Abstract. Scientists working in the field of Alzheimer’s disease and, in particular, cognitive enhancers are very productive. The review on Drugs interacting with Enzymes was accepted in August 2012. However, this field is very dynamic. New potential targets for the treatment of Alzheimer’s disease were identified. This update describes drugs interacting with 60 enzymes versus 43 enzymes in the first paper. Some compounds progressed in their development, while many others were discontinued. The present review covers the evolution of research in this field through April 2014.

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

1. INTRODUCTION

As of May 2, 2014, there are 28,230 entries in PubMed under the term cognitive enhancers, 28,255 entries under the term nootropic, and 313 entries under the term cognition enhancers. Scifinder lists 5,698 references under the research topic nootropic, 655 references under the term cognitive enhancer, and 11,248 references for cognition enhancers. The Thomson Reuters Pharma database lists 1,249 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 Corneliu 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 (ADHD), 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 Maître [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)
In Part 1, drugs interacting with receptors were described [5]. In Part 2, we described drugs interacting with enzymes [6] and in Part 3, drugs interacting with targets 3 to 10 and compounds and preparations of categories 11 to 19 [7]. However, this field is very dynamic. New potential potential targets were identified. Some compounds progressed in their development, while many others were discontinued. Therefore an update is appropriate.

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- and 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
- 2.1.1.11.1. Dual AChE inhibitors and platelet activating factor antagonists
- 2.1.1.12. Dual AChE and serotonin transporter inhibitors
2.13. Drugs interacting with Carnitine Acetyltransferase
2.14. Drugs interacting with Caspases
2.15. Drugs interacting with Catechol-O-methyltransferase
2.16. Drugs interacting with Cathepsin
2.17. Drugs interacting with Cholesterol 24S-Hydroxylase (CYP46A1)
2.18. Drugs interacting with Cytochrome P450 (COX)
2.19. Drugs interacting with Cytochrome P450 (CYP) isoforms (≠ CYP46A1)
2.20. Drugs interacting with D-Amino Acid Oxidase
2.21. Drugs interacting with Dipeptidylpeptidase
2.22. Drugs interacting with Glutaminyl Cyclase
2.23. Drugs interacting with Glyceraldehyde-3-Phosphate Dehydrogenase
2.24. Drugs interacting with Glycogen Synthase Kinase-3 (GSK-3β/H9252)
2.25. Drugs interacting with Guanylyl Cyclase
2.26. Drugs interacting with Heme Oxygenase
2.27. Drugs interacting with Histone Deacetylases (≠ Sirtuins)
2.28. Drugs interacting with HMG-CoA Reductase
2.29. Drugs interacting with Insulin-Degrading Enzyme
2.30. Drugs interacting with Insulin-Regulated Aminopeptidase
2.31. Drugs interacting with Kinases (≠ GSK-3β and ≠ PKC)
2.32. Drugs interacting with Kynurenine Mono-Oxynzyme and Kynurenine Transaminase II
2.33. Drugs interacting with 5-Lipoxygenase
2.34. Drugs interacting with Lysozyme Specific Histone Demethylase I
2.35. Drugs interacting with Monoacylglycerol Lipase
2.36. Drugs interacting with Monoamine Oxidase
2.37. Drugs interacting with Myeloperoxidase
2.38. Drugs interacting with Neprilysin
2.39. Drugs modulating O-linked N-Acetylglocosaminidase
2.40. Drugs interacting with Peptidyl-Prolyl cis-trans Isomerase D
2.41. Drugs interacting with Phosphodiesterases
2.42. Drugs interacting with Phospholipases A2 and D2

2.43. Drugs interacting with Plasminogen Activator Inhibitor
2.44. Drugs interacting with Poly ADP-Ribose Polymerase
2.45. Drugs interacting with human Presenence Protease
2.46. Drugs interacting with Prolyl Endopeptidase
2.47. Drugs interacting with Prostaglandin D & E Synthases
2.48. Drugs interacting with Protein Kinase C (PKC)
2.49. Drugs interacting with Protein Phosphatase Slingshot Homolog 2
2.50. Drugs interacting with Protein Tyrosine Phosphatase
2.51. Drugs interacting with Rac1 GTPase
2.52. Drugs interacting with Ras Farnesyl Transferase
2.53. Drugs interacting with Rho GTPase
2.54. Drugs interacting with S-Adenosylhomocysteine Hydrolase
2.55. Drugs interacting with Serine Palmitoyltransferase
2.56. Drugs interacting with Sirtuin
2.57. Drugs interacting with Steroid Sulphatase
2.58. Drugs interacting with Synaptotagmin I
2.59. Drugs interacting with Transglutaminase
2.60. Drugs interacting with Ubiquitin Carboxyl-terminal Hydroxylase (Usp14).

2.1. Drugs interacting with acetyl- and butyrylcholinesterase

Since the publication of the cholinergic hypothesis of AD by Bartus and colleagues in 1982 [8], tremendous efforts have been undertaken to find either selective acetylcholine receptor agonists (described in Part 1) or acetylcholinesterase (AChE) inhibitors. 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. For reviews on cholinesterase inhibitors for AD, see [9, 10]. Interestingly, APOE and BChE were identified as modulators of cerebral amyloid-β deposition in a genome-wide association study (GWAS) [723].

Donepezil (Aricept; E2020; co-developed by Eisai, Tokyo 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
Launched acetylcholinesterase inhibitors. NAL-8812 is a 3-day patch formulation co-developed with NAL Pharmaceuticals (Hong Kong) since November 2012 (Thomson Reuters Pharma, update of May 6, 2014). NAL-8817 is an orally dissolving film formulation of donepezil using the BIO-FX fast-onset oral cavity drug delivery system technology (Thomson Reuters Pharma, update of January 17, 2014). Deuterated donepezil (DeuteRx, a spin-off from Deuteria Pharmaceuticals, Andover, MA) is investigated for the potential treatment of AD (Thomson Reuters Pharma, update of March 17, 2014). Donepezil + memantine (ADS-8704, MDX-8704; Arimenda; Namenda XR; Adams Pharmaceuticals, Emeryville, CA in collaboration with Forest Laboratories, New York), a once-daily fixed dose combination extended release formulation, is currently tested in Phase III clinical trials in the US and in EU. First clinical results were presented [27]. US NDA filing is planned for 2014 and launch is expected in 2015 (Thomson Reuters Pharma, update of February 4, 2014).

Fig. 1. Launched acetylcholinesterase inhibitors.

**Donepezil** interacts with the active site of AChE and the peripheral anionic site of the enzyme [13]. Its long terminal disposition half-life of 70 hours supports once-daily administration [14].

The sales for donepezil reported by Eisai for 2012 were USD 1.178 billion (Thomson Reuters Pharma, update of May 6, 2014). There are currently 2,635 publications on donepezil listed in PubMed (as of May 2, 2014). A 10-year perspective on donepezil was presented [15]. Two meta-analyses of the efficacy of donepezil, rivastigmine, galantamine, and memantine for the treatment of AD were published [16, 17]. Broader considerations of higher doses of donepezil in the treatment of mild, moderate, and severe AD were communicated [18], in particular on the question of the case of the 23 mg dose [19, 20]. For the effects of donepezil on levels of cholinesterases in the cerebrospinal fluid (CSF) of AD patients, see [21]. Donepezil combined with natural biradun improved the clinical symptoms of patients with mild-to-moderate AD [22]. A combination treatment of donepezil and memantine showed beneficial effects in AD patients in reducing cognitive worsening [23, 24]. Donepezil was used for the treatment of patients with Parkinson’s disease (PD) [25] and for the treatment of memory impairment in multiple sclerosis (MS) patients [26].

**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 [11]. It forms a carbamoylated complex with the active-site serine inactivating it for about 10 hours producing a “pseudo-irreversible” inhibition. Rivastigmine was launched for the treatment of mild to moderate AD in 2000 in EU and the US and in 2010 in Japan. It was approved for the treatment of mild to moderately severe dementia associated with idiopathic PD. Rivastigmine transdermal patch was launched in EU in 2007 and in Japan in 2011 in collaboration with the Japanese licensee Ono Pharmaceuticals.

Sales for rivastigmine for 2013 by Novartis were USD 1.032 billion; sales by Ono for 2012 were USD 48.8 million (Thomson Reuters Pharma, update of June 3, 2014). There are currently 1,341 publications on rivastigmine listed in PubMed (as of May 2, 2014).
Rivastigmine was evaluated for the treatment of dementia in PD [28]. Rivastigmine was also effective in patients with dementia with Lewy bodies. Benefits were seen on tests of attention, working memory, and episodic secondary memory [29]. Rivastigmine was successfully applied for the treatment of vascular dementia [30–33], for treatment of hallucinations in Creutzfeldt-Jakob disease [34], and memory deficits induced by electroconvulsive therapy [35].

Many reviews exist on results of clinical trials using the rivastigmine transdermal patch describing enhanced tolerability and significantly less side effects. A 24 week, randomized, controlled trial of rivastigmine patch 13.3 mg/24 h versus 4.6 mg/24 h demonstrated superior efficacy of the 13.3 mg/24 h patch over the 4.6 mg/24 h patch on the Severe Impairment Battery and the AD Cooperative Study–Activities of Daily Living scale–Severe Impairment Version [36, 37] (Thomson Reuters Pharma, update of June 9, 2014).

Rivastigmine transdermal patch formulation (Samyang, Seoul) is in Phase I clinical evaluation since November 2013 (Thomson Reuters Pharma, update of January 7, 2014).

Rivastigmine transfilm is a sustained release transdermal patch formulation of Tesa Labtech (Langefeld, Germany) in preclinical development (Thomson Reuters Pharma, update of January 7, 2014).

Galantamine (Razadyne, Reminyl, Nivalin; Janssen Pharmaceutica, Beeser, BIE, part of Johnson & Johnson, Shire and Takeda under license from SanofiAventis; Fig. 1) is an alkaloid extracted from the bulbs of the Amaryllidaceae family that include daffodils and the common snowdrop (Galanthea Lycopodium). It blocks AChE (E.C. 3.1.1.7) with an IC50 of 7,320 nM [11]. Galantamine was launched in China for the treatment of AD in 1995. The IC50 of 800 nM and BChE (E.C. 3.1.1.8) with an IC50 of 7,320 nM [11]. Galantamine was launched in 2001 for the treatment of mild to moderate AD in EU and the US and in March 2011 in Japan.

The sales of galantamine in 2011 for Johnson & Johnson were USD 470 million, for Shire in 2012 USD 38 million and for Takeda in 2012 USD 105 million (Thomson Reuters Pharma, update of May 6, 2014).

There are currently 1,786 publications on galantamine (or galanthamine) listed in PubMed (as of May 27, 2014). A commercial scale process of galantamine hydrobromide was presented by chemists of Aurobindo Pharma [39, 40].

The binding interactions of galantamine with amyloid-β (Aβ) peptide were elucidated [41]. 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 [42].

Long-term effects of galantamine treatment on brain functional activities were measured by positron emission tomography (PET) in AD patients [43]. For galantamine in PD, see [44], in schizophrenia patients [45]; in vascular dementia [46].

Johnson & Johnson (New Brunswick, NJ) and Shire (Basingstoke, UK) under the license of Synaptex (Spokane, WA) developed and launched Razadyne ER (Reminyl XL), an extended release capsule formulation, in April 2005 in the US [47, 48] (Thomson Reuters Pharma, update of June 3, 2014).

NAL-8801 (NAL Pharmaceuticals, Hong Kong) 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 January 17, 2014).

Memogain (GLN-1062; Neurodyn, Charlotte, Canada) under license from Galantas Pharma; Heidelberg) is a prodrug, the benzoyl ester, of galantamine administered as an intranasal formulation [49]. In December 2013, the 2-part, single ascending dose Phase Ia trial was initiated in the Netherlands. In January 2014, the double-blind, placebo-controlled, two single ascending dose (5.5 and 11 mg) was completed in healthy young subjects (n = 16). Interim data reported that the drug was safe and well tolerated and significantly enhanced working memory in the healthy subjects (Thomson Reuters Pharma, update of February 25, 2014).

Huperzine A (Cerebra; Shanghai Institute of Material Medica; Fig. 1) is a natural Lycopodium alkaloid found in extracts from Huperzia serrata [50]. 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. Its pharmacology, efficacy and safety was extensively described [724–728]. See also Part 3, Chapter 13. Natural products.

A large-scale synthesis resulted from a joint venture by process chemists of Shasun Pharma (UK and India), Rhodia Pharma (USA), and Debiopharm (Switzerland) [51]. Shasun Pharmaceuticals and Debiopharm entered into a licensing agreement for the manufacturing and commercialization of Huperzine A (Thomson Reuters Pharma, update of August 29, 2013).

There are currently 455 publications on huperzine A listed in PubMed (as of May 27, 2014). The mechanism of Huperzine A seems to play via Wnt/β-catenin signaling [52]. Chronic administration
of huperzine A to double transgenic mice led to an increase in ADAM10 and a decrease in BACE1 and amyloid-β protein precursor (AβPP) protein levels. Huperzine A was also evaluated in triple transgenic mice confirming the improvement of cognitive performance and the non-amyloid pathway activation [53]. Huperzine A reduced iron levels in brains of AD mice [54].

**XEL-001HP** (Xel Pharmaceuticals, Draper, UT in collaboration with Guangzhou Xiangxue Pharmaceutical, Guandong) is a once-weekly sustained release transdermal patch formulation. This formulation was tested in a Phase I clinical trial in China starting in September 2008. The drug is in Phase II trials in China since March 2011 (Thomson Reuters Pharma, update of December 31, 2013).

**XEL-001HG** (Xel Pharmaceuticals, Draper, UT) is a sustained release topical gel formulation in preclinical evaluation (Thomson Reuters Pharma, update of January 3, 2014).

**Posiphen** (the (+)-enantiomer of phenserine, QR Pharma, Berwyn, PA under license from TorreyPines Therapeutics, La Jolla, CA; Fig. 2) is in Phase II clinical trials for the oral treatment of AD since June 2009. Posiphen also blocked the expression of brain α-synuclein [55, 56]. Posiphen is a candidate drug to lower CSF AβPP, Aβ peptide, and tau levels in humans [57]. The synthesis of its primary metabolic products was described [58]. For its neurotrophic actions, see [59] (Thomson Reuters Pharma, update of December 23, 2013).

**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-aminoacridine succinate, a dual cholinesterase inhibitor in Phase II clinical trials since March 2011 (Thomson Reuters Pharma, update of December 31, 2013).

**Bisnorcymserine** (QR Pharma, Radnor, PA under license from TorreyPines Therapeutics, La Jolla, CA; Fig. 2) is a dual BChE and AβPP inhibitor. In June 2012 a Phase I, single-ascending-dose, safety study was planned in elderly volunteers (expected n = 72). In July 2012, the trial was initiated and was to be conducted by the NIA/NIH clinical research group under an NIH clinical trial agreement. In November 2012, a second Phase I trial was initiated (Thomson Reuters Pharma, update of April 26, 2013).
There are several cholinesterase inhibitors in preclinical evaluation (in alphabetical order): 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 [61].

The most potent AChE inhibitor is the molecule syn-1 (Fig. 3) with \( K_d \) of 77 fM synthesized at the Scripps Research Institute (La Jolla, CA) linking a tacrine part via click chemistry to a phenanthridium unit. The tacrine part is binding to the catalytic site, the phenanthridium piece is located at the peripheral site of AChE [62].

