Recent Advances in the Development of Hybrid Molecules/Designed Multiple Compounds with Antiamnesic Properties

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Abstract: Novel compounds have been developed that (in many cases) inhibit cholinesterases and concomitantly interact with at least one further pharmacological target, such as 5-HT_3 or H_3 receptors. But also enzymes like monoamine oxidase and the serotonin transporter have been targeted. Hybrid molecules can also incorporate antioxidant or neuronal Ca^{2+}-channel-blocking structures.

Key Words: Hybrid molecules, Multiple ligands, AChE inhibitors, Serotonin transporter (SERT), monoamine oxidase (MAO), lipoic acid, 5-HT_3 receptor, Ca^{2+}-channel blockers.

INTRODUCTION

Dementia, especially Alzheimer`s disease (AD), is characterized by progressive impairment in memory and cognitive functions leading to a disability to perform basic daily living activities. Although memory impairment correlates with a decrease in cholinergic neurotransmission in the cortex [1], the multiple processes leading to AD are complex and not yet understood. It is therefore improbable that a single pharmacological tool can lead to a comprehensive therapy of dementia.

As a novel strategy in order to target these complex processes leading to AD "designed multiple compounds" or "hybrid molecules" have been developed in the last years: by one single molecule two or more pharmacological actions are addressed synergistically. In most cases this is possible by connecting covalently two distinct pharmacophores in a suitable manner/by a designed spacer (hybrid molecules). But also one (multiple) pharmacophore can act at (at least) two distinct targets (designed dual or multiple compounds). These strategies have the additional advantage to provide more predictable pharmacokinetics and –dynamics due to administration of only one compound and concomitantly an improved compliance of the patient.

In the majority until now of cases the first target is acetylcholinesterase (AChE), inhibitors of which represent the established therapy for AD. The second part of the hybrid molecule interacts with a different pharmacological target, so that either cognition is further enhanced or cell death associated with the progression of AD can be prevented.

The design strategy for obtaining hybrid molecules and designed multiple ligands should be differentiated from the so-called "bivalent ligand approach", in which also two (often identical) pharmacophores are linked by a spacer, but these bivalent ligands aim at the same pharmacological target. In many cases this approach has led to remarkable increases in affinity and selectivity [2]. The bivalent ligand approach has also been successfully applied to cholinesterase (ChE) inhibitors [3]: Heterobivalent inhibitors of AChE have been developed that bind to two different sites of AChE (see also below). Although in some cases both the heterobivalent ligand and the hybrid approach can describe the same path and are hardly distinguished in the literature, in this review the main focus will be on molecules that target two distinct pharmacological actions.

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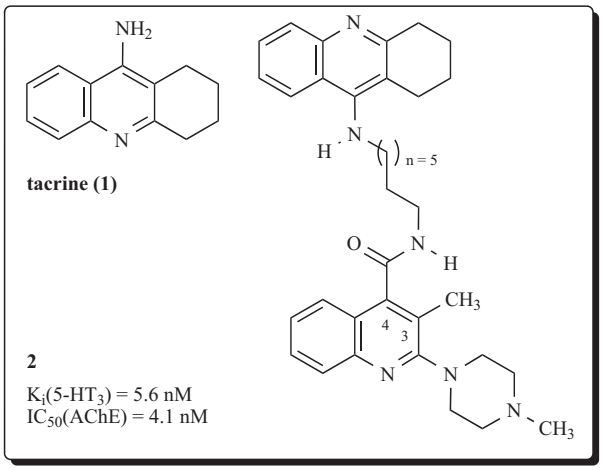
1. HYBRID MOLECULES INTERACTING WITH THE 5-HT_3 RECEPTOR AND ACHE

The 5-HT_3 receptor is a ligand-gated ion channel that allows depolarizations through influx of sodium, potassium, magnesium and calcium [4]. A number of potent and highly selective antagonists like odansetron have been developed and are applied in therapy for emesis control especially associated with anticancer chemotherapy [5]. The 5-HT_3 receptors also mediate the inhibitory control of ACh release in the cortex [6]. The potent AChE inhibitor tacrine (**1**) was connected by a heptamethylene-spacer to a piperazinylquinoline yielding compound (**2**) [7].



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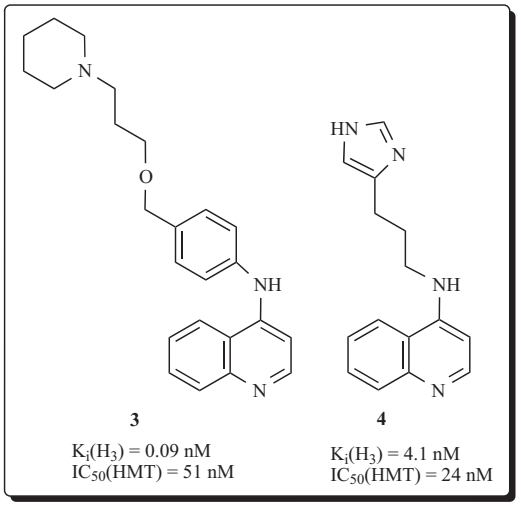
The latter compound (**2**) was yielded as a potent 5-HT_3 antagonists after intensive structure-activity relationships (SARs), which revealed streric tolerance in positions 3 and 4 of the quinoline nucleus therefore allowing functionalization with a tacrine-connected spacer [7]. Compound (**2**) shows nanomolar affinity towards the 5-HT_3 receptor combined with nanomolar inhibitory activity at AChE and a tenfold selectivity over butyrylcholinesterase (BChE). Since the heteroarylpiperazine 5-HT_3 antagonists are devoid of AChE activity, the tacrine moiety binds to the active centre and the heteroarylpiperazine moiety additionally interacts with the so-called peripheral anionic site (PAS) of AChE. The PAS is of special interest for a potential treatment of AD, because its inhibition prevents formation of β-amyloid plaques [8].

