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Haider Alam *et al*, Cognizance Journal of Multidisciplinary Studies, Vol.5, Issue.8, August 2025, pg. 651-668
**(An Open Accessible, Multidisciplinary, Fully Refereed and Peer Reviewed Journal)**
**ISSN: 0976-7797**
**Impact Factor: 5.183**
**Index Copernicus Value (ICV) = 77.57**

# Detection of Aβ Aggregation by Aggregation-Induced Emission (AIE) Probes in Alzheimer's Disease

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**DOI: 10.47760/cognizance.2025.v05i08.029**

**Abstract:**
Alzheimer's disease (AD) remains one of the most challenging neurodegenerative disorders, characterized by the extracellular accumulation of amyloid-β (Aβ) plaques and intracellular tau tangles. Among these, soluble Aβ oligomers are now recognized as the most neurotoxic species, disrupting synaptic function, calcium homeostasis, and neuronal survival. Conventional diagnostic methods, including antibody-based assays, electrochemical sensors, and classical fluorescent dyes such as Thioflavin T and Congo Red, suffer from limited sensitivity, poor selectivity, and incompatibility with early-stage or in vivo detection. Aggregation-induced emission (AIE) probes have emerged as transformative tools to overcome these barriers. AIE luminogens remain non-emissive in their monomeric state but exhibit strong fluorescence upon aggregation, offering high signal-to-noise ratios and minimal background interference. Recent advances include AIE nanoparticles and supramolecular assemblies capable of penetrating the blood–brain barrier, enabling real-time visualization of Aβ oligomers, fibrils, and plaques. Moreover, multifunctional AIE probes integrate detection with therapeutic functions, including inhibition of aggregation and photodynamic therapy. These developments highlight the potential of AIE-based systems for early diagnosis and theranostic applications in AD.

**Keywords:** Alzheimer's Disease, Aβ Aggregation, Aggregation-Induced Emission, AIE Probes, inhibition of Aβ Aggregation

 

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## Introduction

Alzheimer's disease (AD), Parkinson's disease, and other chronic neurodegenerative disorders have emerged as major public-health challenges, threatening the well-being of elderly populations worldwide [1]. AD is one of the most common clinical degenerative disorders of the central nervous system, manifesting as progressive impairments in memory, language (aphasia), visuospatial skills, and executive function [2]. At the molecular level, AD is characterized by two essential pathological hallmarks, extracellular deposition of amyloid-β (Aβ) plaques and intracellular accumulation of hyperphosphorylated tau neurofibrillary tangles (NFTs) [3]. Aβ is a 4 kDa peptide fragment generated by sequential cleavage of β-amyloid precursor protein via α- and β-secretase activities, with Aβ1–40 and Aβ1–42 being the predominant isoforms; the longer Aβ1–42 species serves as the principal initiator and structural component of senile plaques, exerting direct neurotoxic effects on neuronal cells [4]. Current diagnostic protocols rely on clinical symptomatology supplemented by neuroimaging modalities computed tomography, magnetic resonance imaging, and positron emission tomography that, despite their value, are cumbersome, expensive, of limited specificity, prone to radiation exposure risks, and often incapable of detecting early or subtle pathological change [4]. The multifactorial pathogenesis of AD also encompasses cholinergic neuronal deficits, excitatory amino acid toxicity, and neuroinflammation, the latter of which can both induce and be exacerbated by Aβ deposition and tau hyperphosphorylation, ultimately promoting neuronal apoptosis and varying degrees of cognitive dysfunction [5]. Pathologically, AD is a complex disorder marked by progressive synaptic dysfunction and neuronal loss, particularly within the hippocampus and cerebral cortex. Beyond protein aggregation, chronic neuroinflammation driven by activated microglia and astrocytes that release pro-inflammatory cytokines such as TNF-α and IL-1β and oxidative stress resulting from mitochondrial dysfunction further exacerbate neuronal injury. Misfolded amyloid-β (Aβ) and tau proteins exhibit prion-like propagation across synaptic networks, following the characteristic spatiotemporal progression described by Braak staging [6]. Concurrently, vascular pathologies such as cerebral amyloid angiopathy and disruption of the blood–brain barrier compromise clearance mechanisms and exacerbate neuroinflammation within the central nervous system. Moreover, emerging evidence implicates genetic factors such as the APOE4 allele and modifiable lifestyle determinants (e.g., dyslipidemia, physical inactivity) in influencing the onset and progression of AD [7]. Aβ1–42 though comprising only 10–15% of total Aβ is approximately 50 times more prone to self-assembly than Aβ1–40, leading to rapid oligomerization and fibrillogenesis. Soluble Aβ oligomers, detectable at nanomolar concentrations in the interstitial fluid, bind to and dysregulate NMDA and AMPA receptors, precipitating calcium overload, endoplasmic reticulum stress, and early synaptic failure. As these oligomers coalesce into protofibrils and mature plaques sometimes occupying up to 30% of

 

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cortical tissue in late-stage AD they act as potent activators of surrounding glia, driving a chronic neuroinflammatory milieu via release of cytokines and reactive oxygen species (ROS) that further compromise neuronal integrity [8].

Concurrently, tau protein normally essential for microtubule stabilization undergoes pathological hyperphosphorylation by kinases including GSK3β, ERK/MAPK, and CDK5. Hyperphosphorylated tau detaches from axonal microtubules, forming paired helical filaments that obstruct axonal transport and disrupt synaptic communication. Cross-talk between Aβ and tau amplifies neurotoxicity [9]. In addition to these protein-centric mechanisms, glial cells play pivotal roles in propagating pathology. Microglia, initially protective via TREM2- and CD33-mediated Aβ phagocytosis, adopt a proinflammatory phenotype upon chronic Aβ exposure, releasing ROS and cytokines that exacerbate neuronal injury. Astrocytes similarly undergo reactive transformation, impairing glutamate uptake and contributing to excitotoxicity. Collectively, these dysfunctional glial responses fail to clear protein aggregates and instead amplify synaptic and neuronal damage, perpetuating the feed-forward cycle of Aβ and tau pathology in AD [10] Soluble Aβ oligomers are now recognized as the primary neurotoxic species in AD; they bind NMDA and AMPA receptors, disrupt calcium homeostasis, trigger endoplasmic reticulum stress, and inhibit long-term potentiation, precipitating early synaptic failure. As these oligomers nucleate into protofibrils and mature plaques, they continue to activate complement-mediated synapse elimination.

Aβ exists in a dynamic equilibrium of monomers, low-n oligomers (dimers, trimers, and dodecamers such as Aβ*56), protofibrils, and mature fibrils. Low-n oligomers are the most synaptotoxic at nanomolar concentrations, correlating strongly with memory impairment independent of plaque burden [11]. Cryo-EM has revealed distinct fibril polymorphs U-shaped and S-shaped β-sheet architectures that differ in stability, seeding capacity, and metal ion ($Zn^{2+}$, $Cu^{2+}$) binding, likely underlying clinical heterogeneity and variable therapeutic responses. The biophysical environment (pH, ionic strength, lipid membrane interactions) dictates these conformational landscapes, underscoring the need for conformation-specific diagnostics and therapeutics [12].

The crucial role of Aβ, they disrupt glutamate receptor movement while also damaging calcium balance and blocking synaptic plasticity processes like long-term potentiation (LTP). As oligomers develop into protofibrils and dense-core plaques, they become less acutely toxic but continue to drive chronic inflammation through glial activation and metal ion sequestration, which worsens oxidative damage [13]. For these reasons, Aβ oligomers are considered the most prion factor in the disease's progression. Detection of Aβ oligomers is challenging due to their structural instability. In the past, researchers employed some techniques for the detection and

 

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monitoring of amyloid β aggregation for the diagnosis of AD, which show many limitations. To overcome these limitations, AIE must be a suitable tool for the recognition of amyloid beta aggregation [14].

