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# Coumarins as cholinesterase inhibitors: A review

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ABSTRACT

The first report in literature of the isolation of coumarin was in the year 1820. After this report, other papers were published demonstrating the isolation and synthesis of coumarin and analogues. These compounds have been studying along the years for several different pathologies. One of these pathologies was Alzheimer's disease (AD), being the main cause of dementia in the contemporary world. There are two hypotheses to explain the pathogenesis mechanism and disease symptoms, then having the "amyloid hypothesis" and the "cholinergic hypothesis". Some drugs for AD are based on the theory of "cholinergic hypothesis", which objective is to increase the concentration of ACh in the synaptic cleft by the inhibition of cholinesterases. Over the last twenty years, many studies with coumarins compounds were reported as cholinesterases inhibitors. The aim of the present review is to discuss the studies and development of new compounds for AD treatment.



**Contents**



## 1. Introduction

The first literature report about the isolation of coumarin (**1**) was executed by Vogel in 1820 [1] from tonka beans found in plants of the species *Dipteryxodorata*, commonly known as *cumaru*. After this initial report different other papers were published demonstrating the isolation [2–5] and synthesis [6–8] of coumarin and analogues from many others plants. For example, Tilden and Burrows, in 1902 [9], isolated precursors of citropten (**2**), also known as 5,7-dimethoxycoumarin, which is present in some essential oils of citrus fruit like lemon. These precursors were use after few years by Schmidt for synthesis ofcitropten [10]. The structure of coumarin (**1**) and citropten (**2**) are shown in Fig. 1.

Along the years, several reviews were demonstrating the abundance of synthetic and isolation of coumarins from plants, and the related biologic activity of these compounds [11,12]. Dean in

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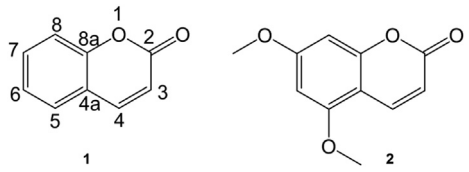

**Fig. 1.** Structure and numeration of coumarin (**1**) and citropten (**2**).

1952 [13] developed the first compilation of occurrence of coumarins in plants up to that time.

Coumarin is characterized by 1,2-benzopyrone or benzopyran-2-ones, groups which are the most common oxygen heterocyclic compounds studied in academic society. The great interest about these compounds is due to their biological activities against different pathologies, which motivate the development of several drugs that are mainly antithrombotics, like warfarin (**3**), acenocoumarol (**4**) and phenprocoumon (**5**) (Fig. 2), being vitamin k antagonists [14]. With this condition, these compounds are also used for preliminary studies of antibacterials [15], antivirals [16], antifungals [17], antiparasitics [18], anticancer [19], antiinflammatory [20], antihyperlipidemic [21] and anticholinesterase activities [22].

Currently, the actual treatment of Alzheimer's Disease (AD) is very scarce, despite this disease being the main cause of dementia in the contemporary world. AD is normally characterized for memory decrease and cognitive dysfunction [23]. To explain the mechanism of AD pathogenesis and these symptoms were created two hypothesis based on morphological and biochemical changes in the patient's brain, then having the amyloid and cholinergic hypothesis [24]. The "amyloid hypothesis" is characterized by intracellular deposits of tau proteins, which affect intracellular transport and leads to cell death, and extracellular deposits of β-amyloid peptides, this deposit is accompanied by oxidative stress and inflammation which leads to neuron degeneration [25]. The "cholinergic hypothesis" is characterized by the main biochemical alteration presented in the patient's brain. The decrease of acetylcholine (ACh) in cholinergic neurons presents the hippocampus and cerebral cortex [26]. ACh is a neurotransmitter produced from acetylation reaction with choline and Acetyl-CoA by the enzyme choline acetyltransferase, which is generated in Meynert*nucleus basalis*. With AD patients, the Meynert*nucleus basalis* is stunted, leading to deficiency of ACh. In the synaptic cleft ACh is degraded by Acetylcholinesterase (AChE) and Butyrylcholinesterase (BuChE), forming acetate and choline (Fig. 3), which are recaptured by the pre-synaptic neurons [27].