Interestingly, computational analysis showed that compound (**2**) binds in a similar manner to the 5-HT_3 receptor as it binds to AChE using a "peripheral" site (in this case occupied by the tacrine moiety) [7].

2. HYBRID MOLECULES INTERACTING WITH THE H_3 RECEPTOR AND ACHE / HMT

H_3 receptor antagonists may be applied in cognitive disorders associated with modulation of the central histaminergic system due to their ability to stimulate the histaminergic system by interaction with presynaptic receptors resulting in an interrution of the negative feedback. Therefore H_3 antagonists showed cognitive enhancing properties in *in vivo* assays for cognitive improvement [9].

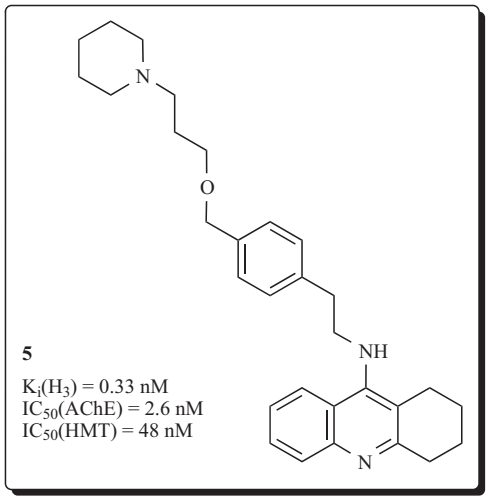
In order to enhance their overall potencies, dual acting hybrid molecules were prepared that are both H_3 antagonists and inhibitors of histamine *N*-methyltransferase (HMT) [10, 11], which is the main enzyme for metabolizing histamine in the human brain [12]. As the results of intensive SARs an aminoquinoline moiety (a structural feature for HMT inhibition) was connected with a piperidino group (for H_3 antagonism) either *via* an alkylene spacer (yielding highly potent HMT inhibitors with moderate to high H_3 affinity) or *via* an *p*-phenoxypropyl spacer, which yielded compounds with very high H_3 affinities like compound (**3**) [10]. Also imidazole derivatives like compound (**4**) resembling the natural neurotransmitter histamine could be obtained exhibiting a similar binding profile [11].



3
$K_i(H_3)$ = 0.09 nM
IC_{50}(HMT) = 51 nM

4
$K_i(H_3)$ = 4.1 nM
IC_{50}(HMT) = 24 nM

It was shown that the AChE-inhibiting drug tacrine (**1**) also inhibits HMT very potently [13]. Out of this reason selected hybrid molecules with a tacrine-like structure were also tested for ChE inhibition [14]. Indeed, several compounds turned out to act at all three targets. For example compound (**5**) is a subnanomolar H_3 antagonist, a nanomolar AChE inhibitor, and a nanomolar HMT inhibitor, respectively. Therefore a triple acting compound has been designed and identified [14]. Related compounds proved unsuccessful in *in vivo* experiments for modulation of brain histamine levels [10]. Nevertheless, the design strategy seems to be very promising for finding novel cognitive enhancing drugs.



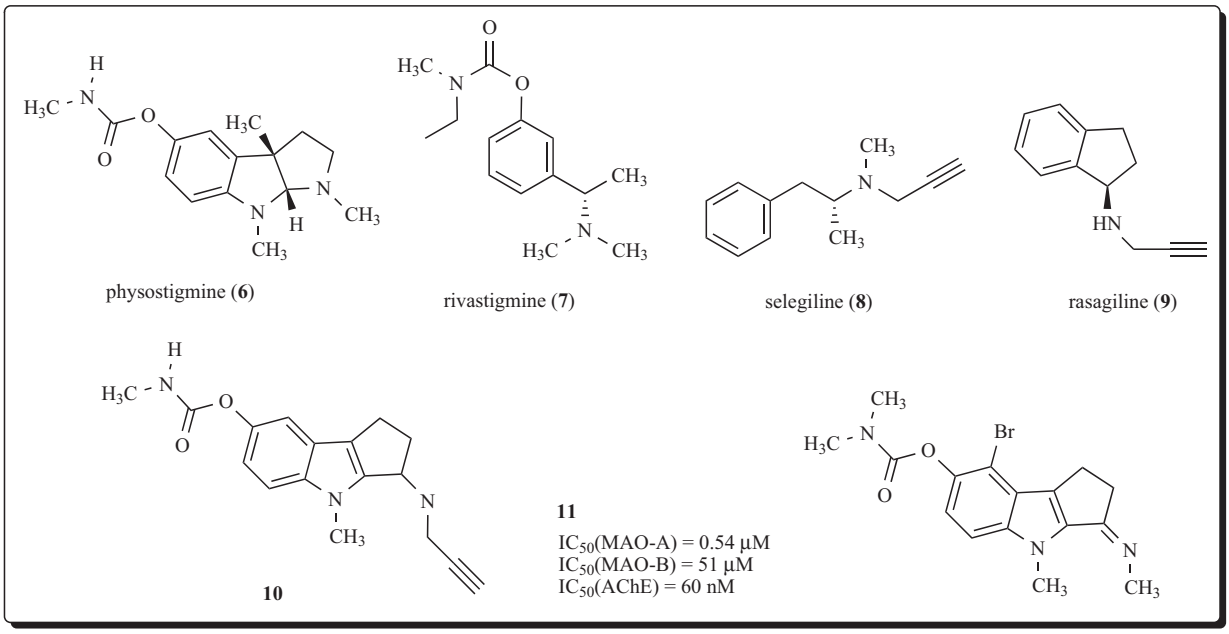
5
$K_i(H_3)$ = 0.33 nM
IC_{50}(AChE) = 2.6 nM
IC_{50}(HMT) = 48 nM

