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Planar AlEgens with Enhanced Solid-State Luminescence and ROS-Generation for Multidrug-Resistant Bacteria Treatment

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Abstract: Planar luminogens have encountered difficulties in overcoming intrinsic aggregation-caused emission quenching by intermolecular π - π stacking interactions. Although excited-state double-bond reorganization (ESDBR) can guide us on designing planar aggregation-induced emission (AIE) luminogens (AIEgens), its mechanism has yet been elucidated. Major challenges in the field include methods to efficiently restrict ESDBR and enhance AIE using without bulkv substituents performance (e.q. tetraphenylethylene and triphenylamine). In this study, we rationally developed fluoro-substituent AIEgens with stronger intermolecular H-bonding interaction for restricted molecular motions and increased crystal density, leading to decreased nonradiative decay rate by one order of magnitude. The adjusted ESDBR properties also show a corresponding response to variation in viscosity. Furthermore, their aggregation-induced reactive oxygen species (ROS) generations have been discovered. The application of such planar AlEgen in treating multidrug-resistant bacteria has been demonstrated in a mouse model. The relationship between ROS generation and distinct E/Z-configurational stacking behaviors have been further understood, providing a design principle for synthesizing planar AIEgen-based photosensitizers.

Introduction

the document.

Fluorescent materials have attracted much attention due to their potential in the field of optoelectronics and biomedical engineering.^[1] However, aggregation-caused quenching (ACQ) remains a significant limitation of traditional organic fluorophores, which presents annihilated emission in the aggregation state due to strong intermolecular π - π stacking interactions of their planar aromatic structures.^[2] On the contrary, aggregation-induced emission (AIE) luminogens (AIEgens) presents dim emission in aqueous solution but strong luminescence in solid, through the substitution using twisted structures to effectively prevent π - π stacking interactions in the aggregation or solid states.^[3] Over the past two decades, a series of mechanisms have been explored to interpret diverse AIE phenomena,^[4] including restriction of intramolecular motions,^[4b] twisted

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intramolecular charge transfer,^[5] anion- π^+ interaction,^[6] restriction of access to dark state,^[4c] intramolecular throughspace conjugation,^[4d] excited-state intramolecular proton transfer,^[7] and excited-state double-bond reorganization (ESDBR).^[8] However, certain types of AIEgens have been rarely developed, primarily those with planar luminophores, resulting from poorly understood working mechanism and intractable intermolecular π - π stacking associated with ACQ. Nevertheless, planar materials usually possess tight crystal density and good electron-delocalization for enhanced photophysical properties,^[9] making them attractive for constructing advanced fluorescent probes

Typical planar luminophores, such as organoboron, have rigid backbones that favor overlapping of molecular orbitals between highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), leading to increased radiative process.^[10] They thus have bright emission with high quantum yields (QYs) in solution but not in the solid state,[11] resulting from severe ACQ effect. To overcome the hurdle, we demonstrated that planar AIEgens can be feasibly developed by introducing an imino-double bond into organoboron architectures to facilitate ESDBR effect.^[8] In the aggregation or solid states, ESDBR is restricted, enabling planar AIEgens to emit intensively. Although ESDBR offers guidance on developing planar AlEgen, its mechanism is not fully understood. Additionally, methods to efficiently restrict ESDBR for further intensified AIE effect in solid state still has not been elucidated in detail. As such, systematically understanding the mechanism of enhanced solidstate luminescence through tuning ESDBR effect in planar AlEgens is of high importance, which will provide insight into molecular design strategy for new AlEgens.

In this work, we rationally designed and synthesized three pairs of planar AlEgens and comprehensively investigated their photophysical properties through experimental studies that support our theoretical hypothesis. The results suggest that the QYs of AlEgens in solid state can be significantly enhanced through introducing fluoro-substitutes in the aromatic ring. This can be attributed to the promoted intermolecular H-bonding interactions in the aggregation and solid states with suppressed nonradiative processes. Additionally, improved AIE performance and suitable energy barrier between the single and triplet states



- Structural optimization for AIEgens
- H-bond enhanced AIE property
- Viscosity study vs ESDBR
- Isomeric ROS generation
- Bactericidal treatment
- * $\alpha_{AIE} = \Phi_{solid} / \Phi_{THF}$

Scheme 1. Design strategy of fluoro-substituted planar AlEgens. Φ_{solid} and Φ_{THF} are the quantum yields of AlEgens in solid powder and THF solution, respectively.

