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BMCL Digest

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

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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

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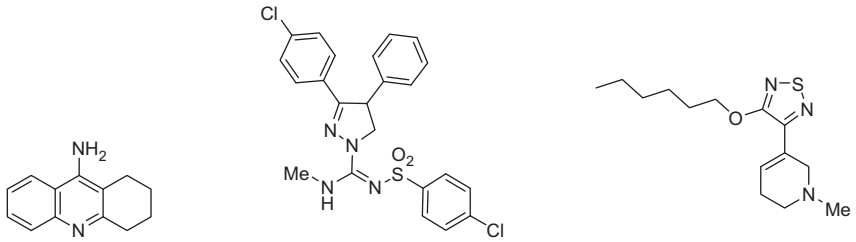


tacrine (**1**) (*Z*)-3-(4-Chlorophenyl)-*N*′-((4-chlorophenyl)sulfonyl)-*N*-methyl-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidamide (**2**) Xanomeline (**3**)

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.

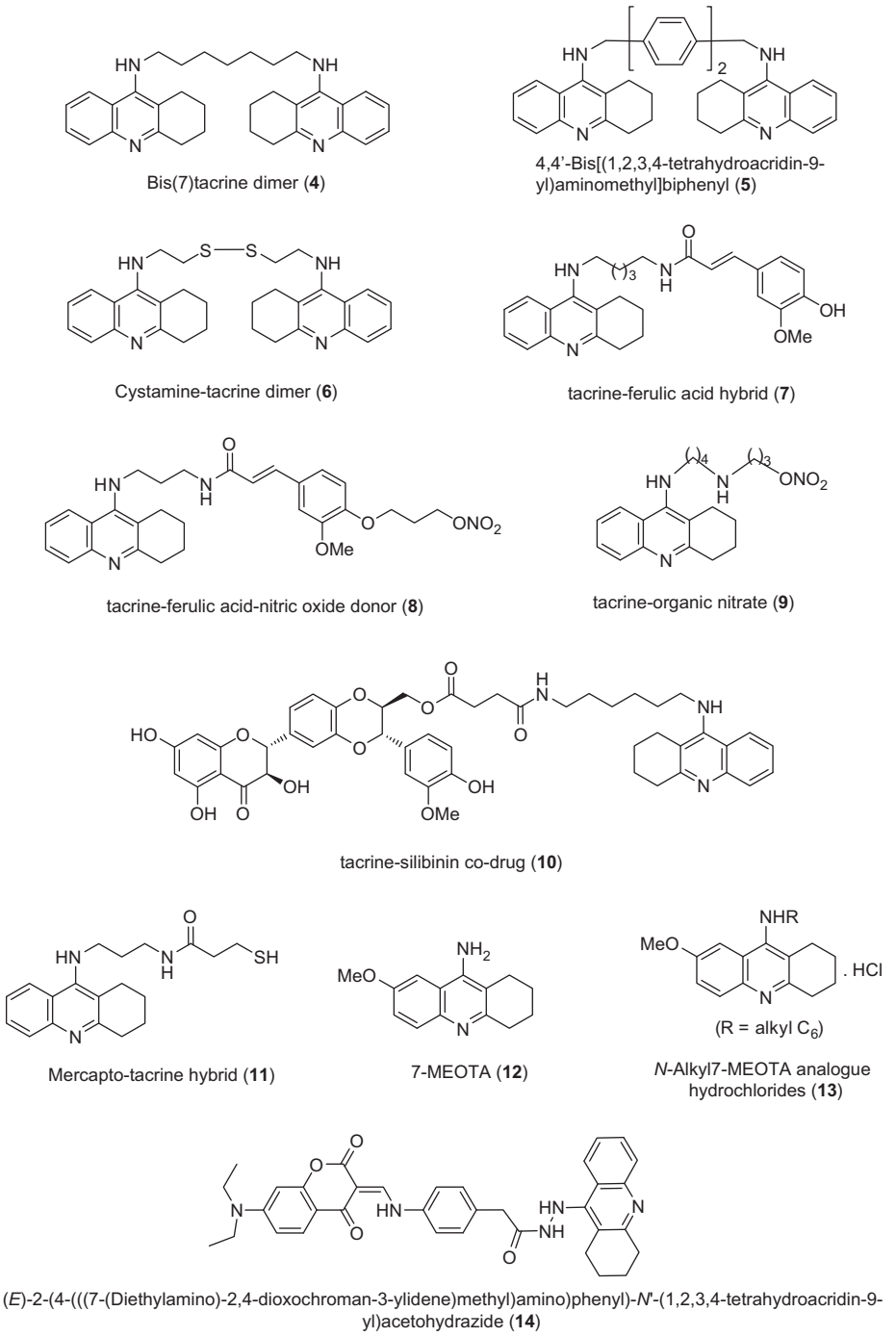
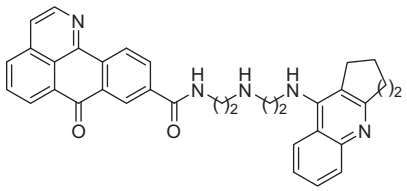


Figure 2. Structure of tacrine derivatives and hybrid compounds (**4**–**14**).

