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Review

Recent Progress on Biological Activity of Amaryllidaceae and Further Isoquinoline Alkaloids in Connection with Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a progressive age-related neurodegenerative disease recognized as the most common form of dementia among elderly people. Due to the fact that the exact pathogenesis of AD still remains to be fully elucidated, the treatment is only symptomatic and available drugs are not able to modify AD progression. Considering the increase in life expectancy worldwide, AD rates are predicted to increase enormously, and thus the search for new AD drugs is urgently needed. Due to their complex nitrogen-containing structures, alkaloids are considered to be promising candidates for use in the treatment of AD. Since the introduction of galanthamine as an antimentia drug in 2001, Amaryllidaceae alkaloids (AAs) and further isoquinoline alkaloids (IAs) have been one of the most studied groups of alkaloids. In the last few years, several compounds of new structure types have been isolated and evaluated for their biological activity connected with AD. The present review aims to comprehensively summarize recent progress on AAs and IAs since 2010 up to June 2021 as potential drugs for the treatment of AD.

Keywords: isoquinoline alkaloids; Alzheimer's disease; acetylcholinesterase; butyrylcholinesterase; prolyl oligopeptidase; monoaminooxidase; neuroprotective activity; docking study

1. Introduction

Alzheimer's disease (AD), a multifactorial neurodegenerative disease that affects the elderly population, is the most common form of dementia that is generally diagnosed in individuals over the age of 65 years, and the one with the strongest social impact with regard to incidence, prevalence, mortality rate, and cost of care [1–3]. The prevalence of AD is growing rapidly, in line with an increase in the age of the population. AD currently affects over 50 million people worldwide and is estimated to nearly triple by 2050 [4]. The exact cause of AD is constantly under debate and review. Several hypotheses have been put forward, including cholinergic, amyloid beta (A β), hyperphosphorylation of τ -protein, calcium dyshomeostasis, and oxidative stress [5,6]. Pathological changes in the brain of a patient with AD can occur more than twenty years before clinical symptoms are apparent [7]. From a neuropathological point of view, the most pronounced selective cholinergic neuronal loss is accompanied by the formation of intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated τ -protein and extracellular senile plaques (SPs) mediated by β -amyloid peptide (A β) [8]. SPs are extracellular deposits composed of various peptide fragments (A β _(1–40) and A β _(1–42)) derived from the amyloid precursor protein

(APP) [9]. These proteins generate deposits in specific areas of the brain and are considered critical factors for memory loss and cognitive impairment in AD patients [10].

Acetylcholinesterase (AChE, EC 3.1.1.7) is a serine-protease that plays a pivotal role in cholinergic transmission in the central nervous system and at the neuromuscular junctions (NMJ). The physiological function of AChE is to hydrolyze acetylcholine (ACh) to afford choline (Chol) and acetic acid, thus playing a key role in cholinergic neurotransmission within the autonomic and somatic nervous system [11]. AChE is mainly expressed in nervous tissue, neuromuscular junctions, plasma and red blood cells [2,12]. In the human brain, there are two structural types of AChE: type G4 (tetramer, highly prevalent) and monomer G1 (in minor amount). The proportion of G1 (monomer) is significantly increased in AD [13].

Similar to AChE, another cholinesterase, butyrylcholinesterase (BuChE, EC 3.1.1.8) can also inactivate ACh. Whilst, under normal conditions, BuChE is responsible for 20% of the total brain cholinesterase activity, in the later stages of AD the activity of BuChE increases to 40–90% in certain brain regions. This dramatic switch between the AChE/BuChE ratio implies a change from a supportive role to a leading role for BuChE in hydrolyzing the excess of ACh [14]. The two enzymes have different abilities to hydrolyze substrates. These differences are probably caused by changes in the arrangement of amino acids in the aromatic cavity. Altered expression of AChE in the brain of patients with AD suggests that AChE activity increases at the periphery of the amyloid plaque (around the A β plaques) and A β actually affect the levels of AChE. It has been found that different forms of AChE in the brain and cerebrospinal fluid of patients with AD are changed in connection with abnormal glycosylation [15]. While the role of AChE in neurodegenerative diseases is relatively well known, that of BuChE is still not completely clarified. This pseudocholinesterase does not have natural substrates in the organism [13]. Some studies have shown that BuChE may indirectly contribute to the pathogenesis of type 2 diabetes mellitus (T2DM) by causing insulin resistance [16]. Sharing the pathological similarities between AD and T2DM (enhanced amyloid beta aggregation, abnormal levels of cholinesterase) gave rise to the hypothesis that cholinesterase inhibitors (ChEIs) can potentially treat both these disorders. Although ChEIs afford mostly a symptomatic response to AD patients, the development of new ChEIs (e.g., multifunctional ligands, selective BuChE inhibitors) remains of interest to treat neurodegenerative diseases. ChEIs may also be used as a treatment for an autoimmune disease named myasthenia gravis, by targeting nicotinic acetylcholine receptors at the neuromuscular junction, and as a prophylactic treatment against organophosphorus nerve agent poisoning [17,18].

Excitatory glutamatergic neurotransmission via the N-methyl-D-aspartate receptor (NMDAR) is critical for synaptic plasticity and the survival of neurons. Glutamate is the most abundant excitatory neurotransmitter in the mammalian CNS. It is extensively distributed in the CNS, where it is almost exclusively located intracellularly [19]. However, excessive NMDAR activity causes excitotoxicity and promotes cell death, underlying a potential mechanism of neurodegeneration that occurs in AD. The glutamatergic hypothesis postulates that the progressive cognitive decline seen in AD patients is due to neuronal cell death caused by the overactivation of NMDA receptors and the subsequent pathological increase in intracellular calcium. Several studies have shown that both soluble A β oligomers and τ -protein can interact with several glutamate signaling proteins, such as NMDA receptors and proteins involved in glutamate uptake and recycling, leading to glutamate excitotoxicity [20]. Several current AD treatments target glutamatergic signaling, including memantine, which is an FDA-approved low-affinity NMDA receptor antagonist.

As mentioned above, one of the neuropathological characteristics of AD is the presence of NFTs, in which the formation enzyme glycogen synthase kinase-3 β (GSK-3 β , EC 2.7.11) plays an important role. GSK-3 β is a multifunctional serine/threonine kinase, which is recognized as a key component of multiple signaling pathways [2]. It plays a crucial role in cellular functions, including cell-cycle regulation, differentiation, and proliferation. More recently, GSK-3 β has been found to play a crucial role in neurodegeneration in

general and AD in particular [21]. In AD, the overactivity and/or overexpression of GSK-3 β accounts for memory impairment, tau hyperphosphorylation, increased β -amyloid production and local plaque-associated microglial-mediated inflammatory responses, which are hallmarks of the disease [22]. Since the phosphorylation of τ -proteins is primarily dependent on GSK-3 β and cyclin-dependent kinase 5 (CDK5, EC 2.7.11.22) [23], inhibition of GSK-3 β and CDK5 is accepted as a promising strategy for the treatment of AD [24].

In pathological processes such as neurodegeneration and depression, low levels of monoamine neurotransmitters have been found. Studies have shown that activated monoamine oxidase (MAO) in the brain of patients with AD is a biomarker for the disease, and it is presumed to induce overproduction of hydroxyl radicals in the brain triggering a biochemical cascade connected to the deposition of A β plaques [25,26]. MAO exists in two isoenzymes in humans—MAO-A and MAO-B—which are distinct due to different amino acid sequences, three-dimensional structures, distribution in organs and tissue, inhibitor sensitivities and substrate specificity [61]. Activated MAO-B leads to cognitive dysfunction, destroys cholinergic neurons, causes disorder of the cholinergic system and contributes to the formation of amyloid plaques [27]. MAO inhibitors have neuroprotective effects related to oxidative stress, which are desirable properties for the development of multi-target drugs for AD.

In recent years, the enzyme prolyl oligopeptidase (POP, EC 3.4.21.26) has gained importance as a target for the treatment of schizophrenia (SZ), bipolar affective disorder (BD) and cognitive disturbances, such as those present in Alzheimer's disease (AD). POP is a serine protease of the S9 protein family that cleaves peptide bonds at the carboxyl end of proline [28]. POP is primarily expressed in the hippocampus, hypothalamus, amygdala, cortex and striatum regions of the brain [29]. It has been discussed that reduced POP activity correlated to the tau pathology and severity of AD [30]. Moreover, POP is associated with learning and memory because it degrades several neuro-peptides; thus, inhibition of POP can impose an interesting alternative for AD treatment [31].

The current treatment, based on the cholinergic hypothesis, is only symptomatic and mainly involves the restoration of ACh levels through AChE inhibition [11]. Three AChE inhibitors, namely, donepezil, galanthamine, and rivastigmine, and one fixed-combination of donepezil and memantine (approved in 2014) are currently used as the main therapeutic option for AD treatment [32,33]. These available drugs are marketed for mild to severe stages of AD. They are able to alleviate cognitive and behavioral symptoms for only a limited period (few months after the start of treatment) [32].

In July 2021, a new AD drug named aducanumab, sold under the brand name Aduhelm, was approved in the USA by the FDA. Aducanumab, a human IgG1 monoclonal antibody, is the first drug with a putative disease-modifying mechanism for the treatment of this devastating disorder, namely, the removal of β -amyloid (or A β) plaques from the brain [34]. The decision was highly controversial and led to the resignation of three FDA advisers because of the absence of evidence that the drug is effective, as clinical trials gave conflicting results on its effectiveness [35,36].

Natural products represent an important source of clinical drugs, especially for their structural diversity and a wide range of biological activities [37]. Alkaloids are, without a doubt, the most intriguing templates of natural origin [38]. Given the fact that Alzheimer's disease has become an important topic in recent years, and a large number of papers have been published on this subject, this review covers the recent progress on Amaryllidaceae alkaloids and further isoquinoline alkaloids, and their biological activity related to AD published between 2010 and 2021. Previous results can be found in the following review articles [39–42]. Recently, a detailed review on cholinesterase inhibitors from marine organisms has been published [41].

2. Isolation of Alkaloids from Plant Material for Biological Evaluation

The critical step in the biological evaluation of AAs is their isolation from plant materials, and thus much of the activity has been directed towards the development

optimum methods for the isolation of alkaloids and alkaloid mixtures. Because the alkaloids usually occur in plants as salts of organic plant acids and inorganic acids, together with complex mixtures of water-soluble compounds, it is often a problem to remove all of the non-alkaloidal compounds during isolation and purification [43–45]. Most alkaloids are insoluble in water and more or less soluble in such organic solvents as ether, chloroform, dichloromethane, and ethyl acetate, whereas their salts have just the opposite solubility characteristics [46].

The general methods of extraction and isolation of alkaloids include the separation of them from the main bulk of the non-alkaloidal substances with solvents such as methanol and ethanol; in some studies, *n*-butanol has also been used [44,47]. The crude concentrated extract is often subjected to successive extractions with ether, ethyl acetate, chloroform or dichloromethane using the acid-base properties of alkaloids. When the crude extract is exposed to an alkaline medium, the alkaloidal salts are readily converted to the corresponding alkaloid bases to form a concentrated alkaloidal extract. These concentrated alkaloidal extracts are subsequently separated by either silica gel or aluminum oxide column chromatography (CC), flash chromatography (FC), preparative high-performance liquid chromatography (HPLC), preparative thin layer chromatography (TLC), and crystallization [43,46]. CC is used especially when a higher amount of plant material is available for the isolation of AAs (normally over 1 kg). Because of the possible formation of isolation artifacts of alkaloids (like *N*-chloromethyl-, methoxy-, ethoxy- and butoxy-derivatives), it is necessary to specify the used solvents within all steps of the phytochemical study to identify if the isolated compound is really a natural product [48–50]. Alcohols can react with a carboxylic group to form esters, and with hemiacetals to form acetals. As a result of the interaction of alcoholic solvents (e.g., methanol and ethanol) with hydroxy groups, methoxy and ethoxy functions can be detected within isolated products. Within Amaryllidaceae alkaloids (AAs), butoxy-derivatives have also been described when *n*-butanol has been used within the phytochemical study [49,51]. Halogen-containing solvents are very unstable, because of their direct interaction with molecules, and because of the presence of contaminants as well [52]. It has been reported that chloroform can directly react with alkaloids, as in the case of AAs and protoberberine-type isoquinoline alkaloids [53]. Furthermore, chloroform can accelerate the decomposition processes of compounds, especially when the solutions of fractions and subfractions are not stored in the dark [52].

3. Amaryllidaceae Alkaloids

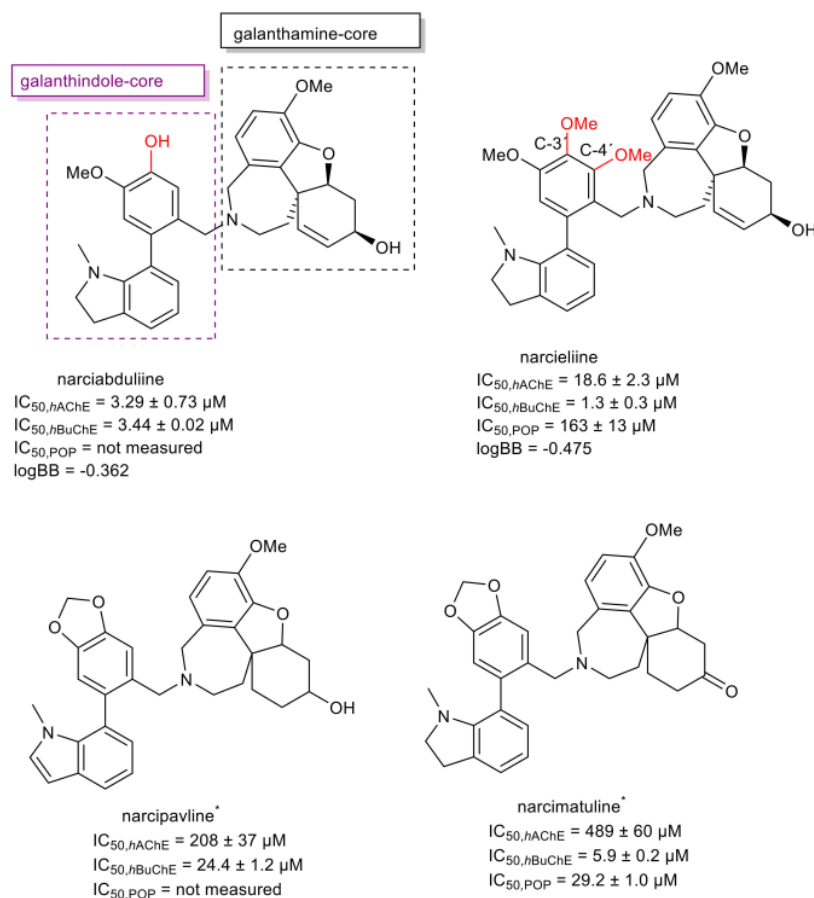
AAs are one of the most studied groups of secondary metabolites in connection with AD. Chemically, they represent a large group of isoquinoline alkaloids, which are produced exclusively by plants of the Amaryllidaceae family and are reported as a separate group of alkaloids. These alkaloids are derived from the aromatic acids phenylalanine and tyrosine, which are used to produce key intermediates in the biosynthesis of the AA 4-*O*-methylnorbelladine [54]. This compound subsequently undergoes different types of intramolecular oxidative couplings, which leads to the formation of the basic structural types of AAs: galanthamine, lycorine, haemanthamine, crinine, homolycorine, tazettine, and montanine.

The biological activity of Amaryllidaceae plants is connected with the presence of AAs, which demonstrate a wide range of biological activities, including antitumor, antibacterial, antioxidant, antiparasitic, antifungal, anti-inflammatory and insect antifeedant effects, as well as acetylcholinesterase and butyrylcholinesterase inhibitory activities [47,55,56]. The most known AA is galanthamine, originally isolated from *Galanthus woronowii* Losinsk. [57], which is a reversible, competitive acetylcholinesterase inhibitor. Additionally, galanthamine binds to the allosteric sites of nicotinic receptors, which causes a conformational change [58]. This allosteric modulation increases the nicotinic receptor's response to acetylcholine. The activation of presynaptic nicotinic receptors increases the release of acetylcholine, further increasing its availability [59].

34

Galanthamine was approved by the FDA (Food and Drug Administration [85]) in 2001 for the treatment of mild to moderate stages of AD. In the early 21st century, it was reported that the acetylcholinesterase activity of AAs is mainly associated with the galanthamine- and lycorine- structural types [60], but in the last decade, new structural types of AAs have been identified as interesting cholinesterase inhibitors (Table 1).

Two new structural types of AAs, named narcikachnine- and carltonine-type, have been isolated in the last five years from various Amaryllidaceae plants. The former combines in its structure both the galanthamine- and galanthindole-type. So far, five AAs of this structural type have been isolated from *Zephyranthes citrina*, *Narcissus pseudonarcissus* cv. Carton, *N. pseudonarcissus* cv. Dutch Master, and *N. poeticus* cv. Pink Parasol [61–64], and four of them were screened for hAChE/hBuChE inhibition potential (Table 1, Figures 1 and 2).



*absolute configuration has not been determined

Figure 1. Newly isolated narcikachnine-type AAs together with biological activities connected with AD.

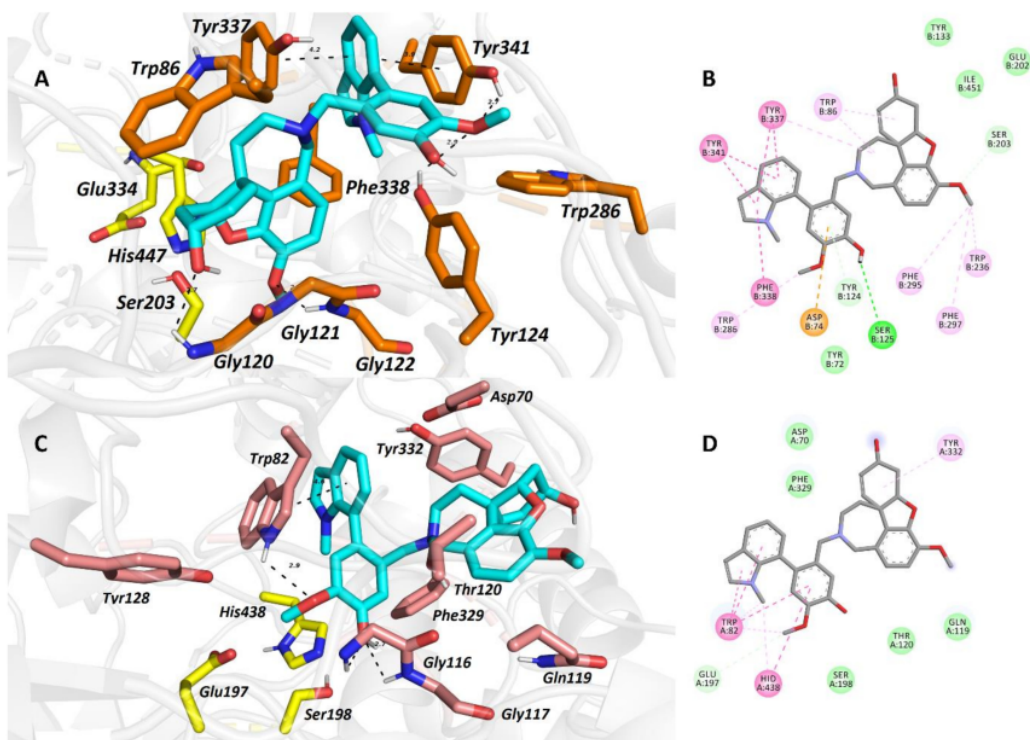


Figure 2. The top-scored docking poses of narciabduliine in *hAChE* ((A,B); PDB ID: 4EY6) and *hBuChE* ((C,D); PDB ID: 4BDS) active sites, with important interactions. Spatial orientation for each ligand is presented as three-dimensional (A,C) and two-dimensional (B,D) diagrams, respectively (taken from [64]).

