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Abstract. Scientists working in the fields of Alzheimer’s disease and, in particular, cognitive enhancers are very productive. The review “Cognitive enhancers (nootropics): drugs interacting with receptors” was accepted for publication in July 2012. Since then, new targets for the potential treatment of Alzheimer’s disease were identified. This update describes drugs interacting with 42 receptors versus 32 receptors in the first paper. Some compounds progressed in their development, while many others were discontinued. The present review covers the evolution of research in this field through March 2014.

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

INTRODUCTION

As of April 19, 2014, there are 28,192 entries in PubMed under the term cognitive enhancers, 28,218 entries under the term nootropic, and 312 entries under the term cognition enhancers. Scifinder lists 5,687 references under the research topic nootropic, 651 references under the term cognitive enhancer, and 11,214 references for cognition enhancers. The Thomson Reuters Pharma database lists 1,249 drugs as nootropic agents or cognition enhancers and gives zero results under the term cognitive enhancer. The term nootropics was coined by the father of piracetam, Corneliu Giurgea, in 1972/1973 [1, 2]; NOOS = mind and TROPEIN = toward.

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, 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 (+ Receptors)
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
   16.2 Inhibitors of serum amyloid P component binding
17. Drugs interacting with tau, prion, and α-synuclein
   17.1 Small molecules preventing tau, prion, and α-synuclein aggregation
   17.2 Ligands interacting with tau and α-synuclein
   17.3 Vaccines against tau and α-synuclein
   17.4 Antibodies against tau, α-synuclein and ApoE
18. Stem Cells
19. Miscellaneous

In Part 1 drugs interacting with receptors were described [6], in Part 2 drugs interacting with enzymes were detailed [7], and in Part 3 drugs interacting with targets 3 to 10 and compounds and preparations of categories 11 to 19 [8] were described. However, this field is very dynamic. New targets were identified. Some compounds progressed in their development, many others were discontinued. Therefore an update is appropriate.

## 1. DRUGS INTERACTING WITH RECEPTORS

Researchers have been investigating drugs interacting with a wide variety of receptors in order to identify valuable cognitive enhancers [9–13]. These receptors (and drugs) are:

### 1.1. Acetylcholine Receptors

1.1.1. Muscarinic Acetylcholine Receptors
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   1.1.1.2. Allosteric mACh M1 Receptor Agonists
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1.4. Amylin Receptors
1.5. Androgen Receptors
1.6. Angiotensin Receptors
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1.9. Chemokine Receptors
1.10. Corticotropin Releasing Factor Receptors
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   1.17.2 NMDA Receptors
   1.17.3 NMDA Receptors’ Glycine-Site
   1.17.4 Metabotropic Glutamate Receptors
1.18. G-protein coupled Orphan Receptors
1.19. Histamine Receptors
1.20. Imidazoline Receptors
1.21. Insulin Receptors
1.22. Liver X Receptors
1.23. Melatonin Receptors
1.24. Neurotensin Receptors
1.25. Nociceptin (ORL1) Receptors
1.26. Opioid Receptors
1.27. Peripheral Benzodiazepine Receptors
1.28. Peroxisome Proliferator-Activated Receptors
1.29. Prostaglandin Receptors
1.30. Purinergic Receptors
1.31. Receptor for Advanced Glycation End Products
1.32. Retinoid X Receptors
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1.34. Scavenging Receptor Class A
1.35. Serotonin Receptors
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1.35.2 5-HT2 Receptors
1.35.3 5-HT3 Receptors
1.35.4 5-HT4 Receptors
1.35.5 5-HT6 Receptors
1.36. Sigma Receptors
1.37. Somatostatin Receptors
1.38. Sortilin Receptors
1.39. Sphingosine-1-Phosphate Receptors
1.40. Tachykinin Receptors
1.41. Tumor Necrosis Factor Receptors 1/2
1.42. Vitamin D Receptors

1.1. Acetylcholine receptors

After the publication of the cholinergic hypothesis of AD by Bartus et al. in 1982 [14] 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.

1.1.1. Muscarinic acetylcholine receptors

Nobel prize winner Brian K. Kobilka and 17 expert colleagues described the X-ray crystal structures of the muscarinic acetylcholine M1 receptor bound to the high affinity agonist iperoxo [15].

1.1.1.1. Orthosteric muscarinic acetylcholine M1 receptor agonists. Hundreds of (wo)men years went into syntheses and characterization of M1 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 [16, 17].

Cevimeline (AF-102B, SNK-508, Exovac, hydrochloride hemihydrate, Israel Institute for Biological Research, Ness-Ziona; Fig. 1), a spiro-quinuclidine derivative, is probably the best investigated selective M1 muscarinic acetylcholine receptor (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 Sjogren’s disease (xerostomia; marketed by Snow Brand Milk Products, Tokyo and Daiichi Pharmaceuticals, Tokyo) [18–20]. The receptor profile of cevimeline according to [21] is: M1: EC50 = 23 nM, Emax = 82%, M2: EC50 = 1.04 μM, Emax = 98%, M1 selectivity over M2: 78 fold; M2: EC50 = 48 nM, Emax = 75%, M1 selectivity over M2: 2 fold, M4: EC50 = 1.31 μM, Emax = 50%, M1 selectivity over M4: 58 fold, M3: EC50 = 63 nM, Emax = 43%, M1 selectivity over M3: 3 fold. Cevimeline (AF-102B) decreased the levels of total amyloid-β (Aβ) in cerebrospinal fluid (CSF) of patients with AD [22] (Thomson Reuters Pharma, update of March 14, 2014).

Fig. 1. Structures of orthosteric muscarinic acetylcholine receptor ligands.
AZPET (FluoroPharma, Montclair, NJ in collaboration with the Massachusetts General Hospital, Boston, MA, 18F-RS-86, Sandoz, now Novartis; Fig. 1) is evaluated for the potential diagnosis of AD (Thomson Reuters Pharma, update of May 27, 2014).

The development of several orthosteric M1 selective mAChR agonists was terminated (in alphabetical order): of MCD-386 (CDD-0102A; Mithridion under license from the University of Toledo; [23–26]), MI-09018, MI-08-016/35, and MI-10-022 (Mithridion) and of Sabcomeline (BrainCells under license from Proximagen and GSK, [27–29]).

1.1.1.2. Allosteric muscarinic acetylcholine M1 receptor agonists. An important breakthrough was achieved in 2002 at ACADIA Pharmaceuticals (San Diego, CA), 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 [30–33].

 MK-7622 (Merk, Whitehouse Station, NJ) is a M1 positive allosteric modulator (PAM) for the potential oral treatment of mild to moderate AD. In November 2013, a Phase Ib clinical trial was initiated in the US [34] (Thomson Reuters Pharma, update of May 16, 2014). Its structure was not communicated.

AC-262271 (Allergan, Irvine, CA, 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 November 7, 2013). Its structure was not communicated.

HTL-9936 (Heptares Therapeutics, Welwyn Garden City, Hertfordshire, UK) is an allosteric M1 subtype selective muscarinic acetylcholine agonist for the potential treatment of schizophrenia and AD. In December 2013 a Phase I trial was initiated in healthy volunteers (expected > 100) in the UK to evaluate the safety, tolerability, and pharmacokinetics of HTL-9936 for AD (Thomson Reuters Pharma, update of April 30, 2014). The structure was not communicated.

There are currently several allosteric M1 mAChR agonists in preclinical development (in alphabetical order): ANAVEX 3-71 (AF-710B; Anavex Life Sciences, New York, NY under license from the Israel Institute for Biological Research, Ness Ziona; Fig. 2) is a M1 muscarinic allosteric modulator and a sigma 1 receptor agonist with neuroprotective and cognition enhancing properties (Thomson Reuters Pharma, update of May 29, 2014).

ASN-51 (Asceneuron, Lausanne, Switzerland) is a M1-selective muscarinic AChR PAM for the potential treatment of AD. Data from mouse primary neuron cultures demonstrated that ASN-51 had shown efficacy at nanomolar concentrations and modulated only the M1 subtype. In vivo data showed that the drug elicited a dose-dependent increase in inositol monophosphate levels after one single oral dose (Thomson Reuters Pharma, update of March 25, 2014). The structure was not disclosed.

AstraZeneca presented gem-difluoro bicyclics as novel M1 muscarinic receptor agonists (Fig. 2), which showed enhanced metabolic stability in comparison to the non-fluorinated analogues. A more potent derivative PPH1 (Fig. 2) was presented recently with a pEC50 of 8.34 in human M1 AChRs. AstraZeneca, under license from Vanderbilt University, is investigating compounds that act on the M1 mAChR for the potential treatment of neurological conditions including psychosis, AD and schizophrenia (Thomson Reuters Pharma, update of April 22, 2014).

Dainippon Sumitomo Pharma (Osaka, Fig. 2) is evaluating M4 mAChR agonists for the potential treatment of psychotic disorders due to AD and schizophrenia (Thomson Reuters Pharma, update of April 16, 2013).

Dainippon Sumitomo Pharma (Osaka, Fig. 2) is evaluating M4 mAChR agonists for the potential treatment of schizophrenia (Thomson Reuters Pharma, update of November 28, 2013).

Merk (Westpoint, PA) scientists presented a more advanced compound (Fig. 2) with good bioavailability in rats and dogs of 68 and 62%, respectively (Thomson Reuters Pharma, update of October 10, 2012). For the medicinal chemistry, see [35–42]. A review on patents claiming allosteric M1 receptor modulators was presented [43].

The development of AM-831 (Acadia Pharmaceuticals in collaboration with Meiji Seika), BQCA (Merk, [44–48]), of TPBB, VU0255035 (ML012) [49, 50] and VU0415248 (all Vanderbilt University) was terminated.

1.1.2. Nicotinic acetylcholine receptors

Nicotinic acetylcholine receptors (nAChRs) are ion channel receptors belonging to the same class as 5-HTx, GABA_A, and strychnine-sensitive glycine receptors [51]. 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 ([52–54]). >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 [55]. In the α4β2 receptor (consisting of 2 α4 and 3 β2 subunits) there are two, in the α7 homopentamer there are five ACh binding sites.

1.1.2.1. α4β2 and α3β4 nicotinic acetylcholine receptor agonists. Ispronicline (TC-1734; AZD-3480; Targacept, Winston-Salem, NC; Fig. 3) is developed for potential oral treatment of AD and ADHD [56–63]. Results of a Phase IIb AD trial were reported [64]. Targacept has completed recruitment of patients for another Phase Ib AD trial were reported [64]. Targacept has completed recruitment of patients for another Phase Ib study of TC-1734 as a treatment for mild to moderate AD. Targacept expects to report top-line results from the study in mid-2014. The drug was also under development for schizophrenia-associated cognitive deficits, but failed to meet the primary endpoints [65]. AstraZeneca returned all rights of ispronicline to Targacept (Thomson Reuters Pharma, update of May 8, 2014).

Pozanicline (ABT-089, AbbVie, NorthChicago, IL; Fig. 3) 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 [66] (Thomson Reuters Pharma, update of December 4, 2013).

ABT-560 (AbbVie, NorthChicago, IL under license from NeuroSearch, Ballerup, DK) is an α4β2 subtype selective nAChR agonist in Phase I clinical trials since July 2007 (Thomson Reuters Pharma, update of January 4, 2013). The structure was not communicated.

18F-Flutabine (norchloro-fluoro-homo-epibatidine, NCFHEB; University of Leipzig), which targets the neuronal α4β2 nicotinic AChRs, is evaluated as a positron emission tomography (PET) imaging agent for the potential diagnosis and imaging of AD in Phase I clinical trials since October 2011 (Thomson Reuters Pharma, update of August 5, 2013). There are several α4β2 subtype selective nAChR agonist in preclinical evaluation (in alphabetical order):

Aniona (Copenhagen, a spin-out from NsDiscovery, previously a division of Neurosearch, Ballerup, DK) is investigating α4β2 subtype allosteric modulators for the potential treatment of cognitive disorders (Thomson Reuters Pharma, update of November 22, 2013). Structures were not communicated.

S-35836-1 (Servier; Fig. 3) and S-38232-1 are a new cyclopropanamine derivatives for the potential treatment of age-related cognitive disorders [67, 68]. A potential follow-up compound is S-47952, whose structure was not communicated (Thomson Reuters Pharma, update of June 26, 2013).

SUVN-911 (Suven Life Sciences, Hyderabad) is an oral α4β2 nAChR antagonist, for the potential treatment of mood disorders and major depressive disorders. Other α4β2 nAChR antagonists are evaluated.
for the potential treatment of schizophrenia, pain and cognitive disorders (Thomson Reuters Pharma, update of April 11, 2014). Structures were not communicated. ZY-1 (Shanghai Jiao Tong University, Fig. 3) is an α4β2 nAChR agonist, which enhanced cognitive functions in a transgenic model of AD [69]. It also promoted proliferation and migration of adult hippocampal neural stem/progenitor cells [70].

Carbon-11 labeled pyridyl ethers for in vivo imaging of α4β2 nAChRs in brain were described [71]. The development of several compounds was terminated (in alphabetical order): of lobeline (Ceptaris Therapeutics, formerly Yaupon Therapeutics), NS-9283 (A-969933; NeuroSearch in collaboration with Abbott; [72–74]), sazetidine-A (AMOP-H-OH; Axeuron Therapeutics), sofinicline (ABT-894; AbbVie under license from NeuroSearch), SR-16584 and SR-17080 (non-competitive α3β4 nAChR antagonists; SRI International) and of SUVN-F91201 (Suven Life Sciences).

