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Synthesis and evaluation of dihydropyrimidinone-derived selenoesters as multi-targeted directed compounds against Alzheimer's disease

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ABSTRACT

This paper describes the synthesis and evaluation of new dihydropyrimidinone (DHPM)-derived selenoesters as potential multi-targeted agents for the treatment of Alzheimer's disease. A series of DHPM-derived selenoesters were obtained with high structural diversity through a short and modular synthetic route. The antioxidant activity was evaluated by TBARS and iron chelation assays. These compounds were also evaluated as acetylcholinesterase inhibitors (AChEi). The compounds demonstrated good antioxidant activity, since they presented excellent lipid peroxidation inhibition and good iron chelation activity. In addition, they showed acetylcholinesterase inhibition activity and some of them presented activity superior to that of the standard drug galantamine. The in silico predictions showed that the compound **1h** may present a good pharmacokinetic profile. Therefore, the series of DHPM-derived selenoesters described herein displayed good potential for the development of antioxidant and anticholinesterasic agents in the search for new multi-targeted therapeutics for the treatment of Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease, affecting millions of people worldwide, and the prognosis is that this number will increase with population aging.[1] The disease is characterized by progressive memory loss and cognitive impairment, and it presents a complex pathophysiology, being described as a multifactorial disease.[2] Diverse factors such as amyloid-β deposits,[3] decreased levels of acetylcholine,[4] τ-protein aggregation[5] and oxidative stress[6] play significant roles in the progression of the disease.

Oxidative stress plays a pivotal role in the pathophysiology of AD, being one of the main causes of neuronal death.[7] Reactive oxygen species (ROS) are overproduced in the brain of AD patients due to abnormal mitochondrial function that produces more O_2^-, which increases the concentration of H_2O_2 in the cytoplasm.[8] The decreased concentrations of ferritin and increased free iron concentrations contribute to free radical generation through Fenton reactions.[9] ROS damage membranes, proteins and DNA, as do lipid peroxidation products, e.g., reactive aldehydes, which present much longer half-lives in the cell than the radicals, thus reacting with cell constituents leading to damage.[10]

Until now, the strategy of using single-targeted drugs has failed and the multi-targeted drug strategy is becoming a focus of research for the development of new drugs for the treatment of AD. The concept of multi-targeting is fully applicable to AD because of its multifactorial pathogenic mechanisms.[11] Nowadays, most of the palliative treatments available are drugs that inhibit acetylcholinesterase (AChE), based on the deficiency of acetylcholine in the central nervous system, e.g., tacrine,[12] galantamine,[13] donepezil[14] and rivastigmine,[15] but their clinical usefulness is limited.[16]

Dihydropyrimidinones (DHPMs) are easily obtained via Biginelli multi-component reaction, and are reported as good antioxidants acting against lipid peroxidation and being effective as radical

Abbreviations: AD, Alzheimer's disease; ROS, reactive oxygen species; AChE, acetylcholinesterase; DHPMs, dihydropyrimidinones; GPx, glutathione peroxidase; TBARS, thiobarbituric acid reactive substances; NMR, nuclear magnetic resonance; IR, infrared spectroscopy; HMRS, high resolution mass spectrometry; APPI, atmosphere pressure photoionization; DPDS, diphenyl diselenide; BHT, butylated hydroxytoluene; MDA, malondialdehyde; mp, melting point.

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scavengers.[17–19] Some analogs are better radical scavengers than resveratrol.[20] Also, this class of compounds presents AChE inhibitory activity,[21,22] potent examples being reported with activities comparable to the standard drug galantamine.[23] Recently, we reported the synthesis and biological evaluation of a series of DHPMs functionalized with selenocyanides as potential multi-targeted therapeutics against AD.[24]

Organoselenium compounds are very useful in synthetic transformations[25–27] and also for biological purposes, since such compounds are well known antioxidants and glutathione peroxidase (GPx) mimetics,[26,28–34] which is one of the most important natural antioxidant enzymes in the brain.[35] Very recently, Kumar and Engman showed that ebselenols are very good antioxidants, being more efficient than α-tocopherol for quenching peroxyl radicals, and better GPx mimetics than ebselen.[36] Selenium might contribute in several ways against the progression of AD.[37] This element has been shown to modulate the cholinergic system and prevent oxidative damage in animal models of AD.[38] Diphenyl diselenide and its analogs, have also been studied in various animal models. These compounds can enhance the cognitive performance without inducing neurotoxicity,[39,40] inhibit AChE activity, protect against β-amyloid induced neurotoxicity and improve the memory of mice,[41–44] due to their antioxidant properties.

