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NJC

Cite this: *New J. Chem.*, 2011, **35**, 1128–1132

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PAPER

The synthesis and $^1O_2$ photosensitization of halogenated asymmetric aniline-based squaraines†

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Received (in Montpellier, France) 1st December 2010, Accepted 8th March 2011
DOI: 10.1039/c0nj00949k

The halogenated (brominated or iodinated) squaraines have promising potential in the application of photodynamic therapy (PDT). Though aniline-based squaraines are the most classical squaraine dyes, no halogenated derivatives with the halogen atoms directly incorporated in the conjugation skeleton of the squaraine chromophore have been reported so far. In this work, a stepwise synthetic approach, *i.e.* by way of the halogenated semi-squaraines, was applied successfully to prepare halogenated asymmetric aniline-based squaraines. Such a structure makes iodine atoms be able to exert significant heavy atom effect on the intersystem crossing (ISC) efficiency of the squaraine dye. As a result, the iodinated asymmetric squaraine (SQ–OH–I) exhibits a singlet oxygen ($^1O_2$) quantum yield as high as 0.54. In contrast, the $^1O_2$ quantum yield of the non-halogenated squaraine analogue (SQ–OH) is only 0.02.

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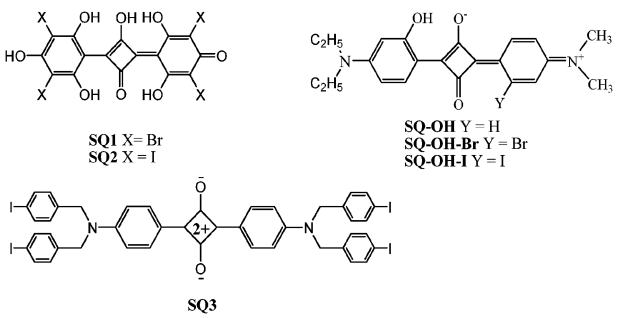
Introduction

Photodynamic therapy (PDT) is a noninvasive method for the treatment of a variety of cancers by the interactions of three elements: light, a photosensitizer, and oxygen. When exposed to proper wavelengths of light, the photosensitizer can be activated and undergo electron/energy transfer through its triplet excited state to generate cytotoxic reactive oxygen species (ROS), mainly singlet oxygen ($^1O_2$).[1] Although several porphyrin photosensitizers, *e.g.* Photofrin, are approved for clinical treatment of certain types of cancers, they are far from being ideal photosensitizers.[2] One of the main drawbacks of these photosensitizers is the relatively weak absorbance in the phototherapeutic window of 600–900 nm. Therefore, great efforts have been made to search for new and more effective photosensitizers, including porphyrin photosensitizers such as chlorin and bacteriochlorin, and nonporphyrin photosensitizers such as BODIPY, cyanine dyes, and squaraines.[3]

Squaraines are versatile organic dyes which have been extensively used in photoconductivity, optical data storage, solar cells, low-gap polymers, nonlinear optics, and chemosensors, due to the unique photophysical properties, particularly sharp and intense absorption and fluorescence in the red to near-infrared (NIR) region.[4] The intense absorption of squaraines in the NIR region makes them suitable for PDT application, however, the low intersystem crossing (ISC) efficiency severely hampers the $^1O_2$ generation ability and thus the photodynamic activity of squaraines. In order to increase the ISC efficiencies of squaraines, Ramaiah and co-workers first introduced heavy atoms (Br, I) into the phloroglucinol-based squaraines (SQ1 and SQ2 shown in Scheme 1) over a decade ago.[5] The heavy atom effect from Br or I atoms[6] endows SQ1 and SQ2 good $^1O_2$ sensitization abilities, but the absorption bands of SQ1 and SQ2 are not mainly within the phototherapeutic window. Since then, many heavy atom-containing squaraines, such as benzothiazole, benzoselenazole, quinoline, pyrrole, and quinaldine-based squaraines, were synthesized for PDT applications, with absorption bands fully falling in the phototherapeutic window.[7] Interestingly and surprisingly, though aniline-based squaraines are the most



Scheme 1 The chemical structures of the examined squaraines and the related squaraines.

