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INVITED REVIEW

Heterocyclic compounds as key structures for the interaction with old and new targets in Alzheimer's disease therapy

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Abstract
Nowadays, Alzheimer's disease (AD) is widely recognized as a real social problem. In fact, only five drugs are FDA approved for the therapy of this widespread neurodegenerative disease, but with low results so far. Three of them (rivastigmine, donepezil and galantamine) are acetylcholinesterase inhibitors, memantine is a N-methyl-D-aspartate receptor antagonist, whereas the fifth formulation is a combination of donepezil with memantine. The prevention and treatment of AD is the new challenge for pharmaceutical industry, as well as for public institutions, physicians, patients, and their families. The discovery of a new and safe way to cure this neurodegenerative disease is urgent and should not be delayed further. Because of the multiple origin of this pathology, a multi-target strategy is currently strongly pursued by researchers. In this review, we have discussed new structures designed to better the activity on the classical AD targets. We have also examined old and new potential drugs that could prove useful future for the therapy of the pathology by acting on innovative, not usual, and not yet fully explored targets like peroxisome proliferator-activated receptor (PPARs).

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Introduction
Among the neurodegenerative diseases (NDs), Alzheimer's disease (AD) is nowadays a big social problem, especially in the countries where the population's age is increasing. This awful pathology, indeed, affects the elderly population and its progression in the United States is estimated from 5 million of 2014 up to 13.8 million by 2050, excluding the development of medical innovations to prevent, slow or stop the disease (Alzheimer's Association, 2014; Hiremathad, 2017). The prevention and treatment of this neurodegenerative disease is one the most urgent challenge for pharmaceutical industry, but also for public institutions, physicians, patients, and their families (Piemontese, 2017a).

Only few drugs have been available for AD therapies over the years: just five symptomatic molecules were approved and one of them (tacrine) was recently withdrawn from the market, due to its side effects. The only non-cholinergic drug is memantine, N-methyl-D-aspartate (NMDA) receptor antagonist, that acts by restoring the Aβ-induced Ca^{2+} imbalance and is able to decrease neuronal death (Small et al., 2011; Santos et al., 2016a; Hiremathad, 2017). Donepezil, rivastigmine, and galantamine, instead, are AchE inhibitors (AchEIs) like tacrine. These molecules are able to delay the onset of the disease for a few years and, if administered in time, can improve cognitive abilities of the patients. Therefore, it is fundamental to find new and more effective therapies, in order to decrease the high costs of public health systems and improve the quality of life of patients and their families (Piemontese, 2017a, b).

AD is widely recognized as a multifactorial disease, and this multiple origin of the pathology suggests that a key strategy for the preparation of new drugs could be found in the so-called "multi-target ligands" approach. This methodology is based on the identification of multifunctional molecules designed in order to act simultaneously on two or more targets with the aim of achieving synergistic actions and, in this way, improving the therapeutic efficacy (Santos et al., 2016a, b; Chaves et al., 2017; Piemontese, 2017a). To date, inhibition of cholinesterases (ChEIs), monoaminoxidases (MAOs) and/or beta-secretase (BACE), NMDA receptor antagonism, antioxidant activity, inhibition of beta amyloid plaques (Aβ) aggregation, and chelation of heavy metal cations (copper, iron, zinc) are among the most common investigated targets (Santos et al., 2016a, b; Piemontese, 2017a). In particular, the removal and/or redistribution of metal ions at the level of the central nervous system (CNS) can significantly reduce the formation of Aβ and thus of reactive oxygen species

(ROS), which are typical of the first stages of AD (Santos et al., 2016b).

In the last two decades, many research groups have addressed their activity on the discovery of novel bioactive moieties attempting to obtain better therapeutic action and lesser side effects. Many natural and synthetic compounds became potential candidates that can protect the neurons against the degeneration. In particular, several studies were addressed to rationalize the importance of 5- and 6-terms heterocyclic rings-based compounds (reviewed by Martorana et al., 2016).

