THERANOSTICS IN ALZHEIMER'S DISEASE: A PARADIGM SHIFT IN DIAGNOSIS AND TREATMENT

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Abstract

Introduction: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive decline in cognitive function and has become one of the greatest socioeconomic and health burdens worldwide. Although significant advances have been made in understanding the pathology of AD, effective treatments remain limited.

Purpose of this thesis: This study aims to explore how a theranostic approach—combining diagnostic imaging with selective, targeted therapeutic interventions—creates new opportunities for the early detection, monitoring, and management of Alzheimer's disease, based on the latest published literature.

Method of work: A comprehensive review of existing literature on theranostics in Alzheimer's disease was conducted, with particular emphasis on recent developments in diagnostic imaging and therapeutic approaches. Data sources included PubMed, ResearchGate, and Google Scholar.

Results and Discussion: The application of theranostic agents in Alzheimer's disease has shown considerable promise, particularly in improving early diagnosis and enabling personalized treatment. Various PET imaging studies using amyloid and tau tracers have demonstrated that these radiopharmaceuticals can specifically detect abnormal protein accumulations in the brain, which are considered key pathological hallmarks of AD.

Conclusion: Theranostics offers a novel strategy for addressing Alzheimer's disease by integrating therapeutic methods that deliver individualized and effective treatments. With the expanding use of advanced imaging technologies and progress in targeted therapies, theranostics has the potential to revolutionize Alzheimer's disease management—shifting from symptom control toward proactive, personalized care.

Keywords: Alzheimer's disease, theranostics

INTRODUCTION

Alzheimer's disease (AD) is among the most common neurological disorders. Clinically, it is classified as a syndrome of progressive dementia, where early symptoms may be subtle or inconspicuous [1]. This pathology primarily affects older populations and is more prevalent among women [2,3].

A positive family history, head trauma with concussion, birth order, and maternal age at birth have been identified as potential risk factors for the development of AD. Memory loss, especially of recent events, is often the first symptom to manifest, gradually progressing to dementia and spreading to other cognitive domains, including language and visuospatial abilities. Additional symptoms may include disorientation, impaired judgment, poor concentration, aphasia, and apraxia [4].

In the final stages of the disease, patients often become rigid, mute, incontinent, and bedridden. These symptoms necessitate assistance with basic activities such as eating, dressing, and toileting, which can lead to complications such as malnutrition, secondary infections, pulmonary embolism, or heart disease [5].

AD is a major global public health concern, currently affecting nearly 50 million people

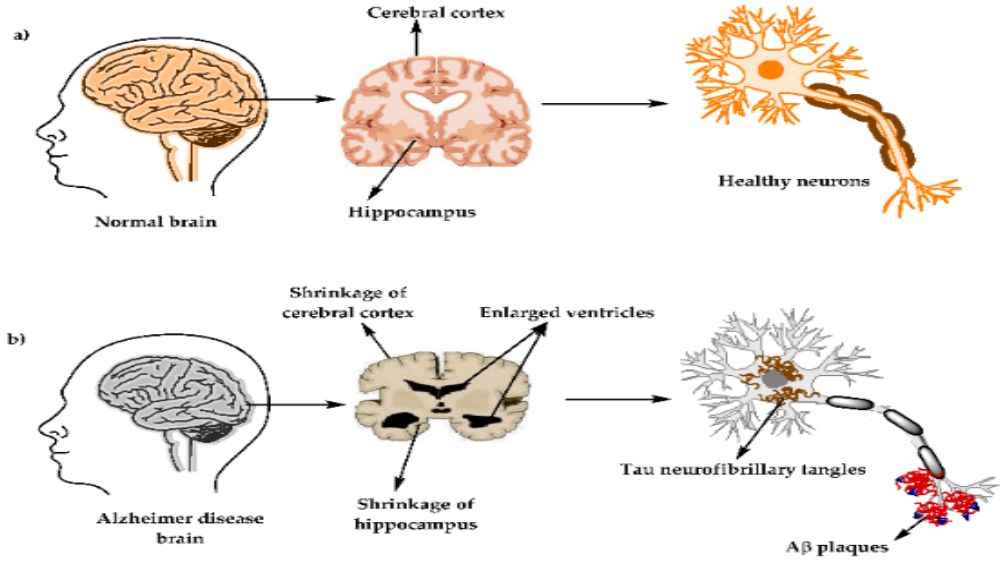

Figure 1. The physiological structure of the brain and neurons in (a) a healthy brain and (b) an Alzheimer's disease (AD) brain (e-Paula VJ, Radanovic M, Diniz BS, Forlenza OV. Alzheimer's disease. Subcell Biochem. 2012;65:329–352.)