The University of Nebraska Medical Center (UNMC, Omaha, NE) investigates an \(^{18}\)F labeled 2′-deoxy-3′-fluorothymidine derivative (Fig. 3), which binds irreversibly and inhibits BChE and may be useful as a diagnostic agent for imaging of AD [63] (Thomson Reuters Pharma, update of April 3, 2013).

Many new scaffolds for AChE inhibitors were discovered recently, such as isoxazoles [64], quinolino-donepezils [65], new semicarbazones of 4-aminopyridine and 7-methoxytacrine-adamantyl-lamine heterodimers [66–68] and phenylcinnamide derivatives [729]. 1,2,3,4-Tetrahydrobenzo[h][1,6]naphthyridines were described as potent peripheral-to-midgorge-site inhibitors of AChE [69]. For alkaloids as a source of potential AChE inhibitors, see [70].

Excellent reviews describe novel virtual screening techniques [71, 72].

The development of many AChE inhibitors was terminated (in alphabetical order): of bis-(7)-tacrine (Mayo Foundation; [73]), huprines (Universitat Autonoma de Barcelona [74–88]), methanesulfonyl fluoride (SNX-001; SeneXta; [89–95]), NP-0336 (Noscira), \((-\)-phenserine (Axonys under license from NIH and Daewoong Pharmaceuticals; [96–99]); it was proposed to retest \((-\)-phenserine by avoiding methodological deficiencies of the first clinical trial; [100]), protexia (PEGylated recombinant human butyryl-cholinesterase; PharmAthene under license from Nexia Biotechnologies; [101, 102]), SPH-1285 and SPH-1359 (Sanochemia) and of WIN-026 (NN-176, KR-WAP-026; WhanLn, Seoul under license from Scigenic & Scigen Harvest; [103, 104]).

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” [105, 106].

2.1.1.1. Dual AChE inhibitors and AChE receptor ligands. The development of MHP-133 (an AChE inhibitor interacting with \( M_4 \) muscarinic acetylcholine, 5-HT\(_4\) and \( I_\beta \) imidazoline receptors, Medical College of Georgia; [107, 108]) and of Ro-46-5934 (a dual AChE inhibitor and \( M_2 \) AChR antagonist, Roche; [109]) was discontinued.

2.1.1.2. Dual AChE and amyloid-\( \beta \) inhibitors. AChE colocalizes with A\( \beta \) peptide deposits in the brains of
AD patients and promoted Aβ fibrillogenesis by forming stable AChE-Aβ complexes. A new motif in the N-terminal of AChE triggers Aβ aggregation and deposition [110].

**AVCRI-104P** (University of Barcelona and Fundacio Bosch I Gimpera, Fig. 4) is a multifunctional therapeutic that inhibited Aβ aggregation including AChE- and self-induced Aβ aggregation, BACE1 and AChE and BChE for the potential treatment of AD (Thomson Reuters Pharma, update of April 10, 2014).

**Meserine** (Shanghai Jiao Tong University School of Medicine, Fig. 4) is a potent AChE inhibitor (IC50 = 274 nM) lowering Aβ42 levels by 42% in AβPP/PS1 transgenic mice cerebrum after i.p. injection of 7.5 mg/kg [111].

This is an area of research with numerous novel contributions presenting O-hydroxyl or O-aminobenzylamine-tacrine hybrids [112], phenylthiazole-tacrine hybrids [113], benzo[e][1, 2, 4]triazin-7(1H)-one and [1, 2, 4]triazine[5,6-ji]carbazol-6-one derivatives [114] and N'-(4-benzylpiperidin-/piperazin-1-yl)acylhydrazone derivatives [115]. Thioflavin- and deferiprone-based molecules acted as AChE inhibitors and dissociated toxic Aβ aggregates [116]. Sym-triazines and 1,4-substituted 4-(1H)-pyridylene-hydrazones inhibited Aβ fibril formation and AChE [117–119], as did tacrine-benzothiazole hybrids [120] and novel tacrine analogs [121, 122]. Rhein-sutrine hybrids showed AChE and BChE inhibiting properties and BACE1, dual Aβ42, and tau anti-aggregating activities [123]. Genstein-O-alkylbenzylamines showed good AChE inhibitory activity and significant inhibition of Aβ aggregation [124]. D-ring opened galantamine analogues showed potent inhibition of AChE and good Aβ42 aggregation inhibitory activity [125]. A ruthenium(II) polypyridyl complex showed AChE and Aβ aggregation inhibiting properties [126]. Benzylisouquinoline derivatives showed strong AChE inhibitory activity and inhibited self-induced Aβ aggregation [730].

The development of NP-61 (NP-0361; Noscira, previously Neuropharma; [127, 128]) was terminated.

2.1.1.3. Dual AChE inhibitors and antioxidants. Several dual-acting drugs with potent AChE inhibiting activity and antioxidant properties were presented, such as novel 4-dimethylaminonitroflavonoid derivatives, which exhibited high AChE and BChE inhibitory activity and showed potent oxygen radical absorbance capacity [129]. 3,4-dihydroxybenzoic acid derivatives acted as antioxidants and AChE inhibitors [130]. Fused donepezil and ebuses were disclosed [131, 132], as were chromenotacrine [133], novel tacrine-carbazole hybrids [134], quinolone-benzylpiperidine derivatives [135], melatonin-N,N-dibenzyl-N-methylamine hybrids [136] and 1H-phenanthro[9,10-d]imidazoles [731].

2.1.1.4. Dual AChE and β-secretase-1 or γ-secretase inhibitors. Tacrine-flurbiprofen hybrids showed superior AChE inhibitory activities [137, 138]. Other tacrine-flurbiprofen hybrid compounds acted as potential BChE inhibitors with vasorelaxation activity [139].

2.1.1.5. Dual AChE inhibitors and calcium channel blockers. The development of bio(7)-tacrine (Mayo Foundation; [73]) was terminated.

2.1.1.6. Dual AChE inhibitors and cannabinoid receptor antagonists. Novel CB2 cannabinoid agonists with additional BChE inhibiting properties were disclosed [140].

The development of Compound 29 (Solvay, now AbbVie, North Chicago, IL) was terminated [141].

2.1.1.7. Dual AChE & fatty acid amide hydrolase inhibitors. MIQ-001 (MetaIQ Aps, Aarhus, Denmark) is a fatty acid metabolism inhibitor for the potential treatment of AD. A Phase 1 healthy volunteer study was performed starting in February 2010 (Thomson Reuters Pharma, update of May 3, 2013). The structure was not communicated.

2.1.1.8. Dual AChE inhibitors and histamine H1 receptor antagonists. A computational analysis of
novel drugs designed for use as AChE inhibitors and histamine H3 receptor antagonists for AD was described [142].

2.1.1.9. Dual AChE and monoamine oxidase inhibitors. Ladostigil (TV-3326; Avraham Pharmaceuticals, Yavne, Israel under license from Yissum Research Development, a wholly owned company of the Hebrew University of Jerusalem; Fig. 5) combines the carbamate moiety of the BChE inhibitor rivastigmine with the propargylamine pharmacophore of the MAO-B inhibitors selegiline and rasagiline. Ladostigil is currently in Phase IIb 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 (MCI) (Thomson Reuters Pharma, update of August 29, 2013). See also section 2.36. Drugs interacting with Monoamine Oxidase.

Spanish and Italian medicinal chemists described potent dual cholinesterase and MAO inhibitors [143–145]. One example is ASS234 (Universitat Autonoma de Barcelona and CSIC, Madrid; Fig. 5), which is also an antioxidant, inhibited Aβ aggregation and protected from Aβ-induced apoptosis in vitro (Thomson Reuters Pharma, update of July 22, 2013). See also section 2.36. Drugs interacting with Monoamine Oxidase.

Scientists of the University of Wisconsin (Madison, WI) investigated acetyl-CoA:lysine acetyltransferase (ATase1/2) inhibitors such as Compound 9 (Fig. 5) for the potential prevention and treatment of AD [150]. ATase1/2 inhibitors reduced BACE1 and Aβ levels in an AβPP/95sw mouse model of AD. One compound decreased BACE1 and Aβ levels and prevented synaptic and cognitive defects (Thomson Reuters Pharma, update of November 27, 2013).

2.2. Drugs interacting with acetyltransferases

α-secretase cleaves AβPP at the Lys16-Leu17 bond within the Aβ sequence to generate the soluble N-terminal AβPP fragment (sAβPPs) and the membrane bound CTF83 (carboxy-terminal fragment of 83 residues in length) thus precluding the formation and subsequent deposition of Aβ.

Bryostatin-1 (Neurotrope BioScience, Plantation, FL in collaboration with the Blanchette Rockefeller Neurosciences Institute, Morgantown, WV) is a naturally occurring PKC activator isolated from the Californian marine bryozoan Bugula neritina. In April 2014 the program was listed as being in Phase IIa development for familial AD, clinical development for fragile X syndrome, and in lead optimization for ischemic stroke and traumatic brain injury. Bryostatin-1 improved survival and reduced ischemic brain injury in aged rats after acute ischemic stroke [151] (Thomson Reuters Pharma, update of June 5, 2014). See also Chapter 2.48. Drugs interacting with Protein Kinase C.

APH-1104 (Amylon LLC, a spin-off of Aphios, Woburn, MA) is a potent α-secretase modulator for the potential oral treatment of mild to moderate AD, cognitive disorders, and other CNS disorders including Down’s syndrome and glaucoma. In November 2013, preclinical data were reported. It is more potent than the PKC modulator APH-0703 (see Chapter 2.48; Thomson Reuters Pharma, update of November 21, 2013). The structure was not communicated.

DIA-10-D (Arizona State University, Tempe, AZ and the Roskamp Institute, Sarasota, FL) is a bispecific tandem single chain (scFv) antibody combining iBSEC1 with the ASec1A, which simultaneously inhibited BACE and promoted α-secretase processing of AβPP. The iBSEC1 scFv was selected, since it recognizes the BACE1 cleavage site on AβPP but does
not bind the adjacent highly antigenic N-terminal of Aβ [152, 153] (Thomson Reuters Pharma, update of February 7, 2013).

The development of etazolate (EHT-0202; SQ-20009; Diaxonhit, formerly Exonhit) and of NP-17, NP-21, NPM-01, NPM-05B1, and NPM-05B2 (orally available α-secretase activators of marine origin; Noszira, Madrid) was terminated.

2.4. Drugs interacting with beta secretase

In the amyloidogenic pathway, AβPP is first cleaved by BACE1 (EC 3.4.23.46; [154, 155]) between residue methionine 671 and aspartic acid 672 to release a 100 kDa NT-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. The splice variants of BACE1 were reviewed [156]. The transcriptional and post-transcriptional regulation of BACE1 was described [157]. The normal and pathologic roles of β-secretase BACE1 was described [732]. A physiological regulator of BACE1 stability and activity is Rheb GTPase, which induced mammalian target of rapamycin activity [158].

There are many interesting reviews on the pharmacology and medicinal chemistry of BACE inhibitors (in chronological order): 2012 [159], 2013 [160–162], 2014 [163, 164].

MK-8931 (SCH-900931; Schering-Plough, now Merck, Whitehouse Station, NJ; Fig. 6) is a potent inhibitor of BACE. Single doses of MK-8931 from 2.5 to 550 mg were well-tolerated [165]. In November 2013 a Phase III trial in prodromal AD patients was initiated in the US. In March 2014, the trial was underway (Thomson Reuters Pharma, update of April 24, 2014).

CTS-21166 (ASP-1702, ATG-Z1; Astellas Pharma, Tokyo and CoMentis, South San Francisco, CA) is a BACE1 inhibitor in Phase I clinical trials since June 2007. In 48 volunteers, the drug was safe and well tolerated (Thomson Reuters Pharma, update of January 31, 2014). The structure was not communicated.

E-2609 (Eisai, Tokyo) is a BACE 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 April 24, 2014). The structure was not communicated.

HPP-854 (TTP-854; High Point Pharmaceuticals, High Point, NC; a spin-out from TransTech Pharma, High Point, NC) is a BACE inhibitor in Phase I clinical trials since November 2009 (Thomson Reuters Pharma, update of November 13, 2013). The structure was not communicated.

Shionogi (Osaka, in collaboration with Janssen Pharmaceuticals, Titusville, NJ, Fig. 6) is investigating conformationally restricted BACE inhibitors [173, 174]. In March 2013 the drug program was listed as being in Phase I in Europe (Thomson Reuters Pharma, update of June 6, 2014).

TAK-070 (University of Tokyo under license from Takeda, Osaka; Fig. 6) is a BACE and Aβ aggregation inhibitor [175, 176]. By December 2013 a Phase I study was underway (Thomson Reuters Pharma, update of January 28, 2014).

Vitae Pharmaceuticals (Fort Washington, PA) in collaboration with Boehringer Ingelheim and the Technical University of Munich [208, 209] is exploring orally active BACE 1 inhibitors. In February 2014 Phase I trials were initiated in the US and in Germany (Thomson Reuters Pharma, update of February 21, 2014). Structures were not communicated.

Several BACE inhibitors of known structure are in preclinical evaluation (in alphabetical order): Arogen (Thousand Oaks, CA; Fig. 6) investigated series of 2-aminooquinolines and 2-aminopyridines as BACE1 inhibitors including AMG-0683 [177]. Hydroxyethylamine and aminoheterocyclic xanthenes containing BACE inhibitors were described
Fig. 6. Beta-secretase inhibitors.

recently [178–182] (Thomson Reuters Pharma, update of April 1, 2014). Array BioPharma (Boulder, CO; Fig. 6) in collaboration with Genentech (South San Francisco, CA) presented novel spirocyclic BACE1 inhibitors [183, 184] (Thomson Reuters Pharma, update of January 23, 2014).

AZ-4217 (AstraZeneca, Fig. 6) is a high potency BACE1 inhibitor (IC50 = 160 pM). A one month treatment significantly lowered Aβ deposition in 12 month old Tg2576 mice [185]. Scientists of the Beijing Institute of Pharmacology and Toxicology presented the potent BACE1 Inhibitor VIa (Fig. 6) with an IC50 = 5.9 nM for BACE1 and good selectivities against BACE2, cathepsinD and renin. In cellular assays 1 nM of BACE1 inhibitor VIa reduced Aβ1-42 by 40% [186].

DIA-10-D (Arizona State University, Tempe, AZ and the Roskamp Institute, Sarasota FL) is a bispecific tandem single chain (scFv) antibody combining iBSEC1 with the ASec1A, which simultaneously inhibited BACE and promoted α-secretase processing.
of AβPP. The iBSEC1 scFv was selected, since it recognizes the BACE1 cleavage site on AβPP but does not bind the adjacent highly antigenic N-terminal of Aβ [152, 153] (Thomson Reuters Pharma, update of February 7, 2013).

ER-901356 (Eisai, Tokyo), a BACE1 inhibitor with an IC₅₀ of 8 nM was administered to rats (3 and 10 mg/kg po) and at 6 h the 10 mg/kg dose significantly reduced Aβ₄₀ levels by 55%, 85%, and 70% in plasma, CSF, and brain, respectively. In Cynomolgus monkeys administered 0.3 to 10 mg/kg p.o. of ER-901356, there was a dose-dependent reduction in plasma and CSF levels of Aβ₁₋₄₀ reduction at the highest doses was 87% and 60% in plasma and CSF, respectively (Thomson Reuters Pharma, update of March 12, 2013). The structure was not communicated.

