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 Aβ 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.

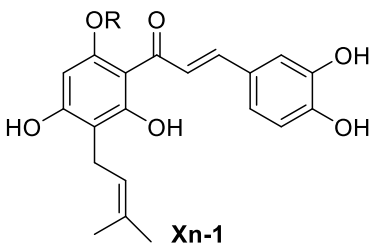
Xanthohumol (Xn) naturally presents in hops (Humulus lupulus L). Studies have shown that it has anti-lipoperoxidative, anti-inflammatory, anti-proliferative activities, antiangiogenic and antioxidant effects, which further illustrates its potential therapeutic for AD. However, the bio-incompatibility and blood-brain barrier impermeability of Xanthohumol hindered it 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 Aβ-plaques but do not have therapeutic potential such as neuroprotection against Aβ induced toxicity. Herein, we designed and synthesized a series of oligomeric Aβ 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 Aβ aggregation, significant neuroprotection effect against the Aβ-induced toxicities, and suppression on Aβ-induced ROS

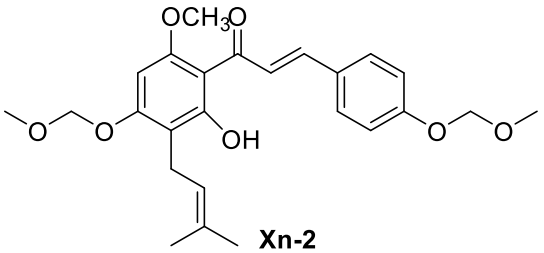
generation. indicating its great promise as a useful theragnostic agent for the early diagnosis and therapy of AD.

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@SiO$_2$@F-SLOH**. More surprising is that the two NIR/MR dual-modal probes show excellent biological properties, including the ability to inhibit Aβ aggregation to a certain extent, neuroprotective effects on cytotoxicity caused by different forms of Aβ species, blood-brain barrier (BBB) permeability, and high stability.

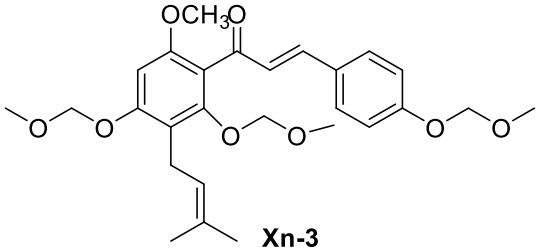
All of these newly designed and synthesized molecules were characterized with ^{1}H NMR, ^{13}C NMR, and HRMS and found to show good agreement with the desired structures. The photophysical properties and biological properties of these novel designed and synthesized fluorescent probe such as UV-vis absorption,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



