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Review

A review on coumarins as acetylcholinesterase inhibitors for Alzheimer's disease

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ABSTRACT

Acetylcholinesterase (AChE) enzyme inhibition is an important target for the management of Alzheimer disease (AD) and AChE inhibitors are the main stay drugs for its management. Coumarins are the phytochemicals with wide range of biological activities including AChE inhibition. The scientists have attempted to explore the coumarin template for synthesizing novel AChE inhibitors with additional pharmacological activities including decrease in beta-amyloid (Aβ) deposition and beta-secretase inhibition that are also important for AD management. Most of the designed schemes have involved incorporation of a catalytic site interacting moiety at 3- and 4-positions of the coumarin ring. The present review describes these differently synthesized coumarin derivatives as AChE inhibitors for management of AD.

Contents

1. Introduction

Alzheimer's disease (AD) is a progressive, degenerative disorder of the brain and is the most common form of dementia among the elderly especially in industrialized countries. AD is associated with a loss of cholinergic system with decreased levels of acetylcholine in the brain areas dealing with learning, memory, behavior and emotional responses. Neuropathologically, AD is characterized by the presence of beta-amyloid (Aβ) plaques, neurofibrillary tangles and degeneration/atrophy of the basal forebrain cholinergic neurons.[1] The loss of basal forebrain cholinergic cells results in reduction of synaptic availability of acetylcholine (ACh) leading to the cognitive impairment in AD.[2] Accordingly, the most promising approach for the symptomatic treatment of AD is to increase the synaptic levels of ACh in the brain by inhibiting the acetylcholinesterase (AChE) enzyme, which is primarily responsible for its hydrolysis and termination of action. Therefore, AChE inhibitors such as galanthamine, donepezil, rivastigmine and tacrine are the main stay drugs for the clinical management of AD.[3]

The accumulation of Aβ in the different brain areas is critical for the induction of AD and its accumulation results in a cascade of biochemical events involving free radical generation, inflammation, calcium dysregulation and neuronal cell membrane damage leading to neuronal dysfunction.[4] The various therapeutic approaches for AD management have been directed to decrease Aβ production or aggregation, or increase its removal. The studies have suggested that AChE is also responsible for several non-catalytic actions including pro-aggregating activity of Aβ.[5] AChE interacts with Aβ and promotes amyloid fibril formation through a pool of amino acids located in proximity of the peripheral anionic site (PAS) of the enzyme.[6] The molecules that interact either exclusively with

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PAS or with both catalytic and peripheral binding sites of AChE prevent the pro-aggregating activity of AChE toward Aβ.[7] Furthermore, studies have also revealed that several AChE inhibitors not only facilitate cholinergic transmission, but also interfere with the synthesis, deposition and aggregation of toxic Aβ. [8] Thus, AChE inhibition has been documented as a critical target for the effective management of AD because of an increase in the synaptic availability of ACh in the brain regions and decrease in the deposition of Aβ. Accordingly, compounds showing dual binding with the AChE, that is, with catalytic and peripheral sites represent new therapeutic agents for effective management of AD.[8]