3. COMBINED MAO AND ACHE INHIBITORS

MAO-A is the prominent form of monoamine oxidase (MAO) in the central nervous system (CNS) responsible for degradation of norepinephrine and 5-HT. Therefore selective MAO-A inhibitors are used as antidepressants. MAO-B is responsible for degradation of dopamine in the striatum. This enzyme is irreversibly inhibited by selegiline, which is applied in the therapy of Parkinson`s disease.

Two different observations led to increased interest in MAO inhibitors for the treatment of AD. On the one hand depression is commonly associated with AD probably due to decreased noradrenergic and serotoninergic activity within the limbic system [15]. On the other hand MAO-B activation is increased in certain brain regions of AD patients, which is responsible for increased levels of hydrogenperoxide and oxidative free radicals, which are in turn correlated with β-amyloid plaque formation [16].

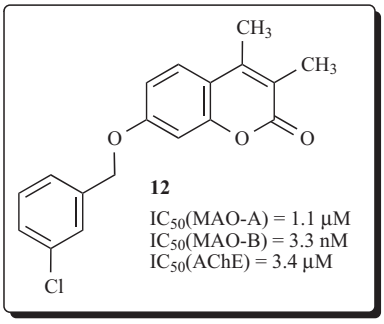
Out of this reason AChE inhibitors were combined with MAO-B inhibiting molecules. In a first approach the structural motive of the AChE inhibitor physostigmine (**6**) was combined with the one of the irreversible MAO inhibitors selegiline (**8**) and rasagiline (**9**) to yield dual inhibitors like (**10**) [17]. Interestingly, biological testing of the synthetic imine precursors identified them as weak combined inhibitors, in which MAO inhibition is reversible. Structural modification led to the identification of several combined inhibitors like compound (**11**), which show high affinity at AChE and both MAOs. Halogen substitution *ortho* to the carbamate



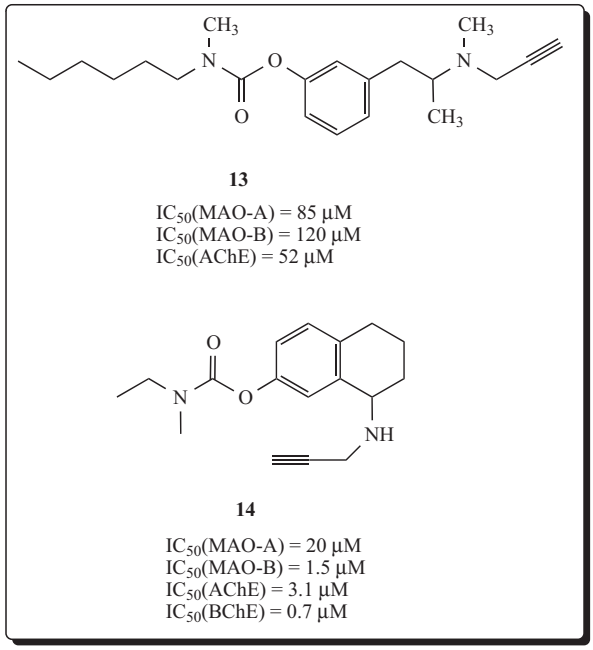
moiety turned out to be responsible for a strong activity increase [17].

Further development of these kinds of compounds was terminated due to low oral activity either due to poor oral availibility or poor penetration of the blood-brain barrier (BBB) [17].

Although not hybrid molecules, some coumarin-derived MAO inhibitors showed moderate ChE inhibiting activities, and therefore behave as dual inhibitors [18]. Compound (**12**) was the best inhibitor in the series of compounds synthesized, which differed in the substituition pattern of the benzyloxy group. It is a micromolar AChE, and a nanomolar MAO-B inhibitor with good selectivity over MAO-A [19]. What makes these findings especially interesting is the fact that these coumarins are noncompetitive AChE inhibitors, and therefore seem to bind to the PAS (, and therefore they may be inhibitors of β-amyloid fibril formation) [19, 20].



