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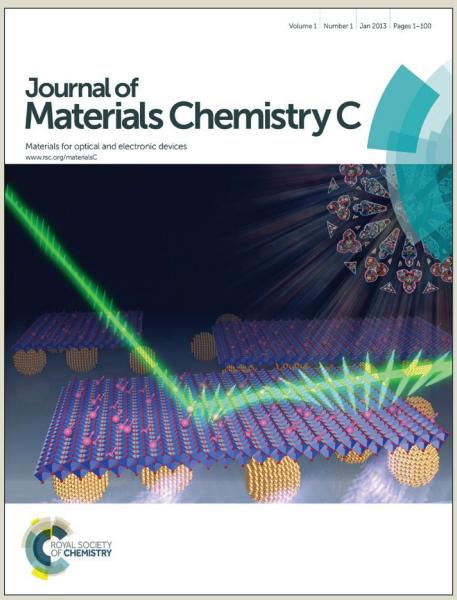

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HIGHTLIGHT

Long wavelength AIEgen of quinoline-malononitrile†

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Development of novel building blocks as long wavelength aggregation-induced emission (AIE)-active fluorophore/chromophore is at high demand for high performance luminescent and optical bioimaging agents. In this Highlight, we summarize some recent advances in the area of red to near-infrared (NIR) fluorescent AIE-active organic materials derived from our established building block of quinoline-malononitrile (QM), focusing on AIE menchanism process, water-soluble and shape-specific effects, hybridized dye-doped prodrug, as well as facile scale-up and fast preparation for AIE-active nanoparticles through flash nanoprecipitation.

Introduction

Construction of high performance fluorescent materials with bioimaging functionality is at high demand for practically biomedical applications.[1-6] To better track physiological behaviors within complex and dynamic biological systems, fluorescent materials should bestow durable high brightness and good biocompatibility. However, the traditional molecular emitters are often in the aggregated states with considerable intermolecular interactions that usually result in the typical aggregation-caused quenching (ACQ) effect. The ubiquitous ACQ effect has become a thorny obstacle for constructing high performance organic luminescent materials. Since the intriguing discovery of aggregation-induced emission (AIE) phenomenon by Prof. Tang, great efforts have been moved to exploration of AIE materials with their biological applications.[7-13] Particularly, unprecedented target of AIE-active nanomaterials in application of cancer diagnosis and therapy *in vivo* has become a fascinating area of research.

Fluorescent AIE materials generally feature a unique turn-on characteristic in aggregation while faintly in molecularly dissolved state.[7] The fascinating advantage leading to good brightness makes AIE fluorophores ideally suitable for biosensing and imaging *in vivo*,[10] especially in high concentration of fluorescent dyes. In the past decade, great efforts have focused on elucidating AIE mechanisms, building novel AIE-active luminogens (AIEgens), tailoring their wavelength and morphological nanostructures, and further exploring their potential applications. Up to date, the solid-state enhanced emission AIE systems are still mostly focused on silole,[14] tetraphenylethene[7-9] and cyanostilbene derivatives[12], severely limited to the short-wavelength fluorescence in the range of 400-600 nm, resulting in the short penetration depth in tissue and auto-fluorescence of body. In contrast, the long wavelength like near-infrared (NIR) emission can greatly facilitate in vivo bioimaging of molecular processes since NIR photons can relatively deeply penetrate into tissues with less damage to biological samples.[6] In this regard, exploration of long wavelength AIEgens is in urgent attention.

In this highlight, we summarize some latest advances in the area of red to NIR fluorescent AIE-active organic materials *via* tailoring novel building block of quinoline-malononitrile (QM, Fig. 1). Firstly, we examine our hypothesis to the AIE-active building block of QM, then present some novel examples based on the AIE-active QM derivatives, followed by the discussion on potential biomedical imaging applications by making use of the AIE effect. Particular emphasis is placed on illustrating how to take insight into molecular structure-property relationship, extend AIE-active fluorescent systems to long emissive wavelength, and enable organic aggregates with desirable morphology and nanoaggregates for bioimaging or therapy.