GNE-629 and GNE-892 (Genentech, South San Francisco, CA; both Fig. 6) are BACE inhibitors in preclinical development [187–189].

GRL-8234 (Johns Hopkins University, Baltimore, MD and Georgetown University, Washington, DC, previously investigated by the Oklahoma Medical Research Foundation, Oklahoma City; Fig. 7) is a potent inhibitor of BACE (IC₅₀ = 1.8 nM) and Aβ synthesis for the potential i.v. treatment of AD. It rescued age-related cognitive decline in AβPP transgenic mice [190] (Thomson Reuters Pharma, update of March 17, 2014).

HL-0362 (2,2′,4′-trihydroxychalcone; Shanghai Institute of Materia Medica of the Chinese Academy of Sciences), isolated from Glycyrrhiza glabra, a new inhibitor of BACE1 efficiently ameliorated memory impairment in mice [191]. Structure optimization is currently ongoing (Thomson Reuters Pharma, update of September 11, 2013).

Johnson & Johnson (presumably JNJ-715754, Fig. 7) is evaluating compounds from a series of aminopiperazines with an IC₅₀ of 40 nM in a BACE1 enzymatic assay, of 28 nM for hAβ₁₋₄₂, and 25 nM for hAβTotal. Medicinal chemistry papers were communicated [192–197] (Thomson Reuters Pharma, update of July 5, 2013).

L-655240 (Merck, Fig. 7) is a thromboxane A2 antagonist, which was re-discovered as a BACE1 inhibitor with IC₅₀ of 4.47 μM by Chinese authors [198].

Novartis (Fig. 7) investigated a series of cyclic sulfoxide hydroxyethylamine BACE1 inhibitors. The compound reduced CSF and brain Aβ₄₀ 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 [199–202] (Thomson Reuters Pharma, update of January 31, 2014).

Perrigo (Dublin, Ireland; following the acquisition of Elan) is investigating a series of small-molecule inhibitors of BACE1. Data on hydroxyethylamine
BACE1 inhibitors showed IC50 values against BACE1 of 12 nM and an ED50 value of 2.1 nM in a HEK-293 cellular assay. Novel dihydroisoquinoline BACE1 inhibitors were presented (Thomson Reuters Pharma, update of December 19, 2013).

Pfizer scientists published on spirocyclic sulfamides as BACE inhibitors (Fig. 7) [206, 207] (Thomson Reuters Pharma, update of August 2, 2013).

ProMediTech (Scoul)/LG Life Sciences (Scoul) and the Seoul National University are investigating BACE inhibitors for the potential treatment of AD (Thomson Reuters Pharma, update of November 8, 2013). Structures were not communicated.

Bi-functional small molecule inhibitors of β- and γ-secretase (Hadassah University Hospital and the Hadassah Medical Research Services and Development, Jerusalem) are investigated for the potential treatment of AD. In vitro data had demonstrated that two compounds reduced amyloid-β levels in PC12 cells in low micromolar concentrations (Thomson Reuters Pharma, update of May 14, 2014).

Dual α7 nicotinic acetylcholine receptor activators and BACE1 inhibitors are investigated in a program at the University of Maryland, College Park, MD (Thomson Reuters Pharma, update of November 29, 2013). No structures were communicated.

BBS-1 BACE inhibitor mAb vaccine (NavVax, Ness Ziona, Israel 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 BACE1 to cleave AβPP (Thomson Reuters Pharma, update of January 22, 2014).

Brain-targeted BACE1 antibody (Genentech, South San Francisco, CA, Roche Holding) is a bi-specific antibody against BACE1 and the transferrin receptor to allow transcytosis across the blood-brain barrier (BBB) [210–212]. Safety liabilities of transferrin receptor bispecific antibodies that cross the BBB were addressed [213] (Thomson Reuters Pharma, update of July 26, 2013).

Excellent papers on theoretical calculations on BACE1 inhibitors were presented (in chronological order): 2013 [217, 213]; 2014 [217].

The development of BACE inhibitors (Actelion, Bristol-Myers Squibb; [218–224]; the Genetics Co (CallistoGen), Ligand, Locus Pharmaceuticals, Medivir [225, 226], Nosica and Plexxikon), GRL-11097 (Purdue University and Astellas Pharma), GSK-188909 (GSK, [227–235]), heparinoid β-secretase inhibitors (IntelliHep), LY-2886721 (Eli Lilly; [236–241]), PP-05297909 (Pfizer), RG-7129 (Roche from a research collaboration with Siena Biotech; [242–244]), and WAY-258131 (Wyeth, now Pfizer; [245–261]) was terminated.

2.5. 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. The enzyme consists of four protein components: presenilin 1 or 2, which contains the catalytic domain, nicasin, Apl-1 (anterior pharynx-1), and Pen-2 (presenilin enhancer-2) in a 1:1:1:1 ratio [262].

There are many interesting publications on medicinal chemistry and pharmacology of γ-secretase inhibitors and modulators (in chronological order): 2012 [263, 264], 2013 [265, 264], 2014 [266].

2.5.1. Gamma-secretase inhibitors

Several γ-secretase inhibitors are in preclinical evaluation (in alphabetical order):

FLZ is a synthetic cyclic derivative of squamosamide from Anomura glabra. It attenuated AβPP processing and decreased Aβ production in mitochondria by selectively inhibiting γ-secretase [267, 268].

Harvard Medical School scientists (Boston, MA) are investigating a series of Notch-sparing γ-secretase inhibitors for the potential treatment of AD (AD-1209, AD-1065, AD-1221, AD-1215, AD-1138, and AD-904; one structure shown in Fig. 8). One of the compounds (AD-1068) had an IC50 value of 9 nM against Aβ42 and an IC50 value of 1.8 μM for Notch. An excellent review was published [269] (Thomson Reuters Pharma, update of July 25, 2013).

NGP-555 (NeuroGenetic Pharmaceuticals, Del Mar, CA, Fig. 8) has an IC50 of 8.3 nM for Aβ. It reduced levels of Aβ42 in brain and plasma at doses up to 100 mg/kg p.o. (Thomson Reuters Pharma, update of March 22, 2013).

Pfizer (Ann Arbor, MI; Fig. 8) presented a novel γ-secretase inhibitor containing a bicyclo-[1.1.1]-pentanoyl moiety with an IC50 of 0.178 nM being equipotent to avagacestat (IC50=0.196 nM) [270] (Thomson Reuters Pharma, update of July 30, 2012).

RO-02 (Roche; Fig. 8) inhibited enzyme activity with an IC50 inhibition IC50 of 500 nM of 1209, AD-1065, AD-1221, AD-1215, AD-1138, and AD-904, one structure shown in Fig. 8). One of the compounds (AD-1068) had an IC50 value of 9 nM against Aβ42 and an IC50 value of 1.8 μM for Notch. An excellent review was published [269] (Thomson Reuters Pharma, update of July 25, 2013).

Critical Outcome Technologies (London, Ontario) is investigating orally available, dual β- and γ-secretase inhibitors.
inhibitors for the potential treatment of AD (Thomson Reuters Pharma, update of January 29, 2013).

The development of many γ-secretase inhibitors was terminated (in alphabetical order), of avagacestat (BMS-708163; Bristol-Myers Squibb; [272–289]), BMS-932481 (Bristol-Myers Squibb; E-2212; Eisai; [290]), GSI-1 (L-685,458; SCH-900229; Merck; [291–297, 291, 298–315]), MK-0752 (Merck; terminated for the indication AD, but in Phase II for the treatment of cancer [316]; Thomson Reuters Pharma, update of May 28, 2014); MRK-560 (SCH-1375975; Schering-Plough, now Merck; [291–293], [317–327]), NGP-328 (NeuroGenetic Pharmaceuticals), peptide-based γ-secretase inhibitors (Pepscan Therapeutics), NIC5-15 (Humanetics under license from the Mount Sinai School of Medicine), PF-03084014 (Pfizer; terminated for the indication AD, but in Phase I for the treatment of cancer; [328–331]; Thomson Reuters Pharma, update of April 29, 2014).

2.5.2. Gamma-secretase modulators

γ-secretase modulator photoaffinity probes revealed distinct allosteric binding sites on presenilin [332]. γ-secretase modulators were effective also in preparations containing AβPP mutations [333].

Several reviews on γ-secretase modulators were presented (in chronological order): 2012: [334–336], 2013: [337, 338], 2014: [339].

CHF-5074 (CereSpir, New York, NY under license from Chiesi Farmaceutici, Parma; Fig. 9) is a γ-secretase modulator in vitro and inhibited plaque deposition and reversed memory deficits in vivo in transgenic mouse models of AD. Tg2576 mice fed with standard diet displayed an impairment of recognition memory. This deficit was completely reversed after long term treatment with CHF-5074 for 13 months [340]. It restored visual memory ability [341] and interacted with the AβPP intracellular domain and impaired its nuclear activity [342]. In July 2012 data from the 12-week, double-blind, dose-range study were presented at the Alzheimer’s
Association International Conference 2012 in Vancouver, Canada. Patients were randomized to receive 200, 400, and 600 mg of CHF-5074 p.o. daily (n = 72) or placebo (n = 24). CHF-5074 was well tolerated. Profile of MCI and healthy patients were similar. The drug dose-dependently affected CSF biomarkers of neuroinflammation in man [343] (Thomson Reuters Pharma, update of April 3, 2014). The structures were not communicated.

EVP-0962 (FORUM Pharmaceuticals, previously EnVivo Pharmaceuticals, Watertown, MA) 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. In November 2012, a randomized, double-blind, parallel-assigned, Phase II study was initiated in healthy subjects or subjects (expected n = 52) with MCI or AD in the US to assess the safety, tolerability, efficacy, and pharmacokinetics. Preclinical data on a close analogue EVP-091562 were published recently [344] (Thomson Reuters Pharma, update of April 3, 2014). The structures were not communicated.

Several γ-secretase modulators are in preclinical evaluation (in alphabetical order):
- AS-2715348 (Astellas Pharma, Tsukuba; Fig. 9) is a γ-secretase modulator, which reduced both cell-free and cellular production of Aβ42 without increasing levels of AβPPβ-carboxy-terminal fragment or inhibiting Notch signaling [345].
- Asceneuron (Lausanne, Switzerland) investigates small Aβ peptides targeting γ-secretase for the potential treatment of AD (Thomson Reuters Pharma, update of July 18, 2013). The structures were not communicated.
- BIIB-042 (Biogen Idec, Weston, PA; Fig. 9) 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 (Thomson Reuters Pharma, update of March 27, 2012).
- Dainippon Sumitomo Pharma (Osaka; Fig. 9) is evaluating γ-secretase modulators for the potential treatment of AD. Medicinal chemistry was published [346] (Thomson Reuters Pharma, update of February 25, 2014).
- HCT-1026 (NicOx, Sophia-Antipolis, France; Fig. 9) is a nitric oxide (NO)-releasing flurbiprofen derivative. Recent research showed that it alleviated functional muscle ischemia and may be valuable to treat Duchenne muscular dystrophy [347] (Thomson Reuters Pharma, update of November 13, 2013).
- The University of California San Diego is investigating γ-secretase modulators which inhibit the production of Aβ42 for the potential treatment of AD [348] (Thomson Reuters Pharma, update of June 13, 2013).
- The development of γ-secretase modulators of Aβ42 was terminated. Also the development of AZ1136, AZ-3303 and AZ-4800 (AstraZeneca; [350–354]), of SPI-014, SPI-1802, SPI-1810, and SPI-1865 (Satori Pharmaceuticals; [355–357]) and of tarenflurbil (MPC-7869; (R)-flurbiprofen, Flurizan, Myriad Genetics, Loma Linda University; [358–367]) was discontinued.

2.5.3. Inhibitors of gamma-secretase activating protein

γ-secretase activating protein (GSAP) interacts both with γ-secretase and its substrate, the AβPP carboxy-terminal fragment (AβPP-CTF). The role of GSAP in the regulation of γ-secretase and Aβ generation was reviewed [368].

Imatinib (Gleevec, STI-571; Novartis, launched in 2001) is an inhibitor of GSAP 3xTg mice treated with imatinib showed a significant reduction in GSAP expression levels, brain Aβ levels and a reduction of tau phosphorylation [369].

ITI-009 series (Intra-Cellular Therapies, New York, NY) are GSAP inhibitors for the potential treatment of AD. A previous compound IC-200155 is no longer followed up (Thomson Reuters Pharma, update of April 8, 2014). Structures were not communicated.

2.5.4. Notch pathway inhibitors

AGT-0031 (AxoGlia Therapeutics, Luxembourg; Fig. 10) is an inhibitor of the Notch pathway, which is involved in astrocyte differentiation and inflammatory activation for the potential treatment of MS and AD [370] (Thomson Reuters Pharma, update of February 28, 2014).

2.6. Drugs interacting with aminoacylase 3

The University of California Los Angeles is investigating aminoacylase 3 inhibitors for the potential treatment of AD, PD, and other neurodegenerative diseases. Inhibition of aminoacylase 3 protected cortex neuronal cells from the toxicity of 4-hydroxy-2-nonenal [371].

2.7. Drugs interacting with amyloid binding alcohol dehydrogenase

The discovery that Aβ, present in mitochondria, specifically binds to amyloid binding alcohol dehydrogenase (ABAD) opened up a new area of AD research.
A recent review described the evidence that the prevention of Aβ binding to ABAD may be a valuable drug target for the treatment of AD [372]. The first paper on structure-based design and synthesis of benzothiazole phosphonate analogues inhibiting human ABAD-Aβ was published by researchers of the University of Kansas [373]. Small molecule ABAD inhibitors crossing the BBB and their pharmacokinetics were described [374].

2.8. Drugs interacting with angiotensin converting enzyme (ACE)

Preclinical and clinical data of the topic ACE and memory were discussed [375–378]. The use of ACE inhibitors in older adults with AD was associated with a slower rate of cognitive decline independent of hypertension as was shown in a four-year prospective multicenter cohort study in France [379]. Centrally acting ACE inhibitors reduced the rate of cognitive decline in patients with dementia [380, 381]. The prescription of ACE inhibitors is a protective factor for cognitive deterioration [382]. Overexpression of angiotensin-converting enzyme in myelo-monocytes prevented AD-like cognitive decline in mice [383].

Captopril (Capoten, Capozide; Bristol-Myers Squibb, launched in 1981; Fig. 10) attenuated the age-related decline in spatial learning and memory both in spontaneously hypertensive rats as in Wistar-Kyoto rats [384]. Captopril, but not losartan, a selective AT1 receptor antagonist, improved learning in an active avoidance task, whereas both drugs were effective in enhancing retention of memory when administered prior to the training of mice [385]. Captopril facilitated memory retrieval after a two month retention interval in mice [386] and delayed the onset of scopolamine-induced impairment [387]. Captopril and enalapril improved cognition and depressed mood in hypertensive patients [388].

Perindopril (Aceon, Coversyl, Servier and Kyowa Hakko Kirin, launched in 1988; Fig. 10) is a long-acting ACE inhibitor. Several reports showed that perindopril improved learning and memorizing in mice [389–393] and rats [394–396]. Perindopril did not show any adverse cognitive effects in elderly [397]. Perindopril was associated with a reduced rate of functional decline in patients with AD without association with mood or behavior suggesting that perindopril may slow disease progression in AD [383].

Trandolapril (Gopten, Mavik, Odirik; Roussel-Uclaf, now sanofi, launched in Japan in 1993 and in the US in 1997; Fig. 10) attenuated acquisition of conditioned avoidance in rats [398]. Captopril and trandolapril improved learning and memory in active and passive avoidance tests in rats comparable to the effects of the nootropic drug oxiracetam [399].