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worldwide—a figure projected to rise to 150 million by 2050 [6]. Although the pathological mechanisms of AD are multifactorial, β-amyloidopathy and tauopathy are considered its primary hallmarks. The prevailing hypothesis in AD research, though still debated, posits that the disease results from the self-aggregation of amyloid-β (Aβ) peptides—mainly Aβ1–40 and Aβ1–42—forming soluble misfolded structures that eventually evolve into insoluble fibrils with β-sheet-rich configurations, known as senile plaques [7,8].

1.2. Role of Molecular Imaging in Alzheimer's Disease

Molecular imaging has emerged as a noninvasive and highly specific tool for diagnosing neurological syndromes, offering significant advantages over previous imaging modalities [10]. It enables the detection of molecular and cellular changes that occur before clinical or pathological manifestations, thereby facilitating early diagnosis and allowing for the timely implementation of appropriate therapeutic strategies [11].

Positron Emission Tomography (PET):

PET imaging, in particular, utilizes radiotracers specific to amyloid and tau proteins, enabling the in vivo visualization of these pathological markers.

•Amyloid Imaging: Radiotracers such as [^{18}F] florbetapir and [^{11}C]PiB have been developed to detect Aβ plaques. Amyloid PET imaging is of great importance for early diagnosis, as amyloid accumulation often precedes the onset of clinical symptoms.

•Tau Imaging: Tau PET tracers, such as [^{18}F] flortaucipir, allow the visualization of tau tangles, which correlate with the degree of neurodegeneration and cognitive decline. Tau imaging is increasingly used as a biomarker in clinical trials to monitor the effects of anti-tau therapies [12].

Magnetic Resonance Imaging (MRI):

MRI-based measurements of brain and ventricular volumes, as well as the assessment of atrophy in specific regions, provide valuable insights into neurodegenerative progression. In particular, medial temporal lobe atrophy is strongly associated with AD-related neurodegeneration and is routinely evaluated using MRI [13].

[^{18}F]FDG-PET:

There is strong evidence that hypometabolism in the posterior cingulate and temporoparietal regions is an early sign of neurodegeneration in AD. This can be evaluated using the [^{18}F]-labelled glucose analog in FDG-PET imaging [13]. Although this technique offers high specificity and sensitivity for predicting AD risk and disease progression—based on characteristic metabolic patterns observed in the more advanced stages—its clinical use remains limited [14].

1.3. Theranostic Agents in Alzheimer's Disease

Theranostic agents in Alzheimer's disease (AD) are bifunctional compounds that enable both imaging and targeted treatment. These agents typically consist of a diagnostic moiety (e.g., radiotracer) conjugated to a therapeutic molecule that specifically targets AD pathology [16].

1.3.1. Nanoparticle-Based Theranostics

Nanotechnology holds significant promise in advancing theranostic strategies for Alzheimer's disease. Among the most extensively studied

