

RESEARCH MONOGRAPH . COMPOUND PROFILE

Sunifiram

A piperazine-derived cognition enhancer synthesized at the University of Florence as a molecular simplification of unifiram, distinguished from the racetam class by four-orders-of-magnitude greater antiamnesic potency in rodent models and a mechanism operating through the glycine-binding site of the NMDA receptor with downstream CaMKII and PKC-alpha activation, though lacking any human clinical data or formal toxicology record.

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ABSTRACT

Sunifiram (DM-235; 1-benzoyl-4-propanoylpiperazine; CAS 314728-85-3; molecular formula C₁₄H₁₈N₂O₂; molecular weight 246.31 g/mol) is a synthetic piperazine-derived nootropic compound first disclosed at the University of Florence in approximately 2000 by the Gualtieri research group as a molecular simplification of unifiram (DM-232), itself a bicyclic diazabicyclononanone derivative of the racetam pharmacophore. Despite frequent categorization in the research-chemical literature as an ampakine or racetam analogue, sunifiram is structurally distinct from both classes: it lacks the pyrrolidone ring system that defines the racetam family and does not directly potentiate AMPA receptor currents in the manner of canonical ampakines such as CX-516 or aniracetam. The compound was identified through a program of systematic structural simplification of the piracetam scaffold, in which opening of the pyrrolidone ring and substitution with an acyl piperazine yielded a series of agents with substantially enhanced anti-amnesic potency in the mouse passive avoidance test. Sunifiram prevents scopolamine-induced amnesia in mice at intraperitoneal doses of 0.001 to 0.1 mg/kg and at oral doses of 0.01 to 0.1 mg/kg, placing its molar potency approximately four orders of magnitude greater than piracetam and comparable on a per-weight basis to the most potent nootropic agents in the preclinical literature. The compound additionally reverses amnesia induced by mecamylamine (a nicotinic antagonist), baclofen (a GABA-B agonist), and clonidine (an alpha-2 adrenergic agonist), indicating broad-spectrum anti-amnesic activity across multiple neurotransmission systems rather than a single-receptor

mechanism. In vitro, sunifiram does not display measurable affinity for any of the major central nervous system receptor classes (glutamate, GABA, serotonin, dopamine, adrenergic, histamine, acetylcholine, or opioid) at concentrations up to 10 micromolar in standard radioligand displacement assays. However, the compound enhances long-term potentiation in mouse hippocampal CA1 slices at nanomolar concentrations (10 to 100 nM) with a bell-shaped dose-response relationship, an effect blocked by 7-chlorokynurenic acid (a glycine-site NMDA receptor antagonist) but not by ifenprodil (a polyamine-site NMDA receptor antagonist). This pharmacological dissection, reported by Bhatt et al. (2013), established the glycine-binding site of the NMDA receptor as the principal locus of sunifiram action, with downstream activation of calcium/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C-alpha (PKC-alpha) mediating the synaptic potentiation and the behavioral antiamnesic effect. In the olfactory bulbectomized (OBX) mouse model of cognitive deficit and depression, Moriguchi et al. (2013) demonstrated that oral sunifiram at 0.01 to 1.0 mg/kg daily for 7 to 12 days significantly improved spatial reference memory (Y-maze) and short-term recognition memory (novel object recognition) and restored hippocampal long-term potentiation, without ameliorating depressive behaviors in the tail suspension test. The dissociation between cognitive and affective endpoints supports a mechanism localized to glutamatergic synaptic plasticity rather than monoaminergic mood regulation. Sunifiram increases the release of acetylcholine from rat cerebral cortex in vitro, an effect shared with unifiram and potentially contributing to the procognitive profile. The compound does not impair motor coordination on the rotarod test, does not modify spontaneous locomotor activity on the Animex apparatus, and does not alter

inspection activity on the hole board test at effective anti-amnesic doses, indicating a clean behavioral profile at therapeutic-range concentrations. As of the most recent monograph revision, sunifiram has not been subjected to formal toxicology testing in any species, has not entered human clinical trials in any jurisdiction, is not approved for medical use anywhere in the world, and is classified by the United States Food and Drug Administration as an unapproved new drug with unlawful use in dietary supplements, food, or medicine. The compound is sold as a research chemical by multiple vendors at purities typically exceeding 98 percent by HPLC. Research-grade vendor literature suggests human doses of 5 to 10 mg per administration, scaled from rodent allometric conversion, but this dose range has not been validated by human pharmacokinetic or safety data. This monograph reviews the chemistry, synthesis, and structure-activity relationships of sunifiram; the glycine-site NMDA receptor mechanism in molecular and electrophysiological detail; the preclinical pharmacology across multiple amnesia models; the absent pharmacokinetic and clinical record; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event signal; and a comparative assessment of five nootropic cognition enhancers against sunifiram on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Proposed International Nonproprietary Name: Sunifiram (not formally assigned; the name is used in the primary pharmacological literature and in the research-chemical market).

Development code: DM-235 (University of Florence laboratory designation). The development code is the canonical identifier in the earliest pharmacological publications and is the identifier under which the original Ghelardini et al. (2002) disclosure was published [1].

Related compounds: Unifiram (DM-232), the bicyclic parent compound from which sunifiram was derived by ring-opening simplification. Sapunifiram (MN-19), a further analogue in the same structural series [2, 3].

Chemical Abstracts Service registry number: 314728-85-3.

International Union of Pure and Applied Chemistry name: 1-(4-benzoylpiperazin-1-yl)propan-1-one. The compound is an N,N'-diacylpiperazine bearing a benzoyl group on one nitrogen and a propanoyl group on the other.

1.2 Structural class and chemistry

Sunifiram is a piperazine-derived nootropic that arose from the systematic structural simplification of the piracetam (2-oxo-1-pyrrolidineacetamide) pharmacophore. The design trajectory proceeded from piracetam through the bicyclic diazabicyclo[4.3.0]nonan-9-one scaffold of unifiram (DM-232) to the open-ring acylpiperazine scaffold of sunifiram, in which the pyrrolidone ring is replaced by a piperazine bearing two exocyclic acyl substituents [1, 4]. The structural class places sunifiram outside the racetam family (which requires an intact 2-pyrrolidone ring) and outside the canonical ampakine class (which requires a sulfonamide, benzamide, or related scaffold that directly modulates the AMPA receptor desensitization gate). The "ampakine-like" descriptor applied in some literature reflects the functional endpoint (cognition enhancement through glutamatergic facilitation) rather than a shared molecular mechanism.