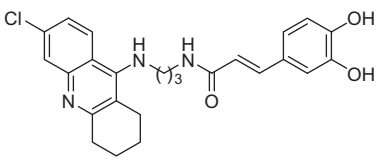
It is interesting to highlight tacrine derivative **14** (Fig. 2), a high-affinity, fluorescent cholinesterase inhibitor able to bind to amyloid structures, described by Gütschow and co-workers.[35]

In the search for more effective tacrine derivatives, Tang et al.,[36] designed a series of hybrids of tacrine-oxoisoaporphine. These compounds exhibit high AChE inhibitory activity with IC_{50} values in the nanomolar range in most cases, the most potent being compound **15** (IC_{50} *Ee*AChE = 3.4 ± 0.2 nM) (Fig. 3), clearly more potent than tacrine. Interestingly, all the synthesized compounds presented a good inhibitory potency on self-induced $A\beta_{1-42}$ aggregation and the AChE-induced $A\beta_{1-40}$ aggregation, being more potent than tacrine and curcumin.

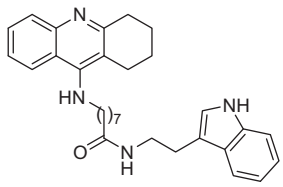
Using the same strategy, tacrine-caffeic acid hybrids were designed as multifunctional agents for AD treatment.[37] Among these, the hybrid **16** (Fig. 3) showed the highest selectivity in inhibiting AChE over BuChE, suggesting that this tacrine binds to both catalytic and peripheral anionic sites (CAS, PAS) of AChE, has low toxicity and Cu^{2+}-chelating properties as well as neuroprotective effects against two oxidative stress inducers, H_2O_2 and glutamate, in the prevention of cell death in HT22, a mouse hippocampal cell line. Furthermore, compound **16** also inhibited self- or AChE-induced $A\beta_{1-40}$ aggregation. Taken together, this hybrid compound may represent a valuable anti-AD candidate for further development.



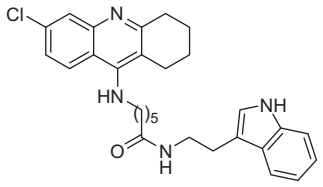
tacrine-oxoisoaporphine hybrid **15**



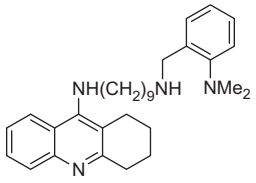
tacrine-caffeic acid hybrid **16**



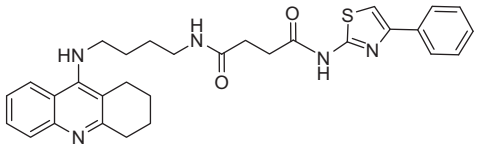
tacrine-melatonin hybrid **17**



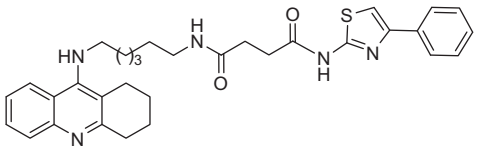
tacrine-melatonin hybrid **18**



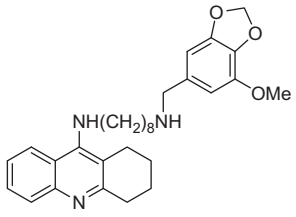
tacrine-*O*-aminobenzylamine hybrid **19**



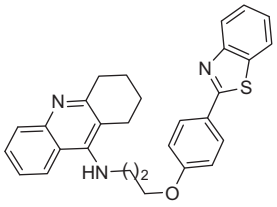
tacrine-phenylthiazole hybrid **20**



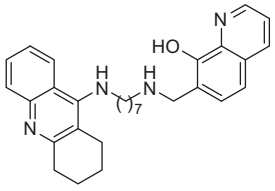
tacrine-phenylthiazole hybrid **21**



tacrine-multialkoxybenzene hybrid **22**



tacrine-phenylbenzoheterocyclic hybrid **23**



tacrine-8-hydroxyquinoline hybrid **24**

Figure 3. Novel tacrine-based hybrids (**15**–**24**).