 (ΔE_{ST}) can contribute to promoted reactive oxygen species (ROS) generation upon excitation.^[12] After thorough examination, we discovered that one fluoro-substituted planar AlEgen, DMA-AB-F, has shown efficient ROS generation in the aggregation state. Thus, it's *in situ* anti-bacteria ability in photodynamic therapy (PDT) has also been demonstrated using a mouse model with multidrug-resistant (MDR) bacterial infection. These insights into the working mechanism and the successful application in biomedical practice can open new doors to explore more planar AlEgens for advanced tasks.

Results and Discussion

The structures of synthesized AlEgens (Scheme S1) and their molecular characterizations are included in the Supporting Information. We initially discovered that the position of electrondonating substitution of alkylamino-group (DMA-AB and AB-DMA) exerts higher influence on ESDBR effect than that of methoxyl-group (MeO-AB and AB-OMe), and the energy barrier of E/Z-configurational interchange could be tuned up by substituting with electron-withdrawing group (DMA-AB-F, DMA-AB-CF₃, F-AB-DMA and CF₃-AB-DMA). Specifically, one AlEgen pair with fluoro-substituted aromatic ring (DMA-AB-F and F-AB-DMA; Scheme 1) have evident solid-luminescence with high QYs (47.4% and 72.5%). DMA-AB-F and F-AB-DMA were obtained at 85-92% yield by a two-step reaction (Scheme S2). Their photophysical properties were investigated and summarized in Figures 1a-d and S1 and Table S1. Although the two molecules exhibit similar UV/vis spectra, F-AB-DMA has more red-shifted emission and larger Stokes shift than DMA-AB-F. According to Lippert-Mataga equation, Stokes shift is mainly ascribed to intramolecular charge transfer (ICT) process and is consistent with the difference of dipole moment ($\Delta \mu$) between the ground and excited states (Table S2 and the inset of Figures 1c and d). The $\Delta \mu$ value of F-AB-DMA (13.59 D) is calculated to be twice the value of DMA-AB-F (6.92 D), implying that the former is more sensitive to the solvent polarity changes with stronger ICT effect. As such, F-AB-DMA shows a more distinct solvatochromism effect (Figure 1d), in which its maximum emission wavelength displays an obvious red-shift from nonpolar (466 nm in hexane) to polar solvent (611 nm in N,Ndimethylformamide). To investigate AIE performance, their fluorescent profiles were further measured in tetrahvdrofuran (THF) and THF/water mixtures with different water fractions (Figures 1b and S2). In THF solution, DMA-AB-F showed a blueshifted photoluminescence (PL) maximum (467 nm) than F-AB-DMA (568 nm) owing to its weaker ICT and stronger ESDBR (vide infra). The PL intensity of DMA-AB-F gradually rises with the increased water fraction (f_w) from 0 to 95% (v/v), demonstrating a typical AIE behavior.^[13] On the contrary, the PL intensity of F-AB-DMA was guenched rapidly upon addition of water due to strong ICT effect, but increases slightly at higher fw value (>80%) on account of AIE effect.^[5b] Estimated by the ratio of absolute quantum yield in solid powder (Φ_{solid}) to that in THF solution (Φ_{THF}), the AIE effect (α_{AIE}) values of DMA-AB-F and F-AB-DMA are 47.4 and 3.7 respectively. The higher α_{AIE} values from fluoro-substituted AIEgens can be attributed to the

significant enhanced Φ_{solid} values (47% and 73% for DMA-AB-F and F-AB-DMA) in comparison with their non-fluoro-substituted counterparts (25% and 35% for DMA-AB and AB-DMA).^[8]



Figure 1. (a) Normalized ultraviolet-visible (UV/vis) and photoluminescence (PL) spectra of AlEgens in tetrahydrofuran (THF) at 10 μ M. (b) Plots of AlE curves of AlEgen in THF solutions with different water fractions (vol%). PL spectra of DMA-AB-F (c) and F-AB-DMA (d) in different solvents. The inset is molecular dipole moments of AlEgens in the ground (S₀) and excited (S₁) states calculated with time-dependent density functional theory (TD-DFT). μ and μ^* denote the dipole moments of geometries in S₀ and S₁ states, respectively. $\Delta\mu$ denotes the difference of dipole moments between S₀ and S₁ states. Hex: hexane; DBE: dibutylether; Tol: toluene; DMSO: dimethyl sulfoxide; DMF: *N*,*N*-dimethylformamide.

