

Full-length Review

Piracetam and other structurally related nootropics

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Abstract

Nearly three decades have now passed since the discovery of the piracetam-like nootropics, compounds which exhibit cognition-enhancing properties, but for which no commonly accepted mechanism of action has been established. This review covers clinical, pharmacokinetic, biochemical and behavioural results presented in the literature from 1965 through 1992 (407 references) of piracetam, oxiracetam, pramiracetam, etiracetam, nefiracetam, aniracetam and rolziracetam and their structural analogues. The piracetam-like nootropics are capable of achieving reversal of amnesia induced by, e.g., scopolamine, electroconvulsive shock and hypoxia. Protection against barbiturate intoxication is observed and some benefit in clinical studies with patients suffering from mild to moderate degrees of dementia has been demonstrated. No affinity for the α_1 -, α_2 -, β -, muscarinic, 5-hydroxytryptamine-, dopamine, adenosine- A_1 -, μ -opiate, γ -aminobutyric acid (GABA) (except for nefiracetam (GABA_A)), benzodiazepine and glutamate receptors has been found. The racetams possess a very low toxicity and lack serious side effects. Increased turnover of different neurotransmitters has been observed as well as other biochemical findings, e.g., inhibition of enzymes such as prolylendopeptidase. So far, no generally accepted mechanism of action has, however, emerged. We believe that the effect of the racetams is due to a potentiation of already present neurotransmission and that much evidence points in the direction of a modulated ion flux by, e.g., potentiated calcium influx through non-L-type voltage-dependent calcium channels, potentiated sodium influx through α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor gated channels or voltage-dependent channels or decreases in potassium efflux. Effects on carrier mediated ion transport are also possible.

Key words: Memory; Cognition; Nootropics; Piracetam derivative; Mechanism; Membrane excitability; Pharmacokinetics

1. Introduction

Almost thirty years have now passed since the discovery of the piracetam-like nootropics. The term nootropic^{92,94,95} was coined by Giurgea in 1972, from Greek *noos* (*νοος*) (mind) and Greek *tropos* (*τροπος*) (turn), to describe the then newly discovered properties of these compounds: (1) enhancement of learning and memory; (2) facilitation of the flow of information between the cerebral hemispheres; (3) enhancement of the resistance towards chemical and physical injuries; and (4) lack of the usual psychological and general cardiovascular pharmacological activity of psychopharmaca.

A great deal of different biochemical and behavioural results have been reported for these compounds, the mechanism of action of these protective and cognition enhancing drugs having, however, not yet been elucidated.

The aim of the present review is therefore to summarise and discuss the biochemical events, behavioural events, pharmacokinetic properties and clinical results which have been reported and furthermore, to show the classes of chemical structures which, from 1965 to 1992, have been tested for nootropic properties. In doing this we hope to inspire research in the area of cognition enhancers, which hopefully will elucidate the mechanism of action of these compounds and lead to even more efficient compounds for the treatment of cognitive disorders.

This review has been prepared after perusal of the original literature in the case of core papers and of abstracts from Chemical Abstracts and Medline as far as more peripheral articles are concerned.

The information on piracetam presented consolidates the contents of previous reviews by others^{5,49,83,122,214,221,230,231,234,236,259,283,319,346,378} and the results of a CD-ROM Medline search covering the period 1991–1992. Literature on oxiracetam, pramiracetam, etiracetam, nefiracetam, aniracetam, rolziracetam and dupracetam has been retrieved through a CD-ROM Medline search covering the period 1983–1992. Additional material, also concerning analogues of the above-mentioned compounds, was retrieved by means of a Chemical Abstract online search (The Scientific and Technical Information Network (STN), File CAOLD, covering 1965–1967, and File CA, covering 1967–) based on the following substructure (1) (Fig. 1):

Altogether data concerning 1666 compounds (many of which contain the 2-oxopyrrolidineacetic acid derivative (racetam) substructure as part of a peptide sequence) were retrieved. Of these approximately 660 were deemed worthy of further consideration. Further supplementary information concerning chemical, bibliographic and historical data has been retrieved by searches in Martindale¹⁹⁴, Merck Index¹⁹⁷ and finally Beilstein, Handbook of Organic Chemistry (ONLINE, DIALOG Base 390).

Thus, this review deals with most compounds corre-

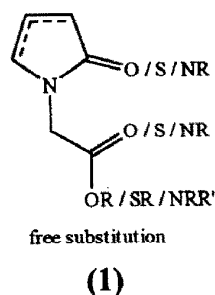


Fig. 1. Substructure used for CA-ONLINE search.

sponding to the substructure plus additional subject matter referred to in the literature in our file. For practical reasons analogues of compounds such as aniracetam, rolziracetam and other compounds containing only the 2-pyrrolidinone moiety (but not a side chain analogous to that of piracetam) which have been tested for nootropic activity are briefly mentioned where appropriate, but not treated exhaustively.

Furthermore, non-racetams like tenilsetam have often been categorized together with the nootropics of the piracetam type regardless of their chemical dissimilarity. Such compounds lie outside the scope of this review.

Information on pre-1983 work with piracetam and oxiracetam has been located through previous reviews^{92–94,282,333,345,391}, and is only treated through these (see also the nootropil monography³⁶⁴). For gen-

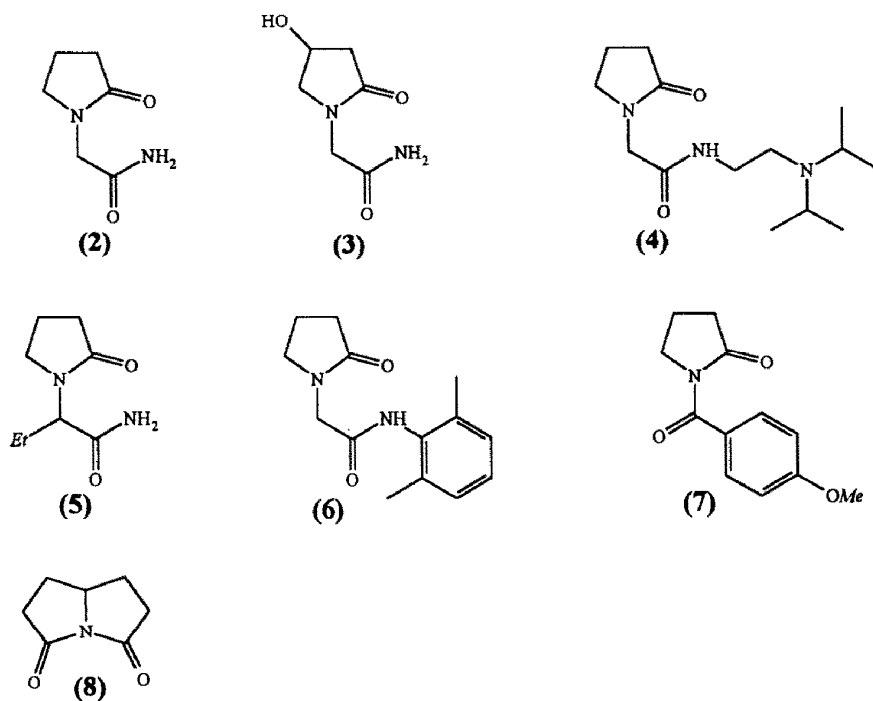
eral reviews on cognition enhancers see refs. 74,198,256,283,320 and especially Frösl and Maître⁷⁴, which contain a large number of chemical structures tested.

Information on the synthesis and chemistry of the piracetam-like nootropics, plus tables of all (about 660) recorded compounds containing the 2-oxopyrrolidineacetic acid substructure (with their CA registry numbers) can be found in our parallel review on the chemistry of piracetam related nootropics¹⁰⁶.

2. The most investigated compounds

Some 2-oxopyrrolidineacetamide nootropics have been investigated more thoroughly than others. Most of these compounds have been assigned a drug name. The named compounds are piracetam (2), oxiracetam (3), pramiracetam (4), etiracetam (5) and nefiracetam (6). Also aniracetam (7) and rolziracetam (8) have, among other compounds, been categorised as piracetam analogues (see Fig. 2).

Most previous reviews have categorised information on these nootropics according to their biochemical properties without regard for the fact that different structures are involved. Small changes in structure often lead to compounds with different chemical properties. A striking example is the poor hydrolytic stability of aniracetam and rolziracetam compared to the highly stable piracetam.



A large diversity of biochemical properties and behavioural events have been reported in the vast extant literature on nootropics and Mondadori et al.²¹⁴ have stated that the dependence of their action on steroids was the first reported common property exhibited by the nootropics. With this background and the many different structures in mind we have chosen to treat each compound separately, even though this means that some repetition in the following compilations of biochemical results cannot be avoided.

This approach allows to profile each individual compound on its own merits and leads to predictions of which additional biochemical experiments, if any, would be required for further progress.

As mentioned above, no commonly accepted mechanism for the racetam nootropics has yet been established. They do not seem to act on any well characterised receptor site with the exception of nefiracetam which has high affinity for GABA_A receptors (see Table 1). They can all to a certain degree pass the

Table 1

Receptor competition studies

- A. Muscimol is a selective GABA_A agonist, showing 417 times higher affinity for GABA_A sites than for GABA_B sites¹⁶¹.
 B. Nefiracetam failed to displace 20% of the specifically bound [³H]muscimol.
 C. L-Pyroglutamate has been included in this table because of its structural similarity with the sole metabolite of rolziracetam.
 D. Experiments performed in the presence of the dopamine antagonist (+)-butaclamol¹³⁰.
 E. The butyrophenone derivative spiroperidol possesses multiple receptor ligand activities with the following relative affinities¹²⁵: D₂(33) > 5-HT₂(1) > α₁(1/18) > 5-HT_{1A}(1/40) > 5-HT_{1C}(1/769) > α₂(< 1/1667) ≈ H₁(< 1/1667) > 5-HT_{1B}(1/3125) ≈ 5-HT_{1C}(1/3125)
 F. Both haloperidol and spiroperidol show generally the highest affinity for dopamine D₂ receptors, but the differentiation between D₁ and D₂ receptors is tissue-dependent¹³².
 G. [³H]Quinuclidinyl benzilate does not, to our knowledge, distinguish between the muscarinic subreceptors.
 H. Cortex.
 I. Hippocampus.
 J. The α₁ competitive antagonist WB-4101 shows also high affinity for 5-HT_{1A} sites (IC₅₀ ≈ 2 nM), but much less affinity for other 5-HT receptor subtypes (IC₅₀ ≈ 4–63 μM)¹²⁴.
 K. Clonidine, an α₂-selective agonist, with additional weak H₂ agonist properties⁴⁷.
 L. Only known to us as a β-receptor-selective ligand¹⁹⁰.
 M. Naloxone is a μ-opiate preferring antagonist, showing the following relative affinities: μ(1) > κ(1/9) > δ(1/14)²⁹².
 N. Although only referred to as an adenosine receptor ligand, it is highly selective for the adenosine-A₁ receptor subtype, A₁(300) >> A₂(1) (ref. 141). The experiments were performed in the presence of the phosphodiesterase inhibitor and weak nonselective adenosine antagonist (K_i = 14 μM, displacement of [³H]cyclohexyladenosine) theophylline¹⁴².

Receptor	Receptor ligand	Compound	IC ₅₀	Refs.
GABA	[³ H]GABA	piracetam	18.0 mM	20
		piracetam	> 10 μM	288, 289
		pramiracetam	> 10 μM	288, 289
GABA _A	[³ H]muscimol ^A	nefiracetam	8.5 nM ^B	222
		aniracetam	0.2 mM	222
		piracetam	17.0 mM	20
Benzodiazepine	[³ H]flunitrazepam	piracetam	> 1 mM	288, 289
		pramiracetam	> 1 μM	288, 289
		l-pyroGlu ^C	> 100 μM	16
Glutamate	[³ H]glutamate	piracetam	1.3 mM	20
		l-pyroGlu ^C	28.1 μM	16
5-HT	[³ H]5-HT ^D	piracetam	34.0 mM	20
		pramiracetam	> 10 μM	288, 289
5-HT ₂	[³ H]spiroperidol ^E	pramiracetam	> 10 μM	288, 289
		piracetam	> 10 μM	288, 289
		piracetam	> 20 mM	20
Dopamine	[³ H]spiroperidol ^{E,F}	pramiracetam	> 10 μM	288, 289
		pramiracetam	> 10 μM	288, 289
Muscarinic	[³ H]QNB ^G	piracetam	> 30 mM	20, 288, 289
		oxiracetam	> 1 mM	203
		pramiracetam	> 10 μM	288, 289
		aniracetam ^H	4.4 μM	203
		aniracetam ^I	6.9 μM	203
α ₁	[³ H]WB-4101 ^J	pramiracetam	> 10 μM	288, 289
		piracetam	> 10 μM	288, 289
α ₂	[³ H]clonidine ^K	l-pyroGlu ^C	> 100 μM	16
β	[³ H]dihydroalprenolol ^L	pramiracetam	> 10 μM	288, 289
		piracetam	> 10 μM	288, 289
		l-pyroGlu ^C	> 100 μM	16
μ-Opiate	[³ H]naloxone ^M	piracetam	57.0 mM	20
Adenosine-A ₁	[³ H]N ⁶ -cyclohexyladenosine ^N	pramiracetam	> 10 μM	288, 289

blood–brain barrier while spanning the whole range of the lipophilicity scale, from the strongly hydrophilic piracetam to highly lipophilic compounds like aniracetam (see Table 2).

We will first examine the oldest of the racetams, i.e., piracetam, immediately followed by some of its analogues (see Fig. 3 for structures marked in bold), which do not fit readily under any of the following subheadings.

2.1. Piracetam

2.1.1. Chemical, bibliographic and historical data

Synonyms: 2-pyrrolidoneacetamide, 2-pyrrolidinoneacetamide (2).

Drug codes: UCB 6215, CI-871.

CAS RN (number of refs. 1967–Dec. 26, 1992): [7491–74–9] (699 refs.).

Molecular formula: $C_6H_{10}N_2O_2$.

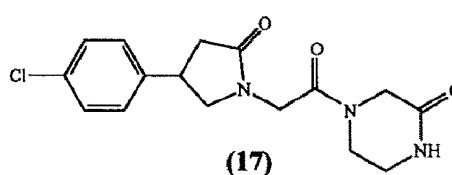
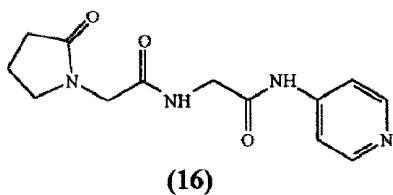
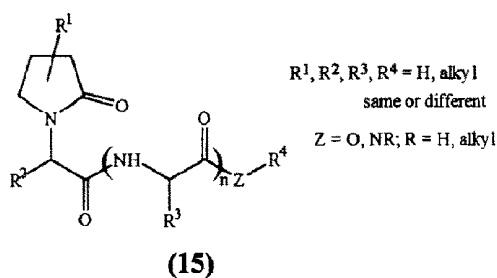
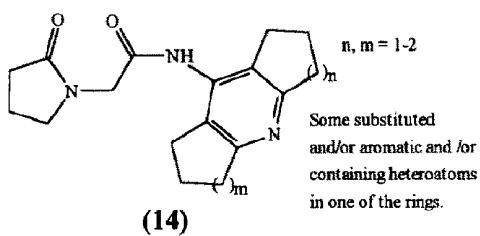
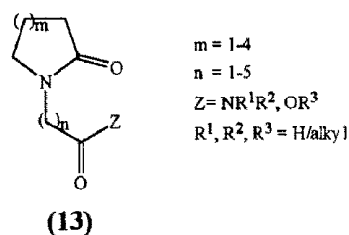
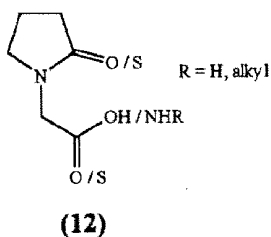
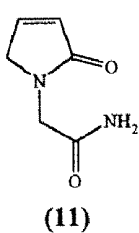
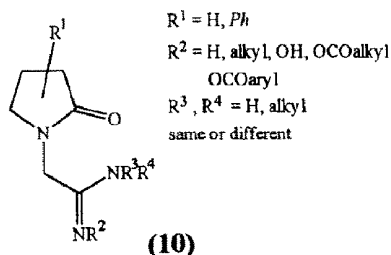
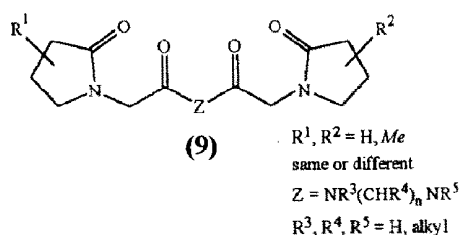


Table 2

Calculated^A *n*-octanol / water distribution coefficients (*P*)

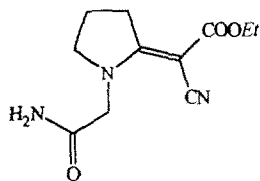
A From Craig⁵² except for OPPA.

B 5-Oxo-2-pyrrolidinepropanoic acid (OPPA), the sole metabolite of rolziracetam. Calculated at pH = 7 (ref. 23).

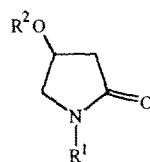
C Nebracetam = 3-benzylaminomethyl-2-pyrrolidone.

D It is not stated whether pramiracetam is ionised, but judged by its high lipophilicity it must be the unionised form.

Compound	log <i>P</i>	% in <i>n</i> -octanol	% in water
OPPA ^B	-4.07	< 0.1	> 99.9
Piracetam	-1.49	3.1	96.9
Oxiracetam	-1.35	4.3	95.7
Etiracetam	-0.65	18.3	81.7
Nebracetam ^C	-0.33	31.9	68.1
Rolziracetam	+0.46	74.3	25.7
Aniracetam	+0.70	83.4	16.6
Pramiracetam ^D	+0.76	85.2	14.8



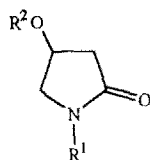
(18)



R¹ = Et, allyl, CH₂CCH, CH₂COOEt, CH₂CONH₂,
CH₂CH₂CONH₂, CONHEt, CH(allyl)CONH₂

R² = H, Me, allyl, Ac, benzoyl, all with (±)-configuration

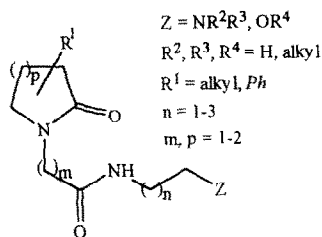
(19)



R¹ = H, Ac, CH₂COOH, CH₂COOEt, CH₂CONH₂,
CH₂CH₂CONH₂

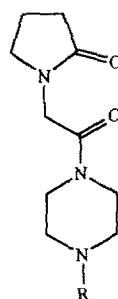
R² = H, allyl, Ac, benzoyl, all with (±)-configuration

(20)



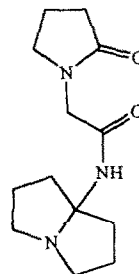
Z = NR²R³, OR⁴
R², R³, R⁴ = H, alkyl
R¹ = alkyl, Ph
n = 1-3
m, p = 1-2

(21)



R = H, alkyl, aryl,
COalkyl, COOalkyl

(22)



(23)

Mol. wt.: 142.15 g/mol.

Martindale ID: 13124-x.

Beilstein cit.: V 21/6, p. 360.

First reported: for treatment of motion sickness in 1966 (refs. 365,367) and 1967 (ref. 99).

Discovery of effects on memory: spinal cord fixation experiments in 1968 (ref. 219) and 1971 (ref. 96), protection against hypoxia-induced amnesia in 1971 (ref. 98) and enhancement of acquisition in passive avoidance experiments with rats in 1971 (ref. 395).

Preparation: refs. 62, 66, 171, 365, 367.

Physical data (melting points): m.p. 145–147°C (from isopropanol)⁶², m.p. 146–149°C (from isopropanol)⁶², m.p. 148–150°C (from isopropanol)⁶², m.p. 151–152°C

Fig. 3 (continued).

(ref. 66), m.p. 151–152°C (ref. 171), m.p. 151.5–152.5°C (ref. 365), m.p. 151.5–152.5°C (ref. 367).

LD₅₀: > 8 g/kg i.v. (rats), > 10 g/kg p.o. (rats, dogs, mice)⁹⁴.

2.1.2. Clinical findings

There exist in the literature at least six reviews which summarise the clinical merits of piracetam^{83,94,97,236,345,378}.

In general, piracetam seems to be effective in patients with mild to moderate dementia (see, e.g., Herrmann et al.¹²³), while it has also been shown that piracetam can be effective in patients suffering from Alzheimer's disease^{272,253}, with an EEG pattern change corresponding to an increase in vigilance²⁷².

Piracetam intensifies the anticonvulsive effect of antiepileptics^{119,215,216,255} and has been shown to be

effective in parkinsonism and in the psychotic state of schizophrenics¹⁴⁶.

Finally, treatment with piracetam has led to some improvement in dyslexia^{3,181} (for a review, see Wilsher³⁹⁰ and Dimond⁶¹).

Piracetam is well tolerated and without serious side effects in man (see, e.g., Coper and Herrmann⁴⁹).

2.1.3. Pharmacokinetics

Piracetam is absorbed very well after p.o. administration, with a bioavailability of almost 100% and reaches peak plasma levels (about 50 μg/ml plasma, corresponding to a total concentration (bound and free) of 350 μM) 30–40 min after a 2 g p.o. dose in humans¹⁰³. After a 800 mg p.o. dose to humans the peak plasma concentration is 18 μg/ml (127 μM)³⁴⁶. In the rat the corresponding plasma concentration

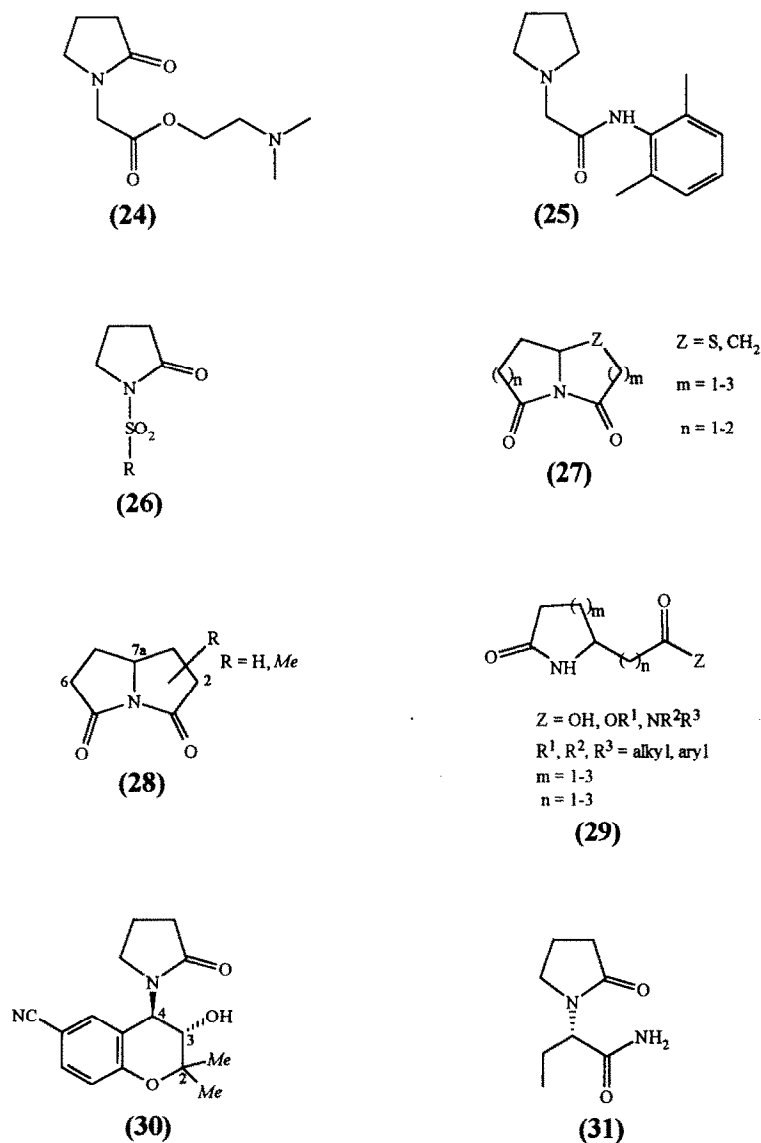


Fig. 3 (continued).

after a 300 mg/kg orally administered dose is about 180 $\mu\text{g/ml}$ (1.3 mM)¹⁰³.

Piracetam is excreted practically unchanged in the urine and completely eliminated after 30 h. The CNS half-life (7.7 h) is greater than the plasma half-life (5 h), after a 2 g p.o. dose to humans, resulting in some accumulation in the brain with time¹⁰³.

Piracetam crosses the blood–brain barrier slowly because of its high hydrophilicity (see Table II) and reaches peak CSF levels (about 10 $\mu\text{g/ml}$ CSF, corresponding to a total concentration (bound and free) of 70 μM) 3 h after a 1 g i.v. dose³⁵.

A determination of the protein bound fraction of piracetam would be of benefit in the determination of the maximal effective dose to be administered.

2.1.4. Antiamnesic and memory-enhancing properties of piracetam

The anti-amnesic and memory-enhancing properties of piracetam have been demonstrated in numerous studies with animals (see tables in refs. 83, 319, 378 or discussions in refs. 214, 230, 231, 259, 346 for a summary).

2.1.5. Interaction with γ -aminobutyric acid neurotransmission

Receptor binding studies show that piracetam has no significant effect on GABA receptors, does not affect the synaptosomal uptake of GABA (18% inhibition at 10 mM)^{20, 214} and does not affect GABA levels in either brain or plasma⁹³.

2.1.6. Interaction with glutamate neurotransmission

Bering and Müller²⁰ suggest that piracetam could accomplish some of its effects through binding to glutamate receptors, since the concentration of piracetam should be in the region of 0.1–1 mM (after 1 g i.v., man). According to Gobert¹⁰³, however, the peak CSF concentration in humans is rather 0.07 mM (after 1 g i.v., man), a factor of 260 less than the concentration needed (without even considering that some of the piracetam may be bound to plasma constituents) for reaching the IC_{50} for glutamate displacement. Bering and Müller²⁰ also suggest that this may explain why so high doses must be used in order to observe an effect.

Micromolar amounts of piracetam enhance the efficacy, but not the potency of AMPA-induced calcium influx in cerebellar granule cells, an effect which persists in the presence of the voltage sensitive L-type³⁵⁹ calcium channel blocker nifedipine⁴⁸.

The AMPA receptor-associated ion channel is not permeable to Ca^{2+} , but it has been shown that the AMPA and kainate receptor activation causes an increase in intracellular free (Ca^{2+}) by calcium influx, which is partly sensitive to the L-type³⁵⁹ calcium chan-

nel blocker verapamil (40% reduction in calcium influx by verapamil channel blockade)⁷².

NMDA receptor activation increases only partly the intracellular free calcium concentration by calcium influx and causes also a co-mobilisation of calcium from intracellular stores, whereas metabotropic glutamate receptor activation causes the increase in intracellular free (Ca^{2+}) solely by intracellular calcium mobilisation⁷².

The remaining part of the AMPA-induced calcium influx (verapamil insensitive) could be due to a co-influx through N-type (or T-type) calcium channels, supported by observations like those of Keith et al.¹⁵² who showed that some of the excitatory amino acid induced release of [³H]NA is caused by influx of calcium through N-type calcium channels.

The potentiated increase in AMPA-induced calcium influx caused by piracetam should therefore be a potentiation of the verapamil insensitive calcium influx and, if the increase is through N-type calcium channels, it should be blocked by ω -conotoxin³⁶⁰. Copani et al.⁴⁸ have also suggested an increase in the intracellular free calcium concentration by means of $\text{Na}^+/\text{Ca}^{2+}$ antiport activation.

Piracetam also increases the maximal density of specific binding sites for [³H]AMPA in synaptic membranes from rat cortex⁴⁸. The authors suggest that this is due to recruitment of a subset of AMPA receptors which do not normally contribute to synaptic transmission.

A potentiation of ibotenate and glutamate-induced inositol monophosphate formation by chronic treatment of rats with piracetam (400 mg/kg i.p. 15 days) is observed in 16-months-old rats, but not in 2-months-old rats. No change in the number or affinity of the recognition sites for [³H]glutamate was observed, but the authors suggest that an increased coupling between glutamate receptors and phospholipase C should be responsible for the observed effects³⁷. Another possibility would be activation of phospholipase C by an increased concentration of intracellular free calcium.

Sharma and Kulkarni³²⁵ have shown that MK-801, an NMDA channel blocker, inhibits some of the memory improving properties of piracetam (150 mg/kg i.p., rats/mice), possibly due to inhibition of LTP induction, which seems to be involved in the memory process. The AChE inhibitor physostigmine reverses both scopolamine and MK-801 induced acquisition deficits, suggesting a cooperation between the muscarinic and the glutamatergic neurotransmission³²⁵.

A potentiation of response to glutamate and aspartate through the glycine site of the NMDA receptor by piracetam has been reported in a Russian study¹⁵⁶. Another study showed that piracetam and aniracetam at 100 μM do not affect MK-801 binding in the presence of NMDA and glycine¹⁵¹. If piracetam acts on the

glycine regulatory site of the NMDA receptor¹⁵⁶ the presence of glycine could obscure the potentiating effect of piracetam.

It is known¹⁸⁶ that introduction of small substituents in the α -position of glycine reduces its agonist activity and that the introduction of larger substituents generates antagonists (some, however, with partial agonist activity). Piracetam, a 2-pyrrolidinone derivative, could therefore, if of any activity at the glycine modulatory site of the NMDA receptor, be expected to exhibit antagonist properties, just like the potent 2-pyrrolidinone derivative HA-966 ((*R*)-*N*-hydroxy-3-amino-2-pyrrolidinone).

Unfortunately, in the study described above by Kaneko et al.¹⁵¹, piracetam and aniracetam were not tested for their effects on AMPA and kainate responses as were other compounds. It would be reasonable to expect a potentiation of the AMPA response if piracetam somehow acts as an activator as mentioned above.

A Chinese study⁴⁰⁷ supports the involvement of the glutamatergic system in the anti-amnesic action of piracetam, since the memory improving properties of piracetam can be inhibited by ketamine, an NMDA channel blocker. Furthermore, piracetam (500 mg/kg i.p.) decreases mouse brain glutamate content and the glutamate/GABA ratio, indicating an increase in excitatory activity. Confirming this is the fact that piracetam (1–10 μ M) potentiates K^+ -induced release of glutamate from rat hippocampal slices¹⁹².