Coumarins are naturally occurring phytochemicals in many plant species with a wide range of biological activities such as anti-inflammatory,[9] anti-tumor,[10] hepatoprotective, anti-allergic, anti-HIV-1, antiviral, antifungal, antimicrobial, antiasthmatic,[11] anti-oxidant,[12] antinociceptive,[13] anti-diabetic and antidepressant effects.[14] The studies have also shown that naturally occurring as well as the chemically synthesised coumarin analogs exhibit potent AChE inhibitory activity.[15] Furthermore, functionalization of the aromatic center of coumarins has led to development of novel analogs that are capable of inhibiting Aβ aggregation.[16] The studies have also documented the anti-amnestic and the memory restorative functions of coumarin derivatives in different experimental models of amnesia.[17] The recognition of key structural features within coumarin template has helped in designing and synthesizing new analogs with improved AChE inhibitory activity and additional pharmacological activities including beta secretase (BACE) inhibition associated with decreased Aβ deposition[18] and monoamine oxidase (MAO) inhibition. Furthermore, coumarin derivatives also provide protection to neurons against Aβ-induced oxidative stress and free radicals.[19] A plant derived coumarin is reported to attenuate intracerebroventricular injection of Aβ-induced memory impairment in mice.[20] It has been well known that coumarins primarily interact with PAS of AChE[21] and accordingly, most of the scientists have put their efforts in synthesising dual inhibitors of AChE by incorporating a catalytic site interacting moiety with coumarin through an appropriate spacer. The present review mainly discusses the development in the area of design and synthesis of coumarin derivatives as AChE inhibitors followed by some key salient finding related to structural activity relationship (SAR) along with description of plant derived coumarins as AChE inhibitors.

2. Synthetic coumarins as AChE inhibitors

Preliminary studies by employing *Torpedo californica* AChE revealed that coumarin and its derivatives are capable of interacting and inhibiting AChE by binding to PAS in a reversible manner.[22] It led the scientists to make modifications in coumarin moiety to synthesize potent AChE inhibitors as potential agents for managing AD.[23] Ensaculin 1 (KA-672 HCl), a coumarin derivative, is composed of benzopyran with a piperazine substituted moiety (Fig. 1) and is under clinical investigation for potential AD management. The studies have shown that ensaculin exhibit multiple actions including AChE inhibition.[24] Based on the structural features of ensaculin, different scientists have attempted to incorporate structural moieties to coumarin template for developing AChE inhibitors.

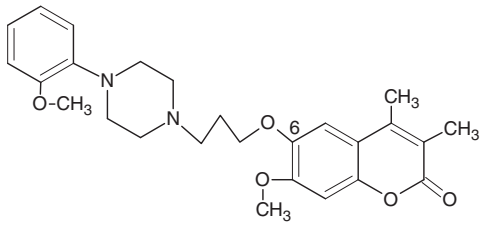

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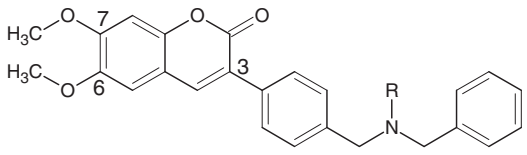
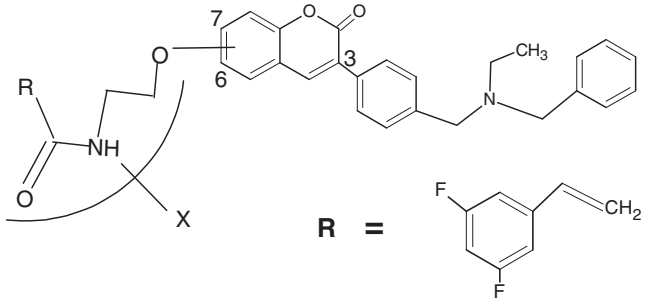
Figure 1. Structure of ensaculin (KA-672) with IC_{50} = 0.36 μM in which benzopyran ring along with piperazine is linked to the coumarin heterocycle at 6th position with four atom linker and is under clinically investigation for potential AD management.

