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Bent-to-planar Si-rhodamines: a distinct rehybridization lights up NIR-II fluorescence for tracking nitric oxide in the Alzheimer's disease brain†

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An ongoing revolution in fluorescence-based technologies has transformed the way we visualize and manipulate biological events. An enduring goal in this field is to explore high-performance fluorogenic scaffolds that show tunability and capability for *in vivo* analysis, especially for small-molecular near-infrared (NIR) fluorophores. We present a unique bent-to-planar rehybridization design strategy for NIR fluorogenic scaffolds, thus yielding a palette of switchable bent/planar Si-rhodamines that span from visible to NIR-II wavelengths. We demonstrate that the rehybridization of *meso*-nitrogen in this innovative NIR scaffold Cl-SiRh results in flipping between the disruption and recovery of the polymethine π -electron system, thereby significantly altering the spectral wavelength with crosstalk-free responses. Using elaborately lighting-up NIR-II probes with ultra-large Stokes shifts (ca. 250 nm), we successfully achieve real-time *in situ* monitoring of biological events in live cells, zebrafish, and mice. Notably, for the first time, the light-up NIR-II probe makes a breakthrough in directly *in situ* tracking nitric oxide (NO) fluctuations in the brains of mice with Alzheimer's disease. This *de novo* bent-to-planar rehybridization strategy of NIR-II probes opens up exciting opportunities for expanding the *in vivo* imaging toolbox in both life science research and clinical applications.

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Introduction

Fluorescence-based technologies have changed the way we study life science and conduct diagnostics.^{1–5} Most prominent amongst these enabling technologies is the utility of fluorescent probes for *in vivo* tracking of biological events with high resolution.^{6–9} Probes with near-infrared (NIR) emission are extremely important, but the primary hurdle is the lack of novel NIR-II fluorogenic scaffolds, showing powerful tunability and

capability for *in vivo* analysis. Most efforts rely on conjugated π -expansion and donor–acceptor (D–A) adjustment (Fig. 1A).^{10–12} However, most of the current NIR-II fluorophores usually require difficult and laborious synthesis and inflict self-instability along with undesirable quenching.^{12–16} Nowadays, it is urgent to develop an innovative NIR-II fluorogenic framework for highly accurate *in vivo* sensing and clinical translation.

Various fluorophores, including Si-rhodamines, have been widely used across a variety of fields including chemistry and life sciences.^{17–20} For instance, the element-substitution strategy that replaces the oxygen-bridge atom with a silicon atom in the xanthene core could alter the energy level of both HOMO and LUMO simultaneously, thereby narrowing the bandgap to afford considerable spectral red-shifts.²¹ Notably, Si-rhodamines afford a longer wavelength, superior brightness, and photostability, making them an outstanding candidate for *in vivo* bioimaging.^{22,23} However, this merely element-substitution skeleton modification alone limits the emission window expanding into the NIR-II window. Inspired by π -extension from molecular conformation changes, we hypothesize that one reasonable solution for developing an innovative NIR-II fluorogenic platform could be attained by tailoring the conjugated skeleton and switchable delocalization, that is greatly expanding the spectral windows and lighting up NIR fluorescence intensity.

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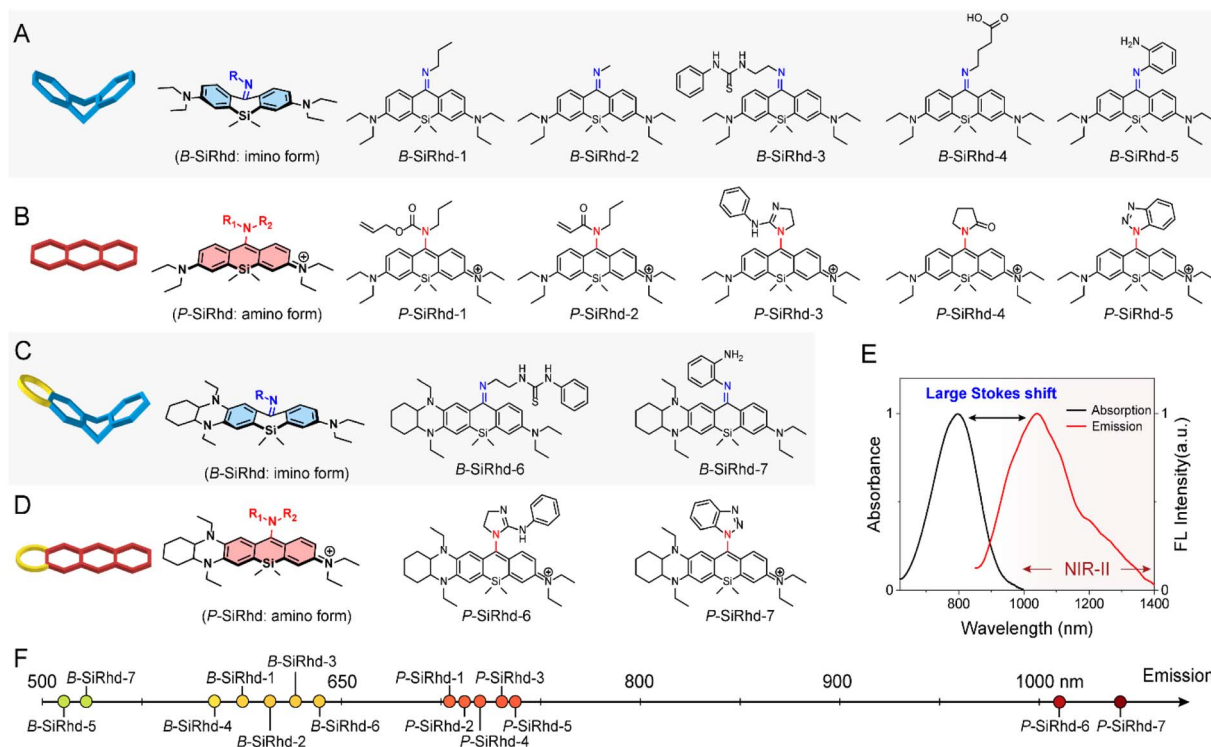


