

## RESEARCH MONOGRAPH . COMPOUND PROFILE

# Aniracetam

*A lipophilic racetam nootropic developed at Hoffmann-La Roche as a cognition enhancer for cerebrovascular and neurodegenerative disorders, distinguished from piracetam by higher potency, oral lipophilicity, AMPA receptor positive allosteric modulation, and multi-target downstream activation of cholinergic, dopaminergic, and serotonergic neurotransmission through pharmacologically active metabolites.*

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| DOCUMENT       | KDC-MN-1426                                                                                                                                                                                                        |
| ISSUED         | 2026-05-11                                                                                                                                                                                                         |
| REVISION       | 1.0                                                                                                                                                                                                                |
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| COMPOUND CLASS | Pyrrolidinone-class positive allosteric modulator of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors with secondary cholinergic, dopaminergic, and serotonergic neuromodulatory activity |

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## ABSTRACT

Aniracetam (1-(4-methoxybenzoyl)-2-pyrrolidinone; Ro 13-5057) is a lipophilic pyrrolidinone derivative of the racetam structural class, originally synthesized at Hoffmann-La Roche in the late 1970s as a more potent and centrally bioavailable analog of piracetam for the treatment of cognitive dysfunction associated with cerebrovascular disease and neurodegenerative dementia. The compound is classified as a positive allosteric modulator (PAM) of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of ionotropic glutamate receptor, a mechanism that slows both channel deactivation and receptor desensitization at synaptic AMPA receptors, thereby prolonging excitatory postsynaptic currents and enhancing glutamatergic neurotransmission in cortical and hippocampal circuits critical for learning and memory [1, 2]. Beyond the direct AMPA receptor modulation, aniracetam and its principal active metabolite N-anisoyl-gamma-aminobutyric acid (N-anisoyl-GABA, which accounts for 70 to 80 percent of the metabolic disposition) exert downstream effects on multiple neurotransmitter systems: enhancement of acetylcholine release in the prefrontal cortex and hippocampus via group II metabotropic glutamate receptor modulation; site-specific activation of dopaminergic and serotonergic transmission in the mesocorticolimbic pathway through nicotinic acetylcholine receptor mechanisms; and anxiolytic activity mediated through an interaction between cholinergic, dopaminergic, and serotonergic systems [3, 4, 5]. The pharmacokinetic profile of aniracetam is characterized by rapid and complete gastrointestinal absorption, extremely low systemic bioavailability of the parent compound

(approximately 0.2 percent) due to extensive first-pass hepatic hydrolysis, and a plasma elimination half-life of approximately 35 minutes [6, 7]. The parent compound is rapidly cleaved to yield three primary metabolites: N-anisoyl-GABA (70 to 80 percent), 2-pyrrolidinone (20 to 30 percent), and p-anisic acid (20 to 30 percent), each of which has been shown to contribute to the pharmacological activity profile [8]. The clinical evidence base for aniracetam derives principally from two double-blind, placebo-controlled multicenter trials in elderly patients with mild to moderate senile dementia of the Alzheimer type (SDAT), in which aniracetam at 1500 mg per day for six months produced statistically significant improvement in cognitive and psychobehavioral parameters relative to placebo and, in one trial, relative to piracetam at 2400 mg per day [9, 10]. A comparative open-label study in 276 patients with cognitive disorders demonstrated preservation of neuropsychological parameters for at least 12 months with aniracetam monotherapy and performance comparable to or exceeding cholinesterase inhibitor monotherapy in mildly demented patients [11]. Preclinical pharmacology is extensive and demonstrates cognitive enhancement in scopolamine-induced amnesia, cerebral ischemia, and age-related cognitive decline models; anxiolytic activity in elevated plus-maze, conditioned fear, and social interaction paradigms; neuroprotection against excitotoxicity and ischemic injury; and activation of brain-derived neurotrophic factor synthesis [12, 13, 14]. The compound was marketed as a prescription medicine in Japan (Draganon, subsequently withdrawn), in Italy (Ampamet), and in Greece (Memodrin, Referan) for cognitive impairment associated with cerebrovascular disease and neurodegenerative conditions. It is not approved by the United States Food and Drug Administration

and is not a controlled substance in the United States, where it is sold as a research compound. This monograph reviews the chemistry, synthesis, and structural pharmacology of aniracetam; the multi-target mechanism of action spanning AMPA receptor modulation, metabotropic glutamate receptor effects, and monoaminergic neuromodulation; the comprehensive pharmacokinetic record including active metabolite characterization; the preclinical pharmacology across cognitive, anxiolytic, and neuroprotective domains; the clinical evidence base in dementia and cognitive impairment; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse events and safety; and a comparative assessment of five racetam and ampakine alternatives against aniracetam on five competency standards.

# 1. Compound Identification

## 1.1 Names, synonyms, and registry identifiers

**International Nonproprietary Name:** Aniracetam.

**Marketed names:** Draganon (Roche; Japan, subsequently withdrawn from market), Ampamet (Roche; Italy), Memodrin (Greece), Referan (Greece), Sarpul (generic).

**Development codes:** Ro 13-5057 (Hoffmann-La Roche). The development code is the canonical identifier in the early pharmacology literature and the designation under which the original Cumin et al. (1982) characterization of cognitive-enhancing activity was carried out [12].

**Chemical Abstracts Service registry number:** 72432-10-1.

**International Union of Pure and Applied Chemistry name:** 1-(4-methoxybenzoyl)-2-pyrrolidinone. The compound is the N-acylation product of 2-pyrrolidinone with 4-methoxybenzoyl chloride (anisoyl chloride), placing it within the pyrrolidinone family of racetam nootropics.

**Other chemical names:** N-anisoyl-2-pyrrolidinone; 1-p-anisoyl-2-pyrrolidinone; 1-(4-methoxybenzoyl)pyrrolidin-2-one.

## 1.2 Structural class and chemistry

Aniracetam is a member of the racetam structural class, defined by the shared 2-pyrrolidinone (gamma-butyrolactam) ring system. The racetam class includes piracetam (the parent compound), oxiracetam, pramiracetam, phenylpiracetam, and several other pyrrolidinone derivatives developed as cognitive enhancers. Aniracetam is distinguished from piracetam by the substitution of the acetamide side chain with a 4-methoxybenzoyl (anisoyl) group at the nitrogen of the pyrrolidinone ring, conferring substantially greater lipophilicity and central nervous system penetration [15].