Piazzi et al. synthesized novel series of coumarin derivatives as potent AChE inhibitors with additional pharmacological activities that are also considered very critical for effective treatment of AD.[25] The scientists specifically designed dual site (PAS as well as catalytic site) interacting derivatives by linking two different moieties through an appropriate spacer. Coumarin as a heterocyclic ring was selected as one of the moiety capable of interacting with PAS of AChE in an effective manner. The other moiety included benzylamino group, an important constituent of potent AChE inhibitors including donepezil and galanthamine, which interacts with the catalytic site of AChE as demonstrated by X-ray crystallographic studies.[26] A phenyl ring as a spacer was used to link two different moieties because of more chances of favorable interactions of phenyl ring with some of the numerous aromatic residues lining the wall of the AChE gorge. In initial studies, compound AP2238 (**2**) was shown to be most potent AChE inhibitor with IC_{50} value of 44.5 ± 6.5 nM with high selectivity for AChE with respect to butyrylcholinesterase (BuChE) with IC_{50} = 48900 ± 3700 nM (Fig. 2). The docking studies also revealed significant interactions of this compound with both peripheral and catalytic sites of AChE. The benzyl group was shown to interact with the indole ring of Trp86 by means of pi–pi stacking; the spacer phenyl ring established pi–pi interaction with the phenol ring of Tyr341 and an OH–pi interaction with the hydroxyl group of Tyr124; the protonated ammonium group interacted with the phenol ring of Tyr337 through pi–cation interactions; the carbonyl group of the coumarin moiety along with endocyclic oxygen established H-bond interactions with the backbone amide group of Phe295 and the aromatic moiety of the coumarin ring interacted with Trp286 by means of a pi–pi stacking (Fig. 3).



R = Me **2 (AP 2238)**

R = Et **3 (AP 2243)**



X at 6th position **4**

X at 7th position **5**

Figure 2. Structures of coumarin derivatives with benzylamino group linked to coumarin at 3rd position with phenyl ring as a spacer with IC_{50} values of **2** = 44.5 ± 6.5 nM; **3** = 18.3 ± 3.2 nM; **4** = 7.16 ± 0.87 μM; and **5** = 4.57 ± 0.59 μM.

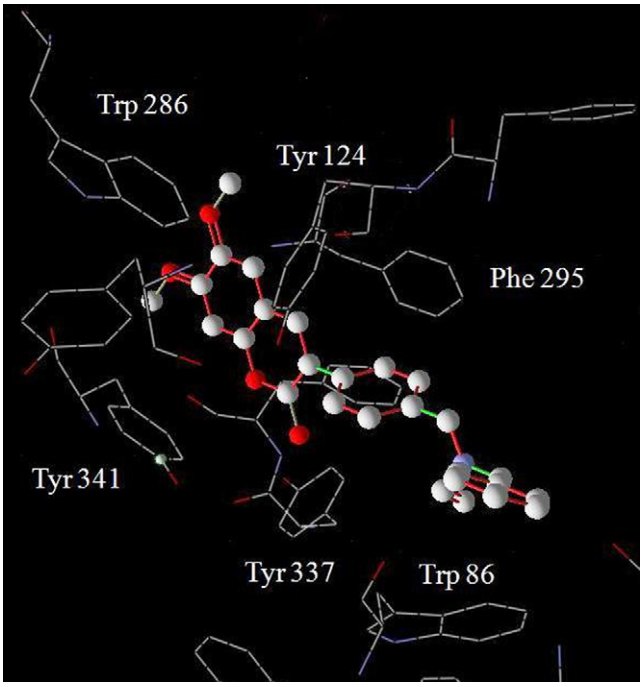


Figure 3. Representation of interactions between compound AP2238 and amino acids of peripheral as well as catalytic site of AChE using the crystallographic structure of enzyme (PDB code 1B41) in Molegro Virtual Docker.

