Cognitive Enhancers (Nootropics). Part 2: Drugs Interacting with Enzymes

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Abstract. Cognitive enhancers (nootropics) are drugs to treat cognition deficits in patients suffering from Alzheimer’s disease, schizophrenia, stroke, attention deficit hyperactivity disorder, or aging. Cognition refers to a capacity for information processing, applying knowledge, and changing preferences. It involves memory, attention, executive functions, perception, language, and psychomotor functions. The term nootropics was coined in 1972 when memory enhancing properties of piracetam were observed in clinical trials. In the meantime, hundreds of drugs have been evaluated in clinical trials or in preclinical experiments. To classify the compounds, a concept is proposed assigning drugs to 19 categories according to their mechanism(s) of action, in particular drugs interacting with receptors, enzymes, ion channels, nerve growth factors, re-uptake transporters, antioxidants, metal chelators, and disease modifying drugs meaning small molecules, vaccines, and monoclonal antibodies interacting with amyloid-β and tau. For drugs whose mechanism of action is not known, they are either classified according to structure, e.g., peptides, or their origin, e.g., natural products. This review covers the evolution of research in this field over the last 25 years.

Keywords: Alzheimer’s disease, cognitive enhancers, donepezil, enzymes, galantamine, memory, rivastigmine

1. INTRODUCTION

As of August 29, 2012, there are 26,677 entries in PubMed under the term cognitive enhancers, 26,680 entries under the term nootropic and 242 entries under the term cognition enhancers. Scifinder lists 5,105 references under the research topic nootropic, 535 references under the term cognitive enhancer, and 9,780 references for cognition enhancers. The Thomson Reuters Pharma database lists 1,106 drugs as nootropic agents or cognition enhancers and gives zero results under the term cognitive enhancer. The term nootropics was coined by the father of piracetam Cornelius Giurgea in 1972/1973 [1, 2], NOOS = mind and TROPEIN = toward.

Nootropics are drugs to treat cognition deficits, which are most commonly found in patients suffering from Alzheimer’s disease (AD), schizophrenia, stroke, attention deficit hyperactivity disorder, or aging. Mark J. Millan and 24 eminent researchers [3] presented an excellent overview on cognitive dysfunction in psychiatric disorders in the February 2012 issue of Nature Reviews Drug Discovery and defined cognition as “a suite of interrelated conscious (and unconscious) mental activities, including pre-attentional sensory gating, attention, learning and memory, problem solving, planning, reasoning and judgment, understanding, knowing and representing, creativity, intuition and insight, spontaneous thought, introspection, as well as mental time travel, self awareness and meta cognition (thinking and knowledge about cognition)”.

Since a first review in 1989 on “Families of Cognition Enhancers” by Froestl and Maitre [4], substantial progress has been made in the understanding of
the mechanism(s) of cognitive enhancers. Therefore, we propose a new classification to assign cognition enhancing drugs to 19 categories:

1. Drugs interacting with Receptors (Part 1)
2. Drugs interacting with Enzymes (Part 2)
3. Drugs interacting with Cytokines (Part 3)
4. Drugs interacting with Gene Expression (Part 3)
5. Drugs interacting with Heat Shock Proteins (Part 3)
6. Drugs interacting with Hormones (Part 3)
7. Drugs interacting with Ion Channels (non-Receptors) (Part 3)
8. Drugs interacting with Nerve Growth Factors (Part 3)
9. Drugs interacting with Re-uptake Transporters (Part 3)
10. Drugs interacting with Transcription Factors (Part 3)
11. Antioxidants (Part 3)
12. Metal Chelators (Part 3)
13. Natural Products (Part 3)
14. Nootropics (“Drugs without mechanism”) (Part 3)
15. Peptides (Part 3)
16. Drugs preventing amyloid-β aggregation (Part 3)
17. Drugs interacting with tau (Part 3)
18. Stem Cells (Part 3)
19. Miscellaneous (Part 3)

In Part 1, drugs interacting with receptors were described [5]. In Part 2, we describe drugs interacting with enzymes and in Part 3, drugs interacting with targets 3 to 10 and compounds and preparations of categories 11 to 19.

2. DRUGS INTERACTING WITH ENZYMES

Researchers have been investigating drugs interacting with a wide variety of enzymes in order to identify valuable cognition enhancers. These enzymes are:

2.1 Drugs interacting with Acetyl- & Butyryl-cholinesterase (AChE & BChE)
2.1.1. Drugs inhibiting AChE and other biological targets
2.1.1.1. Dual AChE inhibitors and AChE receptor ligands
2.1.1.2. Dual AChE and amyloid-β inhibitors
2.1.1.3. Dual AChE inhibitors and antioxidants
2.1.1.4. Dual AChE and β-secretase-1 or γ-secretase inhibitors
2.1.1.5. Dual AChE inhibitors and calcium channel blockers
2.1.1.6. Dual AChE inhibitors and cannabinoid receptor antagonists
2.1.1.7. Dual AChE and fatty acid amide hydrolase inhibitors
2.1.1.8. Dual AChE inhibitors and histamine H3 receptor antagonists
2.1.1.9. Dual AChE and monoamine oxidase inhibitors
2.1.1.10. Dual AChE inhibitors and metal chelators
2.1.1.11. Dual AChE inhibitors and N-methyl-D-aspartic acid receptor channel blockers
2.1.1.12. Dual AChE inhibitors and platelet activating factor antagonists
2.1.1.13. Dual AChE and serotonin transporter inhibitors
2.1.1.14. Dual AChE and sigma receptor inhibitors
2.2. Drugs interacting with β-Secretase
2.3. Drugs interacting with γ-Secretase
2.4. Drugs interacting with γ-Secretase Inhibitors
2.4.1. γ-Secretase Inhibitors
2.4.2. γ-Secretase Modulators
2.4.3. Inhibitors of γ-Secretase Activating Protein
2.4.4. Notch Pathway Inhibitors
2.5. Drugs interacting with β-Hexosaminidase
2.6. Drugs interacting with 11β-Hydroxysteroid Dehydrogenase
2.7. Drugs interacting with Calpain
2.8. Drugs interacting with Carbonic Anhydrase
2.9. Drugs interacting with Caspasas
2.10. Drugs interacting with Catechol-O-methyltransferase
2.11. Drugs interacting with Cathepsin
2.12. Drugs interacting with Cholesterol 24S-hydroxylase (CYP46A1)
2.13. Drugs interacting with Cyclooxygenase
2.14. Drugs interacting with D-Amino Acid Oxidase
2.15. Drugs interacting with Glutaminyl Cyclase
2.16. Drugs interacting with Glyceraldehyde-3-Phosphate Dehydrogenase
2.17. Drugs interacting with Glycogen Synthase Kinase-3
2.18. Drugs interacting with Guanylyl Cyclase
2.19. Drugs interacting with Heme Oxygenase
2.20. Drugs interacting with Histone Deacetylase
2.21. Drugs interacting with HMG-CoA Reductase
2.22. Drugs interacting with HMG-CoA Reductase
2.23. Drugs interacting with Insulin-degrading Enzyme
2.24. Drugs interacting with Kynurenine Mono-oxygenase and Kynurenine Transaminase II
2.25. Drugs interacting with 5-Lipoxygenase
2.26. Drugs interacting with Monoamine Oxidase
2.27. Drugs modulating O-linked N-Acetylglucosaminidase
2.28. Drugs interacting with Peptidyl-prolyl cis-trans Isomerase D
2.29. Drugs interacting with Phosphodiesterases
2.30. Drugs interacting with Phospholipases A2 and D2
2.31. Drugs interacting with Plasminogen Activator Inhibitor
2.32. Drugs interacting with Poly ADP-Ribose Polymerase
2.33. Drugs interacting with Prolyl Endo Peptidase
2.34. Drugs interacting with Prostaglandin D & E Synthases
2.35. Drugs interacting with Protein Kinase C
2.36. Drugs interacting with Protein Tyrosine Phosphatase
2.37. Drugs interacting with Rac1 GTPase
2.38. Drugs interacting with Ras Farnesyl Transferase
2.39. Drugs interacting with S-Adenosylhomocysteine Hydrolase
2.40. Drugs interacting with Sirtuin
2.41. Drugs interacting with Steroid sulfatase
2.42. Drugs interacting with Transglutaminase
2.43. Drugs interacting with Ubiquitin Carboxy-terminal Hydroxylase (Usp14).

2.1. Drugs interacting with Acetyl- and Butyrylcholinesterase

Since the publication of the cholinergic hypothesis of AD by Bartus et al. in 1982 [6], tremendous efforts have been undertaken to find either selective acetylcholine receptor agonists (described in Part 1) or acetylcholinesterase (AChE) inhibitors [7–15]. The history of the cholinergic hypothesis was traced back [16]. In retrospect, the latter approach (i.e., AChE inhibitors) turned out to be more successful than the big efforts to find selective acetylcholine receptor agonists.

Tacrine (tetrhydroaminoacridine, Cognex; Warner-Lambert, Pfizer) was approved by the Food and Drug Administration (FDA) in 1993 and was launched in 1995 for the treatment of AD. It potently blocks butyrylcholinesterase (BChE) (IC50 = 47 nM) and AChE (IC50 = 190 nM) [17]. Tacrine has a short half-life (2–3 hours) and must be administered 4 times a day. The major problem is its severe, though reversible, hepatotoxicity [17, 18].

Donepezil (Aricept; E2020; co-developed by Eisai and Pfizer, Fig. 1) was approved by the FDA in November 1996 and was launched in the US in January 1997 for the treatment of mild-to moderate AD. In October 2006, FDA approval for the treatment of severe AD was granted. It potently blocked AChE (IC50 = 23 nM), whereas blockade of BChE was 320 times weaker (IC50 = 7,420 nM) [17]. The Japanese inventors disclosed values of IC50 = 5.7 nM for AChE and IC50 = 7,140 nM for BChE (factor 1250) [19]. Donepezil interacts with the active site of AChE and the peripheral anionic site of the enzyme [20]. Its long terminal disposition half-life of 70 hours supports once-daily administration [18]. Interestingly, the two enantiomers of donepezil racemize rapidly in vivo [21, 22].

The sales for donepezil reported by Eisai for 2011 totaled USD 1.853 billion (Thomson Reuters Pharma, update of August 24, 2012). 2,301 publications on donepezil are listed in PubMed (as of August 29, 2012).

For the synthesis and medicinal chemistry of donepezil, see [19, 23], for an efficient process for large-scale synthesis of donepezil [24, 25], and for molecular modeling of donepezil [26, 27].

Many preclinical and mechanistic reviews have been published [28–37]. Interestingly, donepezil eliminated the suppressive effects of amyloid-β (Aβ)42 on long-term potentiation (LTP) in rat hippocampal slices [38, 39]. Synergistic effects of donepezil and the 5-HT4 receptor agonist RS-67333 on the object recognition were observed in mice [40]. Pharmacokinetic
considerations for donepezil dosing strategies were presented [41].

There is extensive literature available on clinical trial results; see (in chronological order) [42–66]. Broader considerations of higher doses of donepezil in the treatment of mild, moderate, and severe AD were communicated recently [67], in particular on the question of the case of the 23 mg dose [68]. For the effects of donepezil on levels of cholinesterases in the cerebrospinal fluid (CSF) of AD patients, see [69]. For safety and tolerability of donepezil, see [70–72], for pharmacoeconomics [73–81].

Donepezil significantly improved abilities in daily lives of young adults with Down syndrome [82] and in female Down syndrome patients [83], whereas in children with Down syndrome of age 10–17 years, donepezil did not show any benefit versus placebo [84].

Donepezil was used for the treatment of patients with Parkinson’s disease [85–87] and for the treatment of memory impairment in multiple sclerosis patients [88].

Many galenical forms have been developed. Donepezil hydrochloride fine granule formulation was launched in Japan in September 2001. Donepezil rapid oral disintegration tablet was launched in Japan in July 2004 and in the US in June 2005. Donepezil oral jelly formulation was launched in Japan in December 2009. Donepezil oral sustained release high-dose (23 mg) tablet formulation was launched in the US in August 2010. The US NDA donepezil once weekly transdermal formulation in collaboration with Teikoku Seiyaku was submitted in June 2010. A dry syrup formulation administered by suspending the dry syrup in water is in pre-registration in Japan. A fast dissolving oral film strip formulation in collaboration with Applied Pharma Research and Labtec is in clinical evaluation, as is donepezil oral rapid disintegration film in collaboration with Kyukyu Pharmaceuticals. Donepezil transdermal patch with Labtec, donepezil hydrochloride transdermal patch with Nitto Denk and Kowa, and NAL-8812, a 3-day patch formulation co-developed with NAL Pharmaceuticals are in preclinical evaluations, as is the Immediate Suspension encapsulation by ALRISE Biosystems. NAL-8817 is an orally dissolving film formulation of donepezil using the BIO-FX fast-onset oral cavity drug delivery system technology in preclinical evaluation (Thomson Reuters Pharma, update of May 31, 2012).
Deuterated donepezil is investigated by the company Deutria Pharmaceuticals for the potential treatment of AD (Thomson Reuters Pharma, update of August 10, 2012).

Donepezil + memantine (ADS-8704, Arimenda; Adams Pharmaceuticals), a once-daily fixed dose combination extended release formulation, is currently tested in Phase II clinical trials. In May 2012, the FDA approved Phase III studies in an end-of-Phase II meeting. First clinical results were presented [89] (Thomson Reuters Pharma, update of July 5, 2012).

Rivastigmine (Exelon, SDZ-ENA-713, SDZ-212-713; ENA-713; Novartis, Fig. 1) is a potent BChE inhibitor (IC_{50} = 37 nM). It blocks AChE with an IC_{50} = 4.150 nM, a factor of 112 times less than BChE [17]. It forms a carbamylated complex with the active-site serine inactivating it for about 10 hours producing a “pseudo-irreversible” inhibition. For an excellent review on the neurobiology of BChe, see [90, 91]. Rivastigmine was launched for the treatment of mild to moderate AD in 2000 in the EU and the US and in 2010 in Japan. It was approved for the treatment of mild to moderately severe dementia associated with idiopathic Parkinson’s disease. Rivastigmine transdermal patch was launched in the EU in 2007 and in Japan in 2011 in collaboration with the Japanese licensee Ono Pharmaceuticals.

Sales for rivastigmine for 2011 were USD 1.067 billion representing a 6% increase on 2010 (Thomson Reuters Pharma, update of August 24, 2012). There are currently 1,181 publications on rivastigmine listed in PubMed (as of August 29, 2012). Several syntheses of rivastigmine were published [92–96]. Excellent papers on the preclinical characterization of rivastigmine were communicated [97–102]. Extensive literature exists on the clinical trial results of rivastigmine in AD (in chronological order) [103–112]. Rivastigmine at doses of up to 12 mg/day had useful efficacy in patients with mild-moderate dementia of the Alzheimer type. Reports from larger Phase III studies confirmed these findings. The t.i.d. administration is the more efficacious regimen and had comparable tolerability to the t.i.d. regimen. Rivastigmine was evaluated for the treatment of dementia in Parkinson’s disease [113–120]. Oral rivastigmine 3–12 mg/day for 24 weeks was significantly more effective than placebo in ameliorating cognitive and functional decline, including attentional deficits, in patients with Parkinson’s disease dementia. Rivastigmine was also effective in patients with dementia with Lewy bodies. Benefits were seen on tests of attention, working memory, and episodic secondary memory [121]. Rivastigmine was successfully applied for the treatment of vascular dementia [122–125], for treatment of hallucinations in Creutzfeldt-Jakob disease [126], and memory deficits induced by electroconvulsive therapy [127].

For safety and tolerability of rivastigmine, see [50, 74, 128]; for pharmaco-economics [78, 80, 129].

Many reviews exist on results of clinical trials using the rivastigmine transdermal patch [130–154] describing enhanced tolerability and significantly less side effects.

NAL-8822 (NAL Pharmaceuticals) is a one-day patch formulation of rivastigmine using its Bio-D3 transdermal drug delivery system technology in preclinical evaluation (Thomson Reuters Pharma, update of May 31, 2012).

Galantamine (Razadyne, Reminyl, Nivalin; Janssen Pharmaceutica, part of Johnson & Johnson, Shire and Takeda under license from Sanochemia; Fig. 1) is an alkaloid extracted from the bulbs of the Amaryllidaceae family that include daffodils and the common snowdrop (Galanthus woronowii [155]). It blocks AChE (E.C. 3.1.1.7) with an IC_{50} of 800 nM and BChE (E.C. 3.1.1.8) with an IC_{50} of 7,320 nM [17]. Galantamine was launched in 2001 for the treatment of mild to moderate AD in Europe and the US and in March 2011 in Japan. In 2005, Johnson & Johnson launched an extended release capsule formulation. The sales of galantamine in 2011 for Johnson & Johnson were USD 470 million, for Shire USD 40 million, and for Takeda USD 34 million (Thomson Reuters Pharma, update of August 27, 2012).

There are currently 1,602 publications on galantamine (and galanthamine) listed in PubMed (as of August 29, 2012).

To a small extent, galantamine is still produced from snowdrops [156, 157]. However, chemical syntheses have taken over. A technical process for an efficient nine-step procedure, which affords (−)-galanthamine in 12% overall yield, was presented by Sanochemia [158]. The synthetic schemes from academic laboratories were not scaled up [159–163]. The pharmacological characterization of galantamine was described in depth [164–175]. Galantamine weakly inhibited hERG channels [176]. Interestingly, galantamine not only blocks AChE and BChe, but also acts as a positive allosteric modulator of nicotinic acetylcholine receptors enhancing the concentrations of acetylcholine in the brain by a second mechanism [177–182].
The pharmacokinetics of galantamine were reported [183–187]. Many publications described the clinical trial results of galanthamine in AD (in chronological order) [188–201 [1]]. Galantamine improved and stabilized cognitive performance, activities of daily living, and behavioral symptoms over the course of 6 months, and its efficacy and tolerability are comparable with those of other AChE inhibitors (rivastigmine and donepezil). Galantamine proved to be one of the standard first-line medications for mild-to-moderate AD. For galantamine in Parkinson’s disease, see [201]; in schizophrenic patients [202]; in vascular dementia [203].

For safety and tolerability, see [72]; for pharmacoeconomics [78, 80, 204], the historical development of galantamine as a clinically used drug was traced back [205].

Johnson & Johnson developed and launched Raza-dyne ER (Reminyl XL), an extended release capsule formulation, in April 2005 in the US. Patients treated with the extended release formulation had better overall Alzheimer’s Disease Assessment Scale (ADAS-cog/11) scores than the placebo group after six months (Thomson Reuters Pharma, update of May 31, 2012).

NAL-8801 (NAL Pharmaceutical) is a one day patch formulation of galantamine using the Bio-D3 transdermal drug delivery system technology in preclinical evaluation (Thomson Reuters Pharma, update of May 31, 2012).

Memogain (GLN-1062, Galantos Pharma) is a prodrug, the benzoyl ester, of galantamine administered as an intranasal formulation. Memogain has more than 15 times higher bioavailability in the brain than the same dose of galantamine. It is cleaved enzymatically to galantamine [206]. It is in Phase I since November 2011 (Thomson Reuters Pharma, update of December 28, 2011).

