Review

Cognitive Enhancers (Nootropics). Part 1: Drugs Interacting with Receptors

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Accepted 1 July 2012

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

Keywords: Alzheimer’s disease, cognitive enhancers, memantine, memory, nootropics, receptors

INTRODUCTION

As of May 28, 2012 there are 26,364 entries in PubMed under the term cognitive enhancers, 26,429 entries under the term nootropic, and 217 entries under the term cognition enhancers. Scifinder lists 5,029 references under the research topic nootropic, 504 references under the term cognitive enhancer, and 9,552 references for cognition enhancers. The Thomson Reuters Pharma database lists 1,081 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.

Cognitive enhancers (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. Cognition refers to a capacity for information processing, applying knowledge, and changing preferences. According to Astrid Nehlig [3], it involves memory, attention, executive functions, perception, language, and psychomotor functions. Mark J. Millan and 24 eminent researchers [4] presented an excellent overview on cognitive dysfunction in psychiatric disorders in the February 2012 issue of Nature Reviews Drug Discovery and define 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,

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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 [5], 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
2. Drugs interacting with Enzymes
3. Drugs interacting with Cytokines
4. Drugs interacting with Gene Expression
5. Drugs interacting with Heat Shock Proteins
6. Drugs interacting with Hormones
7. Drugs interacting with Ion Channels
8. Drugs interacting with Nerve Growth Factors
9. Drugs interacting with Re-uptake Transporters (Psychostimulants)
10. Drugs interacting with Transcription Factors
11. Antioxidants
12. Metal Chelators
13. Natural Products
14. Nootropics (“Drugs without mechanism”)
15. Peptides
16. Drugs preventing amyloid-β aggregation
16.1. Ligands interacting with amyloid-β binding
16.2. Inhibitors of serum amyloid P component binding
16.3. Vaccines against amyloid-β
16.4. Antibodies against amyloid-β
17. Drugs interacting with tau
17.1. Small molecules preventing tau aggregation
17.2. Ligands interacting with tau
17.3. Vaccines against tau
17.4. Antibodies against tau
18. Stem Cells
19. Miscellaneous

In Part 1, drugs interacting with receptors are described, in Part 2 drugs interacting with enzymes, and in Part 3 drugs interacting with targets 3 to 10 and compounds and preparations of categories 11 to 19.

1. DRUGS INTERACTING WITH RECEPTORS

Researchers have been investigating drugs interacting with a wide variety of receptors in order to identify valuable cognitive enhancers. These receptors (and drugs) are:

1.1. Acetylcholine Receptors
1.1.1. Muscarinic Acetylcholine Receptors (mAChRs)
1.1.1.1. Orthosteric mACh M1 Receptor Agonists
1.1.1.2. Allosteric mACh M1 Receptor Agonists
1.1.1.3. Vincamine-type Compounds
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1.2. Adenosine Receptors
1.3. Adrenergic Receptors
1.4. Angiotensin Receptors
1.5. Cannabinoid Receptors
1.6. Chemokine Receptors
1.7. Dopamine Receptors
1.8. Endothelin Receptors
1.9. Estrogen Receptors
1.10. GABA Receptors
1.10.1. GABA A Receptors
1.10.2. GABA B Receptors
1.10.3. GABA C Receptors
1.11. Galanin Receptors
1.12. Glutamate Receptors
1.12.1. AMPA Receptors
1.12.1.1. Piracetam-type compounds
1.12.1.2. AMPAkines
1.12.1.3. Biarylpropylsulfonamides
1.12.1.4. Benzothiadiazides
1.12.1.5. 1-Hydroxyazoles
1.12.2. NMDA Receptors
1.12.3. Metabotropic Glutamate Receptors
1.13. G-protein coupled Orphan Receptors
1.14. Histamine Receptors
1.15. Insulin Receptors
1.16. Liver X Receptors
1.17. Neurotensin Receptors
1.18. Noceceptor (OGL)1 Receptors
1.19. Opioid Receptors
1.20. Peripheral Benzodiazepine Receptors (PIRs)
1.21. Peroxisome Proliferator-activated Receptors (PPARs)
1.22. Prostaglandin Receptors
1.23. Purinergic Receptors
1.24. Receptor for Advanced Glycation End products (RAGE)
1.25. Retinoid X Receptors
1.26. Ryanodine Receptors
1.27. Serotonin Receptors
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  1.27.3. 5-HT_3 Receptor Antagonists
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1.30. Sphingosine-1-phosphate Receptor Modulators
1.31. Tachykinin Receptor
1.32. Tumor Necrosis Factor Receptor 1 Negative Allosteric Modulators

1.1. Acetylcholine receptors

Acetylcholine is important for memory processes ([6–14]). The roles of cholinergic receptor subtypes in cognition, emotion, and vigilance control were discussed recently [15]. After the publication of the cholinergic hypothesis of AD by Bartus et al. in 1982 [16] showing by biochemical, electrophysiological, and pharmacological evidence that cholinergic dysfunction is responsible for age-related memory disturbances, tremendous efforts have been undertaken by academics and by researchers from the pharmaceutical industry to find selective acetylcholine receptor agonists (and acetylcholinesterase inhibitors) to counteract cholinergic dysfunction. The search started with M_1 selective orthosteric muscarinic acetylcholine receptor (mAChR) agonists, was continued with efforts to find selective presynaptic M_2 receptor antagonists, shifted later to nicotinic acetylcholine (partial) agonists and since 2002 came back to allosteric M_1 mAChR agonists. Excellent reviews on the cholinergic system in aging and neuronal degeneration have been published [17–26]. The history of the cholinergic hypothesis was also described [27].

1.1.1. Muscarinic acetylcholine receptors

mAChRs are widely expressed throughout the central nervous system (CNS). Five mAChRs have been cloned, of which M_1, M_3, and M_5 mAChRs couple via G_4(11) proteins to activated phospholipase-C and mobilize intracellular calcium. M_2 and M_4 mAChRs signal through G_4(11) proteins to inhibit adenylyl cyclase and reduce intracellular concentrations of cAMP [28]. Activation of mAChRs M_1 and M_3 stably transfected into HEK cells leads to an increase of soluble amyloid-β protein precursors AbPPs and a concomitant reduction of amyloid-β (Aβ) by activating the α-secretase pathway [29, 30]. Muscarinic receptor pharmacology and circuitry for the modulation of cognition was described recently [31]. Muscarinic agonists for the treatment of cognition in schizophrenia was reviewed [32]. Loss of M_1 mACh receptors exacerbated AD pathology and cognitive decline [33].

1.1.1.1. Orthosteric muscarinic acetylcholine M_1 receptor agonists. All “first generation” muscarinic cholinergic agonists interacted with the orthosteric acetylcholine binding site. The orthosteric binding pocket is a hydrophobic network of aromatic residues contributed by the exofacial domains of transmembrane domains TM3, TM4, TM6, and TM7. Site directed mutagenesis experiments have shown that the binding of classic agonists such as carbachol is mediated by two highly conserved residues tyrosine-381 and asparagine-382 in TM6 [34]. Additional studies revealed that also Trp-101 (3.28), Tyr-404 (7.39), and Tyr-408 (7.43) contribute to orthosteric agonist binding [35].

Hundreds of (wo)man years went into syntheses and characterization of M_1 selective muscarinic cholinergic agonists, five of which were followed up into extended Phase III clinical trials before their development was terminated due to unacceptable side effects [28, 36]. The best known compounds are shown in Fig. 1.

Cevimeline (AF-102B, SNK-508, Exovac, hydrochloride hemihydrate, Israel Institute for Biological Research; Fig. 1), a spiro-quinuclidine derivative, is probably the best investigated selective M_1 mAChR agonist. It was in Phase III clinical trials for the treatment of AD patients in the US, Japan, and Israel. It is the only orthosteric acetylcholine receptor agonist, which made it to the US and Japanese markets in 2001 for the treatment of dry mouth of patients suffering from Sjögren’s disease (xerostomia; marketed by Snow Brand Milk Products and Daiichi Pharmaceuticals [37–39]). The receptor profile of cevimeline according to [40] is: M_1: EC_{50} = 25 nM, E_{max} = 82%; M_2: EC_{50} = 1.84 µM, E_{max} = 98%; M_1 selectivity over M_2: 78 fold; M_3: EC_{50} = 48 nM, E_{max} = 75%; M_1 selectivity over M_3: 2 fold; M_4: EC_{50} = 1.31 µM, E_{max} = 50%; M_1 selectivity over M_4: 58 fold; M_5: EC_{50} = 63 nM, E_{max} = 43%; M_1 selectivity over M_5: 3 fold. Cevimeline decreased the levels of total Aβ in cerebrospinal fluid (CSF) of patients with AD [41].

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**Xanomeline** (LY-246708, monotartrate salt, Lilly and Novo Nordisk; Fig. 1) was in Phase III clinical trials for the treatment of AD patients in Denmark and in Phase II in the US [42–44]. More recently, xanomeline has also been tested as a novel treatment approach of cognition deficits in schizophrenic patients [32, 45–51]. The receptor profile of xanomeline according to [40] is: M1: EC50 = 0.3 nM, Emax = 87%; M2: EC50 = 92.5 nM, Emax = 98%; M1 selectivity over M2: 275 fold; M3: EC50 = 5 nM, Emax = 111%; M1 selectivity over M3: 15 fold; M4: EC50 = 52 nM, Emax = 80%; M1 selectivity over M4: 154 fold; M5: EC50 = 22 nM, Emax = 68%; M1 selectivity over M5: 126 fold. In animal experiments, xanomeline was also effective for the treatment of neuropathic pain [52].

**Milameline** (CI-979, RU-35926, PD-129409, hydrochloric acid salt; Parke-Davis, now Pfizer and Roussel-Uclaf, now sanofi; Fig. 1) was in Phase III clinical trials for the treatment of AD patients in the US and Canada [53–56]. The receptor profile was not published.

**Alvameline** (LU-25-109, L-(+)-tartrate salt; Lundbeck; Forest; Fig. 1) was in Phase III clinical trials for the treatment of patients with AD in Denmark and the US [58, 59]. The receptor profile was not published.

**Talsaclidine** (WAL 2014 FU, fumarate salt, Boehringer-Ingelheim; Fig. 1) was in Phase II clinical trials for the treatment of patients with AD in Germany and the US [60–62]. The receptor profile of talsaclidine according to [40] is: M1: EC50 = 18 nM, Emax = 73%; M2: EC50 = 1.535 μM, Emax = 86%; M1 selectivity over M2: 87 fold; M3: EC50 = 143 nM, Emax = 76%; M1 selectivity over M3: 8 fold; M4: EC50 = 1.02 μM, Emax = 64%; M1 selectivity over M4: 57 fold; M5: EC50 = 700 nM, Emax = 33%; M1 selectivity over M5: 40 fold. Talsaclidine stimulated the non-amyloidogenic α-secretase processing of AβPP in vitro and in vivo [63, 64].

**AF267B** (NGX-267, TorreyPines Therapeutics under license from Life Science Research Israel; Fig. 1) was in Phase I clinical trials in the US for the treatment of patients with AD. It is a spiro-piperidine derivative from the laboratories of Abraham Fisher and colleagues (Israel Institute for Biological Research, Ness-Ziona [65–67]). The receptor profile of NGX-267 according to [40] is: M1: EC50 = 30 nM, Emax = 82%; M2: EC50 = 1.57 μM, Emax = 85%; M1 selectivity over M2: 52 fold; M3: EC50 = 44 nM, Emax = 109%; M1.
selectivity over M₁: 1.5 fold; M₄: EC₅₀ = 1.56 µM, Emax = 55%; M₁ selectivity over M₄: 52 fold; M₅: EC₅₀ = 850 nM, Emax = 34%; M₁ selectivity over M₅: 28 fold. In an in depth study in triple transgenic mice (APPps192Δ, tauP301L, and PS1M146V knock-in), it was shown that AF267B caused a selective activation of ADAM17 (α-secretase) thereby shifting AβPP processing towards the non-amyloidogenic pathway [68]. This shift is mediated by PKC and ERK 1/2 activation [69]. In addition a decrease of GSK-3β activity led to a reduction of tau pathology [68].

**WAY-132983** (Wyeth, now Pfizer, Fig. 1), a highly potent M₁ mAChR agonist, reduced cognitive impairment in rats at doses of 0.03 mg/kg/day [70, 71]. The receptor profile of WAY-132983 according to [40] is: M₁: EC₅₀ = 0.3 nM, Emax = 96%; M₂: EC₅₀ = 22 nM, Emax = 97%; M₁ selectivity over M₂: 78 fold; M₄: EC₅₀ = 2 nM, Emax = 114%; M₁ selectivity over M₄: 5 fold; M₅: EC₅₀ = 33 nM, Emax = 92%; M₁ selectivity over M₅: 116 fold; M₁: EC₅₀ = 16 nM, Emax = 61%; M₁ selectivity over M₅: 56 fold. The compound was also evaluated in animal models of chronic pain [72].

**Sabcomeline** (SB-2022026, BC-224, CEAD-242, Memrec, hydrochloride salt, SK&F, now GSK; Fig. 1) was in Phase III clinical trials for the treatment of patients with AD in the UK. BrainCells (under license from Proximagen and GSK) is developing sabcomeline for the potential treatment of schizophrenia in Phase II clinical trials since November 2011 [73, 74] (Thomson Reuters Pharma, update of March 29, 2012). The receptor profile of sabcomeline according to [40] is: M₁: EC₅₀ = 0.2 nM, Emax = 83%; M₄: EC₅₀ = 10 nM, Emax = 95%; M₁ selectivity over M₄: 48 fold; M₅: EC₅₀ = 0.1 nM, Emax = 95%; M₁ selectivity over M₅: 0.6 fold; M₄: EC₅₀ = 5.5 nM, Emax = 71%; M₁ selectivity over M₄: 26 fold; M₁: EC₅₀ = 1 nM, Emax = 45%; M₅ selectivity over M₁: 5 fold. Sabcomeline produced a greater response than xanomeline in releasing acetylcholine and dopamine in the medial prefrontal cortex of rats at a dose of 1 mg/kg s.c. [46].

William S. Messer and coworkers at the University of Toledo have prepared the tetrahydropyrimidine derivative MCD-386 (DDE-0102A, Fig. 1). The compound was formulated as a controlled release tablet and is evaluated in Phase I clinical trials by Mithridion. A transdermal formulation of MCD-386 is also currently evaluated (Thomson Reuters Pharma, update of May 31, 2012). Potential back-up compounds are MI-00918, MI-08-01635, and MI-10-022 (Thomson Reuters Pharma, updates of October 28, October 25, and December 6, 2011, respectively). The structures were not communicated.

**AZPET** (FluoroPharma in collaboration with the Massachusetts General Hospital, 18F-RS-86, ex-Sandoz, Fig. 1) is evaluated for the potential diagnosis of AD (Thomson Reuters Pharma, update of June 19, 2012).

The development of many other orthosteric M₁ selective mAChR agonists was also terminated in earlier phases of clinical development (in alphabetical order): of A-720555 (Abbott Laboratories); AF-30 (Israel Institute for Biological Research [79–82]; AF-150 and AF-151 (Israel Institute for Biological Research and Snow Brand Milk Products [66, 83–85]); arecoline transdermal patch (Cogent Pharmaceuticals); CDD-34, CDD-0038, CDD-0097, CDD-190, CDD-0193, CDD-0199-J, CDD-0235-J, CDD-0322, CDD-0325 (Mithridion under license from the University of Toledo); CI-1017 (Warner-Lambert, now Pfizer [86–88]; CP-172607 (Pfizer); ET-126 (University of Florence, a muscarinic M₁ receptor antagonist [91]; FP-7832 (Faust Pharmaceuticals, now Domain Therapeutics); FPL-14995 and FPL-15467 (Fisons, now sanofi; a M₁ & M₂ agonist and M₃ antagonist); itumeline (RU-47213, Roussel-Uclaf, now sanofi [90]; KAD-1931R (Kyorin Pharmaceuticals Co.,): KW-6055 (Kyowa Hakko Kogyo Co. [91]; L-658903 (Merck [92]); L-680648 (Merck [93]); L-687306 (Merck [94, 95]); L-689,660 (Merck [96]); L-705106 (Merck); L-354006 and LY-593093 (Lilly); MCna-343 (McNeill Pharmaceuticals, now Johnson & Johnson); NC-11-314, NC-11-1585, and NC-11-1607 (Novo Nordisk); NGX-292 (TorreyPines Therapeutics); PD-151832 (CI-1017: Parke-Davis, now Pfizer); RS-86 (Sandoz, now Novartis [97, 98]; SDZ-210-086 (Sandoz, now Novartis [99]; SK-946 (Sanwa Kagaku Kenkyusho [100–106]); SR-46559A (sanofi [107, 108]); T-588 (Toyama [109–117]); tazomeline (Lilly); thiopilo-carpine (SDZ-ENS-163; Sandoz, now Novartis [44, 118–123]); U-80816 (Pharmacia & Upjohn, now Pfizer); VRTX-3 (Vertex); and of YM-796 and YM-954 (Yamanouchi, now Astellas [124–126]).

The main problem of all these compounds was unacceptable side effects, such as severe gastrointestinal distress, bradycardia, salivation, and sweating (sabcomeline; M₁ selectivity = 0.6; NGX-267: M₃/M₁ selectivity = 0.5; cevimeline; M₃/M₁ selectivity = 2; WAY-132983: M₃/M₁ selectivity = 5; talsacline; 354006, CI-1017, PD-151832, YM-796, YM-954).
M1/M4 selectivity = 8; xanomeline, M3/M1 selectivity = 15 [40]. The current opinion is that the orthosteric binding site is highly conserved among mAChRs, which makes the design of subtype selective compounds extremely difficult [28, 35].

The development of the selective muscarinic M1 receptor antagonist LK-12 (All Russian Research Institute of Pharmaceutical Chemistry) was also terminated as was the development of the selective M4 receptor antagonist tropicamide (Harvard Medical School [127]).

