

RESEARCH MONOGRAPH . COMPOUND PROFILE

IDRA-21

A benzothiadiazine derivative developed at the Nathan S. Kline Institute as a partial negative allosteric modulator of AMPA receptor desensitization, distinguished from cyclothiazide and the racetam-class ampakines by partial intrinsic activity, prolonged duration of cognitive enhancement, absence of neurotoxicity at pharmacologically active doses, and oral bioavailability with central nervous system penetration in rodent and primate species.

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ABSTRACT

IDRA-21 (7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine S,S-dioxide; CAS 22503-72-6; molecular formula C₈H₉ClN₂O₂S; molecular weight 232.69 g/mol) is a benzothiadiazine derivative that acts as a positive allosteric modulator of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type glutamate receptors by attenuating receptor desensitization. The compound was synthesized and characterized at the Nathan S. Kline Institute for Psychiatric Research in Orangeburg, New York, under the direction of Erminio Costa and Alessandro Guidotti in the early 1990s, and was advanced through preclinical development by Fidia Farmaceutici SpA of Abano Terme, Italy, before discontinuation in October 2003 without entry into human clinical trials.

The mechanism of action is partial negative allosteric modulation of AMPA receptor desensitization, a pharmacological property that distinguishes IDRA-21 from the full modulators cyclothiazide and diazoxide. In cultured cerebellar granule neurons, IDRA-21 increases the sodium transient with a threshold concentration approximately 10-fold higher than cyclothiazide and an intrinsic activity significantly lower than that of cyclothiazide, producing a shorter-lasting calcium transient and, critically, complete absence of neurotoxicity at concentrations up to 100 micromolar in the presence of AMPA, compared to the severe neurotoxicity produced by cyclothiazide at 5 to 25 micromolar under identical conditions. The partial modulator mechanism therefore provides

a wide therapeutic index between the concentrations that enhance cognition and those that produce excitotoxic neuronal injury.

The compound is a chiral molecule possessing one stereocenter at the 3-position of the benzothiadiazine ring. Enantiomeric resolution by Uzunov et al. (1995) using a custom chiral stationary phase demonstrated that the dextrorotatory (+)-IDRA-21 enantiomer is the pharmacologically active form in rat water maze performance, whereas the levorotatory (-)-enantiomer is devoid of activity at comparable doses. The racemate has been used in all published in vivo behavioral studies.

Preclinical cognitive enhancement has been documented across multiple species, behavioral paradigms, and impairment models. In rat passive avoidance and water maze tasks, racemic IDRA-21 at oral doses of 1 to 3 micromol/kg reverses cognitive deficits induced by alprazolam (a GABAergic positive modulator) and scopolamine (a muscarinic antagonist), with effect persisting for 3 to 4 hours after a single oral dose. In patas monkeys working in a complex operant learning task, IDRA-21 at 3 to 5.6 mg/kg orally antagonized alprazolam-induced learning deficits and was estimated to be approximately 10-fold more potent than aniracetam in this paradigm. In young adult and aged rhesus monkeys performing a delayed matching-to-sample task, oral IDRA-21 at 0.15 to 10 mg/kg produced robust improvements in task accuracy, with effects sustained to 48 hours after a single dose and accuracy on long-delay (most difficult) trials increased by up to 34 percent of vehicle at the individualized best dose. In young macaques performing a visual recognition memory task, oral IDRA-21 significantly improved performance on the longest delay condition.

A secondary pharmacological activity has been characterized: IDRA-21 negatively modulates NMDA receptor function in cultured cerebellar granule cells, with partial selectivity for NR2B-containing receptor assemblies. The NMDA receptor inhibition is neither competitive nor voltage-dependent and may contribute to the neuroprotective and cognitive profiles by tempering excessive NMDA receptor activation while potentiating AMPA receptor currents.

The principal safety concern identified in preclinical studies is the enhancement of ischemic neuronal injury. Yamada et al. (1998) demonstrated that IDRA-21 at 12 and 24 mg/kg orally increases CA1 hippocampal neuron loss following 10 minutes of global ischemia in rats, and that glutamate plus IDRA-21 produces AMPA receptor-dependent neurotoxicity in cultured hippocampal neurons. This finding has implications for any future clinical development in populations at risk of cerebrovascular events.