Huperzine A (Cerebra, Shanghai Institute of Mate- ria Medica; Fig. 1) is a natural Lycopodium alkaloid found in extracts from Huperzia serrate [207]. It was launched in China for the treatment of AD in 1995. The drug is administered in low oral doses of 0.1 mg four times a day. Huperzine A blocked AChE with an IC\textsubscript{50} of 62 nM and BChE with an IC\textsubscript{50} of 74.43 \mu M [208, 209]. Huperzine A is 35-fold more potent than (+)-huperzine A (K\textsubscript{i} = 6.2 nM and 210 nM, respectively [210]), corroborating earlier K\textsubscript{i} values of 8 nM and 300 nM [211]. Molecular modeling studies revealed that huperzine A binds to the bottom of the binding cavity of AChE with its ammonium group interacting with Trp-84, Phe-330, Glu-199, and Asp-72 (catalytic site) and to the opening of the gorge with its ammonium group interacting with Trp-279 (peripheral site) [212]. Tyr-337 is essential for inhibition of recombi- 

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Currently huperzine A is produced in large scale from natural sources, in particular from Phlegmariu- 

rus squarrosus, a member of the Huperziaceae [215], although several chemical synthesis schemes were worked out [208, 216–222]. A large-scale synthetic route resulted from a joint venture by process chemists of Shasun Pharma (UK and India), Rhodia Pharma (USA), and Debiopharm (Switzerland) [223].

There are currently 358 publications on huperzine A listed in PubMed (as of August 29, 2012). Excellent reviews on the pharmacology of huperzine A have been published (in chronological order) [224–230]. In particular, the neuroprotective effects of huperzine A have been investigated in great detail, e.g., protective effects against Aβ- 

associated neurotoxicity [231–235]. Huperzine A dose 
dependently increased secretary amyloid-β protein precursor (AβPP) release suggesting a modulatory effect of huperzine A on α-secretase activity [236, 237]. These findings were confirmed independently [238, 239]. This mechanism seems to play via Wnt/β-catenin signaling. Chronic administration of huperzine A to double transgenic mice led to an increase in ADAM10 and a decrease in β-secretase-1 and AβPP\_{66} protein levels [240]. Recently huperzine A was also evaluated in triple transgenic mice con- firming the improvement of cognitive performance and the non-amyloid pathway activation [241].

Reviews on results of clinical trials of huperzine A were published [242–244]. A Phase II clinical study in 210 AD patients treated with either placebo, 200 \mu g bid, or 400 \mu g bid of huperzine A (70 patients per arm) showed no effect in the 200 \mu g group, but huperzine A 400 \mu g bid showed a 2.27 point improvement in ADAS-cog at 11 weeks versus a 0.29 decline in the placebo group (p = 0.001) [245] (Thomson Reuters Pharma, update of February 20, 2012).

The company Xel Pharmaceuticals (Draper, Utah) is developing the once-weekly sustained release transder- 
al patch formulation XEL-001HP. This formulation is currently tested in a Phase I clinical trial in China since September 2008. Xel Pharmaceuticals is also investigating the sustained release topical gel formulation XEL-001HG in preclinical evaluation
Novartis chemists synthesized novel analogues of huperzine A. The program was terminated [246].

WIN-026 (INM-176, KR-WAP-026; WhanIn under license from Scigenic & Scigen Harvest) is an AChE inhibitor with antioxidant and anti-Aβ properties containing a 95% extract of Angelica gigas Nakai in the pre-registration phase [247]. In June 2008, a Phase III clinical trial for the treatment of AD was initiated, which was completed by May 2011. The results were submitted to the Korean FDA. Launch is expected for the second half of 2012. The memory ameliorating effects of INM-176 in mice were described [248] (Thomson Reuters Pharma, update of May 30, 2012).

Posiphen (the (+)-enantiomer of phenserine, QR Pharma under license from TorreyPines Therapeutics, Fig. 2) is in Phase II clinical trials for the oral treatment of AD since June 2009. It was effective to lower Aβ levels in cell cultures and in mice [249]. Interestingly, posiphen also blocked the expression of brain α-synuclein [250, 251]. Posiphen is a candidate drug to lower CSF AβPP, Aβ peptide, and tau levels in humans [252] (Thomson Reuters Pharma, update of July 25, 2012).

Shen Er Yang (Changchun Huayang High Technology Co Ltd., Shanghai, Fig. 2) is a tablet formulation of 1,2,3,4,5,6,7,8-octohydro-9-phenylacetamidoacridine, a dual cholinesterase inhibitor in preclinical evaluation (in alphabetical order):

Bisnorcymserine (QR Pharma, under license from TorreyPines Therapeutics; Fig. 2) is a dual BChE and AβPP inhibitor. An IND was cleared by the FDA in December 2010. The inhibition of serum BChE by bisnorcymserine was reported [260]. For the crystal structure of the complex, see [261] (Thomson Reuters Pharma, update of July 25, 2012).

Bis(7)-tacrine (Mayo Foundation; Fig. 2) was one of the first homodimers reported in the literature with increased potency as AChE inhibitor (IC50 = 0.4 nM with significantly less affinity to BChE (IC50 = 390 nM), selectivity for AChE is a factor of 980) [262]. For a more detailed description of bis(7)-tacrine, see section 2.1.1.5. Dual AChE inhibitors and calcium channel blockers.

FS-0311 (Shanghai Institute for Materia Medica; Fig. 2) is a bis-huperzine B derivative with similar potency for the inhibition of AChE as donepezil but higher potency than huperzines A and B. It antagonized cognitive deficits induced by scopolamine or by transient brain ischemia [263].

Huprines (tacrine-huperzine A hybrids, Fig. 2) were presented by scientists of the University of Autonoma de Barcelona [264–269] and independently from the University of Hong Kong [270]. French scientists also significantly contributed to novel huprine derivatives [271–273]. The best characterized huprines are huprine-X (3-chloro-9-ethyl), huprine-Y (3-chloro-9-methyl), and huprine-Z (3-fluoro-9-methyl). They are very potent AChE inhibitors with KI values of 0.026 nM for huprine-X and 0.033 nM for huprine Y versus 31 nM for tacrine, 1.1 nM for donepezil, and 4.6 nM for huprinez A [267]. Other scientists measured IC50 values of 0.78 nM for (±)-huprine-Y and 4.58 nM for (±)-huprine-Z in human AChE preparations [274]. (±)-Huprine-X is an agonist at M1 muscarinic acetylcholine receptors (K I = 338 nM) and at M2 mAChRs (K I = 4.66 μM) [275]. The binding of huprine-X to Torpedo californica AChE was resolved in an X-ray structure at 2.1 Å resolution [276]. Huprine-X facilitated learning and memory in the Morris water maze [277]. Chronic treatment of TG2576 (AβPP+++) mice and of 3xTgAD mice with 0.12 μmol/kg huprine-X i.p. for 21 days caused a significant reduction of insoluble Aβ40 by 40% (p < 0.05) in the hippocampus of 3xTgAD mice while showing no effect in AβPP+++ mice [278]. Additional data on huprine X in triple transgenic mice were disclosed recently [241].

Another way to create huperzine A-tacrine hybrids is to link the primary amino group of huperzine A to the primary amino group of tacrine with methylene groups [279]. The best compounds showed KI values against...
human AChE of 6.4 nM versus 0.026 for huprine-X. A group of Spanish and Italian scientists described huprine-tacrine heterodimers [280, 281].

Dimerization of an inactive fragment of huperzine A led to bis-(12)-hupyridone (Hong Kong University, Fig. 3) displaying an IC50 = 52 nM versus 115 nM for huperzine A [282]. The tether length of 12-13 methylene groups is consistent with simultaneous binding to both the catalytic and the peripheral site of AChE (see Fig. 5). Bis-(12)-hupyridone may also act via α7 nicotinic acetylcholine receptors [283].

NP-0336 (Noscira) is a BChE inhibitor in preclinical evaluation (Thomson Reuters Pharma, update of July 19, 2011). The structure was not communicated.
**Fig. 3.** Acetylcholinesterase inhibitors in preclinical evaluation II.

**Fig. 4.** Dual acetylcholinesterase and muscarinic M₃ ACh receptor blocker.

**SPH-1285** (Sanochemia Pharmazeutika, formerly Waldheim Pharmazeutika; Fig. 3 shows SPH-1286) is a neuroprotective derivative of galantamine for the potential treatment of glaucoma (Thomson Reuters Pharma, update of January 3, 2012).

The most potent AChE inhibitor is the molecule syn-1 (Fig. 3) with $K_d$ of 77 fM synthesized at the Scripps Research Institute linking a tacrine part via click chemistry to a phenanthridium unit. The tacrine part is binding to the catalytic site (see Fig. 5), the
Fig. 5. Indole-tacrine heterodimers binding simultaneously to the catalytic and the peripheral anionic site of acetylcholinesterase [381]. With permission from ACS Publications.

phenanthridium piece is located at the peripheral site (see Fig. 5) [284].

Many new scaffolds for AChE inhibitors were discovered recently, such as benzoxazolinones [285], indolizinoquinoline [286], isoindoline-1,3-diones [287], pyrrolo thiazoles [289], quinazolines [290], and quinoline derivatives [291] acting as AChE inhibitors. Also tacrin-ferulic acid-nitric oxide (NO) donor trihybrids were presented [292].

Excellent reviews describe quantitative structure activity relationships (QSAR) [293, 294], virtual screening techniques [295], and the use of support vector machines for a classification of AChE inhibitors [296]. High throughput screening and molecular modeling for novel AChE inhibitors was discussed [297].

The development of many AChE inhibitors was terminated (in alphabetical order) of amiridin (ipi-dacrine hydrochloride; Nikken Chemicals [298–300]), AP-2238 (University of Bologna [301–303]), BZYX (Zhejiang University), CI-1002 (Parke-Davis, now Pfizer), CHF-2822 and CHF-2957 (Chiesi), EN-101 (a orally active 20-base antisense oligonucleotide directed against an AChE sequence; Amarin under license from Yissum [304]), etaptastigmine (MF-201; Mediolanum [305–309]), ER-127528 (Eisai), F-3796 (Pierre Fabre), FR-152558 (Fujisawa), galantamine liposomal (Sanacemia), ganstigmine (CHF-2819; Chiesi [310–315]), Hoe-065 (Hoechst, now sanofi [316–318], HIP-290 (Hoechst, now sanofi), icopezil (CP-118954; Pfizer [319]), JES-9501 (dehydroxyo-diamine hydrochloride, DHED; Feil Pharmaceuticaless in collaboration with Seoul Univ.), LB-1003 (Lifelike Biomatic), metrifonate (BAY-a-9826, ProMen; Bayer [320–324]; MF-268 and MF-8615 (Mediolanum), MIPA-133 (Medical College of Georgia), mimopezil (DEBio-9902, ZT-1; Debiopharm under license from the Shanghai Institute of Materia Medica; a once–daily produg, a Schiff base of hyponine A with 2-hydroxy-3-methoxy-5-chloro-benzaldehyde [319], NP-7557 (Nastech [325]), XXX-866 (Astra), P26 (Phytopharm), P-10358, P-11012, P-11149, and P-11467 (Hoechst Marion Roussel, now sanofi), phenserine and (-)-phenserine (Axonyx under license from NIH, Daewoong Pharmaceuticals [326–329]), of controlled release and transdermal formulations of physostigmine (Forest Laboratories, Lohmann Therapie Systeme [330–332]), protezia (PEG-rBChe; PEGylated recombinant human butyrylcholinesterase; PharmAtheyne under license from Nexia Biotechnologies; a protein produced in the milk of goats in a pegylated formulation; the development as post-exposure therapy for chemical nerve agent, currently in Phase I trials, is ongoing [333, 334]), Ro-46-5934 (Roche; a dual AChE inhibitor and M_2 muscarinic acetylcholine receptor antagonist), RS-1439 (Sankyo; a dual AChE and serotonin re-uptake inhibitor), S-9977 (Servier; a dual AChE and serotonin re-uptake inhibitor), SDZ-ENX-792 (Sandoz, now Novartis), SM-10888 (Sumitomo [335–337]), SPH-1359 (Sanacemia), stacofylline (S-9977; Servier [338–341]), suronacrine (HIP-128; Hoechst, now sanofi [342, 343]), T-82 (SS Pharmaceuticals, a subsidiary of Boehringer Ingelheim and Arena [344, 345]), toberine (Astonyx under license from NIH [346–349], UCB-11056 (UCB), velnacrine (HIP-029; Hoechst, now sanofi [350, 351]), of zanapezil (TAK-147; Takeda [352, 353]) and of zifrosilone (MDL-73745, Hoechst Marion Roussel, now sanofi [354–356]).

2.1.1. Drugs inhibiting AChE and other biological targets

Tremendous efforts have been undertaken to combine AChE inhibition and interaction with multiple targets thought to be responsible for AD pathogenesis to create “multi-target-directed ligands” [357–370].
2.1.1.1. Dual AChE inhibitors and AChE receptor ligands. Caproctamine (University of Bologna; Fig. 4) is a potent AChE inhibitor (IC₅₀ = 104 nM) and a competitive M₄ muscarinic acetylcholine receptor antagonist (IC₅₀ = 410 nM) [371].

MHP-133 (Medical College of Georgia; Fig. 4) is an AChE inhibitor interacting with M₄ muscarinic acetylcholine, 5-HT₄, and I₂ imidazoline receptors [372, 373].

Ro-46-5934 (Hoffmann-La Roche, Fig. 4) is a dual AChE inhibitor and M₂ AChR antagonist for the potential treatment of AD. The development was discontinued [374].

An attempt to combine tacrine and xamensoline led to hybride compounds displaying potent acetyl and BChE inhibition (pIC₅₀’s of 8.2 and selectivity ratio of 1.0). The hybrides did not bind as agonists to the orthosteric muscarinic acetylcholine M₄ receptor but as antagonists to an allosteric site of the M₁ AChR thereby reducing the amount of acetylcholine [375].

2.1.1.2. Dual AChE and amyloid-β inhibitors. AChE colocalizes with Aβ peptide deposits in the brains of AD patients and promoted Aβ fibrillogenesis by forming stable AChE-Aβ complexes. AChE bound through its peripheral site to the Aβ nonamyloidogenic form and acted as a pathological chaperone inducing a conformational transition to the amyloidogenic form [376–380].

One approach is to design ligands binding to both the catalytic as well as to the peripheral anionic site of AChE inhibitors (Fig. 5) [381].

After first attempts [301, 302, 371, 382–384] an important breakthrough was achieved with NP-61.

NP-61 (NP-0361, Noscira, previously Neurorhema) is a once-daily dual binding site AChE and Aβ secretion inhibitor currently in Phase 1 clinical trials for the treatment of AD. The structure was not disclosed, but is probably a combination of 6-chloro-tacrine (binding to the catalytic binding site) linked via a methylene bridge from the primary amine to the amide nitrogen of indole propionamide binding at the peripheral binding site [381]. Key biological data on NP-61 were published: inhibition of AChE: IC₅₀ = 20 pM, inhibition of BChE: IC₅₀ = 2.9 nM, inhibition of Aβ₄₀ aggregation with human AChE: in the thioflavin T test: IC₅₀ = 2.3 µM, inhibition of Aβ₄₀ aggregation without AChE in the thioflavin T test: 49% at 100 µM [385, 386]. NP-61 was able to reverse cognitive impairment tested in the Morris water maze and to reduce plaque load in cortex and hippocampus of 6 month-old human AβPP (Swedish mutation) transgenic mice treated once daily by oral gavage for three months (the doses were not communicated) (Thomson Reuters Pharma, update of May 10, 2012).

IDN-5706, a hyperforin derivative, decreased the content of AChE associated with different types of Aβ plaques in 7-month-old double AβPP/PS1 transgenic mice after treatment with IDN 5706 for 10 weeks [387]. See also Part 3, Chapter 13. Natural Products.

IQM-622 (Neuroscience Group and CSIC, Madrid; Fig. 6) significantly decreased the brain Aβ deposits after treatment of AβPP/PS1 mice for four weeks. It promoted the degradation of intracellular Aβ in astrocytes and protected against Aβ toxicity in cultured astrocytes and neurons (chemistry: [388]; biology: [389]).

This is an area of research with numerous novel contributions presenting new piperidinium-type compounds [390], new piperidine derivatives [391], donepezil-type inhibitors [392], novel pyrazolo[3,2-c]quinoline-6-chlorotacrine hybrids [393], pyridylidenedane hydrazones [394], novel bis(7)-tacrine derivatives [395], hybrid compounds combining donepezil and AP2238 [303], heterodimers of entanipure huprine X or Y and donepezil-type derivatives [396], 2,4-disubstituted pyrimidine derivatives [397, 398], novel triazole-containing berberine derivatives [399], huprine-tacrine heterodimers [400, 401], isaimdigu-tone derivatives [402], and oxosaporphine-based inhibitors [403]. Berberine derivatives act as multifunctional agents of antioxidant, inhibitors of AChE, BChE, and Aβ aggregation [404].

Bisnoryclosmerine (QR Pharma, under license from TorreyPines Therapeutics; see Fig. 2) is a dual BChE and AβPP inhibitor.

2.1.1.3. Dual AChE inhibitors and antioxidants. Lipocrine (University of Bologna; Fig. 6) is a combination of 6-chloroatracine with α-lipoic acid [405]. It has been shown that α-lipoic acid is an universal antioxidant [406–408], which protected rat cortical neurons against cell death induced by Aβ. Lipocrine inhibited AChE with an IC₅₀ of 0.25 nM and BChE with 10.8 nM within 1 minute. It inhibited the aggregation of Aβ with an IC₅₀ of 45 µM and showed significant antioxidant activity against formation of reactive oxygen species in SH-S15Y cells after treatment with tert-butylhydroperoxide at 5 µM (p < 0.01), 10 µM (p < 0.001), and 50 µM (p < 0.001) [409].

Memoquinn (University of Bologna; Fig. 6) is a combination of the polyamine amide caproctamine [371] showing AChE and M₄ muscarinic ACh receptor blocking properties with a 1,4-benzoquinone
Fig. 6. Dual acetylcholinesterase inhibitors with amyloid-β inhibitor, antioxidant, BACE-1 inhibitor, and calcium channel blocker activities.

functionality derived from coenzyme Q or idebenone as a radical scavenger [366, 410, 411]. It inhibited AChE with an IC50 of 1.55 nM, human AChE-induced aggregation of Aβ[1-40] with an IC50 of 28.3 μM and Aβ[1-42] self-aggregation with an IC50 of 5.93 μM. NAD(P)H:quinone oxidoreductase 1 (NQO1) is the enzyme responsible for the regeneration and maintenance of the CoQ-reduced state. Memoquin is a good substrate for NQO1 with a Km of 12.7 μM. In addition, memoquin also effectively blocked β-secretase-1 with an IC50 of 108 nM. The compound reduced the number of Aβ plaques in transgenic AD11 mice after oral administration and rescued behavioral deficits in an object recognition test in transgenic AD11 mice [412].

Introduction of methyl groups in the α-position of the terminal benzylamine moieties (Fig. 6; Memoquin, R = Me, both in (R)-configuration) led to an improved derivative (inhibition of AChE with IC50 of 0.5 nM, inhibition of human AChE-induced aggregation of Aβ[1-40] with IC50 of 9.34 μM [413, 414].

Combination of the 2,5-diamino-benzoquinone scaffold with curcumin derived substituents is another way to multitarget-directed ligands [415]. Dual-acting drugs with extremely potent AChE inhibiting activity and antioxidant properties were presented [416]. Hybrids between 6,8-dichlorotacrine and melatonin showed an IC50 of 8 pM against human AChE and potent peroxyl radical absorbance
Berberine derivatives act as multi-functional agents of antioxidant, inhibitors of AChE, BChE, and Aβ aggreg- 

tion [422].

2.1.1.4. Dual AChE and β-secretase-1 or γ-secretase inhibitors. Memoquin (University of Bologna, Fig. 6) is a potent inhibitor of AChE with an IC_{50} of 1.55 nM and of β-secretase-1 with an IC_{50} of 108 nM (see previous section 2.1.1.3.).

