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Short communication

Synthesis, biological assessment and molecular modeling of new multipotent MAO and cholinesterase inhibitors as potential drugs for the treatment of Alzheimer's disease

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ABSTRACT

The synthesis, biological evaluation and molecular modeling of new multipotent inhibitors of type **I** and type **II**, able to simultaneously inhibit monoamine oxidases (MAO) as well as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), is described. Compounds of type **I** were prepared by sequential reaction of 2,6-dichloro-4-phenylpyridine-3,5-dicarbonitrile (**14**) [or 2,6-dichloropyridine-3,5-dicarbonitrile (**15**)] with prop-2-yn-1-amine (or *N*-methylprop-2-yn-1-amine) and 2-(1-benzylpiperidin-4-yl)alkylamines **22**–**25**. Compounds of type **II** were prepared by Friedländer type reaction of 6-amino-5-formyl-2-(methyl(prop-2-yn-1-yl)amino)nicotinonitriles **32** and **33** with 4-(1-benzylpiperidin-4-yl)butan-2-one (**31**). The biological evaluation of molecules **1**–**11** showed that most of these compounds are potent, in the nanomolar range, and selective AChEI, with moderate and equipotent selectivity for MAO-A and MAO-B inhibition. Kinetic studies of compound **8** proved that this is a *Ee*AChE mixed type inhibitor ($IC_{50} = 16 \pm 2$; $Ki = 12 \pm 3$ nM). Molecular modeling investigation on compound **8** confirmed its dual AChE inhibitory profile, binding simultaneously at the catalytic active site (CAS) and at the peripheric anionic site (PAS). In overall, compound **11**, as a potent and selective dual AChEI, showing a moderate and selective MAO-A inhibitory profile, can be considered as an attractive multipotent drug for further development on two key pharmacological targets playing key roles in the therapy of Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative process characterized by a progressive memory loss, decline in language skills and other cognitive impairments [1]. Although the etiology of AD is not known, amyloid-β (Aβ) deposits [2], τ-protein aggregation, oxidative stress [3] and low levels of acetylcholine [4] are thought to play significant roles in the pathophysiology of the disease [5]. The cholinergic theory [6] suggests that the loss of cholinergic neurons in AD results in a deficit of acetylcholine (ACh) in specific brain regions that mediate learning and memory functions [7]. Consequently, a number of acetylcholinesterase inhibitors (AChEI) such as tacrine [8], rivastigmine [9], donepezil [10] and galanthamine [11] have been developed, but with limited therapeutic benefits, mainly due to the multifactorial nature of AD. The multi-target-directed ligand (MTDL) approach, based on the "one molecule, multiple target" paradigm [12], has been the subject of increasing attention by many research groups, which have developed a number of compounds acting simultaneously on different receptors implicated in AD [13]. In this context, alterations in other neurotransmitter systems, especially the serotoninergic and

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dopaminergic, are also thought to be responsible for the observed behavioral disturbances [14,15]. Monoamine oxidase (MAO; EC 1.4.3.4) is an important target to be considered for the treatment of AD, as catalyzes the oxidative deamination of a variety of biogenic and xenobiotic amines, with the concomitant production of hydrogen peroxide [16]. MAO is a FAD-containing enzyme bound to mitochondrial outer membrane of neuronal, glial and other cells [17]. MAO exists as two isozymes: MAO-A and MAO-B, showing different substrate specificity, sensitivity to inhibitors, and amino-acid sequences. MAO-A preferentially oxidizes norepinephrine and serotonine, and is selectively inhibited by chlorgyline, while MAO-B preferentially deaminates β-phenylethylamine and is irreversibly inhibited by l-deprenyl [18]. X-ray crystal structures of human MAO-A [19] and MAO-B [20] have been reported.