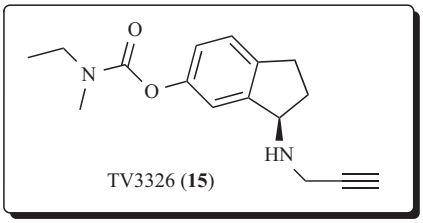
Sterling *et al.* have synthesized a large series of compounds to find dual inhibitors of MAO and AChE by combining the propargylamine pharmacophores of selegiline (**8**) and the MAO-B selective inhibitor rasagiline (**9**) with the AChE inhibiting carbamate pharmacophore of rivastigmine (**7**) [and physostigmine (**6**)]. The propargylamine pharmacophore exhibits neuroprotective properties independent of its MAO inhibition [21-23]. Such hybrid compounds can therefore also be regarded as triple acting compounds. Within the series of compounds synthesized, one phenylethylamine (**13**) and two compounds with an indan and a tetralin ring system (**14**), respectively, were identified as moderately potent (micromolar and equipotent) MAO-B and AChE inhibitors without MAO-A selectivity [24].



For the *N*-propargylaminoindans synthesized, MAO and AChE inhibitory potency of the carbamates decreased as a function of position 4>6>7 for the carbamyloxyphenyls. For both the *N*-propargylaminoindans and the *N*-propargylphenylethylamines AChE inhibitory activity depends primarily on

on the carbamoyl nitrogen substituents, with methyl and ethyl being the least potent ones. In both classes of compounds *N*-methylation at the propargylamine nitrogen increases MAO and decreases AChE inhibition [24].

A compound very closely related to the ones synthesized by Sterling *et al.* is TV3326 (**15**), which can also be regarded as a hybrid out of MAO-B inhibitor rasagiline (**9**) and ChE

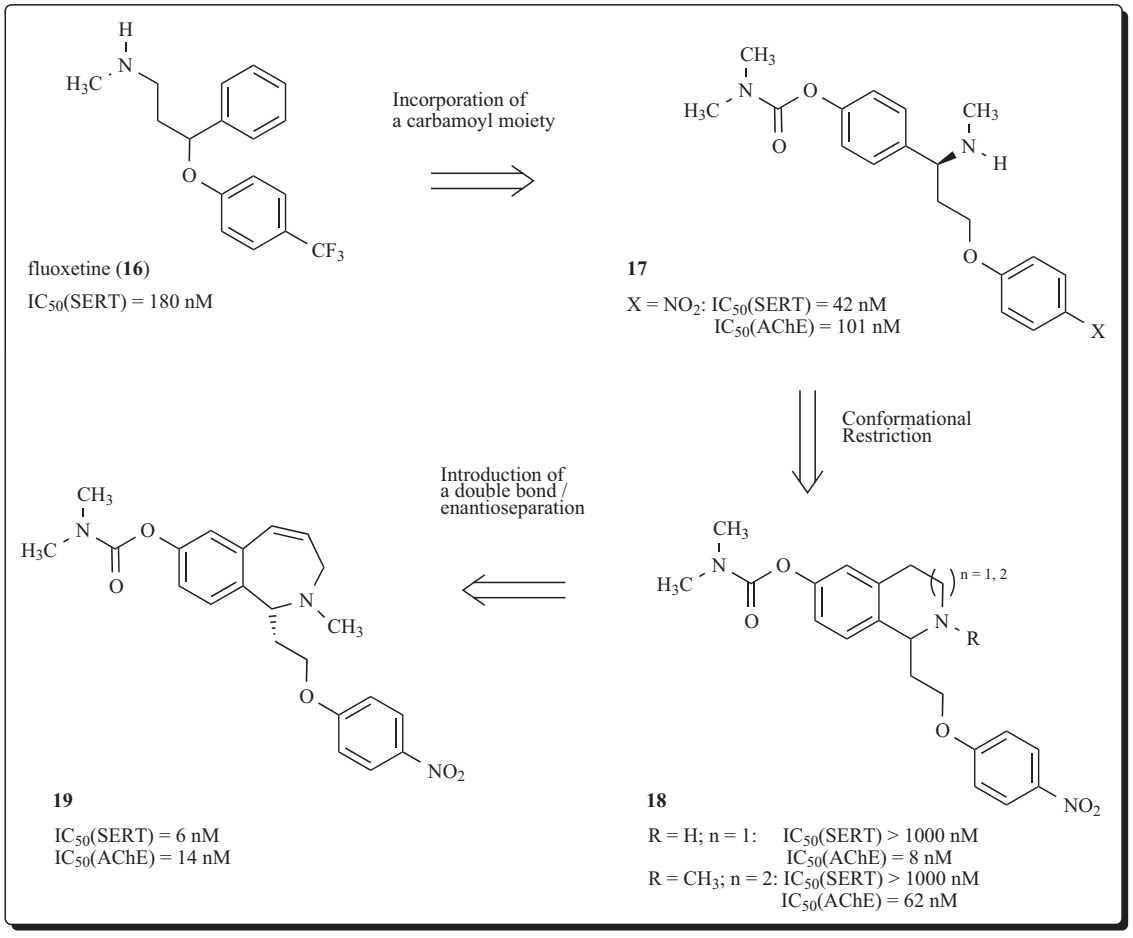


TV3326 (**15**)

inhibitor rivastigmine (**7**) [25]. This compound is of special pharmacological interest, because it has no significant effect on peripheral MAO and therefore does not attenuate the cardiovascular response after tryptamine resorption [26]. More interestingly, TV3326 (**15**) increases neurotrophic/-protective soluble amyloid precursor protein α (sAPPα) secretion by activation of mitogen-activated protein (MAP) kinase in rat PC12 cells and thereby prevents the formation of β-amyloid plaques; these effects seem to be associated with the *N*-propargylamine pharmacophore [27]. α-Secretase inhibitors inhibited the TV3326-induced sAPPα release, clearly showing that the action of this compound is mediated through α-secretase activity. [27].