To gain insight into the solid-state emission of planar AlEgens, the crystal structures were analyzed by single-crystal X-ray diffraction (Figures 2 and S3-5 and Table S3). The results are interpreted as following: (i) they have highly coplanar molecular structure with very small dihedral angles (only 0.22-6.28°), which are different from the traditional AIEgens based on bulky rotors;^[2b] (ii) Z-configurational DMA-AB-F and Econfigurational F-AB-DMA molecules have been identified; (iii) the molecular packing with large distance (Figures 2a and S3) or intercross mode (Figures 2b and S4) could avoid ACQ effect by reducing intermolecular π - π interactions; (iv) the multiple intermolecular interactions, such as C-H…F (2.50-2.66 Å) and C-H··· π (2.76-2.86 Å), restrict the molecular motions to reduce their nonradiative decay rate (k_{nr}) of energy loss for strong solid-state luminescence;^[14] (v) the molar crystal density of DMA-AB-F (4.24 mmol cm⁻³) is increased with more abundant intermolecular H-bonding (C-H···F) in comparison with nonfluoro-substituted AIEgens DMA-AB (4.17 mmol cm⁻³). Because both of them have four Z-configurational molecules in the packing unit, the results imply that tighter molar crystal density with higher luminous density per unit can lead to inhibited nonradiative process and enhanced solid-state QY. Hence, the promoted intermolecular H-bonding by fluoro-substitution can be

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a facile and effective method to restrict the intramolecular motions including ESDBR, leading to advanced planar AlEgens.



Figure 2. Single-crystal X-ray diffraction (SCXRD) crystallographic packing units and structures of DMA-AB-F (a and b) and F-AB-DMA (c and d). The inset numbers present the distance with a unit of Å.

To understand their photophysical properties in solution, the theoretical calculations for ground (S₀) and excited (S₁) states of AIEgens were carried out with a time-dependent density functional theory (TD-DFT) at the level of PBE1PBE/6-31G(d) based on solvation of THF (Figures S6-8 and Tables S4-6). Combining ESDBR guidance, their emissive behaviors in solution (The inset of Figures 3a and 3b) depend on the iminodouble bond (C=N) torsions in the light of the potential energy surface (PES; Figures 3a-3b and S9-10), instead of their high oscillator strength (f) values of electronic transition. The smaller energy barriers of E/Z-configurational interchange (ΔE_{EZI}) for DMA-AB-F (0.26-0.37 eV), compared with F-AB-DMA (0.37-0.50 eV), bring about lower emission in THF. This reveals that the excited DMA-AB-F molecules can be efficiently deactivated to So state projected vertically by S1 (S0//S1) through the conical intersection.

The nonradiative decay rate (k_{nr} , 2.3 × 10⁹ s⁻¹) of DMA-AB-F in THF solution is extremely greater than the radiative decay rate (k_r , 2.4 × 10⁷ s⁻¹) by two orders of magnitude (Figure S1 and Table S1). On the contrary, those rates of F-AB-DMA are in the same order of magnitude $(1.5 \times 10^8 \text{ and } 6.7 \times 10^8 \text{ s}^{-1} \text{ for } k_r \text{ and } k_r$ k_{nr} , respectively). Due to the AIE mechanism, the intramolecular motions including ESDBR are restricted in the aggregation and solid states. Hence, planar AIEgens usually have diminished nonradiative process in solid by one order of magnitude than that in solution.^[15] As a result, the solid-state k_r/k_{nr} ratios for fluoro-modified AIEgens (0.90 and 2.62 for DMA-AB-F and F-AB-DMA) are higher than that for unmodified ones (0.33 and 0.54 for DMA-AB and AB-DMA). This is resulting from the efficiently restricted ESDBR effect by the intermolecular Hbonding interaction upon fluoro-substitution. Furthermore, according to Förster-Hoffmann power-law relationship, the relative PL intensity of AIEgens should increase in high-viscous environment due to the limited molecular motions.^[16] We further carried out a viscosity study to confirm the ESDBR effect in the synthesized AIEgens (Figures 3c-3d). The viscosity parameter (χ) can be estimated from the slope of corresponding plots (Figures S11-17). The highest χ value, which is related to viscosity-sensitive behavior, appears in DMA-AB molecule with the lowest ΔE_{EZI} value (Figure 3c). This result from Figure 3c evidently demonstrates that the viscosity-dependent PL intensity will become more and more unresponsive along with the increased ΔE_{EZI} value for a series of AlEgens. This indicates that ESDBR effect can be adjusted strategically through regulating ΔE_{EZI} value, which guides the emissive behavior of planar AlEgens in the solution phase.