Molecular formula: C₁₄H₁₈N₂O₂.

Exact mass: 246.1368 g/mol (monoisotopic).

Molecular weight: 246.31 g/mol.

Physical properties: White to off-white crystalline powder. Computed partition coefficient (cLogP) approximately 1.45, indicating moderate lipophilicity suitable for gastrointestinal absorption and blood-brain barrier penetration. Molecular weight, hydrogen bond donor count (one, the piperazine NH), hydrogen bond acceptor count (three), and logP are within the Lipinski rule-of-five space, predicting favorable oral drug-likeness. Soluble in dimethyl sulfoxide and in aqueous solutions at acidic pH; sparingly soluble in water at neutral pH.

Stereochemistry: Sunifiram contains no stereocenters. The compound is achiral and is supplied as a single constitutional isomer. No enantiomeric or diastereomeric purity considerations apply.

1.3 Synthesis

The published synthesis of sunifiram proceeds through acylation of piperazine at both nitrogen atoms [1, 4]. In the most direct route, piperazine is monoacylated with propanoyl chloride (or propionic anhydride) under controlled stoichiometric conditions to produce 1-propanoylpiperazine, which is then acylated with benzoyl chloride to yield 1-benzoyl-4-propanoylpiperazine (sunifiram). Alternatively, the order of acylation can be reversed, with benzoylation preceding propanoylation, though the selectivity of the first acylation step for monosubstitution requires careful temperature and stoichiometry control to minimize diacylation side products. The product is purified by recrystallization from appropriate solvent systems (ethyl acetate, ethanol, or isopropanol) or by silica gel column chromatography and is characterized by nuclear magnetic resonance spectroscopy (¹H and ¹³C), mass spectrometry, infrared spectroscopy, and melting point determination. Yields are typically moderate to good (60 to 80 percent for each acylation step). The synthesis is straightforward by medicinal chemistry standards and is accessible to any laboratory equipped for small-molecule organic synthesis; the principal synthetic challenge is the controlled monosubstitution of the symmetrical piperazine diamine.

Manetti et al. (2003) reported extensive structure-activity relationship studies on the sunifiram scaffold, including variations of the acyl chain length, aromatic ring substitution, ring size (five- to seven-membered diazacycloalkanes), and inversion

of the exocyclic amide orientation [4]. Martini et al. (2009) extended this program to further analogues of sunifiram and sapunifiram, demonstrating that the benzoyl-propanoyl-piperazine motif is near-optimal within the explored chemical space and that substantial modifications generally reduce anti-amnesic potency [3].

2. Abstract

Sunifiram (DM-235) is a synthetic piperazine-derived cognition enhancer first disclosed at the University of Florence in approximately 2000 by Gualtieri, Ghelardini, and colleagues as part of a program of systematic structural simplification of the piracetam pharmacophore [1]. The compound prevents scopolamine-induced amnesia in the mouse passive avoidance test at intraperitoneal doses of 0.001 to 0.1 mg/kg and at oral doses of 0.01 to 0.1 mg/kg, a potency approximately four orders of magnitude greater than piracetam (effective at 30 to 100 mg/kg intraperitoneally) and comparable on a per-weight basis to the most potent preclinical nootropic agents including unifiram and noopept [1, 5, 6].

The anti-amnesic activity is not restricted to cholinergic blockade: sunifiram additionally reverses amnesia induced by mecamylamine (nicotinic acetylcholine receptor antagonist), baclofen (GABA-B receptor agonist), and clonidine (alpha-2 adrenergic receptor agonist) in the same passive avoidance paradigm, indicating broad-spectrum efficacy across multiple neurotransmission systems [1]. This polypharmacological anti-amnesic profile, combined with the absence of measurable affinity for any of the major central nervous system receptor classes in radioligand displacement assays, suggested from the outset that sunifiram acts through a mechanism distinct from classical receptor agonism or antagonism.

The mechanism was substantially clarified by two studies from the Fukunaga laboratory at Tohoku University. Bhatt et al. (2013) demonstrated that sunifiram enhances long-term potentiation (LTP) in mouse hippocampal CA1 slices at 10 to 100 nM through the glycine-binding site of the NMDA receptor, with downstream activation of CaMKII and PKC- α [7]. Moriguchi et al. (2013) extended these findings to the olfactory bulbectomized mouse model of cognitive deficit, showing that oral sunifiram at 0.01 to 1.0 mg/kg daily for 7 to 12 days restored spatial and recognition memory and hippocampal LTP through the same glycine-site NMDA receptor mechanism [8].

The compound increases acetylcholine release from rat cerebral cortex *in vitro* [5] and does not impair motor coordination, spontaneous locomotion, or inspection activity at effective anti-amnesic doses [1]. The behavioral profile is therefore selec-

tive for cognition without sedative, stimulant, or motor side effects at the doses studied.

Sunifram has not been subjected to formal toxicology testing in any species. No human clinical trials have been conducted. The compound is not approved for medical use in any jurisdiction and is classified by the United States Food and Drug Administration as an unapproved new drug. It is sold as a research chemical by multiple vendors. Research-grade vendor literature suggests human doses of 5 to 10 mg per administration based on allometric scaling from rodent data, but this dose range has not been validated by human pharmacokinetic, safety, or efficacy studies.

3. Discovery and Development History

3.1 Origin

Sunifiram (DM-235) was synthesized at the Department of Pharmaceutical Sciences (formerly the Department of Preclinical and Clinical Pharmacology), University of Florence (Universita degli Studi di Firenze), in approximately 2000 as part of a medicinal chemistry program led by Fulvio Gualtieri and Maria Novella Romanelli. The program sought to identify cognition-enhancing agents through systematic structural simplification of the piracetam scaffold, beginning with the observation that the 2-pyrrolidone ring system of piracetam could be replaced by fused bicyclic diazacycloalkane systems without loss of anti-amnesic activity [1, 9].