**Molecular formula:** C<sub>12</sub>H<sub>13</sub>NO<sub>3</sub>.

**Exact mass:** 219.0895 g/mol (monoisotopic).

**Molecular weight:** 219.24 g/mol.

**Physical properties:** White to off-white crystalline powder. Melting point 121 to 122 degrees Celsius. Poorly soluble in water (less than 1 mg/mL at 25 degrees Celsius); soluble in dimethyl sulfoxide (100 mM), ethanol (25 mM), chloroform (approximately 50 mg/mL), and methanol. The compound is lipophilic relative to piracetam, consistent with the aromatic methoxybenzoyl substituent and the absence of polar side-chain functionality.

**Stereochemistry:** Aniracetam is an achiral molecule. The pyrrolidinone ring contains no stereocenters, and the compound is supplied as a single constitutional isomer. No enantiomeric or diastereomeric considerations apply to sourcing or quality verification.

## 1.3 Synthesis

The published synthesis of aniracetam proceeds by a single-step N-acylation reaction: 2-pyrrolidinone is treated with 4-methoxybenzoyl chloride (anisoyl chloride) in the presence of triethylamine as an acid-binding agent [16]. The standard procedure involves addition of 4-methoxybenzoyl chloride to 2-pyrrolidinone in anhydrous diethyl ether or toluene at 0 to 10 degrees Celsius with stirring, followed by warming to room temperature and reflux for 2 to 3 hours. The triethylamine hydrochloride precipitate is removed by filtration, and the product is isolated by concentration of the filtrate and recrystallization from ethanol or ethyl acetate. Yields of 70 to 85 percent are achieved under optimized conditions with temperature control below 50 degrees Celsius during reagent addition [16]. Alternative synthesis methods described in the patent literature include catalytic approaches using Lewis acid catalysts in toluene at 40 to 110 degrees Celsius, achieving comparable yields with improved scalability. The product is characterized by nuclear magnetic resonance spectroscopy, melting point determination, and high-performance liquid chromatography. Industrial syntheses optimize the N-acylation step for yield, purity (typically greater than 99 percent by HPLC), and removal of residual triethylamine and solvent.

## 2. Abstract

Aniracetam (Ro 13-5057) is a lipophilic pyrrolidinone-class nootropic and a positive allosteric modulator of AMPA-subtype ionotropic glutamate receptors, with secondary neuromodulatory activity encompassing cholinergic facilitation, dopaminergic and serotonergic activation in mesocorticolimbic circuits, metabotropic glutamate receptor modulation, and anxiolytic effects mediated through multi-transmitter interactions [1, 2, 3, 4, 5]. The compound was developed at Hoffmann-La Roche in the late 1970s as a more potent, lipid-soluble structural analog of piracetam and was advanced through clinical development for cognitive dysfunction associated with senile dementia of the Alzheimer type and cerebrovascular disease.

The principal molecular mechanism is positive allosteric modulation of AMPA receptors at a binding site within the dimer interface of the ligand-binding domain. Aniracetam slows both the rate of receptor deactivation (channel closing after glutamate removal) and the rate of desensitization (channel closing while glutamate remains bound), thereby prolonging excitatory postsynaptic currents and enhancing the fidelity of glutamatergic synaptic transmission in cortical and hippocampal circuits [1, 2]. The functional consequence is facilitation of long-term potentiation (LTP) and enhancement of synaptic plasticity, the cellular substrates of learning and memory.

Beyond AMPA receptor modulation, aniracetam and its principal metabolite N-anisoyl-GABA exert downstream effects on cholinergic neurotransmission through enhancement of acetylcholine release in the prefrontal cortex and hippocampus, mediated in part by group II metabotropic glutamate receptor modulation [3]. Systemic administration of aniracetam enhances dopamine and serotonin release in the prefrontal cortex, basolateral amygdala, and dorsal hippocampus through cholinergic and glutamatergic mechanisms involving nicotinic acetylcholine receptors in the ventral tegmental area and raphe nuclei [4]. The anxiolytic activity, demonstrated in elevated plus-maze, conditioned fear stress, and social interaction tests, is mediated through an interaction between nicotinic acetylcholine, dopamine D2, and 5-HT2A receptor systems and is partially attributable to the metabolite p-anisic acid [5].

The pharmacokinetic profile is dominated by extensive first-pass hepatic hydrolysis. Oral bioavailability of the parent compound is approximately 0.2 percent, with a plasma elimination half-life of approximately 35 minutes [6, 7]. The parent compound is rapidly cleaved to three primary metabolites: N-anisoyl-GABA (70 to 80 percent of metabolic disposition), 2-pyrrolidinone, and p-anisic acid, each of which crosses the blood-brain barrier and contributes to pharmacological activity [8]. N-anisoyl-GABA has a substantially longer half-life than the parent compound and is detected in cerebrospinal fluid after chronic dosing, supporting the interpretation that the metabolites are the principal effectors of the sustained clinical and behavioral activity observed at therapeutic doses.

Clinical evidence derives from two pivotal double-blind, placebo-controlled multicenter trials in elderly patients with mild to moderate Alzheimer-type dementia. Aniracetam at 1500 mg per day for six months produced significant improvement in cognitive and psychobehavioral parameters, with statistically and clinically significant separation from placebo in both trials and superiority to piracetam at 2400 mg per day in one trial [9, 10]. An open-label comparative study in 276 patients confirmed preservation of cognitive function for 12 months with aniracetam monotherapy and comparable or superior performance to cholinesterase inhibitor monotherapy in mildly demented patients [11].

The compound is well tolerated. The most commonly reported adverse events are mild and transient: anxiety, restlessness, insomnia, headache, and gastrointestinal discomfort, none of which necessitated treatment withdrawal in published clinical trials [9, 10, 11]. No hepatotoxicity, cardiac conduction abnormalities, or hematological toxicity has been reported. Animal reproductive toxicity studies have raised concerns that have not been addressed by long-term human data.

Aniracetam was marketed as a prescription medicine in Japan (Draganon, subsequently withdrawn), Italy (Ampamet), and Greece (Memodrin, Referan). It is not approved by the United States Food and Drug Administration and is not classified as a controlled substance in the United States.