Finally, piracetam does not inhibit the synaptosomal uptake of glutamate (24% inhibition at 20 mM)²⁰.

2.1.7. Interaction with acetylcholine neurotransmission

See Pepeu and Spignoli²⁵⁹ for a review of piracetam-like nootropics and a cholinergic mechanism.

Piracetam ameliorates or reverses the amnesic effect^{42,179,271,376} (see also refs. 83 and 319 for other references) and the decrease in glucose utilisation induced by the muscarinic antagonist scopolamine. This could indicate a reestablishment of cholinergic activity.

Piracetam's effect on high-affinity choline uptake (HACU) is somewhat ambiguous. Low doses of piracetam (3–100 mg/kg i.p., rats) increase HACU activity in hippocampal synaptosomes, whereas higher doses do not (300–500 mg/kg i.p., rats)³¹⁹. Spignoli et al.³³⁵ observed a transient increase in HACU activity in rat hippocampus at 300 mg/kg i.p. and an increase in HACU has also been observed by Pedata et al. (see references in Vernon et al.³⁷⁸), but other studies — (300 mg/kg i.p., rat, cortex/hippocampus)⁷⁹, (100 mg/kg chronic, rats, hippocampus)²⁵⁷, (100, 500 mg/kg i.p., rat hippocampus)³²⁶ — failed to confirm this finding.

Piracetam attenuates amnesia, but potentiates ACh depletion induced by hemicholinium-3 (refs. 73,335)

and Wurtman et al.³⁹⁹ observed a piracetam-induced decrease in the ACh content without change in the choline levels in rat hippocampus, indicating an increase in ACh release. In other studies^{336,337} piracetam did not change the steady state levels of ACh.

Piracetam antagonises lethality due to hemicholinium-3 (refs. 116) and neuromuscular blockade in the cat caused by *d*-tubocurarine²⁷⁶. Pilch and Müller²⁷⁶ suggest that this is an effect of a stimulation of ACh synthesis by piracetam acting on HACU.

Electroconvulsive shock (ECS)-induced decrease in the ACh content in cortex and hippocampus remained unaffected by piracetam³³⁷, but the amnesia was attenuated³⁵⁵.

Chronic treatment with piracetam (500 mg/kg 1–2 weeks p.o., rats) causes an increase in the muscarinic receptor number and in the affinity for ligands. These effects were observed in both young and old rats³⁷⁹. Pilch and Müller²⁷⁶ only observed an effect on the density of the cortical muscarinic receptors in aged rats.

A restoration of age related deficits of the central muscarinic cholinergic receptor function is also observed in mice treated with piracetam (500 mg/kg p.o., chronic)³⁴². According to the authors³⁴² this is caused by a decrease in the number of receptors in the desensitised state.

Finally, piracetam did not change choline acetyltransferase (CAT) activity at 10–100 μ M as did oxiracetam²⁰³.

2.1.8. Interaction with noradrenaline / dopamine / 5-hydroxytryptamine neurotransmission

An increase in the firing rate of noradrenergic neurons is observed in the rat locus coeruleus after piracetam treatment²⁴⁵, and increases in NA turnover in the rat brain stem have been observed after piracetam treatment²⁶⁵. High doses of piracetam (600 mg/kg p.o., 5 days, rats) reverse amnesia induced by the dopamine β -hydroxylase inhibitor potassium ethyl-xanthogenate^{86,87}. Piracetam also increases HVA/DA^{257,288,300} and dopamine release³⁹⁸, indicating an increase in the turnover of DA, but does not affect the uptake of 5-HT²⁸⁶. Very high doses of piracetam (5 g/kg i.p. over 14 days) inhibit exploratory behaviour in rats and also modify the content of NA, DA and 5-HT in different areas of the rat brain⁶⁸.

Piracetam reverses the age related decrease in biogenic amine content in old rats³³⁹.

Piracetam (600 mg/kg daily for 30 days) causes a 20% decrease in the activity of MAO in vivo. In vitro piracetam at 100 mM inhibited MAO²⁹⁰. Another study³³⁸ observed an inhibition of MAO_A and MAO_B in the striatum, but a stimulation in the hypothalamus. The overall effect on MAO was stimulation. A recent Russian study³¹ showed that concentrations of 0.1–1

mM are needed to stimulate MAO_A and MAO_B *in vitro*.

2.1.9. Interaction with steroids

Steroids are known to exert both positive and negative effects on memory²⁰⁶, perhaps by influencing protein synthesis or gene expression.

Adrenalectomy, inhibition of steroid biosynthesis by aminoglutethimide and blockade of aldosterone receptors by epoxymexrenone completely suppress the memory improving effect of piracetam. This implies that aldosterone receptors might be involved in the mechanism for piracetam and since epoxymexrenone does not suppress improvements by cholinomimetics, this suggests different modes of action for the cholinomimetics and the 2-oxopyrrolidineacetamide nootropics. Neither adrenalectomy nor aminoglutethimide or epoxymexrenone treatment alone caused any significant decrease in the learning ability of the rats. Only the beneficial effects of piracetam were suppressed^{206,211,213}. Administration of aldosterone or corticosterone to adrenalectomised rats restores the memory-enhancing effects of piracetam-like nootropics²¹², further confirming the importance of steroids in the mechanism of action of these nootropics.

High doses of aldosterone or corticosterone abolish the memory improving effects of both piracetam-like nootropics and cholinomimetics, but not the ability to learn²¹⁰. The authors therefore suggest that the high levels of steroids in Alzheimer patients may be responsible for the lack of beneficial effects of the piracetam-like nootropics.

Corticosterone and aldosterone exert negative feedback on ACTH secretion and ACTH peptide analogues have shown to improve memory in aged monkeys³⁷⁵, see also Frösl and Maître⁷⁴. Häusler et al.¹¹⁸ were unable to observe significant changes in the ACTH level after adrenalectomy, due to large variations of plasma ACTH concentrations.

2.1.10. Interaction with protein / lipid metabolism

Cycloheximide, a protein synthesis inhibitor, induces amnesia which is ameliorated by piracetam⁵³ and piracetam enhances both phospholipid and protein synthesis^{93,258,293} (see Davis and Squire⁵⁶ for a review on protein synthesis and memory).

The membrane fluidity decrease with age or induced by scopolamine is reversed by piracetam and this has been suggested to be caused by its normalising effects on the lipid content of the synaptosomes^{29,362} (see also Müller²²¹).

Piracetam exerts a non-specific stabilising effect on lipid membranes in stress situations where an increase in lipid peroxidation is seen. This effect could not be directly related to specific enzymes²⁹⁸.

Inhibition of the T-cell component of the immune

system is accompanied by an increase in lipid peroxidation. Piracetam favours the normalisation of immunity by affecting lipid peroxidation³⁷⁷.

2.1.11. Other effects

Piracetam activates brain adenylate kinase²³³ and produces a significant increase in the cerebral glucose utilisation in the whole brain of rats¹¹². Also in man an increase in glucose utilisation can be observed¹²¹; furthermore it has been observed that piracetam (1 g/kg) enhances the compensatory capacity of mitochondria during the development of traumatic edema of the brain in rats²⁴¹ and the synthesis or turnover of cytochrome *b*₅ has been reported to be increased by piracetam³⁹². Piracetam has also been observed to increase the blood flow in some situations, probably because of decreased platelet aggregation, enhancement of red blood cell deformability and reduction in adherence of damaged erythrocytes to endothelial cells (see discussion in Vernon and Sorokin³⁷⁸). Results like these have often led to the classification of the piracetam-like nootropics as cerebral metabolic enhancers.

High doses of piracetam (600 mg/kg daily for 30 days, rats) cause a 20% decrease in the activity of Na⁺/K⁺-ATPase *in vivo*. *In vitro* piracetam did not affect Na⁺/K⁺-ATPase at 100 mM²⁹⁰.

Piracetam increases the survival rate of rats subjected to hypoxia⁷⁵ and decreases the time of recovery from hypoxia and also the time required to normalise the EEG³⁷⁸. Piracetam, combined with other drugs such as, e.g., vitamin B₆ and flunarizine, has been analysed for its effect on the EEG pattern and shown to possess an enhanced antihypoxic effect compared to single drug treatment^{237,363}. What may be very important in support of our hypothesis concerning the mechanism of action of these compounds (see subsection 3.2.2) is the fact that it has been suggested that the beneficial effects of piracetam in hypoxia experiments are due to an alleviation of hypoxia-induced memory retrieval deficit, rather than due to protection against hypoxic brain cell injury⁴¹.

Piracetam also ameliorates the biochemical effects of alcohol withdrawal and thus functions as a protective substance²⁵⁴. Rats treated prenatally with alcohol show pronounced memory deficits which can be ameliorated with piracetam. The benzodiazepine agonist diazepam, on the other hand, leads to further impairment²⁶⁷.

Finally, piracetam has been shown to enhance synaptosomal phospholipase A activity³³³ and to inhibit cortical release of the amnesic²⁷⁰ amino acid L-proline²³².

2.2. Analogues of piracetam

Oxiracetam, pramiracetam, nefiracetam and etiracetam may, of course, all be considered as close ana-

logues of piracetam as may their derivatives, but since these compounds have been the subject of much interest they are treated separately.

Under this subheading we will treat compounds chemically related to piracetam which cannot be regarded as close analogues of the above-mentioned special derivatives.

2.2.1. Substituted 2-oxopyrrolidineacetamides

Piracetam and a number of *N*-substituted 2-oxopyrrolidineacetamide derivatives were originally prepared as agents for the treatment of motion sickness and as antiemetics^{229,365,367}.

N-Phenyl substitution of piracetam, which may be considered as a close analogue of nefiracetam, leads to a compound with psychotropic and depressant activity²⁴⁸.

4-Phenyl substitution of piracetam leads to a compound with psychostimulatory activity at low doses and behaviour inhibitory activity at high doses²⁴. 4-Phenylpiracetam has a higher potency than its hydrazide¹⁰¹. The *N*-adamantyl derivative of 4-phenylpiracetam is inactive¹⁰¹. Other *N*-substituted 4-phenyl analogues of piracetam have been tested for effects on GABA uptake, but were all of low intrinsic activity and potency¹⁵⁷.

Different *duplex* compounds (**9**) connected through the acetamide group have been prepared²⁶. Of these dupracetam (*Z* = NHH) has proved to antagonise the lethal effect of hemicholinium-3 (30 mg/kg *i.p.*, mice)¹¹⁶.

The kinetics of dupracetam hydrolysis has been determined³²⁹. In neutral media dupracetam is resistant to 30 h of heating, whereas it hydrolyses to 2-oxopyrrolidineacetic acid hydrazide and 2-oxopyrrolidineacetic acid upon 1.5 h boiling in acidic media. Dupracetam is thus stable to uncatalysed hydrolysis, but whether dupracetam is subject to reduction by reductases *in vivo*, which would generate piracetam, is unknown.

Other substituted 2-oxopyrrolidineacetamides have been prepared and tested for nootropic activity^{22,58,100,183,185,246,247,277,294,322,341,343,383} (see also Gouliaev et al.¹⁰⁶).

2.2.2. 2-Oxopyrrolidineacetic acid, its hydrazide and ester derivatives

α -Phenoxy-2-oxopyrrolidineacetic acid has been tested for analgesic activity³⁸⁷.

Hydrazides and esters of piracetam nootropics have been prepared and screened for nootropic activity²⁴⁸. It seems that psychotropic and stimulant activities are associated with the hydrazides as in the case of piracetam.

drazides and esters have been prepared and tested^{172,173,174,294} (see also Gouliaev et al.¹⁰⁶).

2.2.3. Amidines and amidoximes of piracetam

Amidine^{340,384} and amidoxime¹⁰² analogues (**10**) of piracetam, some of which show nootropic activity similar to piracetam, have been prepared.

2.2.4. 2-Oxopyrroline derivatives

The 3-pyrroline analogue (**11**) of piracetam as well as other pyrroline derivatives have been prepared²⁷⁵.

Benzo[*d*]piracetam has been synthesised, but no data concerning nootropic activity are available from Valenta et al.³⁶⁸

2.2.5. Thiocarbonyl analogues

A number of thiocarbonyl analogues (**12**) of piracetam derivatives have been prepared^{109,110,111,147,148,165}. The thiocarbonyl analogues all show antihypoxic, anti-convulsant and psychotropic effects at lower doses than piracetam, perhaps because of better diffusion across the blood–brain barrier.

Biotransformation studies have been carried out. The dithiocarbonyl analogue of piracetam yields piracetam on biotransformation or undergoes intramolecular cycloaddition, elimination of H₂S and reductive loss of sulfur which finally leads to 5,6-dihydro-7*H*-pyrrolo[1,2-*a*]imidazole. Elimination of H₂S, yielding the corresponding nitrile, has also been observed. None of the metabolites surpass the antihypoxic activity of the parent compound¹⁶⁵.

2.2.6. Cyclo- and side chain-modified homologues

Ring or side-chain-expanded analogues of 2-oxopyrrolidineacetamides have been prepared^{15,131,277,281,294,295} (**13**).

It seems that the 5-membered ring is crucial for the psychotropic effects although the 6-membered ring compounds also show some effect²⁸¹.

2.2.7. Tacrine analogues

A considerable number of close analogues containing substituents in the amide group of piracetam, which may be related to the AChE inhibitor tacrine, have been prepared (**14**). An increase in the activity of HACU at concentrations of 10 nM and an improvement in brain function (13% at 100 nM) in rats^{218,240} have been reported. According to two Russian studies^{29,30} the anti-amnesic effect of tacrine and amiridine (an analogue) is not due to their effects on AChE, since they show anti-amnesic effects at 0.1 mg/kg, a concentration in which they do not affect AChE.

2.2.8. Peptide analogues

Peptide-like compounds (**15**) have been shown to be

Some of the different peptide analogues of piracetam such as, e.g., *N*-carbamoylmethylprolinamide have been prepared in order to test the possibility of the existence in the brain of receptors for piracetam-like nootropics. SAR investigations support this hypothesis and suggest that the endogenous ligands should resemble pyroglutamate (agonist) or proline (antagonist). Furthermore the *D*-form of pyroglutamylglycineamide causes amnesia while the *L*-form has anti-amnesic properties¹¹⁴. *D*-Pyroglutamate itself, however, is known to be anti-amnesic whereas *L*-proline has amnesic properties^{114,270,334}.

2.2.9. Prolylleucylglycine analogues

3-Prolylamino-2-oxopyrrolidineacetamide, a rigid prolylleucylglycine (PLG) analogue, has been prepared as part of structure–activity study and shown to enhance [³H]ADTN (2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene, a dopamine agonist) binding to membranes and/or modulate dopamine receptor supersensitivity^{145,291,370,406}. Furthermore, this compound inhibits the GTP-induced conversion of the dopamine D₂ receptor from its high affinity to a low-affinity state²⁰¹. The dopamine D₂, but not the D₁ receptors, in the caudate nucleus seem to play a specialised role in the memory process¹³⁷.

2.2.10. Thyrotropin-releasing hormone analogues and prolylendopeptidase inhibitors

Thyrotropin-releasing hormone (TRH) is known to improve memory and scopolamine-induced deficits in volunteers^{27,205}. TRH and other neuropeptides like, e.g., vasopressin are degraded by prolylendopeptidase (PEP) and inhibitors of PEP should therefore possess anti-amnesic properties.

Pramiracetam, aniracetam and piracetam inhibit PEP^{50,403}. They have, together with other analogues of piracetam, been subjected to a QSAR study⁵⁰.

2.2.11. Renin inhibitors

Compounds containing the 2-oxopyrrolidineacetic acid or amide moiety, but not necessarily close analogues of piracetam, have been tested as renin inhibitors^{57,242,350,351,389}.

2.2.12. Angiotensin-converting enzyme inhibitors

Different compounds containing the 2-oxopyrrolidineacetic acid moiety have been investigated as angiotensin-converting enzyme (ACE) inhibitors^{153,323,352–354}. Inhibition of ACE appears to cause improvements of cognitive performance (for a review, see Pavia et al.²⁵⁶), although this could be due to some of the structural similarities between the ACE inhibitors and the piracetam-like nootropics and may therefore not be due to inhibition of ACE nor that of renin, but the possibility can, of course, not be ruled out.

2.2.13. Other analogues of piracetam

In this section we will treat the remaining 2-oxopyrrolidineacetamide compounds which have been tested for nootropic activity. Compounds which have been prepared, but not subjected to screening tests, will not be cited.

Compound (16) improves passive avoidance by 39% at 100 mg/kg p.o. in rats²³⁸. Analogues of (16) have also been prepared. This compound is a rather complex drug because it is a combination of piracetam, glycine (which may play some role in the early phase of memory processing after a passive avoidance task²⁰⁹) and 4-aminopyridine which is known as a non-selective potassium channel blocker³⁶¹. Blocking of the potassium channels with 4-aminopyridine has been shown to cause increased release of ACh through delay of repolarisation³²⁰. 3,4-Diaminopyridine (0.1 mg/kg i.p., rats) affects sodium-dependent choline uptake, but 4-aminopyridine (0.01–3.0 mg/kg i.p., rats) does not³²⁶. For a blockade of potassium channels to occur 4-aminopyridine must be released by hydrolysis of the amide bond in (16).

Analogues of CGP25248, cebracetam (17) have been prepared and shown to possess a high activity in the Mondadori–Waser passive avoidance test at 3 mg/kg i.p. in mice⁴³. Opening of the pyrrolidinone ring gives a compound containing the 4-amino-3-(4-chlorophenyl)butyric acid moiety. (*R*)-4-Amino-3-(4-chlorophenyl)butyric acid, also known as (*R*)-baclofen, is a GABA_B agonist, whereas the (*S*)-form is inactive¹⁶². GABA_B receptors are probably involved in the release of other neurotransmitters¹⁶⁰ and regulate induction of LTP⁵⁵.

Finally, (18) has been shown to be effective as anticonvulsant and antihypoxic agent at doses lower than those necessary with piracetam and its thiocarbonyl analogues¹⁴⁷.

2.3. Oxiracetam

2.3.1. Chemical, bibliographic and historical data

Synonyms: 4-hydroxy-2-oxo-1-pyrrolidineacetamide, hydroxypiracetam (3).

Drug codes: (±)-form: CT-848, ISF 2522.

CAS RN (number of refs. 1967–Dec. 26, 1992): (*R*)-form: [68252–28–8] (8 refs.), (*S*)-form: [88929–35–5] (4 refs.), (±)-form: [68567–97–5] (4 refs.), unspecified form: [62613–82–5] (106 refs.).

Molecular formula: C₆H₁₀N₂O₃.

Mol. wt.: 158.16 g/mol.

Martindale ID: 16922-v.

Beilstein cit.: V 21/12, p. 19.

First reported/first reported as nootropic: unspecified form: 1977 (ref. 274), (±)-form: 1978 (ref. 217), (*R*)-form: 1978 (ref. 15), (*S*)-form: 1984 (ref. 13).

Preparation: refs. 15, 273 and 274

Spectroscopic data: ref. 273

Physical data (melting points): (*R*)-form: m.p. 135–136°C (from acetone/water), $[\alpha]_D = +36.2^\circ$ ($c = 1$, water); (*S*)-form: m.p. 135–136°C (from acetone/water), $[\alpha]_D = -36.2^\circ$ ($c = 1$, water); (\pm)-form: m.p.

Table 3

*Effect of oxiracetam on various types of chemically / physically induced amnesia, lethality and recovery after insult**Measurement:* Passive, passive avoidance test; active, active avoidance test; lethality, lethality test; recovery, recovery after insult; maze, different maze tests; learning, different learning tests with or without physical or chemical insult (more than one test, passive and/or active avoidance/maze).*Administration form:* A, administered prior to the learning test/insult; B, administered immediately after the learning test/insult; C, administered before the retention test; D, More than one treatment prior to the learning/retention test or insult.

* = Concentrations in mg/kg unless otherwise indicated.

Stereochemistry: S, (*S*)-form; R, (*R*)-form*Effect of treatment:* NS, no significant effect; AA, attenuation of drug induced amnesia; RE, reversal of drug induced amnesia; I, reduced recovery time after insult or improvement in performance.

Treatment in mg/kg*	Measure	Species	[oxiracetam] in mg/kg*	Effect	Refs.
<i>None:</i>					
	Maze	Rats	30, 100 i.p.	NS	189
	Learning	Rats	10 i.p.	I	164
	Learning	Rats	10–60 i.p./p.o.	I	14
	Learning	Mice		I	371
	Active	Mice	25, 50 i.p. ^D	I	312
	Active	Mice	50	I	310
	Active	Mice	30	I	166
	Active	Mice	50 ^D	NS	308
	Active	Mice	25, 50 ^D	I	309
	Passive	Mice	50	NS	310
	Passive	Mice	16–475 i.p. ^A	NS	376
<i>Modulation of Glu neurotransmission:</i>					
<i>AP-5</i>					
6 mg/2 ml i.c.v. ^A	Passive	Rats	50–500 s.c. ^A	RE	250
<i>Modulation of ACh neurotransmission:</i>					
<i>Scopolamine</i>					
3 i.p. ^A	Passive	Mice	16–474 i.p. ^D	NS	376
0.63–0.66 s.c. ^A	Passive	Rats	50, 100 s.c.	RE	91
		Rats	2–20 nM i.c.v.	RE	280
0.6 s.c. ^A	Passive	Rats	50, 100 s.c. ^A	RE	260
	Passive	Rats	50, 100 i.p. ^A	AA	336
	Passive	Rats	300 s.c. ^A	NS	260
0.2 s.c. ^A	Maze	Rats	30 s.c. ^A	RE	260
	Maze	Rats	100 s.c. ^A	NS	260
	Maze	Rats	30 i.p.	RE	189
<i>Nicotine</i>					
1 i.p. ^A	Active	Mice	50 i.p. ^D	RE	310
<i>Mecamylamine</i>					
2.5, 5 i.p.	Active	Mice	50, 100 i.p.	AA	311
	Passive	Mice	50, 100 i.p.	NS	311
<i>Hemicholinium-3</i>					
149 i.p. ^A (= LD ₅₀)	Lethality	Mice	300 i.p. ^A	RE	116
15 µg i.c.v.	Active	Rats	100 i.p.	RE	335
<i>Blockade of Ca²⁺ channels:</i>					
<i>Diltiazem</i>					
10 ^A	Passive	Rats	10 ^B	RE	25
<i>ECS:</i>					
	Passive	Mice		AA	38
	Passive	Rats		RE	229
	Passive	Rats	100, 300 i.p. ^A	RE	337
	Learning	Rats	30, 100 i.p.	AA	207
<i>Hypoxia:</i>					
	Recovery	Rats	100 i.v. ^B	I	155

165–168°C from (acetone/water)²⁷³, m.p. 160–162°C (ref. 15), m.p. 161–163°C (ref. 274).

LD₅₀: > 10 g/kg p.o. (mice, rats and dogs), > 500 mg/kg i.v. (dogs)²³⁴.

2.3.2. Clinical findings

Oxiracetam has been investigated for potential use in different forms of dementia and is reported to be well tolerated and without any side effects^{134,204,252,303,374,380,381}.

The use of oxiracetam in patients suffering from Alzheimer's dementia (800 mg p.o. b.i.d. for 3 months), epilepsy (800 mg p.o. t.i.d.) or long-term exposure to organic solvents (1.2 g p.o. b.i.d. for 3 months) has not met with convincing success^{4,67,81,126}.

On the other hand, many studies report beneficial effects on logical performance, attention/concentration, memory and orientation after chronic use of oxiracetam (800–2400 mg p.o. once or twice a day for 1–6 months) in dementia of mild to moderate degree^{17,134,191,204,252,381}. Also in elderly patients⁸², patients suffering from exogenic post-concussion syndrome²⁹⁹ and other dementias or organic brain syndromes^{64,303} has there been an improvement after treatment with oxiracetam. Oxiracetam seems more effective than the prototype nootropic piracetam⁸² (for a review on clinical results see Maina et al.¹⁹¹).

2.3.3. Pharmacokinetics

Methods for determining oxiracetam in plasma and urine have been developed^{178,382}. It has been shown that oxiracetam is well absorbed from the GI after p.o. administration, with a bioavailability of 68–82%^{263/56%}¹¹³ and mainly excreted by renal clearance^{113,263,264}. As much as 84% is recovered as unchanged oxiracetam in the urine after a single 800 mg p.o. dose. The peak level of oxiracetam is reached within 1–3 h after a single 800 mg p.o. or 2000 mg p.o. dose, with a serum concentration of 19–31 µg/ml (corresponding to a total concentration (bound and free) of 120–196 µM)²⁶⁴ and 40 µg/ml (250 µM)²⁶³, respectively. The terminal plasma half-life after a 800 mg p.o. dose in healthy people is about 8 h, whereas patients suffering from renal impairment may exhibit long half-lives of 10–68 h^{176,177}. Oxiracetam does, to some extent, penetrate the BBB^{113,251} and a concentration of 2.8 µg/ml a total concentration (bound and free) of 18 µM, corresponding to 5.3% of the serum concentration, is reached 1 h after a single 2 g i.v. dose²⁵¹. This contradicts a study by Mondadori and Petschke²¹³ who could not observe any significant amounts of tritium in the rat brain by autoradiography after a 10 mg/kg i.v. dose of [³H]oxiracetam.

The plasma steady-state concentration of oxiracetam, after administration of 800 mg b.i.d. to persons with a creatine clearance ranging from 9 to 95 ml/min,

has been estimated to range from 530 µM to 60 µM (total concentration: bound and free)¹⁷⁷.

Oxiracetam is found with the highest concentrations in the septum, followed by the hippocampus, the cerebral cortex and with the lowest concentration in the striatum after a 200 mg/kg p.o. administration to rats. A similar distribution pattern is observed after i.c.v. administration^{280,347}.

2.3.4. Antiamnesic and memory-enhancing properties of oxiracetam

Table 3 summarises selected antiamnesic and memory-enhancing properties of oxiracetam (see the text for discussion).

2.3.5. Interaction with glutamate neurotransmission

Treatment of rats with AP-5, an NMDA antagonist, prior to training impairs passive avoidance performance. This can be prevented by pretreatment with oxiracetam or D-pyroglytamic acid²⁵⁰. Oxiracetam (0.1–100 µM) provokes a concentration-dependent (maximum effect at 1 µM) prolonged increase in neurotransmission in the CA1 rat hippocampal region and application of AP-5 (50 µM), which prevents induction of LTP, blocks this effect of oxiracetam²⁸⁷. The effect of oxiracetam is dose-dependent, and oxiracetam in high concentrations (100 µM–1 mM) actually inhibits pyramidal neuronal excitability, diminishing the EPSP and causing a slight hyperpolarisation²⁴⁴. These results imply that NMDA receptors might be involved in the action of oxiracetam either directly or indirectly, but since it is also known that oxiracetam (10 nM–1 µM) increases the release of glutamate from depolarised rat hippocampal slices, but not the spontaneous release¹⁹², this finding could support an indirect mechanism. Further support of oxiracetam's stimulating actions on the glutamate receptor system stems from the result that pretreatment of rats with oxiracetam reverses the AP-7 (an NMDA antagonist)-induced increase in ACh content²⁷⁹. AP-7 is known to inhibit NMDA stimulated ACh release in vitro³³⁰.

Micromolar amounts of oxiracetam enhance the efficacy, but not the potency of AMPA-induced calcium influx in cerebellar granule cells, an effect which persists in the presence of the voltage sensitive L-type³⁵⁹ calcium channel blocker nifedipine. The effect exerted by oxiracetam was specific for signal transductions mediated by the AMPA sensitive glutamate receptor. Only AMPA, but not NMDA nor kainate-induced calcium influx was augmented (see also discussion in subsection 2.1.6). Furthermore, oxiracetam did not affect phosphoinositol turnover, indicating that it does not act on the metabotropic glutamate receptor⁴⁸.

Copani et al.⁴⁸ suggest that the oxiracetam-induced release of glutamate, is secondary to the selective potentiation of the AMPA response. The induced release

of glutamate could then be a result of retrograde messenger stimulation, for which arachidonic acid, nitric oxide or carbon monoxide seem to be likely candidates³²⁸.

Oxiracetam, like piracetam, increases the maximal density of specific binding sites for [³H]AMPA in synaptic membranes from rat cortex⁴⁸.

This may also support the hypothesis that the effect on NMDA receptors is indirect. Much seems to indicate a role of LTP in memory mechanisms and it is known that glutamate cannot induce LTP through NMDA receptors without concomitant activation of the acceptor cells via other receptors, among which the AMPA receptors seem to be good candidates³²⁸. Potentiation of the AMPA response would thus ease the induction of LTP.

2.3.6. Interaction with acetylcholine neurotransmission

Oxiracetam stimulates choline uptake into isolated hippocampal slices from spontaneously hypertensive rats with sodium chloride induced cerebrovascular lesions, which without oxiracetam display a decrease in both choline uptake and incorporation of choline in lipids²²⁸. Chronic treatment with oxiracetam (100 mg/kg i.p., rats) increases HACU activity^{257,335} with concomitant increase in ACh utilisation and without affecting the steady-state ACh level^{2,335}.

Reduction in ACh content and HACU activity can be achieved by physical interruption of corticostriatal pathways. The muscarinic agonist oxotremorine (0.8 mg/kg i.p., rats) and the dopaminergic agonist apomorphine (1 mg/kg i.p., rats), which normally increase the ACh content, could not restore HACU activity nor the ACh content. On the other hand, oxiracetam (100 mg/kg i.p., rats) restores HACU activity and also the normal activity of oxotremorine and apomorphine. The authors suggest that this should be due to an increase in choline availability⁴⁶.

In frontal cortically deafferented rats a decrease in the number of [³H]hemicholinium binding sites, but no change in affinity is observed. This decrease in the number of binding sites is reversed by oxiracetam, leaving the affinity unchanged⁷¹. Finally the lethal effect of hemicholinium-3 (30 mg/kg i.p., mice) is antagonised by oxiracetam (30–300 mg/kg i.p., mice)¹¹⁶.

Oxiracetam ameliorates/antagonises amnesia and the ACh depletion induced by ECS³³⁷ or scopolamine in the hippocampus and the frontal cortex^{91,189,260,336} in a bell-shaped dose-response manner. The rather high subcutaneous dose of 300 mg/kg oxiracetam administered to rats is ineffective²⁶⁰.