Aggregation-induced emission (AIE) probes represent a significant advancement in this field. AIE molecules produce stronger fluorescence when they aggregate, which sets them apart from traditional fluorophores that experience aggregation-caused quenching (ACQ). The unique properties of these molecules render them ideal for detecting Aβ aggregates within biological systems [15]. The new AIE probes like PTPA-QM and QM-FN-SO demonstrate strong BBB penetration and beta-amyloid fibril selectivity while emitting near-infrared light, which provides enhanced contrast imaging at greater depths. The combination of biocompatibility and high photostability makes these tools effective for diagnosing AD early and monitoring disease progression and therapeutic responses [16]. Aggregation Induced Emission (AIE) probes address many of these shortcomings by remaining non-fluorescent in monomeric form and "lighting up" only upon binding to aggregated Aβ species. This turns on a mechanism that virtually eliminates background fluorescence and enables highly sensitive detection of oligomeric and fibrillar assemblies [17]. Rational design strategies such as extending π conjugation for strong near infrared emission, incorporating zwitterionic or sulfonated groups to boost aqueous solubility and minimize nonspecific interactions, and tuning lipophilic hydrophilic balance to facilitate blood–brain barrier penetration have yielded probes like PTPA QM, which displays over 30 fold fluorescence enhancement at low nanomolar concentrations and permits noninvasive in vivo imaging in transgenic mouse models, and QM FN SO, whose sulfonated moiety enables high resolution two photon microscopy of dense core plaques in live brain slices. Beyond simple visualization, some AIE luminogens have been functionalized for multimodal applications [18].

By integrating near-infrared (NIR) fluorescence with MRI contrast agents or photodynamic therapy, AIE-based systems offer a comprehensive theranostic platform. Importantly, AIE detection represents a transformative advance over conventional approaches, enabling real-time, non-invasive, and highly specific monitoring of amyloid-β (Aβ) aggregation dynamics [19].

This review highlights current strategies for detecting Aβ aggregation, with particular emphasis on the emerging role of aggregation-induced emission (AIE) probes. We first discuss the pathological importance of Aβ oligomers and fibrils in Alzheimer's disease, followed by an assessment of traditional recognition methods such as antibody-based assays, electrochemical biosensors, and photochemical dyes, underscoring both their strengths and limitations. We then examine AIE probe design, mechanisms, and performance in recognizing Aβ species, emphasizing their superior sensitivity, selectivity, and capacity for real-time in vivo imaging. Finally, we consider ongoing challenges, potential theranostic applications, and future directions

 

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for advancing AIE-based technologies as powerful tools for early diagnosis and disease monitoring in Alzheimer's research

**Traditional diagnostic methods**

Traditional approaches to detecting amyloid β (Aβ) oligomers have predominantly relied on electrochemical sensors, photochemical dyes, and antibody-based assays, each offering specific advantages. yet hindered by significant limitations [20]. Electrochemical biosensors, for instance, capitalize on the high affinity of aptamers or antibodies immobilized on electrode surfaces to transduce Aβ binding into quantifiable electrical signals using techniques such as differential pulse voltammetry (DPV) or electrochemical impedance spectroscopy (EIS) [21]. By incorporating nanostructured materials like gold nanoparticles or graphene oxide, these platforms can, in theory, attain femtomolar to picomolar detection limits. However, their practical deployment is compromised by the need for intricate, multistep electrode functionalization, which poses challenges in reproducibility and large-scale manufacturing [22]. Furthermore, in complex biological matrices such as serum or cerebrospinal fluid, nonspecific adsorption (biofouling) frequently generates background noise that obscures true signals. Crucially, distinguishing toxic oligomeric assemblies from monomeric or fibrillar forms demands exquisitely selective bioreceptors, the development of which remains laborious and costly [23].

Photochemical detection methods exemplified by Thioflavin T/S and Congo Red staining exploit the affinity of these dyes for β-sheet-rich fibrillar aggregates, facilitating both histological visualization and bulk fluorescence assays. While these dyes are straightforward to use and have underpinned decades of amyloid research, they suffer from aggregation-caused quenching when bound to densely packed fibrils, limiting their fluorescence yield [24]. In addition, the inability of conventional dyes to discriminate between soluble oligomers and mature fibrils results in poor selectivity, and the inherently high background fluorescence further diminishes sensitivity. Importantly, photochemical approaches are largely invasive, as they typically require fixed or postmortem tissue samples and are incompatible with real-time, in vivo monitoring of early Aβ pathology [25].

Antibody-based platforms, including enzyme-linked immunosorbent assays (ELISA), Western blots, and immunohistochemistry, offer molecular specificity by targeting defined epitopes with monoclonal antibodies such as 6E10, 4G8, A11, or OC [26]. Nevertheless, these assays contend with cross-reactivity among different Aβ species, as overlapping epitopes can generate false positives, and conformational heterogeneity may mask antigenic sites, reducing detection accuracy. Moreover, the requirement for cerebrospinal fluid or brain tissue samples imposes significant barriers to minimally invasive screening, precluding their routine use for early diagnosis [27]. Although advanced biosensors employing Aβ-specific aptamers or antibodies

 

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have demonstrated rapid, picomolar-level detection suitable for point-of-care applications, and novel fluorescent probes have enabled dynamic visualization of amyloid aggregation in vitro, the collective drawbacks of traditional methodologies underscore the pressing need for safer, more selective, and truly non-invasive diagnostic tools [28].

**Role of amyloid-β oligomers in plaques**

Soluble amyloid-β (Aβ) oligomers are now widely regarded as the most synaptotoxic Aβ species and key drivers of early Alzheimer's disease (AD) pathophysiology, with effects that are only partly captured by plaque burden alone [2]. Oligomers form along the monomer → low-n oligomer → protofibril → fibril continuum and can seed plaque nucleation as well as sustain plaque growth via secondary nucleation at fibril surfaces [28]. Compared with Aβ1–40, Aβ1–42 displays markedly higher oligomerization and fibrillization propensities, making it the principal initiator and structural contributor to senile plaques [29]. Functionally, nanomolar oligomers bind and dysregulate glutamatergic receptors (NMDA/AMPA), perturb calcium homeostasis, trigger ER stress, and acutely inhibit long-term potentiation—mechanisms closely linked to early memory impairment independent of total plaque load [30]. At the circuit level, oligomers propagate in a prion-like fashion and template further misfolding, helping explain the characteristic spatiotemporal progression of pathology [31].

Within plaques, oligomers are enriched in the diffuse "halo" surrounding dense-core fibrils, creating a highly reactive microenvironment. Although mature fibrils are less acutely synaptotoxic, they act as scaffolds that (i) catalyze the surface-mediated generation of new oligomers, (ii) concentrate redox-active metal ions ($Cu^{2+}$/$Zn^{2+}$), and (iii) sustain chronic microglial and astroglial activation. Microglia initially attempt to clear Aβ but transition toward a pro-inflammatory phenotype with sustained Aβ exposure, releasing cytokines and ROS that exacerbate synaptic loss. Astrocytes become reactive and impair glutamate uptake, further amplifying excitotoxicity [32]. Complement-tagged synapses near plaques are selectively eliminated, and periplaque synaptic dystrophy correlates better with oligomer burden than with total fibrillar mass. Vascular deposition (cerebral amyloid angiopathy) and blood–brain barrier changes can additionally reduce peptide clearance and intensify perivascular oligomer accumulation [33].