With these ideas in mind, and based on our previous work in the synthesis and biological evaluation of MAO inhibitors (MAOI) [21] and AChE inhibitors (AChEI) [22], we have now designed new multipotent MAO and ChE inhibitors (**I** and **II**, Chart 1) for the potential treatment of AD. This approach has been previously analyzed with success by other laboratories [23–26]. What is new and original in our strategy is that the design of our molecules based on a conjunctive approach that combines for the first time the *N*-benzyl piperidine and the *N*-propargylamine moieties present in the AChE inhibitor donepezil [10], and PF9601N, a well known MAOI [21], respectively, connected through an appropriate linker to a central pyridine (or 1,8-naphthyridine) ring (Chart 1). In this preliminary communication, we report the synthesis and pharmacological evaluation of polyfunctionalized pyridines **1**–**8**, naphthyridines **9**–**11** (Table 1), and the identification of compound **11**, as a potent, in the nanomolar range, and selective dual AChEI, showing a moderate and selective MAO-A inhibitory profile.

2. Results and discussion

2.1. Chemistry

Type **I** compounds (Chart 1) were prepared by sequential reaction of 2,6-dichloro-4-phenylpyridine-3,5-dicarbonitrile (**14**) [27] (or 2,6-dichloropyridine-3,5-dicarbonitrile (**15**) [28]) with commercially available prop-2-yn-1-amine (or *N*-methylprop-2-yn-1-amine) and 2-(1-benzylpiperidin-4-yl)alkylamines **22-25** (Chart 2). Compounds of type **II** were prepared by Friedländer type reaction of 6-amino-5-formyl-2-(methyl(prop-2-yn-1-yl)amino)nicotinonitriles **32** and **33** with 4-(1-benzylpiperidin-4-yl)butan-2-one (**31**) (Supplementary data).

The *in vitro* activity of these new molecules against *Ee*AChE and eqBuChE was determined using Ellman's method [29] (Supplementary data) with tacrine and donepezil as reference compounds (Table 1). From these data some interesting SAR can be obtained. The IC_{50} values suggest that most of these molecules are

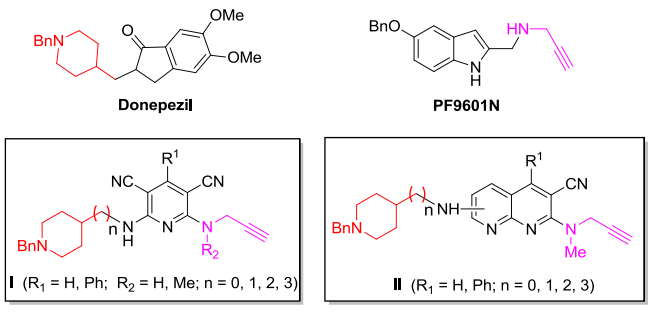


Chart 1. General structure of PF9601N, and the MAO and ChE inhibitors **I** and **II**.

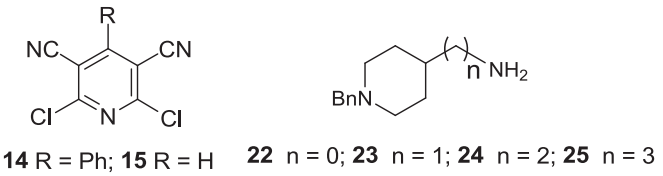


Chart 2. Structure of precursors: Pyridines **14**,**15**, and amines **22**–**25**.

potent, in the nanomolar range, and selective *Ee*AChE inhibitors, the most potent are compounds **3**, **4**, **6**, and **8** [IC_{50} (*Ee*AChE) = 13–16 nM], which are more potent than tacrine, but equipotent with donepezil for the *Ee*AChE inhibition.