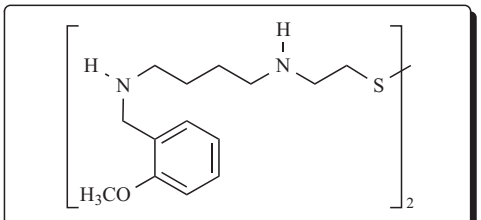
4. COMBINED ACHE AND SERT INHIBITORS

Apart from MAO inhibitors, blockers of the serotonin transporter (SERT) are widely used in the therapy of depression [28]. Out of this reason a carbamate moiety was incorporated into the structure of the established SERT inhibitor fluoxetine (**16**) to yield compounds like (**17**) [29-31]. It was shown that *para*-substitution by the carbamate moiety and a nitro-group for substituent X on the phenyl ether moiety is crucial for dual potent inhibitory activities [29, 31]. In further studies the dual inhibitory structure of (**17**) was incorporated into conformationally restricted six- and seven-membered ring-system (**18**). The six-membered 1,2,3,4-tetrahydroisochinoline derivatives and also the saturated seven-membered ring-systems showed increased (nanomolar) AChE activity, but lost SERT activity completely [31]. The introduction of a double bond led to a nanomolar inhibitor (**19**) of both AChE and SERT, the (*R*)-enantiomer turned out to be a low nanomolar inhibitor exhibiting only weak activity towards BChE, choline acetyltransferase and norepinephrine/dopamine transporters, respectively [30].

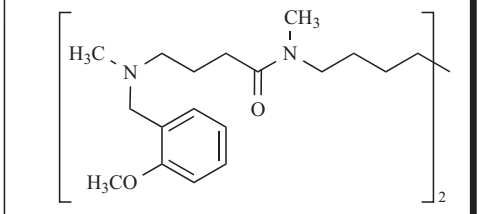


5. HYBRIDS OUT OF ACHE INHIBITORS AND M_2-ANTAGONISTS

Another interesting target for cognitive enhancement is the presynaptic muscarinic M_2 autoreceptor, because its inhibition facilitates ACh release [32]. Combining AChE inhibitory activity with M_2 autoreceptor inhibition should therefore act in a synergistical manner for cognitive enhancement. The irreversible α-adrenoreceptor benextramine (**20**) exhibits M_2 affinity and potentiates ACh effects due to AChE inhition [33]. Melchiorre`s group therefore used benextramine (**20**) as a lead and found out that the disulfide bridge is not necessary for AChE inhibition and compounds bearing an octamethylene spacer between the amino groups show optimum M_2 affinity [34]. Diamine diamides were synthesized and SARs showed that caproctamine (**21**) inhibits both AChE and M_2 receptors with submicromolar affinty, showing some selectivity compared to BChE and good selectivity compared to M_1 and M_3 receptors, respectively [35].



benextramine (20) IC_{50}(AChE) = 7.2 μM
IC_{50}(BChE) = 6.2 μM



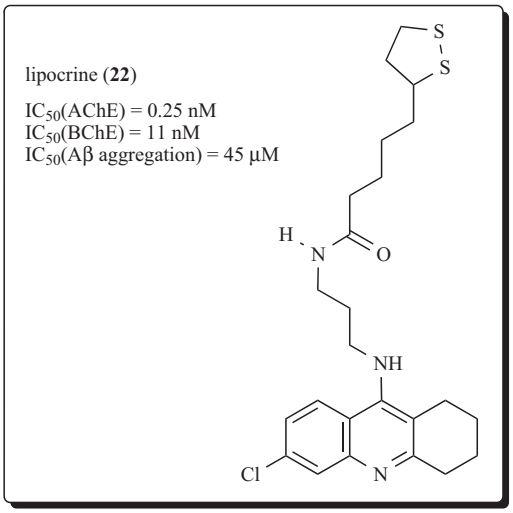
caproctamine (21) IC_{50}(AChE) = 0.17 μM
IC_{50}(BChE) = 12 μM
pA_2 (M_1) = 5.66
pA_2 (M_2) = 6.39
pA_2 (M_3) = 5.55

Furthermore, kinetic measurements and molecular dynamics simulations indicate that caproctamine (**21**) may also interact with the PAS and therefore prevent β-amyloid aggregation [35].