Fig. 2 Regulation π -electron delocalization induced spectral shift in Si-rhodamine fluorophores. Chemical structures of (A and C) bent-Si-rhodamine (B-SiRhod) and (B and D) planar-Si-rhodamine (P-SiRhod) fluorophores. (E) Normalized absorption and fluorescence spectra of representative asymmetric P-SiRhod-7 with a large Stokes shift. (F) Emission maxima peaks of bent/planar Si-rhodamines are visualized graphically on the electromagnetic spectrum.

rhodamine dyes, we expect that Cl-SiRhod has great potential for the development of *in vivo* fluorescent diagnostic reagents. To gain further insight into the structure–property relationship of the spectral changes, *via* nucleophilic amination, a series of *meso*-nitrogen substituted Si-rhodamines were portable synthesized (Fig. 2).

As is well-known, it's extremely difficult to regulate the emission spectra in a “given” Si-rhodamine scaffold with a large Stokes shift.^{23,26,34} However, our obtained Si-rhodamine probes show unprecedented and distinct spectral changes: (i) the resulting imino form of Si-rhodamines (such as B-SiRhod-1; $\lambda_{em} = 600$ nm) showed short-wavelength emission (Fig. 2F and S1–S3†); (ii) when *meso*-nitrogen becomes more electron poor, the corresponded amination of Si-rhodamines (such as P-SiRhod-1; $\lambda_{em} = 700$ nm) displayed long-wavelength emission (Fig. 2F and S4–S7†). Thus, these changes of the *meso*-nitrogen substituent in the conjugation play a key role in both absorption and emission spectral changes. As mentioned above, the hybridized nature of the *meso*-nitrogen substituent in this Cl-SiRhod scaffold responsible for the significant spectral shift is highly unusual in a “given” Si-rhodamine scaffold and needs to be further investigated.

Starting from the initial B-SiRhod-1 and P-SiRhod-1, we engineered a series of wavelength-regulable Si-rhodamines using the following guidelines (Fig. 1B): (i) starting with Cl-SiRhod as the fluorogenic motif; (ii) regulating *meso*-nitrogen with nucleophilic substituents. This strategy unlocks a great opportunity

to rapidly establish a library of Si-rhodamines for studying the regularity of their spectra. Specifically, we employed propylamine, 1-(2-aminoethyl)-3-phenylthiourea, and 4-aminobutyric acid, thus forming imine-type structures; while allyl propylcarbamate, guanidine derivatives, and pyrrolidinone as amine-type structures (Fig. 2). To our delight, all the resulting imino forms of Si-rhodamines displayed relative short-wavelength emission (Fig. S8†), whereas their corresponding amino forms of Si-rhodamines exhibited much longer emission (Fig. S9†). More importantly, when we elaborately constructed an asymmetric Si-rhodamine fluorogenic scaffold, the resulting Si-rhodamines (P-SiRhod-6 and P-SiRhod-7) achieved unexpected maximum NIR-II emission around 1050 nm (Fig. 2E, F and S10†). As far as we know, for the first time, a simple and generalizable Si-rhodamine engineering strategy was formulated to induce large spectral shifts spanning from the visible to NIR-II range (emission from 520 nm to over 1050 nm).

Revealing the bent-to-planar configuration changes

To get a deeper understanding of these significant spectral shifts, it's critical to obtain the molecular geometries/configuration of these Si-rhodamines. It has been revealed that modifying the amino group at the *meso*-position of the xanthene scaffold could significantly alter the spectral properties of Si-rhodamines.^{35–37} Fortunately, we acquired single crystals of B-SiRhod-5 and P-SiRhod-2 (Fig. 3A and B). Specifically, B-SiRhod-5 possesses a large dihedral angle (around 37.15°)



between two benzene units (Fig. 3A). With the attachment of the amino-group with an acryloyl unit, the resulting P-SiRhd-2 exhibits an almost coplanar configuration (Fig. 3B, with merely a 5.76° dihedral angle between two benzene groups). According to single-crystal analysis, the dihedral angle between two benzene rings is distinctly different from the electron density perturbation of *meso*-nitrogen substituents. These results elucidated that the regulation of the *meso*-nitrogen substitution of these B-SiRhd/P-SiRhd chromophores plays a key role in their molecular configuration. Thus, we reasoned that B-SiRhd-5 has a bent configuration with a shorter emission due to its obviously disrupted π -conjugation system. In contrast, P-SiRhd-2 with much longer emission exhibits planar configuration, maintaining the “unbroken” polymethine π -delocalization.