Before the results of the inhibition potency of newly isolated and tested alkaloids are discussed, it is worth mentioning that, for the determination of cholinesterase inhibition potential, it is important that the source of the used enzymes is reported, e.g., electric eel acetylcholinesterase (*EeAChE*), human acetylcholinesterase *hAChE*, mouse brain acetylcholinesterase, equine serum BuChE (*EqBuChE*), and human BuChE (*hBuChE*). The use of different types of enzyme can result in dramatic differences in the obtained IC_{50} values. This can be demonstrated with acetylcaranine, which showed interesting activity against *EeAChE* ($IC_{50} = 11.7 \pm 0.7 \mu M$) [65]. When *hAChE* was used for the study, acetylcaranine was evaluated as a weak inhibitor ($IC_{50} = 443.7 \pm 62.4 \mu M$) [66]. This phenomenon has also been described recently for 1-O-acetyllycorine [66], reported as a strong *EeAChE* inhibitor ($IC_{50} = 0.96 \pm 0.04 \mu M$) [67,68], but inactive against *hAChE* ($IC_{50} = > 1000 \mu M$) [66]. In Tables 1 and 2, the source of enzyme for each IC_{50} value is stated.

Table 1. Biological activities of Amaryllidaceae alkaloids, either newly isolated or tested in the last decade, in connection with Alzheimer's disease (includes only alkaloids with an IC₅₀ value ≤ 30 μM for AChE or BuChE; IC₅₀ ≤ 200 μM for POP; any results for GSK-3β are included).

Alkaloid	Structural Type	Source	IC ₅₀ AChE (μM)	IC ₅₀ BuChE (μM)	IC ₅₀ POP (μM)	GSK-3β (μM)	Ref.
N-nongalanthamine	galanthamine	<i>Pancratium maritimum</i> <i>Lycoris longituba</i>	2.76 ± 0.65 ^a 8.85 ± 0.58 ^b	76.4 ± 3.7 ^c	n.s.	n.s.	[69,70]
11β-hydroxygalanthamine	galanthamine	<i>Lycoris longituba</i>	3.04 ± 0.61 ^a	n.s.	n.s.	n.s.	[70]
narcicabutiline	narcikachnine	<i>Narcissus pseudonarcissus</i> cv. Carlton	3.29 ± 0.73 ^b	3.44 ± 0.02 ^c	n.s.	n.s.	[64]
N-methylcrinasidine	narciclasine	<i>Lycoris longituba</i>	4.23 ± 1.13 ^a	n.s.	n.s.	n.s.	[70]
N-(chloromethyl)galanthamine	galanthamine	<i>Lycoris longituba</i>	5.55 ± 0.6 ^a	n.s.	n.s.	n.s.	[70]
O-demethyllycoramine	galanthamine	<i>Lycoris longituba</i>	8.13 ± 1.49 ^a	n.s.	n.s.	n.s.	[70]
deoxypretazetine	tazettine	<i>Lycoris longituba</i>	8.44 ± 0.83 ^a	n.s.	n.s.	n.s.	[70]
acetykaranine	lycorine	<i>Amargyllis belladonna</i>	11.7 ± 0.7 ^a >30 ^b	n.s.	>200	n.s.	[65,66]
narcicline	narcikachnine	<i>Zephyranthes citrina</i>	18.7 ± 2.3 ^b	1.34 ± 0.31 ^c	163 ± 13	n.s.	[63]
undulatine	crinine	<i>Chlidanthus fragrans</i> <i>Nerine bowdenii</i>	23.5 ± 1.2 ^b	>100 ^c	>200	43.3 ± 4.0 ^e	[66,71,72]
8-hydroxy-9-methoxycrinine	crinine	<i>Pancratium maritimum</i>	25.3 ± 1.8 ^a	>365 ^d	n.s.	n.s.	[69]
N-(chloromethyl)lycoramine	galanthamine	<i>Lycoris longituba</i>	25.76 ± 1.09 ^a	n.s.	n.s.	n.s.	[70]
powelline	crinine	<i>Nerine bowdenii</i>	29.1 ± 1.6 ^b	>30 ^c	>200	n.s.	[66]
cartonine B	belladine	<i>Narcissus pseudonarcissus</i> cv. Carlton	>30 ^b	0.031 ± 0.001 ^c	n.s.	n.s.	[56]
cartonine A	belladine	<i>Narcissus pseudonarcissus</i> cv. Carlton	>30 ^b	0.913 ± 0.020 ^c	143 ± 12	n.s.	[56]
narcimatuline	narcikachnine	<i>Narcissus pseudonarcissus</i> cv. Dutch Master	>30 ^b	5.9 ± 0.2 ^c	29.2 ± 1.0	20.7 ± 2.4	[62]
cartonine C	belladine	<i>Narcissus pseudonarcissus</i> cv. Carlton	>30 ^b	14.8 ± 1.1 ^c	n.s.	n.s.	[56]
narcipavline	narcikachnine	<i>Narcissus pecticus</i> cv. Pink Parasol	>30 ^b	24.4 ± 1.2 ^c	n.s.	n.s.	[61]
zephyranthine	lycorine	<i>Hippastrum hybridum</i> cv. Ferrari	>30 ^b	>30 ^c	142 ± 10	n.s.	[73]
9-O-demethylgalanthine	lycorine	<i>Zephyranthes robusta</i>	>30 ^b	>30 ^c	150 ± 20	50.9 ± 8.9 ^e	[74]
homolycorine	homolycorine	<i>Narcissus pecticus</i> cv. Pink Parasol	>30 ^b	>30 ^c	173 ± 41	54.4 ± 8.9 ^e	[61]
nerinine	homolycorine	<i>Zephyranthes citrina</i>	>30 ^b	>30 ^c	190 ± 10	n.s.	[63]
masonine	homolycorine	<i>Narcissus pecticus</i> cv. Pink Parasol	>30 ^b	>30 ^c	>200	27.81 ± 0.05	[61,72]
caranine	lycorine	⁹⁵ <i>Nerine bowdenii</i>	>30 ^b	>30 ^c	>200	30.75 ± 0.04	[66,72]
9-O-demethylhomolycorine	homolycorine	<i>Narcissus pecticus</i> cv. Pink Parasol	n.s.	n.s.	n.s.	30.01 ± 0.04	[72]

^a *Ec*AChE; ^b *h*AChE; ^c *h*BuChE; ^d *Lq*BuChE; ^e % inhibition at concentration of 50 μM HPTLC bio-autography assay.

The recently [82] isolated narcibaduliine from *N. pseudonarcissus* cv. Carton demonstrated a similar inhibitory activity towards both cholinesterases, with IC_{50} values of $3.29 \pm 0.73 \mu M$ for *hAChE*, and $3.44 \pm 0.02 \mu M$ for *hBuChE* [64]. The best *hBuChE* inhibition activity within the narcikachnine-type AAs has been demonstrated by narceliine ($IC_{50} = 1.3 \pm 0.3 \mu M$) [63]. The only structural difference from narcibaduliine was found in a C-3',C-4'-substitution [59] the galanthindole moiety (Figure 1; differences marked in red). Narceliine was also subjected [101] to enzyme kinetics analysis to determine the kinetics of *hAChE/hBuChE* inhibition. Enzyme velocity curves [113] were recorded at several concentrations of narceliine, and analysis of them revealed a competitive type of inhibition for *hAChE* and a mixed type of inhibition for *hBuChE*. Due to the isolation of only a low amount of narcibaduliine, the type of inhibition of this alkaloid has not been studied. To determine the critical structure aspects responsible for the *hAChE/hBuChE* activities of narceliine and narcibaduliine, molecular modeling studies were applied [63,64]. In the case of narcibaduliine, the top-scored position in the cavity of *hAChE* revealed that the galanthamine moiety is bound to the catalytic anionic site (CAS), whereas the galanthindole core is lodged peripherally. Interaction of narcibaduliine with the oxyanion hole, formed by Gly120-122 residues, is mediated via hydrogen bonds to both the hydroxyl group of the cyclohex-2-en-1-ol moiety and the methoxy group of the phenyl ring. Moreover, the hydroxyl group seems to stand aside from the Ser203 residue, and rotation of Ser203 to a plausible interaction with the hydroxyl moiety may [103] occur. The galanthindole moiety is sandwiched between Tyr337 and Tyr341 by parallel π - π stacking, hampering the hydrogen-bond donor contact between the hydroxyl group of Tyr337 to nitrogen from an azepine ring in narcibaduliine. In general, the overall topology of narcibaduliine in *hAChE* shares a high similarity to that of galanthamine, but the galanthindole core allowed additional spanning of narcibaduliine into the peripheral anionic site (PAS) of the enzyme. The best scoring pose of narcibaduliine in the active site of *hBuChE* indicated that the ligand adopted an inverse accommodation to that observed for the *hAChE* complex. The galanthindole moiety is buried inside the enzyme's cavity, whereas the galanthamine core of narcibaduliine is situated distally. The critical interaction for galanthindole is distorted π - π stacking between the 1-methyl-2,3-dihydro-1*H*-indole moiety of narcibaduliine and Trp82, a hydrogen bond between the oxygen [112] of the methoxy group and hydrogen at the 1-methyl-2,3-dihydro-1*H*-indole moiety, two hydrogen bonds between the phenolic hydroxyl functionality of narcibaduliine and glycine residues 116 and 117, and plausible hydrogen contact to Ser198 from the catalytic triad. The galanthamine moiety seems to contribute less to the overall ligand anchoring, forming hydrophobic contacts with Tyr332 and Gln119 only (Figure 2) [64].

Similar interactions have been observed for narceliine, which expands the catalytic anionic site (CAS) of *hAChE* entirely, with several apparent interactions. The "galanthamine" core is lodged centrally, and the "galanthindole" part is protruding out of the gorge, contacting several other amino acid residues. A closer view of the interaction between narceliine and *hBuChE* revealed that the galanthindole moiety is anchored in the vicinity of the catalytic triad, but not involved in direct contact with this part of the enzyme [63].

Narceliine was also tested for its POP inhibition potential, reaching the same magnitude of inhibition ($IC_{50} = 163 \pm 13 \mu M$) as that of berberine, which is recognized as a natural POP inhibitor ($IC_{50} = 142 \pm 21 \mu M$) [75]. The highest POP inhibition potential within the isolated narcikachnine type alkaloids has been shown by narcimatuline, isolated from *N. poeticus* cv. Dutch Master, with an IC_{50} value of $29.1 \pm 1.0 \mu M$ (Table 1, Figure 1). This alkaloid also showed interesting *hBuChE* activity ($IC_{50} = 5.9 \pm 0.2 \mu M$) and has been identified as a mild GSK-3 β inhibitor ($IC_{50} = 1115 \pm 2.4 \mu M$) [62].

Since the prediction of CNS availability is critical for the development of drugs for neurodegenerative diseases, the logBB values of the most active [13] compounds have been calculated. This value predicts the logarithmic ratio between the concentration of the compound in the brain (C_{brain}) and blood (C_{blood}) [76]. The obtained logBB values for narcibaduliine and narceliine (Figure 1) indicated that both alkaloids should be able

to reach the target area in the CNS. Moreover, the PAMPA-BBB screening method was applied for narceline to predict passive diffusion through biological membranes, employing a brain lipid porcine membrane [77,78]. The obtained result for the in vitro permeability of narceline ($P_e = 14.1 \pm 1.0 \cdot 10^{-6} \text{ cm s}^{-1}$) indicated that it can cross the BBB by passive diffusion. Narciabduline was unable to be studied for in vitro permeability due to the isolation of only a low amount of this alkaloid [64].

Taken together, the narcikachnine type is an interesting group of AAs with promising biological activities in connection with the potential treatment of AD. Unfortunately, these compounds are present in plants only in low concentration; thus, the development of a synthetic route is of interest.

The second newly discovered structural type of AAs, the carltonine-type, contains in its structure a belladine moiety combined with a lycosinine fragment (Figure 3). In the *hAChE* assay, all members of the carltonine-type displayed marginal inhibition potency (Table 1). On the other hand, these compounds showed promising inhibition activity towards *hBuChE* (Table 1). Carltonine A and carltonine B displayed IC_{50} values in the nanomolar range (*hBuChE* IC_{50} = 910 nM, and 31 nM, respectively). From the structural perspective, both AAs are endowed with the same core structure, differing only in the substitution at positions C-5' and C-6', respectively (Figure 3). The presence of a 1,3-dioxalane ring in carltonine B compared with its opened dimethoxybenzene analogue carltonine A is plausibly responsible for the almost 30 times drop in *hBuChE* inhibition activity (Figure 3; the differences marked in blue). The last carltonine-type alkaloid, carltonine C, contains in its structure an additional lycosinine fragment (Figure 3); this additional part of the structure is connected with a dramatic decline in the *hBuChE* inhibition activity ($IC_{50} = 14.8 \pm 1.1 \text{ } \mu\text{M}$) [56].

Molecular modeling studies were applied to reveal fundamental interactions and to identify structure details responsible for the dramatic drop in *hBuChE* inhibition activity. The in silico observations deduced that the higher inhibition potency of carltonine B over carltonine A might be attributed to the presence of the 2*H*-1,3-benzodioxole moiety for its "extended" aromatic properties that, especially in the *pseudo*-enantiomer, broaden the range of hydrophobic interactions between ligand and enzyme [56].

Due to the isolated amounts, only carltonine A has been studied for POP inhibition potency. It showed activity in the same range as that of berberine (Table 1). The significant *hBuChE* inhibition activity of alkaloids of this structural type and the fact that these alkaloids are present in plants only in trace amounts (from 30 kg of fresh bulbs of *N. pseudonarcissus* cv. Carlton, 70 mg of carltonine A, 6 mg of carltonine B, and 7 mg of carltonine C were isolated) mean that the total synthesis of these compounds is a future challenge for medicinal chemistry.

Close derivatives with a norbelladine framework (*N*-benzyl-2-phenylethan-1-amine congeners) have been developed by Carmona-Vigilanco et al. [79] and screened for their *AChE*/*BuChE* potency (Figure 4). Generally, these derivatives yielded moderate to weak inhibition potency against both cholinesterases with IC_{50} values above 10 μM . The structure of the best *AChE*/*BuChE* inhibitor within this study (1) is displayed in Figure 3, together with belladine-type AAs. The latest study published by Al Mamun et al. [80] reported synthesis of compounds with the same fundamental unit, but the developed compounds possessed different substitution patterns within the A-ring (Figure 3). Seven compounds of the twenty synthesized possessed a strong and selective *hBuChE* inhibition profile, with IC_{50} values below 1 μM [80]. The most potent one showed nanomolar range activity with an IC_{50} value of 72 nM and an excellent selectivity pattern over *AChE*, reaching almost 1400 (Figure 3). The top-ranked compound (2) was further studied by enzyme kinetics, along with in silico techniques, to reveal the mode of inhibition. The prediction of CNS availability estimates that all synthesized compounds within the survey can pass through the blood–brain barrier (BBB), as disclosed by the BBB score. These synthetic compounds, inspired by the norbelladine structural type of AAs, display an interesting structure scaffold for further development of selective *hBuChE* inhibitors [80].

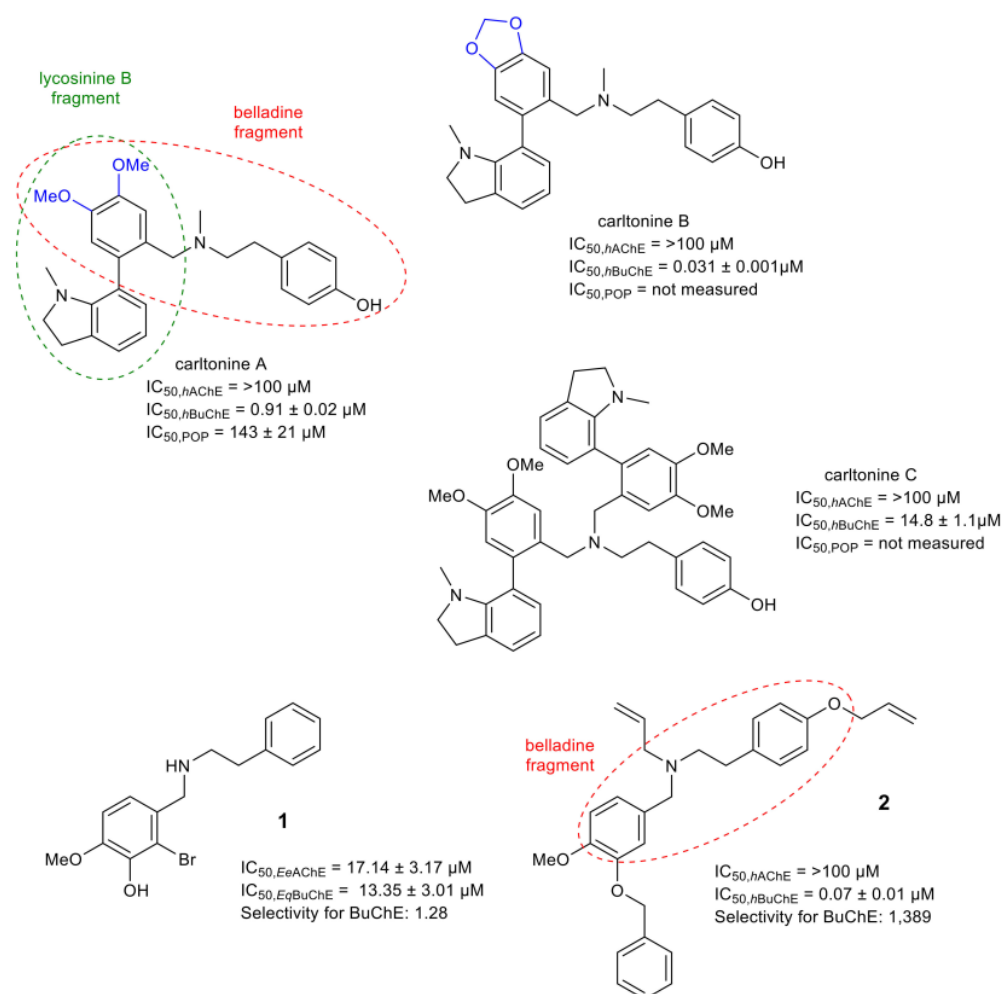


Figure 3. Recently isolated belladine-type *Ar*¹²²lidaceae alkaloids and the selected synthetic compounds inspired by AAs together with biological activities connected with Alzheimer's disease.