## 3. Discovery and Development History

### 3.1 Origin

Aniracetam was synthesized at Hoffmann-La Roche in Basel, Switzerland, in the late 1970s as part of a systematic medicinal chemistry program to develop more potent and lipophilic analogs of piracetam, the prototypical nootropic agent developed at UCB Pharmaceuticals (Belgium) and introduced in the early 1970s [15]. The design rationale was to increase central nervous system penetration by replacing piracetam's hydrophilic acetamide side chain with a lipophilic aromatic acyl group. The 4-methoxybenzoyl (anisoyl) substitution was selected from a series of N-acyl-2-pyrrolidinone candidates on the basis of superior potency in rodent passive avoidance and active avoidance learning paradigms, favorable oral bioavailability of active metabolites, and acceptable acute and subchronic toxicology. The compound was assigned the development code Ro 13-5057 and was patented in 1978.

### 3.2 Preclinical characterization

The initial pharmacological characterization of aniracetam was published by Cumin et al. (1982), who demonstrated that the compound ameliorated impaired learning and memory in rodent models of cognitive dysfunction, including scopolamine-induced amnesia and electroconvulsive shock-induced retrograde amnesia, at oral doses of 10 to 100 mg/kg [12]. The compound was approximately 3 to 8 times more potent than piracetam by weight in these paradigms. Subsequent preclinical work through the 1980s extended the cognitive enhancement profile to cerebral ischemia models, age-related cognitive decline in senescent rodents, and multiple learning and memory paradigms.

### 3.3 Identification of the AMPA receptor mechanism

The molecular mechanism of aniracetam was clarified by Ito et al. (1990) and subsequently by Vyklícky et al. (1991) and Isaacson and Nicoll (1991), who demonstrated that aniracetam selectively potentiates AMPA receptor-mediated synaptic currents in hippocampal neurons without affecting NMDA receptor currents [1, 17]. The compound was found to slow both deactivation and desensitization of AMPA

receptors, placing it in the class of positive allosteric modulators subsequently termed "ampakines." The Lawrence et al. (2003) study of the mechanism of action at synaptic AMPA receptors further defined the binding site within the dimer interface of the AMPA receptor ligand-binding domain and separated the direct and indirect effects on desensitization [2]. Jin et al. (2005) demonstrated that aniracetam and cyclothiazide, though both AMPA PAMs, operate through kinetically distinguishable mechanisms at the same allosteric site [18]. Ahmed and Bhatt (2010) characterized the piracetam binding site on AMPA receptors, confirming that racetam-class compounds and other ampakines share a common allosteric binding region at the dimer interface [19].

### 3.4 Clinical development and registration

Clinical trials in elderly patients with senile dementia of the Alzheimer type were conducted in the late 1980s and early 1990s. The pivotal Senin et al. (1991) double-blind, placebo-controlled multicenter trial in 109 patients demonstrated statistically significant cognitive improvement at 1500 mg per day for six months [9]. A second multicenter trial compared aniracetam to piracetam, with aniracetam demonstrating superiority [10]. On the basis of these trials and additional clinical pharmacology data, aniracetam received marketing authorization as a prescription medicine in Japan (for cerebrovascular disease-associated cognitive impairment, marketed as Draganon by Roche), in Italy (as Ampamet), and in Greece (as Memodrin and Referan).

### 3.5 Post-registration trajectory

In Japan, Draganon was subsequently withdrawn from the market in the 1990s following reassessment of clinical benefit in the post-stroke cognitive impairment indication. Marketing authorization persisted in Italy and Greece into the 2000s, though the compound has been progressively replaced by cholinesterase inhibitors (donepezil, rivastigmine, galantamine) as first-line therapy for Alzheimer-type dementia. The compound has not been submitted for regulatory review in the United States. It is sold as a research compound and dietary supplement in the United States, where it is not classified as a controlled substance. In Australia, aniracetam is classified as a Schedule 4 substance (prescription only).

The research literature on aniracetam has continued to expand through the 2000s and 2020s, with particular emphasis on the multi-target neurotransmitter pharmacology (cholinergic, dopaminergic, serotonergic), the anxiolytic mechanism, the active metabolite pharmacology, neuroprotective potential, and application to attention deficit hyperactivity disorder (ADHD) models [3, 4, 5, 14, 20].

## 4. Molecular Pharmacology

Aniracetam is a multi-target neuromodulatory agent. Its principal molecular activities, characterized in heterologous expression systems, brain slice preparations, and in vivo microdialysis studies, are positive allosteric modulation of AMPA-type ionotropic glutamate receptors; modulation of group II metabotropic glutamate receptors; enhancement of cholinergic neurotransmission; activation of dopaminergic and serotonergic transmission in mesocorticolimbic pathways; and anxiolytic activity mediated through interactions between cholinergic, dopaminergic, and serotonergic systems. Several of these downstream activities are attributable to the active metabolites rather than to the parent compound.

### 4.1 AMPA receptor positive allosteric modulation

The AMPA receptor (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) is a tetrameric ionotropic glutamate receptor composed of GluA1 through GluA4 subunits, mediating the majority of fast excitatory synaptic transmission in the central nervous system. AMPA receptors are expressed at high density on pyramidal neurons of the hippocampus and neocortex and on interneurons throughout the brain; they are the principal postsynaptic receptors at excitatory synapses and are essential for synaptic plasticity, long-term potentiation, and memory formation.

Aniracetam binds to the AMPA receptor at a site within the dimer interface of the extracellular ligand-binding domain, distinct from the glutamate binding site [2, 18, 19]. The binding is allosteric: aniracetam does not activate the receptor in the absence of glutamate but modulates the receptor response to glutamate. Two functionally distinguishable consequences of binding have been characterized [1, 2]:

First, aniracetam slows deactivation, the process by which the ion channel closes after glutamate dissociates from the binding site. The consequence is prolongation of the excitatory postsynaptic current beyond the duration determined by glutamate clearance from the synaptic cleft. Second, aniracetam slows desensitization, the process by which the ion channel closes while glutamate remains bound.

Desensitization ordinarily limits the peak amplitude and duration of synaptic currents at AMPA receptors; reduction of desensitization by aniracetam increases peak current amplitude and prolongs the decay time constant.

Lawrence et al. (2003) demonstrated that aniracetam exerts both indirect effects on desensitization (by slowing deactivation, which reduces the probability of entering the desensitized state) and direct effects on the desensitization process itself [2]. Jin et al. (2005) showed that aniracetam and cyclothiazide, though binding at the same dimer-interface site, modulate AMPA receptor gating through kinetically distinct mechanisms: cyclothiazide primarily blocks desensitization, while aniracetam primarily slows deactivation [18].

The functional consequence of AMPA receptor positive allosteric modulation in hippocampal slices is facilitation of long-term potentiation (LTP), the cellular substrate of learning and memory. Aniracetam enhances LTP induction in the Schaffer collateral-CA1 pathway and in the mossy fiber-CA3 pathway at concentrations of 1 to 5 millimolar [1, 17]. In intact animals, this translates to improved performance in learning and memory tasks dependent on hippocampal and cortical circuit function.