Figure 3. The potential energy surfaces (PES) of *E/Z* configurational interchange (EZCI) of DMA-AB-F (a) and F-AB-DMA (b). The insets show cuvettes containing THF solutions of AIEgens under UV-light irradiation at 365 nm. The *f* value denotes the oscillator strength. (c) The energy difference of EZCI (ΔE_{EZI}) versus viscosity parameter (χ) of Förster–Hoffmann power-law relationship. ΔE_{EZI} is estimated from the average energy barriers of EZCI, calculated from PES. (d) The molecular structures of the synthesized AIEgens.

AlEgens usually have single molecule formation in good solvent, in which the active intramolecular motions favor nonradiative relaxation of the excitons with diminished intersystem crossing (ISC) process.^[12b] On the contrary, the suppressed molecular motions of AIEgens in the aggregation state are favorable for ISC, which is named as the aggregationinduced ISC.^[12c] It has been reported that some aggregated AlEgens can strengthen the energy matches of ΔE_{ST} value by energy spitting, which will increase the ISC rate and prolong the lifetime of the triplet state.^[17] Therefore, the AIEgens may exhibit improved ROS-generation efficiency in the aggregation state. Herein, we investigated the ROS-generating ability of the planar AIEgens in THF solution with different phosphate buffered saline (PBS) fractions (vol%) using 2',7'-dichlorodihydrofluo-rescein (DCFH) as an indicator under white light irradiation (40 mW cm⁻² for 90s). AlEgens produce almost no ROS in 0 and 50 vol% of PBS fractions (Figures 4a-b and S18-20), owing to the active molecular motions in solution and incompact aggregation. This facilitates the excitons relaxation via nonradiative process, further leading to decreased ISC process. Thanks to AIE

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mechanism, AlEgens show obvious ROS-generating ability in high PBS fractions due to the greatly suppressed nonradiative decay. Additionally, the relative emission intensity ($III_0 - 1$) of DCFH mixed with the aggregated DMA-AB-F in PBS ($f_w = 99$ vol%) is enhanced by one order of magnitude than that of DCFH mixed with the aggregated F-AB-DMA (Figures 4a-b).



Figure 4. Time course of relevant changes in fluorescence intensities (*III*₀ – 1) at 523 nm of DCFH/DMA-AB-F (a) and DCFH/F-AB-DMA (b) in THF solutions with different PBS fractions upon white light irradiation (40 mW cm⁻²). Concentrations: 10 µM for AlEgens and 1 µM for DCFH. (c) Time-dependent changes of fluorescence intensities (*III*₀ – 1) at 512 nm for HPF with AlEgens. (d) Time-dependent changes of absorption intensities (*Al*₄₀) at 379 nm for ABDA with rose bengal (RB) or AlEgens. Relative energy level of DMA-AB-F (e) and F-AB-DMA (f) trimers. S₁ and T_n are first singlet and multi-triplet states, respectively. ISC is intersystem crossing between S₁ and T_n states. The solid and dashed arrows refer to the major and minor ISC channels, respectively.

