

Natural products as a source of Alzheimer's drug leads

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This review focuses on recent developments in the use of natural products as therapeutics for Alzheimer's disease. The compounds span a diverse array of structural classes and are organized according to their mechanism of action, with the focus primarily on the major hypotheses. Overall, the review discusses more than 180 compounds and summarizes 400 references.

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1 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects approximately 36 million people worldwide as of 2010.¹ The disease was originally described in 1906 by Alois Alzheimer based on the observation of amyloid plaques, neurofibrillary tangles and vascular anomalies during the autopsy of Auguste Deter, a patient who died with severe cognitive defects.² The pathogenesis of the disease is complex, with both genetic and environmental factors³ likely contributing to varying degrees (reviewed by Jakob-Roetne⁴) with death occurring approximately 9 years after diagnosis. Genetic factors that correlate with early-onset AD include mutations in amyloid precursor protein (APP)^{5,6} and presenilin 1 & 2 (PS1 & PS2)⁷ along with APP gene duplication,⁸ but the causative factors of late-onset or sporadic AD are less well understood. However, a strong correlation does exist with mutations in the $\epsilon 4$ allele of apolipoprotein (APOE),⁹ which can induce endocytosis of APP.¹⁰

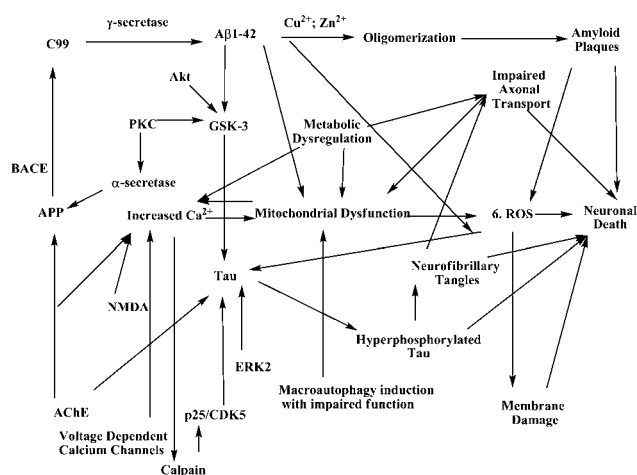


Fig. 1 Summary of relevant Alzheimer's disease pathways.

Ultimately, the biochemical rationale for targeting a particular pathway stems from pathological, genetic, or epidemiological observations. The observation of amyloid plaques gave rise to the amyloid cascade hypothesis^{11,12} and compounds designed to reduce the rate of APP processing or abundance of plaques. Ubiquitous hyperphosphorylated neurofibrillary tangles in AD patients resulted in the tau hypothesis^{13,14} and the development of kinase inhibitors to modulate this aberrant phosphorylation. Microglial activation gave rise to hypotheses based on prolonged inflammation,^{15,16} while abnormal levels of calcium,¹⁷ glucose,¹⁸ metals,^{19,20} and neurotransmitters, particularly acetylcholine (ACh), in AD patients have sparked treatments designed to restore normal concentrations. Fig. 1 summarizes several pathways implicated in AD pathology for which natural product leads have been reported. A full discussion is unfortunately beyond the scope of this review, and interested readers are encouraged to consult the relevant references in this paragraph for detailed discourses.



Philip Williams

Philip Williams received his undergraduate education at the University of Calgary, Canada, and his Ph.D. from the University of Hawaii at Manoa in 2003 under the guidance of the late Professor Richard Moore. After postdoctoral work at the Scripps Institution of Oceanography in San Diego, California, from 2003–2006 with William Fencial, he returned to the University of Hawaii to join the faculty as an assistant professor. His research interests since then have focused on natural products

chemistry, isolation and structure determination, and natural products methodologies.



Analia Sorribas

Analia Sorribas received her B.A. in chemistry from Williams College (Massachusetts, US) in 2006, where she participated in multiple research projects including tracing allelopathic agents in ferns and measuring PCB levels in river sediments and fishes. In 2004, she was awarded a Howard Hughes International Research Scholar Internship with Dr Ferenc Nagy at the Hungarian Academy of Sciences. Analia later attended graduate school at the University of Hawaii at Manoa to pursue

her interest in marine natural products. Her research on Alzheimer's drug leads from marine organisms, under the guidance of Dr Philip Williams, recently resulted in her M.S. in chemistry.

Currently, there are five prescribed treatments in the United States and Europe for AD. These are symptomatic treatments that do not actually slow or reverse the progression of the disease. Four of these drugs are acetylcholinesterase (AChE) inhibitors, while one modulates *N*-methyl-D-aspartic acid (NMDA) receptors. Given the prevalence of AD and the lack of effective long-term therapies, there is a pressing need to discover viable leads that can be developed into clinically approved drugs with disease-modifying effects. There has been a heavy focus on developing drugs against amyloid plaques, although ultimately a clinical validation of either plaques or tangles as a target capable of exerting a disease-modifying effect is still lacking. The challenges here are substantial, in part because of the pharmacokinetic issues associated with central nervous system (CNS) drug therapy (blood–brain barrier (BBB) permeability and P-glycoprotein efflux), in part because of the lengthy clinical trials that are required to observe statistically significant cognitive differences in patients *vs.* controls for neurological diseases, and in part because of the uncertainty regarding the role and timing of the two key pathological events, the formation of amyloid plaques and tau tangles. This latter fundamental issue is complicated by the fact that disease initiation and the manifestation of clinical symptoms are usually separated by decades; early and accurate validated methods of clinical diagnosis for patients prior to the onset of mild cognitive impairment is still a major unmet need facing the field.

1.1 Scope of the review

This review summarizes the natural products that have been reported as leads in the area of AD. The focus of this review is primarily molecules that were either recently described or in which significant advances have been reported in the last five years. Both terrestrial and marine sources have been considered. In the case of the latter, this review represents one of the first attempts to summarize the relevant literature in a number of years, while for terrestrial sources this manuscript builds on the summaries by Viegas²¹ and Houghton *et al.*²² Readers are



Melanie-Jayne Howes

Melanie-Jayne Howes obtained her B.Pharm. degree at King's College London (KCL) in 1996, being the recipient of six prizes. After registering as a pharmacist with the Royal Pharmaceutical Society of Great Britain in 1997, she was awarded a scholarship from the latter for a PhD at KCL on the chemistry and biological activity of plants with uses relevant to Alzheimer's disease, under the supervision of Professor P. Houghton. She received her PhD in 2001 and was awarded the GlaxoSmithKline Prize for Best PhD Thesis. Her post-doctoral work at the Royal Botanic Gardens, Kew, has focused on authentication and quality control of plants, but she has continued her interest in natural products relevant to neurodegenerative disorders.

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directed towards the recent article by Cichewicz and workers (see DOI: 10.1039/c0np00017e) for information on therapeutic leads for other neurodegenerative diseases.

In many instances, there is a close parallel between cancer targets, which have been investigated heavily by the natural product community,²³ and neurodegenerative targets, particularly in the area of kinases.²⁴ In those cases, we have chosen to focus on molecules in which a direct application to AD has been described. The underlying etiology of AD is complex, and while significant advances have been made, numerous competing hypotheses still exist.^{11,13,25–30} Every effort has been made to include compounds relevant to the major targets, but those in which only a few natural product leads have been reported or without significant new developments in the last few years have been omitted.

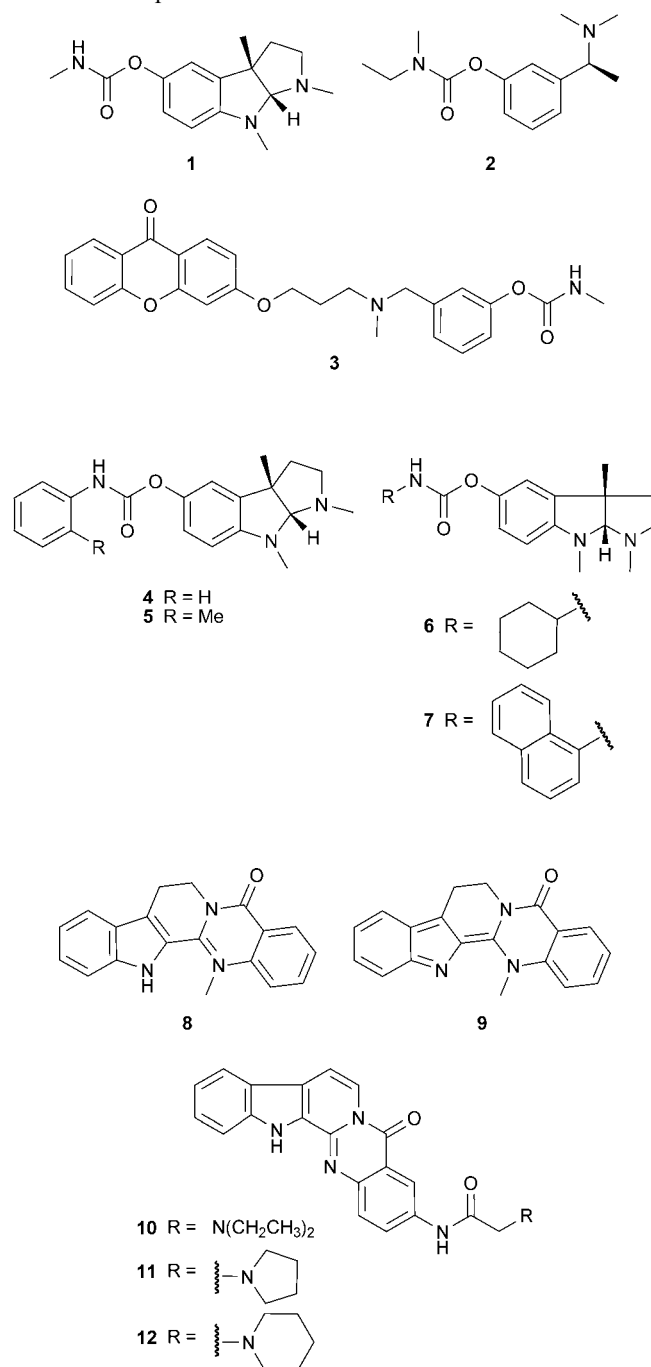
2 Acetylcholinesterase (AChE) inhibitors (cholinergic hypothesis)

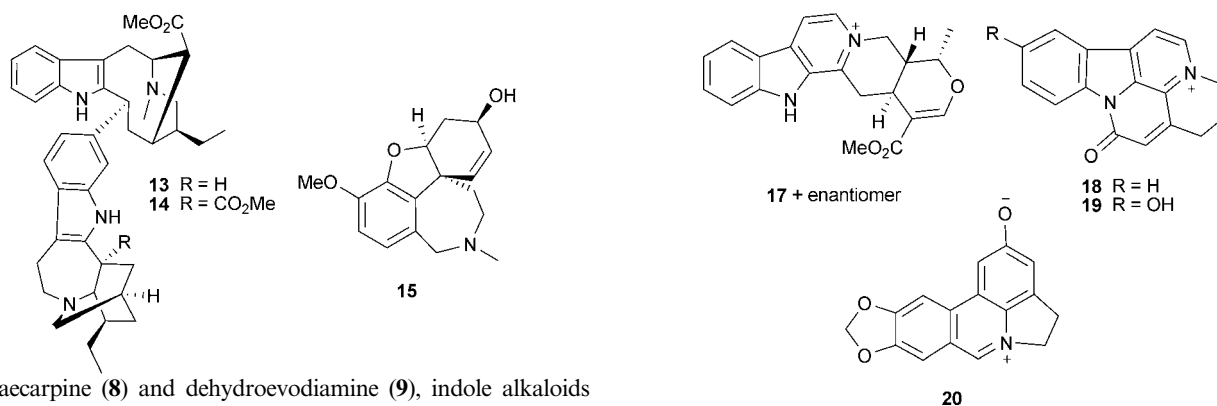
Acetylcholinesterase (AChE), mainly present in the central nervous system (CNS), catalyzes the hydrolysis of the neurotransmitter acetylcholine (ACh) to choline. This process is necessary to return an activated cholinergic neuron to a resting state. It was deficits in this neurotransmitter, which were noted in AD patients, that led to the cholinergic hypothesis.³¹ Two of the drugs currently licensed to alleviate cognitive symptoms in dementia are AChE inhibitors derived from natural products (galantamine and rivastigmine). Consequently, extensive research has been directed towards the identification of other AChE inhibitors, with the majority of these arising from the plant kingdom. While structurally diverse, these compounds are primarily alkaloids. There have also been numerous attempts to develop semi-synthetic or synthetic derivatives of these naturally derived AChE inhibitors, with the aim of improving inhibitory potency and selectivity, or for some structures, engineering dual modes of action relevant to AD therapy.

2.1 Alkaloids as AChE inhibitors

Physostigmine (eserine) (**1**) is an alkaloid with a pyrroloindole skeleton from *Physostigma venenosum* Balf. (Leguminosae) seeds that is a potent, short-acting and reversible inhibitor of AChE.^{32,33} Reviewed in Houghton *et al.*,²² physostigmine has been shown to improve cognitive functions *in vivo* and in both normal and AD patients.³⁴ To improve the pharmacokinetic profile and efficacy of **1**, numerous analogs have been investigated, with the most therapeutically successful being the carbamate-type reversible AChE inhibitor rivastigmine (**2**), now licensed for the symptomatic treatment of mild to moderate dementia in AD or Parkinson's disease (PD). Not surprisingly, there have been numerous attempts to synthesise AChE inhibitors using **1** as a template, with the aim of developing drugs with therapeutic advantages over **2**. Some of these potent and selective AChE inhibitors have been pharmacomodulated for dual modes of action, to target both cognitive and depressive symptoms in AD.^{35,36} Some analogs of the carbamate derivative xanthostigmine (**3**) inhibit AChE-induced β -amyloid aggregation³⁷ and a phenylcarbamate derivative of **1**, phenserine (**4**), inhibits AChE and APP,³⁸

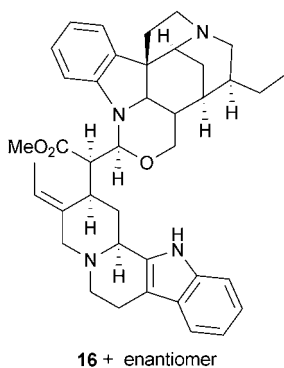
suggesting their potential application in modulating AD symptoms and pathology. (–)-Phenserine enhances cognition *in vivo*³⁹ and in AD patients (20 patients; 30 mg/day),⁴⁰ but Phase III trials with AD patients did not show different effects from the placebo; the (+)-enantiomer (Posiphen™) has been investigated in Phase I trials but additional clinical studies are not planned.³⁸ Methyl substitution at the C-2' position of **4** produces tolserine (**5**), which has improved selectivity for AChE compared to butyrylcholinesterase (BChE).³⁹ More recently, other analogs of **1** with a cyclic alkyl carbamate of eseroline (**6** and **7**) showed more potent AChE inhibition and selectivity than **4**.⁴¹ In general, although numerous derivatives of **1** have been developed, few have reached advanced stages of clinical development for AD.





Rutaecarpine (**8**) and dehydroevodiamine (**9**), indole alkaloids from *Evodia rutaecarpa* (Juss.) Benth. (Rutaceae), have been used as templates to synthesise new AChE inhibitors, since the plant extract and **9** inhibit AChE *in vitro* and reverse scopolamine-induced memory impairment *in vivo*.⁴² Some of these synthetic analogs have included structural features of the AChE inhibitor tacrine, but disappointingly showed greater selectivity for BChE,⁴³ whilst other 3-aminoalkanamido-substituted 7,8-dehydrorutaecarpine derivatives (**10**, **11** and **12**) were more potent and showed selectivity for AChE.⁴⁴ Of four bisindole alkaloids isolated from the root of *Tabernaemontana divaricata* (L.) R.Br. ex Roem. & Schult. (Apocynaceae), only 19,20-dihydrotabernamine (**13**) and 19,20-dihydroervahanine A (**14**) inhibited AChE more potently than galantamine (**15**) *in vitro*;⁴⁵ effects *in vivo* have not been studied, although a root ethanol extract inhibits cortical AChE activity *in vivo*.⁴⁶

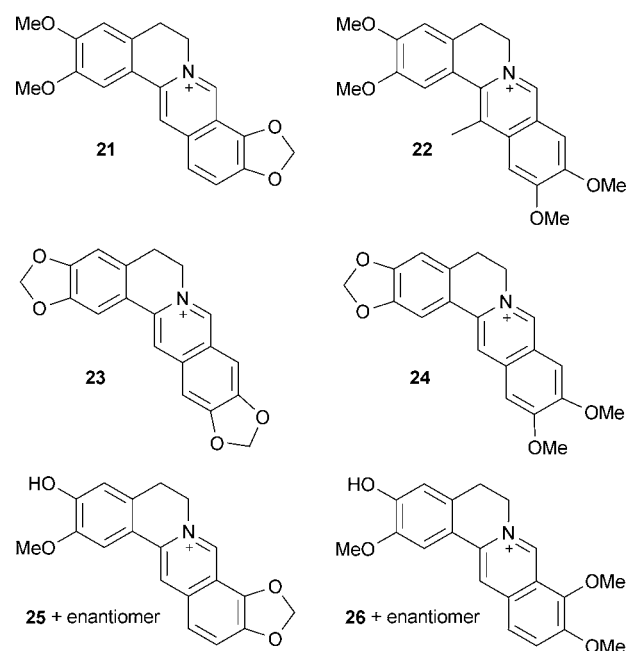
Another AChE-inhibitory indole alkaloid, geissospermine (**16**), was considered to largely explain the cognitive effects of an alkaloid fraction from *Geissospermum vellosii* Allemão (Apocynaceae) stem bark, which reduced scopolamine-induced amnesia *in vivo*.⁴⁷ Although *Catharanthus roseus* (L.) G. Don (Apocynaceae) is a source of the anti-cancer drugs vincristine and vinblastine, an AChE inhibitory alkaloid, serpentine (**17**), from the roots was 10-fold more potent than **15**,⁴⁸ but has not been studied further, perhaps because cytotoxicity may limit its clinical development. Other relevant indole alkaloid derivatives (**18** and **19**) are from the fungus *Cortinarius infractus* Berk. (Cortinariaceae), which could be promising candidates for development since they inhibit AChE with greater selectivity than galantamine (**15**) (due to a lack of π - π interactions in BChE), they comply with Lipinski rules and are predicted to cross the blood-brain barrier (BBB).⁴⁹