6. ACHE INHIBITOR HYBRIDS WITH ANTIOXIDANT PROPERTIES

As mentioned for the AChE/MAO hybrids in chapter 3, antioxidant properties of MAO inhibitors are beneficial pharmacological effects on their own. Concerning the etiology of AD, preventing free radical formation and oxidative cell damage has revealed new targets upstream the neurodegenerative cascade [36, 37]. Lipoic acid (LA) is a well described antioxidant [38], and its was proved that LA is able to prevent neurotoxicity of β-amyloid [39].

Melchiorre`s group has synthesized hybrid molecules like compound (**22**) out of tacrine (**1**) and LA, in which the linking amide group is separated through three to seven methylene groups from the tacrine moiety [40]. Optimum affinity was reached with a propylene spacer, but all hybrids synthesized show nanomolar affinities. Introduction of chlorine atoms into the acridine system furnished lipocrine (**22**). Lipocrine (**22**) showed further increased inhibitory activity yielding subnanomolar activity. Again, kinetic measurements showed that interaction with the PAS was possible, which was proved by inhibition of β-amyloid aggregation [40].

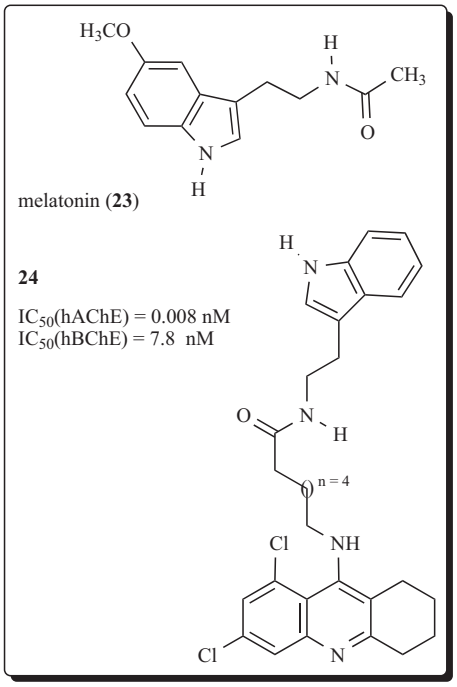


Interestingly, cell viability was not influenced at concentration up to 50 μM, but intracellular antioxidant activity against the formation of reactive oxygen species (ROS) was very high. A strong ROS decrease was observed at 5 μM, therfore surpassing the antioxidant properties of the parent compound LA [40].

A second antioxidant component applied for the synthesis of tacrine (**1**) hybrids is the pineal neurohormone melantonin (**23**) [41]. Melatonin has been described as an antioxidant that directly scavenges ROS [42], and it also shows protective effects against β-amyloid-induced apoptosis in microglial cells [43]. Melatonin was connected as to tacrine (**1**) (or its 6-chloro, 8-chloro- or 6,8-dichloro-analogues, respectively,) by a similar manner as in lipocine (**22**) with a penta- or a hexamethylene spacer [41].

The hexamethylene-linked compounds showed higher potencies than the pentmethylene-linked ones. 6-Chloro- and 6,8-dichloro-substitution further increased activity and AChE selectivity [41]. Also removal of the methoxy-substituent of melatonin yielded in higher potencies. Compound (**24**) is therefore one of the most potent (picomolar) hAChE inhibitors described to date with almost 1000fold selectivity compared to BChE [41].

Concerning the determination of the antioxidant properties of compound (**24**), an oxygen radical absorbance assay using fluorescein (ORAC-FL) was applied, in which the vitamin E analogue trolox was used as a standard. Melatonin (**23**) showed 2.3-fold trolox equivalent activity and compound (**24**) showed an activity 2.5-fold higher than trolox [41].



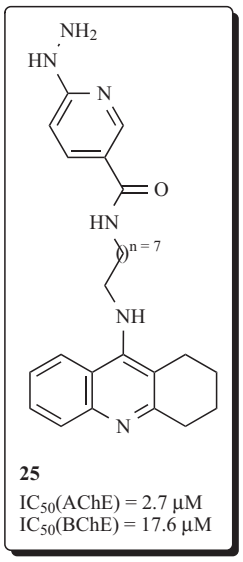
Interestingly, unsubstituted tacrine moieties and the ones with 8-chloro-substitution showed higher radical scavenging values, whereas 6-chloro- and 6,8-dichloro-substitution showed an activity drop. Brain penetration was evaluated by a parallel artificial membrane penetration assay (PAMPA) for the blood-brain barrier (BBB) using lipid extract of porcine brain. Almost all melatonin-tacrine hybrids synthesized should be able to pass the BBB according to this assay [41].

7. AD DIAGNOSTICS AND NEUROPROTECTIVE HYBRIDS

The amount of AChE decreases dramatically during progression of AD, whereas the amount of BChE stays the same or is up-regulated [44]. It might therefore be useful to develop AChE-selective compounds for functional imaging in order to get a tool for the otherwise difficult diagnosis of AD. The hybrid approach has been applied for this purpose: Tacrine (**1**) was connected *via* variable spacer lengths (n = 2, 3, 6, 8) to hydrazine nicotinate (HYNIC), which is able to bind technetium-99m (^{99m}Tc) [45, 46], a radiotracer for single photon emission computed tomography (SPECT). Although tacrine (**1**) itself shows some BChE-selectivity, the hybrids synthesized show improved selectivities towards AChE. Especially the octamethylene-bridge compound (**25**) shows a 7fold AChE-selectivity and a 10fold increase in inhibitory activity compared to tacrine [46].