A direct injection into the lateral ventricles of the rat of 2–20 nmol oxiracetam, which corresponds to the estimated amount reaching the brain after 200 mg/kg p.o. or 100 mg/kg i.a. administration, reverses scopolamine (0.66 mg/kg s.c.)-induced amnesia²⁸⁰. The pe-

ripherally acting muscarinic antagonist methylscopolamine (0.2 mg/kg s.c., rat) does not decrease performance as observed with scopolamine (0.2 mg/kg s.c., rat), indicating centrally mediated effects of scopolamine on memory. Peripheral effects of methylscopolamine (0.63 mg/kg s.c., rat) can on the other hand also be induced by scopolamine (0.63 mg/kg s.c., rat). These effects remain unperturbed by oxiracetam¹⁸⁹.

The effects of a rather high concentration of scopolamine (3 mg/kg i.p., mice) could not be reversed by oxiracetam as they were by piracetam and etiracetam³⁷⁶. Lower doses of oxiracetam than of piracetam are normally sufficient to attenuate or reverse amnesia and observations like these could therefore indicate differential modes of action.

Oxiracetam potentiates the memory improvement, in mice, by secoverine, a presynaptic muscarinic blocker and combining the two in concentrations which by themselves are inactive results in a significant improvement of the performance in a passive avoidance task⁶.

Oxiracetam (50 mg/kg, i.p., rats) also acts synergistically with nicotine (0.5 mg/kg, i.p.) and reverses the inhibitory effect of higher concentrations of nicotine (1 mg/kg, i.p.) in an active avoidance test. It therefore seems reasonable to suppose that oxiracetam's main mechanism does not involve nicotinic receptor activation³¹⁰.

Mecamylamine (2.5–5 mg/kg i.p., mice), a nicotinic antagonist with preference for CNS located receptors, suppresses both passive and active avoidance learning in mice. Oxiracetam (50–100 mg/kg i.p., mice) prevents suppression of active avoidance learning, but not of passive avoidance. The authors suggest that the prevention of mecamylamine-induced suppression of active avoidance performance may indicate that central nicotinic mechanisms are involved in the improvement seen with this nootropic drug³¹¹. The previously mentioned results by Sansone et al.³¹⁰, however, only indicate an indirect action of oxiracetam on nicotinic receptor response.

Oxiracetam (10–100 μ M) enhances K⁺-induced ACh release from rat hippocampal slices and stimulates CAT, but does not affect the concentration curve for the displacement of [³H]QNB by the muscarinic agonist carbachol. Moreover oxiracetam alone does not affect [³H]QNB binding in cerebral cortex and hippocampus and changes neither K_d nor B_{max} for [³H]QNB binding after repeated treatment (100 or 500 mg/kg p.o.) of old rats. Finally, oxiracetam did not affect AChE activity in mouse brain homogenate. The authors suggest an enhancement of the presynaptic cholinergic function²⁰³.

A selective decrease in central noradrenergic and dopaminergic, but not 5-HT, pathways abolishes the beneficial effect of oxiracetam on scopolamine-induced amnesia and decreased ACh levels⁹¹.

2.3.7. Interaction with noradrenaline / dopamine neurotransmission

Oxiracetam (50 mg/kg i.p., 7 days, mice) acts synergistically with methamphetamine to effect an improvement of active avoidance without influencing the locomotor effects of methamphetamine. Oxiracetam alone gave no significant improvement. This could imply that for the improvement by oxiracetam to be possible some 'pre-alertness' must be present in this type of test³⁰⁸.

Treatment with oxiracetam (100 mg/kg, s.c., 5 days, rats) does not change the levels of DA and of the metabolite HVA²⁵⁷.

2.3.8. Interaction with calcium channels

Blockade of L-type calcium channels by dihydropyridines causes a reduction in memory retention when given prior to training, but not if administered after. Furthermore, a two-fold reduction in the density of L-type³⁵⁹ calcium channels is observed in rat cerebral cortex after treatment with the calcium channel blocker diltiazem. These effects can be completely reversed by oxiracetam administered immediately after training or prevented by pretreatment or chronic treatment^{25,63}.

2.3.9. Interaction with steroids

Adrenalectomy, inhibition of steroid biosynthesis by aminoglutethimide and blockade of aldosterone receptors by epoxymexrenone completely suppress the memory improving effect of oxiracetam (see previous discussion in subsection 2.1.9).

2.3.10. Interaction with protein / lipid metabolism

A change in lipid composition might be important in excitable membranes²⁶¹ and it has been observed that oxiracetam reverses the decrease in phospholipids, especially in the hippocampus and the cortex, observed in spontaneously hypertensive rats with cerebrovascular lesions^{261,362}. An increase in phospholipid synthesis is only seen after some time indicating that oxiracetam acts on the turnover of phospholipids rather than on their rate of synthesis³⁶². Another explanation would be that the increase in phosphatidylcholine synthesis may be secondary to an increased choline uptake²²⁸.

Oxiracetam (100 mg/kg, i.p.) stimulates protein kinase C in rats. Higher concentrations of oxiracetam inhibit PKC (ref. 107). This stimulatory effect on PKC could, however, be a secondary effect due to an increase in the intracellular free calcium ion concentration.

A number of GABOB analogues (**19**) have been investigated for effects on protein synthesis and phospholipid synthesis in brain slices from rats pretreated with the compound to be tested²⁵⁸.

Of these, only oxiracetam and 4-acetoxy-2-oxopyrrolidine-1-acetamide were able to increase phospho-

lipid synthesis significantly. Some of the other compounds even inhibited phospholipid synthesis.

The 4-acyloxyethyl esters enhanced protein synthesis as did the 4-hydroxyamides. The rest did not significantly promote protein synthesis, some derivatives inhibited it.

Only oxiracetam enhanced both protein and phospholipid synthesis.

2.3.11. Other effects

No effect on locomotor activity has been observed after treatment (25–50 mg/kg i.p., mice) with oxiracetam³¹².

Prenatal treatment of mice with oxiracetam makes them more interactive with their environment and they perform better in a maze test. These results suggest an enhanced cognitive development upon prenatal oxiracetam treatment. No effects on weight, sensory motor reflexes and motility were observed^{7,8}. Treatment of pregnant rats with methylazoxymethanol, an antimetabolic compound, prevented the development of neurons in the cortex and hippocampus of the offspring. Oxiracetam reverses this effect¹².

Pretreatment with oxiracetam (400–800 mg/kg i.p.) ameliorates the decrease in glucose utilisation induced by occlusion of the left middle cerebral artery in rats¹²⁸.

Pretreatment with oxiracetam also antagonises the reduction, induced by either low glucose or low oxygen supply, in the amplitude of evoked potentials (rat cerebral cortical slices) in a dose dependent manner (10^{-5} – 10^{-6} M)¹²⁹.

2.4. Analogues of oxiracetam

2.4.1. 4-Alkoxy-/4-acyloxy-2-oxopyrrolidineacetic acid derivatives

Different analogues of 4-hydroxy-2-pyrrolidinone, 4-alkoxy-2-pyrrolidinone and 4-acyloxy-2-pyrrolidinone derived nootropics (**20**) have been subjected to nootropic tests¹³.

All these compounds were without acute toxicity at the highest tested dose of 1 g/kg i.p. in rats. It was shown that alkylation and acetylation of the hydroxy-group as well as side chain elongation reduced the beneficial effect in passive avoidance and pole climbing tests. Changing the amide to an acid or ester group also led to a lesser beneficial effect in the pole climbing test (perhaps because of easy hydrolysis of the ester and difficulty for the acid to pass the BBB). Of the compounds tested those containing $R^1 = H$, CH_2COOH , $CH_2CH_2CONH_2$ were not significantly better than saline in passive avoidance (100 mg/kg i.p.). Changing the *N*-acetamide to an *N*-acetyl group gives a compound with about the same efficiency in the passive avoidance, but less in the pole climbing test.

There were no differences in the beneficial effects of (*R*)-, (*S*)- or (\pm)-oxiracetam. This would appear strange if oxiracetam should act as the ring opened compound on GABA receptors, since (*R*)-GABOB is known to inhibit GABA_B binding and (*S*)-GABOB to be inactive¹⁶³.

2.4.2. 3-Hydroxy-analogues of oxiracetam

N-Substituted 3-hydroxy, 3,4-dihydroxy, *O*-alkyl and *O*-acyl derivatives of 2-oxopyrrolidineacetamide have been prepared and shown to be effective in improving performance in passive avoidance at 0.01–50 mg/kg p.o. in rats^{9,159}.

2.5. Pramiracetam

Pramiracetam stands out from the other pyrrolidoneacetamide nootropics, which chemically seen are neutral compounds, by being a basic compound.

2.5.1. Chemical, bibliographic and historical data

Synonyms: *N*-(2-(diisopropylamino)ethyl)-2-oxo-1-pyrrolidineacetamide*, amacetam* (4) (* prepared as a sulfate or hydrochloride).

Drug code: CI-879.

CAS RN (number of refs. 1967–Dec. 26, 1992): [68497–62–1] (34 refs.), sulfate: [72869–16–0] (3 refs.).

Molecular formula: C₁₄H₂₇N₃O₂.

Mol. wt.: 269.39 g/mol.

Martindale ID: 16967-a.

Beilstein cit.: ONLINE DIALOG BASE 390, Record No. 1539543.

First reported/first reported as nootropic: 1978 (ref. 183).

Preparation: refs. 183 and 185.

Physical data (melting and boiling points): m.p. 47–48°C (monohydrate)¹⁸⁵, b.p. 164°C^{20 Pa} 183,185.

LD₅₀: sulfate: 5.434 g/kg p.o. (male mice), 4.355 g/kg p.o. (female mice)²⁸⁶.

2.5.2. Clinical findings

As is the case for most of the 2-oxopyrrolidine-1-acetamide nootropics, pramiracetam is well tolerated and without side effects^{33,195}. Pramiracetam, 400 mg t.i.d. for 10 months, was given as a treatment of males with sustained brain injuries. An improvement was observed which was also present one month after ended treatment¹⁹⁵. Doses up to 4 g daily were without benefit to patients suffering from Alzheimer's disease in one study⁴⁴, but showed encouraging activity in another³³.

2.5.3. Pharmacokinetics

Oral absorption of pramiracetam is moderately rapid, peak plasma concentrations (2.7–9.0 μg/ml, corresponding to a total concentration (bound and

Table 4

Effect of pramiracetam on various types of chemically / physically induced amnesia, lethality and recovery after insult

For an explanation of terms used, see Table 3.

Treatment in mg / kg *	Measure	Species	(pramiracetam) in mg / kg *	Effect	Ref.
<i>None</i>					
	Learning	Rats	30 i.p. ^A	I	65
	Maze	Rats	7.5–15 i.p. ^D	I	220
	Learning	Monkeys	0.5 p.o. ^D	I	286
	Learning	Rats	1.25 p.o. ^A	I	286
<i>Modulation of ACh neurotransmission:</i>					
<i>HC-3</i>					
113 i.p. ^A (= LD ₅₀)	Lethality	Mice	100 i.p. ^A	RE	116
1.5 μg i.c.v. ^A	Passive	Mice	100 i.p. ^A	RE	73
<i>ECS:</i>					
	Active	Mice	1.25–80 i.p. ^B	RE	33
	Learning	Mice	5–160 p.o. ^A	AA	286

free) of 10.0–33.4 μM) being reached 2–3 h after a 400–1600 mg p.o. dose given to healthy volunteers^{39,40}. The harmonic mean elimination half-life (4.5–6.5 h), the total body clearance (4.45–4.85 ml/kg/min), the mean renal clearance (1.8–3.0 ml/kg/min) and the mean apparent volume of distribution (1.8–2.9 l/kg) have been shown to be independent of dose⁴⁰. Chang et al.⁴⁰ suggest that the clearance values are relatively small compared to the hepatic blood flow, suggesting that little or no first-pass metabolism will occur, provided that the drug is not metabolised in the gut. Unidentified metabolites, together with unchanged pramiracetam which is mainly excreted through the urine have, however, previously been observed by Young and Chang in rats and monkeys⁴⁰⁵.

2.5.4. Antiamnesic and memory-enhancing properties of pramiracetam

Table 4 summarises selected antiamnesic and memory-enhancing properties of pramiracetam. See the text for discussion.

2.5.5. Interaction with γ -aminobutyric acid neurotransmission

Pramiracetam does not affect GABA uptake (10% inhibition at 50 μM)²⁸⁶.

2.5.6. Interaction with acetylcholine neurotransmission

Pramiracetam reverses scopolamine effects on choline transport across the BBB, which might be regulated by cholinergic innervation of brain endothelial cells according to Brust²⁸.

Pramiracetam increases HACU in hippocampus, cortex and striatum in a dose responsive manner^{79,257,289,326}, but the effect disappears 24 h after

administration⁷⁹. Pramiracetam reverses hemicholinium-3-induced amnesia⁷³.

Pramiracetam improves avoidance learning as do physostigmine and oxotremorine, as opposed to the peripherally acting AChE inhibitor neostigmine and the peripheral muscarinic antagonist methylatropine¹⁰⁸.

2.5.7. Interaction with noradrenaline / dopamine / 5-hydroxytryptamine neurotransmission

Pramiracetam (100 mg/kg i.p., rats) does not change the concentration of NA²⁸⁹ nor the concentration or turnover of 5-HT²⁸⁹ and DA in striatum and hippocampus^{257,289}. Furthermore, pramiracetam does not affect 5-HT uptake (12% inhibition at 50 μ M)²⁸⁶.

2.5.8. Interaction with steroids

Adrenalectomy, inhibition of steroid biosynthesis by aminoglutethimide and blockade of aldosterone receptors by epoxymexrenone completely suppress the memory improving effect of pramiracetam (see previous discussion in subsection 2.1.9).

2.5.9. Other effects

Pramiracetam inhibits ($K_i = 11 \mu$ M) the enzyme prolylendopeptidase (PEP) in some brain areas, but not in others. Inhibition was observed with the highest effect in the mesencephalon, followed by the striatum, cerebellum, hippocampus and hypothalamus, but no inhibition was observed in the cerebral cortex and the medulla oblongata^{50,403}.

Pramiracetam normalises the EEG pattern of aged rats to resemble that observed in young rats in a bell-shaped dose responsive manner^{284,285}.

Pramiracetam have also been shown to increase cerebral blood flow²⁸.

2.6. Analogues of pramiracetam

N-Substitution of piracetam leads, in general, to more active compounds^{33,184}. *N*-(Aminoethyl)-2-oxopyrrolidine-1-acetamide derivatives^{89,169} (**21**) and *N*-(1-piperazidinyl)-2-oxopyrrolidine-1-acetamide derivatives^{369,402} (**22**) inhibit the amnesia induced by the protein synthesis inhibitor cycloheximide as well as ECS-induced amnesia. In the ECS-induced amnesia test, compounds containing 2-(*N,N*-diisopropylamino)ethyl-pramiracetam) or 2-(2,6-dimethylpiperidin-1-yl)ethyl-substituents were most efficient. The (CH₂)₂ side chain length, the acetamido moiety and the pyrrolidone ring were important for activity. Compounds containing a (CH₂)_{3–4} side chain, a propanamide moiety or a piperidone ring either had lower intrinsic activity, were less potent or had a smaller activity range³³. *N*-(2-Hydroxyethyl)piracetam and *N*-(2-alkoxyethyl)piracetam (**21**) which may be considered

as nonbasic analogues of pramiracetam, are equipotent with piracetam⁸⁹.

Structurally related is (**23**). It exhibits brain function activating activity at 1–10 mg/kg p.o. and protective activity at 0.1–10 mg/kg p.o. in rats and mice^{167,168}.

Amides of acetylcholine are known to be inactive as cholinergic agonists³⁸⁸ and pramiracetam has no significant affinity for muscarinic receptors. 2-Oxopyrrolidine-1-acetic acid 2-(*N,N*-dimethylamino)ethyl ester (**24**), which may be considered as a combined analogue of pramiracetam and ACh, does, however, significantly improve the performance of rats (40 mg/kg s.c.) in passive avoidance³⁶⁸.

2.7. Etiracetam

2.7.1. Chemical, bibliographic and historical data

Synonyms: α -ethyl-2-oxo-1-pyrrolidineacetamide (**5**).

Drug codes: (*R*)-form: UCB L059, (*S*)-form: UCB L060, unspecified form: UCB 6474.

CAS RN (number of refs. 1967–Dec. 26, 1992): (*R*)-form: [103765–01–1] (3 refs.), (*S*)-form [102767–28–2] (4 refs.), (\pm)-form [103833–73–4] (1 refs.), unspecified form [33996–58–6] (12 refs.).

Molecular formula: C₈H₁₄N₂O₂.

Mol. wt.: 170.11 g/mol.

Beilstein cit.: ONLINE DIALOG BASE 390, Record No. 1529106.

First reported/first reported as nootropic: unspecified form: 1971 (ref. 343), (\pm)-form: 1985 (ref. 105), (*R*)-form: 1985 (ref. 105), (*S*)-form: 1985 (ref. 104).

Preparation: refs. 104, 105, 343 and 366

Physical data (melting point): unspecified form: m.p. 122°C (refs. 343,366).

2.7.2. Antiamnesic and memory-enhancing properties of etiracetam

Table 5 summarises selected antiamnesic and memory-enhancing properties of etiracetam. See the text for discussion.

2.7.3. Interaction with acetylcholine neurotransmission

UCB LO59, known as (*S*)-etiracetam (54 mg/kg i.p., mice), ameliorates the amnesic effect of scopolamine (3 mg/kg i.p.) whereas its enantiomer UCB LO60, (*R*)-etiracetam, has no effect. (*S*)-Etiracetam completely antagonises the amnesia when administered repeatedly³⁷⁶.

The amnesic effect of i.c.v. hemicholinium-3 in mice is also reversed⁷³, whereas the hemicholinium-3-induced ACh depletion is not reversed^{73,400}.

(*S*)-Etiracetam causes contraction of a guinea pig ileum preparation in a dose-dependent manner, the contraction being inhibited by atropine, tetrodotoxin and by ACh depletion, but potentiated by AChE inhibition with physostigmine. (*S*)-Etiracetam does not af-

Table 5

Effect of etiracetam on various types of chemically / physically induced amnesia, lethality and recovery after insult

For an explanation of terms used, see Table III.

Treatment in mg / kg *	Measure	Species	[etiracetam] in mg / kg *	Effect	Ref.
<i>None:</i>					
	Learning	Rats	20-30 i.p. ^D	I	393
	Learning	Rats	20-30 i.p. ^D	I	394
<i>Modulation of ACh neurotransmission:</i>					
Hemicholinium-3					
1.5 μ g i.c.v. ^A	Passive	Mice	30, 100 i.p. ^A	RE	73
Scopolamine					
3 i.p. ^A	Passive	Mice	^S 14,27,108 i.p. ^A	NE	376
			^S 54 i.p. ^A	AA	376
			^R 14,27,54,108 i.p. ^A	NE	376
<i>ECS:</i>					
	Learning	Rats	50 i.p. ^C	AA	314
		Rats	^R 0.17 p.o. ^A	AA	105
<i>Hypoxia:</i>					
	Lethality	Mice	^S 5.5 p.o. ^A	I	104

fect AChE activity. Regeneration of twitch response after hemicholinium-3/veratridine preinduced ACh depletion is facilitated by (*S*)-etiracetam, but not by (*R*)-etiracetam. This effect was not further augmented by coadministration of choline. The facilitated twitch

recovery after administration of (*S*)-etiracetam was inversely correlated to the concentration of Ca^{2+} in the medium⁴⁰⁰.

These results could indicate some facilitatory effect of (*S*)-etiracetam on the release of ACh. Wülfert et al.⁴⁰⁰ further suggest that the facilitated twitch recovery is especially pronounced in the absence of calcium-dependent ACh release (see also subsection 3.1).

2.7.4. Other effects

Etiracetam (170 mg/kg i.v., rabbits) is effective against severe barbiturate (80 mg/kg i.v.) intoxication, while piracetam does not confer any protection⁹³.

(*R*)-Etiracetam has been shown to be active against ECS induced amnesia in rats¹⁰⁵.

The EEG pattern dependency on etiracetam treatment has been investigated in man³⁰⁷. In elderly people and patients with memory deficits the EEG is dominated by an increase in δ and θ activity and less α and α -adjacent β activity compared to the activity seen in healthy persons. Etiracetam is capable of reversing these effects, leading to higher vigilance³⁰⁵.

2.8. Nefiracetam

2.8.1. Chemical, bibliographic and historical data

Synonyms: 2-Oxopyrrolidineacetic acid 2,6-dimethylanilide (6).

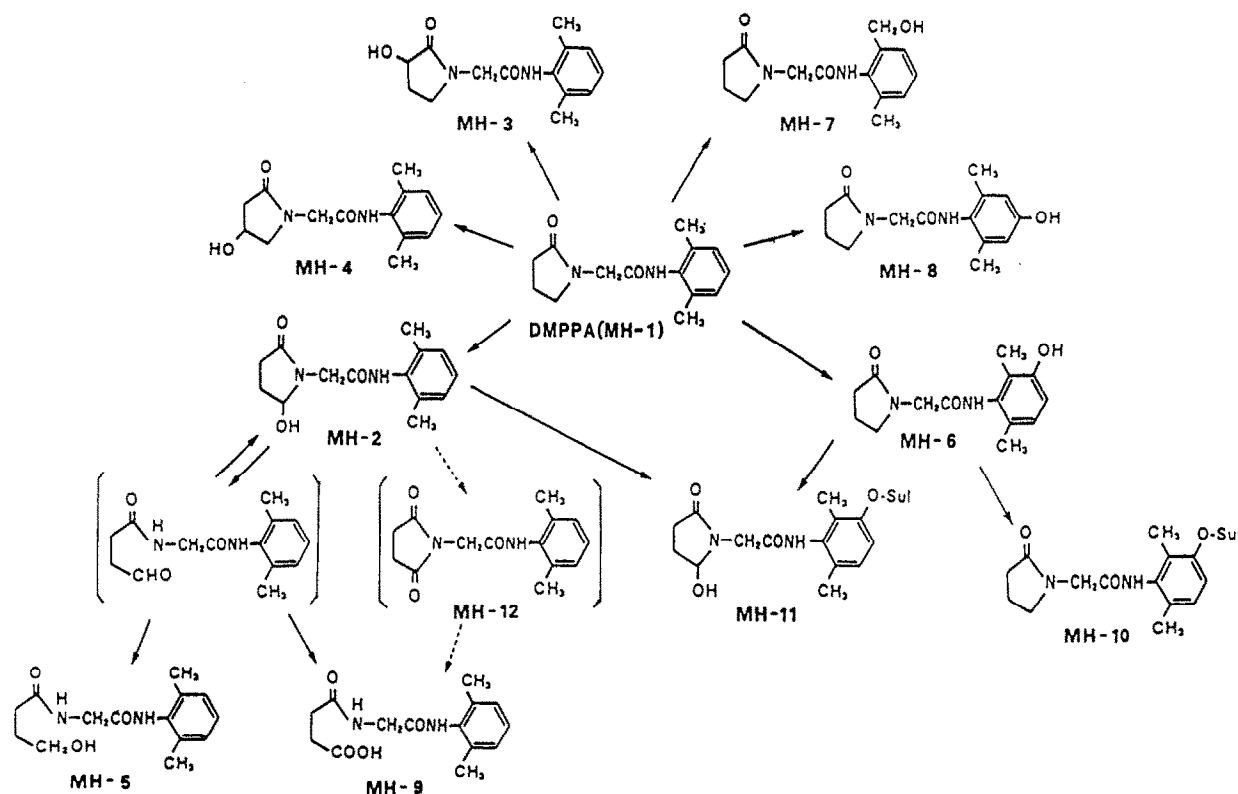


Fig. 4. Metabolism of nefiracetam. From Fujimaki et al.⁷⁶.

Drug code: DM-9384.

CAS RN (number of refs. 1967–Dec. 26, 1992): [77191–36–7] (19 refs.).

Molecular formula: C₁₄H₁₈N₂O₂.

Mol. wt.: 246.31 g/mol.

First reported/first reported as a nootropic: 1980 (ref. 21.).

Preparation: ref. 21

2.8.2. Pharmacokinetics

The metabolism of nefiracetam has been investigated in man^{76,77,78} (Fig. 4); it is initiated by extensive hydroxylation of the pyrrolidone ring and of the phenyl group. The hydroxylated compounds are subsequently subject to further degradation or sulfate conjugation. The main metabolites of nefiracetam have been identified as *N*-(2,6-dimethylphenyl)-4-hydroxy-2-pyrrolidinone (MH-4 in Fig. 4), *N*-(2,6-dimethylphenyl)-5-hydroxy-2-pyrrolidinone (MH-2 in Fig. 4) and *N*-(2,6-dimethylphenyl)carbamoylmethylsuccinamic acid (MH-9 in Fig. 4)⁷⁷. Cleavage of the pyrrolidone ring, leading to *N*-(2,6-dimethylphenylcarbamoylmethyl)-GABA, was not observed and less than 8% of the orally administered dose was excreted unchanged in the urine⁷⁶.

The peak serum concentration (10 nM) was reached 2 h after a low dose of nefiracetam (100 mg p.o., man).

2.8.3. Antiamnesic and memory-enhancing properties of nefiracetam

Table 6 summarises selected antiamnesic and memory-enhancing properties of nefiracetam (see the text for discussion).

2.8.4. Interaction with γ -aminobutyric acid neurotransmission

The role of GABA in memory mechanisms is not completely understood. Picrotoxin is known as a GABA_A receptor-related chloride channel blocker and inhibits GABA neurotransmission. Picrotoxin and bicuculline (a GABA_A antagonist) can induce impairment of memory consolidation^{222,223,226}. This impairment of memory consolidation can be reversed by administration of GABA agonists²²³.

Picrotoxin and bicuculline can, however, also be shown to improve memory consolidation¹³⁸ and picrotoxin may facilitate acquisition²²⁶. Furthermore, the GABA_A agonist muscimol, administered before training, causes amnesia²²⁶, whereas post-training treatment attenuates amnesia induced by scopolamine, cycloheximide and GABA antagonists²²⁶, but can also be shown to result in amnesia¹³⁹.

Further complicating is the fact that post-training intraamygdala microinjection of the GABA_B agonist baclofen impairs memory (see Izquierdo and Medina¹³⁸ for references) whereas inhibition of GABA_B autore-

Table 6

Effect of nefiracetam on various types of chemically / physically induced amnesia, lethality and recovery after insult

For an explanation of terms used, see Table 3.

Treatment mg / kg *	Measure	Species	[nefiracetam] mg / kg *	Effect	Ref.
<i>None:</i>					
	Active	Rats	10 p.o. ^D	I	302
<i>Modulation of GABA neurotransmission:</i>					
<i>Picrotoxin</i>					
3 s.c. ^B	Passive	Mice	30–60 p.o. ^A	AA	222
3 s.c. ^B	Passive	Mice	15–90 p.o. ^B	NS	222
<i>Bicuculline</i>					
2 s.c. ^B	Passive	Mice	15–30 p.o. ^{AB}	AA	222
<i>Ethanol</i>					
2000 p.o. ^A	Passive	Mice	5–15 p.o. ^A	AA	226
<i>Chlordiazepoxide (CDP)</i>					
10 s.c. ^A	Passive	Mice	5–15 p.o. ^A	AA	226
<i>CDP + bicuculline</i>					
10 s.c. ^A + 1 i.p. ^B	Passive	Mice	3–15 p.o. ^A	NS	226
<i>CDP + flumazenil</i>					
10 s.c. ^A + 10 i.p. ^B	Passive	Mice	15 p.o. ^A	AA	226
<i>CDP + scopolamine</i>					
10 s.c. ^A + 1 i.p. ^B	Passive	Mice	15 p.o. ^A	AA	226
<i>Modulation of ACh neurotransmission:</i>					
<i>Scopolamine</i>					
1 i.p. ^A	Passive	Rats	1–30 p.o. ^A	RE	302
<i>Inhibition of protein synthesis:</i>					
<i>Cycloheximide (CXM)</i>					
30 s.c. ^B	Passive	Mice	5–15 p.o. ^{ABC}	AA	227
<i>CXM + bicuculline</i>					
30 s.c. ^B + 0.5–1 i.p. ^B	Passive	Mice	5 p.o. ^A	NS	227
<i>CXM + picrotoxin</i>					
30 s.c. ^B + 0.5–1 i.p. ^B	Passive	Mice	5 p.o. ^A	NS	227
<i>CXM + scopolamine</i>					
30 s.c. ^B + 1 i.p. ^B	Passive	Mice	5 p.o. ^A	NS	227
<i>ECS:</i>					
	Passive	Rats	1–3 p.o. ^A	RE	302
<i>Hypoxia:</i>					
	Lethality	Mice	10–100 p.o. ^A	I	301
<i>Other:</i>					
<i>Basal forebrain lesion</i>					
	Maze	Rats	1, 3 p.o. ^D	AA	225
	Passive	Rats	3 p.o. ^D	AA	225
<i>Old animals</i>					
	Active	Rats	30 p.o. ^A	I	149

ceptors (which down regulate the release of GABA) blocks the induction of LTP⁵⁵.

A complicating factor is also the effect of anxiety during testing, since it is known that a high level of anxiety causes enhanced release of endogenous benzodiazepine receptor ligands from the amygdala, septum and hippocampus, which inhibits the memory consolidation process (see refs. 138, 140 and 182 for references and discussion of endogenous benzodiazepine receptor ligands and learning/memory).

Binding studies and bicuculline experiments suggest that nefiracetam might attenuate the drug-induced im-

pairment of memory consolidation through a direct or indirect interaction with GABA_A receptors²²². Ethanol is known to interact with the GABA-benzodiazepine-chloride channel receptor complex and thereby to enhance its affinity for benzodiazepines²²⁶. Results with the benzodiazepine agonist chlordiazepoxide (CDP) and ethanol-induced amnesia also seem to support a mechanism in which nefiracetam interacts with GABA_A receptors³⁵⁷ and not through muscarinic and benzodiazepine receptors, since the attenuation by nefiracetam of CDP and ethanol-induced amnesia is antagonised by bicuculline, but not scopolamine or the benzodiazepine antagonist flumazenil²²⁶.

Nefiracetam inhibits the decrease in the number of GABA receptors caused by cycloheximide in rats¹⁵⁰.