Upon further measurement of ROS generation using hydroxyl radical probe (hydroxyphenyl fluorescein; HPF) and singlet oxygen probe (2,2'-(anthracene-9,10-diylbis(methylene))-dimalonic acid; ABDA), the major ROS produced by AlEgens are originating from type I reaction (Figures 4c-d and S21-22). Additionally, DMA-AB-F displays faster generating rate of hydroxyl radicals, which is ~23.8 and 6.5 times as high as F-AB-DMA and the standard photosensitizer, chlorin e6 (Ce6), respectively (Figures 4c and S21e). These results clearly demonstrate the great potential of DMA-AB-F as a photosensitizer. To unveil the causes that lead to such distinct

ROS-generating abilities of the two AlEgens, theoretical calculation was performed using a TD-DFT method with a trimer model. As expected, the $\Delta E_{\rm ST}$ value of DMA-AB-F trimer is obviously smaller and more positive than that of F-AB-DMA trimer even if they have the similar number of ISC channels (Figures 4e-f and Tables S7-8). According to Kohn-Sham frontier orbital analysis,^[18] the energy gap below 0.3 eV is possible for triggering ISC process. As such, it can explain the experimental results that DMA-AB-F has better ability of ROS generation in comparison with F-AB-DMA.

In efforts to reduce MDR incidences in clinical practice, development of alternative therapeutic approaches is of great importance to reduce our dependence on traditional antibioticbased antibacterial treatments.^[19] On the basis of its profound aggregation-induced ROS-generating ability, DMA-AB-F can further serve as a photosensitizer (PS) of PDT^[20] to treat MDR bacteria. We first evaluated the antibacterial ability of DMA-AB-F through the traditional colony-forming unit (CFU) counting method. MDR bacteria incubated with different concentrations of PS were irradiated by white light (8 mW cm⁻²) for different times (Figures 5a-b and S23-24). PS at a concentration of 10 µM could efficiently kill MDR E. coli and MRSA upon irradiation for 15 min and 30 min, respectively. These results indicate that DMA-AB-F has a profound killing efficacy on MDR bacteria. Fluorescence imaging results suggest that DMA-AB-F can stain both MDR bacteria by electrostatic and hydrophobic interactions and then emit intense fluorescent signal (Figures S26-27).[21]



Figure 5. Bacteria survival rates of *E. coli* (a) and *MRSA* (b) incubated with the various concentrations of DMA-AB-F upon white light irradiation (8 mW cm⁻²) for 0, 5, and 15 min, respectively. (c) SEM images of *E. coli* and *MRSA* treated with PS+white-light irradiation (PS@Light), PS only (PS@Dark), PBS only (PBS@Dark), and PBS+white-light irradiation (PBS@Light), respectively. PS is DMA-AB-F photosensitizer and PBS is phosphate buffer saline. Scale bar is 1 μ m.

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Figure 6. (a) Representative photographs of burned wounds infected by MDR *E. coli* and treated with PS+white-light irradiation (PS@Light), PS only (PS@Dark), PBS only (PBS@Dark), and PBS+white-light irradiation (PBS@Light), respectively. The power density of light irradiation is 8 mW cm⁻². The burning wounds were created on the flanks of Balb/c mice. (b) Relative changes of wound area (A/A_0) post different treatments. Statistical significance: 0 < *p < 0.0005. (c) Colony-forming unit (CFU) counting of bacterial amounts collected from skin wounds at day 5 and day 10 post treatment. Statistical significance: 0 < *p < 0.0005. (d) CFU counting of bacterial amounts from livers and spleens at day 5 and day 10 post treatment. Statistical significance: 0 < *p < 0.0005. (e) Hemotoxylin & eosin (H&E) staining and (f) Masson's trichrome staining of the sectioned tissues from wounds on mice at day 5 and day 10 post treatment.

Scanning electron microscope analysis was further performed to visualize the morphological features of MDR *E. coli* and *MRSA* before and after PDT (Figure 5c). The bacteria in PS@Light (DMA-AB-F+light irradiation) group show cell wall lysis, while the bacteria in other test groups show intact morphology and cell walls. Thus, DMA-AB-F functions as a good anti-bacteria PS *in vitro* and has great potentials to be used for bacteria treatment *in vivo*. It is worth noting that the PS shows negligible cytotoxicity to normal 3T3 and 293T cells at the same condition (Figure S25).