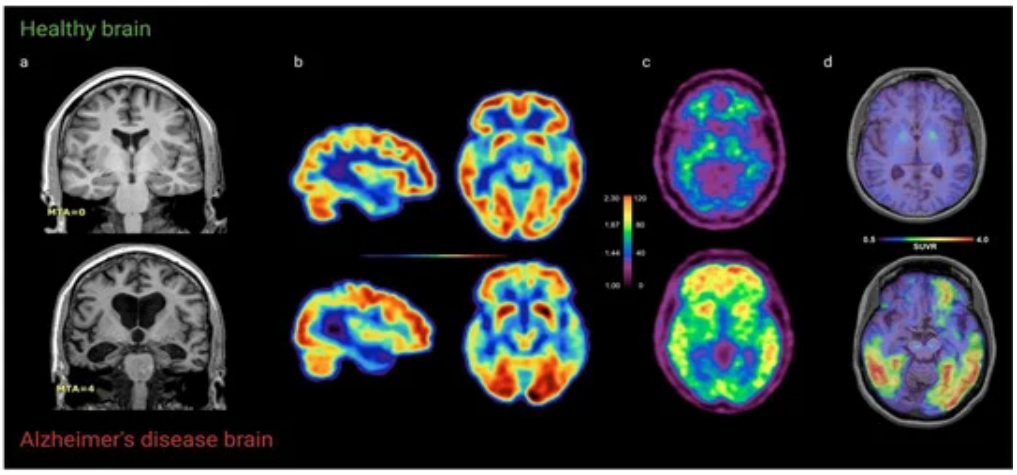

Figure 2. Neuroimages of the healthy versus the Alzheimer's disease (AD) brain. Neuroimaging with (a) structural MRI, (b) FDG-PET, (c) amyloid-PET with PiB, and (d) tau-PET with ^{18}F-AV1451 in both healthy and AD brains (Jack CR, Dickson DW, Parisi JE, Xu YC, Cha RH, O'Brien PC, Edland SD, Smith GE, Boeve BF, Tangalos EG, et al. Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. Neurology. 2000).

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compounds in this context is curcumin, a polyphenolic compound known for its neuroprotective properties. However, poor bioavailability has been a major limitation in translating curcumin into clinical use. Nanoparticle-based delivery systems can enhance the transport of curcumin across the blood–brain barrier (BBB), thereby increasing its therapeutic potential.

Curcumin has demonstrated efficacy in inhibiting pathological processes associated with AD, including the reduction of amyloid plaques and oxidative stress. To improve its bioavailability, curcumin has been encapsulated in nanocarriers such as liposomes and dendrimers. These nanocarriers not only enhance the pharmacokinetic profile of curcumin but also serve as potential diagnostic imaging agents, embodying a dual diagnostic and therapeutic function—the defining feature of theranostic agents.

Recent studies indicate that nanoparticle-based formulations of curcumin can effectively cross the BBB and selectively target amyloid plaques within the brain, underscoring their potential as both diagnostic and therapeutic tools in Alzheimer's disease [17–18].

1.3.1. (continued) Other Nanoparticle-Based Theranostics

Besides curcumin, various other nanoparticles have been engineered - some loaded with neuroprotective agents - to target specific biomarkers associated with Alzheimer's disease (AD). These nanoparticles can be designed to bind selectively to amyloid-β (Aβ) or tau proteins, providing both therapeutic and diagnostic imaging capabilities. The use of such multifunctional formulations has the potential to revolutionize AD diagnosis and treatment by enabling a personalized and highly effective approach to disease management [16].

Special emphasis should be given to near-infrared fluorescence (NIRF) theranostics. These compounds possess unique properties, including the ability to modify fluorescence upon binding to AD biomarkers, the capacity to absorb and emit light in the far-red to near-infrared spectrum (approximately 600–800 nm), and the potential to modulate protein aggregation processes [28].

1.3.2. Therapeutic Efficacy Monitoring and Personalized Treatment

In essence, theranostics provides a feedback-driven approach, enabling real-time monitoring of therapeutic responses and allowing dynamic adjustments to treatment protocols. For instance, positron emission tomography (PET) imaging can be utilized to quantify the levels of amyloid or tau before and after therapy to assess treatment efficacy.

This approach allows clinicians to tailor interventions individually, based on patient-specific responses—something that is not achievable through conventional treatment methods. Periodic imaging further provides valuable insight into disease progression. By visualizing Aβ accumulation and tau tangles over time, clinicians can monitor biomarker dynamics, predict patient outcomes more accurately, and modify therapeutic strategies accordingly [20].

PURPOSE OF THIS THESIS

This study, entitled "Theranostics in Alzheimer's Disease: A Paradigm Shift in Diagnosis and Treatment," delineates the evolving role of theranostics in transforming the management and treatment of Alzheimer's disease. Specifically, this study aims to:

•Analyze how this therapeutic modality - combining diagnostic imaging with selective, targeted therapeutic interventions - creates new opportunities for early detection, monitoring, and management of Alzheimer's disease.

•Review recent advancements in theranostic techniques and evaluate their effectiveness in personalizing treatment plans, enhancing patient outcomes, and reducing disease progression.

METHOD OF WORK

A comprehensive review study was conducted to examine the latest research on theranostics in Alzheimer's disease, with particular emphasis on recent developments in diagnostic imaging modalities and targeted therapeutic approaches.

Data were collected from reputable academic databases, including PubMed, ResearchGate, and Google Scholar. The information was critically analyzed to assess how theranostic strategies are redefining current paradigms in AD management - specifically, by integrating diagnostic imaging with precision-targeted therapies.