These mechanistic insights have direct implications for molecular recognition. Conventional dyes (ThT/Congo Red) preferentially report β-sheet–rich fibrils and have limited ability to discriminate early, diffusible oligomers, leading to poor sensitivity/specificity for the most neurotoxic assemblies. By contrast, aggregation-induced emission (AIE) luminogens exhibit "off-to-on" fluorescence upon the restriction of intramolecular motion (RIM), dramatically reducing background and enabling the selective detection of aggregated Aβ species in complex

 

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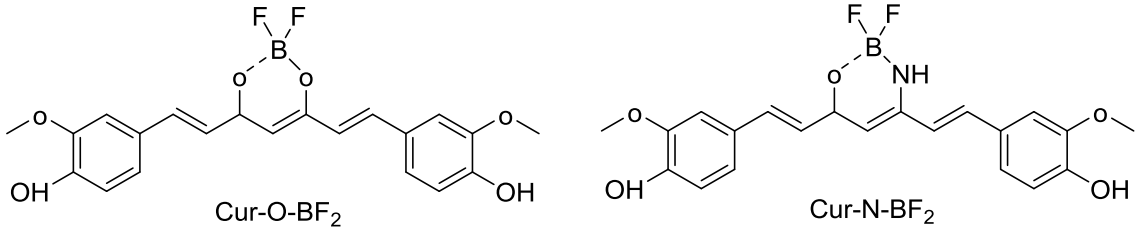
matrices and in vivo. Recent AIE probes engineered for near-infrared (NIR) emission and BBB penetration (e.g., PTPA-QM; QM-FN-SO□ ) demonstrate robust plaque imaging in transgenic models and can report viscosity/conformation changes associated with oligomer/protofibril formation [34, 35]. Importantly, iterative AIE designs now explicitly target oligomeric epitopes with high affinity and ultrahigh S/N, allowing early-stage detection and longitudinal tracking of oligomer-to-plaque transitions that better mirror synaptotoxic risk than fibril-selective dyes. In addition to imaging, multifunctional AIE systems can inhibit fibrillation or disassemble preformed aggregates, opening theranostic avenues that couple oligomer reporting with modulation of aggregation pathways. Together, oligomer-aware AIE probes align the diagnostic readout with the species most relevant to synaptic injury, offering improved sensitivity for preclinical detection and a rational platform to evaluate anti-aggregation therapeutics in vivo [36].

## AIE and its relevance to β-amyloid detection

Yaqi Yang developed a multifunctional AIE-active probe, Cur-N-BF2 and Cur-O-BF2, as shown in **Scheme 1**, for light-up detection of Aβ fibrils and plaques, inhibition of Aβ fibrillation, disassembly of the preformed Aβ fibrils, and efficient protection of neuronal cells from the damage of Aβ fibrils.




**Scheme 1**. Active AIE Probe Cur-N-BF2 and Cur-O-BF2 for light-up detection of Aβ fibrils and plaques.

Cur-N-BF2, an AIE-based probe, demonstrated superior performance compared with curcumin and ThT in detecting Aβ1–42 fibrils. Unlike curcumin and ThT, which suffer from aggregation-caused quenching (ACQ) at higher concentrations, Cur-N-BF2 exhibited strong fluorescence enhancement even at elevated levels as shown in **Figure 1**, owing to its binding to hydrophobic domains of fibrils and restriction of intramolecular motion. Selectivity assays confirmed that Cur-N-BF2 selectively recognized Aβ fibrils over other proteins, enabling high-contrast staining of Aβ plaques in APP/PS1 transgenic mouse brain slices. Beyond detection,

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Cur-N-BF2 effectively inhibited Aβ fibrillation and promoted the disassembly of preformed fibrils, as verified by ThT fluorescence assays, TEM imaging, and CD spectroscopy, which revealed suppression of β-sheet formation. These findings highlight Cur-N-BF2 as a promising probe for both selective imaging and therapeutic intervention against Aβ aggregation [37].

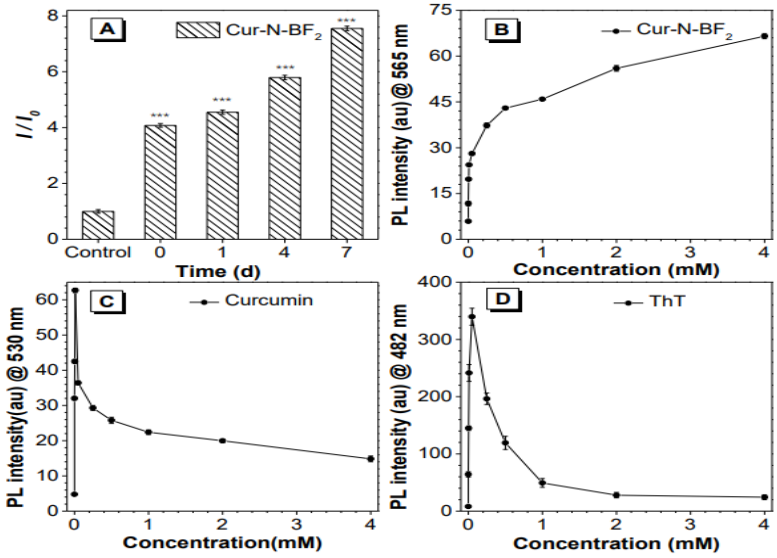


**Figure 1.** The PL intensity changes (I/I0) of Cur-N-BF2 at 565 nm for detection of Aβ1-42 fibrils formed at 0, 1, 4, 7 days, respectively; λex = 426 nm; [Cur-N-BF2] = 10 μM, [Aβ1-42] = 50 μM, ***P<0.001; (B-D) In the presence of Aβ1-42 fibrils (20 μM), the PL intensity changes with increasing concentrations of Cur-N-BF2, curcumin, and ThT; For Cur-N-BF2, λex = 426 nm, λem = 565 nm; for curcumin, λex = 425 nm, λem = 530 nm; for ThT, λex = 430 nm, λem = 482 nm adopted from ref [37].

In another study, Yan Fang synthesized AIE fluorescent probes PTPA-QM **(Figure 2)** employing the QM and triphenylamine aldehyde derivative as the AIE building block. The constructed probe, PTPA-QM, has good optical activity. In low-viscosity solutions, it has a very weak fluorescence due to the intramolecular distorted internal charge transfer (TICT) effect between the α,β-unsaturated bonds. With the increase in solution viscosity, the emission of red wavelengths is greatly enhanced. In addition, owing to the low cytotoxicity and excellent photostability, PTPA-QM can be used for fluorescence imaging with PC12 cells. To our delight, PTPA-QM can image Aβ in the brains of 5XFAD mice and classical inflammatory cognitive impairment mice. Our AIE probe holds great promise for exploring the early diagnosis of diseases caused by Aβ.