No human clinical trials have been conducted with IDRA-21. The compound was discontinued from development by Fidia Farmaceutici in October 2003. It remains available from multiple research-grade chemical suppliers at greater than 98 percent purity and is used as a reference compound in AMPA receptor pharmacology research and as a tool compound for the study of glutamatergic contributions to cognition and synaptic plasticity.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Research designation: IDRA-21. The designation is the internal compound identifier from the research program at the Nathan S. Kline Institute for Psychiatric Research. The name is canonical in all published pharmacology and behavioral literature.

Chemical Abstracts Service registry number: 22503-72-6 (racemate).

International Union of Pure and Applied Chemistry name: 7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide. Alternative IUPAC representations include 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine S,S-dioxide and the equivalent systematic name with explicit stereodescriptors for the active enantiomer.

Other synonyms: 7-chloro-3-methyl-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine 1,1-dioxide. The compound has been described in some literature as a diazoxide derivative owing to its structural relationship to the potassium channel opener diazoxide (7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide), from which IDRA-21 differs by saturation of the 3,4-double bond, producing a chiral center at the 3-position [1, 2].

Development code: No formal development code from Fidia Farmaceutici has appeared in the published literature. The compound is identified exclusively as IDRA-21 in all primary publications.

UNII: 689UW7PT68 (United States FDA Unique Ingredient Identifier, racemate).

1.2 Structural class and chemistry

IDRA-21 is a 1,2,4-benzothiadiazine 1,1-dioxide, a structural class that includes the thiazide diuretics (hydrochlorothiazide, chlorothiazide), the potassium channel opener diazoxide, and the AMPA receptor modulator cyclothiazide. The benzothiadiazine scaffold is a fused bicyclic system consisting of a benzene ring annulated with a six-membered ring containing two nitrogen atoms and a sulfonyl group. The

7-chloro substitution on the benzene ring and the 3-methyl substitution on the thiazine ring define the specific pharmacological and physicochemical properties of IDRA-21.

Molecular formula: C₈H₉ClN₂O₂S.

Molecular weight: 232.69 g/mol.

Exact mass: 232.0074 g/mol (monoisotopic).

Physical properties: White to off-white crystalline powder. Insoluble in water. Soluble in dimethyl sulfoxide (approximately 250 mg/mL with ultrasonic agitation), ethanol, methanol, and dilute aqueous base (the latter owing to the sulfonamide NH acidity). Melting point has been reported in the range of 235 to 240 degrees Celsius.

Stereochemistry: IDRA-21 contains one stereocenter at the 3-position of the thiazine ring. The compound is typically supplied as the racemate. Uzunov et al. (1995) resolved the enantiomers using a custom chiral stationary phase derived from (R)-N-(3,5-dinitrobenzoyl)allylglycine 2,6-dimethylanilide [3]. The (+)-enantiomer eluted at 37.5 minutes and the (-)-enantiomer at 44.3 minutes under the described chromatographic conditions. Behavioral testing in the rat water maze demonstrated that (+)-IDRA-21 is the pharmacologically active enantiomer; (-)-IDRA-21 was completely inactive at comparable doses [3, 4]. Investigators acquiring research-grade IDRA-21 should be aware that all commercial preparations are racemic unless explicitly labeled as enantiopure, and that the active enantiomer represents approximately half the administered mass.

1.3 Synthesis

The published synthesis of IDRA-21 proceeds from commercially available 2-amino-4-chlorobenzenesulfonamide through condensation with acetaldehyde (or an equivalent acetaldehyde surrogate) under acidic conditions to form the 3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide ring system. The reaction is a Mannich-type cyclization producing the racemate. Purification is typically by recrystallization from appropriate solvents, with the product characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and high-performance liquid chromatography [3]. Resolution into individual enantiomers requires chiral chromatographic separation, as the synthesis produces a racemic mixture. The compound is structurally related to hydrochlorothiazide and diazoxide but differs

in the saturation state at the 3-position (dihydro versus the unsaturated diazoxide) and in the absence of the 6-chloro substituent present in hydrochlorothiazide. Industrial synthesis is straightforward, and the compound is manufactured by multiple research-grade suppliers at purities greater than 98 percent by HPLC.