Galantamine (**15**) is produced by *Galanthus woronowii* Losinsk., some species of *Narcissus* and *Leucojum aestivum*

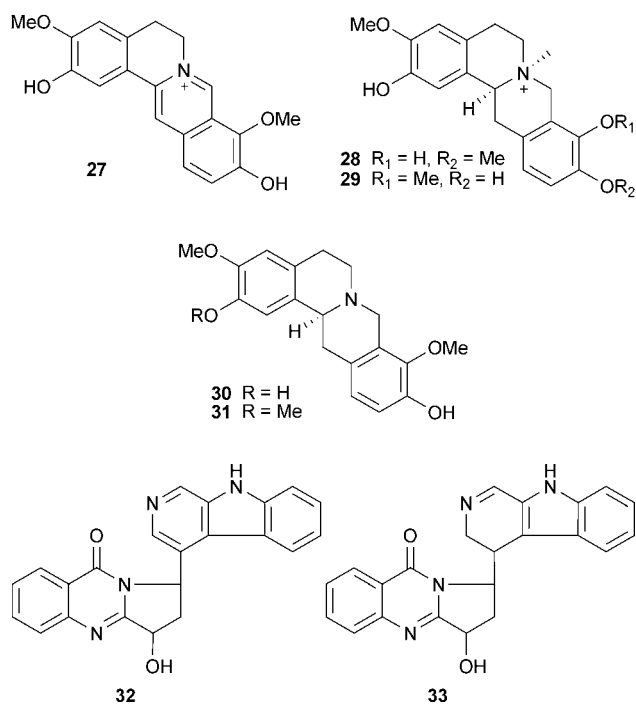
L. (Amaryllidaceae). It is a drug licensed to treat symptoms of mild to moderate dementia in AD, and thus has been extensively studied for its AChE inhibitory activity and is reviewed elsewhere.^{22,34} Numerous synthetic derivatives of **15** have been investigated, with some (heterodimeric alkenyl linked bis-galantamine derivatives) inhibiting AChE more potently than **15**,³⁹ although their potential for clinical use is undetermined. Of particular therapeutic relevance is Memogain® (Gln-1062), a prodrug of **15**, which has improved cognitive effects in an animal model of amnesia and bioavailability (15-fold) in the brain compared to **15**, with fewer adverse gastrointestinal effects.⁵⁰ Numerous other Amaryllidaceae alkaloids inhibit AChE and are reviewed by Houghton *et al.*²² and Jin.⁵¹ Notably, ungeremine (**20**), isolated from *Nerine bowdenii* W. Watson and from species of *Galanthus* and *Narcissus* showed stronger AChE inhibition than **15**.⁵²⁻⁵⁴

Isoquinoline alkaloids from *Colchicum speciosum* Steven (Colchicaceae) corms are reversible inhibitors of both AChE and BChE *in vitro*,⁵⁵ and several benzylisoquinoline alkaloids from *Coptis* (Ranunculaceae) and *Corydalis* (Papaveraceae) species inhibit AChE.^{22,56,57} Some of the most potent inhibitors from the latter include epiberberine (**21**), 13-pseudodehydrocorydaline (**22**), pseudocoptisine (**23**) and pseudoberberine (**24**),⁵⁸ with **23**

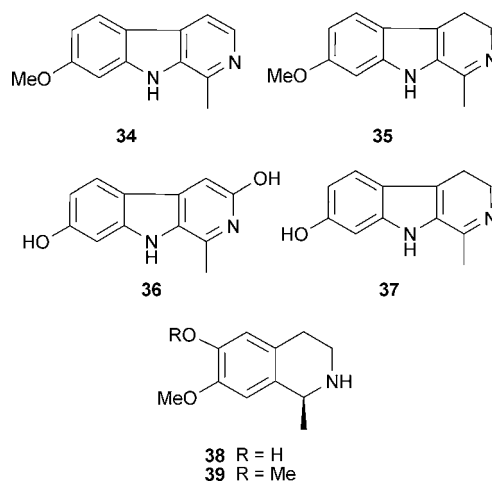


and **24** alleviating scopolamine-induced memory impairment *in vivo*.^{59,58} The berberine structure has been used as a template to synthesise more potent AChE inhibitors; one derivative (berberine linked with phenol by 4-carbon spacers) was more active than berberine (IC₅₀ 0.1, 0.4 μM, respectively) and was suggested to bind to the peripheral anionic site of AChE.⁶⁰ Some anti-AChE alkaloids from *Coptis chinensis* Franch. rhizomes display non-competitive β-secretase (BACE1) inhibitory activities (**21** and groenlandicine (**25**)) and are antioxidant (**25** and jateorrhizine (**26**));⁶¹ thus, **25** in particular shows multiple activities relevant to AD therapy.

Structure–activity studies with protoberberine alkaloids from *Stephania venosa* Spreng. (Menispermaceae) show the important inhibitory features to be a positive charge at the nitrogen of the tetrahydroisoquinoline portion, steric substitution at the nitrogen, and planarity of the molecule or substitutions at C-2, -3, -9, and -10; thus stepharanine (**27**), cyclanoline (**28**) and *N*-methyl stepholidine (**29**) were more potent inhibitors than stepholidine (**30**) and corydalmine (**31**).⁴⁵ Several quinoline and β-carboline alkaloids, including two new alkaloids (nigellastrines I (**32**) and II (**33**)) from the seeds of *Peganum nigellastrum* Bunge (Zygophyllaceae) showed AChE inhibitory activity in a TLC bioautographic assay, with results suggesting harmine (**34**), harmaline (**35**), harmol (**36**) and harman (**37**) show similar activity to gal-

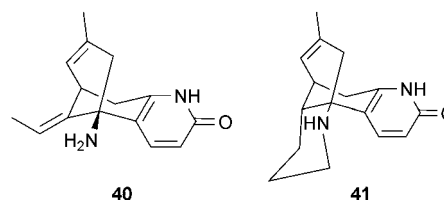


antamine (**15**),⁶² although more quantitative data is needed. Extracts from aerial parts of *Salsola oppositifolia* Pall., *S. soda* L. and *S. tragus* L. (Chenopodiaceae), inhibited cholinesterase (ChE) *in vitro*, the latter showing the highest AChE inhibitory activity, which could be attributed to the tetrahydroisoquinoline alkaloid content, particularly salsoline (**38**) and salsolidine (**39**).⁶³ Although the potency and selectivity of several alkaloids from *Stephania venosa*, *P. nigellastrum* and *Salsola* species have shown promise in these preliminary



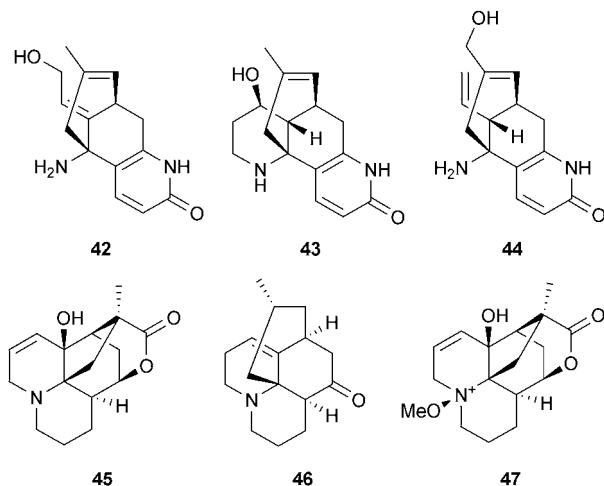
studies, their pharmacological potential requires further evaluation.

Huperzine A (**40**) from *Huperzia serrata* (Thunb.) Trevis. (Lycopodiaceae) is a widely-studied reversible AChE inhibitor which improves cognitive functions in animal studies and in clinical trials with elderly, AD and vascular dementia patients, with limited adverse effects.³⁴ Huperzine A (**40**), which is also neurotrophic⁶⁴ and neuroprotective,⁶⁵ has been used to treat AD symptoms in China and is marketed as powdered *H. serrata* in the US for memory impairment.⁶⁶ A recent meta-analysis of the efficacy and safety of **40** showed it to be well-tolerated and to significantly improve cognitive performance and activities of daily living in patients with AD.⁶⁷ Huperzine B (**41**), also from *H. serrata*, is a less potent AChE inhibitor than **40**,⁶⁸ which may explain why it has not been investigated as extensively for potential clinical use. Numerous structural analogs and hybrids based on **40** and **41** have been investigated for their AChE inhibitory effects and are reviewed by Howes & Houghton.³⁴

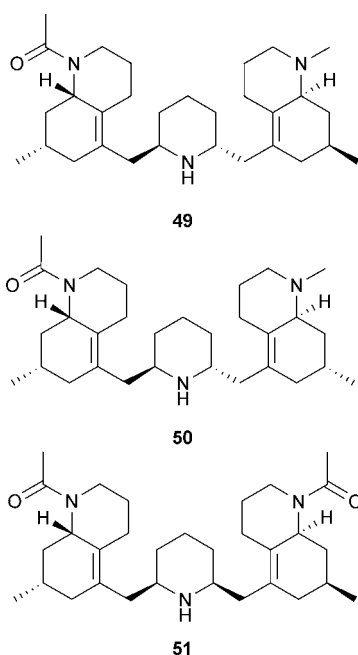
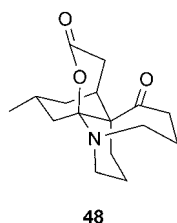


AChE inhibitors structurally related to the huperzines are carinatamins A (**42**) and B (**43**) (IC₅₀ 4.6 and 7.0 μM, respectively), isolated from *Lycopodium carinatum* Desv. ex. Poir. (Lycopodiaceae), but these were not as potent as **40** (IC₅₀ 0.8 μM).⁶⁹ Lycopin C (**44**) (which lacks the carboxylic acid at C-15 and the *N*-methyl groups in the inactive lycopin A and B) from *L. casuarinoides* Spring⁷⁰ and annotine (**45**) from *L. annotinum* L.⁷¹ also inhibit AChE but, unlike the huperzines, none of these alkaloids appear to have been pursued for therapeutic relevance. Of ten alkaloids isolated from *L. annotinum* ssp. *alpestre* (Hartm.) Á. Löve & D. Löve, the most potent AChE inhibitors were anhydrolycodoline (**46**) and annotine *N*-oxide (**47**) but these were still considerably less potent (IC₅₀ 191, 404 μM, respectively) than physostigmine (**1**) (IC₅₀ 0.8 μM).⁷² The low activity was explained by structure–activity studies. Although these alkaloids appeared

to fit into the same AChE binding site as **40** and hydrogen-bond acceptors or donors are present, they formed weak interactions with the amino acid residues in this pocket. As **46** was suggested to be more tightly enclosed in the enzyme's binding site compared to the other alkaloids tested, it is being considered as a template structure to synthesise analogs of increased potency.⁷²

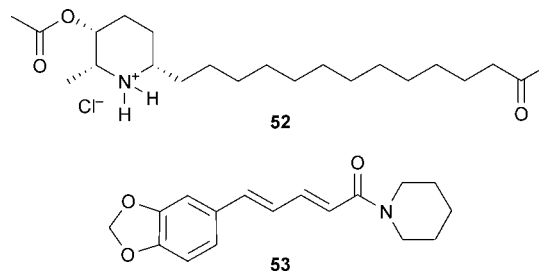


A more relevant therapeutic candidate has been recently discovered from *L. japonicum* Thunb.; lycojapodine A (**48**) is a novel C₁₆N-type alkaloid with a 6/6/6/7 tetracyclic ring system that shows

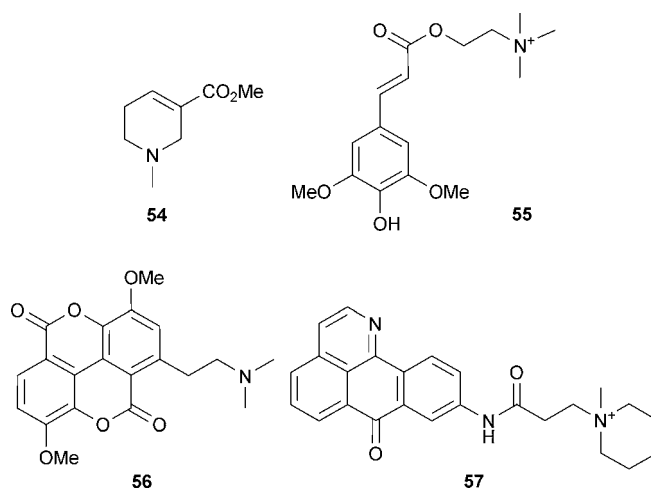


comparable AChE inhibitory activity to **40**.⁷³ Although a number of the AChE inhibitory alkaloids reported from *Lycopodium* species are structurally related to the quinolizidines,^{69–71} cryptadines A (**49**) and B (**50**) from *L. cryptomerianum* Maxim. consist of a piperidine ring and two octahydroquinoline rings. These AChE inhibitors⁷⁴ closely resemble lycoperine A (**51**), an AChE inhibitor from *L. hamiltonii* Spreng.⁷⁵

Piperidine alkaloids and their synthetic derivatives are less well-documented as AChE inhibitors, compared to other alkaloids such as the indole and isoquinoline structural classes, and thus are generally not as advanced in their development for clinical use. Piperidine alkaloids showing some therapeutic relevance for cognitive disorders are derived from *Cassia spectabilis* DC. (Leguminosae) and include some semi-synthetic derivatives patented as AChE inhibitors with potential to treat pathologies affecting the cholinergic system.³⁶ The rationale for investigating (–)-spectaline and the (–)-3-*O*-acetyl derivative from *C. spectabilis* flowers is that they contain structural features similar to that of ACh; the synthetic derivative (2*R*,3*R*,6*S*)-2-methyl-6-(13-oxotetradecyl)-piperidin-3-yl acetate hydrochloride (LASSBio-767) (**52**) inhibits rat brain AChE more selectively than BChE and reverses scopolamine-induced amnesia *in vivo*.^{76,77} Piperine (**53**), from *Piper* species (Piperaceae) improves memory impairment and neurodegeneration *in vivo*, which are effects associated with increased neuron density and AChE inhibition in the hippocampus.⁷⁸ It also inhibits monoamine oxidases,⁷⁹ suggesting it may also alleviate depressive symptoms in dementia.



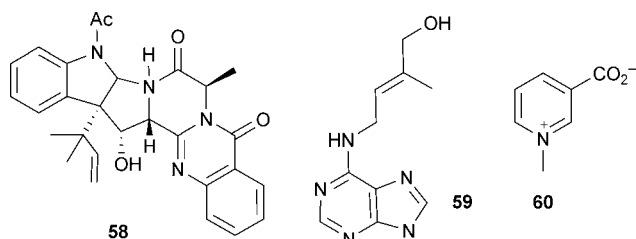
A number of steroidal alkaloids from *Sarcococca* and *Buxus* species (Buxaceae) have shown anti-ChE activities and these, including their structure–activity relationships, have been recently reviewed.^{80,22,34} Several steroidal alkaloids from *Fritillaria* species (Liliaceae) inhibit ChE^{81,82} but pharmacological and



clinical efficacy in relation to cognition has not been determined. Arecoline (**54**), a reduced pyridine alkaloid derivative from *Areca catechu* L. (Arecaceae) (commonly known as betel nut), has been shown to inhibit AChE *in vitro* and in the nervous tissue of the mollusc *Lymnaea acuminata*, but in a separate study, arecoline did not inhibit AChE, even though an extract and fractions from *A. catechu* did produce inhibition.⁸³ Arecoline (**54**) improves scopolamine-induced cognitive impairment and passive avoidance performance *in vivo*^{84,85} and improves cognitive function and recognition skills in AD patients;^{86,87} these effects suggest a cholinergic action that may be due to AChE inhibition (although evidence for this is inconclusive) or by binding to muscarinic receptors.^{88,89}

Other alkaloids that are of therapeutic interest include sinapine (**55**) (an ester of sinapic acid and choline, that occurs in several plants including *Raphanus sativus* L. (Brassicaceae)), which potently inhibits AChE *in vitro* and in brain tissue,³⁶ and tapsine (**56**) (a protoalkaloid from *Magnolia × soulangiana* Soul.-Bod. (Magnoliaceae) leaves) which produces long-acting and concentration-dependent inhibition of AChE (IC₅₀ 0.3 μM) and was more potent than galantamine (**15**) (IC₅₀ 3.2 μM).⁹⁰ Tapsine (**56**) is suggested to bind closely to the catalytic triad in AChE. This is facilitated by π-stacked interactions between the planar aromatic ligand and Trp84 and Phe330 of AChE, anchoring of the cationic side chain with His444 reaching into the catalytic site, and H-bonding with active site water molecules and Ser122.⁹⁰ Semi-synthetic derivatives (including **57**) of some oxoisoporphine alkaloids, which occur in *Menispermum dauricum* DC. (Menispermaceae), are being investigated for their potential to treat AD, since the 1-azabenzanthrone moiety in their chemical structure binds to the peripheral anionic site of AChE, so inhibiting activity.³⁶

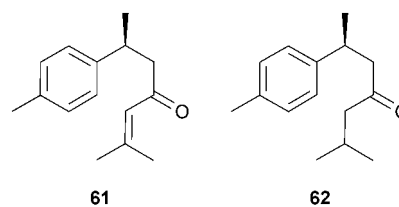
Several non-alkaloidal but potent AChE inhibitors have been isolated from fungal sources.²² Recently, a novel alkaloid, 16α-hydroxy-5*N*-acetylardeemin (**58**) from the fungus *Aspergillus terreus*, has shown AChE inhibitory activity almost as potent as tacrine.⁹¹ Zeatin (**59**) is a cytokinin phytohormone.⁹² This isopentenyl purine derivative is of therapeutic interest as it inhibits AChE,⁹³ protects against β-amyloid-induced neurotoxicity *in vitro* and scopolamine-induced cognitive impairments *in vivo*.⁹⁴ An alkaloid fraction from *Trigonella foenum-graecum* L. (Leguminosae) and the component alkaloid trigonelline (**60**) also inhibit AChE;⁹⁵ interestingly, intake of coffee (*Coffea arabica* L., Rubiaceae), which also contains **60**, has been associated with a reduced risk of dementia.⁹⁶



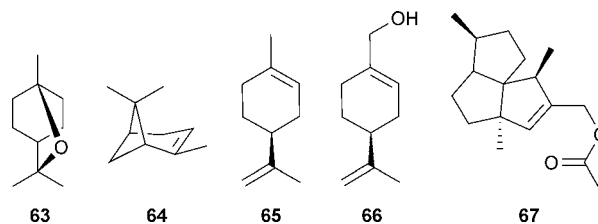
2.2 Terpenoids as AChE inhibitors

Numerous essential oils (or oil absolutes) have shown inhibitory activity against ChE, including those from *Narcissus poeticus* L.