### 1.1.2.2. Alpha7 nicotinic acetylcholine receptor agonists

For excellent reviews, see [75, 76]. A recent review described the α7 nAChR agonists in human clinical AD trials [77] and in Down’s syndrome [563].

Encenicline (EVP-6124, MT-4666, FORUM Pharmaceuticals, previously EnVivo, Watertown, MA, under license from Bayer and Mitsubishi Tanabe Pharma, Osaka; Fig. 4) is an α7 nAChR partial agonist. In October 2012 a randomized, double-blind, placebo-controlled, Phase III trial began in the US in patients (expected n = 640) with schizophrenia (Thomson Reuters Pharma, update of April 23, 2014).

A potential follow-up compound is EVP-4473 (Thomson Reuters Pharma, update of April 3, 2014). The structure of EVP-4473 was not communicated.

ABT-126 (AbbVie, North Chicago, IL; Fig. 4) is an α7 neuronal nicotinic receptor modulator for the potential treatment of AD and for cognitive deficits in schizophrenia. In January 2013 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) was started (Thomson Reuters Pharma, update of April 24, 2014).

GTS-21 (DMXB; CoMentis, South San Francisco, CA, licensed from the University of Florida; Fig. 4) is an α7 nAChR partial agonist in Phase II clinical trials for the treatment of AD, cognition deficits in schizophrenia, and ADHD [78–84]. The improvement of cognitive performance of rhesus monkeys by GTS-21 was described recently [85] (Thomson Reuters Pharma, update of April 17, 2014).

ABT-272 (AbbVie Laboratories, North Chicago, IL) is an α7 nAChR modulator for the potential treatment of pain in Phase I clinical trials since January 2013 (Thomson Reuters Pharma, update of January 3, 2013). The structure was not communicated.
**Fig. 4. α7 nicotinic acetylcholine receptor agonists.**

**BMS-933043** (Bristol-Myers Squibb) is a selective α7 nAChR agonist in Phase I clinical trials in healthy subjects (n = 135) in the US since July 2012 (NCT01605994; Thomson Reuters Pharma, update of December 31, 2013). The structure was not communicated.

**SKL-A4R** (SKL-15508; SK Biopharmaceuticals, Fair Lawn, NJ, formerly SK Life Science) is a novel α7 nAChR partial agonist displaying pro-cognitive and neuroprotective effects. By September 2013 a Phase Ia trial had been initiated (Thomson Reuters Pharma, update of May 23, 2014). The structure was not communicated.

There are many selective α7 neuronal nicotinic receptor (partial) agonists in preclinical evaluation (in alphabetical order):
A-867744 (AbbVie, North Chicago, IL; Fig. 4) and ABT-779 are PAMs of the α7 nAChR (Thomson Reuters Pharma, update of January 4, 2013). The extensive preclinical characterization of A-867744 (Fig. 4) allowed the elucidation of its broad-spectrum cognition-enhancing properties [86].

ADispell (Rochester, NY under license from Cornell University) investigates small molecules with target a novel site on the nAChR (α7?) for the potential treatment of AD. Three lead compounds were identified, a novel site on the nAChR (α7?) for the potential treatment of AD. Three lead compounds were identified, which increased cognition performance in multiple in vivo studies. In March 2011, the Alzheimer’s Drug Discovery Foundation awarded a grant to ADispell (Thomson Reuters Pharma, update of October 10, 2013). The structures were not communicated.

Ann761 (NSD-761; Asona, Copenhagen, a spin-out from NsDiscovery, previously a division of NeuroSearch, Ballerup, DK) is an α7 nAChR agonist for the treatment of cognitive disorders including schizophrenia (Thomson Reuters Pharma, update of April 29, 2014). The structure was not communicated.

BNC-259, BNC-375, BNC-1881, BL-10343, and BL-010362 (Bionomics, Adelaide) are PAMs of α7 nAChRs for the potential memory improvement treatment in AD and schizophrenia (Thomson Reuters Pharma, update of February 24, 2014). Structures were not communicated.

Lu AF-58801 (Lundbeck A/S, Valby, DK; Fig. 4) is a novel, selective, and brain penetrant PAM of α7 nAChRs. It attenuated subchronic phencyclidine-induced cognitive deficits in a novel object recognition task in rats following oral administration [87].

PheTQS (Promaxigen, London, UK, a subsidiary of Upsher-Smith Laboratories, Maple Grove, MN, under license from GSK; Fig. 4) showed an EC50 value of 20 nM as PAM of α7 nAChRs in transfected GH41C cells (Thomson Reuters Pharma, update of April 16, 2014).

PTT-125 (Pain Therapeutics, Austin, TX) is a small molecule targeting a specific novel site on filamin A preventing the filamin A-α7-nAChR association and A1R-42 tumoral toxic signaling [88] (Thomson Reuters Pharma, update of February 27, 2014). The structure was not communicated.

SEN34625/WYE-103914 (Siena Biotech and Pfizer; Fig. 4) is an optimized agonist at α7 nAChRs with an EC50 of 70 nM with excellent in vitro and in vivo profiles [89] [90] (Thomson Reuters Pharma, update of April 9, 2014).

SEN15924/WAY-361789 (Siena Biotech and Pfizer; Fig. 4) is a potent, selective, and orally active full agonist at α7 nAChRs with excellent efficacy in rodent behavioral cognition models, such as novel object recognition and auditory sensory gating [91, 92] (Thomson Reuters Pharma, update of April 9, 2014).

UCI-40083 (University of California at Irvine; Fig. 4) is an isoxazole-acetamide derived α7 nAChR PAM for the potential treatment of cognitive disorders including schizophrenia and ADHD [94]. At the 243rd ACS Meeting in San Diego in March 2012, a novel pyridine structure was disclosed (Fig. 4; Thomson Reuters Pharma, update of October 15, 2013). A novel hybrid series of potent and selective agonists at the α7 nAChR was described [564].

Therapeutic vaccines comprised of synthetic peptide fragments of the α7 nAChR used to generate antibodies that block Aβ binding to neurons are explored at Pharma Bio, Moscow, Russia (Thomson Reuters Pharma, update of January 31, 2014). The development of several compounds of BMS-902483 (Bristol-Myers Squibb, JNJ-1930942 (Johnson & Johnson; [95]), 14C-NN-12857 and 14C-NS-14492 (NeuroSearch and University of Copenhagen) and of TC-5619 (bromadinolide; Targacept; [96, 97]) was terminated.

1.2. Adenosine receptors

Adenosine receptors have been implicated in the modulation of cognitive functions. Chronic treatment with the A1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DCPCX) worsened long-term memory in AβPP/PS1dE9 transgenic mice [98]. The topic “Using caffeine and other adenosine receptor antagonists and agonists as therapeutic tools against neurodegenerative diseases” was reviewed [99].

The best known A2A adenosine receptor antagonist is caffeine (27,247 entries in PubMed as of April 30, 2014). The K0 values of caffeine at human A1 receptors are 12 μM, at A2A receptors 2.4 μM, at A2B receptors 13 μM, and at A3 receptors 80 μM [100]. The association between caffeine and cognitive decline in both sexes was re-evaluated [101]. Beneficial effects of caffeine in a transgenic model of AD-like tau pathology were shown [102]. A functional imaging study revealed the cortical areas affected by caffeine ingestion [565].
Tozadenant (SYN-115; Biotie Therapies Holding, formerly Synosia Therapeutics, Basel, Switzerland under license from Roche; Fig. 5) is a potent and selective A2A receptor antagonist for the potential treatment of PD in Phase IIb clinical trials since April 2011 [103]. In December 2012, topline-data were reported demonstrating that the trial met its primary endpoint of statistically significant decrease in ‘off’ time and increase in ‘on’ time compared with placebo. Improved Unified Parkinson’s Disease Rating Scale (UPDRS) part III and UPDRS parts I-III combined scores and improvements on clinician- and patient-assessed global impression scores were obtained (Thomson Reuters Pharma, update of April 25, 2014).

Heptares Therapeutics (Welwyn Garden City, Hertfordshire, UK) is investigating a series of A2A receptor antagonists for the potential treatment of PD, cognition deficits, and other CNS disorders. Two papers describing 1,2,4-triazine derivatives were published [104, 105] (Thomson Reuters Pharma, update of December 17, 2013).

1.3. Adrenergic receptors

The α1-adrenoceptor agonist guanfacine improved performance in an attention test in aged rhesus monkeys [106, 107]. β-Adrenergic receptors and G protein-coupled receptor kinase-2 may be new targets for drugs to treat AD [108]. Aβ peptides activated α1-adrenergic cardiovascular receptors [109].

ORM-12741 (Janssen Pharmaceuticals, Titusville, NJ under license from Orion Corporation, Espoo, Finland) 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. A Phase II trial in Raynaud’s disease was initiated in the UK (n = 18) in August 2011. At three months, the memory scores for those who received the placebo pill had worsened by 33%, whereas the scores improved by 4% for those patients who took ORM-12741. Janssen initiated a Phase II study in AD patients in the US in December 2013 (Thomson Reuters Pharma, update of February 11, 2014). The structure was not communi-
cated.

ODM-102 (Janssen Pharmaceuticals, Titusville, NJ under license from Orion Corporation, Espoo, Finland) is an α2C adrenoceptor antagonist for the potential treatment of AD in Phase I clinical studies since April 2013 in healthy males (expected n = 27) in Finland.
Aβ and human amylin-induced reduction of long-term potentiation without affecting baseline transmission [126]. The structure was not communicated. The development was terminated (Thomson Reuters Pharma, update of May 16, 2013).

### 1.5. Androgen receptors

**RAD-140** (Radius Health, Cambridge, MA, Fig. 5) is a nonsteroidal selective androgen receptor modulator (SARM). In *vitro* RAD-140 protected neurons from neuronal apoptosis by mimicking testosterone activation of a MAPK pathway. In male Sprague-Dawley rats, RAD-140 induced androgen responses in muscle and brain, but not in reproductive tissues. For the design, synthesis and preclinical characterization of RAD-140, see [127, 128].

The development of the androgen receptor agonist **ACP-105** (Acadia) and **dehydroepiandrosterone (DHEA; Fidelin; Fig. 5)** was terminated [129]. Part of DHEA's pharmacology may also be due to its interaction with sigma-1 receptors [130]. The enantiomer ent-DHEAS protected against Aβ1-42 peptidemediated toxicity in *vitro* and in *vivo* in mice [131].

### 1.6. Angiotensin receptors

2,056 papers were published on the brain renin-angiotensin system (PubMed citations as of April 30, 2014). The impact of angiotensin receptor blockers on AD neuropathology was discussed [132–136]. For the differential effects of angiotensin II receptor blockers on Aβ generation, see [566]. Angiotensin receptor blockers as treatments for inflammatory brain disorders were presented [137]. Central angiotensin II induced tau phosphorylation in normal rat brains [138]. Drug repositioning for the treatment of AD was described recently [139].

**Dhexa** (MM-201; M3 Biotechnology, Pullman, WA, Fig. 5) is an angiotensin IV analogue for the potential treatment of AD. It improved cognitive function of rats with AD-like mental impairment [140] (Thomson Reuters Pharma, update of November 20, 2013).

### 1.7. Calcium-sensing receptors

Aβ protein activated Ca2+ permeable channels through calcium-sensing receptors [141]. The findings were compiled in a recent review [142]. Pharmacotherapy of diverse disorders can be approached via the calcium-sensing receptor [143].
NPS-2143 (NPS Pharmaceuticals, Bedminster, NJ in collaboration with GSK), a calcium-sensing receptor antagonist, specifically blocked the increased secretion of endogenous Aβ42 [144]. The development was terminated (Thomson Reuters Pharma, update of November 7, 2013).

1.8. Cannabinoid receptors

Cannabinoid receptor 1 deficiency in a mouse model of AD led to enhanced cognitive impairment [145]. A review on the CB2 receptor and amyloid pathology in AD patients was presented [146].

**Dronabinol** (ultrapure THC, Namisol; Echo Pharmaceuticals, Nijmegen, NL), 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, multiple sclerosis, and AD patients since February 2012. It enhanced extinction learning in anxious humans [147] (Thomson Reuters Pharma, update of April 9, 2014).

**Cannabidiol** on chronic treatment improved social and object recognition in double transgenic AβPPswe/PS1/Delta1E9 mice [148].

**Sativex** (GW Pharmaceuticals, Salisbury, Wiltshire, UK), a launched mixture of Δ9-tetrahydrocannabinol and cannabidiol improved dopamine neurotransmission [149].

Natural cannabinoids improved dopamine neurotransmission and tau and amyloid pathology in a mouse model of tauopathy [150].

**SMM-189** (The University of Tennessee Health Science Center, Knoxville, TN, Fig. 5) is a novel cannabinoid receptor 2 inverse agonist, for the potential treatment of traumatic brain injury (Thomson Reuters Pharma, update of November 25, 2013).

1.10. Corticotropin releasing factor receptors

Corticotrophin releasing factor accelerated neuropathology and cognitive decline in a mouse model of AD [157]. For a report on cortical concentrations of corticotropin-releasing hormone and its receptor in Alzheimer-type dementia and major depression, see [158].