In this review, we have focused our attention on simple and complex heterocyclic structures, recently used in the design, synthesis and biological evaluation of multi-target compounds as potential new drugs for the treatment of AD. We have searched in literature for new molecules designed in order to better the activity on the classical AD targets, and for old and new potential drugs that could be useful in the future for the therapy of the pathology by acting on innovative, not usual, and not yet fully explored targets.

We selected and reviewed papers dealing on new molecules inspired by the already known structures of tacrine, donepezil and rivastigmine (two or more pharmacophoric structures that act on different targets, linked with a variable-length backbone) as well as completely different ligands that have a multi-target action, but that are designed with a different approach (single pharmacophore, active on different targets). Concerning the new possible targets for AD therapy reported in literature, we focused in the last part of the review on the peroxisome proliferator-activated receptors (PPARs). These nuclear receptors have been recently demonstrated to be involved in the process of inflammation connected with the aluminum-induced changes in media prefrontal cortex (Rafati et al., 2015). Moreover, the activation of PPARs showed *in vitro* (Pang et al., 2014) or *in vivo* (Gupta et al., 2012; Xiang et al., 2012; Barbiero et al., 2014) important improvements in the neuronal protection. Herein, we report the main results obtained studying the effect of heterocyclic compounds with PPAR activity that have shown in the recent past promising preliminary results for the treatment of AD.

Heterocyclic Compounds as Anti-AD Agents

New heterocyclic compounds have been developed in the last years in order to find new bioactive molecules in many research fields (Piemontese et al., 2010, 2013). In particular, as far as the treatment of AD is concerned, as mentioned above, several research groups have designed and synthesized numerous ligands containing at least one heterocyclic scaffold using the multi-target approach and exploring new possible biological targets.

Prati et al. (2015) have reported on the first class of BACE-1/glycogen synthase kinase-3 beta (GSK-3β) dual inhibitors based on a dihydroxy-1,3,5,triazin-2-one scaffold. Remarkably, compound **1** (**Additional Table 1**) showed inhibition against BACE-1 and GSK-3β (IC_{50} = 16 and 7 μM respectively) and exhibited significant neuroprotective and neurogenic activities, with no neurotoxicity in cell based assay as well. *In vivo* pharmacokinetic studies showed good brain permeability.

Moreover, another research group (Khan et al., 2015), has demonstrated the biological activities of two series of N-heterocyclic compounds (triazolothiadiazoles and triazolothiadiazines). Fascinatingly, these molecules showed good inhibition for the acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Among all screened compounds, compound **2a** (**Additional Table 1**) exhibited highest inhibition with IC_{50} = 0.117 ± 0.007 μM against AChE, while **2b** (**Additional Table 1**) showed strong inhibition with IC_{50} = 0.056 ± 0.001 μM against BuChE. Another series of compounds, and in particular the molecules designed as **3a** and **3c** (**Additional Table 1**), showed clear selectivity over AChE and interesting IC_{50} value (0.065 ± 0.005 and 0.075 ± 0.001 μM on AChE and BuChE, respectively). Further, the same research group has tested the same molecules for their monoaminoxidases (MAO-A and MAO-B) inhibition: compounds **2c** and **3b** (**Additional Table 1**) resulted active against MAO-A with IC_{50} value of 0.11 ± 0.005 μM and 0.011 ± 0.001 μM respectively, whereas, compounds **2b** (**Additional Table 1**) inhibited MAO-B.

Several N-pyridinyl naphthyridinamines were recently selected instead as hit compounds by Rombouts et al. (2017) after a mini-high throughput screening (HTS) on four-thousand molecules identified through 2D fragment-based similarity and 3D pharmacophoric and shape similarity. A modest selectivity was observed for compound **4** (**Additional Table 1**) as a potent binder to the aggregated tau *versus* Aβ aggregation. Since further investigation showed that fluorination is the key point to increase the potency and selectivity, they introduced a fluoroalkyl-substitution optimizing physicochemical and kinetic properties, and obtained compound **5** (**Additional Table 1**), that was identified as a potent and selective tau aggregate binder with potential use as a tau PET tracer (Rombouts et al., 2017).