## 4.2 Metabotropic glutamate receptor modulation

The active metabolite N-anisoyl-GABA modulates group II metabotropic glutamate receptors (mGluR2 and mGluR3), which are Gi/Go-coupled receptors that function as presynaptic autoreceptors on glutamatergic terminals and as heteroreceptors on cholinergic and monoaminergic terminals [3]. Group II mGluR modulation by N-anisoyl-GABA enhances acetylcholine release in the prefrontal cortex and hippocampus, providing a cholinergic facilitation mechanism that operates downstream of and in parallel with the direct AMPA receptor modulation by the parent compound.

## 4.3 Cholinergic enhancement

Aniracetam and N-anisoyl-GABA enhance acetylcholine release from cholinergic terminals in the prefrontal cortex, hippocampus, and striatum [3]. The mechanism involves both the group II mGluR-mediated facilitation described above and direct activation of neuronal nicotinic acetylcholine receptors. The cholinergic enhancement has been demonstrated by *in vivo* microdialysis in freely moving rats and is

blocked by mecamylamine (a nicotinic antagonist), confirming the nicotinic receptor involvement [4, 5]. The cholinergic facilitation is relevant to the cognitive enhancement profile because cholinergic neurotransmission in the hippocampus and cortex is essential for attention, encoding, and memory consolidation, and cholinergic deficits are a hallmark of Alzheimer-type dementia.

## 4.4 Dopaminergic and serotonergic activation

Nakamura and Shirane (2001) demonstrated that systemic aniracetam administration enhances dopamine and serotonin release in the prefrontal cortex, basolateral amygdala, and dorsal hippocampus of stroke-prone spontaneously hypertensive rats (SHRSP) [4]. Shirane and Bhatt (2001) showed that this activation is site-specific within the mesocorticolimbic pathway and is mediated through nicotinic acetylcholine receptors in the ventral tegmental area (for dopamine) and dorsal raphe nuclei (for serotonin) [21]. The monoaminergic activation is relevant to both the cognitive enhancement profile (dopaminergic and serotonergic contributions to working memory and executive function) and the anxiolytic profile (serotonergic and dopaminergic contributions to emotional regulation).

## 4.5 Anxiolytic mechanism

The anxiolytic activity of aniracetam was formally characterized by Nakamura and Kurasawa (2001) in three mouse models of anxiety: the elevated plus-maze, the conditioned fear stress test, and the social interaction test [5]. Aniracetam at 10 to 100 mg/kg oral administration produced significant anxiolytic effects in all three paradigms. The anxiolytic effects were blocked by haloperidol (a dopamine D2 receptor antagonist), mecamylamine (a nicotinic acetylcholine receptor antagonist), and ketanserin (a 5-HT<sub>2A</sub> receptor antagonist), indicating that the anxiolytic mechanism involves an interaction between nicotinic cholinergic, dopamine D2, and serotonin 5-HT<sub>2A</sub> receptor systems. Different metabolites mimicked the anxiolytic effects in different paradigms: p-anisic acid reproduced the elevated plus-maze effect, while specific combinations of metabolites were required for the conditioned fear and social interaction effects [5].

## 4.6 Neuroprotective mechanisms

Aniracetam has demonstrated neuroprotective activity against excitotoxicity and ischemic injury in in vitro and in vivo models [13, 14]. The neuroprotective mechanism is multifactorial and includes promotion of brain-derived neurotrophic factor (BDNF) synthesis through AMPA receptor-mediated calcium signaling, reduction of oxidative stress through antioxidant pathways, and modulation of apoptotic signaling. The neuroprotective profile supports the therapeutic rationale for use in cerebrovascular disease and neurodegenerative conditions.

## 5. Pharmacokinetics

### 5.1 Absorption

Aniracetam is rapidly and completely absorbed from the gastrointestinal tract after oral administration. Time to peak plasma concentration (T<sub>max</sub>) is approximately 0.4 hours (24 minutes), indicating very rapid absorption [6, 7]. The compound is lipophilic and crosses the intestinal epithelium efficiently. However, absolute systemic bioavailability of the parent compound is extremely low, approximately 0.2 percent, due to extensive first-pass hepatic hydrolysis [6].

### 5.2 Distribution

The volume of distribution of the parent compound has not been precisely characterized in humans owing to the extremely low systemic bioavailability and rapid elimination. In animal studies, aniracetam distributes readily to the brain, with central nervous system penetration substantially greater than that of piracetam, consistent with the lipophilic character of the molecule [22]. The parent compound and its metabolites cross the blood-brain barrier; N-anisoyl-GABA and 2-pyrrolidinone have been detected in cerebrospinal fluid of patients treated with aniracetam for 12 weeks, confirming central penetration of the active metabolites [8]. Plasma protein binding data for the parent compound are limited; the rapid hydrolysis precludes conventional protein-binding equilibrium studies.

### 5.3 Metabolism

Aniracetam undergoes extensive first-pass hepatic metabolism, principally by hydrolytic cleavage of the amide bond linking the anisoyl group to the pyrrolidinone ring [6, 7, 8]. The total body clearance from blood (approximately 10 liters per minute in humans) exceeds cardiac output, indicating that extrahepatic clearance sites (lung, gastrointestinal tract) contribute to presystemic elimination [6].

Three primary metabolites are produced:

**N-anisoyl-GABA (4-p-anisamidobutyric acid):** The principal metabolite, accounting for 70 to 80 percent of metabolic disposition. N-anisoyl-GABA is pharmacologically active, enhancing acetylcholine release through group II metabotropic glutamate receptor modulation and contributing to the cognitive enhancement and anxiolytic profiles. The metabolite has a substantially longer plasma half-life than the parent compound, supporting sustained pharmacological activity after single and repeated dosing [8].

**2-Pyrrolidinone:** Accounts for 20 to 30 percent of metabolic disposition. 2-Pyrrolidinone is the gamma-butyrolactam ring released by hydrolysis and has modest pharmacological activity in some in vitro systems.

**p-Anisic acid (4-methoxybenzoic acid):** Accounts for 20 to 30 percent of metabolic disposition. p-Anisic acid is pharmacologically active and has been shown to reproduce the anxiolytic effect of the parent compound in the elevated plus-maze test [5].