The Clayton Foundation for Research (Houston, TX) is investigating corticotropin releasing factor receptor-1 (CRF-R1) antagonists for the potential treatment of neurodegenerative diseases including AD. In November 2013 development was ongoing (Thomson Reuters Pharma, update of November 8, 2013).

1.11. Cysteinyl leukotriene receptor 1 (CysLT1R)

Intrahippocampal injection of Aβ1-42 resulted in a significant decline of spatial learning and memory of mice in the Morris water maze and Y-maze tests together with a serious depression of in vivo hippocampal long-term potentiation in the CA1 region of the mice. This treatment caused significant increases in Cysteinyl leukotriene receptor 1 (CysLT1R) expression and subsequent NF-κB signaling, caspase-3 activation and Bcl-2 downregulation in the hippocampus or prefrontal cortex. Oral administration of the CysLT1R antagonist pranlukast [159] at 0.4 or 0.8 mg/kg for 4 weeks significantly reversed Aβ1-42-induced impairments of cognitive function and hippocampal long-term potentiation in mice. Furthermore, pranlukast reversed Aβ1-42-induced CysLT1R upregulation and markedly suppressed the Aβ1-42-triggered NF-κB pathway, caspase-3 activation and Bcl-2 downregulation in the hippocampus and prefrontal cortex in mice [160, 161].

**Montekulast** ameliorated Aβ1-42-induced memory impairment and neuroinflammatory and apoptotic responses in mice [162].

1.12. Dopamine receptors

**Brexpiprazole** (Otsuka, Tokyo and Lundbeck, Valby, DK; Fig. 6) is an orally active dopamine D2/D3 receptor partial agonist, a 5-HT1a receptor partial ago-
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Fig. 6. A chemokine R ligand, six dopamine R modulators and an endothelin-A R antagonist.

nist, and a 5-HT2a antagonist for the potential treatment of schizophrenia (in Phase III clinical trials since October 2011), agitation associated with AD (in Phase III clinical trials since July 2013), and as adjunctive treatment for major depressive disorders (in Phase III clinical trials since July 2011). Its pharmacology was described [163] (Thomson Reuters Pharma, update of April 18, 2014).

Dexpramipexole (KNS-760704; BIIB-050; Knopp Neurosciences, Pittsburgh, PA, under license from the University of Virginia, Charlottesville, VA; Fig. 6) 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 (n = 804) in the US, Canada, Europe, and Australia [164–169]. Phase III data were reported in January 2013 [170] (Thomson Reuters Pharma, update of October 22, 2013).

There are currently several dopamine receptor drugs in preclinical evaluation:

AG-0029 (Angita Pharmaceuticals, Groningen, the Netherlands, Fig. 6) is a dual D2 receptor agonist and H3 receptor antagonist (EC50 and IC50 values of 1.1 and 519 nM, respectively) for the potential oral treatment of PD. In 6-OHDA rats AG-0029 (0.1 and 1 mg/kg s.c.) decreased striatal dopamine and striatal acetylcholine activity at D2 autoreceptors (Thomson Reuters Pharma, update of November 25, 2013).

AG-0098 (Angita Pharmaceuticals, Groningen, the Netherlands, Fig. 6) is a dual D2 receptor agonist and histamine H3 receptor antagonist (EC50 and IC50 values of 22.4 and 63 nM, respectively) for the potential treatment of PD and schizophrenia. AG-0098 antag-
onized phencyclidine-induced locomotor activity and phencyclidine-disrupted novel object recognition in rats (Thomson Reuters Pharma, update of November 18, 2013).

**Dinosynline** (Purdue University, West Lafayette, IN, Fig. 6), which acts as a potent full agonist at all five dopamine receptor subtypes [174], is evaluated for the potential treatment of cognitive diseases including dementia and psychiatric disorders such as schizophrenia (Thomson Reuters Pharma, update of July 23, 2013).

**DW-1066** (Dong Wha, Seoul in collaboration with the Korea Research Institute of Chemical Technology KRICT) is a dopamine receptor antagonist for the potential treatment of schizophrenia (Thomson Reuters Pharma, update of August 6, 2013). The structure was not communicated.

The development of **PF-03800130** (a D2 and a 5-HT1A partial agonist, Pfizer; [175]) was terminated.

1.13. Endothelin receptors

**ENDG-6010** (EndogenX, Los Gatos, CA) is an endothelin receptor antagonist for the potential treatment of AD and dementia including vascular dementia in preclinical evaluation (Thomson Reuters Pharma, update of August 12, 2013). The structure was not communicated. **IRL-1620** (University of Illinois, Urbana, IL) prevented Ab-induced oxidative stress and cognitive impairment in normal and diabetic rats [567].

**Zhototentan** (University of Bristol as part of the Medical Research Council/AstraZeneca compound collaboration, Fig. 6), a selective reversible endothelin-A receptor antagonist, is investigated for the potential treatment of AD (Thomson Reuters Pharma, update of March 7, 2014).

1.14. Estrogen receptors

A number of clinical studies suggested that estrogen therapy may delay the onset or contribute to the prevention and/or attenuation of AD [176, 177].

The Kronos Early Estrogen Prevention Study (KEEPS) was a five year study initiated in 2005 to re-examine estrogen beneficial effects when initiated at the beginning of the menopause [178, 179].

**MF-101** (Menopause Formula-101, Menerba; Bionovo, Emeryville, CA) is a plant-derived mixture that interacts with the estrogen receptor (ER)-β as agonist and contains liquiritigenin (Fig. 7) in Phase II clinical trials since February 2006 (Thomson Reuters Pharma, update of April 4, 2014).

**Phyto-β-SERM** (University of Southern California, Los Angeles, CA) is an ER-β-selective phytoestrogenic formulation comprised of three phyto-estrogens for the potential treatment of AD. By July 2011 Phase II studies were ongoing in the US. Early intervention prolonged survival, improved spatial recognition memory, and slowed progression of amyloid pathology in a female mouse model of AD [180, 181] (Thomson Reuters Pharma, update of September 27, 2013).

There are currently several estrogen receptor drugs in preclinical evaluations:

**Estradiol** enhanced object recognition memory in Swiss female mice by activating hippocampal estrogen receptor α [182].

**Liquiritigenin** (7,4′-dihydroxy-flavanone; Fig. 7) is a highly selective ER-β agonist discovered in a traditional Chinese medicine in the roots of *Glycyrrhiza uralensis* Fisch [183]. Liquiritigenin attenuated Ab1-25,38-induced impairment of learning in rats [184].

Co-administration of the selective androgen receptor agonist **ACP-105** with the selective ER-β agonist...
AC-186 (Acadia, Fig. 7) increased the Aβ degrading enzymes neprilysin and insulin-degrading enzyme and decreased Aβ levels in the brain as well as improved cognition in triple transgenic mice [185] (Thomson Reuters Pharma, update of August 20, 2013).

1.15. GABA receptors

1.15.1. GABA \textsubscript{A} receptors

The cognitive deficits in Down’s syndrome are attributed to an excessive hippocampal inhibition, which can be alleviated by GABA\textsubscript{A} and GABA\textsubscript{B} receptor antagonists [186–188]. CTP-354 (C-21191; CoNCERT Pharmaceuticals, Lexington, MA) is a deuterated α5 GABA\textsubscript{A} receptor inverse agonist derived from Merck’s L-838,417 (Fig. 8), which showed good metabolic stability [189]. In March 2013 a randomized, double-blind, placebo-controlled, single ascending dose, Phase I study to assess the safety, tolerability, and pharmacokinetics of CTP-354 was initiated in healthy volunteers in the US (Thomson Reuters Pharma, update of July 15, 2013).

RG-1662 (Roche, Fig. 8) is a α5 GABA\textsubscript{A} inverse agonist. A randomized, double-blind, parallel-assignment, multicenter, placebo-controlled, Phase II trial (NCT02024789; BP27832; 2013-001263-23; CLEMATIS) will be initiated in adults and adolescent subjects (expected n = 180) with Down’s syndrome in New Zealand and Singapore to evaluate the safety, efficacy and tolerability of RG-1662 (Thomson Reuters Pharma, update of April 16, 2014).

There are many α5 GABA\textsubscript{A} receptor inverse agonists or negative allosteric modulators (NAMs) in preclinical evaluation (in alphabetical order): Dart NeuroScience LLC (San Diego, CA) is investigating GABA\textsubscript{A} receptor modulators for the potential treatment of cognitive impairment in AD patients (Thomson Reuters Pharma, update of January 30, 2013). The structures were not disclosed.

GABA\textsubscript{A} receptor α5 inverse agonists are explored at AgeneBio, Carmel, IN (Thomson Reuters Pharma, update of May 6, 2014). Structures were not disclosed.

GABA\textsubscript{A} α5 inverse agonists (Université Pierre et Marie Curie, Paris) are investigated for the potential treatment of Down’s syndrome. In October 2013, data were presented at the 26th European College of Neuropsychopharmacology Congress in Barcelona, Spain (Thomson Reuters Pharma, update of October 8, 2013). Structures were not disclosed.

GABA\textsubscript{A} receptor α5 PAMs improved cognitive function in aged rats with memory impairment [190].

GABA\textsubscript{A} receptor α5 subtype selective antagonists are investigated jointly by scientists of the University of Wisconsin at Milwaukee and of Metabolic Solutions Development Co. for the potential treatment of anxiety, amnesia, and alcoholism. The lead compound XLI-093 is a dimer of imidazobenzodiazepines (Fig. 9) [191, 192]. Other compounds under evaluation include RY-023, RY-024, PWZ-029, and 3-propoxy-beta-carboline (3-PBC) (Thomson Reuters Pharma, update of April 9, 2014).

HZ-166 (Addiction Therapeutix, Wauwatosa, WI, under license from the University of Wisconsin-Milwaukee; Fig. 9) at doses from 0.03 to 0.3 mg/kg, i.v. reversed ketamine-induced cognitive impairment in a dose-dependent manner in male Rhesus monkeys (Thomson Reuters Pharma, update of December 6, 2013).

NP-260 (NeuroTherapeutics Pharma, Chicago, IL, and NeuroSolutions, Coventry, UK) is a GABA\textsubscript{A} receptor antagonist for the potential treatment of neurological disorders (Thomson Reuters Pharma,
update of May 31, 2013). The structure was not communicated.

**RO-4938581** (Roche; Fig. 9) and the dichloro-analogue **RO-4882224** (Fig. 9) are inverse agonists at α5βγ2 GABA<sub>A</sub> receptors [193–197]. In February 2013, preclinical data were published demonstrating the drug to reverse neurological deficits the Ts65Dn mouse model of Down’s syndrome. Abnormalities of nerve cell number and function in the brain were improved [198] (Thomson Reuters Pharma, update of March 1, 2013).

**UC-1011** (Umecrine Cognition, Vasterbottens, Sweden and licensee CleveXel Pharma, Maisons Alfort, Ile-de-France; Fig. 9) is a GABA<sub>A</sub> receptor antagonist for the treatment of memory and learning disturbances associated with AD [199] (Thomson Reuters Pharma, update of December 20, 2012).

The development of a pyrido[2,3-d]pyrimidine-4 (1H)-one by **Kyowa Hakko Kirin** [200] was terminated.

### 1.15.2. GABA<sub>B</sub> receptors

GABA<sub>B</sub> receptor antagonists proved to be valuable cognitive enhancers as was shown in many animal experiments and in two clinical trials (vide infra).

**CGP-36742** (SGS-742, National Institute of Health, Bethesda, MD acquired the rights from Lundbeck, who bought Saegis Pharmaceuticals in 2006, who licensed the drug from Ciba-Geigy, now Novartis in 2001; Fig. 10) showed pronounced cognition enhancing properties in mice, young and old rats, and in *Rhe- sus* monkeys [201–205]). It was taken into two Phase
II clinical trials first in patients with mild cognitive impairment (MCI) in 2002 and in mild to moderate AD patients in 2005 [206, 207]. It significantly improved attention and working memory in MCI and patients with mild AD, but not in patients with moderate AD, as was found eight years later in Phase III studies of solanezumab (Lilly). In December 2013, the National Institute of Neurological Disorders and Stroke initiated a randomized, double-blind, crossover-assignment, Phase II/III trial (NCT02019667; 140033, 14-N-0033) in patients (expected $n = 22$) with succinic semialdehyde dehydrogenase deficiency in the US. For the biological background, see [208–211] (Thomson Reuters Pharma, update of December 31, 2013). 

ADX-71441 (Addex Therapeutics, Geneva, Switzerland), a potent GABAg receptor PAM demonstrated a robust, dose-dependent, and long-lasting suppression of alcohol intake in mice in a preclinical model of alcohol binge drinking [212] and showed efficacy in a rodent model of overactive bladder [213]. Addex and the National Institute of Drug Abuse entered a collaboration to advance both ADX-71441 and ADX-88178 (a mGluR4 PAM; see Chapter 1.16.4. Metabotropic Glutamate Receptors) for treatment of drug abuse and addiction (Thomson Reuters Pharma, update of April 7, 2014). The structure was not communicated.

1.15.3. GABA$_{	ext{C}}$ receptors

The development of ($R$)-ACBPA and ($S$)-ACBPA (University of Sydney) was terminated.

1.16. Galanin receptors

The roles of neuropeptides including galanin were discussed [216].

