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Propargylamine-derived multitarget-directed ligands: fighting Alzheimer's disease with monoamine oxidase inhibitors

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Abstract Alzheimer's disease (AD) is a complex neurodegenerative disorder with a multifaceted pathogenesis. There are at present three Food and Drug Administration-approved drugs based on the "one drug, one target" paradigm (donepezil, galantamine and rivastigmine) that improve symptoms by inhibiting acetylcholinesterase. However, apart from the beneficial palliative properties, cholinergic drugs have shown little efficacy to prevent the progression of the disease evidencing the unsuitability of this strategy for the complex nature of AD. By contrast, the multifactorial nature of this neurodegenerative disorder supports the most current innovative therapeutic approach based on the "one drug, multiple targets" paradigm, which suggests the use of compounds with multiple activities at different target sites. Accordingly, the also called multitarget-directed ligand (MTDL) approach has been the subject of increasing attention by many research groups, which have developed a variety of hybrid compounds acting on very diverse targets. The therapeutic potential of monoamine oxidase inhibitors (MAOI) in AD has been suggested due to their demonstrated neuroprotective properties besides their enhancing effect on monoaminergic transmission. Especially, those containing a propargylamine moiety are of particular interest due to their reported beneficial actions. Therefore, targeting MAO enzymes should be considered in therapeutic interventions. This review makes a special emphasis on MTDLs that commonly target MAO enzymes. There is at present an urgent need for real disease-modifying therapies for AD and the MTDL approach makes a breakthrough for the development of new drugs capable of addressing the biological complexity of this disorder.

Keywords Multitarget-directed ligand · Propargylamine · Neuroprotection · Alzheimer's disease · Monoamine oxidase · Cholinesterases

Abbreviations

AD	Alzheimer's disease
FDA	Food and Drug Administration
AChE	Acetylcholinesterase
MAO	Monoamine oxidase
MTDL	Multitarget-directed ligand
NFT	Neurofibrillary tangles
SP	Senile plaques
Aβ	Amyloid β
NMDA	N-methyl-D-aspartate
FAD	Flavin adenine dinucleotide
PD	Parkinson's disease
ROS	Reactive oxygen species
OS	Oxidative stress

Introduction

Among neurodegenerative disorders, Alzheimer's disease (AD) appears as the fourth leading cause of death and the most common cause of dementia in the elderly population afflicting more than seven million people worldwide (Wimo et al. 2010). The predominant clinical manifestation is progressive memory deterioration and changes in brain

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function, including disordered behaviour and impairment in language and comprehension (Tsolaki et al. 2001), which progressively worsen over 5–10 years (Bayer and Reban 2004). Most of these cognitive symptoms result from a depletion of basal forebrain cholinergic neurons leading to decreased cholinergic neurotransmission (Perry et al. 1977; Geula and Mesulam 1999). Besides the cognitive deficits, patients frequently exhibit neuropsychiatric symptoms such as depression, psychosis and agitation (Ballard et al. 2008). From the histopathological viewpoint, two characteristic hallmarks accompany these features: the neurofibrillary tangles (NFT) which are intracellular fibrillar deposits mainly composed of the microtubule-associated protein tau (Goedert et al. 1989), and the senile plaques (SP), formed by deposition of the aggregated amyloid-β peptide (Aβ) (Glenner and Murphy 1989).

Despite the significant advances in the last few decades, the pathogenesis of AD is not yet fully understood. Nevertheless, at present the scientific consensus is quite firm in describing it as a multifactorial disease caused by genetic, environmental and endogenous factors. These factors include, beyond the excessive protein misfolding and aggregation (Terry et al. 1964; Grundke-Iqbal et al. 1986) and the cholinergic dysfunction, oxidative stress (Coyle and Puttfarcken 1993; Perry et al. 2000; Gella and Durany 2009), mitochondrial dysfunction (Swerdlow and Khan 2009), metal dyshomeostasis (Huang et al. 2004), excitotoxic and neuroinflammatory processes (Mishizen-Eberz et al. 2004). In addition, disturbances in other neurotransmitter systems such as the monoaminergic have also been reported to account for AD symptoms (Baker and Reynolds 1989; Cross 1990).

Current anti-Alzheimer therapies

The most noticeable evidence pointing to the complexity of AD is that to date no drug can prevent the neurodegenerative process. Pharmaceutical research has only been able to develop drugs that, at best, slightly modulate the symptoms in patients suffering from AD.