Discovery of novel AIE building block of QM

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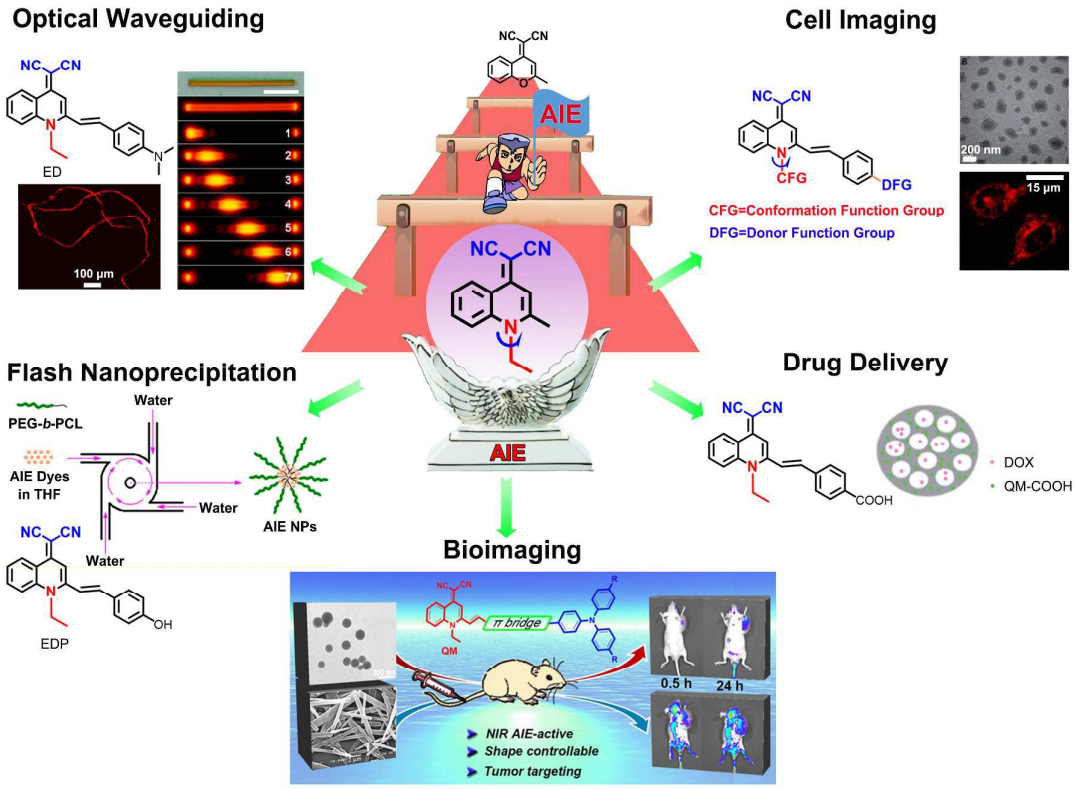

Fig. 1 Schematic illustration of molecular engineering for AIE-active QM derivatives and its application. Redrawn from ref 20, 21, 23a, 24 and 22a. Copyright American Chemical Society, Royal Society of Chemistry and Wiley.

There is still a continuous interest in search for novel AIE-active fluorophore/chromophore units for designing multiple functional optical bioimaging agents. Among a variety of luminescent materials, the dicyanomethylene-4*H*-pyran chromophores (DCM) have attracted considerable interest from material chemists owing to its excellent luminescent properties.[15] In 1989, a DCM derivative was firstly reported by Kodak Company Tang *et al.* as highly red-emitting fluorescent dopants in organic electroluminescent diodes (OLEDs).[16,17] Up to date, many DCM derivatives have been shed light due to their characteristic intramolecular charge transfer (ICT) and excellent opto-electronic properties. In general, the DCM chromophore has typical Donor-π-Acceptor (D-π-A) feature with a broad absorption band resulting from an ultra-fast ICT process.[15] However, the conventional DCM derivatives, such as Kodak- patented DCJTB, can only be utilized as dopant emitter because they always suffer from sever ACQ effect.[17]

The discovery of intriguing AIE phenomenon brings promising benefits since AIE-active materials exhibit turn-on fluorescence in aggregation while faintly in solution. In general, high hydrophobicity of the emitting centers in aromatic hydrocarbons make conventional luminophores form aggregates with ACQ effect in aqueous solutions. While, in the AIE process, the aggregate formation of luminescent chromogens brings out emitting efficiently. It implies that the diverse chromophore structure and packing interaction might exert great effect on the ACQ or AIE in fluorescent processes. Specifically, in a particular system which one of ACQ and AIE prevails depends strongly on the chromophore structure and intermolecular packing interaction. Evidently, tuning the intermolecular interactions associated with molecular stacking, ordering or restriction of intramolecular rotation (RIR) based on rational molecular design has been empolyed as an efficient approach to design AIE-active organic materials.[9]