Coumarin derivatives are also dual human AChE and β-secretase-1 inhibitors [423]. Inhibitions of AChE with IC_{50} of 180 nM and of β-secretase-1 with IC_{50} of 150 nM were measured.

Researchers from the Shanghai Institute of Materia Medica presented a dual inhibitor of AChE: IC_{50} = 1.83 μM and of β-secretase-1: IC_{50} = 0.507 μM [424].

A tacrine-chromene derivative with cholinergic, antioxidant, Aβ reducing, and BACE1 inhibiting properties showed the following values: AChE: IC_{50} = 75 nM, BChE: IC_{50} = 1 nM, β-secretase-1: IC_{50} = 2.8 μM [425]. Quinoxaline-based hybrid compounds with AChE, histamine H3 receptor, and β-secretase-1 inhibitory activities were described [426].

Galantamine-based hybrid molecules with AChE, BChE; and γ-secretase inhibiting activities have been presented recently [427].

2.1.1.5. Dual AChE inhibitors and calcium channel blockers. Bis(7)-tacrine (Mayo Foundation, see Fig. 2), first synthesized in 1996 [262], is a very potent AChE inhibitor with IC_{50} of 0.4 nM [434]. It caused an elevation of the cytosolic concentration of Ca^{2+} in fura 2-loaded bovine chromaffin cells from concentrations of 10 to 250 nM, which was related to the induction of protein synthesis relevant for cell survival. This cytoprotective action of ITH-4012 was reversed by the protein synthesis inhibitor cycloheximide.

ITH-12118 (CSIC Madrid, Fig. 6), a tacrypryne, combines tacrine and a L-type voltage-dependent calcium channel blocker of the nimodipine type. The synthetic work was described in [435, 436] and the extensive biological characterization in [437] showing that ITH12118 could be a paradigmatic multitarget compound having selective brain effects with smaller peripheral side effects. Additional chemical and pharmacological studies were published [438].

The development of NP-34 (or NP-04634, Noscira, formerly Neuropharma), a natural product derived from the marine sponge Aplysina cavernicola with calcium channel blocking and AChE inhibiting properties was terminated [439].

2.1.1.6. Dual AChE, inhibitors and cannabinoid receptor antagonists. CB1 receptor antagonists increased ACh release in certain brain areas including cortical regions and the hippocampus [440]. The CB1 antagonist scaffolds of diaryl-pyrazolines and diaryl-imidazoles [441, 442] were combined with tacrine. Compound 20 (Solvay, now Abbott, Fig. 7) displayed an IC_{50} of 316 nM for acetylcholinesterase and a K_{i} of 48 nM for CB1 receptors. The K_{i} for CB2 receptors was > 1 μM [443].

2.1.1.7. Dual AChE & fatty acid amide hydrolase inhibitors. In regions of Aβ-enriched neuritic plaques an increased activity of the enzyme fatty acid amide hydrolase (FAAH) was selectively demonstrated [444]. Inhibitors of FAAH may regulate endocannabinoid signaling and may counteract neuroinflammation. First dual cholinesterase and FAAH inhibitors were synthesized at the University of Bologna [445]. One carbamate derivative (shown in Fig. 7) displayed IC_{50} of 50 nM for FAAH, 74.9 nM for human AChE, and 1.57 nM for human BChE.

MIQ-001 (Meta-IQ Aps) is a fatty acid metabolism inhibitor for the potential treatment of AD. A Phase I healthy volunteer study was performed with doses from 6 to 100 mg/day starting in February 2010. No side-effects were observed. Meta-IQ generated excel-
Fig. 7. Dual acetylcholinesterase & fatty acid amide hydrolase inhibitor, dual acetylcholinesterase inhibitor & cannabinoid, and histamine H3 receptor antagonists.

In lent preclinical data showing efficacy in restoration of short and long term memory in an AD mouse model (Thomson Reuters Pharma, update of June 25, 2012). The structure was not communicated.

The development of AMR-109 (Amarin Corp., ultra-pure eicosapentanoic acid), a modulator of omega-3 fatty acids, was terminated. For the neuroprotective effects of eicosapentenoic acid against Aβ induced impairment of LTP and memory, see [446–448]. For a review on polyunsaturated fatty acids as cognitive enhancers see [449].

2.1.1.8. Dual AChE inhibitors and histamine H3 receptor antagonists. FUB833 (Freie University of Berlin; Fig. 7) is a potent AChE inhibitor (IC50 = 2.6 nM), BChE inhibitor (IC50 = 8.8 nM), hH3 receptor antagonist (Ki = 0.33 nM) inhibiting also histamine N-methyltransferase (HMT with IC50 = 48 nM) [450].

University of Parma medicinal chemists described potent dual non-imidazole histamine H3 receptor antagonists and AChE inhibitors [451]. Quinoxaline-based hybrid compounds with AChE, histamine H3 receptor, and β-secretase-1 inhibitory activities were described [452].

2.1.1.9. Dual AChE and monoamine oxidase inhibitors. Increased monoamine oxidase (MAO) B activity was found in AD brains [453]. A combination of AChE and of MAO B inhibitors in one molecule was attempted already in 1996 [454, 455]. The breakthrough was achieved with Ladostigil.

Ladostigil (TV-3326; Avraham Pharmaceuticals under license from Yissum Research Development, a wholly owned company of the Hebrew University of Jerusalem; Fig. 8) combines the carbamate moiety of the BChE inhibitor rivastigmine with the propargylamine pharmacophore of the MAO-B inhibitors selegiline and rasagiline. Ladostigil is more potent against BChE (IC50 = 1.7 µM) than against AChE (IC50 = 51 µM). It is a central nervous system (CNS)-selective inhibitor of MAO-A and MAO-B with little inhibition of liver and small intestine MAO.
Propargylamines are irreversible inhibitors of MAO, therefore the long-term daily administration results in a cumulative effect. 50 μmol/kg given daily for 7 and 14 days inhibited both MAO-A and MAO-B by >60%. 80% inhibition of the brain enzymes was achieved with a dose of 75 μmol/kg given once daily for 2 weeks [456]. Ladostigil was extensively characterized [357, 457–472].

Ladostigil is currently in Phase Ib clinical trials in 190 patients in Europe since December 2010 for the oral treatment of AD. In February 2012 a Phase II trial was initiated in Israel and Europe in patients suffering from mild cognitive impairment (Thomson Reuters Pharma, update of May 18, 2012). See also section 2.26. Drugs interacting with Monoamine Oxidase.

Spanish medicinal chemists described potent dual cholinesterase and MAO inhibitors [473–475].

2.1.1.10. Dual AChE inhibitors and metal chelators. HLA20A (Technion Haifa, Fig. 8) is a combination of an 8-hydroxy-quinoline metal chelator, which was carbamoylated at the 8-hydroxy function to interact with AChE as does rivastigmine [476, 477]. Inhibition of AChE was measured with IC50’s of 0.5 μM and for BChE with 42.58 μM. Interaction with AChE readily cleaved the carbamoyl moiety to release the chelator readily forming complexes with FeSO4 and CuSO4. The prochelator is nontoxic to human SH-SY5Y cells at 25 or 50 μM. A recent review described the field in great detail [478].

Novel indanone derivatives were designed as AChE inhibitors and metal-chelating agents [479].

2.1.1.11. Dual AChE inhibitors and N-methyl-D-aspartic acid receptor channel blockers. Carbacrine (University of Bologna, Fig. 9), a potent AChE inhibitor (IC50 = 2.15 nM), and weak inhibitor of BChE (IC50 = 296 nM), blocked AChE-induced Aβ aggregation to 58% at 100 μM and Aβ self-aggregation to 36% at 50 μM and inhibited NMDA receptors with an IC50 of 0.74 μM. It is a noncompetitive open-channel blocker. In the ORAC test carbacrine was a good antioxidant (IC50 = 0.07 μM), more potent than trolox [480].

University of Jena researchers presented bivalent β-carbolines as dual AChE inhibitors and NMDA receptor blockers such as compound 22b (Fig. 9): IC50 = 0.5 nM for AChE, 5.7 nM for BChE, and 1.4 μM for the NMDA receptor, respectively [481].

Bis(7)-tacrine (Mayo Foundation, Fig. 2, see section 2.1.1.5. Dual AChE inhibitors and calcium channel blockers) inhibited NMDA receptors with an IC50 of 763 nM [431].

2.1.1.12. Dual AChE inhibitors & platelet activating factor antagonists. PMS-777 (University of Paris 7-Denis Diderot and Shanghai Jiao Tong University, Fig. 10), synthesized in 1996 [482, 483], is a tetrahydrofuran derivative, which inhibited AChE (IC50 = 2.48 μM), BChE (IC50 = 4.47 μM), and acted as platelet factor antagonist (IC50 = 12.5 μM) [484–490]. It inhibited Aβ-induced human neuroblastoma SH-SYSY cell apoptosis in a concentration dependent manner. It decreased reactive oxygen species up to 32%, NO production up to 5 times, and TNFα release by 33% (Thomson Reuters Pharma, update of June 20, 2012).
Fig. 9. Dual acetylcholinesterase inhibitors and NMDA receptor blockers.

PMS-1339 (University of Paris 7-Denis Diderot and Shanghai Jiao Tong University; Fig. 10) is a novel piperazine derivative, which inhibited AChE (IC₅₀ = 4.4 μM) and BChE (IC₅₀ = 1.09 μM), Aβ aggregation (recombinant human AChE-induced: IC₅₀ = 45.1 μM), and acted as platelet factor antagonist (IC₅₀ = 332 nM) [491] (Thomson Reuters Pharma, update of June 20, 2012).

2.1.1.13. Dual AChE and serotonin transporter inhibitors. RS-1259 (BGC-20-1259; BRG under license from Daiichi Sankyo; Fig. 10) is a dual inhibitor of AChE (IC₅₀ = 101 nM) and of the serotonin transporter (IC₅₀ = 42 nM). It significantly ameliorated the age-related short-term memory impairment at a dose of 1 mg/kg in rats 24-25 months of age [492]. At 2 mg/kg RS-1259 was also effective in recovering from memory deficits. For the design, synthesis and structure-activity relationships see [493–495]. Its development was terminated.

2.1.1.14. Dual AChE and sigma receptor inhibitors. SP-04 (Samaritan Pharmaceuticals; Fig. 10) is an inhibitor of ACHE and of sigma-1 receptors. For synthesis and biological evaluation, see [496] (Thomson Reuters Pharma, update of March 23, 2011).

The development of igmaesine (JO-1784; Jouveinal, now Pfizer) was terminated. See Part 1, Chapter 1.28, Drugs interacting with Sigma receptors.

2.2. Drugs interacting with alpha-secretase

α-Secretase cleaves AβPP at the Lys16-Leu17 bond within the Aβ sequence to generate the soluble N-terminal AβPP fragment (sAβPPα) and the membrane bound CTF83 (carboxy-terminal fragment of 83 residues in length) thus precluding the formation and subsequent deposition of Aβ. The activation of the α-secretase processing of AβPP as a therapeutic approach in AD was reviewed [497–501]. The activation of α-secretase is controlled by the protein phosphorylation signal transduction pathway of protein kinase C (PKC). A review on α-, β-, and γ-secretases in AD was published [502].

Etazolate (EHT-0202; SQ-20009; Exonhit; Fig. 10) is an orally active phosphodiesterase (PDE) 4 inhibitor and anxiolytic GABAA receptor modulator. Etazolate dose-dependently increased the secreted levels of non-amyloidogenic sAβPPα in cortical neurons of rats thus shifting AβPP processing toward the α-secretase pathway [503]. Etazolate improved the memory performance in aged rats [504]. The results of the first Phase II 3-month, randomized, placebo-controlled, double-
blind study in AD patients were reported [505]. The drug was shown to be safe and well tolerated (Thomson Reuters Pharma, update of September 13, 2011). 

Bryostatin-1 (Blanchette Rockefeller Neuroscience Institute) is a naturally occurring PKC activator isolated from the Californian marine bryozoan Bugula neritina. Bryostatin-1 increased brain levels of sAβPP and reduced brain Aβ40 levels, which may be explained by activation of α-secretase [499, 506]. In February 2012, the Institute was preparing to initiate clinical trials in neurological disorders. Chemistry and biology of bryostatins was reviewed [507] (Thomson Reuters Pharma, update of February 24, 2012). See also section 2.35. Drugs interacting with Protein Kinase C.

NP-17, NP-21, NPM-01, NPM-05B1, and NPM-05B2 (Noscira) are orally available α-secretase activators of marine origin for the potential treatment of AD (Thomson Reuters Pharma, updates of July 27, 2011). The structures were not communicated.

Many compounds shifted AβPP processing toward the α-secretase pathway in in vitro experiments, such as muscarinic acetylcholine receptor agonists, MAO-B inhibitors, statins, non-steroidal anti-inflammatory drugs (NSAIDs), neuropeptides such as PACAP, estrogen, and others [499]. However, the benefit for AD patients in clinical trials was (so far) disappointing.

2.3. Drugs interacting with β-secretase

In the amyloidogenic pathway, AβPP is first cleaved by β-secretase (BACE1, EC 3.4.23.46 [508, 509]) between residue methionine 671 and aspartic acid 672 to release a 100 kDa N-terminal fragment sAβPP and a 12 kDa membrane bound CFT99, which is subsequently cleaved by γ-secretase within the transmembrane region to form C-terminal Aβ peptides ranging from 38 to 43 residues. β-secretase was cloned simultaneously by five groups in 1999 and early 2000: at Amgen [510, 511]; at Elan [512], at Pharmacia & Upjohn, now Pfizer [513], at GSK [514], and at the Oklahoma Medical Research Foundation [515]. It is a 501 amino acid protein with two active
site motifs at amino acids 93-96 and 289-292. It is structurally related to renin, cathepsins D and E, pepsinogens A and C, and the retroviral aspartic proteases [516, 517]. The β-secretase-1 gene was described [518] as was the cell biology, regulation, and inhibition of β-secretase-1 [519]. For the enzymatic activities of β-secretase-1 and β-secretase-2 (BACE2; EC 3.4.23.45) in AD, see [520]. β-secretase-1 is also required for myelination and correct bundling of axons by Schwann cells [521, 522].

An X-ray crystal structure of β-secretase-1 bound to an octapeptidic inhibitor OM99-2 was published [523, 524]. Apo and inhibitor complex structures of β-secretase-1 at the resolution of 1.75 Å were determined [525]. X-ray crystal structures of β-secretase-1 bound to a macrocyclic peptidomimetic [526] and to a spiropepiderine iminohydantoin were communicated [527], as was the crystal structure of an active form of β-secretase-1 [528].

β-secretase-1 knockout mice are healthy despite lacking the primary β-secretase activity in the brain [529, 530]. β-secretase-1 null mice are rescued by Aβ-dependent hippocampal memory deficits [531]. A rare gene mutation in the AβPP was identified in an Icelandic population by scientists of deCode genetics, which protects against AD and age-related cognitive decline. This A671T mutation is directly associated with cognitive decline. This A673T mutation is directly associated with cognitive decline.

In view of the importance of the amyloid hypothesis for AD, it is not surprising that many pharmaceutical companies embarked on medicinal chemistry programs to discover β-secretase inhibitors (in alphabetical order): Actelion, Ailostera, ALSp, Amgen, Archer Pharmaceuticals, Astellas, Astex Therapeutics, AstraZeneca, BACE Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, CoMentis (company of Prof. Jordan Tang), Critical Outcome Technologies, De Novo Pharmaceuticals, DuPont Pharma, Elan, Envoy Therapeutics, Evotec, Genetics Company, GlaxoSmithKline, IntellHept, JADO Technologies, Johnson & Johnson, Kyoto University, LG Life Sciences, Ligand Pharmaceuticals, Lilly, Locus Pharmaceuticals, Medivir, Merck, NasVax, Noscira, Novartis, Pfizer, ProMediTech, Roche, Samada Research, sanofi, Schering-Plough, Senex Biotechnology, Shionogi, Sibia, Sunesis Pharmaceuticals, Takeda, Trans-Tech Pharma, Vertex Pharma, Vitae Pharmaceuticals, and Wyeth. In addition, there are numerous excellent papers by competent synthetic organic chemists and molecular modelers working at universities. The problems of β-secretase inhibitors are mostly due to their peptidomimetic structures displaying high molecular weight, high polar surface area, low oral bioavailability, metabolic instability, low blood brain barrier penetration, and susceptibility to P-glycoprotein transport out of the brain.


LY-2886721 (Eli Lilly) was in two Phase I clinical trials since June 2010 (n = 50) and December 2010 (n = 60) in the US. The studies were completed in October 2010 and in April 2011, respectively. In April 2012 a randomized, double-blind, placebo-controlled, Phase II study (NCT01561430) was initiated in patients with mild cognitive impairment due to AD (expected n = 129) in the US and is scheduled to complete in December 2013. For medicinal chemistry, see [582–586] (Thomson Reuters Pharma, update of July 27, 2012). The structure was not communicated.

CTS-21166 (ASP-1702, ATG-Z1; Astellas Pharma and CoMentis) is a β-secretase-1 inhibitor in Phase I clinical trials since June 2007. In 48 volunteers, the drug was safe and well tolerated (Thomson Reuters Pharma, update of July 10, 2012). The structure was not communicated.

E-2609 (Eisai) is a β-secretase inhibitor in Phase I clinical trials since December 2010 in the US in healthy young and elderly volunteers (n = 48). The trial was completed in May 2012. Multiple ascending oral doses of E-2609 (25 to 400 mg for 14 days) were studied at a single site in the US in this ongoing trial in healthy human volunteers of 50 to 85 years of age (both genders). The drug was safe and well tolerated with minor adverse effects. Reductions of Aβ in CSF and plasma were demonstrated following both single and repeated administrations (Thomson Reuters Pharma, update of August 07, 2012). The structure was not communicated.

HPP-854 (TTP-854; High Point Pharmaceuticals, a spin-out from TransTech Pharma) is a β-secretase inhibitor in Phase I clinical trials since November 2009 (Thomson Reuters Pharma, update of April 5, 2012). The structure was not communicated.

MK-8931 (SCH-900931; Schering-Plough, now Merck; Fig. 11) is an inhibitor of β-secretase in Phase I clinical trials since October 2009 (n = 40). In April 2012 data were presented from a two-part,
Fig. 11. Beta-secretase inhibitors.
randomized, double-blind, placebo-controlled single rising-dose study (n = 40). Single doses of MK-8931 from 2.5 to 550 mg were well-tolerated [587]. For medicinal chemistry, see [548, 588-593] (Thomson Reuters Pharma, update of August 13, 2012).

For further documentation on the impressive β-secretase-1 inhibitor research program ongoing at Merck see (in chronological order): [594–621 [2]].

At the occasion of the 244th ACS meeting in Philadelphia Merck presented a bicyclic iminoheterocycle compound (Fig. 11) with an optimized thiazidine subunit with high affinity for β-secretase. RG-7129 (Roche from a research collaboration with SigmaBiotec) is a small molecule β-secretase (BACE) inhibitor in Phase I development since September 2011 (Thomson Reuters Pharma, update of August 8, 2012). The structure was not communicated. See also the interesting papers [621, 622].

Several β-secretase inhibitors of known structure are in preclinical evaluation (in alphabetical order).

- **Amgen** (presumably AC-3; AMG-0683; Fig. 11) investigated series of 2-aminooquinolines and 2-aminopyridines as β-secretase-1 inhibitors [623]. Hydroxyethylamine containing β-secretase inhibitors were described very recently [624, 625] (Thomson Reuters Pharma, update of July 31, 2012).

- **AZ-13** (Astellas Pharmaceuticals and AstaZeneca; Fig. 11) at 50, 75, 100, or 300 mmol/kg achieved a concentration-dependent decrease in Aβ42, Aβ40, and sAβPP levels in brain and plasma of C57BL/6 mice. For medicinal chemistry, see [626–629] (Thomson Reuters Pharma, update of August 2, 2012).