The Food and Drug Administration (FDA)-approved drugs for the treatment of the cognitive deficits of AD are mainly based on the "Cholinergic Hypothesis of AD" (Davies and Maloney 1976) which gives a central role to decreased cholinergic neurotransmission and thus proposes the use of anticholinergic drugs as an approach for improving cognitive function (Bartus et al. 1982). These drugs include rivastigmine (**1**), donepezil (**2**), galantamine (**3**) and tacrine (**4**) (Fig. 1) (Birks et al. 2000; Birks and Harvey 2006; Loy and Schneider 2004; Waldholdz 1993). The latter is now rarely used because of its hepatotoxicity. Memantine (**5**) is an N-methyl-D-aspartate (NMDA) receptor antagonist that improves glutamatergic neurotransmission and a unique non-cholinergic approved drug (Fig. 1) (Areosa et al. 2005).

In the search for more effective therapies, a combination of different anti-Alzheimer's drugs has also been attempted. The multidrug medication or drug "cocktail" therapy consists in the use of multiple drugs targeting different sites of action, the efficacy of which is determined by the additive or synergistic effect of each medicine and relief of adverse effects. Different strategies have been reported in clinical trials investigating the potential of very diverse formulations, including those combining rivastigmine (**1**), donepezil (**2**) or galantamine (**3**) with memantine (**5**) (for review see Patel and Grossberg 2011). Recent trials have assessed, among others, the use of drugs exerting nerve growth factor (NGF)-like activity (Alvarez et al. 2011), histamine inverse agonists (Cho et al. 2011) and peroxisome proliferators-activated receptor gamma (PPARγ) agonists (Harrington et al. 2011) in combination with anticholinesterase drugs. Additional formulations envisage the incorporation of antioxidant molecules such as vitamin D, E and C (Annweiller et al. 2001; Morris et al. 2005). Also, studies with inhibitors of relevant enzymes such as β-secretase (BACE) or phosphodiesterase-9 (PD9) are underway.

Although it has been suggested that the combination provides long-term benefits linked to cognitive and functional improvement, there is still much scepticism regarding the likelihood of success of some of the cocktail combinations, since to date clinical trials have given controversial results, particularly those involving antioxidants, due to methodological problems and poorly matched epidemiological studies. The current ongoing studies will help to elucidate this question and develop better formulations.

Multitarget-directed ligands (MTDLs) strategy

Despite the recent advances in the knowledge of the several factors involved in the aetiology of AD, slowing or halting the neurodegenerative process has not yet been accomplished and neuroprotection is thus still considered an unmet need. Several authors have pointed out that the lack of effectiveness of the current anticholinergic therapies may be related to the multifactorial and extremely complex nature of AD, which makes one single drug hitting a single pathway or target inadequate as treatment (Buccafusco and Terry 2000; Youdim and Buccafusco 2005; Sterling et al. 2002). In this context, it is now widely accepted that a more effective therapy would result from the use of compounds able to target the multiple mechanisms underlying the aetiology of AD (Fig. 2). This emerging paradigm, called the MTDL approach, describes compounds whose multiple biological profile is rationally designed to combat a particular disease (Cavalli et al. 2008).