Furthermore, the compound AP2238 was also shown to exhibit an Aβ anti- aggregating action which was accounted for its significant interactions with PAS of AChE. The Aβ deposition has been considered as one of the central events in the pathogenesis of AD and accordingly, Aβ anti-aggregating action is also considered crucial for effective management of AD.[27] The same group of scientists made modification in compound AP 2238 by replacing methyl substituent at basic nitrogen of benzyl amino group with ethyl group to yield the compound AP 2243 (**3**) with higher potency IC_{50} = 18.3 ± 3.2 nM which was attributed to its probable increase in lipophilicity (Fig. 2). Furthermore, the authors deduced from SAR of synthesized AChE inhibitors that –OCH_3 substitutions at 6th and 7th position of coumarin along with positioning of *N*-benzyl-*N*-methyl group in the *para*-position conferred the best AChE inhibitory activity. Any substitution at *orthro, meta* and *para*-positions in terminal phenyl ring of benzylamino group was associated with decrease in AChE activity indicating that unsubstituted *N*-benzyl group completely filled the bottom of AChE gorge and no increase in hindrance on that part of molecule was allowed.[28] These scientists made further modifications in compound AP 2243 by introducing halophenyl alkylamidic group in position 6th or 7th of coumarin moiety to obtain multi targeted coumarins as AChE and BACE inhibitors as potential anti-Alzheimer compounds (**4, 5**) (Fig. 2). BACE is a transmembrane aspartyl protease responsible for N terminal cleavage of amyloid precursor protein leading to production of Aβ peptide whose deposition is associated with development of AD.[29] Accordingly, BACE inhibition has also emerged as potential drug target for AD management.[30] The replacement of –OCH_3 group at 6th or 7th position with bulkier group led to decrease in AChE inhibitory activity. This decrease in activity was more significant with bulkier halophenyl substituents suggesting that molecule carrying bulky groups were not allowed to penetrate into AChE gorge to establish interactions. However, halophenyl alkyl amidic substituted coumarins were shown to be potent BACE inhibitors with IC_{50} = 99 nM for most potent derivative.[16]

Previously, Bruhlmann and co-workers[31] synthesized multi-targeted 7-benzyloxy coumarin derivatives as dual inhibitors of AChE and MAO based on the studies that inhibition of both the enzymes are critical for effective management of AD.[32] The studies have shown an increased activity of MAO in AD patients[33] which in-turn is correlated with deposition of Aβ plaque in different areas of the brain[34] that may result in increased production of free radicals to contribute the neuronal damage particularly in the hippocampus.[35] The replacement of 7-OH group of coumarin with benzyloxy moiety led to significant increase in AChE as well as MAO inhibitory activities. These 7-benzyloxycoumarin derivatives exhibited non-competitive inhibition of AChE suggesting that these compounds interacted with peripheral site of AChE. The substitution of coumarin with chromone nucleus led to decrease in AChE inhibitory activity suggesting the critical role of coumarin ring itself in AChE inhibition. 3-Methyl substituted coumarin derivatives exhibited higher AChE as well as MAO inhibitory activities. Moreover, substitution in *orthro, meta,* and *para*-positions of the phenyl ring of benzyloxy moiety by either electron donating groups such as –CH_3, –OH, –OCH_3 or electron with-drawing groups such as –F, –Cl exhibited decrease in AChE inhibition as well MAO-inhibition as compared to compound with unsubstituted phenyl ring of benzyloxy moiety of coumarin except 3′-chloro benzyloxy coumarin (**6**) which was reported as most potent AChE as well as MAO inhibitor with pK_i = 5.47 and pIC_{50} = 5.95. Furthermore, the length of the ether bridge of benzyloxy ring also played a crucial role in