(Amaryllidaceae),⁹⁷ *Melaleuca* species (Myrtaceae),⁹⁸ *Acorus calamus* L. (Acoraceae),⁹⁹ *Eucalyptus camaldulensis* Dehnh.,¹⁰⁰ *Marlierea racemosa* Kiaersk. (Myrtaceae),¹⁰¹ *Cymbopogon schoenanthus* Spreng. (Poaceae)¹⁰² and several oils from the Lamiaceae.^{39,103–106} Many constituents of these oils have been identified as AChE inhibitors including monoterpenoids (e.g. geranial, neral and linalool)^{103,107,108} and sesquiterpenoids (e.g. caryophyllene oxide, (+)-(*S*)-*ar*-tumerone (**61**))^{109,110} and some phenylpropanoids (e.g. eugenol, α- and β-asarone).^{103,99,111,112} AChE structure–activity relationships for monoterpenoids have been discussed previously.^{22,113} More recently, structure–activity studies with bisabolane-type sesquiterpenoids, derived from *Peltophorum dasyrachis* Kurz ex Baker (Leguminosae), inhibited AChE in the following order of potency: ketones > alcohols > hydrocarbons; oxidation at C-9 and a single-bond between C-10–C-11 were also concluded to be important in the bisabolane-type inhibitors.¹¹⁰ Although this study revealed (+)-(*S*)-*ar*-tumerone (**61**) and (+)-(*S*)-dihydro-*ar*-tumerone (**62**) in *P. dasyrachis* oil were potent inhibitors (IC₅₀ 191, 82 μM, respectively), they were not as active as galantamine (**15**) (IC₅₀ 3 μM).¹¹⁰

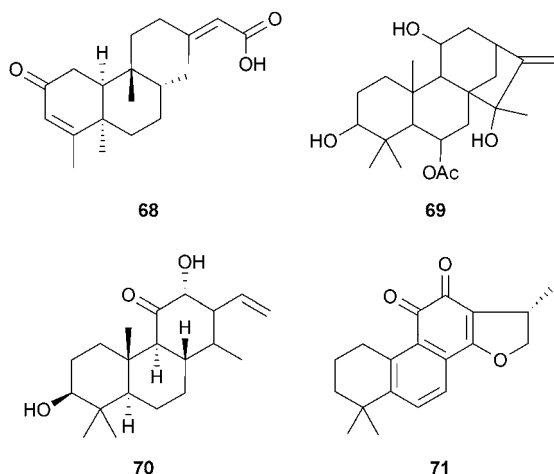


Although documented as AChE inhibitors, relatively few of these oils and their constituents have been investigated for their potential effects in cognitive disorders. Those studied more extensively include the steam-distilled oils from *Salvia officinalis* L. and *S. lavandulifolia* Vahl. (Lamiaceae), which inhibited AChE *in vitro* and positively influenced cholinergic function and cognition *in vivo*.^{114,115} 1,8-Cineole (**63**) and α-pinene (**64**) are considered to be the most active AChE inhibitory components of *S. lavandulifolia* oil (the latter is also an anti-AChE component of *S. potentillifolia* Boiss. & Heldr. ex Benth. oil),¹¹⁶ although other oil constituents may inhibit AChE, perhaps synergistically.^{108,109} An extract from the aerial parts of another member of the Lamiaceae, *Teucrium polium* L., is anti-amnesic *in vivo* and inhibits AChE *in vitro*,¹¹⁷ although the compounds responsible have not been determined. Limonene (**65**) and perillyl alcohol (**66**), components of *Citrus* (Rutaceae) essential oils, improve scopolamine-induced memory impairment, which is suggested to be due to AChE inhibition (observed *in vitro*).¹¹⁸ Sesquiterpenoids from the root of *Leontopodium alpinum* Cass. (Asteraceae) increased extracellular ACh in rat brains, but only silphiperfolene acetate (**67**) inhibited AChE activity *in vitro*, although weakly.¹¹⁹



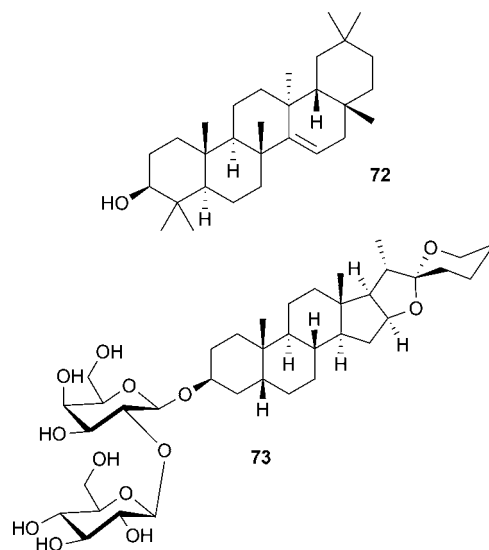
Numerous diterpenoids inhibit AChE;^{22,120} however, few have demonstrated potencies that have stimulated further

investigation. $5\alpha,8\alpha$ -(2-Oxokolavenic acid) (**68**) was the most potent of several clerodane diterpenoids from the fruit of *Detarium microcarpum* Harms (Leguminosae) to inhibit AChE, but it was 10-fold less potent than galantamine (**15**).¹²¹ The ent-kaurane diterpenoid melissoidesin (**69**), from leaves of *Isodon wightii* (Benth.) H.Hara (Lamiaceae), inhibits AChE *in vitro*, but further studies to confirm inhibitory potency are required.¹²² The isopimarane diterpenoids 7β -hydroxyisopimara-8,15-dien-14-one and 14α -hydroxyisopimara-7,15-dien-1-one, from the leaves of *Hypoestes serpens* R.Br. (Acanthaceae), required 50- and 20-fold higher concentrations than **15**, respectively, to inhibit AChE in a TLC bioautographic assay.¹²³ Thus, structural modification may be necessary to optimise the AChE inhibitory potency of these less active diterpenoids. A more potent AChE inhibitor (only 2-fold less potent than **15**) is the cassane diterpene niloticane (**70**), from *Acacia nilotica* subsp. *kraussiana* (Benth.) Brenan (Leguminosae) bark, which also showed selective inhibition of cyclooxygenase-1 (COX-1),¹²⁴ an effect that has also been considered relevant in dementia treatment. Of more therapeutic relevance are the first diterpenoids shown to inhibit AChE from *Salvia miltiorhiza* Bunge (Lamiaceae), particularly cryptotanshinone (**71**),¹²⁵ which ameliorates scopolamine-induced learning impairments in rodents.^{126,127} Although a promising drug candidate, pharmacokinetic studies show penetration of **71** across the BBB may be limited *in vivo*.¹²⁸



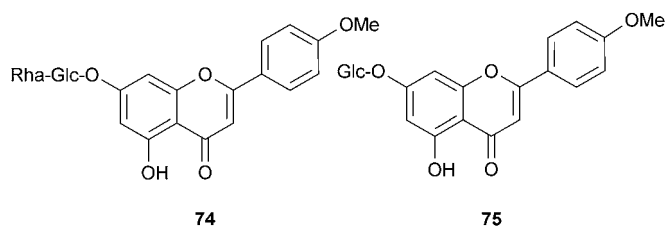
Compared to alkaloids, relatively few triterpenoid or steroidal derivatives have been discovered as AChE inhibitors, and in many cases their potency is weak. Nevertheless, weak to moderate AChE inhibitors are frequently used as template structures for the synthesis of more potent and therapeutically relevant inhibitors. Jujubogenin glycosides occur in *Bacopa monnieri* Wettst. (Scrophulariaceae),¹²⁹ a plant widely-studied for its effects on cognition;¹³⁰ semi-synthetic derivatives are described in a patent as AChE inhibitors for potential use in AD.³⁶ Other triterpenoid or steroidal derivatives have not been considered as leads for drug development as potent AChE inhibitors, but possess additional activities relevant to dementia treatment. For example, taraxerol (**72**) is a triterpenoid from *Clitoria ternatea* L. (Leguminosae) that inhibits AChE *in vitro* and in the brain of rodents *in vivo*.^{131,132}

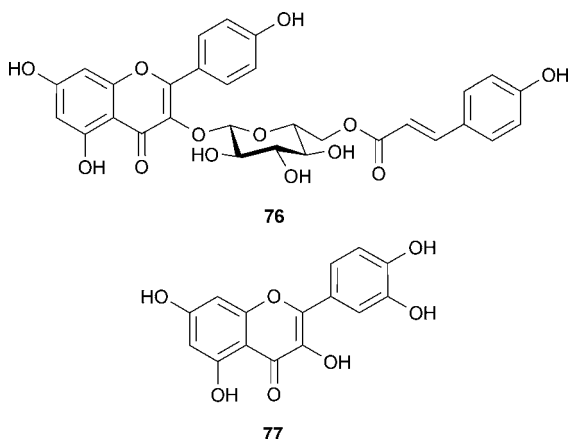
Extracts from aerial parts and roots of this plant attenuate memory deficits in rats, but this was not directly correlated with AChE inhibition,¹³³ suggesting other modes of action; particularly since **72** was not as potent as physostigmine (**1**) when tested for AChE inhibition.^{131,132} Timosaponin AIII (**73**), a steroidal saponin from *Anemarrhena asphodeloides* Bunge (Asparagaceae) significantly reversed the scopolamine-induced learning deficits and expression of tumor necrosis factor- α (TNF- α) and interleukin- 1β (IL- 1β) in the brain, and increased hippocampal ACh levels *in vivo*.¹³⁴ Although anti-inflammatory mechanisms could contribute to these observed cognitive effects, AChE inhibition (reported *in vitro*) is considered the principal mode of action.¹³⁴



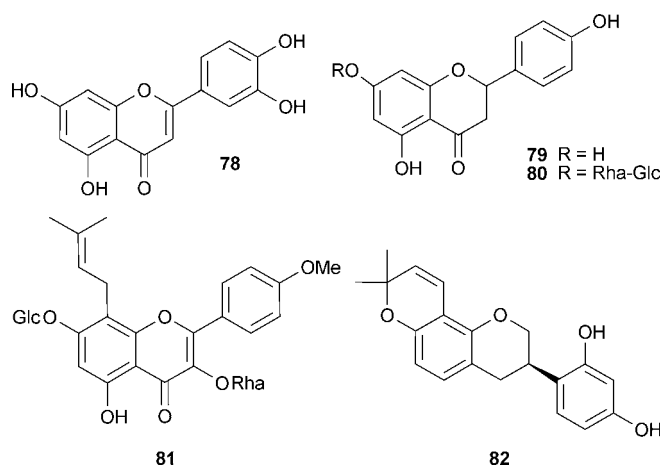
2.3 Shikimate-derived compounds as AChE inhibitors

Compared to alkaloids, a relatively low number of shikimate-derived compounds are documented as AChE inhibitors. One structure-activity relationship study focused on 17 flavonoids, including those from *Buddleja davidii* Franch. (Buddlejaceae) leaves, but only linarin (**74**) (shown in a separate study to inhibit AChE)¹³⁵ and tilianin (**75**) inhibited AChE, thus a 4'-OMe group, a 7-O-sugar, and the length of the interglycosidic links of the sugar chain were considered important structural features for AChE inhibition.¹³⁶ Other flavonoid inhibitors of AChE include quercitrin, 3-methoxyquercetin, tiliroside (**76**) and quercetin (**77**) from *Agrimonia pilosa* Ledeb. (Rosaceae); although these flavonols were not as active as tacrine and berberine, **76** and **77** were almost two-fold more active than the alkaloid dehydroevodi-amine (**9**).^{137,138}





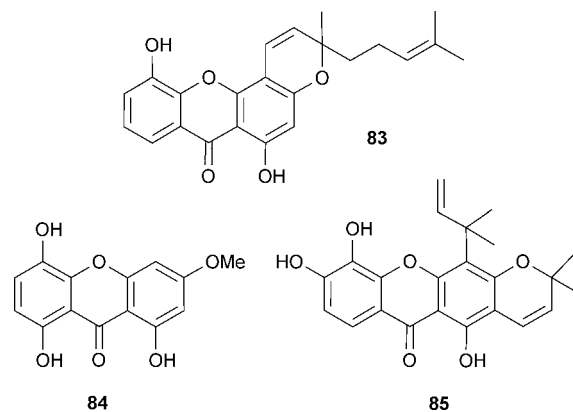
Generally, there is limited evidence for *in vivo* cognitive effects of flavonoids in relation to ChE activity. Luteolin (**78**), a common flavone, inhibits AChE ($IC_{50} > 0.1$ mM) and BChE *in vitro*^{139,140} and is anti-amnesic *in vivo*, protecting against β -amyloid-induced toxicity and inhibiting AChE activity (increasing ACh levels) in the cerebral cortex.¹⁴¹ Although naringenin (**79**) did not inhibit AChE in the study by Fan *et al.*,¹³⁶ in a different study this flavanone dose-dependently inhibited AChE *in vitro*, perhaps explaining why it also ameliorated scopolamine-induced amnesia in rodents;¹⁴² the 7-neohesperidoside, naringin (**80**), also alleviates cognitive impairment and oxidative stress, and attenuates brain AChE activity *in vivo*.¹⁴³ The prenylflavone icariin (**81**) from *Epimedium* species (Berberidaceae) improves cognitive impairments in mice, which was attributed to increasing monoamine levels, inhibiting oxidative damage and also decreasing AChE activity.¹⁴⁴ The isoflavan glabridin (**82**) from the roots of *Glycyrrhiza* species (Leguminosae) antagonised scopolamine-induced amnesia in mice, an effect associated with a reduction of brain ChE activity.¹⁴⁵



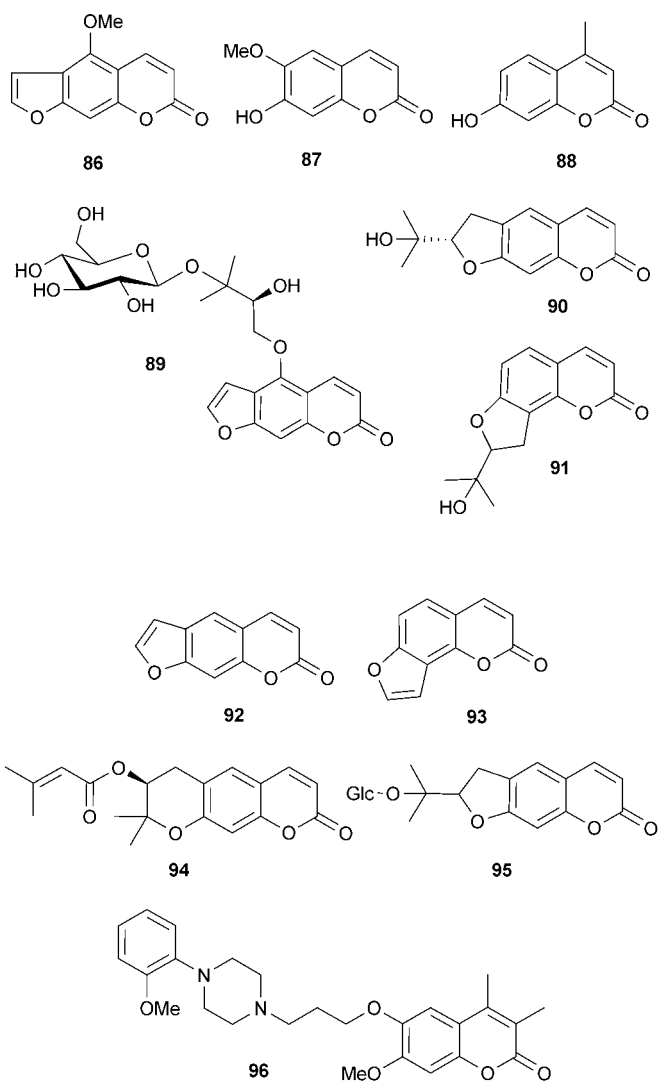
A diet of soy isoflavones for 16 weeks in aged male rats produced AChE inhibition in the cortex, basal forebrain and hippocampus,¹⁴⁶ although other modes of action may explain the cognitive effects observed with these isoflavones.^{147,148} The potential AChE inhibitory effects of compounds with isoflavone structures have been confirmed by the evaluation of synthetic

flavonoid derivatives. Of the derivatives based on chalcone, flavone, flavanone and isoflavone structures, the most potent and selective AChE inhibitors were the isoflavone derivatives; 6,7-dimethoxy-3-[4-(pyrrolidin-1-ylmethyl)-phenyl]-4*H*-chromen-4-one was even more potent than donepezil.¹⁴⁹ Other isoflavones that inhibit AChE are osajin and pomiferin and their *iso*-derivatives from fruits of *Maclura pomifera* (Raf.) C.K.Schneid. (Moraceae), but IC_{50} values were in mM (0.1–2.7) concentrations.¹⁵⁰

A screen of 45 non-alkaloid natural compounds found six of the seven AChE inhibitors to be xanthenes. The most potent (**83**) had an additional cyclic component and a hydrophobic side-chain (not features of the other active xanthenes), which are considered important structural features for AChE inhibition.¹⁵¹ Other xanthenes from *Gentiana campestris* L. (Gentianaceae) leaf inhibit AChE; optimum inhibitory activity was associated with the absence of a glucopyranosyl, and a methoxy group present in position C-3, since the most potent inhibitor, bellidifolin (**84**), was similar in potency to galantamine (**15**).¹⁵² Macluraxanthone (**85**) (occurs in some Guttiferae) is a potent non-competitive AChE inhibitor,¹³⁷ but it also inhibits platelet aggregation,¹⁵³ therefore therapeutic development could be limited due to the potential for drug interactions with anti-platelet/anti-coagulant drugs.