A further research group (Lee et al., 2014) has focused its researches on Aβ aggregation, metal ion dyshomeostasis, and oxidative stress. The prototype compound **6** (**Additional Table 1**) showed water solubility, and brain permeability as well. The *in vitro* studies demonstrated that the ligand **6** suppresses Aβ aggregation and toxicity induced by the free metal ions, and controls the formation and presence of free radical which causes the oxidative stress. Therefore, they concluded that compound **6** is a small molecule that can target and modulate several targets involved in AD.

Among the cholinesterase inhibitors, the main class of drugs available in market, tacrine (TAC) was the first molecule used in the therapy of AD. However, due to its hepatotoxicity, it was recently withdrawn from the market. Therefore, many researchers are currently making an effort to improve the drug properties through chemical modifications of the starting structure. Keri et al. (2013) have reported a series of TAC-benzothiazole (BTA) conjugates with potential

activity in AD treatment. Among all the molecules tested, compound **7a** (**Additional Table 1**) proved to be the best AChE inhibitor with IC_{50} = 0.34 μM, whereas compound **7b** (**Additional Table 1**) showed the highest anti-$A\beta_{42}$ self-aggregation activity (61.3%, at 50 μM).

In order to evaluate other AD classical targets (such as accumulation of Aβ plaques related to the oxidative damage and dyshomeostasis of redox-active biometals), in 2016 the same group has explored another set of TAC and S-allyl or propargyl cysteine hybrids (Keri et al., 2016). Using docking simulations, they have optimized the linker length for the interaction with AChE active sites. Furthermore, the compounds were explored for their *in vitro* activities for AChE and $A\beta_{42}$ self-aggregation inhibition, as well as for their neuroprotective activity towards Aβ- and ROS-induced cellular toxicity. Remarkably, compound **8a** (**Additional Table 1**) showed the best AChE inhibition (IC_{50} = 0.30 μM), though it did not show a relevant Aβ aggregation inhibition. Compound **8b** (**Additional Table 1**), on the other side, prevented the superoxide production and Aβ-induced cellular toxicity. Hiremathad et al. (2016), instead, have attempted to discover tri-hybrids compounds for AD target studies. The designed and synthesized tri-hybrids and the resulting compounds were analyzed for their biological activity as AChE inhibitors, anti-oxidants, monoaminoxidase inhibitors, and finally for their Aβ-aggregation inhibition ability. Interestingly, many compounds turn out to be more potent than TAC. In particular, chloro-substitution in position 1 increased AChE inhibition and all hybrids showed almost the same activity on the enzyme, with a range of inhibition (calculated as IC_{50}) of 0.27–0.37 μM. Moreover, compounds **9a** and **9b** (**Additional Table 1**) showed good Aβ-anti-aggregation ability (78.2 and 77.2 % respectively) as well. The compound with propargyl and longer linker (**9c**, **Additional Table 1**) showed the best MAO inhibitor profile. To sum up, the conjugation of three molecules improved the *in vitro* experimental results (Hiremathad et al., 2016).

Following similar goals, Quintanova et al. (2015) reported on the synthesis and the biological activity of tacrine-cinnamate and tacrine-cinnamylidene acetate conjugates as multi-target AD ligands. All synthesized hybrids showed AChE inhibition between micromolar and nanomolar range of concentrations, and among all compounds, **10a** and **10b** (**Additional Table 1**) displayed the better activity (IC_{50} = 0.09 μM). Noticeably, cinnamate derivatives with hydroxyl substituents and extended allyl conjugation showed good antioxidant capacity. In addition, these compounds showed good neuroprotective effect (Quintanova et al., 2015).