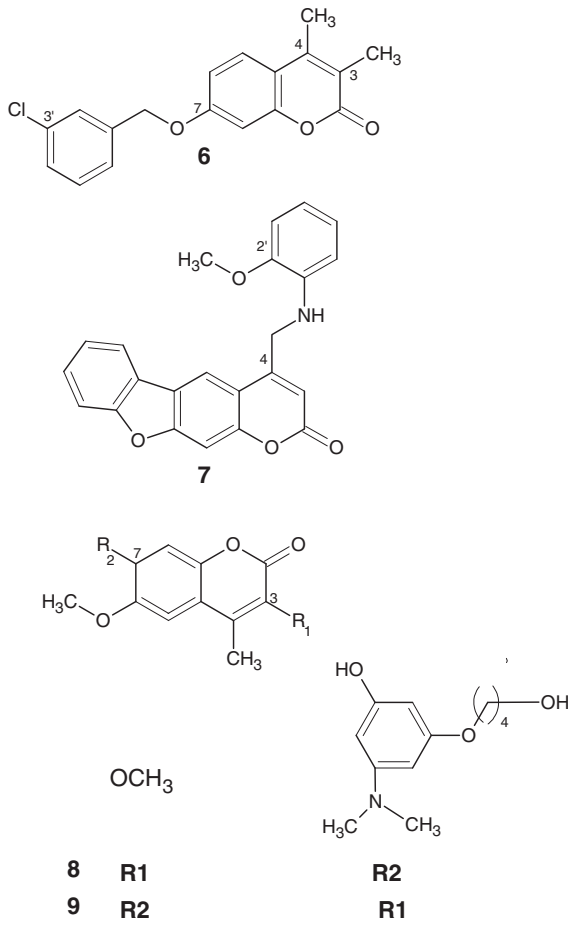


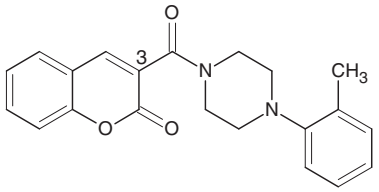
Figure 4. Structure of differently substituted coumarins with benzyloxy group linked to 7th position in compound **6** with pK_i = 5.47; anilino group with a methyl linker linked to 4th position of benzofuran fused coumarin in compound **7** with IC_{50} = 0.19 ± 0.01 μM; *N*,*N*-dimethylanilino linked to coumarin at 3rd position in compound **8** with IC_{50} = 275 nM or 7th position in compound **9** with IC_{50} = 0.236 nM.

influencing AChE inhibitory activity. An increase in the length of the ether bridge with additional methylene group was associated with significant drop of AChE inhibitory activity without change in MAO inhibitory activity.[31] (Fig. 4).

Shen et al.[36] synthesized coumarin derivatives by fusing benzofuran ring to coumarin heterocycle and substituting arylamino group (anilino) with one atom linker to 4th position of the coumarin. The synthesized compounds exhibited moderate AChE inhibitory activity with IC_{50} value range in μM comparable to tacrine. Two factors seemed to influence the AChE inhibitory activity, that is, the type of substitution on the anilino moiety and the type of linker linking the anilino moiety to coumarin. The compounds with strong electron donating groups such as $–OCH_3$, $–NH_2$ and –OH on the phenyl ring of anilino moiety exhibited more potent AChE inhibitory activity as compared to compounds with weak electron donating group such as $–CH_3$. Furthermore, it was reported that mono substituted compounds with one of the substituent at either 2′ or 4′ position of the phenyl ring of anilino moiety conferred more potent activity than di-substituted compounds at both 2′ and 4′positions. The presence of bulkier groups led to significant decrease in inhibitory activity indicating that both steric and electronic effects play a significant role in influencing the AChE activity. The nature of linker also influenced the activity as the compounds with methyl group as linker were more potent than compounds with methylene group or unsaturated group. Furthermore, the compounds with methyl linker selectivity inhibited AChE as compared to BuChE. It was deduced that compound (**7**) with mono-substituted anilino moiety with 2′-OCH_3 linked to coumarin fused benzofuran with methyl group was most potent with IC_{50} = 0.19 ± 0.01 μM. Furthermore, it was reported that fusion of aniline substituted furan ring to the coumarin led to significant loss of AChE inhibitory activity (Fig. 4).