In this context, recent reports demonstrate the effective strategy of merging organoselenium compounds with known AChE inhibitors in the design of potential multi-targeted therapeutics for AD. Ebselen and donepezil were merged together in the same structure in order to develop potent human AChE inhibitors as well as good GPx mimics with the ability to penetrate the central nervous system with no acute toxicity.[45,46] Also, some hybrids formed with tacrine and ebselen were also designed and they presented potent inhibitory activity against AChE and butyrylcholinesterase as well as being effective against hydrogen peroxide and peroxynitrite oxidants.[47] Recently, Wang and co-workers reported the synthesis and evaluation of clioquinol seleno-derivatives which demonstrated excellent antioxidant activities, inhibition of Cu(II)-induced amyloid-β aggregation and also good blood–brain barrier penetration in vitro.[48]

As part of our wider research program aim at designing and developing biologically active new organoselenium compounds as well as eco-friendly processes,[24,49–53] herein we report the design, synthesis and biological evaluation of a series of novel DHPM-derived selenoesters. The compounds were evaluated as antioxidants through the inhibition of lipid peroxidation in the thiobarbituric acid reactive species (TBARS) assay and also as iron chelating agents. The most active compounds were screened as inhibitors of the enzyme AChE, turning them into potential multi-targeted compounds for the treatment of Alzheimer's disease.

2. Results and discussion

2.1. Chemistry and biological evaluation

The synthesis of the DHPM-derived selenoesters **1a**–**h** was performed in a two-step pathway, affording the final compounds in moderate yields (Scheme 1). The intermediates 6-chloromethyl-DHPMs (**2a**–**h**) were synthesized in good yields from the three-component Biginelli reaction, using aromatic aldehydes (**3a**–**g**), ethyl 4-chloroacetoacetate (**4**) and urea (**5a**) or *N*-Me-urea (**5b**) at 100 °C, under solvent-free conditions, catalyzed by HCl.[24] These 6-chloromethyl-DHPMs were reacted with the selenocarboxylate (**6**), generated in situ from the reaction of NaSeH with *p*-toluoyl chloride, at room temperature for 1 h, affording the target seleno-DHPM **1a**–**h** in 30–58% isolated yields.

A series of selenoesters functionalized with electron donating or withdrawing groups on the DHPM aromatic portion, as well as bicyclic aromatic structures were synthesized and the structures of the desired DHPM-derived selenoesters are shown in Figure 1. All compounds are stable at room temperature, even when exposed to light and an air atmosphere for prolonged times, and their analytical and spectroscopic data are in agreement with the expected structures.

In ^{1}H NMR spectra, the *N*-H resonance signals are usually registered as singlets in the ranges of ca. 5.51–8.14 ppm and 7.34–9.10 ppm. The aromatic protons of the DHPM nucleus appear at between 6.60 and 8.18 ppm and the two doublets of the aromatic moiety attached to the selenoester at 7.18 and 7.83 ppm. The proton of the carbon near to the NH appears as a doublet between 5.06 and 6.15 ppm. The two protons of the methylene that links the selenium to the DHPM core appear as an AB quartet at around 4.24 and 4.55 ppm. The characteristic quartet and triplet of the ethyl ester moiety appear at around 1.10 and 4.10 ppm, respectively. The ^{13}C NMR spectra show the characteristic

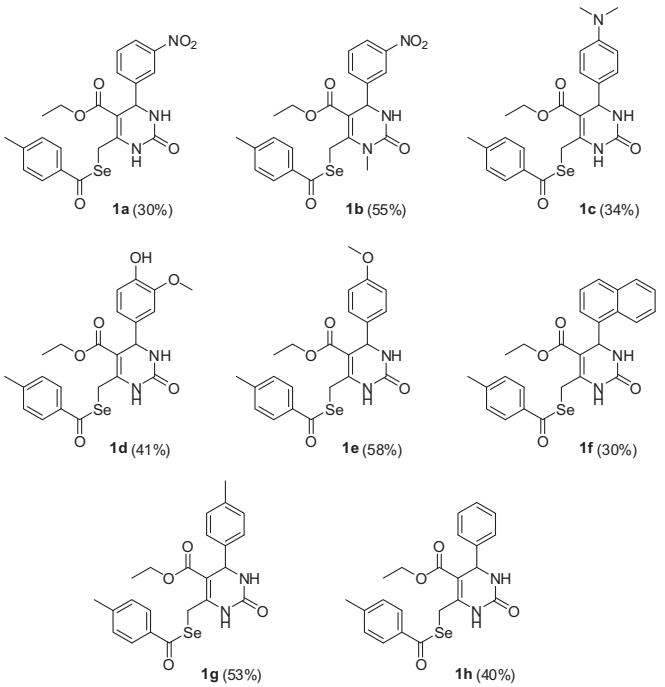
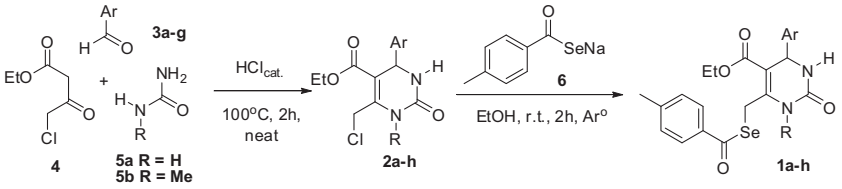


Figure 1. Structures and yields of DHPM-derived selenoesters.



Scheme 1. Synthesis of DHPM-derived selenoesters.