HT-2157 (SNAP-37889; Dart NeuroScience, San Diego, CA following the acquisition of Helcion Therapeutics, San Diego, CA, licensed from Lundbeck; Fig. 10) is a galanin-3 receptor antagonist for the treatment of major depressive and cognitive disorders such as memory loss in Phase II development in the US (Thomson Reuters Pharma, update of January 30, 2013).

NeuroTargets (Guildford, UK) in collaboration with the University of Bristol is investigating allosteric modulators of galanin receptor 2 for the potential treatment of multiple sclerosis and AD (Thomson Reuters Pharma, update of February 11, 2014). Structures were not communicated.

1.17. Glutamate receptors

1.17.1. AMPA receptors

1.17.1.1. Piracetam-type compounds. Piracetam (UCB-6215; Nootropil, UCB, Brussels, Belgium; Fig. 11) was discovered more than forty years ago [217]. 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. Piracetam enhanced mitochondrial membrane potential and ATP production and reduced sensitivity to apoptosis [218]. Molecular docking and quantum calculations were performed on piracetam [219]. Analgesic effects of piracetam were discovered in the chronic constriction injury of sciatic nerve in rats suggesting investigations for the treatment of neuropathic pain [568] (Thomson Reuters Pharma, update of April 18, 2014).

Dimiracetam (NT-11624; BND-11624; Neurotune, Zurich, Baranzate, Italy, Fig. 11) is in Phase II clinical trials for the treatment of HIV-associated pain in South Africa since April 2009. 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 (Thomson Reuters Pharma, update of December 30, 2013).

NT-24336 (NiK-13317; Baranzate, Italy, after its spin-off from Nikem Research; Fig. 11) is in preclinical evaluation for the treatment of diabetic neuropathy and neuropathic pain (Thomson Reuters Pharma, update of December 30, 2013).

The development of nefiracetam (DM-9384; Motiva; Translon; Neuren Pharmaceuticals uner license from Daiichi Sankyo; [220–224]) was terminated.

1.17.1.2. AMPAkines. The groups of Gary Lynch of the University of California Irvine and of Gary A. Rogers of the University of California Santa Barbara presented the first benzamide drug 1-BCP (BA-14) [225, 226]. The drug crossed the blood-brain barrier (BBB) 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. 

**CX-1739** (Cortex Pharmaceuticals, Irvine, CA) is investigated 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. The drug enhanced the social interaction in the BTBR mouse model of autism [227] (Thomson Reuters Pharma, update of November 24, 2013). The structure was not communicated. 

**CX-717** (Cortex Pharmaceuticals, Irvine, CA) is an AMPA kinase for the potential treatment of ADHD, AD, and respiratory disorders. It is also evaluated to alleviate the effects of sleep deprivation [228]. Oral and i.v. formulations were evaluated. The development of oral CX-717 was terminated, whereas CX-717 i.v. is currently in Phase I clinical trials for the potential treatment of respiratory disorders (Thomson Reuters Pharma, update of May 16, 2013). The structure was not communicated. 

Cortex is developing several other AMPA kinases, whose structures were not disclosed, such as **CX-1942** and **CX-2007** (Thomson Reuters Pharma, updates of May 16 and May 3, 2013, respectively). 

**JAMII1001A** (Colorado State University, Fort Collins, CO, University of Strathclyde, Glasgow, Morehouse School of Medicine, Atlanta, GA and Merck Research Laboratories, Boston, MA; Fig. 12) is a novel PAM of AMPA receptors derived from a structure-based drug design strategy [229].

The development of **CX-717 oral** (Cortex Pharmaceuticals) was terminated. 

1.17.1.3. Biarylpropylsulfonamides. **PF-04958242** (Pfizer; Fig. 12) is an AMPA receptor potentiator for the potential treatment of cognitive defects associated with schizophrenia 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 [230] (Thomson Reuters Pharma, update of April 18, 2013). 

**PF-04778574** (Pfizer, Fig. 12) is a potential follow-up compound of PF-04958242 for the treatment of cognitive deficits in schizophrenia [231] (Thomson Reuters Pharma, update of November 11, 2013). 

1.17.2. NMDA receptors 

A review on the NMDA receptor as a target for cognitive enhancement was published [232]. 

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, Frankfurt am Main; Fig. 13). Sales for Namenda by Forest in 2012 were USD 1.52 billion, sales for Ebixa by Lundbeck in 2012 USD 484 million and sales for Daiichi Sankyo in 2012 USD 300 million (Thomson Reuters Pharma, update of April 30, 2014). 

There are currently 2,393 papers on memantine listed in PubMed (as of April 30, 2014). Two meta-
analyses of the efficacy of donepezil, rivastigmine, galantamine and memantine for the treatment of AD were published [233, 234].

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 launched in the US in June 2013 (Thomson Reuters Pharma, update of April 16, 2014).

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 [235]. These benefits were confirmed in AD patients [236, 237].
ADS-8704 (Arimenda; MDX-8704, Adamas Pharmaceuticals, Emeryville, CA, and licensee Forest Laboratories, New York) is a memantine + donepezil fixed dose combination in an extended release formulation. Phase III studies started in December 2013 in the EU and the US. In October 2013 Forest was planning to file an NDA in 1H14 and launch in 2015 (Thomson Reuters Pharma, update of April 30, 2014).

Neramexane (MRZ-2/579; KRP-209; Merz, Frankfurt am Main, Fig. 13) is currently in Phase III clinical trials for the treatment of tinnitus, severe acne, and as preemptive analgesic, as add-on therapy to opioids in the management of postoperative pain and as add-on therapy to opioids in cancer patients for the management of chronic pain attributable to skeletal metastases. Japanese licensee Kyorin is codeveloping the drug in Japan (Thomson Reuters Pharma, update of April 23, 2014).

EVT-101 (Fig. 13) and EVT-103 (Janssen Pharmaceuticals, formerly Ortho-McNeil, Titusville, NJ under license from Evotec, Hamburg under exclusive license from Roche) are orally active NMDA NR2B subtype specific antagonists for the potential treatment of treatment-resistant depression and AD (Thomson Reuters Pharma, update of May 29, 2014). The structure of EVT-103 was not communicated.

Johns Hopkins University (Baltimore, MD) is investigating modulators of NMDA glutamate receptor for the potential treatment of AD (Thomson Reuters Pharma, update of June 4, 2013). The structures were not communicated.

MeN-061016-1 (Lijun International Pharmaceutical, Hong Kong, Fig. 13) is a memantine prodrug as a nicotinic acid amide in preclinical evaluation in China (Thomson Reuters Pharma, update of April 10, 2014). Mnemosyne Pharmaceuticals (Providence, RI) is investigating small molecule NR2B allosteric modulators to improve cognitive dysfunction in AD (Thomson Reuters Pharma, update of July 2, 2013). The structures were not communicated.

NRX-20xx (Naurex, Evanston, IL) are NMDA receptor partial agonists for the potential oral treatment of autism, neurological diseases including AD, and neuropathic pain (Thomson Reuters Pharma, update of May 26, 2014). The structures were not communicated.

SGE-301 (Sage Therapeutics, Cambridge, MA) is a potent and selective PAM of NMDA receptor function. In preclinical studies, treatment with SGE-301, a synthetic analogue of the major brain cholesterol metabolite 24(S)-hydroxy-cholesterol, showed rever- sal of cognitive and social deficits in rats [238] (Thomson Reuters Pharma, update of March 31, 2014). The structure was not communicated. The development of NRX-1059 (Naurex, Evanston, IL) was terminated.

1.17.3. NMDA receptors’ glycine-site

For a review on the glycine site of the NMDA receptor see [239].

GLYX-13 (Naurex, Evanston, IL) is a tetrapeptide and NMDA receptor glycine site functional partial agonist for the potential i.v. treatment of psychiatric disorders such as depression and neuropathic pain. It enhanced cognition and produced antidepressant effects without the psychomimetic side effects of NMDA receptor antagonists [240, 241]. It is in Phase II clinical trials for treatment-resistant depression since May 2011 in the US. In December 2012 a Phase IIb trial began. It was claimed that GLYX-13 has a therapeutic potential for treatment of autism [242] (Thomson Reuters Pharma, update of February 11, 2014).

1.17.4. Metabotropic glutamate receptors

Neuroprotective and symptomatic effects of targeting group III mGlu receptors in neurodegenerative diseases were reviewed [243].

ADX-71149 (Janssen Pharmaceuticals, formerly Ortho-McNeil, Titusville, NJ under license from Addex Therapeutics, Geneva, Switzerland; Fig. 14) is a PAM of metabotropic glutamate receptor 2 for the treatment of psychiatric disorders including schizophrenia, anxiety, AD, and depression. In June 2012 a multicenter, double-blind, placebo-controlled, Phase II trial of the drug as an adjunct to antidepressant treatment was initiated in 94 adult patients with major depressive disorder who are also suffering from anxiety symptoms in Ukraine, Romania, Hungary, and Bulgaria. Subjects will receive oral twice daily ADX-71149 (25 to 150 mg) as an adjunct to antidepressant therapy and the primary endpoint would be the change from baseline in the Hamilton Anxiety Rating Scale (HAM-A6) score. Janssen Research & Development LLC has completed enrollment of 150 patients in a multicenter, double-blind, Phase II study of ADX-71149 in adults with major depressive disorder who are also suffering from anxiety symptoms. Medicinal chemistry papers were published [244, 245] (Thomson Reuters Pharma, update of April 7, 2014).

RG-1578 (R-1578; RO-4995819, Roche) is a small-molecule mGluR2/3 NAM in a Phase II study in patients with major depressive disorders (n = 480) since December 2011 in the US. By February 2012,
RG-1578 had shown antidepressant and cognitive enhancing effects in a broad range of preclinical models (Thomson Reuters Pharma, update of April 17, 2014). The structure was not disclosed.

Basimglurant (RG-7090, RO-4917523; Roche, Fig. 14) is an mGluR5 antagonist for the potential treatment of treatment-resistant depression and fragile X syndrome. 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. In September 2013 the trial was completed. In January 2013, a randomized, double-blind, placebo-controlled, Phase II study started to assess the safety and efficacy and pharmacokinetics of RG-7090 in pediatric patients (estimated n = 45) in the US with fragile X syndrome (Thomson Reuters Pharma, update of April 17, 2014).

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

**ADX-88178** (Addex Therapeutics, Geneva, Switzerland in collaboration with the National Institute of Drug Abuse, Bethesda, MD; Fig. 14) is an orally available PAM of metabotropic glutamate receptor 4 (mGluR4 PAM) for the potential treatment of nicotine and cocaine dependence (Thomson Reuters Pharma, update of November 5, 2013).

**DT-2442** (Domain Therapeutics, Illkirch-Graffenstaden, France; Fig. 14) is an mGluR2 NAM for the potential treatment of AD and depression [246] (Thomson Reuters Pharma, update of April 7, 2014).

**LSN-2463359** (Eli Lilly, Fig. 14) is an mGluR5 PAM, which modulated motor, instrumental and cognitive effects of NMDA receptor antagonists in rats [247–249] (Thomson Reuters Pharma, update of January 3, 2014).

**Pfizer** is investigating mGluR2 PAMs (lead structure shown in Fig. 14) for the treatment of CNS disorders [250–252]. (Thomson Reuters Pharma, update of March 24, 2011). For a highly potent mGluR5 NAM of Pfizer, see [253].

**Sanofi** is investigating mGluR2 PAMs for the potential treatment of cognitive impairment associated with schizophrenia (Thomson Reuters Pharma, update of February 8, 2013). Structures were not communicated.

**STX-110** (Roche under license from Seaside Therapeutics, Cambridge, MA under license from Vanderbilt...
University, Nashville, TN) is a mGluR5 inhibitor for the potential treatment of fragile X syndrome and autism (Thomson Reuters Pharma, update of February 13, 2014). The structure was not communicated.

VU-0430644 (ML-254; Janssen Pharmaceutica, Beerse, Belgium under license from Vanderbilt University, Nashville, TN; Fig. 14) is a 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. Other evaluated compounds are VU-0469942 (ML-337), VU-0405372, VU-0404251, INI-42659604, VU-0360172 (VU-172), and VU-0092273. The medicinal chemistry was presented [254] (Thomson Reuters Pharma, update of February 11, 2014).

The development of ADX-47273 (mGluR5 PAM; Addex Therapeutics; [255]), ADX-50938 (mGluR5 PAM; [256]), ADX-63365 (mGluR5 PAM; [257]) and EVT-501 (EDC-2) and EVT-502 (EDC-3; Evotec, Hamburg) are small molecule H3 receptor antagonists for the potential treatment of cognitive and sleep disorders (Thomson Reuters Pharma, update of March 19, 2013). The structures were not communicated.

LGD-3437 (Ligand Pharmaceuticals, San Diego, CA), a histamine H3 receptor antagonist, is investigated for the potential treatment of excessive daytime somnolence. By June 2013 LGD-3437 had demonstrated a favorable PK/ADME and safety profile in preclinical studies (Thomson Reuters Pharma, update of April 24, 2014). The structure was not communicated.

SUVN-G1031, SUVN-G3031, and SUVN-G1010034 (Seven Life Sciences, Hyderabad, India) are potent selective H3 receptor antagonists/inverse agonists for the potential treatment of cognitive disorders such as AD (Thomson Reuters Pharma, update of August 10, 2012). Structures were not communicated.

SAR-110068 (Sanofi-Aventis US, Bridgewater, NJ; Fig. 15) is a H3 receptor antagonist for the potential treatment of sleep disorders including narcolepsy [271, 272] (Thomson Reuters Pharma, update of April 10, 2014).