The mechanism of hydrolysis of acetylcholine (ACh) by acetylcholinesterase (AChE) with the presence of water is shown in Fig. 4. The principal amino acids for the active site of AChE are serine (Ser203), histidine (His447) and glutamic acid (Glu332), which are directly involved on ACh hydrolysis [27,28].

Some drugs used for AD are based on the theory of cholinergic hypothesis, which objective is to increase the concentration of ACh in the synaptic cleft by the inhibition of cholinesterases (ChE) [29]. Until now, it is known that four drugs have been approved for the treatment with this mechanism of action. These drugs are tacrine (**6**), donepezil (**7**), galanthamine(**8**) and rivastigmine (**9**)(Fig. 5) [30]. Tacrine was the first approved by Food and Drug Administration (FDA) for the treatment in 1993 but it is known that cause hepatotoxicity and has low bioavailability, these facts limited and discontinuedin United States (USA) the use of this drug [31]. It was a noncompetitive and reversible inhibitor of AChE and BuChE making a strong link near the catalytically active site of the AChE [32]. After that, donepezil was introduced to therapeutic of AD being the second drug approved by FDA in 1996. This drug is relatively selective and reversible AChE inhibitor with low toxicity [33]. Galanthamine is the only natural product derivative, an alkaloid that is reversible and competitive inhibitor of AChE and also agonist of nicotinic receptors activity [34]. Rivastigmine is the only pseudo irreversible AChE inhibitor with relatively less BuChE activity. The carbamate portion of this compound is slowly hydrolyzed after binding to AChE. It is indicated for the treatment of Parkinson's disease as well [35].

Among the currently available drugs for the treatment of AD, memantine was the last to be approved by FDA and it is the only one who acts by a different mechanism of action, acting as an antagonist of glutamate receptors of N-methyl-D-aspartate (NMDA) type. This drug avoids excessive influx of calcium ($Ca^{2+}$) ions and it has been proposed because in the synapses after stimulation of the pre-synaptic neuron occurs glutamate release, which binds to the NMDA receptor and stimulates the entry of $Ca^{2+}$ ions in the neuron cytoplasm. The $Ca^{2+}$ions influx induces the production of nNOS (neuronal nitric oxide synthase), an enzyme which leads to the release of nitric oxide (NO) in the pos-synaptic neurons, functioning as a messenger for the pre-synapse and restarting the entire process. With this, the excessive release of glutamate causes a high concentration of neurotransmitter in the synaptic cleft which generates a toxic process leading to cell death. Because of this provision, memantine is indicated for patients with moderate to severe phase [36].

All drugs display beneficial effects on cognitive, functional, and behavioral symptoms of AD, by improving cholinergic deficit. However, these drugs are extremely limited because they are able to treat only the symptoms without causing it to stop or reverse its progression, and also considerable side effects due to cholinergic stimulation of peripheral tissues of the brain [37].

Some alternative treatments for patients with AD have shown to be effective in promoting the improvement of cognition. Among the substances used, one can highlight the herbal containing *Ginkgo biloba*, in which there are substances that promote increased cerebral blood supply and the reduction of free radicals in the body. As a result, it is believed to have neuroprotective effects. Another substance suitable as a supplement for patients with AD is α-

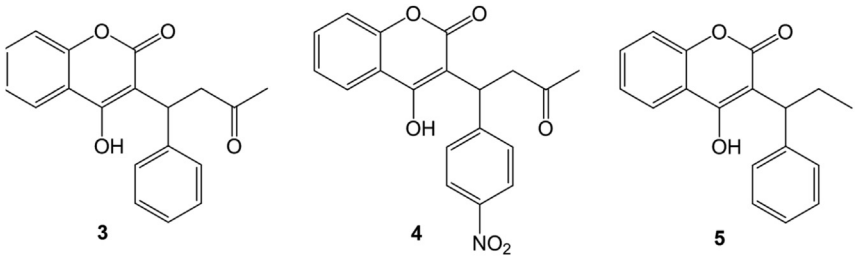

**Fig. 2.** Structure of warfarin (**3**), acenocoumarol (**4**) and phenprocoumon (**5**).