2. Abstract

IDRA-21 (7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine S,S-dioxide) is a positive allosteric modulator of AMPA-type glutamate receptors that enhances cognition by attenuating the rapid desensitization of the receptor following agonist binding [1, 4]. The compound was developed at the Nathan S. Kline Institute for Psychiatric Research by the Costa and Guidotti laboratory in the early 1990s and advanced through preclinical pharmacology by Fidia Farmaceutici SpA before discontinuation in 2003 without human clinical trials.

The pharmacological mechanism is partial negative allosteric modulation of AMPA receptor desensitization. Unlike the full modulator cyclothiazide, which produces maximal attenuation of desensitization and dose-dependent neurotoxicity through excessive calcium influx, IDRA-21 acts as a partial modulator with significantly lower intrinsic activity at the desensitization-modulatory site [5]. The consequence is that IDRA-21 enhances AMPA receptor-mediated synaptic currents sufficiently to promote long-term potentiation and cognitive performance while maintaining a wide margin between effective and neurotoxic concentrations. In hippocampal slice preparations, IDRA-21 at 500 micromolar increased the amplitude and half-width of field excitatory postsynaptic potentials and promoted the induction of long-term potentiation with stimulation paradigms that were only partially effective in the absence of the drug [6].

The preclinical cognitive evidence base spans rodent and primate models. In rats, oral IDRA-21 at 1 to 3 micromol/kg reverses learning deficits induced by the benzodiazepine alprazolam and the muscarinic antagonist scopolamine, with the compound estimated to be 10- to 30-fold more potent than aniracetam in these paradigms and with effect duration of 3 to 4 hours after a single dose [4, 7]. In patas monkeys, oral IDRA-21 at 3 to 5.6 mg/kg antagonized alprazolam-induced learning impairment in a complex operant schedule, with potency approximately 10-fold greater than aniracetam [7]. In young adult and aged rhesus monkeys performing a delayed matching-to-sample task, oral IDRA-21 produced sustained improvements in accuracy lasting up to 48 hours after a single dose, with long-delay trial accuracy increased by up to 34 percent of vehicle [8]. In young macaques, IDRA-21 improved visual recognition memory performance at the longest delay intervals [9].

A secondary pharmacological activity is negative modulation of NMDA receptor function, with partial selectivity for NR2B-containing assemblies in cultured cerebellar granule cells [10]. The NMDA receptor modulation may contribute to the overall cognitive and neuroprotective profile.

The principal safety limitation is the potential for enhanced ischemic neuronal injury through AMPA receptor potentiation. Yamada et al. (1998) demonstrated that oral IDRA-21 at 12 to 24 mg/kg increased CA1 hippocampal neuron loss following global ischemia in rats [11]. This finding represents a class-specific risk for AMPA receptor positive modulators and has implications for any future clinical translation in neurologically vulnerable populations.

IDRA-21 has not been studied in human subjects. No Phase 1, Phase 2, or Phase 3 clinical trials have been conducted. The compound is available as a research-grade chemical from multiple suppliers and is used as a tool compound in AMPA receptor pharmacology, glutamatergic neuroscience, and cognitive enhancement research.

3. Discovery and Development History

3.1 Origin

IDRA-21 was synthesized at the Nathan S. Kline Institute for Psychiatric Research in Orangeburg, New York, as part of a structure-activity investigation of benzothiadiazine derivatives for modulation of AMPA-type glutamate receptor desensitization. The research program was directed by Erminio Costa and Alessandro Guidotti, with the pharmacological and behavioral characterization conducted by Ivan Zivkovic, Donald M. Thompson, Mario Bertolino, Doncho Uzunov, Maria DiBella, and colleagues. The rationale for the program was the observation that cyclothiazide, a thiazide diuretic, potentially attenuated AMPA receptor desensitization and enhanced glutamatergic synaptic transmission but produced dose-limiting neurotoxicity through excessive AMPA receptor-mediated calcium influx. The goal was to identify congeners with sufficient modulation of desensitization to enhance cognition while retaining a wide margin to neurotoxic concentrations [1, 4, 5].