Nefiracetam increases the activity of GAD and the turnover of GABA in the cortex³⁸⁶, indicating an increase in the activity of GABAergic neurons.

The results achieved with nefiracetam on the GABA receptor system are difficult to interpret (see also Sarter³¹⁵) because of the unresolved influence of GABA on the memory process. Furthermore, the concentration of picrotoxin used by Nabeshima et al.^{222,226} was 3 mg/kg (s.c.), quite high compared to the LD₅₀ value in mice of 4–7 mg/kg (i.p.). Finally, it is important to stress that the above-mentioned attenuation of amnesia did not exceed a level of about 50%.

2.8.5. Interaction with acetylcholine neurotransmission

Scopolamine is able to inhibit the anti-amnesic effect of nefiracetam on cycloheximide, but not CDP-induced amnesia. This suggests that muscarinic receptors play a different role in these two situations²²⁷. Nefiracetam is, however, capable of attenuating amnesia induced by hemicholinium-3 and scopolamine alone^{224,302} and nefiracetam increases the turnover of ACh in the cortex³⁸⁶.

Nefiracetam (1–30 mg/kg p.o.) does not affect the ACh level, but attenuates the depletion induced by scopolamine in murine hippocampus, frontal cortex, amygdala and striatum more than physostigmine².

Nefiracetam increases the number of muscarinic receptors in rats¹⁵⁰.

Treatment of rats with nefiracetam caused an increase in CAT activity in the fronto-parietal cortex²²⁵, but antagonised only slightly the marked fall in the activity of cerebrocortical CAT in another study¹⁵⁴.

2.8.6. Interaction with noradrenaline / dopamine / 5-hydroxytryptamine neurotransmission

A decrease in the tissue DA level and an increase in the HVA/DA level is observed in the striatum, whereas the opposite is observed in the hippocampus after ischemia in gerbils. Nefiracetam does not affect these ischemic effects¹⁸⁸.

During ischemia a decrease in the tissue level of NA and an increase in MHPG/NA can be observed in the hippocampus, hypothalamus and colliculus superior in gerbils¹⁸⁸. Nefiracetam was unable to counteract the decrease in NA level, but some attenuation of the increased MHPG/NA level was observed at 30 mg/kg nefiracetam in the hypothalamus.

A decreased tissue 5-HT level and an increased 5-HIAA/5-HT level is observed in several brain areas except the cortex after ischemia in gerbils. No major effect of nefiracetam on these phenomena could be observed, except for a small increase in the 5-HT content in the striatum¹⁸⁸.

2.8.7. Interaction with protein / lipid metabolism

Nefiracetam has been shown to inhibit amnesia induced by the protein synthesis inhibitor cycloheximide which, *inter alia*, causes a decrease in the number of GABAergic and muscarinic receptors. Nefiracetam inhibits the decrease in the number of GABA receptors and increases the number of muscarinic receptors¹⁵⁰.

Nefiracetam's reversal of the action of cycloheximide seems to involve GABA_A and ACh receptors since, as previously mentioned, the amnesia reversal was inhibited by picrotoxin, bicuculline and scopolamine²²⁷, whereas the reversal of amnesia by CDP as already mentioned only seems to involve GABA_A receptors.

2.8.8. Other effects

Improvement is observed in old rats treated with nefiracetam (30 mg/kg p.o.) of active avoidance performance¹⁴⁹ and nefiracetam has been suggested as an effective drug against SDAT¹¹⁷.

Nefiracetam shows a bell-shaped dose-response curve³⁰², and nefiracetam attenuates ischemia-induced decreases in ATP and pyruvate/lactate ratio, but does not influence the glucose uptake and utilisation in normal mice³⁰¹.

At first glance one is struck by the resemblance between nefiracetam (6) and the local anaesthetic pyrocaine⁵¹ (25).

Local anaesthetic properties of nefiracetam could perhaps explain the protective properties of nefiracetam, but there is a significant difference between it and typical local anaesthetics. Nefiracetam contains a carbonyl group in position 2 of the pyrrolidine ring and thus the amino group which is necessary for local anaesthetic effects by channel blockade is transformed into an amide group which is very much less basic, probably with loss of all channel blocking effects.

2.9. Aniracetam

2.9.1. Chemical, bibliographic and historical data

Synonyms: 1-(4-methoxybenzoyl)-2-pyrrolidinone, 1-(*p*-anisoyl)-2-pyrrolidinone (7).

Table 7

Effect of aniracetam on various types of chemically / physically induced amnesia, lethality and recovery after insult

For an explanation of terms used, see Table 3.

Treatment mg / kg *	Measure	Species	[aniracetam] mg / kg *	Effect	Ref.
<i>None:</i>					
	Active	Rats	100 p.o. ^D	NS	88
	Passive	Rats	1–300 p.o.	NS	59
	Passive	Rats	30, 50 i.p. ^D	I	401
	Learning	Monkeys	12.5, 25, 50 p.o. ^A	I	278
	Learning	Rats	50 i.p.	I	262
	Maze	Rats	100–800 p.o. ^A	I	193
<i>Modulation of GABA neurotransmission:</i>					
<i>Picrotoxin</i>					
3 s.c. ^B	Passive	Rats	15–90 p.o. ^A	NS	222
	Passive	Rats	15–90 p.o. ^B	NS	222
<i>Bicuculline</i>					
2 s.c. ^B	Passive	Rats	30–90 p.o. ^A	AA	222
	Passive	Rats	30–60 p.o. ^B	AA	222
<i>Chlordiazepoxide (CDP)</i>					
10 s.c. ^A	Passive	Mice	5–30 p.o. ^A	NS	226
<i>Ethanol</i>					
2000 p.o. ^A	Passive	Mice	5–15 p.o. ^A	NS	226
<i>Modulation of ACh neurotransmission:</i>					
<i>Scopolamine</i>					
0.63 i.p. ^A	Passive	Rats	100 p.o. ^A	RE	336
	Passive	Rats	300 p.o. ^A	NS	336
0.56 i.p.	Learning	Rats	10–100 p.o.	AA	243
0.25 i.p.	Maze	Rats	10, 30 p.o.	AA	348
20 mg i.c.v.	Maze	Mice	10, 20 p.o. ^A	RE	136
30 µg/kg i.m. ^A	Learning	Monkeys	12.5, 25, 50 p.o. ^A	NE	278
20 µg/kg i.m. ^A	Learning	Monkeys	12.5, 25, 50 p.o. ^A	RE	278
	Passive	Rats	100 p.o.	RE	60
1 i.p. ^A	Passive	Rats	1–30 p.o. ^A	AA	302
<i>Hemicholinium-3</i>					
119 i.p. ^A (= LD ₅₀)	Lethality	Mice	300 i.p. ^A	RE	116
<i>Modulation of NA neurotransmission:</i>					
<i>Clonidine</i>					
0.1 i.p. ^B	Active	Rats	50 ^D	RE	175
0.1 i.p.	Passive	Rats	50 ^D	RE	86
<i>Diethylthiocarbamate (DEC)/ potassium ethylxanthogenate (PEX)</i>					
300 i.p. (DEC)	Passive	Rats	50 ^D	RE	86
100 i.p. (PEX)	Passive	Rats	50 p.o. ^D	RE	87
<i>Inhibition of protein synthesis:</i>					
<i>Cycloheximide (CXM)</i>					
30 s.c. ^B	Passive	Mice	3–30 p.o. ^{ABC}	AA	227
<i>ECS:</i>					
	Maze	Mice	20 p.o. ^A	RE	136
	Passive	Rats	10 p.o. ^A	AA	302
<i>Hypoxia:</i>					
	Learning	Man	10, 100 i.v. ^D	AA	306
	Learning	Rats	32, 100 p.o.	AA	243
	Passive	Mice	3–30 p.o.	RE	348
	Passive	Rats	30 p.o.	AA	60
<i>Other:</i>					
<i>Basal forebrain lesion</i>					
	Maze	Rats	3, 10 p.o. ^A	AA	225
	Passive	Rats	3, 10 p.o. ^A	NS	225

Drug code: Ro 13–5057.

CAS RN (number of refs. 1967–Dec. 26, 1992): [72432–10–1] (83 refs.).

Molecular formula: $C_{12}H_{13}NO_3$.

Mol. wt.: 219.10 g/mol.

Martindale ID: 16511-s.

First reported/first reported as nootropic: 1979 (ref. 127).

Preparation: ref. 127

Physical data (melting point): m.p. 121–122°C (from ethanol)¹²⁷.

LD₅₀: 4.5 g/kg p.o. (rats), 5.0 g/kg p.o. (mice)⁵³.

2.9.2. Clinical findings

Aniracetam has recently been shown to improve the condition of elderly patients suffering from slight to moderate mental deterioration (1.5 g daily)³⁶, of geriatric patients with cerebrovascular insufficiency⁷⁰ and in one SDAT study³²⁴, while aniracetam showed no effect (1 g daily for 3 months) in patients who suffered from long-term exposure to organic solvents³³¹ and in another SDAT study³³².

2.9.3. Pharmacokinetics

Aniracetam is absorbed very rapidly from the GI after p.o. administration, but its bioavailability is low due to extensive first-pass metabolism. According to Guenzi and Zanetti¹¹⁵, the total body clearance of aniracetam is as high as 10 l/min. The imide compounds aniracetam and rolziracetam are quite unstable in vivo and are transformed to the more stable amide and acid. In humans the main metabolite of aniracetam is *N*-anisoyl-GABA (70%) and the remaining 30% appear as 4-methoxybenzoic acid and 2-pyrrolidinone¹¹⁵.

2.9.4. Antiamnesic and memory-enhancing properties of aniracetam

Table 7 summarises selected antiamnesic and memory-enhancing properties of aniracetam. See the text for discussion.

2.9.5. Interaction with γ -aminobutyric acid neurotransmission

Aniracetam affects GABA receptors weakly. It only ameliorates (maximally about 33%) bicuculline-induced amnesia, but not CDP induced amnesia and is unable to reverse picrotoxin-induced amnesia^{222,226}. Finally, the response of GABA receptors to GABA, at 1 mM aniracetam, is not affected¹³⁵.

2.9.6. Interaction with glutamate neurotransmission

Micromolar amounts of aniracetam enhance the efficacy, but not the potency, of AMPA-induced calcium influx in cerebellar granule cells, an effect which persists in the presence of the voltage sensitive L-type³⁵⁹

calcium channel blocker nifedipine⁴⁸. Aniracetam does not change the receptor binding affinity for AMPA nor the ion conductance selectivity¹³⁵.

Aniracetam only affects the fast synaptic currents mediated by the ionotropic quisqualate receptor and only AMPA, but not NMDA or kainate, EPSC is enhanced by aniracetam (0.1–5 mM)^{135,151,249,349}. Piracetam and 2-pyrrolidinone were inactive¹³⁵. (See also discussion in subsection 2.1.6).

The decay of glutamate-induced EPSCs is slowed 2–3 fold and the magnitude of stimulus evoked EPSC is doubled by aniracetam. L-Glutamate activated single channel response lengths are increased by aniracetam and aniracetam (10^{-8} – 10^{-7} M, but not 10^{-6} M) augments LTP in the hippocampal CA3 area³¹⁸.

Simulations suggest that aniracetam acts via a post-synaptic mechanism by slowing the entry into a desensitised state, decreasing the rate constant for ion channel gating^{133,135,249,349,385} or, as suggested for oxiracetam, by recruitment of a subset of AMPA receptors which do not normally contribute to synaptic transmission⁴⁸. Recently it was shown that the mechanism underlying LTP formation in the guinea pig hippocampal CA1 region is unrelated to aniracetam's enhancement of EPSC (ref. 10).

2.9.7. Interaction with acetylcholine neurotransmission

Aniracetam exerts its effect on scopolamine-induced amnesia in a dose responsive manner, since 10–100 mg/kg p.o. to rats ameliorates amnesia^{60,136,243,278,297,348,377} whereas a dose of 300 mg/kg p.o. is less effective or without effect^{336,358}. Furthermore, the scopolamine-induced decrease in striatum, cerebral cortex and hippocampal ACh content is ameliorated in the hippocampus and the cerebral cortex by aniracetam (100–300 mg/kg p.o., rats)^{336,358}. Aniracetam (100–300 mg/kg p.o., rats) also increases the ACh content in the absence of scopolamine-induced depletion in the hippocampus and the cerebral cortex, but not in the corpus striatum. The choline content is neither increased in the hippocampus nor in the corpus striatum³⁵⁸ and sodium-dependent high-affinity choline uptake is not affected by aniracetam (10–200 mg/kg p.o., rats)³²⁶. Lethal neuromuscular blockade by hemicholinium-3 is antagonised by aniracetam (30–300 mg/kg i.p., mice)¹¹⁶.

Aniracetam (10–100 μ M) does not affect CAT activity in hippocampal slices²⁰³.

Finally, i.p. injection of pirenzepine, an M₁ selective antagonist, results in contralateral turning behaviour in mice which can be reversed by muscarinic agonists, AChE inhibitors and aniracetam, but not by the GABA_A agonist muscimol or the 5-HT uptake inhibitor citalopram, nor by the α -sympathomimetic amphetamine³⁹⁷.

2.9.8. Interaction with noradrenaline / dopamine / 5-hydroxytryptamine neurotransmission

It has been reported that aniracetam (50 mg/kg p.o., rat) decreases the DA level in the striatum and the hypothalamus²⁶⁵. This is probably not due to the fact that aniracetam activates monoamine oxidase B (MAO_B), but inhibits MAO_A in the striatum and the hypothalamus³³⁸, since dopamine seems to be a substrate of both enzymes⁴⁰⁴. The overall effect on MAO is inhibition³³⁸ and the decrease in DA level could therefore indicate an increased release of DA.

A study on the effect of prolonged aniracetam administration (50 mg/kg, p.o., b.i.d., 7 days, rats) on peripheral adrenergic neurons in blood vessels has been performed³⁵⁶. It seems that some modulation of the contractile response to NA is possible, mostly as a potentiating effect.

Activation of α_2 receptors by clonidine induces memory impairment whereas blockade of these receptors by, e.g., atipamezole²³⁵ improves memory retention, but not retrieval of memory. Aniracetam reverses the memory impairment induced by clonidine^{86,175}. Likewise aniracetam (50 mg/kg p.o., 5 days, rats) completely abolishes the amnesic effect of the dopamine β -hydroxylase inhibitor *N,N*-diethyldithiocarbamate^{85,86} and potassium ethylxanthogenate⁸⁷.

The 5-HT level is decreased in the hypothalamus, but increased in the cortex and the striatum by aniracetam (50 mg/kg p.o., rats)²⁶⁵. 5-HT turnover was delayed in the hypothalamus, but accelerated in the cortex, brain stem and striatum²⁶⁵.

The decrease in brain biogenic monoamine content with age is ameliorated by aniracetam³³⁹.

2.9.9. Interaction with steroids

Adrenalectomy, inhibition of steroid biosynthesis by aminoglutethimide and blockade of aldosterone receptors by epoxymexrenone completely suppress the memory improving effect of aniracetam (see previous discussion in subsection 2.1.9).

2.9.10. Interaction with protein / lipid metabolism

Aniracetam antagonises the amnesia induced by the protein synthesis inhibitor cycloheximide²²⁷.

2.9.11. Other effects

Aniracetam inhibits ($K_i = 160 \mu\text{M}$) prolylendopeptidase (PEP) in the mesencephalon, striatum, cerebellum, hippocampus and hypothalamus, but is inactive in the cerebral cortex and the medulla oblongata⁴⁰³.

Aniracetam is well tolerated, has no influence on food and fluid intake¹⁴³ and does not affect locomotor activity in rats^{144,401}. No physical or psychic dependence is observed in monkeys¹⁷⁰.

2.10. Analogues of aniracetam

2.10.1. Phenyl-substituted analogues

The *p*-fluoro, *p*-chloro, *p*-demethoxy- and *p*-(2-oxopyrrolidinyl)-analogues of aniracetam have been prepared and tested; they cause improvement of memory consolidation^{268,269}.

2.10.2. 1-Acyl-2-pyrrolidinones

1-Valproyl-2-pyrrolidinone has been prepared and tested. This compound ameliorates scopolamine-induced amnesia, protects against hypoxia and reduces the glutamate and aspartate content in hippocampal slices²⁰².

Valproic acid is known as an antiepileptic drug, but with the amide being more effective than the acid. Since the main metabolite of aniracetam is *N*-anisoyl-GABA one could expect the same for 1-valproyl-2-pyrrolidinone. A comparable metabolism would generate an amide of valproic acid. Further support is found in a study by Sasaki et al.³¹⁷, showing anticonvulsant and anti-amnesic properties of a number of 1-acyl-2-pyrrolidinones, especially the 1-dodecanoyl derivative. They were shown to generate GABA after treatment with mouse liver homogenate in vitro³¹⁷.

2.10.3. 1-Sulfonyl-2-pyrrolidinones

2-Oxopyrrolidine-1-sulfonic acid derivatives (**26**) have been prepared as analogues of aniracetam. Substituted 1-(phenylsulfonyl)-2-pyrrolidinones have been claimed to possess cognition enhancing properties²⁹⁶ whereas other 2-oxo-1-pyrrolidinesulfonic acid derivatives were devoid of activity in tests where aniracetam was active³⁸.

2.10.4. Other analogues of aniracetam

The 3-hydroxy-analogue of aniracetam has been tested in hyperventilation-induced EEG changes in young humans (1.5 g p.o.). It was as effective as aniracetam¹⁵⁸.

2.11. Rolziracetam

2.11.1. Chemical, bibliographic and historical data

Synonyms: tetrahydropyrrolizine-3,5-dione; 3,5-dioxohexahydropyrrolizine; dihydro-1*H*-pyrrolizine-3,5-(2*H*,6*H*)-dione (8).

Drug code: CI-911.

CAS RN (number of refs. 1967–Dec. 26, 1992): [18356–28–0] (23 refs.).

Molecular formula: C₇H₉NO₂.

Mol. wt.: 139.15 g/mol.

Beilstein cit.: V 21/10, 69; IV 21/10, 4668.

First reported: 1947 (refs. 180,187).

First reported as nootropic: 1982 (ref. 32).

Preparation: refs. 45, 180, 187, 199, 200 and 321.

Spectroscopic data: refs. 1, 69, 199 and 373.

Physical data (melting points): m.p. 175–182°C (from ethanol)⁴⁵, m.p. 176–177°C (from ethanol)¹⁸⁰, m.p. 181°C (from benzene)¹⁸⁰, m.p. 181.5–182°C (from ethanol)³²¹, m.p. 181.5–182°C (from water)³²¹, b.p. 173°C (665 Pa)⁴⁵.

2.11.2. Pharmacokinetics

The metabolic disposition of rolziracetam has been investigated in monkeys, dogs and rats after both p.o. and i.v. doses²³.

When rolziracetam is given i.v. it is eliminated rapidly from the systemic circulation, having a $t_{1/2}$ of less than 25 min, leaving 5-oxo-2-pyrrolidinepropanoic acid, the sole metabolite of rolziracetam, in circulation. The hydrolysis of rolziracetam is presumably mediated through nonspecific esterases/amidases which are distributed throughout the body. After oral doses only traces of intact drug can be detected in the plasma, but the metabolite is reaching peak levels 0.5–1 h after administration, indicating a fast absorption. Rolziracetam and its metabolite are excreted almost solely by renal elimination. Only small amounts concentrate in the brain because of the very polar structure of the metabolite²³ (see Table II). The amount of rolziracetam reaching the brain may, however, be trapped there.

2.11.3. Interaction with acetylcholine neurotransmission

The amnesic effect of a high concentration of scopolamine (3 mg/kg i.p.), given to mice before an acquisition trial, could not be reversed by rolziracetam (14–460 mg/kg i.p.)³⁷⁶.

2.11.4. X-ray structure of rolziracetam

Rolziracetam has been subjected to an X-ray analysis¹¹, but since it is rapidly transformed into the active metabolite 5-oxo-2-pyrrolidinepropanoic acid in vivo, this structure analysis does not reveal anything about the structure of a potential receptor site.

2.12. Analogues of rolziracetam

Different analogues (27) and (28) of rolziracetam have been prepared and tested as anti-amnesic compounds in ECS tests in mice^{23,32,34}. The compounds were given after learning and ECS, but before the retention test.

It seems that the 5,5- and 5,6-ring systems possess equal activity. The 5,7- and 6,6-bicyclic compounds displayed less activity. Replacement of a methylene group by sulfur leads to compounds with less activity. 2-Methyl or 2,6-dimethyl derivatives were also less effective, whereas the 7a-methyl compound seemed more active. Reduction of one carbonyl group to an

alcohol group gave a compound with less activity, perhaps because of increased stability towards hydrolysis.

The possible metabolites of the above-mentioned compounds have been synthesised and tested (29).

The length of the side chain has little influence on the activity. However, the compound with $n = 2$, corresponding to the metabolite of the parent 5,5-bicyclic compound, seems most active and the one with $n = 1$ least active. Esters and amides are somewhat less active than the corresponding acids. This is contrary to expectation, since the esters and amides should be more lipophilic.

Introduction of a sulfur atom or of a double bond in the side chain reduces the activity. The potency varied with the ring size of the lactams in the order 6- > 5- >> 7-membered. The intrinsic activity of the 5-membered lactam was highest, it also showed the broadest activity range. Finally, the potential metabolites seemed more potent than the parent compounds²³. In this context it is interesting that the compound with $n = 0$, $m = 1$ and $R = OH$ corresponds to pyroglutamate the D-form of which possesses anti-amnesic properties. Generally speaking there is a good correlation between the activities of the parent compounds and their metabolites.

3. General discussion

A great deal of different biochemical and behavioural findings have been presented throughout the years. As evident from the presentation above and up to now no key mechanism for the cognition enhancing and protective effect of these compounds has been established.

We would like to stress that there appears good reason to assume that the nootropics improve the cognitive state (see also Poschel²⁸³) by exerting effects on the brain activity. A few selected results taken from above should emphasise this.

The EEG of elderly people, of healthy volunteers treated with diazepam and of patients with memory deficits is dominated by an increase in δ and θ activity and less α and α -adjacent β activity compared to the activity seen in healthy persons. Aniracetam, piracetam and etiracetam are capable of reversing these effects, leading to greater vigilance^{90,304,305,313} and pramiracetam normalises the EEG pattern of aged rats towards that observed with young rats^{284,285}.

3.1. Structure–activity relationships

If one looks at the structures involved it seems that they only have the pyrrolidone ring in common which also seems to be important for their activity. This is interesting, since 2-pyrrolidone has been found to occur naturally in man²⁸³. In the series of analogues of

piracetam, oxiracetam, pramiracetam and etiracetam it seems that the acetamide moiety is important for activity.

4-Hydroxy-substitution increases the potency, since lower doses of oxiracetam are often required for equipotency with piracetam. The hydroxy-group could well be involved in crucial hydrogen bonding since the corresponding alkoxy- and acyloxy-compounds are less active. Another possibility would be that oxiracetam is oxidised *in vivo*, which is very unlikely for the acyloxy- and alkoxy-analogues. Oxidised metabolites of oxiracetam have, however, not been observed *in vivo*.

N-Substitution, with crucial dependence on side chain length, as in the case of pramiracetam also increases the activity. Part of the increased activity might be due to higher lipophilicity. Interference with cation channels, due to the basic amino group, may also cause some effects.

Very interesting is the stereospecificity of the biological action of etiracetam. This fact may well turn out to be a powerful tool in the elucidation of the mechanism of action. Only the (*S*)-form of etiracetam ameliorates the amnesic effect of scopolamine, as mentioned above. Biochemical experiments should therefore be conducted with the pure enantiomers of etiracetam. Biochemical findings which show significantly higher activity of the (*S*)-form at clinically relevant concentrations could very well be linked to the anti-amnesic action of these compounds, but the possibility of a stereospecific transport mechanism for etiracetam can, of course, not be ruled out. Unfortunately, this powerful tool has not been used much (only two studies^{376,400} have been conducted so far with the pure enantiomers). The apparent stereospecificity should, however, perhaps be regarded with caution, since (*R*)-etiracetam has been shown to be active against ECS induced amnesia (the (*S*)-form was not tested)¹⁰⁵.

The structure–activity relationships for aniracetam and rolziracetam have been discussed above. When considering structure–activity relationships for these one should bear in mind the rapid metabolism *in vivo*, leading to γ -carbonylaminobutyric acid structures. *In vitro* and *in vivo* results are therefore not necessarily well correlated (see Sasaki et al.³¹⁷ for the stability of acylpyrrolidinones in different media).

Finally, the study by Gudasheva et al.¹¹⁴ should be recalled. Ligands for possible nootropic binding sites in the brain are likely to resemble proline or pyroglutamate.

3.2. Mechanisms of action

In the previous sections we have attempted to be as objective as possible in our presentation and critique of the results found in the literature and not to exclude any hypothesis of a mechanism of action.

In this section we present a short discussion of previously suggested mechanisms of action followed by our own view on a possible mechanism of action, based on the available evidence.

3.2.1. Previously suggested mechanisms of action

It has been proposed in the literature that the piracetam-like nootropics should exert their effect by a nonspecific action, but it seems more reasonable to assume a specific mode of action, since the piracetam-like nootropics exhibit bell-shaped dose response curves (see, e.g., refs. 33, 286, 289, 336, 358 and 285).

Thus, Poschel et al.²⁸⁵ observed a therapeutic window with pramiracetam for changes of EEG (1–160 mg/kg p.o., rats), learning behaviour (1–160 mg/kg p.o., rats) and single neuron (ventral pallidum) firing rates (2–16 mg/kg i.v., anaesthetized (ketamine) rats) and the decrease in activity at higher doses were shown not to be due to toxic effects.

The bell-shaped dose–response relationships are, however, not unique to the piracetam-like nootropics, since they have also been observed in behavioral studies with other cognitive activator agents (see Pugsley et al.²⁸⁹ for references).

The stereospecific biological action observed in the case of etiracetam and the fact that oxiracetam is subject to saturable binding in the rat brain^{196,347} also supports a specific mode of action.

From Table I it is, however, evident that the piracetam-like nootropics do not exhibit high affinity for any of the receptor types tested so far (except for nefiracetam, which shows some activity at GABA_A receptors) and they do not share any of the side effects associated with analeptics or psychostimulants (see refs. 5, 92 and 95 for a discussion of drug classification and 49, 122 for a comparison of nootropics, psychostimulants and analeptics).

There has been much discussion on whether the racetams exert their effect by a centrally or by a peripherally mediated mechanism. It would be attractive and, of course, straightforward to link the anti-amnesic action of these compounds to their centrally mediated effects, but how can we then account for the peripheral effects observed?

Investigations like those of Mennini et al.¹⁹⁶ and Taddei et al.³⁴⁷ who observed saturable binding of oxiracetam in the rat brain, support a centrally mediated mechanism of action and in the early years of investigation it was also suggested that piracetam should act selectively on telencephalic functions, since it lacks reticular and limbic effects as well as activity on hypothalamic and pituitary functions⁹³.

Further indications for a centrally mediated mechanism of action arise from the fact that even the least lipophilic compounds like piracetam and oxiracetam (see Table II) are capable of entering the CNS, al-

though with some delay, but then with longer half-lives in the brain. They alter the EEG pattern, i.c.v. injection of, e.g., oxiracetam is able to reverse scopolamine-induced amnesia which also can be reversed by the cholinomimetics physostigmine, oxotremorine and the nootropic pramiracetam, but not the peripherally acting cholinomimetic neostigmine and anticholinergic methylatropine¹⁰⁸.

Much interest has been devoted in the literature to a possible cholinergic mechanism for the actions of the racetams (see Pepeu and Spignoli²⁵⁹ for a review on piracetam-like nootropics and cholinergic mechanisms). The cholinergic system, however, is probably not directly affected by the racetams and Mondadori et al.²⁰⁹ have investigated the effects of different drugs on the memory consolidation process at different times after a learning trial. The results of this study reveal that stimulation of memory consolidation through a blockade of strychnine sensitive glycine receptors is possible up to 1 h after a learning trial whereas stimulation of memory consolidation through the cholinergic system is feasible up to 2 h after a learning trial. The piracetam-like nootropics (piracetam, oxiracetam, pramiracetam and aniracetam) stimulate the memory consolidating process up to 8 h after a learning trial.

The piracetam-like compounds do, however, exert some effects (probably of secondary origin, see below) on the cholinergic system such as, e.g., reversal of scopolamine or hemicholinium-3-induced amnesia and even the peripheral cholinergic system is susceptible to their effects such as reversal of *d*-tubocurarine-induced neuromuscular blockade and lethality due to neuromuscular paralysis by hemicholinium-3.

Furthermore, the action of the piracetam-like nootropics is, as previously mentioned, dependent on steroids. This is not the case for the cholinomimetics arecoline and physostigmine²⁰⁶.

Mondadori et al. suggest that activation of aldosterone receptors might be an absolute prerequisite for any nootropic effect or that the piracetam-like nootropics might modulate the effect of steroids on memory²⁰⁶.

The steroid dependency, together with the above mentioned time dependency, would indeed imply that the piracetam-like nootropics have effects beyond an action on the cholinergic system which may then be classified as secondary, but nonetheless very important, effects.

On the other hand, the cholinomimetics and the nootropics share the property of inhibition of their activity by high steroid levels²¹⁰.

3.2.2. Modulation of ion fluxes, the mechanism of action?

The question is how to account for the somewhat puzzling fact that the racetams are capable of influenc-

ing so many different processes and still being so nontoxic.

Most of the various biochemical findings such as, e.g., effects on MAO, HACU, protein and lipid metabolism, are in our view probably secondary to some specific primary effect and we think that the racetams exert their effect on some species present in the membranes of all excitable cells, i.e., the ion carriers or ion channels and that they somehow accomplish an increase in the stimulatory response. This is supported by observations like the piracetam reversal of *d*-tubocurarine-induced neuromuscular blockade by a combined effect of an increase in neurotransmitter release and excitability of motor nerve terminals¹¹⁶.

Such effects could be a consequence of, e.g., increased sodium influx, decreased potassium efflux or increased calcium influx and could explain the observed augmentation of LTP seen at very low doses (10–100 nM) of aniracetam³¹⁸ and oxiracetam's enhancement of depolarisation induced glutamate release¹⁹². Furthermore, these effects are linked to the nerve impulse as observed by Marchi et al.¹⁹² since, e.g., etiracetam's effect on guinea pig ileum contraction is completely blocked by the sodium channel blocker tetrodotoxin⁴⁰⁰ while oxiracetam increases the release of glutamate induced by depolarisation, but not the spontaneous release¹⁹².