To overcome severe ACQ effect, Tang *et al.* developed a structural design strategy by simply modifying the conventional ACQ chromophores with AIE fluorogens.[18,19] For example, Tang and Liu *et al.* designed a triphenylamine (TPA)-modified DCM derivative (TPA-DCM, Fig. 2) as ACQ chromophore, then two tetraphenylethene (TPE) as AIE-active units were introduced to the periphery of the TPA-DCM core. The adduct (TPE-TPA-DCM) is AIE-active, which can emit bright far-red/NIR light in the aggregate state. In the aggregate state, the propeller shape of AIE units in the molecules prevents π-π stacking and efficiently blocks the ACQ pathway. TPE-TPA-DCM loaded with protein nanoparticles was demonstrated as good imaging contrast for *in vitro* and *in vivo* bioimaging using MCF-7 breast-cancer cells and a tumor-bearing mouse model. However, this directly covalent integration with AIE luminogens into DCM derivatives could severely limit the synthetic flexibility in the molecular design and structural modification. Our group has recently developed a novel

emitter ED (Figs. 1 and 3) based on quinoline-malononitrile (QM), with an impressive alternative approach to modify the typical π-electron acceptor in DCM derivatives.[20] Unexpectedly, the QM-based ED displays the amazing AIE-active characteristic with strong red-emission in solid state upon only replacing the oxygen atom in DCM moiety with *N*-ethyl group, which is in contrast with the severe ACQ effect of DCM-based BD.

In the isolated molecular state of pure THF solution, BD emits strong red fluorescence at 636 nm (λ_{ex} = 507 nm); however, a characteristic blue-shift weak fluorescence at 594 nm (λ_{abs} = 430 nm) of ED was observed owing to the introduction of *N*-ethyl group in the acceptor of ED disturbing the direction of dipole-dipole interaction along the D-π-A system (Figs. 3C and 3D). Also the DFT calculation indicates that QM has the weaker electron withdrawing ability compared with the acceptor in BD.

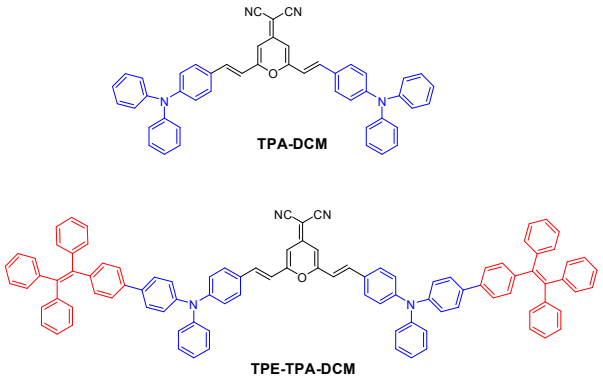

Fig. 2 Simply modifying the conventional ACQ chromophores with AIE fluorogens from TPA-DCM to TPE-TPA-DCM.

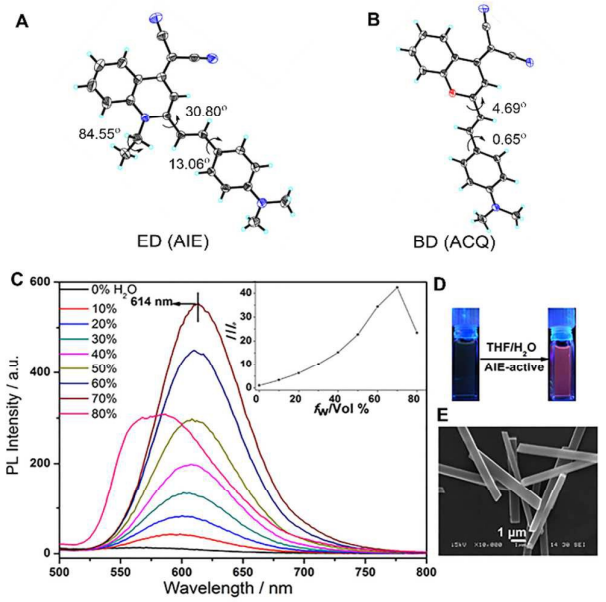

Fig. 3 Molecular structure of ED and BD and its photophysical properties: single crystals of (A) ED and (B) BD; (C) emission spectra of ED in H_2O/THF mixtures; (D) fluorescence images of ED (0 and 70% H_2O) under 365 nm illumination; (E) SEM image of microrods obtained from ED suspension (70% H_2O). Redrawn from ref 20. Copyright American Chemical Society.