The metabolic pathway does not involve cytochrome P450 enzymes as the principal transformation; the initial hydrolytic step is mediated by esterases and amidases. Subsequent conjugation and elimination of the metabolites proceeds through standard phase II pathways.

## 5.4 Elimination

The plasma elimination half-life of aniracetam in humans is approximately 35 minutes (0.47 to 0.49 hours), consistent with the extensive first-pass hydrolysis [6, 7]. Maximum plasma concentrations after a single 400 mg oral dose in healthy Chinese male volunteers were achieved at approximately 0.4 hours, with rapid decline thereafter [7]. The metabolites N-anisoyl-GABA and p-anisic acid have longer elimination half-lives, contributing to sustained pharmacological activity. Elimination of metabolites is principally renal, with conjugated forms excreted in urine.

## 5.5 Routes of administration

The standard route of administration is oral. The registered dosing regimen in clinical trials and marketed formulations is 1500 mg per day, typically administered as 750 mg twice daily or 500 mg three times daily. Some clinical protocols have used

doses of 1000 to 1500 mg per day. The compound is supplied as tablets, capsules, or granules in marketed formulations and as bulk powder in research-grade preparations.

Intravenous and intraperitoneal administration have been used in preclinical research but are not registered routes for human use. The extremely low bioavailability of the parent compound via oral administration is offset by the pharmacological activity of the metabolites, which achieve higher and more sustained plasma concentrations than the parent compound.

## 5.6 Special populations

Pharmacokinetic studies in elderly patients (the target population for the dementia indication) have not identified clinically significant differences in absorption or metabolic disposition compared to younger adults, though the limited data available do not exclude age-related alterations in esterase activity or metabolite clearance. Renal impairment may affect elimination of the conjugated metabolites; dose adjustment has not been formally studied. Hepatic impairment may alter the rate and extent of first-pass hydrolysis; formal dose-adjustment recommendations are not available.

## 6. Preclinical Pharmacology

### 6.1 Cognitive enhancement in learning and memory models

The original Cumin et al. (1982) characterization demonstrated that aniracetam ameliorated impaired learning and memory in multiple rodent paradigms at oral doses of 10 to 100 mg/kg [12]. Specific models included:

Scopolamine-induced amnesia: Aniracetam produced partial (in rats) or complete (in mice) prevention of scopolamine-induced short-term amnesia in passive avoidance tasks, demonstrating interaction with cholinergic mechanisms of memory formation [12, 13].

Electroconvulsive shock-induced retrograde amnesia: Aniracetam attenuated the retrograde amnesic effects of electroconvulsive shock in rodents, supporting activity on memory consolidation processes [12].

Cerebral ischemia models: Aniracetam ameliorated impairment of working memory induced by transient forebrain ischemia in gerbils and improved pre- and post-synaptic cholinergic indices in gerbil hippocampus following ischemic injury [13].

Age-related cognitive decline: Aniracetam improved performance in aged rodents in multiple paradigms including the Morris water maze, consistent with enhancement of synaptic plasticity in senescent hippocampal circuits [14].

### 6.2 Anxiolytic activity

The Nakamura and Kurasawa (2001) study demonstrated anxiolytic effects in three mouse models at oral doses of 10 to 100 mg/kg [5]. In the elevated plus-maze, aniracetam increased open-arm entries and time. In the conditioned fear stress test, aniracetam reduced freezing behavior. In the social interaction test, aniracetam increased total social interaction time, principally reflecting increased trunk

sniffing and following behavior. The anxiolytic effects were dose-dependent and were blocked by haloperidol, mecamylamine, and ketanserin, establishing the multi-transmitter mechanism.

## 6.3 Neuroprotection

In vitro studies demonstrated that aniracetam protects cultured neurons against glutamate excitotoxicity and oxidative stress [14]. In vivo studies in ischemia models demonstrated neuroprotective effects on hippocampal neuronal survival and function. The neuroprotective mechanism involves promotion of BDNF synthesis through AMPA receptor-mediated calcium signaling pathways and modulation of apoptotic cascades.

## 6.4 Monoaminergic neurotransmission

Microdialysis studies in freely moving rats demonstrated that systemic aniracetam administration enhances extracellular dopamine concentrations in the prefrontal cortex, nucleus accumbens, and striatum, and enhances extracellular serotonin concentrations in the prefrontal cortex, basolateral amygdala, and dorsal hippocampus [4, 21]. The activation pattern is site-specific and is consistent with activation of the mesocorticolimbic dopaminergic pathway (originating in the ventral tegmental area) and the serotonergic projection system (originating in the dorsal raphe nucleus). The monoaminergic effects are mediated through nicotinic acetylcholine receptors, as demonstrated by blockade with mecamylamine [4].

## 6.5 ADHD models

Recent preclinical work has demonstrated that aniracetam ameliorates attention deficit hyperactivity disorder behavior in adolescent mice, restoring the excitation-inhibition balance of neurotransmitters in the prefrontal cortex [20]. This finding extends the therapeutic rationale beyond dementia and anxiety to neurodevelopmental conditions characterized by prefrontal cortical dysfunction.

## 6.6 Amyloid-beta pathology

Love (2024) presented an evidence-based model for aniracetam's potential role in preventing the accumulation of amyloid-beta plaques in Alzheimer's disease, integrating the AMPA receptor modulation, BDNF promotion, and neuroprotective

mechanisms into a composite anti-amyloidogenic rationale [23]. The preclinical evidence supports further investigation of aniracetam in amyloid-related neurodegenerative disease models.

## 7. Clinical Evidence Base

### 7.1 Senile dementia of the Alzheimer type: pivotal trials

Two double-blind, placebo-controlled, multicenter clinical trials constitute the principal clinical evidence base for aniracetam in cognitive impairment.

The Senin et al. (1991) trial enrolled 109 elderly patients with mild to moderate cognitive impairment fulfilling NINCDS-ADRDA criteria for probable dementia of the Alzheimer type [9]. Patients were randomized to aniracetam 1500 mg per day or placebo for six months. The aniracetam group showed statistically significant improvement in psychobehavioral parameters versus baseline and statistically significant separation from the placebo group by the end of the six-month treatment period. The placebo group showed steady deterioration consistent with the natural history of the disease. Tolerability was excellent; adverse events were mild and did not require treatment withdrawal.

A second multicenter trial compared aniracetam 1500 mg per day to piracetam 2400 mg per day and to placebo over six months in elderly patients with mild to moderate SDAT [10]. Aniracetam produced statistically and clinically significant improvement in cognitive function relative to both placebo and piracetam, establishing superiority to the parent compound at the tested doses. The difference between aniracetam and piracetam was attributed to the greater potency, improved central nervous system penetration, and multi-target mechanism of aniracetam relative to piracetam.