2.9. Drugs interacting with beta-hexosaminidase

Amicus Therapeutics (Cranbury, NJ) was 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. The development was terminated (Thomson Reuters Pharma, update of March 12, 2014).

2.10. Drugs interacting with 11β-hydroxysteroid dehydrogenase

The topic 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1), brain atrophy, and cognitive decline was reviewed [400].

UE-1961, UE-2811, and UE-2343 (University of Edinburgh in collaboration with Argenta Discovery, Harlow, UK; Fig. 11) are inhibitors of 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) for the treatment of age-related cognitive disorders. 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. In January 2013 a randomized, double-blind, placebo-controlled Phase I study to assess safety, efficacy, pharmacokinetics, and pharmacodynamics in healthy subjects (expected n = 48) was initiated in the UK (Thomson Reuters Pharma, update of September 26, 2013).

KR-1-2 (Korea Research Institute of Chemical Technology, Daejon, South Korea) suppressed cortisol by inhibiting 11β-hydroxysteroid dehydrogenase type 1. The drug is intended for the treatment of glaucoma, non-insulin dependent diabetes, and dementia (Thomson Reuters Pharma, update of December 2, 2013). The structure was not communicated.

The development of ABT-384 (Abbott Laboratories) was terminated [401].

2.11. Drugs interacting with calpain

Neuronal overexpression of the endogenous inhibitor of calpains, calpastatin, in [A30P] α-synuclein transgenic mice reduced human α-synuclein processing, aggregation, and synaptic impairment [402].

A-705253 (AbbVie, North Chicago, IL, a spin-out of Abbott Laboratories, formerly Knoll, Bayreuth, Germany; Fig. 11) is an orally active calpain inhibitor for the potential treatment of AD. A-705253 significantly reduced cholinergic neurodegeneration caused by Aβ in a dose-dependent manner in rats [403–409]. It also prevented stress-induced tau hyperphosphorylation in vitro and in vivo [410, 411] (Thomson Reuters Pharma, update of January 4, 2013).

ABT-957 (AbbVie, North Chicago, IL, a spin-out of Abbott Laboratories) is a calpain inhibitor for the potential treatment of neurological disorders including AD (Thomson Reuters Pharma, update of January 4, 2013). The structure was not communicated.

Conjugated linoleic acid (CLA) is a specific calpain inhibitor. CLA showed neuroprotective effects against neurotoxins as Aβ in SH-SY5Y cells and inhibited Aβ oligomerization/fibrillation and Aβ-induced Zona Occludens-1 degradation [413].

SNJ-1945 (Senju Pharmaceutical Co, Osaka; Fig. 11) is a potent calpain inhibitor for the potential oral treatment of age-related macular degeneration, retinopathy, and optic neuritis (Thomson Reuters Pharma, update of March 25, 2013).

2.12. Drugs interacting with carbonic anhydrase

Carbonic anhydrase dysfunction impaired cognition and was associated with mental retardation, AD, and aging [414].

The Blanchette Rockefeller Neurosciences Institute (Morgantown, WV) 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 April 18, 2014).

Ethylene bis-imidazoles are highly potent and selective activators for isozymes VA and VII of carbonic anhydrase with potential nootropic effects [415].

2.13. Drugs interacting with carnitine acetyltransferase

Mildronate (THP, MET-88, Meldonium, Quaterine; Grindeks, Riga, Latvia; Fig. 11) is a launched carnitine acetyltransferase inhibitor [416] and nootropic drug, which improved cognition and reduced Aβ pathology in transgenic AD mice [417–419].

2.14. 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.
Caspase-6 activity predicts lower episodic memory ability in aged individuals [420, 421].

NWL-53 (New World Laboratories, Laval, Quebec) is a peptidomimetic and selective inhibitor of caspase-3 for the potential treatment of neurological diseases including stroke, spinal cord injury, traumatic brain injury, MS, PD, AD, myocardial infarction, and cancer (Thomson Reuters Pharma, update of January 24, 2013). The structure was not communicated.

NWL-117 (New World Laboratories, Laval, Quebec) 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.

NWL-149 (New World Laboratories, Laval, Quebec) is a selective caspase 1/4 modulator for the potential treatment of inflammatory and autoimmune degenerative diseases including MS, AD, and heart disease (Thomson Reuters Pharma, update of January 24, 2013). The structure was not communicated.

NWL-154 (New World Laboratories, Laval, Quebec) is a peptidomimetic and selective caspase 6 modulator for the potential treatment of AD and Huntington’s disease (HD) (Thomson Reuters Pharma, update of January 24, 2013). The structure was not communicated.

2.15. Drugs interacting with catechol-O-methyltransferase (COMT)

SOM-0226 (SOM Biotech, Barcelona) is the COMT inhibitor tolcapone for the potential oral prevention and treatment of transthyretin amyloidosis in Phase II clinical trials since May 2012 in Spain (Thomson Reuters Pharma, update of April 17, 2014).

Cerecor (Baltimore, MD under license from Merck) is investigating COMT inhibitors for the potential treatment of schizophrenia including cognition (Thomson Reuters Pharma, update of February 18, 2014). Structures were not communicated.

Tolcapone (Tasmar; Roche, launched in 1997) and Entacapone (Comtan; Orion in collaboration with Novartis, launched in 1999) blocked fibril formation of α-synuclein and Aβ and protected against Aβ-induced toxicity [422]. Both agents acted as tau-derived hexapeptide (306)VVQIVYK(311) aggregation inhibitors [423].
2.16. Drugs interacting with cathepsin

Decreased expression of Cathepsin D is related to the defective degradation of amyloid β in AD [733]. VBY-036 and VBY-129 (Virobay, Menlo Park, CA) are cathepsin S inhibitors for the potential oral treatment of AD. In May 2013 Virobay initiated a Phase I, double-blind, randomized, placebo-controlled study to evaluate escalating doses of VBY-036 in healthy subjects (Thomson Reuters Pharma, updates of February 26, 2014 and March 13, 2013, respectively). The structures were not communicated.

Aloxistatin (E64d; AB-007; ALP-496; American Life Science Pharmaceuticals, San Diego, CA; Fig. 11) is an inhibitor of cathepsin B for the potential treatment of AD and traumatic brain injury [424]. E64d reduced brain pyroglutamate Aβ [425]. Aloxistatin was previously evaluated for the treatment of Duchenne muscular dystrophy by Taisho Pharmaceuticals, but this development was terminated (Thomson Reuters Pharma, update of April 8, 2014).

2.17. Drugs interacting with cholesterol 24S-hydroxylase (CYP46A1)

Researchers elucidated the binding site of cholesterol within the Aβ peptide in the linear fragment 22–35 of Aβ [426, 427]. For a debate, "is cholesterol a causative factor in AD", see [428]. Two recent reviews deal with the role of cholesterol metabolism in the pathogenesis of AD [734, 735].

AAV-CYP46A1 (INSERM in collaboration with sanofi) is an adeno-associated virus gene therapy encoding cholesterol 24-hydroxylase (CYP46A1 gene) for the potential injectable treatment of AD. Reduced Aβ peptides, amyloid deposits, and trimeric oligomers were observed in AβPP23 mice. Significant improvements in cognitive function assessed by the Morris water maze were also seen in Tau22 mice [429] (Thomson Reuters Pharma, update of June 6, 2012). See also Part 3, Chapter 4. Drugs interacting with Gene Expression.

2.18. Drugs interacting with cyclooxygenase (COX)

COX (EC 1.14.99.1) is the enzyme responsible for the formation of prostaglandins, prostacyclin, and thromboxane. NSAIDs exert their effects through inhibition of COX.

COX-1 inhibition by SC-560 reduced amyloid pathology and improved memory deficits in a mouse model of AD [430]. Short-term treatment with tolmetinic acid improved cognitive functions in AD mice [431]. It downregulated BACE1 after daily treatment for one month [432]. A review describes the use of anti-inflammatory drugs in the therapy of AD [433]. Aβ42-lowering NSAIDs constitute the founding members of the new class of γ-secretase modulators, vide supra Chapter 2.5.2.

2.19. Drugs interacting with cytochrome P450 (CYP) isoforms

Sodium benzoate, a D-amino acid oxidase inhibitor, was tested in 60 patients with amnestic MCI and mild AD in Taiwan. The preliminary results showed promise for D-amino acid oxidase inhibition as a novel approach for early dementing processes [434]. AS-2651816-00 (Astellas Pharma, Tokyo, Fig. 11) is a novel DAAO inhibitor for the potential treatment of schizophrenia with an IC50 of 1.5 nM against human DAAO [435] (Thomson Reuters Pharma, update of January 13, 2014).

Cerecor (Baltimore, MD) is investigating D-amino acid oxidase (DAAO) inhibitors to enhance the activity of D-serine for the potential treatment of schizophrenia (Thomson Reuters Pharma, update of August 12, 2013). Structures were not communicated.

2.20. Drugs interacting with D-Amino acid oxidase

Saxagliptin (Onglyza; BMS-477118; OPC-262; Bristol-Myers Squibb and AstraZeneca, launched in 2009; Fig. 12) ameliorated streptococin-induced AD
Glutaminyl cyclase (IC50 = 17 nM) and totally inhib-
many; Fig. 12) is a potent inhibitor of human
2014). The structure was not communicated.
(Thomson Reuters Pharma, update of February 17,
Pharmacokinetics was found to be dose-proportional
ated with relevant therapeutic levels in blood and CSF.
Oral administration of PQ-912 was safe and well toler-
ascending dose trials in >120 healthy volunteers were
placebo-controlled, blinded, single- and multiple-
less than elevated concentration of unmodified Aβ [441].
PQ-912 (Probiodrug, Halle Sachsen-Anhalt, Ger-
many) is a potent QC inhibitor in Phase I clinical
studies with single- and multiple ascending dose,
blinded, placebo-controlled, randomized, healthy volunteers (n = 100) since November 2011. In November
2013 data from three Phase I, randomized, placebo-controlled, blinded, single- and multiple-
ascending dose trials in >120 healthy volunteers were
presented at the 43rd SFN Meeting in San Diego, CA. Oral administration of PQ-912 was safe and well toler-
ated with relevant therapeutic levels in blood and CSF. Pharmacokinetics was found to be dose-proportional
(Thomson Reuters Pharma, update of February 17, 2014). The structure was not communicated.
PBD-150 (Probiodrug, Halle, Sachsen-Anhalt, Ger-
many; Fig. 12) is a potent inhibitor of human glutaminyl cyclase (IC50 = 17 nM) and totally inhib-
ited formation of Aβ1-42[3H] in cell culture at 1 μM (Thomson Reuters Pharma, update of March 7, 2014). A potential follow-up compound is PQ-1228 (Struc-
ture was not communicated).
Novel benzimidazole derivatives were described
(Fig. 12) [442]. One compounds had an IC50 value of
0.07 μM and Ki value of 0.023 μM against human QC
(Thomson Reuters Pharma, update of March 7, 2014).

2.2. Drugs interacting with glutaminyl cyclase

Glutaminyl cyclase (QC) is an enzyme that catalyzes
the formation of pyrog glutamic peptides or proteins
from an N-terminal glutamine residue. When Aβ is
cleaved between amino acids 2 and 3, a peptide with an
N-terminal glutamate is formed, which is cyclized by
QC to the N-terminal pyroglutamate. A review “Focusing
the amyloid cascade hypothesis on N-truncated Aβ peptides as drug targets against AD” was pub-
lished [736]. Pyroglutamate-3 Aβ deposition in the
brains of humans, non-human primates, canines and
AD-like transgenic mouse models was investigated
[438]. The structural analysis of the pyroglutamate-
modified isoform of the AD-related Aβ using NMR
spectroscopy was described [439]. Pyroglutamylated
amyloid-β peptide reversed cross β-sheets by a prion-
like mechanism [737]. Increased glutaminyl cyclase
expression was found in peripheral blood of AD patients [440]. Elevated pGlu-Aβ load showed a bet-
ter correlation with the decline in Mini-Mental State
Examination scores than elevated concentration
of unmodified Aβ [441].

Omagapil (SNT-317, TCH-346, CGP-3466; San-
thera, Liestal, Switzerland under license from
Novartis, Basel, Switzerland; Fig. 12) is an orally
bioavailable glyceraldehyde 3-phosphate dehydroge-
nase modulator with anti-apoptotic properties for
the treatment of PD and amyotrophic lateral sclerosis
(ALS) in Phase I clinical trials since November 2011
(Thomson Reuters Pharma, update of September 5, 2013).

Glyceraldehyde 3-phosphate dehydrogenase–
Siah cell death cascade inhibitors are investigated
by scientists of the Johns Hopkins University (Balti-
more, MD) for the potential treatment of degenerative
diseases like AD, PD, stroke, and cardiomyopathy
(Thomson Reuters Pharma, update of March 15, 2014).
Structures were not communicated.

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

GSK-3β (EC 2.7.11.26, 47 kDa) is a ser-
ine/threonine protein kinase ubiquitously expressed
and involved in many cellular signaling pathways play-
ing a key role in the pathogenesis of AD [443]. Crucial
is the phosphorylation at serine 9. The cited papers are
listed in chronological order: 2012: [444–451], 2013:
[452, 453, 454].

There is currently no GSK-3β inhibitor in clinical
development, but there are many in preclinical evalua-
tion (in alphabetical order):

AX-9839 (ActinX Biosciences, La Jolla, CA and
Kyorin Pharmaceuticals, Tokyo; Fig. 12) is an inhibitor of GSK-3β for the potential treatment of diabetes, AD,
and various CNS disorders [455] (Thomson Reuters
Pharma, update of March 21, 2014).

Benfolamine (a synthetic 5-acyl derivative of
thiamine, i.e., vitamin B1, Shanghai Rixin Bio-
Technology under license from Fudan University,
Shanghai; Fig. 12) significantly reduced Aβ produc-
tion in cells and enhanced the ratio of phosphorylated
GSK-3 together with consistent down-regulation of
GSK-3 activity. It showed beneficial effects on cog-
Fig. 12. Two dipeptidyl peptidase inhibitors, two glutaminyl cyclase inhibitors, a glyceralddehyde 3-phosphate dehydrogenase modulator and 9 GSK-3β inhibitors.

Bofinamide and Aβ deposition in AβPP/PS1 transgenic mice [456, 457]. In July 2013, an IND was filed in China (Thomson Reuters Pharma, update of April 24, 2014).

Bristol-Myers Squibb is investigating novel isonicotinamides as selective GSK-3 inhibitors for the potential treatment of AD. The lead compound inhibited GSK-3α and β with IC_{50} values of 0.3 and...
0.9 nM, respectively, and lowered hyperphosphorylation of tau with an IC₅₀ value of 40 nM (Thomson Reuters Pharma, update of March 26, 2014). Structures were not communicated.

Celon Pharma (Łomianki, Poland) is investigating a GSK-3β inhibitor for the potential treatment of AD (Thomson Reuters Pharma, update of March 14, 2013). The structure was not communicated.

Cyclacel Pharmaceuticals (Berkeley Heights, NJ, Fig. 12) is investigating GSK-3β inhibitors for the potential oral treatment of type 2 diabetes [458] (Thomson Reuters Pharma, update of December 27, 2013).

**Dual GSK-3/casein kinase (CK) 2 modulators** (University of Illinois at Chicago and the University of Illinois at Urbana-Champaign) are investigated for the potential treatment of AD (Thomson Reuters Pharma, update of November 4, 2013). Structures were not communicated.