Leonetti et al.[37] designed novel AChE inhibitors by linking edrophonium, that is, 3-hydroxy-*N*,*N*-dimethylanilino derivatives (interacting with catalytic site) to 7th position of coumarin (interacting primarily with PAS) with a suitable linker. These compounds exhibited potent AChE inhibition in the range of nM to subnanomolar range with high selectivity for AChE than BuChE. The compounds with quarternary ammonium salts were more potent as compared to corresponding 3° amines (IC_{50} = 275 versus 1.0 nM) for most of the compounds of the two series. The length of spacer linking the coumarin and edrophonium also influenced the AChE inhibitory activity. The compounds with spacer consisting tetramethylene units (**8**) were more potent than the corresponding derivatives with trimethylene units. The same group of scientists extended their previous work to establish SAR by taking 3° amines derivatives of coumarin and 3-hydroxy-*N*,*N*-dimethylanilino derivatives.[38] Though in the previous study, quarternary compounds were reported to be more potent, yet, the tertiary amine derivatives were further investigated due to their ability to cross blood brain barrier. In these compounds, an introduction of pentamethylene linker led to sharp decrease in activity. The replacement of central methylene unit with *N*-methyl group also led to decrease in activity. Furthermore, introduction of more rigid linker, that is, *meta*-xylyl and 1,4-butenyl also decreased activity. Therefore, it was concluded that tetramethylene linker is an ideal spacer in terms of length and conformational flexibility for connecting coumarin and 3-hydroxy-*N*,*N*-dimethylanilino group. Furthermore, the influence of the type and the number of substitutions on the coumarin moiety was also assessed. The compounds with substitutions at both 3rd and 4th positions were more potent than unsubstituted or mono-substituted ones. An increase in potency was related to an increase in lipophilicity and the derivatives with methoxy, chloro and trifluoromethyl substituents were significantly more potent. However, the substitution with high lipophilic groups such as 3,4-cyclohexyl and 3,4-benzo fused ring led to attenuation of activity probably due to steric hindrance exerted by bulkier groups. Furthermore, the position of linker with respect to coumarin ring also influenced the activity. The compounds with 3-hydroxy-*N*,*N*-dimethylanilino attached by a linker to 3rd position of coumarin were more potent compared to corresponding 6th and 7th substituted regioisomers that in turn were more potent than 4th, 5th and 8th positioned compounds. The most potent compound was 6,7-dimethoxy-3-substituted coumarin (**9**) linked with 3-hydroxy-*N*,*N*-dimethyl aniline by a tetramethylene linker with IC_{50} = 0.236 nM and AChE/BChE selectivity >300,000[38] (Fig. 4).

Zhou et al.[39] designed coumarin analogs on the basis of structural features of ensaculin which has a benzopyran with piperazine moiety linked to the coumarin heterocycle at 6th position with four atoms linker. Three series of coumarin based compounds were synthesized by linking phenylpiperazine moiety at different positions, that is, 3rd, 4th or 6th position of coumarin nucleus with compounds **10, 11** and **12**, respectively. The compounds with phenylpiperazine substitution at 3rd and 4th position of coumarin exhibited moderate AChE inhibitory activity with IC_{50} value range in μM. The most of 6-substituted coumarin analogs did not exhibit anti-AChE activity which is in contrast to ensaculin with potent AChE inhibitory activity with phenylpiperazine moiety at 6th position. The difference was attributed to the difference in the number of atoms in the linker chain between coumarin moiety and phenylpiperazine moiety. The longer linker chain (four atoms) in ensaculin enables the coumarin to enter into gorge which is not possible for 6-substituted phenylpiperazine coumarin analogs with one atom linker. Based on the results, it was deduced that coumarin heterocycle interacted with PAS, one of nitrogen atom in the piperazine ring acted as positive charge center to interact with catalytic center of AChE and the phenyl ring linked to piperazine acted as choline binding site (Fig. 5).