As described in subsection 2.1.9, the piracetam-like nootropics show a dependency of their beneficial effect on the stimulation of aldosterone receptors. One possible explanation, in the case of adrenalectomised animals, would then be an electrolyte imbalance caused by a cation transmembrane transport change in the kidneys which could have been counteracted by the administration of aldosterone to the adrenalectomised animals for 8 days, causing the beneficial effects of the nootropics to reappear.

This would also require some electrolyte imbalance to appear 26 h after treatment with the aldosterone antagonist epoxymexrenone and the steroid synthesis inhibitor aminoglutethimide, since these also inhibit the beneficial effect of the piracetam-like nootropics. Other reasons for the dependence on aldosterone receptor stimulation can, of course, not be excluded.

Some effect on ion fluxes is supported by the fact that the activity of the Na⁺/K⁺-ATPase decreases in vivo after treatment with high doses of piracetam (600 mg/kg daily for 30 days, rats)²⁹⁰. The transport carrier is not affected in vitro, probably indicating that it is not a question of direct allosteric inhibition of the carrier. A decrease in activity could perhaps indicate a decrease in the number of carriers.

It would therefore seem that the racetams act as potentiators of an already present activity (also causing the increase in glucose utilisation observed) rather than possessing any activity of their own, in keeping

with their very low toxicity and lack of serious side effects. The result of their action is therefore an increase in general neuronal sensitivity towards stimulation.

Such a link between the effect of the nootropics and an already present activity would also explain why different results have been observed under different experimental conditions, such as, e.g., the dependence on the intensity of the foot shock used²⁰⁸ or the learning ability of the animals to be tested²⁶⁶. Active avoidance tests, passive avoidance tests, mazes and other learning systems may cause different neurochemical events and may cause anxiety or arousal to a different extent, which would influence the neuronal activity and thereby the experimental parameter to be measured.

An increased basal activity would also be expected to increase the effect of the piracetam-like nootropics, which is seen in the case of co-treatment with oxiracetam and methamphetamine³⁰⁸, nicotine³¹⁰ or the presynaptic muscarinic blocker secoverine⁶. An enhancement of stimulatory pathways would also counteract the inhibitory effects of, e.g., barbiturates and scopolamine.

The question is now which kind of ion transport mechanism is affected.

The decay of glutamate induced excitatory postsynaptic currents (EPSCs) is slowed, the magnitude of evoked EPSC enhanced and L-glutamate activated single channel response lengths are increased by aniracetam³⁸⁵. Simulations suggest that aniracetam acts via a postsynaptic mechanism by slowing the transition to a desensitised state, thus decreasing the rate constant for ion channel gating^{133,135,249,349,385}.

This could be an indirect indication of increased sodium or calcium influx.

The results by Wülfert et al.⁴⁰⁰ showed that the effect of etiracetam on twitch recovery after ACh depletion in the guinea pig was inversely correlated to the extracellular calcium concentration. It is known that a modest decrease in the extracellular concentration of Ca^{2+} can decrease excitation thresholds¹²⁰ and could thereby synergise the effect of the piracetam-like nootropics.

Another possible mode of action would, as already mentioned, be via a decreased potassium efflux and piracetam has indeed shown to decrease potassium efflux from erythrocytes³⁴⁴.

It is in this context interesting to note some of the structural similarities between piracetam, oxiracetam, pramiracetam, etiracetam, nefiracetam and the potassium channel openers of the benzopyran type³⁶¹, e.g., lemakalim (30). A comparison of these nootropics with lemakalim shows that the unionisable hydroxy-group in position 3 of lemakalim has been exchanged for an unionisable amino group in the form of an amide moiety in the nootropics. Furthermore the active (*S*-

form of etiracetam (31) has an absolute configuration opposite to that of lemakalim (30). It would therefore be interesting to clarify whether the observed changes result in a potassium channel closing activity of the nootropics compared to the channel opening activity of lemakalim.

One may further speculate whether the effect of the piracetam-like nootropics involves receptor gated channels, voltage-dependent channels or ion carriers.

Aniracetam, piracetam and oxiracetam enhance, as previously mentioned, *selectively* the efficacy, but not the potency, of AMPA-induced calcium influx in cerebellar granule cells⁴⁸ without change in ion conductance selectivity¹³⁵ and Ito et al.¹³⁵ imply that the effect of aniracetam should resemble the glycine-NMDA receptor interaction and not the benzodiazepine-GABA receptor interaction, since the latter changes its affinity for agonists and it is therefore more likely that aniracetam modifies the properties of the AMPA-associated cation channel.

Glutamate is the main excitatory neurotransmitter in the brain and a general increase in excitatory activity would also be expected to cause a general increase in the activity and turnover of other transmitters, but since the piracetam-like nootropics elicit both peripheral and central effects some effects have to be elicited through receptor gated channels or voltage-dependent channels present both centrally and peripherally.

It was shown recently that the mechanism underlying LTP formation in the guinea pig hippocampal CA1 region is unrelated to aniracetam's enhancement of EPSC (ref. 10), thus possibly indicating effects beyond the AMPA system.

The mediation of the possible effect on ion channels may be a direct allosteric one, but action on G-proteins in G-protein modulated ion channels cannot, at present, be ruled out nor can a possible action on ion carriers.

The effect of compounds with the suggested mechanism, i.e., a potentiation of depolarisation evoked increase in sodium or calcium influx or by decreasing potassium efflux, would result in a potentiated release and response to depolarizing neurotransmitters, but only a potentiation in the release of inhibitory neurotransmitters.

The mechanism described would also explain the rather unusual bell-shaped dose response curves observed with these compounds, since the increase in response from depolarizing neurotransmission may be counteracted by an increase in the release of inhibitory neurotransmitters. This also means that at some ratio of excitatory/inhibitory activity no net response to the racetams may be seen, since the effect is fully counteracted. If on the other hand, there is, e.g., an increase in excitatory activity, this increase might be potentiated (cf. subsection 3.2.1).

Such a mechanism of action, i.e., a potentiation of neurotransmission, would demand some degree of activity present, otherwise no effect will be seen and effects should be especially pronounced in situations of physiological (or pharmacological) augmentation of specific neuronal pathways (e.g., in the learning/memory process) which would be further potentiated.

3.3. Clinical potential

The investigation of the beneficial effects of the piracetam-like nootropics has revealed that these effects are especially pronounced in situations of imbalance (e.g., a change in the *normal* excitatory/inhibitory ratio), but only to a certain degree. This would correlate well with the idea that they are dependent on activity already present.

In healthy subjects the beneficial effects also seem less pronounced, indicating some sort of negative feedback^{283,285}. Such negative feedback (e.g., by a potentiation in the release of inhibitory transmitters) might be present in subjects without any receptor plasticity deficits (see refs. 221, 372 and 396 for a discussion on the decrease in receptor plasticity with age). The known decrease in receptor number, receptor sensitivity and receptor-effector coupling (coupling to secondary messenger systems) with age may be involved in the decreased receptor plasticity.

The piracetam-like nootropics increase the general activity, which may cause the piracetam-induced increase in the receptor number seen in drug treated or old animals. This would then increase the synaptic efficacy and result in a generally improved performance.

Beneficial effects of these compounds are therefore to be expected in patients with mild to moderate dementia. In more progressed dementia the activity along some neuronal pathways may be so low that improvement is no longer to be expected (see also refs. 231 and 234). In the case of advancing dementia co-treatment with other drugs may very well be beneficial.

The racetams' presumed action as potentiators of neurotransmission might also explain the benefit for Parkinson patients of treatment with piracetam¹⁴⁶ and, since other single drug treatments are known to increase some specific neuronal transmission (e.g., L-dopa reinforces the dopaminergic effects, physostigmine the cholinergic effects, etc.), co-treatment with piracetam-like compounds should especially potentiate these neuronal transmissions.

If the above described hypothesis, i.e., a potentiation of already present neurotransmission, accounts for the actual mechanism, other possible uses of the racetams could become interesting, especially in co-treatment with other drugs.

Possible examples of uses, beyond that in patients suffering from mild to moderate dementia, would then involve diseases such as myasthenia gravis (possibly as part of a co-treatment with AChE inhibitors), schizophrenia (possibly in a co-treatment regimen with neuroleptics, reducing the anticholinergic and extrapyramidal effects associated with the latter; increases in glutamic neurotransmission may increase the release of neurotransmitters, thereby further adding to the benefit), Parkinson's disease (possibly as co-treatment with L-dopa, reducing the dose of L-dopa needed and allowing to extend the time range of possible treatment with L-dopa), depression (possibly as co-treatment with tricyclic antidepressants, reducing the amount of antidepressant needed and decreasing the anticholinergic side effects), epilepsy (co-treatment with valproate should increase GABA neurotransmission further) and in congestive heart failure (possibly by co-treatment with the Na⁺/K⁺-ATPase inhibitor ouabain).

3.4. Final comments

Discrepancies between the effects on memory in animal and human studies of nootropic compounds have been reported. This might be due to ill-defined patient collectives (see Gainotti et al.⁸⁰), to progressed dementia in some patient collectives and to the concentrations used.

In animal experiments the amounts used are often much higher (often higher than 100 mg/kg) than the concentrations used in man (a dose of 2 g corresponds to about 20–40 mg/kg). The peak CSF total concentration (bound and free) reached in humans is about 10–15 μ M after 2 g oxiracetam (p.o.). One should, however, remember that the piracetam-like nootropics exhibit a therapeutic window and overdosing is therefore possible. Finally, the piracetam-like nootropics in their present state of development seem to be most efficient in long-term treatment, which would allow beneficial effects on receptor plasticity.

It is, in general, also important to point out, as has been done by others (especially by Sarter³¹⁵ and Sarter et al.³¹⁶), that the choice of the animal model in screenings of possible cognition enhancing drugs (see Sarter^{315,316}) is very important for the achievement of acceptable validity, i.e., in order to avoid confusion by false positive cognition enhancers.

We hope that our overview and critique of the available biochemical data will contribute to the generation and testing of new ideas concerning the mechanism of action of piracetam related nootropics and, of course, especially tests of our working hypothesis.

We would therefore particularly like to encourage *in vitro* experiments such as, e.g., patch clamp experiments with the pure enantiomers of etiracetam.

Our final conclusion is that the establishment of the mechanism of action for these prototype compounds, followed by a full SAR investigation, would bode well for the development of drugs with well-balanced pharmacokinetics and activity and which as such or perhaps especially as part of a co-treatment regimen will be of benefit in cognitive disease states and also in additional indications.

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Abbreviations

ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChE	acetylcholinesterase
ACTH	adrenocorticotrophic hormone
ADTN	2-amino-6,7-dihydroxy-1,2,3,4-tetrahydro-naphthalene
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AP-5	2-amino-5-phosphonoheptanoic acid
AP-7	2-amino-7-phosphonoheptanoic acid
ATP	adenosine 5'-triphosphate
BBB	blood-brain barrier
b.i.d.	bis in die
b.p.	boiling point
CAT	choline acetyl transferase
CDP	chlordiazepoxide
CNS	central nervous system
CSF	cerebrospinal fluid
DA	dopamine
ECS	electroconvulsive shock
EEG	electroencephalogram
EPSC	excitatory postsynaptic current
EPSP	excitatory postsynaptic potential
GABA	γ -aminobutyric acid
GABOB	γ -amino- β -hydroxybutyric acid
GAD	glutamic acid decarboxylase
GI	gastrointestinal
Glu	glutamate
HACU	high-affinity choline uptake
5-HT	5-hydroxytryptamine
5-HIAA	5-hydroxyindoleacetic acid
HVA	homovanillic acid
i.a.	intraarterially
i.c.v.	intracerebroventricularly
i.p.	intraperitoneally
i.v.	intravenously
LTP	long-term potentiation

MAO	monoamine oxidase
MHPG	3-methoxy-4-hydroxyphenylglycol sulfate
m.p.	melting point
NA	noradrenaline
NMDA	<i>N</i> -methyl-D-aspartate
PEP	prolylendopeptidase
PKC	protein kinase C
PLG	prolylleucylglycine
p.o.	per oral
QNB	quinuclidinyl benzilate
QSAR	quantitative structure-activity relationship
SAR	structure-activity relationship
s.c.	subcutaneously
SDAT	senile dementia of Alzheimer's type
t.i.d.	ter in die
TRH	thyrotropin-releasing hormone

References

- 1 Aasen, A.J., Culvenor, C.C.J. and Willing, R.I., Shielding of 7 β -H in pyrrolizidine derivatives, *Aust. J. Chem.*, 24 (1971) 2575–2580.
- 2 Abe, E., Reversal effect of DM-9384 on scopolamine-induced acetylcholine depletion in certain regions of the mouse brain, *Psychopharmacology*, 105 (1991) 310–316.
- 3 Ackerman, P.T., Dykman, R.A., Holloway, C., Paal, N.P. and Gocio M.Y., A trial of piracetam in two subgroups of students with dyslexia enrolled in summer tutoring, *J. Learn. Disabil.*, 24 (1991) 542–549.
- 4 Aldenkamp, A.P., Van Wieringen, A., Alpherts, W.C., Van Emde-Boas, W., Haverkort, H.A., De Vries, J. and Meinardi, H., Double-blind placebo-controlled, neuropsychological and neurophysiological investigations with oxiracetam (CGP 21690E) in memory-impaired patients with epilepsy, *Neuropsychobiology*, 24 (1990–1991) 90–101.
- 5 Amaducci, L., Angst, J., Bech, P., Benkert, O., Bruinvels, J., Engel, R.R., Gottfries, C.G., Hippus, H., Levy, R., Lingjaerde, O., López-Ibor Jr., J.J., Orgogozo, J.M., Bull, C., Saletu, B., Stoll, K.D. and Woggon, B., Consensus conference on the methodology of clinical trials of 'Nootropics', Munich, June 1989, Report of the Consensus Committee, *Pharmacopsychiatry*, 23 (1990) 171–175.
- 6 Ammassari-Teule, M., Castellano, C. and Sansone, M., Enhancement by oxiracetam of passive avoidance improvement induced by the presynaptic muscarinic antagonist secoverine in mice, *Behav. Brain Res.*, 47 (1992) 93–95.
- 7 Ammassari-Teule, M., D'Amato, F.R., Sansone, M. and Olive-rio, A., Enhancement of radial maze performances in CD1 mice after prenatal exposure to oxiracetam: possible role of sustained investigative responses developed during ontogeny, *Physiol. Behav.*, 42 (1988) 281–285.
- 8 Ammassari-Teule, M., D'Amato, F.R., Sansone, M. and Olive-rio, A., Avoidance facilitation in adult mice by prenatal administration of the nootropic drug oxiracetam, *Pharmacol. Res. Commun.*, 18 (1986) 1169–1176.
- 9 Aschwanden, W.K.E. and Kyburz, E. (F. Hoffmann-La Roche und Co. AG), Pyrrolizidine derivatives, *Ger. Offen.*, DE 3,227,649 (1983) CA98:160582t.
- 10 Asztely, F., Hanse, E., Wigström, H. and Gustafsson, B., Aniracetam-evoked potentiation does not interact with long-term potentiation in the CA1 region of the hippocampus, *Synapse*, 11 (1992) 342–345.

- 11 Bandoli, G., Grassi, A., Liégeois, C., Lumbroso, H., Montoneri, E. and Pappalardo, G.C., X-Ray crystal structure, dipole moment and theoretical molecular orbital study of the cognition activator rolziracetam, *Eur. J. Med. Chem.*, 24 (1989) 81–85.
- 12 Banfi, S., Dorigotti, L., Abbracchio, M.P., Balduini, W., Coen, E., Ragusa, C. and Cattabeni, F., Methylazoxymethanol microencephaly in rats: neurochemical characterization and behavioral studies with the nootropic oxiracetam, *Pharmacol. Res. Commun.*, 16 (1984) 67–83.
- 13 Banfi, S., Fonio, W., Allievi, E., Pinza, M. and Dorigotti, L., Cyclic GABA-GABOB analogs. IV. Activity on learning and memory, *Farmacol. Ed. Sci.*, 39 (1984) 16–22.
- 14 Banfi, S. and Dorigotti, L., Experimental behavioral studies with oxiracetam on different types of chronic cerebral impairment, *Clin. Neuropharmacol.*, 9 Suppl. 3 (1986) 19–26.
- 15 Banfi, S., Pellegata, R., Pifferi, G. and Pinza, M. (I.S.F.S.p.A.), 4-Hydroxypyrrolidin-2-on-1-ylalkylcarboxylic acid esters and N-ethyl-2-(4'-hydroxypyrrolidin-2-on-1-yl)acetamide, *Ger. Offen.*, DE 2,758,937 (1978) CA89:197330z.
- 16 Barone, D. and Spignoli, G., Investigations on the binding properties of the nootropic agent pyroglutamic acid, *Drugs Exp. Clin. Res.* 16 (1990) 85–99.
- 17 Baumel, B., Eisner, L., Karukin, M., MacNamara, R., Katz, R.J. and Deveaugh-Geiss, J., Oxiracetam in the treatment of multi-infarct dementia, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 13 (1989) 673–682.
- 18 Bencze, W., Kamber, B. and Storni, A. (Ciba-Geigy AG), Pyrrolidinone derivatives, *Eur. Pat. Appl.*, EP 115,472 (1984) CA102:25041b.
- 19 Bencze, W., Kamber, B. and Storni, A. (Ciba-Geigy AG), Substituted pyrrolidinone derivatives, *Eur. Pat. Appl.*, EP 115,473 (1984) CA102:46254p.
- 20 Bering, B. and Müller, W.E., Interaction of piracetam with several neurotransmitter receptors in the central nervous system, *Arzneim.-Forsch. / Drug Res.*, 35 (1985) 1350–1352.
- 21 Betzing, H., Biedermann, J., Materne, C. and Neuser, V., (A. Nattermann und Cie. GmbH), Pyrrolidin-2-on-1-ylacetic acid 2,6-dimethylanilide and pharmaceutical compositions containing it, *Ger. Offen.*, DE 2,924,011 (1980) CA94:156740t.
- 22 Betzing, H., Biedermann, J. and Materne, C., (A. Nattermann und Cie. GmbH), Pyrrolidinones and pharmaceutical compositions containing them, *Ger. Offen.*, DE 2,923,975 (1980) CA94:156739z.
- 23 Black, A. and Chang, T., Metabolic disposition of rolziracetam in laboratory animals, *Eur. J. Drug Metab. Pharmacokin.*, 12 (1987) 135–143.
- 24 Bobkov, Yu.G., Morozov, I.S., Glozman, O.M. and Nerobkova, L.N., Pharmacological characteristics of 4-phenylpiracetam, a new phenyl analog of piracetam, *Byull. Eksp. Biol. Med.*, 95 (1983) 50–53.
- 25 Bobkov, Yu.G., Plev, P.V., Machula, A.I., Val'dman, E.A., Soldatov, N.M. and Dudkin, S.M., Participation of dihydropyridine-sensitive calcium channels in psychotropic effects of nootropic drugs, *Byull. Eksp. Biol. Med.*, 110 (1990) 386–389.
- 26 Boltze, K.H., Dell, H.D. and Jacobi, H., (Troponwerke GmbH und Co. K.G.), 2-Oxo-1-pyrrolineacetic acid derivatives, *Ger. Offen.*, DE 2,757,680 (1979) CA91:107887a.
- 27 Brambilla, F., Aguglia, E., Massirone, R., Maggioni, M., Grillo W., Castiglioni, R., Catalano, M. and Drago, F., Neuropeptide therapies in chronic schizophrenia: TRH and vasopressin administration, *Neuropsychobiology*, 15 (1986) 114–121.
- 28 Brust, P., Reversal of scopolamine-induced alterations of choline transport across the blood-brain barrier by the nootropics piracetam and pramiracetam, *Arzneim.-Forsch. / Drug Res.*, 39 (1989) 1220–1222.
- 29 Burov, Yu.V., Robakidze, T.N., Kadyшева, L.V., Voronin, A.E. and Shaposhnikova, G.I., Study of anti-amnesic activity of amiridine in a model of amnesic syndrome, *Byull. Eksp. Biol. Med.*, 111 (1991) 614–617.
- 30 Burov, Yu.V., Robakidze, T.N., Kadyшева, L.V. and Sukhanova, S.A., Experimental study of the effects of amiridine and tacrine on learning and memory, *Byull. Eksp. Biol. Med.*, 111 (1991) 612–614.
- 31 Burov, Yu.V., Baimanov, T.D., Tat'yanenko, L.V., Sokolova, N.M. and Tereshchenkova, I.M., Effects of amiridine and tacrine, drugs effective in Alzheimer's disease, on the activity of monoamine oxidase A and B, *Byull. Eksp. Biol. Med.*, 113 (1992) 149–150.
- 32 Butler, D.E., (Warner-Lambert Company), The use of dihydro-1H-pyrrolizine-3,5(2H,6H)-dione as a cognition activator, pharmaceutical compositions containing that compound and the production of such compositions, *Eur. Pat. Appl.*, EP 0.048.132 (1982) CA96:223312m.
- 33 Butler, D.E., Nordin, I.C., L'Italien, Y.J., Zweisler, L., Poschel, P.H. and Marriott, J.G., Amnesia-reversal activity of a series of N-(disubstituted amino)alkyl)-2-oxo-1-pyrrolidineacetamides, including pramiracetam, *J. Med. Chem.*, 27 (1984) 684–691.
- 34 Butler, D.E., Leonard, J.D., Caprathe, B.W., L'Italien, Y.J., Pavia, M.R., Hershenson, F.M., Poschel, P.H. and Marriott, J.G., Amnesia-reversal activity of a series of cyclic imides, *J. Med. Chem.*, 30 (1987) 498–503.
- 35 Calliauw, L. and Marchau, M., Clinical trials of piracetam in disorders of consciousness due to head injury, *Acta Anaesthesiol. Belg.*, 26 (1975) 51–60.
- 36 Canonico, V., Forgione, L., Paoletti, C., Casini, A., Colonna, C.V., Bertini, M., Acito, R. and Rengo, F., Efficacy and tolerance of aniracetam in elderly patients with primary or secondary mental deterioration, *Riv. Neurol.*, 61 (1991) 92–96.
- 37 Canonico, P.L., Aronica, E., Aleppo, G., Casabona, G., Copani, A., Favita, A., Nicoletti, F. and Scapagnini, U., Repeated injections of piracetam improve spatial learning and increase the stimulation of inositol phospholipid hydrolysis by excitatory amino acids in aged rats, *Funct. Neurol.*, 6 (1991) 107–111.
- 38 Cerri, A., Farina, C., Pinza, M. and Banfi, S., Synthesis and nootropic activity of 2-oxo-1-pyrrolidinesulfonic acid derivatives, *Farmacol.*, 46 (1991) 959–966.
- 39 Chang, T. and Young, R.M., Gas chromatographic assay of pramiracetam in human plasma using nitrogen specific detection, *J. Chromatogr.*, 274 (1983) 346–349.
- 40 Chang, T., Young, R.M., Goulet, J.R. and Yakatan, G.J., Pharmacokinetics of oral pramiracetam in normal volunteers, *J. Clin. Pharmacol.*, 25 (1985) 291–295.
- 41 Chleide, E., Bruhwiler, J. and Mercier, M., Enhanced resistance effect of piracetam upon hypoxia-induced impaired retention of fixed-interval responding in rats, *Pharmacol. Biochem. Behav.*, 40 (1991) 1–6.
- 42 Chopin, P. and Briley, M., Effects of four non-cholinergic cognitive enhancers in comparison with tacrine and galanthamine on scopolamine-induced amnesia in rats, *Psychopharmacology*, 106 (1992) 26–30.
- 43 Ciba-Geigy AG, Preparation of piperazinyloxy-pyrrolidinone derivatives for treatment of amnesia and retention defects, *Jpn. Kokai Tokkyo Koho*, JP 62,185,068 (1987) CA108:167500y.
- 44 Claus, J.J., Ludwig, C., Mohr, E., Giuffra, M., Blin, J. and Chase, T.N., Nootropic drugs in Alzheimer's disease: symptomatic treatment with pramiracetam, *Neurology*, 41 (1991) 570–574.
- 45 Colonge, J. and Pouchol, J.M., Préparation de pyrrolidones-2 et de γ -aminoacides, *Bull. Soc. Chim. Fr.*, 598–603 (pp. 598, 601).
- 46 Consolo, S., Salmoiraghi, P., Amoroso, D. and Kolasa, K., Treatment with oxiracetam or choline restores cholinergic biochemical and pharmacological activities in striata of decorticated rats, *J. Neurochem.*, 54 (1990) 571–577.
- 47 Cooper, D.G., Young, R.C., Durant, G.J. and Ganellin, C.R.,

- Histamine Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 3*, Elsevier Science/Pergamon, Oxford, 1990, p. 360.
- 48 Copani, A., Genazzani, A.A., Aleppo, G., Casabona, G., Canonico, P.L., Scapagnini, U. and Nicoletti, F., Nootropic drugs positively modulate α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-sensitive glutamate receptors in neuronal cultures, *J. Neurochem.*, 58 (1992) 1199–2204.
 - 49 Coper, H. and Herrmann, W.M., Psychostimulants, analeptics, nootropics: an attempt to differentiate and assess drugs designed for the treatment of impaired brain functions, *Pharmacopsychiatry*, 21 (1988) 211–217.
 - 50 Cosentino, U., Moro, G., Pitea, D., Todeschini, R., Brossa, S., Gualandi, F., Scolastico, C. and Giannesi, F., Pharmacophore identification in amnesia-reversal compounds using conformational analysis and chemometric methods, *Quant. Struct.-Act. Relat.*, 9 (1990) 195–201.
 - 51 Craig, P.N., Drug Compendium. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 6*, Pergamon Press, Oxford, 1990, p. 819.
 - 52 Craig, P.N., Drug Compendium. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 6*, Pergamon Press, Oxford, 1990, pp. 237–965.
 - 53 Cumin, R., Bandle, E.F., Gamzu, E. and Haefely, W.E., Effects of the novel compound aniracetam (Ro 13–5057) upon impaired learning and memory in rodents, *Psychopharmacology*, 78 (1982) 104–111.
 - 54 Reference deleted.
 - 55 Davies, C.H., Starkey, S.J., Pozza, M.F. and Collingridge, G.L., GABA_B autoreceptors regulate the induction of LTP, *Nature*, 349 (1991) 609–611.
 - 56 Davis, H.P. and Squire, L.R., Protein synthesis and memory: a review, *Psychol. Bull.*, 96 (1984) 518–559.
 - 57 De, B., Dellaria, J.F., Baker, W.R., Zydowsky, T.M., Rosenberg, S.H. and Jae, H.S. (Abbott Laboratories), Preparation of heterocyclic peptides as renin and retroviral protease inhibitors, *Eur. Pat. Appl.*, EP 365,992 (1990) CA114:43580d.
 - 58 De Lanno, J. (UCB S.A.), 1,3-Disubstituted ureas and 2-thioureas, *Ger. Offen.*, DE 2,805,769 (1978) CA89:197313w.
 - 59 DeNoble, V.J., Vinpocetin enhances retrieval of a step-through passive avoidance response in rats, *Pharmacol. Biochem. Behav.*, 26 (1987) 183–186.
 - 60 DeNoble, V.J., Repetti, S.J., Gelpke, L.W., Wood, L.M. and Keim, K.L., Vinpocetine: nootropic effects on scopolamine-induced and hypoxia-induced retrieval deficits of a step-through passive avoidance response in rats, *Pharmacol. Biochem. Behav.*, 24 (1986) 1123–1128.
 - 61 Dimond, S.J., Drugs to improve learning in man: Implications and neuropsychological analysis. In R.M. Knights and D.J. Bakker (Eds.), *Neuropsychol. Learn. Disord., Proc. Int. Conf.*, Univ. Park Press, Baltimore, MD, pp. 367–379.
 - 62 Djokic, S., Gaspert, B., Simunic, B., Tomic, M. and Maasbol, A., (PLIVA Tvornica Farmaceutskih i Kemijskih Proizvoda, Helm, Karl O.), *Ger. Offen.*, DE 2,701,450 (1977) CA87:135051j.
 - 63 Dudkin, S.M., Plev, P.V. and Soldatov, N.M., Calcium entry blockers and oxiracetam have opposite effects on the density of dihydropyridine receptors in rat cerebral cortex, *Brain Res.*, 525 (1990) 319–321.
 - 64 Dysken, M.W., Katz, R., Stallone, F. and Kuskowski, M., Oxiracetam in the treatment of multi-infarct dementia and primary degenerative dementia, *J. Neuropsychiatry Clin. Neurosci.*, 1 (1989) 249–252.
 - 65 Ennaceur, A., Cavoy, A., Costa, J.C. and Delacour, J., A new one-trial test for neurobiological studies of memory in rats. II: Effects of piracetam and pramiracetam, *Behav. Brain Res.*, 33 (1989) 197–207.
 - 66 Espinos, T., Jose, M. and Bofill Auge, J.A., *N*-Substituted pyrrolidinone, *Ger. Offen.*, DE 2,507,576 (1975) CA84:59183z.
 - 67 Falsaperla, A., Monici-Preti, P.A. and Oliani, C., Selegiline versus oxiracetam in patients with Alzheimer-type dementia, *Clin. Ther.*, 12 (1990) 376–384.
 - 68 Felinska, W. and Bien, E., Central pharmacological effects of long-term application of piracetam in rats, *Pol. J. Pharmacol. Pharm.*, 43 (1991) 7–13.
 - 69 Flitsch, W., Einfluß der Ringgröße auf die Eigenschaften cyclischer Imide, *Chem. Ber.*, 97 (1964) 1548–1554 (pp. 1548, 1549, 1550, 1552).
 - 70 Foltyn, P., Luckner, P.W., Schnitker, J. and Wetzelsberger, N., A test model for cerebrally active drugs as demonstrated by the example of the new substance aniracetam, *Arzneim.-Forsch./Drug Res.*, 33 (1983) 865–867.
 - 71 Forloni, G., Angeretti, N., Amoroso, D., Addis, A. and Consolo, S., Decrease in (³H)hemicholinium binding to high-affinity choline uptake sites in deafferented striatum: restoration by oxiracetam, *Brain Res.*, 530 (1990) 156–160.
 - 72 Frandsen, Aa. and Schousboe, A., Mobilization of dantrolene-sensitive intracellular calcium pools is involved in the cytotoxicity induced by quisqualate and *N*-methyl-D-aspartate but not by 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionate and kainate in cultured cerebral cortical neurons, *Proc. Natl. Acad. Sci. USA*, 89 (1992) 2590–2594.
 - 73 Franklin, S.R., Sethy, V.H. and Tang, A.H., Amnesia produced by intracerebroventricular injections of hemicholinium-3 in mice was prevented by pretreatment with piracetam-like compounds, *Pharmacol. Biochem. Behav.*, 25 (1986) 925–927.
 - 74 Fröstl, W. and Maître, L., The families of cognition enhancers, *Pharmacopsychiatry*, 22 Suppl. (1989) 54–100.
 - 75 Fujii, T., Kuraishi, Y., Ueda, M. and Satoh, M., Specific binding sites for bifemelane in the hippocampus of the guinea pig, relevant to its pharmacological actions, *Neuropharmacology*, 30 (1991) 1291–1295.
 - 76 Fujimaki, Y., Hashimoto, K., Sudo, K. and Tachizawa, H., Biotransformation of a new pyrrolidinone cognition-enhancing agent: isolation and identification of metabolites in human urine, *Xenobiotica*, 20 (1990) 1081–1094.
 - 77 Fujimaki, Y., Sudo, K. and Hokusui, H., Simultaneous determination of nefiracetam and its metabolites by high-performance liquid chromatography, *J. Chromatogr.*, 575 (1992) 261–268.
 - 78 Fujimaki, Y., Sudo, K. and Tachizawa, H., High-performance liquid chromatographic determination of a new nootropic, *N*-(2,6-dimethylphenyl)-2-(2-oxo-1-pyrrolidinyl)acetamide, in human serum and urine, *J. Chromatogr.*, 433 (1988) 235–242.
 - 79 Funk, K.F. and Schmidt, J., Effect of nootropics on choline uptake, *Biomed. Biochim. Acta*, 47 (1988) 417–421.
 - 80 Gainotti, G., Benedetti, N., Caltagirone, C. and Nocentini, U., Cognitive improvement in clinical trials with nootropic drugs: when can it be expected and how to clarify its meaning?, *Clin. Neuropharmacol.*, 9 Suppl. 3 (1986) 65–69.
 - 81 Gainotti, G., Nocentini, U. and Sena, E., Can the pattern of neuropsychological improvement obtained with cholinergic drugs be used to infer a cholinergic mechanism in other nootropic drugs?, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 13 Suppl. 1989 47–59.
 - 82 Gallai, V., Mazzotta, G., Del-Gatto, F., Montesi, S., Mazzetti, A., Dominici, P. and Della-Monica, A., A clinical and neurophysiological trial on nootropic drugs in patients with mental decline, *Acta Neurol. Napoli*, 13 (1991) 1–12.
 - 83 Gamzu, E.R., Hoover, T.M., Gracon, S.I. and Ninteman, M.V., Recent developments in 2-pyrrolidinone-containing nootropics, *Drug Dev. Res.*, 18 (1989) 177–189.
 - 84 Gava, R. and Schifano, F., Oxiracetam, *G. Clin. Med.*, 70 (1989) 69–72.