3.2 Structural evolution from piracetam to sunifiram

The design trajectory proceeded through three principal stages. First, Gualtieri and colleagues explored bicyclic diazabicyclononanone derivatives, identifying unifiram (DM-232, a 1,4-diazabicyclo[4.3.0]nonan-9-one bearing an acyl substituent) as a potent anti-amnesic agent approximately four orders of magnitude more potent than piracetam [5, 9]. Second, the observation that the bicyclic ring system could be opened to a piperazine without catastrophic loss of activity led to the synthesis of sunifiram (DM-235), in which the pyrrolidone-derived bicyclic core was replaced by an acylated piperazine [1]. Third, the Manetti et al. (2003) structure-activity relationship study systematically varied the acyl substituents, ring size, and amide orientation around the piperazine core, establishing that the 1-benzoyl-4-propanoyl substitution pattern of sunifiram represents a near-optimal configuration within the explored chemical space [4].

3.3 Initial pharmacological characterization

The first full pharmacological disclosure of sunifiram was the Ghelardini et al. (2002) publication in Naunyn-Schmiedeberg's Archives of Pharmacology, which reported the anti-amnesic activity across multiple amnesia models, the dose-response relationship, the absence of motor or behavioral side effects, and the comparative potency against piracetam, aniracetam, and rolipram [1]. This was followed by the

Galeotti et al. (2003) study demonstrating AMPA receptor involvement in the anti-amnesic mechanism [10] and by the Romanelli et al. (2006) comprehensive pharmacological review, which placed both unifiram and sunifiram in the context of the broader nootropic pharmacology field [5].

3.4 Expansion to electrophysiology and molecular mechanism

Beginning in 2013, the Fukunaga laboratory at Tohoku University published two reports that substantially advanced the mechanistic understanding. Bhatt et al. (2013) characterized the LTP enhancement mechanism through the glycine-binding site of the NMDA receptor in hippocampal slices [7], and Moriguchi et al. (2013) extended the findings to the olfactory bulbectomized mouse cognitive deficit model with oral dosing [8]. These studies moved the mechanistic characterization beyond the behavioral level to molecular pharmacology and electrophysiology.

3.5 Industrial and clinical trajectory

Sunifiram has not been advanced to industrial development, patent protection for a therapeutic indication, or human clinical trials by any pharmaceutical company or academic institution. The Romanelli and Gualtieri (2015) retrospective review, published in the *Journal of Enzyme Inhibition and Medicinal Chemistry* under the title "Unifi nootropics from the lab to the web: a story of academic (and industrial) shortcomings," documented the failure to advance either unifiram or sunifiram from academic pharmacology to clinical development, attributing the gap to insufficient toxicology funding, absence of commercial pharmaceutical interest in nootropic agents without a clearly defined clinical indication, and the subsequent uncontrolled diffusion of the compounds into the online research-chemical market without safety data [11].

The compound is currently sold as a research chemical by multiple vendors worldwide. It is not approved for medical use in any jurisdiction. The United States Food and Drug Administration has issued advisories classifying sunifiram as an unapproved new drug that may not be lawfully used in dietary supplements, food, or medicine [11].

4. Mechanism of Action

Sunifiram operates through a mechanism that is functionally distinct from classical receptor agonism, antagonism, or allosteric modulation at any single identified receptor. The compound does not display measurable affinity in radioligand displacement assays for the glutamate (AMPA, NMDA, kainate), GABA (GABA-A, GABA-B), serotonin (5-HT1 through 5-HT7), dopamine (D1 through D5), adrenergic (alpha-1, alpha-2, beta-1, beta-2), histamine (H1 through H3), muscarinic acetylcholine (M1 through M5), nicotinic acetylcholine, or opioid (mu, delta, kappa) receptors at concentrations up to 10 micromolar [5]. This absence of direct receptor binding in standard assays, combined with potent behavioral activity, defines the pharmacological puzzle of sunifiram and its structural relatives.

4.1 Glycine-site NMDA receptor facilitation

The Bhatt et al. (2013) study in Hippocampus provided the most complete mechanistic characterization [7]. In mouse hippocampal CA1 slices, sunifiram at 10 nM (the optimal concentration in a bell-shaped dose-response) significantly enhanced the magnitude of LTP induced by theta-burst stimulation. The enhancement was blocked by 7-chlorokynurenic acid (7-ClKN), a selective antagonist at the glycine-binding site of the NMDA receptor, at concentrations that did not affect baseline LTP. The enhancement was not blocked by ifenprodil, an antagonist at the polyamine site (NR2B-preferring) of the NMDA receptor. Furthermore, pretreatment with a saturating concentration of glycine (300 micromolar) occluded the sunifiram effect, indicating that sunifiram and glycine compete for, or converge on, the same modulatory site [7].

The glycine-binding site of the NMDA receptor (located on the NR1/GluN1 subunit) is a co-agonist site that must be occupied for NMDA receptor channel opening in response to glutamate binding at the NR2/GluN2 subunit. At typical synaptic glycine concentrations (estimated at 1 to 10 micromolar in the hippocampus), the glycine site is partially but not fully saturated; agents that increase glycine-site occupancy therefore enhance NMDA receptor function and the downstream calcium influx that triggers LTP. Sunifiram appears to facilitate glycine-site function at con-

centrations (10 to 100 nM) far below those required for direct glycine displacement, suggesting an indirect facilitation mechanism rather than direct agonism at the glycine site.

4.2 Downstream kinase activation

The Bhatt et al. (2013) study further demonstrated that sunifiram treatment enhanced the phosphorylation of CaMKII (calcium/calmodulin-dependent protein kinase II) at threonine 286, the autophosphorylation site that converts the kinase to a calcium-independent constitutively active form [7]. CaMKII activation is a canonical downstream consequence of NMDA receptor-mediated calcium influx and is a molecular requirement for LTP induction and maintenance in the hippocampal CA1 region.

In parallel, sunifiram enhanced the phosphorylation of PKC-alpha (protein kinase C-alpha), a kinase implicated in AMPA receptor trafficking to the postsynaptic membrane. The Bhatt et al. (2013) data indicated that PKC-alpha activation by sunifiram proceeds through Src family kinase activation, suggesting a signaling cascade in which glycine-site facilitation of the NMDA receptor produces calcium influx, Src kinase activation, PKC-alpha activation, and consequent phosphorylation of AMPA receptor subunits (particularly GluA1 at serine 831) that increases their synaptic insertion and single-channel conductance [7].

The net molecular effect is therefore enhancement of both NMDA receptor function (through glycine-site facilitation) and AMPA receptor function (through PKC-alpha-mediated phosphorylation and trafficking), producing a coordinated potentiation of glutamatergic synaptic transmission that is the molecular basis for LTP enhancement and the behavioral antiamnesic effect.