1.1.1.2. Allosteric muscarinic acetylcholine M1 receptor agonists. An important breakthrough was achieved in 2002 at ACADIA Pharmaceuticals in San Diego, where scientists screened a library of 145,000 structurally diverse small organic molecules for agonist activity on M1, M3, and M5 muscarinic receptors using a cell-based functional assay. They identified allosteric agonists acting at a site removed from the orthosteric site to directly activate the receptor in the absence of acetylcholine, such as AC-42 (Fig. 3 [34, 128–130]), which was later optimized to AC-260,584 (Fig. 3 [131]). The receptor profile of AC-260,584 according to [40] is: M1; EC50 = 2 nM, Emax = 8%; M2; EC50 = 470 nM, Emax = 68%; M1 selectivity over M2: 220 fold; M1; EC50 = 415 nM, Emax = 41%; M1 selectivity over M1: 195 fold (!!); M4; EC50 >10 μM, Emax = 0%; M1 selectivity over M4: >5,000 fold; M1; EC50 = 189 nM, Emax = 32%; M1 selectivity over M1: 89 fold.

Studies on M3 receptors with point mutations established that the allosteric binding site is located adjacent to the orthosteric site on the opposite face of residue Trp-101 (3.28) [35, 128], see Fig. 2 [132, 133].

AC-262271 (Allergan under license from ACADIA Pharmaceuticals) is being developed for the treatment of glaucoma in Phase I clinical trials since August 2007 (Thomson Reuters Pharma, update of March 28, 2012). Its structure was not communicated.

AM-831 (ACADIA Pharmaceuticals in collaboration with Meiji Seika, Tokyo) is a muscarinic M1 partial agonist with dopamine D2 and 5-HT2A antagonistic properties for the potential oral treatment of schizophrenia and AD in Phase I trials in healthy volunteers (Thomson Reuters Pharma, update of May 16, 2012). The structure was not communicated.

Glaxo SmithKline scientists found a highly selective and systemically active M1 positive allosteric modulator (PAM), which did not activate the receptor directly, but potentiated the activation of the receptor by endogenous acetylcholine, i.e., 77-LH-28-1 [40] does not cause down-regulation of M1 mACh receptors [134, 135]. Further optimization led to the Phase I compound GSK-1034702 (Fig. 3), which was well tolerated [136, 137] (Thomson Reuters Pharma, update of August 4, 2011).

There are currently several allosteric M1 mAChR agonists in preclinical development (in alphabetical order):

- **AstraZeneca** (Fig. 3) presented gem-difluorobicyclics as novel M1 muscarinic receptor agonists, which showed enhanced metabolic stability in comparison to the non-fluorinated analogues (Thomson Reuters Pharma, update of April 18, 2012).

- **Novartis** (ACP-104; Fig. 3) was identified as an allosteric modulator of mAChRs [138, 139]. There is evidence that its cognition enhancing effects derive from the muscarinic M1 receptor agonist interaction [46]. The receptor profile according to [40] is: M1; EC50 = 3 nM, Emax = 85%; M2; EC50 = 295 nM, Emax = 89%; M1 selectivity over M2: 107 fold; M3; EC50 = 31 nM, Emax = 102%; M1 selectivity over M3: 11 fold; M4; EC50 = 1.23 μM.
Fig. 3. Structures of allosteric muscarinic acetylcholine ligands.

$E_{\text{max}} = 68\%$; $M_1$ selectivity over $M_4$: 443 fold; $M_5$: $E_{\text{max}} = 53\%$; $M_1$ selectivity over $M_5$: 18 fold. Note that N-desmethylclozapine interacts with the $M_1$ mAChR at a third site positioned above the orthosteric binding site [35, 128].

Heptares Therapeutics is investigating allosteric $M_1$ subtype selective muscarinic acetylcholine agonists for the potential treatment of schizophrenia and AD (Thomson Reuters Pharma, update of April 26, 2012). The structures were not communicated.
Lu AE51090 (Lundbeck, Fig. 3) is a compound with "unprecedented selectivity" (EC50 at M1: 61 nM and Emax = 83%; Emax at M2, M3, M5 receptors, respectively). In a delayed alternation Y-maze, the drug produced a significant increase in correct alternation at doses of 10 and 20 mg/kg s.c. in mice [140].

Merck & Co conducted a screen on >1,000,000 compounds to identify a PAM at M1 mAChRs, i.e., BQCA (benzyl quinolone carboxylic acid, Fig. 3) [141]. BQCA reduced the concentration of acetylcholine required to activate M1 receptors up to 129 fold. No potentiation, agonism, or antagonism on the other subtypes of mAChRs were observed up to 100 μM. BQCA had no activity in >300 radioligand binding assays at 10 μM and did not significantly potentiate eight other class A G protein coupled receptors at 100 μM. BQCA had no activity in >300 radioligand binding assays at 10 μM and did not significantly potentiate eight other class A G protein coupled receptors at 100 μM. BQCA had no activity in >300 radioligand binding assays at 10 μM and did not significantly potentiate eight other class A G protein coupled receptors at 100 μM. Studies in M1 (–/–) mice demonstrated that BQCA required M1 to promote inositol phosphate turnover in primary neurons and to increase c-fos and arc RNA expression and extracellular signal-regulated kinase (ERK) phosphorylation in the brain. BQCA binds to Y179 in the loop between transmembrane domains 4 and 5 and to W400, which precedes transmembrane domain 7. BQCA reversed scopolamine induced memory deficits in contextual fear conditioning with doses of 10 and 30 mg/kg i.p., which neither TBPB (vide infra) nor AC-42 (vide supra) did. BQCA increased blood flow to the cerebral cortex and increased wakefulness while reducing delta sleep. BQCA induced β-arrestin recruitment to M1 suggesting a role for this signal transduction mechanism.

Scientists at Vanderbilt University also investigated BQCA and found that it restored discrimination reversal learning in a transgenic AD mouse model. BQCA regulated non-amyloidogenic AβPP processing in vitro suggesting that M1 PAMs have the potential to provide both symptomatic and disease modifying effects in AD patients [142].

Merck scientists presented a more advanced compound (Fig. 3) with good bioavailabilities in rats and dogs of 68 and 62%, respectively (Thomson Reuters Pharma, update of May 31, 2012). For excellent medicinal chemistry, see [143–150].

TBPB (Vanderbilt University, Fig. 3) is a PAM at muscarinic M1 receptors, which had effects on the processing of AβPP toward the non-amyloidogenic pathway [151–153]. Further optimization efforts led to VU-0357017 (ML-071) and VU034572 (Fig. 3) [154–158].

ML169 (VU-0405652; Vanderbilt University, Fig. 3) is an optimized, brain penetrant M1 PAM based on VU0366369 (ML157) [159, 160].

Vanderbilt University and Seaside Therapeutics are also investigating allosteric M1 mAChR antagonists for the potential treatment of fragile X syndrome and autism. VU0415248 (Fig. 3) is the most recent optimized compound based on VU/0255035 (ML121; Fig. 3) [161, 162].

The development of ACP-104 (N-desmethylclozapine) and PCAP-1 and PCAP-2 (all ACADIA Pharmaceuticals) were terminated.

1.1.1.3. Vincamine-type compounds: In an early review [5], vincamine-type compounds were described as a chemical class, because the mechanism of their cognition enhancing effects was unknown. Surprisingly, it turned out that (−)-eburnamonine (Vinburnine; Fig. 4) and vincamine (Fig. 4) (Vinburnine; Fig. 4) and vincamine (Fig. 4) (Vinburnine; Fig. 4) and vincamine (Fig. 4) (Vinburnine; Fig. 4) and vincamine (Fig. 4) (Vinburnine; Fig. 4) acted as allosteric M1 to M4 muscarinic ligands [163–166]. The affinities to the subtypes of mAChRs are modest (measurements of binding of [3H]NMS in the presence of increasing concentrations of the allosteric ligands, for vincamine: M1: Kd = 17.3 μM, M2: 8.12 μM, M3: 1.85 μM, M4: 58.9 μM; for (−)-eburnamonine: M1: Kd = 7.54 μM, M2: 68.9 μM, M3: 6.67 μM, M4: 23.7 μM [164].
Medicinal chemists of Gedeon Richter explored trans-vincamine derivatives and identified RGH-10885 (Fig. 4) as a novel cognition enhancer active at an oral dose of 5 mg/kg in rats, which also inhibited lipid peroxidation [167]. Its development was terminated as was the development of Vintoperal (RT-3003; Gedeon Richter [168, 169]), Vincomate (OM-853; Omnium [170–180]), and Apovincamine, the 2-nitroxyethyl ester of (+)-eburnamenine-14-carboxylic acid (VA-045; Taisho [181–188]), which protected mice against traumatic brain injury-induced retrograde and anterograde amnesia [189, 190].

1.1.1.4. Muscarinic acetylcholine M2 receptor antagonists. An alternative approach to achieve improved cholinergic transmission is to antagonize central presynaptic muscarinic M2 receptors leading to an increased release of acetylcholine. This approach was mainly followed up by scientists at Schering-Plough, Boehringer-Ingelheim, GSK, and Roche and was described in an excellent review [36]. For earlier work, see [191]. Best known compounds are BIBN-99 (Boehringer-Ingelheim; Fig. 5; M2: Kᵢ = 9 nM, ratio M₁/M₂ = 26) and SCH-217443 (Schering-Plough; Fig. 5; M2: Kᵢ = 0.4 nM, ratio M₁/M₂ = 623, ratio M₂/M₃ = 250, ratio M₂/M₄ = 35, ratio M₂/M₅ = 58). SCH-217443 showed excellent oral bioavailability and cognition enhancing effects in rats at low oral doses of 0.001, 0.01, and 0.1 mg/kg. As M₂ receptors are also present in cardiac tissue, an increased heart rate in rats was observed at doses of 3 mg/kg p.o. [192].

It appears that safety concerns about potential cardiac side effects [28] led to the termination of the development of BIBN-140, SCH-57790, SCH-72788, and SCH-226206. Also himbacine analogues were actively pursued by scientists from Kyorin and Schering-Plough. Their development was also abandoned.

1.1.2. Nicotinic acetylcholine receptors

Nicotinic acetylcholine receptors (nAChRs) are ion channel receptors belonging to the same class as 5-HT₃, GABAᵢ, and strychnine-sensitive glycine receptors [193]. Each subunit has a large N-terminal extracellular domain, a transmembrane domain comprising four segments (TM1-TM4) and a small C-terminal. They form pentamers with the M2 domain at the inside of the channel, which is permeable to Na⁺ and K⁺ ions. The nAChRs are encoded by 17 genes. Of these nine α subunits (α₂–α10) and three β subunits (β₂–β4) are expressed in the brain [194–196]. >90% of the nAChR in the CNS contain α₄ and β₂ subunits forming α-bungarotoxin insensitive receptors. Another subtype consists of a homopentamer of α₇ subunits, α-bungarotoxin sensitive receptors [197]. The acetylcholine binding site lies at the interface between an α-type subunit (the principal component) and a non-α-type subunit (the complementary component). In the α₄β₂ receptor (consisting of 2 α₄ and 3 β₂ subunits) there are two, and in the α₇ homopentamer there are five ACh binding sites. The localization of nAChRs in the hippocampus was elucidated [198]. Functional brain imaging of nicotinic effects on higher cognitive functions remains...
processes have been reported [199]. The topic nicotinic receptors, Aβ, and synaptic failure was discussed [200]. Excellent reviews on selective nAChR agonists as potential therapies to treat cognitive impairment associated with schizophrenia and AD were published recently [201, 202].

1.1.2.1. α4β2 and α3β4 nicotinic acetylcholine receptor agonists. α4β2 nAChRs have a role in cognitive function [203, 204]. Medicinal chemists and pharmacologists succeeded to identify agonists with improved safety and therapeutic profiles in comparison to nicotine [205]. Treating cognitive deficits of schizophrenic patients with α4β2 neuronal nicotinic receptor agonists was discussed [206]. α6β2 and α4β2 nAChRs as drug targets for Parkinson’s disease were reviewed [207]. Peroxisome proliferator-activated receptor (PPAR) ligands are important negative modulators of α4β2 nAChRs on dopaminergic neurons [208].

Varenicline (Chantix, Champix; CP-526555; Pfizer; Fig. 6) is a partial agonist for α4β2 nAChRs and a full agonist at α7 neuronal nicotinic receptors [209]. The drug was launched in 2006 as an aid to smoking cessation treatment [210–227]. Sales in 2011 were USD 720 million. Partial agonists at the α4β2 subtype in the mesolimbic system stimulate dopamine release to reduce craving when quitting, whereas the
antagonistic properties inhibit nicotine reinforcement when smoking [228]. A Phase II clinical trial in subjects with mild to moderate AD has started in early 2010. However, by February 2011 the development of varenicline tartrate had been discontinued for the treatment of cognition deficits in AD patients (Thomson Reuters Pharma, update of June 25, 2012).

**Pozanicline (ABT-089; Abbott; Fig. 6)** was already characterized preclinically in 1997 [229, 230]. The drug was tested in AD, ADHD, schizophrenia, and smoking cessation. The indication schizophrenia was abandoned. Two Phase II trials in children afflicted by ADHD gave negative results. Efficacy and safety of ABT-089 in adults with ADHD was reported [231] (Thomson Reuters Pharma, update of February 8, 2012).

**Ispronicline (TC-1734; AZD-3480; Targacept and AstraZeneca; Fig. 6)** is tested in clinical Phase II trials both in patients suffering from AD and from ADHD. In January 2012 AstraZeneca decided to advance the drug in AD. It appears that a Phase II trial with AZD-1446 as an adjunct treatment to donepezil will be initiated in patients with mild to moderate AD (Thomson Reuters Pharma, update of May 17, 2012). AZD-1446 (TC-6683; AstraZeneca in collaboration with Targacept) is tested in clinical Phase II trials both in patients with ADHD since January 2007. In June 2008 it was reported that the drug was safe and generally well tolerated. A formulation of sofinicline for potential use in ADHD was reported [231] (Thomson Reuters Pharma, update of June 6, 2012). The structure was not disclosed.

**Lobeline (derived from lobelia inflata; Ceptaris Therapeutics, formerly Yaupon Therapeutics, Fig. 6)** is being developed for the potential treatment of methamphetamine addiction and ADHD in Phase II trials since July 2008. By January 2010, the trials in both indications were completed [242, 243] (Thomson Reuters Pharma, update of January 6, 2012). The structure was not disclosed. SR-17080 has a $K_i$ value of 2.6 nM at the high sensitivity $\alpha_4\beta_2$ nAChR isofrom [249–251] (Thomson Reuters Pharma, update of March 09, 2012). A neurosearch is evaluating the drug for smoking cessation (Thomson Reuters Pharma, update of February 27, 2012).

**Compound 64** (Prof. A. P. Kozikowski and coworkers at the University of Illinois at Chicago, Fig. 6) was identified as a potent agonist acting at the high sensitivity $\alpha_4\beta_2$ nAChR isofrom [249–251] (Thomson Reuters Pharma, update of March 09, 2012). Aurogen is evaluating the drug for smoking cessation (Thomson Reuters Pharma, update of February 27, 2012).

**SUVN-F91201 (Suvan Life Sciences)** is a non-competitive $\alpha_3\beta_4$ nAChR antagonist. SR-17080 has a $K_i$ value of 2.6 nM at $\alpha_3\beta_4$ nAChRs compared with 476 nM at $\alpha_4\beta_2$ receptors. The aim is potential treatment of AD [256] (Thomson Reuters Pharma, update of January 25, 2011).

**SUVN-9111 (Suvan Life Sciences)** is an oral $\alpha_4\beta_2$ nAChR antagonist, for the potential treatment of mood disorders and major depressive disorders. Other $\alpha_4\beta_2$ nAChR antagonists are evaluated for the potential treatment of schizophrenia, pain, and cognitive disorders (Thomson Reuters Pharma, update of February 8, 2012). Structures were not communicated.
Carbon-11 labeled pyridyl ethers for in vivo imaging of nAβ2 nAChRs in brain were described [257].

The development of several well-known compounds was terminated (in alphabetical order): of A-82695 (Abbott Laboratories [258–260]), ABT-418 (Abbott [261–268]), altinicline (SIB-1508Y; Sibia, now Merck for the indication of Parkinson’s disease [269–271]), ATG-901 (CoMentis), DHR-83 (University of Florence [272, 273]), dianicline (SSR-591813; sanofi for the indication of smoking cessation [274–276]), of a nicotine patch (Japan Tobacco), rivanicline (RJR-2403, TC-2403; Targacept, previously RJ Reynolds Tobacco [277–281]), RJR-1401 (RJ Reynolds Tobacco), of TC-1827, TC-2429 (RJR-2429), TC-2559, and TC-4959 (AVE-3183; Targacept in collaboration with Aventis, now sanofi), of TC-5214 (S(+)-mecamylamine; Targacept and AstraZeneca; a selective α4β2 nAChR antagonist [282–284]), of tebanicline (ABT-594; Abbott [285] and A-366833 [286]), both for the indication of pain and neuropathy and of UB-165 (University of Bristol [287–290]).

1.1.2.2. Alpha7 nicotinic acetylcholine receptor agonists. α7 nAChRs are highly expressed in the hippocampus. Gene knockout and antisense experiments have shown a role for α7 nAChRs in learning and memory ([291–293]. Deletion of the α7 nAChR gene improves cognitive deficits in a mouse model of AD [294]. For excellent reviews, see [308]).

ABT-126 (Abbott Laboratories) is an α7 neuronal nicotinic receptor modulator for the potential treatment of AD and for cognitive deficits in schizophrenia (CDS) in Phase II clinical trials. In October 2009 a multicenter, randomized, double-blind, placebo- and active-controlled Phase II was initiated in 274 mild to moderate AD patients in the US, Bulgaria, the Czech Republic, Slovakia, South Africa, and the UK (NCT00948909). In March 2010 a randomized, double-blind, placebo controlled Phase II study in 210 CDS patients began in the US (NCT01095562). In March 2009 a randomized, double-blind Phase I trial began to assess the safety, tolerability, and pharmacokinetics of ABT-126 (20 mg four times a day (qd) for 10 days and 35 mg qd for 21 days in 30 elderly subjects; NCT00867399). In February 2012 a randomized, double-blind, placebo and active controlled Phase II study to evaluate the efficacy and safety of ABT-126 in patients with mild to moderate AD (n=410; NCT01527916) was expected to start (Thomson Reuters Pharma, update of March 13, 2012). The structure of ABT-126 was not communicated.