Subsequently, we investigated the role of *meso*-substituent in switching the intramolecular π -electron delocalization. Two (or more) consecutive carbon-carbon single bonds generally

disrupt the π -electron delocalization in a conjugated system. Indeed, the bent B-SiRhd-5 (imino form) possesses an obvious double bond (1.29 Å) of the C=N bond between *meso*-nitrogen and central-carbon C₅, and therefore this sp² hybridization of the N atom leads to two consecutive single bonds C₄-C₅ and C₅-C₆ in this Si-rhodamine (Fig. 3A and C). In contrast, the planar P-SiRhd-2 (amino form) exhibits a single bond (1.45 Å) of the C-N bond between *meso*-nitrogen (sp³ hybridization) and central-carbon atoms. Importantly, in P-SiRhd-2, no consecutive single carbon bonds are found in its skeleton (Fig. 3B and D), thereby affording much longer emission than that of B-SiRhd-5. Collectively, these results elucidate that the hybridization of *meso*-nitrogen in these B-SiRhd/P-SiRhd skeletons could switch the π -electron delocalization: (i) C=N bond formation disrupts π -electron delocalization with a bent fluorophore scaffold (Fig. 3A and C); (ii) *meso*-nitrogen undergoing sp³-hybridization restores π -electron delocalization with a planar fluorophore scaffold (Fig. 3B and D). Given that changing the molecular