A phytochemical study of bulbs of *Lycoris longituba* yielded thirteen AAs that have been screened for their neuroprotective, and electric eel AChE (*EeAChE*) inhibition activity [70]. The natural existence of isolated alkaloids with a *N*-chloromethyl moiety in the structure, as in *N*-(chloromethyl)galanthamine and *N*-(chloromethyl)lycoramine isolated from this plant must be first reinvestigated, because when halogenated solvents are used during the isolation process, this can result in the formation of *N*-chloromethyl alkaloid derivative artifacts (Figure 4) [48,49]. The best *EeAChE* inhibitors belong to the galanthamine type (e.g., *N*-norgalanthamine ($IC_{50} = 2.76 \pm 0.65 \mu M$) and 11 β -hydroxygalanthamine ($IC_{50} = 3.04 \pm 0.61 \mu M$)). Interesting activity was also obtained for AAs of further structural types (e.g., narciclassine type AA *N*-methylcrinasiadine ($IC_{50} = 4.23 \pm 1.13 \mu M$; Table 1)) [70]. Some of the isolated alkaloids also showed promising neuroprotective effects against $CoCl_2$, H_2O_2 , and $A\beta_{25-35}$ -induced neuronal cell death in dopaminergic neuroblastoma SH-SY5Y cells. Incartine, triphaeridine, *N*-(chloromethyl)galanthamine, sanguinine, *O*-demethyllycoramine, and deoxypretazettine showed significant neuroprotective

effects against all three injury models [70]. Lycolongirine C and *N*-methylcrinasiadine exhibited significant neuroprotective activities against H_2O_2 and $A\beta_{25-35}$ -induced cell death [70]. Homolycorine- and galanthamine-type AAs isolated from the bulbs of *L. aurea* showed significant neuroprotective effects against $CoCl_2$ -induced SH-SY5Y cell injury, while *N*-norgalanthamine, *N*-(chloromethyl)galanthamine, *N*-(chloromethyl)lycoramine, 2 α -hydroxy-6-*O*-methyldoline, 2 α -hydroxy-6-*O*-*n*-butyldoline, *O*-*n*-butyllycoramine, *O*-methyllycoramine-*N*-oxide and pluviine showed obvious neuroprotective effects against H_2O_2 -induced SH-SY5Y cell death [51]. The same models have been used for the evaluation of neuroprotective alkaloids isolated from *L. sprengeri*. Two alkaloids, namely, *O*-methyllycoramine and hippadine, exhibited significant neuroprotective effects against H_2O_2 -induced SH-SY5Y cell death; lycosprenine, *O*-methyllycoramine, and tortuosine showed obvious neuroprotective effects against $CoCl_2$ -induced SH-SY5Y cell injury [81]. The results obtained within the mentioned studies indicate that AAs of homolycorine-, lycorine-, and galanthamine-type may have potential for further development as neuroprotective compounds. The cited studies are one of the few that have addressed the neuroprotective activity of individual AAs. Most of the studies dealing with the neuroprotective activity of AAs have used complex alkaloidal extracts accompanied by GC/MS analysis [82–84]. However, studies performed on mixtures are not able to identify which compound is responsible for the studied activity. Moreover, synergistic effects can occur. It is highly unlikely that a complex mixture will be used for the treatment of AD, and thus studies of individual compounds are required.

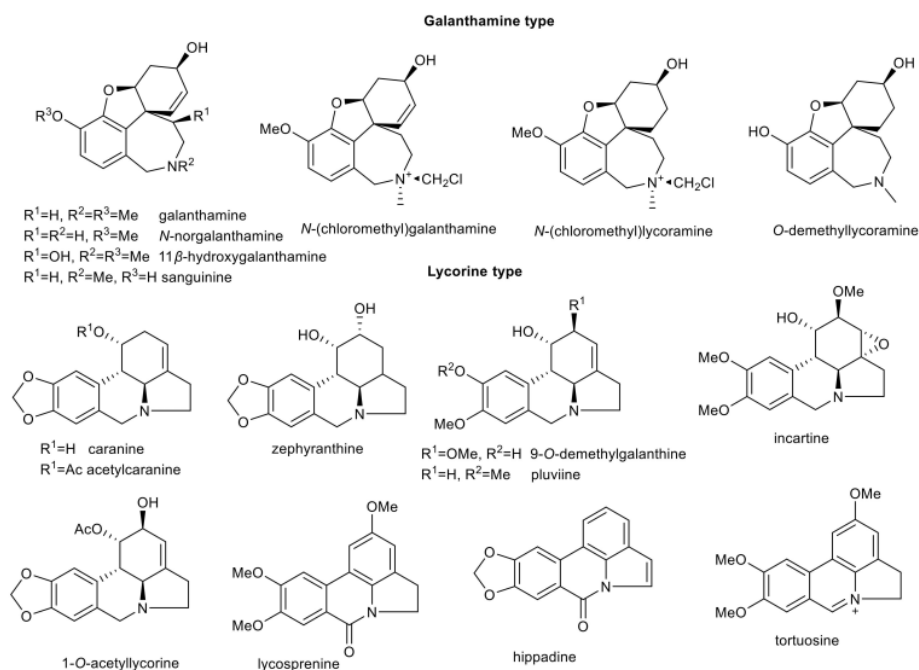


Figure 4. Amaryllidaceae alkaloids of galanthamine- and lycorine-type with interesting biological activity in connection with AD.

Under pathological conditions, such as in AD, the imbalance of the neurotransmitter leads to excitotoxic processes. There is an increase in the intraneuronal concentrations of Ca^{2+} , which causes mitochondrial dysfunction, the activation of proteases and the accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [85]. The brain is particularly vulnerable to damage caused by ROS and RNS, due to the high

consumption [88] oxygen and its high lipid content [86]. Galanthamine is able to stabilize free radicals due to the presence of the enol group in its structure [87]. It is well known that molecules with phenolic groups have a greater capacity to stabilize ROS and RNS. On the other hand, it has been shown that these groups are inefficient when crossing the BBB [88], a pharmacokinetic limitation for drugs which should reach the CNS area, as in the treatment of AD. Recently, the antioxidant activity of several fractions of alkaloids isolated from Amaryllidaceae species has been studied using a model of glutamate (Glu) excitotoxicity in rat cortical neurons [89]. The study showed a possible neuroprotective mode of action of the alkaloidal fractions of *Eucharis bonplandii* bulbs, *E. caucana* bulbs and *Clivia miniata* leaves due to the presence of phenol and enol groups in the structures of the AAs. Additionally, the pair of free electrons on the N is spatially close to hydroxyl groups, which benefits the cleavage of this group and consequently the stabilization of the generated O[•] [89].

The alkaloidal extract of *Hippeastrum reticulatum* bulbs (AHR) has been studied for its ameliorating effects on memory and cognitive dysfunction in a scopolamine-induced rodent model of AD using a Y-maze, the novel object recognition test (NORT), and the Morris water maze (MWM) test [90]. Sixty Swiss male mice, divided into six groups, received samples for 15 days. The normal group received saline and the scopolamine-treated group scopolamine (1.5 mg/kg, intraperitoneal injection). The test group received AHR 10 and 15 mg/kg, per os) and the positive control group donepezil (5 mg/kg, per os), administered 1 h before the test; scopolamine was injected 30 min prior to testing. The results of in vivo studies showed that AHR (15 mg/kg) significantly increased spontaneous alternation performance in the Y-maze test, and significantly increased the time spent exploring the novel object compared with the scopolamine-treated group. In the MWM test, administration of AHR at doses of 10 and 15 mg/kg significantly decreased escape latency and swimming distance to the platform, which indicates learning and spatial memory abilities of the mice [90].

Two standardized alkaloidal extracts of *Zephyranthes carinata* (bulbs and leaves) were evaluated for their in vitro and in vivo neuroprotective potential. In order to select the most promising extract for in vivo study in a triple transgenic mouse model of AD (3xTg-AD), an in vitro excitotoxicity model was used. The extracts of bulbs of *Z. carinata* (BZC) protected neurons against a Glu-mediated toxic stimulus in vitro, and consequent in vivo experiments showed the effects of the intraperitoneal administration of BZC extract (10 mg/kg) every 12 h for 1 month on learning and spatial memory of 3xTg-AD (18 months old) [91]. Histopathologically, a significant reduction in tauopathy and astrogliosis was observed, as well as a significant decrease in the proinflammatory marker COX-2, which indicates the potential of BZC alkaloids for further biological evaluation.

Further A36, isolated and tested in the last decade, with interesting biological activity related to AD are summarized in Table 1 and Figures 4 and 5.

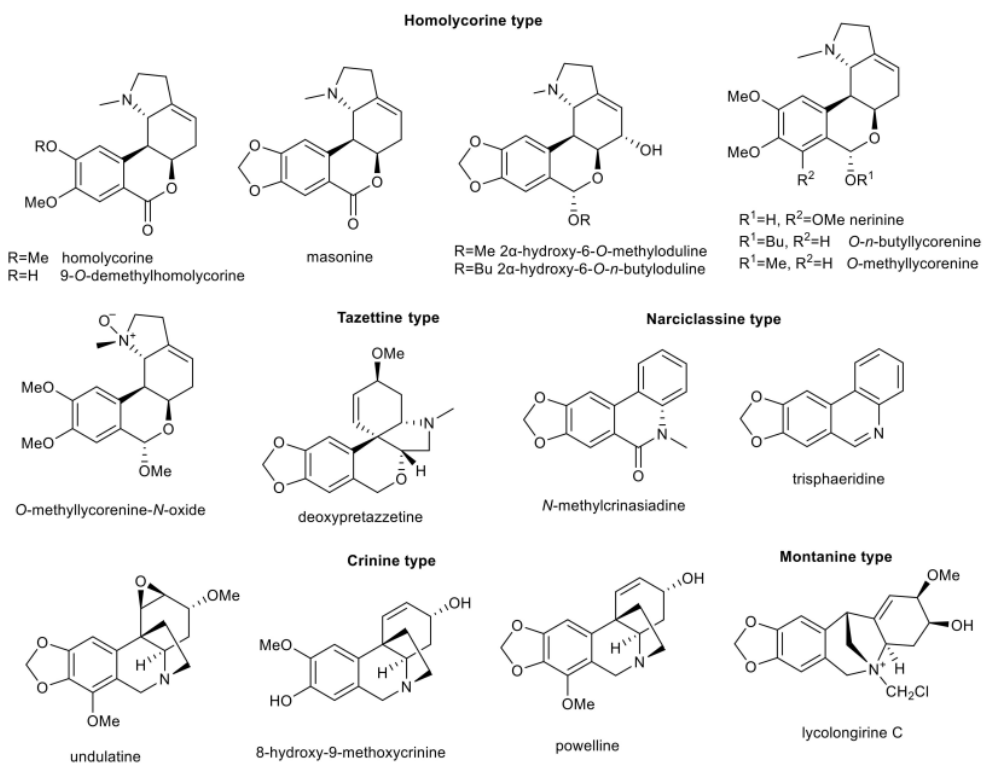


Figure 5. Amaryllidaceae alkaloids of homolycorine-, tazettine-, narciclasine-, crinine, and montanine-type with interesting biological activity in connection with AD.

4. Further Isoquinoline Alkaloids

Isoquinoline alkaloids (IAs) belong to one of the most complex families of plant alkaloids. They are widely distributed in plants coming from the families Papaveraceae, Rutaceae, Berberidaceae, Menispermaceae, Ranunculaceae, and Annonaceae [92]. Several species of Magnoliaceae and Convolvulaceae are also rich in these alkaloids and have been intensively investigated for their various biological activities [93]. Based on different degrees of oxygenation, intramolecular rearrangements, distribution, and the presence of additional rings connected to the main system, they may be divided into eight subgroups: benzyloisoquinoline, aporphine, protoberberine, benzo[c]phenanthridine, protopine, phthalideisoquinoline, morphinan, and emetine alkaloids. The largest and most studied group among the listed subgroups is protoberberines, the activity of which on cholinesterases has been evaluated by numerous authors, mainly regarding the quaternary compounds berberine and palmatine [94–96]. In the last decade, several new IAs with interesting biological activity towards AD have been isolated.

The detailed phytochemical study of the alkaloidal extract of the root bark of *Berberis vulgaris* (Berberidaceae) led to the isolation of ten isoquinoline alkaloids. Compounds isolated in sufficient amounts were evaluated for their *in vitro* hAChE, hBuChE, POP and GSK-3 β inhibitory activities [97]. Significant hBuChE inhibition potential was demonstrated by the newly isolated bisbenzyloisoquinoline alkaloids aromoline ($IC_{50} = 0.82 \pm 0.10 \mu M$), and berbostrejdine ($IC_{50} = 6.9 \pm 1.0 \mu M$). Both alkaloids were only weak hAChE inhibitors. On the other hand, aromoline showed only slightly lower POP inhibition potency than the used standard, berberine (Table 2). The balanced hBuChE and POP inhibitory abilities of aromoline initiated its screening for GSK-3 β inhibition activity at a concentration of 10 μM .

Unfortunately, the assayed compound showed only weak inhibition potency (Table 2). Kinetic studies of aromoline indicated that it acts as a mixed inhibitor of hBuChE. To identify structural determinants responsible for the ligand binding, a molecular modeling simulation exploiting the crystal structure of hBuChE (PDB ID: 4BDS) was carried out [98]. Aromoline was seen to be lodged near all of the catalytic triad residues establishing parallel π - π interactions of the phenolic moiety with His438. This part of the molecule of aromoline was implicated in a conventional hydrogen bond with Ser198. Additionally, Glu104 showed van der Waals forces with aromoline, and Tyr332, enabling the formation of T-shaped π - π stacking with one of the 1,2,3,4-tetrahydroisoquinoline moieties.

The whole plant of *Berberis vulgaris* is generally considered a rich source of the quaternary protoberberine alkaloids berberine and palmatine, which have been identified as AChE inhibitors. The biological activities of these compounds in relation to AD have been recently summarized in various articles and detailed information can be found in the following reviews [38,99–108].

Extensive phytochemical study of whole plants of *Corydalis mucronifera* (Papaveraceae) yielded previously undescribed IAs, named mucroniferanines A–M, together with 26 known IAs [109,110]. The isolated alkaloids were evaluated using EeAChE [110] and selected IAs also with equine serum BuChE [109]. Of the newly isolated compounds, the most promising activities have been shown by the quaternary protoberberine alkaloid mucroniferanine H, with IC_{50} values of $2.31 \pm 0.20 \mu M$ for EeAChE, and $36.71 \pm 1.12 \mu M$ for EqBuChE. Interesting inhibition potency has also been obtained for further mucroniferanines (Table 2). The type of inhibition and identification of structural determinants responsible for the ligand binding have not been determined.

Twelve IAs were isolated from the whole plant of *Corydalis saxicola* (Papaveraceae) and screened for their EeAChE and EqBuChE inhibition potential [96]. Six of the isolated IAs, including berberine and palmatine, showed potent inhibition of EeAChE activity (Table 2). Structure-activity studies demonstrated that the nitro substituent in the structure of protoberberines, such as in 1-nitroapocavidine, increases AChE inhibition potency. All of the studied alkaloids were inactive against EqBuChE ($IC_{50} > 200 \mu M$) [96].

Multi-step chromatography was used for the isolation of alkaloids from the root extract of *Zanthoxylum rigidum* (Rutaceae) [111]. Eight purified IAs were isolated, which were tested for EeAChE, hAChE and EqBuChE inhibitory activity, as well as for monoamine oxidase (MAO-A and B) and $A\beta$ aggregation. Two quaternary benzophenanthridine alkaloids, nitidine and avicine, were identified as multi-target ligands. Both alkaloids presented inhibitory activities against both forms of AChE with IC_{50} values in the (sub)micromolar concentration range (Table 2) and showed preferential activity for AChE. Moreover, avicine also demonstrated significant EqBuChE activity ($IC_{50} = 0.88 \pm 0.08 \mu M$), with an EqBuChE/hAChE selectivity index of 1.67, confirming the dual inhibitory character of this compound. Kinetic studies indicated that avicine and nitidine are reversible-mixed inhibitors of both cholinesterases. In the MAO inhibition assay, both alkaloids demonstrated inhibition potency against isoform A of human recombinant monoamine oxidase in micromolar concentrations (Table 2) but were inactive against MAO-B ($IC_{50} > 100 \mu M$). In addition, these alkaloids presented moderate $A\beta_{1-42}$ anti-aggregation activity (Table 2).

Seven IAs isolated from *Chelidonium majus* and *Corydalis yanhusuo* were evaluated for their potency to inhibit isoforms of recombinant MAOs. All alkaloids were first screened at a concentration of $20 \mu M$; chelerythrine was selected for the determination of the IC_{50} for MAO-A, and corydaline for MAO-B. Chelerythrine showed similar selective MAO-A inhibition potency ($IC_{50} = 0.55 \pm 0.042 \mu M$) as avicine, as discussed above [113]. The time-dependence, reversibility and kinetic study of MAO-A inhibition by chelerythrine was also studied. No changes in activity were observed after a 30 min preincubation; thus, chelerythrine interacts with MAO-A instantaneously and acts as a reversible competitive inhibitor of MAO-A ($K_i = 0.22 \pm 0.033 \mu M$). Docking simulation implied that Cys323 and Tyr444 of MAO-A are key residues for hydrogen-bond interaction with chelerythrine [113].

Table 2. Biological activities of further IAs, isolated and tested in connection with potential treatment of Alzheimer's disease, from 2010 (alkaloids only included with an IC₅₀ value ≤ 30 µM for AChE or BuChE; an IC₅₀ ≤ 200 µM for POP; all results for MAO-A and inhibition of Aβ-aggregation are included).