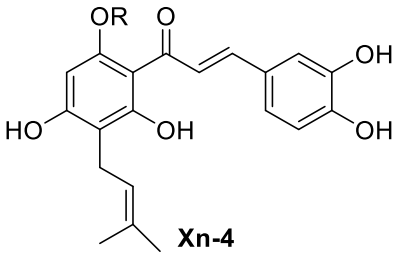
Xn-1



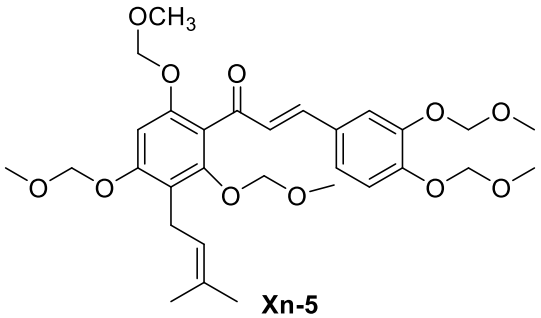
Xn-2



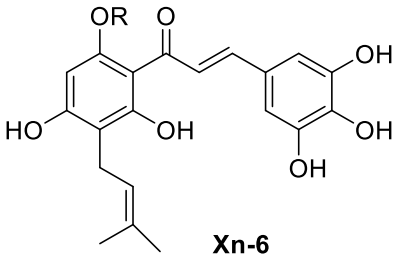
Xn-3



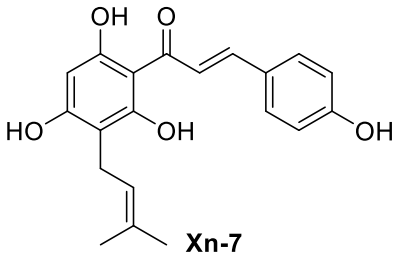
Xn-4



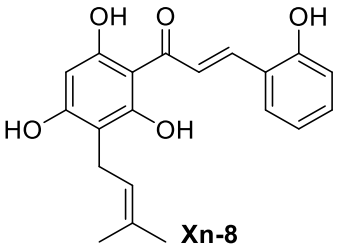
Xn-5



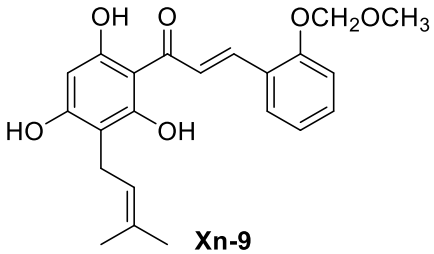
Xn-6



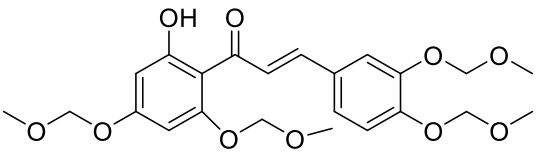
Xn-7



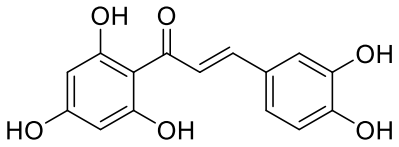
Xn-8



Xn-9



C-1



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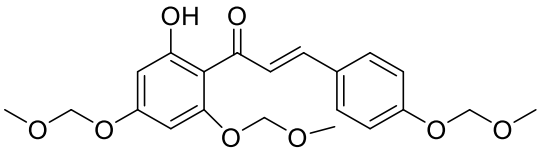

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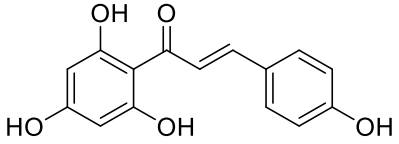

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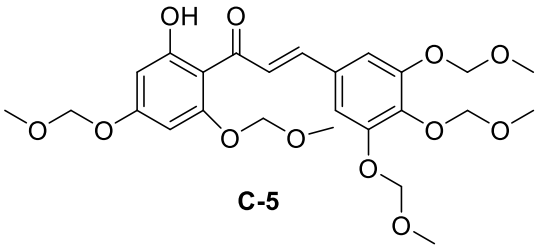

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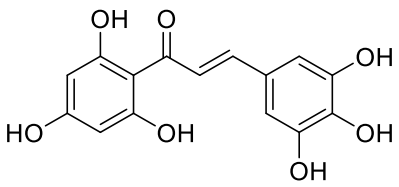

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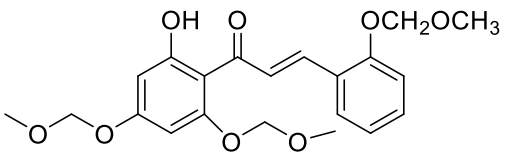

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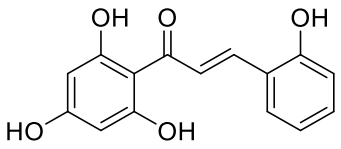

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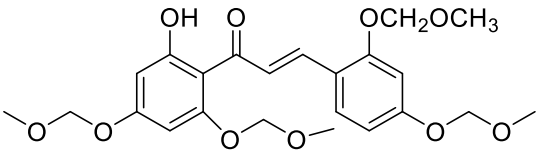