- **Bristol-Myers Squibb** (Fig. 11) is investigating a series of 7-aza-indole compounds with IC50 values of 10 nM against BACE-1 and 800 nM against BACE-2. For medicinal chemistry, see [630–635] (Thomson Reuters Pharma, update of August 8, 2011).

- **Elan** (Fig. 11) presented data on hydroxyethylamine β-secretase-1 inhibitors with IC50 values against β-secretase-1 of 12 nM and an ED50 value of 2.1 nM in a HEK-293 cellular assay. For medicinal chemistry, see [636–643] (Thomson Reuters Pharma, update of August 13, 2012).

- **Johnson & Johnson** (presumably NJ-J-71574s, Fig. 11) is evaluating compounds from a series of aminopiperazines with an IC50 of 40 nM in a β-secretase-1 enzymatic assay, of 28 nM for hAβ40, and 25 nM for hAβ42Total. Many medicinal chemistry papers were communicated [644–649] (Thomson Reuters Pharma, update of January 18, 2012).

- **KMI-000**, **KMI-358**, **KMI-370**, **KMI-426**, **KMI-429**, **KMI-574**, **KMI-1027**, and **KMI-1303** (Kyoto Pharmaceutical University) are potent BACE1 inhibitors [650–665]. KMI-429 (Fig. 12) is a β-secretase-1 inhibitor with enhanced cell membrane permeability (IC50 = 3.9 nM). KMI-574 (Fig. 12) is a β-secretase inhibitor produced by substituting the side chain of KMI-429 with a bioequivalent material to enhance blood-brain barrier permeability (IC50 = 5.6 nM). KMI-1027 (Fig. 12) is a low molecular weight β-secretase inhibitor with enhanced in vivo enzyme stability and blood-brain barrier permeability (IC50 = 50 nM). KMI-1303 (Fig. 12) is a β-secretase-1 inhibitor with higher affinity for active site pockets (IC50 = 9 nM). The structures were obtained from the Wako Online Catalog. Research for Alzheimer’s Disease, edition November 2011.

- **L-655240** (Merck, Fig. 12) is a thromboxane A2 antagonist, which was re-discovered as a BACE1 inhibitor with IC50 of 4.47 μM by Chinese authors [666].

- **Novartis** (Fig. 11) investigated a series of cyclic sulf oxide hydroxyethylamine β-secretase-1 inhibitors. The compound reduced CSF and brain Aβ1-42 levels in a dose-dependent manner and showed good efficacy at a 10 fold lower dose, when co-administered with the CYP3A4 inhibitor ritonavir in various animal models. For medicinal chemistry, see [667–671]. (Thomson Reuters Pharma, update of July 5, 2011).

- **TAK-070** (University of Tokyo under license from Takeda) is a β-secretase and Aβ aggregation inhibitor (Thomson Reuters Pharma, update of June 8, 2012). The structure was not communicated.

- **WAY-258131** (Wyeth, now Pfizer; Fig. 11) inhibited β-secretase-1 with an IC50 value of 10 nM and reduced Aβ1-40 with an IC50 value of 20 nM. For medicinal chemistry, see [672–689] (Thomson Reuters Pharma, update of August 15, 2012).

Several companies have β-secretase inhibitors in preclinical development, whose structures were not communicated (in alphabetical order): Allosterix, BACE Therapeutics, Boehringer Ingelheim, Envoy Therapeutics [690], Evotec [691, 692], II Dong Pharma (Seoul), Intellilife (heparinoid β-secretase inhibitors), LG Life Sciences [693], ProModTech, Samuda Research, Vitae Pharmaceuticals in collaboration with Boehringer Ingelheim and the Technical University of Munich [694, 695].

A dual β-secretase-1 inhibitor and metal chelator was described [696].

Dual α7 nicotinic acetylcholine receptor activators and β-secretase-1 inhibitors are investigated in a program at the University of Maryland (Thomson Reuters Pharma, update of February 24, 2012).
Fig. 12. Beta-secretase inhibitors II.
JADO Technologies synthesized a membrane-anchored version of a β-secretase transition-state inhibitor by linking it to a sterol moiety. This inhibitor reduced enzyme activity much more efficiently than the free inhibitor in cultures and in vivo [697].

BBS-1 BACE inhibitor mAb vaccine (NasVax under license from Ramot at Tel Aviv University) is investigating a vaccine based on its lead mAb candidate BBS-1 (blocking β-site-1), which inhibits the ability of β-secretase-1 to cleave AβPP (Thomson Reuters Pharma, update of July 30, 2011).

Antibodies directed against the β-secretase cleavage site of AβPP were described [698, 699].

Brain-targeted BACE1 antibody (Genentech, Roche Holding) is a bs-specific antibody against β-secretase-1 and the transferrin receptor to allow transcytosis across the blood-brain barrier [700, 701] (Thomson Reuters Pharma, update of May 14, 2012). This technique was pioneered by W. M. Paradigm of UCLA [702–708].

Excellent papers on β-secretase-1 inhibitors from universities were presented (in alphabetical order of their location): Mahidol University Bangkok [709, 710], University of Darmstadt [711], TU Dresden [712], University of Duisburg-Essen [713], Gwangju Institute of Science and Technology Korea [714], Linköping University [715], University of Liverpool [716, 717], University of Marseille [718], Max-Planck-Institut für Biochemie Martinsried [719], University of Montpellier [720–722], Technical University Munich [695], Peking University [723], University of Pisa [724–726], Purdue University [536, 559, 561, 727, 728], Sapienza University Rome [729], Shanghai Institute of Materia Medica [730, 731], Shujitsu University [732], Stockholm University [733–735], University of South Florida Tampa [736], University of Tokyo [665], SISSA-IBAS Trieste [737], CNRS Valbonne [738, 739], and Uppsala University [740–743].


Several companies or institutions seem to have abandoned the search for novel β-secretase-1 inhibitors, such as Actelion, De Novo, the Genetics Co (Callisto-Gen), Ligand, Locus Pharmaceuticals, Medivir [779], Noscira, and Plexxikon.

The development of allosteric peptide BACE-1 inhibitors (Allosterix), of ARC-069 (Archer Pharmaceuticals), AZD-3839 (AstraZeneca [780, 781]), BACE inhibitors (BACE Therapeutics, Evotec, Samada Research, and ProMediTech/LG Life Sciences), GRL-8234 (Oklahoma Medical Research Foundation [782]), GSX-188999 (GSX [783–791]), LY-2811376 (Lilly [792]), SIB-1281 (Sibia), of TAK-070 (Takeda [793, 794]), and of TC-1 (Merck under license from Sunesis [795, 796]) was terminated.

2.4. Drugs interacting with γ-secretase

γ-secretase is an aspartyl protease that cleaves its substrates within the transmembrane region in a process termed regulated-intramembrane-proteolysis (RIP). The enzyme consists of four protein components: presenilin 1 or 2, which contains the catalytic domain, nicastrin, Aph-1 (anterior pharynx-1), and Pen-2 (presenilin enhancer-2) in a 1:1:1:1 ratio [797]. It is hypothesized that the free N-terminus of a γ-secretase substrate first binds to the ectodomain of nicastrin (a 709 amino acid type 1 membrane glycoprotein), which may facilitate its interaction with the docking site on presenilin followed by relocation to the active site on presenilin, where it is cleaved [798–812]. γ-secretase cleaves AβPP transmembrane domain in a progressive stepwise manner at the e, ζ, and γ-sites, resulting in Aβ species of varying length. This stepwise cleavage may occur via two different routes. They initiate with the formation of Aβ1–42 and Aβ1–40 and then proceed via the cleavage at approximately every three residues, i.e., every helical turn of the substrate. The two product lines are e40–46–43–38–40 and e48–44–42. Further cleavage will subsequently generate the other isoforms Aβ1–39, Aβ1–38, and Aβ1–37, of which Aβ1–38 results from the product line containing Aβ1–40 [813–816]. The mechanism of γ-secretase dysfunction in familial AD was addressed [817].

γ-secretase also cleaves other protein substrates, e.g., Notch, Jagged, and Nectin 1 [818–821]. γ-secretase cleavage of Notch leads to the release of the smaller cytosolic fragment NICD (Notch intracellular domain) important in signal transduction pathways. γ-secretase inhibitors that are not Notch-sparing may cause severe gastrointestinal toxicity and interfere with the maturation of B- and T-lymphocytes in mice [822–827]. Note that AβPP interacts with Notch receptors [828].

The first proof that γ-secretase inhibitors reduced Aβ peptide levels in the brain was published already in 2001 by Elan scientists [829].

In view of the importance of the amyloid hypothesis for AD, it is not surprising that many pharmaceutical companies embarked on medicinal chemistry
programs to discover γ-secretase inhibitors and modulators (in alphabetical order): Archer Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb, Cellzome, Eisai, Eli Lilly, EnVivo Pharmaceuticals, Harvard Medical School, Intra-Cellular Therapies, Janssen, Lilly, Merck, Myriad Genetics, NeuroGenetic Pharmaceuticals, Ortho-McNeil, Pfizer, Roche, TorreyPinesTherapeutics and Wyeth (now Pfizer). There are many highly interesting publications on medicinal chemistry and pharmacology of γ-secretase inhibitors and modulators reviewed (in chronological order) 2002: [539, 830–834]; 2003: [835]; 2004: [836, 837]; 2005: [838, 839]; 2006: [556, 557, 840–843]; 2007: [819]; 2008: [844]; 2009: [809, 845–847]; 2010: [848, 849]; 2011: [577, 850]; 2012: [851, 852]. A review on the molecular modeling and the design of γ-secretase inhibitors was presented [607]. Many excellent reviews on the therapeutic potential of γ-secretase inhibitors and modulators were published [850, 853–863].

2.4.1. Gamma-secretase inhibitors

Avagacestat (BMS-708163; Bristol-Myers Squibb; Fig. 13) is an orally active γ-secretase inhibitor that selectively inhibited Aβ production. A Phase II trial in 200 AD patients was initiated in February 2009; a second Phase II trial in 270 prodromal AD (mild cognitive impairment) patients over a period of 104 weeks was initiated in May 2009. First reports on the tolerability profile, pharmacokinetic parameter, and pharmacodynamics markers were published [864–866] [3]. A sensitive and selective LC-MS/MS method for determination of avagacestat in plasma and CSF was published [867, 878] (Thomson Reuters Pharma, update of January 2012). The structures were not communicated. For medicinal chemistry, see [885, 916–919, 895, 896, 920–927] (Thomson Reuters Pharma, update of November 24, 2011).

NGP-555 (NeuroGenetic Pharmaceuticals, Fig. 14) has an IC50 value of 8.3 nM. It reduced levels of Aβ42 in brain and plasma at doses up to 100 mg/kg p.o. Chronic treatment with 50 mg/kg for 7 months significantly reduced the percentage area of plaques in mouse brains. There was no evidence of notch-mediated GI toxicity [928]. A potential follow-up compound may be NGP-328, whose structure was not disclosed (Thomson Reuters Pharma, update of June 4, 2012).

Pepscan Therapeutics is investigating a series of peptide-based γ-secretase inhibitors for the potential treatment of AD (Thomson Reuters Pharma, update of April 1, 2011). The structures were not communicated.

Pfizer (Fig. 14) presented a novel γ-secretase inhibitor containing a bicyclo-[1.1.1]-pentanyl moiety with an IC50 of 0.178 nM being equipotent to avagacestat (IC50 = 0.196 nM) [929]. For additional medicinal chemistry papers from Pfizer, see [930–935] (Thomson Reuters Pharma, update of July 30, 2012).

E-2212 (Eisai), a γ-secretase inhibitor, is in Phase I clinical evaluation since January 2010 (n = 91). The structure of E-2212 was not communicated. E-2212 replaces the abandoned γ-secretase modulator E-2012 (Thomson Reuters Pharma, update of March 15, 2011).

\[ \text{E-2212 (Eisai), } \gamma \text{-secretase inhibitor, is in Phase I clinical evaluation since January 2010 (n = 91).} \]

The structure of E-2212 was not communicated. E-2212 replaces the abandoned γ-secretase modulator E-2012 (Thomson Reuters Pharma, update of March 15, 2011).

\[ \text{E-2212 (Eisai), } \gamma \text{-secretase inhibitor, is in Phase I clinical evaluation since January 2010 (n = 91).} \]

The structure of E-2212 was not communicated. E-2212 replaces the abandoned γ-secretase modulator E-2012 (Thomson Reuters Pharma, update of March 15, 2011).

\[ \text{E-2212 (Eisai), } \gamma \text{-secretase inhibitor, is in Phase I clinical evaluation since January 2010 (n = 91).} \]
Excellent papers on theoretical calculations on γ-secretase inhibitors have been presented (in chronological order) [960–967].

Critical Outcome Technologies is investigating orally available, dual β- and γ-secretase inhibitors (Thomson Reuters Pharma, update of June 24, 2011).

The development of several γ-secretase inhibitors was terminated, of ARC-069 (Archer Pharmaceuticals, Roskamp Institute), begacestat (GSI-953; WAY-210953; PF-5212362; Wyeth, now Pfizer [809, 968–974]), BMS-299897 (Bristol-Myers Squibb; [975–978]), BMS-433796 (Bristol-Myers Squibb [869, 979]), E-2012 (Eisai), ELND-006 and ELND-007 (both Elan [944–946, 980, 981]; GSI-136; Wyeth, now Pfizer [982]), MK-0752 (Merck; in Phase II for the treatment of cancer, but terminated for the indication of AD [983]), PF-03084014 (Pfizer; in Phase I for the treatment of cancer, but terminated for the indication of AD [984–987]), RO-4929097 (RG-4733; Roche, for the indication breast cancer [988–993]), semagacestat (LY-450,139; Eli Lilly [931, 932, 994–1010]) and of SR-973 (DuPontScios, now Bristol-Myers Squibb).

2.4.2. Gamma-secretase modulators

A γ-secretase modulator interacts with allosteric binding sites at the protease complex shifting the proteolytic processing of AβPP toward higher production of shorter Aβ species such as Aβ40 at the expense of the highly toxic Aβ42 isoform. Impairment of Notch processing and signaling was not observed [1011]. Reviews on γ-secretase modulators were presented (in chronological order) 2005: [1012]; 2006: [556, 557, 1013]; 2007: [1014, 1015]; 2008: [833, 1016–1019]; 2010: [821]; 2011: [1020, 1021]; 2012: [1022–1024].

Tarenflurbil (MPC-7869; (R)-flurbiprofen, Flurizan, Myriad Genetics, Loma Linda University; Fig. 14) is a COX inhibitor and γ-secretase modulator that selectively reduced the levels of Aβ42 in vivo [1025, 1026]. The IC₅₀ values for the inhibition of COX-1 are 44 μM, of COX-2: 123 μM, and of Aβ42: 280 μM [1027]. Chronic administration of R-flurbiprofen attenuated learning impairments in transgenic AβPPswe mice [1028]. Tarenflurbil upregulated nerve growth factor and brain-derived neurotrophic factor protecting both human neuroblastoma cell lines and primary neurons from cytotoxicity associated with exposure to Aβ42 or hydrogen peroxide [1029].
Tarenflurbil was tested in a Phase II study in 210 patients with doses of 400 mg and 800 mg twice per day or placebo for 12 months. Patients with mild AD in the 800 mg tarenflurbil group had lower rates of decline than those in the placebo group concerning activities of daily living. In patients with moderate AD 800 mg tarenflurbil twice a day had no significant effects on ADCS-ADL and ADAS-cog [1030].

Tarenflurbil was tested in a Phase III study in 1,684 patients, of which 1,046 completed the trial. Tarenflurbil had no beneficial effect on the co-primary outcomes for ADCS-ADL and for ADAS-cog [1031]; for commentaries see [1032–1034] (Thomson Reuters Pharma, update of August 24, 2012).

With the termination of the development of tarenflurbil, the NO-releasing flurbiprofen derivative HCT-1026 (NicOx) was also stopped. CHF-5074 (Chiesi Farmaceutici; Fig. 14) showed a concentration dependent inhibitory activity on Aβ/secretion (IC50 = 40 µM). At 300 µM, an inhibitory effect was detected on COX-1 (~40%), but not on COX-2 [1035]. It is devoid of Notch-interfering activities in vitro [1036]. Treatment of 6 months old hAβPP transgenic mice for 6 months significantly reduced the number of plaques in cortex and hippocampus, whereas ibuprofen did not reduce Aβ burden [1037].

CHF-5074 treatment of Tg2576 mice from 6 to 15 months of age resulted in a significant attenuation of the neurogenesis impairment in hippocampus [859, 1038]. For the reduction of the accumulation of hyperphosphorylated tau, see [1039], for the restoration of hippocampal plasticity in Tg2576 mice [1040] and for the effects in a mouse model of scrapie [1041].

CHF-5074 was tested in a double-blind, placebo-controlled Phase I ascending oral dose study in 48 healthy males with 200, 400, and 600 mg/day for 14 days (n=12 each per dose level and 12 receiving placebo). The drug was well tolerated. In March 2011, a Phase II trial was initiated in the US and in Italy (n=96). Trial completion is expected for July 2012 (Thomson Reuters Pharma, update of July 23, 2012).

EVP-0962 (EnVivo Pharmaceuticals) is a γ-secretase modulator in Phase I clinical evaluation since June 2011 in healthy volunteers. By June 2012, the Phase I trial was completed (Thomson Reuters Pharma, update of August 14, 2012). Its structure was not communicated.

Fig. 14. γ-secretase inhibitors and modulators.
Several γ-secretase modulators are currently in preclinical evaluation (in alphabetical order):

Amgen (Fig. 15) presented preclinical data on a novel γ-secretase modulator at the occasion of the 41st SFN Meeting in Washington in November 2011 (Thomson Reuters Pharma, update of December 6, 2011).

AZ-4800 (AstraZeneva; Fig. 15) at 75, 150, and 300 μmol/kg caused a dose dependent decrease of brain Aβ42 1.5 hours after administration to C57 mice (Thomson Reuters Pharma, update of April 1, 2011). For medicinal chemistry, see [1042, 1043]. AstraZeneva scientists described the detailed pharmacological evaluation of the γ-secretase modulators AZ3303 and AZ1136 (both Fig. 16) [1044, 1045]. The second generation γ-secretase modulators have different modes of action regarding Notch processing [1046] (Thomson Reuters Pharma, update of July 4, 2012).

BIIB-042 (Biogen Idec; Fig. 15) is a γ-secretase modulator, which significantly reduced brain Aβ42 levels in CF-1 mice and in Fisher rats and plasma Aβ42 levels in cynomolgus monkeys. For medicinal chemistry, see [1047, 1048] (Thomson Reuters Pharma, update of March 27, 2012).

GSM-2 (Merck UK [1049], Fig. 15), as was investigated by scientists of Astellas [1050], significantly ameliorated memory deficits in Tg2576 mice and did not affect normal cognition in wild-type mice. In contrast γ-secretase inhibitors avagacestat (BMS-708163) and semagacestat (LY-450139) on subchronic dosing impaired normal cognition in 3 month old Tg2576 mice. GSM-10h (GSK, Fig. 15) is an orally active piperidine-derived γ-secretase modulator [1051–1054]. GSK is also investigating γ-secretase modulators derived from pyridazines (Fig. 15) [1055] and from pyridines (Fig. 15) [1056] (Thomson Reuters Pharma, update of January 13, 2012).