4.3 AMPA receptor involvement

The Galeotti et al. (2003) study demonstrated that the AMPA receptor antagonist NBQX (2,3-dioxo-6-nitro-7-sulfamoylbenzo[f]quinoxaline), administered intracerebroventricularly, reversed the antiamnesic effect of sunifiram in the mouse passive avoidance test [10]. This finding established that AMPA receptor activation is a necessary component of the antiamnesic mechanism. However, subsequent work clarified that sunifiram does not directly potentiate AMPA receptor currents in the manner of canonical ampakines (CX-516, CX-546, aniracetam). The AMPA receptor

involvement is therefore downstream of the primary glycine-site NMDA receptor facilitation, mediated through the CaMKII and PKC-alpha kinase cascade that enhances AMPA receptor phosphorylation and synaptic expression [5, 7, 10].

4.4 Acetylcholine release

Both unifiram and sunifiram increase the release of acetylcholine from rat cerebral cortex slices in vitro [5]. The cholinergic facilitation is likely a secondary consequence of enhanced glutamatergic transmission in cortical circuits that project to cholinergic neurons in the basal forebrain, though a direct presynaptic mechanism has not been excluded. The cholinergic component may contribute to the anti-amnesic activity, particularly in the scopolamine model where restoration of cholinergic tone would directly oppose the muscarinic antagonist-induced deficit.

4.5 Composite mechanism summary

The composite mechanism of sunifiram is best described as glycine-site facilitation of NMDA receptor function, producing enhanced calcium influx through the NMDA receptor channel, activation of CaMKII and PKC-alpha through Src kinase, increased phosphorylation and synaptic insertion of AMPA receptors, potentiation of hippocampal long-term potentiation, facilitation of cortical acetylcholine release, and consequent improvement in memory acquisition and consolidation in behavioral paradigms that depend on hippocampal glutamatergic synaptic plasticity. The mechanism is functionally convergent with the ampakine class (both produce enhanced AMPA receptor-mediated transmission and LTP) but molecularly distinct (sunifiram acts upstream at the NMDA receptor glycine site rather than directly at the AMPA receptor desensitization gate).

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

No formal pharmacokinetic studies of sunifiram have been published in any species. Oral bioavailability has not been measured. The computed physicochemical profile (molecular weight 246.31 Da, cLogP approximately 1.45, one hydrogen bond donor, three hydrogen bond acceptors, zero violations of Lipinski's rule of five) predicts favorable gastrointestinal absorption and oral bioavailability [5]. The behavioral activity of sunifiram after oral administration at doses as low as 0.01 mg/kg in mice confirms that the compound achieves functionally relevant central nervous system concentrations after oral dosing [1, 8].

5.2 Distribution

Distribution data are not available. The physicochemical profile (moderate lipophilicity, low molecular weight, low polar surface area) predicts adequate blood-brain barrier penetration, which is confirmed indirectly by the robust central nervous system activity after systemic administration. The volume of distribution, plasma protein binding, and tissue partitioning have not been characterized.

5.3 Metabolism

No metabolic studies have been published. The principal hepatic cytochrome P450 enzymes involved in sunifiram biotransformation have not been identified. The molecular structure (two amide bonds, an aromatic ring, and an aliphatic chain) suggests susceptibility to amide hydrolysis, aromatic hydroxylation (likely CYP-mediated), and N-dealkylation as plausible metabolic pathways, but these are predictions from structural analysis and have not been confirmed experimentally.

5.4 Elimination

Elimination half-life has not been measured in any species. The relatively short duration of behavioral activity in rodent studies (sunifiram is typically administered 20 minutes before behavioral testing, with peak cognitive effects aligning with this timeframe) suggests a relatively brief plasma elimination phase, but this inference is indirect and confounded by the possibility of rapid central nervous system equilibration followed by slower peripheral elimination.

5.5 Routes of administration

Two routes have been used in published preclinical studies: intraperitoneal injection (the principal route for acute passive avoidance studies, 0.001 to 0.1 mg/kg) and oral gavage (used in both acute passive avoidance studies, 0.01 to 0.1 mg/kg, and in the chronic olfactory bulbectomized mouse studies, 0.01 to 1.0 mg/kg daily for 7 to 12 days) [1, 8]. No intravenous, subcutaneous, or other parenteral routes have been reported in the published literature.

Research-chemical vendors supply sunifiram as a powder or in solution for sublingual or oral administration in human research contexts. The sublingual route has not been studied in published preclinical or clinical literature and its bioavailability relative to oral administration is unknown.

5.6 Special populations

No data exist for any special population (pediatric, geriatric, hepatic impairment, renal impairment, pregnancy, lactation, or pharmacogenomic subgroups). The absence of any human pharmacokinetic data renders population pharmacokinetic analysis impossible.

6. Preclinical Pharmacology

6.1 Passive avoidance test

The passive avoidance test in mice is the principal behavioral assay in which sunifiram has been characterized. In this paradigm, mice learn to avoid a dark compartment in which they received a mild foot shock; amnesia is induced by pharmacological agents administered before or after training, and anti-amnesic compounds restore the avoidance behavior when administered before or after the amnesic insult.

Ghelardini et al. (2002) reported that sunifiram prevented scopolamine-induced amnesia (scopolamine 1.5 mg/kg intraperitoneally) at intraperitoneal doses of 0.001 to 0.1 mg/kg (administered 20 minutes before training) and at oral doses of 0.01 to 0.1 mg/kg [1]. The dose-response relationship was bell-shaped, with maximal effect at 0.01 to 0.1 mg/kg and reduced effect at higher doses. The anti-amnesic potency was comparable to that of piracetam at 30 to 100 mg/kg intraperitoneally, aniracetam at 100 mg/kg orally, and rolipram at 30 mg/kg orally, confirming the approximately 1000-fold potency advantage on a per-weight basis [1].

Sunifiram additionally prevented amnesia induced by mecamylamine (20 mg/kg intraperitoneally, a nicotinic acetylcholine receptor antagonist), baclofen (2 mg/kg intraperitoneally, a GABA-B receptor agonist), and clonidine (0.125 mg/kg intraperitoneally, an alpha-2 adrenergic receptor agonist) in the same passive avoidance paradigm [1]. The broad-spectrum anti-amnesic activity across cholinergic, GABAergic, and adrenergic amnesia models indicates that sunifiram acts at a convergent point downstream of these individual neurotransmitter systems, consistent with the glycine-site NMDA receptor mechanism subsequently identified.