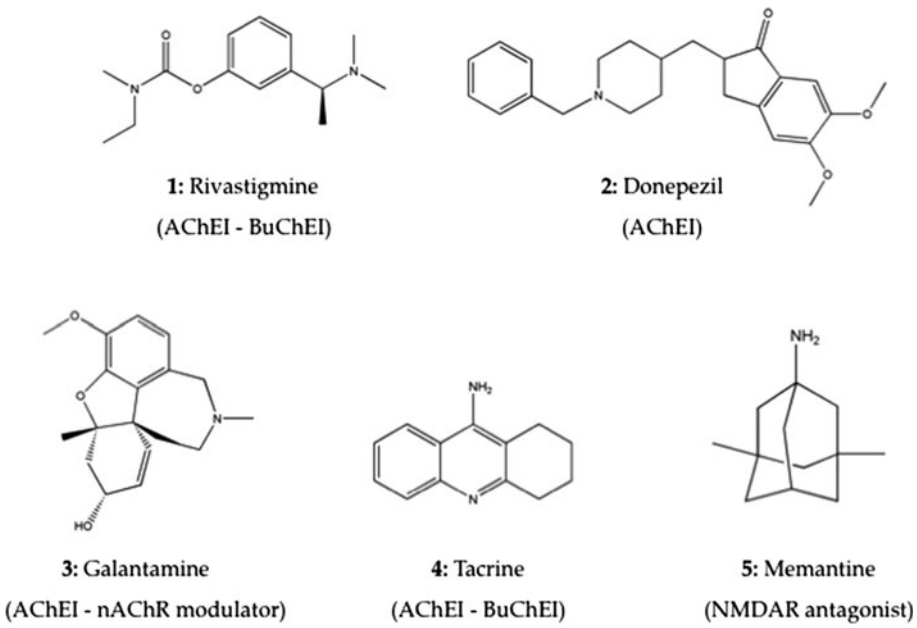

Fig. 1 Chemical structures of the currently available FDA-approved drugs for AD treatment. Action mechanisms are indicated in parenthesis. *AChEI* acetylcholinesterase inhibitor, *BuChEI* butyrylcholinesterase inhibitor, *NMDAR* N-methyl-D-aspartate receptors, *nAChR* nicotinic acetylcholine receptors

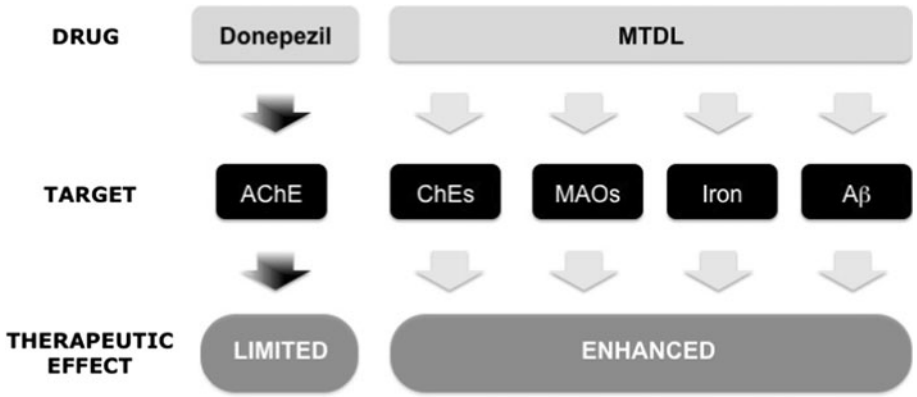

Fig. 2 Pathways leading to the discovery of new drugs. On the left, the "one target–one molecule" paradigm (donepezil) and on the right, the "multitarget-directed ligand" (MTDL) approach. *AChE* acetylcholinesterase, *ChEs* cholinesterases, *MAOs* monoamine oxidases, *Aβ* amyloid-β protein. Adapted from Cavalli et al. 2008

The MTDLs design strategy involves the incorporation of distinct pharmacophores of different drugs in the same structure to get hybrid molecules. Principally, each pharmacophore of the hybrid drug should retain the ability to interact with its specific site(s) on the target producing the consequent pharmacological response. In the context of AD, the most widely adopted approach is to combine the structure of an FDA-approved cholinesterase inhibitor with another drug whose biological properties would be useful for the treatment. MTDLs approach has gained increasing acceptance and has therefore been the subject of increasing attention from many research groups, which have developed a wide variety of compounds acting on very diverse type of targets, such as Aβ peptide aggregation, γ-secretase, serotonin transporter, reactive oxygen species, calcium channels and metals (Rodríguez-Franco et al. 2005; Rosini et al. 2003; Van der Schyf et al. 2006; Elsinghorst et al. 2007; Fang et al. 2008; Zheng et al. 2009).

In this review, we will describe the reasons for considering monoamine oxidase (MAO) an interesting potential target in the design of MTDLs. We will also focus on the current status of reported multifunctional compounds targeting MAO. Particularly, we will focus on propargylamine-derived compounds as promising neuroprotective agents with a potential disease-modifying activity towards AD. As mentioned before, a wide amount of interesting MTDLs have been designed to combat AD. Many of them do not include MAO enzymes as target, so, although interesting, this is an extensive field which is beyond the scope of this review.

Therapeutic potential of MAO inhibitors

Monoamine oxidase (MAO, E.C.1.4.3.4) is an FAD-containing enzyme that catalyses the oxidative deamination of a variety of biogenic and xenobiotic amines (Youdim et al. 1988),

including monoamine neurotransmitters such as serotonin, noradrenaline and dopamine, in a reaction shown below:

$$RCH_2NH_2 + H_2O + O_2 \rightarrow RCHO + NH_3 + H_2O_2.$$

The final products of the reaction are the corresponding aldehyde, hydrogen peroxide and ammonia (in case of primary amines) or a substituted amine (in case of secondary and tertiary amines) (Tipton et al. 2004). MAO exists as two distinct enzymatic isoforms, MAO-A and MAO-B, based on their substrate and inhibitor specificities (Johnston 1968).