- 85 Genkova, M.G. and Lazarova, M.B., Influence of nootropic drugs on the learning- and memory-impairing effect of diethyldithiocarbamate in albino rats, *Methods Find. Exp. Clin. Pharmacol.*, 10 (1988) 369–375.
- 86 Genkova-Papasova, M. and Lazarova-Bakarova, M., Influence of nootropic drugs on the memory-impairing effect of diethyldithiocarbamate and clonidine in 'step down' passive avoidance in albino rats, *Acta Physiol. Pharmacol. Bulg.*, 14 (1988) 36–41.
- 87 Genkova-Papasova, M. and Lazarova-Bakarova, M., Learning and memory impairment in albino rats after potassium ethylxanthate. Effects of nootropic agents, *Acta Physiol. Pharmacol. Bulg.*, 17 (1991) 75–83.
- 88 Getova, D. and Petkov, V., The effects on the learning process of 4 pyrrolidine derivatives and of cytidine (experiments on rats in a water maze), *Eksp. Med. Morfol.*, 29 (1990) 39–44.
- 89 Giannessi, F., Ghirardi, O., Misiti, D., Tinto, M.O. and Scolastico, C. (Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.), Preparation of 2-pyrrolidone derivatives as enhancers for learning and memory, *Eur. Pat. Appl.*, EP 408,524 (1991) CA115:92061q.
- 90 Giaquinto, S., Nolfi, G. and Vitali, S., EEG changes induced by oxiracetam on diazepam-medicated volunteers, *Clin. Neuropharmacol.*, 9 Suppl. 3 (1986) 79–84.
- 91 Giovannini, M.G., Spignoli, G., Carla, V. and Pepeu, G., A decrease in brain catecholamines prevents oxiracetam antagonism of the effects of scopolamine on memory and brain acetylcholine, *Pharmacol. Res.*, 24 (1991) 395–405.
- 92 Giurgea, C., A drug for the mind, *ChemTech*, 10 (1980) 360–365.
- 93 Giurgea, C., Nootropic and related drugs interacting with the integrative activity of the brain, *Dev. Psychiatry (Biol. Psychiatry Today, Vol. B)*, 2 (1978) 876–881.
- 94 Giurgea, C., Vers une pharmacologie de l'activité intégrative du cerveau. Tentative du concept nootrope en psychopharmacologie, *Actual. Pharmacol.*, 25 (1972) 115–156.
- 95 Giurgea, C., The nootropic concept and its prospective implications, *Drug Dev. Res.*, 2 (1982) 441–446.
- 96 Giurgea, C. and Mouravieff-Lesuisse, F., Pharmacological studies on an elementary model of learning. Fixation of an experience at spinal level. I. Pharmacological reactivity of the spinal cord fixation time, *Arch. Int. Pharmacodyn. Ther.*, 191 (1971) 279–291.
- 97 Giurgea, C. and Salama, M., Nootropic drugs, *Prog. Neuro.-Psychopharmacol.*, 1 (1977) 235–247.
- 98 Giurgea, C., Lefevre, D., Lescrenier, C. and David-Remacle, M., Pharmacological protection against hypoxia induced amnesia in rats, *Psychopharmacologia*, 20 (1971) 160–168.
- 99 Giurgea, C., Moeyersoons, F.E. and Evraerd, A.C., A GABA-related hypothesis on the mechanism of action of the antimotion sickness drugs, *Arch. Int. Pharmacodyn.*, 166 (1967) 238–251.
- 100 Glasky, A.J., Multifunctional pharmaceutical compounds and methods of use, *PCT Int. Appl.*, WO 91 14,434 (1991) CA116:15822g.
- 101 Gluzman, O.M., Morozov, I.S., Zhmurenko, L.A. and Zagorevskii, V.A., Synthesis and anticonvulsive activity of 4-phenyl-2-pyrrolidinone-1-acetic acid amides, *Khim.-Farm. Zh.*, 14 (1980) 43–48.
- 102 Gluzman, O.M., Voronina, T.A., Orlova, E.K., Meshcheryakova, L.M., Rakhmankulova, I. Kh., Kazanskaya, A.A., Smirnov, L.D., Rostock, S. and Siegemund, H., Synthesis and pharmacological activity of amidoximes of (2-oxopyrrolidino)alkanoic acids and O-acyl derivatives, *Khim.-Farm. Zh.*, 23 (1989) 1147–1152.
- 103 Gobert, J.G., Genèse d'un médicament: le piracetam, métabolisation et recherche biochimique, *J. Pharm. Belg.*, 27 (1972) 281–304.
- 104 Gobert, J., Geerts, J.P. and Bodson, G. (UCB S.A.), (S)- α -Ethyl-2-oxo-1-pyrrolidineacetamide, *Eur. Pat. Appl.*, EP 162,036 (1985) CA105:18467d.
- 105 Gobert, J., Giurgea, C., Geerts, J.P. and Bodson, G. (UCB S.A.), (R)- α -Ethyl-2-oxo-1-pyrrolidineacetamide, *Eur. Pat. Appl.*, EP 165,919 (1985) CA105:97305a.
- 106 Gouliaev, A., Sørensen, J.B., Vedsø, M. and Senning, A., Synthetic and analytical aspects of the chemistry of piracetam-type nootropics, *To be published*.
- 107 Govoni, S., Lucchi, L., Battaini, F. and Trabucchi, M., Protein kinase C increase in rat brain cortical membranes may be promoted by cognition enhancing drugs, *Life Sci.*, 50 (1992) 125–128.
- 108 Gower, A.J. and Tricklebank, M.D., The effects of cholinergic drugs support an avoidance learning hypothesis of brief foot shock-induced analgesia, *Neuropharmacology*, 25 (1986) 1161–1166.
- 109 Granik, V.G., Golovko, T.V., Glushkov, R.G., Mashkovskii, M.D., Roshchina, L.F., Polezhaeva, A.I., Parimbetova, R.B., Bobkov, Y.G., Losev, A.S. and Ivanova, I.A., Synthesis and pharmacological activity of 1-thiocarbamoylmethylpyrrolidine-2-thione, *Khim.-Farm. Zh.*, 23 (1989) 1186–1193.
- 110 Granik, V.G., Stezhko, T.V., Glushkov, R.G., Mashkovskii, M.D., Roshchina, L.F., Polezhaeva, A.I., Parimbetova, R.B., Bobkov, Y.G., Losev, A.S. and Ivanova, I.A., (S. Ordzhonikidze All-Union Scientific-Research Chemical-Pharmaceutical Institute, Scientific-Research Institute of Pharmacology, Academy of Medical Sciences, U.S.S.R.), Preparation of 1-(thiocarbamoylmethyl)-2-pyrrolidinethione with antihypoxic and nootropic activity, *PCT Int. Appl.*, WO 88 01,620 (1988) CA110:94987s.
- 111 Granik, V.G., Stezhko, T.V., Glushkov, R.G., Mashkovskii, M.D., Roshchina, L.F., Polezhaeva, A.I., Parimbetova, R.B., Bobkov, Y.G., Losev, A.S. and Ivanova, I.A. (S. Ordzhonikidze All-Union Scientific-Research Chemical-Pharmaceutical Institute, Institute of Pharmacology, Academy of Medical Sciences, U.S.S.R.), Preparation of 1-(thiocarbamoylmethyl)pyrrolidine-2-thione as a psychotropic agent, *U.S.S.R.*, SU 1,414,845 (1988) CA110:8039e.
- 112 Grau, M., Montero, J.L. and Balasch, J., Effect of piracetam on electrocortigram and local cerebral glucose utilization in piracetam on electrocortigram and local cerebral glucose utilization in the rat, *Gen. Pharmacol.*, 18 (1987) 205–211.
- 113 Gschwind, H.P., Schütz, H., Wigger, N. and Bentley, P., Absorption and disposition of 14 C-labelled oxiracetam in rat, dog and man, *Eur. J. Drug Metab. Pharmacokinet.*, 17 (1992) 67–82.
- 114 Gudasheva, T.A., Ostrovskaya, R.U., Trofimov, S.S., Kosoi, M.Y., Yenkina, F.V., Burov, Y.V. and Skoldinov, A.P., Peptide analogs of piracetam as ligands of putative nootropic receptors, *Khim.-Farm. Zh.*, 19 (1985) 1322–1329, Eng. transl. in Gudasheva, T.A., Ostrovskaya, R.U., Trofimov, S.S., Kosoi, M.Y., Yenkina, F.V., Burov, Y.V. and Skoldinov, A.P., Peptide analogs of piracetam as ligands for hypothetical nootropic receptors, *Pharmaceutical Chem. J.*, 19 (1985) 762–769.
- 115 Guenzi, A. and Zanetti, M., Determination of aniracetam and its main metabolite, N-anisoyl-GABA, in human plasma by high-performance liquid chromatography, *J. Chromatogr.*, 530 (1990) 397–406.
- 116 Hall, E.D. and Von Voigtlander, P.F., Facilitatory effects of piracetam on excitability of motor nerve terminals and neuromuscular transmission, *Neuropharmacology*, 26 (1987) 1573–1579.
- 117 Hara, C. and Ogawa, N., Characteristic of learning deficit induced by ibotenic acid lesion of the frontal cortex related with the nucleus basalis of Meynert in rats, *Adv. Behav. Biol.*, 38A (1990) 735–738.
- 118 Häusler, A., Persoz, C., Buser, R., Mondadori, C. and Bhatnagar, A., Adrenalectomy, corticosteroid replacement and their

- importance for drug-induced memory-enhancement in mice. *J. Steroid. Biochem. Mol. Biol.*, 41 (1992) 785–789.
- 119 Hawkins, C.A. and Mellanby, J.H., Piracetam potentiates the antiepileptic action of carbamazepine in chronic experimental limbic epilepsy, *Acta Neurol. Scand.*, 74 Suppl. 109 (1986) 117–121.
- 120 Haynes Jr., R.C., Agents affecting calcification: calcium, parathyroid hormone, calcitonin, vitamin D and other compounds. In A. Goodman Gilman, T.W. Rall, A.S. Nies and P. Taylor (Eds.), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th edn., Elsevier Science/Pergamon Press, New York, 1990, p. 1498.
- 121 Heiss, W.D., Szelies, B., Kessler, J. and Herholz, K., Abnormalities of energy metabolism in Alzheimer's disease studied with PET, *Ann. NY Acad. Sci.*, 640 (1991) 65–71.
- 122 Herrmann, W.M. and Coper, H., Are nootropics a separate class of drugs? A differentiation in various models, *Methods Find. Exp. Clin. Pharmacol.*, 9 (1987) 173–182.
- 123 Herrmann, W.M. and Stephan, K., Efficacy and clinical relevance of cognition enhancers, *Alzheimer Dis. Assoc. Disord.*, 5 Suppl. 1 (1991) 7–12.
- 124 Hibert, M.F., Mir, A.K. and Fozard, J.R., Serotonin (5-HT) Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 3*, Elsevier Science/Pergamon Press, Oxford, 1990, pp. 574, 583.
- 125 Hibert, M.F., Mir, A.K. and Fozard, J.R., Serotonin (5-HT) Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 3*, Elsevier Science/Pergamon Press, Oxford, 1990, pp. 574, 591, 592.
- 126 Hjorth, A., Browne, E., Jakobsen, K., Viskum, P. and Gyntelberg, F., Organic brain syndrome treated with oxiracetam. A double-blind randomized controlled trial, *Acta Neurol. Scand.*, 75 (1987) 271–276.
- 127 Hoffmann-La Roche, F. und Co. AG, Pyrrolidine derivatives, *Jpn. Kokai Tokkyo Koho*, JP 54,117,468 (1979) CA92:41755t.
- 128 Hokonohara, T., Sako, K., Shinoda, Y., Tomabechi, M. and Yonemasu, Y., The effects of oxiracetam (CT-848) on local cerebral glucose utilization after focal cerebral ischemia in rats, *Jpn. J. Pharmacol.*, 58 (1992) 127–135.
- 129 Hokonohara, T., Shinoda, Y. and Hori, N., Effects of oxiracetam on the decrease in population spikes in hypoxic and low glucose media, *Nippon Yakurigaku Zasshi*, 99 (1992) 123–133.
- 130 Horn, A.S., Dopamine Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 3*, Elsevier Science/Pergamon Press, Oxford, 1990, pp. 238, 264, 273.
- 131 ICS, Consulting und Service Co., AG, Heterocyclic carboxylic acid hydrazides and their pharmaceutically compatible salts, *Austrian*, AT 371.437 (1983) CA99:139783v.
- 132 Ince, F., Peripheral Dopamine Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 3*, Elsevier Science/Pergamon Press, Oxford, 1990, pp. 312, 319.
- 133 Isaacson, J.S. and Nicoll, R.A., Aniracetam reduces glutamate receptor desensitization and slows the decay of fast excitatory synaptic currents in the hippocampus, *Proc. Natl. Acad. Sci. U.S.A.*, 88 (1991) 10936–10940.
- 134 Itil, T.M., Menon, G.N., Songar, A. and Itil, K.Z., CNS pharmacology and clinical therapeutic effects of oxiracetam, *Clin. Neuropharmacol.*, 9 Suppl. 3 (1986) 70–72.
- 135 Ito, I., Tanabe, S., Kohda, A. and Sugiyama H., Allosteric potentiation of quisqualate receptors by a nootropic drug, aniracetam, *J. Physiol.*, 424 (1990) 533–543.
- 136 Itoh, J., Nabeshima, T. and Kameyama, T., Utility of an elevated plus-maze for the evaluation of memory in mice: effects of nootropics, scopolamine and electroconvulsive shock, *Psychopharmacology*, 101 (1990) 27–33.
- 137 Izquierdo, I., Dopamine receptors in the caudate nucleus and memory processes, *TiPS*, 13 (1992) 7–8.
- 138 Izquierdo, I. and Medina, J.H., GABA_A receptor modulation of memory: the role of endogenous benzodiazepines, *TiPS*, 12 (1991) 260–265.
- 139 Izquierdo, I., Da-Cunha, C., Huang, C.H., Walz R., Wolfman, C. and Medina, J.H., Post-training down-regulation of memory consolidation by a GABA-A mechanism in the amygdala modulated by endogenous benzodiazepines, *Behav. Neurol. Biol.*, 54 (1990) 105–109.
- 140 Izquierdo, I., Medina, J.H., Da-Cunha, C., Wolfman, C., Jerusalinsky, D. and Ferreira, M.B.C., Memory modulation by brain benzodiazepines, *Braz. J. Med. Biol. Res.*, 24 (1991) 865–881.
- 141 Jacobsen, K.A., Adenosine (P₁) and ATP (P₂) Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 3*, Elsevier Science/Pergamon Press, Oxford, 1990, p. 618.
- 142 Jacobsen, K.A., Adenosine (P₁) and ATP (P₂) Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 3*, Elsevier Science/Pergamon Press, Oxford, 1990, p. 625.
- 143 Janicke, B. and Coper H., Effects of age and drugs on food and fluid intake, *Growth Dev. Aging*, 55 (1991) 139–150.
- 144 Janicke, B. and Wrobel, D., Changes in motor activity with age and the effects of pharmacologic treatment, *Exp. Gerontol.*, 19 (1984) 321–328.
- 145 Johnson, R.L., Long, Y.K., Taraporewala, I., Mishra, R.K. and Rajakumar, G., Conformationally restricted analogs of Pro-Leu-Gly-NH₂, *Pept. Struct. Funct., Proc. Am. Pept. Symp. 9th*, (1985) 671–674.
- 146 Kabeš, J., Erban, L., Hanzlič, L. and Skondia, V., Biological correlates of piracetam clinical effects in psychotic patients, *J. Int. Med. Res.*, 7 (1979) 277–284.
- 147 Kadushkin, A.V., Golovko, T.V., Granik, V.G., Glushkov, R.G., Parimbetova, R.B., Parshin, V.A. and Mashkovskii, M.D., New derivatives of pyrrolidine-2-thione and 2-methylenepyrrolidine: synthesis and pharmacological study, *Khim.-Farm. Zh.*, 23 (1989) 1301–1304.
- 148 Kadushkin, A.V., Golovko, T.V., Granik, V.G., Glushkov, R.G., Parimbetova, R.B., Parshin, V.A. and Mashkovskii, M.D., Novel piracetam derivatives and their thio analogs: synthesis and pharmacological study, *Khim.-Farm. Zh.*, 23 (1989) 1193–1196.
- 149 Kamei, C., Tsujimoto, S. and Tasaka, K., Effects of cholinergic drugs and cerebral metabolic activators on memory impairment in old rats, *J. Pharmacobio-Dyn.*, 13 (1990) 772–777.
- 150 Kameyama, T., Nabeshima, T., Tohyama, K., Ogawa, S., Murasc, K. and Ishihara, S., DM-9384, a pyrrolidone derivative, ameliorates basal forebrain lesion-induced amnesia and inhibits cycloheximide-induced decrease in the number of GABA and acetylcholine receptors, *Adv. Behav. Biol.*, 38B (1990) 371–374.
- 151 Kaneko, S., Sugimura, M., Inoue, T. and Satoh, M., Effects of several cerebroprotective drugs on NMDA channel function: evaluation using *Xenopus* oocytes and (3H)MK-801 binding, *Eur. J. Pharmacol.*, 207 (1991) 119–128.
- 152 Keith, R.A., Mangano, T.J., U'Prichard, D.C. and Salama, A.I., Inhibition of excitatory amino acid-induced neurotransmitter release by ω -conotoxin GVIA, an inhibitor of neuronal voltage-sensitive calcium channels, *Neurol. Neurobiol.: Front. Excitatory Amino Acid Res.*, 46 (1988) 47–50.
- 153 Klutchko, S., Hoefle, M.L., Smith, R.D., Essenburg, A.D., Parker, R.B., Nemeth, V.L., Ryan, M., Dugan, D.H. and Kaplan, H.R., Synthesis and angiotensin-converting enzyme inhibitory activity of 3-(mercaptomethyl)-2-oxo-1-pyrrolidineacetic acids and 3-(mercaptomethyl)-2-oxo-1-piperidineacetic acids, *J. Med. Chem.*, 24 (1981) 104–109.
- 154 Kojima, H., Kawajiri, S., Sakurai, T. and Yamasaki, T., Effect of

- DM-9384, a new pyrrolidone derivative, on passive avoidance and cerebral choline acetyltransferase activity in rats, *Adv. Behav. Biol.*, 38B (1990) 367–370.
- 155 Kometani, M., Okada, M., Takemori, E., Hasegawa, Y., Nakao, N. and Inukai, T., Effect of oxiracetam on cerebrovascular impairment in rats, *Arzneim.-Forsch. / Drug Res.*, 41 (1991) 684–689.
- 156 Komissarov, I.V., Abramets, I.I. and Samoilovich, I.M., The aspartate/NMDA-sensitizing effect of piracetam, *Dokl. Akad. Nauk. SSSR*, 316 (1991) 501–503.
- 157 Kovalev, G.I., Raevskii, K.S., Kovalev, G.V., Grineva, V.S., Kiseleva, I.N. and Perekalin, V.V., Effect of substances structurally related to β -phenyl- γ -aminobutyric acid (phenibut) on the accumulation of labeled (^3H)GABA in rat brain synaptosomes, *Tr. Volgogr. Gos. Med. Inst.*, 31 (1979) 40–43.
- 158 Kraaier, V., van-Huffelen, A.C. and Wieneke, G.H., The hyper-ventilation-induced ischaemia model in human neuropharmacology: neurophysiological and psychometric studies of aniracetam and 3-OH aniracetam, *Eur. J. Clin. Pharmacol.*, 36 (1989) 605–611.
- 159 Kretschmar, G. and Hock, F. (Hoechst AG), Preparation of *N*-substituted 3,4-dihydropyrrolidin-2-ones as psychotropic agents, *Eur. Pat. Appl.*, EP 338,435 (1989) CA112:198119t.
- 160 Krogsgaard-Larsen, P., Amino Acid Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 3*, Elsevier Science/Pergamon Press, Oxford, 1990, p. 503.
- 161 Krogsgaard-Larsen, P., Amino Acid Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 3*, Elsevier Science/Pergamon Press, Oxford, 1990, p. 505.
- 162 Krogsgaard-Larsen, P., Amino Acid Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 3*, Elsevier Science/Pergamon Press, Oxford, 1990, pp. 510, 512.
- 163 Krogsgaard-Larsen, P., Amino Acid Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry, Vol. 3*, Elsevier Science/Pergamon Press, Oxford, 1990, p. 511.
- 164 Krylova, I.N., Antonova, L.V., Kamenskii, A.A. and Yasnetsov, V.V., A comparative study of the nootropic properties of piracetam and oxiracetam, *Farmakol. Toksikol.*, 54 (1991) 14–16.
- 165 Kuleshova, E.F., Kadushkin, A.V., Anisimova, O.S., Solov'eva, N.P., Sheinker, Y.N., Golovko, T., Granik, V.G., Glushkov, R.G., Parshin, V.A. et al., Biotransformation of 1-thiocarbamoylmethylpyrrolidine-2-thione, *Khim.-Farm. Zh.*, 24 (1990) 7–11.
- 166 Kuribara, H. and Tadokoro S., Facilitating effect of oxiracetam and piracetam on acquisition of discrete two-way shuttle avoidance in normal mice, *Jpn. J. Pharmacol.*, 48 (1988) 494–498.
- 167 Kurono, M., Hayashi, M., Suzuki, T., Miura, K., Matsumoto, K. and Miyano, S. (Sanwa Kagaku Kenkyusho Co., Ltd.), Preparation of 7a-(2-oxopyrrolidinoacetamidoalkyl)pyrrolizidine derivatives for the treatment of brain dysfunction, *Jpn. Kokai Tokkyo Koho*, JP 61,254,587 (1986) CA106:169057s.
- 168 Kurono, M., Hayashi, M., Suzuki, T., Miura, K., Kumagai, Y., Matsumoto, K., Miyano, S. and Sumoto, K. (Sanwa Kagaku Kenkyusho Co. Ltd.), Preparation of 2-pyrrolidinone derivatives as preventive and therapeutic agents for brain disorders, *Jpn. Kokai Tokkyo Koho*, JP 62,22,785 (1987) CA107:77618t.
- 169 Kurono, M., Suzuki, T., Suzuki, T., Hirooka, K., Matsumoto, Y., Ozawa, H. and Sawai, K. (Sanwa Kagaku Kenkyusho Co. Ltd.), Piracetam-related 1-pyrrolidineacetamide derivatives, processes for their preparation and their pharmaceutical compositions for therapy of cerebral dysfunction, *Eur. Pat. Appl.*, EP 299,495 (1989) CA111:7217v.
- 170 Kuwahara, A., Kubota, A., Hakkei, M. and Nakamura, K., Drug dependence test on a cerebral insufficiency improver, aniracetam, *Nippon Yakurigaku Zasshi*, 89 (1987) 33–46.
- 171 Lange, F.W. and Müller, J. (Chemisches Laboratorium Fritz-Walter Lange GmbH und Co. KG), Psychopharmaceutical *N*-((1-ethyl-2-pyrrolidiny)-methyl)-2-methoxy-5-sulfamoylbenzamide, *Ger. Offen.*, DE 2,253,463 (1974) CA81:91342z.
- 172 Lange, F.W. and Müller, J. (Chemisches Laboratorium Fritz-Walter Lange GmbH und Co. KG), Oxopyrrolidino- and oxopiperidinoalkanoic acid hydrazides, *Ger. Offen.*, DE 2,745,907 (1979) CA91:56814q.
- 173 Lange, F.W., Jacobi, H. and Müller, J. (Chemisches Laboratorium Fritz-Walter Lange GmbH und Co. KG), (2-Oxopyrrolidino)-1-acetic acid hydrazide, *Swiss*, CH 618,426 (1980) CA93:204453e.
- 174 Lange, F.W., Jacobi, H. and Müller, J. (Chemisches Laboratorium Fritz-Walter Lange GmbH und Co. KG), (2-Oxo-1-pyrrolidino)acetic acid hydrazides, *Can.*, CA 1,065,875 (1979) CA92:180999p.
- 175 Lazarova-Bakarova, M.B. and Genkova-Papasova, M.G., Influence of nootropic drugs on the memory-impairing effect of clonidine in albino rats, *Methods Find. Exp. Clin. Pharmacol.*, 11 (1989) 235–239.
- 176 Lecaillon, J.B., Dubois, J.P., Coppens, H., Darragon, T., Theobald, W., Reumond, G. and Beck, H., Pharmacokinetics of oxiracetam in elderly patients after 800 mg oral doses, comparison with non-geriatric healthy subjects, *Eur. J. Drug Metab. Pharmacokinet.*, 15 (1990) 223–230.
- 177 Lecaillon, J.B., Dubois, J.P., Coppens, H., Darragon, T., Reumond, G., Pozet, N., Traeger, J. and Lambrey, G., Pharmacokinetics of oxiracetam in patients with renal impairment after a 800 mg single oral dose, *Eur. J. Drug Metab. Pharmacokinet.*, 15 (1990) 231–237.
- 178 Lecaillon, J.B., Souppart, C., Le-Duigou, F. and Dubois, J.P., Determination of oxiracetam in plasma and urine by column-switching high-performance liquid chromatography, *J. Chromatogr.*, 497 (1989) 223–230.
- 179 Lenègre, A., Chermat, R., Avril, I., Stéru, L. and Porsolt, R.D., Specificity of piracetam's anti-amnesic activity in three models of amnesia in the mouse, *Pharmacol. Biochem. Behav.*, 29 (1988) 625–629.
- 180 Leonard, N.J., Hruda, L.R. and Long, F.W., Synthesis of pyrrolizidines, *J. Am. Chem. Soc.*, 69 (1947) 690.
- 181 Levinson, H.N., Dramatic favorable responses of children with learning disabilities or dyslexia and attention deficit disorder to antimotion sickness medications: four case reports, *Percept. Mot. Skills*, 73 (1991) 723–738.
- 182 Lister, R.G., The effects of benzodiazepines and 5-HT_{1A} agonists on learning and memory. In R.J. Rodgers and S.J. Cooper (Eds.), *5-HT_{1a} Agonists, 5-HT₃ Antagonists and Benzodiazepines. Their Comparative Behavioural Pharmacology*, John Wiley, New York, 1991, pp. 267–280.
- 183 L'Italien, Y.J. and Nordin, I.C. (Parke, Davis and Co.), *N*-(Substituted aminoalkyl)-2-oxo-1-pyrrolidine acetamides, *Ger. Offen.*, DE 2,808,067 (1978) CA90:22798b.
- 184 L'Italien, Y.J. (Warner-Lambert Co.), Quaternary derivatives of *N*-(substituted aminoalkyl)-2-oxo-1-pyrrolidineacetamides as cognition activators, *U.S.*, US 4,372,960 (1983) CA98:160585w.
- 185 L'Italien, Y.J. and Nordin, I.C. (Parke, Davis and Co.), *N*-(Substituted aminoalkyl)-2-oxo-1-pyrrolidineacetamides, *U.S.*, US 4,145,347 (1979) CA91:39332p.
- 186 Lodge, D., Ligands for NMDA receptor modulatory sites, in P. Krogsgaard-Larsen and J.J. Hansen, *Excitatory Amino Acid Receptors, Design of Agonists and Antagonists*, Ellis Horwood, Chichester, 1991, pp. 207.
- 187 Lukes, R. and Sorm, F., Symmetrical amino dicarboxylic acids and their cyclization, *Coll. Czech. Chem. Commun.*, 12 (1947) 278–291 (pp. 278, 287).