 

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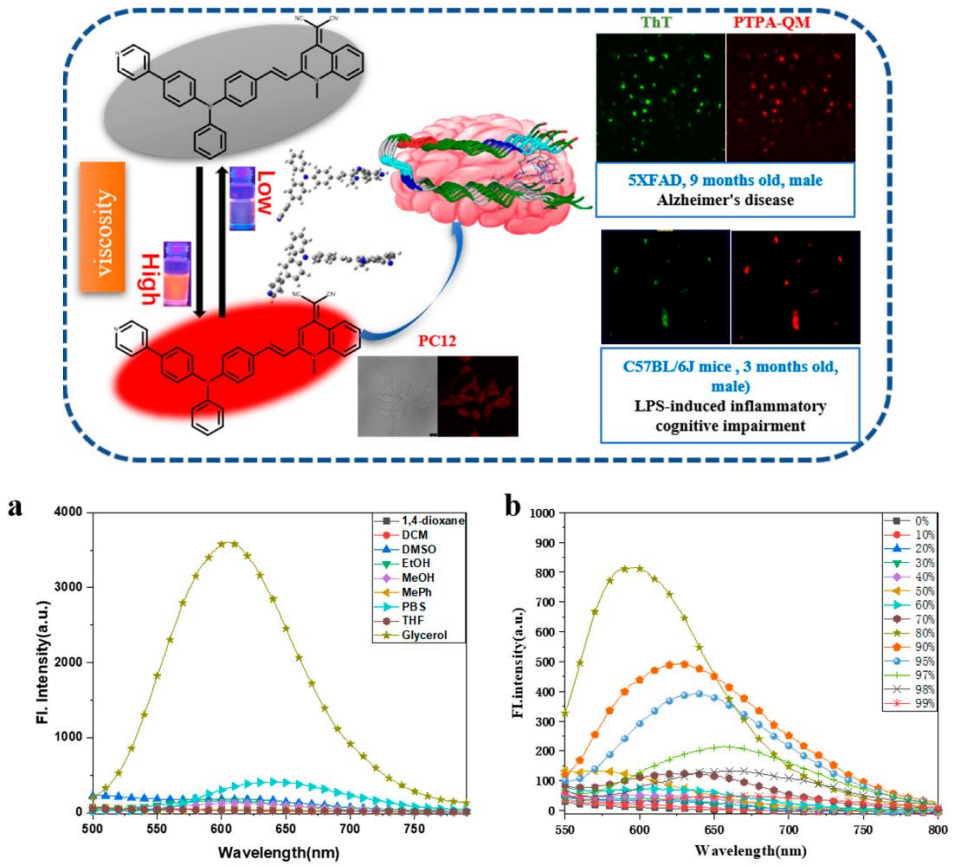


**Figure 2.** Schematic diagram of PTPA-QM monitoring of viscosity fluctuations and Aβ images in different mouse models. (a,b) Fluorescence emission spectra of PTPA-QM (**a**) in different solvents and (**b**) in PBS-DMSO mixture with different DMSO volume fractions (10 μM).

To evaluate the solvent effect, the fluorescence spectra of PTPA-QM were measured in different systems (Fig. 2a). In PBS (low viscosity), PTPA-QM showed weak emission at 645 nm, while in glycerol (high viscosity) strong red fluorescence at 605 nm was observed, with an ~8-fold enhancement and quantum yields of 0.09% (THF) and 3.93% (glycerol). In other organic solvents, fluorescence was negligible. The probe also displayed aggregation-induced emission (AIE) characteristics in PBS/DMSO mixtures (Fig. 2b). When the PBS fraction exceeded 60%, fluorescence increased sharply (~12-fold) with a slight blue shift, indicating nanoaggregate formation, consistent with visible colour changes under UV light [16].

The QM-FN-SO3 fluorescent probe, previously developed for in situ amyloid fiber mapping, was also found to detect amorphous aggregates due to its D–π–A structure and dimethylaminophenylene donor group (Fig. 3A). It quantitatively monitored aggregate formation

 

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in vitro and, with strong membrane permeability, illuminated both amyloid fibers and amorphous aggregates in *E. coli* BL21(DE3) (Fig. 3B). Notably, QM-FN-SO3 distinguished aggregation propensities in vivo and enabled evaluation of chaperone activity, revealing that SurA exhibited stronger in vivo anti-aggregation function than Skp, despite weaker inhibition in vitro. These findings establish QM-FN-SO3 as a versatile tool for detecting protein aggregates and assessing chaperone function, with potential applications in drug discovery targeting pathogenic protein aggregation [18].

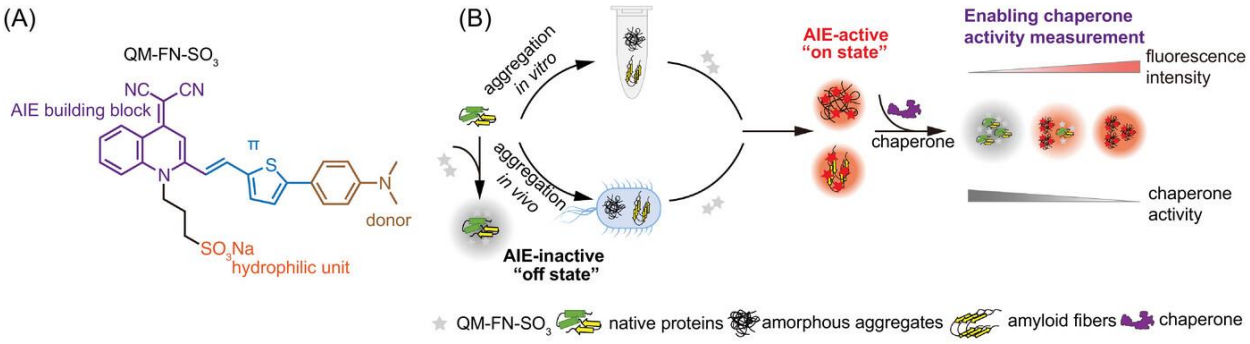


**Figure 3. Aggregate detection via the near-infrared (NIR) AIE-active probe, QM-FN-SO3**. (A) QM-FN-SO3 structure. (B) Schematic illustrations of the applications of the QM-FN-SO3 probe in detecting amorphous aggregates, amyloid fibers, and chaperone activity both in vitro and in vivo [18].

Wang et al (2018) design and synthesize a series of AIE-active molecules with nearly planar donor–acceptor structures, which facilitate molecular insertion into the binding site, causing RIM and thus enhanced fluorescence (**Fig. 4**). The probes emit negligible fluorescence in solution, while in the aggregated state, they emit strong fluorescence due to RIM.6 Piperidine and dimethylamino-substituted groups are introduced into the molecular structures as electron donating and also binding groups for Ab. DM-BZ, PD-BZ and PD-NA were synthesized by a typical nucleophilic addition reaction of aldehydes and 2-(4-bromophenyl) acetonitrile with high yields of 75–85% (Scheme S1, ESI†). PD-NA-TEG was synthesized by Suzuki reaction [38].

 

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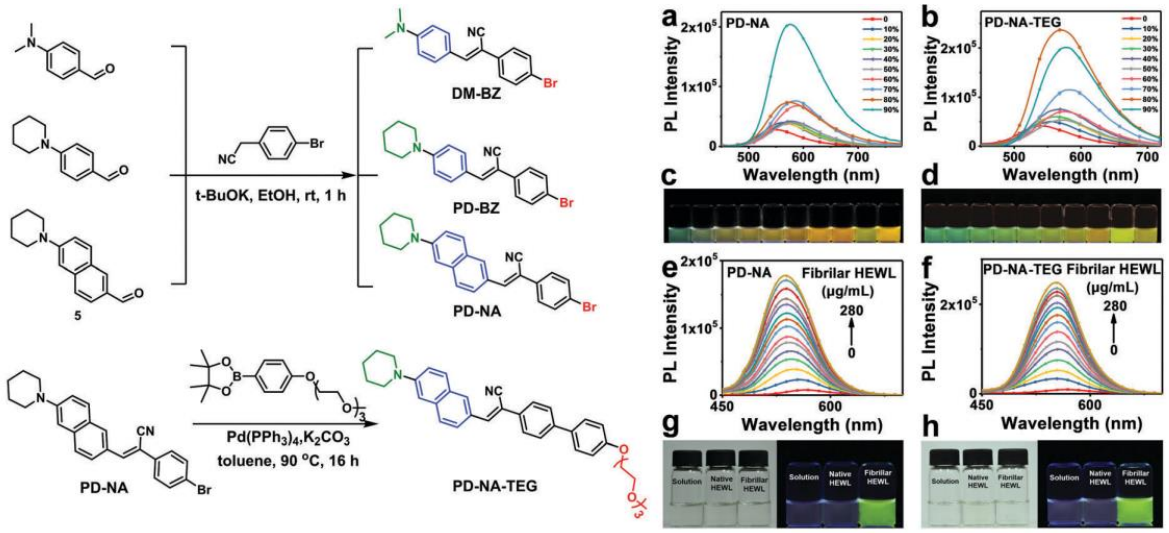