Isoquinoline Alkaloid	Structural-Type	Plant Source	IC ₅₀ AChE (µM)	IC ₅₀ BuChE (µM)	IC ₅₀ POP (µM)	IC ₅₀ MAO-A (µM)	IC ₅₀ Aβ (µM)	Ref.
avicine	benzophenanthridine	<i>Zanthoxylum rigidum</i>	0.15 ± 0.01 ^a 0.52 ± 0.05 ^b	0.88 ± 0.08 ^c	n.s.	0.41 ± 0.02	5.56 ± 0.94	[111]
nitidine	benzophenanthridine	<i>Zanthoxylum rigidum</i>	0.65 ± 0.09 ^a 1.25 ± 0.09 ^b	5.73 ± 0.60 ^c	n.s.	1.89 ± 0.17	1.89 ± 0.40	[111]
6-ethoxydihydrocherythrine	benzophenanthridine	<i>Chelidonium majus</i>	0.83 ± 0.04 ^b	4.20 ± 0.19 ^d	n.s.	n.s.	n.s.	[112]
chelythrine	benzophenanthridine	<i>Chelidonium majus</i>	1.54 ± 0.07 ^b 3.78 ± 0.15 ^a	6.33 ± 0.93 ^c 10.34 ± 0.24 ^d	n.s.	0.55 ± 0.04	4.20 ± 0.43	[113,114]
sanguinarine	benzophenanthridine	<i>Corydalis saxicola</i>	1.93 ± 0.01 ^a	>200 ^c	n.s.	n.s.	n.s.	[96]
mucroniferanine H (racemic mixture)	protoberberine	<i>Corydalis mucronifera</i>	2.31 ± 0.20 ^a	36.71 ± 1.12 ^c	n.s.	n.s.	n.s.	[109]
6-ethoxydihydrosanguinarine	benzophenanthridine	<i>Chelidonium majus</i>	3.25 ± 0.24 ^b	4.51 ± 0.31 ^d	n.s.	n.s.	n.s.	[112]
hydroxydrastinine	simple isoquinoline	<i>Corydalis mucronifera</i>	9.13 ± 0.15 ^a	>100 ^c	n.s.	n.s.	n.s.	[109]
dehydrocavidine	protoberberine	<i>Corydalis saxicola</i>	9.92 ± 0.24 ^a	>200 [*]	n.s.	n.s.	n.s.	[96]
mucroniferanine G (diastereoisomeric mixture 1:1)	phthalideisoquinoline	<i>Corydalis mucronifera</i>	11.3 ± 0.8 ^a	n.s.	n.s.	n.s.	n.s.	[110]
mucroniferanine F (diastereoisomeric mixture 1:1)	phthalideisoquinoline	<i>Corydalis mucronifera</i>	12.2 ± 0.2 ^a	n.s.	n.s.	n.s.	n.s.	[110]
(+)-canadine	protoberberine	<i>Corydalis cava</i>	12.4 ± 0.9 ^b	>100 ^d	152.0 ± 12.5	n.s.	n.s.	[115–117]
bendersine B	benzylisoquinoline	<i>Corydalis mucronifera</i>	14.22 ± 0.34 ^a	>100 ^c	n.s.	n.s.	n.s.	[109]
7,8-dihydro-1,2,3-dioxolo[4,5-g]isoquinoline	simple isoquinoline	<i>Stephania rotunda</i>	18.4 ± 1.4 ^c	n.s.	n.s.	n.s.	n.s.	[95]
caryachine	pavine	<i>Eschscholzia californica</i>	19.6 ± 0.4 ^b	>100 ^d	n.s.	n.s.	n.s.	[118]
(+)-canadiline	benzylisoquinoline	<i>Corydalis cava</i>	20.1 ± 1.1 ^b	85.2 ± 2.2 ^d	n.s.	n.s.	n.s.	[115]
remetine	aporphine	<i>Stephania rotunda</i>	20.7 ± 1.3 ^c	n.s.	n.s.	n.s.	n.s.	[95]
chelidone	benzophenanthridine	<i>Chelidonium majus</i>	26.8 ± 1.2 ^b	31.9 ± 1.4 ^d	n.s.	n.s.	n.s.	[112]
(-)-mucroniferanine D	phthalideisoquinoline	<i>Corydalis mucronifera</i>	28.3 ± 0.4 ^a	n.s.	n.s.	n.s.	n.s.	[110]
aromoline	bisbenzylisoquinoline	<i>Berberis vulgaris</i>	>100 ^b	0.82 ± 0.10 ^d	189 ± 32	n.s.	n.s.	[97]
berbostejidine	bisbenzylisoquinoline	<i>Berberis vulgaris</i>	66.0 ± 8.0 ^b	6.9 ± 1.0 ^d	n.s.	n.s.	n.s.	[97]
N-methylcodaurine	benzylisoquinoline	<i>Peumus boldus</i>	>100 ^b	15.0 ± 1.4 ^d	n.s.	n.s.	n.s.	[119]
1-(3-hydroxy-4-methoxybenzyl)-2-methyl-6,7-methylenedioxyl-2,3,4-tetrahydroisoquinoline	benzylisoquinoline	<i>Eschscholzia californica</i>	>100 ^b	27.8 ± 0.4 ^d	n.s.	n.s.	n.s.	[118]
sinactine	protoberberine	<i>Fumaria officinalis</i>	>100 ^b	>100 ^d	53 ± 2	n.s.	n.s.	[120]
californidine iodide	pavine	<i>Eschscholzia californica</i>	36.7 ± 0.9 ^b	>100 ^d	55.6 ± 3.5	n.s.	n.s.	[118,121]
bersavine	bisbenzylisoquinoline	<i>Berberis vulgaris</i>	68.0 ± 11.0 ^b	>100 ^d	67 ± 6	n.s.	n.s.	[97]
parfumidine	spirobenzylisoquinoline	<i>Fumaria officinalis</i>	>100 ^b	>100 ^d	99 ± 5	n.s.	n.s.	[120]

Table 2. Cont.

Isoquinoline Alkaloid	Structural-Type	Plant Source	IC ₅₀ AChE (μM)	IC ₅₀ BuChE (μM)	IC ₅₀ POP (μM)	IC ₅₀ MAO-A (μM)	IC ₅₀ Aβ (μM)	Ref.
dihydrosanguinarine	benzophenanthridine	<i>Madaya cordata</i> <i>Corydalis mucronifera</i>	>100 ^b	n.s.	99.1 ± 7.6	n.s.	n.s.	[110,121]
corypalmine	protoberberine	<i>Corydalis cava</i>	>100 ^b	>100 ^d	128.0 ± 10.5	n.s.	n.s.	[117,121]
N-methylauretamine	aporphine	<i>Peumus boldus</i>	>100 ^b	>100 ^d	135.0 ± 11.7	n.s.	n.s.	[119,121]
sinoacutine	morphine	<i>Peumus boldus</i>	>100 ^b	>100 ^d	143.1 ± 25.4	n.s.	n.s.	[119]
bicuculline	phthalideisoquinoline	<i>Fumaria officinalis</i>	>100 ^b	>100 ^d	190 ± 50	n.s.	n.s.	[120]

^a EcAChE; ^b hAChE; ^c EqBuChE; ^d hBuChE; * rat cortex AChE; * origin of used enzymes not specified within this study.

For the next study, roots and aerial parts of *Chelidonium majus* (Papaveraceae) were used; eight AAs of different structural types were isolated and screened for *hAChE/hBuChE* inhibitory activity [112]. Two compounds, identified as 6-ethoxydihydrosanguinarine and 6-ethoxydihydrochelerythrine, should be recognized as isolation artifacts, as in the presence of common solvents such as MeOH, EtOH and CHCl_3 , the free benzophenanthridine alkaloids (sanguinarine and chelerythrine) easily produce adducts [122]. On the other hand, these artifacts showed balanced cholinesterase inhibition activity, with IC_{50} values lower than 526 nM; 6-ethoxydihydrochelerythrine was the more potent (Table 2). These compounds can be used as templates for further development of antidementia drugs bearing a benzophenanthridine scaffold in the structure. [57]

Column chromatography and preparative TLC of the alkaloid extract of dried tubers of *Corydalis cava* (Papaveraceae) led to the isolation of fifteen IAs belonging to six structural types [117]. Two protoberberine alkaloids, (+)-canadine and (+)-canadoline, were recognized as moderate *hAChE* inhibitors ($\text{IC}_{50} = 12.4 \pm 0.9$ and 20.1 ± 1.1 μM , respectively; Table 2). As a part of an ongoing study, (+)-canadine showed POP inhibition potency comparable with that of the used standard, berberine [115].

Repeated column chromatography, preparative TLC, and crystallization led to the isolation of fourteen IAs from the roots and aerial parts of *Eschscholzia californica* (Papaveraceae). Most of the isolated alkaloids were recognized as weak inhibitors of *hAChE/hBuChE*. Moderate *hAChE* activity was shown by the pavinane-type alkaloid caryachine ($\text{IC}_{50} = 19.6 \pm 0.4$ μM), and moderate *hBuChE* inhibition potency by the newly isolated benzylisoquinoline alkaloid 1-(3-hydroxy-4-methoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline ($\text{IC}_{50} = 27.8 \pm 0.4$ μM) [118].

Extensive purification of the alkaloidal extract of whole plants of *Fumaria officinalis* (Papaveraceae) afforded twenty alkaloids. Compounds isolated in sufficient amounts have been screened for *hAChE*, *hBuChE*, POP and GSK-3 β inhibition activity. Of the studied alkaloids, only parfumidine and sinactine exhibited interesting inhibition potency against POP ($\text{IC}_{50} = 99 \pm 5$ and 53 ± 2 μM , respectively) [120]. The other isolated IAs have been considered inactive.

Two benzophenanthridine IAs (sanguinarine, chelerythrine) were evaluated for their potential to inhibit $\text{A}\beta_{1-42}$ aggregation [123]. [36] obtained results indicate that the benzophenanthridine nucleus of both alkaloids is directly involved in the inhibitory effect on $\text{A}\beta_{1-42}$ aggregation.

Dauricine, a bisbenzylisoquinoline alkaloid isolated from the rootstock of *Menispermum dauricum* (Menispermaceae) [124], has been studied for its neuroprotective effects in a murine neuroblastoma cell line (N2a) stably transfected with the human Swedish mutant form of amyloid protein precursor (APP), an AD-like cell model [125]. Employing this cell model, which overexpresses APP and hyperphosphorylates tau protein [126], and ELISA and Western blot analysis, it has been revealed that dauricine inhibited APP processing and reduced $\text{A}\beta$ accumulation [125]. [31]

Another bisbenzylisoquinoline alkaloid, tetrandrine, originally isolated from the dried root of *Stephania tetrandra* [127], attenuated spatial memory impairment and hippocampal inflammation by inhibiting NF- κB activation in a rat model of AD induced by $\text{A}\beta_{1-42}$ [128].

Pronuciferine, a naturally occurring proaporphine alkaloid isolated from *Berberis coletioidea* [129], has been investigated for its neuroactive effect against H_2O_2 -induced apoptosis in SH-SY5Y cells [130]. It did not show any toxicity when SH-SY5Y cells were treated with a concentration of 100 μM or less. The effect of pronuciferine on cell metabolites and brain-derived neurotrophic factor (BDNF) level in SH-SY5Y has been also investigated. Pronuciferine significantly increased the intracellular BDNF protein expression at 10 μM , and thus this alkaloid can be recognized as a neuroactive molecule that might act as a neuroprotective agent to prevent apoptosis in neurodegenerative diseases.

An overview of the IAs isolated and tested in the last decade, with interesting biological activity related to AD, are summarized in Table 2 and Figures 6–8.

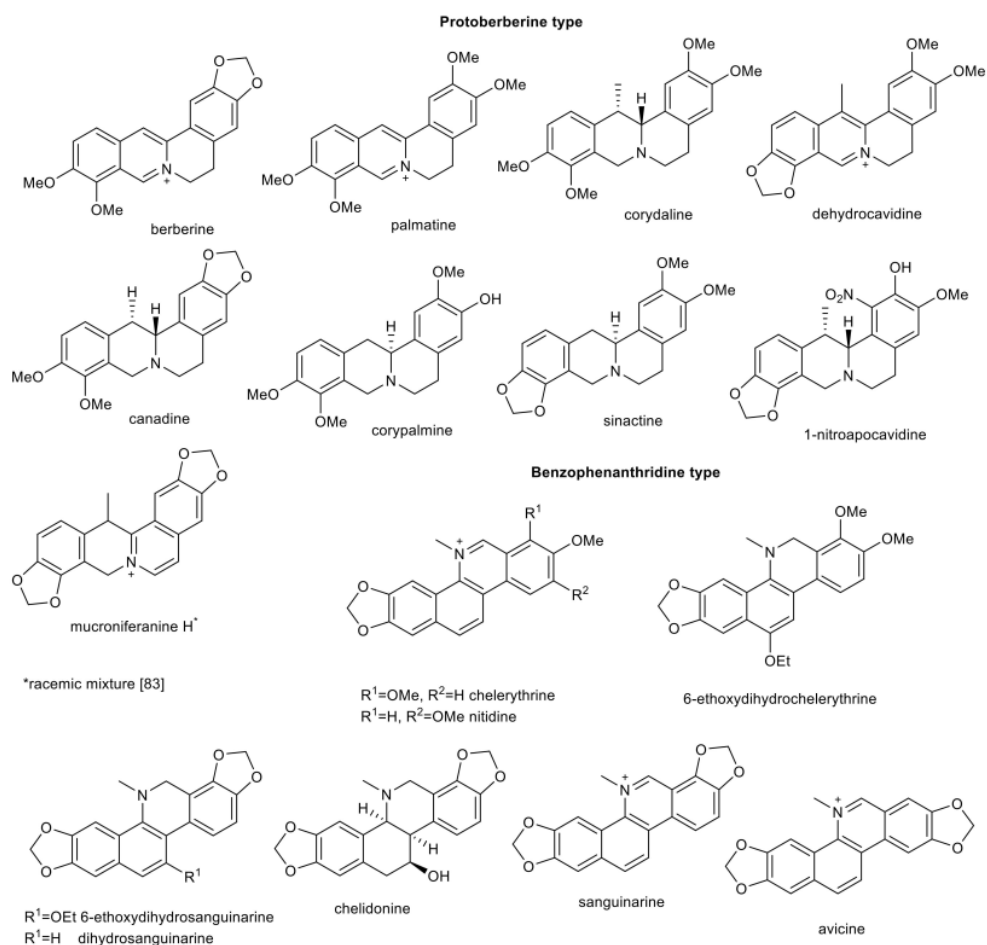


Figure 6. Isoquinoline alkaloids of protoberberine- and benzophenanthridine-type with interesting biological activity in connection with AD.

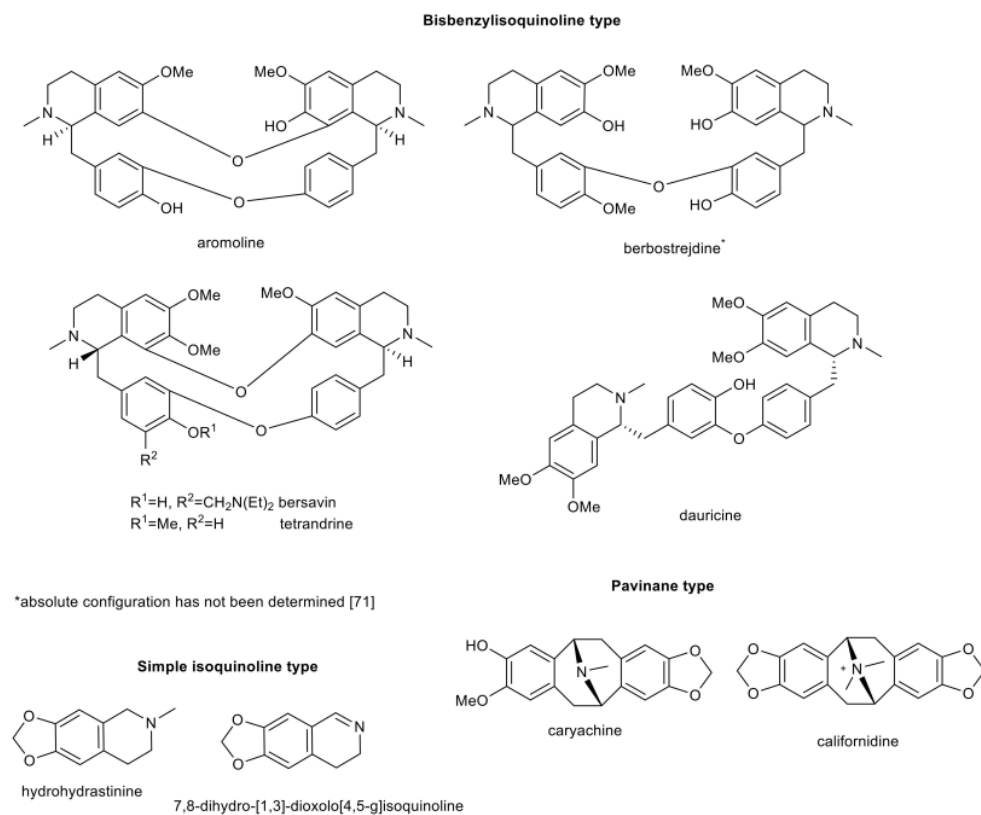


Figure 7. Isoquinoline alkaloids of bisbenzylisoquinoline- and pavinane-types and simple isoquinoline alkaloids with interesting biological activity in connection with AD.

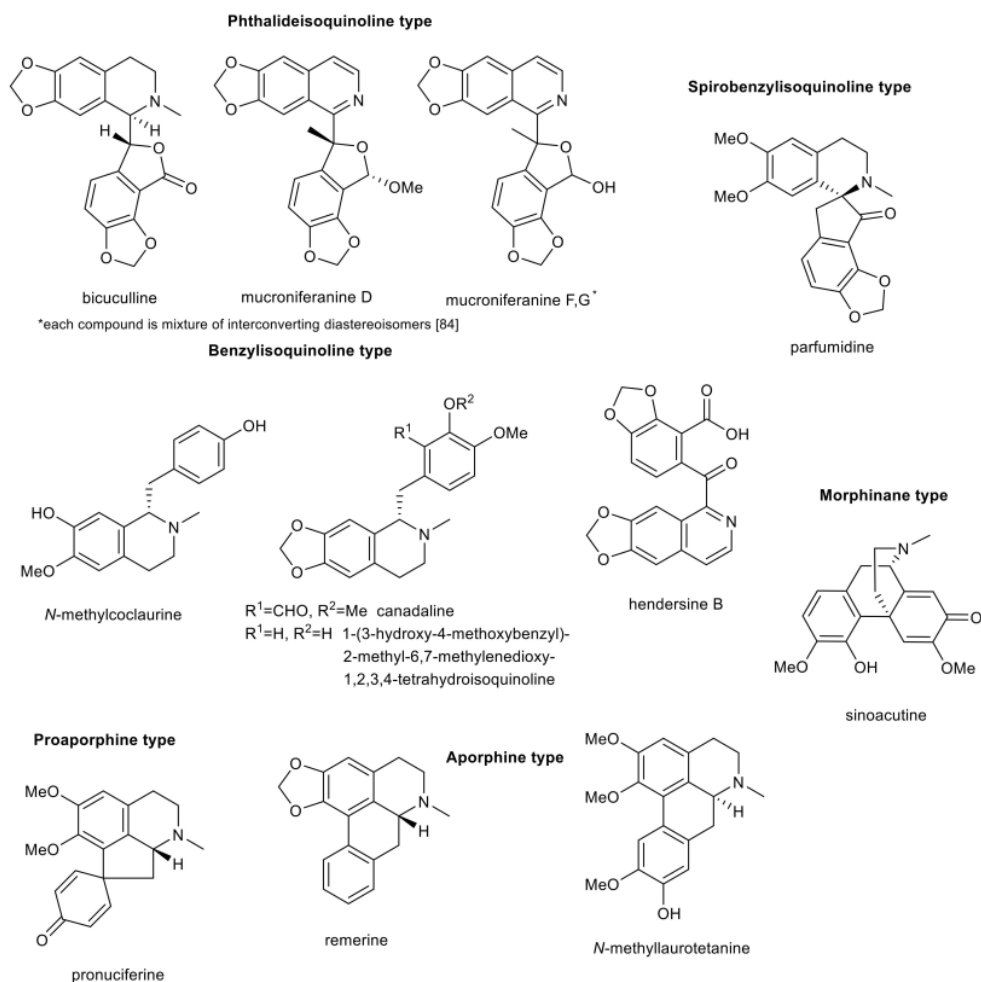


Figure 8. Isoquinoline alkaloids of phthalideisoquinoline-, spirobenzylisoquinoline-, benzylisoquinoline-, morphinane-, proaporphine-, and aporphine-type with interesting biological activity in connection with AD.

5. Selected Semisynthetic Derivatives of Amaryllidaceae and Isoquinoline Alkaloids as Inspiration for Drug Development for Neurodegenerative Diseases

Since AAs and IAs display promising biological activities and some of them are available from plant material in gram amounts [56,62,73], different semisynthetic derivatives have been developed in the last ten years and screened for biological activities connected with AD.

Two series of aliphatic and aromatic esters of haemanthamine were synthesized by Kohelová et al. [131] and Peřinová et al. [132]. The free hydroxyl group on C-11 of haemanthamine was esterified with different anhydrides and also acylated with differently substituted benzoyl chlorides affording the corresponding esters [131]. The strongest *hAChE* inhibition capacity within twenty-four haemanthamine derivatives was demonstrated by the 11-*O*-(2-nitrobenzoyl)- (3), 11-*O*-(3-nitrobenzoyl)- (4) and 11-*O*-(2-chlorobenzoyl)- (5) derivatives of haemanthamine with IC₅₀ values of 9.9 ± 0.5 μM for 3, 4.0 ± 0.3 μM for 4, and 13 ± 1 μM for 5 (Figure 9). More interestingly, compounds 3 and 4 displayed a selec-

tive *hAChE* inhibition profile with a selectivity index (SI) higher than 10 (Figure 9) [132]. From *hBuChE* data, two derivatives exerted 1 μ M micromolar inhibition activity, namely, 11-O-(2-methoxybenzoyl)haemanthamin (96) with an IC_{50} value of $3.3 \pm 0.4 \mu$ M and 11-O-(2-chlorobenzoyl)haemanthamine (5) with an IC_{50} value of $5.6 \pm 0.6 \mu$ M (Figure 9). Moreover, compound 5 also showed interesting *hAChE* inhibition potency and can be considered a dual non-selective cholinesterase inhibitor. The BBB permeability was investigated applying the PAMPA assay to predict CNS availability. The obtained results indicated that all developed derivatives should be centrally active, crossing the BBB by passive diffusion [132].