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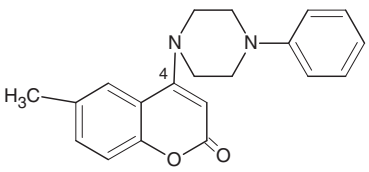

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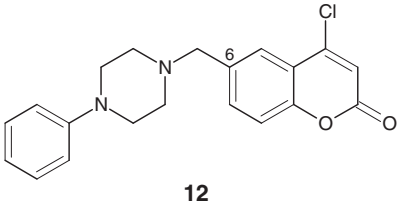

12

Figure 5. Structure of coumarin derivatives by linking phenylpiperazine moiety to coumarin nucleus at different positions, that is, 3rd (compound **10** with IC_{50} = 6.7 ± 0.02 μM), 4th (compound **11** with IC_{50} = 4.5 ± 0.03 μM) and 6th position (compound **12** with IC_{50} = 19 ± 0.1 μM).

3. Plant derived coumarin as AChE inhibitors

There have been several studies showing that plant derived coumarins exhibit potent AChE inhibitory activity.[40] The methanolic extract of *Angelica gigas* (Umbelliferae) has been shown to exhibit AChE inhibitory activity which was attributed to presence of coumarins. Decursinol (**13**) was reported to exhibit the most potent AChE inhibition with IC_{50} in the range of 0.28 μM (Fig. 6).[41] The presence of different 4-phenylcoumarins in hexane extract of the bark of *Mesua elegans* (Clusiaceae) including mesuagenin A, B, C and D was reported to confer AChE inhibitory activity with Mesuagenin B (**14**) being the most potent inhibitor with IC_{50} of 0.7 μM (Fig. 6).[42] The virtual screening followed by experimental in vitro studies documented the potent AChE inhibitory activity of *Scopolia carniolica* derived scopoletin (**15**) and its glucoside scopolin (**16**) (Fig. 7). Furthermore, the in vivo experiments also revealed an increase in the extracellular ACh following its administration.[43] The presence of furanocoumarins in the hexane and CH_2Cl_2 extracts of *Citrus hystrix* fruits including (*R*)-(+)-6′-hydroxy-7′-methoxybergamottin (**17**) and (*R*)-(+)-6′,7′-dihydroxybergamottin (**18**) showed IC_{50} values of 11.2 ± 0.1 and 15.4 ± 0.3 μM, respectively (Fig. 7).[44] Furthermore, studies have also shown that coumarins of *Psoraleae Fructus* including psoralen and isopsoralen alleviate scopolamine-induced amnesia in rats[17] suggesting the memory restorative effects of plant derived coumarins for management of AD.

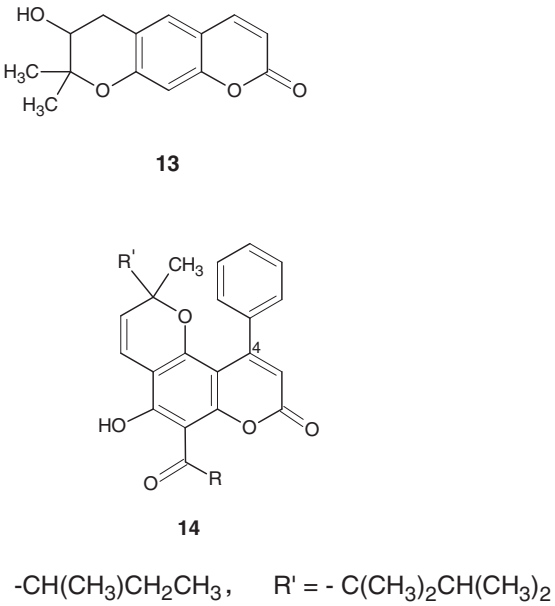

Figure 6. Decursinol (**13**) and mesuagenin (**14**) as plant derived coumarins possessing AChE inhibitory activities with IC_{50} values 0.28 and 0.7 μM, respectively.