3.2 Characterization of mechanism

The first published characterization of IDRA-21 appeared in the *Journal of Pharmacology and Experimental Therapeutics* in 1995, authored by Zivkovic, Thompson, Bertolino, Uzunov, DiBella, Costa, and Guidotti [4]. This report demonstrated that IDRA-21 attenuated the rapid autodesensitization of AMPA-selective glutamate receptors, increased excitatory synaptic strength, and improved cognitive performance in rats subjected to water maze and passive avoidance tests when performance was impaired by alprazolam or scopolamine. The compound was shown to cross the blood-brain barrier after oral administration and to act stereoselectively, with the behavioral effect residing in the (+)-enantiomer [3, 4].

3.3 Primate behavioral studies

Thompson et al. (1995) published in the *Proceedings of the National Academy of Sciences* the first primate demonstration that IDRA-21 reverses pharmacologically induced cognitive impairment [7]. In patas monkeys working in a multiple-schedule operant task with separate learning and performance components, oral IDRA-21

at 3 and 5.6 mg/kg antagonized the large disruptive effects of alprazolam on the learning component without affecting the performance component, and was approximately 10-fold more potent than aniracetam in this paradigm. The selectivity of effect on learning (but not performance) was interpreted as evidence for a genuine cognitive mechanism rather than a nonspecific psychostimulant effect.

3.4 Safety characterization

Impagnatiello et al. (1997) published in the Proceedings of the National Academy of Sciences the critical safety characterization demonstrating that IDRA-21 is a partial modulator of AMPA receptor desensitization devoid of neurotoxicity at pharmacologically active concentrations [5]. In cultured cerebellar granule neurons, IDRA-21 at concentrations up to 100 micromolar in the presence of AMPA produced no neurotoxicity, whereas cyclothiazide at 5 to 25 micromolar under identical conditions was highly neurotoxic. The margin between cognitive-enhancing doses (1 to 3 micromol/kg in rats) and the absence of toxicity at 100 micromolar in vitro was interpreted as a favorable therapeutic index for the partial-modulator mechanism.

3.5 Fidia Farmaceutici and discontinuation

Fidia Farmaceutici SpA of Abano Terme, Italy, held development rights to IDRA-21 and advanced the compound through preclinical pharmacology studies. A patent application (WO1995015759A1) covering the use of benzothiadiazide derivatives as nootropic agents was filed in 1994, naming the compound class and the cognitive enhancement application [12]. Development was discontinued by Fidia in October 2003 for the cognition disorders indication. The reasons for discontinuation have not been publicly disclosed but likely reflect the challenging regulatory and commercial landscape for cognitive enhancement compounds lacking an established clinical endpoint and the general difficulty of translating rodent and primate cognitive pharmacology to human registration trials. No human clinical studies were initiated prior to discontinuation.

3.6 Subsequent research

Following discontinuation of commercial development, IDRA-21 continued as a research tool compound. Buccafusco et al. (2004) extended the primate evidence with a study in young adult and aged rhesus monkeys demonstrating sustained cognitive enhancement lasting 48 hours after a single oral dose [8]. Terry et al. (2011) at Johns

Hopkins and the Medical College of Georgia published a visual recognition memory study in young macaques confirming the AMPA receptor-mediated cognitive enhancement in a second primate species and paradigm [9]. The compound is now established as a standard reference positive AMPA receptor modulator alongside CX516, CX614, and aniracetam in the neuropharmacology literature.

4. Mechanism of Action

IDRA-21 is a positive allosteric modulator of the AMPA subtype of ionotropic glutamate receptors. Its principal molecular activity is the attenuation of AMPA receptor desensitization, a process by which the receptor ion channel closes despite continued binding of glutamate at the orthosteric site. A secondary activity is negative modulation of NMDA receptor function. These activities operate at distinct concentration ranges and receptor sites and contribute differentially to the observed cognitive enhancement, synaptic plasticity facilitation, and safety profile.

4.1 AMPA receptor desensitization and its modulation

The AMPA receptor is a tetrameric ligand-gated ion channel assembled from combinations of GluA1, GluA2, GluA3, and GluA4 subunits. It mediates the majority of fast excitatory synaptic transmission in the central nervous system. Upon binding of glutamate released from presynaptic terminals, the receptor channel opens for approximately 1 to 2 milliseconds and then enters a desensitized state, closing the channel while glutamate remains bound. Desensitization occurs on a time scale of approximately 5 to 15 milliseconds and limits the amplitude and duration of the excitatory postsynaptic current. The molecular basis of desensitization involves rearrangement of the dimer interface of the ligand-binding domains, disrupting the coupling between agonist binding and channel gating [13, 14].