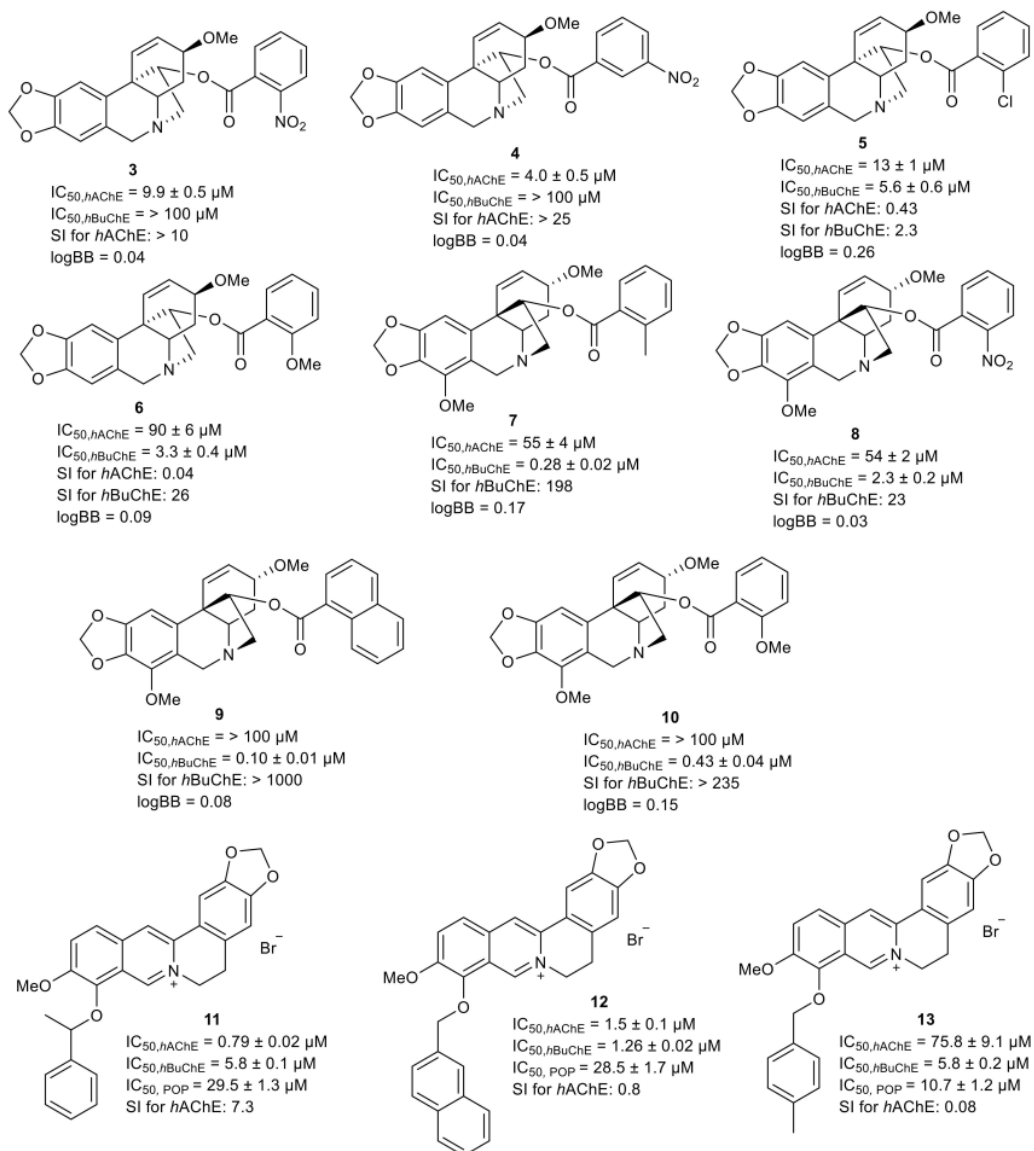


Figure 9. Derivatives of selected AAs and IAs together with biological activities connected with Alzheimer's disease.

The same procedure for preparation of semisynthetic derivatives has been used in the case of ambelline, which differs from haemanthamine only in the orientation of the 5,10b-ethano bridge and by possessing an additional methoxy group at C-7 (Figure 9). Comparison of the *hAChE/hBuChE* inhibition potencies of the analogues with the same substitution related to both ambelline and haemanthamine show the critical role of the absolute configuration of the 5,10b-ethano bridge in terms of its biological activity [133]. Within twenty ambelline derivatives, only three of them were identified as *hAChE* inhibitors, namely, 11-*O*-(2-methylbenzoyl)- (7), 11-*O*-(2-nitrobenzoyl)- (8), and 11-*O*-(4-nitrobenzoyl)ambelline, but these revealed only rather moderate inhibition, with IC_{50} values of 55 ± 4 , 54 ± 2 , and 48 ± 2 μ M, respectively. On the other hand, four aromatic derivatives with either different substitutions on the aromatic ring or with a naphthyl ring exerted strong inhibitory potency against *hBuChE* ($IC_{50} < 1$ μ M). The strongest *hBuChE* inhibition was shown by 11-*O*-(1-naphthoyl)ambelline (9), 11-*O*-(2-methylbenzoyl)ambelline (7), and 11-*O*-(2-methoxybenzoyl)ambelline (10) with IC_{50} values of 0.10 ± 0.01 , 0.28 ± 0.02 , and 0.43 ± 0.04 μ M, respectively (Figure 9). Moreover, the results for 7 and 10 showed a selective inhibition pattern for *hBuChE* with a selectivity index (SI) higher than 100 (Figure 9) [133]. The *in vitro* results were supported by computational studies predicting plausible binding modes of the strongest inhibitors in the active site of *hBuChE* [133].

As discussed earlier, berberine possesses an interesting multipotent pharmacological profile potentially applicable for AD treatment. Hence, a series of twenty-two berberine derivatives was developed by Sobolová et al. in 2020 and tested *in vitro* for inhibition potential against *hAChE/hBuChE* and POP [134]. The berberine core was substituted at position 86-O of its aromatic ring region. All the derivatives displayed *hAChE* inhibition ability in the micromolar to sub-micromolar range. The most active compound, 9-*O*-(α -methylbenzyl)berberine bromide (11), displayed inhibitory activity, with an IC_{50} value of 0.79 ± 0.02 μ M [134]. In the *hBuChE* assay, all derivatives exerted inhibition activity with IC_{50} values in the micromolar range (1.26–21.5 μ M), all being more potent than the parent, berberine ($IC_{50} = 47.2 \pm 3.3$ μ M). The top-ranked compound was 9-*O*-(naphth-2-yl)berberine bromide ($IC_{50} = 1.26 \pm 0.02$ μ M) (12). All the berberine derivatives were also screened for their POP inhibition activity; 9-*O*-(4-methylbenzyl)berberine bromide (13) was the best POP inhibitor with an IC_{50} value of 10.7 ± 1.2 μ M (Figure 9) [134].

6. Conclusions and Future Perspectives

The present review demonstrates that, during the last decade, a number of AAs and IAs have been isolated and tested against various targets connected with the potential treatment of AD. Two new structural types of AAs have been isolated, identified and screened for biological activity connected with AD. Compounds of the carltonine-type have been identified as strong selective inhibitors of BuChE, and compounds of the narcikachnine-type showed inhibitory activity against both cholinesterases. Several IAs have been identified as multitarget ligands for AD. Moreover, some of the active compounds have also been investigated through molecular docking studies to identify the sites of interaction between the chemical scaffold and the enzymatic amino acid residues.

As described in Chapter 5, several AAs and IAs can be isolated in gram amounts, allowing for their structure modification, as demonstrated for ambelline, haemanthamine (both AChE/BuChE inactive) and berberine. Thus, the preparation of derivatives of major AAs and IAs may be a new direction in the development of AD drugs. In the case of a low presence of AAs and IAs in plant material, their structures can be used as structural scaffolds for the total synthesis of new compounds, as discussed in the case of molecules structurally inspired by alkaloids isolated from *N. pseudonarcissus* cv. Carlton.

Conclusively, we have shown that AAs and IAs still have promising neuropharmacological potential for further exploration and structure optimization into multitargeted drugs for AD. Nowadays, *in vivo* and clinical trials are especially needed to be more adequately addressed in order to generate a more coordinated and focused means of developing new AD drugs.

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References

- Marešová, P.; Klímová, B.; Novotný, M.; Kuča, K. Alzheimer's and Parkinson's diseases: Expected economic impact on Europe—A call for a Uniform European Strategy. *J. Alzheimers Dis.* **2016**, *54*, 1123–1133. [\[CrossRef\]](#)
- Silva, T.; Reis, J.; Teixeira, J.; Borges, F. Alzheimer's disease, enzyme targets and drug discovery struggles: From natural products to drug prototypes. *Ageing Res. Rev.* **2014**, *15*, 116–145. [\[CrossRef\]](#)
- Ballard, C.; Gauthier, S.; Corbett, A.; Brayne, C.; Aarsland, D.; Jones, E. Alzheimer's disease. *Lancet* **2011**, *377*, 1019–1031. [\[CrossRef\]](#)
- Nichols, E.; Szeoke, C.; Vollset, S.; Abbasi, N.; Abd-Allah, F.; Ebro, J.; Aichour, M.; Akinyemi, R.; Alahdab, F.; Asgedom, S.; et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **2019**, *18*, 88–106. [\[CrossRef\]](#)
- Hardy, J.; Selkoe, D.J. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science* **2002**, *297*, 353–356. [\[CrossRef\]](#)
- Mehta, D.C.; Short, J.L.; Hilmer, S.N.; Nicolazzo, J.A. Drug access to the central nervous system in Alzheimer's disease: Preclinical and clinical insights. *Pharm. Res.* **2015**, *32*, 819–839. [\[CrossRef\]](#) [\[PubMed\]](#)
- Anand, R.; Gill, K.D.; Mahdi, A.A. Therapeutics of Alzheimer's disease: Past, present and future. *Neuropharmacology* **2014**, *76*, 27–50. [\[CrossRef\]](#) [\[PubMed\]](#)
- Dubey, H.; Gulati, K.; Ray, A. Recent studies on cellular and molecular mechanisms in Alzheimer's disease: Focus on epigenetic factors and histone deacetylase. *Rev. Neurosci.* **2018**, *29*, 241–260. [\[CrossRef\]](#) [\[PubMed\]](#)
- Hampel, H.; Schneider, L.S.; Giacobini, E.; Kivipelto, M.; Sindi, S.; Dubois, B.; Broich, K.; Nisticò, R.; Aisen, P.S.; Lista, S. Advances in the therapy of Alzheimer's disease: Targeting amyloid beta and tau and perspectives for the future. *Expert Rev. Neurother.* **2015**, *15*, 83–105. [\[CrossRef\]](#) [\[PubMed\]](#)
- Garcia, M.L.; Cleveland, D.W. Going new places using an old MAP: Tau, microtubules and human neurodegenerative disease. *Curr. Opin. Cell Biol.* **2001**, *13*, 41–48. [\[CrossRef\]](#)
- Hampel, H.; Mesulam, M.M.; Cuello, A.C.; Farlow, M.R.; Giacobini, E.; Grossberg, G.T.; Khachaturian, A.S.; Vergallo, A.; Cavedo, E.; Snyder, P.J.; et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain* **2018**, *141*, 1917–1933. [\[CrossRef\]](#) [\[PubMed\]](#)
- De Almeida, J.P.; Saldanha, C. Nonneuronal cholinergic system in human erythrocytes: Biological role and clinical relevance. *J. Membr. Biol.* **2010**, *234*, 227–234. [\[CrossRef\]](#)
- Cahlíková, L.; Macáková, K.; Benešová, N.; Chlebek, J.; Hošťálková, A.; Opletal, L. Chapter 6—Natural compounds (small molecules) as potential and real drugs of Alzheimer's disease: A critical review. In *Studies in Natural Products Chemistry*, 1st ed.; Rahman, A., Ed.; Elsevier: Oxford, UK, 2014; Volume 42, pp. 153–194. ISBN 978-0-444-63281-4.
- Ciro, A.; Park, J.; Burkhard, G.; Yan, N.; Geula, C. Biochemical differentiation of cholinesterases from normal and Alzheimer's disease cortex. *Curr. Alzheimer Res.* **2012**, *9*, 138–143. [\[CrossRef\]](#)
- García-Ayllón, M.S.; Silveyra, M.X.; Sáez-Valero, J. Association between acetylcholinesterase and beta-amyloid peptide in Alzheimer's cerebrospinal fluid. *Chem. Biol. Interact.* **2008**, *175*, 209–215. [\[CrossRef\]](#)
- Sridhar, G.R.; Nirmala, G.; Apparao, A.; Madhavi, A.S.; Sreelatha, S.; Rani, J.S.; Vijayalakshmi, P. Serum butyrylcholinesterase in type 2 diabetes mellitus: A biochemical and bioinformatics approach. *Lipids Health Dis.* **2005**, *4*, 18. [\[CrossRef\]](#)
- Paz, M.L.; Barrantes, F.J. Autoimmune attack of the neuromuscular junction in myasthenia gravis: Nicotinic acetylcholine receptors and other targets. *ACS Chem. Neurosci.* **2019**, *10*, 2186–2194. [\[CrossRef\]](#)
- Bajgar, J. Organophosphates/nerve agent poisoning: Mechanism of action, diagnosis, prophylaxis, and treatment. *Adv. Clin. Chem.* **2004**, *38*, 151–216. [\[CrossRef\]](#)
- Wang, R.; Reddy, P.H. Role of glutamate and NMDA receptors in Alzheimer's disease. *J. Alzheimers Dis.* **2017**, *57*, 1041–1048. [\[CrossRef\]](#)
- Kornhuber, J.; Wiltfang, J. The role of glutamate in dementia. *J. Neural. Transm. Suppl.* **1998**, *53*, 277–287. [\[CrossRef\]](#)

21. Hernández, F.; Avila, J. The role of glycogen synthase kinase 3 in the early stages of Alzheimer's disease. *FEBS Lett.* **2008**, *582*, 3848–3854. [\[CrossRef\]](#)
22. Hooper, C.; Killick, R.; Lovestone, S. The GSK3 hypothesis of Alzheimer's disease. *J. Neurochem.* **2008**, *104*, 1433–1439. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Plattner, F.; Angelo, M.; Giese, K.P. The roles of cyclin-dependent kinase 5 and glycogen synthase kinase 3 in tau hyperphosphorylation. *J. Biol. Chem.* **2006**, *281*, 25457–25465. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Martinez, A.; Perez, D.I. GSK-3 inhibitors: A ray of hope for the treatment of Alzheimer's disease? *J. Alzheimers Dis.* **2008**, *15*, 181–191. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Cai, Z. Monoamine oxidase inhibitors: Promising therapeutic agents for Alzheimer's disease (Review). *Mol. Med. Rep.* **2014**, *9*, 1533–1541. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Ramsay, R.R.; Popovic-Nikolic, M.R.; Nikolic, K.; Uliassi, E.; Bolognesi, M.L. A perspective on multi-target drug discovery and design for complex diseases. *Clin. Transl. Med.* **2018**, *7*, 3. [\[CrossRef\]](#)
27. Schedin-Weiss, S.; Inoue, M.; Hromádková, L.; Teranishi, Y.; Yamamoto, N.G.; Wiehager, B.; Bogdanovic, N.; Winblad, B.; Sandebring-Matton, A.; Frykman, S.; et al. Monoamine oxidase B is elevated in Alzheimer disease neurons, is associated with γ -secretase and regulates neuronal amyloid β -peptide levels. *Alzheimers Res. Ther.* **2017**, *9*, 57. [\[CrossRef\]](#)
28. Svarcbaš, R.; Jäntti, M.; Kilpeläinen, T.; Julku, U.H.; Urvás, L.; Kivioja, S.; Norrbacka, S.; Myöhänen, T.T. Prolyl oligopeptidase inhibition activates autophagy via protein phosphatase 2A. *Pharmacol. Res.* **2020**, *151*, 104558. [\[CrossRef\]](#)
29. Szeltner, Z.; Polgár, L. Structure, function and biological relevance of prolyl oligopeptidase. *Curr. Protein Pept. Sci.* **2008**, *9*, 96–107. [\[CrossRef\]](#) [\[PubMed\]](#)
30. Laitinen, K.S.; van Groen, T.; Tanila, H.; Venäläinen, J.; Männistö, P.T.; Alafuzoff, I. Brain prolyl oligopeptidase activity is associated with neuronal damage rather than beta-amyloid accumulation. *Neuroreport* **2001**, *12*, 3309–3312. [\[CrossRef\]](#)
31. García-Horsman, J.A.; Männistö, P.T.; Venäläinen, J.I. On the role of prolyl oligopeptidase in health and disease. *Neuropeptides* **2007**, *41*, 1–24. [\[CrossRef\]](#)
32. Zemek, F.; Drtinová, L.; Nepovimová, E.; Šepsová, V.; Korábečný, J.; Klimeš, J.; Kuča, K. Outcomes of Alzheimer's disease therapy with acetylcholinesterase inhibitors and memantine. *Expert Opin. Drug Saf.* **2014**, *13*, 759–774. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Matsunaga, S.; Kishi, T.; Iwata, N. Combination therapy with cholinesterase inhibitors and memantine for Alzheimer's disease: A systematic review and meta-analysis. *Int. J. Neuropsychopharmacol.* **2014**, *18*, pyu115. [\[CrossRef\]](#)
34. Lalli, G.; Schott, J.M.; Hardy, J.; De Strooper, B. Aducanumab: A new phase in therapeutic development for Alzheimer's disease? *EMBO Mol. Med.* **2021**, *13*, e14781. [\[CrossRef\]](#)
35. Mahase, E. Three FDA advisory panel members resign over approval of Alzheimer's drug. *BMJ* **2021**, *373*, n1503. [\[CrossRef\]](#)
36. Servick, K. Alzheimer's drug approval spotlights blood tests. *Science* **2021**, *373*, 373–374. [\[CrossRef\]](#)
37. Wang, S.; Dong, G.; Sheng, C. Structural simplification of natural products. *Chem. Rev.* **2019**, *119*, 4180–4220. [\[CrossRef\]](#)
38. Konrath, E.L.; Passos Cdos, S.; Klein, L.C., Jr.; Henriques, A.T. Alkaloids as a source of potential anticholinesterase inhibitors for the treatment of Alzheimer's disease. *J. Pharm. Pharmacol.* **2013**, *65*, 1701–1725. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Murray, A.; Faraoni, M.; Castro, M.; Alza, N.; Cavallaro, V. Natural AChE inhibitors from plants and their contribution to Alzheimer's disease therapy. *Curr. Neuropharmacol.* **2013**, *11*, 388–413. [\[CrossRef\]](#)
40. Dos Santos, T.C.; Gomes, T.M.; Pinto, B.A.S.; Camara, A.L.; Paes, A.M.D.A. Naturally occurring acetylcholinesterase inhibitors and their potential use for Alzheimer's disease therapy. *Front. Pharmacol.* **2018**, *9*, 1192. [\[CrossRef\]](#)
41. Moodie, L.W.K.; Sepčić, K.; Turk, T.; Frangež, R.; Svenson, J. Natural cholinesterase inhibitors from marine organisms. *Nat. Prod. Rep.* **2019**, *36*, 1053–1092. [\[CrossRef\]](#)
42. Panda, S.S.; Jhanji, N. Natural products as potential anti-Alzheimer agents. *Curr. Med. Chem.* **2020**, *27*, 5887–5917. [\[CrossRef\]](#)
43. Svendsen, A.B.; Verpoorte, R. (Eds.) Chapter 4—Isolation of alkaloids. In *Chromatography of Alkaloids*; Elsevier: Amsterdam, The Netherlands, 1983; Volume 23A, pp. 51–58. ISBN 978-0-444-42145-6.
44. Lee, K.T. Quantitative isolation of alkaloids from plant materials. *Nature* **1960**, *188*, 65–66. [\[CrossRef\]](#)
45. Sasidharan, S.; Chen, Y.; Saravanan, D.; Sundram, K.M.; Latha, L.Y. Extraction, isolation and characterization of bioactive compounds from plants' extracts. *Afr. J. Tradit. Complement. Altern. Med.* **2011**, *8*, 1–10. [\[CrossRef\]](#)
46. Maldoni, B. Alkaloids: Isolation and purification. *J. Chem. Educ.* **1991**, *68*, 700–703. [\[CrossRef\]](#)
47. Kornienko, A.; Evidente, A. Chemistry, biology, and medicinal potential of narciclasine and its congeners. *Chem. Rev.* **2008**, *108*, 1982–2014. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Cahliková, L.; Breiterová, K.; Opletal, L. Chemistry and biological activity of alkaloids from the genus *Lycoris* (Amaryllidaceae). *Molecules* **2020**, *25*, 4797. [\[CrossRef\]](#)
49. Berkov, S.; Osorio, E.; Viladomat, F.; Bastida, J. Chapter Two—Chemodiversity, chemotaxonomy and chemoecology of Amaryllidaceae alkaloids. In *The Alkaloids: Chemistry and Biology*; Knölker, H.J., Ed.; Academic Press: Cambridge, MA, USA, 2020; Volume 83, pp. 113–185. ISBN 978-0-12-820981-3.
50. Xu, T.; Chen, W.; Zhou, J.; Dai, J.; Li, Y.; Zhao, Y. Virtual screening for reactive natural products and their probable artifacts of solvolysis and oxidation. *Biomolecules* **2020**, *10*, 1486. [\[CrossRef\]](#)
51. Jin, A.; Li, X.; Zhu, Y.Y.; Yu, H.Y.; Pi, H.F.; Zhang, P.; Ruan, H.L. Four new compounds from the bulbs of *Lycoris aurea* with neuroprotective effects against CoCl_2 and H_2O_2 -induced SH-SY5Y cell injuries. *Arch. Pharm. Res.* **2014**, *37*, 315–323. [\[CrossRef\]](#) [\[PubMed\]](#)