The key findings were synthesized to highlight the benefits, limitations, and future directions of theranostics in Alzheimer's disease, with the ultimate goal of establishing a comprehensive perspective on its potential to improve patient care and clinical outcomes.

RESULTS AND DISCUSSION

The application of theranostic agents in Alzheimer's disease has proven highly promising, particularly in advancing early diagnosis and personalized treatment. Numerous PET imaging studies using amyloid and tau tracers have demonstrated that these radiopharmaceuticals can specifically detect abnormal protein accumulations in the brain—hallmarks of AD pathology.

Theranostic approaches integrate diagnostic imaging techniques with targeted therapeutic interventions. PET imaging with amyloid and tau tracers has yielded significant benefits in identifying the preclinical stages of AD, before overt symptoms appear. Radiotracers such as [^{18}F]-florbetapir and [^{11}C]-PiB have been used to detect Aβ plaques that

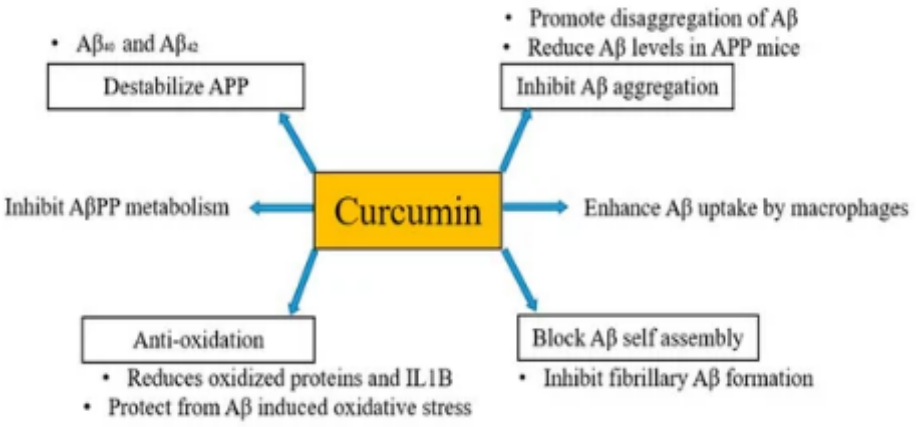

Figure 3. Anti-amyloid properties of curcumin. Curcumin regulates Aβ metabolism and inhibits Aβ aggregation in several ways (Fiala M, Liu PT, Espinosa-Jeffrey A, Rosenthal MJ, Bernard G, Ringman JM, Sayre J, Zhang L, Zaghi J, Dejbakhsh S. Innate immunity and transcription of MGAT-III and Toll-like receptors in Alzheimer's disease patients are improved by bisdemethoxycurcumin. Proc Natl Acad Sci U S A. 2007).

accumulate many years prior to symptom onset, while [^{18}F]-flortaucipir enables the visualization of tau tangles that correlate with neurodegeneration and cognitive decline. These imaging methods allow non-invasive, real-time assessment of disease pathology, greatly facilitating early detection and therapeutic monitoring.

Following the comprehensive review by Bolognesi et al. on fluorescent theranostics, Chen and co-workers reported the development of the first phenothiazine-based theranostic agent targeting Aβ aggregation—a key pathological factor in Alzheimer's disease [21].

These compounds were engineered using a donor–acceptor (D–A) structure with π-electron conjugated chains. The researchers employed phenothiazine as the core scaffold, enhanced by rhodanine moieties, although the rationale behind this combination was not fully explained [22–24].

•Phenothiazine is known for its anti-aggregation and antioxidant properties and is commonly used in central nervous system drugs such as promethazine and chlorpromazine [25].

•Rhodanine has demonstrated anti-tau aggregation activity. Given the interplay between Aβ and tau aggregates, its inclusion was likely intended to target both types of protein misfolding. Moreover, rhodanines exhibit versatile binding properties, potentially improving their efficacy as Aβ-binding theranostic agents [26].

The emission wavelengths were found to be ≥640 nm for all tested compounds, making them suitable for near-infrared fluorescence (NIRF) imaging applications. Fluorescence "turn-on" upon complexation with $A\beta_{1-42}$ aggregates ranged from 2.3- to 13.1-fold, while no significant fluorescence change was observed upon interaction with Aβ monomers. It was hypothesized that these compounds interact with hydrophobic pockets within $A\beta_{1-42}$ aggregates, where restricted molecular rotation leads to an increase in quantum yield [21].