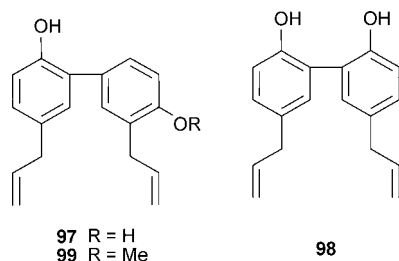


Several coumarins and derivatives inhibit AChE, including bergapten (**86**), scopoletin (**87**), 4-methylumbelliferone (**88**), ferionelloside (**89**), marmesin (**90**) and columbianetin (**91**).^{22,34,36} The inhibitory potency of simple coumarins (*e.g.* **87**) and furanocoumarins (*e.g.* **86**) is considered to be moderate to low, and large substituents (*e.g.* benzyloxy) in position C-7 of the coumarin nucleus, or at positions 5 and 8 of the furanocoumarin nucleus, improve inhibitory potency compared to smaller substituents (*e.g.* hydroxyl and methoxy).¹⁵⁴ Few AChE-inhibitory coumarins have been investigated for their cognitive effects *in vivo*, but psoralen (**92**), isopsoralen (**93**) (furanocoumarins from *Psoralea* species (Leguminosae)), decursin (**94**) and nodakenin (**95**) reverse scopolamine-induced cognitive impairments in rodents, correlating with AChE inhibition.³⁴ The coumarin analog ensaculin (**96**) inhibits AChE, modulates dopaminergic, serotonergic and adrenergic function and is an NMDA receptor antagonist,¹⁵⁵ and thus is further advanced in clinical development for AD as the HCl salt (KA-672).

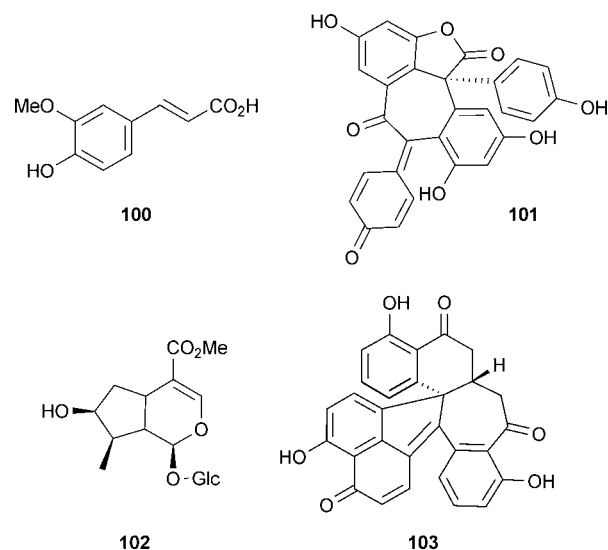


2.4 Miscellaneous compounds as AChE inhibitors

Magnolia officinalis Rehder & E.H.Wilson (Magnoliaceae) extracts have shown numerous biological activities relevant to dementia treatment, and the component lignans honokiol (**97**) and magnolol (**98**) inhibit AChE.¹⁵⁶ More recently, an extract and 4-*O*-methylhonokiol (**99**) from the bark of this species prevented scopolamine-induced memory impairment and the increase in brain AChE in mice; the latter inhibited AChE *in vitro* (IC₅₀ 12 nM; tacrine: 135.4 nM),¹⁵⁷ thus lignans from *M. officinalis* warrant further study for their therapeutic potential in AD.



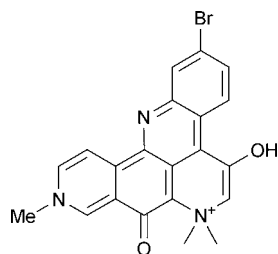
Although ferulic acid (**100**) is a competitive inhibitor of AChE,¹⁵⁸ it has been subjected to pharmacomodulation to produce tacrine–ferulic acid hybrids for dual anti-AChE (tacrine moiety) and antioxidant (ferulic acid moiety) activities, with some being both antioxidant and more potent AChE inhibitors than tacrine.¹⁵⁹ Another phenolic compound that inhibits AChE is hopeahainol A (**101**) (from *Hopea hainanensis* Merr. & Chun (Dipterocarpaceae) stem bark), which shows comparable potency to huperzine A (**40**)¹⁶⁰ and is also neuroprotective *in vitro*,¹⁶¹ providing two mechanisms of interest for AD. Also of interest for further study are procyanidin-containing extracts from lotus (*Nelumbo nucifera* Gaertn. (Nelumbonaceae)) seeds, and *Cornus officinalis* Siebold & Zucc. (Cornaceae) fruit extract and its constituent iridoid glycoside, loganin (**102**), since they could improve cognitive impairments and decrease brain AChE activity *in vivo*.^{162–164}



Other recently discovered AChE inhibitors include synthetic derivatives of cardanol (a non-isoprenoid phenolic lipid from *Anacardium occidentale* L. (Anacardiaceae)), which correlate with the AChE binding effects of rivastigmine (**2**)¹⁶⁵ and an unusual polyketide, sporothrin A (**103**), from an endophytic marine fungus *Sporothrix* sp. (Ophiostomataceae), which is described as a strong AChE inhibitor (although not compared with a positive control).¹⁶⁵

In general, AChE inhibitors of marine, fungal or bacterial origin are less well-documented compared to those from plant origin, and have been reviewed previously.^{22,166} More recently discovered AChE inhibitors of marine origin include a steroidal alkaloid, 4-acetoxylplakinamine B from the sponge *Corticium* sp.,³⁴ a cambranoid, crassumolide E from the coral *Lobophytum* sp.,¹⁶⁷ the plastoquinones sargaquinoic acid and sargachromenol from the alga *Sargassum sagamianum*,¹⁶⁸ and phlorotannins (eckstonol, eckol, phlorofucofuroeckol A, dieckol, 2- and 7-phloroecol) from another alga, *Ecklonia stolonifera*,¹⁶⁹ but all were either less potent than alkaloid positive controls, or did not report a positive control. However, the pentacyclic pyridoacridine alkaloid petrosamine (**104**) from the sponge *Petrosia* n. sp., was a more potent AChE inhibitor than galantamine (**15**) *in vitro*,¹⁷⁰ so could be of interest for further study. Extracts from

the sponge *Topsentia ophiraphidites*¹⁷¹ and the seaweeds *Gracilaria gracilis*,¹⁷² *G. edulis*, *Ulva reticulata*, *Hypnea valentiae* and *Padina gymnospora*¹⁷³ also inhibit AChE, but identification of the compounds responsible and any therapeutic potential requires further study.



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Although AChE inhibition is one of the major pharmacological targets for AD at present, new therapeutic strategies have emerged (*vide infra*). Thus, the continued clinical relevance of AChE inhibitors for symptomatic treatment of AD may eventually be superseded by new and more effective disease-modifying drugs targeting other pathophysiological processes.

3 Protease inhibitors (amyloid cascade hypothesis)

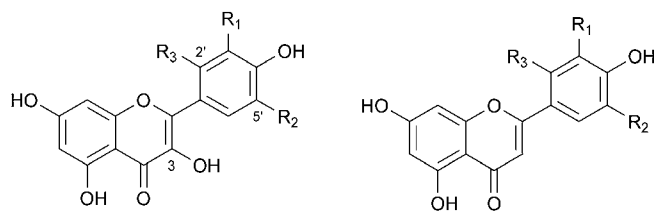
The build-up of amyloid plaques is one of the hallmarks of AD. This observation has led to the proposal by Hardy¹¹ that these sessile plaques are critical to the observed neurodegeneration (amyloid cascade hypothesis), which is supported by familial mutations. Recent modification¹⁷⁴ of this original hypothesis implicates the precursors (oligomers of A β ₄₂) as the causative agent. Two distinct therapeutic strategies consistent with this proposal have been investigated, including inhibiting the proteolytic enzymes involved in forming the A β ₄₂ building blocks (secretase modulation), and reducing the concentration of A β ₄₂ oligomers either by inhibiting aggregation or increasing the rate that the monomers or oligomers are cleared. Recent *in vivo* kinetic data suggests this latter issue may be at the heart of the observed A β ₄₂ build-up, rather than APP overproduction or secretase overactivity, as rates of clearance in transgenic AD mice models are essentially half of those in controls.^{175,176}

The two major enzyme targets in the amyloidogenic pathway of A β formation are the aspartic proteases, β - and γ -secretases. While aspartic proteases have been successfully targeted as HIV therapeutics, developing β - and γ -secretase inhibitors has been more problematic. The latter have potential target toxicity as NOTCH, which is crucial in cell-cell signaling, is a substrate for γ -secretase, while the former possesses an active site large enough to require molecules that suffer from poor BBB (MW >500). To date though, several synthetic γ -secretase inhibitors and one inhibitor of β -secretase (Comentis' CTS-21166) have been evaluated in clinical trials. While the exact structure of this latter clinical candidate has not been revealed yet, it is a transition state analog of peptide hydrolysis and would likely be considered a natural product mimic under the classification system of Newman and Cragg.¹⁷⁷ Interestingly, no direct inhibitor of γ -secretase has yet been reported from natural sources, although the fungal metabolite beauverolide modifies this process indirectly.¹⁷⁸ As of July 2010, 49 β -secretase inhibitors have been

reported (IC₅₀ <100 μ M), of which three have IC₅₀ values of less than 1 μ M (bastadin 9 (**134**), luteolin (**78**), neocorylin (**112**)). However, no natural product has yet displayed the <100 nM potency of the most promising synthetic pre-clinical candidates. The vast majority of the reported inhibitors are plant-derived flavonoids, including flavones, and related phenolic compounds. Interestingly, while β -secretase (BACE1) inhibitors derived from synthetic lead discovery programs are competitive inhibitors,¹⁷⁹ many of these natural products are non-competitive inhibitors that were active in FRET assays, with few demonstrating potency in cell or animal models. It has been suggested that these compounds might bind to either a β -secretase subsite or to a regulatory domain,¹⁸⁰ but more detailed structural work is needed to clarify these issues.

3.1 Shikimate-derived compounds as secretase inhibitors

By far the largest class of natural product BACE1 inhibitors reported is shikimic-acid-derived. Shimmyo *et al.* reported SAR data for a series of related flavonols (myricetin (**105**), quercetin (**77**), kaempferol (**106**), morin (**107**)) and a flavone (apigenin (**108**)).¹⁸¹ While in FRET-based enzymatic assays all four flavonols displayed moderate BACE1 inhibition (1.4 μ M to 40 μ M), only **105** and **77** reduced BACE1 activity (by approximately 20–30%) and A β ₄₂ production in a cellular system. This led to the hypothesis that the C-3 hydroxyl group was critical for the observed effect, as the corresponding flavone (**108**) was the weakest inhibitor. Docking studies suggest that this hydroxyl group stabilizes the enzyme–inhibitor complex by hydrogen-bonding to Asp32 of BACE1 (one of two catalytic Asp residues involved in the hydrolysis), while hydroxy groups at 5' and 3' also participate in hydrogen bonding. In 2009, the flavone luteolin (**78**), from *Perilla frutescens* var. *acuta* (Thunb.) Kudô (Lamiaceae), was discovered to be a BACE1 inhibitor in an enzyme assay. With an IC₅₀ value of 0.5 μ M, it is one of the most potent natural product inhibitors of BACE1 to date.¹⁸⁰ A comparison of the planar structure of this compound and the inactive **108** indicates the C-5 hydroxyl group is responsible for the two order of magnitude increase observed in potency. Assuming no change in the binding conformation compared to **105**–**108**, this increase in potency could be partially attributed to an additional H-bond to the Trp198 residue in the binding pocket. Since the identical structural variation between myricetin (**105**) and quercetin (**77**) results in only a marginal increase in activity, the explanation must involve other factors. Counter-screens indicate luteolin (**78**) does not inhibit serine proteases (trypsin, chymotrypsin), AChE or TNF- α converting enzyme (TACE; a putative γ -secretase) at

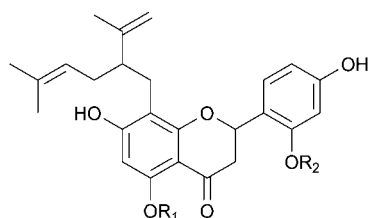


105 R₁ = OH, R₂ = OH, R₃ = H
77 R₁ = OH, R₂ = H, R₃ = H
106 R₁ = H, R₂ = H, R₃ = H
107 R₁ = H, R₂ = H, R₃ = OH

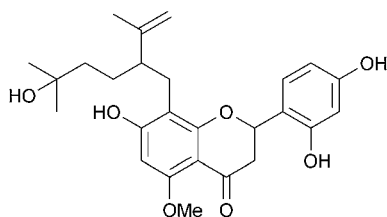
108 R₁ = H, R₂ = H, R₃ = H
78 R₁ = H, R₂ = OH, R₃ = H

100 μM , but additional work is needed to assess selectivity against more structurally relevant aspartic proteases.

Hwang *et al.* reported a series of lavandulyl flavanones (**109**–**110**) isolated from *Sophora flavescens* Aiton (Fabaceae) that displayed similar potency (1–10 μM) in an *in vitro* assay system.¹⁸² Biochemical analyses indicated these non-competitive inhibitors reduced soluble APP β levels (the extracellular BACE1 cleavage product), but did not affect intracellular full-length APP, suggesting selective *in vivo* BACE1 inhibition. Minor structural variations resulted in negligible potency differences, with the exception of hydroxylation at C-4'' of the lavandulyl moiety in **111** which abolished activity.

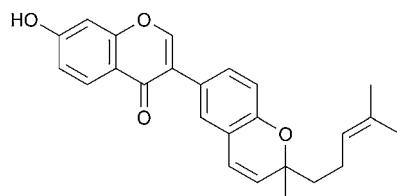


109 R₁ = H, R₂ = H
110 R₁ = H, R₂ = Me



111

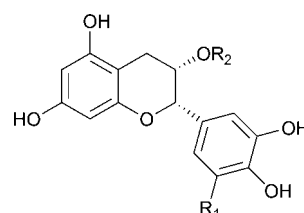
Neocoylin (**112**), an isoflavone from the seeds of *Psoralea corylifolia* L. (Fabaceae),¹³⁹ potently inhibited BACE1 cleavage of APP (0.7 μM) in a FRET assay system. That this compound retains significant activity despite substitution at C-3 suggests an alternative binding conformation or site than the flavonols in which hydroxylation was shown to be critical for binding (**105**–**108**; *vide supra*). Several other phenolic compounds were also isolated although they lack the C-3 2*H*-chromene moiety and are less active. Soy isoflavones have also attracted attention as an Alzheimer's treatment. Currently, a pilot study on 60 patients is being conducted to evaluate the potential effects of soy isoflavone supplements (Novasoy[®]) on cognitive function for men and women with AD (NCT00205179).



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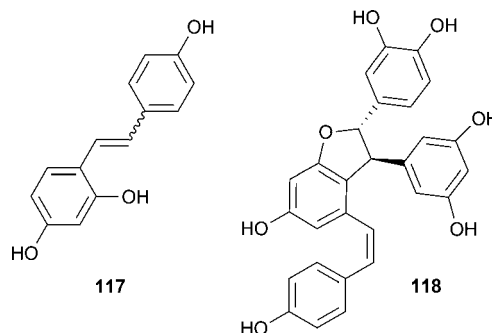
Another potent naturally occurring BACE1 inhibitor is (–)-gallocatechin gallate (**113**), isolated from green tea, *Camellia sinensis* L. (Theaceae), after an examination of 260 species of herbal drugs.¹⁸³ Compounds **113**–**115** were the first examples of non-peptidic natural product β -secretase inhibitors and

non-competitively inhibited BACE1 in a dose-dependent manner with K_i values of 0.17, 0.27 and 5.3 mM, respectively. Preliminary SAR data indicates that the pyrogallol moiety is essential for activity, as removal of one of the hydroxyl groups (as in **116**) resulted in an inactive compound. Continued development of these compounds has resulted in on-going Phase II/III clinical trials using 200–800 mg/day of epigallocatechin gallate (EGCG) (**115**) (NCT00951834), based primarily on the observed neuro-protective effects in cell and animal studies. Multiple pathways are being modulated in addition to BACE1 though, including increasing non-amyloidogenic α -secretase processing, preventing the aggregation of A β , as well as antioxidant effects (see section 6) and modulation of mitochondrial function.



113 2*R* R₁ = OH R₂ = galloyl
114 2*R* R₁ = OH R₂ = H
115 2*S* R₁ = OH R₂ = galloyl
116 2*S* R₁ = H R₂ = galloyl

Active stilbenoids and phenylpropanoid esters were isolated from the dried rhizomes of *Smilax china* L. (Smilacaceae).¹⁸⁴ These compounds include *trans*-*cis*-resveratrol, oxysresveratrol, veraphenol and *cis*-scripusin. Again, IC₅₀ values for these non-competitive inhibitors were in the single-digit micromolar range. Specifically, *trans*-resveratrol (**117**) and *cis*-scripusin (**118**) had IC₅₀ values of 7.5 and 10 μM , respectively. All compounds were tested for selectivity against TACE, elastase, chymotrypsin and elastase, and found to be inactive at up to 100 μM .