52. Maltese, F.; van der Kooy, F.; Verpoorte, R. Solvent derived artifacts in natural products chemistry. *Nat. Prod. Commun.* **2009**, *4*, 447–454. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Miana, G.A. Tertiary dihydropyprotoberberine alkaloids of *Berberis lycium*. *Phytochemistry* **1973**, *12*, 1822–1823. [\[CrossRef\]](#)
54. Kilgore, M.B.; Kutchan, T.M. The Amaryllidaceae alkaloids: Biosynthesis and methods for enzyme discovery. *Phytochem. Rev.* **2016**, *15*, 317–337. [\[CrossRef\]](#)
55. Nair, J.J.; Wilhelm, A.; Bonnet, S.L.; van Staden, J. Antibacterial constituents of the plant family Amaryllidaceae. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4943–4951. [\[CrossRef\]](#)
56. Al Mamun, A.; Maříková, J.; Hulcová, D.; Janoušek, J.; Šafratová, M.; Nováková, L.; Kučera, T.; Hrabínová, M.; Kuneš, J.; Korábečný, J.; et al. Amaryllidaceae alkaloids of belladine-type from *Narcissus pseudonarcissus* cv. carlton as new selective inhibitors of butyrylcholinesterase. *Biomolecules* **2020**, *10*, 800. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Fulton, B.; Benfield, P. Galanthamine. *Drugs Aging* **1996**, *9*, 60–65. [\[CrossRef\]](#)
58. Raskind, M.A.; Peskind, E.R.; Wessel, T.; Yuan, W. Galanthamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology* **2000**, *54*, 2261–2268. [\[CrossRef\]](#)
59. Kotra, L.P.; Park, J. 5.14—Therapeutic approaches to MS and other neurodegenerative diseases. In *Comprehensive Medicinal Chemistry III*; Chackalamannil, S., Rotella, D., Ward, S.E., Eds.; Elsevier: Oxford, UK, 2017; pp. 439–473. ISBN 978-0-12-803201-5.
60. López, S.; Bastida, J.; Viladomat, F.; Codina, C. Acetylcholinesterase inhibitory activity of some Amaryllidaceae alkaloids and *Narcissus* extracts. *Life Sci.* **2002**, *71*, 2521–2529. [\[CrossRef\]](#)
61. Šafratová, M.; Hošťálková, A.; Hulcová, D.; Breiterová, K.; Hrabcová, V.; Machado, M.; Fontinha, D.; Prudêncio, M.; Kuneš, J.; Chlebek, J.; et al. Alkaloids from *Narcissus poeticus* cv. Pink Parasol of various structural types and their biological activity. *Arch. Pharm. Res.* **2018**, *41*, 208–218. [\[CrossRef\]](#)
62. Hulcová, D.; Maříková, J.; Korábečný, J.; Hošťálková, A.; Jun, D.; Kuneš, J.; Chlebek, J.; Opletal, L.; De Simone, A.; Nováková, L.; et al. Amaryllidaceae alkaloids from *Narcissus pseudonarcissus* L. cv. Dutch Master as potential drugs in treatment of Alzheimer's disease. *Phytochemistry* **2019**, *165*, 112055. [\[CrossRef\]](#)
63. Kohelová, E.; Maříková, J.; Korábečný, J.; Hulcová, D.; Kučera, T.; Jun, D.; Chlebek, J.; Jenčo, J.; Šafratová, M.; Hrabínová, M.; et al. Alkaloids of *Zephyranthes citrina* (Amaryllidaceae) and their implication to Alzheimer's disease: Isolation, structural elucidation and biological activity. *Bioorg. Chem.* **2021**, *107*, 104567. [\[CrossRef\]](#)
64. Maříková, J.; Mamun, A.A.; Shammari, L.A.; Korábečný, J.; Kučera, T.; Hulcová, D.; Kuneš, J.; Malaník, M.; Vašková, M.; Kohelová, E.; et al. Structure elucidation and cholinesterase inhibition activity of two new minor Amaryllidaceae alkaloids. *Molecules* **2021**, *26*, 1279. [\[CrossRef\]](#)
65. Sibanyoni, M.N.; Chaudhary, S.K.; Chen, W.; Adhami, H.-R.; Combrinck, S.; Maharaj, V.; Schuster, D.; Viljoen, A. Isolation, in vitro evaluation and molecular docking of acetylcholinesterase inhibitors from South African Amaryllidaceae. *Fitoterapia* **2020**, *146*, 104650. [\[CrossRef\]](#) [\[PubMed\]](#)
66. Vaněčková, N.; Hošťálková, A.; Šafratová, M.; Kuneš, J.; Hulcová, D.; Hrabínová, M.; Doskočil, I.; Štěpánková, Š.; Opletal, L.; Nováková, L.; et al. Isolation of Amaryllidaceae alkaloids from *Nerine bowdenii* W. Watson and their biological activities. *RSC Adv.* **2016**, *6*, 80114–80120. [\[CrossRef\]](#)
67. Elgorashi, E.E.; Stafford, G.I.; van Staden, J. Acetylcholinesterase enzyme inhibitory effects of Amaryllidaceae alkaloids. *Planta Med.* **2004**, *70*, 260–262. [\[CrossRef\]](#)
68. Nair, J.J.; Aremu, A.O.; van Staden, J. Isolation of narciprimine from *Cyrtanthus contractus* (Amaryllidaceae) and evaluation of its acetylcholinesterase inhibitory activity. *J. Ethnopharmacol.* **2011**, *137*, 1102–1106. [\[CrossRef\]](#) [\[PubMed\]](#)
69. Orhan, I.E.; Senol Deniz, F.S.; Eren, G.; Sener, B. Molecular approach to promising cholinesterase inhibitory effect of several Amaryllidaceae alkaloids: Further re-investigation. *S. Afr. J. Bot.* **2021**, *136*, 175–181. [\[CrossRef\]](#)
70. Zhu, Y.Y.; Li, X.; Yu, H.Y.; Xiong, Y.F.; Zhang, P.; Pi, H.F.; Ruan, H.L. Alkaloids from the bulbs of *Lycoris longituba* and their neuroprotective and acetylcholinesterase inhibitory activities. *Arch. Pharm. Res.* **2015**, *38*, 604–613. [\[CrossRef\]](#) [\[PubMed\]](#)
71. Cahliková, L.; Hrabínová, M.; Kulhánková, A.; Benešová, N.; Chlebek, J.; Jun, D.; Novák, Z.; Macáková, K.; Kuneš, J.; Kuča, K.; et al. Alkaloids from *Chlidanthus fragrans* and their acetylcholinesterase, butyrylcholinesterase and prolyl oligopeptidase activities. *Nat. Prod. Commun.* **2013**, *8*, 1541–1544. [\[CrossRef\]](#)
72. Hulcová, D.; Breiterová, K.; Siatka, T.; Klímová, K.; Davani, L.; Šafratová, M.; Hošťálková, A.; De Simone, A.; Andrisano, V.; Cahliková, L. Amaryllidaceae alkaloids as potential glycogen synthase kinase-3 β inhibitors. *Molecules* **2018**, *23*, 719. [\[CrossRef\]](#)
73. Al Shammari, L.; Hulcová, D.; Maříková, J.; Kučera, T.; Šafratová, M.; Nováková, L.; Schmidt, M.; Pulkrábková, L.; Janoušek, J.; Soukup, O.; et al. Amaryllidaceae alkaloids from *Hippeastrum X hybridum* cv. Ferrari, and preparation of vittatine derivatives as potential ligands for Alzheimer's disease. *S. Afr. J. Bot.* **2020**, *137*, 137–146. [\[CrossRef\]](#)
74. Šafratová, M.; Novák, Z.; Kulhánková, A.; Kuneš, J.; Hrabínová, M.; Jun, D.; Macáková, K.; Opletal, L.; Cahliková, L. Revised NMR data for 9-O-demethylgalanthine: An alkaloid from *Zephyranthes robusta* (Amaryllidaceae) and its biological activity. *Nat. Prod. Commun.* **2014**, *9*, 787–788. [\[CrossRef\]](#)
75. Tarrago, T.; Kichik, N.; Seguí, J.; Giral, E. The natural product berberine is a human prolyl oligopeptidase inhibitor. *ChemMedChem* **2007**, *2*, 354–359. [\[CrossRef\]](#)
76. Muehlbacher, M.; Spitzer, G.M.; Liedl, K.R.; Kornhuber, J. Qualitative prediction of blood-brain barrier permeability on a large and refined dataset. *J. Comput. Aided Mol. Des.* **2011**, *25*, 1095–1106. [\[CrossRef\]](#)

77. Di, L.; Kerns, E.H.; Fan, K.; McConnell, O.J.; Carter, G.T. High throughput artificial membrane permeability assay for blood–brain barrier. *Eur. J. Med. Chem.* **2003**, *38*, 223–232. [\[CrossRef\]](#)
78. Zenaro, E.; Piacentini, G.; Constantin, G. The blood–brain barrier in Alzheimer’s disease. *Neurobiol. Dis.* **2017**, *107*, 41–56. [\[CrossRef\]](#) [\[PubMed\]](#)
79. Carmona-Vigilanco, F.; Zaragoza-Puchol, D.; Parravicini, O.; Garro, A.; Enriz, R.D.; Feresin, G.E.; Kurina-Sanz, M.; Orden, A.A. Synthesis, biological evaluation and molecular modeling studies of substituted *N*-benzyl-2-phenylethanamines as cholinesterase inhibitors. *N. J. Chem.* **2020**, *44*, 9466–9476. [\[CrossRef\]](#)
80. Mamun, A.A.; Pidaný, F.; Hulcová, D.; Maříková, J.; Kučera, T.; Schmidt, M.; Catapano, M.C.; Hrabínová, M.; Jun, D.; Múčková, L.; et al. Amaryllidaceae alkaloids of norbelladine-type as inspiration for development of highly selective butyrylcholinesterase inhibitors: Synthesis, biological activity evaluation, and docking studies. *Int. J. Mol. Sci.* **2021**, *22*, 8308. [\[CrossRef\]](#) [\[PubMed\]](#)
81. Wu, W.M.; Zhu, Y.Y.; Li, H.R.; Yu, H.Y.; Zhang, P.; Pi, H.F.; Ruan, H.L. Two new alkaloids from the bulbs of *Lycoris sprengeri*. *J. Asian Nat. Prod. Res.* **2014**, *16*, 192–199. [\[CrossRef\]](#)
82. Trujillo-Chacón, L.M.; Alarcón-Enos, J.E.; Céspedes-Acuña, C.L.; Bustamante, L.; Baeza, M.; López, M.G.; Fernández-Mendivil, C.; Cabezas, F.; Pastene-Navarrete, E.R. Neuroprotective activity of isoquinoline alkaloids from of Chilean Amaryllidaceae plants against oxidative stress-induced cytotoxicity on human neuroblastoma SH-SY5Y cells and mouse hippocampal slice culture. *Food Chem. Toxicol.* **2019**, *132*, 110665. [\[CrossRef\]](#)
83. Cortes, N.; Posada-Duque, R.A.; Alvarez, R.; Alzate, F.; Berkov, S.; Cardona-Gómez, G.P.; Osorio, E. Neuroprotective activity and acetylcholinesterase inhibition of five Amaryllidaceae species: A comparative study. *Life Sci.* **2015**, *122*, 42–50. [\[CrossRef\]](#)
84. Ibrakaw, A.S.; Omoruyi, S.I.; Ekpo, O.E.; Hussein, A.A. Neuroprotective activities of *Boophone haemanthoides* (Amaryllidaceae) extract and its chemical constituents. *Molecules* **2020**, *25*, 5376. [\[CrossRef\]](#)
85. Yang, E.J.; Park, G.H.; Song, K.S. Neuroprotective effects of liquiritigenin isolated from licorice roots on glutamate-induced apoptosis in hippocampal neuronal cells. *Neurotoxicology* **2013**, *39*, 114–123. [\[CrossRef\]](#)
86. Niedzielska, E.; Smaga, I.; Gawlik, M.; Moniczewski, A.; Stankowicz, P.; Pera, J.; Filip, M. Oxidative stress in neurodegenerative diseases. *Mol. Neurobiol.* **2016**, *53*, 4094–4125. [\[CrossRef\]](#)
87. Traykova, M.; Traykov, T.; Hadjimitova, V.; Krikorian, K.; Bojadgieva, N. Antioxidant properties of galantamine hydrobromide. *Z. Naturforsch. C J. Biosci.* **2003**, *58*, 361–365. [\[CrossRef\]](#)
88. Bakhtiari, M.; Panahi, Y.; Ameli, J.; Darvishi, B. Protective effects of flavonoids against Alzheimer’s disease-related neural dysfunctions. *Biomed. Pharmacother.* **2017**, *93*, 218–229. [\[CrossRef\]](#)
89. Cortes, N.; Castañeda, C.; Osorio, E.H.; Cardona-Gomez, G.P.; Osorio, E. Amaryllidaceae alkaloids as agents with protective effects against oxidative neural cell injury. *Life Sci.* **2018**, *203*, 54–65. [\[CrossRef\]](#) [\[PubMed\]](#)
90. Hoang, T.H.X.; Ho, D.V.; Van Phan, K.; Le, Q.V.; Raal, A.; Nguyen, H.T. Effects of *Hippeastrum reticulatum* on memory, spatial learning and object recognition in a scopolamine-induced animal model of Alzheimer’s disease. *Pharm. Biol.* **2020**, *58*, 1107–1113. [\[CrossRef\]](#) [\[PubMed\]](#)
91. Cortes, N.; Sabogal-Guaqueta, A.M.; Cardona-Gomez, G.P.; Osorio, E. Neuroprotection and improvement of the histopathological and behavioral impairments in a murine Alzheimer’s model treated with *Zephyranthes carinata* alkaloids. *Biomed. Pharmacother.* **2019**, *110*, 482–492. [\[CrossRef\]](#) [\[PubMed\]](#)
92. Bisset, N.G. Plants as a source of isoquinoline alkaloids. In *The Chemistry and Biology of Isoquinoline Alkaloids. Proceedings in Life Sciences*; Phillipson, J.D., Roberts, M.F., Zenk, M.H., Eds.; Springer: Berlin/Heidelberg, Germany, 1985; pp. 1–22. ISBN 978-3-642-70130-6.
93. Kukula-Koch, W.A.; Wideliski, J. Chapter 9—Alkaloids. In *Pharmacognosy: Fundamentals, Applications and Strategies*; Badal, S., Delgoda, R., Eds.; Academic Press: Cambridge, MA, USA, 2017; pp. 163–198. ISBN 978-0-12-802104-0.
94. Ingkaninan, K.; Phengpa, P.; Yuenyongsawad, S.; Khorana, N. Acetylcholinesterase inhibitors from *Stephania venosa* tuber. *J. Pharm. Pharmacol.* **2006**, *58*, 695–700. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Hung, T.M.; Nguyen, H.D.; Kim, J.C.; Jang, H.S.; Ryoo, S.W.; Lee, J.H.; Choi, J.S.; Bae, K.H.; Min, B.S. Alkaloids from roots of *Stephania rotunda* and their cholinesterase inhibitory activity. *Planta Med.* **2010**, *76*, 1762–1764. [\[CrossRef\]](#)
96. Huang, Q.Q.; Bi, J.L.; Sun, Q.Y.; Yang, F.M.; Wang, Y.H.; Tang, G.H.; Zhao, F.W.; Wang, H.; Xu, J.J.; Kennelly, E.J.; et al. Bioactive isoquinoline alkaloids from *Corydalis saxicola*. *Planta Med.* **2012**, *78*, 65–70. [\[CrossRef\]](#) [\[PubMed\]](#)
97. Hošťálková, A.; Maříková, J.; Opletal, L.; Korábečná, J.; Hulcová, D.; Kuneš, J.; Nováková, L.; Perez, D.I.; Jun, D.; Kučera, T.; et al. Isoquinoline alkaloids from *Berberis vulgaris* as potential lead compounds for the treatment of Alzheimer’s disease. *J. Nat. Prod.* **2019**, *82*, 239–248. [\[CrossRef\]](#)
98. Nachon, F.; Carletti, E.; Ronco, C.; Trovaslet, M.; Nicolet, Y.; Jean, L.; Renard, P.Y. Crystal structures of human cholinesterases in complex with huprine W and tacrine: Elements of specificity for anti-Alzheimer’s drugs targeting acetyl- and butyrylcholinesterase. *Biochem. J.* **2013**, *453*, 393–399. [\[CrossRef\]](#) [\[PubMed\]](#)
99. Zhao, C.; Su, P.; Lv, C.; Guo, L.; Cao, G.; Qin, C.; Zhang, W. Berberine alleviates amyloid β -induced mitochondrial dysfunction and synaptic loss. *Oxid. Med. Cell. Longev.* **2019**, *2019*, 7593608. [\[CrossRef\]](#) [\[PubMed\]](#)
100. Wai, A.; Yeung, A.W.K.; Erdogan Orhan, I.; Aggarwal, B.; Battino, M.; Belwal, T.; Bishayee, A.; Daglia, M.; Devkota, H.; El-Demerdash, A.; et al. Berberine, a popular dietary supplement for human and animal health: Quantitative research literature analysis—A review. *Anim. Sci. Pap. Rep.* **2020**, *38*, 5–19.