Effects. Since July 2011 a Phase Ib study of S-38093 is underway in 600 mild to moderate AD patients. The trial is expected to complete in April 2014 (Thomson Reuters Pharma, update of May 21, 2014).

PD-9475 (betahistine; P2D Biosciences, Cincinnati, OH; Fig. 15) is an oral formulation of the H3 receptor antagonist betahistine in a Phase Ib trial since February 2011 for the treatment of ADHD in the US [270] (Thomson Reuters Pharma, update of March 31, 2014). There are several histamine H3 receptor antagonists or inverse agonists in preclinical evaluation (in alphabetical order):

Angitia Pharmaceuticals (Groningen, the Netherlands) investigates a dual N-acetyltransferase reuptake inhibitor and histamine H3 receptor antagonist for the potential oral treatment of cognitive disorders. (Thomson Reuters Pharma, update of March 14, 2014). The structure was not communicated.

EVT-501 (EDC-2) and EVT-502 (EDC-3; Evotec, Hamburg) are small molecule H3 receptor antagonists for the potential treatment of cognitive and sleep disorders (Thomson Reuters Pharma, update of March 19, 2013). The structures were not communicated.

LGD-3437 (Ligand Pharmaceuticals, San Diego, CA), a histamine H3 receptor antagonist, is investigated for the potential treatment of excessive daytime somnolence. By June 2013 LGD-3437 had demonstrated a favorable PK/ADME and safety profile in preclinical studies (Thomson Reuters Pharma, update of April 24, 2014). The structure was not communicated.

Oxygen Healthcare Research (Ahmedabad, India) is investigating histamine H3 receptor antagonists/inverse agonists for the potential treatment of cognitive disorders such as AD (Thomson Reuters Pharma, update of August 10, 2012). Structures were not communicated.

SAR-110068 (Sanofi-Aventis US, Bridgewater, NJ; Fig. 15) is a H3 receptor antagonist for the potential treatment of sleep disorders including narcolepsy [271, 272] (Thomson Reuters Pharma, update of April 10, 2014).

SUVN-G1031, SUVN-G3031, and SUVN-G1010034 (Seven Life Sciences, Hyderabad, India) are potent selective H3 receptor antagonists for the potential treatment of cognitive deficits. A 4.5-dihydrobenzo[1,4]oxazepine-3-one (Fig. 15) was presented at the 243rd ACS Meeting in San Diego March 2012. The compound increased the release of cognitive-enhancing neurotransmitters. SUVN-G3031 displayed gains in object recognition at doses of 1 and 3 mg/kg and dose-dependently reduced path length and latency in a water maze test at doses from 0.03 to 10 mg/kg p.o. It
had a $K_i$ value of 8.7 nM and it showed an $ED_{50}$ value of 0.30 mg/kg with up to 85% receptor occupancy (Thomson Reuters Pharma, update of April 11, 2014). UCB (Brussels, Belgium) investigates $H_3$ receptor antagonists for the potential treatment of cognitive disorders including AD (Thomson Reuters Pharma, update of October 2, 2012).

The development of ABT-288 (AbbVie; [273–275]), GSK-239512 (GSK, the development for the indication AD was terminated but the drug is in Phase II clinical trials for the potential oral treatment of multiple sclerosis; Thomson Reuters Pharma, update of April 17, 2014), Irdabliban (CEP-26401; Cephalon, now Teva; [276–291]), JNJ-10181457 (Johnson & Johnson; [292, 293]), MK-3134 (Merck; [294]) and SAR-110894 (sanofi; [296]) was terminated.

1.20. Imidazoline receptors

Targeting the imidazoline $I_2$ receptor emerged as a new mechanism of action to inhibit tissue plasminogen activator-induced signaling in neurons for the treatment of AD [297].

1.21. Insulin receptors

For reviews on impaired insulin signaling and mechanisms of memory loss, see [298, 299]. The relationship between diabetes and cognitive impairment was described [300, 301]. Impaired glycemia increased disease progression in MCI [302]. Infusion of insulin increased plasma concentrations of Aβ42 [303]. The common pathological processes in AD and diabetes were reviewed [300–313]. Genetic ablation of tau mitigated cognitive impairment induced by type 1 diabetes [314]. Conversely, insulin dysfunction and tau pathology was discussed [315]. Type 2 diabetic and AD mice present similar behavioral, cognitive, and vascular abnormalities [316]. The impact of metabolic syndrome on cognition and brain was reviewed [317], as was the topic diabetes and the brain [570]. The common pathway of both diseases seems to be serine phosphorylation of insulin receptor substrate 1 (IRS-1). ADDLs activated the JNK/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) [318]. Another possible link between AD and type 2 diabetes may be aberrant insulin signaling and inflammation [319]. The insulin receptor expression and activity in the brains of nondiabetic sporadic AD cases was analyzed recently [320]. A review deals with the insulin-like growth factor-1 and the risk of Alzheimer dementia and brain atrophy [571]. Insulin-like growth factor-1 receptor stimulating activity is associated with dementia [572]. There is emerging evidence that insulin-like growth factor 2 may act as a memory enhancer [573].
sNN-0465 (NeuroNova AB, Stockholm, a wholly owned subsidiary of Newron Pharmaceuticals, Milano) is a formulation of exenatide, a peptide glucagon-like peptide-1 agonist and neurogenesis stimulator, for the potential treatment of PD in Phase II clinical trials since June 2011 (Thomson Reuters Pharma, update of December 18, 2012). See reference (321).

SYN-20090510RU (SalXen; SynBio LLC, Moscow in collaboration with Xenetic Biosciences; London) is a long-acting insulin formulation, which incorporates bacterial polysialic acid for the potential injectable treatment of type 1 and 2 diabetes and neurological disorders such as AD [322]. Phase I studies in diabetic patients were started in August 2011 and in patients with neurological disease in November 2012 (Thomson Reuters Pharma, update of December 4, 2013).

There are several drugs interacting with insulin receptors in preclinical evaluations:

CB-211 (CohBar, Pacific Palisades, CA) is a mitochondrial-derived peptide that acts as cytoprotective and improved mitochondrial function by interaction with the insulin receptor. It is evaluated for the potential treatment of type 2 diabetes and AD (Thomson Reuters Pharma, update of December 7, 2012). The structure was not communicated.

Humanin analogues (CohBar, Pacific Palisades, CA) such as CB-102, HNG6FA, and S14G-humanin are peptides encoded within the mitochondria for the potential treatment of AD and type 2 diabetes [323–327]. Humanin may be a possible linkage between AD and type 2 diabetes [328] (Thomson Reuters Pharma, update of May 24, 2013). The structures were not communicated.

Liraglutide (Victoza, NN-2211, NNC-90-1170; licensed from Scios, Sunnyvale, CA and Massachusetts General Hospital, Boston, MA) is a recombinant protein, a once-daily stable analog of glucagon-like peptide-1 for s.c. administration. It ameliorated aberrant insulin receptor localization and signaling in parallel with decreasing both Aβ plaque and glial pathology in a mouse model of AD [329]. Liraglutide protected against Aβ protein-induced impairment of spatial learning and memory in rats [330] and reversed memory impairment and synaptic loss and reduced plaque load in aged AβPP/PS1 mice [331]. Subcutaneous administration of liraglutide ameliorated AD-associated tau hyperphosphorylation in rats with type 2 diabetes [332]. Sales reported by Novo Nordisk for 2012 were USD 1.640 billion (Thomson Reuters Pharma, update of April 15, 2014).

NA-135 (Nerve Access, Chicago Ridge, IL) is a nasal formulation of insulin, which enters the CNS without having to cross the BBB for the potential treatment of AD [Thomson Reuters Pharma, update of April 3, 2014].

NA-753 (Nerve Access, Chicago Ridge, IL) is a nasal formulation of insulin and clioquinol that enters CNS without having to cross the BBB and acts by enhancing regenerative capacity of the CNS for the potential treatment of neurodegenerative diseases, including AD (Thomson Reuters Pharma, update of October 8, 2013).

AGT-160 (ArmaGen Technologies, Calabasas, CA) 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 BBB for the potential detection and treatment of AD [333, 334] (Thomson Reuters Pharma, update of September 20, 2013).

1.22. Liver X receptors

The liver X receptors (LXRs and LXRβ) are members of the nuclear hormone receptor family and are involved in the regulation of cholesterol and lipid metabolism. LXRs may be an emerging target for AD [335]. Hypercholesterolemia induced short-term spatial memory impairments in mice [336]. Pre- and post-traumatic brain injury treatment of mice with T0901317 (Fig. 16) [337] increased ABCA1 levels at 24 hours post-injury and reduced the post-traumatic brain injury-induced increase of Aβ [338]. The ATP-binding cassette transporter A1 mediated the beneficial effects of the LXR agonist GW39665 (GSK, Fig. 16) on object recognition memory and Aβ burden in AβPP/PS1 mice [339]. Reduction of LXR expression in primary rat neurons by antisense oligonucleotides decreased secreted Aβ levels [340].

XL-652 (XL-014; Bristol-Myers Squibb under license from Exelixis, South San Francisco, CA, formerly X-CEPTor Therapeutics) is a LXR agonist in Phase I clinical trials since March 2008 for the treatment of atherosclerosis (Thomson Reuters Pharma, update of February 11, 2014). The structure was not communicated.

MAD-8100 (Madera Biosciences, San Diego, CA) is a small molecule therapeutic that increased apolipoprotein E and ATP binding cassette transporter 1 (ABCA1) levels in the brain. Targeted diseases are
Fig. 16. Two liver X receptor agonists, a melatonin R antagonist and seven ligands for PBRs.
AD, age-related macular degeneration, and traumatic brain injury (Thomson Reuters Pharma, update of May 22, 2014). The structure was not communicated.

1.23. Melatonin receptors

Melatonin facilitated short-term memory [341]. The melatonin receptor agonist agomelatine blocked the adverse effect of stress on memory and enabled spatial learning of rats [342]. Memory enhancing effects of agomelatine were also observed in the novel recognition memory paradigm in rats [343].

Piromelatine (Neu-P11; Neurim Pharmaceuticals, Tel Aviv; Fig. 16) is a melatonin MT1, MT2 and MT3 agonist, a 5-HT1A, 5-HT1B and 5-HT1D agonist and 5-HT2b antagonist. It also inhibits P2X3, TRPV12 and NaV1.7 channels. It is in Phase II clinical trials for the treatment of insomnia since November 2011 in Israel [344]. The company is also investigating Neu-P11 for the treatment of MCI in early-stage AD. Neu-P11 facilitated memory performance and improved cognitive impairment in a rat model of AD [345] (Thomson Reuters Pharma, update of November 29, 2013).

1.24. Neurotensin receptors

NTSR3 is now called sortilin receptor [346]. See Chapter 1.35. Sortilin Receptor.

NT-69-L (Mayo Foundation, Rochester, MN) is a neurotensin hexapeptide of disclosed structure acting as neurotensin receptor agonist for the potential treatment of pain, schizophrenia, AD, PD, nicotine and alcohol dependence, and schizophrenia-associated cognitive impairment [347–355]. The development was terminated in 2013 (Thomson Reuters Pharma, update of February 26, 2013).

1.25. Nociceptin (ORL1) receptors

LY-2940094 (Lilly) is a nociceptin/orphanin FQ peptide (ORL1) receptor modulator in Phase II clinical trials for the potential treatment of pain, schizophrenia, AD, PD, nicotine and alcohol dependence, and schizophrenia-associated cognitive impairment [347–355]. The development was terminated in 2013 (Thomson Reuters Pharma, update of October 24, 2013). The structure was not communicated.

The development of PF-454583 and PF-4926965 (Pfizer) was terminated.

1.26. Opioid Receptors

A review on the opioid system and AD was published [356].

1.27. Peripheral benzodiazepine receptors

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 peripheral benzodiazepine receptors (PBRs or translocator protein) [357, 358]. This increase of PBRs can be measured quantitatively via PET imaging. A review on the translocator protein as a drug target in AD was published [359].

18F-BAY-85-8102 (18F-DPA-714, F-18-DPA-714; Bayer in collaboration with INSERM under license from the University of Sydney, Fig. 16) is in Phase I clinical evaluations for the imaging of patients with brain disease since June 2008 in France and since October 2009 in Finland. INSERM is developing the compound for the potential imaging of neuroinflammation. In June 2013 data from a neuroinflammation clinical study were presented. MRI imaging results showed increased 18F-DPA-714 uptake in the infarct tissue reflecting BBB breakage in the infarcted area and this was thought to relate to activation of microglia and a different radiotracer kinetic in the injured and normal tissues (Thomson Reuters Pharma, update of February 12, 2014).

11C-DPA-713 (National Institutes of Health, Bethesda, MD) is a PBR PET ligand for the potential imaging of epilepsy. In January 2013 a Phase I study was initiated in the US. The study will compare 11C-PBR-28 (vide infra) and 11C-DPA-713. Uptake of 11C-DPA-713 was comparable to that of 11C-R-PK-11195 (vide infra), but 11C-DPA-713 showed lower non-specific binding (Thomson Reuters Pharma, update of August 2, 2013). The structure was not communicated.