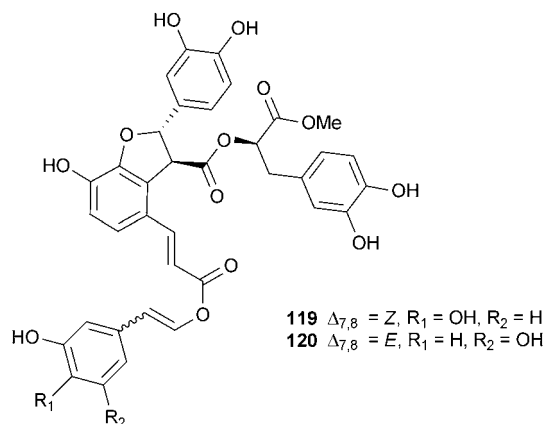


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118

The need for counterscreens to assess selectivity is illustrated by our report of two related phenylpropanoid esters from *Cordia sebestena* L. (Boraginaceae), which is commonly known as the Geiger tree.¹⁸⁵ Initial biological evaluation indicated a dose-dependent inhibition of BACE1 in a complementation-based enzyme assay for sebestenoids C (**119**) and D (**120**). In contrast to the related compound *cis*-scripusin (**118**), these compounds also inhibited chymotrypsin in a standard chemiluminescence assay, although at slightly lower concentrations. Further testing revealed this inhibition was strongly affected by the addition of detergent, as assays performed in the presence of 0.01% Triton X-100 resulted in 4-fold lower IC₅₀ values. These results are

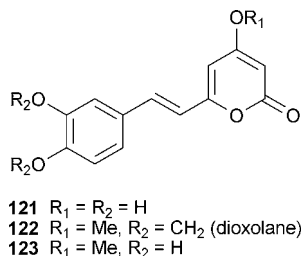
consistent with the non-competitive inhibition expected from a non-specific aggregation inhibitor, as has been outlined elegantly by the Shoichet's lab.¹⁸⁶



Several other complex aromatics have been reported as inhibitors. An investigation of pomegranate husk *Punica granatum* L. (Lythraceae) identified the complex phenolic ellagic acid and punicalagin as weak inhibitors of BACE1,¹⁸⁷ while more potent glucopyranoside galloyl derivatives were isolated from *Sanguisorba officinalis* L. var. *officinalis* or var. *longifolia* (Bertol.) T.T.Yu & C.L.Li.¹⁸⁸ Finally, weak (>100 μM) furanocoumarin inhibitors of BACE1 were reported from the roots of *Angelica dahurica* L. (Apiaceae), and phlorotannin inhibitors were reported from the marine kelp *Eisenia bicyclis* Setchell (Lessoniaceae) with low micromolar potency.¹⁸⁹

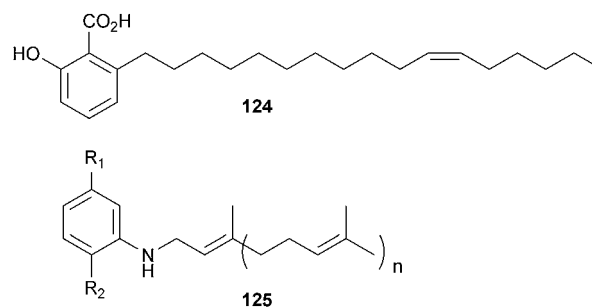
3.2 Polyketides as secretase inhibitors

A screen of 256 plant and fungal extracts led to the identification of the polyketide-derived hispidin (**121**) from a fungal mycelium of *Phellinus linteus* (Hymenochaetales),¹⁹⁰ although this compound had been previously isolated from *P. pomaceus*.¹⁹¹ In the course of a total synthesis, analogs **122** and **123** were generated and tested. These analogs were an order of magnitude less potent than hispidin with IC_{50} values of 40 and 72 μM respectively, which led the authors to suggest "a catechol moiety might not be necessary for stronger activity."¹⁹⁰ Selectivity was evaluated against chymotrypsin, trypsin, elastase, PEP (prolyl peptidase), TACE, with hispidin displaying equipotency towards BACE1 and PEP.

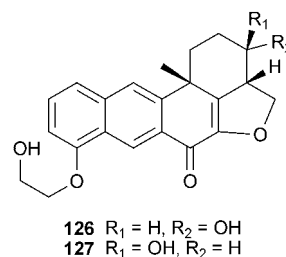


Taine *et al.*¹⁹² reported four alkylphenolic acids as inhibitors of BACE1. These compounds were isolated from perennial Araceae herbs, which are widely distributed in southern China and used as a traditional Chinese medicine. Represented by **124**, the other analogs differ in the chain length and positions of oxidation, but

the potency is essentially unaffected by these minor variations. The position of these double-bonds is odd perhaps indicating that their biogenesis may begin with a 6-hydroxy-2-methylbenzoic rather than 6-hydroxybenzoic acid. These 7 μM non-competitive inhibitors are also reminiscent of NP-12 (**125**), a phenylprenyl derivative isolated from the marine sponge *Sarcotragus* sp. by Noscira.¹⁹³ These compounds were put forth as clinical candidates that inhibited both BACE1 and GSK3 (the latter phosphorylates tau) at micromolar concentrations, thus being able to simultaneously modulate both major histopathological hallmarks of AD.¹⁹⁴ Treatment with NP-12, also known as Nypta or Tideglusib, was tolerated over a 20-week period and produced a positive impact on patients' cognitive performance in a Phase IIa trial, although given the small sample size, this trial did not reach statistical significance, which is not unexpected.¹⁹⁵ A larger Phase IIb trial is scheduled for later in 2010 to evaluate the compound more fully.

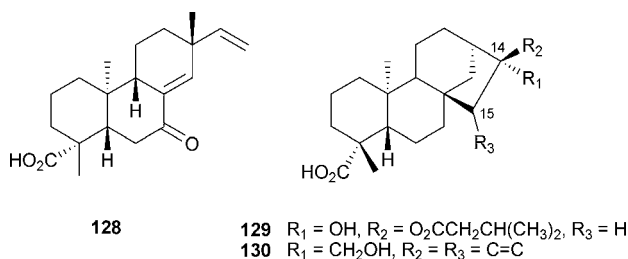


Investigation of the marine sponge *Xestospongia* sp. Schmidt (Petrosiidae) yielded xestosaprols D–M that weakly inhibited β -secretase.^{196,197} The configuration of the hydroxyl group on the D-ring of xestosaprol H (**126**) was found to be important for the observed inhibition, as the corresponding epimer, xestosaprol F (**127**) was significantly less active. While the activity of these compounds was weak, given their small size and hydrophobic nature, their BBB permeability is predicted to be high, which suggests further evaluation may be warranted.

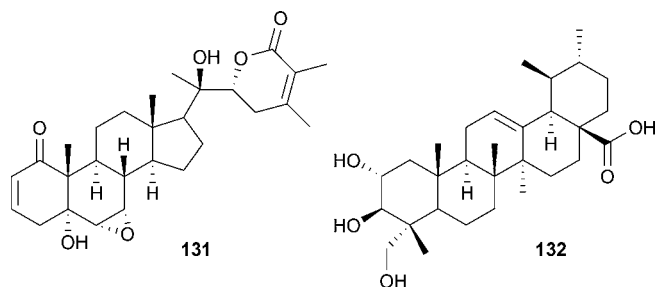


3.3 Terpenoids as secretase inhibitors

Terpenoid inhibitors of BACE1 are relatively rare. From the roots of the edible herb *Aralia cordata* Thunb. (Araliaceae), one *ent*-pimarane (**128**) and two *ent*-kaurane-type diterpenes (**129**–**130**) were isolated which inhibited BACE1.⁵⁶ Modest activity was observed for these compounds in an enzyme assay (**128**: 24.1; **129**: 18.6, **130**: 23.4 μM). The identification of an inactive analog, possessing an epoxide at C-14/15, hints at the importance of the bicyclic system for the observed inhibition.

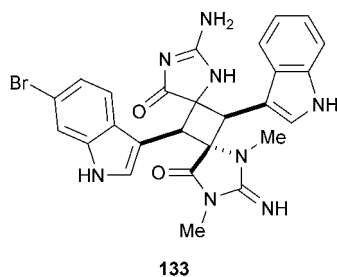


Withania somnifera (L.) Dunal (Solanaceae) and *Centella asiatica* (L.) Urb. (Apiaceae) are recommended as memory and intellect enhancers in traditional Ayurvedic medicinal systems. Chan *et al.* investigated the major components. Treatment of neuronal cells with withanolide A (**131**) and asiatic acid (**132**) (from *W. somnifera* and *C. asiatica*, respectively) significantly affected APP processing.¹⁹⁸ In both cases, BACE1 processing was down-regulated while non-amyloidogenic α -secretase processing was increased. While the exact mechanism is unknown, direct inhibition of BACE1 is known to increase non-amyloidogenic processing, as these pathways are mutually exclusive. In this case, evidence suggests a direct activation of α -secretase, in addition to activation of A β clearance mechanisms, occurs upon treatment in cells. The authors reiterate the proposal that “multifunctional” and “multilevel” activity may be required in an Alzheimer’s drug for true efficacy.^{199,200}



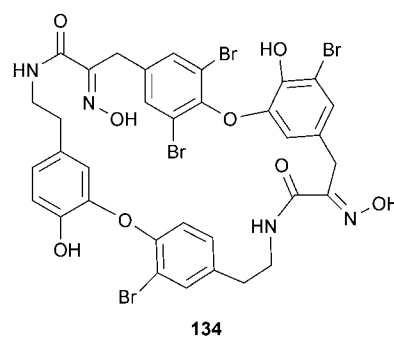
3.4 Alkaloids as secretase inhibitors

Despite the large number of synthetic alkaloids known to inhibit BACE1, few naturally occurring alkaloids have been reported with this activity. Marine sponges belonging to the family Thorectidae, and the genus *Smenospongia* in particular, are well-known sources of indole alkaloids, and an examination of a Panamanian species of *S. cerebriformis* Duchassaing & Michelotti (Thorectidae) identified an unusual bis-2-amino-imidazolone, dictazole A (**133**), which weakly inhibited BACE1.²⁰¹ This compound may be of interest for further development, as the 2-imino-imidazolidinone moiety is considered a privileged



subunit responsible for the observed activity against BACE1 in many structurally unrelated compounds.²⁰²

The marine natural product bastadin 9 (**134**), isolated from *Ianthella basta* Pallas (Lanthellidae), is also reported to reduce APP processing *via* inhibition of BACE1.²⁰³ This compound is part of a larger family of metabolites that consists of more than 26 members,²⁰⁴ which have been reported to display a range of biological activities.^{205–208} Bastadin 9 inhibited BACE1 cleavage of APP with IC₅₀ values of 0.3 and 2.8 μM in enzyme- and cell-based assays, respectively. Although other analogs inhibited BACE1 as well, they were less potent.²⁰³ In 2008, Bristol-Myers Squibb patented a series of oxime-based cyclic nanomolar BACE1 inhibitors that resembled the upper half of the bastadins, and were able to permeate the BBB with nanomolar potency.²⁰⁹ These data suggest a critical evaluation of the BACE1 inhibitory effect of the bastadin structural class is warranted.



4 Compounds promoting anti-aggregation and clearance

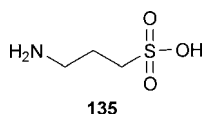
While A β peptides are common in the brains of individuals with or without AD, the physiological role of A β is still unclear. It has been implicated in myelin sheath formation in developing cells,²¹⁰ and early lethality has been recently noted in transgenic mice,²¹¹ thus a drug that prevents A β formation could have unknown consequences. Reducing the concentration of A β ₄₂ oligomers by either inhibiting aggregation or increasing the rate of clearance of the soluble oligomers or insoluble fibril plaques is another possible therapeutic strategy that has been investigated.²¹² An ideal anti-aggregation drug would prevent the formation of A β aggregates, destabilize plaques, and reduce existing deposits. Although the oligomers are more toxic than their insoluble fibril plaque counterparts, both cause neurodegeneration though through two different apoptotic pathways,²¹³ so an ideal drug would inhibit both processes.

Most of the compounds described below are only able to inhibit fibrillogenesis, but inhibitors of oligomerization would be more valuable. In general, these compounds are proposed to disrupt the weak bonds between residues in the β -sheet fibrils, through interfering with hydrogen-bonding or electrostatic interactions. These compounds are often small (low molecular weight) and are either lipophilic or possess a number of polar substituents capable of competing for hydrogen bonds. Few of these small molecules show activity in the μM or nM range, and those that have the greatest activity have other problems (such as the lack of bioavailability, inability to cross the BBB, or lacking

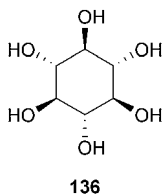
specificity) that prevent them from becoming likely drug candidates. However, many of these compounds are non-toxic and have multiple bioactivities (*i.e.*, antioxidant, anti-inflammatory, enzyme inhibitors) that could provide multi-prong therapeutics for fighting the diverse pathologies of AD.

4.1 Compounds in clinical trials with these mechanisms

One of the first natural products with an anti-aggregation mechanism to be investigated was tramiprosate (**135**).²¹⁴ The active ingredient is homotaurine, or 3-aminopropanesulfonic acid, which occurs naturally in seaweed.²¹⁵ The synthetic compound was evaluated as tramiprosate, Alzhemed™, and Cerebril™. It is a glycosaminoglycan (GAG) mimetic that competes for GAG-binding sites in soluble A β and prevents the formation of fibrils. *In vivo* studies using TgCRND8 transgenic mice showed that tramiprosate specifically binds to soluble A β , preventing the β -sheet conformation, as well as reducing the amount of plaque, and the soluble and insoluble forms of A β_{40} and A β_{42} in the brain.²¹⁴ While tramiprosate (Alzhemed, homotaurine, 3-aminopropanesulfonic acid) potentially inhibits A β , it promotes undesired tau aggregation.²¹⁶ This drug failed Phase III clinical trials in the US, and Phase III trials were halted in the EU due to statistically inconclusive results.²¹⁷ Ultimately, this compound may not have had the necessary potency to demonstrate a clear effect. In a controversial move, Bellus Health, formerly Neurochem, opted to market homotaurine as the “memory protective” nutraceutical Vivimind™ in Canada and on the internet.²¹⁸



Scyllo-cyclohexanehexol (**136**), which occurs naturally in dogwood²¹⁹ *Cornus florida* L. Spach (Cornaceae) and coconut palm²²⁰ *Cocos nucifera* L. (Arecaceae), is being evaluated in clinical trials by Transition Therapeutics and Élan, as AZD-103/ELND-005. In 2006, JoAnne McLaurin, Peter St. George-Hyslop, and colleagues at the University of Toronto demonstrated that AZD-103 lowered the amount of insoluble A β_{40} and A β_{42} , lowered the amount of soluble A β oligomers, and reduced A β plaque load in the brains of transgenic mice.²²¹ The resulting reversal of memory deficits was attributed to the inhibition and disaggregation of A β oligomers (20–60% decrease).²²¹ In fact, the *scyllo*-treated mice navigated the water maze just as well as controls after several days of testing. Measurements of synaptic loss and glial inflammation also showed marked improvement. Results of Phase I clinical trials suggested the compound was well-tolerated and resulted in Phase IIa trials at multiple doses for mild to moderate AD (NCT00568776).²²¹ However, the two highest-dose trials (1000 mg and 2000 mg dosed twice daily) were



discontinued earlier this year (2010) due to nine deaths, while the lower-dose trial (250 mg dosed twice daily) continues.²²²

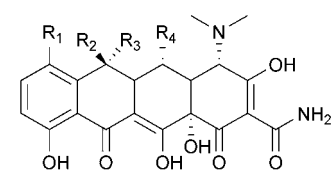
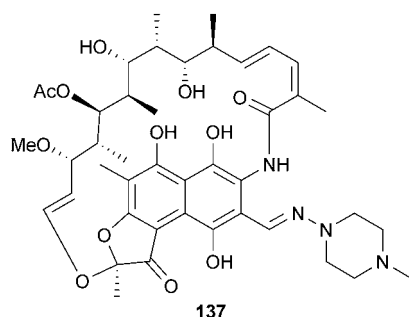
An active area of development is the use of vaccines or antibodies to facilitate disruption of aggregates and increase clearance, which is based on the early work by the Schenk *et al.* with transgenic mice.²²³ Bapineuzumab²²⁴ is a humanized monoclonal antibody developed by Wyeth and Élan in Phase III clinical trials.²²⁵ It is widely considered one of the most promising candidates. Previous clinical trials using β -amyloid vaccinations (AN-1792) were halted when several patients developed aseptic meningoencephalitis.²²⁶ However, almost no plaques were observed in brain autopsies of these two subjects, despite them reaching severe end-dementia.²²⁷ The significance of these findings – that A β levels were reduced with AN-1792 treatment, but neurodegeneration continued – is still debated. Some argue it signifies the end of the amyloid cascade hypothesis, while others suggest that earlier treatment is necessary to stop the neurodegeneration initially triggered by A β . A more recent Phase II study evaluating the efficacy of bapineuzumab showed no significant results, although reversible vasogenic edema occurred more frequently in patients who were on higher doses and had APOE ϵ 4 risk factors.²²⁸ Based on an *a posteriori* analysis, a Phase III clinical trial is currently being conducted in individuals without the APOE ϵ 4 mutation, who appeared to show a five-point improvement, as compared to a two- or three-point improvement with AChE inhibitors such as Aricept,²²⁹ on the standard Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-COG) in the Phase II trial.²³⁰ Ponezumab (PF-04360365; Pfizer) is another antibody vaccination that successfully completed two Phase I studies in patients with mild to moderate AD.²³¹ This vaccination is now undergoing Phase II clinical trials.