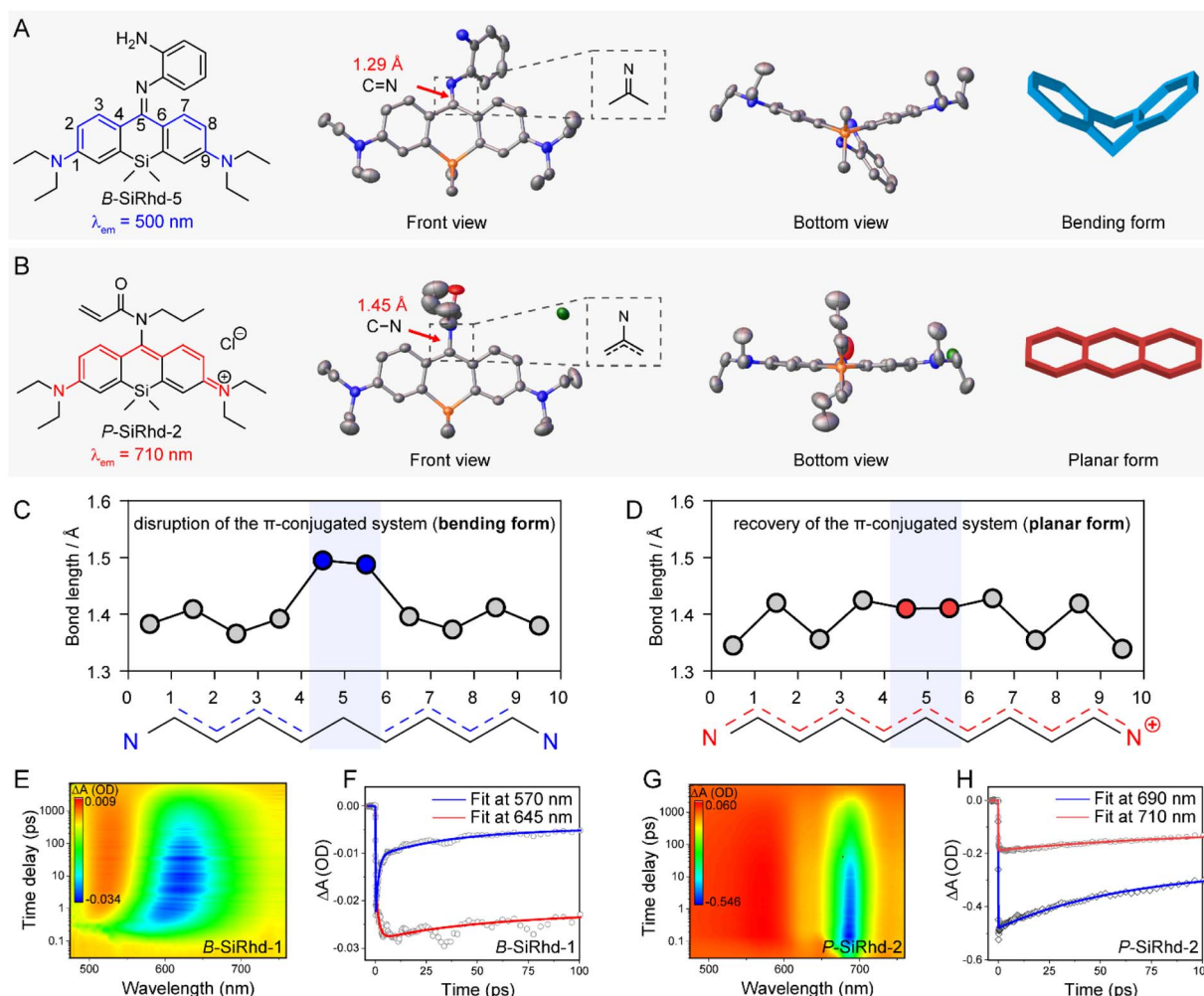


Fig. 3 Revealing the molecular bent-to-planar configuration change between imino and amino forms resulting in a significant wavelength shift. Chemical structures and single-crystal X-ray structures of (A) B-SiRhd-5 and (B) P-SiRhd-2. Note: solvent molecules and H atoms are omitted for clarity. Bond lengths of the carbon-carbon and carbon-nitrogen bonds of B-SiRhd-5 (C, bent-form) and P-SiRhd-2 (D, planar-form) along the conjugated path according to the crystal structure. (E) Femtosecond time-resolved transient absorption (TA) spectroscopy (contour plot) of B-SiRhd-1 in CH₃CN. (F) A comparison of the B-SiRhd-1 TA kinetic traces at 645 and 570 nm ($\lambda_{\text{ex}} = 460$ nm). (G) TA spectroscopy (contour plot) of P-SiRhd-2 in CH₃CN. (H) A comparison of the P-SiRhd-2 TA kinetic traces at 710 and 690 nm ($\lambda_{\text{ex}} = 680$ nm).



skeletal conformation could expand the π -conjugation,^{38,39} it is believed that tailoring the nature of the *meso*-position substituent in the conjugated system would play a key role in the development of NIR Si-rhodamine scaffolds.

According to single-crystal analysis, distinctly different π -delocalization was observed from *meso*-nitrogen substituted Si-rhodamines due to the electron density perturbation, and therefore the configuration in the molecular solution-state should be further investigated. With this in mind, we subsequently carried out femtosecond time-resolved transient absorption (TA) spectroscopy experiments. As shown in Fig. 3E, the time-resolved experiments of B-SiRhd-1 showed a red shift stimulated emission band, which is in agreement with the flexible molecular geometry (*i.e.*, bent configuration) of B-SiRhd-5 from the single-crystal analysis. More importantly, the transient absorption of B-SiRhd-1 kinetic traces at 570 nm and 645 nm clearly denotes an internal conversion in the excited state^{40–42} (Fig. 3F and S11†), further confirming that the B-SiRhd scaffold is flexibly bent in the molecular solution state. In contrast, P-SiRhd-2 displayed a still stimulated emission band over time (Fig. 3G and H), which implies that the Si-rhodamine scaffold is rigid in both the crystalline solid-state and solution-state (*i.e.*, planar configuration). All these results further confirm that the regulation of the *meso*-nitrogen substituent in the Cl-SiRhd scaffold can switch intramolecular π -electron delocalization, thereby resulting in flipping between the disruption and recovery of the polymethine π -electron system.

Constructing ratiometric NIR probes with minimized spectral crosstalk

The above experiments demonstrated that the alteration of π -electron delocalization in Si-rhodamines could generate a crosstalk-free dual-channel response. We thus hypothesized that high-performance ratiometric fluorescent probes^{43–48} could be designed *via* switching Si-rhodamines between the bent and planar configurations (Fig. 4A). Consequently, the following functionalized B-SiRhd/P-SiRhd probes were designed: B-SiRhd-3 with a 1-(2-aminoethyl)-3-phenylthiourea group for sensing Hg²⁺, B-SiRhd-4 with a 4-aminobutyric acid group for sensing phosgene and P-SiRhd-1 with the allyl propylcarbamate group for sensing Pd(0). As shown in Fig. 4B–J and S12–S15,† the crosstalk-free ratiometric responses were observed in all test assays.

For example, upon the addition of Hg²⁺, B-SiRhd-3 exhibited a remarkable shift in the absorption spectra, along with an obvious color change from yellow to green. Specifically, the absorption peak at 488 nm sharply decreased, and an increasing band centered at 690 nm was simultaneously observed, along with a distinct isosbestic point at around 550 nm (Fig. 4C). Concomitantly, when excited at an isosbestic point of 550 nm, an obvious decrease in the emission spectra at 610 nm and a sharp increase at 710 nm were also observed in the emission spectra (Fig. 4D, S16 and S17†). Importantly, this crosstalk-free ratiometric response not only contributes to the accurate measurement of dual-channel emission intensity, but

also results in a huge ratiometric value (Fig. S18†). To our delight, similar emission profiles and crosstalk-free responses were also observed in B-SiRhd-3 and P-SiRhd-1 towards phosgene and Pd(0), respectively (Fig. S19 and S20†). Furthermore, the crosstalk-free ratiometric bioimaging in cells and zebrafish demonstrated that B-SiRhd-3 can real-time track the uptake of Hg²⁺ in living cells and zebrafish (Fig. 4K, L and S21†). All these above results showed that the bent/planar switchable Si-rhodamines enable crosstalk-free ratiometric analysis and serve as a generalizable platform for detecting various chemical species.

Enabling simultaneously activatable NIR-II, photoacoustic, and photothermal signals

It remains quite challenging to rationally regulate absorption and emission in the NIR-II region, and these bottlenecks severely hinder the applicability of such probes for *in vivo* biosensing.^{49–54} Given that the asymmetric bent form (B-SiRhd with NIR-I emission) could be transformed to planar-form Si-rhodamines (P-SiRhd with NIR-II emission) (Fig. 2F and 5A), rational modulation of the NIR-II emission could be achieved *via* bent-to-planar configuration change. In this regard, various NIR-II fluorescent probes could be constructed *via* using our B-SiRhd/P-SiRhd chromophores.