With the aim to synthesize multi-target compounds with metal chelation activity, in 2013 Nunes et al. starting from the structure of 3-hydroxy-4-pyridinone (3,4-HP), a nucleus that is known to have affinity for iron and Aβ peptides, projected a new series of derivatives. In particular, they explored the conjugation of the benzothiazole (BTA) nucleus with HP instead of the TAC (as reported for compounds **9a**–**c**, **Additional Table 1**) and studied their capacity to inhibit AChE and antioxidant ability, as well as Aβ-self-aggregation inhibition in absence of zinc and zinc-mediated. Their studies showed moderate AChE inhibition activity (IC_{50} = 14–19 μM). Over all, this series exhibited a good Aβ anti-aggregation effect: compound **11** (**Additional Table 1**) showed the best results, with 68% inhibition and the improvement of the cell viability. Compound **12** (**Additional Table 1**), showed, on the other side, the best antioxidant capacity (147 μM), and the best Aβ-self-aggregation inhibition activity in absence of zinc. Lastly, the authors evaluated the effects of selected compounds on the viability of neuronal cells stressed with $A\beta_{42}$ protein (Keri et al., 2013).

Starting from these results, Chand et al. (2016) projected and synthesized TAC and hydroxybenzoyl-pyridone (HBP) hybrids as well, introducing the benzoyl group in the HP structure and coupled it with TAC and exploring them for their biological activities (AChE, anti-oxidant capacity) and bio-metal chelating property. Remarkably, all hybrids showed AChE inhibition in sub-micromolar range (IC_{50} = 0.57–0.78 μM) and, among them, compound **13** (**Additional Table 1**) displayed the best profile (IC_{50} = 0.50 ± 0.05 μM). The radical scavenging activity was good (DPPH, 2–2 diphenyl-1-picrylhtdrazyl, free radical method: EC_{50} = 204–249 μM), and chelating capacity towards biometals was moderate to good (pFe = 13.9, pCu = 6.0 and pZn = 6.0 at pH 6.0, C_L/C_M = 10, $C_M = 10^{-6}$ M).

Following a similar approach, Xie et al. (2013) reported on the design, synthesis and biological evaluation of novel TAC and coumarin hybrids. Many of these compounds inhibited ChE enzymes as well as Aβ plaques formation. Particularly, compound **14** (**Additional Table 1**) showed the highest AChE inhibition (IC_{50} = 0.092 μM) and also good BuChE inhibition (IC_{50} = 0.234 μM) as well as good metal chelation activity. In addition, molecular modeling studies revealed that compound **14** interacts with both central (CAS, catalytic active site), and peripheral (PAS, peripheral anionic site) sites with a mixed type AchE inhibition system.

TAC-carbazole derivatives were developed by Thiratmatrakul et al. (2014) instead. These molecules exhibited good AChE inhibition (IC_{50} = 0.48–1.03 μM) with selectivity on BuChE and good radical scavenging capacity. In addition, they were able to reduce the neuronal death induced by oxidative stress. The ability to improve the cognitive impairments was studied by *in vivo* studies. Compound **15** (**Additional Table 1**, AchE IC_{50} = 0.48 μM) was designed as the most promising molecule and it can be considered for further studies for drug development in AD (Xie et al., 2013).

The first study of hybrids that combines the steroidal alkaloid with tacrine moiety was reported by García et al. (2015). The isolation of steroidal alkaloid Solanocapsine from *S. pseudocapsicum* and its subsequent derivatization by chemical modifications were performed with the aim to modify the reactive groups in order to achieve a better AChE inhibition. A Structure-Activity Relationship (SAR) study was performed as well: the introduction of a

lipophilic group linked to the primary amine decreased inhibitory potency, whereas the effects of various substituents (with different electronic and steric characteristics) on the aromatic ring were not clearly observed. Interestingly, the authors remarked that at least one free amino group is necessary to achieve a nanomolar-range enzyme inhibition. Compound **16** (**Additional Table 1**) showed the most potent inhibitor activity against the AChE with IC_{50} value of 90 nM. The molecular simplification induced a significant decrease in the activity, confirming that the tetrahydroacridin moiety is crucial for the inhibition process. For this reason, this appears as an important key to develop new solanocapsine derivatives as novel pharmacophore for the AD treatment.