EVP-6124 (MT-4666, EnVivo under license from Bayer and Mitsubishi Tanabe Pharma; Fig. 7) is an α7 nAChR partial agonist in Phase I b clinical trials for the treatment of cognition deficits in patients with AD since May 2010 and in schizophrenia patients since January 2010; Thomson Reuters Pharma, update of June 14, 2012). An improvement of working and recognition memory in rodents at doses of 0.3 to 1 mg/kg p.o. was recognized [309]. Additional in vitro and in vivo characterization was disclosed recently [310].

A potential follow-up compound is EVP-4473 (Thomson Reuters Pharma, update of Dec. 23, 2011). The structure of EVP-4473 was not communicated.

GTS-21 (DMXB; CoMentis licensed from the University of Florida; Fig. 7) is an α7 nAChR partial agonist in Phase II clinical trials for the treatment of AD, CDS, and ADHD [311–317] (Thomson Reuters Pharma, update of March 14, 2012).

TC-5619 (Targacept, Fig. 7) is a full agonist at α7 nAChRs and is currently in Phase II clinical trials for the treatment of schizophrenia in the US and Eastern Europe (n=450) since December 2011. Another Phase II trial in 80 patients with inattentive-predominant ADHD was initiated in the US in November 2011. For efficacy in animal models, see [318] (Thomson Reuters Pharma, update of June 6, 2012).

ABT-272 (Abbott Laboratories) is an α7 nAChR modulator for the potential treatment of pain in Phase I clinical trials (Thomson Reuters Pharma, update of November 24, 2011). The structure of ABT-272 was not communicated.

There are many selective α7 neuronal nicotinic receptor agonist (partial) agonists in preclinical evaluation (in alphabetical order):

A-867744 (Abbott Laboratories; Fig. 7) and ABT-779 are PAMs of the α7 nAChR [319, 320]; Thomson Reuters Pharma, update of September 27, 2011). Extensive preclinical characterization of A-582941 (Fig. 7) described the broad-spectrum cognition-enhancing properties [321] (Thomson Reuters Pharma, update of October 21, 2011).

α7 nAChR agonists (Napogenex in collaboration with Ceptaris Therapeutics, formerly Yaupon Pharmaceauticals) are plant extracts discovered by plant-genomics technology (Thomson Reuters Pharma, update of January 6, 2012). In a second program, N-methyl-D-aspartic acid (NMDA) receptor and α7 nAChR inhibitors are evaluated.

APL-1 (Galantos Pharma) is a nAChR allosteric potentiating ligand (nAChR APL), which
Fig. 7. \( \alpha_7 \) nicotinic acetylcholine receptor agonists.

Specifically targets \( \alpha_7 \) subtypes for the potential treatment of AD (Thomson Reuters Pharma, update of February 6, 2012). The structure was not communicated.

AZT-2 (Lundbeck) is an \( \alpha_7 \) nAChR PAM for the potential treatment of cognitive dysfunctions (Thomson Reuters Pharma, update of December 6, 2011). The structure was not communicated.
Bio-Link is investigating positive allosteric α7 nAChR modulators for the potential treatment of cognitive disorders (Thomson Reuters Pharma, update of February 13, 2012). The structures were not communicated.

BMS-902483 (Bristol-Myers Squibb; Fig. 7) is a partial α7 nAChR agonist with an EC50 of 9.3 nM. It demonstrated excellent brain penetration and α7 nAChR occupancy at low plasma concentrations in rodents. The compound showed hepatotoxicity in dogs (Thomson Reuters Pharma, update of April 3, 2012).

BNC-1881 (Biometrics) is a PAM of α7 nAChR for the potential memory improvement treatment in AD and schizophrenia (Thomson Reuters Pharma, update of June 28, 2012). The structure was not communicated.

Cholinergic therapeutics (Ophiodon) are siRNA mediated lynx-1 modulators, which regulate α7 nAChR receptors [322–324] (Thomson Reuters Pharma, update of June 15, 2012). Structures were not communicated.

JNJ-1930942 (Johnson & Johnson; Fig. 7) is a selective, and orally active facinicline for the potential treatment of CDS, Parkinson’s disease, AD, and ADHD. It does not act on α4β2, α3β4 nAChRs, or on the related 5-HT1 channel. It increased peak and net charge response to choline and acetylcholine mainly by affecting receptor desensitization characteristics [325] (Thomson Reuters Pharma, update of February 15, 2011).

11C-NS-12857 and 11C-NS-14492 (NeuroSearch, University of Copenhagen; Fig. 7) are positron emission tomography (PET) ligands for the assessment of neurological disorders including AD and schizophrenia (Thomson Reuters Pharma, update of November 16, 2010).

PheTQS (Promaxigen under license from GSK; Fig. 7) showed an EC50 value of 20 nM as PAM of α7 nAChRs [326–332] (Thomson Reuters Pharma, update of March 2012, a novel pyridine structure was disclosed (Fig. 7; Thomson Reuters Pharma, update of June 8, 2012). The structure was not communicated.

Dual α7 nicotinic acetylcholine receptor activators and BACE-1 inhibitors are investigated in a program by the University of Maryland [338] (Thomson Reuters Pharma, update of February 24, 2012). The development of several well-known compounds was terminated, e.g., of ABT-107 (Abbott [339–341]), AR-R-17779 (Astra Arcus, now AstraZeneca), AZD-0328 (AstraZeneca [342–344]), AZD-6319 (AstraZeneca), CP-810123 (PNU-120596; Pfizer [345–347]), facinicline (MEM-3454, R3487, RO5313334; Memory Pharmaceuticals, now Roche [348, 349]), JN403 (Novartis [350–352]) and JN711 (Novartis [353, 354]), MEM-63908 (RG-4996; Memory Pharmaceuticals, now Roche), NNC-90-0270 (Novo Nordisk), PHA-543613 and PHA-568487 (both Pfizer), SAR-130479 (sanoﬁ), SIB-1553A, SIB-1663, SIB-1765F, SIB-1926, SIB-2182 (Sibia, now Merck [355–362], for the treatment of cognitive dysfunctions see [197]), SSR-180711 (sanoﬁ [347, 363]), W-56203 (Mitsubishi Tanabe Pharma), and of XY-4083 (Xytis).

1.2. Adenosine receptors

Adenosine receptors have been implicated in the modulation of cognitive functions. The assessment of adenosine receptor antagonists for the treatment of cognitive dysfunction in animal studies was reviewed [364]. In particular selective inactivation of A2A adenosine receptors enhanced learning and memory functions [365, 366]. Mice lacking A2A adenosine receptors displayed improved spatial recognition memory [367]. The best known A2A adenosine receptor antagonist is caffeine (25,381 entries in PubMed as of May 28, 2012). The K0 values of caffeine at human A1
receptors are 12 μM, at A2A receptors 2.4 μM, at A1 receptors 13 μM, and at A3 receptors 80 μM [368]. Experiments were carried out in wild-type and in A1 and A2A knock-out mice at doses of 15, 10, and 5 mg/kg i.p. of caffeine. In wild-type mice the dose of 15 mg/kg significantly increased wakefulness by 1.5, 2.9, and 2.1 fold during the first, second, and third hour after injection, respectively. In contrast, in A2A knockout mice, the dose of 15 mg/kg did not show any change in time spent in wakefulness, whereas A1 R knockout mice showed the same increase in wakefulness as wild-type mice confirming that the arousal effect of caffeine is due to A2A receptors [369–371].

The psychomotor stimulant effects of caffeine are generated by affecting a particular group of projection neurons located in the striatum expressing high levels or A2A adenosine receptors [372]. A1–A2A receptor heteromers were identified in the striatum [373]. Caffeine has the ability to release the pre- and postsynaptic brakes that adenosine imposed on dopaminergic neurotransmission [374].

Astrid Nehlig [3] reviewed the topic: “Is caffeine a cognitive enhancer?” Caffeine facilitated learning in tasks in which information is presented passively. In tasks in which material is learned intentionally, caffeine had no effect. Caffeine facilitated low-difficulty performance in low-load memory tasks and impaired it on high-load tasks, probably due to over-arousal. In the longitudinal Three City Cohort Study including 4,197 healthy women and 2,820 healthy men over 65 years, women consuming over 3 cups of caffeine daily for over 4 years showed less decline in verbal retrieval and visuospatial memory than women consuming one cup or less. The protective effect of caffeine increased with age with a maximal effect in women over 80 years. No relation was found between caffeine intake and cognitive decline in men [375]. Caffeine, but not theophylline, exerted disease-modifying effects in AD mice including a direct reduction of Aβ production through suppression of both β- and γ-secretase levels [376–378]. This may be due to increased plasma levels of granulocyte-colony stimulating factor [379]. High blood caffeine levels in patients with mild cognitive impairment (MCI) are linked to a lack of progression to dementia [380].

Rabbits fed on a 2% cholesterol-enriched diet showed enhanced levels of Aβ and tau phosphorylation and increased levels of reactive oxygen species and isoprostanes. Caffeine at 0.5 and 30 mg/kg per day in drinking water reduced the cholesterol-induced increase in Aβ, phosphorylated tau, and oxidative stress levels suggesting that even very low doses of caffeine might protect against sporadic AD-like pathology [381]. Rifampicin and caffeine caused an upregulation of the low-density lipoprotein receptor related protein-1. The brain efflux index of Aβ in rifampicin and caffeine treated mice was significantly higher (82% and 80%, respectively) than the brain efflux index of control mice (62%). It appears that a yet to be identified transporter/receptor plays a significant role in Aβ clearance, which is upregulated by rifampicin and caffeine [382]. Caffeine at 10 mg/kg improved memory recognition on scopolamine-induced impairment of memory in mice [383]. In the novel object recognition task, pre-treatment with caffeine prevented disruption of short- and long-term memory by scopolamine. In the inhibitory avoidance task caffeine prevented short-term, but not long-term, memory disruption by pre-training with scopolamine. These results confirmed previous data in humans [384].

In a very large prospective study in 229,229 men and 173,141 women during 1995 and 2005, coffee consumption was found to be inversely associated with total and cause-specific mortality [385]. Some effects of caffeine are unrelated to interactions with adenosine receptors. Caffeine also acts as a competitive, non-selective phosphodiesterase inhibitor [370, 386].

Tozadenant (SYN-115; Biotie Therapies Holding, formerly Synosia Therapeutics under license from Roche; Fig. 8) is a potent and selective A2A receptor antagonist for the potential treatment of Parkinson’s disease in Phase Ib clinical trials since April 2011 [387] (Thomson Reuters Pharma, update of May 29, 2012). Shire (under license from Heptares Therapeutics) is investigating a series of A2A receptor antagonists for the potential treatment of Parkinson’s disease, cognition deficits, and other CNS disorders (Thomson Reuters Pharma, update of May 2, 2012).

The development of a potent adenosine A1 and A2A receptor dual antagonist ASP-5854 (Astellas Pharma) was terminated [388, 389].

1.3. Adrenergic receptors

The serotonergic and adrenergic mechanisms of cognition have been reviewed [390]. Long-term α1-adrenergic receptor stimulation improved synaptic plasticity, cognitive function, mood, and longevity in transgenic mice [391]. The beneficial effects of desipramine on cognitive function of chronically stressed rats are mediated by α1-adrenergic
receptors [392]. The α2-adrenoceptor agonist guanfacine improved performance in an attention test in aged Rhesus monkeys [393]. The roles of β-adrenergic receptors in AD were discussed [394].

Buflomedil (Loptyl, Laboratoire L. Lafon, later Cephalon, now Teva) is an α1A/α1B adrenoceptor antagonist (Kᵢ = 4 μM and 6.84 μM, respectively [395]) with partial calcium channel antagonist activity launched for the treatment of peripheral vascular disease and cognitive disorders [396–401]. An interesting case study was presented [402].

ORM-12741 (Orient Corporation) is an α2C adrenoceptor antagonist for the potential treatment of neurological diseases such as AD and Raynaud’s disease. By April 2011, a randomized, double-blind, placebo-controlled Phase II trial in AD patients (n = 99) was started in Finland and is expected to terminate in June 2012. A Phase II trial in Raynaud’s disease was initiated in the UK (n = 18) in August 2011 (Thomson Reuters Pharma, update of February 21, 2012). The structure was not communicated.

Curvedilol, an α1, β1, and β2 adrenoceptor blocker, re-established long term potentiation in mouse models of AD [403–406].

The development of dabeholine (S-12024-2, Servier), an adrenoceptor agonist and nootropic agent, was discontinued [407–412], as was the development of idazoxan (Pierre Fabre), an α2 adrenoceptor
antagonist [413], of 5-fluoro-methoxy-idazoxan F-14413 (Pierre Fabre), of S-32212, S-34324 and S-35966 (Servier, dual $\alpha_2$ adrenoceptor antagonists and serotonin and noradrenaline re-uptake inhibitors) and of SDZ-NVI-085 (a selective, centrally acting $\alpha_1$ adrenoceptor agonist; Sandoz, now Novartis [414–419].

1.4. Angiotensin receptors

1,818 papers have been published on the brain renin-angiotensin system (PubMed citations as of May 28, 2012). There are plausible explanations for the cognitive facilitation noted in human clinical trials conducted with AT1 antagonists [420, 421]. The formation of angiotensin II interferes with memory acquisition. Preventing the formation of angiotensin II should facilitate cognitive processing. Preventing the formation of angiotensin II also releases the inhibition of potassium-induced exocytosis of acetylcholine. Preclinical findings of the brain renin-angiotensin system in cognitive function and implications for the prevention and treatment of dementia were communicated [422, 423]. An AT1 receptor blocker may have greater cognition protective effects that angiotensin-converting enzyme (ACE) inhibitors [424]. The effects of renin-angiotensin system blockade on cognitive function in patients aged 55 years and older were investigated [425]. The effects of the ACE inhibitor ramipril, and a combination of the drugs were evaluated in 25,620 patients. Meta-regression analysis did not show any benefits of blood-pressure lowering on cognition over several years of treatment. The current standing of the benefits of blood-pressure lowering on cognition over patients. Meta-regression analysis did not show any combination of the drugs were evaluated in 25,620 patients [425]. The effects of renin-angiotensin system blockade on cognitive function in patients aged 55 years and older were investigated [425].

Losartan (DUP-753; Merck, launched in 1994; Fig. 8) is a brain penetrating selective AT1 receptor antagonist. Losartan administered intranasally to AβPP/PS1 transgenic mice for two months decreased Aβ plaques by 3.7 fold [427]. Losartan also showed memory-enhancing properties in an active avoidance task in mice [428, 429], which is due to involvement of the cholinergic system [430]. Losartan significantly increased the score of the word list memory and the word list recall test in elderly hypertensive patients [431]. Cognitive enhancement following acute losartan in normotensive young adults was reported [432].

Candesartan (Takeda, launched in 1998; Fig. 8) improved memory decline in mice [433] and in older patients with hypertension [434].

Telmisartan (Boehringer Ingelheim, launched in 1999; Fig. 8) prevented Aβ caused cognitive decline, which may be partly due to an activation of PPAR-γ [435–439]. It improved cognitive function in elderly hypertensive patients [440].

Valsartan (Novartis, launched in 1996; Fig. 8) lowered brain Aβ protein levels [441].

Also Eprosartan (GSK, launched 1999; Fig. 8) penetrated the blood-brain barrier [442] as did Irbesartan (sanoft, launched 1997; Fig. 8) [443, 444].

The development of RS-66252 (an angiotensin I receptor antagonist; Syntex, now Roche) and of WSU-2088 (an angiotensin 4 receptor agonist of the Washington State University) has been terminated.

1.5. Cannabinoid receptors

The endocannabinoids and the CB1 receptors have been implicated in the control of cognition [445–447]. Cannabinoids and prefrontal cortical functions have been studied [448]. Significantly lower levels of the endocannabinoid anandamide and its precursor 1-stearoyl-2-docosahexaenoyl-sn-glycero-phosphoethanolamine-N-arachido-noyl (NArPE) were found in postmortem brain samples from AD patients in comparison to brains from control subjects [449]. Anandamide and NArPE levels in midfrontal cortex of the study subjects inversely correlated with levels of Aβ$_{1-40}$ while showing no association with Aβ$_{40}$ levels, amyloid plaque load, or tau protein phosphorylation.

Dronabinol (ultrapure THC; Namisol, Echo Pharmaceuticals), a natural product and cannabinoid receptor agonist, is tested as a sublingual 1.5 mg tablet in Phase II clinical trials to evaluate efficacy, safety, and tolerability in chronic pancreatitis, MS, and AD patients (Thomson Reuters Pharma, update of June 7, 2012).

Rimonabant (SR-141716A, sanoft, withdrawn from the market) improved memory in a delayed radial maze task [450]. Also the development of drinabant (AVE-1625; Aventis, now sanoft [451]). Org-50189 (Organon, now Merck [452–455]). SILV-330 (Solvay Pharmaceuticals, now Abbott Laboratories [456, 457]) and of TAK-937 (Takeda [458]) was terminated.

1.6. Chemokine receptors

CC chemokine receptor 2 deficiency aggravated cognitive impairments and amyloid pathology in a transgenic mouse model of AD [459]. The role of the CC-chemokine receptor 5 signaling pathway in cognitive deficits induced by Aβ was
described [460]. CC chemokine receptor 5 regulated olfactory and social recognition in mice [461]. Fractalkine receptor (CX3CR1) signaling protected against plaque-independent cognitive deficits in a mouse model of AD [462].