The X-ray single crystal structures of ED and BD (Figs. 3A and 3B) also provide a further insight into its AIE mechanism. ED and BD are both *trans*-conformation in their solid state. ED takes a more twisted conformation, but BD takes a graphene-like planar structure. Especially, the *N*-ethyl group in quinolone unit of ED takes a torsional angle of 84.5° from the quinolone unit. The strong π-π interaction between aromatic ring of BD leads to strong face-to-face stacking with a typical ACQ effect in solid state. In contrast, the introduction of *N*-ethyl group on the acceptor of QM can efficiently suppresses the close stacking of molecules in its aggregate process. The AIE-active ED feature easily to form 1D ordered nanostructures (Fig. 3E) is well-demonstrated, along with the excellent optical waveguide behaviors.[20] As a consequence, a novel AIE building block of QM was introduced to the original DCM family, which is highly beneficial for a better understanding of the molecular structure-property relationship.

Insight into AIE characteristics of water-soluble QM Derivatives

The water-soluble, long wavelength and red-emitting AIE-active systems are highly desirable for tracing important biological species *in vivo* owing to the predominated aqueous physiological environment. However, a better understanding of the fascinating AIE molecular structure-property relationship in aqueous environment is still need to make clear, which could provide the guidelines for preprogramming specific molecular design so as to fine-tune the AIE-active emitting characteristics with response to biological species in a specific aggregation model.

Based on our established AIE-active building block of QM, we further explored novel water-soluble red-emitting AIE chromophores for biomedical applications *in vivo*.[21] The sulfonate groups were decorated with the building block of QM at the different substitution positions to systematically shed light on their difference in the intrinsic hydrophilicity, emitting color and AIE properties. In EDS, sulfonate unit ($-SO_3^-$) was incorporated as conformation function group (CFG) into the AIE-active building block of QM moiety (Fig. 4A). While in EDPS**,** when slightly changing the sulfonate unit from the CFG position to the DFG position in the backbone (Fig. 4B), there exhibit completely different AIE characteristics with EDS in aqueous system. Only EDS shows distinct light-up AIE-active fluorescence signal alteration by biomolecular binding, but EDPS has rarely any response in the same condition. Definitely, the different substitution positions of sulfonate group for EDPS and EDS in the QM-based AIE-active system bring forth great differences in aqueous solubility and AIE characteristics.

Unlike the previous AIE-active materials containing sulfonate groups,[8,10] which are generally in the molecularly dissolved state in aqueous system, the large volume aggregates will be formed in the presence of proteins, along with light-up characteristics. However, in the case of EDS, both

dynamic light scattering (DLS) and transmission electron microscopy (TEM) demonstrated that it is just a well dispersed form in aqueous or buffer solution rather than being molecularly dissolved. Whereas, for EDPS, the conversely solvent AIE phenomena are observed. DLS and cell tracking confirmed that the EDS aggregation in pure water is capsule-like with loosely packing characteristic (Fig. 4C), which still has a large internal free volume to consume the energy, resulting in nearly no fluorescence. Intriguingly, its loosely packing could be transformed into the tight packing possibly due to both hydrophobic and electrostatic interactions between EDS and specific protein like BSA, resulting in the specific turn-on AIE characteristic. Moreover, upon addition of trypsin as hydrolysis cleavage catalyst of protein, the tight packing of EDS could go back to initial loosely packing aggregation state (Fig. 4C). Obviously, attaching functional groups as CFG unit can well behave as modulating the aggregation conformation, predominately affecting the AIE characteristic than that of DFG group in QM-based fluorophores.

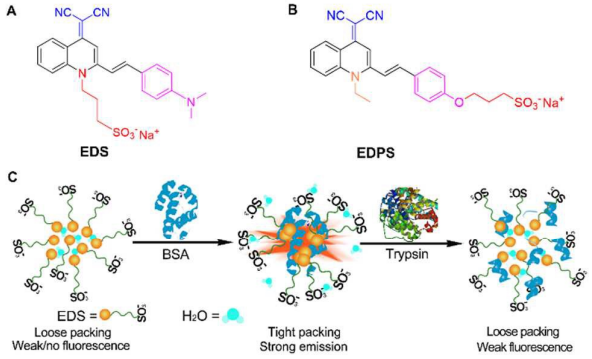

Fig. 4 Molecular structure of (A) EDS, (B) EDPS and (C) schematic illustration of the interaction of EDS and protein (BSA), and its disassembly in the presence of trypsin. Redrawn from ref 21. Copyright Royal Society of Chemistry.