18F-FEDAA-1106 (ZK-6032924, BAY-85-8101; Bayer Schering, Berlin under license from Taisho Pharmaceuticals, Tokyo; Fig. 16) is an i.v. injectable PET ligand for potential diagnostic imaging of AD and multiple sclerosis (Thomson Reuters Pharma, update of August 2, 2013).

11C-PBR-28 (National Institutes of Health, Bethesda, MD; Fig. 16) is a PET tracer for the potential imaging of neuronal inflammation. In April 2013 a Phase I trial was initiated in the US (Thomson Reuters Pharma, update of February 5, 2014).

18F-Flutamiclaimide (GE Healthcare, Pollards Wood, UK; Fig. 16) is a PET tracer for the potential imaging of neuronal inflammation. In April 2013 a Phase I trial was initiated in the US (Thomson Reuters Pharma, update of February 5, 2014).

11C-PBR-28 (National Institutes of Health, Bethesda, MD; Fig. 16) is a PET tracer for the potential imaging of neuronal inflammation. In April 2013 a Phase I trial was initiated in the US (Thomson Reuters Pharma, update of February 5, 2014).
expected to complete in July 2014. The in vivo radioligand binding correlated with the severity of AD measured by scans with \(^{11}C\)-PBB [360]. This ligand may be useful for longitudinal studies to mark conversion from MCI to AD (Thomson Reuters Pharma, update of May 30, 2014).

\(^{11}C\)-DA-A-1106 (Tainbo Pharmaceuticals, Tokyo, Fig. 16) has a very high affinity to PBRs in mitochondrial fractions of rat (K\(_i\) = 0.043 nM) and monkey (K\(_i\) = 0.188 nM) brains. LogP is 3.65. This compound has a four times higher uptake in vivo than PK11195 in monkey brain [361–366] (Thomson Reuters Pharma, update of December 5, 2011).

\(^{11}C\)-PK11195 (Fig. 16) was used for PET scans in a clinical study with 13 AD patients and 10 controls. Voxel-wise statistical parametric mapping analysis showed small clusters of significantly increased (R)-\(^{11}C\)-PK11195 binding potential in the occipital lobes in AD dementia patients compared with healthy control subjects [367].

\(^{11}C\)-SSR-180875 (sanofi, Fig. 16) is a valuable tool to measure neuroinflammation in the brain [368, 369] (Thomson Reuters Pharma, update of February 25, 2014).

\(^{11}C\)-Vinpocetine (Gedeon Richter, Budapest) displayed a significantly higher brain uptake than \(^{11}C\)-(R)-PK11195 to reach PBRs in human brain [370, 371].

1.28. Peroxisome proliferator-activated receptors

The mechanisms underlying the rapid peroxisome proliferator-activated receptor gamma (PPAR\(\gamma\))-mediated A\(_\beta\) clearance and reversal of cognitive deficits in a marine model of AD were described [372]. Peroxisome proliferators reduced spatial memory impairment in double transgenic AD mice [373]. The potential roles of peroxisomes in AD were described [374]. The PPAR\(\gamma\)-co-activator-1\(\alpha\) (PGC-1\(\alpha\)) reduced A\(_\beta\) generation [375]. Its overexpression exacerbated A\(_\beta\) and tau deposition in a transgenic mouse model of AD [376]. The upregulation of PGC-1\(\alpha\) by an AD-associated pathway was described [377]. The modulation of microglia activity by PPAR\(\gamma\) agonists may provide a promising therapy for PD [378]. For a review on PPARs in AD, see [379].

Rosiﬂ glitazone (Avandia, GSK, launched in 1999; Fig. 17) enhanced synaptic plasticity in experimental animals [380–382]. Cognitive enhancement with rosiﬂ glitazone is linking the hippocampal PPAR\(\gamma\) and ERK-MAPK signaling pathways [383–385] (Thomson Reuters Pharma, update of April 24, 2014).

Pioglitazone (Actos, Takeda, Osaka, launched in 1999; Fig. 17) was tested in five randomized controlled Phase II trials on cognition in AD patients [386–388]. In August 2013 Takeda and Zinfandel initiated a global, multicenter, double-blind, placebo-controlled, parallel-group, Phase III study (TOMMORROW) to investigate a genetic-based biomarker risk assignment algorithm to predict the risk of developing MCI due to AD within a 5-year period and to evaluate the efficacy of low-dose pioglitazone in delaying the onset of MCI due to AD in cognitively normal individuals (expected n = 5,800) at high risk as determined by the risk assignment algorithm. The primary endpoint was time to diagnosis of MCI due to AD for placebo-treated, high-risk subjects versus placebo-treated, low-risk subjects.

Pioglitazone improved reversal learning and exerts mixed cerebrovascular effects in a mouse model of AD with combined A\(_\beta\) and cerebrovascular pathology [389]. It reduced glial inflammation and A\(_\beta\)-\(\eta\)-42 levels in A\(_\beta\)PPV717I transgenic mice [390]. Pioglitazone improved scopolamine-induced memory impairment in mice [391], see also [392]. Sales of pioglitazone in 2012 were USD 1.548 billion (Thomson Reuters Pharma, update of April 30, 2014).

MSDC-0160 (Mitoglitazone, Metabolic Solutions Development Co., Kalamazoo, MI; Fig. 17), the active metabolite of pioglitazone, is an insulin-sensitizing, PPAR\(\gamma\)-sparking thiazolidine-dione with antihyperglycemic and lipid-lowering properties. The novel insulin sensitizer modulated nutrient sensing pathways and maintained \(\beta\)-cell phenotype in human islets [393]. In September 2013 data from the 29-patient trial were presented at the 14th International Conference on Alzheimer’s Drug Discovery, Jersey City, NJ. Data demonstrated that glucose metabolism was maintained in non-diabetic AD-related dementia patients treated with MSDC-0160, in key regions of brain associated with cognitive decline due to AD as confirmed by FDG-PET imaging (Thomson Reuters Pharma, update of January 21, 2014).

DSP-9658 (Dainippon Sumitomo, Osaka, one compound of this series is shown in Fig. 17) is a dual PPAR\(\alpha\)/\(\gamma\) agonist, which also reduces A\(_\beta\) 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 December 30, 2013).

Other PPAR agonists are currently in preclinical evaluation (in alphabetical order):

Bezafibrate (Bezalip, Bezatol; Boehringer Mannheim, now Roche, co-marketed with Kissei Pharmaceuticals, Nagano, launched in 1977), a drug...
Fig. 17. Seven PPARγ agonists, two prostaglandin E2R, a thromboxane A2R and two RAGE antagonist(s).
for the treatment of hyperlipidemia, is a pan-PPAR agonist, which improved behavioral deficits and tau pathology in P301S mice exerting a preventive effect [394] (Thomson Reuters Pharma, update of February 19, 2014).

GFT-1803 (Genit, Loos, France and University of Bonn, Germany), a novel potent PPAR agonist that activates all the three PPAR isoforms (α/β/γ), protected APP/PS1 mice from amyloid deposition and cognitive deficits [574]. The structure was not communicated.

Glimepiride (sanofi, launched in 1996 by Hoechst) is a medium- to long-acting sulfonylurea antidiabetic drug with PPAR-δ activating all the three PPAR isoforms (NR1F1) for the potential treatment of inflammation early in the AD course [400]. Positive and negative effects of prostaglandins in AD were described [401]. AD-associated inflammation was suppressed via microglial prostaglandin-E2 EP4 receptor signaling [402].

Amgen (Thousand Oaks, CA) is investigating EP2 antagonists for the potential treatment of AD. A lead compound (Fig. 17) was identified with moderate i.v. phamaco-kinetic properties in mice, a Cmax of 1.2 μM and an oral bioavailability of 31%. The compound demonstrated good CNS permeability and significantly increased Aβ phagocytosis with an IC50 value of 8 nM for EP2 receptors. The development was terminated (Thomson Reuters Pharma, update of May 12, 2014).

CNTX-5126 and CNTX-5129 (University of Pennsylvania, Philadelphia, PA; one compound is shown in Fig. 17) are thromboxane A2-prostanoid receptor antagonists in preclinical evaluation for the potential treatment of AD (Thomson Reuters Pharma, update of June 5, 2013).

TG-6101 (Emory University, Atlanta, GA; Fig. 17) is the lead compound of prostaglandin EP2 receptor antagonists for the potential treatment of inflammation associated with neurological disease such as AD, PD, stroke, traumatic brain injury, migraine, and neuropathic pain [403] (Thomson Reuters Pharma, update of December 10, 2012).

1.30. Purinergic receptors

Silencing of the P2X7 receptor enhanced Aβ phagocytosis by microglia [404]. Loss of P2Y2 receptors enhanced early pathology in a transgenic mouse model of AD [405]. P2Y4 receptor-mediated pinocytosis contributed to Aβ-induced self-uptake by microglia [406]. Activation of the purinergic receptor P2X7 stimulated AβPP release from mouse neuroblastoma cells expressing human AβPP [407]. The development of P2X7 purinoceptor antagonists of Axxam was terminated.

1.31. Receptor for advanced glycation end products

RAGE is a member of the microglial scavenger receptors [408–411]. Hypertension induced brain Aβ accumulation, cognitive impairment, and memory deterioration through activation of RAGE [412].
TTP-488 (PF-0494700; Trans Tech Pharma, High Point, NC in collaboration with Pfizer) is a small molecule and orally active RAGE antagonist in a multi-center, randomized, double-blind, placebo-controlled, Phase Ib trial in the US in 400 subjects with mild-to-moderate AD since December 2007. In October 2012 data were reported from the trial demonstrating 26% benefit relative to placebo in cognitive decline over 18 months in patients receiving a 5 mg dose. Patients with mild AD showed a 46% benefit over placebo. Extensive post-hoc analyses showed a consistent signal indicative of a therapeutic benefit at the 5 mg dose level. At 18-month, decline in ADAS-cog11 was reduced to 26% compared to placebo. Pharmacokinetic and pharmacodynamic data showed statistically significant differences in ADAS-cog11 from month 6 through 18 in population through plasma concentrations in an optimal range. The drug was safe and well tolerated. The FDA granted Trans Tech Pharma fast track designation for TTP-488 for the treatment of AD. The results of a Phase IIb trial with 5 mg/d and 20 mg/d for 18 months in patients with mild AD showed a consistent signal indicative of a therapeutic benefit at the 5 mg dose level. Patients with mild AD showed a 34% benefit over placebo. At 18-month, decline in ADAS-cog11 was reduced to 26% compared to placebo. Pharmacokinetic and pharmacodynamic data showed statistically significant differences in ADAS-cog11 from month 6 through 18 in population through plasma concentrations in an optimal range. The drug was safe and well tolerated. The FDA granted Trans Tech Pharma fast track designation for TTP-488 for the treatment of AD. The results of a Phase IIb trial with 5 mg/d and 20 mg/d for 18 months in patients with mild AD showed a 46% benefit over placebo. Extensive post-hoc analyses showed a consistent signal indicative of a therapeutic benefit at the 5 mg dose level.

The development of small molecule RAGE antagonists by Perjeta Pharma Oy (Helsinki) and by MabPrex (San Diego, CA) was terminated.

1.32. Retinoid X receptors

Stimulation of the retinoid X receptor facilitated Aβ clearance across the BBB [418]. For a review, see [419]. More precisely, only retinoic acid α agonists (e.g., AM-580, Roche) reduced the number of Aβ plaques, whereas retinoic acid β (e.g., CD-2019) or retinoic acid γ agonists (e.g., CD-437) had no effect on plaque load [420, 421]. The Aβ production is attenuated by direct inhibition of γ-secretase-mediated cleavage of AβPP [422]. Retinoic acid-elicited RARα/RXRs signaling attenuated the Aβ production by direct inhibition of γ-secretase-mediated cleavage of AβPP [423]. The retinoic acid-inducible gene-1 (RIG-1) receptor is significantly elevated in the temporal cortex and plasma in patients with MCI [424]. A recent review was disclosed [425].

IRX-4204 (AGN-194204; Ie Therapeutics, Santa Ana, CA, under license from Allergan, Irvine, CA, Fig. 18) is a second generation orally active retinoid X receptor agonist for the potential treatment of prostate cancer and AD in Phase II clinical trials since October 2011 (Thomson Reuters Pharma, update of April 10, 2014).

Acitretin (Roche, launched IN 1997) up-regulated the α-secretase ADAM10 [426, 427].

All-trans retinoic acid rescued memory deficits and neuropathological changes in a mouse model of streptozocin-induced dementia of Alzheimer-type [428].

Bexarotene (Targetretin, LGD-1069; Eisai, Fig. 18) is a retinoid X receptor agonist, which after oral administration to a murine model of AD caused enhanced clearance of soluble Aβ within hours in an ApoE-dependent manner. ApoE expression is transcriptionally induced through the action of the nuclear receptors PPARy and LXR in coordination with

Medifron DBT (Seoul, Fig. 17) published a paper on ligand-based design, synthesis, and biological evaluation of 2-aminopyrimidines, a novel series of RAGE inhibitors [414, 415] (Thomson Reuters Pharma, update of February 25, 2014).

Pfizer scientists published the pharmacokinetics and lung distribution of a humanized anti-RAGE antibody in wild-type and in RAGE−/− mice [416].

An aqueous orally active vaccine targeted against the RAGE/Aβ complex was described by scientists from Georgia Health Sciences University, Augusta, GA [417].

The development of small molecule RAGE antagonists by Perjeta Pharma Oy (Helsinki) and by MabPrex (San Diego, CA) was terminated.