**Figure 4.** Schematic synthesis and optical properties of AIE. Synthesis route and structure of DM-BZ, PD-BZ, PD-NA and PD-NA-TEG (left). Emission spectra of (a) PD-NA and (b) PD-NA-TEG in THF-water with different water contents, (the excitation wavelength is 405 nm). The concentration of dyes is kept at 1.0 105 M. Fluorescence spectra of (c) PD-NA and (d) PD-NA-TEG in THF-water with different water contents under 365 nm irradiation. Emission spectra of (e) PD-NA and (f) PD-NA-TEG in 30% EtOH/H2O with different fibrillar HEWL contents (the excitation wavelength is 405 nm). The concentration of the dyes is kept at 3 mM. Photos of (g) PD-NA and (h) PD-NA-TEG in 30% EtOH/H2O, with native HEWL (280 mg $mL^{-1}$) and fibrillar HEWL (280 mg $mL^{-1}$) under room light (left) and 365 nm irradiation (right) adopted from [38].

Wei Fu describes a molecular rational design strategy to create ultrasensitive off−on NIR probes for Aβ plaques, relying on the alteration of substituted electron-donating and hydrophilic functional groups to regulate well the aggregated behaviour (**Figure 5**). By virtue of harnessing this strategy, the elaborated probe QM-FN-SO3 could achieve high-fidelity in situ mapping of Aβ plaques, bestowing the following extraordinary features: (i) ultrahigh signal-to-noise (S/N) ratio with integrating background minimization and fidelity signal amplification, (ii) remarkable binding affinity to Aβ plaques with efficient BBB penetrability, and (iii) NIR AIEactive emission with excellent photostability. As far as we know, this is the first report of finely tuning molecular aggregation for NIR light-up identifying and binding to Aβ plaques in living mice, even being capable of higher-fidelity mapping than commercial ThT for histological staining [18].

 

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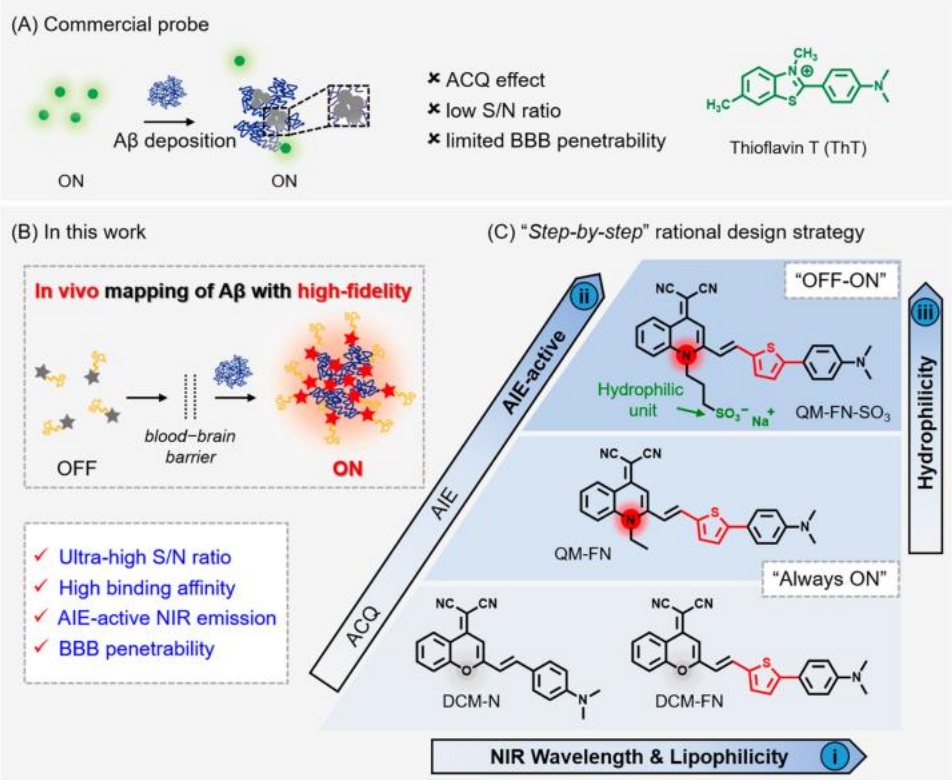


**Figure 5.** Rational design of NIR AIE-active probes for Aβ deposition. (A) Commercial probe ThT based on the always-on pattern. (B, C) The "step-by-step" strategy to address the inherent defects of commercial ThT and create ultrasensitive off−on NIR probes: (i) introducing a lipophilic πconjugated thiophene-bridge for extending the wavelength to the NIR region with BBB penetrability, (ii) replacing the ACQ to AIE building block, and (iii) tuning the sulfonate-substituted position for guarantee fluorescence-off state before binding to Aβ deposition [18].

Jie Zheng proposed a new hypothesis and introduced ROF2, an aggregation-induced emission (AIE) molecule with multifunctional roles as both an amyloid probe and a screening tool for inhibitors (Fig. 6a). Unlike its ACQ analogue ROF1 and conventional probes such as ThT, ROF2 offers long-wavelength orange–red emission, easy one-pot synthesis, good cell permeability, and superior sensitivity to early-stage amyloid species (Fig. 6 b, c). Competitive binding studies confirmed ROF2's enhanced performance over ThT, particularly in discriminating between aggregation stages. Importantly, a novel strategy was proposed: using ROF2 fluorescence quenching as a readout for inhibitor screening. Applying this approach to 30 FDA-approved cardiovascular drugs identified Ali5, Tic11, Amb3, and Ang27 as effective amyloid inhibitors, with Ali5 and Tic11 further reducing amyloid-induced cytotoxicity in cell and worm models

 

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(Fig. 6d). This dual detection–screening strategy underscores the broader potential of AIE probes in both amyloid sensing and therapeutic discovery [39].

