

DOCTORAL THESIS

Organic molecules for diagnosis and therapy of Alzheimer's disease

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ABSTRACT

Alzheimer's disease has become one of the most common diseases jeopardizing the health of the human being. The main pathological feature of AD is the accumulation of A β in the brain to form senile plaques. Therefore, it is of great significance to develop new and efficient drugs targeting at amyloid- β for the detection, diagnosis and therapeutics for Alzheimer's disease.

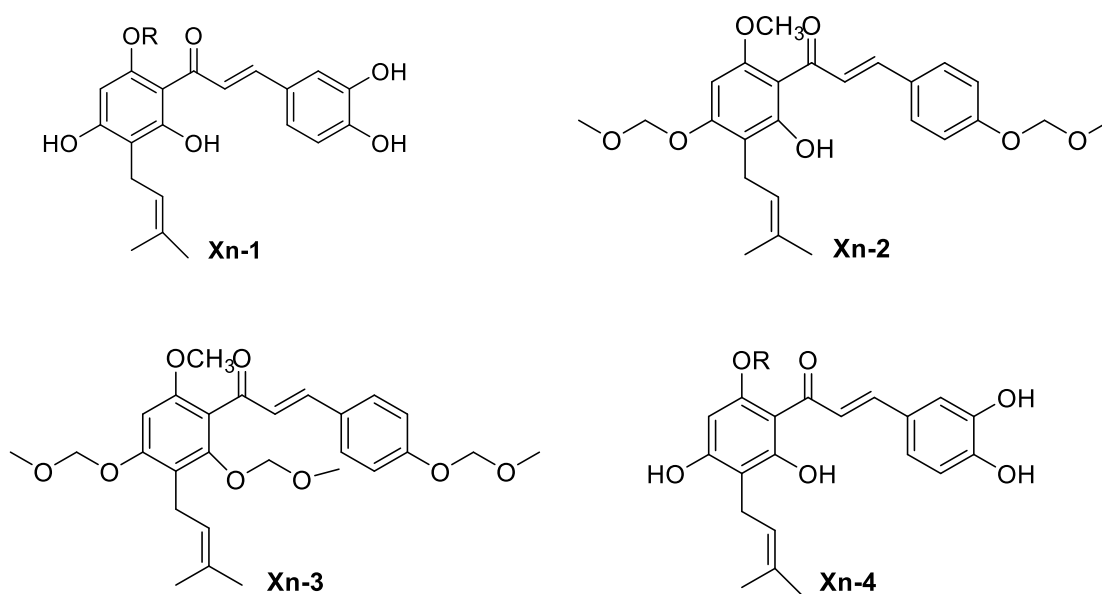
Xanthohumol (Xn) naturally presents in hops (*Humulus lupulus* L). Studies have shown that it has anti-lipoperoxidative, anti-inflammatory, anti-proliferative activities, antiangiogenic and antioxidant effects, which further illustrates its potential therapeutic for AD. However, the bio-incompatibility and blood-brain barrier impermeability of Xanthohumol hindered its *in vivo* efficacy potential for treating Alzheimer's disease. Thus, we designed and prepared a series of Xanthohumol derivatives, namely, **Xn-n, (n = 1-9)** and its chalcone derivatives **C-n, (n = 1-10)** to enhance the desirable physical, biological and pharmacological properties, especially the blood-brain barrier permeability for intervention of AD.