Janssen described a novel series of bicyclic heterocycles as potent γ-secretase modulators [1057]. Merck (Fig. 16) is investigating γ-secretase modulators with fused 5,6-bicyclic heterocycles. The best compound had an EC50 of 122 nM for the inhibition of Aβ42 and exhibited good selectivity over overall γ-secretase inhibition (IC50 ratio of 38 fold). In rats, the compound reduced Aβ42 in the CSF by 26% after 3 hours at 30 mg/kg p.o. Medicinal chemistry was described (1058–1063). Important mechanistic insights were contributed [1064] (Thomson Reuters Pharma, update of August 15, 2012).

Pitzer medicinal chemists presented novel dihydrobenzofuran amides as orally bioavailable, centrally active γ-secretase modulators [1068] (Thomson Reuters Pharma, update of July 30, 2012).

Roche presented novel γ-secretase modulators at the occasion of the Alzheimer’s Association International Conference in Paris, France, July 16–21, 2011. One compound (Fig. 16) had an Aβ42 EC50 value of 0.1 μM and demonstrated dose-dependent efficacy in transgenic AβPPsw mice. CSF Aβ42 levels were reduced in non-transgenic rats for longer than 8 hours. A good pharmacokinetic profile was seen (Thomson Reuters Pharma, update of July 27, 2012).

SPI-014, SPI-1802, SPI-1810, and SPI-1865 (Satori Pharmaceuticals, Figure 16) are γ-secretase modulators reducing the levels of Aβ42 without altering total Aβ levels in cell lines and in animal models of AD (Thomson Reuters Pharma, update of July 31, 2012). The structures were not communicated.

TorreyPines Therapeutics presented a novel class of aminothiazoles as γ-secretase modulators. Compound 3 (Fig. 16) displayed an IC50 for Aβ42 of 5 nM [1069]. Excellent papers on theoretical calculations on γ-secretase modulators were presented from the University of Munich [1081, 1082], the University of Duesseldorf [1075], Emory University [1076], from the Mayo Clinic [1077], the Memorial Sloan-Kettering Cancer Center [1078–1080], the University of Munich [1081, 1082], and the University of Tokyo [1083]. Excellent papers on theoretical calculations on γ-secretase modulators were presented from the University of Duesseldorf [1084], the Massachusetts General Hospital [1085–1087], and Vanderbilt University [1088].

Dual modulators of γ-secretase and peroxisome proliferator-activated receptor γ (PPARγ) were presented to produce compounds with IC50 (Aβ42) of 5.1 μM and EC50 (PPARγ) of 6.6 μM [1089, 1090]. The development of JNJ-4018677 and JNJ-42601572 [Janssen, formerly Ortho-McNeil Pharmaceuticals, under license from Cellzome] [1091] was discontinued.

2.4.3. Inhibitors of gamma-secretase activating protein
 γ-secretase activating protein (GSAP) interacts both with γ-secretase and its substrate, the AβPP...
Fig. 15. γ-secretase modulators.
carboxy-terminal fragment (AβPP-CTF). Reducing GSAP concentrations in cell lines decreased Aβ concentrations, hence GSAP may be a new therapeutic target for AD [1092]. For a commentary, see [1093]. The immunohistochemical characterization of γ-secretase activation protein expression in AD brains was described [1094]; the purification and characterization of human GSAP [1095].

IC-200155 (Intra-Cellular Therapies) is a compound that decreases Aβ levels in the brain by
2.4.4. Notch pathway inhibitors

AGT-0031 (AxoGlia Therapeutics; Fig. 16) is an inhibitor of the Notch pathway, which is involved in astrocyte differentiation and inflammatory activation for the potential treatment of multiple sclerosis and AD (Thomson Reuters Pharma, update of February 29, 2012).

2.5. Drugs interacting with beta hexosaminidase

The first report of short-term memory deficits in a murine model of lysosomal storage diseases including Sandhoff disease was described [1096]. Amicus Therapeutics is investigating small molecule pharmacological chaperones that bind to and activate the lysosomal enzyme beta-hexosaminidase for the potential oral treatment of AD. These compounds lowered the levels of GM2 and GM3 gangliosides associated with Aβ aggregation (Thomson Reuters Pharma, update of March 28, 2012). No structures were communicated.

2.6. Drugs interacting with 11 beta hydroxysteroid dehydrogenase

The topic 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1), brain atrophy, and cognitive decline was reviewed [1097, 1098]. 11β-HSD1 expression was enhanced in the aged mouse hippocampus and caused memory impairment [1099]. Enhanced hippocampal LTP and spatial learning was found in 11β-HSD1 knockout mice [1100, 1101]. Partial deficiency or short term inhibition of 11β-HSD1 improved cognitive function in aged mice [1102, 1103]. Inhibition of 11β-hydroxysteroid dehydrogenase by carbenoxolone (100 mg three times per day) improved cognitive function in elderly men [1104]. ABT-384 (Abbott Laboratories) is in a double-blind safety/efficacy Phase II trial since May 2010 in patients (n = 260) with mild to moderate AD in the UK. Despite being safe, well tolerated and tested at doses associated with full inhibition of brain 11β-HSD-1 activity, it did not induce symptomatic improvement in...
mild to moderate AD during the 12-week trial period. Therefore the trial was terminated (Thomson Reuters Pharma, update of July 18, 2012). The structure of ABT-384 was not communicated.

KR-1-2 (Korea Research Institute of Chemical Technology) suppressed cortisol by inhibiting 11β-hydroxysteroid dehydrogenase type 1. The drug is intended for the treatment of glaucoma and dementia (Thomson Reuters Pharma, update of February 27, 2012).

UE-1961, UE-2811 (Univ. of Edinburgh in collaboration with Argenta Discovery), and UE-2343 (Univ. of Edinburgh in collaboration with Argenta Discovery) are inhibitors of 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) for the potential treatment of age-related cognitive disorders, such as memory loss [1102]. UE-2343 showed cognition enhancement in aged transgenic Tg2576 mice after one month of treatment in a passive avoidance test and a significant reduction of their Aβ plaque load (Thomson Reuters Pharma, update of March 15, 2012). Another class of 11β-HSD1 inhibitors, i.e., 1,5-substituted 1H tetrazoles, was described [1105].

2.7. Drugs interacting with calpain

The mechanistic involvement of the calpain-calpastatin system in AD neuropathology was reviewed [1106]. Calpain inhibitors for the treatment of AD were discussed [1107, 1108]. Over-activated calpain caused a down-regulation of cAMP-dependent protein kinase in AD brain [1109]. Neuronal over-expression of the endogenous inhibitor of calpains, calpastatin, in a mouse model of AD reduced Aβ pathology [1110].

A-705253 (Abbott, formerly Knoll; Fig. 17) is an orally active calpain inhibitor for the potential treatment of AD. A-705253 significantly reduced cholinergic neurodegeneration in a dose-dependent manner in rats [1111–1117]. It also prevented stress-induced tau hyperphosphorylation in vitro and in vivo [1118, 1119] (Thomson Reuters Pharma, update of May 16, 2011).

ABT-957 (Abbott) is a calpain inhibitor for the potential treatment of neurological disorders including AD (Thomson Reuters Pharma, update of March 2, 2012). The structure was not communicated.

SNJ-1945 (Senju Pharmaceutical; Fig. 17) is a potent calpain inhibitor for the potential oral treatment of age-related macular degeneration, retinopathy, and optic neuritis. Preclinical data were reported [1121–1124]. Medicinal chemistry papers were contributed [1125–1128] (Thomson Reuters Pharma, update of April 18, 2012).

The development of calpain inhibitors BDA-410 (Mitsubishi-Tokyo Pharmaceuticals), CEP-3122 (Cephalon, now Teva), EP-475 (University of Tennessee), MDL-28170 (Hoechst Marion Roussel, now sanofi [1129–1131]), and of TH-3501 (University of Virginia) was terminated.

2.8. Drugs interacting with carbonic anhydrase

Carbonic anhydrase dysfunction impaired cognition and was associated with mental retardation, AD, and aging [1132].

The Blanchette Rockefeller Neurosciences Institute is investigating phenylalanine compounds acting as carbonic anhydrase activators for the potential treatment of attention deficit disorders and memory problems in AD (Thomson Reuters Pharma, update of February 16, 2012).

2.9. Drugs interacting with caspases

Caspases, or cysteine-aspartic proteases or cysteine-dependent aspartate-directed proteases, are a family of cysteine proteases that play essential roles in apoptosis (programmed cell death), necrosis, and inflammation. For a review on caspase-6 and neurodegeneration, see [1133]; for the role of caspases in AD, see [1134–1138].

NWL-117 (New World Laboratories) is an irreversible inhibitor of active caspase-6 for the potential treatment of AD (Thomson Reuters Pharma, update of July 18, 2012). The structure was not communicated.

2.10. Drugs interacting with Catechol-O-methyltransferase (COMT)

The topic COMT, cognition, and psychosis was reviewed [1139–1141]. The potential role of COMT inhibitors for the treatment of cognitive deficits associated with schizophrenia was described [1142, 1143]. Tolcapone and Entacapone (Comtan; Orion in collaboration with
Novartis launched in 1999 blocked fibril formation of α-synuclein and AβI and protected against AβI-induced toxicity [1145].

The company Cerecor is investigating COMT inhibitors for the potential treatment of schizophrenia including cognition (Thomson Reuters Pharma, update of April 12, 2012). Structures were not communicated.

2.11. Drugs interacting with cathepsin

Reduction of cathepsin B in transgenic mice expressing human wild-type AβPP resulted in significantly decreased brain AβI [1146, 1147]. Higher cathepsin B levels were found in plasma of AD patients compared to healthy controls [1148].

Aloxistatin (E-64d; AB-007; ALP-496; ALSP; Fig. 17) is an inhibitor of cathepsin B for the potential treatment of AD and traumatic brain injury [1149–1152]. Aloxistatin was previously evaluated for the treatment of Duchenne muscular dystrophy by Taisho Pharmaceuticals, but the development was terminated (Thomson Reuters Pharma, update of June 29, 2012).

Acetyl-L-leucyl-L-valyl-L-lysinal (ALSP) is a cysteine protease inhibitor, which caused a significant reduction in brain AβI and β-secretase activity by approximately 50% after i.c.v. administration of 0.06 mg/g brain weight/day for 28 days [1153] (Thomson Reuters Pharma, update of June 28, 2012).

The development of CEL-5A (University of California at Irvine; a cathepsin D inhibitor) and eystatin C (New York University/Nathan Kline Institute, a cysteine protease inhibitor) was terminated.

2.12. Drugs interacting with cholesterol

Abnormal induction of the cholesterol-catabolic enzyme CYP46 in glial cells of AD patients was already recognized in 2001 by researchers at the Karolinska Institute [1154], followed by [1155–1157]. It was shown that polymorphism in the cholesterol 24S-hydroxylase (CYP46A1) gene (CYP46A1) is an enzyme that is responsible for the formation of prostaglandins, prostacyclin, and thromboxane. NSAIDs exert their effects through inhibition of COX. Oligomers of Aβ1-42 induced the activation of COX-2 in astrocytes [1169].

Epidemiological studies have documented a reduced prevalence of AD among users of NSAIDs [1170, 1171, 1026, 1172–1178]).

In the Rotterdam study, 6,989 subjects 55 years of age or older were analyzed for the association of NSAIDs use and AD. The relative risk of AD was 0.95 in subjects with short-term use (1 month) of NSAIDs, 0.62 in subjects with intermediate-term use (1 to 24 months), and 0.20 in those with long-term use (more than 24 months) [1179]. Several clinical trials using indomethacin, diclofenac/misoprostol, naproxen, nimesulide, celecoxib, and rofecoxib showed no benefit for AD patients, reviewed by [1177]. The ADAPT research group could not show a prevention of AD dementia in a clinical trial using naproxen and celecoxib [1180, 1181].

The NSAIDs ibuprofen, indomethacin, and sulindac sulfide preferentially decreased the highly amyloidogenic Aβ1-42 peptide [1172]. This effect was not mediated by inhibition of COX, but by an allosteric modulation of γ-secretase [1064] and by a change in presenilin 1 conformation [1182]. A list of compounds decreasing the formation of Aβ1-42 peptide comprising diclofenac, (R)-flurbiprofen, fenoprofen, ibuprofen, indomethacin, meclofenamic acid, and sulindac was presented [1183]. NSAIDs dose-dependently destabilized preformed Aβ fibrils in vitro [1184, 1185]. These effects were also shown in transgenic mice in vivo [1025, 1177].
Aβ42-lowering NSAIDs constitute the founding members of the new class of γ-secretase modulators [1186], vide supra section 2.4.2.

2.14. Drugs interacting with D-amino acid oxidase

The therapeutic potential of D-amino acid oxidase (DAAO) inhibitors was described [1187]. Several susceptibility genes for psychiatric disorders have been identified, among others G72, which is the D-amino acid oxidase activator [1188–1191].

AS-2651816-00 (Astellas Pharma) is a novel DAAO inhibitor for the potential treatment of schizophrenia (DAAO) inhibitors was described [1187]. Several susceptibility genes for psychiatric disorders have been identified, among others G72, which is the D-amino acid oxidase activator [1188–1191]. It is a 3-hydroxy-pyridazin-4(1H)-one, but the precise structure was not communicated.

Eisai following the acquisition of MGI Pharma was investigating DAAO inhibitors to enhance the activity of D-serine. The compound 6-chlorobenzo[d]isoxazol-3-ol (CBIO) showed an IC₅₀ of 200 nM. Its development was terminated. Also the development of DAAO inhibitors of Merck and Pfizer and of Eisai following the acquisition of MGI Pharma was investigated. The compound 6-chlorobenzo[d]isoxazol-3-ol (CBIO) showed an IC₅₀ of 200 nM. Its development was terminated. Also the development of DAAO inhibitors of Merck and Pfizer and of Eisai following the acquisition of MGI Pharma was investigated.

2.15. Drugs interacting with Glutaminyl Cyclase

Glutaminyl cyclase (QC) is an enzyme that catalyzes the formation of pyroglutamic peptides or proteins from a N-terminal glutamine residue. Human QC can perform in parallel the conversion of a N-terminal glutamate of a peptide to a pyroglutamated peptide. When Aβ is cleaved between amino acids 2 and 3, a peptide with a N-terminal glutamate is formed, which is cyclized by QC to the N-terminal pyroglutamate. This transformation renders the molecule more hydrophobic and increases its aggregation velocity [1192–1197]. Hence a QC inhibitor could prevent the formation of this species [1198–1204]. Secondary glutaminyl-cyclase inhibitor interactions were presented [4].

PB1-150 (Probiodrug; Fig. 18) is a potent inhibitor of human glutaminyl cyclase (IC₅₀ = 17 nM) and totally inhibits formation of Aβ1–11(EP)36-42 in cell culture at 1 μM (Thomson Reuters Pharma, update of February 24, 2012). A second generation of compounds was evaluated, in which the 1-propyl imidazole residue was replaced by the more rigid benzimidazole.

PQ-912 (Probiodrug) is a potent QC inhibitor in Phase I clinical studies with single- and multiple ascending dose, blinded, placebo-controlled, randomized in healthy volunteers (n = 100). First results showed that oral administration of PQ-912 was safe and well tolerated with relevant therapeutic levels in blood and CSF (Thomson Reuters Pharma, update of January 4, 2012). The structure of PQ-912 was not communicated.

2.16. Drugs interacting with glyceraldehyde-3-phosphate dehydrogenase

A proteomics analysis of the AD hippocampal proteome showed an increase of the levels of glyceraldehyde-3-phosphate dehydrogenase [1205]. A decrease of the activity of cerebral glyceraldehyde-3-phosphate dehydrogenase in different animal models of AD was observed [1206].

Omigapil (SNT-317, TCH-346, CGP-3466; Sanothers under license from Novartis; Fig. 18) is an orally bioavailable glyceraldehyde-3-phosphate dehydrogenase modulator with anti-apoptotic properties for the treatment of Parkinson’s disease and amyotrophic lateral sclerosis in Phase I clinical trials [1207–1221] (Thomson Reuters Pharma, update of April 11, 2012).

2.17. Drugs interacting with glycogen synthase kinase-3β (GSK-3β)

GSK-3β (EC 2.7.11.26, 47 kDa) is a serine/threonine protein kinase ubiquitously expressed and involved in many cellular signaling pathways playing a key role in the pathogenesis of AD. It is probably the link between Aβ and tau pathologies. GSK-3β induces memory deficits in vivo. Crucial is the phosphorylation at serine 9. The cited papers are listed in chronological order: 1999: [1222]; 2002: [1223–1225]; 2004: [1226–1228]; 2005: [1229]; 2006: [1230–1232]; 2007: [1233, 1234]; 2008: [1235–1240]; 2009: [1241–1243]; 2010: [1244, 1245]; 2011: [1246–1252]; 2012: [1253–1260]. GSK-3β was crystallized and the crystal structure was resolved [1261]. 3D-QSAR studies were reported [1263, 1264]. Ligand-based virtual screening was elucidated [1265]. Scoring functions were applied [1266].

Tideglsufib (NP-12, NP-031112; Nysta; Noscira, previously known as Neuropharma; Fig. 18) is the
Fig. 18. A glyceraldehyde 3-phosphate dehydrogenase modulator, a glutaminyl cyclase inhibitor, 10 glycogen synthase-3 and one HDAC inhibitor.
lead compound of a series of orally active thiazolidinediones, potent inhibitors of GSK-3 [1267]. A Phase Ib clinical trial in AD patients was initiated in Spain, Germany, Finland, and the UK in April 2011. In January 2012, randomization of patients (n = 308) was completed in the double-blind trial. Preliminary results are expected by the end of 2012. In December 2009, a Phase II trial for progressive supranuclear palsy was initiated in the US and in Europe. Enrollment was completed in October 2010 (n = 125). The drug was granted orphan status for progressive supranuclear palsy in November 2009. First positive results of a clinical pilot study were reported [1268]. (Thomson Reuters Pharma, update of July 23, 2012).

There are currently many GSK-3β inhibitors in preclinical evaluation (in alphabetical order):

AX-9839 (Actrix Biosciences, Kyorin Pharmaceuticals, Fig. 18) is an inhibitor of GSK-3β for the potential treatment of diabetes, AD, and various CNS disorders [1269] (Thomson Reuters Pharma, update of April 18, 2012).

CG-9, CG-701338, CG-701446, and CG-701448 (Crystal Genomics) are lead compounds from a series of GSK-3 inhibitors for the potential treatment of cancer, AD, and schizophrenia (Thomson Reuters Pharma, update of May 02, 2012). The structures were not communicated.

CP-70949 (Pfizer, Fig. 18) is a selective inhibitor of GSK-3β in preclinical evaluation [1270] (Thomson Reuters Pharma, update of July 11, 2011).

Dual GSK-3β/casein kinase 2 modulators (University of Illinois at Chicago) are investigated for the potential treatment of Alzheimer’s disease. (Thomson Reuters Pharma, update of September 20, 2012). Structures were not communicated.

GSK-3β inhibitors (Pfizer, Fig. 18) investigated a series of oxazole derivatives. The shown compound had an IC₅₀ of 5 nM and a more than 100-fold selectivity against all other kinases and met safety criteria (Thomson Reuters Pharma, update of Aug. 28, 2012).

JI-7263 (Jeil Pharmaceuticals) is the lead compound from a series of GSK-3β inhibitors for the potential treatment of AD and amyotrophic lateral sclerosis (Thomson Reuters Pharma, update of May 7, 2012). The structure was not communicated.

Mitsubishi-Tanabe (Fig. 18) presented a potent GSK-3β inhibitor at the AIMECS 11 meeting in Tokyo with an IC₅₀ of 12 nM (Thomson Reuters Pharma, update of January 24, 2012).

NNI-362 (NNI-AD; NeuroNascent) is a multikinase and GSK-3β modulator inhibiting several tau phosphorylation sites. Other orally active compounds that stimulate neuron formation are NNI-X01, NNI-C, and NNI-251 (Thomson Reuters Pharma, update of July 19, 2012). The structures were not communicated.