### 7.2 Comparative open-label study

Koliaki et al. (2012) conducted a prospective, open-label comparative study in 276 patients (mean age 71 years) with cognitive disorders [11]. Four treatment groups were evaluated: no treatment (n = 75), aniracetam monotherapy (n = 58), cholinesterase inhibitor (ChEI) monotherapy (n = 68), and combined aniracetam plus ChEI therapy (n = 68). Follow-up assessments were conducted at 3, 6, and 12 months.

Mildly demented patients (Mini-Mental State Examination score 15 to 25) treated with aniracetam monotherapy maintained all neuropsychological parameters at 3, 6, and 12 months of follow-up. The comparison between aniracetam and ChEIs in mildly demented patients revealed significantly better cognitive performance with aniracetam at 6 months and improved functionality at 3 months. In moderately demented patients, ChEIs and combined therapy showed better outcomes than aniracetam monotherapy. The study concluded that aniracetam is a promising option for patients with cognitive deficit of mild severity and appeared to exert a favorable effect on emotional stability [11].

### 7.3 Post-stroke cognitive impairment

Clinical use in Japan under the Draganon brand was directed at cognitive impairment following cerebrovascular events. Published clinical data from this indication are limited in the English-language literature; the Japanese regulatory experience supported initial marketing authorization but not sustained marketing, as the compound was subsequently withdrawn.

### 7.4 Emotional and behavioral effects

Clinical observations across the published trials suggest that aniracetam may exert a mood-stabilizing or anxiolytic-like effect in demented patients, consistent with the preclinical anxiolytic pharmacology [5, 11]. Koliaki et al. (2012) noted a favorable effect on emotional stability in aniracetam-treated patients [11]. Formal clinical trials of aniracetam as an anxiolytic agent in non-demented populations have not been conducted.

### 7.5 Limitations of the clinical evidence base

The clinical evidence base for aniracetam is substantially smaller than that for cholinesterase inhibitors and memantine. The pivotal trials enrolled relatively small patient populations (109 and comparable cohorts) and predated contemporary standards for cognitive endpoint assessment in Alzheimer's disease registration trials (including the ADAS-Cog and CDR-SB scales used in current regulatory submissions). No Phase 3 registration trial meeting current United States or European regulatory standards has been conducted. The comparative open-label study provides supportive but not definitive evidence. Far more clinical trials are needed to validate the promising indications suggested by the existing data.

## 8. Sourcing and Quality Verification

Research-grade aniracetam is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Tocris, Cayman Chemical, MedChemExpress, Santa Cruz Biotechnology, APExBIO, InvivoChem, others) at greater than 98 percent purity by HPLC. Supply is in milligram to multi-gram quantities as the free base. Pricing is moderate, in the range of \$20 to \$100 per gram of research-grade material at the time of monograph preparation.

Pharmaceutical-grade aniracetam (Ampamet brand or equivalent) is available in jurisdictions where the compound retains marketing authorization. The pharmaceutical material is supplied as oral tablets or capsules, typically in 750 mg unit doses.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (220.10 for the protonated molecule  $[M+H]^+$ , or 219.09 for the molecular ion)
- Melting point determination (121 to 122 degrees Celsius for the pure compound)
- Nuclear magnetic resonance spectroscopy confirmation of the expected  $^1H$  and  $^{13}C$  patterns for the anisoyl-pyrrolidinone structure
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis (gas chromatography for common synthesis solvents: diethyl ether, toluene, ethanol, ethyl acetate)

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) provide independent confirmation of vendor certificates of analysis. The research-grade aniracetam market is well established; however, as with all unregulated research compounds, lot-to-lot variability is observed and on-receipt analytical confirmation is appropriate for any investigation where dose-response precision is important.

Investigators should be aware that aniracetam has been identified as an undeclared ingredient in some commercially marketed dietary supplements sold as cognitive enhancers in the United States [24]. This raises quality and regulatory compliance considerations for both research and consumer-grade sourcing.

## 9. Reconstitution and Handling

Aniracetam is supplied as a white to off-white crystalline powder. For oral research applications, the compound is typically administered as powder in capsules, suspended in a suitable vehicle, or dissolved in dimethyl sulfoxide for in vitro work. The compound is poorly soluble in water (less than 1 mg/mL) but dissolves readily in DMSO (up to 100 mM), ethanol, and chloroform.

For in vitro electrophysiology and cell culture studies, stock solutions are typically prepared at 50 to 100 mM in DMSO and diluted to working concentrations (0.5 to 5 mM) in physiological recording solutions. The final DMSO concentration should not exceed 0.1 percent to avoid solvent-mediated effects on ion channel function.

For in vivo animal studies, aniracetam is commonly suspended in 0.5 percent carboxymethylcellulose or dissolved in a small volume of DMSO followed by dilution in saline or corn oil. Oral gavage is the standard route for preclinical dosing studies.

Storage of the solid compound at room temperature in a dry, light-protected environment is appropriate. The compound is stable under these conditions for extended periods (years) when stored in sealed containers with desiccant. Solutions in DMSO are stable at minus 20 degrees Celsius for at least 6 months; aqueous suspensions should be prepared fresh before use.

The compound is not classified as hazardous under standard chemical safety frameworks. Standard laboratory personal protective equipment (gloves, laboratory coat, eye protection) is appropriate for handling.

## 10. Stack Interactions and Combinations

Aniracetam interacts with several drug classes through its glutamatergic, cholinergic, and monoaminergic mechanisms. Investigators conducting research with aniracetam, especially in chronic dosing regimens or in combination with other research compounds, should consider:

**Cholinergic agents:** Concurrent acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) produce additive cholinergic activity. The combination has been studied clinically by Koliaki et al. (2012), who found that combined aniracetam plus ChEI therapy produced outcomes comparable to or modestly better than either agent alone in moderately demented patients [11]. The combination is pharmacologically rational and appears well tolerated.

**Other racetams:** Concurrent use with piracetam, oxiracetam, or pramiracetam is pharmacologically plausible given overlapping but not identical mechanisms. Piracetam and aniracetam bind at a common allosteric site on AMPA receptors [19], suggesting competitive rather than additive interactions at the receptor level. The combination has not been formally studied in controlled clinical trials.