6.2 Olfactory bulbectomized mouse model

The Moriguchi et al. (2013) study used the bilateral olfactory bulbectomized (OBX) mouse as a model of cognitive deficit with relevance to Alzheimer's disease and depression [8]. OBX produces hippocampus-dependent memory impairment, reduced

hippocampal LTP, and depressive-like behaviors, providing a chronic neurodegenerative-like cognitive phenotype that is more translationally relevant than acute pharmacological amnesia.

Sunifiram was administered orally at 0.01, 0.1, and 1.0 mg/kg once daily for 7 to 12 days. Spatial reference memory assessed by the Y-maze test and short-term recognition memory assessed by the novel object recognition task were significantly improved at all three doses. Hippocampal LTP, impaired in untreated OBX mice, was restored by sunifiram treatment. The cognitive improvement was blocked by gavestinel (GV150526), a glycine-site NMDA receptor antagonist, confirming the glycine-site mechanism in vivo [8].

Sunifiram did not ameliorate depressive-like behavior as assessed by the tail suspension test in OBX mice, indicating selectivity for cognitive rather than affective endpoints [8]. This dissociation is consistent with a mechanism operating through hippocampal glutamatergic synaptic plasticity (which subserves spatial and recognition memory) rather than through monoaminergic circuits (which subserve mood regulation).

6.3 Hippocampal slice electrophysiology

Bhatt et al. (2013) recorded field excitatory postsynaptic potentials (fEPSPs) in the CA1 region of mouse hippocampal slices [7]. Sunifiram at 10 nM significantly enhanced LTP magnitude induced by theta-burst stimulation. The dose-response relationship was bell-shaped, with peak enhancement at 10 nM and reduced enhancement at 100 nM. The bell-shaped dose-response is a common feature of glycine-site modulators and partial agonists and may reflect desensitization or receptor internalization at higher concentrations.

The enhancement was abolished by 7-chlorokynurenic acid (10 micromolar) and was occluded by pretreatment with glycine (300 micromolar), establishing the glycine-binding site as the site of action. The enhancement was not affected by ifenprodil (3 micromolar), excluding the polyamine (NR2B) site [7].

Biochemical analysis of hippocampal slice lysates demonstrated that sunifiram increased phosphorylation of CaMKII at threonine 286, phosphorylation of PKC- α , and phosphorylation of GluA1 (the principal AMPA receptor subunit in hippocampal pyramidal neurons) at serine 831, the CaMKII phosphorylation site that increases single-channel conductance [7].

6.4 Acetylcholine release

Romanelli et al. (2006) reported that both unifiram and sunifiram increase the release of acetylcholine from superfused rat cerebral cortex slices [5]. The concentration-response relationship and the magnitude of the cholinergic facilitation relative to known cholinergic agents were not reported in sufficient detail to characterize the potency or efficacy of this effect. The cholinergic facilitation may contribute to the anti-amnesic effect, particularly in cholinergic deficit models.

6.5 Behavioral safety profile

Ghelardini et al. (2002) reported that sunifiram at the highest effective anti-amnesic doses (0.1 mg/kg intraperitoneally) did not impair motor coordination on the rotarod test, did not modify spontaneous locomotor activity on the Animex apparatus, and did not alter inspection activity on the hole board test [1]. These negative findings indicate the absence of sedative, stimulant, anxiolytic, or motor-impairing effects at therapeutic-range doses and support a selective cognitive profile.

7. Clinical Evidence Base

7.1 Human clinical trials

No human clinical trials of sunifiram have been conducted in any jurisdiction. No Phase 1 safety, tolerability, or pharmacokinetic studies have been published. No Phase 2 or Phase 3 efficacy studies exist. The compound has not been investigated in any human disease population through formal clinical research [5, 11].

7.2 Human use in the research-chemical context

Sunifiram is sold as a research chemical by multiple online vendors and is used by individuals in the nootropic community at self-selected doses typically in the range of 5 to 10 mg per administration, one to three times daily, by oral or sublingual routes. These doses are derived from allometric scaling of the rodent effective dose range (0.01 to 0.1 mg/kg in mice, scaling to approximately 0.001 to 0.01 mg/kg in humans by standard body surface area conversion, or approximately 0.06 to 0.6 mg for a 60 kg human). The commonly used doses of 5 to 10 mg substantially exceed the allometrically scaled range, and the basis for the higher doses in the research-chemical market is unclear [11].

Anecdotal reports from the nootropic community describe subjective cognitive enhancement, improved verbal fluency, enhanced visual perception, and increased motivation at doses of 5 to 10 mg. Reported adverse effects in anecdotal use include headache, insomnia, anxiety, and overstimulation at higher doses. These reports are not controlled, not blinded, subject to expectancy effects, and cannot be used to draw conclusions about efficacy or safety.

7.3 Regulatory status

Sunifiram is not approved for medical use in any jurisdiction worldwide. In the United States, the compound is classified as an unapproved new drug; its use in dietary supplements, food, or medicine is unlawful under the Federal Food, Drug, and Cosmetic Act. The compound is not specifically scheduled under the Controlled Substances Act in the United States or under equivalent legislation in

most other jurisdictions, which permits its sale as a "research chemical" in many markets [11]. Investigators should consult local regulatory authorities before any research application involving human subjects.

8. Sourcing and Quality Verification

Research-grade sunifiram is supplied by multiple chemical and pharmaceutical research suppliers (Cayman Chemical, MedChemExpress, Sigma-Aldrich, InvivoChem, GlpBio, BocSci, others) at purities typically exceeding 98 percent by HPLC. Supply is in milligram to gram quantities as the free base. Pricing is low to moderate, in the range of \$30 to \$150 per gram of research-grade material at the time of monograph preparation, reflecting the straightforward synthesis and low raw-material cost.

The research-chemical market also includes consumer-oriented vendors that supply sunifiram in capsule or powder form for the nootropic market. These consumer-grade products may or may not carry certificates of analysis and are subject to less rigorous quality control than pharmaceutical or research-grade suppliers.