NP-101020 (Nosicra) is a GSK-3β inhibitor for the potential treatment of AD (Thomson Reuters Pharma, update of January 12, 2012). The structure was not communicated.

SN-2127 (AstraZeneca, Fig. 18) is one of several GSK-3β inhibitors in evaluation by AstraZeneca as SN-2568, SN-3728, and others (Thomson Reuters Pharma, update of April 4, 2012).

Takeda (Fig. 18) presented a very potent GSK-3β inhibitor with IC₅₀ of 2 nM. After oral administration a significant reduction of tau phosphorylation was observed in aged JNPL3 mice [1271–1273]. Thomson Reuters Pharma, update of January 04, 2012. The compound MMBO (Fig. 18) decreased tau phosphorylation and ameliorated cognitive deficits in a transgenic model of AD [1274].

TWS-119 (Scripps Research Institute; Fig. 18) is a compound that can induce neurogenesis in murine embryonic stem cells. The target of TWS-119 was shown to be GSK-3β by affinity-based and biochemical methods [1275].

VPL.15 (CSIC Madrid and University of Toronto, Fig. 18) is a dual GSK-3 and PDE7 inhibitor acting as an antipsychotic and cognitive enhancer in C57BL/6J mice [1276, 1277]. Extensive programs to identify GSK-3β inhibitors have been ongoing at AstraZeneca [1226, 1278–1280], at ChemDiv [1281], at GSK (e.g., SB-415286 and others [1282–1287]), at GVK Biosciences [1288], at Johnson & Johnson [1289–1292], at Kemira [1293], at Lilly [1294–1296], at Roche [1297], at Vertex [1298]), and at Yuyu in collaboration with CrystalGenomics [1299].

Potent GSK-3β inhibitors were described by researchers at universities (in alphabetical order of their location): University of Athens [1300], University Autonoma de Barcelona [1301], Technical University of Braunschweig [1302], University of Caen [1303, 1304], University of Illinois at Chicago [1305–1310], Technical University of Darmstadt [1311, 1312, 1313], Martin-Luther University Halle [1313], University of La Rochelle [1314], University of Leuven [1231, 1239–1241], CSIC Madrid [1315–1318], University of Louisiana at Monroe [1319], CNRS/Institut Curie Orsay [1320], Peking University [1321], Indian Institute of Technology Roorkee [1322], Korea Institute of Science and Technology Seoul [1323], Fudan University Shanghai [1324], and the University of Talca, Chile [1325].
SAR studies on GSK-3β inhibitors were published by researchers at the Technical University Darmstadt, University of Naples, University of Leuven, and Tel Aviv University [1326].

The Broad Institute is investigating ATP noncompetitive and allosteric inhibitors of GSK-3β (Thomson Reuters Pharma update of June 3, 2011).

DM-204 (DiaMedica following its acquisition of Sanomune) is a monoclonal antibody that inhibits GSK-3β (Thomson Reuters Pharma update of June 15, 2012).

The development of AR-A014418 (AstraZeneca) was terminated [1226, 1278–1280] as was NP-103 (Noscira) and UDA-680 (SAR-502250; Mitsubishi Pharma and sanofi). Also the development of Propentofylline (IWA 285; Hoechst Werke Albert, now sanofi) for AD and for vascular dementia has been terminated after results of the 72 week propentofylline long-term use (PLUS) clinical trial showed no treatment differences between the propentofylline-treated group and the placebo-treated group [1327–1331]. Propentofylline attenuated tau hyperphosphorylation by reducing the activated form of GSK-3β and by increasing the inactivated form of GSK-3β [1332]. Propentofylline is also a potent inhibitor of PDEs (see section 2.29.). The development of SAN-161 (Sanomune, a subsidiary of DiaMedica), SB-216763 (SmithKline Beecham, now GSK [1333], and the 4000 series (Xcellsyz, Lonza group) was terminated.

2.18. Drugs interacting with guanylyl cyclase

Soluble guanylyl cyclase may be required for emotional learning and for both reference and working memory [1334]. A selective irreversible inhibitor of soluble guanylyl cyclase, i.e., 1H-[1,2,4]-oxadiazole[4,3-a]-quinoxaline-1-one at doses of 5, 10, and 20 mg/kg impaired retention for the passive avoidance task in rats. Activation of soluble guanylyl cyclase and cGMP formation in the brain represents one element of effective neuroprotective pathways mediated by NO [1335]. The design and synthesis of nonmethylated oxadiazoles as NO-chimeras for neurodegenerative therapy was described [1336].

sGC-1016 (sGC Pharma) is a sustained-release NO mimetic for the potential treatment of AD in Phase I clinical trial, which was completed in July 2012 showing high bioavailability (Thomson Reuters Pharma, update of July 17, 2012). The structure was not communicated.

GT-715 and GT-1061 (Cita NeuroPharmaceuticals, Vernalis) were prototypes of engineered NO mimetics, which activated soluble guanylyl cyclase and increased cGMP formation. They improved task acquisition in cognitively impaired animals and in the 6-OHDA model of Parkinson’s disease [1337–1341]. The development of both compounds was terminated.

2.19. Drugs interacting with heme oxygenase

Glycine heme oxygenase-1 expression in AD and mild cognitive impairment was reviewed [1342–1346]. OB-28 (Osta Biotechnologies) is a heme oxygenase-1 inhibitor for the potential injectable treatment of AD showing statistically significant improvement in behavioral deficits in double transgenic (AβPPSWE/PS1dE9) mice (n=105) after treatment with 15 or 30 mg/kg/day for 4 months (Thomson Reuters Pharma update of August 6, 2012). The structure of OB-28 was not communicated.

2.20. Drugs interacting with histone deacetylase (HDAC)

An in depth overview shows how to target “the correct” HDAC(s) to treat cognitive disorders [1347]. The roles of HDAC inhibition in neurodegenerative conditions were discussed [1348]. The role of HDAC6 in Alzheimer’s disease was discussed [1349]. The loss of HDAC5 impaired memory function [1350]. EVP-0334 (EnVivo under license from Methyl-Gene) is developing the orally active HDAC inhibitor as a cognition enhancer for the potential treatment of AD. A Phase I clinical trial was started in May 2009 and finished in May 2010. Phase II trial are underway since November 2011. Medicinal chemistry papers were published [1351, 1352] (Thomson Reuters Pharma, update of August 10, 2012).

4-Phenylbutyrate (Digna Biotech SL) ameliorated cognitive deficits and reduced tau pathology in an AD mouse model [1353–1355], reduced Aβ plaques, and rescued cognitive behavior in AD transgenic mice [1356, 1357]. The drug is in Phase I clinical trials for the potential treatment of AD since April 2010 (Thomson Reuters Pharma update of May 30, 2012).

Other HDAC inhibitors are currently in preclinical evaluation (in alphabetical order): CHDI-390576 and CHDI-00381817 (HDAC4 inhibitors) are investigated by the CHDI Foundation in collaboration with BioFocus DPI (Thomson Reuters Pharma update of August 10, 2012). The structures were not disclosed.

Crebainostat (Harvard Medical School, Fig. 18) is a novel HDAC inhibitor and enhancer of CREB-
regulated transcription and modulator of chromatin-mediated neuroplasticity [1358].

KAR-3010, KAR-3084, and KAR-3166 (Karus Therapeutics) are HDAC6 inhibitors for the potential oral treatment of immune and inflammatory disease including AD (Thomson Reuters Pharma update of July 05, 2012). The structures were not disclosed.

LB-201 and LB-205 (Liste Biotechnology) are drugs that target HDAC and prevent the degradation and restore the activity of glucocerebrosidase for the treatment of neurological disorders such as Gaucher’s disease [1359] (Thomson Reuters Pharma update of April 05, 2012). The structures were not disclosed.

Dual PKC activators and HDAC inhibitors were described [1360]. The development of EHT-0205 (ExonHit) was terminated.

2.21. Drugs interacting with HMG-CoA reductase

The enzyme 3-hydroxy-3-methyl-glutaryl-CoA reductase (EC 1.1.1.88) is the rate-controlling enzyme of the mevalonate pathway, which produces cholesterol and other isoprenoids. It is the target of the statins (or HMG-CoA reductase inhibitors). In a large study comprising 9,844 participants at ages from 40 to 45 years the risk of AD was evaluated in relation to cholesterol levels. The analyses revealed that cholesterol levels >220 mg/dL were a significant risk factor for AD [1361]. See also the review [1362].

A lower prevalence of probable AD in a cohort of patients taking lovastatin or pravastatin between 60 and 73% (p < 0.001) lower than the total patient population or compared with patients taking other medications typically used for the treatment of hypertension or cardiovascular disease was found [1363–1367]. Excellent reviews were provided [1368–1375]. The link between altered cholesterol metabolism and AD was described [1376]. Statins, risk of dementia, and cognitive function were discussed [1377].

Statins can shift AβPP processing to the non-amyloidogenic α-secretase pathway, e.g., simvastatin, which in addition prevented neuroinflammation and oxidative stress [1378, 1379], atorvastatin, which in addition prevented neuroinflammation [1380, 1381] and lovastatin, which in addition stimulated the upregulation of α7 nicotinic acetylcholine receptors [1382, 1383]. Aβ42 blocked cerebral perivascular sympathetic α7-nAChRs, which was prevented by statins such as mevastatin and lovastatin [1384, 1385].

Pitavastatin attenuated celecoxib- and streptozotocin-induced experimental dementia [1386]. Atorvastatin and pitavastatin reduced senile plaque and phosphorylated tau in aged AβPP mice [1387, 1388].

These promising biological results in experimental animals were not confirmed in extensive clinical trials. Only a slight reduction of cognitive decline in a large study including 3,334 participants was found [1389]. A post hoc analysis from three double-blind, placebo-controlled, clinical trials of galantamine in patients with AD was done [1390]. Patients were divided into four treatment groups, statin plus galantamine (n = 42), statin alone (n = 50), galantamine alone (n = 614), and placebo (n = 619). Galantamine was associated with a significant beneficial effect on cognitive status (p < 0.001). The use of statins did not produce a significant beneficial effect (p = 0.083).

A proof-of-concept randomized controlled trial of Atorvastatin (Lipitor, Pfizer, launched in 1996) indicated a trend for symptomatic benefit in mild to moderate AD patients [1391–1393]. But the large LEAD (Lipitor’s effect in Alzheimer’s Dementia) study in 640 patients, who were randomized to atorvastatin 80 mg/day or placebo for 72 weeks followed by a double-blind, 8-week atorvastatin withdrawal phase did not show a significant benefit for cognition as measured by ADAS-cog (p = 0.26) or for global function as measured by ADCS-Clinical Global Impression of Change (p = 0.73) compared with placebo [1394, 1395].

Pravastatin (Pravachol, Mevalonat; Daiichi Sankyo, launched in 1989) was evaluated in PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) in 5,804 participants at six different time points. No difference in cognitive decline was found in patients treated with pravastatin compared to placebo (p > 0.05). During a three year follow-up period no effect on cognitive decline was observed [1396].

Simvastatin (Zocor, MK-0733; Merck launched in 1989) was evaluated in a 406 patient Phase III study conducted by the National Institute of Aging. Patients were treated with 20 mg simvastatin per day for six weeks and with 40 mg/day simvastatin for an additional 18 months. Simvastatin lowered lipid levels, but had no effect on change of ADAS-cog score or on secondary outcome measures [1397–1403]. Chronic simvastatin treatment rescued cognitive function in a transgenic mouse model of AD and enhanced LTP in the CA1 region of the hippocampus in slices from C57BL/6 mice via inhibition of farnesylat [1404–1406].
NST-0037 (Neuron BioPharma; Fig. 19) is a natural small molecule HMG-CoA-reductase inhibitor, which also has neuroprotective, antioxidant, and anti-convulsive activity. The synthesis was described [1407]. Potential follow-up compounds are NST-0005 and NST-0060, whereas the development of NST-0021 was terminated (Thomson Reuters Pharma, update of June 13, 2012).
2.22. Drugs interacting with insulin-degrading enzyme

The role of insulin-degrading enzyme in AD was discussed [1408, 1409]. The expression and functional profiling of insulin-degrading enzyme in elderly and AD patients was reported [1410] as was the characterization in human serum [1411].

The company Inventram is investigating insulin-degrading enzyme activators for the potential treatment of type 2 diabetes and AD (Thomson Reuters Pharma, update of April 20, 2012). No structures were communicated.

2.23. Drugs interacting with Kinases (≠ GSK-3β and ≠ PKC)

Advances in the development of kinase inhibitor therapeutics for AD were presented [1412]. Note-worthy is that acetetyl-L-carnitine (ST-200, Nicetile, Zibren; launched by Sigma-Tau in Italy in 1985 and in South Korea in 1995 as a memory enhancer) ameliorated spatial memory deficits induced by inhibition of phosphoinositol-3-kinase and PKC [1413]. Also clioquinol seems to operate in a similar way [1414].

Masitinib (AB-1010, AB Science, Fig. 19) is an inhibitor of c-kit, Lyn and PDGF-R kinases. It was evaluated in a Phase II clinical trial as an adjunct therapy to cholinesterase inhibitor and/or memantine in 26 patients with mild-to-moderate AD versus placebo (n = 8). The masitinib treated patients showed improvements in MMSE scores, the ADAS-Cog and improvements in ADL Inventory with statistical significance (p = 0.016 and 0.030, respectively) [1415]. In September 2010, EMA approved a pivotal Phase III trial in 300 AD patients to assess safety and efficacy of 6 mg/kg/day masitinib over 24 weeks. The biological characterization was described [1416] (Thomson Reuters Pharma, update of August 14, 2012). Structures were not communicated.

DYRK-1 alpha protein kinase inhibitors (Carma Biosciences) is a program in the stage of lead optimization. (Thomson Reuters Pharma, update of March 16, 2012). Structures were not communicated.

DYRK-1 alpha protein kinase inhibitors (Afraxis) showed IC50 values of 23, 58, and 14 nM for p21-activated kinase. The drugs have a potential for the treatment of fragile X syndrome, autism, schizophrenia, and AD (Thomson Reuters Pharma, update of August 14, 2012). Structures were not communicated.

G-2019S (Zenobia Pharmaceuticals in collaboration with Johns Hopkins University) is a LRRK2 inhibitor for the potential treatment of Parkinson’s disease (Thomson Reuters Pharma, update of March 13, 2012). The structure was not communicated.

Hydroxy-fasudil (Fig. 19, Asahi Kasei Pharma Corp.), a rho kinase (ROCK) inhibitor, improved spatial learning and working memory in rats in a water radial-arm maze [1420]. ROCK inhibition led to an increase of Rac1 activity and to an activation of PKC, which in turn phosphorylated KIBRA involved in the formation of memory [1421].
ROCK inhibition prevented tau hyperphosphorylation [1422].

KIBRA pathway modulators (Amneisix Inc., a wholly owned subsidiary of SYGNIS Pharma) offer a new genetic link to cognition that may benefit patients suffering from AD. For the association of KIBRA and late onset AD, see [1423], for enhancement of cognition in anxiety disorders [1424] (Thomson Reuters Pharma, update of August 14, 2012).

LDN-22684 (Sirtris Pharmaceuticals) is a LRRK2 inhibitor for the potential treatment of Parkinson’s disease [1425] (Thomson Reuters Pharma, update of June 17, 2011). The structure was not communicated.

LRRK2 inhibitors (Arriend Pharmaceuticals) are investigated for the potential oral treatment of Parkinson’s disease (Thomson Reuters Pharma, update of May 18, 2012). The structures were not communicated.

LRRK2 inhibitors (Genentech, Fig. 19) are investigated for the potential treatment of Parkinson’s disease. The medicinal chemistry was described [1426]. (Thomson Reuters Pharma, update of June 26, 2012). The lead structure was communicated.

LRRK2 inhibitors (Genosome, Oscotec Inc.) are investigated for the potential treatment of Parkinson’s disease (Thomson Reuters Pharma, update of April 20, 2012). The structures were not communicated.

LRRK2 inhibitors (Ontodesign Biotechnology) are investigated for the potential treatment of cancer and CNS diseases including Parkinson’s disease (Thomson Reuters Pharma, update of April 2, 2012). The structures were not communicated.

LRRK2 inhibitors (Oregens GmbH) are investigated for the potential treatment of Parkinson’s disease (Thomson Reuters Pharma, update of May 11, 2012). The structures were not communicated.

LRRK2 inhibitors (Pfizer) are investigated for the potential treatment of Parkinson’s disease (Thomson Reuters Pharma, update of June 20, 2012). The structures were not communicated.

LRRK2 inhibitors (Vernalis/Lundbeck) are investigated for the potential treatment of Parkinson’s disease (Thomson Reuters Pharma, update of June 20, 2012). The structures were not communicated.

MARK inhibitors (microtubule affinity regulating kinase; Medical Research Council Technology, MRCT) are investigated for the inhibition of tau phosphorylation (Thomson Reuters Pharma, update of June 1, 2012). The structures were not communicated.

MARK3 inhibitors (microtubule affinity regulating kinase 3; CDC5L-associated kinase 1; Merck) are in preclinical evaluation for the potential treatment of AD. The pyrazolo[1,5-a]pyridine compound (Fig. 19) showed t1/2’s in rat, dog, and Rhesus monkey of 3.5, 2.3, and 1.4 hours, respectively (Thomson Reuters Pharma, update of April 14, 2011).

Minokine (MW01-2-069A-SRM; Northwestern University; Fig. 19) is a p38 MAP kinase inhibitor for the potential oral treatment of neurodegenerative diseases including AD (Thomson Reuters Pharma, update of April 27, 2011).

NNI-351 (NNI-depression, NNI-DS, NeuroVascents; Fig. 19) is an orally active compound preventing stress-induced neurogenesis reduction via inhibition of dual specificity tyrosine-phosphorylation-regulated kinase 1 alpha (DYRK-1α) protein (Thomson Reuters Pharma, update of March 22, 2012).

P-005 (NB Health Laboratory) is a small molecule highly selective kinase inhibitor for the potential treatment of AD (Thomson Reuters Pharma, update of December 23, 2011). The structure was not communicated.

Protein kinase inhibitors (ManRos Therapeutics) are evaluated as AD medication (Thomson Reuters Pharma, update of February 24, 2011). The structures were not communicated.

SEL-103 (Selvita Life Sciences Solutions) is a program in collaboration with Orion Corporation, Espoo Finland, to investigate novel, orally bioavailable and highly selective small molecules for the potential treatment of multiple cognitive disorders including AD (Thomson Reuters Pharma, update of July 4, 2012).

SEL-141 (Selvita Life Sciences Solutions) is a program targeting kinases involved in tau phosphorylation for the potential treatment of AD, Down syndrome, and cognitive disorders. Focus is on DYRK1A (Thomson Reuters Pharma, update of July 4, 2012). Structures were not communicated.

Sorafenib, a small molecular inhibitor of tyrosine protein kinases (VEGFR and PDGFR) and of raf restored working memory in AβPPsw/25 transgenic mice [1427].

TTT-3002 (Taurixis) is a multi-targeted kinase inhibitor that can inhibit the LRRK2 gene and tumor growth for the potential treatment of Parkinson’s disease, AD, and cancer (Thomson Reuters Pharma, update of January 25, 2012). The structure was not communicated.