Shape-specific effects of QM nanoaggregates

Rational design of high performance materials for cancer-specific imaging *in vivo* is still of great challenge, particularly for development of imaging contrasts that can differentiate tumors from normal tissues in cancer diagnosis.[1-3] As known, there is the critical interdependent role of particle shape, size and surface chemistry in nanomaterial bioimaging.[22] Conventional organic materials with well-defined sizes and shapes are often suffered from the inherent ACQ effect during aggregate formation, thereby limiting their application as imaging contrasts. In contrast, the fascinating merits that AIE-active molecules exhibit highly bright fluorescence in aggregation while faintly in solution make them ideally suitable for bioimaging or therapy *in vivo*.

The AIE effect provides a new platform for researchers to insight into emitting processes from nanoaggregates, especially in understanding molecular structure–property relationships in AIE-active luminescence processes. Tailoring AIE-active organic molecules to control and form aggregated nanostructures with desirable morphologies, and therefore the high performance optical properties for bioimaging is anticipated. Very recently, we presented a novel molecular design strategy to generate tailor-made AIE-active QM nanoaggregates emitting from red to NIR region with defined morphologies (from rod-like to spherical shapes).[22a] As demonstrated, these AIE-active fluorescent organic nanoaggregates with ideal biological geometries can feature specific shape dependence on tumor-targeting ability in bioimaging.

Through elongating the π-conjugated system and changing the π-bridge from thiophene to 3,4-ethylenedioxythiophene (EDOT), six red to NIR emitting AIE-active derivatives (QM1 to QM6) along with various morphologies in the aggregation state were specifically developed (Fig. 5A). Indeed, rod-like self-assembly structures of QM1, QM2 and QM3 can emit red to NIR fluorescence obtained with thiophene unit as a π-bridge by attaching the electron donor groups from methyl to triphenylamine, even to alkoxytriphenylamine (Fig. 5B). In contrast, QM4, QM5 and QM6 form spherical nanoparticles during their aggregating process upon changing the π-bridge from thiophene to EDOT, which is possibly due to the flexibility of epoxy ethyl group. The structural and conformational differences of QM derivatives are responsible for the different aggregated microenvironment, thus resulting in different AIE-active spectral features.

Their significant differences in the aggregate morphology make diverse properties for biological events in living systems. Notably, the NIR spherical QM-5 nanoaggregates exhibits excellent tumor-targeting performance in mice, while the same is not true for the rod-like aggregates of QM-2 (Figs. 5C and 5D). All these modulations in delicate molecular structures induced morphology of QM derivatives from rod-like to spherical were confirmed by SEM, TEM, CLSM images and LLS studies. Particularly, TEM images of tissues and cells exposed to the QM nanoprobes strongly confirmed that QM aggregates almost maintain their initially aggregated morphologies *in situ* and *in vivo*. Moreover, QM nanoaggregates tend to retain long term in the cytoplasm of living cells and extend blood circulation time *in vivo* with high photostability with respect to commercial dyes ICG (the FDA-approved NIR contrast agent). Although size, shape, surface chemistry are all fundamental properties of micro/nanoparticles which are critically important for biological applications such as circulation, phagocytosis and distribution *in vivo*, here these shape-tailored organic QM nanoprobes may open new opportunities for particle geometry of AIEgens on tumor imaging and therapy *in vivo* (Figs. 5E and 5F).[22]