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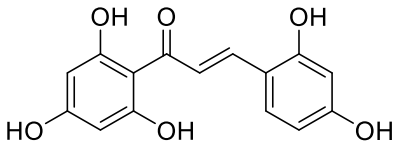

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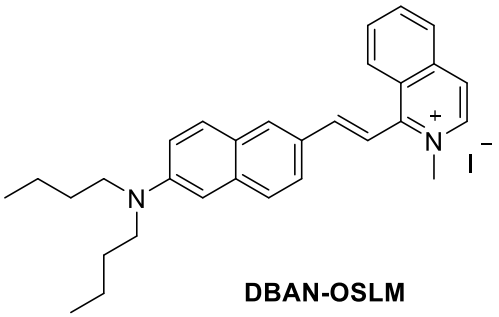
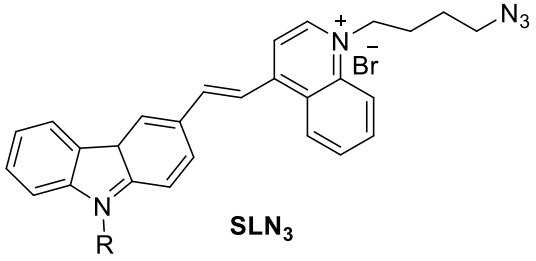
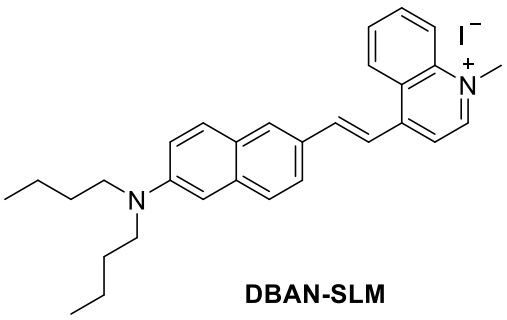


DBAN-OSLM



SLN_3



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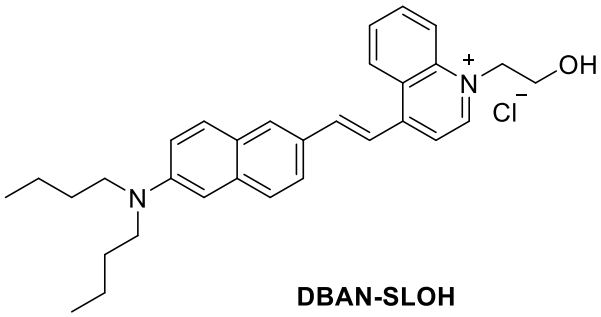
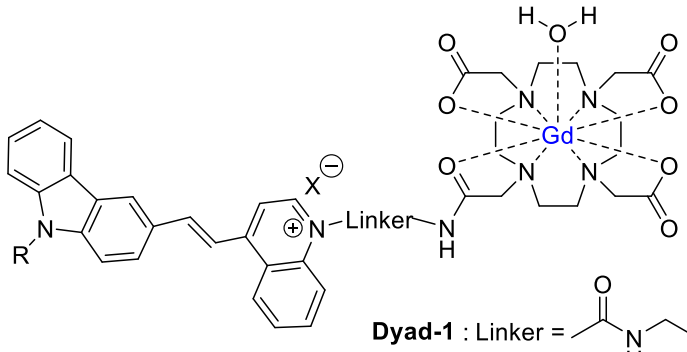
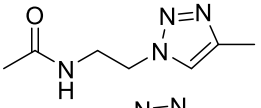
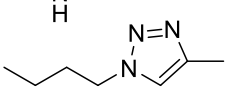


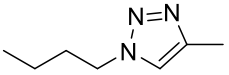
DBAN-SLOH



R=$CH_2CH_2OCH_2CH_2OCH_3$

Dyad-1 : Linker =  X = Cl

Dyad-2 : Linker =  X = Br

Dyad-3 : Linker =  X = CF_3CO_2

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