Another example of this strategy is represented by tacrine-melatonin hybrids.[38] Molecular modeling studies showed that these hybrids target both the CAS and PAS of AChE. In order to evaluate the pharmacological profile, compounds **17** and **18** (Fig. 3) were more potent and selective *h*AChEIs than tacrine, with IC_{50} in the subnanomolar range. These compounds showed interesting neuroprotective properties against several toxic insults such as rotenone, H_2O_2 and $A\beta_{25-35}$ peptide in the human neuroblastoma SH-SY5Y cell line. They also displayed an important inhibitory potency on self-induced Aβ peptide aggregation and the AChE-induced Aβ peptide aggregation. Finally, they exhibited low toxicity and may be able to penetrate the CNS, according to an in vitro parallel artificial membrane permeability assay for the blood–brain barrier (PAMPA-BBB) analysis.[39] All these new tacrine—melatonin hybrids can be considered interesting structures in the search for new agents of potential application in AD.

O-Hydroxyl- or *O*-amino benzylamine-tacrine heterodimers[40] were obtained by reacting *N*-(aminoalkyl)tacrine with salicylic aldehyde or derivatives of 2-aminobenzaldehyde. Relative to tacrine, which had an IC_{50} value of 109 nM, a selection of these hybrids were potent as *h*AChEIs with IC_{50} values in the nano- and subnanomolar range, and also exhibited very good BuChE inhibitory activities (nanomolar range). Among the synthesized compounds, compound **19** (Fig. 3) exhibited the greatest inhibitory potency towards AChE (IC_{50} = 0.55 nM). All the hybrids have potential complexation abilities for biometals such as Cu^{2+}, Fe^{2+}, and Zn^{2+}, and in addition, most of them showed antioxidative activity as well as a favorable effect on $A\beta_{1-42}$ peptide aggregation inhibition.

Recently, a series of multipotent phenylthiazole-tacrine hybrids has been reported.[41] Screening results showed that these compounds were potent inhibitors of AChE and BuChE, and they efficiently prevented $A\beta_{1-42}$ self-aggregation. Furthermore, compounds **20** and **21** (Fig. 3) displayed the blockade effect on Ca^{2+} overload in the primary cultured cortical neurons. This blocking could represent a valuable strategy for preventing cell death, and consequently, phenylthiazole-tacrine hybrids will have an additional biological property for the therapy of AD.

In this line, a new series of tacrine-multialkoxybenzene hybrids was designed.[42a] All the tested compounds, an particularly hybrid **22** (IC_{50} *Ee*AChE = 7.98 ± 0.12 nM) (Fig. 3), showed significant ChEs inhibitory activity and 1- to 11.5-fold of inhibition selectivity for BuChE over AChE, which were similar to or better than those of tacrine. This is important, since as AChE is the abundant form of cholinesterases in the brain, the role of BuChE has been usually overlooked. However, during the development of AD, BuChE activity increases by 40–90%[42b] in the most affected brain areas such as the temporal cortex and hippocampus, while at the same time AChE activity declines. Moreover, high levels of BuChE are found to have a role in Aβ aggregation during the early stages of senile plaque formation as well as in other pathological characteristics of AD.[42b] Therefore, inhibition of BuChE, not only AChE, may have clinical benefits in treating symptoms and alleviating the manifestation of neurodegenerative diseases and dementia.[42b] The new hybrids could bind to both the CAS and PAS of AChE, in good agreement with the results of molecular modeling studies. These hybrids also prevented $A\beta_{1-42}$ self-aggregation with percentages of inhibition higher than the reference compound, curcumin.

Tacrine-phenylbenzoheterocyclic hybrids[43] are excellent multifunctional drug candidates for AD. Particularly, compound **23** (Fig. 3) was the most potent *Ee*AChE mixed-type inhibitor (IC_{50} = 0.017 ± 0.002 μM), 18-fold more potent than tacrine, demonstrating also similar Aβ aggregation inhibitory activity to that of curcumin. These results indicate that these new tacrine derivatives are useful templates for the development of new multifunctional anti-AD drugs.