The asymmetric Si-rhodamine probes B-SiRhd-6 and B-SiRhd-7 were obtained by using a 1-(2-aminoethyl)-3-phenylthiourea moiety as the Hg²⁺ responsive site, and an *o*-phenylenediamine moiety as the nitric oxide (NO) responsive site, respectively. To our delight, both B-SiRhd-6 (Fig. S22–S26†) and B-SiRhd-7 displayed remarkable lighting-up NIR-II fluorescence in response to their respective target analytes. For example, B-SiRhd-7 initially displayed two main absorptions at 420 and 580 nm with an emission peak at 520 nm. The detection of NO resulted in a new sharply increased NIR-I absorption band centered at 800 nm (Fig. 5B), accompanied by a reduction of the original absorption bands with a limit of detection of 0.3 μ M (Fig. S27†). Concomitantly, a new significantly increased emission band in the NIR-II region around 1050 nm ($\lambda_{\text{ex}} = 800$ nm) was observed, along with the decrease of the 520 nm emission (Fig. 5C, D and S28–S33†). Such an obvious NIR-II fluorescence enhancement (20-fold) is attributed to the NO-induced bent-to-planar transformation of Si-rhodamine (Fig. 5A). We summarize these photophysical properties of Cl-SiRhd-based fluorophores (Table S1†). Impressively, P-SiRhd-7 exhibits excellent photostability compared to the traditional NIR-II fluorophore, which is a critical property in *in vivo* fluorescence imaging (Fig. S34†). All these results demonstrated that our bent-to-planar strategy enables not only the construction of dual-channel crosstalk-free ratiometric probes, but also the construction of turn-on probes with NIR-II fluorescence.

Inspired by the NO-induced sharp enhancement of the absorption at 800 nm, we reasoned that B-SiRhd-7 could be a promising chromophore for activatable photothermal (PT) therapy and photoacoustic (PA) imaging.^{55–60} As shown in Fig. 5E, upon treatment with NO, the probe B-SiRhd-7 exhibited a clear NIR-photothermal effect upon exposure to 808 nm NIR