**Choline sources:** Alpha-GPC (alpha-glycerophosphocholine), CDP-choline (citicoline), and choline bitartrate are commonly co-administered with racetams in nootropic research protocols on the rationale that enhanced cholinergic demand from racetam use requires supplemental choline substrate. The pharmacological rationale is supported by the demonstrated cholinergic facilitation by aniracetam and N-anisoyl-GABA [3]. Formal clinical data on the combination are absent.

**Ampakines and AMPA PAMs:** Concurrent use with other AMPA receptor positive allosteric modulators (CX516, CX717, sunifiram) produces additive or potentially supraadditive effects on AMPA receptor function and should be approached with caution, as excessive AMPA receptor potentiation could theoretically lower seizure threshold.

**GABAergic agents:** Concurrent benzodiazepines, barbiturates, or other GABA-A receptor agonists may functionally oppose the excitatory glutamatergic effects of AMPA receptor potentiation. Aniracetam's anxiolytic mechanism is not GABAergic and is not expected to produce additive sedation with GABAergic agents.

**Serotonergic agents:** Aniracetam enhances serotonin release through cholinergic mechanisms [4, 21]. Concurrent use with selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or monoamine oxidase inhibitors should be monitored for potential additive serotonergic effects, though the magnitude of aniracetam's serotonergic contribution is modest at therapeutic doses and clinically significant serotonin syndrome has not been reported.

**Dopaminergic agents:** Aniracetam enhances dopamine release in the mesocorticolimbic pathway [4, 21]. Concurrent use with dopamine agonists, levodopa, or stimulant medications should be considered for potential additive dopaminergic effects. The clinical significance of this interaction has not been formally characterized.

# 11. Adverse Events and Safety

## 11.1 Common adverse events

The principal adverse events reported in clinical trials at registered doses (1500 mg per day) are mild and transient:

- Anxiety, restlessness, uneasiness (the most commonly reported category)
- Insomnia
- Headache
- Vertigo, dizziness
- Mild gastrointestinal discomfort (stomach pain, nausea, diarrhea)
- Urinary urgency (rare)
- Rash (rare)

These adverse events did not necessitate treatment withdrawal in published clinical trials [9, 10, 11]. The overall tolerability profile is favorable, and aniracetam has been described as having a high level of tolerability and safety in the published clinical literature.

## 11.2 Hepatic and cardiac safety

No clinically significant hepatotoxicity has been reported in clinical trials or post-marketing surveillance. Liver enzyme elevations have not been identified as a safety signal. No cardiac conduction abnormalities, QT prolongation, or arrhythmias have been reported, distinguishing aniracetam from some other centrally active compounds in its safety profile.

## 11.3 Reproductive toxicity

Animal reproductive toxicity studies have identified potential concerns that have not been resolved by human data [24]. The nature and magnitude of the animal reproductive toxicity findings have not been fully characterized in the publicly avail-

able English-language literature. The absence of long-term human reproductive safety data is a significant limitation of the safety profile. Use in pregnancy and lactation is not recommended.

## 11.4 Long-term safety

The principal limitation of the aniracetam safety database is the absence of long-term human studies. Most clinical trials have lasted weeks to six months. The long-term safety of chronic aniracetam use (years) in humans is unknown. Investigators conducting chronic dosing studies should implement appropriate safety monitoring including hepatic function tests, renal function tests, and periodic clinical assessment.

## 11.5 Overdose

No cases of clinically significant aniracetam overdose have been reported in the published literature. The lethal dose in rodents (LD50) is high relative to the therapeutic dose range, indicating a wide therapeutic index. The compound does not produce respiratory depression, cardiovascular collapse, or other life-threatening acute toxicity at doses studied.

## 12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative racetam, ampakine, and cognitive-enhancement compounds against aniracetam, evaluated on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal compounds sharing structural class or mechanism with aniracetam that have substantive clinical or preclinical pharmacology programs.

### 12.1 Piracetam

**Mechanism:** The prototypical racetam nootropic. Positive allosteric modulator of AMPA receptors at the same dimer-interface binding site as aniracetam, though with lower potency and efficacy [19]. Additional effects on membrane fluidity, rheological properties of erythrocytes, and cerebral blood flow.

**Development trajectory:** Piracetam (UCB-6215) was developed at UCB Pharmaceuticals (Belgium) and introduced in the early 1970s as the first nootropic agent. It is marketed in numerous European and Asian jurisdictions for cognitive impairment, vertigo, myoclonus, and dyslexia. It is not approved by the FDA.

**Novelty:** Low. Piracetam is the oldest and most extensively studied racetam. All subsequent racetam development has been measured against piracetam.

**Effect size:** Modest in clinical trials of cognitive impairment. Multiple meta-analyses have found small but statistically significant effects on cognitive function in dementia, with substantial heterogeneity across trials. Aniracetam demonstrated superiority to piracetam at tested doses in head-to-head comparison [10].

**Promising potential:** Low to moderate. The compound is well established but has not produced convincing large-scale Phase 3 registration data by contemporary regulatory standards. It persists as a widely used nootropic and prescription medicine outside the United States.

**Side-effect profile:** Excellent. Piracetam is well tolerated with a very low incidence of adverse events. The principal side effects are nervousness, insomnia, and weight gain, generally mild.

**Overall validation:** Moderate. Extensive clinical and preclinical literature spanning over 50 years. The effect sizes are modest and the regulatory trajectory incomplete by current standards.

**Comparison to aniracetam:** Aniracetam is 3 to 8 times more potent than piracetam by weight in preclinical cognitive models and demonstrated clinical superiority in a head-to-head trial. Aniracetam has the additional multi-target pharmacology (cholinergic, dopaminergic, serotonergic, anxiolytic) that piracetam lacks. Piracetam has a more extensive clinical database, longer market history, and a more favorable aqueous solubility for formulation.

## 12.2 Oxiracetam

**Mechanism:** Racetam-class nootropic with AMPA receptor positive allosteric modulation. Also reported to enhance cholinergic neurotransmission and to promote phospholipid metabolism.

**Development trajectory:** Developed by ICF (Italy) in the 1970s. Clinical trials in dementia and cognitive impairment have been conducted in Europe and Asia, with mixed results. Marketed in some European and Asian jurisdictions.

**Novelty:** Low. The mechanism is closely related to piracetam and aniracetam within the racetam class.

**Effect size:** Modest. Clinical trials have reported small improvements in cognitive function in demented patients, generally similar in magnitude to piracetam and smaller than aniracetam.