The beneficial properties of monoamine oxidase inhibitors (MAOIs) have been extensively reported. Thus, selective inhibitors for MAO-A have been shown to be effective antidepressants, whereas MAO-B inhibitors are useful for the treatment of Parkinson's disease (PD) (Cesura and Pletscher 1992). The neuroprotective effect of MAOIs in these disorders may result not only from the increased amine neurotransmission, but also from prevention of neurotoxic product formation, which promotes reactive oxygen species (ROS) generation and may ultimately contribute to increased neuronal damage (Lamensdorf et al. 2000; Kristal et al. 2001; Burke et al. 2004). Despite some disadvantages found in using MAOIs in clinical practice, such as hepatotoxicity and the so-called "cheese-effect", which describes the hypertensive crisis produced by the consumption of tyramine-rich food, especially cheese (Callingham 1993), MAO enzymes remain in the focus of drug design targeting neurodegenerative disorders (Carradori et al. 2012; Binda et al. 2011). Nevertheless, it seems at present unlikely that the neuroprotective activities of MAOIs are exclusively related to the ability to decrease the production of free radicals and toxic aldehydes via the inhibition of enzymatic activity. With regard to this, several studies have suggested that they are rather related to the anti-apoptotic properties of the propargyl group present in these molecules (Tatton et al. 2003; Weinreb et al. 2006; Naoi et al. 2007).

Propargylamines are molecules containing a propargyl moiety that typically inhibits MAO-B including the well-characterised compounds selegiline (l-deprenyl) (**6**), rasagiline (**7**) and PF9601N (**8**) (Fig. 3). While selegiline was the first selective MAO-BI used clinically for the treatment of Parkinson's disease, rasagiline (**7**) and PF9601N (**8**) belong to a second generation of MAO-BIs that, unlike selegiline (**6**), do not generate amphetamine derivatives when metabolised (Chen et al. 2007; Valoti 2007). These compounds possess anti-apoptotic properties independent of their ability to inhibit MAO-B.

Diverse mechanisms have been suggested to be involved in the neuroprotective properties of propargylamine-containing compounds (Fig. 4). One of these mechanisms involves a significant antioxidant potency arising from the increase in the activities of superoxide dismutase (SOD) and catalase (CAT) enzymes (Carrillo et al. 2000), besides the prevention of the MAO reaction products formation, which are potentially neurotoxic since they contribute to oxidative stress and the formation of ROS. Moreover, the anti-apoptotic activity of these molecules has been attributed to their ability to prevent the fall in mitochondrial membrane potential (Ψm) and the blockade of the permeability transition pore (PTP) opening as a consequence of the up-regulation of Bcl-2 family protein (Youdim and Weinstock 2001; Mayurama et al. 2001) and activation of protein kinase C (PKC) and mitogen-activated protein kinase (MAPK) (Yogev-Falach et al. 2002). These pathways may be additionally involved in the effect of propargylamines on the enhanced release of the non-amyloidogenic α-secretase form of soluble amyloid precursor protein (sAPPα), which precludes the formation of amyloid derivatives promoting the non-amyloidogenic pathway of APP processing (Youdim and Weinstock 2001). Further neuroprotective effects have been related to the induced increase in the expression of neurotrophic factors such as BDNF and GDNF (Bar-Am et al. 2005).

Targeting MAO in AD

Renewed interest has regarded MAO inhibition as a potential target in AD. MAO-B increases with age and its activity is found elevated in AD patients, particularly around SP, resulting in an elevation of brain levels of neurotoxic free radicals and thus contributing to OS (Saura et al. 1997; Riederer et al. 2004). This appears early in the disease and so some authors have suggested that fighting OS is an imperative requirement in the therapy against AD (Gella and Bolea 2011).

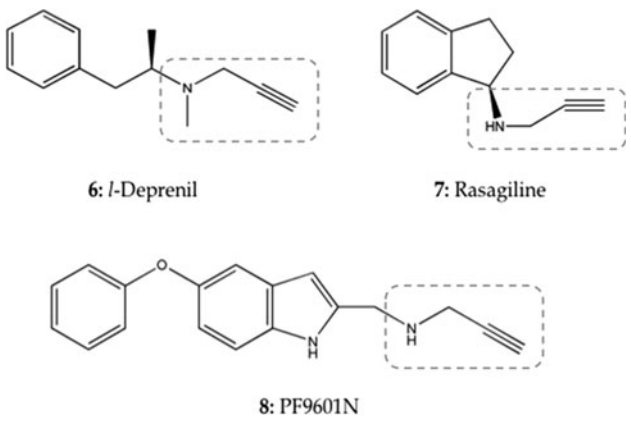

Fig. 3 Chemical structures of some propargylamine-derived MAOIs with neuroprotective properties. The propargylamine moiety is highlighted with *dotted lines*