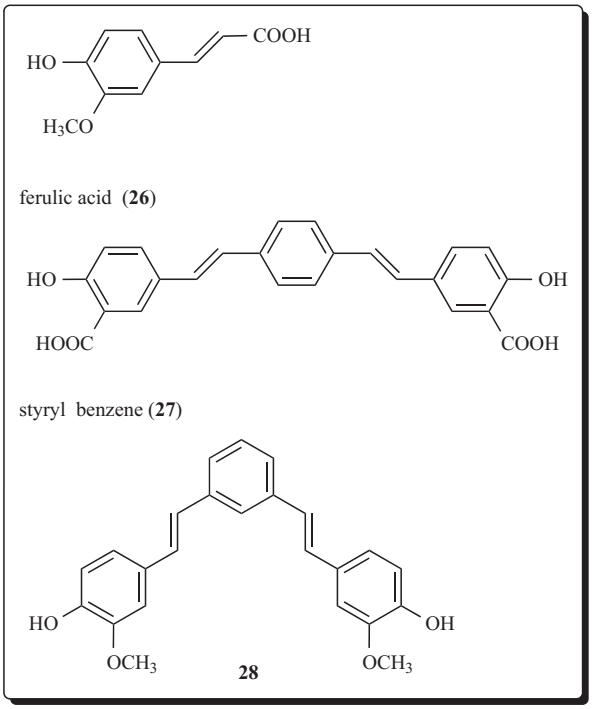
Although the optimum in activity and selectivity is not yet reached, the hybrid approach also works for the development of radiotracers designed for diagnostic purposes.

A completely different class of hybrids specifically targeting amyloid-related disorders is represented by compound (**28**) [47]: There is some evidence that AD-specific fibrils are formed through oligomeric β-amyloid assembly intermediates, which seem to be more toxic than the polymeric fibrils [48]. Because of distinct pathways only β-amyloid$_{42}$ forms



protofibril-type oligomers [49]. Stryryl benzene (**27**) has been described as a fibril specific molecule such as congo red [50]. Also ferulic acid (**26**) displays antidementive activity, a fact that suggests this structural unit might represent a kind of minimum pharmacophore [51].

Out of these reasons hybrid molecules like compound (**28**) were designed and synthesized for amyloid fibril inhibition [47].



Interesting results were obtained for hybrid compound (**28**), which could be readily obtained by Wittig-olefination: Toxicity induced by β-amyloid$_{42}$ could be alleviated and fibril formation be inhibited with an EC$_{50}$ of 0.5 μM [47]. As expected, binding of compound (**28**) to non-fibrous mono-

mer-like β-amyloid was shown using surface plasmon resonance. Interestingly, styryl benzene (**27**) did not alleviate β-amyloid toxicity, although compound (**27**) was described as a compound with high fibril affinity [52]. It seems that 4-hydroxy and 3-methoxyl moieties are important pharmacophoric features. Also the *meta*-substitution of the styryl groups is an important feature, as no alleviative effect can be observed for *para*-substituted styryl benzene (**27**) [47].

8. CALCIUM CHANNEL BLOCKING AGENTS WITH ACHE INHIBITING PROPERTIES

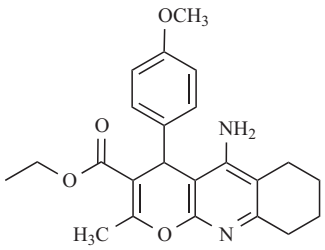
Of special interest both from the medicinal chemical as from the pharmacological point of view are hybrid molecules, in which Ca^{2+} channel blocking and nicotinic ACh receptor modulating properties are incorporated into a tacrine (**1**) molecule [53-55]. In these works the tacrine molecule was not just attached to other pharmacophoric moieties, but the tacrine molecule itself was modulated: on the one hand by changing the ring size of the alicycle (from five- to eight membered alicycles), on the other hand by replacing the benzene ring by variously substituted pyridines, 1,4-dihydropyrans, thiophenes and furans, respectively, in order to achieve affinity to nicotinic receptors and modulation of voltage-dependent calcium channels [53-55].

This rationale was developed due to the fact that alteration of calcium homeostasis plays a pivotal role in AD pathogenesis and that nicotinic receptor ligands exhibit neuroprotective effects [56, 57]. Tacrine itself served as a lead, because it both inhibits calcium channels [58] and the binding of nicotinic receptor ligands [59]. A large set of target compounds were prepared by Friedländer reaction from cycloalkanones and the respective aromatics (e. g. 6-amino-5-cyano-4*H*-pyrans and 6-amino-5-cyano-pyridines) to yield compounds like (**29**) and (**30**).

A whole set of compounds is able to inhibit the nicotinic ACh receptor and to block the L-type calcium channel [53, 55].