Intensive care is required for treating tertiary burns, where the wound recovery can be further complicated by high infection rates caused by some anaerobic and facultative anaerobic pathogens. Accordingly, we established a standard third-degree burn infection mouse model to assess the in vivo sterilization effect of AlEgen. Here, the burned wounds on the flank were infected with MDR E. coli and then randomly divided into four groups for the following treatments: PS@Light, PS@Dark, PBS@Dark and PBS@Light (Figure 6). The PBS@Light group is PDT group while the other three groups are control groups. At day 3 and day 5 post burns and treatments, the surfaces of wounds in control groups show severe ulceration accompanied by a large amount of pus accumulation. On the other hand, the wound sites in PDT group are much cleaner at the same time points. At day 8 post burn, the wound size of PDT group is significantly smaller than the others. At day 10, the wounds of PDT group have almost recovered with proper wound closure, while other groups showed lesser recovery status. Severe ulceration with pustules after uncovering the scab was observed due to the incomplete clearance of the bacteria. At day 5 and day 10, we collected the skin tissues from the wounds for bacterial culture. The results suggest that there is negligible amount of pathogens in PDT group, while other groups are

largely still infected by the pathogens (Figures 6c and S28). Similar phenomena have been observed in the in vitro bacterial culture experiments using liver and spleen tissues collected from each group at day 10 (Figures 6d and S29). These results indicate that the protection of deep organs from further infection has been achieved by fast eliminating bacteria in burn wounds through efficient PDT therapy.^[22] These results imply that DMA-AB-F has an excellent bactericidal efficacy on inhibiting the further infection of bacteria from skin into deep organs.^[23] In addition, hematoxylin and eosin (H&E) staining results show intact and thick epidermis in the regenerated skin of PDT group on day 5 (Figure 6e). At day 10, hair follicles and blood vessels appear on the H&E stained sections from the same group, indicating the good wound healing efficacy in PDT group. Similarly, Masson's trichrome staining images indicate that the visible collagen fibers are neat and the layers are clearly visible in the regenerated skin of PDT group (Figure 6f). On the contrary, delayed and incomplete skin regeneration progresses were observed by the histological staining results of skin tissues collected from other three control groups. As such, DMA-AB-F can act as an effective photosensitizer for PDT to eliminate MDR E. coli. Infection in vivo.

Conclusion

In this work, we show a significantly boosted AIE effect in planar AIEgens through introducing a fluorine substituent and unveil the mechanism of this facile approach through theoretical calculation and experimental data. Changing the position of substituents can lead to differed optical properties. Particularly, DMA-AB-F has a blue-shifted but weaker emission compared to

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F-AB-DMA in THF solution due to its weaker ICT and stronger ESDBR. Resulting from fluorine substitution, intermolecular Hbond is strengthened to further restrict the intramolecular motions including ESDBR in the aggregation and solid states. As a result, the solid-state luminescence and AIE performance are dramatically enhanced. Interestingly, by accident of the different E/Z-configurational stacking behaviors, only DMA-AB-F has a suitable driving force to facilitate ISC from S₁ to T₁ states to produce ROS in the aggregated state. As a result, DMA-AB-F can serve as a photosensitizer for PDT to successfully eliminate MDR bacteria both in vitro and in vivo. Noteworthy is that we demonstrate a new strategy to design highly emissive AIEgens using H-bonding restricted ESDBR property, which offers an alternative approach to the design principle of traditional AlEgens by introducing bulky rotor-substituents. This investigative elucidation will not only break the structural limit for typical AlEgen design, but also assist to expand new planar AlEgens with novel properties for advanced biomedical applications.

Experimental Section

The experimental details were described in the supporting information.

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Keywords: aggregation-induced emission • organoboron • photodynamic therapy • H-bond • conical intersection

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RESEARCH ARTICLE

The excellent aggregation-induced emission and ROS-generation performances of planar luminophores, stemmed from intermolecular Hbonding interactions, served as photosensitizers for photodynamic therapy of bacterial infection.



Jen-Shyang Ni, Tianliang Min, Yaxi Li, Menglei Zha, Pengfei Zhang, Chun Loong Ho, and Kai Li*

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Planar AlEgens with Enhanced Solidstate Luminescence and ROS-Generation for Multidrug-Resistant Bacteria Treatment