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 (expected $[M+H]^+$ at m/z 247.14 for $C_{14}H_{18}N_2O_2$)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) to confirm structural identity and exclude positional isomers or synthetic impurities
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography if the synthesis route involves solvents of toxicological concern (dichloromethane, dimethylformamide)

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) provide independent confirmation of vendor certificates of analysis. The sunifiram research-chemical market is established but not as well characterized as the markets for more widely studied compounds; lot-to-lot variability and occasional misidentification have been reported in the consumer-grade segment. On-receipt analytical confirmation is strongly recommended for any investigation where dose-response precision is important.

No pharmaceutical-grade (Good Manufacturing Practice-compliant) source of sunifiram exists, as the compound has not been registered as a medicine in any jurisdiction.

9. Reconstitution and Handling

Sunifiram is supplied as a white to off-white crystalline powder with moderate water solubility at acidic pH and limited solubility at neutral pH. For in vitro research applications, the compound is typically dissolved in dimethyl sulfoxide (DMSO) to prepare concentrated stock solutions (10 to 100 mM) which are then diluted into aqueous assay buffers at the desired final concentration. Final DMSO concentration in assay media should be kept below 0.1 percent (v/v) to avoid solvent effects on cellular or electrophysiological preparations.

For in vivo research applications (rodent studies), sunifiram has been administered as a suspension in 1 percent carboxymethylcellulose for oral gavage or dissolved in saline with pH adjustment for intraperitoneal injection [1, 8].

Storage of the solid material should be at room temperature in a dry, dark location, or refrigerated (2 to 8 degrees Celsius) for long-term storage. The compound is chemically stable under standard storage conditions; the two amide bonds are resistant to hydrolysis at neutral pH and room temperature. Aqueous solutions should be prepared fresh or stored refrigerated and used within 7 to 14 days. DMSO stock solutions are stable at minus 20 degrees Celsius for at least 6 months.

For consumer-grade research applications, sunifiram powder is typically weighed on a milligram-precision analytical balance and administered orally in capsule form or sublingually. The low doses (5 to 10 mg) require accurate weighing; volumetric dosing from a pre-prepared solution is recommended over direct powder measurement to ensure dose consistency.

10. Stack Interaction Considerations

Sunifiram interacts with several drug classes through its glutamatergic mechanism of action. Investigators conducting research with sunifiram, especially in combination with other research compounds, should consider the following:

Other glutamatergic agents: Concurrent administration with other NMDA receptor modulators (D-cycloserine, sarcosine, glycine, D-serine) may produce additive or synergistic effects at the glycine-binding site. The bell-shaped dose-response observed in hippocampal slice electrophysiology [7] suggests that excessive glycine-site activation may be counterproductive; combination with high-dose glycine or D-serine could push the system past the optimal point on the dose-response curve.

Racetams and ampakines: Concurrent administration with piracetam, aniracetam, oxiracetam, or other racetams produces a theoretical risk of additive glutamatergic facilitation. Aniracetam in particular, which directly modulates AMPA receptor desensitization, could interact with the indirect AMPA receptor potentiation produced by sunifiram through CaMKII and PKC-alpha. The combination has not been studied in published research.

Cholinergic agents: Concurrent acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine, huperzine A) or cholinergic precursors (alpha-GPC, citicoline) may produce additive cholinergic activity given the acetylcholine-releasing property of sunifiram [5]. The combination is commonly used in the nootropic community but has not been studied in controlled research.

GABAergic agents: Concurrent benzodiazepines, barbiturates, or other GABAergic sedatives may oppose the glutamatergic facilitation produced by sunifiram. The baclofen amnesia model, in which sunifiram reversed GABA-B agonist-induced cognitive deficit [1], suggests functional antagonism between GABAergic inhibition and sunifiram-mediated glutamatergic facilitation.

Stimulants: Concurrent caffeine, amphetamine, or modafinil may produce additive cognitive activation and additive risk of overstimulation, insomnia, or anxiety. No published interaction data exist.

NMDA receptor antagonists: Concurrent memantine, ketamine, or dextromethorphan (NMDA channel blockers) may oppose the glycine-site facilitation produced by sunifram. The functional interaction between glycine-site facilitation and channel blockade is complex and has not been studied with sunifram specifically, though the general pharmacology of NMDA receptor modulation predicts partial opposition.

11. Adverse Events and Safety

11.1 Preclinical safety

The published preclinical behavioral safety data are limited to the Ghelardini et al. (2002) report demonstrating absence of motor impairment, sedation, or behavioral activation at effective anti-amnesic doses in mice [1]. No formal preclinical toxicology studies (acute toxicity, subacute toxicity, subchronic toxicity, chronic toxicity, reproductive toxicity, genotoxicity, carcinogenicity) have been conducted or published for sunifiram in any species [5, 11].

The absence of formal toxicology is the most significant safety limitation of the compound and is the principal reason that sunifiram has not been advanced to clinical development. The Romanelli and Gualtieri (2015) retrospective attributed this gap to insufficient funding for the toxicology studies required for an Investigational New Drug application and to the absence of pharmaceutical industry interest in the compound [11].

11.2 Theoretical safety considerations

The glycine-site NMDA receptor facilitation mechanism raises several theoretical safety considerations:

Excitotoxicity risk: Excessive NMDA receptor activation produces calcium overload and excitotoxic neuronal death. Glycine-site facilitation at therapeutic doses is expected to produce modest enhancement of physiological NMDA receptor function, not pathological overactivation. The bell-shaped dose-response in hippocampal slices [7] provides some reassurance that the system is self-limiting at higher concentrations. However, the excitotoxicity risk at supratherapeutic doses, in combination with other glutamatergic agents, or in disease states with compromised glutamatergic homeostasis (epilepsy, acute stroke, traumatic brain injury) has not been evaluated.

Seizure risk: Enhanced glutamatergic transmission is a theoretical risk factor for seizure induction. No seizures have been reported in published rodent studies at effective doses, but formal seizure threshold testing (pentylenetetrazol threshold,

maximal electroshock) has not been conducted.

Chronic exposure effects: The effects of chronic sunifiram administration on NMDA receptor expression, glycine-site sensitivity, glutamatergic homeostasis, and neuronal viability have not been studied. The Moriguchi et al. (2013) study administered sunifiram orally for up to 12 days without reported adverse effects in OBX mice [8], but this duration is insufficient to characterize chronic safety.