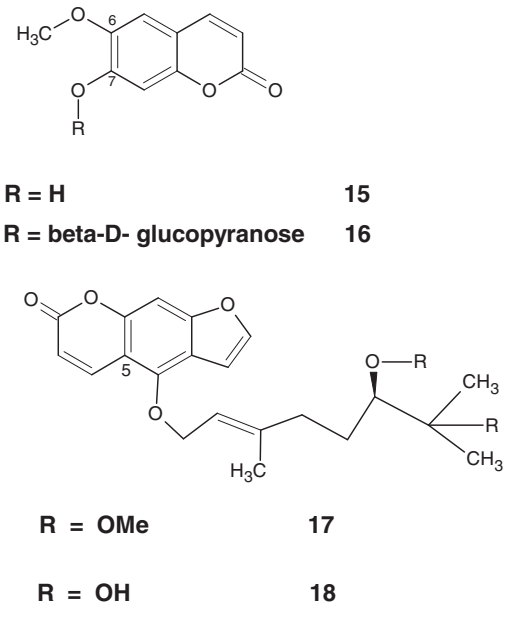

Figure 7. Scopoletin (**15**), scoploetin glycoside (**16**), (*R*)-(+)-6′-hydroxy-7′-methoxybergamottin (**17**) with IC_{50} = 11.2 ± 0.1 μM and (*R*)-(+)-6′,7′-dihydroxybergamottin (**18**) with IC_{50} = 15.4 ± 0.3 μM.

4. Salient findings related to SAR

a. The compounds with coumarin as heterocyclic moiety have appreciable AChE inhibitory activity. Coumarin ring seems to be essential for the optimal activity and its replacement with related structural moiety such as chromone is associated with loss of AChE inhibitory activity.
b. The different studies have shown that coumarin primarily interacts with PAS of AChE. Accordingly, different moieties capable of interacting with catalytic site of AChE including benzylamino, phenylpiperazines and anilino have been linked to coumarin heterocycle using appropriate spacer to obtain dual site interacting derivatives.
c. The dual site interacting coumarins have been demonstrated to exhibit other pharmacological activities beneficial for the management of AD including decrease in amyloid deposition due to Aβ anti-aggregating activities. Furthermore, some of these compounds also exhibit significant MAO and BACE inhibitory activities.
d. The length of spacer (linker) linking coumarin heterocycle and catalytic site interacting moiety is an important parameter influencing AChE inhibitory activity. Most of the studies have reported that compounds with tetramethylene or phenyl linker are more potent AChE inhibitors.
e. The 3rd or 4th position of coumarin moiety has been described as the most favorable for linking catalytic site interacting moiety for obtaining potent dual site interacting AChE inhibitors. Such substitution at 6th or 7th position generally does not increase the potency of compounds.
f. The substituents at coumarin moiety particularly at 6th and 7th position also influence the activity in a significant manner. The presence of electron-donating groups such as $–OCH_3$, –OH, and $–NH_2$ increase the activity and it has been generally attributed to increase in lipophilicity of compounds. In general, 6,7-dimethoxycoumarin derivatives are reported to exhibit superior AChE inhibition as compared to others.
g. The presence of bulkier substituents at 6th and 7th positions of the coumarin is associated with significant loss in AChE inhibitory activity indicating the critical role of electronic as well as steric effects in influencing the AChE inhibitory activity.

5. Conclusion

AChE inhibitors are the main stay drugs for the clinical management of AD. However, due to limitations in clinically available AChE inhibitors, there is a need for exploring new AChE inhibitors. The studies indicating that the coumarins are capable of inhibiting AChE by binding to its PAS have spurred the designing and synthesis of novel coumarin derivatives as potent AChE inhibitors. The studies demonstrating the potent AChE inhibitory and memory

restorative activities of plant derived coumarins have also projected coumarins as potential lead molecules for the synthesis of effective therapeutic agents for AD management. Most of the scientists have incorporated a catalytic site interacting moiety to coumarin template through an appropriate spacer to yield potent and dual site interacting coumarin analogs as AChE inhibitors. Furthermore, these coumarin analogs have also exhibited additional pharmacological actions including MAO and BACE inhibition with a consequence of decrease in Aβ deposition that are also very useful for effective management of AD.

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