- 188 Luthman, J., Lindqvist, E., Dell'anna, E., Kojima, H., Shiotani, T., Tachizawa, H. and Olson, L., Effects of DM-9384, a pyrrolidone derivative, on ischemia-induced changes in the central monoamine systems, *Pharmacol. Biochem. Behav.*, 41 (1992) 231–234.
- 189 Magnani, M., Pozzi, O., Biagetti, R., Banfi, S. and Dorigotti, L., Oxiracetam antagonizes the disruptive effects of scopolamine on memory in the radial maze, *Psychopharmacology*, 106 (1992) 175–178.
- 190 Main, B.G., β -Adrenergic Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry*, Vol. 3, Elsevier Science/Pergamon Press, Oxford, 1990, p. 193.
- 191 Maina, G., Fiori, L., Torta, R., Fagiani, M.B., Ravizza, L., Bonavita, E., Ghiazza, B., Teruzzi, F., Zagnoni, P.G. and Ferrario, E., Oxiracetam in the treatment of primary degenerative and multi-infarct dementia: a double-blind, placebo-controlled study, *Neuropsychobiology*, 21 (1989) 141–145.
- 192 Marchi, M., Besana, E. and Raiteri, M., Oxiracetam increases the release of endogenous glutamate from depolarized rat hippocampal slices, *Eur. J. Pharmacol.*, 185 (1990) 247–249.
- 193 Martin, J.R., Cumin, R., Aschwanden, W., Moreau, J.L., Jenck, F. and Haefely, W.E., Aniracetam improves radial maze performance in rats, *Neuroreport*, 3 (1992) 81–83.
- 194 Martindale, *The Extra Pharmacopoeia*, 29th edn., The Pharmaceutical Press, London, 1989.
- 195 McLean Jr., A., Cardenas, D.D., Burgess, D. and Gamzu, E., Placebo-controlled study of pramiracetam in young males with memory and cognitive problems resulting from head injury and anoxia, *Brain Inj.*, 5 (1991) 375–380.
- 196 Mennini, T., Taddei, C., Cagnotto, A. and Ponzio, F., In-vivo radiolabelled oxiracetam binding to rat brain, *J. Pharm. Pharmacol.*, 42 (1990) 171–174.
- 197 *Merck Index*, The, 11th edn., Merck & Co. Inc., Rahway, NJ, USA, 1989.
- 198 Merlini, L. and Pinza, M., Trends in searching for new cognition enhancing drugs, *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 13 (1989) 61–75.
- 199 Micheel, F. and Albers, H., Pyrrolizidine derivatives, *Liebigs Ann. Chem.*, 581 (1953) 225–227 (pp. 225, 226, 233).
- 200 Micheel, F. and Flitsch, W., Pyrrolizidine derivatives. III. A simple synthesis of 3,4-dioxopyrrolizidine, *Chem. Ber.*, 88 (1955) 509–510 (p. 509).
- 201 Mishra, R.K., Srivastava, L.K. and Johnson, R.L., Modulation of high-affinity CNS dopamine D_2 receptor by L-Pro-L-Leu-glycinamide (PLG) analog 3(R)-(N-L-prolylamino)-2-oxo-1-pyrrolidin acetamide, *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, 14 (1990) 821–827.
- 202 Miyazaki, C., Matsuyama, K., Ichikawa, M., Goto, S. and Yamamoto, J., Synthesis of valproyl-2-pyrrolidinone and its evaluation as a cognitive drug with the ability to modulate acidic amino acids in the brain, *J. Pharmacobiodyn.*, 13 (1990) 70–75.
- 203 Mochizuki, D., Sugiyama, S. and Shinoda, Y., Biochemical studies of oxiracetam (CT-848) on cholinergic neurons, *Nippon Yakurigaku Zasshi*, 99 (1992) 27–35.
- 204 Moglia, A., Sinfiorani, E., Zandrini, C., Gualtieri, S. and Corsico, R., Arrigo, A., Activity of oxiracetam in patients with organic brain syndrome: a neuropsychological study, *Clin. Neuropharmacol.*, 9 Suppl. 3 (1986) 73–78.
- 205 Molchan, S.E., Sunderland, T., Mellow, M., Lawlor, A., Cohen, R.M., Cohen, M.R., Weingartner, H. and Murphy, D.L., *Pep-tidergic neuromodulation of scopolamine-induced memory impairment by thyrotropin-releasing hormone in humans*. 27th Annu. Meet. Am. College Neuropsychopharmacology (Dec. 11–16, San Juan), 189 (1988).
- 206 Mondadori, C., Bhatnagar, A., Borkowski, J. and Häusler, A., Involvement of a steroidal component in the mechanism of action of piracetam-like nootropics, *Brain Res.*, 506 (1990) 101–108.
- 207 Mondadori, C., Classen, W., Borkowski, J., Ducret, T., Buerki, H. and Schade, A., Effects of oxiracetam on learning and memory in animals: comparison with piracetam, *Clin. Neuropharmacol.*, 9 Suppl. 3 (1986) 27–38.
- 208 Mondadori, C., Ducret, T. and Borkowski, J., The memory-enhancing effects of the piracetam-like nootropics are dependent on experimental parameters, *Behav. Brain Res.*, 33 (1989) 79–82.
- 209 Mondadori, C., Ducret, T. and Borkowski, J., How long does 'memory consolidation' take? New compounds can improve retention performance, even if administered up to 24 hours after the learning experience, *Brain Res.*, 555 (1991) 107–111.
- 210 Mondadori, C., Ducret, T. and Häusler, A., Elevated corticosteroid levels block the memory-improving effects of nootropics and cholinomimetics, *Psychopharmacology*, 108 (1992) 11–15.
- 211 Mondadori, C., Ducret, T. and Petschke, F., Blockade of the nootropic action of piracetam-like nootropics by adrenalectomy: an effect of dosage?, *Behav. Brain Res.*, 34 (1989) 155–158.
- 212 Mondadori, C. and Häusler, A., Aldosterone receptors are involved in the mediation of the memory-enhancing effects of piracetam, *Brain Res.*, 524 (1990) 203–207.
- 213 Mondadori, C. and Petschke, F., Do piracetam-like compounds act centrally via peripheral mechanisms?, *Brain Res.*, 435 (1987) 310–314.
- 214 Mondadori, C., Petschke, F. and Häusler, A., The effects of nootropics on memory: new aspects for basic research, *Pharmacopsychiatry*, 22 Suppl. 2 (1989) 102–106.
- 215 Mondadori, C. and Schmutz, M., Synergistic effects of oxiracetam and piracetam in combination with antiepileptic drugs, *Acta Neurol. Scand. Suppl.*, 109 (1986) 113–116.
- 216 Mondadori, C., Schmutz, M. and Baltzer, V., Potentiation of the anticonvulsant effects of antiepileptic drugs by 'Nootropics': a potential new therapeutic approach, *Acta Neurol. Scand.*, 69 Suppl. 99 (1984) 131–132.
- 217 Monguzzi, R. and Pifferi, G. (I.S.F.S.p.A.), 4-Hydroxypyrrolidin-2-on-1-ylalkylcarboxylic acid esters, *Ger. Offen.*, DE 2,759,033 (1978) CA90:22797a.
- 218 Morita, S., Saito, K., Ninomiya, K., Tobe, A., Nitta, K. and Kanno, M. (Mitsubishi Kasei Corp.), Preparation of 9-acylamino-tetrahydroacridine derivatives as memory improvers, *Jpn. Kokai Tokkyo Koho*, JP 03 02,166 (1991) CA115:71418w.
- 219 Mouravieff-Lesuisse, F. and Giurgea, C.E., Pharmacological reactivity of an experimental model of memory: the spinal cord fixation, *Arch. Int. Pharmacodyn. Ther.*, 176 (1968) 471–472.
- 220 Murray, C.L. and Fibiger, H.C., The effect of pramiracetam (CI-879) on the acquisition of a radial arm maze task, *Psychopharmacology*, 89 (1986) 378–381.
- 221 Müller, W.E., Restoration of age-related receptor deficits in the central nervous system, a common mechanism of nootropic action?, *Methods Find. Exp. Clin. Pharmacol.*, 10 (1988) 773–783.
- 222 Nabeshima, T., Noda, Y., Tohyama, K., Itoh, J. and Kameyama, T., Effects of DM-9384 in a model of amnesia based on animals with GABAergic neuronal dysfunctions, *Eur. J. Pharmacol.*, 178 (1990) 143–149.
- 223 Nabeshima, T., Noda, Y. and Kameyama, T., GABAergic modulation of memory with regard to passive avoidance and conditioned suppression task in mice, *Psychopharmacology*, 94 (1988) 69–73.
- 224 Nabeshima, T., Noda, Y., Tohyama, S. and Kameyama, T., Antiamnesic effects of DM-9384, a pyrrolidone derivative on drug-induced amnesia animal models, *Psychopharmacology*, 96 Suppl. (1988) 305 (P32.02.22).
- 225 Nabeshima, T., Ogawa, S., Kameyama, T., Shiotani, T., Takasu, Y., Sakurai, T., Hasegawa, M. and Hasegawa, T., Effects of

- DM-9384 and aniracetam on learning in normal and basal forebrain-lesioned rats, *Res. Commun. Psychol. Psychiatry Behav.*, 16 (1991) 1–14.
- 226 Nabeshima, T., Tohyama, K. and Kameyama, T., Effects of DM-9384, a pyrrolidone derivative, on alcohol- and chlordiazepoxide-induced amnesia in mice, *Pharmacol. Biochem. Behav.*, 36 (1990) 233–236.
- 227 Nabeshima, T., Tohyama, K., Murase, K., Ishihara, S., Kameyama, T., Yamasaki, T., Hatanaka, S., Kojima, H., Sakurai, T. and Takasu, Y., Effects of DM-9384, a cyclic derivative of GABA, on amnesia and decreases in GABA_A and muscarinic receptors induced by cycloheximide, *J. Pharmacol. Exp. Ther.*, 257 (1991) 271–275.
- 228 Nardella, C., Terracina, L., Brunetti, M., Avellini, L., De-Medio, G.E., Gaiti, A., Belfiore, P. and Mariani, O., Choline incorporation into phospholipids in brain areas from spontaneously hypertensive rats: effect of oxiracetam treatment, *Farmaco*, 46 (1991) 1051–1059.
- 229 Naumova, V.I., Krylova, I.N., Drozd, Yu.V., Polev, P.V., Bashnin Yu.I., Comparative influence of nootropic preparations on the emetic effect of morphine, *Byull. Eksp. Biol. Med.*, 107 (1989) 711–713.
- 230 Nicholson, C.D., Nootropics and metabolically active compounds in Alzheimer's disease, *Biochem. Soc. Trans.*, 17 (1989) 83–85.
- 231 Nicholson, C.D., Pharmacology of nootropics and metabolically active compounds in relation to their use in dementia, *Psychopharmacology*, 101 (1990) 147–159.
- 232 Nickolson, V.J. and Wolthuis, O.L., Differential effects of the acquisition enhancing drug pyrrolidoneacetamide (piracetam) on the release of proline from visual and parietal rat cerebral cortex in vitro, *Brain Res.*, 113 (1976) 616–619.
- 233 Nickolson, V.J. and Wolthuis, O.L., Effect of the acquisition-enhancing drug piracetam on rat cerebral energy metabolism. Comparison with naftidrofuryl and methamphetamine, *Biochem. Pharmacol.*, 25 (1976) 2241–2244.
- 234 Nicolaus, B.J.R., Chemistry and pharmacology of nootropics, *Drug Dev. Res.*, 2 (1982) 463–474.
- 235 Nieminen, S.A., Huttunen, L., Haapalinna, A. and Airaksinen, M.M., Comparison of memory effects in posttraining and pretesting administrations of atipamezole in the passive avoidance test in rats, *Acta Physiol. Scand. Suppl.*, 146 (1992) P2.44.
- 236 Nietsch, P., Piracetam zur Behandlung von Hirnleistungen, neuere Doppelblindstudien und die therapeutischen Konsequenzen, *Therapiewoche*, 39 (1989) 230–234.
- 237 Nikolova, M., Pyramem combinations. Quantitative electroencephalographic studies as a basis for evaluating their effects on brain function, *Med.-Biol. Inf.*, 1 (1989) 3–8.
- 238 Ninomiya, K., Saito, K., Morita, S., Tobe, A. and Nitta, I. (Mitsubishi Kasei Corp.), Preparation of (5-oxopyrrolidine-1-yl)acetylglucylaminopyridine derivatives as cognitive performance enhancers, *Eur. Pat. Appl.*, EP 308,337 (1989) CA111:115750x.
- 239 Ninomiya, K., Saito, K., Morita, S., Tobe, A. and Nitta, I. (Mitsubishi Kasei Corp.), Preparation of 4-piperidinecarboxamide derivatives as psychoanaleptics, *Eur. Pat. Appl.*, EP 308,319 (1989) CA112:7374q.
- 240 Ninomiya, K., Saito, K., Sugano, M., Tobe, A., Morinaka, Y., Bessho, T. and Harada, H. (Mitsubishi Kasei Corp.), Preparation of 4-acylamino-pyridine derivatives for treatment of Alzheimer's disease, *Eur. Pat. Appl.*, EP 427,636 (1991) CA115:136076e.
- 241 Novikov, V.E and Sharov, A., The effect of GABA-ergic agents on oxidative phosphorylation in the brain mitochondria in traumatic edema, *Farmakol. Toksikol.*, 54 (1991) 44–46.
- 242 Ocain, T.D., Timothy, D. and Deininger, D.D. (American Home Products Corp.), Preparation of peptide renin inhibitors, U.S., US 5,023,338 (1991) CA115:256655q.
- 243 Ohno, M., Yamamoto, T., Kitajima, I., Ueki, S., WEB 1881 FU ameliorates impairment of working memory induced by scopolamine and cerebral ischemia in the three-panel runway task, *Jpn. J. Pharmacol.*, 54 (1990) 53–60.
- 244 Olpe, H.R., Pozza, M.F., Jones, R.S. and Haas, H.L., Comparative electrophysiological investigations on oxiracetam and piracetam, *Clin. Neuropharmacol.*, 9 Suppl. 3 (1986) 48–55.
- 245 Olpe, H.R. and Steinman, W.M., The effect of vincamine, hydergine and piracetam on the firing rate of locus coeruleus neurons, *J. Neural Transmission*, 55 (1982) 101–109.
- 246 Oshiro, Y., Sakurai, Y., Tanaka, T., Kikuchi, T., Hirose, T. and Tottori, K., Novel cerebroprotective agents with central nervous system stimulating activity. 2. Synthesis and pharmacology of the 1-(acylamino)-7-hydroxyindan derivatives, *J. Med. Chem.*, 34 (1991) 2014–2023.
- 247 Oshiro, Y., Ueda, H. and Nakagawa, K., (Otsuka Pharmaceutical Co. Ltd.), 2,3-Dihydro-1H-indene derivatives and pharmaceutical compositions containing them, *Eur. Pat. Appl.*, EP 173,331 (1986) CA105:42509q.
- 248 Ostrovskaya, R.U., Molodavkin, G.M., Trofimov, S.S., Popova, R.Ya., Gudashcheva, T.A. and Skoldinov, A.P., Neuropharmacological properties of piracetam derivatives, *Byull. Eksp. Biol. Med.*, 94 (1982) 62–65.
- 249 Ozawa, S., Iino, M. and Abe, M., Excitatory synapse in the rat hippocampus in tissue culture and effects of aniracetam (sic!), *Neurosci. Res.*, 12 (1991) 72–82.
- 250 Paoli, F., Spignoli, G. and Pepeu, G., Oxiracetam and D-pyroglytamic acid antagonize a disruption of passive avoidance behaviour induced by the N-methyl-D-aspartate receptor antagonist 2-amino-5-phosphonovalerate, *Psychopharmacology*, 100 (1990) 130–131.
- 251 Parnetti, L., Mecocci, P., Gaiti, A., Cadini, D., Lombardi, F., Visconti, M. and Senin, U., Comparative kinetics of oxiracetam in serum and CSF of patients with dementia of Alzheimer type, *Eur. J. Drug Metab. Pharmacokinet.*, 15 (1990) 75–78.
- 252 Parnetti, L., Mecocci, P., Petrini, A., Longo, A., Buccolieri, A. and Senin, U., Neuropsychological results of long-term therapy with oxiracetam in patients with dementia of Alzheimer type and multi-infarct dementia in comparison with a control group, *Neuropsychobiology*, 22 (1989) 97–100.
- 253 Passeri, M.A., A multicentre study of piracetam in patients with late onset senile dementia. In *Symposium on Piracetam: 5 Years' Progress in Pharmacology and Clinics*, Tecnicas Graficas Formas, Madrid, 1990, pp. 75–80.
- 254 Paula-Barbosa, M.M., Brandao, F., Pinho, M.C., Andrade, J.P., Madeira, M.D. and Cadete-Leite, A., The effects of piracetam on lipofuscin of the rat cerebellar and hippocampal neurons after long-term alcohol treatment and withdrawal: a quantitative study, *Alcohol. Clin. Exp. Res.*, 15 (1991) 834–838.
- 255 Paulus, W., Ried, S., Stodieck, S.R. and Schmidt, D., Abolition of photoparoxysmal response in progressive myoclonus epilepsy, *Eur. Neurol.*, 31 (1991) 388–390.
- 256 Pavia, M.R., Davis, R.E. and Schwarz, R.D., Cognition enhancers, *Ann. Rep. Med. Chem.*, 25 (1990) 21–29.
- 257 Pavlik, A., Benesova, O. and Dlohozkova, N., Effects of nootropic drugs on brain cholinergic and dopaminergic transmission, *Act. Nerv. Super. Praha*, 29 (1987) 62–65.
- 258 Pellegata, R., Pinza, M., Pifferi, G., Gaiti, A., Mozzi, R., Tirillini, B. and Porcellati, G., Cyclic GABA-GABOB analogs. III. Synthesis and biochemical activity of new alkyl and acyl derivatives of 4-hydroxy-2-pyrrolidinone, *Farmaco Ed. Sci.*, 36 (1981) 845–855.

- 259 Pepeu, G. and Spignoli, G., Nootropic drugs and brain cholinergic mechanisms, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 13 Suppl. (1989) 77–88.
- 260 Pepeu, G., Spignoli, G., Giovannini, M.G. and Magnani, M., The relationship between the behavioral effects of cognition-enhancing drugs and brain acetylcholine. Nootropic drugs and brain acetylcholine, *Pharmacopsychiatry*, 22 Suppl. 2 (1989) 116–119.
- 261 Perini, S., Brunetti, M., Parnetti, L., De-Medio, G.E., Trovarelli, G., Banfi, S., Dorigotti, L. and Gaiti, A., The effect of oxiracetam treatment on alterations of lipid metabolism in brain areas from spontaneously hypertensive rats, *Pharmacol. Res.*, 21 (1989) 313–323.
- 262 Perio, A., Terranova, J.P., Worms, P., Bluthe, R.M., Dantzer, R. and Biziere, K., Specific modulation of social memory in rats by cholinomimetic and nootropic drugs, by benzodiazepine inverse agonists, but not by psychostimulants, *Psychopharmacology*, 97 (1989) 262–268.
- 263 Perucca, E., Albrici, A., Gatti, G., Spalluto, R., Visconti, M. and Crema, A., Pharmacokinetics of oxiracetam following intravenous and oral administration in healthy volunteers, *Eur. J. Drug Metab. Pharmacokinet.*, 9 (1984) 267–274.
- 264 Perucca, E., Parini, J., Albrici, A., Visconti, M. and Ferrero, E., Oxiracetam pharmacokinetics following single and multiple dose administration in the elderly, *Eur. J. Drug Metab. Pharmacokinet.*, 12 (1987) 145–148.
- 265 Petkov, V.D., Grahovska, T., Petkov, V.V., Konstantinova, E. and Stancheva, S., Changes in the brain biogenic monoamines of rats, induced by piracetam and aniracetam, *Acta Physiol. Pharmacol. Bulg.*, 10 (1984) 6–15.
- 266 Petkov, V.D. and Kehayov, R., Individually determined differences in the effects of psychotropic drugs on memory (experiments on rats), *Acta Physiol. Pharmacol. Bulg.*, 13 (1987) 30–36.
- 267 Petkov, V.D., Konstantinova, E.R., Petkov, V.V. and Vaglenova, J.V., Learning and memory in rats exposed pre- and postnatally to alcohol. An attempt at pharmacological control, *Methods Find. Exp. Clin. Pharmacol.*, 13 (1991) 43–50.
- 268 Petkov, V.D., Lazarova, M.B., Belcheva, S., Getova, D., Petkova, B., Petkov, V.V., Stancheva, S., Alova, L., Konstantinova, E. and Todorov, I., Memory effects of a group of newly synthesized pyrrolidine derivatives with putative nootropic effect, *Acta Physiol. Pharmacol. Bulg.*, 17 (1991) 61–74.
- 269 Petkov, V.D., Mosharraf, A.H., Milenkov, B. and Enev, V., Learning and memory effects of four newly synthesized aniracetam analogues, *Acta Physiol. Pharmacol. Bulg.*, 15 (1989) 18–27.
- 270 Pico, R.M., Keller, E., Cherkin, A. and Davis, J.L., Brain glutamate inhibition and amnesia: evidence provided by proline analog action, *Dev. Brain Res.*, 9 (1983) 227–230.
- 271 Piercey, M.F., Vogelsang, G.D., Franklin, S.R. and Tang, A.H., Reversal of scopolamine-induced amnesia and alterations in energy metabolism by the nootropic piracetam: implications regarding identification of brain structures involved in consolidation of memory traces, *Brain Res.*, 424 (1987) 1–9.
- 272 Pierlovisi-Lavaivre, M., Michel, B., Sebban, C., Tesolin, B., Chave, B., Sambuc, R., Melac, M., Gastaut, J.L., Poitrenaud, J. and Millet, Y., The significance of quantified EEG in Alzheimer's disease. Changes induced by piracetam, *Neurophysiol. Clin.*, 21 (1991) 411–423.
- 273 Pifferi, G. and Pinza, M., Cyclic GABA(4-aminobutyric acid)-GABOB(4-amino-3-hydroxybutyric acid) analogs. I. Synthesis of new 4-hydroxy-2-pyrrolidinone derivatives, *Farmaco Ed. Sci.*, 32 (1977) 602–613.
- 274 Pifferi, G. and Pinza, M. (I.S.F.S.p.A.), Pharmaceutical pyrrolidin-2-one derivatives, *Ger. Offen.*, DE 2,635,853 (1977) CA86:171253q.
- 275 Pifferi, G. and Pinza, M. (I.S.F.S.p.A.), Pharmaceutical pyrrolidin-2-one derivatives, *Ger. Offen.*, DE 2,635,854 (1977) CA86:171252p.
- 276 Pilch, H. and Müller, W.E., Piracetam elevates muscarinic cholinergic receptor density in the frontal cortex of aged but not of young mice, *Psychopharmacology*, 94 (1988) 74–78.
- 277 PLIVA, Tvornic Farmaceutskih i Kimijskih Proizvoda Firma Helm K.O., 2-Oxo-1-pyrrolidine derivatives, *Neth. Appl.*, NL 77 00,408 (1977) CA88:23392k.
- 278 Pontecorvo, M.J. and Evans, H.L., Effects of aniracetam on delayed matching-to-sample performance of monkeys and pigeons, *Pharmacol. Biochem. Behav.*, 22 (1985) 745–752.
- 279 Ponzio, F., Belfiore, P. and Dorigotti, L., Effect of oxiracetam on cerebral cholinergic imbalance secondary to an NMDA-receptor blockade, *Pharmacol. Res.*, 21 Suppl. 1 (1989) 103–104.
- 280 Ponzio, F., Pozzi, O., Banfi, S. and Dorigotti, L., Brain entry and direct central pharmacological effects of the nootropic drug oxiracetam. Oxiracetam: brain entry and pharmacological effects, *Pharmacopsychiatry*, 22 Suppl. 2 (1989) 111–115.
- 281 Popova, R., Gudasheva, T.A., Trofimov, S.S., Ostrovskaya, R.U. and Skoldinov, A.P., Pharmacological activity of piracetam analogs and cyclohomologs, *Khim.-Farm. Zh.*, 17 (1983) 1439–1445.
- 282 Poschel, B.P.H., New pharmacological perspectives on nootropic drugs. In L.L. Iversen, S.D. Iversen and S.H. Snyder (Eds.), *Psychopharmacology of the Aging Nervous System (Handbook of Psychopharmacology)*, Vol. 20, Plenum Press, New York, 1988, pp. 437–469.
- 283 Poschel, B.P.H., Recent pharmacologic developments in the search for cognition enhancing drugs. Developments in psychiatry, *Proceedings of the IVth World Congress of Biological Psychiatry, Biological Psychiatry*, 7 (1985) 1328–1330.
- 284 Poschel, B.P.H., Ho, P.M. and Ninteman, F.W., Arousal deficit in aged rats demonstrated by quantitative EEG and the ameliorative action of pramiracetam compared to piracetam, *Experientia*, 41 (1985) 1433–1435.
- 285 Poschel, B.P.H., Ho, P.M., Ninteman, F.W. and Callahan, M.J., Pharmacologic therapeutic window of pramiracetam demonstrated in behavior, EEG and single neuron firing rates, *Experientia*, 41 (1985) 1153–1156.
- 286 Poschel, B.P.H., Marriott, J.G. and Gluckman, M.I., Pharmacology of the cognition activator pramiracetam (CI-879), *Drugs Exp. Clin. Res.*, 9 (1983) 853–871.
- 287 Pugliese, A.M., Corradetti, R., Ballerini, L. and Pepeu, G., Effect of the nootropic drug oxiracetam on field potentials of rat hippocampal slices, *Br. J. Pharmacol.*, 99 (1990) 189–193.
- 288 Pugsley, T.A., Poschel, B.P.H., Downs, D.A., Shih, Y.H. and Gluckman, M.I., Some pharmacological and neurochemical properties of a new cognition activator agent, pramiracetam (CI-879), *Psychopharmacology Bull.*, 19 (1983) 721–726.
- 289 Pugsley, T.A., Shih, Y.H., Coughenour, L. and Stewart, S.F., Some neurochemical properties of pramiracetam (CI-879), a new cognition-enhancing agent, *Drug. Dev. Res.*, 3 (1983) 407–420.
- 290 Qian, Z.N., Gu, Z.L., Jin, L.Q., Xie, M.L. and Chen, B.Q., Effects of piracetam on Na⁺-K⁺-ATPase and monoamine oxidase in rat brain and its antioxidation effect, *Chung Kuo Yao Li Hsueh Pao*, 13 (1992) 48–50.
- 291 Rajakumar, G., Naas, F., Johnson, R.L., Chiu, S., Yu, K.L. and Mishra, R.K., Down-regulation of haloperidol-induced striatal dopamine receptor supersensitivity by active analogs of L-prolyl-L-leucyl-glycinamide (PLG), *Peptides*, 8 (1987) 855–861.
- 292 Rees, D.C. and Hunter, J.C., Opioid Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry*, Vol. 3, Elsevier Science/Pergamon Press, Oxford, 1990, p. 828.