**RAP-310** (RAPID Pharmaceuticals) is a small stabilized receptor active peptide targeting the CCR5 receptor for the potential treatment of AD. Preclinical data demonstrated that the number of activated microglia within the dentate gyrus and CA3 hippocampal areas were reduced on treatment with RAP-310 compared to lipopolysaccharide-infused rats. Significant reduction in the number of hypertrophic astrocytes and expression of NFκB was also observed on treatment with RAP-310 (Thomson Reuters Pharma, update of June 13, 2011). The structure was not communicated.

### 1.7. Dopamine receptors

The dopaminergic enhancement of cognitive function was discussed in detail [463]. Research in experimental animals suggested that stimulation of dopamine D1 receptors in the prefrontal cortex can ameliorate spatial working memory related cognitive deficits and may even enhance cognitive function in healthy animals. Prefrontal dopamine had specific functions in attentional control and working memory, which was mediated mainly through D1 receptors [464]. Activation of D1/D5 dopamine receptors by the selective agonist SKF-81297 protected neurons from synapse dysfunction induced by Aβ oligomers [465]. Low doses of dopamine D2 receptor agonists such as bromocriptine and pergolide may be able to enhance working memory and executive functions [463]. Dopamine D2 receptor antagonism improved certain cognitive domains [466].

**Dexpramipexole** (KNS-760704; Knopp Neurosciences and Biogen Idec under license from the University of Virginia; Fig. 9) is the (R)-enantiomer of pramipexole with weak affinities to D2 and D3 receptors (IC50’s of 1800 nM and 610 nM, respectively). The compound is in Phase III clinical trials for an oral treatment of amyotrophic lateral sclerosis patients since March 2011 (∼804) in the US, Canada, Europe, and Australia and in Phase II trials for AD (∼20) in the US [467–471]. (Thomson Reuters Pharma, update of June 21, 2012).

**Seridopidine** (ACR-343; A. Carlsson Research AB, now NeuroSearch, Fig. 9) is a dopaminergic stabilizer for the potential oral treatment of Parkinson’s disease and schizophrenia. A Swedish Phase I trial began in December 2007. The planned Phase II study was delayed due to additional toxicological examinations of a metabolite. In the Thomson Reuters Pharma update of June 25, 2012 the drug is reported to be
suspended in favor of the Phase III compound pridopidine (ARC16; Fig. 9) for the treatment of Huntington’s disease [472–474].

PB-03000130 (Pfizer; Fig. 9) is a dopamine D2 and a 5-HT1A partial agonist, a potent 5-HT2B antagonist and a moderately potent serotonin re-uptake inhibitor for the potential treatment of manic and depressive symptoms in bipolar disorder and schizophrenia in pre-clinical evaluation [475] (Thomson Reuters Pharma, update of May 23, 2011).

A dual D2 receptor agonist and histamine H3 receptor antagonist is investigated by Angita Pharmaceuticals for the potential treatment of cognitive disorders (Thomson Reuters Pharma, update of May 9, 2012).

A dual N-acetyltransferase re-uptake inhibitor and histamine H3 receptor antagonist is investigated by Angita Pharmaceuticals for the potential treatment of cognitive disorders (Thomson Reuters Pharma, update of May 10, 2012).

The development of many dopamine receptor ligands was terminated, i.e., of A-412997 (Abbott; a D2 receptor agonist [476–478]), adrogeside (ABT-431, DAS-431, Abbott Laboratories and Drug Abuse Sciences, a dopamine D2 receptor agonist for the potential treatment of cocaine addiction and cognitive disorders [479–481]), dilydroxidine (DAR-0100; DarPharma under license from Purdue University, a dopamine D2 receptor agonist for the potential treatment of cocaine addiction and cognitive disorders [479–481]), dinydroxidine (DAR-201; DalPharma; a dopamine D2 agonist [487–489]), PRX-5007 (Proximagen; a D1 dopamine receptor agonist), RGB-1756 (Gedeon Richter; a dopamine D3 receptor agonist [490]), S-33138 (Servier; a D3 receptor antagonist), SB-277011-A (GSK; a D3 dopamine receptor antagonist [491–493]), seridotidine (A. Carlsson Research, now NeuroSearch; a dopamine D1 receptor modulator).

1.8. Endothelin receptors

Endothelin-1 is elevated in AD and upregulated by Aβ. Endothelin-A receptor antagonists prevented Aβ-induced increase in ETA receptor expression, oxidative stress, and cognitive impairment [494]. These findings provide evidence of overactivity of the endothelin system in AD supporting the suggestion that endothelin receptor antagonists may be of value for the treatment of this disease [495, 496]. Reduction of endothelin levels may lead to an improved brain perfusion.

ENDG-6010 (EndogenX Inc.) is an endothelin receptor antagonist for the potential treatment of AD and dementia including vascular dementia in pre-clinical evaluation (Thomson Reuters Pharma, update of November 22, 2011). The structure was not communicated.

The development of S-0139 (SB-737004; Shionogi), an endothelin-A antagonist, was terminated [497–499].

1.9. Estrogen receptors

A number of clinical studies have suggested that estrogen therapy may delay the onset or contribute to the prevention and/or attenuation of AD [500–503]. Several comprehensive reviews were published [504–506].

The results of the Women’s Health Initiative, a large, prospective study in which 16,608 post-menopausal women were randomized to receive either conjugated equine estrogen (0.625 mg per day) plus medroxyprogesterone (2.5 mg per day) or placebo clearly indicated that, after a mean of 5.2 years of follow-up, the use of oral conjugated estrogen and medroxyprogesterone not only did not reduce the risk of heart disease, but led to a 29% increase in the risk of non-fatal myocardial infarction and heart disease death, a 41% increase in the risk of stroke, a 111% increase in the risk of venous thromboembolism and a 26% increase in the risk of breast cancer compared with placebo-treated subjects [507]. Data from the Women’s Health Initiative Memory Study indicate that treatment with estrogens either alone or in combination with progesterin failed to prevent age-related memory decline and dementia [508–511]. A follow-up Women’s Health Initiative study on cognitive aging reported that treatment impaired verbal memory [512–515]. There may be a “critical period” around the time of menopause [517]. There may be a “critical period” around the time of menopause during which the prescription of estrogen therapy may reduce the risk of developing AD in later life. This effect may be most significant in women under 49 years. Prescription of estrogen therapy after this point may have a neutral or negative effect, particularly when initiated in women over 60–65 years [518, 519].

Despite the controversial clinical reports, many interesting preclinical papers appeared on the effects
of estrogen on markers of AD. Estrogen stimulated degradation of Aβ peptide by upregulating neprilysin [520]. 17β-estradiol increased intracellular trafficking of AβPP and hence reduced maximal Aβ generation within the trans-Golgi network [521]. The fundamental mediator of the neuroprotective effects of estrogen seems to be seladin-1 (the selective AD indicator-1 [522]; for a commentary see [523]). Estrogen protected from Aβ neurotoxicity by restoring integrin expression and cell-cycle control [524].

Phyto-beta-SERM (University of Southern California) is an estrogen receptor beta selective phytoestrogenic formulation comprised of three phytoestrogens for the potential treatment of AD. By July 2011 Phase III studies were ongoing (Thomson Reuters Pharma, update of August 4, 2011).

Despite big efforts the work on selective estrogen receptor modulators (SERMs), NeuroSERMs [525] and on selective estrogen receptor-β agonists did not produce useful cognitive enhancers for clinical development. It appears that AstraZeneca, Bayer-Schering, Celera, Celgene, GSK, J&J, Lilly, Merck-Organon, Novartis, QuatRx Pharmaceuticals, sanofi, and SRI International have all terminated their programs on SERMs. Only ACADIA Pharmaceuticals has a SERM program ongoing (Thomson Reuters Pharma, update of March 6, 2012).

A highly selective estrogen receptor-β agonist was discovered by investigating traditional Chinese medicine in the roots of Glycyrrhiza uralensis Fisch, i.e., liquiritigenin (7,4′-dihydroxy-flavanone; Fig. 10) [526]. Liquiritigenin was able to attenuate Aβ25-35 induced impairment of learning in rats [527]. Biomovo is developing MF-101 (Menopause Formula-101, Menerba), a plant-derived mixture that interacts with the estrogen receptor-β as agonist and contains liquiritigenin in Phase II clinical trials (Thomson Reuters Pharma, update of April 2, 2012).

(-)-Epigallocatechin-3-gallate (EGCG; Fig. 10) present in green tea acts as an estrogen receptor-α (ER-α) agonist setting in motion receptor tyrosine phosphorylation of the p85 regulatory subunit of PI3K. Subsequently PIP₂ is converted to PIP₃, which activates Akt. Akt interacts with AβPP by phosphorylating C-terminal tyrosine sites. Interaction with ADAM10 favors the promotion of the non-amyloidogenic α-secretase processing of AβPP [528, 529]. EGCG reduced Aβ-mediated cognitive impairment presumably via flavonoid-mediated presenilin-1 phosphorylation, which reduced AD Aβ production [530–532]. EGCG prevented lipopolysaccharide-induced elevation of Aβ generation [533]. The cell signaling pathways and iron chelation were described [534–540]. Also ERK and NFκB pathways are involved [533]. A special formulation of EGCG in nanolipidic particles to improve its bioavailability was presented [541].

Neurocrine tested the androgen receptor agonist dehydroepiandrosterone (DHEA; Fidelin; Fig. 10) in Phase II/III double-blind, placebo-controlled, clinical trials in Canada, New Zealand, Australia, South Africa, and Europe. In one center, DHEA was given to 58 subjects with AD in a 6 month treatment (50 mg p.o. twice a day) versus placebo. DHEA did not significantly improve cognitive performance or overall rating of change in severity in this study [542]. Part of DHEA’s pharmacology may also be due to its interaction with sigma-1 receptors [543].

The development of E2-CDN (estradiol-chemical delivery system; Pharmos under license from the
1.10. GABA receptors

1.10.1. GABA\(_A\) receptors

Many studies describe that inverse agonists of \(\alpha5\)\(\gamma2\) GABA\(_A\) receptors, particularly abundant in the hippocampus, display valuable cognition enhancing properties (in chronological order) [544–555].

Big efforts have been made particularly by scientists at Merck UK during many years to produce first L-655,708 (Fig. 11) [556, 557] followed by \(\alpha5\)IA (Fig. 11), which was converted \textit{in vivo} to a highly insoluble hydroxymethyl isoxazole metabolite [558–561]. \(\alpha5\)IA restored cognitive deficits in Down syndrome mice [562, 563]. MK-016 (Fig. 11) was well tolerated in young, but not in elderly volunteers [564]. For excellent medicinal chemistry see [565, 566].

RG-1662 (Roche), a small-molecule \(\alpha5\) GABA\(_A\) inverse agonist and negative allosteric modulator (NAM), is evaluated in a multicenter, randomized, double-blind, placebo-controlled, multiple dose, Phase I study in Down syndrome patients \((n = 33)\) in the US to assess the safety and tolerability of RG-1662 since September 2011 (Thomson Reuters Pharma, update of April 18, 2012). Its structure was not disclosed.

There are many \(\alpha5\) GABA\(_A\) receptor inverse agonists or NAMs in preclinical evaluation (in alphabetical order):

- AC-4402 (Dainippon Sumitomo Pharma) is a partial inverse GABA\(_A\) receptor agonist for the potential treatment of AD. Its structure was not communicated (Thomson Reuters Pharma, update of December 6, 2011).
- C-21191 (CoNCERT Pharmaceuticals) is a deuterated \(\alpha5\) GABA\(_A\) receptor inverse agonist derived from Merck’s L-838,417 (Fig. 11), which was considered to have an unsuitable pharmacokinetic profile. The deuterated derivative showed good metabolic stability [567] (Thomson Reuters Pharma, update of March 6, 2012).
- GABA\(_A\) receptor \(\alpha5\) inverse agonists are explored at AgeneBio (Thomson Reuters Pharma, update of December 29, 2010). The structures were not disclosed.
- GABA\(_A\) receptor \(\alpha5\) subtype selective antagonists are investigated jointly by scientists of the University of Wisconsin at Milwaukee and of MSD for the potential treatment of anxiety, amnesia, and...
alcoholism. The lead compound XLi-093 is a dimer of imidazo-benzodiazepines (Fig. 12) [568, 569] (Thomson Reuters Pharma, update of July 12, 2011).

Medicinal chemists at Kyowa Hakko Kirin produced the pyrido[2,3-d]pyrimidine-4-one derivative (Fig. 12) [570]. It appears that the development was terminated.

RO4938581 (Roche; Fig. 12) and the dichloro-analogue RO4882224 (Fig. 12) are inverse agonists at α5β2γ2 GABAA receptors [571–575].

UC-1011 (Umecrine; Fig. 12) is a GABAA receptor antagonist with neurosteroid structure for the treatment of memory and learning disturbances associated with AD [576] (Thomson Reuters Pharma, update of January 31, 2012).

The development of FG-8094 (Ferrosan), HT-2678 (Helicon Therapeutics), radequinil (AC-3933; AVE-3933, SX-3933; Dainippon Sumitomo [577]), RU-33965 (Roussel-Uclaf, now sanofi [578–580]), S-135 (Shionogi [581]), S-8510 (SB-737552; Shionogi and GSK [582–584]), SAR-501788 (sanofi), of sarmanzenil (Roche [585]), suritizole (MDL-26479; Hoechst Marion Roussel, now sanofi [586–590]) and of ZK-91296 and ZK-93426 (Bayer Schering Pharma [591–594]) was terminated.

1.10.2. GABAB receptors

GABAB receptor antagonists proved to be valuable cognitive enhancers as was shown in many animal experiments and in two clinical trials (vide infra). It is still unclear which GABAB1 receptor isoforms contribute to cognitive processes. Both GABAB1A (−/−) and GABAB1B (−/−) mice were impaired relative to wildtype controls in a continuous spontaneous alternation behavior test of working spatial memory. GABAB1A (−/−) mice were impaired in familiar and novel object recognition tests, but neither GABAB1A (−/−) nor GABAB1B (−/−) mice were deficient in a passive avoidance task [595].

CGP36742 (SGS742; Saegis Pharmaceuticals under license from Ciba-Geigy, now Novartis; Fig. 13) showed pronounced cognition enhancing properties in mice, in young and old rats, and in Rhesus monkeys [596–600]. It was taken into two Phase II clinical trials, first in patients with MCI and in mild to moderate AD patients. It significantly improved attention and working memory in MCI and patients with mild AD, but not in patients with moderate AD [601, 602]. CGP36742 was characterized in binding and electrophysiological experiments [603]. Repeated administration of CGP36742 upregulated
GABA\(_B\) receptor binding sites in cortex and spinal cord [604–606], which may be predictive of potential antidepressant effects according to a hypothesis first presented in 1984 [607]. CGP36742 enhanced the release of somatostatin [608–611]. Single administration of CGP36742 enhanced the levels of both mRNA and protein of nerve growth factor and brain-derived neurotrophic factor (BDNF) in brain and spinal cord of rats [612]. Administration of CGP36742 (SGS742) reduced the levels of CREB2 in the hippocampi of rats [613]. It was shown that the effects of CGP36742 were strain dependent in mice [614, 615]. Major signaling cascades were not involved in the memory enhancing effects of CGP36742 [616], but phosphorylated protein kinase A and synapsin isoform levels were linked to spatial memory enhancement [617, 618]. CGP36742 also antagonized actions of \(/\)-hydroxybutyrate [619, 620]. Special GC-MS methodology was required to determine plasma and brain levels of CGP36742 [621, 622]. CGP36742 was also able to suppress spike and wave discharges in an animal model of absence epilepsy (GAERS, genetic absence epilepsy rats of Strasbourg [623–627]).

CGP36742 and CGP51176 (AVE-7398; Ciba-Geigy, now Novartis outlicensed to Aventis, now sanofi; Fig. 13) showed pronounced antidepressant properties in several animal experiments [628–631], which may be due to the enhanced release of BDNF [612] and/or to the upregulation of GABA\(_B\) receptor binding sites [604, 632]. Three reviews were published [633–635].

The high affinity GABA\(_B\) receptor antagonists CGP56433 and CGP63360 (Fig. 13) improved learning and memory in active and passive avoidance tests in mice and rats at low doses of 0.1 mg/kg p.o. [624, 636, 637].

PAMs of GABA\(_B\) receptors are currently investigated at Addex Therapeutics, at Hoffmann-La Roche, and at AstraZeneca. For a patent survey on novel GABA\(_B\) receptor positive modulators, see [638]. The Addex compounds ADX-1a, ADX-1b, ADX-71441, and ADX-18200 were characterized in animal models of pain, fragile X syndrome, urinary incontinence, and gastroesophageal reflux disease (Thomson Reuters Pharma, update of June 19, 2012). Structures were not communicated.

1.10.3. GABA\(_C\) receptors

Researchers of the University of Sydney presented the first selective and brain penetrating GABA\(_C\) receptor antagonists (R)-ACBPA and (S)-ACBPA (Fig. 14). (S)-(3-amino-cyclopentenyl)-\(\alpha\)-butyl-phosphinic acid had a higher affinity to \(\rho_1\) receptors \((K_\text{b} = 5 \mu\text{M for } \rho_1\) and 11 \(\mu\text{M for } \rho_2\) receptors). The (R)-(enantiomer showed a higher affinity for \(\rho_2\) receptors \((K_\text{b} = 60 \mu\text{M for } \rho_1\) and 6 \(\mu\text{M for } \rho_2\) receptors). Both compounds showed dose dependent learning and memory enhancing effects in an object recognition test in mice at doses of 10 and 100 mg/kg i.p. [639, 640]. One of the compounds will be developed by NeuroTherapeutics (Thomson Reuters Pharma, update of January 24, 2012). Novel cyclic phosphinic acids as GABA\(_C\) receptor antagonists were discovered [641]. Two reviews on the medicinal chemistry of GABA\(_C\) receptors were published [642, 643].
GABA receptors are also evaluated for the potential treatment of vascular eye disease at Aarhus University (Thomson Reuters Pharma, update of December 13, 2011).

1.11. Galanin receptors

Galanin and galanin receptors are overexpressed in limbic brain regions associated with cognition in AD [644, 645]. Galanin impairs cognitive abilities in rodents. GAL-R1 receptors play a role in aversive memories [646–648].