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† Electronic supplementary information (ESI) available: The absorption and fluorescence spectra of SQ–OH and SQ–OH–Br, intensity changes of DPBF fluorescence with the illumination time of squaraines. See DOI: 10.1039/c0nj00949k

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classical squaraines and exhibit intense absorption bands totally in the phototherapeutic window,[8] no heavy atom-containing derivatives can be found until 2007 when Smith and co-workers reported the first iodinated aniline-based squaraine (SQ3 shown in Scheme 1).[9] Nevertheless, the iodine atoms are attached to the side chains of the two aniline moieties rather than on the squaraine conjugation skeleton, limiting the heavy atom effect that the iodine atoms should have. In this work, we present a new strategy to synthesize asymmetric aniline-based squaraines, SQ–OH–Br and SQ–OH–I shown in Scheme 1, with a Br or I atom incorporated into one of the two conjugation branches. Such a strategy may also allow for the independent structure optimization of the non-halogenated branch to tune absorption wavelength, water solubility, biocompatibility, as well as targeting property for application in PDT.

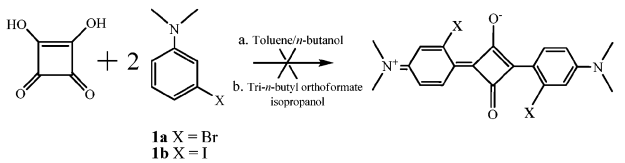
Results and discussion

Synthesis of the halogenated aniline-based squaraines

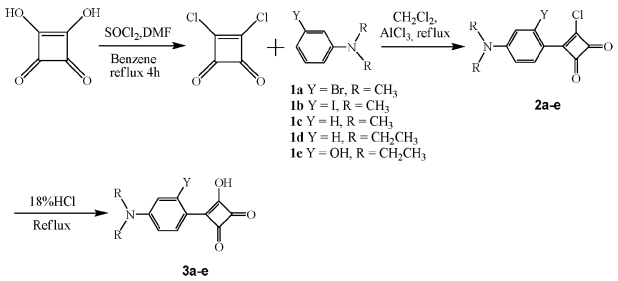
To synthesize halogenated aniline-based squaraines, the most straightforward strategy is to carry out condensation reactions between 1 equiv. of squaric acid and 2 equiv. of halogenated aniline derivatives. As shown in Scheme 2, squaric acid and 3-bromo-*N*,*N*-dimethyl aniline (or 3-iodo-*N*,*N*-dimethyl aniline) were refluxed either in toluene/*n*-butanol mixed solvent or in isopropanol/tri-*n*-butyl orthoformate mixed solvent.[10] Though tried many times at varied reaction temperatures and reaction durations, neither of the two procedures can lead to the production of the target symmetric halogenated squaraines. Because the production of aniline-based squaraines highly depends on the nucleophilic attack of the aniline derivatives to the electron-deficient cyclobutene ring of squaric acid, the failure of the condensation reactions most likely results from the reduced nucleophilicity of **1a** and **1b** due to the presence of the electron-withdrawing atom of Br or I.

Then, we attempted to synthesize halogenated aniline-based squaraines in a stepwise manner, *i.e.* through the semi-squaraine intermediates. Using reported methods as shown in Scheme 3,[11] five aniline-based semi-squaraines (**3a–e**) were all synthesized successfully, including brominated and iodinated semi-squaraines **3a** and **3b**, presumably resulting from the stronger reactivity of 3,4-dichlorocyclobut-3-ene-1,2-dione than that of squaric acid.