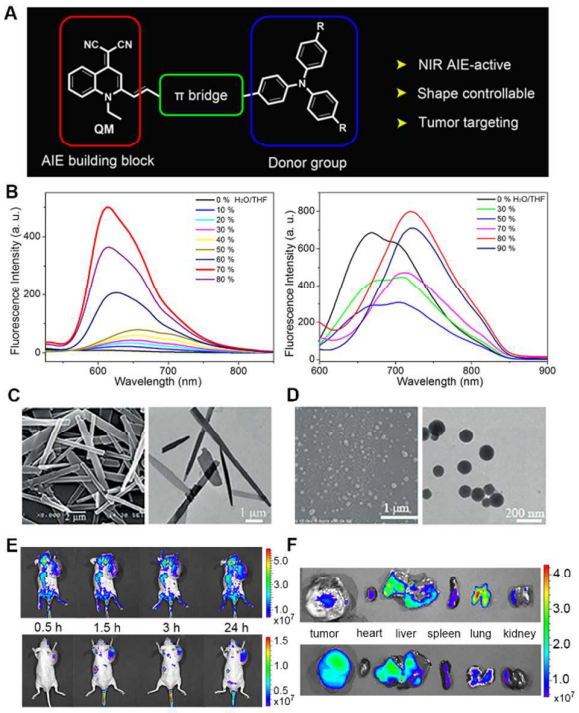

Fig. 5 (A) Molecular structure design of QM derivatives; (B) photoluminescence properties of QM-2 (left) and QM-5 (right) in THF-water mixtures with different water fraction (f_w); SEM and TEM imaging of QM-2 (C) and QM-5 (D) aggregates; (E) *In vivo* non-invasive imaging of tumor-bearing mice after intravenous injection of QM-2 (up) and QM-5 (down) at different periods of time (0.5, 1.5, 3 and 24 h); (F) *ex vivo* fluorescence images of the internal organs of mice sacrificed at 24 h post-injection with QM-2 (up) and QM-5 (down). Redrawn from ref 22. Copyright of Wiley.

Hybridized AIE-active QM nanoparticles for drug release and bioimaging

Mesoporous silica nanoparticles (MSNs) have been intensively pursued as drug delivery vehicles due to their large surface areas, large pore volume, tunable pore sizes, good biocompatibility, and the ease of surface functionalization. Very recently, Tian's group has detailed reviewed the development of AIE-active fluorescent nanoparticles (FNPs) for biomedical applications, as the good guidance to construct novel AIE functional materials in the future.[23b] Owing to our QM-based AIEgen with good stability and relative high-temperature resistance, we constructed fluorescent mesoporous silica nanoparticles (FMSNs) by hybridizing MSNs with the silylated QM derivative (AIE luminogen molecules),[23] thereby fabricating uniform FMSNs with particle size of around 110 nm via hybridizing MSNs with a silylated QM derivative AIE luminogen (Fig. 6A). DOX can be effectively stored as a typical anticancer drug into the pores of FMSNs. As well demonstrated, the corresponding DOX@FMSNs prodrug could be released pH-dependently (Fig. 6B). Meanwhile, the resulting FMSNs showed good biocompatibility with normal human liver cells L02, and the DOX-loaded FMSNs displayed a high cytotoxicity for MCF-7 cancer cells given that the FMSNs-delivered DOX can retain its pharmaceutical activity (Fig. 6C). The hybridized AIE-active QM nanomaterials are expected to be a promising multifunctional candidate for both bio-imaging and cancer therapy.

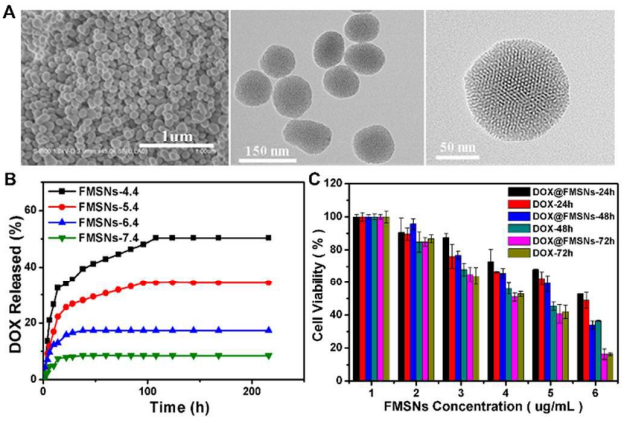

Fig. 6 (A) SEM and TEM images of FMSNs; (B) Release profiles of DOX@FMSNs at 37 °C under different pH values; (C) *In vitro* cell viabilities of MCF-7 cells incubated at same concentration of DOX for 24 , 48 and 72 h. Redrawn from ref 23a. Copyright Royal Society of Chemistry.