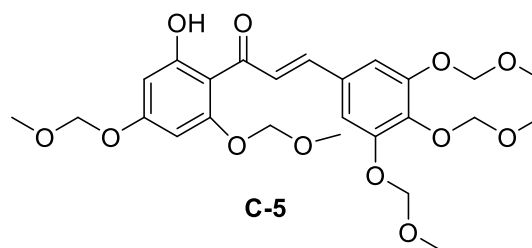
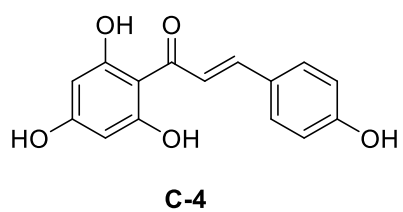
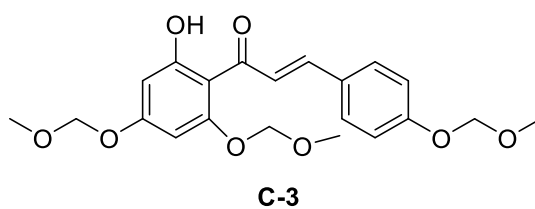
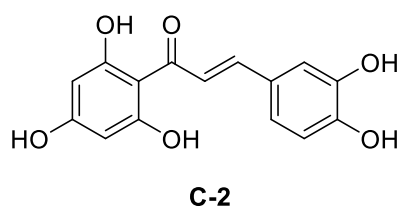
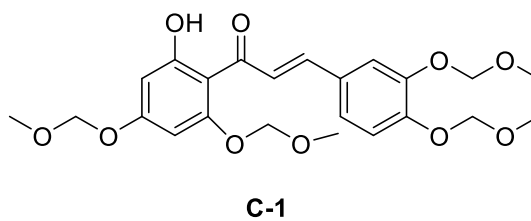
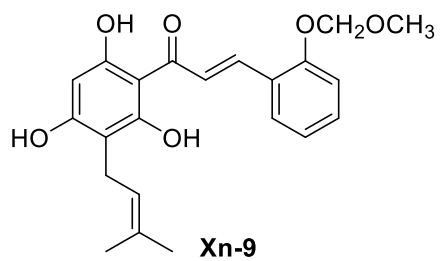
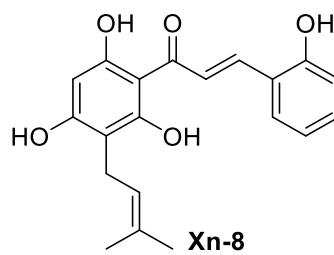
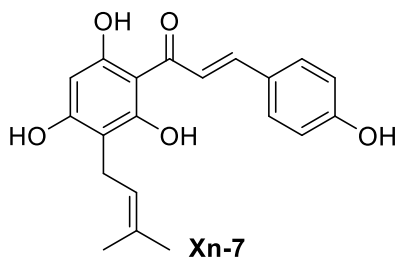
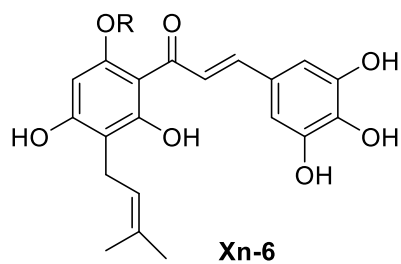
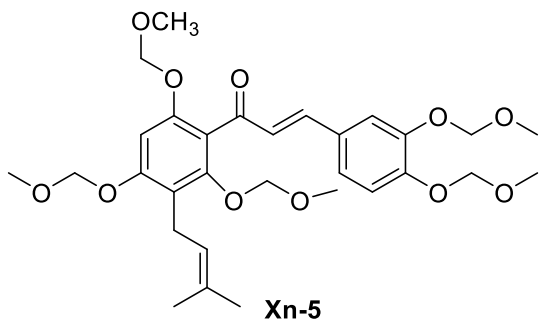
As an effective technique for *in vivo* visualization, Near-infrared fluorescence imaging based on organic small molecule probes has a promising application in the diagnosis of Alzheimer's disease. However, most of the reported imaging probes can only visualize A β -plaques but do not have therapeutic potential such as neuroprotection against A β induced toxicity. Herein, we designed and synthesized a series of oligomeric A β targeted near infrared (NIR) fluorescent probes for the diagnosis and therapeutics of Alzheimer's disease, namely **DBAN-SLM, DBAN-SLOH, DBAN-OSLM** which showed remarkably effective inhibitory effect on A β aggregation, significant neuroprotection effect against the A β -induced toxicities, and suppression on A β -induced ROS