With the five semi-squaraines (**3a–e**) in hand, we tried our best to prepare halogenated aniline-based squaraines. The reactions of **3d** or **3e** with **1a** or **1b** did not yield the desired halogenated asymmetric aniline-based squaraines either (Scheme 4). In contrast, the condensation reactions between **3c** and *N*,*N*-diethylaniline or 3-hydroxy-*N*,*N*-diethylaniline



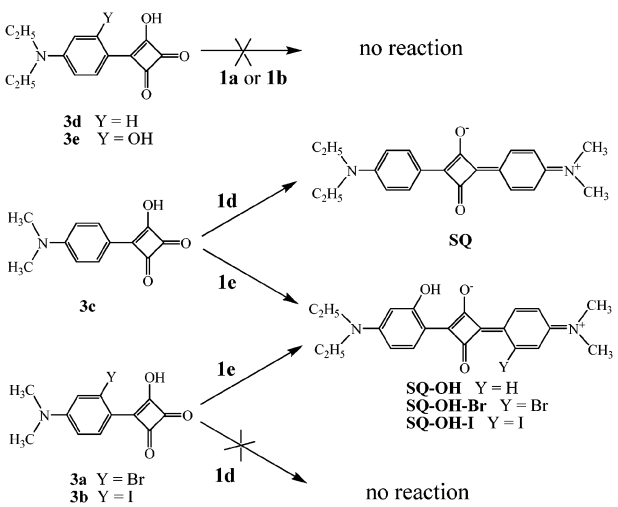
Scheme 2 The unsuccessful trials for the synthesis of symmetric halogenated aniline-based squaraines.



Scheme 3 The synthetic routes for aniline-based semi-squaraines.

can give the desired asymmetric squaraines in good yields (45% for SQ–OH), reflecting again the lower nucleophilic activities of **1a** and **1b** with respect to their non-halogenated analogues.

Finally, we used **3a** or **3b** as starting material to prepare halogenated asymmetric squaraines. Interestingly, *N*,*N*-diethylaniline cannot react with **3a** or **3b** whereas SQ–OH–Br and SQ–OH–I were obtained in moderate yields (30% for SQ–OH–Br and 25% for SQ–OH–I) by condensation reactions between 3-hydroxy-*N*,*N*-diethylaniline and **3a** or **3b** (Scheme 4). Compared to the fact that **3c** is able to react with both *N*,*N*-diethylaniline and 3-hydroxy-*N*,*N*-diethylaniline to yield the corresponding squaraines, one may reach the conclusion that the electrophilic activities of **3a** and **3b** are lower than that of **3c**. However, due to the electron-withdrawing character of Br or I atoms, it is expected that **3a** and **3b** should have stronger electrophilicity than **3c**. Ramaiah and coworkers also found that the bromination or iodination may improve the electrophilicity of quinaldine-based semi-squaraines.[7e] Therefore, there must be some factors other than the electronic induction effect of Br or I atoms to influence the electrophilic reactivity of **3a** and **3b**, and we tentatively attribute it to the steric effect. A Br or I atom is at the 3-position in **1a** and **1b**, which leads to the close proximity between the two large atoms and the cyclobutene ring in **3a** and **3b**. Gaussian calculation reveals that the optimized conformation of **3a** or **3b** does not adopt a coplanar strategy between the halogenated aniline



Scheme 4 The synthesis of squaraines starting from the semi-squaraines **3a–e**.

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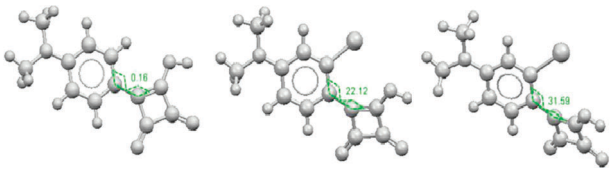

Fig. 1 The optimized conformations of semi-squaraines **3a** (middle), **3b** (right) and **3c** (left).

moiety and the cyclobutene ring, having a dihedral angle of 22.12° for **3a** and 31.59° for **3b**, while the optimized conformation of **3c** is in a coplanar manner (a dihedral angle of only 0.16°), Fig. 1. The non-coplanar conformation may either decrease the electrophilic activity of **3a** and **3b** or destabilize the reaction transition state, resulting in no reaction between *N*,*N*-diethylaniline and **3a** or **3b**. Due to the lower nucleophilicity of **1a** and **1b** than *N*,*N*-diethylaniline, it is not strange that **3a** and **3b** cannot react with **1a** and **1b** to gain the corresponding squaraines. Benefited from the higher nucleophilicity of 3-hydroxy-*N*,*N*-diethylaniline, which in turn results from the electron-donating property of the hydroxy substituent, two halogenated asymmetric aniline-based squaraines, SQ–OH–Br and SQ–OH–I, are obtained successfully.