Positive allosteric modulators of AMPA receptors that slow desensitization increase the amplitude and duration of AMPA receptor-mediated currents, producing stronger and longer-lasting excitatory postsynaptic potentials. This enhancement of glutamatergic transmission promotes the induction and maintenance of long-term potentiation, the principal cellular correlate of learning and memory in the hippocampus and cortex.

4.2 IDRA-21 binding and partial modulation

IDRA-21 binds at the dimer interface of the AMPA receptor ligand-binding domain, the same general site occupied by cyclothiazide, aniracetam, and the biarylpropyl-sulfonamide modulators [5, 14]. The binding attenuates the rate of desensitization,

producing longer channel open times and increased integrated synaptic current per glutamate-binding event. The critical distinction from cyclothiazide and other full modulators is that IDRA-21 acts as a partial modulator. In cultured cerebellar granule neurons, IDRA-21 increases the intracellular sodium transient with a threshold of approximately 5 micromolar, compared to a threshold approximately 10-fold lower for cyclothiazide, and with an intrinsic activity (maximal effect on current amplitude) significantly lower than that of cyclothiazide [5].

The partial modulator property produces a self-limiting ceiling effect on AMPA receptor activation. Where cyclothiazide can drive AMPA receptor-mediated calcium influx to neurotoxic levels, IDRA-21 produces a smaller and shorter-lasting calcium transient that is insufficient to trigger excitotoxic cascades under normal physiological conditions. In the Impagnatiello et al. (1997) study, cyclothiazide at 5 to 25 micromolar in the presence of AMPA was highly neurotoxic to cultured cerebellar granule neurons, killing the majority of cells, while IDRA-21 at concentrations up to 100 micromolar under identical conditions was completely devoid of neurotoxicity [5]. The therapeutic index between cognition-enhancing concentrations and neurotoxic concentrations is therefore several orders of magnitude for IDRA-21, compared to a narrow index for cyclothiazide.

4.3 Enhancement of long-term potentiation

In hippocampal slice preparations, IDRA-21 at 500 micromolar increased the amplitude and half-width of field excitatory postsynaptic potentials recorded from the CA1 region following Schaffer collateral stimulation [6]. At concentrations that facilitated synaptic transmission, IDRA-21 promoted the induction of long-term potentiation: full potentiation was obtained with stimulation paradigms (weak tetanic protocols) that were only partially effective in the absence of the drug. The result supports the hypothesis that drugs which enhance AMPA receptor-mediated currents facilitate the induction of long-term potentiation by increasing postsynaptic depolarization sufficiently to relieve the voltage-dependent magnesium block of NMDA receptors, permitting calcium influx through NMDA receptor channels and activating the downstream calcium-dependent kinases (calcium/calmodulin-dependent protein kinase II, protein kinase C) that consolidate potentiation [6].

4.4 NMDA receptor modulation

In addition to its primary AMPA receptor activity, IDRA-21 negatively modulates NMDA receptor function. In cultured cerebellar granule cells, IDRA-21 reduced NMDA receptor whole-cell currents through a mechanism that was neither competitive nor voltage-dependent [10]. In transfected HEK293 cells, the inhibitory effect was stronger on NR1a-NR2B recombinant receptors than on NR1a-NR2A assemblies, indicating partial selectivity for the NR2B subunit. Both NMDA miniature excitatory postsynaptic current decay and nucleated patch current decay were shortened by the compound, suggesting that the effect is mediated through an increase in receptor deactivation kinetics rather than through channel block [10].

The NR2B-preferring NMDA receptor inhibition may contribute to the cognitive profile by two mechanisms. First, NR2B-containing NMDA receptors are enriched at extrasynaptic sites, where their tonic activation by ambient glutamate promotes excitotoxic signaling cascades; preferential inhibition of extrasynaptic over synaptic NMDA receptors would shift the balance toward neuroprotection. Second, the combination of enhanced AMPA receptor currents (promoting long-term potentiation induction) with reduced extrasynaptic NMDA receptor currents (reducing long-term depression and excitotoxicity) could produce a favorable bidirectional modulation of synaptic plasticity.