101. Chen, Y.; Chen, Y.; Liang, Y.; Chen, H.; Ji, X.; Huang, M. Berberine mitigates cognitive decline in an Alzheimer's Disease Mouse Model by targeting both tau hyperphosphorylation and autophagic clearance. *Biomed. Pharmacother.* **2020**, *121*, 109670. [CrossRef]
102. Dahua, F.; Liping, L.; Zhengzhi, W.; Meiqun, C. Combating neurodegenerative diseases with the plant alkaloid berberine: Molecular mechanisms and therapeutic potential. *Curr. Neuropharmacol.* **2019**, *17*, 563–579. [CrossRef]
103. Cai, Z.; Wang, C.; Yang, W. Role of berberine in Alzheimer's disease. *Neuropsychiatr. Dis. Treat.* **2016**, *12*, 2509–2520. [CrossRef]
104. Liang, Y.; Huang, M.; Jiang, X.; Liu, Q.; Chang, X.; Guo, Y. The neuroprotective effects of Berberine against amyloid β -protein-induced apoptosis in primary cultured hippocampal neurons via mitochondria-related caspase pathway. *Neurosci. Lett.* **2017**, *655*, 46–53. [CrossRef]
105. Huang, M.; Jiang, X.; Liang, Y.; Liu, Q.; Chen, S.; Guo, Y. Berberine improves cognitive impairment by promoting autophagic clearance and inhibiting production of β -amyloid in APP/tau/PS1 mouse model of Alzheimer's disease. *Exp. Gerontol.* **2017**, *91*, 25–33. [CrossRef]
106. Ahmed, T.; Gilani, A.H.; Abdollahi, M.; Daglia, M.; Nabavi, S.F.; Nabavi, S.M. Berberine and neurodegeneration: A review of literature. *Pharmacol. Rep.* **2015**, *67*, 970–979. [CrossRef]
107. Ji, H.F.; Shen, L. Berberine: A potential multipotent natural product to combat Alzheimer's disease. *Molecules* **2011**, *16*, 6732–6740. [CrossRef]
108. Long, J.; Song, J.; Zhong, L.; Liao, Y.; Liu, L.; Li, X. Palmatine: A review of its pharmacology, toxicity and pharmacokinetics. *Biochimie* **2019**, *162*, 176–184. [CrossRef] [PubMed]
109. Zhang, J.; Zhang, C.; Xu, F.C.; Quesheng, Zhang, Q.Y.; Tu, P.F.; Liang, H. Cholinesterase inhibitory isoquinoline alkaloids from *Corydalis mucronifera*. *Phytochemistry* **2019**, *159*, 199–207. [CrossRef] [PubMed]
110. Zhang, J.; Zhang, Q.Y.; Tu, P.F.; Xu, F.C.; Liang, H. Mucroniferanines A–G, isoquinoline alkaloids from *Corydalis mucronifera*. *J. Nat. Prod.* **2018**, *81*, 364–370. [CrossRef] [PubMed]
111. Plazas, E.; Hagenow, S.; Avila Murillo, M.; Stark, H.; Cuca, L.E. Isoquinoline alkaloids from the roots of *Zanthoxylum rigidum* as multi-target inhibitors of cholinesterase, monoamine oxidase A and $A\beta_{1-42}$ aggregation. *Bioorg. Chem.* **2020**, *98*, 103722. [CrossRef]
112. Čahlíková, L.; Opletal, L.; Kurfürst, M.; Macáková, K.; Kulhánková, A.; Hošťálková, A. Acetylcholinesterase and butyrylcholinesterase inhibitory compounds from *Chelidonium majus* (Papaveraceae). *Nat. Prod. Commun.* **2010**, *5*, 1751–1754. [CrossRef]
113. Baek, S.C.; Ryu, H.W.; Kang, M.G.; Lee, H.; Park, D.; Cho, M.L.; Oh, S.R.; Kim, H. Selective inhibition of monoamine oxidase A by chelerythrine, an isoquinoline alkaloid. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2403–2407. [CrossRef]
114. Brunhofer, G.; Fallarero, A.; Karlsson, D.; Batista-Gonzalez, A.; Shinde, P.; Gopi Mohan, C.; Vuorela, P. Exploration of natural compounds as sources of new bifunctional scaffolds targeting cholinesterases and beta amyloid aggregation: The case of chelerythrine. *Bioorg. Med. Chem.* **2012**, *20*, 6669–6679. [CrossRef]
115. Chlebek, J.; Simone, A.; Hošťálková, A.; Opletal, L.; Perez, C.; Perez, D.; Havlíková, L.; Čahlíková, L.; Andrisano, V. Application of BACE1 immobilized enzyme reactor for the characterization of multifunctional alkaloids from *Corydalis cava* (Fumariaceae) as Alzheimer's disease targets. *Fitoterapia* **2016**, *109*, 241–247. [CrossRef]
116. Chlebek, J.; Macáková, K.; Čahlíková, L.; Kurfürst, M.; Kuneš, J.; Opletal, L. Acetylcholinesterase and butyrylcholinesterase inhibitory compounds from *Corydalis cava* (Fumariaceae). *Nat. Prod. Commun.* **2011**, *6*, 607–610. [CrossRef]
117. Siatka, T.; Adamcová, M.; Opletal, L.; Čahlíková, L.; Jun, D.; Hrabínová, M.; Kuneš, J.; Chlebek, J. Cholinesterase and prolyl oligopeptidase inhibitory activities of alkaloids from *Argemone platyceras* (Papaveraceae). *Molecules* **2017**, *22*, 1181. [CrossRef] [PubMed]
118. Čahlíková, L.; Macáková, K.; Kuneš, J.; Kurfürst, M.; Opletal, L.; Cvačka, J.; Chlebek, J.; Blunden, G. Acetylcholinesterase and butyrylcholinesterase inhibitory compounds from *Eschscholzia californica* (Papaveraceae). *Nat. Prod. Commun.* **2010**, *5*, 1035–1038. [CrossRef] [PubMed]
119. Hošťálková, A.; Opletal, L.; Kuneš, J.; Novák, Z.; Hrabínová, M.; Chlebek, J.; Čegan, L.; Čahlíková, L. Alkaloids from *Peumus boldus* and their acetylcholinesterase, butyrylcholinesterase and prolyl oligopeptidase inhibition activity. *Nat. Prod. Commun.* **2015**, *10*, 577–580. [CrossRef]
120. Chlebek, J.; Novák, Z.; Kassemová, D.; Šafratová, M.; Kostelník, J.; Malý, L.; Ločárek, M.; Opletal, L.; Hošťálková, A.; Hrabínová, M.; et al. Isoquinoline alkaloids from *Fumaria officinalis* L. and their biological activities related to Alzheimer's disease. *Chem. Biodivers.* **2016**, *13*, 91–99. [CrossRef]
121. Čahlíková, L.; Hulová, L.; Hrabínová, M.; Chlebek, J.; Hošťálková, A.; Adamcová, M.; Šafratová, M.; Jun, D.; Opletal, L.; Ločárek, M.; et al. Isoquinoline alkaloids as prolyl oligopeptidase inhibitors. *Fitoterapia* **2015**, *103*, 192–196. [CrossRef]
122. Toušek, J.; Dommissie, R.; Dostál, J.; Žák, Z.; Pieters, L.; Marek, R. Configurations and conformations of sanguinarine and chelerythrine free bases stereoisomers. *J. Mol. Struct.* **2002**, *613*, 103–113. [CrossRef]
123. Marasco, D.; Vicidomini, C.; Krupa, P.; Cioffi, F.; Huy, P.D.Q.; Li, M.S.; Florio, D.; Broersen, K.; de Pandis, M.F.; Roviello, G.N. Plant isoquinoline alkaloids as potential neurodrugs: A comparative study of the effects of benzo[c]phenanthridine and berberine-based compounds on β -amyloid aggregation. *Chem. Biol. Interact.* **2021**, *334*, 109300. [CrossRef]
124. Sugimoto, Y.; Yoshida, A.; Uchida, S.; Inanaga, S.; Yamada, Y. Dauricine production in cultured roots of *Menispermum dauricum*. *Phytochemistry* **1994**, *36*, 679–683. [CrossRef]

125. Liu, P.; Chen, X.; Zhou, H.; Wang, L.; Zhang, Z.; Ren, X.; Zhu, F.; Guo, Y.; Huang, X.; Liu, J.; et al. The isoquinoline alkaloid dauricine targets multiple molecular pathways to ameliorate Alzheimer-like pathological changes in vitro. *Oxid. Med. Cell. Longev.* **2018**, *2018*, 2025914. [\[CrossRef\]](#)
126. Thinakaran, G.; Teplow, D.B.; Siman, R.; Greenberg, B.; Sisodia, S.S. Metabolism of the “Swedish” amyloid precursor protein variant in neuro2a (N2a) cells. Evidence that cleavage at the “beta-secretase” site occurs in the golgi apparatus. *J. Biol. Chem.* **1996**, *271*, 9390–9397. [\[CrossRef\]](#) [\[PubMed\]](#)
127. Chen, J.; Liu, J.; Wang, T.; Xiao, H.; Yin, C. Effects of tetrandrine on cAMP and cGMP levels in rabbit corpus cavernosum in vitro. *Nat. Prod. Res.* **2010**, *24*, 1095–1103. [\[CrossRef\]](#) [\[PubMed\]](#)
128. He, F.Q.; Qiu, B.Y.; Zhang, X.H.; Li, T.K.; Xie, Q.; Cui, D.J.; Huang, X.L.; Gan, H.T. Tetrandrine attenuates spatial memory impairment and hippocampal neuroinflammation via inhibiting NF- κ B activation in a rat model of Alzheimer’s disease induced by amyloid- β (1–42). *Brain Res.* **2011**, *1384*, 89–96. [\[CrossRef\]](#)
129. Fajardo, V.; Araya, M.; Cuadra, P.; Oyarzun, A.; Gallardo, A.; Cueto, M.; Diaz-Marrero, A.R.; Darias, J.; Villarroel, L.; Álvarez, C.; et al. Pronuciferine N-oxide, a proaporphine N-oxide alkaloid from *Berberis coletoides*. *J. Nat. Prod.* **2009**, *72*, 1355–1356. [\[CrossRef\]](#) [\[PubMed\]](#)
130. Bayazeid, O.; Nemutlu, E.; Eylem, C.C.; Yalçın, F.N. Neuroactivity of naturally occurring proaporphine alkaloid, pronuciferine. *J. Biochem. Mol. Toxicol.* **2020**, *34*, e22601. [\[CrossRef\]](#) [\[PubMed\]](#)
131. Kohelová, E.; Peřinová, R.; Maafi, N.; Korábečný, J.; Hulcová, D.; Mařiková, J.; Kučera, T.; Martínez González, L.; Hrabínová, M.; Vorčáková, K.; et al. Derivatives of the β -crinane Amaryllidaceae alkaloid haemanthamine as multi-target directed ligands for Alzheimer’s disease. *Molecules* **2019**, *24*, 1307. [\[CrossRef\]](#) [\[PubMed\]](#)
132. Peřinová, R.; Maafi, N.; Korábečný, J.; Kohelová, E.; De Simone, A.; Al Mamun, A.; Hulcová, D.; Marková, J.; Kučera, T.; Jun, D.; et al. Functionalized aromatic esters of the Amaryllidaceae alkaloid haemanthamine and their in vitro and in silico biological activity connected to Alzheimer’s disease. *Bioorg. Chem.* **2020**, *100*, 103928. [\[CrossRef\]](#)
133. Mařiková, J.; Ritomská, A.; Korábečný, J.; Peřinová, R.; Al Mamun, A.; Kučera, T.; Kohelová, E.; Hulcová, D.; Koblřová, T.; Kuneš, J.; et al. Aromatic esters of the crinane Amaryllidaceae alkaloid ambelline as selective inhibitors of butyrylcholinesterase. *J. Nat. Prod.* **2020**, *83*, 1359–1367. [\[CrossRef\]](#) [\[PubMed\]](#)
134. Sobolová, K.; Hrabínová, M.; Hepnarová, V.; Kučera, T.; Koblřová, T.; Benková, M.; Janočková, J.; Doležal, R.; Prchal, L.; Benek, O.; et al. Discovery of novel berberine derivatives with balanced cholinesterase and prolyl oligopeptidase inhibition profile. *Eur. J. Med. Chem.* **2020**, *203*, 112593. [\[CrossRef\]](#)

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Structural Types", Natural Product Communications, 2017

Publication

21

Shiqiang Zhou, Rongbiao Tong. "Three-Step Catalytic Asymmetric Total Syntheses of 13-Methyltetrahydroprotoberberine Alkaloids", Organic Letters, 2017

Publication

<1 %

22

Ling Huang, Tao Su, Xingshu Li. "Natural Products as Sources of New Lead Compounds for the Treatment of Alzheimer's Disease", Current Topics in Medicinal Chemistry, 2013

Publication

<1 %

23

Nicotinic Receptors, 2014.

Publication

<1 %

24

Shidore, Mahesh, Jatin Machhi, Kaushik Shingala, Prashant Murumkar, Mayank Kumar Sharma, Neetesh Agrawal, Ashutosh Tripathi, Zalak Parikh, Prakash Pillai, and Mange Ram Yadav. "Benzylpiperidine-linked diarylthiazoles as potential anti-Alzheimer's agents-synthesis and biological evaluation", Journal of Medicinal Chemistry, 2016.

Publication

<1 %

25

Zhong Jin. "Amaryllidaceae and Sceletium alkaloids", Nat. Prod. Rep., 2016

Publication

<1 %

- | | | |
|----|---|------|
| 26 | tuhat.helsinki.fi
Internet Source | <1 % |
| 27 | Angelo O. Rosa, Manuella P. Kaster, Ricardo W. Binfaré, Susana Morales et al.
"Antidepressant-like effect of the novel thiadiazolidinone NP031115 in mice",
Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2008
Publication | <1 % |
| 28 | Jana Křoustková, Aneta Ritomská, Abdullah Al Mamun, Daniela Hulcová et al. "Structural analysis of unusual alkaloids isolated from Narcissus pseudonarcissus cv. Carlton",
Phytochemistry, 2022
Publication | <1 % |
| 29 | Sonali Mehendale Munj, Pooja Bhagwan Patil.
"Drug Discovery to Drug Development of BACE1 Inhibitor as Antialzheimer's: A Review",
Current Topics in Medicinal Chemistry, 2023
Publication | <1 % |
| 30 | avesis.hacettepe.edu.tr
Internet Source | <1 % |
| 31 | www.labome.org
Internet Source | <1 % |
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Alzheimer's disease", Future Medicinal Chemistry, 2017

Publication

33

Irem Kiris, Merve Karayel Basar, Betul Sahin, Busra Gurel, Julide Coskun, Tomasz Mroczek, Ahmet Tarik Baykal. "Evaluation of the Therapeutic Effect of Lycoramine on Alzheimer's Disease in Mouse Model", Current Medicinal Chemistry, 2021

Publication

<1 %

34

Richard M. van Rijn, In K. Rhee, Robert Verpoorte. " Isolation of acetylcholinesterase inhibitory alkaloids from ", Natural Product Research, 2010

Publication

<1 %

35

Strahil Berkov, Carles Codina, Jaume Basti. "Chapter 3 The Genus Galanthus: A Source of Bioactive Compounds", IntechOpen, 2012

Publication

<1 %

36

Umme Kalsoom, Meshari Alazmi, Hafiz Syed Usama Bin Farrukh, Ka Hang Karen Chung et al. "Structure Dependent Differential Modulation of A β Fibrillization by Selenadiazole-Based Inhibitors", ACS Chemical Neuroscience, 2021

Publication

<1 %

37

repository.nwu.ac.za

Internet Source

<1 %

38

vdoc.pub

Internet Source

<1 %

39

Honghua Zhang, Yan Peng, Linsheng Zhuo, Yuying Wang, Guo Zeng, Shuzhi Wang, Lin Long, Xuelin Li, Zhen Wang. "Recent advance on pleiotropic cholinesterase inhibitors bearing amyloid modulation efficacy", European Journal of Medicinal Chemistry, 2022

Publication

<1 %

40

Eva Mezeiova, Katarina Chalupova, Eugenie Nepovimova, Lukas Gorecki et al. "Donepezil Derivatives Targeting Amyloid- β Cascade in Alzheimer's Disease", Current Alzheimer Research, 2019

Publication

<1 %

41

Juan C. Cedrón, Juan C. Oberti, Ana Estévez-Braun, Ángel G. Ravelo, Marcelino Del Arco-Aguilar, Matías López. " as an Important Source of Amaryllidaceae Alkaloids ", Journal of Natural Products, 2009

Publication

<1 %

42

idr-lib.iitbhu.ac.in:8080

Internet Source

<1 %

43

jglobal.jst.go.jp

Internet Source

<1 %

44

Barry M. Trost, Chao-I Joey Hung, Zhiwei Jiao.
" Enantioselective Divergent Syntheses of (+)-
Bulleyanaline and Related Isoquinoline
Alkaloids from the Genus ", Journal of the
American Chemical Society, 2019

Publication

<1 %

45

Cristiane da Silva Barth, Hugo Guilherme
Tolentino de Souza, Lilian W. Rocha, Camilla
Regina de Souza Madeira et al. "RP-HPLC and
LC–MS–MS determination of a bioactive
artefact from Ipomoea pes-caprae extract",
Revista Brasileira de Farmacognosia, 2019

Publication

<1 %

46

N.A. Masondo, G.I. Stafford, A.O. Aremu, N.P.
Makunga. "Acetylcholinesterase inhibitors
from southern African plants: An overview of
ethnobotanical, pharmacological potential
and phytochemical research including and
beyond Alzheimer's disease treatment", South
African Journal of Botany, 2019

Publication

<1 %

47

"Abstracts The Israel Society for Neuroscience
18th Annual Meeting", Journal of Molecular
Neuroscience, 2009

Publication

<1 %

48

Ana Aradski-Alimpić, Mariana Oalđe-Pavlović,
Smiljana Janković, Petar Marin, Sonja Duletić-
Laušević. "Enzyme inhibitors as controllers of

<1 %

neurodegenerative diseases: An update of in vitro effects of medicinal plants", Lekovite sirovine, 2021

Publication

49

Douglas F. Rambo, Renata Biegelmeyer, Natally S.B. Toson, Roger R. Dresch, Paulo R.H. Moreno, Amélia T. Henriques. "Box–Behnken experimental design for extraction optimization of alkaloids from Erythrina verna Vell. trunk barks and LC Method Validation", Industrial Crops and Products, 2019

<1 %

Publication

50

I. Buendia, E. Parada, E. Navarro, R. León, P. Negredo, J. Egea, M. G. López. "Subthreshold Concentrations of Melatonin and Galantamine Improves Pathological AD-Hallmarks in Hippocampal Organotypic Cultures", Molecular Neurobiology, 2015

<1 %

Publication

51

Jong Min Oh, Hyun-Jae Jang, Won Jun Kim, Myung-Gyun Kang, Seung Cheol Baek, Jae Pil Lee, Daeui Park, Sei-Ryang Oh, Hoon Kim. "Calycosin and 8-O-methylretusin isolated from Maackia amurensis as potent and selective reversible inhibitors of human monoamine oxidase-B", International Journal of Biological Macromolecules, 2020

<1 %

Publication

52

Redondo, Miriam, José Brea, Daniel I. Perez, Ignacio Soteras, Cristina Val, Concepción Perez, Jose A. Morales-García, Sandra Alonso-Gil, Nuria Paul-Fernandez, Rocío Martin-Alvarez, María Isabel Cadavid, María Isabel Loza, Ana Perez-Castillo, Guadalupe Mengod, Nuria E. Campillo, Ana Martinez, and Carmen Gil. "Effect of Phosphodiesterase 7 (PDE7) Inhibitors in Experimental Autoimmune Encephalomyelitis Mice. Discovery of a New Chemically Diverse Family of Compounds", *Journal of Medicinal Chemistry*, 2012.