Other heterocyclic natural compounds inspired the design of original structures. Hydroxylated benzochromenones (urolithins), for example, were synthesized and explored for their biological activities on AD targets by Gulcan et al. (2014). Urolithins are the main bioavailble metabolites and biomarkers of ellagitannins, natural bioactive compounds that are present in various food commodities. This justifies the use of several edible plants in the folk medicine as cognitive enhancer in the treatment of AD and other kind of dementia. Unfortunately, these molecules demonstrated less potential of inhibition of AChE and BuChE. A series of benzochromenone and tetrahydro-benzochromenone, instead, showed potential activity against the same enzymes. The results of biological studies showed inhibitions comparable to the commercial drugs activity both in *in vitro* and *in vivo*. Therefore, ligands **17a**, **17b**, **18**, **19** and **20** (**Additional Table 1**) were indicated as lead compounds for the generation of further active molecules (Gulcan et al., 2014).

Recently, other commercial drugs have inspired the design and synthesis of novel series of multitarget-directed ligands. Starting from the structure of donepezil, C. Rochais et al. (2015) obtained several molecules that exhibited a very interesting dual binding site AChE inhibitory activity and partial serotonergic subtype-4 receptor (5-HT4R) agonist activity in nanomolar range. Among all, ligand **21** (donecopride, **Additional Table 1**) seems to be the most promising compound. In fact, *in vivo* studies revealed pro-congnitive, anti-amnesic effects in NMRI mice and also activity in promotion of the release of sAPPα in C57BL/6 mice.

Very recently, L. Monjas et al. (2017) have developed an innovative synthetic route for the preparation of several donepezil-based glutamic acid derivatives and have evaluated their pharmacological activity *in vivo* considering different AD targets. The studied compounds inhibited the AChE and protected neurons against toxic insults associated with AD. In particular, compound **22** and **23** (**Additional Table 1**) showed the best AChE inhibition (IC_{50} = 0.53 and 0.5 μM respectively).

Other authors reported on their studies about a series of hybrids of donepezil and ebselen (a synthetic organoselenium drug molecule with anti-inflammatory, anti-oxidant and cytoprotective activity, Luo et al., 2013) as multi-target ligands with anti-AD potential therapeutic use. Several compounds did not show relevant activity on the studied target, but interestingly, compound **24** (**Additional Table 1**) exhibited excellent AChE inhibition (IC_{50} = 0.042 μM for electrophorus electricus AChE) and strong BuChE inhibition (IC_{50} = 1.586 μM). In addition, these molecules exhibited good radical scavenging capacity (123.5 μM) and did not show acute toxicity in mice at doses of up to 2000 mg/kg. Moreover, compound **24** seems to be relatively able to penetrate the central nervous system (Luo et al., 2013).

New scutellarin–rivastigmine hybrids were designed and synthesized by Sang et al. (2015) instead. The biological evaluation revealed that these compounds are good AChE and BuChE inhibitors, with neuroprotective and antioxidant effects and good capacity of biometal chelation. Additionally, the *in vivo* studies indicated good neuroprotective effects in scopolamine-induced cognitive impairment. Compound **25** (**Additional Table 1**) showed the most promising enzymatic activity (IC_{50} = 0.57 and 22.61 μM, for AChE and BuChE, respectively) and a promising anti-oxidant activity (1.3 fold of Trolox, used as a reference compound). The *in vitro* studies suggested that **25** could cross the blood-brain barrier as well (Sang et al., 2015).