Photophysical properties of the halogenated aniline-based squaraines

The basic photophysical properties of SQ–OH, SQ–OH–Br, and SQ–OH–I, such as absorption maxima, fluorescence maxima, and fluorescence quantum yields in chloroform, are presented in Table 1, and Fig. 2 shows the absorption and fluorescence spectra of SQ–OH–I (see Fig. S1, ESI†, for the absorption and emission spectra of SQ–OH and SQ–OH–Br). It is clear that the sharp and intense absorption bands of both SQ–OH–Br and SQ–OH–I are mainly located in the phototherapeutic window, with the absorption maximum at 632 nm and 635 nm, respectively. As the result of the heavy atom effect, the fluorescence quantum yields of SQ–OH–Br and SQ–OH–I are lower than that of SQ–OH, particularly in the case of SQ–OH–I, suggesting that SQ–OH–I might have a high efficiency of intersystem crossing (ISC) and a large $^1O_2$ quantum yield, prerequisite properties for PDT application.

Table 1 The photophysical properties of SQ–OH, SQ–OH–Br, and SQ–OH–I in $CHCl_3$

	λ_{max}^{ab}/nm	$\varepsilon/\times 10^5$ M^{-1} cm^{-1}	λ_{max}^{em}/nm	$\Phi_f{}^a$	$\Phi(^1O_2)^b$
SQ–OH	628	3.19	656	0.89	0.02
SQ–OH–Br	632	1.20	664	0.81	0.08
SQ–OH–I	635	1.66	668	0.35	0.54

[a] Fluorescence quantum yield measured using bis[4-(dimethylamino)-phenyl]squaraine (0.45 in CH_2Cl_2) as a reference.[8] [b] $^1O_2$ quantum yield measured *via* the chemical trap method using MB (0.51 in $CHCl_3$) as a reference.[13]

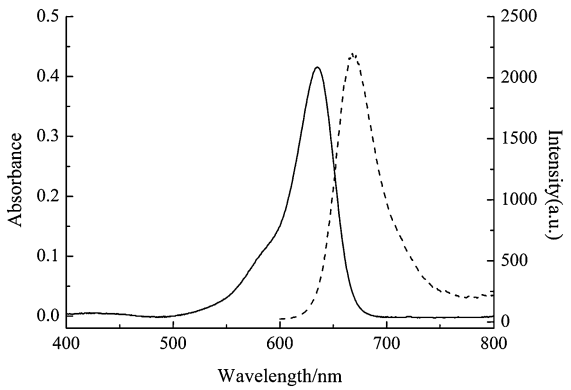

Fig. 2 The absorption and fluorescence spectra of SQ–OH–I in $CHCl_3$.

The absorption and fluorescence properties of the examined squaraines in THF are very similar to those in $CHCl_3$ (Fig. S3 and Table S1, ESI†). However, some differences can be found in CH_3CN and DMSO. Fig. S5(a), ESI†, shows the absorption spectra of SQ–OH–I in $CHCl_3$, THF, CH_3CN and DMSO. Though the concentrations of SQ–OH–I were all kept at 3 μM, the spectra in CH_3CN and DMSO are markedly broadened than those in $CHCl_3$ and THF, suggesting the aggregation of SQ–OH–I in CH_3CN and DMSO. Meanwhile, the fluorescence intensities of SQ–OH–I in CH_3CN and DMSO are significantly lower than those in $CHCl_3$ and THF, also suggesting the aggregation of SQ–OH–I in CH_3CN and DMSO. The aggregation of SQ–OH–I may result from its decreased solubility in CH_3CN and DMSO. SQ–OH and SQ–OH–Br display similar behaviors in CH_3CN and DMSO as SQ–OH–I. The insolubility of the three squaraines limits the property study in aqueous solutions.