Publication

<1 %

53

Santosh R. D'Mello. "When Good Kinases Go Rogue: GSK3, p38 MAPK and CDKs as Therapeutic Targets for Alzheimer's and Huntington's Disease", *International Journal of Molecular Sciences*, 2021

Publication

<1 %

54

Seung-Hwan Kwon, Ha-Kyung Lee, Ji-Ah Kim, Sa-Ik Hong et al. "Neuroprotective effects of chlorogenic acid on scopolamine-induced amnesia via anti-acetylcholinesterase and anti-oxidative activities in mice", *European Journal of Pharmacology*, 2010

Publication

<1 %

55

Willian Orlando Castillo, Andres Felipe Aristizabal-Pachon, Elsa Sakamoto-Hojo,

<1 %

Cristian Aldemar Gasca et al. "Caliphruria subedentata (Amaryllidaceae) decreases genotoxicity and cell death induced by β -amyloid peptide in SH-SY5Y cell line", Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 2018

Publication

56

it.readkong.com

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57

paccon2015.kmutt.ac.th

Internet Source

<1 %

58

uspto.report

Internet Source

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59

Huan-Huan Li, Chengyao Wu, Shi-Long Zhang, Jian-Guo Yang, Hua-Li Qin, Wenjian Tang.

"Fluorosulfate-containing pyrazole heterocycles as selective BuChE inhibitors: structure-activity relationship and biological evaluation for the treatment of Alzheimer's disease", Journal of Enzyme Inhibition and Medicinal Chemistry, 2022

Publication

<1 %

60

Jun Zhang, Chen Zhang, Fu-Chun Xu, Quesheng, Qing-Ying Zhang, Peng-Fei Tu, Hong Liang. "Cholinesterase inhibitory isoquinoline alkaloids from *Corydalis mucronifera*", Phytochemistry, 2019

Publication

<1 %

61

Qi He, Jing Liu, Jin-Shuai Lan, Jiaoli Ding et al. "Coumarin- dithiocarbamate hybrids as novel multitarget AChE and MAO-B inhibitors against Alzheimer's Disease: Design, synthesis and biological evaluation", Bioorganic Chemistry, 2018

Publication

<1 %

62

Radek Marek, Pavlína Sečkářová, Dagmar Hulová, Jaromír Marek, Jiří Dostál, Vladimír Sklenář. " Palmatine and Berberine Isolation Artifacts ", Journal of Natural Products, 2003

Publication

<1 %

63

pure.rug.nl

Internet Source

<1 %

64

www.scielo.br

Internet Source

<1 %

65

Mariela González-Ramírez, Javiera Gavilán, Tiare Silva-Grecchi, Daniel Cajas-Madriaga et al. "A Natural Benzofuran from the Patagonic Aleurodiscus vitellinus Fungus has Potent Neuroprotective Properties on a Cellular Model of Amyloid- β Peptide Toxicity", Journal of Alzheimer's Disease, 2018

Publication

<1 %

66

Zdeněk Novák, Anna Hošťálková, Lubomir Opletal, Lucie Nováková, Martina Hrabínová, Jiří Kuneš, Lucie Cahliková. " (+)-Chenabinol

<1 %

(Revised NMR Data) and Two New Alkaloids from and their Biological Activity ", Natural Product Communications, 2015

Publication

67

antiaging2022.febsevents.org

Internet Source

<1 %

68

jneuroinflammation.biomedcentral.com

Internet Source

<1 %

69

mts.intechopen.com

Internet Source

<1 %

70

"Poster Presentations", Clinical and Experimental Hypertension, 2009

Publication

<1 %

71

Bharat Singh, Ram Avtar Sharma. "Secondary Metabolites of Medicinal Plants", Wiley, 2020

Publication

<1 %

72

Fu-Qian He, Bo-Yun Qiu, Xiao-Hui Zhang, Tian-Ke Li, Qin Xie, De-Jun Cui, Xiao-Li Huang, Hua-Tian Gan. "Tetrandrine attenuates spatial memory impairment and hippocampal neuroinflammation via inhibiting NF- κ B activation in a rat model of Alzheimer's disease induced by amyloid- β (1-42)", Brain Research, 2011

Publication

<1 %

73

Heng-Yi Yu, Cui Hao, Fan-Yu Meng, Xue Li, Zu-Yu Chen, Xi Liang, Han-Li Ruan.

<1 %

"Neuroprotective Lignans from the Stems of *Schisandra glaucescens*", *Planta Medica*, 2012

Publication

74

Imran Kazmi, Fahad A. Al-Abbasi, Muhammad Afzal, Muhammad Shahid Nadeem, Hisham N. Altayb. "Sterubin protects against chemically-induced Alzheimer's disease by reducing biomarkers of inflammation- IL-6/ IL- β / TNF- α and oxidative stress- SOD/MDA in rats", *Saudi Journal of Biological Sciences*, 2023

Publication

75

Javier E. Ortiz, Natalia B. Pigni, Sebastián A. Andujar, German Roitman et al. " Alkaloids from and Their Cholinesterase-Inhibitory Activities: An in Vitro and in Silico Study ", *Journal of Natural Products*, 2016

Publication

76

Nouri, Fakhri, El-Senduny, Sanadgol, Abd-ElGhani, Farzaei, Chen. "On the Neuroprotective Effects of Naringenin: Pharmacological Targets, Signaling Pathways, Molecular Mechanisms, and Clinical Perspective", *Biomolecules*, 2019

Publication

77

Paloma Manzanares, Roberto Martínez, Sandra Garrigues, Salvador Genovés, Daniel Ramón, Jose Marcos, Patricia Martorell. "Tryptophan-Containing Dual Neuroprotective

<1 %

<1 %

<1 %

<1 %

Peptides: Prolyl Endopeptidase Inhibition and Caenorhabditis elegans Protection from β -Amyloid Peptide Toxicity", International Journal of Molecular Sciences, 2018

Publication

78

Rashid Taqui, Mithila Debnath, Safin Ahmed, Ajit Ghosh. "Advances on plant extracts and phytocompounds with acetylcholinesterase inhibition activity for possible treatment of Alzheimer's disease", Phytomedicine Plus, 2022

Publication

<1 %

79

Shalini Sharma, Mukesh K. Pandey. "Positron emission tomography imaging of neuroinflammation", Elsevier BV, 2023

Publication

<1 %

80

Shuiyao Hu, Wern Chern Chai, Lintao Xu, Shaoqiang Li et al. "Catecholic alkaloid sulfonates and aromatic nitro compounds from Portulaca oleracea and screening of their anti-inflammatory and anti-microbial activities", Phytochemistry, 2021

Publication

<1 %

81

Teixidó, Meritxell, Esther Zurita, Laura Mendieta, Benjamí Oller-Salvia, Roger Prades, Teresa Tarragó, and Ernest Giralt. "Dual system for the central nervous system targeting and blood-brain barrier transport of

<1 %

a selective prolyl oligopeptidase inhibitor",
Biopolymers, 2013.

Publication

82

Vincenza Andrisano, Marina Naldi, Angela De Simone, Manuela Bartolini. "A patent review of butyrylcholinesterase inhibitors and reactivators 2010-2017", Expert Opinion on Therapeutic Patents, 2018

Publication

<1 %

83

Zeinab Hosseini, Fatemeh Mansouritorghabeh, Faezeh Sadat Hosseini Kakhki, Mahmoud Hosseini et al. "Effect of Sanguisorba minor on scopolamine-induced memory loss in rat: involvement of oxidative stress and acetylcholinesterase", Metabolic Brain Disease, 2022

Publication

<1 %

84

es.scribd.com

Internet Source

<1 %

85

Anzer A. Shah, Tanveer A. Dar, Parvaiz A. Dar, Showkat A. Ganie, Mohammad A. Kamal. "A Current Perspective on the Inhibition of Cholinesterase by Natural and Synthetic Inhibitors", Current Drug Metabolism, 2017

Publication

<1 %

86

Barbora Svobodova, Eva Mezeiova, Vendula Hepnarova, Martina Hrabanova et al. "Exploring Structure-Activity Relationship in

<1 %

Tacrine-Squaramide Derivatives as Potent Cholinesterase Inhibitors", Biomolecules, 2019

Publication

87

Ceschi, Marco Antonio, Jessie Sobieski da Costa, João Paulo Bizarro Lopes, Viktor Saraiva Câmara, Leandra Franciscato Campo, Antonio César de Amorim Borges, Carlos Alberto Saraiva Gonçalves, Daniela Fraga de Souza, Eduardo Luis Konrath, Ana Luiza Martins Karl, Isabella Alvim Guedes, and Laurent Emmanuel Dardenne. "Novel series of tacrine-tianeptine hybrids: Synthesis, cholinesterase inhibitory activity, S100B secretion and a molecular modeling approach", European Journal of Medicinal Chemistry, 2016.

Publication

<1 %

88

Daniel I. Perez, Valle Palomo, Concepción Pérez, Carmen Gil, Pablo D. Dans, F. Javier Luque, Santiago Conde, Ana Martínez. "Switching Reversibility to Irreversibility in Glycogen Synthase Kinase 3 Inhibitors: Clues for Specific Design of New Compounds", Journal of Medicinal Chemistry, 2011

Publication

<1 %

89

Dighe, Satish N, Girdhar Singh Deora, Eugenio De la Mora et al. "Discovery and Structure-Activity Relationships of a Highly Selective

<1 %

Butyrylcholinesterase Inhibitor by Structure-Based Virtual Screening", Journal of Medicinal Chemistry

Publication

90

Ghulam Hussain, Longbin Zhang, Azhar Rasul, Haseeb Anwar et al. "Role of Plant-Derived Flavonoids and Their Mechanism in Attenuation of Alzheimer's and Parkinson's Diseases: An Update of Recent Data", *Molecules*, 2018

Publication

91

Kin Tak Chu, Tzi Bun Ng. "First report of a glutamine-rich antifungal peptide with immunomodulatory and antiproliferative activities from family Amaryllidaceae", *Biochemical and Biophysical Research Communications*, 2004

Publication

92

Korabecny, Jan, Martin Andrs, Eugenie Nepovimova, Rafael Dolezal, Katerina Babkova, Anna Horova, David Malinak, Eva Mezeiova, Lukas Gorecki, Vendula Sepsova, Martina Hrabnova, Ondrej Soukup, Daniel Jun, and Kamil Kuca. "7-Methoxytacrine-p-Anisidine Hybrids as Novel Dual Binding Site Acetylcholinesterase Inhibitors for Alzheimer's Disease Treatment", *Molecules*, 2015.

Publication

<1 %

<1 %

<1 %

93

Linda Söderberg, Nenad Bogdanovic, Birgitta Axelsson, Bengt Winblad, Jan Näslund, Lars O. Tjernberg. "Analysis of Single Alzheimer Solid Plaque Cores by Laser Capture Microscopy and Nanoelectrospray/Tandem Mass Spectrometry", Biochemistry, 2006

Publication

<1 %

94

Nalin Seixas, Ionara I. Dalcol, Bruno Ravanello, Keiti Alessio, Fábio A. Duarte, Vanessa Bender, Ademir F. Morel. "Evaluation of Acetylcholinesterase and Prolyl Oligopeptidase Inhibition of Novel Amino acid-functionalized Stigmasterol and Ursolic Acid Derivatives", Current Organic Chemistry, 2019

Publication

<1 %

95

Ramón Cacabelos, Vinogran Naidoo, Olaia Martínez-Iglesias, Lola Corzo, Natalia Cacabelos, Rocío Pego, Juan C. Carril. "Chapter 13 Pharmacogenomics of Alzheimer's Disease: Novel Strategies for Drug Utilization and Development", Springer Science and Business Media LLC, 2022

Publication

<1 %

96

Roland Hellinger, Johannes Koehbach, Albert Puigpinós, Richard J. Clark, Teresa Tarragó, Ernest Giralt, Christian W. Gruber. " Inhibition of Human Prolyl Oligopeptidase Activity by

<1 %

97

Seydou Ka, Marco Masi, Natacha Merindol, Roberta Di Lecce et al. "Gigantelline, gigantellinine and gigancrinine, cherylline- and crinine-type alkaloids isolated from *Crinum jagus* with anti-acetylcholinesterase activity", *Phytochemistry*, 2020

Publication

<1 %

98

Sri Sukumaran, Chin Chee, Geetha Viswanathan, Michael Buckle, Rozana Othman, Noorsaadah Abd. Rahman, Lip Chung. "Synthesis, Biological Evaluation and Molecular Modelling of 2'-Hydroxychalcones as Acetylcholinesterase Inhibitors", *Molecules*, 2016

Publication

<1 %

99

Thaiane Coelho dos Santos, Thaís Mota Gomes, Bruno Araújo Serra Pinto, Adriana Leandro Camara, Antonio Marcus de Andrade Paes. "Naturally Occurring Acetylcholinesterase Inhibitors and Their Potential Use for Alzheimer's Disease Therapy", *Frontiers in Pharmacology*, 2018

Publication

<1 %

100

Tran Hung, Nguyen Dang, Jin Kim, Han-Su Jang, Sung-Woo Ryoo, Jeong Lee, Jae Choi,

<1 %

KiHwan Bae, Byung Min. " Alkaloids from
Roots of and Their Cholinesterase Inhibitory
Activity ", Planta Medica, 2010

Publication

101 V. Hepnarova, J. Korabecny, L. Matouskova, P. Jost et al. "The concept of hybrid molecules of tacrine and benzyl quinolone carboxylic acid (BQCA) as multifunctional agents for Alzheimer's disease", European Journal of Medicinal Chemistry, 2018

Publication

102 Yuelin Zhang, Dongli Qi, Yanquan Gao, Chunxia Liang et al. "History of uses, phytochemistry, pharmacological activities, quality control and toxicity of the root of *Stephania tetrandra* S. Moore: A review", Journal of Ethnopharmacology, 2020

Publication

103 Zhao-Hui Li, Li-Quan Yin, Dong-Hai Zhao, Lian-Hai Jin, Ya-Juan Sun, Cheng Tan. "SAR studies of quinoline and derivatives as potential treatments for Alzheimer's disease", Arabian Journal of Chemistry, 2022

Publication

104 bio.gnu.ac.kr

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111	Clara Stiebing, Izabella J. Jahn, Michael Schmitt, Nanda Keijzer et al. "Biochemical Characterization of Mouse Retina of an Alzheimer's Disease Model by Raman Spectroscopy", ACS Chemical Neuroscience, 2020 Publication	<1 %
112	Elgorashi, E.E.. "Quantitative structure-activity relationship studies on acetylcholinesterase enzyme inhibitory effects of Amaryllidaceae alkaloids", South African Journal of Botany, 200605 Publication	<1 %
113	George D. Geromichalos, Fotini N. Lamari, Magdalini A. Papandreou, Dimitrios T. Trafalis et al. "Saffron as a Source of Novel	<1 %

Acetylcholinesterase Inhibitors: Molecular Docking and in Vitro Enzymatic Studies",
Journal of Agricultural and Food Chemistry,
2012

Publication

- 114 Jacobus P. Petzer, Anél Petzer. "Leflunomide, a Reversible Monoamine Oxidase Inhibitor", Central Nervous System Agents in Medicinal Chemistry, 2016 $<1\%$
- Publication
-

- 115 Lawandi, Janice, Sandrine Gerber-Lemaire, Lucienne Juillerat-Jeanneret, and Nicolas Moitessier. "Inhibitors of Prolyl Oligopeptidases for the Therapy of Human Diseases: Defining Diseases and Inhibitors", Journal of Medicinal Chemistry, 2010. $<1\%$
- Publication
-

- 116 Liu, Wei, Ming Lang, Moussa B.H. Youdim, Tamar Amit, Yewei Sun, Zaijun Zhang, Yuqiang Wang, and Orly Weinreb. "Design, synthesis and evaluation of novel dual monoamine-cholinesterase inhibitors as potential treatment for Alzheimer's disease", Neuropharmacology, 2016. $<1\%$
- Publication
-

- 117 Nisha A. Rehuman, Bijo Mathew, Rakesh K. Jat, Orazio Nicolotti, Hoon Kim. "A Comprehensive Review of Monoamine $<1\%$

Oxidase-A Inhibitors in their Syntheses and Potencies", Combinatorial Chemistry & High Throughput Screening, 2020

Publication

- 118 Omer Bayazeid, Emirhan Nemutlu, Cemil Can Eylem, Mert İlhan et al. "Neuroactivity of the naturally occurring aporphine alkaloid, roemerine", Natural Product Research, 2020

Publication

- 119 Veronika Opletalova, Jan Dolezel, Jiri Kunes, Vladimir Buchta, Marcela Vejsova, Marta Kuceroval-Chlupacova. "Synthesis and Antifungal Screening of 2-{{1-(5-Alkyl/arylalkylpyrazin-2-yl)ethylidene}hydrazono}-1,3-thiazolidin-4-ones", Molecules, 2016

Publication

- 120 Zitko, Jan, Barbora Servusová, Pavla Paterová, Jana Mandíková, Vladimír Kubíček, Radim Kučera, Veronika Hrabcová, Jiří Kuneš, Ondřej Soukup, and Martin Doležal. "Synthesis, Antimycobacterial Activity and In Vitro Cytotoxicity of 5-Chloro-N-phenylpyrazine-2-carboxamides", Molecules, 2013.

Publication

- 121 Plant Secondary Metabolism, 1998.

Publication

122 Stephanie Andrade, Maria João Ramalho, Joana Angélica Loureiro, Maria do Carmo Pereira. "Natural Compounds for Alzheimer's Disease Therapy: A Systematic Review of Preclinical and Clinical Studies", International Journal of Molecular Sciences, 2019

Publication

<1 %

123 Zeinab Hosseini, Fatemeh Mansouritorghabeh, Faezeh Sadat Hosseini Kakhki, Mahmoud Hosseini et al. "Effect of Sanguisorba Minor on Scopolamine-induced Memory Loss in Rat: Involvement of Oxidative Stress and Acetylcholinesterase", Research Square Platform LLC, 2021

Publication

<1 %

124 Rafael Rodrigues, Corinne Lengsfeld. "Development of a Computational System to Improve Wind Farm Layout, Part I: Model Validation and Near Wake Analysis", Energies, 2019

Publication

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