URMC-099-C (Califa, the University of Nebraska Medical Center and the University of Rochester) is an inhibitor of mixed lineage kinase-3 for the treatment of HIV-associated neurocognitive disorder (Thomson Reuters Pharma, update of July 26, 2011). The structures were not communicated.
Inhibitors of the protein kinase c-raf1, such as GW-5074 and ZM-336372, protected cortical cells against Aβ toxicity [1428]. The development of A1Kch2 (Allinkki Biopharma; a MAP kinase inhibitor), BA-1001 (BioAxone; a rho kinase inhibitor [1429]), GW-5074 (GSK; a c-raf1 inhibitor), ORS-1006 (Arrien Pharmaceuticals, a LRRK2 inhibitor), Pan-MLK inhibitors (Cephalon, now Teva), PLX-3397 (Pixuxikon, a subsidiary of Dai-ichi Sankyo; an oral small-molecule dual Fms/kit and Flt3-ITD inhibitor; a Phase II trial for the treatment of acute myelogenous leukemia continues), RS-4073 (Daiichi Sankyo; a potentiatior of TrkA and Map kinase activation), SB-203580 (SmithKline Beecham, now GSK; a protein kinase and cytokine suppression binding protein (CSBP)/p38 inhibitor [1430], SCH-323 (Scios, a p38 kinase inhibitor), SRN-003-556 (SIRENADE Pharmaceuticals; an ERK2 inhibitor), and of ZK-808762 (University of Göttingen; a serine protease and Factor Xa inhibitor) was terminated.

2.24. Drugs interacting with kynurenine mono-oxygenase and kynurenine transaminase II

The kynurenine metabolism in AD was described [1431]. Reduction of kynurenic acid formation enhanced hippocampal plasticity and cognitive behavior [1432]. Crystal structure-based selective targeting of kynurenine aminotransferase II for cognitive enhancement was discussed [1433].

CHDI-003940246 and CHDI-00340246 (Evotec in collaboration with the CHDI Foundation) are kynurenine mono-oxygenase inhibitors for the potential treatment of Huntington’s disease (Thomson Reuters Pharma, update of January 10, 2012). The structures were not communicated.

PF-04859989 (Pfizer, Fig. 19) is an inhibitor of kynurenine (oxoglutarate) aminotransferase II for the potential treatment of schizophrenia [1434] (Thomson Reuters Pharma, update of March 21, 2012).

2.25. Drugs interacting with 5-lipoxygenase

The enzyme 5-lipoxygenase (5-LO) catalyzes the conversion of arachidonic acid to 5-hydroxy-peroxy-eicosatetraenoic acid (5-HPETE) and subsequently to 5-hydroxy-icosatetraenoic acid (5-HTETE), which are metabolized to different leukotrienes [1435]. The group of Domenico Pratico found that Aβ deposition in brains of Tg2576 mice lacking 5-LO was reduced by 64 to 80%, suggesting that pharmacological inhibition of 5-LO could provide a novel therapy for AD [1436]. Additional investigations showed that 5-LO regulated the formation of Aβ by activating the cAMP-response element binding protein (CREB), which in turn increased transcription of the γ-secretase complex [1437, 1438].

In a Letter to the Editor of Annals of Neurology, Kenji Hashimoto [1439] suggested to test minocycline, which protected PC12 cells against NMDA-induced injury via inhibiting 5-lipoxygenase activation [1440].

Minocycline (Wyeth, now Pfizer and Takeda launched in 1999) is a second generation tetracycline that effectively crosses the blood brain barrier. It improved cognitive impairment in AD models [1441]. It provided protection against Aβ25-35-induced alterations of the somatostatin signaling pathway [1442, 1443]. It reduced microglial activation [1444, 1445] and Aβ-derived neuroinflammation [1446]. It recovered MTT-formazan exocytosis impaired by Aβ [1447]. Minocycline inhibited β-secretase-1 in a transgenic model of AD-like amyloid pathology [1448]. It reduced the development of abnormal tau species in models of AD [1449–1451]. Minocycline improved negative symptoms in patients with early schizophrenia [1452].

A new class of 5-lipoxygenase inhibitors was communicated recently [1453].

2.26. Drugs interacting with monoamine oxidase

Recent efforts of medicinal chemists to explore ligands targeting MOAs were reviewed [1454]. A patent-related survey on new MOA inhibitors was published [1455]. The changes of MAO A and B in AD were elucidated [1456] as was the platelet MAO B activity in dementia [1457].

Ladostigil (TV-3326, Avraham Pharmaceuticals under license from Yissum Research Development, a wholly owned company of the Hebrew University of Jerusalem; see Fig. 8) is a dual acetycholine esterase and MAO inhibitor currently in Phase II clinical trials in 190 patients in Europe since December 2010 (Thomson Reuters Pharma, update of May 18, 2012). See section 2.1.1.9. Dual ACHE and MAO inhibitors. RG-1577 (RO-4602522; EVT-302, Roche under license from Evotec) is an orally active, selective, and reversible MAO-B inhibitor. The company was planning to start a Phase II trial in patients with AD.
in the second half of 2012 (Thomson Reuters Pharma, update of August 8, 2012). Its structure was not communicated.

OG-45 (Oryzon Genomics) is a dual MAO-B inhibitor and lysine specific demethylase-1 inhibitor. (Thomson Reuters Pharma, update of April 16, 2012). Its structure was not communicated.

VAR-10200 (HILA-29; Varinel; Fig. 20) is a dual iron-chelating agent and MAO-B inhibitor for the potential treatment of age-related macular degeneration [1458] (Thomson Reuters Pharma, update of February 24, 2012).

VAR-10300 (M-30; Varinel, Technion and the Weizmann Institute of Science. Fig. 20) combines the iron-chelating properties of 8-hydroxy-quinoline with the MAO inhibitor moiety of rasagline [470, 1459-1465] (Thomson Reuters Pharma, update of May 15, 2012).

Rasagline (TVP-1012; (R)-enantiomer: Azilect; marketed by Teva and Lundbeck; Fig. 20) proved to be a very valuable drug for the treatment of Parkinson’s disease with sales in 2011 of USD 290 million reported by Teva and USD 221 million reported by Lundbeck. Rasagline was extensively characterized (in chronological order) [1466–1478]. The effects of rasagline on cognitive deficits in cognitively-impaired Parkinson’s disease patients were evaluated [1479]. A compound significantly reduced tau phosphorylation [1480] (Thomson Reuters Pharma, update of August 21, 2012). Its structure was not communicated.

The development of many other MAO inhibitors for the indication AD was terminated, of biflemeline (MC1-2016; SON-216; Sosei under license from Mitsubishi [1492, 1493]), EVT-301 (Evotec under license from Roche), EXP-631 (Bristol-Myers Squibb), 4-fluoro-selageline (Chinoin, now sanofi), HT-1067 (Helicon Therapeutics), indantadol (Vernalis under license from Chiesi), lazabemide (Ro 19-6327; Roche [1494–1496]), milacemide (GD Searle, now Pfizer [1497–1499]), NW-1772 (Newron Pharmaceuticals), PF-9601N (University of Autonoma de Barcelona), Ro-41-1045 (Roche), SL-25.1188 and SL-34.0026 (both sanofi) and of YY-125 (Yuyu Inc.).

2.27. Drugs modulating O-linked N-acetylgalactosaminidase (O-GlcNAcase; OGA)

O-GlcNAcase is the enzyme that plays a role in the removal of N-acetylgalactosamine groups from serine and threonine residues in both the nucleus and the cytoplasm of cells [1500, 1501]. O-GlcNAcase may compete with phosphorylation of the same serine or threonine residues. Studies to elucidate the binding mode were carried out by [1502, 1503]. O-GlcNAcylation directly regulates core components of the pluripotency network [1504].

Alectos Therapeutics/Merck are investigating O-GlcNAcase modulators (Thomson Reuters Pharma updates of July 5, 2012).

GlcNAcstatin (University of Dundee in collaboration with Aquapharm Biodiscvery; Fig. 20) is a marine natural product for the potential treatment of AD [1505, 1506]. For an efficient and versatile synthesis of GlcNAcstatin derivatives, see [1507] (Thomson Reuters Pharma, update of January 23, 2012).

NBuTG (Seoul National University; Fig. 20), a specific inhibitor of O-GlcNAcase, reduced Aβ production by lowering γ-secretase activity both in vitro and in vivo. O-GlcNAcylation takes place at the S708 residue of nicastrin, a component of γ-secretase [1508] = 5]. The synthesis was described by chemists of the Simon Fraser University [6].

SEG-4 (Summit Corporation) inhibited OGA with IC50 and Ki values of 10 and 72 nM, respectively. The compound significantly reduced tau phosphorylation at Thr231, Ser396, and Ser422 in both rat cor-
Fig. 20. Four monoamine oxidase and three O-linked N-acetylglucosaminidase inhibitors.

tex and hippocampus [1509-1512]. For commentaries see [1513, 1514]. Acute thiamet G treatment led to a decrease in tau phosphorylation at Thr181, Thr212, Ser214, Ser262/Ser356, Ser404, and Ser409 and an increase in tau phosphorylation at Ser199, Ser202, Ser396, and Ser422 in mouse brain, probably via stimulation of GSK-3β activity [1515].

2.28. Drugs interacting with peptidyl-prolyl cis-trans isomerase D

Peptidyl-prolyl cis-trans isomerase D or Cyclophilin D (Cyp D; EC 5.2.1.8. Isomerase) is implicated in cell death pathways. Blockade of Cyp D could be a potent therapeutic strategy for degenerative disorders such as AD, ischemia, and multiple sclerosis [1516]. Soluble Aβ is also found in mitochondria, where it interacts with Cyp D, a component of the mitochondrial permeability transition pore. Interference with the normal functions of this protein resulted in disruption of cell homeostasis and ultimately cell death [1517].

The Hep90-associated cis-trans peptidyl-prolyl isomerase-FK506 binding protein 51 (FKBP51) was recently found to co-localize with the microtubule-associated protein tau in neurons and physically interact with tau in brain tissues from humans, who died from AD [1518].

PIN1 is a peptidyl-prolyl isomerase, which catalyzes cis-trans isomerization of peptide bonds N-terminal to specific phospho-serine/threonine-proline motifs. PIN1 isomerizes phosphorylated tau and thus restores the ability of phosphorylated tau to bind microtubules, and eventually promote dephosphorylation of tau by PP2A phosphatase [1519].

Scynexis is investigating a series of Cyp D inhibitors for the potential treatment of muscle injury, ischemia, reperfusion injury, trauma, and neurodegenerative disease (Thomson Reuters Pharma, update of June 28, 2011).

2.29. Drugs interacting with phosphodiesterases

Several excellent reviews on PDE inhibition and cognition enhancement were published [1520–1524]. Based on the expression of PDE mRNA in the human brain, it was suggested that PDE1 and PDE10 inhibitors are strong candidates for the development of cognition enhancers. Chronic PDE type 2 inhibition with BAY60-7550 improved memory in the AβPPsw/P51dE9 mouse model of AD [1525].
medicinal chemistry of PDE4D allosteric modulators [1526], of PDE4 inhibitors [1527], of PDE5 inhibitors [1528, 1529], and of PDE10A inhibitors was reviewed (1530, 1531).

**Etxetolate (EHT-202: SQ-20009; Exonhit; see Fig. 10) is an orally active PDE4 inhibitor and anxiolytic GABAA receptor modulator, which shifts A1PP processing toward the a-secretase pathway [503, 504, 1532–1536].** The results of the first Phase II 3-month, randomized, placebo-controlled, double-blind study in AD patients was reported [505] (Thomson Reuters Pharma, update of September 13, 2011). See also section 2.2. Drugs interacting with a-secretase.

**PF-02545920 (MP-10; Pfizer, Fig. 21) is a PDE10A inhibitor in a randomized, double-blind, placebo-controlled Phase II clinical trial in patients with acute schizophrenia (n=260) since October 2010. PF-02545920 is also evaluated for the treatment of Huntington’s disease [1531], 1537–1540]. (Thomson Reuters Pharma, update of July 19, 2012).**

**Lu-AF11167 (Lundbeck) is an inhibitor of a brain-expressed PDE enzyme for the potential treatment of AD, Huntington’s chorea, and schizophrenia in a Phase I clinical trial since March 2011 (Thomson Reuters Pharma, update of July 19, 2012).**

There are several PDE inhibitors in preclinical evaluation (in alphabetical order):

- **AMG-7980 (Amgen, Fig. 21) is a novel PDE10A inhibitor with a K_i of 0.94 nM useful as tritiated ligand to measure PDE10A target occupancy in rat brain [1541, 1542].**

- **AVE-8112 (Avantis, now sanofi and Michael J. Fox Foundation) is a PDE4 inhibitor for the potential treatment of Parkinson’s disease. In April 2012, a US Phase Ib study was planned (Thomson Reuters Pharma, update of May 30, 2012). The structure was not communicated.**

- **BCCA-909 (BCCA-909: Biotherminger Engelheim under license from biocrea GmbH) is a PDE2 inhibitor for the potential treatment of mild cognitive impairment in schizophrenia and AD (Thomson Reuters Pharma, update of May 30, 2012). The structure was not communicated.**

- **Cilostazol (Otsuka), a selective PDE3 inhibitor, protected against Aβ1-40 induced suppression of viability and neurite elongation [1543].**

- **Dual PDE10/PDE 2 inhibitors (biocrea GmbH) are investigated for the potential treatment of schizophrenia and AD (Thomson Reuters Pharma, update of January 18, 2012). Structures were not communicated.**

- **GEBR-7b (University of Genoa; Fig. 21) is a novel PDE4D selective inhibitor that improves memory in rodents at non-emetic doses [1544] (Thomson Reuters Pharma, update of December 21, 2011).**

- **ITI-002A, IC-200214, and ITI-214 (Takeda under license of Intra-Cellular Therapies) are PDE1 inhibitors for the potential oral treatment of cognitive disorders associated with schizophrenia (Thomson Reuters Pharma, update of July 30, 2012). The structures were not communicated.**

- **OMS-182410 (Omeros) is a PDE10 inhibitor for the potential treatment of schizophrenia (Thomson Reuters Pharma, update of July 19, 2012).**

- **PDE2A inhibitor (Pfizer, Fig. 21) is evaluated for the potential treatment of cognitive impairment associated with schizophrenia. In March 2012, a PDE2A inhibitor with an IC_{50} of 4 nM was presented at the 243rd ACS Meeting in San Diego (Thomson Reuters Pharma, update of August 24, 2012).**

- **Allotsteric PDE4 inhibitors (Tetra Discovery Partners; West Virginia University) are evaluated for the potential treatment of mild cognitive impairment (Thomson Reuters Pharma, update of July 5, 2012). Structures were not communicated.**

- **PDE7 inhibitors (Omeros) are a potential new treatment of Parkinson’s disease (Thomson Reuters Pharma, update of May 23, 2012). The structures were not communicated.**

- **A PDE9 inhibitor (Pfizer, Fig. 21) for the potential treatment of AD was found to penetrate mouse brain and had a half-life of 6.8 hour in dog (Thomson Reuters Pharma, update of April 14, 2011).**

- **A PDE10 inhibitor (biocrea, a spin-out from BioTie Therapeutics following its acquisition of elbion, Fig. 21) is investigated for the potential treatment of Huntington’s disease. (Thomson Reuters Pharma, update of May 29, 2012).**

- **ITI-214 (Takeda)**

- **A PDE2A-selective CNS PET ligand for the potential diagnosis of Alzheimer’s disease. (Thomson Reuters Pharma, update of October 03, 2012).**

- **PF-999 (Pfizer, Fig. 21) is a PDE2A inhibitor for the potential treatment of cognitive impairment associated with schizophrenia. (Thomson Reuters Pharma, update of September 6, 2012).**

- **Sildenafil (Pfizer, launched as Viagra in 1998) and Tadalafil (EHT-202: SQ-20009; Exonhit; see Fig. 10) is a novel PDE4D selective inhibitor that improves memory in rodents at non-emetic doses [1544] (Thomson Reuters Pharma, update of December 21, 2011).**
**THPP-1** (Merck, Fig. 21) is a potent, orally bioavailable PDE10A inhibitor, which improved episodic-like memory in rats and executive function in Rhesus monkeys [1547].

**VP1.15** (CSIC Madrid and University of Toronto, Fig. 18) is a dual GSK-3 and PDE7 inhibitor acting as an antipsychotic and cognitive enhancer in C57BL/6J mice [1276, 1277].

The development of many PDE inhibitors was terminated, of **D-159687** and **DG-071** (deCODE genetics, now DGI Resolution), **denbufylline** (BRL-30892; SmithKline Beecham, now GSK [1548]),
2.30. Drugs interacting with Phospholipase A2 and D2

Phospholipase A2 reduction ameliorated cognitive deficits in a mouse model of AD [1567–1569]. These findings were confirmed by genetic phospholipase A2 and D2 ablation studies [1570–1572].

Rilapladib (SB-659032; GSK using a technology licensed from Human Genome Science; Fig. 21) is a lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitor for the potential oral treatment of atherosclerosis and AD. In October 2011 a randomized, double-blind, placebo-controlled Phase II study was initiated in 120 AD patients with evidence of cardiovascular disease in Europe. The study was scheduled to complete in November 2012 (Thomson Reuters Pharma, update of June 26, 2012).

Icosapent ethyl (AMR-101, SC-111, LAX-101; MND-21; Epaped; ethyl-eicosapentaenoic acid; Mochida Pharmaceutical and Amarin under license from Scotia Holdings), a phospholipase A2 inhibitor, was launched in Japan for the treatment of atherosclerosis and AD. In October 2011 a randomized, double-blind, placebo-controlled Phase II study was initiated in 120 AD patients with evidence of cardiovascular disease in Europe. The study was scheduled to complete in November 2012 (Thomson Reuters Pharma, update of June 26, 2012).

2.31. Drugs interacting with plasminogen activator inhibitor (PAI)

PAI-1 (serpin E1) is a serine protease inhibitor that functions as the principal inhibitor of tissue plasminogen activator (tPA) and urikinase, the activators of plasminogen and hence fibrinolysis [1573]. Elevated serum PAI-1 was associated with a high risk for cognitive dysfunction [1574]. PAI-1 promoted synaptogenesis and protected against Aβ1-42-induced neurotoxicity [7]. PAI-1 was also related to lower speed and visuomotor coordination in elderly subjects [1575]. PAI-1 may be a useful marker for vascular dementia [1576]. The plasmin system of AD patients was discussed [1577].

IMD-4482 (Institute of Medicinal Molecular Design, INMD) is an inhibitor of PAI-1 for the potential treatment of fibrotic diseases. The indication AD is no longer followed up (Thomson Reuters Pharma, update of January 19, 2012).

The development of the PAI aleplasinin (PAZ-417; Wyeth, now Pfizer) was terminated.

2.32. Drugs interacting with poly ADP-ribose polymerase (PARP)

Cognitive impairment can be prevented by PARP-1 inhibitors administered after hypoglycemia [1578, 1579]. Cognitive and motor deficits were reduced in mice deficient in PARP-1 [1580]. E-7016 (Eisai following the acquisition of MGI Pharma, formerly Guilford; presumed to be GPI-21016 under license from Johns Hopkins University, Fig. 22) is an orally active, brain-penetrable, PARP PAR synthase inhibitor currently in Phase II clinical trials for the treatment of stage III/IV melanoma patients [1581]. The indications AD and stroke were abandoned (Thomson Reuters Pharma, update of June 15, 2012).

MP-124 (Mitsubishi Tanabe Pharma) in a PARP inhibitor for the potential treatment of acute ischemic stroke in Phase I clinical trials since December 2008 (Thomson Reuters Pharma, update of February 04, 2011). The structure was not communicated.

AL-309 (Allon Therapeutics), a peptide, is a neuroprotective agent and PARP stimulator in preclinical studies (Thomson Reuters Pharma, update of May 9, 2012).

