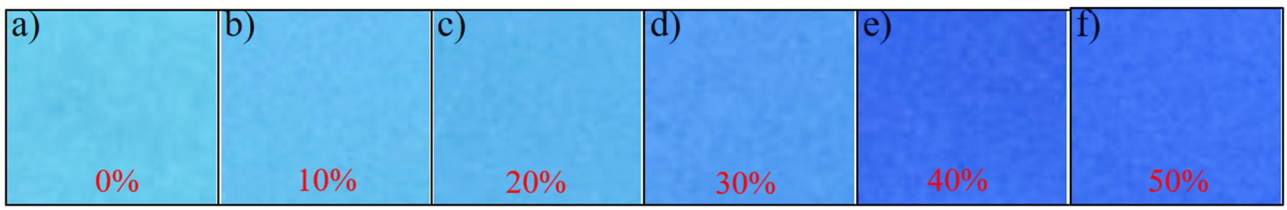


FIGURE 4 | Photographs of thin-layer chromatography (TLC) plates, soaked in the solution of **NE-N_2H_4,** followed by addition of different amounts of hydrazine. **(a)** Water, **(b)** 10% N_2H_4, **(c)** 20% N_2H_4, **(d)** 30% N_2H_4, **(e)** 40% N_2H_4, **(f)** 50% N_2H_4.

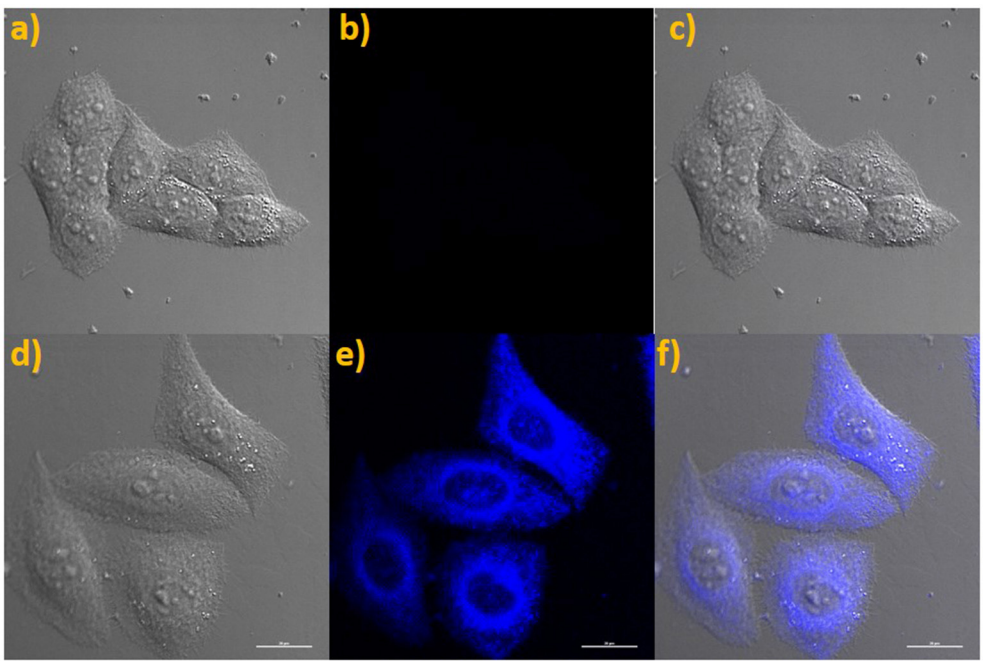


FIGURE 5 | (a) Brightfield image of living HeLa cells costained only with **NE-N_2H_4**. **(b)** Fluorescence images of **(a)** from blue channel. **(c)** Overlay of **(a,b)**. **(d)** Brightfield image of living HeLa cells costained with **NE-N_2H_4** and N_2H_4. **(e)** Fluorescence image of **(d)** from blue channel. **(f)** Overlay of the brightfield image **(d)** and blue channels **(e)**.

could be suitable for the response to N_2H_4 with good selectivity over other interfering molecules in the biosamples.

Application in Gas Detection

According to the above research data, the application of gas detection was operated. The free TLC plates were soaked in the solution of **NE-N_2H_4** (0.1 mM, in DMF). The TLC plates loaded with probe **NE-N_2H_4** were prepared to discriminate N_2H_4 (gas) in different concentrations after drying with a vacuum dryer. Distinctive fluorescence color changes of plates were obtained under UV 365 nm light (**Figure 4**) after exposing TLC plates to the N_2H_4 (gas) for 10 min. Obviously, no obvious change was exhibited in the distilled water (**Figure 4a**). The experimental result indicated that the sensing probe **NE-N_2H_4** may be a practical method to detect N_2H_4 in industrial pollution.

Cytotoxicity and Imaging

Encouraged by the good fluorescent properties of probe **NE-N_2H_4** including sensitive response, good selectivity, and large Stokes shift, a laser confocal microscope was applied to test the potential applications in cell imaging. The cytotoxicity of probe **NE-N_2H_4**was tested for imaging MTT assays in living cells. The living HeLa cells were operated for imaging fluorescent experiments by means of confocal laser scanning microscopy.

MTT assays were operated on living HeLa cells incubated with probe **NE-N_2H_4** (see **Supplementary Figure 4**). The data indicated that this probe **NE-N_2H_4** at different concentrations was almost nontoxic to the living cells [>90% HeLa cells survived after 24 h with **NE-N_2H_4** (10.0 μM) incubation]. Therefore, this probe is fit for imaging N_2H_4 in living HeLa cells.

The probe **NE-N_2H_4** was operated to incubate living HeLa cells for bioimaging of N_2H_4 due to the improved properties. Firstly, the solution of probe **NE-N_2H_4** was used for incubating living HeLa cells for 30 min. No obvious fluorescence emerged in blue channel collected with Nikon A1MP confocal microscopy with a CCD camera (**Figures 5a–c**). Then, probe **NE-N_2H_4** was used to incubate the living HeLa cells for 30 min and treated with N_2H_4 for another 30 min, obvious fluorescence exhibited in blue channel (**Figures 5d–f**). The experimental data indicated that the probe **NE-N_2H_4** was fit for imaging N_2H_4 in living HeLa cells.

CONCLUSION

In conclusion, an organic fluorescent probe has been constructed using diethyl malonate as a recognition site for sensing N_2H_4 with good selectivity and large Stokes shift (125 nm). This novel probe **NE-N_2H_4** was developed for sensing N_2H_4 in living HeLa cells. In addition, this probe **NE-N_2H_4** was applied for gas detection by probe-loaded TLC plate. The above results indicate that the probe **NE-N_2H_4** may be powerful for monitoring N_2H_4 in biosystems and environmental problem.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

J-YW: synthesize and characterize the dyes. JQ: supervise the project, review, and edit manuscript. HZ: supervise the project, review, and edit manuscript. Z-HZ and Z-TW: design, synthesize, characterize the dyes, write and edit manuscript, and manage the research project. All authors: contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2020.602125/full#supplementary-material

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