HT-2157 (SNAP-37889; Dart NeuroScience following the acquisition of Helicon Therapeutics licensed from Lundbeck; Fig. 14) is a galanin-3 receptor antagonist for the treatment of major depressive and cognitive disorders such as memory loss in Phase I/II since August 2011 (n = 28) in the US. The study is estimated to be complete in May 2012 [649–651] (Thomson Reuters Pharma, update of April 24, 2012).

1.12. Glutamate receptors

1.12.1. AMPA receptors

AMPA receptor stands for α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid receptor, which is a non-NMDA-type ionotropic transmembrane receptor for glutamate that mediates fast synaptic transmission in the CNS [652].

1.12.1.1. Piracetam-type compounds

Piracetam (UCB-6215; Nootropil, UCB; Fig. 15) was discovered more than forty years ago [653]. For decades it was considered as “a drug without a mechanism”, i.e., a “nootropic agent” [1, 2]. Now it is firmly established that piracetam acts as a weak positive modulator of AMPA receptors. The X-ray structure of piracetam binding to the S1S2 dimer interface of GluA2 is available [654]. Piracetam can occupy three binding sites, binding site 1 analogous to the binding of aniracetam, binding site 2 analogous to the binding of cyclothiazide, and a unique new binding site 3. An X-ray structure was also obtained for GluA3 in the presence of piracetam. The density in binding site 3 was not as strong as in GluA2. The orientation within this binding site is identical to that of GluA2 and GluA3. For the alternative splicing into flip and flop versions of AMPA receptors, see [655].

A comprehensive review of the pharmacological properties and the clinical uses of piracetam was presented [656] as was an overview on piracetam and piracetam-like drugs [657].

Oxiracetam (SF-2522; Neuromet, ISF, GSK) was launched in 1987, Aniracetam (Ro-13-5057; Draganon, Sarpu, Roche, Toyama) in 1993 [658], and Pramiracetam (CI-879; Neupramir; Pfizer, Lusofarma, licenced from Lundbeck in 1993; see [659, 660]) in 2005. Dimiracetam (NT-11624; BND-11624; Neurontone, Brune Discovery, Fig. 15) is in Phase II clinical trials for the treatment of HIV-associated pain in South Africa. In October 2010 results from 111 patients showed the drug was safe and well tolerated and all subjects had a significant improvement in pain symptoms. For medicinal chemistry, see [659, 660] (Thomson Reuters Pharma, update of May 4, 2012).

NT-24336 (NIK-13317; Neurontone, Brune Discovery, Fig. 15) is in Phase II clinical trials for the treatment of HIV-associated pain in South Africa. In October 2010 results from 111 patients showed the drug was safe and well tolerated and all subjects had a significant improvement in pain symptoms. For medicinal chemistry, see [659, 660] (Thomson Reuters Pharma, update of May 4, 2012).

The development of many piracetam-type compounds was terminated, i.e., of alaptide (VUFB [666, 667]), tebaracetam (Ciba-Geigy, now Novartis [668]), CI-933 (Parke-Davis, now Pfizer), (–)-clausenamide (Chinese Academy of Medical Sciences [669, 670]), fasoracetam (NS-105; LAM-105; Nippon Shinyaku [671, 672]), nebracetam (WEB 181 FU; Boehringer Ingelheim [673–675], rolziracetam
Fig. 15. Piracetam and piracetam analogues.

1.12.1.2. AMPAkines. The first observations of the pharmacological potentiation of AMPA receptors were made via electro-physiological recordings using the nootropic drug aniracetam (Fig. 15) [685–687]. The groups of Gary Lynch of the University of California at Irvine and of Gary A. Rogers of the University of California at Santa Barbara presented the first benzamide drug 1-BCP (BA-14, Fig. 16) [688, 689]. The drug crossed the blood-brain barrier and reversibly increased the amplitude and prolonged the duration of field excitatory postsynaptic potentials. Evidence for improved memory was shown in the Morris water maze and in a radial maze.

Later it was found that AMPAkines enhanced synaptic transmission, lowered the threshold, and increased the magnitude of long term potentiation and increased the release of BDNF [690–692]).

The prototypic AMPAkin CX-516 (BDP-12, BA-74, Ampalex, SPD-420, Org-24292, Cortex Pharmaceuticals; Fig. 16) was tested in several clinical trials in AD and MCI, in schizophrenia, ADHD, sleep disorders, fragile X syndrome, and autism. The development of Ampalex was terminated in December 2006.

CX-516 binds to a different site than other modulators [693]. The compound has been characterized as a type II AMPAkin, as the more potent CX-691 (tarampator). Type I AMPAkines slow the channel closing by factors up to 50, whereas type II AMPAkines accelerate the channel opening by factors up to three.

CX-717 (Cortex) is an AMPAkin for the potential treatment of ADHD, AD, and respiratory disorders in Phase II clinical trials. It is also evaluated to alleviate the effects of sleep deprivation [694]. Oral and i.v. formulations are evaluated (Thomson Reuters Pharma, update of May 16, 2012). The structure was not communicated.

CX-1739 (Cortex) is a potential follow-up compound of CX-717 for the potential treatment of sleep apnea and neurological diseases including ADHD and AD. Phase II results of a sleep apnea trial have been reported in February 2011. Cortex is evaluating oral and injectable formulations (Thomson Reuters Pharma, update of May 16, 2012). The structure was not communicated.

S-47445 (CX-1632; Servier under license from Cortex Pharmaceuticals) is an AMPAkin for the potential treatment of memory and cognitive impairments associated with neurodegenerative disease including AD. A Phase I trial has been completed by Servier in October 2011 (Thomson Reuters Pharma, update of...
April 2, 2012. The structure of S-47445 was not communicated.

CX-546 (Fig. 16) promoted enhancement of glucose utilization by cortical, hippocampal, and cerebellar astrocytes [695]. CX-546 significantly prolonged synaptic responses in CA1 pyramidal cells, but at the same concentrations had only weak modulatory effects in reticular thalamic nucleus neurons [696].

CX-554 (BDP-20; Fig. 16) was useful to elucidate the multiple modulatory sites of AMPA receptors [697]. It was approximately ten-fold more potent than CX-516 (BDP-12) in behavioral effects [698] and was more potent in enhancing feedforward than feedback inhibition [699].

The co-crystal structures of the AMPA receptor GluA2 S1S2 ligand-binding domain in complex with aniracetam (Fig. 8) and with CX-614 (Fig. 9) were presented [700]. Both potentiators bind within the dimer interface adjacent to the hinge in the ligand-binding core clamshell.

Farampator (CX-691; ORG-24481; SCH-900460; Fig. 16) was developed jointly by Cortex and Schering-Plough (formerly Organon; now Merck), but the development was terminated due to concerns about cardiac safety. Farampator enhanced cognitive effects in rats [701].

Cortex is developing several other AMPAkines, whose structures were not disclosed, such as CX-1942, CX-2007, and CX-2076 (Thomson Reuters Pharma, update of May 16, 2012).

New benzoxazinone scaffolds with very high potency were published recently. The readout is the EC2x value, the concentration of the compound, which when perfused onto cultured rat embryonic hippocampal neurons doubled the steady-state current induced by 500 μM glutamate. CX-614 had an EC2x of 2.3 μM, compound 4 (Fig. 16) an EC2x of 0.06 μM and compound 11r (Fig. 17) an EC2x of 0.7 nM, a big improvement over the 5 mM value of aniracetam [702, 703]. Potent AMPAkines with benzotriazinone, benzobistriazinone, and benzopyrimidinone structures were also disclosed [704, 705].

Excellent reviews on AMPA potentiators have been published [706–711].

The development of CX-929, CX-1501, CX-1796, and CX-1837 (Cortex Pharmaceuticals), Org-26576 (Organon, now Merck [712–716]), and of S-70340 (Servier) was terminated.

1.12.1.3. Biarylpropylsulfonamides. PF-04958242 (Pfizer; Fig. 17) is an AMPA receptor potentiator for the potential treatment of CDS in Phase I trials.
in healthy volunteers \( n = 24 \) since August 2010. In addition, a clinical study (NCT01518920) is underway to evaluate the effects of PF-049582432 in subjects with age-related hearing loss \( n = 42 \) in the US \[717\] (Thomson Reuters Pharma, update of May 11, 2012). LY-392098 (Eli Lilly, Fig. 10), LY-404187 (Fig. 17), and its \((R)\)-enantiomer LY-4516146 have been thoroughly investigated in preclinical models as novel antidepressants \[718–733\].

LY-404187 and LY-503430 (Fig. 17) have been characterized in rodent models of Parkinson’s disease \[734–738\]. LY-404187 and mibampator (LY-451395) reversed the central effects of acutely intoxicating doses of ethanol in rats \[739\]. In continuation of their work, Lilly scientists have thoroughly analyzed the properties of two novel PAMs of GluA2 desensitization and deactivation, i.e., compounds CMPDA and CMPDB (Fig. 17) with IC\(_{50}\)’s of 45 nM at GluA2i receptors and 63 nM at GluA2o receptors for CMPDA and EC\(_{50}\)’s of 122 nM at GluA2i and 470 nM at GluA2o receptors for CMPDB, respectively \[740\]. CMPDB attenuated the rate of deactivation for GluA2i and GluA2o receptors by factors of 7 and 5-fold, respectively. CMPDA slowed the rate of deactivation of GluA2o receptors by 2-fold, but had no effect on GluA2i receptor deactivation.

Scientists of GSK (Harlow) discovered novel AMPA receptor modulators, compound 17i (Fig. 18) \[741\] and compound 9a (Fig. 18) \[742\]. The challenges for and the current status of research of positive modulators of AMPA receptors were discussed \[743, 744\]. A HTS hit was optimized to a potent AMPA receptor modulator at Merck UK \[745\]. Compound 5 (Fig. 18) had good bioavailability \[746\]. Compound 19 (Fig. 18) displayed high aqueous solubility and excellent stability in microsomal and hepatocyte preparations \[747\]. For reviews describing the state of the art in 2000 and in 2010, see \[748, 749\].

The AMPA receptor potentiator PF-04778574 of Pfizer (Fig. 18) is a potential follow-up compound of PF-04958242 for the treatment of CDS \[750\]. \((R,R)\)-PIMSD (University of Copenhagen, Fig. 18) is a dimeric positive modulator bridging two identical AMPA receptor binding sites \[751\]. PIMSD showed cognitive enhancing effects on place learning in mice \[752\]. The development of mibampator (LY-451395; Eli Lilly) \[753, 754\]) and of LY-450108 was terminated.

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**Fig. 17.** AMPAkines of the biarylpropylsulfonamide type and novel modulators of AMPA receptor deactivation and desensitization.
1.12.1.4. Benzothiadiazides. **Cyclothiazide** (Fig. 19) is a diuretic and antihypertensive drug launched by Lilly in 1963. In 1993 it was discovered that it acts as a PAM of AMPA receptors [755]. In 2003 it was recognized that it acts as a NAM of GABAA receptors [756, 757]. In 2007 it was found that it acts as a NAM of mGluR1 receptors [758]. In 2008 it was discovered that it acts as a NAM of GABAC receptors [759]. Note that cyclothiazide contains 4 asymmetric centers theoretically giving rise to 16 stereoisomers, which is reduced to 8 due to the geometrical restriction of the methylene bridge. The four diasteromeric racemates have been separated by chromatography. The most potent fraction was resolved further into the two enantiomers by chiral HPLC showing a five times more potent effect in potentiating AMPA transmission than the cyclothiazide mixture [760].

Cyclothiazide eliminated desensitization of GluA2i receptors and significantly slowed the rate of desensitization of GluA2o receptors, but had no effect on deactivation on either GluA2i or GluA2o receptors. Cyclothiazide alters the channel gating events [761, 762].

**IDRA-21** (Fidia-Georgetown Institute for the Neurosciences; Fig. 19) crossed the blood-brain barrier readily and improved alprazolam-induced learning deficits in rats and monkeys [763–765]. Oral administration of IDRA-21 significantly improved performance in a delayed non-matching-to-sample task in young macaques [766]. Racemic IDRA-21 was resolved into the two enantiomers [767]. A significant increase in drug affinity was achieved by alkyl substitution at the 5′-position [768].

**S-18986** (Servier, Fig. 19) was in Phase II clinical trials, but its development was terminated due to rare side effects. Its pharmacology was extensively documented [769–774]. For an elegant asymmetric synthesis see [775]. The development of **BIIR-777** (Boehringer-Ingelheim, Fig. 19) was also terminated.

1.12.1.5. 1-Hydroxyazoles. Novo Nordisk was investigating a series of 1-hydroxyazoles (Fig. 19) as AMPA receptor agonists for the potential treatment of AD. The development activities were suspended [776].

**N-methyl-D-aspartate** is the selective agonist, which binds to this specific type of ionotropic glutamate receptors [777]. A substantial progress in the treatment of patients suffering from AD was achieved with the launch of the NMDA receptor channel blocker **memantine** (Axura, Ebixa, Namenda, Memary; Merz; Fig. 20). The compound was launched by Merz in Germany in
1982 for various neurological syndromes and cognitive dysfunction [778], by Lundbeck in the EU for the treatment of moderate to severe AD in November 2002, by Forest Laboratories in the US in January 2004, and by Daiichi Sankyo in Japan in June 2011. Sales for Namenda by Forest in 2011 were USD 1,400 million, sales for Ebixa by Lundbeck in 2011 were USD 514 million and sales for Daiichi Sankyo in 2011 were USD 123.5 million (Thomson Reuters Pharma, update of June 29, 2012).

There are currently 1960 papers on memantine listed in PubMed (as of May 28, 2012). Memantine is a moderate affinity, voltage-dependent, uncompetitive channel blocking NMDA receptor antagonist first synthesized at Lilly and patented in 1968 [779]. It inhibited NMDA receptors at near resting potential with an approximate affinity of 1 \mu M and blocked NR2A, NR2B, NR2C, and NR2D receptors expressed in Xenopus oocytes with IC_{50}'s of 0.89, 0.40, 0.32, and 0.28 \mu M, respectively [780]. It displaced \[^{3}H\]MK-801 from binding to postmortem human brain with a \(K_i\) of 0.54 \mu M [781]. Memantine blocked NMDA channels activated by high concentrations of L-glutamate at \(-70\) mV with a \(K_{on}\) of 2 to \(4 \times 10^7 \) M^{-1} s^{-1} and a \(K_{off}\) of around \(0.2 \) s^{-1} [780]. Memantine binds to at least two sites within the NMDA receptor channel, a shallow and a deep site [782]. Memantine also binds to \(\alpha 4\beta 2\) nAChRs with an IC_{50} of 6.6 \mu M, to \(\alpha 7\) nAChRs with an IC_{50} of 0.33 \mu M to 1.68 \mu M [780] and to 5-HT_{1A} receptors with an IC_{50} of 2.3 \mu M. Serum levels of memantine in humans with the usual daily maintenance dose of 20 mg are within the range of 0.5 to 1.0 \mu M [783]. Physiologically NMDA receptors are transiently activated by mM concentrations of L-glutamate in the synapse following strong depolarization of the postsynaptic membrane from a resting potential of \(-70\) mV to a value of \(-20\) mV, which rapidly relieves their voltage-dependent blockade by Mg^{2+} ions. The combination of fast-offset kinetics and relatively strong voltage-dependency allows memantine to rapidly leave the NMDA channel upon transient physiological activation by mM concentrations of synaptic glutamate. Under pathological conditions in AD, NMDA receptors are activated by \mu M concentrations of glutamate. Memantine can block this sustained tonic activation in contrast to Mg^{2+} ions. Thus, memantine can differentiate...
between low-level pathological activation of NMDA receptors in AD ("noise") and physiological synaptic NMDA receptor activation ("signal"; "signal to noise hypothesis") [780].

In addition memantine displayed disease-modifying effects on hallmarks of AD. Memantine significantly reduced the levels of insoluble Aβ, of Aβ dodecamers (Aβ1-42), prebrillar soluble oligomers, and brillover oligomers in triple transgenic AD mice of 6, 9, and 15 months of age [784]. Memantine lowered Aβ peptide levels in neuronal cultures and in AβPP/PS1 transgenic mice [785]. Memantine treatment significantly reduced the amount of phosphorylated tau (at Thr181) in the CSF of 13 AD patients treated for one year with 20 mg memantine daily (p = 0.018) [786].

A combination treatment of donepezil and memantine showed synergistic effects in a test for spatial learning and recall in a transgenic mouse model of AD [787]. For further reviews on primarily biological and mechanistic data, see [788–791].

Clinical trials were initiated by the medical team of Merz under Hans Jörg Möbius, who collaborated with many outstanding clinicians. The results of the clinical trials are described in the listed papers [778, 792–820] as were the effects of memantine for the treatment of dementia in adults with Down syndrome [780]. Memantine was also prescribed for the neuroenhancement of healthy individuals [831].

A review on safety and efficacy was published [832] as were pharmacoeconomic reviews [833–836].

Merz and Forest developed memantine extended release (memantine ER; Namenda XR), a once-daily 28 mg extended-release formulation, which was approved by the FDA in June 2010. The formulation was registered (Thomson Reuters Pharma, update of June 12, 2012, respectively). The structures were not communicated.

The development of CR-3394 (Rottapharm Madaus [839, 840], CNS-5161 (Paton, formerly Cambridge Neuroscience), D-cycloserine (a NMDA/glycine receptor agonist and of dexanabinol (HU-211: PA-50211, Sinnabinol; Pharmos, under license from the Hebrew University of Jerusalem) was terminated, as was the development of EVT-101 (Evotec, Roche), an orally active NMDA NR2B subtype specific antagonist and of NT-13 (a partial agonist at the NMDA receptor; Naurex, formerly Nyxis Neurotherapeutics).