Facile scale-up preparation of AIE-active QM nanoparticles

Efficiently creating high performance fluorescent nanomaterials by using a scalable and fast processing method is still highly desirable. In order to apply the AIE-active molecules in bioimaging with high performance, it is very necessary to precise control of the aggregation degree as well as fluorescence.[10] Generally, the degree of aggregation can be traditionally controlled by modulating the solubility in a mixture of good and poor solvent. However, the traditional method to prepare nanoparticles relies on slow self-assembly which is a spontaneous, naturally occurring process. The formed nanoparticles usually show a large size with broad particle size distribution which limits the practical applications of these materials especially in biomedical areas. Recently, we presented the engineered method of flash nanoprecipitation (FNP, Fig. 7A) for processing fluorescent AIE-active NPs, resulting in a narrow size distribution with desirable fluorescence properties.[24] The size and distribution of NPs are easy to be well tuned by the alteration of solvent ratio and stream velocity while maintaining the good stability of NPs. Under the optimized conditions in FNP, the QM-based AIE-active NPs sizes can be well tuned from 20 to 60 nm (Fig. 7B), along with strong AIE properties. Indeed, preparation AIE-active NPs by FNP has unique advantages such as narrow size distribution and convenience in tuning fluorescent properties. Particularly, the FNP method is very simple, easy scalable and fast processing for preparing nanoparticles (NPs) with the assistance of a vortex equipment. As a consequence, encapsulating AIE-active fluorophores in NPs by FNP would be a promising platform to facile manufacturing of high performance bio-imaging nanomaterials.

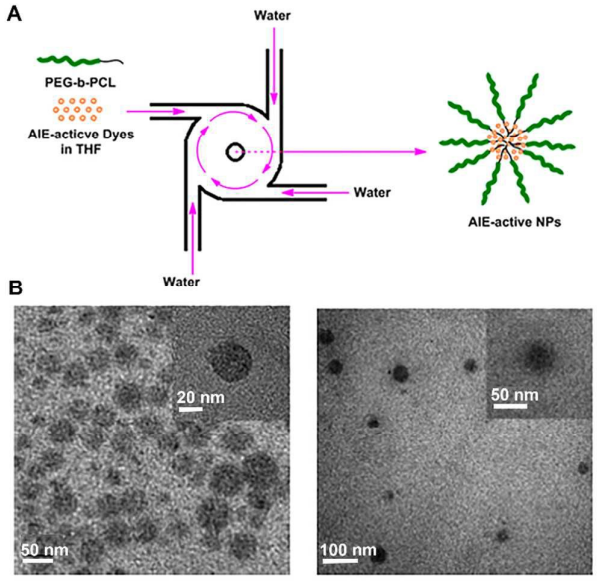

Fig. 7 (A) Schematic diagram of the MIVM system and FNP; (B) TEM images of EDP NPs by the FNP method. Redrawn from ref 24. Copyright American Chemical Society.

Summary and perspectives

The discovery of novel AIE fluorophore offers new opportunities for high tech innovations, especially for optical bioimaging agents. Particularly, novel high performance NIR fluorophores bestowed with excellent photostability and luminescent efficacy are highly preferable as AIE-active contrast agents. In this short highlight, we briefly summarized our recent progress based on the established AIE-active building block of QM. In comparison with other AIEgens, QM derivatives present several advantages: i) easy realization of red to NIR AIE-active luminescence by introducing different donor group and π–bridge beneficial for biomedical application *in vivo*; ii) excellent self-assemble properties by tailoring organic molecular structures to obtain different aggregated morphology; and iii) understanding of the aggregated microenvironment of AIEgens by finely control the morphologies and sizes of organic aggregated nanostructures, and therefore performing the excellent optical properties for bioimaging *in vivo*.

At the moment, there is still a continuous interest in search for novel AIE-active fluorophore/chromophore units for designing multiple functional optical bioimaging agents. It is our hope that this highlight can provide an overview of seminal and current research efforts as well as a mechanism framework for the creation of new AIE parent chromophore. Given that the hydrophilicity, size and shape of dye aggregates play a vital role on the cellular uptake, cytotoxicity and tumor imaging performance,[25-31] the tailoring of their morphology, dimension as well as aqueous dispersibility still remains challenging in exploitation of AIEgens as bioprobes. This highlight may also stimulate work that leads to the development of new functional bioimaging contrasts, the practical exploration of NIR AIE-active imaging contrast, thus giving rise to more effective and economically attractive luminescent biomaterials.

Acknowledgements

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Long wavelength AIEgen of quinoline-malononitrile†

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In this Highlight, we summarize some recent advances in the area of red to near-infrared fluorescent AIE-active organic materials *via* tailoring the building block of quinoline-malononitrile (QM) and its application in bioimaging.