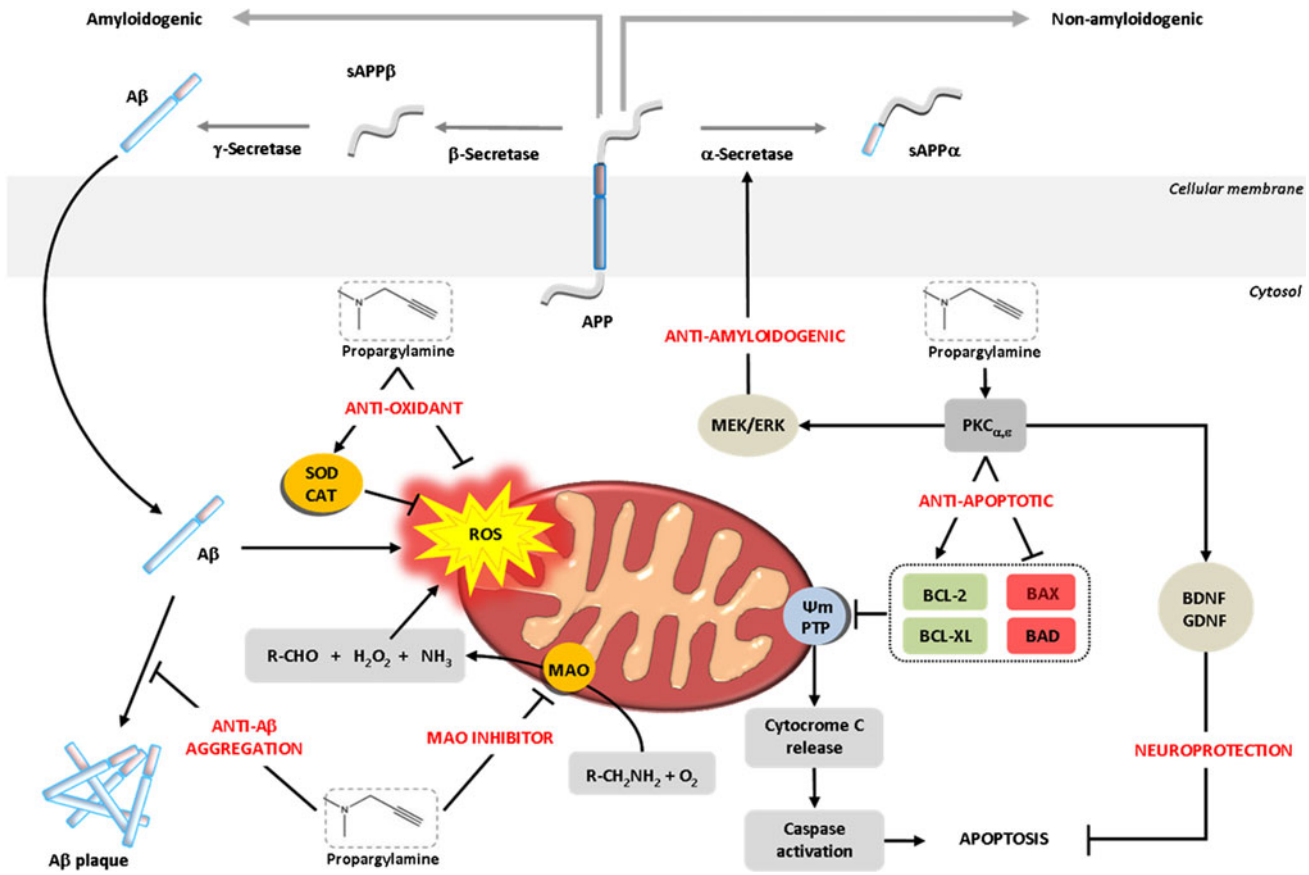

Fig. 4 Schematic representation of the sites of action of propargylamine-derived compounds as potential targets for AD treatment