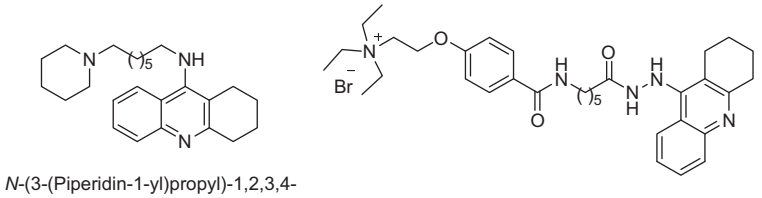
Tacrine-8-hydroxyquinoline hybrids[44] have interesting and noteworthy in vitro biological activity for the treatment of AD. Thus, they exhibit: (1) *h*AChE and *h*BuChE inhibition with IC_{50} values in the nano- and subnanomolar range; (2) inhibited AChE-induced Aβ aggregation; (3) significant antioxidant properties in an oxygen radical absorbance capacity (ORAC) assay, being more potent than the reference compound, trolox (vitamin E analogue); (4) high neuroprotective activity, based on LDH release, against damage caused by mitochondrial free radicals; (5) selective complexation for Cu^{2+}, showing low cellular toxicity, and (6) capability to penetrate the CNS, according to the PAMPA-BBB test. Particularly, compound **24** (Fig. 3) was shown to be a potent dual inhibitor of human AChE (IC_{50} = 20 ± 1 nM) and BuChE. (IC_{50} = 5.0 ± 0.2 nM), antioxidant capacity in the ORAC test (3.3 ± 0.01 μM of Trolox equivalents/μM of tested compound), 3.3-fold more potent than the vitamin E analogue, propidium displacement of 22%, permeability to the brain–blood-barrier (BBB) by passive diffusion, complexed Cu (II) cations, and neuroprotection power showing negligible cell death using rotenone as toxic insult.[44]

Recently, Incerti et al., described a series of tetrahydroaminoacridine hybrids,[45] the most interesting being *N*-(3-(piperidin-1-yl)propyl)-1,2,3,4-tetrahydroacridin-9-amine (**25**) (Fig. 4) that showed nanomolar and selective H3 antagonism with high anticholinesterase activity (95 ± 2 maximum percent inhibition of rat brain cholinesterase; pIC_{50} = 7.69 ± 0.05).

Multipotent tacrine derivatives able to interact simultaneously in the cholinergic system and muscarinic M2 receptor have been described.[46] One of these molecules is the gallamine-tacrine hybrid **26** (Fig. 4). The biochemical analysis proved that derivative **26** was a very potent inhibitor of *Ee*AChE with an IC_{50} value of about 500 pM, exhibiting EC_{50} values around 1 nM. The rational for this choice was based in the well known capacity of gallamine to allosterically modulate muscarinic receptors[47] and that tacrine is an atypical muscarinic allosteric agent.[48]

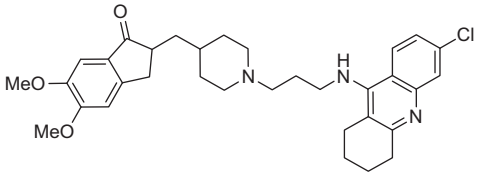
Camps et al., have developed a series of donepezil-tacrine heterodimers.[49] Donepezil is dual binding site AChE inhibitor approved for the treatment of AD. The new hybrids resulted in potent and selective *h*AChE in the nM range, the most active being compound **27** (IC_{50} = 0.27 ± 0.03 nM) (Fig. 4). The novel donepezil-tacrine **27** afforded strong reductions in thioflavin T fluorescence among all the analyzed compounds (57% reduction), as a result of the displacement of the fluorophore at the peripheral site of the enzyme. In agreement with this, hybrid **24** significantly inhibited the *h*AChE-induced aggregation of $A\beta_{1-40}$ by 46.1 ± 9.0% at 100 μM.

As reported above, AD is a multifactorial disease which could be better treated by drugs acting upon more than one of its neuropathological targets.[50] Using the same strategy, Marco-Contelles et al., have synthesized and evaluated a series of 1,8-naphthyridine derivatives related to tacrine.[51] The compounds were dual inhibitors of both AChE and BuChE, with slight selectivity toward AChE. Only compound CR80 (**28**) (Fig. 5) had significant Ca^{2+}-blocking activity (20% blockade). It exhibited interesting neuroprotective activity against oxidative stress induced by two toxic insults of the mitochondrial chain. Tacrine **28**, the best AChE inhibitor of this



N-(3-(Piperidin-1-yl)propyl)-1,2,3,4-tetrahydroacridin-9-amine (**25**)

Gallamine-tacrine hybrid **26**



Donepezil-tacrine hybrid **27**

Figure 4. Tacrine-based hybrids (**25**–**27**).