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Fig. 18. Two retinoid X Rs, three 5-HT₁A Rs agonists, three 5-HT₂A Rs antagonists, three 5-HT₄Rs agonists and one 5-HT₄R antagonist PET ligand.
retinoid X receptors. Aβ plaque area was reduced by 50% within 72 hours [575]. Bexarotene blocked calcium-permeable ion channels formed by neurotoxic Aβ peptides [429]. What did we learn from the bexarotene discussion [430]? Bexarotene analogues with higher affinity to retinoid receptors were described [431] (Thomson Reuters Pharma, update of February 17, 2014).

GT-1036 (MC 1036; Gerinda Therapeutics, Cary, NC, under license from MaxoCore, Solana Beach, CA) is the lead from selective retinoid X receptor agonists which acts by increasing ApoE protein levels for the potential oral treatment of AD (Thomson Reuters Pharma, update of November 18, 2013). The structure was not communicated.

Retinoic acid receptor-α agonists (CoCo Therapeutics, Oxford, UK under license from King’s College, London) are investigated for the potential treatment of AD. They are aryl-amido-aryl compounds (Thomson Reuters Pharma, update of September 4, 2013). The precise structures were not communicated.

The development of Tandospirone (Am80; Nippon Shinyaku, Kyoto, under license from the University of Tokyo; [432–434]) was terminated.

1.34. Scavenging receptors

Scavenger receptors are a group of receptors that recognize modified low-density lipoprotein (LDL) by oxidation or acetylation. This naming is based on a function of cleaning (scavenging). Scavenger receptors widely recognize and uptake macromolecules having a negative charge as well as modified LDL. Class A is mainly expressed in the macrophage with a molecular weight of 80 kDa [436]. It was shown that heptapeptide XD4 activated the class A scavenger receptor (SR-A) on glia by increasing the binding of Aβ to SR-A, thereby promoting glial phagocytosis of Aβ oligomer in microglia and astrocytes and triggering intracellular MAPK signaling cascades. XD4 enhanced the internalization of Aβ monomers to microglia and astrocytes through macropinocytosis or SR-A-mediated phagocytosis. XD4 significantly inhibits Aβ oligomer-induced cytotoxicity to glial cells and decreases the production of proinflammatory cytokines, such as TNF-α and IL-1β, in vitro and in vivo. These findings may provide a novel strategy for AD treatment by activating SR-A [437].

1.35. Serotonin receptors

1.35.1. 5-HT1A Receptor agonists and antagonists

Vortioxetine (Brintelix, Lu-AA21004; Lundbeck, Valby, DK and Takeda, Osaka, Fig. 18) is a 5-HT1A receptor agonist, a 5-HT1B receptor partial agonist, a 5-HT1D, 5-HT3, and 5-HT7 receptor antagonist, and a 5-HT transporter inhibitor launched in the US in October 2013 for the treatment of adult major depressive disorders. Vortioxetine enhanced contextual and episodic memory in rat behavioral models [443, 444]. For the efficacy and safety of vortioxetine in patients, see [445–453]. The outcome of the FOCUS study was presented at ACNP and Brintelix 10 mg and 20 mg demonstrated a statistically significant improvement in cognitive performance as assessed by DANTES Subject Standardized Test and Rey Auditory Verbal Learning Test versus placebo. Vortioxetine received EU approval as well as approval in Iceland, Liechtenstein, and Norway for the treatment of adults with major depressive episodes. First European launches are expected in 2H14 (Thomson Reuters Pharma, update of May 27, 2014).

F-15599 (Pierre Fabre, Burlsats, France, Fig. 18) 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 [454–458] (Thomson Reuters Pharma, update of December 10, 2013). 18F-F15599 was used as a novel radioligand for PET neuroimaging [459].
1.35.2  5-HT₂ receptor antagonists

Disease-specific expression of 5-HT₂C receptors in patients with AD was reported [460].

Aripiprazole (Abilify; Otsuka Pharmaceuticals, Tokyo, launched in 2002) was tested in AD patients. It should only be used in selected patient populations resistant to non-pharmacological treatment with persisting or severe psychotic symptoms and/or agitation [461]. Sales in 2012 reported by Otsuka were USD 5.481 billion (Thomson Reuters Pharma, update of May 31, 2014).

Asenapine (Saphris, Organon, later Schering-Plough, now Merck & Lundbeck, launched in 2009) is a 5-HT₂A and dopamine D₂/D₃ antagonist for the treatment of schizophrenia in adults administered as a sub-lingual formulation. Sales in 2012 reported by Merck were USD 166 million and by Lundbeck at USD 19 million (Thomson Reuters Pharma, update of January 15, 2014).

Blonanserin (Lonasen, AD-5423, DSP-5423; Dainippon Sumitomo Pharmaceuticals, Osaka, Fig. 18) is a 5-HT₂A and dopamine D₂/D₃ antagonist launched in Japan in 2008 for the treatment of schizophrenia. The pharmacological profile was described including reports on the improvement of some types of cognitive function in patients with first-episode and chronic schizophrenia [462]. Sales in 2012 were USD 134 million (Thomson Reuters Pharma, update of May 30, 2014).

Lurasidone (Latuda, SM-13496; Dainippon Sumitomo Pharmaceuticals, Osaka, Fig. 18) is a 5-HT₂A and 5-HT₇ antagonist, 5-HT₁A partial agonist and dopamine D₂ antagonist atypical antipsychotic launched in the US by Dainippon’s US subsidiary Synovion Pharmaceuticals (Marlborough, MA) in February 2011. The product is indicated in the US for the treatment of schizophrenia in adults with depressive episodes associated with bipolar I disorder and cognitive function deficits [463–467]. Sales in 2012 were USD 201 million (Thomson Reuters Pharma, update of May 29, 2014).

Pimavanserin (ACP-103; BVE-036; ACADIA Pharmaceuticals, San Diego, CA; Fig. 18), a 5HT₁A receptor inverse agonist reversed psychosis-like behaviors in a rodent models of AD and PD [468–470]. The compound is in Phase III clinical trials since January 2003 in Europe and since June 2007 in the US. A detailed report on Pimavanserin for patients with PD psychosis: a randomized, placebo-controlled Phase III trial was published [471]. Acadia announced that it had initiated a Phase II feasibility trial designed to examine the efficacy and safety of pimavanserin as a treatment for patients with AD psychosis (Thomson Reuters Pharma, update of May 7, 2014).

ITI-007 (Intra-Cellular Therapies, New York, NY under license from Bristol-Myers Squibb) is a 5-HT₂A receptor antagonist, dopamine D₂ receptor partial agonist, and serotonin reuptake transporter modulator, for the potential treatment of schizophrenia, depression, bipolar disorder, and sleep disturbances in psychiatric and neurodegenerative diseases in Phase II clinical trials since May 2010 in the US. In December 2013, positive results were reported. In March 2014, a Phase III trial (ITI-007-200) was initiated to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of low dose ITI-007. The first part of the trial was a randomized, double-blind, placebo-controlled multiple ascending dose study in which 10 healthy geriatric subjects in each cohort would receive ITI-007 or placebo for 7 days. The second part of the trial would be conducted in dementia patients (expected n = 121) [472] (Thomson Reuters Pharma, update of May 7, 2014). The structure was not communicated.

Quetiapine (Seroquel; AstraZeneca) is an orally active dibenzoazepine atypical antipsychotic with 5-HT₂ and D₂ antagonistic activity launched in the UK and the US in 1997. It attenuated recognition memory impairment and hippocampal oxidative stress in a transgenic mouse model of AD [473] (Thomson Reuters Pharma, update of May 31, 2014).

1.35.3  5-HT₇ receptor antagonists

Cognitive implications for histamine H₃ and 5-HT₇ receptor modulation of cortical cholinergic function were elucidated [474] as was the role of 5-HT₇ receptors in selective animal models of cognition [475].

1.35.4  5-HT₄ receptor (partial) agonists

PRX-3140 (Nanotherapeutics, Alachua, FL, Fig. 18) is a 5-HT₄ receptor agonist in Phase II clinical trials for treatment of AD and post-traumatic stress disorders since December 2009 in the US. Data on the enhancement of cognitive function in vivo were communicated [476] (Thomson Reuters Pharma, update of October 24, 2013).

Velusetrag (TD-5108, Theravance, South San Francisco, CA, Fig. 18) is in Phase I trials for AD in the US in July 2010. In January 2013 a proof-of-concept Phase II trial in gastroparesis in the US and in Italy was initiated. Its in vitro pharmacological profile was published [477]. Another potential use is treatment of gastroduodenal motility disorders [478, 479] (Thomson Reuters Pharma, update of May 27, 2014).
AAT-009 (RQ-0000009, RQ-9; AskAt, following its spin-out from RaQualia, Chita-Gun, Aichi-Ken, Japan and Pfizer) is a selective 5-HT4 receptor partial agonist for the treatment of AD. A Phase I study was initiated in Japan in August 2008, a second Phase I study in February 2013 (Thomson Reuters Pharma, update of January 2, 2014). The structure was not disclosed.

SUVN-D1003019, SUVN-1004028, SUVN-D1108121, SUVN-D4010, and orally bioavailable SUVN-D1104010 (Suven Life Sciences, Hyderabad, India) are selective 5-HT4 receptor agonists for the treatment of MCI, cognition, and AD. A 4-hydroxyquinolinone with good oral exposure, brain penetration, moderate clearance, good half-life in rats, and efficacy in in vivo cognition tests was presented at the 243rd ACS Meeting in San Diego March 2012 (Fig. 18). Preclinical data on SUVN-D1104010 were presented at the Alzheimer’s Association International Conference in Vancouver, July 14–19, 2012 [273]. In November 2013 preclinical studies in AD were ongoing (Thomson Reuters Pharma, update of May 26, 2014).

GSK terminated the development of the 5-HT4 antagonist PET ligand \(^{11}\)C-SB-207145 (Fig. 18; Thomson Reuters Pharma, update of December 4, 2013). The ligand is still extensively used for brain imaging of 5-HT4 receptors in academic settings [480–484]. Also the tritiated ligand \(^{3}\)H-SB-207145 is frequently used for 5-HT4 receptor binding studies [485, 486].

The development of TD-8954 (Theravance; [476, 487–489]) for the indication AD was terminated, but development for the treatment of gastrointestinal motility disorders is continuing (Thomson Reuters Pharma, update of May 27, 2014).

1.35. 5-HT6 receptor antagonists

The topic 5-HT6 receptors and AD was reviewed [490]. Their role in modulating brain neurochemistry was described [491].

Idalopirdine (Lu AES8054; LY-483518; SGS-518; Lundbeck, Valby, DK under license from Lilly; Fig. 19) was in Phase II clinical development since November 2009. Lundbeck and Otsuka Pharmaceutical Co., Tokyo have concluded a license agreement

![Fig. 19. 5-HT6 receptor antagonists.](image-url)
to co-develop and co-commercialize Lu AE58054. In October 2013 the first of four Phase III trials was initiated; the Phase III program will enroll approximately 3,000 patients and assess Lu AE58054 (10 to 60 mg) combined with donepezil. The primary endpoints will be ADAS-cog, activities of daily living, and the Clinical Global Impression of Change Scale. Three studies were started: NCT01955161: Study of Lu AE58054 in patients with mild to moderate AD treated with donepezil (STARSHINE), NCT02006654: Lu AE58054 in patients with mild to moderate AD treated with donepezil (STARBEAM) and NCT02006641: Lu AE58054 in patients with mild to moderate AD treated with an acetylcholinesterase Inhibitor (STAR-BRIGHT) (Thomson Reuters Pharma, update of May 29, 2014). The structure was not disclosed.

AVN-101 (Avineuro Pharmaceuticals, San Diego, CA and Avineyro, Russian Federation under license from Alla Chem LLC, Hallandale Beach, FL) is a 5-HT6 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 May 29, 2014). The structure was not disclosed.

AVN-211 Avineuro Pharmaceuticals, San Diego, CA, and Avineyro, Russian Federation under license from Alla Chem LLC, Hallandale Beach, FL) is a 5-HT6 receptor antagonist for the potential treatment of cognitive symptoms in schizophrenia since June 2009. In February 2011 results from the double-blind, Phase IIIa trial in 50 patients showed the trial met its primary efficacy endpoints and AVN-211 was safe and well tolerated. In July 2013 a Phase IIb schizophrenia trial was initiated (Thomson Reuters Pharma, update of May 29, 2014). The structure was not disclosed.

SAM-760 (PF-05212377, WYE-103760; Wyeth, now Pfizer; Fig. 19) was in Phase I clinical trials for the treatment of AD since October 2009. In January 2013 a placebo-controlled, randomized, double-blind, 18-week, Phase II trial was initiated to assess the safety and efficacy of SAM-760 in patients with mild-to-moderate AD (n = 342) with existing neuropsychiatric symptoms on a stable dose of donepezil (Thomson Reuters Pharma, update of May 16, 2014).

ABT-354 (SLV-354; Abbvie, North Chicago, IL; Fig. 19) is a 5-HT6 receptor modulator in Phase I clinical trials since February 2010 in the UK. In March 2012 another Phase I trial began in schizophrenia patients (n = 221) in the US (Thomson Reuters Pharma, update of May 29, 2014). The structure was not communicated.