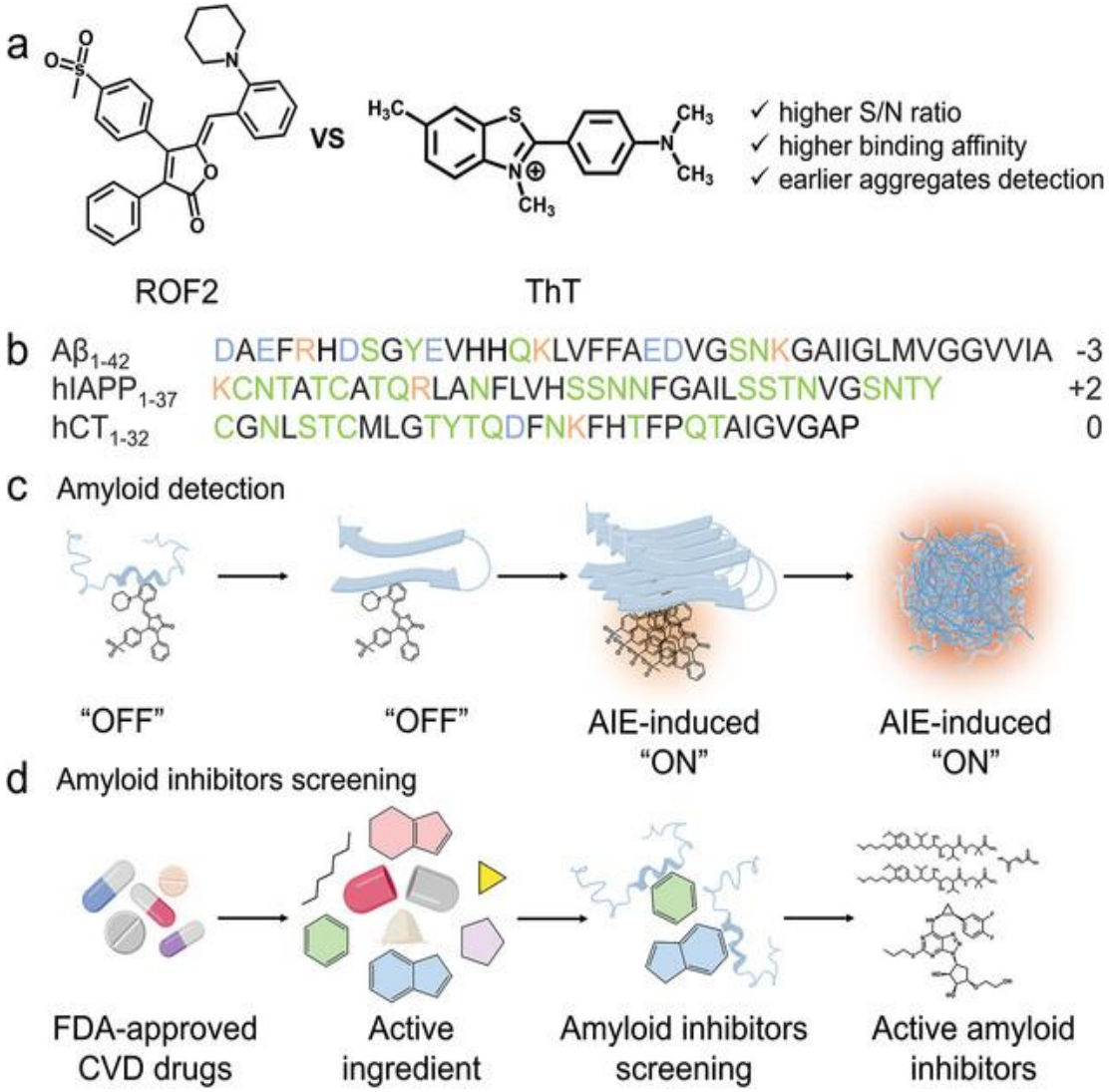


**Figure 6.** Dual-functional ROF2 fluorescence for amyloid detection and amyloid inhibitor screening. Chemical structure of a) ROF2 and ThT. b) A$\beta$ , hI APP, and hCT sequences, with color codes for positively charged residues (orange letters), negatively charged residues (blue letters), polar residues (green), and non-polar residues (black). c) ROF2 serves as an amyloid probe with an "off-on" switch for the detection of amyloid aggregates. d) ROF2 functions as a screening molecule for amyloid inhibitors, aiming to discover potential amyloid inhibitors adopted as [39].

 

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**(An Open Accessible, Multidisciplinary, Fully Refereed and Peer Reviewed Journal)**
**ISSN: 0976-7797**
**Impact Factor: 5.183**
**Index Copernicus Value (ICV) = 77.57**

**Recognition of Aβ aggregate by AIE nanoparticles**

Aggregation-induced emission (AIE) luminogens provide a powerful platform for detecting amyloid-β (Aβ) aggregates, and their nanoparticle formulations further enhance stability, bioavailability, and in vivo applicability. Unlike conventional dyes such as thioflavin T and Congo Red, which suffer from aggregation-caused quenching (ACQ), AIE-based nanoparticles (AIE NPs) exhibit strong fluorescence upon aggregation due to the restriction of intramolecular motion (RIM) [40, 41]. This unique property enables a robust "turn-on" signal when AIE NPs bind to β-sheet–rich structures in Aβ oligomers or fibrils, offering significantly higher sensitivity and signal-to-noise ratios [36]. The nanoparticle formulation also improves aqueous solubility and prevents premature aggregation of the probe itself, which is a major limitation of hydrophobic small-molecule fluorophores [42].

At the mechanistic level, AIE nanoparticles interact selectively with Aβ species, especially the soluble oligomeric and protofibrillar intermediates that are increasingly recognized as the most neurotoxic forms of Aβ. Upon binding, the restricted intramolecular rotations of the AIEgens within the nanoparticle core lead to a pronounced fluorescence emission, allowing real-time monitoring of aggregation kinetics [43]. Many AIE nanoparticles are further functionalized with surface modifications such as polyethene glycol (PEG) or peptide ligands to improve stability in biological media, prolong circulation time, and facilitate blood–brain barrier (BBB) penetration. Targeting moieties can also be incorporated to enhance recognition specificity for Aβ deposits, thereby expanding their application from in vitro assays to in vivo brain imaging in Alzheimer's disease models [44].

A particularly important advantage of AIE nanoparticles is their ability to detect early-stage Aβ assemblies that are often missed by traditional fibril-selective probes. In animal studies, near-infrared (NIR) emissive AIE NPs have successfully illuminated amyloid deposits in the brains of transgenic Alzheimer's models with deep tissue penetration and minimal background autofluorescence [45]. Furthermore, multifunctional AIE NPs have been reported that not only detect Aβ aggregates but also intervene in their formation. Some are designed to inhibit fibrillization or disassemble preformed fibrils, while others generate reactive oxygen species under light irradiation for photodynamic therapy (PDT) [46]. These dual diagnostic and therapeutic (theranostic) functions establish AIE nanoparticles as a cutting-edge technology for Alzheimer's disease, bridging early molecular detection with potential intervention strategies [47].

Using silole-based AIE-GNPs, both monomeric Aβ peptides and fibrils can be sensitively detected in a ratiometric manner. As shown in **Figure 7**, the AIE-GNPs exhibit strong green fluorescence, which is transferred to red-emitting glycoprobes via FRET. Upon binding Aβ, the

 

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nanoparticles disassemble, restoring the AIEgen emission. In contrast, lectin binding produces a distinct ratiometric response, allowing clear discrimination between Aβ and lectins [48].