**Promising potential:** Low. No active clinical development program. Persists as a marketed product and research tool.

**Side-effect profile:** Excellent. Well tolerated with adverse events similar in nature and frequency to piracetam. Insomnia and nervousness are the most commonly reported.

**Overall validation:** Low to moderate. Clinical evidence base is smaller than for piracetam or aniracetam.

**Comparison to aniracetam:** Aniracetam has greater potency, broader multi-target pharmacology, and a larger clinical evidence base. Oxiracetam is water-soluble (unlike aniracetam), facilitating aqueous formulation.

## 12.3 Pramiracetam

**Mechanism:** Racetam-class nootropic. The precise molecular mechanism is less well characterized than that of aniracetam. Pramiracetam enhances high-affinity choline uptake in the hippocampus, facilitating acetylcholine synthesis. AMPA receptor modulation has not been convincingly demonstrated.

**Development trajectory:** Developed by Parke-Davis (Warner-Lambert, now Pfizer) in the late 1970s. Limited clinical trials have been conducted in cognitive impairment and traumatic brain injury. Marketed in some European jurisdictions.

**Novelty:** Low to moderate. The choline uptake mechanism is distinct from the AMPA PAM mechanism of aniracetam, but the compound is otherwise within the conventional racetam space.

**Effect size:** Modest in the limited clinical data available. A single-center trial in traumatic brain injury patients showed improvement in memory and attention.

**Promising potential:** Low. No active clinical development. Available as a research compound.

**Side-effect profile:** Favorable. Well tolerated in published studies. Headache and gastrointestinal discomfort are reported.

**Overall validation:** Low. The clinical evidence base is small, and the molecular mechanism is incompletely characterized.

**Comparison to aniracetam:** Aniracetam has a better characterized molecular mechanism, a broader pharmacological profile, and a larger clinical evidence base. Pramiracetam's choline uptake enhancement provides a theoretically complementary mechanism.

## 12.4 CX516 (Ampalex)

**Mechanism:** Benzamide-class positive allosteric modulator of AMPA receptors (ampakine). CX516 was developed by Cortex Pharmaceuticals as a more potent and selective AMPA PAM than the racetams, designed specifically for the AMPA receptor target.

**Development trajectory:** CX516 advanced through Phase 2 clinical trials for schizophrenia cognitive impairment and Alzheimer's disease in the late 1990s and early 2000s. The Goff et al. (2008) randomized, double-blind, placebo-controlled Phase 2 trial in 105 schizophrenia patients reported no significant improvement on cognitive endpoints at 900 mg three times daily for 4 weeks [25]. Clinical development was discontinued.

**Novelty:** Moderate. CX516 represented the first synthetic ampakine designed specifically for AMPA receptor potentiation, distinct from the racetam class in chemical structure.

**Effect size:** Negative in the pivotal Phase 2 trial. Preclinical effect sizes were promising but did not translate to clinical benefit.

**Promising potential:** Low. Development terminated. Available as a research tool.

**Side-effect profile:** Tolerable in Phase 2 studies. No serious safety concerns identified.

**Overall validation:** Low to moderate. The compound advanced to Phase 2 with negative results, limiting validation of the mechanism at the clinical level.

**Comparison to aniracetam:** CX516 is more selective for the AMPA receptor target but produced negative clinical trial results, whereas aniracetam produced positive results in dementia trials. Aniracetam's multi-target pharmacology (including the active metabolite contributions) may explain the disparity between the clinical outcomes.

## 12.5 Sunifiram (DM-235)

**Mechanism:** Piperazine-class AMPA receptor positive allosteric modulator and glycine-binding site activator. Sunifiram enhances LTP in hippocampal slices at nanomolar concentrations and improves cognitive performance in rodent models at doses approximately 1000-fold lower than piracetam [26].

**Development trajectory:** Developed at the University of Firenze (Italy). Preclinical characterization only. No human clinical trials have been conducted. Available as a research compound.

**Novelty:** Moderate to high. The piperazine scaffold and the potency at nanomolar concentrations distinguish sunifram from the conventional racetam class.

**Effect size:** Substantial in preclinical rodent models. Effect sizes in animal models do not translate predictively to human clinical effect.

**Promising potential:** Low as a clinical candidate (no human studies). Moderate as a research tool for understanding AMPA receptor modulation in cognition.

**Side-effect profile:** Preclinical only. No human safety data.

**Overall validation:** Low. Preclinical research tool with no clinical validation.

**Comparison to aniracetam:** Sunifram is substantially more potent than aniracetam at the AMPA receptor level but has no clinical evidence base. Aniracetam has the advantages of clinical trial data, established safety profile at therapeutic doses, and marketed-product operational history.

## 12.6 Comparator summary

The five compounds occupy distinct positions in the racetam and ampakine pharmacology space. **Piracetam** is the prototypical agent with the longest history and largest literature but modest clinical effect sizes and demonstrated inferiority to aniracetam in head-to-head comparison. **Oxiracetam** is a closely related racetam with a smaller evidence base and comparable or inferior efficacy to aniracetam. **Pramiracetam** has a complementary choline uptake mechanism but an incompletely characterized molecular pharmacology. **CX516** represents the first purpose-designed ampakine but failed to produce clinical cognitive benefit in Phase 2. **Sunifram** is the most potent compound in the panel at the receptor level but lacks any human clinical data.

Aniracetam occupies a unique position in this comparator landscape: it combines AMPA receptor positive allosteric modulation with multi-target downstream pharmacology through active metabolites (cholinergic, dopaminergic, serotonergic, anxiolytic), positive clinical trial data in dementia populations, and a marketed-product history in multiple jurisdictions. The multi-target pharmacology ap-

appears to be a clinical advantage rather than a liability, as the single-target AMPA PAM CX516 failed clinically while the multi-target aniracetam succeeded, suggesting that the composite mechanism may be necessary for clinical translation of AMPA receptor modulation in cognitive disorders.

The principal limitation of aniracetam relative to contemporary drug development standards is the small scale and age of the clinical trials, which predate current regulatory requirements for cognitive endpoint assessment (ADAS-Cog, CDR-SB). A modern, adequately powered, regulatory-standard Phase 3 trial has not been conducted. Investigators considering aniracetam for cognitive research should expect modest effect sizes consistent with the AMPA PAM and racetam class, should manage the rapid parent-compound metabolism and active metabolite pharmacology as determinants of dose-response, and should consider the comparator landscape as the realistic context for clinical-translation expectations. The historical clinical data, the multi-target mechanism, the registration status in selected jurisdictions, and the operational accessibility of the compound combine to support its continued use as a research-clinical tool.

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