AVN-322 (Avineuro Pharmaceuticals, San Diego, CA and Avineyro, Moscow, Russia under license from Alla Chem LLC, Hallandale Beach, FL) was in Phase I clinical trials for the treatment of AD since June 2009. In October 2013 a new Phase I study was initiated in Russia (Thomson Reuters Pharma, update of May 29, 2014). The structure was not disclosed.

SYN-502 (Suven Life Sciences, Hyderabad, Fig. 19), an orally active 5-HT6 receptor antagonist, which increases extracellular levels of acetylcholine and glutamate, is in Phase I clinical trials for the treatment of cognitive disorders in AD, attention deficient hyperactivity, PD, and schizophrenia since June 2008 in Switzerland and since November 2013 in the US (Thomson Reuters Pharma, update of May 26, 2014). SYN-114 and SYN-120 (Biotic Therapeutics, Basel, Switzerland, formerly Synosia Therapeutics under license from Roche, Basel, Switzerland) are currently both in Phase I clinical trials for the treatment of cognitive disorders since January 2007 and March 2009 in the US, respectively (Thomson Reuters Pharma, updates of August 24, 2012 and May 27, 2014, respectively). The structures were not disclosed.

There are many 5-HT6 receptor antagonists in pre-clinical evaluation (in alphabetical order):

AVN-457, AVN-458 and AVN-492 (Avineuro Pharmaceuticals, San Diego, CA) are drugs for the potential treatment of cognitive disorders (Thomson Reuters Pharma, update of May 30, 2014). The structures were not disclosed.

BVA-101 and BVA-601 (Biovista, Charlottesville, VA) are novel formulations of latrepirdine (dimebon) for the potential oral treatment of multiple sclerosis and of epilepsy, respectively (Thomson Reuters Pharma, updates of November 28, 2012 and of November 29, 2012, respectively).

SEL-103 (Selvita Life Sciences Solutions, Krakow, PL) is a program of 5-HT6 receptor inhibitors for the potential treatment of AD and related cognitive disorders (Thomson Reuters Pharma, update of March 13, 2014). No structures were communicated.

5-HT6 receptor antagonists (Abbvie, North Chicago, IL; Fig. 19) are evaluated for the potential treatment of cognitive deficits in patients with AD and schizophrenia. The medicinal chemistry was described [492]. The effects to ameliorate scopolamine-induced memory deficits in object recognition and object location tasks in Wistar rats were reported [493] (Thomson Reuters Pharma, update of January 4, 2013).

5-HT6 receptor antagonists (Proximag, London, UK, a subsidiary of Upsher-Smith Laboratories, Maple Grove, MN, under license from Swedish
Orphan Biovitrum, Stockholm) are evaluated for the potential treatment of cognitive disorders including cognitive disorders in PD. By March 2012 in vivo studies had demonstrated high brain penetration and good oral activity in a novel object recognition test (Thomson Reuters Pharma, update of April 16, 2014). No structures were communicated.

SUVN-507 (Suven Life Sciences, Hyderabad; Fig. 19) is a 5-HT6 receptor antagonist (Kᵢ = 1.3 to 1.6 nM) for the treatment of schizophrenia, MCI and AD in preclinical development. Other compounds in preclinical evaluation are SUVN-501, SUVN-504, SUVN-901, SUVN-976, and SUVN-A60203. SUVN-504 is evaluated as drug for the potential treatment of obesity and metabolic disorders including diabetes. SUVN-512 was presented as a novel 5-HT6 receptor antagonist with drug like properties at the Alzheimer’s Association International Conference in Boston, July 17, 2013 in Abs P4-305 (Thomson Reuters Pharma, update of April 11, 2014).

Novel chemical classes of 5-HT6 receptor antagonists, i.e., aryl aminosulfonamide derivatives with a Kᵢ of 0.02 nM were reported by medicinal chemists at Suven, as were N-1-arylsulfonyl-3-piperazinyl indole derivatives with a Kᵢ of 3.4 nM [494–501].

The development of SB-742457 (GSK; [502–506]) was terminated.

1.36. Sigma receptors

The accumulation of the sigma-1 receptor is common to neuronal nuclear inclusions in various neurodegenerative diseases [507].

Anavex-2-73 (A vex-2-73; AN-2; Anavex Life Sciences, Vancouver, BC; Fig. 20), a sigma-1 receptor agonist, is currently in a Phase I AD trial since March of 2011 [508]. Sigma-1 receptor agonists like Anavex 2-73 are involved in cellular survival by regulating and stabilizing a key cell stress sensor [509]. Blockade of tau hyperphosphorylation and AβPP25-35 generation was reported [510] (Thomson Reuters Pharma, update of May 29, 2014).

ANAVEX PLUS (Anavex Life Sciences, Vancouver, BC) is a combination of Anavex-2-73 and donepezil for the potential treatment of AD. In January 2014 clinical development with the Roskamp Institute (Sarasota, FL) was planned (Thomson Reuters Pharma, update of May 29, 2014).

Anavex-1-41 (Anavex Life Sciences, Vancouver, BC; Fig. 20) is a potential back-up compound [511–513] (Thomson Reuters Pharma, update of May 19, 2014).

Epigen Biosciences (San Diego, CA) is investigating ligands to sigma-1 receptors that regulate nitric oxide production for the potential treatment of AD (Thomson Reuters Pharma, update of February 13, 2014). Structures were not communicated.

Fabomotizole (Afobazol, CM-346, SM-346, GRN-014; Pharmstandard through its subsidiary IBC Generium, Moscow; Fig. 20) is a neuroprotective pan-sigma receptor agonist for the potential treatment of ischemic stroke and neurodegenerative conditions including AD. The drug was launched in Russia in 2005 as an OTC mild anxiolytic. The drug modulates neuronal responses to AβPP25-35 [514, 515] (Thomson Reuters Pharma, update of May 20, 2014).

MC-116 (M’s Science, Kobe) is a sigma receptor agonist for the potential treatment of major depression and CNS diseases including AD (Thomson Reuters Pharma, update of February 28, 2013). The structure was not communicated.

(±)-PPCC (University of Trieste; Fig. 20), a novel sigma-1 receptor ligand, displayed anti-amnesic properties on cognitive dysfunction induced by selective cholinergic lesions in rats [516].

SOM Biotech SL (Barcelona) is investigating a repurposed formulation of an undisclosed sigma-1 agonist, for the potential treatment of amnesia and AD (Thomson Reuters Pharma, update of December 24, 2013). The structure was not communicated.

A novel PET radioligand for imaging of sigma-1 receptors 18F-FTC-146 (Stanford University, Fig. 20) was presented [517, 518].

The development of (-)-MR22 (University of Messina; [519–521]) was terminated.

1.37. Somatostatin receptor agonists

The roles of neuropeptides including somatostatin were discussed [216].

1.38. Sortilin receptor inhibitors

Sortilin is a type I membrane receptor belonging to the vacular protein sorting 10 protein (VPS10P) family of sorting receptors [346], that also includes SorLa and SorCS1,2 and 3 [522]. Previously, sortilin was known as the neureptensin receptor 3 [523]. Sortilin binds to and promotes α-cleavage of AβPP and is responsible for ApoE-mediated cellular uptake and degradation of extracelluar Aβ [524–526]. Significantly increased levels of sortilin were found in human AD brains and in 6-month-old Swedish-AβPP/PS1de9 transgenic mice [527].
BACE1 retrograde trafficking is regulated by the cytoplasmic domain of sortilin [528]. Extracellular Aβ oligomers act as sortilin ligands [529]. In addition, genetic variants in the sortilin-related receptor (SORL1) and the sortilin-related vacuolar protein sorting 10 (VPS10) domain-containing receptor 1 (SORCS1) are associated with increased risk of late-onset AD [530].

AF-38469 (Lundbeck, Valby, DK; Fig. 20) is an orally bioavailable sortilin receptor inhibitor with an IC50 of 330 nM [531]. An X-ray crystal structure of the sortilin-AF-38469 protein-inhibitor complex was published [532] (Thomson Reuters Pharma, update of March 11, 2014).

1.39. Sphingosine-1-phosphate receptor modulators

Sphingolipids are critical players in AD [533]. Plasma sphingomyelins are associated with cognitive progression in AD [534]. The pathological roles of ceramide and its metabolites in metabolic syndrome and AD were described [576].

ABT-363 (AbbVie, North Chicago, IL) is a sphingosine-1-phosphate receptor 5 (S1P5) modulator for the potential treatment of neurological disorders including AD (Thomson Reuters Pharma, update of January 3, 2013). Another S1P1/S1P5 receptor modulator ABT-413 is evaluated in Phase I clinical trials for the treatment of multiple sclerosis and rheumatoid arthritis since June 2011 (Thomson Reuters Pharma, update of January 4, 2013). Neither structure was communicated.

Fingolimod (FTY720; Novartis and Mitsubishi Tanabe Pharma, Osaka, launched in 2010) attenuated Aβ42 induced impairment of spatial learning and memory in rats [535] via increased BDNF expression in neurons [536]. Fingolimod increased BDNF levels and ameliorated Aβ-induced memory impairment [538] (Thomson Reuters Pharma, update of January 7, 2014).

Siena Biotech is investigating S1P antagonists for the potential treatment of neurodegenerative diseases including AD and Huntington’s disease, inflammation, and fibrosis (Thomson Reuters Pharma, update of October 1, 2012). Structures were not communicated.

1.40. Tachykinin receptor antagonists

The roles of neuropeptides including the tachykinin system were discussed [216].
1.4. Tumor necrosis factor receptor 1/2 inhibitors

\[1^41\] Aβ1-40 binds specifically to TNFR1 in SH-SY5Y cells with a \(K_d\) of 0.42 nM [539]. A combination of data on plasma TACE activity, sTNFRs, and Aβ with the presence of the ApoE e4 allele may provide a novel biomarker [540].

**TK-001** (NP-1; Neurokin Pharmaceuticals, Vancouver, BC) is a repurposed form of the TNFα-blocking agent etanercept, a recombinant fusion protein of 934 amino acids (mol. weight: 150 kDa) composed of a dimer of the extracellular portion of human TNFR-2 fused to the Fc fragment of human IgG1 [541, 542]. A rapid cognitive improvement following perispinal etanercept administration (Trendelenburg positioning) to 15 probable-AD patients treated once weekly for 6 months was reported [543–545]. See also the commentary [546]. In December 2010 the drug was in Phase II development in Canada for the potential treatment of neurocognitive impairment following coronary artery bypass graft surgery (Thomson Reuters Pharma, update of August 19, 2013).

3.6-Dithiothalidomide (Fig. 20), a small molecule inhibitor for TNF-α prevents cognitive deficits in a triple transgenic mouse model of AD [547–550].

**PD-2015**, **PD-2016** and **PD-2024** (P2D BioScience, Cincinnati, OH) are small molecule TNFα inhibitors. They are thalidomide analogues. A significant improvement (by 24%) in the Morris water maze performance was observed in mice administered PD-2015 at a 100 mg/kg dose. The working memory in the radial arm maze task and the ability to construct a nest were improved by 42 and 17%, respectively (Thomson Reuters Pharma, update of February 26, 2014). The structures were not communicated.

**TNFR1 NAMs** (Addex Therapeutics) are investigated for the potential oral treatment of rheumatoid arthritis, psoriasis, AD and multiple sclerosis (Thomson Reuters Pharma, update of April 7, 2014).

**TNFR2:Fc fusion protein** (UCB, Brussels, Belgium) is a s.c. formulation of an anti-TNFs agent for the potential treatment of AD [551] (Thomson Reuters Pharma, update of October 26, 2012).

1.42. Vitamin D receptors

Epidemiological studies suggested that vitamin D insufficiency increased the risk of AD. Low serum vitamin D concentrations were observed in AD patients [552, 553]. The role of vitamin D in AD and possible genetic and cell signaling mechanisms were discussed [554]. Reviews on vitamin D, cognition, and dementia were presented [555, 556, 577]. Vitamin D supplementation restored suppressed synaptic plasticity in AD [578]. The major mediator of vitamin D’s actions is the vitamin D receptor. Aβ suppressed the expression of the vitamin D receptor gene [557]. The current knowledge was compiled in a recent review [558]. Vitamin D₃-enriched diet correlated with a decrease of Aβ plaques in the brains of AβPP transgenic mice [559]. 1α,25-Dihydroxyvitamin D3 and resolving D1 retune the balance between Aβ phagocytosis and inflammation in AD patients [560]. Combination of memantine and vitamin D prevented axon degeneration induced by Aβ and glutamate [561].

The level of vitamin D-binding protein (DBP) is increased in the CSF of patients with AD. DBP interacted with Aβ and suppressed Aβ-mediated pathology [562].

CONCLUSIONS

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 four acetylcholinesterase inhibitors launched previously (see Part 2 [7]). The medical team of Meers under Hans Jörg Mobius and the many collaborating clinicians deserve full credit for an important breakthrough for the benefit of AD patients.

So far, the development of 14 Phase III compounds interacting with receptors for the potential treatment of AD was discontinued, i.e., of alfameline, cevimeline, milameline, sabcobeline and xanomeline (NP-1; Neurokin Pharmaceuticals, Vancouver, BC) is a repurposed form of the TNFα inhibitor etanercept. 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 four acetylcholinesterase inhibitors launched previously (see Part 2 [7]). The medical team of Meers under Hans Jörg Mobius and the many collaborating clinicians deserve full credit for an important breakthrough for the benefit of AD patients.

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