4.5 Composite pharmacology and selectivity

The composite pharmacology of IDRA-21 at behaviorally active doses in rodents (1 to 3 micromol/kg orally, corresponding to approximately 0.23 to 0.7 mg/kg) and in primates (0.15 to 10 mg/kg orally) produces AMPA receptor desensitization modulation as the principal mechanism and NMDA receptor NR2B inhibition as a secondary mechanism. The compound does not produce appreciable activity at metabotropic glutamate receptors, GABA receptors, dopamine receptors, serotonin receptors, or noradrenergic receptors at behaviorally relevant concentrations, consistent with a selective glutamatergic mechanism of cognitive enhancement [4, 5]. The absence of monoaminergic receptor activity distinguishes IDRA-21 from the methylxanthine and catecholaminergic psychostimulants that produce cognitive-appearing improvements through arousal and attention modulation rather than through direct synaptic plasticity facilitation.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and oral bioavailability

IDRA-21 is absorbed from the gastrointestinal tract after oral administration in rats, patas monkeys, rhesus monkeys, and macaques. All published behavioral studies demonstrating cognitive enhancement employed the oral route, confirming functionally meaningful oral bioavailability across multiple species [4, 7, 8, 9]. Specific oral bioavailability values (expressed as fraction of intravenous exposure) have not been published for any species. The compound crosses the blood-brain barrier after oral administration, as demonstrated by the central cognitive effects and by the stereoselective activity pattern (the inactive enantiomer produces no central effect, confirming that the behavioral activity requires central receptor engagement rather than peripheral signaling) [3, 4].

5.2 Distribution

Volume of distribution data have not been published. The compound is lipophilic (insoluble in water, soluble in organic solvents and dimethyl sulfoxide), consistent with tissue distribution and central nervous system penetration. The ability of oral IDRA-21 to produce behavioral effects at low doses (1 to 3 micromol/kg in rats, 0.15 mg/kg in rhesus monkeys) suggests adequate brain penetration at pharmacologically relevant plasma concentrations. IDRA-21 has been reported to cross the blood-brain barrier more readily than cyclothiazide, which despite higher intrinsic activity at the AMPA receptor has limited central nervous system access [4, 5].

5.3 Metabolism and elimination

Specific metabolic pathways, cytochrome P450 isoform involvement, metabolite identification, and elimination half-life have not been published for IDRA-21 in any species. The benzothiadiazine scaffold suggests potential metabolic transformations including oxidative metabolism of the thiadiazine ring system, dechlorina-

tion, and conjugation reactions (glucuronidation of the sulfonamide nitrogen). No drug-drug interaction studies or metabolic phenotyping studies have been reported.

The duration of behavioral effect provides an indirect estimate of the effective pharmacokinetic profile. In rats, cognitive enhancement after a single oral dose of 1 to 3 micromol/kg persists for 3 to 4 hours [4]. In rhesus monkeys, cognitive enhancement after a single oral dose at the individualized best dose persists for up to 48 hours [8]. The prolonged duration in primates relative to rodents may reflect species differences in metabolic clearance, volume of distribution, or receptor binding kinetics, and is a notable feature of the compound that distinguishes it from aniracetam (which has a short duration of behavioral effect owing to rapid hydrolysis of the pyrrolidone ring) and from CX516 (which has a half-life of approximately 15 minutes in humans) [8, 15].

5.4 Routes of administration

All published behavioral studies have employed the oral route. In rats, the compound was administered by oral gavage in a vehicle appropriate for the poorly water-soluble compound (typically a suspension in methylcellulose or in a small volume of dimethyl sulfoxide diluted in saline). In primates, the compound was administered orally, with the specific formulation not always described but consistent with oral capsule or oral solution delivery [7, 8, 9].

Intraperitoneal administration has been used in some in vitro-to-in vivo correlation studies. No intravenous, subcutaneous, intramuscular, or intrathecal administration has been reported. The water insolubility of the compound limits the feasibility of aqueous parenteral formulations without cosolvent systems.

5.5 Special populations

No data exist on IDRA-21 pharmacokinetics in any defined special population (pediatric, geriatric, renally impaired, hepatically impaired). The aged rhesus monkey data from Buccafusco et al. (2004) represent the only comparison of drug effect across age groups; the compound produced cognitive enhancement in both young adult and aged animals, though the aged animals showed more variable responses [8].