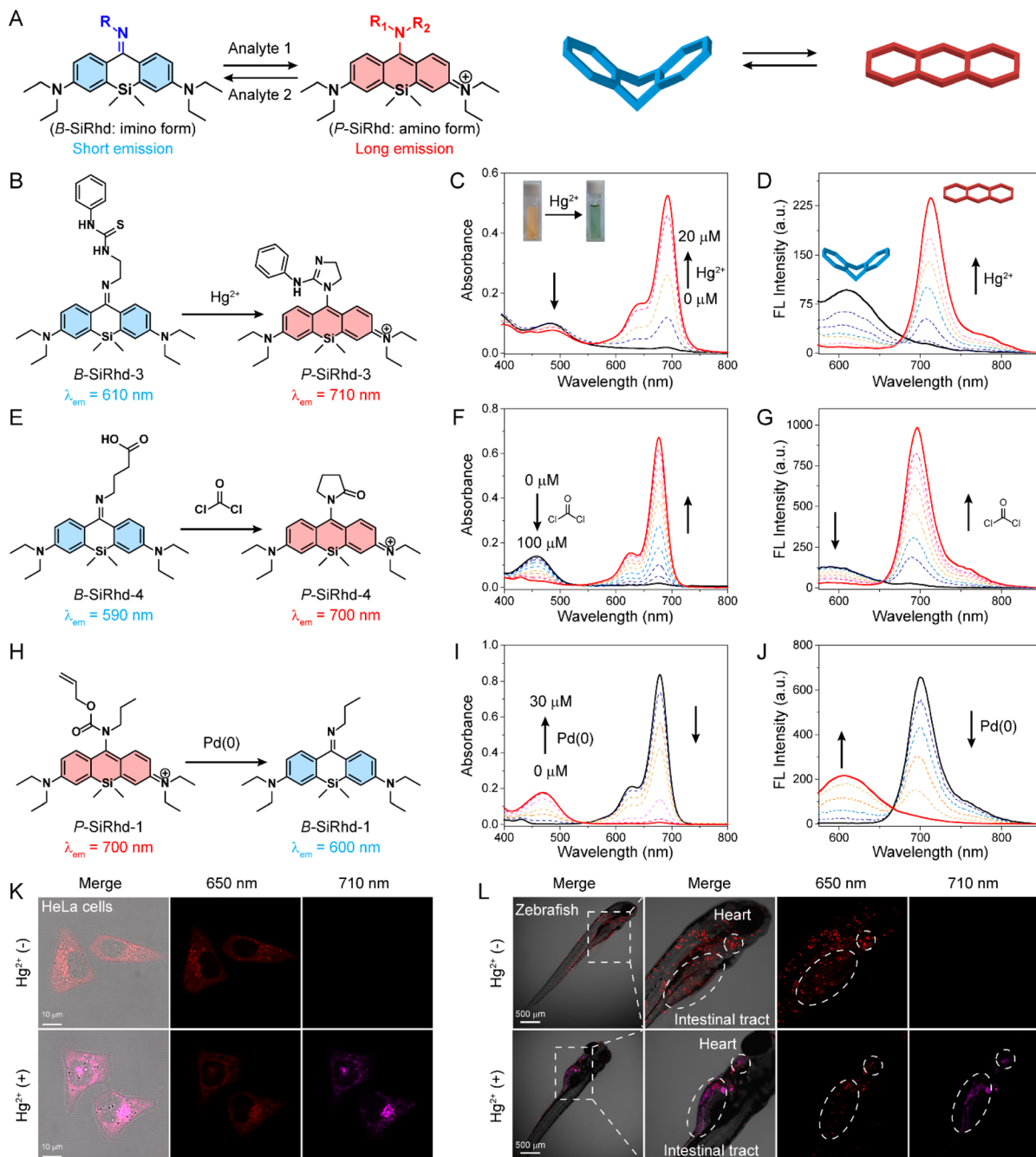


Fig. 4 A generalizable method for ratiometric NIR sensing with minimized crosstalk. (A) Using the designed bent/planar switchable fluorophores, we are able to construct NIR ratiometric probes. Chemical structures of bent/planar switchable probes with different biomolecular-recognition groups towards Hg^{2+} (B), phosgene (E), and $\text{Pd}(0)$ (H). Absorption (C, F and I) and fluorescence (D, G and J) spectra of B-SiRhd-3, B-SiRhd-4, and P-SiRhd-1 for various analytes ($\lambda_{\text{ex}} = 550 \text{ nm}$). (K and L) Dual-channel fluorescence imaging of Hg^{2+} with minimized crosstalk in cells and zebrafish (incubated with B-SiRhd-3, without and with Hg^{2+}).

light laser irradiation. The repeatable temperature increases (even after five cycles of heating and cooling) indicated that this NO-activatable probe B-SiRhd-7 has excellent photo-thermal stability as a potential PTT agent (Fig. 5F and S35–S37[†]). Furthermore, we also explored the NO-induced PA signal from the response of B-SiRhd-7. Notably, the corresponding opto-acoustic signal at approximately 800 nm is enhanced for the

detection of NO with good linear quantifiability (Fig. 5G) and high selectivity (Fig. 5H and S38[†]). Taken together, all these spectral results including single-crystals and time-resolved transient absorption analysis clearly demonstrated that the B-SiRhd/P-SiRhd platform could serve as a generalizable method for engineering activatable NIR-II probes with PT and PA signals.