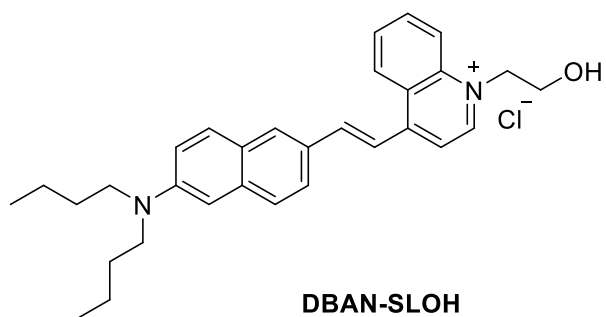
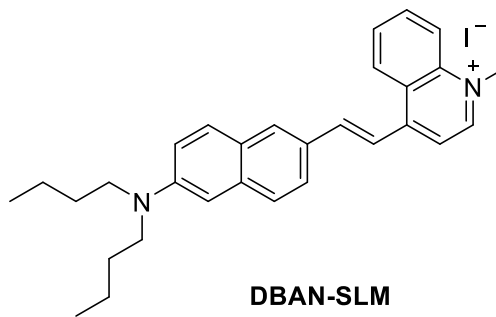
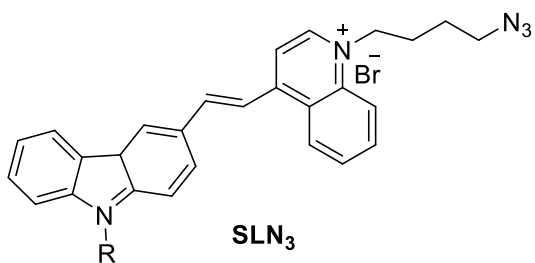
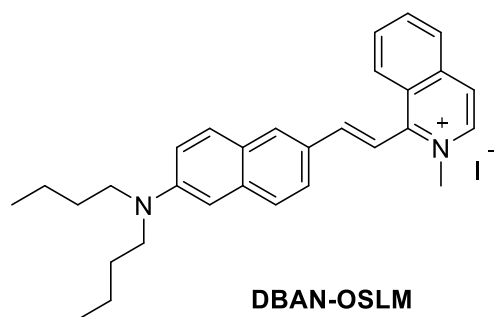
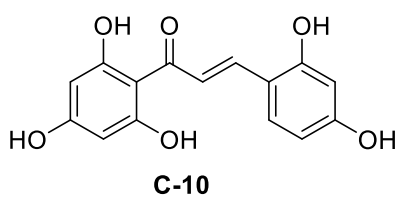
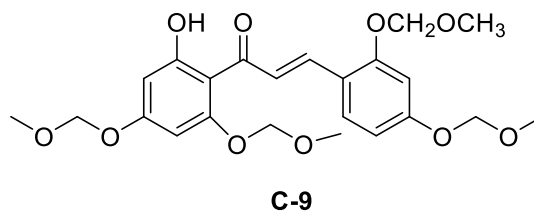
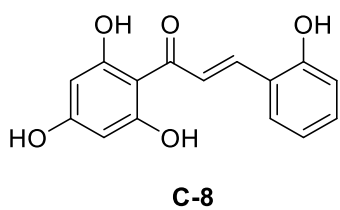
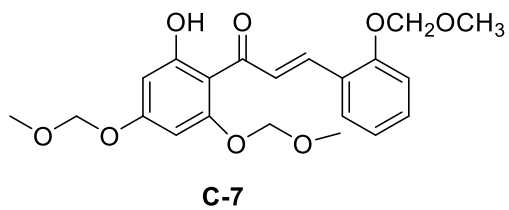
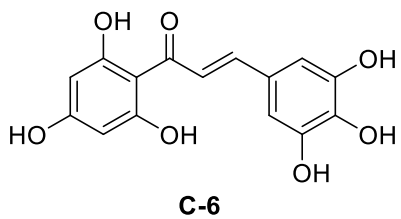
generation. indicating its great promise as a useful theragnostic agent for the early diagnosis and therapy of AD.

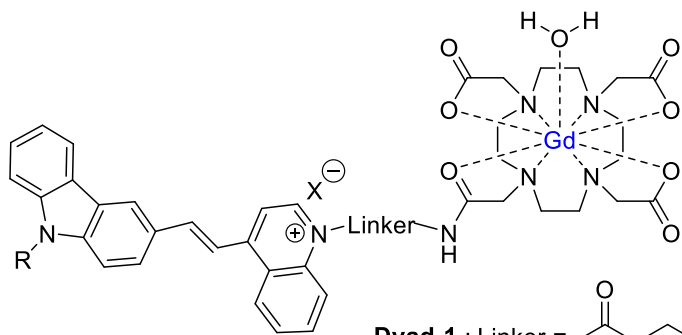
Dual-modal imaging is an important approach to overcome the limitations of single imaging technology in the diagnosis of AD disease. Therefore, based on the dual-modal, we designed and synthesized the NIR/MR dual-modal detection and theragnostic probes namely **Dyad-1**, **Dyad-2**, **Dyad-3** and **NP@SiO₂@F-SLOH**. More surprising is that the two NIR/MR dual-modal probes show excellent biological properties, including the ability to inhibit A β aggregation to a certain extent, neuroprotective effects on cytotoxicity caused by different forms of A β species, blood-brain barrier (BBB) permeability, and high stability.

All of these newly designed and synthesized molecules were characterized with ¹H NMR, ¹³C NMR, and HRMS and found to show good agreement with the desired structures. The photophysical properties and biological properties of these novel designed and synthesized fluorescent probe such as UV-vis absorption, fluorescence emission, dissociation constant determined by fluorescence titration, cytotoxicity assay, neuroprotection, and inhibition of A β aggregation were investigated.









$R = \text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$

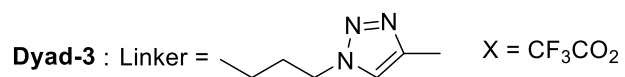
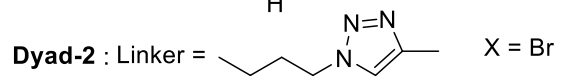
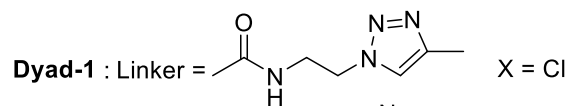


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