6. Preclinical Pharmacology

6.1 Rodent cognitive models

The foundational behavioral pharmacology of IDRA-21 was established in the Zivkovic et al. (1995) report [4]. In rats subjected to the Morris water maze (a spatial learning and memory task requiring hippocampal function), oral IDRA-21 at 1 to 3 micromol/kg reversed the learning deficit induced by alprazolam (a GABA-A receptor positive allosteric modulator that impairs cognition through excessive GABAergic inhibition) and by scopolamine (a muscarinic acetylcholine receptor antagonist that impairs cognition through cholinergic blockade). The compound was 20- to 30-fold more potent than aniracetam in reversing scopolamine-induced deficits and approximately 10-fold more potent than aniracetam in reversing alprazolam-induced deficits in the same paradigms [4, 7].

In passive avoidance tests (a fear-motivated learning paradigm), oral IDRA-21 similarly reversed pharmacologically induced cognitive deficits. The effect persisted for 3 to 4 hours after a single oral dose, suggesting a duration of central receptor engagement consistent with single daily dosing in a research context [4].

The compound did not produce behavioral stimulation, sedation, or motor impairment at cognitive-enhancing doses, supporting the interpretation that the behavioral improvement reflects genuine cognitive enhancement rather than a non-specific arousal or psychomotor effect.

6.2 Primate cognitive models

Three primate studies constitute the principal evidence base for cognitive enhancement by IDRA-21.

Thompson et al. (1995) tested IDRA-21 and aniracetam in patas monkeys working in a multiple-schedule operant task with separate learning (a different four-response chain acquired each session) and performance (the same four-response chain each session) components [7]. Alprazolam at 0.1 or 0.32 mg/kg orally produced large decreases in accuracy and response rate in the learning component. IDRA-21 at 3 or 5.6 mg/kg orally, administered 60 minutes before alprazolam, antag-

onized the disruptive effects on learning without affecting performance, and was approximately 10-fold more potent than aniracetam (30 mg/kg orally) in this paradigm. The selectivity for learning over performance is an important feature, demonstrating that the compound enhances cognitive processes rather than motor or motivational processes.

Buccafusco et al. (2004) tested IDRA-21 in 7 young adult and 7 aged rhesus monkeys performing a delayed matching-to-sample (DMTS) task [8]. Oral administration of IDRA-21 over a dose range of 0.15 to 10 mg/kg produced highly significant improvement in task accuracy in young adults. The effect was sustained to 48 hours after a single dose, a duration that exceeds the known behavioral half-life of any other AMPA receptor modulator tested in primates. At the individualized best dose, task accuracy for long-delay (most difficult) trials was increased by up to 34 percent of vehicle. In aged monkeys, the response was more variable but still positive, with medium-delay trial accuracy increased by up to 18 percent of vehicle at the best dose.

Terry et al. (2011) tested huperzine A and IDRA-21 in young macaques performing visual recognition memory tasks [9]. Oral IDRA-21 significantly improved performance on the longest delay condition of the visual recognition task, extending the primate evidence to a third species (macaque) and a third cognitive paradigm (recognition memory).

6.3 Electrophysiological studies

Arai et al. (1996) studied the effects of IDRA-21 on long-term potentiation in hippocampal slice preparations [6]. IDRA-21 at 500 micromolar significantly increased the amplitude and half-width of field excitatory postsynaptic potentials in the CA1 stratum radiatum following Schaffer collateral stimulation. At this concentration, IDRA-21 promoted the induction of long-term potentiation with weak tetanic stimulation protocols that produced only partial potentiation in control slices. The electrophysiological data provide a direct cellular-level mechanism for the behavioral cognitive enhancement: IDRA-21 lowers the threshold for the induction of synaptic plasticity in the hippocampus, the brain region most directly implicated in spatial learning, episodic memory, and the cognitive paradigms tested in the behavioral studies.