Colostrinin™ (CLN; ReGen Therapeutics) is a mixture of proline-rich polypeptides (PRPs) originally isolated by Polish scientists²³² from ovine (sheep) colostrums. This is a form of milk produced by mammalian mammary glands late in a pregnancy. Some peptide components of CLN were homologous to annexin and β -casein, while other peptide components had unique sequences.²³³ Mechanistically, CLN inhibits A β aggregation and facilitates disassembly of existing aggregates by disrupting β -sheet bonding. In aged mice, CLN facilitated spatial learning and improved incidental learning, while having no negative effect on locomotive skills.²³⁴ In limited human trials, eight out of 15 Alzheimer's patients who were given oral tablets showed an improved mental state and developed new memories better than controls.²³⁵ More extensive double-blind studies with 105 Alzheimer's patients over a 15-week period on low dosages demonstrated that CLN helped to maintain cognitive and daily functions in patients with mild to moderate AD, and that it was well-tolerated.²³⁶ CLN is currently licensed as the non-medical nutraceutical CogniSure in the US and Australia.²³⁷

4.2 Polyketides promoting anti-aggregation and clearance

Rifampicin (**137**) is a semisynthetic polyketide originally derived from *Amycolatopsis rifamycinica* Bala (Pseudonocardiaceae). Popular for its use as a treatment for tuberculosis and leprosy, **137** also appears to inhibit A β aggregation *in vitro*.²³⁸ Rifampicin

is proposed to inhibit the toxicity of A β fibrils by binding to the aggregates and preventing the adhesion of the fibrils to the cell surface.²³⁸ However, it was recently shown that instead of inhibiting the formation of amyloid fibrils, **137** was inhibiting the interaction of fibrils and thioflavin-T, which is used as an indicator in the assay.²³⁹ This result highlights the major difficulty in screening for anti-aggregation inhibitors – specificity. Rifampicin also has poor BBB permeability,²⁴⁰ and thus lacks a crucial prerequisite for a viable neurological drug lead. A randomized trial though assessing the effectiveness of combining rifampicin and doxycycline (**138**) over a three-month period demonstrated a reduction in cognitive decline after six months in patients with mild to moderate AD.²⁴⁰ Doxycycline, a semisynthetic tetracycline antibiotic, was incorporated into the trial due to observations that tetracyclines inhibit the formation and promote disassembly of fibrils (*vide infra*). Presumably, multiple mechanisms are involved in this effect, including anti-inflammatory and anti-aggregation. Currently, a Phase III clinical trial is underway testing the effect of this combination on AD biomarkers in the cerebral spinal fluid.²⁴¹



138 R₁ = H, R₂ = OH, R₃ = Me, R₄ = OH

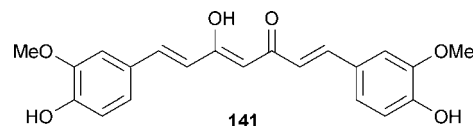
139 R₁ = H, R₂ = OH, R₃ = Me, R₄ = H

140 R₁ = N(Me)₂, R₂ = R₃ = H, R₄ = H

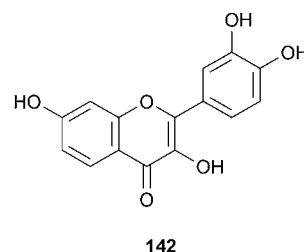
Tetracycline (**139**) is capable of inhibiting the formation of A β fibrils and promoting disassembly of existing A β fibrils *in vitro*.²⁴² Isolated from *Streptomyces* spp., the antibiotic is structurally analogous to Congo red and iododoxorubicin, which are dyes known to bind to amyloid aggregates. Tetracycline interacts with A β fibrils *via* a combination of hydrogen bonding through its polar substituents and hydrophobic interactions through its aromatic groups.²⁴² While **139** is able to penetrate the BBB, it produces minimal beneficial effects.²⁴² A semi-synthetic derivative called minocycline was better able to inhibit A β fibril formation *in vitro* at a molar ratio of 2.5 : 1 (minocycline to A β) in comparison to tetracycline, which only inhibited fibrilization when present in a ratio of 8 : 1. Other results of this same study showed that both tetracycline and minocycline could also inhibit microglial activation.²⁴³ Minocycline (**140**) exhibits neuroprotective effects in both *in vitro* and *in vivo* studies,²⁴⁴ and reduces capase-3 activation and the development of hyperphosphorylated tau species.²⁴⁵

4.3 Shikimate- and sugar-derived compounds promoting anti-aggregation and clearance

Curcumin (**141**), or diferuloylmethane, is a well-known ingredient in traditional Indian cuisine from the turmeric plant *Curcuma longa* L. (Zingiberaceae). This polyphenol effectively inhibits the formation of A β oligomers, binds already existing plaques, as well as reduces amyloid *in vivo*,²⁴⁶ while possessing greater BBB permeability than similar synthetic compounds such as Congo red. Several other beneficial effects have been attributed to **141**, including anti-inflammatory and antioxidant properties.²⁴⁷ These mechanisms may be involved in the observed neuroprotective effect by blocking microglial activation.²⁴⁸ Structure–activity relationship studies suggest optimal activity requires two phenyl groups, one of which has polar substituents for hydrogen bonding, linked by a 8–16 Å spacer containing less than two sp³-hybridized carbons.²⁴⁹ Owing to numerous attractive qualities, including BBB permeability and minimal toxicity,²⁴⁶ Longvida, a curcumin formulation, is being evaluated in a Phase II Alzheimer's clinical trial (NCT01001637).

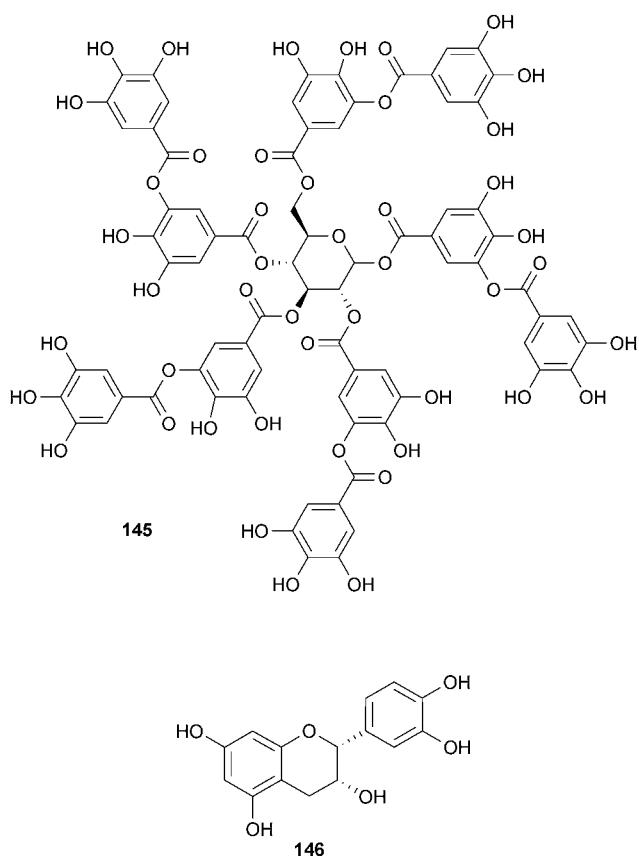
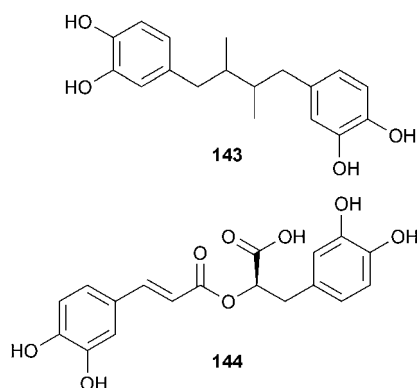


Not surprisingly, a number of flavonoids have been reported as anti-aggregation agents. These compounds include: fisetin (**142**; 3,3',4',7-tetrahydroxyflavone), **77–78**, chrysin, **105–106**, 3',4',7-trihydroxyflavone, 3,3',4'-trihydroxyflavone, 3,3',7-trihydroxyflavone, 5-deoxykaempferol and synthetic derivatives.²⁵⁰ Myricetin (**105**) was the most potent compound, while 3,3',7-trihydroxyflavone, 5-deoxykaempferol, chrysin, and **106** enhanced fibril formation. The key inhibitory pharmacophore in these compounds was the 3',4'-dihydroxyl group of the B ring,²⁵⁰ which facilitates the preferential reversible binding of myricetin to the neurotoxic oligomers rather than monomers.²⁵¹ Compound **105** also interferes with A β conformational changes, inhibits BACE-1, and displays antioxidant activity.²⁵²



Other polyphenols inhibit fibrogenic A β (fA β) formation and increase its degradation. Nordihydroguaiaretic acid (NDGA; **143**) found in *Larrea divaricata* Cav. (Zygophyllaceae), was more potent than rifamycin²⁵³ and as an antioxidant can suppress the accumulation of reactive oxygen species (ROS) and Ca²⁺.²⁵⁴ Rosmarinic acid (**144**), found in various culinary herbs, has comparable activity to **105**, **141**, and **143**.²⁵⁵ While **144** reduces A β accumulation *in vitro*, A β accumulation was noted in an *in vivo* rodent model.²⁵⁶ Rosmarinic acid also affects many Alzheimer's-related pathways, such as ROS formation, lipid

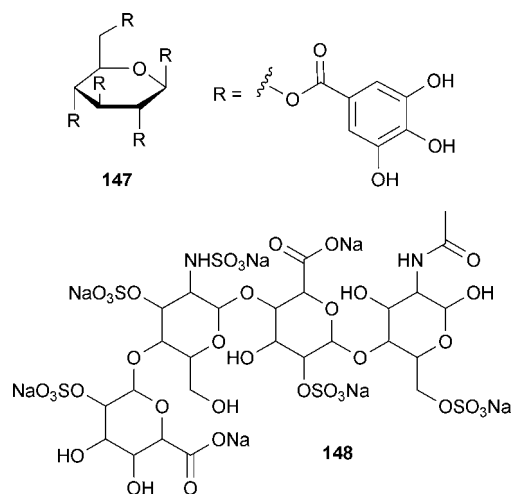
peroxidation, DNA fragmentation, caspase-3 activation, and tau protein hyperphosphorylation.^{257,246} Tannic acid (**145**), widely distributed in wood, is more potent in inhibiting $fA\beta$ *in vitro* than **143**,²⁵⁸ but with its large molecular weight, it is an unrealistic neurological drug candidate. A comparison of these and other active compounds established inhibition, and degradation of the aggregates occurred with the following relative potency: tannic acid (**145**) = NDGA (**143**) = curcumin (**141**) = rosmarinic acid (**144**) = myricetin (**105**) > kaempferol (**106**) = ferulic acid (**100**) > (+)-catechin = (-)-epicatechin (**146**) > tetracycline (**139**).²⁵⁵



Another polyphenol that promotes the decomposition of $A\beta$ aggregates is resveratrol (**117**; *trans*-3,4',5-trihydroxystilbene). Commonly found in grapes, this compound promotes the

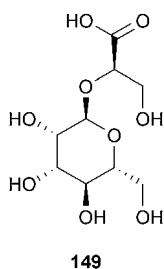
clearance of intracellular $A\beta$ by activating proteasomal degradation.²⁵⁹ A recent study suggests **117** disrupts $A\beta_{42}$ hydrogen bonding thus preventing fibril formation, and it can destabilize preformed $fA\beta_{42}$ *in vitro*,²⁶⁰ but does not prevent oligomerization.²⁶⁰ The ability of **117** to inhibit $A\beta_{42}$ aggregation ranked amongst the highest of the previously studied antioxidants: **117** > catechin > curcumin (**141**) > piceid > ginkgolides.²⁶⁰ Resveratrol is currently in Phase III clinical trials as a nutritional supplement in combination with glucose and malate (Clinical trial # NCT00678431). The underlying rationale is that the glucose and malate prime oxidative metabolism and the Krebs-cycle in the brain, which aids in regenerating the reduced form of resveratrol under normal brain cell metabolism.²⁶¹

1,2,3,4,6-Penta-*O*-galloyl- β -D-glucopyranose (**147**; PGG) is another tannin-type polyphenol that affects $A\beta$ aggregation. Studies have shown that **147** inhibits and destabilizes $fA\beta_{40}$ and $fA\beta_{42}$ both *in vitro* and *in vivo*.²⁶² *In vivo* studies also suggested that it inhibits oligomerization.²⁶² While **147** has activity comparable to curcumin (**141**) and is non-toxic, its high molecular weight and hydrophilicity indicate poor BBB permeability is a serious issue.



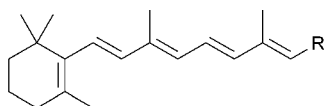
Another sugar derivative with anti-aggregation properties is enoxaparin (**148**), a heparin found in the intestinal mucosa of pigs. Enoxaparin sodium, also known as Lovenox[®], is manufactured by Sanofi-Aventis to prevent deep vein thrombosis. This poly-sulfonated compound was found to reduce $A\beta$ plaque load, reduce the amount of astrocytes surrounding $A\beta$ deposits, and reduce inflammatory effects associated with AD *in vitro*. However, the authors of this study recognize that this compound is not an effective long-term therapy due to its anticoagulant effect and poor bioavailability.²⁶³

The sugar analog α -D-mannosylglycerate (**149**) is a natural extremolyte found in bacteria and archaea that exist in extremely high temperatures. This analog was shown to inhibit aggregation of $A\beta_{42}$ *in vitro* which increased cell survival rates. The authors suggested that **149** had an electrostatic interaction with a lysine residue of the $A\beta_{42}$ that inhibited its aggregation, but acknowledged further confirmation was needed.²⁶⁴ An advantage to this compound is that it is non-toxic even at high concentrations.

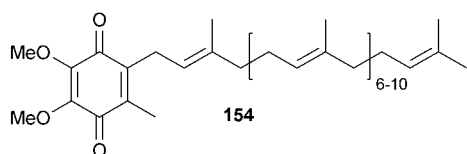
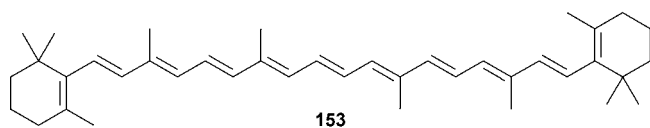


4.4 Terpenoids promoting anti-aggregation and clearance

Terpenoids reported to have anti-aggregation activity are highly lipophilic and include retinol (**150**), retinal (**151**), and retinoic acid (**152**) (components of vitamin A), as well as β -carotene (**153**). Although vitamin A and **153** could inhibit the aggregation of $fA\beta_{40}$ and $fA\beta_{42}$, and destabilize them *in vitro*, these compounds could not depolymerize amyloid fibrils into monomers or oligomers.²⁶⁵ While **150** and **151** have activity comparable to NDGA (**143**), **152** and **153** are less active than **143**. Anti-amyloidogenic and fibril-destabilizing activity are in the order of NDGA = retinol = retinal > β -carotene > retinoic acid.²⁶⁵ A similar result was obtained with coenzyme Q10 (**154**), although it was slightly less potent than **143**.²⁶⁶



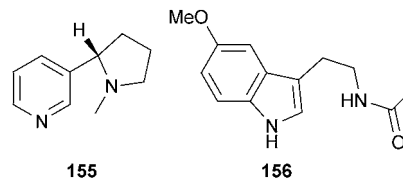
150 R = CH₂OH
151 R = CHO
152 R = COOH



4.5 Alkaloids promoting anti-aggregation and clearance

Only two naturally occurring alkaloids have been reported to directly affect $A\beta$ aggregation. Nicotine (**155**), found in the Solanaceae family, affects multiple stages of amyloidogenesis *in vitro*. It was reported that **155** inhibited the formation and extension of $fA\beta_{40}$ and $fA\beta_{42}$, and was able to destabilize preformed $fA\beta_{40}$ and $fA\beta_{42}$. However, it could not break down the aggregates to their respective oligomers and monomers.²⁶⁷ This anti-amyloidogenic activity was attributed to the *N*-methylpyrrolidine moieties.²⁶⁸ While **155** is less potent than the other inhibitors described above,²⁶⁷ $A\beta$ plaque levels were significantly reduced in transgenic mice after 5.5 months of treatment with **155** versus controls.²⁶⁸ However, *in vivo* studies also suggest **155** increases the aggregation and phosphorylation of tau, which would be an unwanted side-effect.²⁶⁹ Melatonin (**156**) is another

anti-aggregation alkaloid found in many organisms. By disturbing salt bridges between the histidine and asparagine residues in the β -sheet conformation, **156** promotes random coil conformations of $A\beta$ peptides, which facilitates clearance.²⁷⁰ In contrast to many of the compounds mentioned above, **156** can effectively cross the BBB.



5 Kinase modulators (tau and amyloid hypotheses)

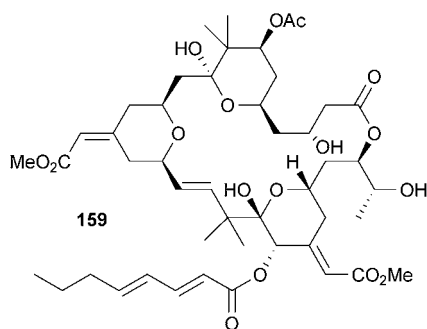
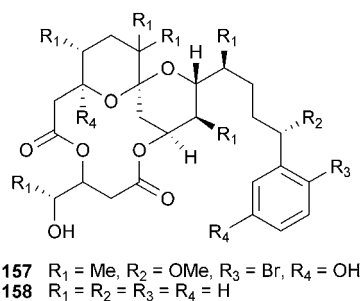
Both activators and inhibitors of kinases have been examined as potential treatments for neurological disorders as kinases regulate a diverse array of cellular functions (reviewed recently by Watterson²⁴). Numerous natural products that interact with kinases have been reported, primarily focusing on their anti-cancer potential.^{271,272} However, there has been comparatively little direct application of natural product kinase inhibitors to the field of Alzheimer's drug discovery.