11.2.3. Metabotropic glutamate receptors (mGluRs)

For a superb review on all eight mGluRs as novel drug targets, see [847]. Activation of mGluRs may lead to a novel approach for the treatment of schizophrenia [848]. A special issue on mGluRs and cognition was published in the European Journal of Pharmacology [849]. Efforts of targeting mGluRs for the treatment of CDS were presented [850, 851]. One publication deals with mGluRs as therapeutic targets for cognitive disorders [852]. Reviews on mGluR2/3, schizophrenia, and cognition were presented [853–855]. The effects of mGluR2/3 agonism and antagonism on schizophrenia-like cognitive deficits were discussed...
orders (Phase II study in patients with major depressive disorder who are also suffering from anxiety symptoms in Ukraine, Russia, Romania, Hungary, and Bulgaria. Subjects would receive oral twice daily treatment was initiated in 94 adult patients with major depressive disorder which was completed in May 2011. A Phase IIa trial was initiated in Europe (n = 105). In June 2012, a multicenter, double-blind, placebo-controlled, Phase II trial of the drug as an adjunct to antidepressant therapy and the primary endpoint would be the change from baseline in the Hamilton Anxiety Rating Scale score (Thomson Reuters Pharma, update of June 19, 2012).

RG-1578 (R-1578; presumed to be RO-4995819, Roche) is a small-molecule mGluR5 NAM in a Phase II study in patients with major depressive disorders (n = 480) since December 2011. By February 2012, RG-1578 had shown antidepressant and cognitive enhancing effects in a broad range of preclinical models (Thomson Reuters Pharma, update of May 22, 2012). The structure of RG-1578 has not been disclosed.

RG-7090 (RO-4917523; Roche, Fig. 21) is a mGluR5 antagonist for the potential treatment of depression and fragile X syndrome in Phase II clinical trials since March 2009, which was completed in September 2011. In February 2012, recruitment began for a randomized, double-blind, parallel-group, Phase II study (n = 315) in the US, Europe, Chile, Mexico, and Taiwan (Thomson Reuters Pharma, update of June 20, 2012).

BC1-838 (MGS-0210; BrainCells Inc. under license from Taisho Pharmaceutical; Fig. 21) is a produg of BC1-632 (MGS-0039, Fig. 21), a mGluR 2/3 antagonist with neurogenesis stimulating properties for the potential treatment of CNS disorders including treatment-resistant depression as well as major depressive disorder and AD in Phase I clinical trials since February 2012 [867, 868] (Thomson Reuters Pharma, update of March 19, 2012).

STX-107 (Seaside Therapeutics under license from Merck; Fig. 21) is a mGluR5 antagonist for the treatment of fragile X syndrome and autism in Phase I trials since September 2009 [869–876] (Thomson Reuters Pharma, update of February 9, 2012).

Other cognition enhancing mGluR ligands are in preclinical evaluation (in alphabetical order):

ADX-63365 (Addex Therapeutics; Fig. 21) shows the structurally similar compound ADX-50938 is an orally available PAM of mGluR5 for the potential treatment of schizophrenia and other indications involving cognitive impairment [877] (Thomson Reuters Pharma, update of March 21, 2012). The biological characterization of a structurally close analogue ADX-47273 (Fig. 21) was described in great detail [878].

Addex Therapeutics is investigating a series of NAMs of mGluR2 for the potential oral treatment of depression and AD (Thomson Reuters Pharma, update of June 19, 2012). The structures were not communicated.

DT-2228 (Domain Therapeutics; Fig. 21) is a mGluR2 NAM for the potential treatment of AD and depression [879] (Thomson Reuters Pharma, update of December 13, 2011). For the original discovery and the following re-exploration of the PHCCC scaffold, see [880–882].

Pfizer is investigating mGluR2 PAMs (lead structure shown in Fig. 21) for the treatment of CNS disorders [883–885] (Thomson Reuters Pharma, update of March 24, 2011).

RO-4491533 (Roche; Fig. 21), a mGluR2/3 dual antagonist, acts as a cognitive enhancer [886–890] (Thomson Reuters Pharma, update of January 19, 2011).

Roche (under license from Seaside Therapeutics under license from Vanderbilt Univ., Nashville TN) is investigating mGluR5 inhibitors for the potential treatment of fragile X syndrome and autism (Thomson Reuters Pharma, update of June 20, 2012). Structures were not communicated.

Sanofi is investigating mGluR2 PAMs for the potential treatment of CDS (Thomson Reuters Pharma, update of May 09, 2011). Structures were not communicated.
Fig. 21. Metabotropic glutamate receptor ligands.

**VU-0430644** (ML-254; Janssen under license from Vanderbilt University, Fig. 21) is an mGluR5 PAM for the potential treatment of schizophrenia. The compound showed efficacy in animal models of cognitive enhancement and was found to effectively treat the positive symptoms of schizophrenia.
The development of AIX-71743 (Addex Therapeutics; a mGluR7 NAM), CTEP (Roche; a mGluR5 receptor antagonist [891, 892]), LX-181837 and LY-487379 (Lilly; PAMs of group II mGluRs [893, 894]) and LY-341495 (Lilly, a mGluR2/3 antagonist [895]) was terminated as was MRZ-8676 (Merz, a NAM of mGlu5 receptors [896]).

1.13. G-protein coupled orphan receptors

The potential of G-protein coupled Orphan Receptors is still largely unexplored.

ESN-502 (Euroscreen) is a G-protein coupled receptor 3 (GPR3) modulator for the potential treatment of AD (Thomson Reuters Pharma, update of April 30, 2012). The structure was not communicated.

G-protein coupled receptor 3 antagonists (GPR3; Galapagos) may be of use for the potential treatment of AD (Thomson Reuters Pharma, update of May 21, 2012). The structures were not communicated.

GPR12, GPR27, GPR31, GPR52, GPR78, GPR123, GPR135, GPR139, GPR151, GPR153, and GPR173 antagonists (Omeros) may be of use for the potential treatment of cognitive disorders and other CNS disorders (Thomson Reuters Pharma, update of May 24, 2012). The structures were not communicated.

Mas-related G-protein coupled receptor antagonists (Omeros) are investigated for the potential treatment of cognitive impairment (Thomson Reuters Pharma, update of May 24, 2012). The structures were not communicated.

RGS-14 (University of Malaga) is a protein regulator of G-protein signaling 14 inhibitor for the potential treatment of memory loss (Thomson Reuters Pharma, update of January 10, 2012). The structure was not communicated. Extensive preclinical investigations were published [897–899].

1.14. Histamine receptors

Memory tests in experimental animals have shown that in particular histamine H3 receptor antagonists are valuable cognitive enhancers. Six recent reviews describe the development of this field in great detail [900–905].

ABT-288 (Abbott) entered a randomized, double-blind, placebo-controlled, Phase II clinical study in patients with schizophrenia (n = 210; NCT01077700) in April 2010 in the US and a second Phase II study in patients with AD in Russia and the Ukraine (n = 242) in March 2010 [903] (Thomson Reuters Pharma, update of May 06, 2011). The structure of ABT-288 was not disclosed.

AZD-5213 (AstraZeneca) was in Phase I clinical trials in the USA since June 2010 to assess safety and pharmacokinetics in 88 healthy volunteers (NCT01548287). In April 2012, a Phase IIa trial to assess the effect on sleep in patients with AD and MCI was initiated (Thomson Reuters Pharma update of July 3, 2012). The structure was not disclosed.

JNJ-17216498 (ALZA Corp, a wholly-owned subsidiary of J&J) is an orally active, selective H3 receptor antagonist for the treatment of narcolepsy in Phase II clinical trials since December 2006, which were completed in December 2007 [906] (Thomson Reuters Pharma, update of March 28, 2011). The structure of JNJ-17216498 was not disclosed.

S-38093 (Servier) and the related structure S-38471-1 (Fig. 22) are lead compounds from a series of histamine H3 antagonists with wakefulness-promoting and cognitive-enhancing effects. Since July 2011 a Phase IB study of S-38093 is underway in 600 mild to moderate AD patients in Australia, Brazil, Bulgaria, Chile, the Czech Republic, France, Germany, Hungary, Mexico, Portugal, Romania, Russia, and South Africa. The trial is expected to complete in April 2014 (Thomson Reuters Pharma, update of September 14, 2011).

SAR-110894 of sanofi is in Phase II clinical trials for the potential oral treatment of cognitive deficits associated with AD, schizophrenia, and attention deficit disorder patients since February 2011 in the US (n = 520; NCT01266525; Thomson Reuters Pharma, update of May 1, 2012). The structure was not disclosed.

Irubisabant (CEP-26401; Cephalon, now Teva; Fig. 22) is a non imidazole containing histamine H3 receptor antagonist in Phase I clinical trials since March 2010 for treatment of cognition deficits in AD. In March 2011 good safety data were communicated. The discovery and characterization was described in all details [907–915] (Thomson Reuters Pharma, update of May 29, 2012).

MK-3134 (Merck) is an oral histamine H3 receptor inverse agonist acting as a cognitive enhancer for the potential treatment of dementia. Phase I trials were initiated in June 2007 in the UK (n = 31), in August 2007 in Belgium (n = 32), and in June 2010 in Belgium (n = 24) in healthy subjects (Thomson Reuters Pharma, update of January 24, 2011). The structure was not communicated.
PD-9475 (betahistine; P2D Biosciences; Fig. 22) is an oral formulation of the H3 receptor antagonist betahistine in a Phase Ib trial since February 2011 for the treatment of ADHD [916] (Thomson Reuters Pharma, update of April 26, 2012).

There are several histamine H3 receptor antagonists or inverse agonists in preclinical evaluation (in alphabetical order):

- **Ciproxifan** (FUB-359; INSERM; Fig. 22) is a cognition enhancer for the potential treatment of dementia, schizophrenia, and AD [917–920] (Thomson Reuters Pharma, update of January 24, 2012).

- **EVT-501** (EDC-2) and **EVT-502** (EDC-3; Evotec) are small molecule H3 receptor antagonists for the potential treatment of cognitive and sleep disorders (Thomson Reuters Pharma, update of May 29, 2012). The structures were not communicated.

- **JNJ-10181457** (Johnson & Johnson; Fig. 22) is in preclinical development for the potential treatment of narcolepsy and cognitive disorders including schizophrenia [921]. Another orally active H3 receptor antagonist **JNJ-39220675** is developed in Phase II trials for allergic rhinitis and for treatment of alcohol dependence [922] (Thomson Reuters Pharma, update of March 26, 2012). The structure of JNJ-39220675 was not disclosed.

- **Ligand Pharmaceuticals** (following its acquisition of Neurogen) is investigating a series of orally active small molecule H3 inverse agonists for the potential treatment of cognitive disorders (Thomson Reuters Pharma, update of May 16, 2012). The structures were not communicated.

- **SUVN-G1031** (Suven Life Sciences) is a potent selective H3 receptor antagonist for the treatment of cognitive deficits. A 4,5-dihydrobenzo[1,4]oxazepine-3-one (Fig. 22) was presented at the 243rd ACS Meeting in San Diego March 2012. The compound increased the release of cognitive-enhancing neurotransmitters and was efficacious in in vivo models of cognition (Thomson Reuters Pharma, update of April 16, 2012).

The development of several cognition enhancing histamine H3 receptor antagonists (or inverse agonists) was terminated, of **ABT-239** (Abbott [923–926]), **ABT-834** (Abbott), **APD-916** (Arena Pharmaceuticals), **AQ-0145** (The Green Cross Corp. & Mitsubishi Chemical [927]), **ATH-90879** (Athersys), **cipralisant** (GT-2331; Gliatech [928]), **FUB-181** (Freie University Berlin [929, 930]), **GSK-189254A**, **GSK-239512**, **GSK-334429**, and **GSK-357868** (GSK [931–936]), **GT-2016** (Gliatech [937]), histamine H3 antagonists (Athersys), **MK-0249** (Merck [938–941]),...
1.15. Insulin receptors

Soluble Aβ oligomers, also referred to as Aβ-derived diffusible ligands (ADDLs), cause a major downregulation of plasma membrane insulin receptors via a mechanism sensitive to calcium calmodulin-dependent kinase II and casein kinase II inhibition. This loss of surface insulin receptors could be completely prevented by insulin. The protection by submaximal doses of insulin was potentiated by the PPARγ agonist rosiglitazone [952]. The common pathological processes in AD and diabetes were reviewed [953–956]. In a population-based neuropathologic study including 553 patients aged >85...
years, it was found that diabetes at baseline doubled the incidence of dementia [957]. Mice with systemic insulin deficiency displayed evidence of reduced insulin signaling pathway activity in the brain that is associated with biochemical and behavioral features of AD [958]. The common pathway of both diseases seems to be serine phosphorylation of insulin receptor substrate 1 (IRS-1). ADDLs activated the JNK/tumor necrosis factor (TNF)-α pathway and induced IRS-1 phosphorylation at multiple serine residues. The neuronal pathology could be prevented by exposure to the glucagon-like peptide 1 receptor agonist exenatide (exendin-4, launched by Amylin Pharmaceuticals and Lilly) [959]. The insulin receptor expression and activity in the brains of nondiabetic sporadic AD cases was analyzed recently [960].

Intranasal insulin (nasal drug delivery device by Kurve Technology) was administered to patients with amniotic MCI (n = 64) and with mild to moderate AD (n = 40) in a randomized, double-blind, placebo-controlled clinical trial. Participants received placebo (n = 30), 20 IU of insulin (n = 36), or 40 IU (n = 38) for 4 months. Treatment with 20 IU of insulin improved delayed memory and both doses of insulin preserved caregiver-rated functional ability [961].

AGT-160 (ArmaGen Technologies) is a recombinant IgG fusion protein formed by the fusion of a single chain Fv (ScFv) antibody against Aβ plaque formation to the company’s human insulin receptor-targeting monoclonal antibody Trojan horse for transport across the blood-brain-barrier for the potential detection and treatment of AD (Thomson Reuters Pharma, update of January 23, 2012).

SYN-20090510RU (SoliXen; SynBio in collaboration with Xeretic Biosciences) is a long-acting insulin formulation, which incorporates bacterial polysialic acid for the potential injectable treatment if type 1 and 2 diabetes and neurological disorders such as AD [962] (Thomson Reuters Pharma, update of June 14, 2012).

1.16. Liver X receptors

The liver X receptors LXRα and LXRβ are members of the nuclear hormone receptor family and are involved in the regulation of cholesterol and lipid metabolism. Disordered cholesterol balance in the brain is a hallmark of several neurological disorders including AD [963, 964]. Treatment with the liver X receptor agonist T0901317 (Fig. 23) ameliorated Aβ pathology and memory deficits caused by high-fat diet in AβPP/PS1 mice [965]. The ATP-binding cassette transporter A1 mediated the beneficial effects of the liver X receptor agonist GW3965 (GSK, Fig. 23) on object recognition memory and Aβ burden in AβPP/PS1 mice [966]. Liver X receptor agonist treatment promoted Aβ degradation and rescued olfactory behavior in Tg2576 mice [967]. Activation of liver X receptors promoted neuroprotection and reduced brain inflammation in experimental stroke [968].

Madera Biosciences is investigating small molecule therapeutics that increase apolipoprotein E and ATP binding cassette transporter 1 (ABCA1) levels in the brain. Pre- and post-traumatic brain injury treatment of mice with the liver X-receptor agonist T0901317 (Fig. 23 [969]) increased ABCA1 levels at 24 hours post-injury and reduced the traumatic brain injury-induced increase of Aβ [970]. Targeted diseases are AD, age-related macular degeneration, and traumatic brain injury (Thomson Reuters Pharma, update of April 20, 2012).

The development of LXR agonists of Anagen Therapeutics and the University of Chicago, of AstraZeneca [963], and of GSK investigating the research tool GW-3965 for the treatment of inflammatory CNS disorders was discontinued [971].

1.17. Neurotensin receptors

The expression levels of neurotensin receptor 1 (NTSR1) and of NTS2 were profoundly decreased in AD, whereas mRNA levels of neurotensin only declined slightly and those of NTSR3 (which is involved in neuronal apoptosis) did not vary [972].

NT-69-L (Mayo Foundation) is a neurotensin hexapeptide of disclosed structure acting as neurotensin receptor agonist for the potential treatment of pain, schizophrenia, AD, Parkinson’s disease, nicotine and alcohol dependence, and CDS [973–978] (Thomson Reuters Pharma, update of February 22, 2011).

1.18. Nociceptin (ORL1) receptors

The nociceptin system and hippocampal cognition in mice was investigated [979]. Activation of the nociceptin receptor impaired recognition memory in rodents [980].

PF-454583 (Fig. 23) and PF-4926965 (Pfizer) are opioid receptor-like 1 (ORL1) receptor antagonists in preclinical development. PF-454583 had a Kᵢ value of 8 nM. At doses of 0.1 and 0.32 mg/kg it’s reversed scopolamine-induced deficits to an extent comparable to that of donepezil at 3.2 mg/kg (Thomson Reuters Pharma, update of August 4, 2011).
The development of NNC-63-0532 and NNC-63-0780 (Novo Nordisk) for treatment of anxiety and dementia was terminated [981, 982].

1.19. Opioid receptors

The interactive influence on pain, cognition, and emotion by endogenous opioid peptides was elucidated [983]. Activation of μ-opioid receptors led to an enhancement of cognition in rats [984]. A review on the opioid system and AD was published in 2012 [985].

The development of GR-86014 and GR-91272 (GSK, potent μ opioid receptor agonists [986–989]) and of RDC-5768 (Alkermes, an antagonist on hσ and δ opioid receptors and a partial agonist at hμ opioid receptors) was terminated [353].

1.20. Peripheral benzodiazepine receptors (PBRs)

AD is associated with local glial responses in the brain parenchyma, which involves activation of microglia. The mitochondria of these cells express increased amounts of PBRs [990, 991]. This increase of PBRs can be measured quantitatively via PET imaging.