In our experiments, we used 1,3-diphenylisobenzofuran (DPBF) as the chemical trap of $^1O_2$[12] and methylene blue (MB, $\Phi(^1O_2) = 0.51$ in $CHCl_3$)[13] as the reference to determine the $^1O_2$ quantum yields of the examined squaraines. The consumption of DPBF was monitored by its fluorescence intensity decrease as shown in Fig. S2, ESI.† Consistent with the trend of the fluorescence quantum yields, the $^1O_2$ quantum yields are in the order of SQ–OH < SQ–OH–Br ≪ SQ–OH–I (Table 1). The $^1O_2$ quantum yield of SQ–OH–I is as high as 0.54, 27-fold higher than that of SQ–OH, fully demonstrating the key role of the heavy atom I in tuning the ISC and $^1O_2$ efficiencies. The relative $^1O_2$ quantum yields in THF are also in the order of SQ–OH < SQ–OH–Br ≪ SQ–OH–I, Fig. S4 and Table S1, ESI.† The $^1O_2$ quantum yields of SQ–OH–I are too low to be accurately measured in CH_3CN and DMSO, probably due to the aggregation of SQ–OH–I in the both solvents.

To further confirm the $^1O_2$ sensitization ability of SQ–OH–I, we performed spin-trapping EPR experiments using 2,2,6,6-tetramethyl-4-piperidone (TEMP) as a spin-trapping agent of $^1O_2$.[14] Upon irradiation (532 nm laser) of the air-saturated chloroform solution of SQ–OH–I and TEMP, a three line EPR signal with equal intensity and a hyperfine coupling constant of $a_N = 16.0$ G was observed (Fig. 3), which is attributable to the adduct product of TEMP and $^1O_2$ (TEMPO).[15] The irradiation, air, and SQ–OH–I are all necessary for the generation of the TEMPO signal. The quenching of the EPR signal by NaN_3 or 1,4-diazabicyclo-[2,2,2]octane (DABCO), the well known $^1O_2$ scavengers, further supports the assignment of the signal. In contrast, in the case of SQ–OH, the TEMPO signal can be neglected upon irradiation, in line with its poor $^1O_2$ quantum yield.

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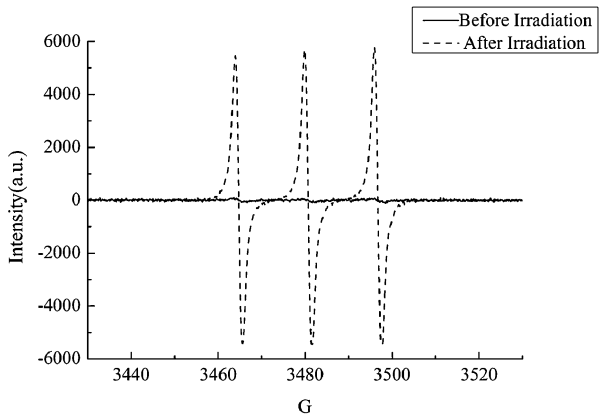

Fig. 3 The EPR spectra of air-saturated solution of SQ–OH–I (0.1 mM) in $CHCl_3$ in the presence of TEMP (50 mM) before and after laser irradiation at 532 nm.

Conclusions

In summary, by way of the halogenated semi-squaraines, we for the first time synthesized halogenated aniline-based squaraines, SQ–OH–Br and SQ–OH–I, with Br or I atoms directly incorporated in the conjugation skeleton of the squaraine chromophore. Such a structure makes iodine atoms be able to exert significant heavy atom effect on the ISC efficiency of the squaraine dye. As a result, SQ–OH–I exhibits a much improved $^1O_2$ yield, as high as 0.54. Further structure modification is in progress to render our halogenated asymmetric squaraines more ideal characters for PDT application, such as water solubility and targeting property.

Experimental section

General

Squaric acid, 3-hydroxy-*N*,*N*-diethylaniline, 3-bromo-*N*,*N*-dimethylaniline, 3-iodoaniline, tri-*n*-butyl-orthoformate, and sodium cyanoborohydride were purchased from Alfa Aesar and used without further purification. 1,3-Diphenylisobenzofuran (DPBF), sodium azide (NaN_3), 2,2,6,6-tetramethyl-4-piperidone (TEMP), and 1,4-diazabicyclo[2,2,2] octane (DABCO) were purchased from Sigma-Aldrich and used without further purification. Other materials, such as *N*,*N*-dimethylaniline, *N*,*N*-diethylaniline, aluminium chloride, thionyl chloride, and solvents were purchased from Beijing Chemical Plant and used as received. 3-Iodo-*N*,*N*-dimethylaniline and 3,4-dichlorocyclobut-3-ene-1,2-dione were synthesized following the literature methods.[16,17]