Moreover, the involvement of monoaminergic neurotransmitter systems, particularly dopaminergic, has been strongly related to the high incidence of depression found in AD patients (Ballard et al. 2008; Gualtiery and Morgan 2008). Indeed, many authors have recently suggested that depression can be considered as a risk factor for AD (for review see Caraci et al. 2010). Interestingly, SP and NFT are more pronounced in the hippocampus of AD patients with depression than those without depression (Rapp et al. 2008). All these data suggest that dual inhibition of MAO-A and MAO-B, rather than MAO-B alone, may be of therapeutic value and, based on this premise, several authors have proposed in the last decade the use of MAO inhibitors as potential drugs for AD (Thomas 2000; Riederer et al. 2004; Youdim and Buccafusco 2005; Youdim et al. 2006). In agreement with these observations, a clinical trial assessing the beneficial properties of MAO-B inhibitor, Selegiline, showed a cognition-improved efficacy in subjects treated with donepezil, suggesting a synergistic effect (Tsunekawa et al. 2008). In addition, there is at present another ongoing clinical trial assessing MAO-B inhibition after repeated dosing with Selegiline in patients with AD and in healthy control subjects (http://clinicaltrials.gov/NCT01701089).

The development of MTDLs showing an MAO inhibitory activity as a key biological feature represents an interesting field of research for providing promising compounds for use as disease-modifying agents in AD, due to their neuroprotective properties, besides their capacity to increase amine neurotransmission. This field is still in its childhood since, in contrast to what occurs with other targets (e.g. AChE, amyloid β), MAO inhibition has not yet substantially captured the attention of scientists. Nevertheless, as described in the present review, in spite of the small number of compounds developed, they show a high therapeutic potential and thus demonstrate the suitability of the strategy. We will report the most advanced and promising compounds.

MTDLs targeting MAO and AChE

An initial work on multipotent MAO/ChE inhibitors was designed by combining a tricyclic indole carbamate moiety of the AChEI physostigmine with the typical propargylamine group of MAOIs (Fink et al. 1996) to give compounds with good dual inhibitory activities. Compound **9** (Fig. 5) showed the most interesting profile with a reversible behaviour towards MAO-A and, hence, lacking the

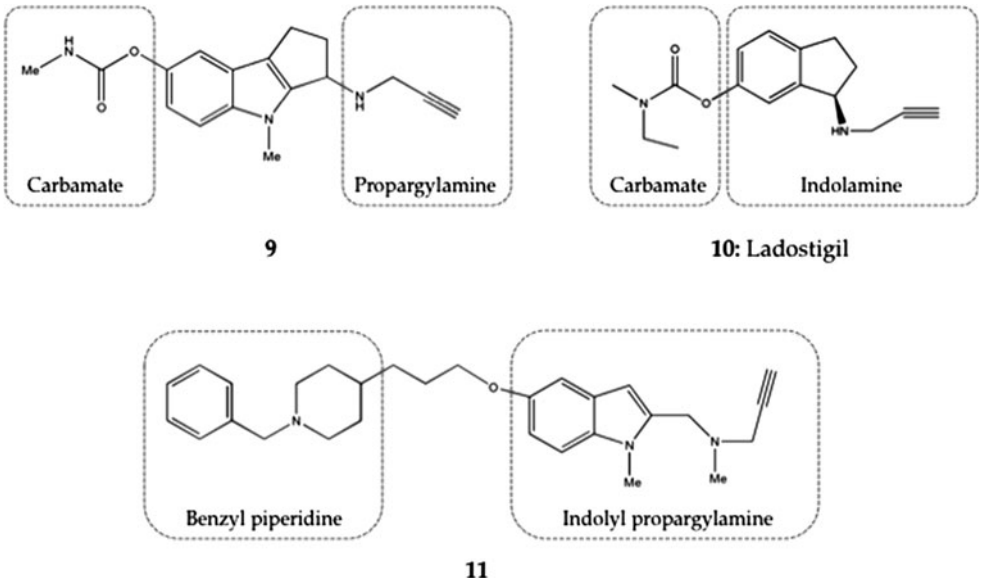

Fig. 5 Chemical structures of propargylamine-containing multitarget-directed ligands (MTDLs) with dual MAO/ChE inhibitory activity

adverse side effects observed by irreversible inhibitors. Although this approach was not developed further due to the low oral activity and poor brain penetration found, this work provided a structural starting point for further development of combined MAO/ChE inhibitors.