In a clinical study, 13 AD patients and 10 controls had [11C-(R)-PK11195 (Fig. 23) PET scans. Region of interest analyses detected a significant 20–35% increase of microglial activation in frontal, temporal, parietal, occipital, and cingulate cortices (<0.05) of the AD subjects. [11C-PBR PET revealed a significant two-fold increase in Aβ load in the same cortical areas (<0.0001). Mini-Mental Status Exam (MMSE) scores in AD subjects correlated with levels of cortical microglial activation but not with Aβ load. The inverse correlation between MMSE and microglial activation is compatible with the role of microglia in neuronal damage [990]. Patients with idiopathic Parkinson’s disease show significantly increased mean levels of [11C-(R)-PK11195 binding in pons, basal ganglia, and frontal and temporal cortical regions compared with control subjects [992]. Similar results were found in patients with progressive supranuclear palsy [993].

11C-Vinpocetine (Gedeon Richter, Fig. 23) displayed a significantly higher brain uptake than [11C-(R)-PK11195 to reach PBRs in human brain [994, 995].

11C-DAA-1106 (Taisho Pharmaceuticals, Fig. 23) has a very high affinity to PBRs in mitochondrial fractions of rat (Kᵣ = 0.043 nM) and monkey (Kᵣ = 0.188 nM) brains. logP is 3.65. This compound has a four times higher uptake in vivo than PK11195 in monkey brain [996–1001]. A comparative autoradiography study in postmortem whole hemisphere human brain slices was reported [1002]. An improved synthesis was worked out [1003]. The development of DAA-1106 as a drug for the potential treatment of anxiety disorders was terminated (Thomson Reuters Pharma, update of December 5, 2011).

11F-FEDAA-1106 (ZK-6032924, BAY-85-8101; Bayer under license from Taisho Pharmaceuticals; Fig. 23) is an i.v. injectable PET ligand for potential diagnostic imaging of AD and multiple sclerosis. For the synthesis, see [1004, 1005]. A Phase I study in AD (n = 55) was initiated in June 2007 in Sweden and the Netherlands, a second Phase I study in January 2009 in MS (n = 30) in Sweden and Australia (Thomson Reuters Pharma, update of March 27, 2012).

SSR-180575 (sanofi, Fig. 23) is a PBR agonist that stimulated nerve growth and was developed for the potential treatment of diabetic neuropathy [1006–1008]. Although its development as an anti-diabetic drug was terminated the radioligand [11C-SSR-180575 is a valuable tool to measure neuromelanin in the brain [1009, 1010]. (Thomson Reuters Pharma, update of February 14, 2011).

BAY-85-8102 (11F-DPA-714, F-18-DPA-714; Bayer in collaboration with INSERM under license from the University of Sydney, Fig. 23) is no longer developed as an imaging agent for patients with AD. It is in Phase I clinical evaluation for the imaging of patients with amyotrophic lateral sclerosis (Thomson Reuters Pharma, update of March 27, 2012).

1.21. Progesterone proliferator-activated receptors (PPARs)

The nuclear receptor PPARγ is a ligand-activated transcription factor, whose biological actions are to regulate glucose and lipid metabolism and to suppress inflammatory gene expression [1011, 1012]. The neuroprotective mechanisms of PPAR agonists in AD were reviewed pointing to the anti-amyloidogenic, anti-inflammatory, insulin-sensitizing, and cholesterol-lowering potential of PPARγ agonists [1013].

Rosiglitazone (Avandia, GSK; Fig. 24) has been evaluated in several Phase III clinical trials for the treatment of AD. The argument was that rosiglitazone may reduce the physiological resistance to insulin, which could potentially reduce the level of Aβ in the blood. Insulin protected against the ADDL-induced downregulation of plasma membrane insulin receptors.
The protection by submaximal doses of insulin was potentiated by rosiglitazone [1014]. In clinical studies, neither the 2 mg nor the 8 mg dose offered a statistically significant therapeutic benefit to mild to moderate AD patients [1015]. GSK discontinued all clinical trials of rosiglitazone in AD. In 2011 rosiglitazone was withdrawn from the market in Europe and is available in the US only under severe restrictions (Thomson Reuters Pharma, update of June 13, 2012). Recent preclinical results confirm that rosiglitazone enhanced synaptic plasticity in experimental animals [1016, 1017].

Pioglitazone (Actos, Takeda, launched in 1999; Fig. 24) has been tested in five randomized controlled Phase II trials on cognition in AD patients [1018]. So far no results have been communicated. In November 2011, Takeda and Zinfandel Pharmaceuticals initiated Phase I trials of pioglitazone using Zinfandel’s TOMM40 biomarker assay to identify subjects at risk of developing AD in the US and in EU. Pioglitazone attenuated mitochondrial dysfunction, cognitive impairment, and inflammation following traumatic brain injury [1019]. For a comment, see [1020]. NMDA receptors are involved in the beneficial effects of pioglitazone on scopolamine-induced memory impairment in mice [1021]. The effect of pioglitazone on insulin resistance correlated with RAGE inhibition [1022] (Thomson Reuters Pharma, update of June 21, 2012).

Mitoglitazone (MSDC-0160; Metabolic Solutions Development Co; Fig. 24), the active metabolite of pioglitazone, is an insulin-sensitizing, PPARγ-sparing thiazolidine-dione with antihypertensive and lipid-lowering properties. In July 2011, a Phase IIa study in mild AD patients began and was finished by February 2012. The data showed this novel once-a-day oral insulin sensitizer, the first in a new class of therapeutic agents called mTOT modulators, met the study’s primary endpoint of significantly reducing fasting plasma glucose in patients diagnosed with type 2 diabetes, and significantly reduced hemoglobin A1c (Thomson Reuters Pharma, update of June 20, 2012).

DSP-8658 (Dainippon Sumitomo, one compound of this series is shown in Fig. 24) is a dual PPARα/γ agonist, which also reduces Aβ levels, for the potential treatment of diabetes and AD. A Phase I clinical trial in patients with AD started in February 2011 in the US (Thomson Reuters Pharma, update of February 21, 2012). The synthesis and pharmacological evaluation of DSP-8658 were published recently [1023, 1024].

G-15750 (Genfit) is active against PPARγ receptors and acts as a nootropic agent (Thomson Reuters...
Pharma, update of November 30, 2010). The structure was not communicated.

Roche is investigating a series of dual gamma secretase/PPARγ modulators based on the structure of 2-(bis(phenethoxy)pyrimidine-2-thio)hexanoic acid in collaboration with scientists from the University of Frankfurt am Main for the potential treatment of AD [1025, 1026] (Thomson Reuters Pharma, update of April 1, 2011).

1.22. Prostaglandin receptors

Impaired cognition was observed in mice lacking the prostaglandin E2 (EP2) receptor [1027]. EP2 stimulated the production of Aβ through internalization of the EP4 receptor [1028]. Improvement of cognitive function was observed in AD AβPP23 mice by genetic and pharmacological inhibition of the EP4 receptor [1029].

Amgen is investigating EP2 antagonists for the potential treatment of AD. A lead compound (Fig. 24) was identified with moderate i.v., pharmacokinetic potential treatment of AD. A compound (Fig. 24) is the lead


Other RAGE antagonists are currently in preclinical evaluation (in alphabetical order):

DBT-066 (Roche under license from Digital Biotech and the Seoul National University) is a RAGE antagonist that blocks the entry of Aβ to the brain (Thomson Reuters Pharma, update of April 28, 2010). The structure was not communicated.

FPS2-BM1 and FPS-ZM1 (Socratech, a spin-off of the University of Rochester; Thomson Reuters Pharma, update of March 15, 2012). The structure of FPS-ZM1 (Fig. 24) deriving from a secondary screen was communicated [1040]. It is a high affinity RAGE-specific inhibitor that blocked Aβ binding to the V domain of RAGE and inhibited Aβol and Aβ42 induced cellular stress in RAGE-expressing cells in vitro and in the mouse brain in vivo. FPS-ZM1 inhibited RAGE-mediated influx of circulating Aβol and Aβ42 into the brain. In brain FPS-ZM1 bound exclusively to RAGE, which inhibited β-secretase activity and Aβ production and suppressed microglia activation and the neuroinflammatory response. Blockade of RAGE actions at the blood-brain barrier and in the brain reduced Aβol and Aβ42 levels in brain markedly and normalized cognitive performance and cerebral blood flow responses in aged AβPP+/− mice.

Hermo Pharma Oy is investigating a series of small molecule RAGE antagonists for the potential treatment of neurodegenerative diseases including AD and pain. The company received a grant from the Alzheimer’s Drug Discovery Foundation (Thomson Reuters Pharma, update of June 23, 2011).

1.24. Receptor for advanced glycation end products (RAGE)

RAGE mediates amyloid-peptide transport across the blood-brain barrier back into the brain leading to a potential accumulation of Aβ in the brain as was shown in in vitro experiments [1036] and in in vivo experiments [1037]. See also [1038]. The role of RAGE as therapeutic target to promote neuroprotection was discussed [1039].

TTP-4000 (Pfizer under license from Trans Tech Pharma) is a fusion protein containing the extracellular portion of the RAGE. In March 2012, a randomized, double-blind, placebo-controlled, Phase I study (NCT01548430) was initiated in patients with AD (expected n = 16) in the US to assess the safety and pharmacokinetics (Thomson Reuters Pharma, update of April 9, 2012). The structure of TTP-4000 was not communicated.

P2X7 receptors were specifically upregulated in the blood-brain barrier back into the brain leading to a potential accumulation of Aβ in the brain as was shown in in vitro experiments [1036] and in in vivo experiments [1037]. See also [1038]. The role of RAGE as therapeutic target to promote neuroprotection was discussed [1039].

Other RAGE antagonists are currently in preclinical evaluation (in alphabetical order):

DBT-066 (Roche under license from Digital Biotech and the Seoul National University) is a RAGE antagonist that blocks the entry of Aβ to the brain (Thomson Reuters Pharma, update of April 28, 2010). The structure was not communicated.

FPS2-BM1 and FPS-ZM1 (Socratech, a spin-off of the University of Rochester; Thomson Reuters Pharma, update of March 15, 2012). The structure of FPS-ZM1 (Fig. 24) deriving from a secondary screen was communicated [1040]. It is a high affinity RAGE-specific inhibitor that blocked Aβ binding to the V domain of RAGE and inhibited Aβol and Aβ42 induced cellular stress in RAGE-expressing cells in vitro and in the mouse brain in vivo. FPS-ZM1 inhibited RAGE-mediated influx of circulating Aβol and Aβ42 into the brain. In brain FPS-ZM1 bound exclusively to RAGE, which inhibited β-secretase activity and Aβ production and suppressed microglia activation and the neuroinflammatory response. Blockade of RAGE actions at the blood-brain barrier and in the brain reduced Aβol and Aβ42 levels in brain markedly and normalized cognitive performance and cerebral blood flow responses in aged AβPP+/− mice.

Hermo Pharma Oy is investigating a series of small molecule RAGE antagonists for the potential treatment of neurodegenerative diseases including AD and pain. The company received a grant from the Alzheimer’s Drug Discovery Foundation (Thomson Reuters Pharma, update of June 23, 2011).
MabPrex is investigating a series of RAGE antagonists for the potential treatment of AD and diabetic nephropathy (Thomson Reuters Pharma, update of August 5, 2011). Structures were not disclosed. A-992401 (Abbott Laboratories) is a monoclonal antibody targeting RAGE (Thomson Reuters Pharma, update of December 1, 2010). Pfizer scientists have published the pharmacokinetics and lung distribution of a humanized anti-RAGE antibody in wild type and RAGE –/– mice [1041].

Aqueous orally active vaccine targeted against a RAGE/AB complex was described in 2012 [1042]. The development of the RAGE antagonist PF-04494700 (TTP-488; Pfizer under license from TransTech Pharma) was terminated. Analysis of the low-dose group (10 mg/d after a 6-d loading dose of 30 mg/d) showed a favorable outcome for Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) at month 18 [1043]. Although there were no safety concerns with this group, the high-dose group (20 mg/d after a loading dose of 60 mg/d) was discontinued at 6 months due to safety concerns as well as increased ADAS-cog decline which appeared to slow after the drug was stopped. The results did not support continued development of PF-04494700 for AD (Thomson Reuters Pharma, update of December 8, 2011).

1.25. Retinoid X receptors

Goodman discussed the topic retinoid receptors, transporters and metabolizers as therapeutic targets in late onset AD already in 2006 [1044]. Retinoids may be valuable therapeutic agents in disorders of social cognition including autism [1045]. Bexarotene (Targretin, LGD-1069; Eisai; Fig. 25) is a retinoid X receptor agonist launched by Eisai in 2006 in the US and in Western Europe for the treatment of cutaneous T-cell lymphoma. Scientists from the Case Western Reserve University found that after oral administration to a murine model of AD bexarotene caused enhanced clearance of soluble Aβ within hours in an apolipoprotein E (ApoE)-dependent manner. ApoE expression is transcriptionally induced through the action of the nuclear receptors PPARγ and liver X receptors in coordination with retinoid X receptors. Aβ plaque area was reduced by 50% within 72 hours. Bexarotene stimulated the rapid reversal of cognitive, social, and olfactory deficits and improved neutral circuit function [1046]. However, it is likely that this approach will be limited for patients having the ApoE4 isoform (Thomson Reuters Pharma, update of February 14, 2012).

Tamibarotene (Am80; Nippon Shinyaku under license from the University of Tokyo; Fig. 25) is a retinoid receptor agonist launched for the treatment of acute promyelocytic leukemia. In a collaboration of the Osaka City University, Itsuu Laboratory, and Kumamoto University, tamibarotene is evaluated as an orally active nootropic agent in a randomized, placebo-controlled, Phase II clinical trial in patients with AD (n = 50) in Japan since May 2010. The dosage is 4 mg four times a day (qid) [1047, 1048] (Thomson Reuters Pharma, update of September 8, 2011).

1.26. Ryanoine receptors

Ryanoine receptors located within the membrane of the endoplasmic reticulum mediate the release of calcium ions into the cytoplasm. Mutations in the genes of presenilin-1 and presenilin-2 significantly increase the expression and activation of ryanoine receptors [1049–1051]. Dantrolene (JHP Pharmaceuticals) is a well-known muscle relaxant and ryanoine receptor inhibitor. It ameliorated cognitive decline and neuropathology in triple transgenic AD mice [1052].

1.27. Serotonin receptors

The topic serotonin and human cognitive performance was reviewed [390, 1053]. Serotonin receptors represent highly favorable molecular targets for cognitive enhancement in schizophrenia and other disorders [1054]. Abundant data revealed that administration of 5-HT2A/2C and 5-HT3 receptor agonists, or of 5-HT1A, 5-HT3, and 5-HT1B antagonists improved memory and had a facilitatory effect on learning in situations involving a high cognitive demand. Also the role of 5-HT1 receptors in the modulation of cognitive processes was studied in depth [1055–1057].

1.27.1. 5-HT1A receptor agonists and antagonists

The role of 5-HT1A receptors in the pathophysiology of schizophrenia was reviewed [1058, 1059]. The role of 5-HT1A receptors in learning and memory was discussed [1060, 1061], as was the modulation of cholinergic functions by serotonin and possible implications in memory with focus on 5-HT1A receptors [1062]. 5-HT1A agonism was adequate to ameliorate the PCP-induced impairment of novel object recognition deficits in rats [1063]. A PET study of 5-HT1A receptors using [11C]-WAY-100635 was carried out in 10 patients with mild to moderate AD [1064].
F-15599 (Pierre Fabre, Fig. 25) is a preferential postsynaptic 5-HT1A receptor agonist showing a favorable profile in models of cognition in comparison to reference 5-HT1A receptor agonists such as F-13714. F-15599 is currently in preclinical evaluation for the potential treatment of depression [1065–1069] (Thomson Reuters Pharma, update of March 14, 2011). [18F]F15599 was used as a novel radioligand for PET neuroimaging [1070]. The development of many 5-HT1A receptor agonists and antagonists was terminated (in alphabetical order), of adatanserin (Wyeth, a combined 5-HT1A agonist and 5-HT2 antagonist), AP-159 (Asahi Kasei Pharma; a 5-HT1A receptor agonist [1071]), F-15063 (Pierre Fabre; a high efficacy 5-HT1A receptor agonist [1072–1074]), of the 5-HT1A receptor antagonist lecozotan (SRA-333) (Wyeth, now Pfizer [1075, 1076]) and of its backup compound SRA-444, robalzotan (NAD-299; AstraZeneca; a 5-HT1A receptor antagonist [1077]), WAY-100635 (Wyeth, Pfizer [1077–1081]), and of xaliproden (sanofi), which stimulated endogenous neurotrophin synthesis and prevented p75-mediated apoptosis [1083]. Xaliproden was evaluated in several Phase III clinical trials in AD and in amyotrophic lateral sclerosis patients, which turned out to be disappointing [1084, 1085].

1.27.2. 5-HT2 receptor antagonists
The role of 5-HT2A receptors in learning was reviewed [1086]. The 5HT2A antagonist mianserin improved performance in selective neurocognitive tests as an add-on medication to typical antipsychotics in chronic schizophrenia patients [1087].

Asenapine (Organon, Schering-Plough, now Merck & H. Lundbeck) is a 5-HT2A and dopamine D1/D2 antagonist launched as a sub-lingual formulation for the treatment of schizophrenia in adults. Asenapine restored cognitive flexibility in rats with medial prefrontal cortex lesions suggesting that asenapine may be beneficial for cognitive deficits in schizophrenic patients [1088]. Asenapine improved phencyclidine-induced object recognition deficits in rats [1089].

The development of AP-267 (AcurePharma AB, a 5-HT2C receptor-modulating compound [1090]), of dual 5-HT2C and 5-HT3 receptor antagonists (Korea Research Institute of Chemical Technology) and of EGIS-11150 (EGIS, now Servier), binding to 5-HT2A and 5-HT3 receptors with Ki values of 3.1 nM and 22 nM and to α1-adrenoceptors with a Ki...
The role of 5-HT4 receptors in learning and memory has been reviewed [1102]. The ligand is still extensively used for brain imaging in vivo cognition tests was presented at the 243rd ACS Meeting in San Diego March 2012 (Fig. 25; Thomson Reuters Pharma, update of April 16, 2012).