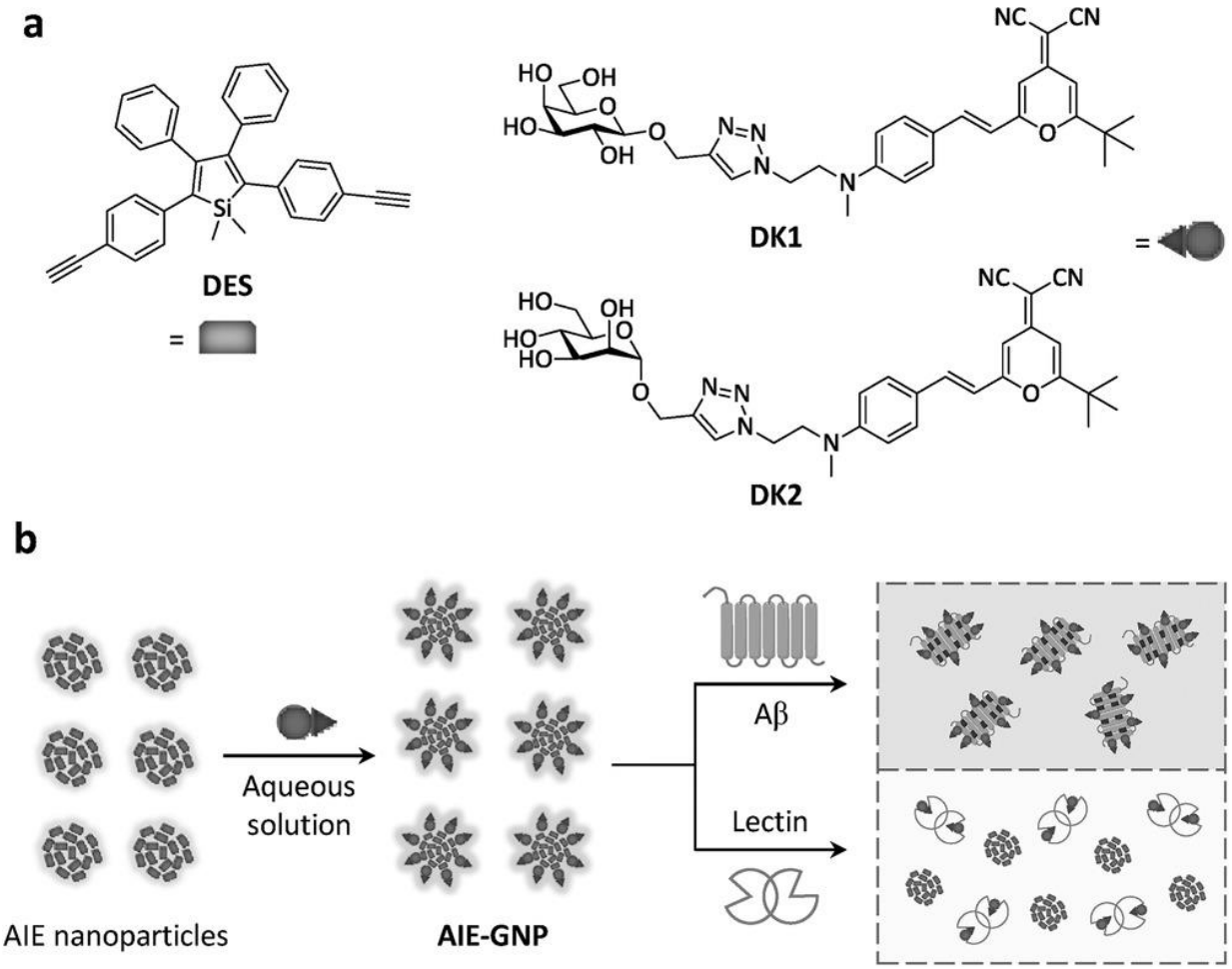


Figure 7. a) Structures of the AIEgen (DES) and glycoprobes (DK1 and DK2) used. b) Schematic illustration of the supramolecular assembly of AIEgen with glycoprobe to produce the AIE-GNP and its use for the ratiometric detection of and discrimination between amyloid *β* (A*β*) and lectin adopted from [48].

## Conclusion

This review underscores the central role of amyloid-β (Aβ) oligomers and fibrils in Alzheimer's disease and highlights the promise of aggregation-induced emission (AIE) probes as next-generation diagnostic and therapeutic platforms. Traditional recognition strategies, though valuable, are hampered by limitations such as low selectivity for oligomers, photobleaching, and

 

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invasiveness, thereby restricting their application for early detection. In contrast, AIE probes provide a distinctive advantage by switching from an "off" to "on" fluorescence state upon binding aggregated Aβ, effectively eliminating background noise and allowing highly sensitive monitoring of disease progression. Nanoparticle formulations further enhance probe stability, solubility, and brain penetrability, enabling real-time in vivo imaging of plaques with deep tissue penetration and near-infrared emission. Supramolecular AIE glyconanoparticles add a further dimension by offering ratiometric detection and discrimination from lectins, increasing diagnostic accuracy in complex biological environments. Importantly, multifunctional AIE platforms not only detect but also modulate Aβ aggregation, demonstrating inhibitory or disassembly effects and, in some designs, generating reactive oxygen species for photodynamic therapy.

Despite these advances, challenges remain in clinical translation, including long-term safety, pharmacokinetics, and standardization of probe design. Nevertheless, AIE-based detection provides a paradigm shift in AD research, bridging molecular pathology with real-time diagnostic imaging and opening new avenues for integrated theranostic strategies.

**Future Directions**

Future research on AIE-based probes for Alzheimer's disease should focus on translating laboratory advances into clinically viable tools. Although current AIE luminogens demonstrate high sensitivity, selectivity, and biocompatibility in preclinical models, long-term biosafety, pharmacokinetics, and metabolic fate remain underexplored. Rational probe design integrating near-infrared emission, high quantum yield, and targeted ligands will be essential for achieving reliable early-stage detection of soluble Aβ oligomers in living patients. Multifunctional theranostic systems combining AIE imaging with drug delivery, photodynamic therapy, or aggregation inhibitors offer exciting opportunities to couple diagnosis with intervention. Furthermore, standardized protocols and multimodal approaches integrating AIE fluorescence with MRI or PET imaging could enhance diagnostic accuracy. Progress will also require interdisciplinary collaboration across chemistry, neuroscience, and clinical medicine to validate probe performance in patient-derived samples and eventually in human trials. Collectively, these directions will help establish AIE platforms as robust diagnostic and therapeutic technologies for Alzheimer's disease.

 