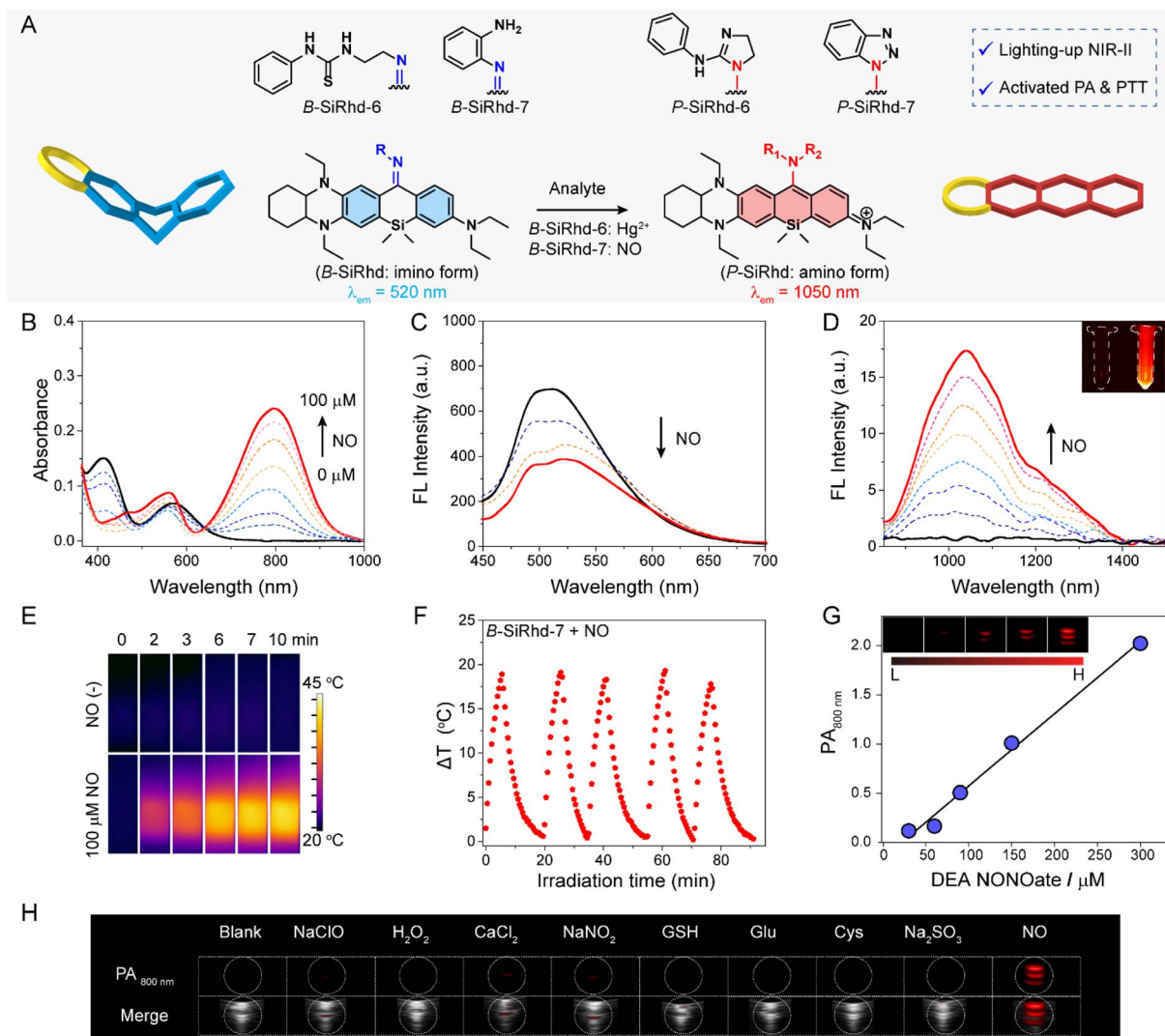


Fig. 5 The molecular bent-to-planar strategy for lighting-up NIR-II sensing. (A) Schematic illustration of the sensing mechanism for B-SiRhd-6 and B-SiRhd-7 towards Hg^{2+} and NO, respectively. Activatable NIR-II response: absorption (B) and fluorescence emission (C and D) spectra of B-SiRhd-7 ($10 \mu\text{M}$) in the presence of NO in a mixed solution. (E) Photothermal activation: thermal infrared image of B-SiRhd-7 ($20 \mu\text{M}$) in the presence of NO under 808 nm laser irradiation (2 W cm^{-2}). (F) Excellent photothermal stability: the variation of temperatures during five cycles of heating-cooling processes under 808 nm laser irradiation of B-SiRhd-7 ($20 \mu\text{M}$) with $100 \mu\text{M}$ NO. (G) Photoacoustic (PA) activation: plot of $\text{PA}_{800 \text{ nm}}$ of B-SiRhd-7 against the concentration of NO. (H) *In vitro* PA images of the solution of B-SiRhd-7 in the presence of various biologically relevant species at 800 nm .

Lighting-up NIR-II fluorescence for real-time *in situ* tracking inflammation in the liver, intestine and AD mice brain

The diagnosis of chronic diseases is of great significance for the timely implementation of medical intervention. Chronic inflammation plays a key role in the development and progression of many chronic diseases, such as inflammatory bowel disease (IBD) and Alzheimer's disease (AD), and can lead to increases in morbidity.^{61,62} Therefore, accurate mapping of inflammation will provide critical information to better understand its role in the onset and progression of chronic diseases. Activatable NIR-II imaging is a powerful approach to interrogate intact living samples in real time with spatial resolution due to its deep penetration and high-fidelity imaging capabilities. It has been widely applied for non-invasive real-time sensing and disease diagnosis in living systems.

Our new method of analyte-controlled molecular configuration changes for lighting-up NIR-II detection fits in well with disease diagnosis in living systems. Herein, to validate our strategy of expanding light-up NIR-II sensors with the real-time *in vivo* imaging capability, we chose the construction of an inflammation sensing system based on effective interaction of inflammatory factors for *in situ* generation of NO in deep tissue. We next assessed the capability of B-SiRhd-7 for *in vivo* monitoring endogenous NO levels in LPS-induced inflammation and Alzheimer's disease mice (Fig. 6). Because NO is a lipid-permeable free radical molecule, liposomal nanoparticles would be better employed to encapsulate B-SiRhd-7 for tracking NO fluctuation. With this in mind, stable lipid-based supramolecular nanoparticles were fabricated by self-assembly of colipids (phosphatidylcholine, DSPE-PEG-