A very successful approach of combined MAO/ChE inhibition came from the combination of the carbamate moiety of rivastigmine (**1**) with the indoleamine present in rasagiline (**7**), a well-known MAO-B inhibitor, leading to the compound ladostigil (**10**) (Fig. 5) (Sterling et al. 2002). Ladostigil (**10**) is able to inhibit both AChE and butyrylcholinesterase (BuChE) for a longer time than the parent compound rivastigmine. This is of particular interest in view of the renewed interest in dual cholinergic inhibitors as therapeutic agents for AD to elicit a larger protective response (Greig et al. 2005). In addition, ladostigil (**10**) selectively inhibits brain MAO-A and MAO-B resulting in an increase in noradrenaline, dopamine and serotonine levels, and thus exerting an antidepressant action. An important aspect of ladostigil (**10**) is that it is selective for brain enzymes and so it is devoid of the classical side effects observed after peripheral MAO inhibition. Ladostigil (**10**) has also been shown to retain the neuroprotective and anti-apoptotic properties observed in the parent compound and propargylamine-derived rasagiline (Weinstock et al. 2003; Yogev-Falach et al. 2002; Sagi et al. 2003). Besides, ladostigil (**10**) also possesses a cognition-enhancing activity and is the most advanced MTDL on its category as demonstrated by the promising results obtained from a phase 2 clinical trial (Youdim et al. 2006). Two other clinical trials are underway to investigate its safety and efficacy in mild to moderate AD (http://clinicaltrials.gov/NCT01354691, http://clinicaltrials.gov/NCT01429623).

More recently, a novel series of multipotent propargylamine-derived ChE/MAO inhibitors with a very promising profile has been reported (Bolea et al. 2011). The design strategy was to combine the *N*-benzylpiperidine moiety of donepezil (**2**) with the indolyl propargylamine of PF9601N (**8**), which is a potent propargylamine-containing MAO-B inhibitor possessing several demonstrated neuroprotective properties (Prat et al. 2000; Cutillas et al. 2002; Pérez and Unzeta 2003; Pérez et al. 2003; Battaglia et al. 2006; Sanz et al. 2008, 2009). Among the large number of evaluated derivatives, compound **11** (Fig. 5) shows a very interesting and promising profile, since it potently inhibits both MAO-A and MAO-B. Interestingly, **11** is able to inhibit both AChE and BuChE enzymes, though the parent compound, donepezil, is not active for BuChE. In addition, besides behaving as a good ChE/MAO inhibitor, **11** is also able to inhibit $A\beta_{1\text{-}42}$ self-induced aggregation as well as AChE-induced $A\beta_{1\text{-}40}$ aggregation. These results demonstrate that **11** is able to interact with the peripheral anionic site of AChE which mediates the amyloid-β (Aβ) peptide pro-aggregating action of AChE (Inestrosa et al. 1996; De Ferrari et al. 2001; Dinamarca et al. 2010). Recent studies show that **11** retains the anti-apoptotic and antioxidant properties observed by the parent compound PF9601N and possesses a favourable blood–brain barrier crossing capability. These findings suggest that **11** is a new promising multitarget drug candidate that can be taken under consideration for the treatment of the multifactorial nature of AD.

MTDLs targeting MAO and iron

Excessive iron occurs at degenerative neuronal sites in AD (Mattson 2004). It has been reported that iron contributes to

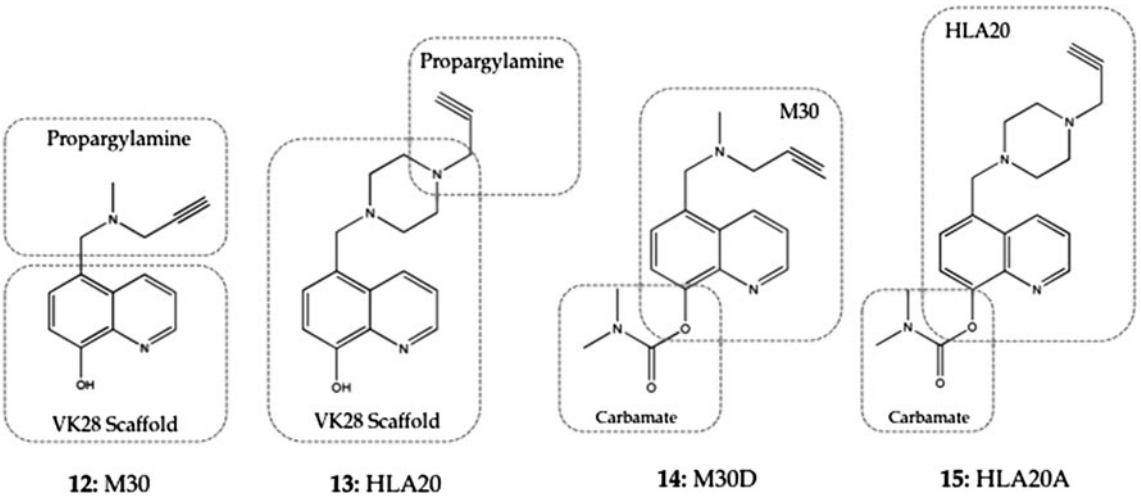

Fig. 6 Chemical structures of propargylamine-containing multitarget-directed ligands (MTDLs) with dual MAO/iron chelation activities (M30 and HLA20) and MAO/iron chelation/ChE inhibitory activitiy (M30D and HLA20D)