GSK terminated the development of the 5-HT4 antagonist PET ligand 1H-SCB-207145 (Fig. 25; Thomson Reuters Pharma, update of April 3, 2012). The ligand is still extensively used for brain imaging of 5-HT4 receptors in academic settings [1109, 1116–1120]. Also the tritiated ligand 3H-SCB-207145 is extensively used for 5-HT4 receptor binding studies [1121, 1122].

The development of BIMU-1 and BIMU-8 (Boehringer Ingelheim [1123–1125]), capeserod (SL-65.0155; sanofi [1101, 1126–1129]), of the 5-HT4 antagonist GR-113808 (GSK [1130, 1131]), ML-10302 (sanofi [1132]), PF-04995274 (Pfizer), RS-56532 and RS-66331 (Roche [1133, 1134]), SC-53116 (Searle, Pfizer [1135, 1136]), TD-8954 (Theravance [1113, 1137]; however, the development for the treatment of gastrointestinal motility disorders is continuing) and of VRX-03011 (Epix Pharma [1138]) was terminated.

1.27.5. 5-HT4 receptor antagonists
5-HT4 receptors are almost exclusively localized in the CNS [1139]. They are positively coupled to adenylyl cyclase. Extensive preclinical research supports a
model of neural circuitry in which the tonic activation of 5-HT\textsubscript{6} receptors expressed on GABAergic neurons leads to an induction of GABA release and in turn to an inhibition of cholinergic and glutamatergic neurons. Blockade of 5-HT\textsubscript{6} receptors effectively removes this tonic GABAergic inhibition of downstream neurons resulting in enhanced neurotransmission of at least acetylcholine and glutamate [1140–1148]. An excellent overview of the effects of 5-HT\textsubscript{6} receptor antagonists in ten cognitive paradigms (Morris water maze, passive avoidance, conditioned operant responding, reward-motivated learning behavior, novel object recognition, social recognition, attentional set shifting, pre-pulse inhibition of acoustic startle, latent inhibition and five-choice serial reaction time and delayed reward tasks) was presented [1149]. A functional human 5-HT\textsubscript{6} receptor assay for high throughput screening [1150] and a chemocentric informatics approach were described [1151].

**Latrepirdine** (Dimebon; Dimebolin; Medivation, Pfizer; Fig. 26) is an orally bioavailable antihistamine drug discovered in Russia used for the treatment of skin allergy and allergic rhinitis since 1983. In 2000, additional preclinical experiments revealed that dimebon improved learning in animal models of AD [1152, 1153] acting as a cognition enhancer [1154]. The
drug was taken into a Phase II clinical trial in AD (n = 183, 10 mg three times a day for 7 days, increased to 20 mg three times a day for the remainder of the study or placebo for 26 weeks) and showed a significant improvement in cognitive function on the ADAS-cog in the dimebon group and worsening in the placebo group (mean change from baseline −1.9 with dimebon, versus −2.1 with placebo, difference −4.0, p < 0.0001 [1155]). Pfizer started several Phase III clinical trials in AD and in Huntington’s disease [1156], but the promising data of the Phase II trial could not be repeated [1157].

Pfizer and Medivation discontinued the development of latrepirdine for the treatment of AD and Huntington’s disease, which was communicated on January 17, 2012.

There is a longstanding debate on the mechanism of action of latrepirdine in AD [1158]. It is a potent 5-HT6 receptor antagonist with acute cognition enhancing properties (Ki = 26 nM for 5-HT6 receptors; Ki = 119 nM for 5-HT6 receptors) [1159, 1160]. The receptor profile is H1 receptors: Ki = 600 nM; inhibition of butyryl cholinesterase: IC50 = 7.9 nM; inhibition of acetylcholinesterase: IC50 = 3.8 nM, H2 receptor: IC50 = 287 nM, α1A and α1D receptors: Ki = 34–86 nM, α1C, α2A, and I2 receptors: Ki = 261–313 nM, but no binding to β adrenoceptors; 5-HT1 receptor: Ki = 8 nM, 5HTB receptor: Ki = 34 nM, 5-HT3 receptor: Ki = 76 nM, 5-HT4 receptor: Ki = 61 nM, D1 = D2S = D2L receptors: Ki = 600 nM; inhibition of butyryl cholinesterase: IC50 = 7.9 μM, inhibition of acetylcholinesterase: IC50 = 42 μM [1161]. The cognition-enhancing properties of dimebon in a rat novel object recognition task are unlikely to be associated with acetylcholinesterase inhibition or NMDA receptor antagonism (Ki = 105 μM) [1162]. Other scientists claim that its main action is the improvement of mitochondrial function in the setting of cellular stress [1163, 1164]. After acute dosing of latrepirdine, extracellular levels of Aβ levels were elevated in vitro and in vivo [1165]. In the brains of TgCRND8 mice chronically treated with dimebon, levels of total Aβ as well as of soluble oligomeric Aβ were unchanged [1166]. Studies in young adult and aged Rhesus monkeys showed that dimebon produced statistically significant increases in delayed matching-to-sample task accuracies [1167]. Dimebon slowed the progression of proteinopathy in γ-synuclein transgenic mice [1168].

The potential PET agent [11C]Dimebon was prepared [1169].

Biovista is evaluating latrepirdine for the potential oral treatment of multiple sclerosis in a novel formulation BVA-101 (Thomson Reuters Pharma, update of December 6, 2011) and for the potential oral treatment of epilepsy in another formulation BVA-601 (Thomson Reuters Pharma, update of October 3, 2011). Lu-AE58054 (LY-483518; SGS-518; Lundbeck under license from Lilly; Fig. 26) is currently in Phase II clinical development since November 2009. In May 2012 Lundbeck reported that the fixed dose, randomized trial conducted in Europe, Canada, and Australia met its primary endpoint. Data demonstrated that Lu-AE58054 plus donepezil (10 mg/day) significantly improved cognitive function in 278 patients with AD compared to placebo plus donepezil, when measured by ADAS-cog. Lu-AE58054 showed positive results in the secondary endpoints including measures of global status and daily living activities compared to donepezil treated patients (Thomson Reuters Pharma, update of May 29, 2012). The reversal of cognitive impairment induced by subchronic phencyclidine in rats was described [1170]. The characterization of the tritiated ligand [3H]Lu AE60157 (Fig. 26) binding to 5-HT3 receptors in vivo was communicated [1171].

SB-742457 (GSK, Fig. 26) entered Phase II clinical trials for the oral treatment of AD in September 2005 (n = 371, 24 weeks treatment of 5 mg, 15 mg, or 35 mg once daily in comparison to placebo). Another Phase II trial was initiated in July 2008 (n = 672, NCT00710684). The results of the clinical studies were reported showing a statistically significant improvement of the patients on the CIBIC+ scale, but not at the ADAS-cog [1172, 1173]. The interaction between risperidone and SB-742457 in healthy men was investigated [1174]. The amelioration of memory deficits induced by scopolamine in Wistar rats was reported [1175, 1176] (Thomson Reuters Pharma, update of October 17, 2011).

AVN-101 (Avineuro Pharmaceuticals and Chem-Div) is a 5-HT1A receptor antagonist for the potential treatment of AD and anxiety. Phase II clinical trials were initiated in February 2010 for AD and anxiety (Thomson Reuters Pharma, update of August 19, 2011). The structure of AVN-101 was not disclosed.

AVN-211 (Avineuro Pharmaceuticals and Chem-Div) is another 5-HT1A receptor antagonist in a Phase II clinical trial for the potential treatment of CDS since June 2009. In February 2011 results from the double-blind, Phase IIa trial in 50 patients showed the trial met its primary efficacy endpoints and AVN-211 was safe and well tolerated (Thomson Reuters Pharma, update of July 14, 2011). The structure of AVN-211 was not disclosed.
derivatives with a \( K_i \) of 0.088 nM [1184–1192] (Thomson Reuters Pharma, update of May 8, 2012).

5-HT₆ receptor antagonists (Abbott Laboratories; Fig. 26) are evaluated for the potential treatment of cognitive deficits in patients with AD and schizophrenia (Thomson Reuters Pharma, update of December 9, 2011). The medicinal chemistry was described [1193]. The effects to ameliorate scopolamine-induced memory deficits in object recognition and object location tasks in Wistar rats were reported [1194].

5-HT₆ receptor antagonists (Galenea) are evaluated for the potential treatment of cognitive impairment associated with schizophrenia (Thomson Reuters Pharma, update of April 17, 2012). No structures were communicated.

Intense medicinal chemistry efforts have been carried out over years in companies such as Bristol-Myers Squibb, Cephalon, Esteve, Galenea, Gedeon Richter, GSK, Merck, Merz, Redix, Roche, Synosia Therapeutics, and Wyeth (Pfizer), which have been described in several excellent reviews [1139, 1143, 1195–1203].

The development of the clinical trial compounds A-964324 (Abbott Laboratories [1193, 1204]), AVN-397 (Avineuro Pharmaceuticals), cerlapiridine (SAM-531, PF-5212365; Wyeth, now Pfizer [1205, 1206]), E-6801 (Esteve [1207]), 11-C-GSK-215083 (GSK [1208]), MEM-66826 (Memory Pharmaceuticals, now Roche), PRX-07034 (Predix Pharmaceuticals [1209]), R-1485 (Roche), Ro-4368554 (Roche [1210–1212]), SAM-315 (WAY-255315; Wyeth, now Pfizer [1213–1216]), SB-258510, SB-258585 (GSK [1210]), SB-271046 (GSK [1217–1223]), SB-357134 and SB-399885 (GSK [1223, 1224]) and WAY-101 (Wyeth, now Pfizer) was terminated.

1.28. Sigma receptors

Excellent reviews on sigma-1 receptors and cognition were published [1225–1227] complementing the exhaustive early reference work [1228].

Fluvoxamine (Solvay, now Abbott; Fig. 27) is a 5-HT re-uptake inhibitor and sigma-1 receptor agonist launched in 1994 for the treatment of depression and obsessive compulsive disorders. Recently it was reported that fluvoxamine improved cognitive impairment in patients with schizophrenia [1229, 1230].
Cutamesine (SA-4503; M’s Science under license from Santen, Fig. 27) is a potent sigma-1 receptor agonist (Ki = 4 nM) in Phase II clinical trials for the treatment of CDS and AD, for post-stroke recovery and depression. The cognition enhancing properties of SA-4503 were elucidated [1231–1235]. SA-4503 attenuated cocaine- and methamphetamine-induced hyperactivity [1236, 1237] (Thomson Reuters Pharma, update of June 20, 2012).

A Sigma-1 receptor antagonist (E-52862; Esteve; Fig. 27) with Ki values of 0.55 nM and 109 nM for sigma-1 and sigma-2 receptors, respectively is in Phase II clinical trials since March 2012 for the indication pain. The indication cognitive and psychotic disorders is no longer followed up [1238] (Thomson Reuters Pharma, update of April 18, 2012).

Anavex-2-73 (AVex-2-73; AN-2; Anavex Life Sciences, Fig. 27), a sigma-1 receptor agonist, is in a
Phase I AD trial since March of 2011 [1239] (Thomson Reuters Pharma, update of June 27, 2012). Anavex-1-41 (Fig. 27) is a potential back-up compound [1240–1242] (Thomson Reuters Pharma, update of June 19, 2012). MC-113 (M’s Science) is a sigma receptor ago-nist for the potential treatment of major depression and CNS diseases including AD (Thomson Reuters Pharma, update of June 20, 2012). The structure was not communicated.

\((\pm)-\)PPCC (University of Trieste; Fig. 27), a novel sigma-1 receptor ligand, displayed anti-amnesic prop-erties on cognitive dysfunction induced by selective cholinergic lesions in rats [1243].

\((-)-MR22\) (University of Catania; Fig. 27) is a selective sigma-1 receptor agonist showing anti-amnesic and neuroprotective actions in rats with selective cholinergic lesions and amyloid infusion [1244–1246].

The development of dehydroepiandrosterone (DHEA; Fidelin, see Fig. 15), an androgen recep-tor agonist with sigma-1 receptor agonistic properties, which may be responsible for its cognition enhanc-ing properties, was terminated [543, 1247] as was the development of igmesine (JO-1784; Jouveinal, now Pfizer) [1248–1256], NEBO-178 (Stegram Pharma-ceuticals, a sigma receptor antagonist that increased estrogen binding to ER-H9252 and dehydroepiandrosterone levels in the brain), PRE-084 (INSERM Montpellier) [1256–1262] and of a sigma-1 receptor ligand (UCB, Fig. 27).

1.29. Somatostatin receptor agonists

The topic somatostatin and AD was reviewed [1263]. The link between somatostatin receptors, memory, and AD was discussed [1264]. Somatostatin receptor subtype 2 and 4 agonists upregulate the activity of neprilysin, which amongst other neuropeptides degrades A\(_{\beta}\) and A\(_{\beta}\) oligomeric forms of A\(_{\beta}\) [1265–1268]. Hippocampal SSTR4 receptors control the selection of memory strategies [1269, 1270].

NCC-26-9100 (Novo Nordisk) was a selective somatostatin subtype-4 receptor agonist (Ki = 6 nM), which on chronic administration enhanced learning and memory in SAMP8 mice and reduced A\(_{\beta}\) brain levels [1271]. It was evaluated for the poten-tial treatment of glaucoma and cancer, but is not followed up.

The development of the somatostatin/serotonin stimulators FK-960 and FK-962 (Fujisawa, now Astellas) was also discontinued. The preclinical char-acterization of FK-960 was described [1272–1281] and of FK-962 [1282, 1283]. Also the development of the somatostatin analogue FK-121196 (Fujisawa, now Astellas) and of L-363377 (a somatostatin receptor subtype 2 agonist of Merck) was terminated.

1.30. Sphingosine-1-phosphate receptor modulators

Mice lacking the sphingosine-1-phosphate receptor 2 displayed working memory deficits [1284]. ABT-363 (Abbott Laboratories) is a sphingosine-1-phosphate receptor 5 (S1P5) modulator for the potential treatment of neurological disorders includ-ing AD (Thomson Reuters Pharma, update of March 1, 2012). Another S1P1/S1P5 receptor modulator ABT-413 is evaluated in Phase I clinical trials for the treatment of multiple sclerosis and rheumatoid arthritis since July 2011 (Thomson Reuters Pharma, update of November 28, 2011). Neither structure was communicated.

1.31. Tachykinin receptor antagonists

The tachykinin (previously known as neurokinin) receptors are involved in more CNS actions than previ-ously thought including sleep disorders, amyotrophic lateral sclerosis, AD, and Machado-Joseph’s disease [1285]. Neurokinin-3 receptor knockout mice showed cognitive deficits [1286, 1287].

SSR-241586 (sanofi) is a dual tachykinin 2/tachykinin 3 (previously known as neurokinin) receptor antagonist for the potential treatment of irritable bowel syndrome and for positive symptoms, depression, and anxiety. Its development was terminated [1288, 1289].

1.32. Tumor necrosis factor receptor 1 negative allosteric modulators

125I-A\(_{\beta}\) binds specifically to TNFR1 in SH-SYSY cells with a K\(_d\) of 0.42 nM [1290]. A\(_{\beta}\) inhibition of long-term potentiation is mediated by TNF [1291, 1292]. The role of the TNF-\(\alpha\) signaling pathway lead-ing to cognitive decline was described [1293, 1294]. TNF-\(\alpha\) contributed to cognitive deficits after traumatic brain injury in mice [1295]. A small molecule inhibitor for TNF-\(\alpha\) (3,6-dithiothalidomide) prevented cognitive deficits in a triple transgenic mouse model of AD [1296, 1297].
130 patients with MCI were followed up for 4–6 years. Those patients, who subsequently developed AD or vascular dementia, had higher levels of sTNFR1 and sTNFR2 in both CSF and plasma already at baseline [1298, 1299]. Elevated plasma levels of soluble CD40, a member of the tumor necrosis factor receptor super-family, have also been found in patients who converted from MCI to AD [1300]. Improvement of cognition was observed in elderly patients with rheumatoid arthritis treated with anti-TNF therapy [1301].

Addex Therapeutics is investigating NAMs of TNFR1 for the potential treatment of rheumatoid arthritis, psoriasis, AD, and multiple sclerosis (Thomson Reuters Pharma, update of June 19, 2012). The structures were not communicated.

PD-2015 and PD-2016 (P2D Bioscience) are small molecule TNF-α inhibitors. PD-2015 improved cognitive deficiency in AD transgenic mice and inhibited neuroinflammation (Thomson Reuters Pharma, update of April 30, 2012). The structures were not communicated.

CONCLUSION

With the launch of the NMDA receptor channel blocker memantine for the treatment of moderate to severe AD in 2002, a valuable medication was added to the four acetylcholinesterase inhibitors launched previously (see Part 2). The medical team of Merz under Hans Jörg Möbius and the many collaborating clinicians deserve full credit and admiration for an important breakthrough for the benefit of AD patients. In January 2012, the development of the Phase III compound interacting with receptors latrepirdine for the potential treatment of AD was terminated. Before latrepirdine, 13 other Phase III compounds were discontinued, i.e., alvameline, cevimeline, milameline (M1 mAChR agonists); fasoracetam, nebracetam, and nefiracetam (NMDA receptor channel blocker); rosiglitazone (PPAR-γ agonists); neramexane (NMDA receptor antagonist); xaliproden (5-HT1A receptor agonist); and tozadentan (adenosine receptor A2A antagonist). ORM-12741 (α2C adrenergic receptor antagonist); HT-2157 (glycinamin-3 receptor antagonist); CX-717 and CX-1739 (AMPKines); ADX-71149, RG-1578, and RG-7090 (eNOSR ligands); ABT-288, S-38093, and SAR-110884 (histamine H3 R antagonists); pioglitazone (PPAR-γ agonists); PRX-3140 (serotonin 5-HT2 R agonist); Lu AE58054, SB-742457, AVN-101, and AVN-211 (serotonin 5-HT3 R antagonists); and entanemine (sigma-1 receptor agonist). In view of the duration of a clinical development, in this indication it will take at least five to six years until one of these compounds will make it to the market.

DISCLOSURE STATEMENT


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