^{1}H NMR spectra were obtained on a Bruker DMX-400 MHz spectrophotometer. High resolution mass spectra were performed on a Bruker APEX IV FT-MS. UV/vis spectra were recorded on an UV-2450 spectrophotometer. Fluorescence spectra were run on a F-4500 spectrophotometer and the fluorescence quantum yields were measured using bis-[4-(dimethylamino)phenyl]squaraine (0.45 in CH_2Cl_2) as a reference.[8] The EPR spectra were recorded at room temperature on a Bruker-ESP-300E spectrometer at 9.8 GHz, X-band with 100 Hz field modulation. Samples were injected quantitatively into quartz capillaries and illuminated in the cavity of the EPR spectrometer with a Nd:YAG laser at 532 nm (5–6 ns of pulse width, 10 Hz of repetition frequency, 30 mJ per pulse energy).

Gaussian calculations were performed with the Gaussian 03 (G03) program package employing the DFT method with Becke's three-parameter hybrid functional and Lee–Yang–Parr's gradient corrected correlation functional (B3LYP). The LanL2DZ basis set and effective core potential were used for the I atom, and the 6-31 G* basis set was applied for H, C, N, O and Br. The ground-state geometries of the compounds were optimized in toluene using the conductive polarizable continuum model (CPCM), and frequency calculations were also performed to verify that the optimized structure is at an energy minimum.

The reaction of $^1O_2$ with DPBF[12] was adopted to measure the $^1O_2$ quantum yields of the examined squaraines using MB as the reference, whose $^1O_2$ quantum yield was measured to be 0.51 in chloroform.[13] A series of 2 mL of air-saturated chloroform solutions containing DPBF and squaraines, in which the absorbance at 630 nm originating from the absorption of the examined squaraines was adjusted to be the same (OD = 0.15), were separately charged into an open 1 cm path fluorescence cuvette and illuminated with the light of 630 nm (obtained from a Hitachi F-4500 fluorescence spectrophotometer). The consumption of DPBF was followed by monitoring its fluorescence intensity decrease at the emission maximum (λ_{ex} = 405 nm, λ_{em} = 479 nm).

Synthesis

Synthesis of 2a–e[17]. Aluminium chloride was dissolved in dichloromethane under reflux. 3,4-Dichlorocyclobut-3-ene-1,2-dione and corresponding aniline derivatives (**1a–e**) were dissolved in dichloromethane, and added dropwise into the refluxed solution over a period of 10 min. After 1.5 h, the resulting solution was poured into ice water in which two drops of concentrated hydrochloric acid were added. Then, the aqueous solution was extracted with dichloromethane for three times. The organic phase was washed with water, dried over $MgSO_4$, and concentrated to dryness. The crude product was purified by column chromatography on silica gel using *n*-hexane/ethyl acetate (3 : 1 in volume ratio) as eluent. The desired product was obtained as yellow solid *via* recrystallization from *n*-hexane/ethyl acetate (10 : 1 in volume ratio). **2a–e** have similar absorption spectra of typical semi-squaraines. **2a**, **2b** and **2d** were also characterized by ^{1}H NMR.

Synthesis of 3a–e. 2a–e were refluxed in the aqueous solution of 18% HCl for 4 h. After the resulting solution cooled to room temperature, the aqueous solution of $NaHCO_3$ was added until a large amount of precipitation was generated. The precipitation was filtered and dried overnight. The product was directly used to synthesize the corresponding squaraines without further purification.

Synthesis of SQ–OH, SQ–OH–Br, and SQ–OH–I. The target squaraine dyes were synthesized by the condensation of semi-squaraine derivatives **3a–c** and 3-hydroxy-*N*,*N*-diethylaniline with azeotropical removal of water in *n*-butanol/toluene (1 : 1 v/v) under reflux. After the resulting solution cooled to room temperature, the precipitation was filtered,

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washed with ether and methanol, and dried overnight. The product was collected as blue powder.