11.3 Anecdotal human adverse events

Reports from the nootropic community describe headache (the most commonly reported adverse event, potentially related to glutamatergic activation or to cholinergic facilitation), insomnia (particularly with evening dosing), anxiety or overstimulation (at doses exceeding 10 mg), jaw tension, and nasal congestion (with sublingual administration). These reports are uncontrolled and cannot be attributed with confidence to sunifiram rather than to expectancy effects, concurrent substances, or confounding factors.

11.4 Pregnancy and lactation

No reproductive toxicity, teratogenicity, or lactation data exist for sunifiram in any species. The compound should be considered contraindicated in pregnancy and lactation in the absence of any safety data.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five nootropic cognition enhancers against sunifiram, evaluated against five competency standards: novelty (of mechanism or approach), effect size (in preclinical or clinical models), promising potential (current development state and trajectory), side-effect profile (clinical or preclinical), and overall validation. The five candidates were selected as the principal agents that share mechanistic overlap with sunifiram (glutamatergic facilitation, AMPA receptor-dependent cognition enhancement, or high-potency preclinical nootropic activity) and against which investigators would most likely consider sunifiram for research applications.

12.1 Piracetam

Mechanism: The prototype racetam nootropic. Piracetam (2-oxo-1-pyrrolidineacetamide) is the structural parent from which the design trajectory leading to sunifiram originated. Mechanism of action remains incompletely characterized despite decades of research; proposed mechanisms include positive modulation of AMPA receptor currents, enhancement of membrane fluidity, and facilitation of inter-hemispheric neurotransmission [12].

Development trajectory: Piracetam was synthesized by UCB Pharma in 1964 and has been marketed as a prescription medicine (Nootropil) in many European and Latin American jurisdictions for cognitive disorders, vertigo, cortical myoclonus, and sickle cell disease. It is not approved by the United States Food and Drug Administration. Clinical trial data span decades and include studies in dementia, post-stroke cognitive recovery, vertigo, and dyslexia, with mixed and generally modest results.

Novelty: Low. Piracetam is the historical prototype nootropic and the reference compound for the class.

Effect size: Modest in human clinical trials. Cognitive effects in dementia and post-stroke populations are small and inconsistently replicated. In rodent passive avoidance models, effective doses are 30 to 100 mg/kg intraperitoneally, approxi-

mately 1000-fold higher than sunifiram [1, 12].

Promising potential: Low for new indications. The compound is extensively studied, generically available, and is not the subject of active clinical development for novel cognitive applications.

Side-effect profile: Favorable. Piracetam has an extensive human safety record spanning decades of clinical use. Adverse events are mild and infrequent (headache, insomnia, gastrointestinal discomfort, weight gain) at registered doses of 2.4 to 4.8 grams daily [12].

Overall validation: Moderate. The compound has extensive human clinical data but modest effect sizes and an incompletely characterized mechanism.

Comparison to sunifiram: Sunifiram is approximately 1000-fold more potent than piracetam on a per-weight basis in rodent anti-amnesic models and has a better-characterized molecular mechanism (glycine-site NMDA receptor facilitation versus the uncertain piracetam mechanism). Piracetam has the decisive advantage of decades of human safety data and registered medical use. Sunifiram has no human safety data at all.

12.2 Aniracetam

Mechanism: A pyrrolidinone derivative with demonstrated positive allosteric modulation of AMPA receptors (reduces AMPA receptor desensitization rate) and additional modulation of metabotropic glutamate receptors, dopamine, and serotonin signaling [13]. The AMPA receptor modulation is the basis for the ampakine classification.

Development trajectory: Aniracetam was developed by Hoffmann-La Roche and is marketed in some European and Asian jurisdictions (notably Japan, as Ampamet/Draganon) for cognitive impairment associated with cerebrovascular disease. It has not been approved by the United States Food and Drug Administration.

Novelty: Low to moderate. The AMPA receptor positive allosteric modulator mechanism was novel when first characterized but is now well established.

Effect size: Moderate in rodent antiamnesic models at 100 mg/kg orally. Human clinical data in cerebrovascular cognitive impairment show modest benefit. The compound is substantially less potent than sunifiram on a per-weight basis [1].

Promising potential: Low. The compound is generically available in some markets and is not the subject of active new clinical development.

Side-effect profile: Favorable. The human safety record is reassuring, with mild and infrequent adverse events (anxiety, insomnia, nausea) at registered doses of 1.5 grams daily.

Overall validation: Moderate. The compound has human clinical data and registered indications, but effect sizes are modest and the clinical development is not actively expanding.

Comparison to sunifiram: Aniracetam acts directly on the AMPA receptor desensitization gate, while sunifiram acts indirectly through glycine-site NMDA receptor facilitation with downstream AMPA receptor potentiation via kinase cascades. Aniracetam has the advantage of human safety data and registered medical use. Sunifiram has the advantage of substantially greater potency and a more precisely characterized molecular mechanism.

12.3 Unifiram (DM-232)

Mechanism: The bicyclic diazabicyclononanone parent compound from which sunifiram was derived. Shares the same antiamnesic activity profile; AMPA receptor involvement confirmed; increases acetylcholine release from cerebral cortex; increases fEPSP amplitude in hippocampal slices [5, 9].

Development trajectory: Synthesized at the University of Florence by the same Gualtieri research group. Pharmacologically characterized in the same series of publications. Not advanced to clinical development for the same reasons as sunifiram (insufficient toxicology funding, absent pharmaceutical interest) [11].

Novelty: Moderate. The bicyclic piperazine scaffold was novel at the time of synthesis. Unifiram is the immediate structural predecessor of sunifiram.

Effect size: Comparable to sunifiram in rodent antiamnesic models. Effective at approximately the same dose range (0.001 to 0.1 mg/kg intraperitoneally in mouse passive avoidance) [5, 9].

Promising potential: Low. Not in clinical development. Available as a research chemical with the same limitations as sunifiram. Less widely available commercially than sunifiram.

Side-effect profile: Similar to sunifiram. No formal toxicology. No motor or behavioral adverse effects at effective doses in rodent studies [5].

Overall validation: Low. Preclinical characterization only. No human data. Slightly less mechanistic depth than sunifiram (the Bhatt and Moriguchi studies focused on sunifiram specifically, not unifiram).

Comparison to sunifiram: Unifiram and sunifiram are closely matched in potency, efficacy, and mechanistic profile. Sunifiram has the advantage of the more detailed mechanistic characterization from the Tohoku University studies. Unifiram has a more complex (bicyclic) structure that is marginally less amenable to large-scale synthesis. The two compounds are essentially interchangeable for most research applications.