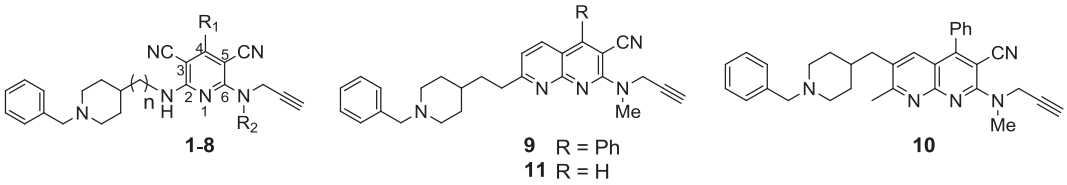
All compounds are less potent than the reference compounds for BuChE inhibition, except compound **4**, 4-fold more potent than donepezil. Regarding the effect of the linker, for compounds **1**–**4** bearing a phenyl group at C4 and a methyl group at N(C6), the inhibition of both *Ee*AChE and eqBuChE increases on going from $n = 0$ to $n = 2$ or 3. For the same length in the linker ($n = 0$), changing only the methyl group by hydrogen (compare compound **1** with **5**), the *Ee*AChE inhibitory potency decreases 3.3-fold, while both compounds remain inactive for eqBuChE inhibition. Similarly, for the same length in the linker ($n = 2$), changing only the phenyl at C4 by a hydrogen (compare compound **3** with **6**), the *Ee*AChE inhibitory potency remains similar, affording the most potent AChEI (**6**) in this series [IC_{50} (*Ee*AChE) = 13 nM], while the eqBuChE potency is reduced, becoming around 3-fold less potent. Very interestingly, the substitution of the methyl group in compound **6** by a hydrogen, with the same length ($n = 2$), results in the potent, but completely selective *Ee*AChEI **8**. However, this potency is lost in inhibitor **7** bearing the same type of substituent, the length of the linker being now $n = 0$. Note also that for $n = 2$, compound **3** with the functional couple Ph(C-4)/N(C-6)Me is equipotent with compound **8** bearing the functional couple H(C-4)/N(C-6)H for the inhibition of *Ee*AChE. Definitively, compound **4** with the longest length ($n = 3$), bearing a phenyl group at C4 and a methyl group at N(C6) remains as the most potent eqBuChe inhibitor [IC_{50} (eqBuChE) = 230 nM].

Based on our previous work on the area [30], and in order to evaluate the presumed critical effect of the pyridine ring in compounds **1**–**8** on the biological activity, we prepared naphthyridine derivatives **9**–**11** [31] (Table 1). According to the observed IC_{50} values (Table 1), these three compounds are also potent and selective AChEI, the most potent is compound **11** [IC_{50} = 37 nM], while compound **10** shows the worst inhibitory potency for both enzymes.

To determine the type of the *Ee*AChE inhibition mechanism on these compounds, a kinetic study was carried out with inhibitor **8** [IC_{50} (*Ee*AChE = 16 ± 2 nM); IC_{50} (eqBuChE > 100000 nM)] (Supplementary data). The type of inhibition was established from the analysis of Lineweaver–Burk reciprocal plots (Fig. 1) showing both increasing slopes (lower V_{max}) and intercepts (higher K_m) with higher inhibitory concentration. This suggests a mixed-type inhibition [32]. The graphical analysis of steady-state inhibition data for compound **8** is shown in Fig. 1. A K_i value of 12.2 nM was estimated from the slopes of double reciprocal plots versus compound **8** concentrations.

Based on these results, compound **8** was analyzed in order to investigate the possible interactions between the inhibitor and the amino acid residues on the catalytic active site (CAS), and in the peripheral anionic site (PAS) of AChE. Ligand docking studies were performed with AUTODOCK VINA [33] using a single catalytic subunit of *Ee*AChE (PDB: 1C2B) (Supplementary data). The docking procedure was applied to the whole protein target ("blind docking"). To account for side chain flexibility during docking, flexible

Table 1
Inhibition of AChE from Electrophorus electricus (EeAChE), equine serum butyrylcholinesterase (eqBuChE) and monoamineoxidase (MAO-A and MAO-B) by compounds **1**–**11**.[a]