Derivative 1a was selected for further investigation despite its moderate fluorescence enhancement of 4.89-fold, due to the following favorable properties:

•High binding affinity to $A\beta_{1-42}$ aggregates (K_d = 7.5 ± 0.4 nM).

•Significant inhibition of $A\beta_{1-42}$ aggregation (IC_{50} = 0.67 ± 0.02 μM).

•Low affinity for non-specific targets such as bovine serum albumin (BSA).

•Minimal cytotoxic effects on SH-SY5Y cells at concentrations up to 50 μM.

In vitro fluorescence staining of brain and eye tissue slices from double transgenic mice (APP^{wtse}/PSEN1, 9 months old) demonstrated the effective targeting capability of compound 1a toward Aβ plaques [21].

Discussion

Integrated therapeutic capabilities within theranostics represent a paradigm shift in the management of Alzheimer's disease (AD). Traditional AD treatments were limited by the inability to detect the disease in its earliest stages. The introduction of theranostic agents now enables clinicians to identify amyloid plaques and tau tangles while simultaneously delivering targeted therapies that can slow disease progression.

Another major advantage of theranostic agents is their capacity to provide real-time feedback on treatment efficacy. Imaging can be performed before and after therapeutic interventions to assess changes in amyloid or tau burden, allowing clinicians to adjust treatment protocols based on individual patient responses. This feedback mechanism makes it possible to design personalized therapeutic strategies tailored to each patient's disease progression.

The results demonstrate that phenothiazine-based derivatives, particularly compound 1a, show great promise as near-infrared fluorescence (NIRF) probes for detecting Aβ aggregates in Alzheimer's disease models. Their high binding affinity, strong inhibition of aggregation, and low cytotoxicity suggest significant potential for in vivo diagnostic applications.

Conclusion

The application of theranostics in Alzheimer's disease marks a significant advancement toward early diagnosis and personalized treatment. This approach integrates diagnostic imaging with therapeutic intervention, allowing clinicians to detect pathological markers such as amyloid-β (Aβ) plaques and tau tangles long before clinical symptoms manifest. Early detection is critical for managing disease progression and tailoring treatment strategies to the individual.

Positron emission tomography (PET) imaging using tracers such as [^{18}F] florbetapir, [^{11}C]PIB, and [^{18}F]flortaucipir has been instrumental in visualizing Aβ plaques and tau tangles in the brain, providing a non-invasive method to diagnose pathology in real time. These imaging techniques not only improve early diagnosis but also enable the continuous monitoring of therapeutic responses through a feedback mechanism that can optimize treatment regimens.

Further studies on phenothiazine-based compounds, particularly derivative 1a, highlight the potential of theranostic agents in AD. The phenothiazine scaffold with appended rhodanine units

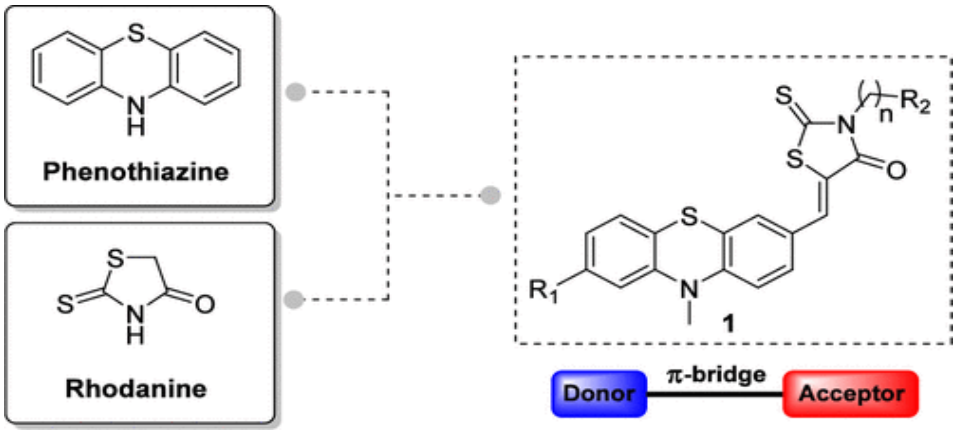

Figure 4. Donor–acceptor design by framework combination of phenothiazine and rhodanine (Francisco TN, Malafaia D, Melo L, Silva AM, Albuquerque HM. Recent advances in fluorescent theranostics for Alzheimer's disease: a comprehensive survey on design, synthesis, and properties. ACS Omega. 2024).

demonstrates high binding affinity to $A\beta_{1-42}$ aggregates, effective inhibition of aggregation, and minimal neuronal toxicity. Owing to its "turn-on" fluorescence upon binding to Aβ aggregates, compound 1a serves as a highly promising NIRF probe.