2.33. Drugs interacting with prolyl endopeptidase

Several reviews on prolyl endopeptidase, also known as prolyl oligopeptidase, as a potential target for the treatment of cognitive disorders were published [1582–1584]. Sustained efforts over many years have gone into the discovery and characterization of potent prolyl endopeptidase inhibitors for the treatment of
memory disorders [1585]. Potent prolyl endopeptidase inhibitors, such as KYP-2047 and JTP-4819, did not increase striatal dopamine, acetylcholine, neurotensin and substance P levels [1586–1588].

Subchronic administration of rosmarinic acid, a natural prolyl oligopeptidase inhibitor, enhanced cognitive performances [1589]. The development of many prolyl endopeptidase inhibitors was terminated, of eurystatin A (Bristol-Myers Squibb [1590–1593]), JTP-4819 (Japan Tobacco [1594–1597]), KYP-2047 (Univ. of Kuopio and Finncovery [1598]), ONO-1603 (Ono Pharmaceuticals [1599, 1600]), S-17092 (Servier [1601–1605]) and S-19825 (Servier [1606]). SUAM-1221 (Chinoin and sanofi [1598, 1607–1610]). Y-29794 (Yoshitomi, now Mitsubishi Pharma Corp. [1611, 1612]), Z-321 (Zeria Pharmaceutical [1613–1615]) and ZTTA [1616].

2.34. Drugs interacting with prostanoid D & E synthases

Reviews on the biochemical, structural, genetic, physiological, and patho-physiological features of lipocalin-type prostanoid D synthase were disclosed [1617, 1618]. The three prostanoid E synthases were described [1619] as was prostanoid E2 synthase inhibition as a therapeutic target [1620] and the COX-1 mediated prostanoid E2 elevation and contextual memory impairment [1621]. Deletion of microsomal prostanoid E synthase-1 protected neuronal cells from the cytotoxic effects of Aβ [1622].

HF-0220 (7-beta-hydroxy-epiandrosterone; Newron Pharmaceuticals; Fig. 22) is a cytoprotective steroid, which stimulated prostanoid D synthase for the potential treatment of AD. A Phase Ia multicenter, double-blind, placebo-controlled, biomarker trial (NCT00357357) in AD patients was initiated in April 2007. The randomized, double-blind, placebo-controlled pilot study enrolled 42 patients in the UK, Sweden, and India. Subjects received 1 to 220 mg/day of the drug and were allowed to continue with their current AD treatment. Results were reported in October 2008. HF-0220 was well tolerated at all doses (Thomson Reuters Pharma, update of August 21, 2012).

AAD-2004 (GNT Pharma, formerly Neurotech and US subsidiary AmKor, Fig. 22) is a prostanoid E synthase-1 inhibitor for the treatment of AD, Parkinson’s disease, and amyotrophic lateral sclerosis. A Phase I study was initiated in April 2010. By December 2011, the Phase Ia single ascending dose trial had been successfully completed. In April 2012, it was reported that a Phase Ib multiple ascending-dose trial to evaluate safety and biomarker profiles was planned for that year (Thomson Reuters Pharma, update of May 4, 2012).

The development of an analogue of AAD-2004, i.e., NG-2006 (GNT Pharma) was terminated.

2.35. Drugs interacting with protein kinase C

Activation of PKC prevents synaptic loss, Aβ elevation, and cognitive deficits in AD transgenic mice [1623, 1624]. The pharmacology of PKC activators was extensively reviewed [1625–1629]. APH-0708 (Aphios Corp.), a potent PKC activator, enhanced the generation of non-amyloidogenic, soluble AβPP in fibroblasts from AD patients. It reduced brain amyloid plaques (Aβ40 and Aβ42) in double-transgenic mice. The drug, formulated using Aphios’s hydrophobic-based and SFS-PNS polymer nanospheres technologies, is in Phase II clinical trials since May 2010 (Thomson Reuters Pharma, update of July 5, 2012). The structure was not communicated. Potent activators of PKC are indirect activators of α-secretase [1630–1632].

Bryostatin-1 (Blanchette Rockefeller Neurosciences Institute) is a naturally occurring PKC activator isolated from the Californian marine bryozoan Bugula neritina. In February 2012, the Institute was preparing to initiate clinical trials in neurological disorders. Dual effects of bryostatin-1 on spatial memory and depression were described [1633–1635]. Postischemic PKC activation to rescue long-term memory was investigated [1636, 1637]. The chemistry and biology of bryostatins was reviewed [504] (Thomson Reuters Pharma, update of February 24, 2012). See also Section 2.2. Drugs interacting with u-secretase.

DCC-PLA (Hyogo College of Medicine; Fig. 22) is an activator of PKC for the potential treatment of stroke and cognitive disorder (Thomson Reuters Pharma, update of May 25, 2012).

PKC epsilon activators (Blanchette Rockefeller Neurosciences Institute) are evaluated for the potential treatment of cognitive disorder (Thomson Reuters Pharma, update of February 17, 2012). The structures were not communicated.

The development of FR-236924 (Fujiwsawa, now Astellas; an activator of PKCε [1638–1641]) and of K-252c (Kyowa Hakko Kogyo; a PKC inhibitor) was terminated.
Fig. 22. A poly ADP-ribose polymerase inhibitor, prostaglandin D and E modulators, a protein kinase C ε activator, a Rac1 GTPase inhibitor and a ras farnesyl transferase inhibitor.

2.36. Drugs interacting with protein tyrosine phosphatase

The role of striatal-enriched protein tyrosine phosphatase in cognition was described [1642] as was the involvement of PTPN5, the gene encoding the striatal-enriched protein tyrosine phosphatase in schizophrenia and cognition [1643]. A genome-wide association study in 700 schizophrenic patients found that three intrinsic SNPs in the protein tyrosine phosphatase receptor type O were associated with learning and memory [1644]. Knockout mice revealed a role for protein tyrosine phosphatase in cognition [1645].

LDN-33960 (Yale University) is a striatal-enriched protein tyrosine phosphatase inhibitor, which increased the phosphorylation of NMDA receptors and of ERK in a dose dependent manner. The drug restored memory in a novel object recognition test in triple transgenic mice. It appears that the development of LDN-33960 was terminated (Thomson Reuters Pharma, update of June 19, 2012).

2.37. Drugs interacting with Rac1 GTPase

The role of Rac1 GTPase in cognitive impairment following cerebral ischemia in the rat was described [1646]. The modulation of synaptic function by Rac1 may be a possible link to fragile X syndrome pathology [1647, 1648].

Cytotoxic Necrotizing Factor 1, a modulator of Rho GTPases including Rac, Rho, and Cdc42 subfamilies improved object recognition in mice [1649].

Sanquinarinium chloride (ExonHit; Fig. 22) is a selective Rac1/1b GTPase nucleotide binding inhibitor with IC\textsubscript{50}'s of 58 μM and 4.6 μM for Rac1 and Rac1b, respectively in nucleotide binding assays in preclinical development (Thomson Reuters Pharma, update of July 20, 2011).

The development of EHT-1864 (EHT-206, EHT-101; ExonHit), an orally active small molecule Rac1 GTPase inhibitor capable of crossing the blood brain barrier was discontinued [1650–1652].
2.38. Drugs interacting with Ras Farnesyl Transferase

Inhibiting farnesylation, but not geranylgeranylation, replicated the enhancement of LTP caused by simvastatin via the activation of Akt [1653]. LNK-754 (OSI-754, CP-609754; AstraZeneca following the acquisition of Link Medicine’s neuroscience assets under license from OSI Pharmaceuticals, a subsidiary of Astellas Pharma, and Pfizer; Fig. 22) is an orally active inhibitor of ras farnesyl transferase. Two Phase I clinical trials were initiated in the US, one in May 2009 in 40 healthy elderly subjects and one in November 2009 in 110 healthy elderly subjects and in patients with mild AD. Treatment of transgenic mice at 6 months of age for 3 months showed a clear reduction of plaques caused by either α-synuclein or Aβ [1654] (Thomson Reuters Pharma, update of July 13, 2012).

2.39. Drugs interacting with S-adenosylhomocysteine hydrolase

Homocysteine potentiated Aβ neurotoxicity [1655]. The S-adenosyl homocysteine hydrolase inhibitor 3-deaza-adenosine prevented cognitive impairment following folate and vitamin E deprivation in mice [1656]. L-002259713 (Merck, Fig. 23) is a potent inhibitor of S-adenosylhomocysteine hydrolase for the potential treatment of AD. The development was discontinued (Thomson Reuters Pharma, update of June 19, 2012).

2.40. Drugs interacting with sirtuin

The neuronal protection by sirtuins in AD was described [1657] as were details on the sirtuin pathway in aging and AD [1658]. Resveratrol (Fig. 23) is a natural phyto compound, which activates Sirtuin-1 [1659–1664]. It reduced Aβ accumulation [1665–1668]. It remodeled soluble oligomers and fibrils of Aβ into off-pathway conformers [1669]. Resveratrol is not a direct activator of SIRT1 enzyme activity [1670]. Resveratrol improved memory deficits in mice fed a high-fat diet [1671]. Subchronic oral toxicity and cardiovascular safety pharmacology studies were carried out [1672]. The biosynthesis of resveratrol in yeast and in mammalian cells was worked out [1673]. The Georgetown
University Medical Center started at Phase II, randomized, double-blind, placebo-controlled study in patients with mild to moderate AD (expected n = 120) in the US in May 2012 (NCT015048549). A novel application in Huntington’s disease was discussed recently [1674] (Thomson Reuters Pharma, update of June 22, 2012).

**Selisistat** (SEN-196, EX-527, SEN-0014196; Siena Biotech under license from Elixir Pharmaceuticals; Fig. 23) is a sirtuin-1 inhibitor for the potential treatment of Huntington’s disease in Phase II trials (PADDINGTON, NCT01485965) in Europe since April 2011 (Thomson Reuters Pharma, update of May 20, 2012).

**INDUS-815C** (Indus Biotech) is a natural NAD-dependent deacetylase sirtuin-2 (SIRT-2) inhibitor for the potential treatment of Huntington’s disease. In addition, the drug is evaluated for the potential treatment of age-related macular degeneration and retinopathy (Thomson Reuters Pharma, updates of August 19, 2011 and August 16, 2011, respectively). The structure was not communicated.

### 2.41. Drugs interacting with steroid sulfatase

Steroid sulfatase is a potential modifier of cognition in attention deficit hyperactivity disorder [1675].

**DU-14** (Dusquesne University, Fig. 23) is a steroid sulfatase inhibitor for the potential enhancement of cognitive function via enhanced levels of plasma dehydro-epiandrosterone and brain acetylcholine [1676–1679]. Its development was terminated.

### 2.42. Drugs interacting with transglutaminase (TG2)

Tissue transglutaminase catalyzes protein cross-linking, an important molecular process in AD. Accumulation of insoluble proteins with isopeptide bonds, products of tissue transaminase activity, are correlated with cognitive impairment [1680].

**CHDI-00339864** (Fig. 23) and CHDI-00316226 (Evotec in collaboration with the CHDI Foundation) are selective TG2 inhibitors (IC50 = 7eM for TG2 for CHDI-00316226) for the potential treatment of Huntington’s disease. It displayed an 85 fold greater selectivity for TG2 over Factor XIA (Thomson Reuters Pharma, update of February 10, 2012).

### 2.43. Drugs interacting with ubiquitin carboxyl-terminal hydrolase (Usp14)

Inhibitors of this enzyme could accelerate the degradation of neurodegenerative disease-related proteins, such as tau, TDP-43, and ataxin-3. Changes in hippocampal synaptic transmission were observed in Usp14-deficient mice [1681].

**Usp14 inhibitors** (Protestas Therapeutics under license from Harvard University) are investigated for the potential treatment of neurodegenerative diseases (Thomson Reuters Pharma, update of August 15, 2012). Structures were not communicated.

### 3. CONCLUSION

With the launch of donepezil (Aricept) in 1996, rivastigmine (Exelon) in 2000, and galantamine (Reminyl) in 2001 (all inhibitors of AChE and BChE), three valuable medications are available for the treatment of patients with mild to moderate AD. Huperzine A was launched in China in 1995, but the four times a day administration makes it less attractive, a problem which will be solved by a transdermal patch currently in Phase I evaluation as XEL-001HP by Xel Pharmaceuticals.

The development of ten Phase III compounds tested for the indication AD was terminated, of the AChE inhibitors amiridin (Nikken), eptastigmine (Medolanum), metrifonate (Bayer), phenserine (Anonyx), and velnacrine (HMR, now sanofi), of the β-secretase inhibitors begacestat (Pfizer) and semagacestat (Lilly), the γ-secretase modulator tarenflurbil (Myriad Genetics), and of the MAO inhibitors rasagiline (Teva) and safinamide (Merck Serono).

Currently there is one compound interacting with enzymes in the pre-registration phase (WIN-026, WhanIN, an AChE inhibitor), one compound in Phase III trials (masitinib, AB Science, a kinase inhibitor), and 15 drugs in Phase II evaluation (posiphen and Shen Er Yang, two AChE inhibitors), ladostigil (a dual AChE and MAO inhibitor), etazolate (an α-secretase activator), avagacestat and NMC5-15 (γ-secretase inhibitors), CHF-5074 (β-secretase modulator), tidegusib (GSK-3β inhibitor), EVP-0334 (HDAC inhibitor), RG-1577 (MAO-B inhibitor), PP-02545920 (PDE10A inhibitor), rilapladib (PLA2 inhibitor), HF-0220 (prostaglandin D synthase stimulator), APII-0703 (PKC activator), and selisistat (sirtuin-1 inhibitor).

It may be that positive results will be obtained from the masitinib Phase III trials within the next two to
three years, whereas results from the Phase II trials will be available only within the next five to six years.

DISCLOSURE STATEMENT

Authors’ disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1508).

REFERENCES


598  W. Frewell et al. / Cognitive Enhancers (Nootropics). Part 2: Drugs Interacting with Enzymes


myasthenia gravis. Synthesis and activities of quater-
nary phenylcarbamates of neostigmine, pyridostigmine

Kinetics of human acetylcholinesterase inhibition by the
novel experimental Alzheimer therapeutic agent, talizine.

[349] Hartman J, Kowert C, Duyen EG, Leckridge O, Greig
NH, Klein J (2007) Excessive hippocampal acetylcholine
levels in acetylcholinesterase-deficient mice are moder-

[350] Zemlan FP (1996) Velnacrine for the treatment of
Hartmann J, Kiewert C, Duysen EG, Lockridge O, Greig
agents for AD.

[351] Hornsperger JM, Collard JN, Heydt JG, Giacobini E,
Hatip-Al-Khatib I, Iwasaki K, Yoshimitsu Y, Arai T,
Hatip-Al-Khatib I, Takashi A, Egashira N, Iwasaki K,
Hatip-Al-Khatib I, Garcia-Palomero E, Valenzuela R,
Martinez A, Medina M (2006) Dual binding site acetyl-

[352] Bonilla ML, Matarra R, Minarini A, Rosini M, Mel-

[353] Bonilla ML, Simonetti E, Rosini M, Minarini A, Tumi-
atti V, Melchiorre C (2011) Multitarget-directed ligands:
innovative chemical probes and therapeutic tools against

drugs for disorders of the central nervous system. *Neu-

[355] Micheliore C, Bolognesi ML, Minarini A, Rosini M, Tumi-
atti V (2010) Polymamides as drug discovery: From the
universal template approach to the multitarget-directed lig-

[356] Leon R, Garcia AG, Marco-Contelles J (2011) Recent
advances in the multitarget-directed ligands approach for

[357] Marco-Contelles J, Soriano E (2011) The medicinal chem-
istry of hybrid-based drugs targeting multiple sites of


multi-target ligands for the treatment of Alzheimer’s dis-

[360] Melchiorre C, Andrisano V, Bolognesi ML, Budorici R,
Cavalli A, Caretti V, Rosini M, Tumiatti V, Recan-
tini M (1998) Acetylcholinesterase noncovalent inhibitors
based on a polyanine backbone for potential use against


[363] Borroni E, Danusma G, Giovacchini C, Mulei V, Jakob-
Rost R, Da PM (1994) A novel acetylcholinesterase
inhibitor, Ro 46-5934, which interacts with muscarinic M2

[364] Fung L, Jumprongt Y, Zhang V, Apponthep D, Fleck C,
Mohr K, Trankle C, Decker M (2010) Hybrid molecules
from xanomeline and lutein-based lutein actions on


with ACHE, H3 receptors and BACE 1 inhibitor activities. Bioorg Med Chem 19, 7158-7167.


W. Froestl et al. / Cognitive Enhancers (Nootropics). Part 2: Drugs Interacting with Enzymes

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620

W. Frenzel et al. / Cognitive Enhancers (Nootropics). Part 2: Drugs Interacting with Enzymes


in plasma and cerebrospinal fluid using deproteinized or formate added 4-ions as precursor ions. J Chro
nomatogr A 1207, 2319-2326.


characterization of Abeta(40) changes in brain and cerebrospinal fluid using the novel gamma-secretase inhibitor N-(cis-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexyl)-1,1,1-trifluoromethane-amides as gamma-secretase inhibitors. Bioorg Med Chem Lett 17, 57-62.


[100] Lanz TA, Hotsey JD, Adams WM, Merchant KM (2004) Studies of Abeta pharmacodynamics in the brain, cerebrospinal fluid, and plasma in young (placebo-free) Tg2576 mice using the gamma-secretase inhibitor N(3-c-3,5-difluorophenyl)cysteineamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideamideam


alternates motor and cognitive deficits following experimental brain injury in the rat. Proc Natl Acad Sci USA 103, 128-133.


Alzheimer disease mice expressing the wild-type, but not the Swedish mutant, beta-secretase site of the amyloid precursor protein. J Biol Chem 283, 7745-7753.


W. Froestl et al. / Cognitive Enhancers (Nootropics). Part 2: Drugs Interacting with Enzymes


novel NO mimetic nitrate ester. Neuropeptider Endocrinology 32, 505-511.


doses with multipotent ligands: A new emerging strategy in the search of new drugs against neurodegenerative dis-

eases. Expert Opin Ther Pat 22, 755-801.


monamine oxidase B activity in dementia: A 4-year follow-up. Dement Geriatr Cogn Disord 9, 74-77.


Dopamine, synthesis, and evaluation of novel bifunctional iron-chelators as potential agents for neuroprotection in

Alzheimer’s, Parkinson’s, and other neurodegenerative diseases. Bioconjug Chem 13, 773-783.

drug with potent iron chelating and brain selective monamine oxidase-B inhibitory activity for Parkinson’s disease. J

Neurotransm Suppl 70, 447-456.

[1458] Youdim MB (2006) The path from anti Parkinson drug selegiline and rasagiline to multifunctional neuropro-


potential of the novel brain-permeable multifunctional iron-chelator-monoamine oxidase inhibitor drug, M30, for the


Neurorescue activity, A PK regulation and amyloid-beta peptide reduction by novel brain-permeable iron-

chelating-antioxidants, m30 and green tea polyphenol, EGCg. Curr Alzheimer Res 4, 403-411.


ase inhibitory moieties as novel phospholipid therapeutic agents for Alzheimer’s disease: A tribute to Monuza Youdim. J

Neurosci 31, 479-492.


monoamine oxidase, M30, has a neuroprotective effect against dexamethasone-induced brain cell apoptosis. Front

Neurosci 4, 180.


aminocyclohexanone (rasagiline) and derivatives. Highly selective and potent inhibitors of monoamine oxidase B. J

Neural Transm Suppl 52, 303-305.


Inhibitors of PDE10A (PDE10A) inhibitors.


de Lima MN, Presti Torres J, Garcia VA, Guimarans MM, Scarl FB, Roeder R, Schorner N (2008) Amelioration of recognition memory impairment associated with iron loading or aging by the type 4-specific phosphodiesterase