**JGK-263** (JL-7263, JGK-216; Jeil Pharmaceutical, Seoul in collaboration with the Seoul National University, Hanyang University and Daegu Haany University) is the lead compound from a series of GSK-3β inhibitors for the potential treatment of AD and ALS (Thomson Reuters Pharma, update of December 4, 2013). The structure was not communicated.

**L803-mts and GSC-7** (Tel Aviv University and the Weizmann Institute, Rehovot, Israel) are peptide GSK-3 inhibitors, which on nasal treatment reduced Aβ burden and improved cognitive effects in 5xFAD mice (Thomson Reuters Pharma, update of January 22, 2014).

Mitsubishi Tanabe Pharma (Osaka; Fig. 12) is investigating GSK-3β inhibitors from a series of 2-(2-phenylmorpholin-4-yl) pyrimidin-4(3H)-ones [459, 460]. The most potent compound had an IC₅₀ value of 12 nM and clearance value of 0.06 ml/min/mg in a human liver microsome assay. In male rats the compound demonstrated significant decrease of tau phosphorylation after oral administration in mice and also exhibited excellent pharmacokinetic profiles (Thomson Reuters Pharma, update of March 26, 2014).

**NNI-362** (NNI-AD; NeuroNascent, Clarksville, MD in collaboration with the National Institute on Aging, Bethesda, MD) is a multikinase and GSK-3β modulator inhibiting several tau phosphorylation sites. Other orally active compounds that stimulate neuron modulator inhibiting several tau phosphorylation sites. SAR studies on GSK-3β inhibitors were published by a joint effort of researchers from the Technical University of Darmstadt, University of Naples, University of Leuven and Tel Aviv University (486). SAR studies on GSK-3α inhibitors were published by a joint effort of researchers from the Technical University of Darmstadt, University of Naples, University of Leuven and Tel Aviv University (486).

Pfizer (Fig. 12) 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 [461] (Thomson Reuters Pharma, update of August 28, 2012).

**SN-2127** (AstraZeneca, Fig. 12) is one of several GSK-3β inhibitors in evaluation by AstraZeneca as are SN-2568, SN-3728, and others [462, 463] (Thomson Reuters Pharma, update of April 5, 2012). Takeda (Osaka) presented very potent GSK-3β inhibitors with 1,3,4-oxadiazole structures with IC₅₀ values of 2 nM [464–466]. The chiral sulfoxide MMBO (Fig. 12) decreased tau phosphorylation and ameliorated cognitive deficits in a transgenic model of AD [467].

**TWS-119** (Scripps Research Institute, La Jolla, CA, Fig. 12) is a compound that induced neurogenesis in murine embryonic stem cells. The target of TWS-119 was shown to be GSK-3β by affinity-based and biochemical methods [468].

**UDA-680** (SAR-502250; Mitsubishi Pharma, Osaka and sanofi, Paris) is a GSK-3β and tau phosphorylating kinase 1 inhibitor for the potential treatment of AD and schizophrenia (Thomson Reuters Pharma, update of November 11, 2013). The structure was not communicated.

**VPL1.15** (CSIC, Madrid and the University of Toronto, Fig. 12) is a dual GSK-3β and PDE7 inhibitor acting as an antipsychotic and cognitive enhancer in C57BL/6J mice [469, 470]. Potent GSK-3β inhibitors were described by researchers at universities (in alphabetical order of their location): Technical University of Darmstadt [471], Martin-Luther University Halle [472–474], Zhejiang University of Technology, Hangzhou, China [475, 476], CSIC Madrid [477–480], Hanyang University College of Medicine, Seoul [481], Fudan University Shanghai [482–484], and Tel Aviv University [485].

SAR studies on GSK-3α inhibitors were published by a joint effort of researchers from the Technical University of Darmstadt, University of Naples, University of Leuven and Tel Aviv University [486].

DM-204 (DiaMedica, Minneapolis, MN following its acquisition of Sanomune, Winnipeg, Manitoba) is a monoclonal antibody that inhibits GSK-3β for the potential treatment of cancer, diabetes, influenza, hypertension, and neuronal disorders such as AD, HD, and tularemia (Thomson Reuters Pharma update of January 23, 2014).

The development of allosteric inhibitors of GSK-3β (Broad Institute) and of AZD-1080 (AstraZeneca) was terminated [487–490], but it is re-investigated by scientists from the University of Leeds for the
potential treatment of glialblastoma; Thomson Reuters Pharma, update of June 14, 2013). Also terminated was a potential treatment of glioblastoma; Thomson Reuters inhibitors; Fig. 13) are investigated by the CHDI (in alphabetical order):

- CG-9, CG-701338, CG-701446, and CG-701448 (CrystalGenomics), CHIR-99014 (Chiron, Novartis), CP-70949 (Pfizer; [491]) and of NP-101020 and tideglibusin (Noscira, previously known as Neuropharma; [492–495]).

2.25. Drugs interacting with guaneryl cyclase

Activation of soluble guanyl cyclase and cGMP formation in the brain represents one element of effective neuroprotective pathways mediated by NO [496].

sGC-1061 (sGC Pharma, Cambridge, MA) is a sustained-release NO-nitric and nonmethanol 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 March 4, 2014). The structure was not communicated.

2.26. Drugs interacting with heme oxygenase

OB-28 (Osta Biotechnologies, Dollard-des-Ormeaux, Québec) was a heme oxygenase-1 inhibitor for the potential injectable treatment of AD showing statistically significant improvement in behavioral deficits in double transgenic (AβPP/PS1dE9) mice (n = 103) after treatment with 15 or 30 mg/kg/day for 4 months. The development was terminated (Thomson Reuters Pharma update of April 4, 2013).

2.27. Drugs interacting with histone deacetylases (\*Sirnats)

The potential of HDAC inhibitors as cognitive enhancers was discussed [497, 498]. The loss of HDAC5 impaired memory function [499]. The class III histone deacetylases, sirtuins 1–7, are described in Chapter 2.56.

FRM-0334 (formerly EVP-0334; FORUM Pharmaceuticals, previously EnVivo, Watertown, MA under license from MethylGene, Montréal) is developing the potential treatment of AD in Phase I clinical trial, which was completed in July 2012 showing high bioavailability (Thomson Reuters Pharma, update of April 4, 2013). The structure was not communicated.

Other HDAC inhibitors are currently in preclinical evaluation (in alphabetical order):

- CHDI-390576 and CHDI-00381817 (HDAC4 inhibitors; Fig. 13) are investigated by the CHDI Foundation (Los Angeles, CA) in collaboration with BioFocus DPI (Saffron Walden, Essex, UK) for the potential treatment of HD (Thomson Reuters Pharma update of February 12, 2014).

- Crebinostat (Harvard University Medical School, Boston, MA; Fig. 13) is a novel HDAC inhibitor and enhancer of CREB-regulated transcription and modulator of chromatin-mediated neuroplasticity [500].

- Entinostat (MS-275. SNDX-275. Syndax Pharmaceuticals, Waltham, MA under license from Bayer Schering Pharma, Berlin; Fig. 13) ameliorated microglial activation and Aβ deposition in the cerebral cortex of transgenic AβPP/PS1 mice [501].

- HDAC inhibitors (BioMarin, Novato, CA, through an asset acquisition from RepliGen, Waltham, MA under license from the Scripps Research Institute, La Jolla, CA; Fig. 13) is a novel HDAC inhibitor and enhancer of CREB-regulated transcription and modulator of chromatin-mediated neuroplasticity [500].

- HDAC inhibitors (BioMarin, Novato, CA, through an asset acquisition from RepliGen, Waltham, MA under license from the Scripps Research Institute, La Jolla, CA; Fig. 13) is a novel HDAC inhibitor and enhancer of CREB-regulated transcription and modulator of chromatin-mediated neuroplasticity [500].

- LB-201 and LB-205 (Lixte Biotechnology, East Setauket, NY; Fig. 13) target HDAC and prevent the degradation and restore the activity of glucocerebrosidase for the potential treatment of neurological disorders, as Gaucher’s disease and traumatic brain injury [504] (Thomson Reuters Pharma update of February 25, 2013 and July 25, 2013, respectively).

- Quinazolin-4-one derivatives are selective HDAC6 inhibitors for the potential treatment of AD [505].

- Sodium butyrate, a pan-HDAC inhibitor, improved memory function in an AD mouse model [506, 507]. It improved cognitive impairments induced by isoflurane exposure in aged rats [508].

- Sodium valproate, a class I HDAC inhibitor (i.e., HDAC1,2,3,8), completely restored contextual memory in a mouse model of AD [509–511].

- Trichostatin A induces the protein expression of gelsolin, which binds to Aβ and inhibits its fibrillation [512].

- Tubastatin A (Fig. 13) is a potent and selective HDAC6 inhibitor [513]. Chronic tubastatin A treatment for two months decreased total tau levels in tg4510 mice [514]. HDAC6 inhibition resulted in tau acetylation and modulated tau phosphorylation [515].

The development of KAR-3010, KAR-3084, and KAR-3166 (Karus Therapeutics) and of
2.28. 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). Statins are more than cholesterol lowering agents in AD [523]. A systematic review on statins and cognitive function was published [524].

In September 2009 a randomized, double blind, parallel assignment, treatment, safety/efficacy, Phase I trial of lovastatin oral capsule began in the US in patients (expected n = 50) with neurofibromatosis type I. By May 2013 data had demonstrated that lovastatin was safe and well tolerated in children and had shown improvements in memory. By May 2013 a Phase II trial had been initiated by the University of California Los Angeles (UCLA).

NST-0037 (Neuron BioPharma, Granada, Spain; Fig. 14) is a natural HMG-CoA-reductase inhibitor, which displayed neuroprotective, antioxidant, and anti-convulsive activities. The synthesis was described [525]. Potential follow-up compounds are NST-0005 and NST-0060 (for both Thomson Reuters Pharma, update of December 26, 2013), whereas the development of NST-0021 was terminated.

Atorvastatin (Lipitor, Pfizer, launched in 1996) prevented amyloid-β peptide oligomer-induced synaptic toxicity and memory dysfunction in rats through a p38 MAPK-dependent pathway [738].

2.29. Drugs interacting with insulin-degrading enzyme

Inventram (Istanbul, Turkey) is investigating insulin-degrading enzyme activators for the potential treatment of type 2 diabetes and AD (Thomson Reuters Pharma, update of March 13, 2014). Structures were not communicated.

2.30. Drugs interacting with insulin-regulated aminopeptidase

Insuline-regulated aminopeptidase (IRAP) is the main target of the hexapeptide angiotensin IV (Ang IV), which on intracerebroventricular injection
Fig. 14. One HMG-CoA reductase, 13 kinase, one kynurenine aminotransferase II and one monoacylglycerol lipase inhibitor(s).
improved memory and learning in rats [526–528]. Deletion of the IRAP gene resulted in mice with an accelerated, age-related decline in spatial memory that was only detected in the Y maze paradigm [529]. It was proposed to search for inhibitors of IRAP as potential enhancers of cognitive function [530–533]. Recently a novel radioligand for IRAP [3H]IVDE77 was described [534].

2.31. Drugs interacting with kinases ($\neq$ GSK-3β and $\neq$ PRC)

Masitinib (AB-1010, AB Science, Paris, France; Fig. 14) 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 Mini-Mental State Examination scores, the Alzheimer's Disease Assessment Scale-cognitive subscale, and the AD Cooperative Study Activities of Daily Living Inventory with statistical significance between treatment arms at week 24 ($p=0.016$ and 0.030, respectively) [535]. 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 [536]. Masitinib is in the Pre-registration Phase in Europe for the treatment of gastro-intestinal tumors since October 2012. Masitinib will also be tested in ALS patients as an adjunct therapy to cholinesterase inhibitor and/or memantine [537] (Thomson Reuters Pharma, update of June 2, 2014). The masitinib treated patients showed improvements in Mini-Mental State Examination scores, the Alzheimer's Disease Assessment Scale-cognitive subscale, and the AD Cooperative Study Activities of Daily Living Inventory with statistical significance between treatment arms at week 12 and/or week 24 ($p=0.016$ and 0.030, respectively) [535]. 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 [536]. Masitinib is in the Pre-registration Phase in Europe for the treatment of gastro-intestinal tumors since October 2012. Masitinib will also be tested in ALS patients (Thomson Reuters Pharma, update of June 2, 2014).

PLX-5622 (Plexxikon, Berkeley, CA, a subsidiary of Daiichi Sankyo, Tokyo) is a fms kinase inhibitor investigated for the potential oral treatment of rheumatoid arthritis, MS, and AD in Phase I clinical trials for rheumatoid arthritis since January 2011 and for AD and MS since November 2013 in the US (Thomson Reuters Pharma, update of March 24, 2014). The structure was not communicated.

Saracatinib (AZD-0530, NSC-73464, AstraZeneca, University of Sheffield and Yale University) is a dual Src/Abl tyrosine kinase inhibitor, which was tested in Phase II clinical trials for the treatment of solid tumors. Yale University researchers are investigating saracatinib for the potential treatment of AD. In July 2013 a Phase I trial was initiated in the US (Thomson Reuters Pharma, update of April 29, 2014).

Many other kinase inhibitor therapeutics are currently in preclinical evaluation (in alphabetical order) for the potential treatment of neurodegenerative diseases:

Apoptosis signal-regulating kinase 1 (ASK1) inhibitors are investigated by Takeda (Osaka) for the potential treatment of various indications including autoimmune diseases, diabetes, inflammatory disorders, cardiovascular disease, and neurodegenerative disorders [537] (Thomson Reuters Pharma, update of May 14, 2014).

Beta carboline alkaloids as harmol (Fig. 14) inhibit dual specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A) and tau phosphorylation ($I_{50}=90$ nM). DYRK1A enhanced tau expression in a dose-dependent manner [538].

Cadeprin (group S8A serine protease) antagonists are investigated by researchers from the Universities of Strathclyde and Glasgow [539] (Thomson Reuters Pharma, update of December 4, 2012). Structures were not communicated.

Casein kinase 1 δ inhibitors (Proteome Sciences, Cribbham, Surrey, UK), such as PS-110 and PS-278, are investigated for the potential treatment of AD. In September 2013 preclinical data were presented (Thomson Reuters Pharma, update of May 29, 2014). Structures were not communicated.

Cdc2-like kinases (Clk) and dual-specificity tyrosine-regulated kinase 1A (DYRK1A) inhibitors are investigated by researchers of the National Center for Advancing Translational Sciences (NCATS, Bethesda, MD) for the potential treatment of Down’s syndrome and AD (Thomson Reuters Pharma, update of May 28, 2013). Structures were not communicated.

CDK5/CDK2 inhibitory peptides (Hong Kong University of Science and Technology) are evaluated for the potential treatment of AD (Thomson Reuters Pharma, update of January 8, 2014). Structures were not communicated.

CDK5/p25 inhibitors (AstraZeneca, the lead compound in shown in Fig. 14) are investigated for the potential treatment of AD. Medicinal chemistry was published [540] (Thomson Reuters Pharma, update of February 13, 2013).

CLFR-1134 (Calfia Bio, San Diego, CA) is a second generation selective mixed lineage kinase-3 inhibitor for the potential treatment of HIV-associated neurocognitive disorder. (Thomson Reuters Pharma, update of November 15, 2013). The structure was not communicated.
Dasatinib (Bristol-Myers Squibb, launched in 2006), a Src tyrosine kinase inhibitor, attenuated Aβ associated microgliosis in a murine model of AD [541].