In conclusion, integrating theranostic approaches—specifically the use of phenothiazine-based probes—offers significant potential for the early diagnosis and treatment of Alzheimer's disease. These agents enable precise detection and real-time monitoring of disease progression, paving the way for personalized therapies aimed at slowing neurodegeneration and improving patient outcomes. Future research should focus on optimizing these compounds for clinical application and evaluating their therapeutic potential in in vivo models of AD.

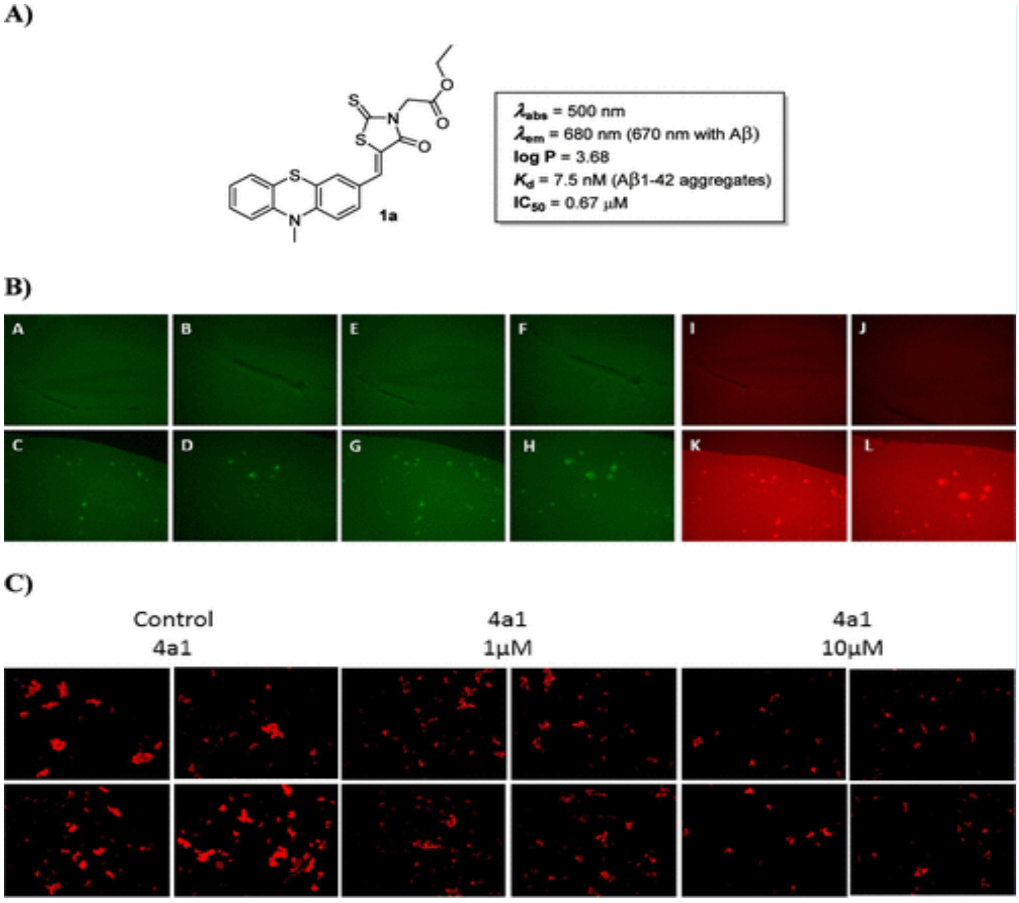

Figure 5. (A) In vitro binding profile of compound 1a. (B) In vitro fluorescent staining assays for Aβ plaques—fluorescent staining of compound 1a on cortical brain slice sections from a double transgenic (Tg) mouse. (C) Inhibition of $A\beta_{1-42}$ self-aggregation followed by fluorescence microscopy using compound 1a (Dao P, Ye F, Liu Y, Du ZY, Zhang K, Dong CZ, Meunier B, Chen H. Development of phenothiazine-based theranostic compounds that act both as inhibitors of β-amyloid aggregation and as imaging probes for amyloid plaques in Alzheimer's disease. ACS Chem Neurosci. 2017).

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