5.1 Compounds that activate protein kinase C

Protein kinase C (PKC) isoforms are a family of serine/threonine kinases,²⁷³ which are central and potentially critical junctions for memory acquisition and loss in both invertebrates and mammals.^{274,275} For example, the retrieval and formation of long- and short-term memories can be blocked by infusion of PKC inhibitors in an isozyme-dependent manner.²⁷⁶ The first indication of a potential casual role for these proteins in this neurodegenerative disorder was the observation of decreased levels of PKC- α in the brains of Alzheimer's patients²⁷⁷ and that soluble β -amyloid is involved in the reduction^{278–280} by increasing non-amyloidogenic APP processing. Both direct and indirect PKC activation of the non-amyloidogenic pathways has been demonstrated. PKC can directly phosphorylate TACE (TNF- α converting enzyme, ADAM17),^{281,282} which is responsible for regulated α -secretase activity,^{283,282} or indirectly activate α -secretase through the MAP kinase ERK1/2.^{284,285}

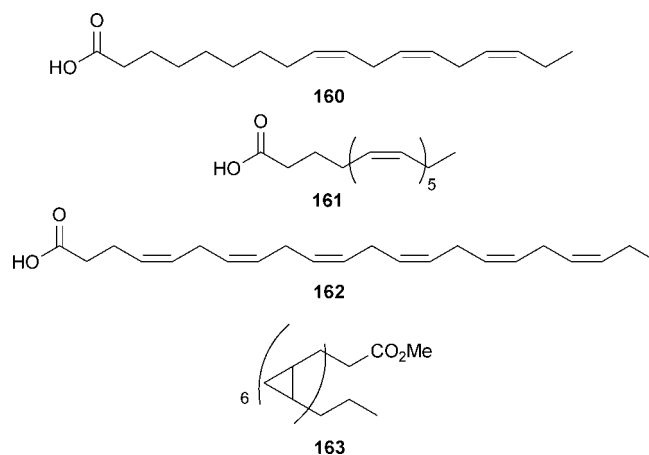
However, most known PKC activators also promote tumor formation. The PKC-activating phorbol esters and indole alkaloids lyngbyatoxin A and teleocidin are widely used in biochemical studies, but are potent co-carcinogens preventing clinical applications. Synthetic compounds have been designed to reduce this effect,^{286,287} or in the case of the tumor-promoting aplysiatoxin (**157**), simplified derivatives (**158**) have been developed that decouple PKC activation from the tumor-promoting effects completely.²⁸⁸ The most notable exception is the natural product bryostatin, discovered in an anti-cancer screen of marine samples by George Pettit²⁸⁹ from the bryozoan *Bugula neritina* L. (Bugulidae). Bryostatin (**159**) enhances α -secretase activation in human fibroblast cells, reduces $A\beta_{42}$ levels, and reduces mortality of transgenic AD mice.²⁹⁰ It also reverses $A\beta_{42}$ produced deficits of PKC and ERK1/2 phosphorylation in cellular models of AD. Phase I and II clinical trials, focused on evaluating its anti-cancer

potential,²⁹¹ have confirmed bryostatin is not tumorigenic despite activating PKC. Blood–brain permeability is clearly a serious obstacle for this compound, and a number of simplified synthetic analogs, “bryologs”, have been developed which may be able to address this issue.²⁹² A Phase II clinical trial using bryostatin remains on-going.



Naturally-occurring polyunsaturated fatty acids (PUFA) from marine oils have been examined as neuroprotective agents against AD (reviewed by Boudrault²⁹³). α -Linolenic acid (**160**), eicosapentaenoic acid (**161**), and docosahexaenoic acid (**162**) are the three major dietary fatty acids, with the last two derived primarily from fish oil. Compound **162** is abundant in the human brain, accounting for 8% of the dry weight. PUFA intake has been evaluated in clinical trials (NCT01058941), the results of which suggest little therapeutic benefit as a treatment for AD, although subgroups of patients with mild cognitive impairment were responsive. Long-term preventative intake over a life-time may be a more viable strategy. Numerous mechanisms have been investigated for these compounds spanning neuroprotective to cholesterol lowering (relating to the APO ϵ 4 mutation). More recently Nishizaki and coworkers²⁹⁴ have demonstrated **160** is capable of selectively activating PKC- ϵ , a novel PKC, in the absence of the other required cofactors (phosphatidylserine and diacylglycerol) facilitating hippocampal synaptic transmission. Cyclopropyl derivatives showing enhanced potency (such as **163**) were prepared separately by Nishizaki²⁹⁴ and Nelson.²⁹⁵ Unlike PKC activators, such as bryostatin and the phorbol esters, that bind to the 1,2-diacylglycerol-binding site and produce prolonged down-regulation, the new activators produced sustained activation of PKC, resulting in a 60–70% reduction in APP-overexpression in human neuronal cell cultures. Endothelin-converting enzyme was also significantly activated, suggesting that the A β -lowering ability of these PKC ϵ activators is caused by increasing the rate of A β degradation by endothelin-converting enzyme, and not by activating non-amyloidogenic amyloid precursor protein metabolism.²⁹⁵ These intriguing

findings further illustrate the complexity of APP processing and A β buildup.

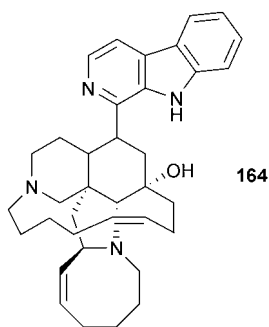


5.2 Compounds that inhibit glycogen-synthase kinase 3 (GSK3)

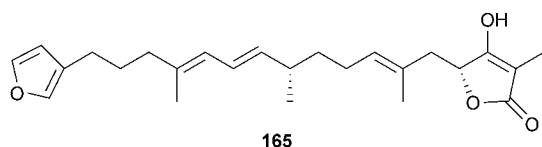
GSK3 is involved in the phosphorylation of tau, a neuronal microtubule-associated phosphoprotein. Tau phosphorylation by GSK3 regulates the binding of tau to microtubules, its degradation and its aggregation. Hyperphosphorylation of tau is the other hallmark of AD, with many arguing this is the critical event. It has been proposed that β -amyloid promotes GSK activation, resulting in this hyperphosphorylation (reviewed by Henandez²⁹⁶). In addition, a “GSK hypothesis of AD” has been proposed by Lovestone and coworkers in which the over-activity of GSK3 results in memory impairment, tau hyperphosphorylation, increased β -amyloid production, and microglial-mediated inflammation.²⁹⁷ Regardless of which hypotheses hold true, inhibiting GSK3 may be a viable therapeutic strategy (reviewed in Martinez¹⁹⁴).

The first direct reversible inhibitor of GSK3 was lithium, discovered in 1996.²⁹⁸ It reduces GSK3 activity by competing with magnesium ions for binding²⁹⁹ and by increasing the inhibitory N-terminal serine phosphorylation of GSK3.³⁰⁰ Treatment with lithium results in decreased tau phosphorylation, which enhances the binding of tau to microtubules and prevents neurotoxicity by reducing the production of β -amyloid in transgenic mouse models.³⁰¹ Clinical trials in Japan and the US are on-going to evaluate the potential of these compounds.

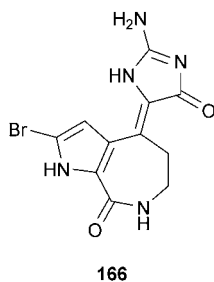
Originally isolated by Higa from an Okinawan sponge of the genus *Haliclona*,³⁰² the alkaloid manzamine A (**164**) was reported as a cellular GSK inhibitor (10 μ M) by Hamann and co-workers in collaboration with NeuroPharm.³⁰³ Manzamine A effectively decreased tau hyperphosphorylation in human neuroblastoma cell lines, thus successfully interfering with tau pathology. Analog semi-synthesis was reported along with structure–activity relationship studies against GSK3, which indicated both the indole and ircinal fragments were required. Selectivity was evaluated against a panel of six kinases, specifically CDK1, PKA, CDK5, MAPK, and GSK3 α . Compound **164** non-competitively inhibited GSK3 β and CDK5, the two kinases involved in tau hyperphosphorylation. These results suggest that **164** constitutes a promising scaffold from which more potent and selective GSK3 inhibitors could be designed as potential therapeutic agents for AD.



Palinurin (**165**) is a linear sesterterpene originally isolated from a marine sponge of the genus *Iricina* Polejaeff (Irciniidae) by Alfano and coworkers in 1979.³⁰⁴ These non-ATP competitive inhibitors of GSK3 (4.5 μ M) were patented by the Spanish biotechnology company NeuroPharm³⁰⁵ in collaboration with PharmaMar. No details have been reported after the initial patent though. Interestingly, a related difuran analog³⁰⁶ was inactive against both GSK3 and CDK5, suggesting the furanone moiety is crucial for activity.

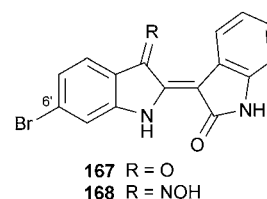


Hymenaldisine (**166**) is a marine alkaloid that belongs to a group of natural products containing both bromopyrrole and guanidine moieties from sponges produced by the Agelasidae, Axinellidae, and Halichondriidae families. As part of a larger screen for kinase inhibitors using a purified library of natural products, Meijer and coworkers³⁰⁷ discovered this compound was a competitive ATP inhibitor of GSK3 β (35 nM) and CDK5/p35 (28 nM) *in vivo*. Both kinases contribute to the phosphorylation of 40 of the 85 available sites on tau. Some degree of selectivity was noted against a broad panel of 40 kinases as most IC₅₀ values were greater than 1 μ M, although CDK1/cyclin B, CDK2/cyclin A, CDK2/cyclin E, and CDK3/cyclin E were also inhibited at low nanomolar concentrations. A crystal structure was obtained with CDK2, but extending these conclusions to identify common structural features for all inhibited kinases was not possible, so additional crystallographic work is required using GSK3 β or CDK5 to better understand hymenaldisine's selectivity against the AD relevant kinases.



Meijer and coworkers also reported that the indirubins were selective GSK3 inhibitors.³⁰⁸ These compounds **167–168**, occurring naturally in gastropod mollusks of the Muricidae and

Thaididae families, have been widely used as components of a dye, known as Tyrian blue, due to their striking purplish-blue color and are the key ingredient in the traditional Chinese medicine '*danggui longhui wan*' used to treat chronic myelocytic leukemia. Compound **167** is derived from a spontaneous non-enzymatic dimerization of two common precursors, istatin and indoxyl. Evaluating both naturally occurring and synthetic analogs revealed that 6'-bromosubstitution on the indirubins conferred strong selectivity for both isoforms of GSK3 (IC₅₀ 22 nM). The selectivity of these competitive ATP kinase inhibitors can be enhanced by converting the ketone **167** to an oxime **168** such that the ERK, MAPKK, and PKC families of kinases were not inhibited up to 10 μ M, while CDK-1, -2, -4 were inhibited at approximately 0.3 μ M. Crystal structures of **167** and other derivatives bound to GSK3 β , CDK5, and CDK2 indicate that the selectivity is due to an unfavorable van der Waals interaction in CDK5 and CDK2 between the 6' bromine atom and the Phe132 residue. In GSK3, a smaller leucine residue is substituted in this position, thus reducing this unfavorable steric interaction. However, given the hydrophobic nature of these compounds, the issue of solubility must be addressed before any clinical application.



A number of other GSK inhibitors have been identified from natural sources over the years (reviewed by Fusetani³⁰⁹ and Alonso³⁰⁵), although as outlined above few have been evaluated in Alzheimer's models. Given the importance of GSK3 in this degenerative disease, a re-evaluation of many of these structural classes as neurological leads may be warranted.

6 Antioxidant natural products

Although oxidative mechanisms are associated with AD pathology, and hypotheses have been proposed,^{310,311,16} clinical trials investigating antioxidants to alleviate AD symptoms have, to date, not been convincing. Evidence for their ability to delay disease progression is limited, with most studies focusing on antioxidant vitamins rather than phytochemicals.^{312–316} Since the pathology of AD is complex, it is too simplistic to assume that antioxidant treatment alone might alleviate or delay cognitive decline in dementia. It should be considered, however, that there is some epidemiological evidence that diets rich in particular antioxidant phytochemicals may reduce the risk of developing dementia.³¹⁷ Thus, a multi-targeted therapeutic approach including antioxidants in combination with drugs or phytochemicals that target other pharmacological mechanisms might be a more rational approach to dementia treatment. It is therefore not surprising that those plants that produce some positive effects on cognition in AD patients have frequently shown antioxidant and other activities relevant to dementia pathology when their modes of action have been investigated *in vitro* and *in vivo*. Those species with a range of relevant neurobiological

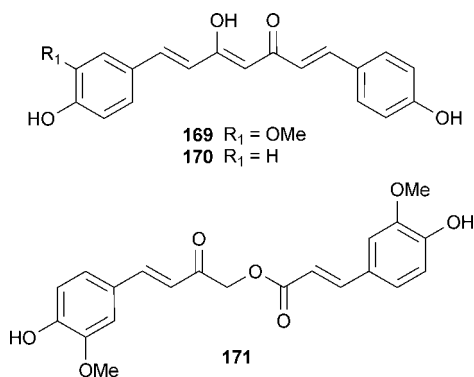
activities, including antioxidant, that have shown some promising effects on cognition in dementia patients include *Salvia officinalis* L. or *S. lavandulifolia* Vahl., *Melissa officinalis* L. (Lamiaceae), *Crocus sativus* L. (Iridaceae) and the extensively studied *Ginkgo biloba* L. (Ginkgoaceae).⁹⁶ *G. biloba* has been the subject of much attention for its antioxidant activity and other modes of action, and for its clinical effects in dementia (recently reviewed by Shi *et al.*³¹⁸ and Perry and Howes⁹⁶). It should be noted however, that a recent Cochrane review concluded that evidence for any predictable or clinically significant benefit of *G. biloba* in dementia or cognitive impairment is inconsistent and unreliable, although it appears to be safe with few adverse effects.³¹⁹ The contradictory data for *G. biloba* clearly suggests further trials are needed.

Consumption of curry is associated with improved cognitive function³²⁰ and a lower prevalence of AD in some populations, which is suggested to be due to a curcumin-rich diet.³¹⁷ Curcumin (**141**) from turmeric (*Curcuma longa* L. (Zingiberaceae)) has numerous activities, including antioxidant, which might explain the beneficial cognitive effects. Curcumin (**141**) is neuroprotective *in vitro*³²¹ and in addition to other compounds from *C. longa* (demethoxycurcumin (**169**), bisdemethoxycurcumin (**170**), calebin A (**171**)) and some synthetic analogs, protects PC12 cells from β -amyloid^{322,323} due to antioxidant effects.³²² Other mechanisms³²⁴ may also contribute to these protective effects though as curcumin (**141**) protects against ethanol-induced brain injury, reduces brain lipid peroxide levels and enhances glutathione, thus reducing oxidative damage, in an *in vivo* dementia model.^{325–327} It also protects against aluminium-induced cognitive dysfunction and ameliorates memory impairment (prevents and treats) *in vivo*.^{111,328} It is reported that the enol structure with the intramolecular hydrogen bond is principally responsible for the free radical scavenging activity of **141**, and the phenolic hydrogens are essential for antioxidant activity and free radical kinetics.³²⁹ An indirect antioxidant mechanism of **141** is its ability to complex with metal ions (observed *in vitro* and *in vivo*),³³⁰ suggested to be *via* the diketone and pairs of phenol and methoxy groups of the structure of **141**.³³¹ It is therefore suggested to reduce metal-induced amyloid aggregation or oxidative neurotoxicity in AD.³³¹ A recent finding is that **141** can maintain the catalytic function of protein disulfide isomerase (PDI), which catalyzes maturation of disulfide-bond-containing proteins; **141** prevents PDI-resistant misfolded protein forms that accumulate with oxidative stress and are involved in the pathogenesis of AD.³³² Other mechanisms of **141** relevant to modulating AD

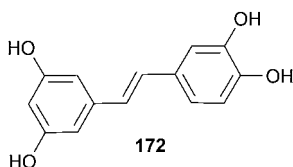
pathology have been recently reviewed.³¹⁷ Evidence for efficacy of **141** in dementia patients is lacking – some clinical studies in AD patients are in progress, but the outcomes are still unknown.³²⁹

Green tea (*Camellia sinensis* (L.) Kuntze (Theaceae)) leaves contain polyphenolic compounds, with catechins as the major constituents, although processing methods influence the chemical composition of tea leaves.³³³ Epidemiological data suggest green tea polyphenols improve age-related cognitive decline and associate tea drinking with a reduced risk of dementia.^{334,335} Catechins are well-documented as antioxidants and scavengers of reactive oxygen species (ROS), and they chelate metal ions.^{317,336,334,337} Tea catechins improve memory acquisition and retention in senescence-accelerated mice (SAM) and suppress oxidative damage to DNA in SAM brains.³³⁴ Epigallocatechin-3-gallate (**115**) is a more potent scavenger of ROS than some other tea catechins, which is attributed to the presence of the trihydroxyl group on the B ring and the gallate moiety at the 3' position in the C ring;^{314,336} this is perhaps why subsequent studies investigating the relevance of tea catechins for AD have focused on **115**. It is the scavenging of ROS that explains a protective effect of **115** on hippocampal neuronal cells exposed to β -amyloid,³³⁸ and *in vivo*, **115** mitigated β -amyloid-induced oxidative stress and reduced hippocampal lipid peroxide.³¹⁷ One mechanism by which **115** protects against β -amyloid-induced oxidative cell death is by enhancing cellular glutathione by elevating mRNA expression of γ -glutamylcysteine ligase, the rate-limiting enzyme in glutathione biosynthesis.³³⁹ It is also suggested that **115** is neuroprotective against oxidative stress by stimulating protein kinase C and modulating cell cycle genes.³⁴⁰ Epicatechin (**146**) increased glutathione levels in astrocytes,³⁴¹ and it improved memory skills and decreased lipid peroxidation and ROS in rats with β -amyloid-induced hippocampal toxicity.³⁴² Other bioactivities of tea catechins relevant to AD have been recently reviewed.^{317,336,337}

Light to moderate alcohol consumption is associated with a reduced risk of AD and some other types of dementia³⁴³ and epidemiological evidence suggests moderate red wine consumption may attenuate clinical dementia in AD.³⁴⁴ Various activities have been associated with wine polyphenols, resveratrol (**117**) in particular, and thus are suggested to explain the possible preventive effects, and have been investigated for possible therapeutic effects for AD. Resveratrol (**117**) (*trans*-3,4',5-trihydroxystilbene) occurs in various plants including grapes (*Vitis vinifera* L. (Vitaceae)) and it produces a number of mechanistic effects, including antioxidant, relevant for AD treatment. Specifically, it scavenges ROS (the 4'-OH group is an important structural feature), up-regulates cellular antioxidants including glutathione and is neuroprotective against oxidative stress *in vitro* and *in vivo*.^{345,317,346} Piceatannol (**172**) (3',4',3,5-tetrahydroxystilbene) occurs in many resveratrol-containing species but at lower concentrations. It is a metabolite of **117** and has also been considered for application in neurodegenerative diseases. Interestingly, **172** is a more efficient scavenger of ROS than **117**, due to the additional 3'-OH group adjacent to the 4'-OH group present in **117**; the 3'-OH hydrogen is shared through a strong intramolecular hydrogen bond between O-3' and O-4', making the abstraction and transfer of the 4'-H atom to a free radical easier, and resulting in the formation of a more stable



semiquinone radical.³⁴⁷ Resveratrol (**117**) protects astrocytes in rat hippocampal slices from H₂O₂-induced oxidative stress by increasing glutathione levels, in addition to other mechanisms.³⁴⁸ It also prevents cognitive impairments and associated oxidative stress *in vivo*^{317,349} and reduces plaque formation in a transgenic model of AD.³⁵⁰ It is apparent there is emerging evidence that **117** may modulate AD pathology due to antioxidant effects, or by various other mechanisms (including activation of sirtuin 1, a histone deacetylase which is involved in responding to molecular damage and metabolic imbalances).^{317,351,352} However, clinical evidence for any potential efficacy on AD progression is still lacking.