Eukaryotic elongation factor-2 kinase (eEF2K) inhibitors (Johns Hopkins University, Baltimore, MD) are investigated for the potential treatment of AD, Down’s syndrome and fragile X mental retardation syndrome (Thomson Reuters Pharma, update of March 14, 2014). Structures were not communicated.

FRAX-120, FRAX-355, and FRAX-486 (Afraxis, La Jolla, CA) showed IC50 values of 23, 58, and 14 nM for p21-activated kinase (PAK). The drugs have a potential for the treatment of fragile X syndrome, autism, schizophrenia, and AD. The rescue of fragile X syndrome phenotypes in Fmr1 knockout mice by the small-molecule PAK inhibitor FRAX-486 was described [542] (Thomson Reuters Pharma, update of May 29, 2014). The structure of FRAX-597 (Fig. 14) was communicated.

Fyn kinase inhibition may provide a novel therapy for AD [543].

G-201995 (Zenobia Pharmaceuticals, San Diego, CA, in collaboration with Johns Hopkins University, Baltimore, MD) is a leucine-rich repeat kinase-2 (LRRK2) inhibitor for the potential treatment of PD (Thomson Reuters Pharma, update of January 27, 2014). The structure was not communicated.

GNE-7915 (Genentech, South San Francisco, CA, and BioFocus, Saffron Walden, Essex, UK; Fig. 14) is a LRRK2 inhibitor for the potential treatment of PD. Medicinal chemistry was described [544, 545] (Thomson Reuters Pharma, update of October 15, 2013).

GSK-2606414 and GSK-2656157 (GSK; Fig. 14) are protein kinase receptor-like endoplasmic reticulum kinase inhibitors for potential treatment of solid tumors and neurodegenerative diseases including AD. Biological data were published [546]. For an excellent commentary, see [547]. Medicinal chemistry was described [548] (Thomson Reuters Pharma, update of January 23, 2014).

Hydroxy-fasudil (Asahi Kasei Pharma Corp., Tokyo), a rho kinase (ROCK) inhibitor, improved spatial learning and working memory in rats in a water radial-arm maze [549]. Fasudil protected against Aβ-induced hippocampal neurodegeneration in rats [550]. ROCK inhibition led to an increase of Rac1 activity and to an activation of PKCζ which in turn phosphorylated KIBRA involved in the formation of memory [551]. ROCK inhibition prevented tau hyperphosphorylation [552].

Imatinib (Gleevec, STI-571; Novartis, launched in 2001) is an inhibitor of tyrosine kinases including Bcr-Abl and c-kit. Imatinib eliminated the cognitive impairment seen following seven consecutive days of LPS-induced peripheral inflammation implicating Aβ peptides as a likely cause of these cognitive deficits [553, 554].

ITT-012 series (Intra-Cellular Therapies, New York, NY) are casein kinase I inhibitors for the potential treatment of AD (Thomson Reuters Pharma, update of April 8, 2014). The structures were not communicated.

LRRK2 inhibitors (Oncodesign Biotechnology, Dijon, France) are investigated for the potential treatment of cancer and CNS diseases including PD utilizing its Nanocyclix technology (Thomson Reuters Pharma, update of April 30, 2013). Structures were not communicated.

LRRK2 inhibitors (Oritgenis GmbH, Martinsried, Bavaria) are investigated for the potential treatment of PD (Thomson Reuters Pharma, update of April 7, 2014). Structures were not communicated.

LRRK2 inhibitors (Perrigo, formerly Elan Pharmaceuticals, Dublin, Ireland) on novel cinnoline scaffolds were published recently [555]. Also triazolopyridazine and cyano-quinoline LRRK2 kinase inhibitors were presented [556, 557].

LRRK2 inhibitors (SignalChem Life Sciences, Richmond, BC, formerly MetSignaI) are investigated for the potential treatment of PD and AD (Thomson Reuters Pharma, update of March 25, 2013). The structures were not communicated.

LRRK2 inhibitors (Vernalis, Winnersh, UK in collaboration with Lundbeck, Valby, Denmark) are investigated for the potential treatment of PD (Thomson Reuters Pharma, update of May 23, 2013). The structures were not communicated.

For LRRK2 interactions with α-synuclein in PD brains and in cell models, see [558].

MARK inhibitors (microtubule affinity regulating kinase inhibitors; Medical Research Council Technology, London) are investigated for the inhibition of tau phosphorylation. The role of individual MARK isoforms in the phosphorylation of tau at Ser262 was investigated [559] (Thomson Reuters Pharma, update of November 1, 2013). Structures were not communicated.

MARK inhibitors (Merck Research Laboratories, Boston, MA) are in preclinical evaluation for the potential treatment of AD. The compound in Fig. 14 showed potent activity with IC50 values of 3 and 56 nM against MARK 3 and 4, respectively. In rats it showed t1/2 and bioavailability values of 3.5 h and 46%, respec-
P-005 (NB Health Laboratory, Sapporo) is a small molecule casein kinase 1 delta (CK-1δ) inhibitor for the potential oral treatment of sleep disturbances including circadian rhythm disorder, in patients with dementia (Thomson Reuters Pharma, update of November 27, 2013). The structure was not communicated.

**ORS-1104 (Arrien Pharmaceuticals, Somerset, NJ)** is the lead compound from a program comprising two series of LRRK2 inhibitors for the potential oral treatment of PD. For a review, see [563] (Thomson Reuters Pharma, update of January 15, 2014). The structure was not communicated.

**P-005** is a small molecule casein kinase 1 delta (CK-1δ) inhibitor for the potential oral treatment of sleep disturbances including circadian rhythm disorder, in patients with dementia (Thomson Reuters Pharma, update of November 27, 2013). The structure was not communicated.

Inhibitors of the **protein kinase c-raf1**, such as GW-5074 and ZM-336372, protected cortical cells against Aβ toxicity [564].

**Protein kinase inhibitors** (ManRos Therapeutics, Roscoff, Bretagne, France, leucetine-L41 is shown in Fig. 14) are evaluated as AD medication. Selectivity, cocrystal structures and neuroprotective properties of leucetines, a family of protein kinase inhibitors derived from the marine sponge alkaloid leucetamine B, were published [565–567] (Thomson Reuters Pharma, update of March 7, 2014).

**SEL-141** (Selvita Life Sciences Solutions, Krakow, PL) is a program targeting DYRK1A kinase and other kinases involved in tau hyperphosphorylation including SLV-01917, SLV-00251, SLV-00125, SLV-00756, SLV-00095, and SLV-01184 for the potential treatment of AD, cancer, and neurological diseases, including Down syndrome, tauopathy, and cognitive diseases (Thomson Reuters Pharma, update of May 23, 2014). Structures were not communicated.

**SKI-G-1141** (Genosco, a subsidiary of Oscotec, Buena Park, CA) is a LRRK2 inhibitor for the potential treatment of PD (Thomson Reuters Pharma, update of September 17, 2013). The structure was not communicated.

**Sorafenib**, a small molecular inhibitor of tyrosine protein kinases (VEGFR and PDGFR) and of raf, restored working memory in AβPP/APP transgenic mice [568].

**Sphingosine kinase-1** protected differentiated N2a cells against Aβ25-35-induced neurotoxicity via the mitochondrial pathway [569].

**T-343** (Arizona State University, Tempe, AZ and Translational Genomics Research Institute, Phoenix, AZ) is a Rho-associated protein kinase (ROCK) I/II inhibitor, for the potential treatment of AD [549]. It showed IC50 values of 1.2 and 0.3 μM against ROCK-I and -II, respectively. In H4-tau cells the ratio of p-tau to total tau was significantly reduced (Thomson Reuters Pharma, update of November 22, 2013). The structure was not communicated.

**TFF-5** (National Institute of Neurological Disorders and Stroke, Bethesda, MD) is a modified truncated peptide from p35, a CDK5 activator, which prevented AD phenotypes in a 5xFAD AD mouse model [570, 571] (Thomson Reuters Pharma, update of May 10, 2013). The structure was not communicated.

**TTBK1 inhibitors** (SignalChem Life Sciences, Richmond, BC, formerly MetaSignal), tau-tubulin kinase 1 inhibitors, are investigated for the potential treatment of PD and AD (Thomson Reuters Pharma, update of March 25, 2013). Structures were not disclosed.

**TTT-3002** (TaiTaTis, Jacksonville, FL) is a multitargeted kinase inhibitor that can inhibit the LRRK2 gene and tumor growth for the potential treatment of PD, AD, and cancer (Thomson Reuters Pharma, update of November 27, 2013). The structure was not communicated.

University of Arizona (Tucson, AZ) chemists in collaboration with the Translational Genomics Research Institute, Phoenix, AZ, and the University of Arizona (Tucson, AZ) chemists in collaboration with the Translational Genomics Research Institute, Phoenix, AZ, developed **TORIRI-1** (Translational Genomics Research Institute, Phoenix, AZ) a LRRK2 inhibitor for the treatment of PD (Thomson Reuters Pharma, update of September 17, 2013). The structure was not communicated.
Institute (Phoenix, AZ) described advances in the search for novel DYRK1A inhibitors [572] (Thomson Reuters Pharma, update of November 7, 2013).

URMC-099-C (Califia, San Diego, CA, the University of Nebraska Medical Center, Omaha, NE and the University of Rochester, NY, Fig. 14) is an inhibitor of mixed lineage kinase-3 for the treatment of HIV-associated neurocognitive disorder [573] (Thomson Reuters Pharma, update of March 19, 2014).

The development of AIK-2, AIK-2a, AIK-2c, and AIK-21 (Allioky Biopharma), CDK5/p25 inhibitors (Pfizer; [574, 575]), CEP-1347 (a mixed lineage kinase-1 inhibitor; Cephalon), CZC-25146 (Cellzome; [576]), dual-specificity tyrosine-regulated kinase (DYRK) 1/H9252/H9251 inhibitors (Diaxonhit, formerlly ExonHit), GSK-2578215A (GSK), KIBRA pathway modulators (Amnestix; [551, 577–579]), LDN-22684 (a LRRK2 inhibitor; Sirtris Pharmaceuticals; [580]), LRRK2 inhibitors (Pfizer), PLX-3397 (an oral small-molecule dual Fms/kit and Flt3-ITD inhibitor; Plexxikon; a Phase II trial for the treatment of acute myelogenous leukemia continues; Thomson Reuters Pharma, update of June 2, 2014) was terminated.

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

For the potential role of kyurenines in dementia and AD, see [581, 582]. Targeting the kynurenine pathway-related alterations in AD may be a future therapeutic strategy [583, 584]. The X-ray structure of kynurenine-3-monooxygenase in complex with the tight-binding inhibitor UPF-648 was resolved [585].

CG-026864 (CrystalGenomics, Seongnam, South Korea) is a small molecule kynurenine mono-oxygenase (KMO) inhibitor for the potential oral treatment of neurodegenerative disorders such as HD and AD (Thomson Reuters Pharma, update of November 29, 2013). The structure was not communicated. CHDI-003940246 and CHDI-00340246 (Evotec, Hamburg, in collaboration with the CHDI Foundation, Los Angeles, CA) are kynurenine mono-oxygenase inhibitors for the potential treatment of HD (Thomson Reuters Pharma, update of October 30, 2012). The structures were not communicated.

PF-04859989 (Pfizer, Fig. 14) is an inhibitor of kynurenine (oxoglutarate) aminotransferase II for the potential treatment of schizophrenia [586, 587] (Thomson Reuters Pharma, update of May 8, 2013).

2.33. 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-eicosatetraenoic acid (5-HETE), which are metabolized to different leukotrienes [588]. The influence of 5-lipoxygenase on tau pathology was investigated [589–591]. Gene knockout of 5-lipoxygenase rescued synaptic dysfunction and improved memory in a triple-transgenic mouse model of AD [592–595]. Also reduction of the 5-lipoxygenase activating protein ameliorated cognitive deficits in a mouse model of AD [596]. Mice receiving MK-591 (quiflapon, a FLAP, 5-lipoxygenase-activating protein inhibitor) had a significant reduction of tau phosphorylation [597]. The role of 5-lipoxygenase for DNA methylation was discussed. The data were compiled in a recent review [598].

Minocycline (Wyeth, now Pfizer and Takeda launched in 1999) is a second generation tetracycline that effectively crosses the BBB. It improved cognitive impairment in AD models [599]. It reduced the development of abnormal tau species in models of AD [600–602].

New classes of 5-lipoxygenase inhibitors were communicated [603].

2.34. Drugs interacting with lysine-specific histone demethylase 1

ORY-2001 (Oryzon Genomics, Barcelona) is a lysine specific demethylase-1 inhibitor for the potential treatment of neurodegenerative disease (Thomson Reuters Pharma, update of May 19, 2014). The structure was not communicated. For a discussion on histone demethylation in pathological processes including neurodegeneration, see [604].

2.35. Drugs interacting with monoacylglycerol lipase (MAGL)

Inactivation of MAGL, the primary enzyme metabolizing the endocannabinoid 2-arachidonoylglycerol in the brain, by the highly selective and potent MAGL inhibitor JZL-184 (Fig. 14) [605, 606] robustly suppressed production and accumulation of BACE1 in a mouse model of AD [607]. For a review on the topic monoacylglycerol lipase as a therapeutic target for AD, see [608].
2.36. Drugs interacting with monoamine oxidase

Monoamine oxidase inhibitors: promising therapeutic agents for AD were described [609]. Recent efforts of medicinal chemists to explore ligands targeting MAOs were reviewed [610–612]. Ladostigil (TV-3326; Avraham Pharmaceuticals, Yavne, Israel under license from Yissum Research Development, a wholly owned company of the Hebrew University of Jerusalem; see Fig. 5) is a dual acetylcholine esterase and MAO inhibitor currently in Phase II clinical trials in 190 patients in Europe since December 2010. In February 2012, a Phase II trial was initiated in Israel and Europe in patients suffering from MCI (Thomson Reuters Pharma, update of August 16, 2013). See Chapter 2.1.1.9. Dual AChE and MAO inhibitors.

RG-1577 (RO-4602522; EVT-302; Roche, Basel, Switzerland and its Japanese subsidiary Chugai, Tokyo under license from Evotec, Hamburg) is an orally active, selective, and reversible MAO-B inhibitor. The company initiated a Phase II trial in patients with AD in September 2012 (Thomson Reuters Pharma, update of April 25, 2014). The structure was not communicated.

HT-1067 (Dart NeuroScience LLC, San Diego, CA presumably under license from Helicon, San Diego, CA) is a reversible MAO-B inhibitor for the potential memory impairment in PD patients. In January 2013 the drug entered Phase I development in the US for cognitive disorders (Thomson Reuters Pharma, update of April 10, 2014). The structure was not communicated.

HT-3951 (Dart NeuroScience LLC, San Diego, CA) is a potential backup compound for the reversible MAO-B inhibitor HT-1067 (Thomson Reuters Pharma, update of January 30, 2013). The structure was not communicated.

OG-45 (Oryzon Genomics, Barcelona) is a dual MAO-B inhibitor and histone specific demethylase-1 inhibitor (Thomson Reuters Pharma, update of April 8, 2014). The structure was not communicated.