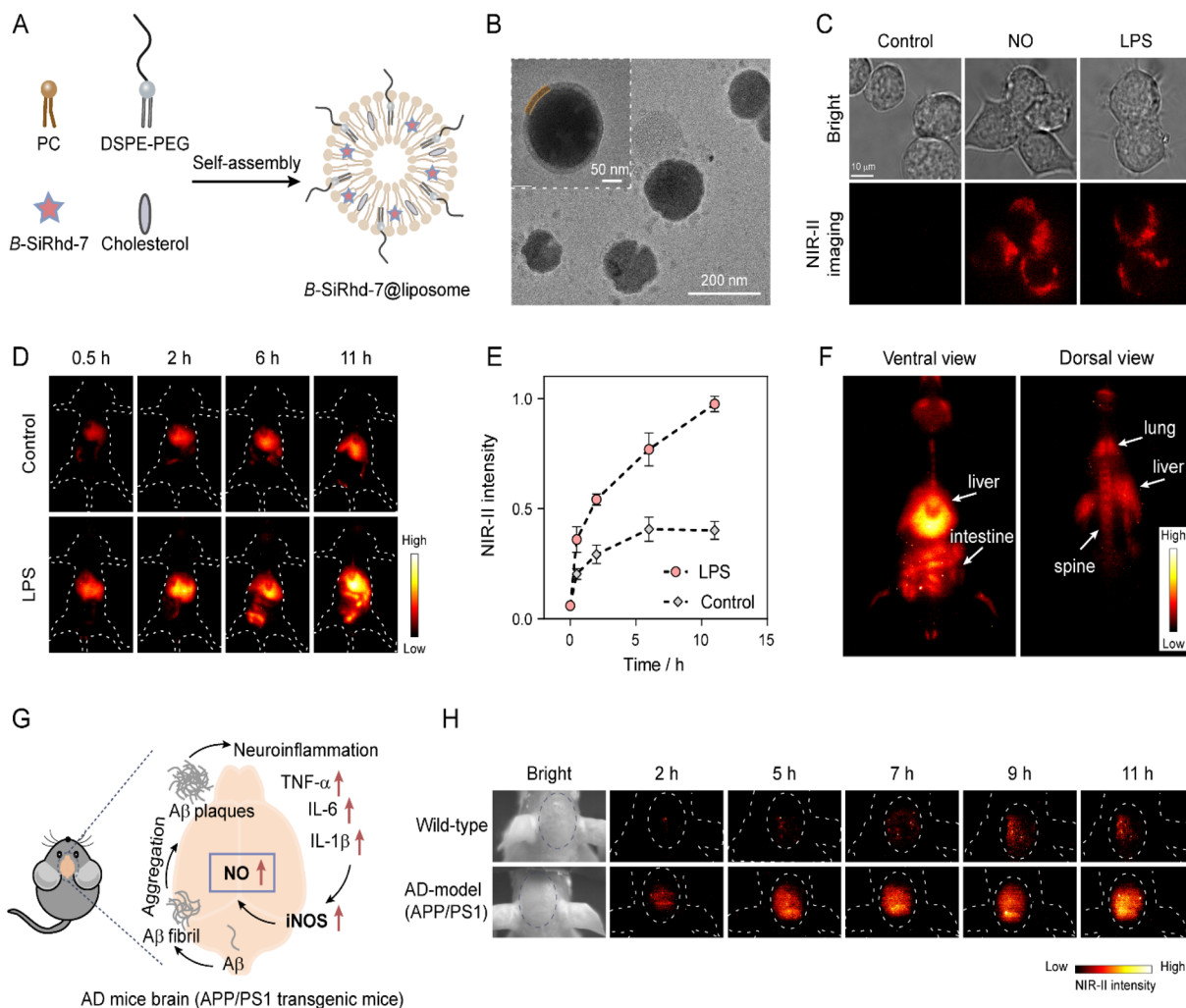


Fig. 6 *In vivo* NIR-II imaging of nitric oxide in LPS-induced inflammation and Alzheimer disease (AD) mice. (A) Schematics showing the synthesis of B-SiRhd-7@liposome. Cholesterol and NO probe B-SiRhd-7 were loaded into a stable liposomal system facilitated by the self-assembly of colipids (DSPE-PEG and phosphatidyl choline (PC)). (B) TEM image showing a B-SiRhd-7@liposome. (C) NIR-II fluorescence imaging of NO in RAW264.7 cells (incubated with B-SiRhd-7@liposome, without and with exogenous or endogenous NO). Notes: $\lambda_{\text{ex}} = 808$ nm, and 900 nm emission filter. (D) Representative images of mice receiving intravenously B-SiRhd-7@liposome (0.4 mM, 200 μL) pretreated with LPS or saline (control) intraperitoneally at a different time point. (E) The normalized fluorescence intensity over time in Fig. 6D. The maximum fluorescence intensity (11 h) is defined as 1.0. Data are presented as mean \pm SD ($n = 3$). (F) Biodistribution of B-SiRhd-7@liposome in the LPS-induced mouse in the ventral view (26 h) and dorsal view (28 h) after tail-vein injection of B-SiRhd-7@liposome. (G) Purposed biological synthesis route of NO in AD mouse brains. (H) *In vivo* fluorescence imaging of NO in wild-type and AD-model (APP/PS1) mice brains for 11 h *via* intravenous injection of 200 μL of 0.4 mM B-SiRhd-7@liposomes. $\lambda_{\text{ex}} = 808$ nm, and 1100 nm long-pass filter.

2000, and cholesterol) facilitated by hydrophilic and hydrophobic interactions. Indeed, hydrophobic B-SiRhd-7 occupies the spaces between the lipid bilayer constituting the B-SiRhd-7@liposome system⁶³ (Fig. 6A). The hydrodynamic diameter was evaluated using dynamic light scattering and was found to be *ca.* 125 nm (Fig. S39 and S40[†]). Transmission electron microscopy revealed the nanoparticles to have a clear structure of the lipid bilayer (Fig. 6B). Taking the above results together, we successfully prepared spherical core-shell structured liposome nanoparticles with a homogeneous particle size.

Firstly, we evaluated the NIR-II fluorescence response ability of B-SiRhd-7@liposome towards NO in living cells, and a RAW 264.7 cell was chosen as a model cell line. As shown in Fig. 6C

and S41[†] when RAW264.7 cells were preloaded with B-SiRhd-7@liposome (10 μM) for 30 min, dim fluorescence was detected in cells. However, after the cells were incubated with NO (10 μM) for another 10 min, a distinct enhancement of NIR-II fluorescence ($\lambda_{\text{ex}} = 808$ nm and 900 nm emission filter) of the cells was observed. Similarly, remarkable NIR-II fluorescence was found in the lipopolysaccharide (LPS, 1 $\mu\text{g mL}^{-1}$) pretreatment group, in which LPS could induce an inflammatory response in cells to produce NO. Cellular test results indicated that B-SiRhd-7@liposome enables real-time tracking of the alteration of endogenous NO levels.

Encouraged by *in vivo* cellular imaging results, we further examined B-SiRhd-7@liposome for monitoring the fluctuation



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