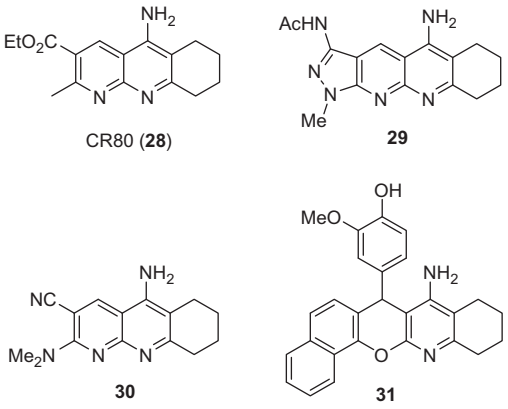


Figure 5. New tacrine analogues reported from Marco-Contelles' laboratory (Refs. 46–50).

series, was able to improve cell viability when exposed to okadaic acid (OA)-induced τ- hyperphosphorylation, and prevented OA-induced protein phosphatase 2 (PP2A) inhibition, as well as protecting against $A\beta_{1-42}$ neurotoxicity in SH-SY5Y cells. Because compound **28** exhibited very good neuroprotective properties in culture cells, it was found, in a more complex model based on the rat hippocampal slice subjected to oxygen and glucose deprivation (OGD) followed by reoxygenation, that tacrine was able to increase cell viability in a concentration-dependent manner (1–30 μM). It would be interesting to test derivative **28** further in in vivo studies with AD models in order to evaluate its therapeutic potential. In this context, the same group has also described a series of attractive multipotent therapeutic molecules, such as 2-aminopyridine- and 2-chloropyridine-3,5-dicarbonitriles,[52] which act on two biological targets that play roles in the progress of AD, such as cholinergic dysfunction and oxidative stress. In general, these compounds showed modest AChE and BuChE inhibition in the micromolar range, although some derivatives were highly selective for AChE or for BuChE. Furthermore, they afforded an important neuroprotectant effect (30%) in the LDH/MTT test in SH-SY5Y cells exposed to two toxic insults.

Marco-Contelles et al., also reported the synthesis and pharmacological analysis of tacrine analogues such as pyrazolo[3,4-*b*]quinoline and benzo[*b*]pyrazolo[4,3-*g*][1,8]naphthyridine derivatives,[53] some of which were potent and selective AChEIs. In particular, tacrine analogue **29** (Fig. 5), the most interesting inhibitor, was able to improve cell viability against two toxic molecules [(rotenone/oligomicin-A)-induced cell death in SH-SY5Y cells (45% neuroprotection value)].

In the same manner, Marco-Contelles et al., synthesized new tacrine analogues from highly substituted 2-aminopyridine-3-carbonitriles; some of these molecules, such as tacrine **30**[54] (Fig. 5) were good AChE inhibitors in the nanomolar range, and quite selective regarding the inhibition of BuChE. The neuroprotective profile shown by these compounds was only moderate.

Recently, Marco-Contelles et al., synthesized a series of very interesting 7-aryl-9,10,11,12-tetrahydro-7*H*-benzo[7,8]chromeno[2,3-*b*]quinolin-8-amines as new racemic tacrine analogues.[55] These compounds are potent and selective inhibitors of *h*AChE, in the low micromolar range. Particularly, tacrine **31** (Fig. 5) had an excellent antioxidant profile as determined in the ORAC experiment (1.47 ± 0.10 trolox equiv), crossed BBB in the PAMPA assay, and had significant neuroprotective effects in cortical neurons against mitochondrial chain blocker-induced cell death; and, unlike tacrine, this compound is not neurotoxic at concentrations lower than 50 μM, and showed less hepatotoxicity in HepG2 cells. These tacrine analogues can be considered as new innovative therapeutic tools against AD.

Summarizing, although the present fashion in AD therapeutics is focused on immunization procedures against Aβ deposition in senile plaques, antiphosphorylating agents to halt neurofibrillary tangle formation, and γ- and β-secretase inhibitors, the above-mentioned results with tacrine-related compounds should not be neglected by the scientific community.[56] Among others, the recent failure in clinical phase III of semagecestat,[57,58] a γ-secretase inhibitor developed by Lilly, as well as the recent news from the Spanish Zeltia group announcing the discontinuation of tideglusib, a GSK-3β inhibitor developed by Noscira, targeting tau protein, are clear examples of the state of confusion that has emerged in the medicinal chemistry of AD.[59] Obviously, the conclusion is clear: the soundest and strongest hypotheses for AD have not yet provided any drug for the clinic. Thus, this may be the moment to revise *old-fashioned therapeutic strategies*. In this arena, and not surprisingly, some researchers have clearly banked on tacrine, considering that *what works, must work better*. The purpose of this BMCL Digest has been to update the most recent reports on this topic, showing the large, latent and unexplored possibilities of this drug.

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