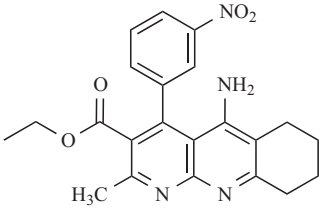
Concerning SARs, compound (**29**) was among the most potent compounds. It was not only a moderate ChE inhibitor, but a good modulator of the nACh receptor. *Meta*-methoxy substituents showed even higher blockade, but had no effect on the L-type Ca^{2+} channels, whereas *ortho*-methoxy substitution again had effects at both targets [53]. In general, nACh receptors seemed to be more sensitive to steric effects of the substituents, whereas voltage-gated channels were more effected by the electronic structure of the substituents [53]. Also analogous pyridine compounds (e. g. **30**) showed both nACh and voltage-dependent Ca^{2+} channel modulation. Compound (**29**) might be well suitable as a lead for neuroprotectives by preventing cell Ca^{2+} overload leading to neuronal degeneration and cell death [60], because its IC_{50} for relaxation of precontracted rat aorta strips was only around 2 μM, a fact that makes peripheral cardiovascular effects less likely [53].

Concerning ChE inhibition, cyclohexane-fused compounds showed the highest activity and *meta*-substitution of the methoxy-group decreased ChE activity [54]. Also conversion of the ethyl ester group into an *i*-propyl group decreased activities. Pyridine (actually [1,8]-naphthyridine)-



29

IC_{50}(AChE) = 0.9 μM
IC_{50}(BChE) = 6.2 μM
Inhibition of nAChR-mediated Ca^{2+}-uptake by a 3 μM solution: 90 %
Inhibition of K^+-induced Ca^{2+}-uptake by a 3 μM solution: 50 %



30

IC_{50}(AChE) = 0.9 μM
IC_{50}(BChE) = 21 μM
Inhibition of nAChR-mediated Ca^{2+}-uptake by a 3 μM solution: 62 %
Inhibition of K^+-induced Ca^{2+}-uptake in the presence of nifedipine (non-L-type): 19 %

compounds like (**30**) inhibit both nACh receptor-mediated and voltage-gated calcium influx. Most members of this family block L-type channels, compound (**30**) also non-L-type channels [55].

The inhibitory potencies and the binding mode of these hybrid molecules are remarkable. Most of the hybrid molecules are micromolar ChE inhibitors with lower potencies than tacrine and some - although not prominent - selectivity towards AChE. But in contrast to tacrine, the hybrid molecules inhibit AChE noncompetitively despite their structural similarity [54]. Molecular dynamics simulations of compound (**29**) showed that its van der Waals volume (~330 Å) greatly exceeds the one of tacrine (~170 Å); the cavity of the active site is estimated to be ~340 Å. These simulations suggest that the binding site of AChE is not flexible enough to accommodate the hybrids, which might therefore exert their activity by interacting at the peripheral site [55]. The β-amyloid fibril aggregation-inhibiting properties of PAS blockers, which these compounds seem to be because of their binding mode, represents an additional advantage of this class of compounds.

9. CONCLUDING REMARKS

AD and other forms of dementia represent diseases, for which treatment options are strongly limited. Even symptomatic treatment provides tremendous help in terms of reducing the costs of the care for patients and of course for the improvement of the life quality of the individual patient.

As an increasingly evolving strategy for the design and development of new drugs, the hybrid molecule approach and the synthesis of designed dual or even multiple acting compounds has been applied to antiamnesic compounds, in many cases based on the ChE inhibitor tacrine. It was possible to develop compounds that act at two or more pharmacological targets at the same time. These targets cover an extremely broad variety of pharmacological structures, such as enzymes, receptors, ion channels, and transporters. But also antioxidant properties have been introduced into therapeutically acting structures to target upstream processes leading to dementia, and the hybrid / designed multiple ligand approach has additionally being applied to diagnostic agents.

What makes this new approach of special value is the fact that is was often not only possible to maintain the pharmacological activities of the parent compounds/structures, but an activity increase and/or modulated selectivities could be obtained. Concerning AChE inhibitors, interaction of hybrids with the PAS can often extend pharmacological activity to a third target (i. e. inhibition of β-amyloid fibril aggregation).

In general the hybrid / designed multiple ligand approach may suffer from certain drawbacks. For instance the optimal and maximal extent to which the first target is effected might differ for the second (and third) target. This means the optimal balance of activities is difficult to find and is not necessarily found with highest activities in order to minimize unwanted side effects.

Due to the broadness of applicability and optimization of therapeutic activity the hybrid / designed multiple ligand approach as a novel strategy in Medicinal Chemistry can be expected to be successfully applied to further targets with remarkable improvement of drug properties.

ABBREVIATIONS

ACh(E) = Acetylcholin(esterase)

AD = Alzheimer`s disease

BBB = Blood-brain barrier

BCh(E) = Butyrylcholin(esterase)

CNS = Central nervous system

H = Histamine

HMT = Histamine *N*-methyltransferase

5-HT = Serotonin

HYNIC = Hydrazine nicotinate

LA = Lipoic acid

MAO = Monoamine oxidase

MAP = Mitogen-activated protein

M receptor = Muscarinic receptor

ORAC = Oxygen radical absorbance assay

PAMPA = Parallel artificial membrane penetration assay

PAS = Peripheral anionic site

ROS = Reactive oxygen species

sAPPα = Soluble amyloid precursor protein α

SAR = Structure-activity relationship

SERT = Serotonin transporter

SPECT = Single photon emission computed tomography

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