12.4 Noopept (GVS-111, N-phenylacetyl-L-prolylglycine ethyl ester)

Mechanism: A synthetic dipeptide nootropic developed at the Russian Academy of Sciences. Proposed mechanisms include facilitation of AMPA receptor function, increase in brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) expression, and modulation of acetylcholine signaling. Active metabolite cycloprolylglycine may mediate some effects [14, 15].

Development trajectory: Noopept was developed in Russia and is marketed as a prescription medicine in Russia and some former Soviet republics for cognitive impairment. It has not been approved in the United States, European Union, or most other jurisdictions. Clinical trials in Russia have reported cognitive benefit in patients with mild cognitive impairment and post-traumatic cognitive deficit.

Novelty: Moderate. The dipeptide scaffold is distinct from both the racetam and piperazine classes. The BDNF/NGF-mediated neurotrophic mechanism, if confirmed, would represent a distinct approach to cognition enhancement.

Effect size: Comparable to sunifiram in terms of weight-adjusted potency in rodent models (effective at approximately 0.5 to 10 mg/kg in mice, somewhat less potent than sunifiram on a molar basis). Russian clinical trials report modest cogni-

tive improvement at 10 to 30 mg daily in human patients [14, 15].

Promising potential: Low to moderate. The compound has some clinical data from Russian trials and is marketed in Russia, but has not produced registration-quality data in Western regulatory frameworks and is not in active Western clinical development.

Side-effect profile: Favorable based on Russian clinical data. Adverse events are mild and infrequent at studied doses. No formal Western regulatory-standard toxicology is publicly available.

Overall validation: Moderate. The compound has clinical data (from Russian trials) and marketing authorization in limited jurisdictions, giving it more human validation than sunifiram. The quality and transparency of the Russian clinical trial data have been questioned by some Western reviewers.

Comparison to sunifiram: Noopept has the advantage of human clinical data and marketing authorization, though limited to Russia. Sunifiram has the advantage of more detailed molecular mechanistic characterization (the Bhatt 2013 glycine-site study). Both compounds are available as research chemicals. The two operate through partially overlapping glutamatergic mechanisms but with distinct molecular targets (glycine-site facilitation for sunifiram; AMPA modulation and neurotrophic factor induction for noopept).

12.5 CX-516 (Ampalex)

Mechanism: A benzamide-class ampakine that directly modulates AMPA receptor desensitization. CX-516 binds at the interface between AMPA receptor subunits and slows the rate of receptor desensitization, prolonging excitatory postsynaptic currents [16].

Development trajectory: Developed by Cortex Pharmaceuticals, CX-516 was advanced through Phase 2 clinical trials for schizophrenia cognitive impairment and for fragile X syndrome. The schizophrenia trials (Goff et al. 2008) reported that CX-516 added to clozapine, olanzapine, or risperidone did not produce significant cognitive improvement on the primary outcome measures [16]. Development was discontinued following the negative Phase 2 results.

Novelty: Moderate at the time of development. CX-516 was among the first ampakines advanced to human clinical trials for cognitive endpoints.

Effect size: Modest in preclinical models. Ineffective in Phase 2 schizophrenia cognitive trials at the doses studied, possibly owing to pharmacokinetic limitations (rapid metabolism, short half-life, insufficient brain exposure) [16].

Promising potential: Low. Development is terminated. The compound served as a proof-of-concept for the ampakine class but was pharmacokinetically insufficient for clinical translation.

Side-effect profile: Favorable. No significant safety concerns were identified in Phase 1 and Phase 2 trials. Adverse events were mild (headache, nausea, dizziness).

Overall validation: Low to moderate. The compound advanced through Phase 2 with negative efficacy results, suggesting that the therapeutic concept (direct AMPA receptor modulation for cognitive enhancement) may require more potent and pharmacokinetically optimized agents. CX-516 remains a reference compound for the ampakine class.

Comparison to sunifiram: CX-516 acts directly on the AMPA receptor desensitization gate, while sunifiram acts indirectly through glycine-site NMDA receptor facilitation. CX-516 has human clinical data (though negative for cognition) and Phase 2 safety data, which sunifiram lacks entirely. Sunifiram has substantially greater pre-clinical potency and a more favorable computed pharmacokinetic profile. The CX-516 clinical failure illustrates the challenge of translating ampakine-class preclinical cognition enhancement to human clinical endpoints.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the nootropic and cognition-enhancement pharmacology space. **Piracetam** is the historical prototype with extensive human safety data but low potency and uncertain mechanism. **Aniracetam** adds a characterized AMPA receptor mechanism and registered indications but is substantially less potent than sunifiram. **Unifiram** is the direct structural predecessor with nearly identical pharmacological profile but less detailed mechanistic characterization. **Noopept** has the advantage of limited human clinical data and Russian marketing authorization, with a partially distinct neurotrophic mechanism. **CX-516** illustrates the challenge of clinical translation of the ampakine concept, having failed in Phase 2 despite a clear molecular mechanism.

Sunifiram occupies a distinctive position in this landscape: it is the most potent of the evaluated compounds in rodent anti-amnesic models (approximately equipotent with unifiram and approximately 1000-fold more potent than piracetam or aniracetam on a per-weight basis), has the most precisely characterized molecular mechanism through the Bhatt et al. (2013) glycine-site NMDA receptor study, and has a favorable computed pharmacokinetic profile for oral bioavailability and blood-brain barrier penetration. Its principal weakness is the complete absence of human clinical data: no Phase 1 safety study, no pharmacokinetic characterization in humans, no formal toxicology in any species, and no regulatory approval anywhere in the world. Among the five comparators, piracetam, aniracetam, and noopept all have substantially more human safety and efficacy data than sunifiram, and even CX-516 (which failed in clinical development) has Phase 2 safety data that sunifiram lacks.

The practical implication for investigators considering sunifiram for research applications is that the compound offers the highest preclinical potency and the best-characterized molecular mechanism among the evaluated agents, but carries the greatest safety uncertainty owing to the complete absence of human data and formal toxicology. The compound is best positioned as a pharmacological tool for fundamental research into glycine-site NMDA receptor facilitation and glutamatergic synaptic plasticity, rather than as a clinical candidate for human cognitive enhancement, until toxicology and Phase 1 studies are completed.

13. References

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