Compound	R_1	R_2	n	IC_{50} (nM)		Selectivity	IC_{50} (μM)		Selectivity
				*Ee*AChE	EqBuChE	BuChE/AChE	MAO-A	MAO-B	MAO-B/MAO-A
1	Ph	Me	0	1200 ± 200	>100 000	>83	>100	>100	>1
2	Ph	Me	1	270 ± 52	5000 ± 700	18.5	>100	>100	>1
3	Ph	Me	2	16 ± 2	1110 ± 30	69.4	>100	>100	>1
4	Ph	Me	3	14 ± 1	230 ± 30	16.4	>100	>100	>1
5	Ph	H	0	4000 ± 100	>100 000	>25	25 ± 1	>100	>4
6	H	Me	2	13 ± 1	3100 ± 300	238.5	>100	>100	>1
7	H	H	0	530 ± 70	>100 000	>188	>100	>100	>1
8	H	H	2	16 ± 2	>100 000	>6250	>100	>100	>1
9				53 ± 3	3500 ± 350	66	>100	32 ± 3	>0.32
10				2300 ± 300	>100 000	>34	>100	97 ± 24	>1
11				37 ± 4	1990 ± 270	54	41 ± 7	>100	>2.4
tacrine				27 ± 2	5.2 ± 0.2	0.19	40 ± 10	>100	>2.5
donepezil				13.4 ± 0.9	840 ± 50	63	>100	15 ± 2	>0.15

[a] Values are expressed as mean ± standard error of the mean of at least three different experiments in quadruplicate.

torsions in the ligand were assigned, and the acyclic dihedral angles were allowed to rotate freely. In the docking simulation, the pose with the lowest docking energy was selected as the best solution. The "blind docking" of the **8**-*Ee*AChE molecules was successful as indicated by the statistically significant scores. Fig. 2 shows the complex of *Ee*AChE with ligand **8**. As can be seen, docking results indicate that the cyano group makes hydrogen bonding with residue Ser203 in the catalytic triad, playing an important role in the molecular recognition as well as in the inhibition process. The pyridine nitrogen of compound **8** is likely to form a hydrogen interaction with the OH Tyr337 side chain, located in the constricted region in the gorge. Additionally, inhibitor **8** seems to stabilize through π–π stacking interactions between the phenyl group and the indole ring of Trp286 in the PAS. Therefore, ligand **8** is a dual *Ee*AChEI, able to simultaneously interact with both, the CAS and PAS of the enzyme, a result that is in good agreement with its mixed-type inhibition profile [34]: the pyridine moiety of this inhibitor binds at the CAS, while the linker spans theactive-sitegorge, and the phenyl ring binds at the PAS [35].

Finally, and in order to test their multipotent profile, compounds **1**–**11** have been evaluated as MAO-A and MAO-B inhibitors (Table 1) (Supplementary data). These results show that pyridines **2**, **3**, **6** and **7** are inactive, and pyridines **1**, **4**, **8**, and naphthyridine **10** are poor MAO inhibitors. Only pyridine **5** (IC_{50} = 25 ± 1 μM) and naphthyridine **11** (IC_{50} = 41 ± 7 μM) were moderate, in the micromolar range, selective MAO-A inhibitors, while pyridine **9** showed selective MAO-B inhibition activity (IC_{50} = 32 ± 3 μM). Thus, the substitution of a phenyl at C4 in compound **9** by a hydrogen in inhibitor **11** drives the MAO selectivity from MAO-B to MAO-A, with the potency remaining similar. In general, the