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# References

1. Jehangir, M., et al., *An Updated Review of Amyloid Beta Oligomer Toxicity Inhibition and Detection for Alzheimer's Disease Diagnosis.* Cognizance Journal of Multidisciplinary Studies, 2024. **4**(7): p. 164-186.
2. Jehangir, M., et al., *Chemical Modulation of Amyloid Beta Oligomer's in Alzheimer's Disease.* American Journal of Chemistry and Pharmacy, 2025. **4**(1): p. 16-28.
3. Jellinger, K.A., *Neuropathological assessment of the Alzheimer spectrum.* Journal of Neural Transmission, 2020. **127**(9): p. 1229-1256.
4. Steiner, H., et al., *Making the final cut: pathogenic amyloid-β peptide generation by γ-secretase.* Cell Stress, 2018. **2**(11): p. 292-310.
5. Chen, Z.-R., et al., *Role of Cholinergic Signaling in Alzheimer's Disease.* Molecules, 2022. **27**(6).
6. Thakur, S., et al., *Neuroinflammation in Alzheimer's Disease: Current Progress in Molecular Signaling and Therapeutics.* Inflammation, 2022. **46**(1): p. 1-17.
7. Chen, F., et al., *The vascular contribution of apolipoprotein E to Alzheimer's disease.* Brain, 2024. **147**(9): p. 2946-2965.
8. Almeida, Z.L. and R.M.M. Brito, *Structure and Aggregation Mechanisms in Amyloids.* Molecules, 2020. **25**(5).
9. Almansoub, H.A.M.M., et al., *Tau Abnormalities and the Potential Therapy in Alzheimer's Disease.* Journal of Alzheimer's Disease, 2019. **67**(1): p. 13-33.
10. Dias, D. and R. Socodato, *Beyond Amyloid and Tau: The Critical Role of Microglia in Alzheimer's Disease Therapeutics.* Biomedicines, 2025. **13**(2).
11. Viola, K.L. and W.L. Klein, *Amyloid β oligomers in Alzheimer's disease pathogenesis, treatment, and diagnosis.* Acta Neuropathologica, 2015. **129**(2): p. 183-206.
12. Puthenveetil, R., E.T. Christenson, and O. Vinogradova, *New Horizons in Structural Biology of Membrane Proteins: Experimental Evaluation of the Role of Conformational Dynamics and Intrinsic Flexibility.* Membranes, 2022. **12**(2).
13. Danysz, W. and C.G. Parsons, *Alzheimer's disease, β-amyloid, glutamate, NMDA receptors and memantine – searching for the connections.* British Journal of Pharmacology, 2012. **167**(2): p. 324-352.
14. Bruggink, K.A., et al., *Methods for Analysis of Amyloid-β Aggregates.* Journal of Alzheimer's Disease, 2012. **28**(4): p. 735-758.
15. Gao, M. and B.Z. Tang, *Fluorescent Sensors Based on Aggregation-Induced Emission: Recent Advances and Perspectives.* ACS Sensors, 2017. **2**(10): p. 1382-1399.
16. Fang, Y., et al., *A Novel Aggregation-Induced Emission Fluorescent Probe for Detection of β-Amyloid Based on Pyridinyltriphenylamine and Quinoline–Malononitrile.* Biosensors, 2023. **13**(6).
17. Mei, J., et al., *Aggregation-Induced Emission: Together We Shine, United We Soar!* Chemical Reviews, 2015. **115**(21): p. 11718-11940.
18. Yan, C., et al., *Preparation of near-infrared AIEgen-active fluorescent probes for mapping amyloid-β plaques in brain tissues and living mice.* Nature Protocols, 2023. **18**(4): p. 1316-1336.
19. He, Q., et al., *Near-infrared aggregation-induced emission materials: Bibliometric analysis and their application in biomedical field.* Aggregate, 2024. **5**(3).
20. Parihar, A., N.K. Choudhary, and R. Khan, *Current challenges and future perspectives for the development of POCT devices for neurodegenerative disorders*, in *Smart Diagnostics for Neurodegenerative Disorders*. 2024. p. 311-346.
21. Bae, M., et al., *Recent Advances in Electrochemical Biosensors for Neurodegenerative Disease Biomarkers.* Biosensors, 2025. **15**(3).
22. Lin, X., et al., *Determination of cell metabolite VEGF165 and dynamic analysis of protein–DNA interactions by combination of microfluidic technique and luminescent switch-on probe.* Biosensors and Bioelectronics, 2016. **79**: p. 41-47.
23. Haes, A.J., et al., *Detection of a Biomarker for Alzheimer's Disease from Synthetic and Clinical Samples Using a Nanoscale Optical Biosensor.* Journal of the American Chemical Society, 2005. **127**(7): p. 2264-2271.
24. Biancalana, M. and S. Koide, *Molecular mechanism of Thioflavin-T binding to amyloid fibrils.* Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 2010. **1804**(7): p. 1405-1412.
25. Walsh, D.M. and D.J. Selkoe, *Aβ Oligomers – a decade of discovery.* Journal of Neurochemistry, 2007. **101**(5): p. 1172-1184.
26. Kayed, R., et al., *Common Structure of Soluble Amyloid Oligomers Implies Common Mechanism of Pathogenesis.* Science, 2003. **300**(5618): p. 486-489.
27. Ida, N., et al., *Analysis of Heterogeneous βA4 Peptides in Human Cerebrospinal Fluid and Blood by a Newly Developed Sensitive Western Blot Assay.* Journal of Biological Chemistry, 1996. **271**(37): p. 22908-22914.

 

**28.** Olsson, B., et al., *CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis.* The Lancet Neurology, 2016. **15**(7): p. 673-684.
**29.** Cacabelos, R., et al., *Pharmacogenomics of Alzheimer's Disease: Novel Therapeutic Strategies for Drug Development*, in *Pharmacogenomics in Drug Discovery and Development*. 2014. p. 323-556.
**30.** Yoon, J.H., et al., *How Can Insulin Resistance Cause Alzheimer's Disease?* International Journal of Molecular Sciences, 2023. **24**(4).
**31.** Ugalde, C.L., et al., *Pathogenic mechanisms of prion protein, amyloid-β and α-synuclein misfolding: The prion concept and neurotoxicity of protein oligomers.* Journal of neurochemistry, 2016. **139**(2): p. 162-180.
**32.** McInnis, J., *Regulation of Neuroinflammation after Ischemic Stroke by Astroglial Endothelin Receptor Type-B Signaling*. 2020: The University of Vermont and State Agricultural College.
**33.** Deng, Q., et al., *Microglia and astrocytes in Alzheimer's disease: significance and summary of recent advances.* Aging and disease, 2024. **15**(4): p. 1537.
**34.** Wang, X., et al., *Amyloid-β oligomer targeted theranostic probes for in vivo NIR imaging and inhibition of self-aggregation and amyloid-β induced ROS generation.* Talanta, 2021. **224**: p. 121830.
**35.** Dao, P., et al., *Design and synthesis of new theranostic agents for near-infrared imaging of β-amyloid plaques and inhibition of β-amyloid aggregation in Alzheimer's disease.* Dyes and Pigments, 2017. **147**: p. 130-140.
**36.** Gour, N., et al., *Synthesis and aggregation studies of a pyridothiazole-based aiee probe and its application in sensing amyloid fibrillation.* ACS Applied Bio Materials, 2019. **2**(10): p. 4442-4455.
**37.** Yang, Y., et al., *An AIE-active theranostic probe for light-up detection of Aβ aggregates and protection of neuronal cells.* Journal of Materials Chemistry B, 2019. **7**(15): p. 2434-2441.
**38.** Wang, Y.-L., et al., *AIE-based super-resolution imaging probes for β-amyloid plaques in mouse brains.* Materials Chemistry Frontiers, 2018. **2**(8): p. 1554-1562.
**39.** Tang, Y., D. Zhang, and J. Zheng, *ROF-2 as an Aggregation-Induced Emission (AIE) Probe for Multi-Target Amyloid Detection and Screening of Amyloid Inhibitors.* Small, 2024.
**40.** Luo, J., et al., *Aggregation-induced emission of 1-methyl-1, 2, 3, 4, 5-pentaphenylsilole.* Chemical communications, 2001(18): p. 1740-1741.
**41.** Haass, C. and D.J. Selkoe, *Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β-peptide.* Nature reviews Molecular cell biology, 2007. **8**(2): p. 101-112.
**42.** Mei, J., et al., *Aggregation-induced emission: the whole is more brilliant than the parts.* Advanced materials, 2014. **26**(31): p. 5429-5479.
**43.** Wu, Q., et al., *Aggregation-induced emission: An emerging concept in brain science.* Biomaterials, 2022. **286**: p. 121581.
**44.** He, B., et al., *Promising applications of AIEgens in animal models.* Small Methods, 2020. **4**(4): p. 1900583.
**45.** Ulanova, M., et al., *Nanoparticles as contrast agents for the diagnosis of Alzheimer's disease: A systematic review.* Nanomedicine, 2020. **15**(7): p. 725-743.
**46.** Tang, Y., et al., *Dual-functional, multi-targeting GNNQQNY-AIE conjugates as amyloid probes and amyloid modulators via amyloid cross-seeding principle.* Advanced Functional Materials, 2022. **32**(45): p. 2208022.
**47.** Balachandran, Y.L. and X. Jiang, *Aggregation-induced fluorogens in bio-detection, tumor imaging, and therapy: a review.* Ccs Chemistry, 2022. **4**(2): p. 420-436.
**48.** Zhang, J.D., et al., *Ratiometric Detection of β-Amyloid and Discrimination from Lectins by a Supramolecular AIE Glyconanoparticle.* Small, 2016. **12**(47): p. 6562-6567.

 