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BMCL Digest

Novel tacrine-related drugs as potential candidates for the treatment of Alzheimer's disease

Alejandro Romero [a,*], Ramón Cacabelos [b], María J. Oset-Gasque [c], Abdelouahid Samadi [d], José Marco-Contelles [d,*]

[a] Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Complutense University of Madrid, 28040-Madrid, Spain
[b] EuroEspes Biomedical Research Center, Institute for CNS Disorders and Genomic Medicine, 15166-Corunna, Spain
[c] Department of Biochemistry and Molecular Biology II, Faculty of Pharmacy, Complutense University of Madrid, 28040-Madrid, Spain
[d] Medicinal Chemistry Laboratory, Institute of General Organic Chemistry (CSIC), Juan de la Cierva, 3, 28006-Madrid, Spain

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ABSTRACT

A summary of the recently published efforts on tacrine derivatives as a renewed potential therapeutic approach for the treatment of Alzheimer's disease is presented.

Alzheimer's disease (AD) is the most prominent form of dementia in the world affecting about 6% of the population aged over 65, its incidence increasing with age.[1] Despite enormous efforts to elucidate the pathophysiology of AD, the disease is still incurable.[2] AD is clinically characterized by memory impairment and progressive deficits in different cognitive domains related to a pronounced degradation of the cholinergic system and to alterations in the glutamatergic and serotoninergic systems.[3] The *cholinergic hypothesis* of AD[4] asserts that the decline of the acetylcholine (ACh) level leads to cognitive and memory deficits, and that sustaining or recovering the cholinergic function is therefore supposed to be clinically beneficial.[5] ACh can be degraded by two types of cholinesterases (ChEs), namely acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Indeed, nowadays AD therapy is mainly founded on AChE inhibitors (AChEIs), able to increase ACh levels in the cholinergic synapses.[6] Thus, the number of approved drugs is limited to only three AChEIs, the moderately active drugs rivastigmine, donepezil and galantamine, and the NMDA antagonist memantine. Unfortunately, instead of curing or preventing neurodegeneration, AChEIs only enable a palliative treatment,[7] and their clinical effectiveness is still under debate.[8]

Because of the multifactorial nature of AD, the traditional 'one molecule, one target' paradigm, the so-called magic bullets, can generally only offer limited and transient benefits. Thus, a strategy named multi-target-directed ligand (MTDL)[9] has recently emerged,[10,11] targeting compounds decorated with additional pharmacological/biochemical properties other than ChE inhibition, being able to bind simultaneously to different receptors or enzymatic systems involved in the disease.

Many aspects of the etiology and pathological pathways of AD remain unclear and subject to speculation. These pathological lesions have been considered to be the causative features of AD, giving rise to several theories about AD pathogenesis, mostly including the β-amyloid cascade[12] and tau[13] hypotheses, oxidative stress, free radical formation and neuroinflammation.[14]

In this complex scenario, tacrine (**1**, Fig. 1), the most potent and clinically effective AChEI,[15] was approved for clinical use by the U.S. FDA in 1993. However, it soon exhibited hepatotoxicity via elevation of *serum alanine aminotransferase* levels, resulting in limited clinical application and, consequently, was withdrawn from the pharmaceutical market shortly after its approval.[16] This is the reason why tacrine is usually considered not a gold standard for AD drug discovery. In fact, although new AChEIs continue to be developed, more recent efforts have been aimed at developing small molecules that target the underlying pathogenic mechanisms of AD. These new approaches, and the fact that most of

* Corresponding author. Tel.: +34 91 562 29 00; fax: +34 91 564 48 53.
E-mail address: iqoc21@iqog.csic.es (J. Marco-Contelles).

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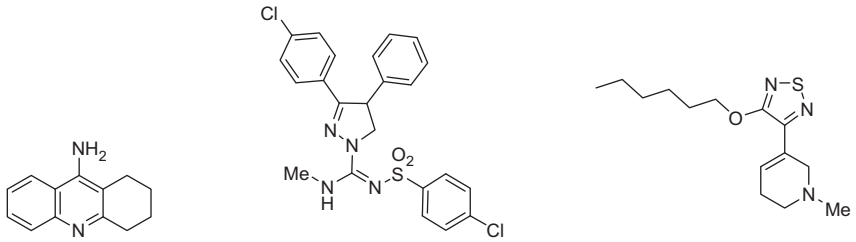

tacrine (**1**) (*Z*)-3-(4-Chlorophenyl)-*N*′-((4-chlorophenyl)sulfonyl)-*N*-methyl-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2**) Xanomeline (**3**)

Figure 1. Structures of tacrine (**1**), (*Z*)-3-(4-chlorophenyl)-*N*′-((4-chlorophenyl)sulfonyl)-*N*-methyl-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2**), and xanomeline (**3**).

the funding agencies declare limited interest in funding ChE inhibitor programs, currently make AChEI drug discovery less relevant from a medicinal chemistry perspective.

It is the purpose of this BMCL Digest to update the most recent reports on this topic, showing the, unexplored possibilities of such drugs.[17a]

Tacrine (**1**) (Fig. 1) has been widely used in the past and in more recent studies to design hybrid or multi-target compounds in order to combine its potent AChE inhibition with other pharmacological properties. This is achieved by covalently connecting tacrine to other pharmacologically active structures,[17b] such (*Z*)-3-(4-chlorophenyl)-*N*′-((4-chlorophenyl)sulfonyl)-*N*-methyl-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2**), a CB1 receptor antagonist (Fig. 1),[18] and xanomeline (**3**) (Fig. 1), a M1 agonist.[19] In addition, the key and critical point was to demonstrate that the newly-designed tacrine molecules were not hepatotoxic, while retaining other beneficial cholinergic properties.