- 293 Rochus, L. and Reuse, J.J., Chlorpromazine and phospholipid metabolism in the rat hypothalamus. Effect of pretreatment with piracetam, *Arch. Int. Physiol. Biochim.*, 82 (1974) 1010–1011.
- 294 Rodriguez, L. and Marchal, L. (UCB S.A.), Lactam-*N*-acetic acids and their amides, *Ger. Offen.*, DE 2,918,523 (1979) CA92:76284r.
- 295 Rodriguez, L. and Marchal, L. (UCB S.A.), Pharmaceutical *N*-substituted lactams, *Ger. Offen.*, DE 2,747,369 (1978) CA89:59834r.
- 296 Roger, P., Choay, P. and Fournier, J.P. (Roussel-UCLAF), Preparation of alkoxy-*N*-(arylsulfonyl)pyrrolidines as psychoanaleptic agents, *Eur. Pat. Appl.*, EP 229,566 (1988) CA 108:5855.
- 297 Rousseva, S., Petkov, V.V., Petkov, V.D., Voronina, T.A., Nerobkova, L.N., Ivanova, I.A., Stoyanova, V., Memory effects of the combination of medazepam with nootropic agents, *Acta Physiol. Pharmacol. Bulg.*, 14 (1988) 27–35.
- 298 Rozhkovskii, Ya.V. and Kresiun, V.I., Activity of marker enzymes and status of the erythrocyte membrane lipid matrix in stress and during its correction using medications, *Ukr. Biokhim. Zh.*, 63 (1991) 74–80.
- 299 Russello, D., Randazzo, G., Favetta, A., Cristaldi, C., Petino, A.G., Carnazzo, S.A. and Latteri, F., Oxiracetam treatment of exogenous post-concussion syndrome. Statistical evaluation of results, *Minerva Chir.*, 45 (1990) 1309–1314.
- 300 Rågo, L.K., Allikmets, L.H. and Zarkovsky, A.M., Effects of piracetam on the central dopaminergic transmission, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 318 (1981) 36–37.
- 301 Sakurai, T., Hatanaka, S., Tanaka, S., Yamasaki, T., Kojima, H. and Akashi, A., Protective effect of DM-9384, a novel pyrrolidone derivative, against experimental cerebral anoxia, *Jpn. J. Pharmacol.*, 54 (1990) 33–43.
- 302 Sakurai, T., Ojima, H., Yamasaki, T., Kojima, H. and Akashi, A., Effects of *N*-(2,6-dimethylphenyl)-2-(2-oxo-1-pyrrolidinyl)acetamide (DM-9384) on learning and memory in rats, *Jpn. J. Pharmacol.*, 50 (1989) 47–53.
- 303 Saletu, B., Linzmayer, L., Grünberger, J. and Pietschmann, H., Double-blind, placebo-controlled, clinical, psychometric and neurophysiological investigations with oxiracetam in the organic brain syndrome of late life, *Neuropsychobiology*, 13 (1985) 44–52.
- 304 Saletu, B. and Grünberger, J., Antihypoxidotic and nootropic drugs: proof of their encephalotropic and pharmacodynamic properties by quantitative EEG investigations, *Prog. Neuro-Psychopharmacol.*, 4 (1980) 469–89, 519.
- 305 Saletu, B. and Grünberger, J., Memory dysfunction and vigilance: neurophysiological and psychopharmacological aspects, *Ann. NY Acad. Sci.*, 444 (1985) 406–427.
- 306 Saletu, B. and Grünberger, J., The hypoxia model in human psychopharmacology: neurophysiological and psychometric studies with aniracetam i.v., *Hum. Neurobiol.*, 3 (1984) 171–181.
- 307 Sannita, W.G., Ottonello, D., Perria, B., Rosadini, G. and Timitilli, C., Topographic approaches in human quantitative pharmacoelectroencephalography, *Neuropsychobiology*, 9 (1983) 66–72.
- 308 Sansone, M., Ammassari-Teule, M. and Oliverio, A., Interaction between nootropic drugs and methamphetamine on avoidance acquisition but not on locomotor activity in mice (*sic!*), *Arch. Int. Pharmacodyn. Ther.*, 278 (1985) 229–235.
- 309 Sansone, M., Castellano, C. and Ammassari-Teule, M., Improvement of avoidance acquisition by the nootropic drug oxiracetam in mice, *Arch. Int. Pharmacodyn. Ther.*, 275 (1985) 86–92.
- 310 Sansone, M., Castellano, C., Battaglia, M. and Ammassari-Teule, M., Effects of oxiracetam-nicotine combinations on active and passive avoidance learning in mice, *Pharmacol. Biochem. Behav.*, 39 (1991) 197–200.
- 311 Sansone, M., Castellano, C., Battaglia, M. and Ammassari-Teule, M., Oxiracetam prevents mecamlamine-induced impairment of active, but not passive, avoidance learning in mice, *Pharmacol. Biochem. Behav.*, 36 (1990) 389–392.
- 312 Sansone, M. and Oliverio, A., Avoidance facilitation by nootropics, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 13 Suppl. (1989) 89–97.
- 313 Santucci, V., Fournier, M., Worms, P., Keane, P. and Biziere, K., Cerebral-activating (EEG) properties of two inverse agonists and of an antagonist at the benzodiazepine receptor in the rat, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 340 (1989) 93–100.
- 314 Sara, S.J., Memory retrieval deficits: alleviation by etiracetam, a nootropic drug, *Psychopharmacology*, 68 (1980) 235–241.
- 315 Sarter, M., Taking stock of cognition enhancers, *TiPS*, 12 (1991) 456–461.
- 316 Sarter, M., Hagan, J. and Dudchenko, P., Behavioral screening for cognition enhancers: from indiscriminate to valid testing. Part I, *Psychopharmacology*, 107 (1992) 144–159.
- 317 Sasaki, H., Mori, Y., Nakamura, J. and Shibasaki, J., Synthesis and anticonvulsant activity of 1-acyl-2-pyrrolidinone derivatives, *J. Med. Chem.*, 34 (1991) 628–633.
- 318 Satoh, M., Ishihara, K., Iwama, T. and Takagi, H., Aniracetam augments and midazolam inhibits, the long-term potentiation in guinea pig hippocampal slices, *Neurosci. Lett.*, 68 (1986) 216–220.
- 319 Schindler, U., Pre-clinical evaluation of cognition enhancing drugs, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 13 Suppl. (1989) 99–115.
- 320 Schwarz, R.D. and Pugsley, T.A., Neurochemistry of cognitive agents: an overview. Developments in psychiatry, *Proceedings of the IVth World Congress of Biological Psychiatry, Biological Psychiatry*, 7 (1985) 1325–1327.
- 321 Scipioni, A., Preparation of γ -oxopimelic acid and some derivatives I, *Ann. Chim. (Rome)*, 42 (1952) 53–61 (pp. 53, 60).
- 322 Scolastico, S. (Gibipharma S.p.A.), Preparation of 2-oxo-1-pyrrolidineacetamide derivatives having nootropic activity, *Eur. Pat. Appl.*, EP 255,149 (1988) CA109:73315k.
- 323 Scott, W.L. (Eli Lilly and Co.), Substituted lactams, *Brit. Pat. Appl.*, GB 2,141,120 (1984) CA103:123348x.
- 324 Senin, U., Abate, G., Fieschi, C., Gori, G., Guala, A., Marini, G., Villardita, C. and Parnetti, L., Aniracetam (Ro 13-5057) in the treatment of senile dementia of Alzheimer's type (SDAT): results of a placebo controlled multicentre clinical study, *Eur. Neuropsychopharmacol.*, 1 (1991) 511–517.
- 325 Sharma, A.C. and Kulkarni, S.K., Evaluation of learning and memory mechanisms employing elevated plus-maze in rats and mice, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 16 (1992) 117–125.
- 326 Shih, Y.H. and Pugsley, T.A., The effects of various cognition-enhancing drugs on in vitro rat hippocampal synaptosomal sodium-dependent high affinity choline uptake, *Life Sci.*, 36 (1985) 2145–2152.
- 327 Sil'vestrov, V.P., Kinitin, A.V. and Chesnokova, I.V., Immunological and metabolic disorders and the means for their correction in patients with chronic bronchitis, *Ter. Arkh.*, 63 (1991) 7–11.
- 328 Skinner, K.J., The chemistry of learning and memory, *Chem. Eng. News*, Oct. (1991) 24–41.
- 329 Smilowski, B., Stability of 2-pyrrolidinone derivatives. Part 4. Analysis and stability of dupracetam, *Pharmazie*, 44 (1989) 272–273.
- 330 Snell, L.D. and Johnson, K.M., Characterization of the inhibition of excitatory amino acid-induced neurotransmitter release in the rat striatum by phencyclidine-like drugs, *J. Pharmacol. Exp. Ther.*, 238 (1986) 938–946.
- 331 Somnier, F.E., Østergaard, M.S., Boysen, G., Bruhn, P. and Mikkelsen, B.O., Aniracetam tested in chronic psychosyndrome

- after long-term exposure to organic solvents. A randomized, double-blind, placebo-controlled cross-over study with neuropsychological tests, *Psychopharmacology*, 101 (1990) 43–46.
- 332 Sourander, L.B., Portin, R., Molsa, P., Lahdes, A. and Rinne, U.K., Senile dementia of the Alzheimer type treated with aniracetam: a new nootropic agent, *Psychopharmacology*, 91 (1987) 90–95.
- 333 Spagnoli, A. and Tognoni, G., 'Cerebroactive' drugs. Clinical pharmacology and therapeutic role in cerebrovascular disorders, *Drugs*, 26 (1983) 44–69.
- 334 Spignoli, G., Magnani, M., Giovannini, M.G. and Pepeu, G., Effect of pyroglutamic acid stereoisomers on ECS and scopolamine-induced memory disruption on brain acetylcholine levels, *Pharmacol. Res. Commun.*, 19 (1987) 901–912.
- 335 Spignoli, G., Pedata, F., Giovannelli, L., Banfi, S., Moroni, F. and Pepeu, G., Effect of oxiracetam and piracetam on central cholinergic mechanisms and active-avoidance acquisition, *Clin. Neuropharmacol.*, 9 Suppl. 3 (1986) 39–47.
- 336 Spignoli, G. and Pepeu, G., Interactions between oxiracetam, aniracetam and scopolamine on behavior and brain acetylcholine, *Pharmacol. Biochem. Behav.*, 27 (1987) 491–495.
- 337 Spignoli, G. and Pepeu, G., Oxiracetam prevents electroshock-induced decrease in brain acetylcholine and amnesia, *Eur. J. Pharmacol.*, 126 (1986) 253–257.
- 338 Stancheva, S.L. and Alova, L.G., Effect of centropheoxine, piracetam and aniracetam on the monoamine oxidase activity in different brain structures of rats, *Farmakol. Toksikol.*, 51 (1988) 16–18.
- 339 Stancheva, S.L., Petkov, V.D., Hadjivanova, C.I. and Petkov, V.V., Age-related changes of the effects of a group of nootropic drugs on the content of rat brain biogenic monoamines, *Gen. Pharmacol.*, 22 (1991) 873–877.
- 340 Stezhko, T.V., Granik, V.G., Glushkov, R.G., Roshchina, L.F., Polezhaeva, A.I. and Mashkovskii, M.D., Synthesis and biological activity of *N*-substituted pyrrolid-2-ones, *Khim.-Farm. Zh.*, 18 (1984) 823–827.
- 341 Stezhko, T.V., Granik, V.G., Kadushkin, A.V., Glushkov, R.G., Roshchina, L.F., Polezhaeva, A.I. and Mashkovskii, M.D., Synthesis and pharmacological study of a series of 1-substituted pyrrolid-2-ones, structurally close to piracetam, *Khim.-Farm. Zh.*, 18 (1984) 1198–1203.
- 342 Stoll, L., Schubert, T. and Muller W.E., Age-related deficits of central muscarinic cholinergic receptor function in the mouse: partial restoration by chronic piracetam treatment, *Neurobiol. Aging*, 13 (1992) 39–44.
- 343 Strubbe, J.H.L. and Linz, R.A. (UCB S.A.), Pharmaceutical (2-oxopyrrolidine)acetamide derivatives, *Ger. Offen.*, DE 2,106,418 (1971) CA75:140681w.
- 344 Stuart, J., Bילו, Y.Y., Player, M., Stone, P.C. and Chalder, S.M., Rheological action of drugs that prevent erythrocyte dehydration, *J. Mal. Vasc.*, 16 (1991) 46–48.
- 345 Suchenwirth, R.M., 6 Jahre Piracetam-Anwendung. Literaturübersicht und eigene Erfahrungen, *Med. Monatsschr. Pharm.*, 3 (1980) 53–55.
- 346 Tacconi, M.T. and Wurtman, R.J., Piracetam: physiological disposition and mechanism of action, *Adv. Neurol.*, 43 (1986) 675–685.
- 347 Taddei, C., Donini, E. and Mennini, T., In vivo (³H)oxiracetam binding to rat brain, *Pharmacol. Res.*, 22 Suppl. 3 (1990) 29–30.
- 348 Tanabe, S., Ikeda, Y., Sugawa, M. and Iwasaki, T., Effects of BY-1949 on three kinds of experimental amnesia in rodents, *Yakubutsu Seishin Kodo*, 10 (1990) 297–305.
- 349 Tang, C.M., Shi, Q.Y., Katchman, A. and Lynch, G., Modulation of the time course of fast EPSCs and glutamate channel kinetics by aniracetam, *Science*, 254 (1991) 288–290.
- 350 Thaisrivongs, S. (Upjohn Co.), Preparation of renin inhibitors having a lactam pseudo dipeptide, *PCT Int. Appl.*, WO 87 05,909 (1987) CA109:150041x.
- 351 Thaisrivongs, S., Pals, D.T., Turner, S.R. and Kroll, L.T., Conformationally constrained renin inhibitory peptides: γ -lactam bridged dipeptide isosteres as conformational restriction, *J. Med. Chem.*, 31 (1988) 1369–1376.
- 352 Thorsett, E.D., Conformationally restricted inhibitors of angiotensin-converting enzyme, *Actual Chim. Ther.*, 13 (1986) 257–268.
- 353 Thorsett, E.D., Harris, E.E., Aster, S.D., Peterson, E.R., Snyder, J.P., Springer, J.P., Hirshfield, J., Tristram, E.W., Patchett, A.A. et al., Conformationally restricted inhibitors of angiotensin-converting enzyme, Synthesis and computations, *J. Med. Chem.*, 29 (1986) 251–260.
- 354 Thorsett, E.D., Harris, E.E., Aster, S., Peterson, E.R., Taub, D., Patchett, A.A., Ulm, E.H. and Vassil, T.C., Dipeptide mimics. Conformationally restricted inhibitors of angiotensin-converting enzyme, *Biochim. Biophys. Res. Commun.*, 111 (1983) 166–171.
- 355 Tobe, A., Yamaguchi, T., Nagai, R. and Egawa, M., Effects of bifemelane hydrochloride (MCI-2016) on experimental amnesia (passive avoidance failure) in rodents, *Jpn. J. Pharmacol.*, 39 (1985) 153–161.
- 356 Todorov, S., Zamfirova, R. and Petkov, V.D., Study of the effects of nootropic agents on the adrenergic neurotransmission in smooth muscles of young and old animals, *Acta Physiol. Pharmacol. Bulg.*, 16 (1990) 38–45.
- 357 Tohyama, K., Nabeshima, T. and Kameyama, T., Effect of DM-9384, a pyrrolidone derivative, on benzodiazepine-induced amnesia, *Psychopharmacology*, 96 Suppl. (1988) 305 (P32.02.23).
- 358 Toide, K., Effects of aniracetam on one-trial passive avoidance tests and cholinergic neurons in discrete brain regions of rats, *Arch. Int. Pharmacodyn. Ther.*, 298 (1989) 25–37.
- 359 Triggie, D.J., Drugs Acting on Ion Channels and Membranes. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry*, Vol. 3, Elsevier Science/Pergamon Press, Oxford, 1990, pp. 1071, 1079, 1085.
- 360 Triggie, D.J., Drugs Acting on Ion Channels and Membranes. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry*, Vol. 3, Elsevier Science/Pergamon Press, Oxford, 1990, p. 1085.
- 361 Triggie, D.J., Drugs Acting on Ion Channels and Membranes. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry*, Vol. 3, Elsevier Science/Pergamon Press, Oxford, 1990, pp. 1086, 1088.
- 362 Trovarelli, G., Gaiti, A., De Medio, G.E., Brunetti, M. and Porcellati, G., Biochemical studies on the nootropic drug, oxiracetam, in brain, *Clin. Neuropharmacol.*, 9 Suppl. 3 (1986) 56–64.
- 363 Tsoneva-Tyutvulkova, N., Nikolov, R., Nikolova, M., Andonova, V., Georgiev, A., Ninov, K., Daskalov, Kh., Nisimov, I., Khadzhiev, D. and Yancheva, S. (Scientific-Research Chemical-Pharmaceutical Institute, Sofia), Antihypoxic agent containing flunarizine and piracetam, *Eur. Pat. Appl.*, EP 408,782 (1991) CA114:157214t.
- 364 UCB Pharmaceutical Sector, *Nootropil*, 4th edn., Brussels, Belgium, 1980.
- 365 UCB S.A., *N*-Carbamoylmethyl lactams, *Brit.*, GB 1,039,113 (1966) CA65:12180c.
- 366 UCB S.A., Pharmacologically active *N*-substituted lactams, *Belg. Pat. Appl.*, BE 762,728 (1971) CA77:114240y.
- 367 UCB S.A., *N*-Substituted lactams, *Neth. Appl.* NL 6,509,994 (1966) CA65:13672a.
- 368 Valenta, V., Holubek, J., Svatek, E., Valchar, M., Krejci, I. and Protiva, M., Potential nootropic agents: synthesis of some (2-oxo-1-pyrrolidinyl)acetamides and some related compounds, *Collect. Czech. Chem. Commun.*, 55 (1990) 2756–2764.

- 369 Valenta, V., Sindelar, K., Holubek, J., Ryska, M., Krejci, I., Diabac, A. and Protiva, M., Potential nootropic agents: synthesis of a series of (2-oxo-1-pyrrolidinyl)acetic acid piperazides, *Collect. Czech. Chem. Commun.*, 55 (1990) 1613–1629.
- 370 Valle, G., Crisma, M., Toniolo, C., Yu, K.L. and Johnson, R.L., Crystal-state structural analysis of two γ -lactam restricted analogs of Pro-Leu-Gly-NH₂, *Int. J. Pept. Protein Res.*, 33 (1989) 181–190.
- 371 Valzelli, L., Baiguerra, G. and Giraud, O., Difference in learning and retention by Albino Swiss mice. Part III. Effect of some brain stimulants, *Methods Find. Exp. Clin. Pharmacol.*, 8 (1986) 337–341.
- 372 Valzelli, L., Bernasconi, S. and Sala, A., Piracetam activity might differ according to the age of the recipient mouse, *Int. Pharmacopsychiatry*, 15 (1980) 150–156.
- 373 Van Binss, G., Steger, Y. and Flitsch, W., Untersuchung der Konformation bicyclischer Imidderivate mit Hilfe der 270 MHz NMR-Spektroskopie, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.*, 30B (1975) 591–599.
- 374 Van Wieringen, A., Meijer, J.W., Van Emde-Boas, W. and Vermeij, T.A., Pilot study to determine the interaction of oxiracetam with antiepileptic drugs, *Clin. Pharmacokinet.*, 18 (1990) 332–338.
- 375 Van Wimers, M. and Greidanus, T.B., MSH/ACTH_{4–10}: a tool to differentiate between the role of vasopressin in memory consolidation or retrieval processes, *Peptides*, 3 (1982) 7–11.
- 376 Verloes, R., Scotto, A.M., Gobert, J. and Wuelfert, E., Effects of nootropic drugs in a scopolamine-induced amnesia model in mice, *Psychopharmacology*, 95 (1988) 226–230.
- 377 Verma, A. and Kulkarni, S.K., Effect of a herbal psychotropic preparation, BR-16A (Mentat), on performance of mice on an elevated plus-maze, *Indian. J. Exp. Biol.*, 29 (1991) 1120–1123.
- 378 Vernon, M.W. and Sorkin, E.M., Piracetam. An overview of its pharmacological properties and a review of its therapeutic use in senile cognitive disorders, *Drugs Aging*, 1 (1991) 17–35.
- 379 Viana, G.S., Marinho, M.M. and Sousa, F.C., Effect of piracetam administration on (³H)-N-methylscopolamine binding in cerebral cortex of young and old rats, *Life Sci.*, 50 (1992) 971–977.
- 380 Villardita, C., Grioli, S., Lomeo, C., Cattaneo, C. and Parini, J., Clinical studies with oxiracetam in patients with dementia of Alzheimer type and multi-infarct dementia of mild to moderate degree, *Neuropsychobiology*, 25 (1992) 24–28.
- 381 Villardita, C., Parini, J., Grioli, S., Quattropiani, M., Lomeo, C. and Scapagnini, U., Clinical and neuropsychological study with oxiracetam versus placebo in patients with mild to moderate dementia, *J. Neural Transm. Suppl.*, 24 (1987) 293–298.
- 382 Visconti, M., Spalluto, R., Crolla, T., Pifferi, G. and Pinza, M., Determination of oxiracetam in human serum and urine by high-performance liquid chromatography, *J. Chromatogr.*, 416 (1987) 433–438.
- 383 Vocke, W., Lohmann, D., Gross, H., Junghänel, H., Sauer, W., Schmidt, J., Morgenstern, E. and Rostock, A. (VEB Isis-Chemie Zwickau), Preparation of 2-oxo-1-pyrrolidineacetamides as pharmaceuticals, *Ger. (East)*, DD 258,982 (1988) CA110:192645y.
- 384 Voronina, T.A., Gluzman, O.M., Orlova, E.K., Meshcheryakova, L.M., Zauer, V., Eckard, R., Garibova, T.L., Rakhmankulova, I.Kh., Rostock, A. and Siegemund, H., Synthesis and pharmacological properties of amidine analogs of pyracetam, *Khim.-Farm. Zh.*, 24 (1990) 26–29.
- 385 Vyklicky Jr., L., Patneau, D.K. and Mayer, M.L., Modulation of excitatory synaptic transmission by drugs that reduce desensitization at AMPA/kainate receptors, *Neuron*, 7 (1991) 971–984.
- 386 Watanabe, S., Yamaguchi, H. and Ashida, S., Effects of DM-9384 a new cognition-enhancing agent, on GABA release and choline uptake in rat cortex, *Neurosci. Abstr.*, 15 (Part I) (1989) 601.
- 387 Wellcome Foundation Ltd., Pyrrolidinones and piperidinones, *Jpn. Kokai Tokkyo Koho*, JP 59 65,071 (1984) CA101:110897j.
- 388 Wess, J., Buhl, T., Lambrecht, G. and Mutschler, E., Cholinergic Receptors. In C. Hansch, P.G. Sammes and J.B. Taylor (Eds.), *Comprehensive Medicinal Chemistry*, Vol. 3, Elsevier Science/Pergamon Press, Oxford, 1990, p. 458.
- 389 Williams, P.D., Veber, D.F., Greenlee, W.J. and Ten Broeke, J. (Merck and Co., Inc.), Preparation and testing of di- or tripeptide renin inhibitors containing conformationally restricted derivatives of (3S,4S)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid, *Eur. Pat. Appl.*, EP 312,283 (1989) CA111:154382y.
- 390 Wilsher, C.R., Effects of piracetam on developmental dyslexia, *Int. J. Psychophysiol.*, 4 (1986) 29–39.
- 391 Wittenborn, J.R., Pharmacotherapy for age-related behavioral deficiencies, *J. Nerv. Ment. Dis.*, 169 (1981) 139–156.
- 392 Woelk, H. and Peiler-Ichikawa, K., The action of piracetam on the formation of ethanalamine plasmalogen by neuronal microsomes of the developing rat brain, *Arzneim.-Forsch. / Drug Res.*, 28 (1978) 1752–1756.
- 393 Wolthuis, O.L., Behavioral effects of etiracetam in rats, *Gov. Rep. Announce. Index (U.S.)*, 81 (1981) 5506.
- 394 Wolthuis, O.L., Behavioral effects of etiracetam in rats, *Pharmacol. Biochem. Behav.*, 15 (1981) 247–255.
- 395 Wolthuis, O.L., Experiments with 2-oxo-1-pyrrolidineacetamide (UCB 6215), a drug which enhances acquisition in rats. Its effects compared with those of metamphetamine, *Eur. J. Pharmacol.*, 16 (1971) 283–297.
- 396 Wong, D.F., Wagner, H.N., Dannals, R.F., Links, J.M., Frost, J.J., Ravert, H.T., Wilson, A.E., Gjedde, A., Douglass, K.H., Petronis, J.D., Folstein, M.F., Toung, J.K., Burns, H.D. and Kuhar, M.J., Effect of age on dopamine and serotonin receptor measured by positron tomography in the living human brain, *Science*, 226 (1984) 1393–1396.
- 397 Worms, P. and Bizière, K., Antagonism by cholinomimetic drugs of the turning induced by intrastriatal pirenzepine in mice, *Psychopharmacology*, 93 (1987) 489–493.
- 398 Wurtman, C.H., Rudolph, E. and Fischer, H.D., Einfluß von Piracetam und Dihydroergotoxin auf die Freisetzung von Dopamin aus Striatumschnitten der Ratte, *Acta Biol. Med. Germ.*, 39 (1980) 983–985.
- 399 Wurtman, R.J., Magil, S.G. and Reinstein, D.K., Piracetam diminishes hippocampal acetylcholine levels in rats, *Life Sci.*, 28 (1981) 1091–1093.
- 400 Wülfert, E., Hanin, I. and Verloes, R., Facilitation of calcium-dependent cholinergic function by UCB L059, a new 'second generation' nootropic agent, *Psychopharmacol. Bull.*, 25 (1989) 498–502.
- 401 Yamada, K., Inoue, T., Tanaka, M. and Furukawa, T., Prolongation of latencies for passive avoidance responses in rats treated with aniracetam or piracetam, *Pharmacol. Biochem. Behav.*, 22 (1985) 645–648.
- 402 Yevich, J.P. and Mattson, R.J. (Bristol-Myers Co.), Preparation of psychogeriatric 1-((4-(2-pyrimidinyl)-1-piperazinyl)methyl)-2-pyrrolidines, *U.S.*, US 4,668,687 (1987) CA107:236740v.
- 403 Yoshimoto, T., Kado, K., Matsubara, F., Koriyama, N., Kaneto, H. and Tsuru, D., Specific inhibitors for prolyl endopeptidase and their anti-amnesic effect, *J. Pharmacobio-Dyn.*, 10 (1987) 730–735.
- 404 Youdim, M.B.H., Finberg, J.P.M. and Tipton, K.F., Monoamine oxidase. In U. Trendelenburg and N. Weiner (Eds.), *Catecholamines I*, Springer, Berlin, 1988, pp. 136–138.

- 405 Young, M.R. and Chang, T., Metabolic disposition of pramiracetam in rhesus monkeys and rats, *Pharmacologist*, 26 (1982) 95 (P15).
- 406 Yu, K.L., Rajakumar, G., Srivastava, L.K., Mishra, R.K. and Johnson, R.L., Dopamine receptor modulation by conformationally constrained analogs of Pro-Leu-Gly-NH₂, *J. Med. Chem.*, 31 (1988) 1430–1436.
- 407 Zhang, L.H. and Zhang, S.S., Relationship between facilitatory effect of piracetam on memory and glutamate receptors, *Chung Kuo Yao Li Hsueh Pao*, 12 (1991) 145–147.

Note added in proof

Our review covered the literature up to December 1992 and we therefore find it appropriate here briefly to mention some of the most interesting observations made in the field of piracetam nootropics recently.

Further support for the idea that the piracetam nootropics are only of benefit in situations of mild to moderate dementia have appeared. Thus, piracetam seems to decrease the progression of cognitive deterioration without improving the status of the disease [5]. Furthermore, oxiracetam gave improvement in patients suffering from dementia after long-term treatment [12,13], but no benefit was observed in patients suffering from Alzheimer's disease [6], multi-infarct or mixed dementia [2].

As concerning the mechanism of action of the piracetam-type nootropics, further support for an interaction of especially aniracetam with the AMPA receptor has appeared [15] (for a short review, see Nicoletti et al. [9]). Aniracetam reduces the anticonvulsant effect of non-NMDA antagonists, but not of NMDA antagonists and without being a convulsant itself [3]. This would seem to confirm the idea that the nootropics do not have any activity of their own, but only potentiate activity already present.

The modulatory effect on AMPA responses does, however, not completely explain the activity of aniracetam, since it has been observed that activation of the metabotropic glutamate receptor (mGluR) causes protection against AMPA, kainate and glutamate-induced neurotoxicity, an effect potentiated by aniracetam. Aniracetam seems to potentiate the mGluR-coupled stimulation of phospholipase C [10]. Furthermore, the modulatory effect on the AMPA receptor does not explain the peripheral effects observed with the piracetam-type nootropics.

Effects on LTP have also been reported. Augmentation is observed by aniracetam [1,14], whereas piracetam is without effect on LTP in the dentate gyrus in vivo [8]. Very interesting is the fact that (*S*)-oxiracetam has higher activity than (*R*)-oxiracetam in an LTP study [4]. This is the first observation of different activity of the enantiomers of oxiracetam.

Finally, micromolar concentrations of oxiracetam enhance the K⁺-induced release of [³H]aspartate and [³H]acetylcholine, but not [³H]GABA, [³H]noradrenaline or [³H]5-hydroxytryptamine [11], but, on the other hand, it has also been reported that aniracetam blocks N-type calcium channels [7], which are known to be involved in the release of transmitters.

Some of the ambiguities with aniracetam might be explained by the fact that aniracetam is quite unstable and may be subjected to metabolism by non-specific esterases/amidases, as rolziracetam is, yielding *N*-anisoyl-GABA, 4-methoxybenzoic acid and 2-pyrrolidone causing different effects.

We would finally like, once more, to encourage the use of (*R*)- and (*S*)-etiracetam and now also (*R*)- and (*S*)-oxiracetam in the search for the mechanism of action of these compounds.

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References to Note added in proof

- 1 Arai, A. and Lynch, G., Factors regulating the magnitude of long-term potentiation induced by theta pattern stimulation, *Brain Res.*, 598 (1992) 173–184.
- 2 Bottini, G., Vallar, G., Cappa, S., Monza, G.C., Scarpini, E., Baron, P., Cheldi, A. and Scarlato, G., Oxiracetam in dementia: a double-blind, placebo-controlled study, *Acta Neurol. Scand.*, 86 (1992) 237–241.
- 3 Chapman, A.G., al-Zubaidy, Z. and Meldrum, B.S., Aniracetam reverses the anticonvulsant action of NBQX and GYKI 52466 in DBA/2 mice, *Eur. J. Pharmacol.*, 231 (1993) 301–303.
- 4 Chiodini, L. and Pepeu, G., Preparation and composition of (*S*)-oxiracetam for use as a nootropic, *PCT Int. Appl.*, WO 93,06,826, CA119:139083y.
- 5 Croisile, B., Trillet, M., Fondarai, J., Laurent, B., Mauguere, F. and Billardon, M., Long-term and high-dose piracetam treatment of Alzheimer's disease, *Neurology*, 43 (1993) 301–305.
- 6 Green, R.C., Goldstein, F.C., Auchus, A.P., Presley, R., Clark, W.S., Van Tuyl, L., Green, L., Hersch, S.M. and Karp, H.R., Treatment trial of oxiracetam in Alzheimer's disease, *Acta Neurol.*, 49 (1992) 1135–1136.
- 7 Koike, H., Saito, H. and Matsuki, N., Inhibitory effect of aniracetam on N-type calcium current in acutely isolated rat neuronal cells, *Jpn. J. Pharmacol.*, 61 (1993) 277–281.
- 8 Molnar, P. and Gaal, L., Effect of different subtypes of cognition enhancers on long-term potentiation in the rat dentate gyrus in vivo, *Eur. J. Pharmacol.*, 215 (1992) 17–22.
- 9 Nicoletti, F., Casabona, G., Genazzani, A.A., Copani, A., Aleppo, G., Canonico, P.L. and Scapagnini, U., Excitatory amino acids and neuronal plasticity: modulation of AMPA receptors as a novel substrate for the action of nootropic drugs, *Funct. Neurol.*, 7 (1992) 413–422.
- 10 Pizzi, M., Fallacara, C., Arrighi, V., Memo, M. and Spano, P.F., Attenuation of excitatory amino acid toxicity by metabotropic glutamate receptor agonists and aniracetam in primary cultures of cerebellar granule cells, *J. Neurochem.*, 61 (1993) 683–689.
- 11 Raiteri, M., Costa, R. and Marchi, M., Effects of oxiracetam on neurotransmitter release from rat hippocampus slices and synaptosomes, *Neurosci. Lett.*, 145 (1992) 109–113.
- 12 Rozzini, R., Zanetti, O. and Bianchetti, A., Effectiveness of oxiracetam therapy in the treatment of cognitive deficiencies secondary to primary degenerative dementia, *Acta Neurol. Napoli*, 14 (1992) 117–126.
- 13 Rozzini, R., Zanetti, O. and Bianchetti, A., Treatment of cognitive impairment secondary to degenerative dementia. Effectiveness of oxiracetam therapy, *Acta Neurol. Napoli*, 15 (1993) 44–52.
- 14 Staubli, U., A peculiar form of potentiation in mossy fiber synapses, *Epilepsy Res. Suppl.*, 7 (1992) 151–157.
- 15 Tsuzuki, K., Takeuchi, T. and Ozawa, S., Agonist- and subunit-dependent potentiation of glutamate receptors by a nootropic drug aniracetam, *Mol. Brain Res.*, 16 (1992) 105–110.