Heterocyclic Compounds as PPAR Agonists: a New Target for AD Therapy

Recently, new targets for the treatment of neurodegenerative diseases were explored, starting from a new consideration of further studies performed on several drugs already used in therapy. In particular, PPAR agonists seem to be very promising new agents for the treatment of AD.

The classical drugs that act through PPARs activation are fibrates and glitazones. These molecules were used over the years in the therapies of atherosclerosis and diabetes. Many efforts have been made in the last 20 years with the aim of obtaining a single ligand able of acting on hyperlipidemia and type 2 diabetes (Fracchiolla et al., 2008, 2012; Carrieri et al., 2013; Laghezza et al., 2015; Piemontese et al., 2015, 2017c), in order to better the compliance of the patients. In fact, these diseases are very often associated (in a condition defined as metabolic syndrome), and the treatment of both pathologies with one drug only was for many years a goal for pharmaceutical industry. Fascinatingly, PPAR ligands, if well projected, seem to be useful in the treatment of NDs as well (Piemontese et al., 2017a).

In a recent study, Cheng et al. (2015) determined the effects of PPARα activation on neuronal degeneration by using a model of $A\beta_{42}$-induced cytotoxicity. They concluded that the mitochondrial-associated AIF/Endo G-dependent pathway can be hindered by activation of receptor in the model. Therefore, they suggest that PPARα activation should be considered as an innovative potential strategy for the treatment of AD.

PPARγ activation was demonstrated, on the other side, to influence the amyloid-β precursor protein (APP) cleavage

by suppressing the transcription of APP processing enzyme BACE-1, thus leading to decreased Aβ levels. Moreover, PPARγ agonists are able to enhance the degradation of Aβ by microglia (Yamanaka et al., 2012) and inhibit pro-inflammatory gene expression (Jiang et al., 1998; Ricote et al., 1998).

In particular, the ligand **26** (**Additional Table 1**) presented a promising *in vitro* activity (γ-secretase: IC_{50} ($A\beta_{42}$) = 6.0 μM; EC_{50} ($A\beta_{38}$) = 1.8 μM and PPARγ: EC_{50} = 11.0 μM, maximum activation: 112%) (Hieke et al., 2010). The pharmacokinetic properties of this molecule were recently studied in order to address further preclinical pharmacodynamic animal studies (Pellowska et al., 2015).

Recently, the anti-diabetic approved drug pioglitazone (PPARγ full agonist) was subjected to clinical studies in order to deepen the possibility of its use for the treatment of AD. The aims of this investigation in Phase II trial, planned as co-administration of the drug with an AChE inhibitor and memantine in patients with mild to moderate AD, were safety and tolerability, and therefore no significant results on cognitive measures were shown. Pioglitazone was well tolerated, with few side effects. This study will permit to calculate the population to be treated in Phase III (Galimberti et al., 2016). Obviously, further studies will clarify the possibility of the use of pioglitazone in the therapeutic protocols for AD.

Conclusion

The use of AchE inhibitors or NMDA receptor antagonist drugs, joint with a correct diet and with the consumption of selected food supplements with antioxidant properties (Piemontese, 2017a, b) is actually the only weapon able to prevent and treat AD in the early stage of pathology.

However, the discovery of a new, safe, selective way to treat AD could provide a breakthrough for physicians, patients and pharmaceutical industry. Along this direction, heterocyclic scaffolds were widely used in the synthesis of new potential drugs over the last twenty years with promising but still partial results.

The identification of molecules with interesting multi-target profile, the screening of old drugs that are proved effective through the interaction with new important targets and the preparation of natural-based synthetic molecules might be the key to finally achieve this fundamental goal and restore hope for Earth's population.

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Additional file: *Additional Table 1 Structure and related anti-AD activity of heterocyclic compounds.*

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