3-Chloro-(2-bromo-4-(dimethylamino)phenyl)cyclobut-3-ene-1,2-dione (2a). Yield, 10%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.85 (d, 1H, J = 9.04 Hz), 7.01 (s, 1H), 6.68 (d, 1H, J = 6.4 Hz), 3.10 (s, 6H).

3-Chloro-4-(2-iodo-4-(dimethylamino)phenyl)cyclobut-3-ene-1,2-dione (2b). Yield, 10%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.57 (d, 1H, J = 8.88 Hz), 7.33 (s, 1H), 6.74 (d, 1H, J = 6.4 Hz), 3.08 (s, 6H).

3-Chloro-4-(4-(diethylamino)phenyl)cyclobut-3-ene-1,2-dione (2d). Yield, 25%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 8.16 (d, 2H, J = 9.16 Hz), 6.90 (d, 2H, J = 8.84 Hz), 3.50 (q, 4H, J = 7.13 Hz), 1.26 (t, 6H, J = 7.12 Hz).

(2-Hydroxy-4-diethylaminio-phenyl)-(4-dimethylamino-phenyl) squaraine (SQ–OH). Yield, 45%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 8.20 (d, 2H, J = 9.00 Hz), 8.09 (d, 1H, J = 9.28 Hz), 6.79 (d, 2H, J = 8.72 Hz), 6.38 (d, 1H, J = 8.04 Hz), 6.12 (s, 1H), 3.50 (q, 4H, J = 6.95 Hz), 3.15 (s, 6H), 1.27 (t, 6H, J = 7.14 Hz); HRMS (ESI), calcd for ($C_{22}H_{24}N_2O_3$ + H^+) 365.18597, found 365.18651. Anal. calcd for $C_{22}H_{24}N_2O_3$: C, 72.49; H, 6.64; N, 7.69; found: C, 72.41; H, 6.54; N, 7.45%.

(2-Hydroxy-4-diethylaminio-phenyl)-(2-bromo-4 dimethylamino-phenyl) squaraine (SQ–OH–Br). Yield, 30%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 8.29 (d, 1H, J = 8.96 Hz), 8.17 (d, 1H, J = 9.44 Hz), 7.37 (s, 1H), 6.74 (d, 1H, J = 9.04 Hz), 6.41 (dd, 1H, J = 7.08, 2.36 Hz), 6.12 (d, 1H, J = 2.4 Hz), 3.53 (q, 4H, J = 7.17 Hz), 3.08 (s, 6H), 1.30 (t, 6H, J = 7.18 Hz); HRMS (ESI), calcd for ($C_{22}H_{23}N_2O_3Br$ + H^+) 443.09648, found 443.09712. Anal. calcd for $C_{22}H_{23}N_2O_3Br$: C, 59.72; H, 5.24; N, 6.33; found: C, 59.65; H, 5.12; N, 6.16%.

(2-Hydroxy-4-diethylaminio-phenyl)-(2-iodo-4-dimethylamino-phenyl) squaraine (SQ–OH–I). Yield, 25%; ^{1}H NMR (400 MHz, $CDCl_3$), δ = 8.27 (d, 1H, J = 8.96 Hz), 8.17 (d, 1H, J = 9.44 Hz), 7.41 (s, 1H), 6.80 (m, 1H), 6.42 (d, 1H, J = 9.48 Hz), 6.12 (d, 1H, J = 2.28 Hz), 3.53 (q, 4H, J = 7.20 Hz), 3.08 (s, 6H), 1.30 (t, 6H, J = 7.16 Hz); HRMS (ESI), calcd for ($C_{22}H_{23}N_2O_3I$ + H^+) 491.08262, found 491.08365; Anal. calcd for $C_{22}H_{23}N_2O_3I$: C, 53.87; H, 4.73; N, 5.71; found: C, 53.81; H, 4.58; N, 5.50%.

Acknowledgements

We greatly appreciate the financial support from NNSFC (20772133, 20873170) and CAS (KJCX2.YW.H08, KGCX2-YW-389).

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