Rasagiline (TVP-1012; (R)-enantiomer; Azilect, Agilect; marketed by Teva, Petach Tikva, Israel and Lundbeck, Valby, DK; Fig. 15) proved to be a very valuable drug for the treatment of PD with sales in 2012 of USD 330 million reported by Teva and USD 211 million reported by Lundbeck. The effects of rasagiline on cognitive deficits in cognitively-impaired PD patients were evaluated [615] (Thomson Reuters Pharma, update May 5, 2014).

The Cleveland Clinic Foundation (Cleveland, OH) is investigating rasagiline for the potential treatment of AD. In May 2014, a clinical trial was being planned (Thomson Reuters Pharma, update of June 5, 2014).

Tesa Labtec (Langenfeld, Germany), the Chongqing Pharmaceutical Research Institute (Chongqing, China) and Teikoku Pharma (San Jose, CA) are independently evaluating sustained release transdermal patch formulations of rasagiline for the potential treatment of PD (Thomson Reuters Pharma, updates of March 15, 2013, of April 2, 2014, and of May 15, 2014, respectively).

Safinamide (FCE-26743; NM-1015; PNU-151774E; Zambon, Milano under license from Newron, Milan, who acquired the rights from Pharmacia and Upjohn, now Pfizer; Fig. 15) is a potent MAO-B inhibitor. Phase III trials in early PD patients began in June 2004. An expert opinion on safinamide in PD was published [616]. In December 2013 the company submitted the MAA to the EMA as an add-on therapy to a stable dose of a single dopamine agonist or levodopa based on treatment of more than 2,000 PD patients treated over four years (Thomson Reuters Pharma, update of April 9, 2014).

Selegiline reversed Aβ25-35-induced cognitive deficits in male mice [617].

2.37. Drugs interacting with myeloperoxidase

Torrey Pines Pharmaceuticals (Del Mar, CA) is investigating myeloperoxidase inhibitors for the potential oral treatment of AD. Increased levels of myeloperoxidase plasma levels were detected in patients with AD [618] (Thomson Reuters Pharma, update January 29, 2014). Structures were not communicated.

2.38. Drugs interacting with neprilysin

Nephrilysin (EC 3.4.24.11, NEP, neutral endopeptidase, enkephalinase, neutrophil cluster-differentiation antigen 10 = CD10, common acute lymphoblastic leukemia antigen = CALLA) is a member of the zinc metalloproteinase family first discovered in the renal
microvillar membrane in 1974 [619]. Cloning revealed a type II integral membrane protein of 749 amino acid residues [620]. Neprilysin cleaves peptides smaller than 5 kDa at the amino side of hydrophobic amino acid residues including Aβ1-40 and Aβ1-42, which is the longest substrate for neprilysin [621]. NEP can also degrade the oligomeric forms of Aβ [622]. Recombinant soluble neprilysin reduced Aβ accumulation and improved memory impairment in AD mice [623]. Novartis scientists are investigating an Fc-neprilysin fusion protein for the potential treatment of AD. The ED50 value of intravenous Fc-neprilysin was 8.5 mg/kg. In vivo, Fc-neprilysin (630 nM i.v.) degraded Aβ. In plaque bearing AβPP23 mice, chronic peripheral dosing of Fc-neprilysin (100 mg/kg q12d to q16d) did not reduce brain Aβ levels. Significant reductions in plasma Aβ1-40 levels were observed with Fc-neprilysin [624] (Thomson Reuters Pharma update of November 27, 2013).

2.39. Drugs modulating O-linked N-Acetylglucosaminidase (O-GlcNAcase; OGA)

O-GlcNAc and neurodegeneration, its biochemical mechanisms and potential roles in AD and beyond were described [625]. The tau O-GlcNAcylation and phosphorylation sites in mouse brain synaptosomes were elucidated [626]. O-GlcNAc may compete with phosphorylation of the same serine or threonine residues. O-GlcNAc levels may directly influence neurodegenerative disease progression [627]. A dynamic view to the modulation of phosphorylation and O-GlcNAcylation was described [628]. Increased O-GlcNAcylation reduced pathological tau without affecting its normal phosphorylation in a mouse model of tauopathy [629]. O-GlcNAc modification of tau directly inhibited its aggregation without perturbing the conformational properties of tau monomers [630]. A comparison of the anti-amyloidogenic effects of O-mannosylation, O-galactosylation, and O-GalNAc glycosylation was presented [631]. Alectos Therapeutics (Burnaby, BC) in collaboration with Merck is investigating O-linked N-acetyl-glucosaminidase (O-GlcNAcase) modulators (Thomson Reuters Pharma update of May 30, 2014). ASN-61 and ASN-461 (Asceneuron, Lausanne, Switzerland) are small molecule inhibitors of O-GlcNAcase for the potential treatment of AD. In a mouse model of tau aggregation, ASN-61 (30 mg/kg po, qdx5) increased tau O-GlcNAcylation in a robust...
manner. In vivo ASN-461 demonstrated a minimal effective dose below 1 mg/kg and at 10 mg/kg the in vivo response was greater than that for Thiamet G (500 mg/kg). At doses between 1.5 and 10 mg/kg ASN-461, total brain protein O-GlcNAcylation was significantly greater than that for the vehicle (Thomson Reuters Pharma update of March 25, 2014). The structures were not communicated.

GlcNAcstatin (University of Dundee; Fig. 15) is a rationally designed glucosidimazole, which inhibited bacterial OGA (bOGA) with a Ki of 4.6 pM for the potential treatment of AD [632, 633] (Thomson Reuters Pharma, update of October 26, 2012).

NBuTG (Seoul National University; Fig. 15) is a specific inhibitor of O-GlcNAcase, which reduced Aβ production by lowering γ-secretase activity both in vitro and in vivo. O-GlcNAcylation takes place at the S708 residue of nicasin [634]. NBuTG attenuated Aβ plaques and rescued memory impairment in 5xTAD mice. The synthesis was described by chemists of the Simon Fraser University (Burnaby, BC) [635].

SEG-4 (Summit Corporation, Abington, UK) inhibited OGA with IC50 and Ki, values of 10 and 72 nM, respectively. The compound significantly reduced tau phosphorylation (Thomson Reuters Pharma, update of April 9, 2014). The structure was not communicated.

Thiamet-G (Simon Fraser University, Burnaby, BC; Fig. 15) is a potent inhibitor of human O-GlcNAcase (Ki = 21 nM) and efficiently reduced phosphorylation of tau at Thr231, Ser396, and Ser422 in both rat cortex and hippocampus [636]. For a commentary, see [637]. 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 [638].

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

Peptidyl-prolyl isomerase activity of FK506 binding protein 12 prevented tau peptide from aggregating [639].

Scyntex (Research Triangle Park, NC) was investigating a series of cyclophilin D inhibitors for the potential treatment of muscle injury, ischemia, reperfusion injury, trauma, and neurodegenerative disease. The program was terminated (Thomson Reuters Pharma, update of January 2, 2013).

2.41. Drugs interacting with phosphodiesterases

Several excellent reviews on PDE inhibition and cognition enhancement were published [640–642]. A review on phosphodiesterases as therapeutic targets for AD was communicated [643]. 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 2 inhibition with BAY60.7550 improved memory in the AβPPsw/Ps1ΔE9 mouse model of AD [644]. Knockdown of the long-form of phosphodiesterase-4D (PDE4D) reversed Aβ42-induced memory deficits in mice [645]. The medicinal chemistry of PDE 4 inhibitors [646], of PDE5 inhibitors [647], and of PDE10A inhibitors was reviewed [648].

HT-0712 (IPL-455903; Dart Neuroscience, San Diego, CA) presumably under license from Helicon, San Diego, CA, under license from Orexo, formerly Biosapox, Uppsala, Sweden; Fig. 16) is a PDE4 inhibitor for the potential treatment of memory disorders [649, 650]. In January 2013 the drug was listed as being in Phase II development for cognitive disorders (Thomson Reuters Pharma, update of April 9, 2014).

OMS-824 (Omeros, Seattle, WA; Fig. 16) is a PDE10 inhibitor for the potential treatment of schizophrenia in Phase II clinical trials since September 2013. The trial enrolled 33 patients. Data were reported in January 2014 showing that OMS-824 was well tolerated and tolerability and pharmacokinetics were not affected by concomitant antipsychotic medications. Omeros initiated a Phase II trial of OMS-824 for HD [651] (Thomson Reuters Pharma, update of June 5, 2014).

PF-02545920 (MP-10; Pfizer; Fig. 16) is a PDE10A inhibitor in a randomized, double-blind, placebo-controlled Phase II clinical trial in patients with acute schizophrenia (n = 280) since October 2010. Development for the indication schizophrenia was terminated. PF-02545920 is now evaluated in a Phase II clinical trial in France for the oral treatment of HD since October 2013 [652] (Thomson Reuters Pharma, update of June 4, 2014).

AVE-8112 (Aventis, now sanofi and The Michael J. Fox Foundation, New York, NY) is a PDE4 inhibitor for the potential treatment of PD. In January 2013 a multiple ascending dose, safety and efficacy Phase I study was initiated in patients with PD (expected n = 32) (Thomson Reuters Pharma, update of March 8, 2013). The structure was not communicated.

ITI-214 (Takeda, Osaka under license of Intracellular Therapies, New York, NY; Fig. 16) is a PDE1
Fig. 16. Eleven phosphodiesterase and one phospholipase A2 inhibitor(s).
inhibitor for the potential oral treatment of cognitive disorders associated with schizophrenia. In February 2013 a randomized, double-blind, placebo-controlled, pharmacokinetic single rise dose phase I trial was completed in healthy subjects (n = 70). Results showed that the drug was safe and well tolerated with a favorable pharmacokinetic profile consistent with once-a-day dosing [653, 654] (Thomson Reuters Pharma, update of April 8, 2014).

Lu-AF11167 (Lundbeck, Valby, DK) is an inhibitor of a brain-expressed PDE enzyme for the potential treatment of AD, HD, and schizophrenia in a Phase I clinical trial since March 2011 (Thomson Reuters Pharma, update of November 15, 2013). The structure was not communicated.

RG-7203 (RO-5545965, Roche) is a PDE 10A inhibitor for the potential treatment of schizophrenia. In October 2012 a Phase I trial began in the Netherlands in healthy male volunteers. Tracer uptake was the highest in the striatum, followed by neocortices and cerebellum (Thomson Reuters Pharma, update of December 3, 2013).

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

AB-63 (Aralcon Biotech, Zaragoza) is a heterocyclic PDE7 inhibitor for the potential treatment of PD (Thomson Reuters Pharma, update of March 17, 2014). The structure was not disclosed.

AMG-7980 (Amgen, Thousand Oaks, CA in collaboration with Envoy Therapeutics, Jupiter, FL, and Columbia University, New York, NY; Fig. 16) is a novel PDE 10A inhibitor with a Ki of 0.94 nM useful as tritiated or PET ligand to measure PDE 10A target occupancy in brain [655-660] (Thomson Reuters Pharma, update of October 13, 2013).

BCR-159 (BCA-159, BioCrea, Radebeul, Germany; Fig. 16) is a PDE 10 inhibitor for the potential treatment of schizophrenia and HD [652] (Thomson Reuters Pharma, update of November 22, 2013).

Cilostazol (Otsuka, Tokyo; launched in 1993), a selective PDE3 inhibitor, protected against Aβ1-40-induced suppression of viability and neurite elongation [661]. It also attenuated Aβ-induced tauopathy via activation of CK2oz/SIRT1 [662].

CPL-204-015 (Celon Pharma, Lomianki, Poland) is a phosphodiesterase 9A (PDE9A) inhibitor and cognition enhancer for the potential treatment of AD (Thomson Reuters Pharma, update of January 6, 2014). The structure was not communicated.

DG-071 (Tetra Discovery Partners, Grand Rapids, MI) is a PDE4b inhibitor for the potential treatment of depression (Thomson Reuters Pharma, update of May 5, 2014). The structure was not communicated.

Icarin, a flavonoid isolated from Epimedi herba, is a phosphodiesterase-5 inhibitor. It inhibited Aβ1-42-induced expression of BACE in rat hippocampus [663] and attenuated Aβ-induced neurotoxicity by inhibition of tau protein hyperphosphorylation in PC12 cells [664]. It attenuated lipopolysaccharide-induced microglial activation and resultant death of neurons by inhibiting TAK1/IKK/NF-κB and JNK/p38 MAPK pathways [665]. It improved memory impairment in AD model mice and attenuated Aβ-induced neurite atrophy [666] and learning and memory in Aβ/PPPS1 transgenic mice by stimulating NOC15/CAMP signal-ing [667]. There seems to be a synergistic effect to improve learning and memory deficits in rats by co-administration of Icarin and Panax notoginseng saponins [668].

OMS-527 (Omeros, Seattle, WA licensed from Asubio Pharma, Kobe, a part of Daichi Sankyo, Tokyo) is a PDE-7 inhibitor investigated for the potential treatment of addiction, compulsive disorder and neurological disorders, including PD, restless legs syndrome, and movement disorders (Thomson Reuters Pharma, update of November 11, 2013). The structure was not communicated.

PDE-4D inhibitors (Tetra Discovery Partners, Grand Rapids, MI) are evaluated for the potential treatment of AD and associated MCI (Thomson Reuters Pharma, update of March 8, 2014) Structures were not communicated.

PDE-9 inhibitor (Lundbeck, Valby, DK; Fig. 16) is investigated for the potential treatment of AD. The compound showed a high potency at PDE-9 (IC50 = 28 nM), good selectivity (PDE-1: IC50 = 240 nM) and a good ADME profile in rats [669] (Thomson Reuters Pharma, update of October 28, 2013).

PDE-9A inhibitor (Pfizer, Fig. 16) for the potential treatment of AD exhibited an IC50 of 32 nM for PDE9A, was 30 fold selective over PDE1C and displayed a brain/plasma ratio of 1.4 in rat [670] (Thomson Reuters Pharma, update of April 22, 2013).
PF-999 (Pfizer, Fig. 16) is a PDE2A inhibitor for the potential treatment of cognitive impairment associated with schizophrenia [671, 672] (Thomson Reuters Pharma, update of September 6, 2012).

Roflumilast (Daxas; Takeda Pharmaceuticals International, Opikon, Switzerland, previously Nycomed), a PDE4 inhibitor launched in 2010, and donepezil are clinically evaluated to reverse scopolamine induced cognitive deficits in healthy adults (NCT02051335). Sales for roflumilast reported by Takeda for 2012 were USD 37.5 million (Thomson Reuters Pharma, update of April 18, 2014).

S14, an inhibitor of PDE7, reduced cognitive impairment and pathological hallmarks in a mouse model of AD [673].

Sildenafil (Viagra, Pfizer, launched in 1998) and Tadalafil (Cialis, Lilly, launched in 2003), potent PDE5 inhibitors, restored cognitive function without affecting Aβ burden in a mouse model of AD [674]. Tadalafil reversed cognitive dysfunction in a mouse model of AD (675–677).

THPP-1 (Merck, Fig. 16) is a potent, orally bioavailable PDE10A inhibitor, which improved episodic-like memory in rats and executive function in Rhesus monkeys [678] (Thomson Reuters Pharma, update of February 22, 2013).

VPL15 (CSIC, Madrid and University of Toronto, see Fig. 12) is a dual GSK-3 and PDE7 inhibitor acting as an antipsychotic and cognitive enhancer in C57BL/6J mice [469]. See also Chapter 2.24. Drugs interacting with GSK-3β.