Aβ aggregation, which in turn contributes to neuronal degeneration through the induction of oxidative stress (Yoshiije et al. 2001). A link between high iron concentration and MAO activity and their involvement in ROS production has also been reported (Shoham and Youdim 2000). To address these problems, Youdim and collaborators have developed compounds with a bi-functional action on iron chelation and MAO inhibition obtained by combining the iron-chelating and antioxidant scaffold of VK28 with the *N*-propargylamine moiety of rasagiline (**7**) (Zheng et al. 2010). The most interesting compounds obtained were M30 (**12**) and HLA20 (**13**) (Fig. 6) possessing iron-chelating activity similar to that of VK28, but holding higher brain permeability (Zheng et al. 2005). M30 (**12**) and HLA20 (**13**) possess neuroprotective properties comparable to rasagiline (**7**) and potently inhibit the iron-induced membrane lipid peroxidation features (Youdim et al. 2004; Zheng et al. 2010). More importantly, M30 (**12**) has been shown to selectively inhibit brain MAO (A and B) enzymes and to increase serotonin, dopamine and adrenaline neurotransmission, which confers to this multipotent compound an antidepressant action besides preventing the potentiation of tyramine-induced cardiovascular activity (Gal et al. 2005). Interestingly, M30 (**12**) inhibits the Aβ aggregation induced by metals and reduces Aβ formation (Amit et al. 2008; Avramovich-Tirosh et al. 2007).

Targeting MAO, AChE and iron

The success of this strategy has led the authors to the recent development of more advanced site-activated chelators by incorporating into the structure of M30 (**12**) or HLA20 (**13**) the carbamate moiety of rivastigmine (**1**), producing compounds M30D (**14**) and HLA20A (**15**), respectively (Fig. 6). This approach holds several advantages over the preceding compounds, since besides the MAO inhibition and iron-chelating activities, M30D (**15**) and HLA20A (**15**) possess an interesting AChE inhibitory capacity (Zheng et al. 2010). The special characteristic of this approach is that the iron chelation capacity becomes activated after inhibition of AChE to release the active chelators M30 (**12**) and HL20 (**13**).

Some of the mentioned compounds were designed to bind to two different targets (MAO/AChE or MAO/iron). However, subsequent pharmacological evaluation of these molecules shows that some of them are even "more multitarget" than expected since they are also able to inhibit other processes such as Aβ aggregation or exert anti-apoptotic and neuroprotective effects by acting on diverse signalling pathways. Due to the multifactorial nature of AD, future improved formulations may deal with the development of compounds able to act simultaneously on more than three targets, including AChE, MAO, iron and other redox-active metals (e.g. Cu^{2+}, Zn^{2+}), Aβ, calcium, BACE and tau, besides exerting anti-apoptotic, neuroprotective and neurorescue properties.

Concluding remarks

Drug development in the Alzheimer's disease field presents a great challenge, since despite the considerable amount of new molecules reported in literature, effective disease-modifying drugs have not yet been discovered. The multifactorial nature of AD supports the emerging innovative approach consisting of the design and synthesis of multipotent compounds specially conceived to incorporate in

their structure the active moieties of already known drugs to obtain the desired effect (Buccafusco and Terry 2000). The reported compounds appear as good lead molecules for the development of further better combinations, which must be warranted to fully address the complexity of AD.

Oxidative stress has been reported to be an early event in the pathogenesis of AD, and thus targeting the source of ROS early in the disease progression is a matter of interest. In this context, MAO appears as a key target to be considered when designing MTDLs against AD, not only due to the increased amine neurotransmission, but also because of the reduction of the neurotoxic products of its catalytic activity. Particularly, propargylamine-containing compounds may possess additional benefits due to the demonstrated neuroprotective properties.

In the search for better anti-AD formulations, other promising compounds not targeting MAO enzymes have been described in literature (Bolognesi et al. 2009; Viayna et al. 2010). Mounting evidence suggests that the incorporation of a propargylamine moiety in the structure of these compounds may further improve their effectiveness. Hence, MAO inhibition represents an emerging and promising feature when designing MTDLs to have better outcomes in the complex nature of AD than the current selective drugs.

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