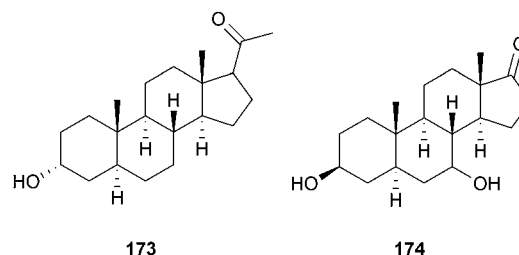


There are numerous other reports of structurally diverse phytochemicals that display antioxidant effects and are suggested as relevant to modulate dementia pathology, although the majority of these studies have focused on structures with phenolic components. The effects of a range of dietary polyphenols on events related to AD pathology have recently been reviewed.^{353,354} There are many flavonoids reported to protect against oxidative stress in neuronal cell-lines and in some brain conditions *in vivo*.^{355,356} Antioxidant mechanisms are considered to explain why some flavonoids protect against oxidative stress [quercetin (**77**), myricetin (**105**), luteolin (**78**),^{357,358} hyperoside,³⁵⁹ fisetin (**142**)³⁶⁰] and β -amyloid-induced toxicity [puerarin,³⁶¹ genistein,³⁶² **77**,³⁶³ naringenin (**79**),³⁶⁴ baicalein, baicalin⁹³] in neuronal cells *in vitro*, and against β -amyloid-induced cognitive impairments *in vivo* [silibinin³⁶⁵]. Several synthetic lipophilic alkenylated 2,3-dehydrosilybin analogs of the flavolignan silibinin are neuroprotective against H₂O₂-induced toxicity *in vitro* and are being investigated for their pharmacological potential in CNS disorders.³⁶⁶

Also of notable interest are studies in rodents showing dietary supplementation with spinach (*Spinacia oleracea* L. (Chenopodiaceae)), strawberry (*Fragaria ananassa* Duchesne (Rosaceae)), or blueberry (*Vaccinium* species (Ericaceae)) extracts reversed brain age-related deficits and behavioral function, and blueberry supplementation effectively reversed cognitive declines in object recognition; these observations were not attributed to antioxidant activity alone.³⁶⁷ However, strawberry and blueberry anthocyanins protect against oxidative stress in neuronal cells *in vitro*³⁶⁸ and in rodent brain *in vivo*, respectively.³⁶⁹ In a recent preliminary trial, wild blueberry (*V. angustifolium* Benth.) juice (containing anthocyanins and phenolic compounds, including chlorogenic acid) consumed for 12 weeks produced neurocognitive benefits in older adults with early memory changes, compared to a placebo beverage absent from natural polyphenolic compounds.³⁷⁰ It is apparent that there is some therapeutic potential for antioxidant phytochemicals in cognitive disorders. However, there is a lack of evidence that the activities of these phytochemicals can be translated to clinically relevant effects in the complex pathology of AD.

7 Neuro-regenerative compounds

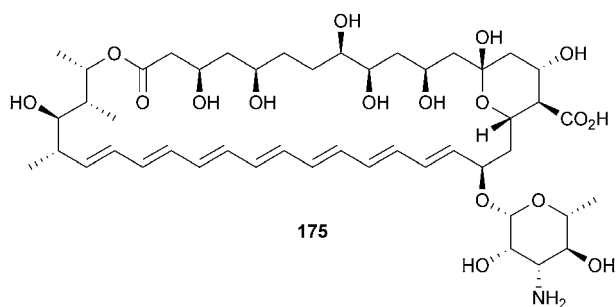
Allopregnanolone (**173**) is a progesterone metabolite produced in embryonic and adult CNS. The abundance of neurosteroids, such as allopregnanolone, decreases during aging, but in particular, in AD patients in a manner that parallels the decline in the proliferative ability of neuronal progenitor cells. Treatment with allopregnanolone has been shown to significantly increase proliferation and survival of neural progenitor cells in rodents and human cells *in vitro*.³⁷¹ These beneficial effects occur *via* GABA_A receptor and L-type Ca²⁺ channel-dependent mechanisms leading to an efflux of chloride and an activation of CREB transcription factors.^{372,371} This activates a key pathway in adult hippocampal neurogenesis that promotes proliferation, survival, and differentiation of neural progenitor cells. Brinton and coworkers recently demonstrated the efficacy of allopregnanolone treatment in a male triple transgenic mouse model of Alzheimer's.³⁷³ In a dose-dependent manner, treatment with **173** prior to the onset of AD pathology restored neural progenitor cell proliferation to normal levels and reversed the cognitive deficits, thus restoring normal learning and memory performance. These findings suggest that treatment with allopregnanolone may serve as a regenerative therapeutic for patients with mild cognitive impairment and AD, at a stage before immunodetectable A β .³⁷³



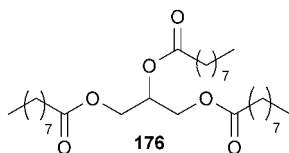
Other steroids have been evaluated as neuroprotective agents. HF0220 is a 7-hydroxy epiandrosterone (**174**). These compounds are produced when CYP450 hydroxylates steroids, such as estradiol, at the 7-position which occurs at high levels in the brain. Pringle and coworkers³⁷⁴ have demonstrated that these hydroxylated metabolites significantly reduced neurotoxicity at concentrations of 10 and 100 nM in a rat model of cerebral ischaemia even when administered after onset. HF0220 (**174**) has been developed further by Hunter-Fleming, which was acquired in 2008 by Newron Pharmaceuticals. This compound has successfully completed safety and tolerability studies in patients with mild to moderate AD. The very high rate of completion of the study by patients, the absence of clinically relevant or statistically significant changes in safety measures, and the very low number of patients experiencing any adverse events, indicate that HF0220 can be safely administered to patients with AD who often experience multiple concomitant illnesses and who are more susceptible to the side-effects of their usual medications.³⁷⁵

Successful axon regeneration in the adult CNS is normally prevented by a number of factors, including the presence of inhibitory molecules that originate from the myelin sheath and glial scars.³⁷⁶ Upon injury to axons, the myelin sheath breaks down, releasing inhibitory components, myelin-associated inhibitors (MAIs) containing Nogo-A proteins, myelin-associated

glycoproteins (MAG), and oligodendrocyte–myelin glycoproteins.³⁷⁷ A glial scar forms shortly after the injury, producing extracellular matrix molecules, such as chondroitin sulfate proteoglycan, that suppress axonal growth.^{378,379} However, only a few compounds have the ability to interrupt these inhibitors in a manner that enhances neurite outgrowth *in vivo*. The Discovery Neurosciences division of Wyeth (now Pfizer Research) initiated a screen of 180 diverse natural products and a 1300-compound drug set to identify antagonizers of these inhibitory molecules. Amphotericin B (**175**) was shown to promote neurite outgrowth and prevent the activities of the major myelin- and glial-associated inhibitors.³⁸⁰ This intriguing effect was not related to amphotericin's antifungal activity, as the structurally and mechanistically related pore-forming antibiotic nystatin had no effect on neurite outgrowth. Comparative screening of a library of kinase inhibitors revealed that this antagonism occurred *via* activation of Akt, which suppressed the activity of GSK3 β .



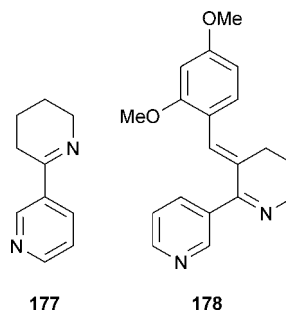
Almost 20% of the body's consumption of glucose occurs in the brain, suggesting metabolic deficits that are noted in AD patients may significantly contribute to pathogenesis. Attempts to compensate for reduced cerebral metabolic rates by supplementing with glucose and insulin have met with some success, although have notable side effects. An alternative strategy is to administer ketone bodies (acetone, acetoacetic acid, and β -hydroxybutyrate), either directly or as their metabolic precursors (medium-chain triglycerides). Accera developed two products along these lines. In a preliminary study, KetasyTM (AC-1202) demonstrated pharmacological activity and statistically significant efficacy in improving short-term memory and attention performance after a single dose in clinical trials. More recently, this formulation has been renamed Axona (the active ingredient being **176**) and it has been approved as a "medical food" intended for the clinical dietary management of the metabolic processes associated with mild-to-moderate AD. Medical foods are specially formulated prescribed foods defined under the US Orphan Drug Act of 1988. These are "intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."



8 Modulators of ion channels

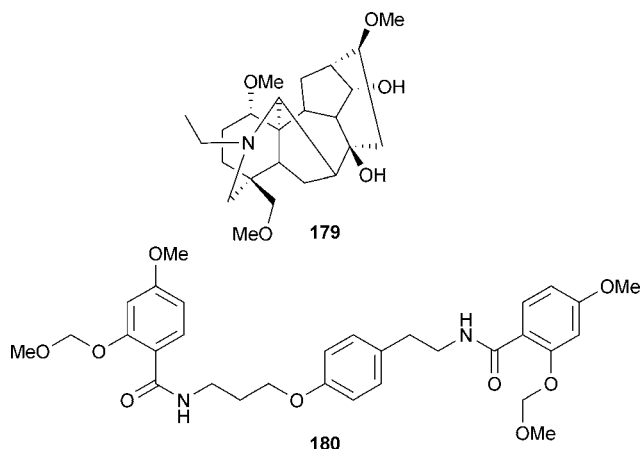
Ion channels have a critical role in maintaining proper CNS function, and have long been suspected as a potential factor in AD.³⁸¹ For example, accumulation of A β peptides in neurons has been shown to activate ion channels, causing an influx of Ca²⁺ that disrupts homeostasis, leading to mitochondria malfunction and oxidative stress and apoptosis of neurons.³⁸² To date, the only successful modulator of these targets for the treatment of AD is the synthetic *N*-methyl-D-aspartate receptor (NMDAR) antagonist, memantine, approved in the EU in 2002 and in the US in 2003³⁸³ for patients with moderate-to-severe AD. Evidence suggests it protects against Ca²⁺ influx without disrupting physiological synaptic activity.³⁸⁴ This beneficial effect is in sharp contrast to other high-affinity NMDAR antagonists that are often neurotoxic.³⁸⁴ However, a clear rationale to explain these discrepancies is still lacking.³⁸⁴ Several synthetic compounds, which target L-type Ca²⁺ (reviewed by Yu³⁸⁵) and nicotinic receptor ion channels (reviewed by Arneric³⁸⁶) are currently undergoing clinical evaluations to determine their efficacy as well.

The first marine natural product to be evaluated as a potential treatment for AD, based on its ability to modulate ion channels, was described by William Kem (reviewed by Kem³⁸⁷). In 1971, Kem reported the discovery of the alkaloid anabaseine (**177**) from several species of marine worms which prompted an extensive evaluation of this compound and synthetic derivatives. This research has culminated in DMXBA [also known as GTS-21; **178**] which recently completed a Phase II clinical trial with Comentis Inc. for schizophrenia, in which patients demonstrated improvements in cognitive function.²³ These beneficial effects are due to the ability of GTS-21 to stimulate selectively $\alpha 7$ nicotinic acetylcholine receptors expressed on CNS neurons and astrocytes.³⁸⁸ GTS-21 counteracts the neurotoxic effects of β -amyloid in neuronal cells from the cerebral cortex, and improves cognitive functions in a variety of animal models. For full details regarding GTS-21, the reader is directed towards the recent review by Toyohara and Hashimoto.³⁸⁹



Natural products that modulate ion channels have been discussed elsewhere,^{390,391} and as such, will only be briefly mentioned. Talatisamine (**179**), an alkaloid in *Aconitum heterophyllum* Wall. (Ranunculaceae), was evaluated for its channel specificity (K⁺, Na⁺ and Ca²⁺) in rat hippocampal neurons.³⁹² Compound **179** specifically inhibited potassium currents (I_K) by binding to the external pore entry of the channel with an IC₅₀ value of 146.0 \pm 5.8 μ M.³⁹² The prenylflavone icariin (**81**), isolated from *Epimedium brevicornum* Maxim. (Berberidaceae), was

shown to reduce behavioral dysfunction and neurodegeneration in rat models,³⁹³ while blocking Ca^{2+} currents disrupted by A β 25-35.³⁹⁴ A synthetic derivative (NP04634, **180**) of the metabolite 11,19-dideoxyfistularin from the sponge *Aplysina cavernicola* Vacelet (Aplysinidae) protected neurons from calcium overload and mitochondrial disruption. Specifically, **180** protects neurons from toxicity induced by 30 μM $\text{K}^+/\text{5Ca}^{2+}/\text{FPL}$ at a concentration of 10 μM , reduces voltage-dependent Ca^{2+} levels and protects mitochondrial disruption by preventing depolarization.³⁹⁵



Voltage-gated K^+ channels (K_V) are responsible for the electrical activity in neurons, and a reduction of K^+ in cells can cause neuronal apoptosis. A study by Yu *et al.* demonstrated that exposure to A β fragments induces cell death by enhancing the delayed rectifier K^+ current (I_K), which causes an efflux of K^+ that consequently leads to apoptosis.³⁹⁶ Since the addition of I_K blockers (TEA, 5 mM) slowed neuronal death in this study, as opposed to the addition of Ca^{2+} blockers, it was suggested that I_K plays a pivotal role in neuronal apoptosis. Further evidence that the K_V 3.4 ion channel, in particular, is involved in amyloid pathology was provided by the observation of overexpression of K_V 3.4 in transgenic mice with the Swedish mutation of APP.³⁹⁷

BDS-I and -II toxins, isolated from *Anemonia viridis* Forskål (Actiniidae), are peptides that were found to block K_V more specifically than talatisamine. Out of the four major potassium channel subfamilies (K_{V1} , K_{V2} , K_{V3} , and K_{V4}), BDS-I and -II

were originally reported to inhibit the K_V 3.4 ion channel with IC_{50} values of 47 nM and 56 nM respectively.³⁹⁸ While Diochot *et al.* reported that BDS-I was able to block K_V 3.4 specifically, Yeung *et al.* showed that BDS-I also inhibits other K_V 3 subfamilies, K_V 3.1 and K_V 3.2.³⁹⁹ Since AD distinctively affects the K_V 3.4 ion channel, there is still a need for blockers that are specific to the K_V 3.4 ion channel.

Many natural products have been identified as potassium channel blockers. For instance, compounds have been isolated from scorpion venom (charybdotoxin, maurotoxin, margatoxin, agitoxin-2, kaliotoxin), sea anemone toxin (ShK toxin), and a Costa Rican tree (correalide) all of which are active at nM and pM concentrations.⁴⁰⁰ All of these compounds serve as examples of very active ion channel blockers from natural sources; however, they also point to the importance of finding a blocker with affinity to the right type of ion channel, as well as to the desired ion channel subfamily.

9 Conclusions

Several conclusions about natural product Alzheimer's drug leads are supported by the literature. First, the majority of the compounds examined to date with a direct relevance to AD are primarily from plants, with comparatively few molecules derived from marine and microbial sources. Also, to date, the greatest successes have come from plant-based AChE discovery programs, which have provided two of the five currently approved drugs for the treatment of AD. This latter fact likely significantly contributes to the former. However, it is widely accepted that these AChE inhibitors are only effective at treating the symptoms of AD in the short term, and a broader range of therapeutics is needed. Given the diverse pathology of AD, these therapeutics might target multiple mechanisms simultaneously. Several compounds noted above, EGCG (**115**), galantamine (**1**), resveratrol (**117**), and withanolide A (**131**), fulfill these requirements, although further study is needed in all cases. As illustrated by this review, and summarized in Table 1, a number of natural products are currently being evaluated for their clinical effects against AD. Whether the requisite properties can be engineered into these leads, either as individual agents or in combination, remains to be seen.

Table 1 Clinical status of selected Alzheimer's natural products or derivatives

Mechanism	Compound	Source	Phase I	Phase II	Phase III	Phase IV
AChE	Galantamine (1)	Plant	✓	✓	✓	✓
	Rivastigmine (2)	Synthetic analog	✓	✓	✓	✓
	Huperzine A (40)	Plant	✓	✓		
Secretase	NP-12 (125)	Marine	✓	✓		
	Homotaurine (135)	Marine	✓	✓	Discontinued	Nutraceutical
Aggregation/Clearance	AZD-103 (136)	Plant	✓	✓		
	Bapineuzmab	Antibody	✓	✓	✓	
	Colostrinin	Mammal				Nutraceutical
	Rifampicin (137)	Bacteria	✓	✓	✓	
	Curcumin (141)	Plant	✓	✓		
	Resveratrol (117)	Plant	✓	✓		
	Bryostatin A (159)	Marine	✓	Recruiting		
Kinases	Lithium	—	✓	✓		
	HF-0220 (174)	—	✓			
Neuroprotein	Axona (176)	—				Medical food
	GTS-21 (178)	Synthetic analog	✓	✓		

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