As a consequence, several tacrine derivatives have been reported, including:

Bis(7)tacrine dimer (**4**, Fig. 2),[20a] which exhibited a 1000-fold higher AChE inhibition potency than the reference drug, dual interaction in the active and peripheral sites of AChE, AChE-induced Aβ aggregation through interaction with its peripheral anionic site[21] and neuroprotective effects related to the interaction with β-secretase enzyme, NMDA and GABA receptors.[22] Very recently, Bolognesi et al., have reported 4,4′-bis[(1,2,3,4-tetrahydroacridin-9-yl)aminomethyl]biphenyl (**5**, Fig. 2) as a new bis(7)-tacrine MTDL ligand showing activity against AChE and amyloid formation and aggregation.[20b]

Cystamine-tacrine dimer (**6**, Fig. 2), endowed with a lower toxicity in comparison to bis(7)tacrine dimer (**4**), able to inhibit AChE/BuChE, self- and AChE-induced Aβ aggregation in the same range of tacrine, exerts a neuroprotective action on the SH-SY5Y neuroblastoma cell line against H_2O_2-inducedoxidative injury.[23]

Tacrine-ferulic acid hybrid (**7**, Fig. 2), is a moderate antioxidant and potent reversible, non-competitive AChEI able to bind the PAS of the AChE, showing an almost equipotent capacity to inhibit *Ee*AChE (IC_{50} = 4.4 ± 1.7 μM) and *eq*BuChE (IC_{50} = 6.7 ± 1.6 μM).[24] Conversely, kinetic measurements for BuChE showed reversible and competitive inhibition by hybrid **7**, revealing that this tacrine derivative competes for the same active site as acetylcholine.

Antioxidant agents tacrine-ferulic acid-nitric oxide (NO) donor hybrids, such as compound **8** (Fig. 2),[25] being fivefold and twofold more active than the parent product **7** toward AChE/BuChE, respectively. In the vascular relaxation assay, inhibitor **8** possessed an activity comparable to the activity of the reference drug isosorbide dinitrate (ISDN). Tested in the scopolamine-induced cognition animal model, tacrine derivative **8** showed significant cognitive improvements. In addition, hepatotoxicity studies confirmed that **8** was much safer than tacrine. Altogether, the multifunctional effects of the new hybrid **8** might be considered a promising lead compound.

Non-toxic tacrine-organic nitrates[26a] are tacrine hybrid compounds with NO-donating nitrate connected to the tacrine scaffold via an alkylenediamine-type linker. All compounds inhibited ChEs. Target compound **9**, in particular, showed 7- to 8-fold higher AChE inhibitory activity compared to tacrine, and moderately relaxed the porcine pulmonary arteries in in vitro vasorelaxation experiments, aided by the NO donor part of the molecule. In the in vivo hepatotoxicity studies, tacrine, but not compound **9**, showed serious hepatotoxicity. These results suggest that these NO donor-tacrine hybrids, especially compound **9**, may be considered to be novel, more potent and safer anti-Alzheimer's drugs. Nitric oxide (NO) is an essential signaling molecule involved in various physiological functions in humans.[26b] The over and under production of NO is responsible for a number of pathological conditions. The biosynthesis of NO by brain neuronal NOS (nNOS) is associated with stroke and chronic neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's diseases.[26c]

Tacrine-silibinin co-drug (**10**, Fig. 2), showed high AChE and BuChE inhibition, neuroprotective effects, lacking tacrine's hepatotoxicity in vitro and in vivo, with the same pro-cognitive effects in vivo as tacrine, being superior to the physical mixture of tacrine and silibinin in all these regards.[27]

Mercapto-tacrine hybrids such as compound **11**[28] (Fig. 2), endowed with cholinesterase inhibition, long-term potentiation enhancement, neuroprotective activity and less hepatotoxicity, are consequently good candidates for further studies directed toward the development of novel drugs for age-related neurodegenerative diseases such as AD.

Particularly interesting among all the tacrine derivatives studied and investigated is the case of 7-MEOTA (9-amino-7-methoxy-1,2,3,4-tetrahydroacridine) (**12**, Fig. 2), an old Czech cholinergic drug first synthesized by Patocka,[29] a potent, centrally-active ChEI, free of the serious side effects related to tacrine.[30–32] In single-administration studies, 7-MEOTA was well tolerated, and thus further research efforts are currently aimed at improving its pharmacological profile.[33] In connection with the results obtained previously,[34] fourteen new *N*-alkyl 7-MEOTA analogue hydrochlorides, which were found to be less toxic than tacrine, were synthesized.[34b] Their activity in vitro on AChE and BuChE showed inhibitory power on a micromolar scale. The inhibitory profile and selectivity index for *h*AChE of the new compounds were compared to standards of tacrine and 7-MEOTA. Compound **13** (Fig. 2) showed the best selectivity ratio for AChE (IC_{50} = 0.10 μM, which is fivefold more potent than tacrine). The molecular docking with compound **13** showed that the 7-MEOTA moiety was bound to the active site cleft between Trp86 and Tyr337 by π–π stacking in the PAS anionic aromatic site.