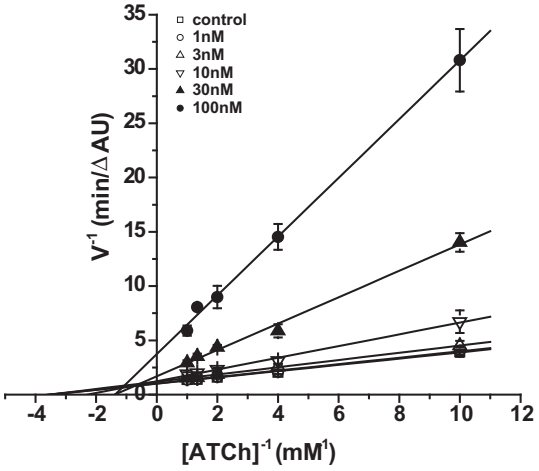


Fig. 1. Steady-state inhibition of AChE hydrolysis of acetylthiocholine (ATCh) by compound **8**. Lineweaver–Burk reciprocal plots of initial velocity and substrate concentrations (0.1–1 mM) are presented. Lines were derived from a weighted least-squares analysis of data.

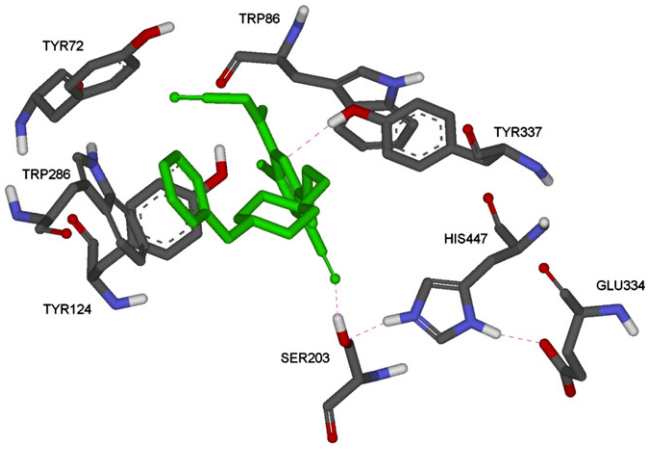


Fig. 2. Binding mode of **8** on *Ee*AChE as the outcome of docking simulations. The compound is rendered as sticks and illustrated in green. The hydrogen bonds are represented in dashed yellow lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

naphthyridine core seems to be a more promising hit. However, no clear SAR can be deduced from these results, and a careful molecular modeling analysis in progress should possibly afford the keys in order to rationalize the observed inhibition trends.

3. Conclusions

To sum up, compounds **1**–**11**, designed as hybrids from donepezil and PF9601N, bearing *N*-benzyl piperidine and propargylamine moieties attached to a central pyridine or naphthyridine ring, have been synthesized and subjected to pharmacological evaluation. The biochemical results clearly identify compound **8**, and particularly, **11** as multipotent drugs showing strong and selective AChE inhibitory activity [(IC_{50} = 37 ± 4 nM)], and moderate, but selective MAO-A inhibitory profile [(IC_{50} = 41 ± 7 μM)]. We conclude that the most sensitive moiety to modulate AChE inhibition is the length of the spacer, which would control the dual interaction of these molecules with both CAS and PAS sites, improving inhibition when both binding sites are spatially targeted at the same time. Compared to tacrine, compound **11** is equipotent for the AChE and MAO-A inhibition, less potent for the inhibition of BuChE and more potent for the inhibition of MAO-B. Compared to donepezil, compound **11** is less potent for the inhibition of AChE, BuChE, and MAO-B, and more potent for the inhibition of MAO-A. Comparing the two pyridine derivatives **9** and **2**, with the same length in the linker, compound **9** (linker: CH_2CH_2) is 5-fold less potent than inhibitor **2** (linker: CH_2NH) for the inhibition of *Ee*AChE, and 1.4-fold less active for the inhibition of eqBuChE. Conversely, regarding MAO inhibition, while pyridine **2** was inactive, naphthyridine **9** showed a moderate, but selective MAO-B inhibitory profile. The pharmacological profile of compound **11**, as well as the fact that it is a readily available compound in a short synthetic sequence, in good chemical yields, prompts us to select it as a lead-compound for further optimization in our current research programme targeted to the preparation of new molecules for the potential treatment of AD. Work is now in progress and will be reported in due course.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.05.048.

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