The development of several PDE inhibitors was terminated: of BCA-909 (Boehringer Ingelheim under license from BioCrea), dual PDE10/ PDE 2 inhibitors (biocrea), etazolate (EHT-202; SQ-20099; also an α-secretase activator; Duxonhit, formerly Exonhit), GEBR-7b (University of Genoa; [679, 680]), PDE 2 inhibitors (BioCrea) and PF-03649423 (a PDE5 inhibitor, Pfizer).

2.42. Drugs interacting with phospholipase A2 and D2

The role of secretory phospholipase A2 in the central nervous system and in neurological diseases was described [681]. Inhibition of phospholipase A2 in rat brain decreased the levels of total tau protein [682].

Rilapladib (SB-659032) GSK using a technology licensed from Human Genome Sciences, Rockville, MD, Fig. 16) 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 [683] (Thomson Reuters Pharma, update of May 6, 2014).

GSK-2647544 (GSK) is a lipoprotein-associated phospholipase A2 inhibitor for the potential treatment of AD in Phase I clinical trials since November 2012 in Australia. In December 2013 another Phase I trial was initiated in the UK (Thomson Reuters Pharma, update of April 17, 2014). The structure was not communicated.

Darapladib (GSK) reduced accumulation of Aβ42 in neurons [684]. The drug is in Phase III for the treatment of atherosclerosis for the potential oral prevention of cardiovascular events in patients with atherosclerosis and coronary artery disease since 2008 (Thomson Reuters Pharma, update of January 22, 2014).

The development of icosapent ethyl (AMR-101, SC-111, LAX-21; Epadel; ethyl eicosapentaenoic acid; Mochida Pharmaceutical Co., Tokyo and Amarin, Dublin, Ireland under license from Scotia Holdings, Guildford, Surrey, UK), a phospholipase A2 inhibitor, in the indication age-associated memory impairment was discontinued (Thomson Reuters Pharma, update of May 6, 2014).

2.43. Drugs interacting with plasminogen activator inhibitor (PAI)

Tissue plasminogen activator could degrade Aβ molecules resulting in a delay of AD pathogenesis [685]. Elevated serum PAI-1 was associated with a high risk for cognitive dysfunction [686]. PAI-1 promoted synaptogenesis and protected against Aβ1-42-induced neurotoxicity [687].

2.44. Drugs interacting with Poly ADP-Ribose polymerase (PARP)

E-7016 (Eisai, Tokyo following the acquisition of MGI Pharma, Bloomington, MN, formerly Guilford, Baltimore, MD; presumed to be GPI-21016 under license from Johns Hopkins University, Baltimore, MD, Fig. 17) is an orally active, brain-penetrable, PARP PAR synthase inhibitor in Phase II clinical trials for the treatment of stage III/IV melanoma patients [688]. The indications AD and stroke were abandoned (Thomson Reuters Pharma, update of May 14, 2014).

MP-124 (Mitsubishi Tanabe Pharma, Osaka) in a PARP inhibitor for the potential treatment of acute ischemic stroke in Phase I clinical trials since December 2008 in the US and since January 2011 in
Canada (Thomson Reuters Pharma, update of February 3, 2014). The structure was not communicated.

The development of AL-309 (Allon Therapeutics, Vancouver, BC), a neuroprotective peptide and PARP stimulator, was suspended.

2.45. Drugs interacting with human presequence protease

Human Presequence Protease (hPreP) is responsible for the degradation of mitochondrial Aβ peptide in human neuronal cells, and is thus an attractive target to increase the proteolysis of Aβ. Therefore, it offers a potential target for AD drug design, by identifying potential activators of hPreP. Medicinal chemists of the University of Kansas applied structure-based drug design combined with experimental methodologies to investigate the ability of various compounds to enhance hPreP proteolytic activity. Small benzimidazole derivatives (Compound 3c is shown in Fig. 17) may provide a promising avenue for AD treatment [689].

2.46. Drugs interacting with prolyl endopeptidase

Prolyl oligopeptidase colocalizes with α-synuclein, Aβ, tau protein and astroglia in the postmortem brain samples with PD and AD [690]. Inhibitors of prolyl oligopeptidase showed a significant antiaggregation effect on α-synuclein [691]. At present there is no drug in clinical or preclinical development.

2.47. Drugs interacting with prostaglandin D & E synthases

Microsomal prostaglandin E synthase-1 is induced in AD [692].

HF-0220 (7β-hydroxy-epiandrosterone; Newron Pharmaceuticals, Milano; Fig. 17) is a cytoprotective steroid, which stimulated prostaglandin D synthase for the potential treatment of AD. A Phase IIa multicenter, double-blind, placebo-controlled, biomarker trial in AD patients was initiated in April 2007. HF-0220 was well tolerated at all doses (Thomson Reuters Pharma, update of June 24, 2013).

AAD-2004 (GNT Pharma, Yongin, South Korea, formerly Neurotech and US subsidiary AmKor; Fig. 17) is a prostaglandin E synthase-1 inhibitor for the treatment of AD, PD, and ALS. A Phase I study was initiated in April 2010. By December 2011 the single ascending dose trial was successfully completed [693] (Thomson Reuters Pharma, update of May 7, 2014).

2.48. Drugs interacting with protein kinase C (PKC)

APH-0703 (Aphios, Woburn, MA), a potent PKC activator and a nanoparticle formulation
of bryostatin-1 and formulated using Aphios’s hydrophobic-based and SFS-PNS polymer nanospheres technologies, is in Phase II clinical trials since May 2010. The development of the i.v. formulation was taken into Phase III clinical trials in September 2013 in the US. An oral nanoparticle formulation is in preclinical evaluation (Thomson Reuters Pharma, updates of June 6, 2014 for both).

**Bryostatin-1** (Neurotrope BioScience, Plantation, FL in collaboration with the Blanchette Rockefeller Neurosciences Institute, Morgantown, WV) is a naturally occurring PKC activator isolated from the Californian marine bryozoan *Bugula neritina*. In April 2014 the program was listed as being in Phase IIa development for familial AD, clinical development for fragile X syndrome and in lead optimization for ischemic stroke and traumatic brain injury. Bryostatin-1 improved survival and reduced ischemic brain injury in aged rats after acute ischemic stroke (Thomson Reuters Pharma, update of June 5, 2014). See also Chapter 2.3. Drugs interacting with *H9251*.

**DCP-LA, DHA-CP6 and BR-111** (Neurotrope BioScience, Plantation, FL in collaboration with the Blanchette Rockefeller Neurosciences Institute, Morgantown, WV) are lipophilic PKC epsilon activators, back-up compounds of bryostatin-1, for the potential treatment of AD. In April 2014 the program was listed as being in Phase I development (Thomson Reuters Pharma, update of June 6, 2014).

**α,β-DCP-LA** (Hyogo College of Medicine, Japan; Fig. 17) is an activator of PKCε for the potential treatment of stroke and cognitive disorder (Thomson Reuters Pharma, update of January 2, 2014).

**Aplysiatoxin derivatives** (Kyoto University), which bind to protein kinase C isozymes, showed high cytostatic and antiproliferative activity when compared to bryostatin-1 [694-696] (Thomson Reuters Pharma, update of October 29, 2013).

A dual PKC activator and HDAC inhibitor that decreases Aβ production is currently evaluated by scientists at the University of Illinois at Chicago for the potential treatment of AD (Thomson Reuters Pharma, update of November 4, 2013). The precise structure was not communicated. It is a modified benzolactam compound.

**Genistein**, the most active molecule of soy isoflavones, inhibited Aβ25-35-induced neurotoxicity in PC12 cells via a PKC signaling pathway [697].

The development of **PKC modulators** (Georgetown University Medical Center, Washington, DC and Neurologic, Rockville, MD) was terminated.

**2.49. Drugs interacting with protein phosphatase slingshot homolog 2**

University of California San Diego researchers are investigating slingshot-2 inhibitors for the potential treatment of cancer and AD (Thomson Reuters Pharma, update of June 11, 2013).
2.5. Drugs interacting with protein tyrosine phosphatase

Knockout mice revealed a role for protein tyrosine phosphatase in cognition [698].

2.51. Drugs interacting with Rac1 GTPase

The development of Sanquinarinium chloride (Diaxonhit, formerly ExonHit) was discontinued.

2.52. Drugs interacting with ras farnesyl transferase

LNK-754 (OSI-754, CP-690754; AstraZeneca following the acquisition of Link Medicine’s neuroscience assets under license from OSI Pharmaceuticals, a subsidiary of Astellas Pharma, and Pfizer) was an orally active inhibitor of ras farnesyl transferase. Treatment of transgenic mice at 6 months of age for 3 months showed a clear reduction of plaques caused by either /H9251-synuclein or A/H9252 [699]. The development was terminated (Thomson Reuters Pharma, update of June 26, 2013).

2.53. Drugs interacting with Rho GTPase

ZCL-278 (East Carolina University, Greenville, NC; Fig. 18) is a small molecule targeting CDC42 Rho GTPase signaling for the potential treatment of AD [700] (Thomson Reuters Pharma, update of July 29, 2013).

2.54. Drugs interacting with S-adenosylhomocysteine hydrolase

The development of L-002259713 (Merck) was terminated.

2.55. Drugs interacting with serine palmitoyl transferase

Serine palmitoyltransferase is upregulated in a subgroup of sporadic AD patient brains [701]. Inhibition of serine palmitoyltransferase by subcutaneous /H9251-cyclohexamine reduced A/H9252 and tau hyperphosphorylation in an AD mouse model (TgCRND8). This may be a safe strategy for the treatment of AD [702].

2.56. Drugs interacting with sirtuin

The class III histone deacetylases, sirtuins 1–7, and the sirtuin activating compounds were reviewed [703]. Reviews on sirtuins in neurodegenerative diseases [704] and in brain aging [705, 706] were published. There are distinct patterns of sirtuin expression during the progression of AD [739].

Resveratrol (Fig. 18) is a natural phyto compound, which activates Siruin-1 and reduced A/H9252 accumulation. It attenuated cerebral ventricular streptococin-induced tau hyperphosphorylation [707]. Resveratrol-fed mice demonstrated increased in GSK-3/H9251 phosphorylation and a 3.8-fold increase of transhydroxin [708]. Dietary resveratrol prevented AD in SAMP8 mice [709].

The Georgetown University Medical Center, Washington, DC, 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 (Thomson Reuters Pharma, update of June 22, 2012).

In order to improve on the unfavorable pharmacokinetics resveratrol-loaded lipid-core nanocapsules (RSV-LNC) were generated. Pre- and co-treatments with RSV-LNC were able to protect cultures against reactive oxygen species formation and cell death induced by A/H9252, possibly through sustained blocking of TNFα, IL1β, and IL-6 release. Furthermore, RSV-LNC was able to increase IL-10 release even in the presence of A/H9252 and prevent or decrease both glial and JNK activation [710].

Resveratrol derivatives were explored as A/H9252 aggregation inhibitors, antioxidants, and neuroprotective agents [711, 712] (Thomson Reuters Pharma, update of March 6, 2014).

Selsisistat (SEN-196, EX-527, SEN-0014196; Siena Biotech under license from Elixir Pharmaceuticals, Cambridge, MA; Fig. 18) is a Sirtuin-1 inhibitor. In November 2011 a randomized, double-blind, Phase II trial was initiated to study the safety and tolerability of selsisistat administered over 12 weeks in HD patients (n = 144). The trial was completed in October 2012. Selsisistat is a racemic compound [715] (Thomson Reuters Pharma, update of April 9, 2014).

Curcumin via activation of SIRT1 blocked the neurotoxicity of amyloid-β1-42 in rat cortical neurons [740].

INDUS-815C (Indus Biotech, Pune, India) is a natural NAD-dependent deacetylase Siruin-2 inhibitor for the potential treatment of HD. The drug was also evaluated for the potential treatment of age-related macular degeneration and retinopathy, but this indication was abandoned (Thomson Reuters Pharma, updates of January 29, 2014 and January 28, 2014, respectively). The structure was not communicated.
2.57. Drugs interacting with steroid sulfatase

Steroid sulfatase is a potential modifier of cognition in ADHD [716].

2.58. Drugs interacting with synaptojanin 1

Synaptojanin 1 (Synj1), a lipid phosphatase mediating the breakdown of PI (4,5)P₂, has been shown to play a role in synaptic vesicle recycling and receptor trafficking in neurons. Heterozygous deletion of Synj1 protected neurons from Aβ-induced synaptic loss and restored learning and memory in a mouse model of AD [717]. Thus, inhibition of Synj1 may ameliorate Aβ-associated impairments, suggesting Synj1 as a potential therapeutic target. A screening assay for Synj1 based on detection of inorganic phosphate liberation from a water-soluble, short-chain PI(4,5)P₂ was developed. The assay displayed saturable kinetics and detected Synj1’s substrate preference for PI(4,5)P₂ over PI(3,4,5)P₃. The assay will enable identification of novel Synj1 inhibitors that have potential utility as chemical probes to dissect the cellular role of Synj1 as well as potential to prevent or reverse AD-associated synaptic abnormalities [718, 719].

2.59. Drugs interacting with transglutaminase (TG2)

Tissue transglutaminase catalyzes protein cross-linking, an important molecular process in AD. Its involvement in the pathogenesis and its potential as a therapeutic target was reviewed recently [720]. Tissue transaminase may also serve as a biochemical marker for AD [721].

CHDI-00339864 and CHDI-00316226 (Evotec; Hamburg, in collaboration with the CHDI Foundation; Los Angeles, CA, US) are selective TG2 inhibitors (IC₅₀ = 7 nM for TG2 for CHDI-00316226) for the potential treatment of HD. It displayed an 85 fold greater selectivity for TG2 over Factor XIA [722] (Thomson Reuters Pharma, update of October 30, 2012).

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

Usp14 inhibitors (Proteostasis Therapeutics, Cambridge, MA) are investigated for the potential treatment of neurodegenerative diseases (Thomson Reuters Pharma, update of March 3, 2014). Structures were not communicated.

3. CONCLUSION

With the launch of donepezil (Aricept) in 1996, rivastigmine (Exelon) in 2000, and galantamine (Reminyl) in 2001 (inhibitors of acetyl and butyryl cholinesterase), 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 may be solved by the transdermal patch XEL-001HP.

So far, the development of 11 Phase III compounds interacting with enzymes for the potential treatment of AD was discontinued, i.e., of the AChE inhibitors amiridin, eptastigmine, metrifonate, phenserine, and velnacrine, of the γ-secretase inhibitors begacestat and semagacestat, the γ-secretase modulator tarenflurbil, the MAO inhibitors rasagiline and safinamide, and the PDE inhibitor propentofylline.

Three compounds interacting with enzymes are currently in Phase III clinical trials for the potential treatment of AD: MK-8931, a BACE inhibitor; masitinib, an inhibitor of c-kit; Lyn and PDGF-R kinases; and APH-0703, a protein kinase C activator.

There are currently 16 compounds interacting with enzymes in Phase II clinical trials for the potential treatment of AD: posiphen, Shen Er Yang, and XEL-001HP (AChE inhibitors), ladostigil (dual AChE and MAO inhibitor), CHF-5074 and EVP-0962 (γ-secretase modulators), FRM-0334 (HDAC inhibitor), RG-1577 (MAO B inhibitor), HT-0712, OMS-824, PF-02545920, and PF-03049423 (phosphodiesterase inhibitors), rilapladib (phospholipase A2 inhibitor), HF-0220 (prostaglandin D synthase stimulator), and resveratrol and selisistat (sirtuin-1 modulators).

It may be that positive results will be obtained from the three Phase III trials within the next two to three years.

DISCLOSURE STATEMENT


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