6.4 NMDA receptor studies

The secondary NMDA receptor activity of IDRA-21 was characterized in cultured cerebellar granule cells [10]. IDRA-21 reduced NMDA receptor whole-cell currents through a noncompetitive, voltage-independent mechanism. In HEK293 cells expressing recombinant NMDA receptor subunits, the inhibitory effect was stronger on NR1a-NR2B assemblies than on NR1a-NR2A assemblies, indicating partial subunit selectivity. The compound shortened both NMDA miniature excitatory postsynaptic current decay and nucleated patch current decay, consistent with an increase in receptor deactivation rate rather than channel block. The NMDA receptor inhibition occurs at concentrations overlapping with the AMPA receptor modulatory range and may therefore contribute to the *in vivo* pharmacological profile by limiting excessive NMDA receptor-mediated calcium influx at extrasynaptic sites while the AMPA receptor component enhances synaptic transmission [10].

6.5 Ischemic injury enhancement

Yamada et al. (1998) reported that IDRA-21 enhances ischemic hippocampal neuron injury in rats [11]. *In vitro*, glutamate plus IDRA-21 killed cultured rat hippocampal neurons through AMPA receptor-dependent mechanisms. *In vivo*, oral IDRA-21 at 12 and 24 mg/kg increased CA1 hippocampal neuron loss following 10 minutes of global ischemia. The effect is mechanistically consistent with AMPA receptor potentiation: during ischemia, excessive glutamate release activates AMPA receptors, and a positive modulator that slows desensitization prolongs the excitotoxic current. The finding establishes a context-dependent safety boundary for AMPA receptor positive modulators: while devoid of neurotoxicity under normal physiological conditions, the compounds may exacerbate neuronal injury in the setting of cerebrovascular ischemia, seizures, or other conditions characterized by pathological glutamate release [11].

7. Clinical Evidence Base

IDRA-21 has not been evaluated in any published human clinical trial. No Phase 1, Phase 2, or Phase 3 studies have been conducted. The compound was discontinued from commercial development by Fidia Farmaceutici in October 2003 before any human dosing occurred.

The absence of human data represents the most significant limitation in the evidence base for IDRA-21. All efficacy data are derived from rodent and nonhuman primate models, and all safety data are derived from in vitro studies and rodent in vivo studies. Translation of AMPA receptor positive modulator pharmacology from preclinical to clinical settings has been historically challenging, as demonstrated by the clinical failure of CX516 (insufficient efficacy at tolerated doses in human schizophrenia trials) and the narrow therapeutic index concerns that have limited development of more potent AMPA receptor modulators [15, 16].

The clinical development pathway for a compound with the pharmacological profile of IDRA-21 would require Phase 1 healthy-volunteer safety and pharmacokinetic studies establishing the human dose range, metabolic profile, and tolerability; Phase 2 proof-of-concept studies in a defined cognitive impairment indication (Alzheimer's disease, schizophrenia cognitive impairment, or age-associated memory impairment are the historically studied populations for ampakines); and Phase 3 registration studies. The regulatory pathway for cognitive enhancement agents remains poorly defined, with no AMPA receptor positive modulator having achieved regulatory approval for a cognitive indication in any jurisdiction as of the date of this monograph.

8. Sourcing and Quality Verification

Research-grade IDRA-21 is supplied by multiple chemical and pharmaceutical research suppliers including Tocris Bioscience (catalog number 1219), Sigma-Aldrich, Cayman Chemical, MedChemExpress, Selleckchem, Santa Cruz Biotechnology, Hello Bio, Alomone Labs, and others. Supply is typically in milligram quantities (5 mg to 500 mg) as the racemic free base at greater than 98 percent purity by HPLC. Pricing is moderate, generally in the range of \$30 to \$150 per 50 mg of research-grade material at the time of monograph preparation.

The compound is not available as a pharmaceutical-grade preparation from any jurisdiction, as it has never been registered as a medicine. All sourcing is therefore research-grade, and investigators should confirm compound identity and purity on every lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ of 233.01 for the protonated molecular ion)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation, particularly to distinguish the 3,4-dihydro form (IDRA-21) from the unsaturated form (diazoxide)
- Chiral HPLC or optical rotation measurement if enantiomeric composition is relevant to the experimental design (commercial preparations are racemic unless otherwise specified)
- Karl Fischer or loss-on-drying analysis for residual water
- Residual solvent analysis where the synthesis route or supplier certificate of analysis indicates potential solvent contamination

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) provide independent confirmation of vendor certificates of analysis. The research-grade IDRA-21 market is established but smaller than markets for more widely used research compounds; lot-to-lot variability has been observed, and on-receipt analytical confirmation is appropriate for any investigation where dose-response or mechanism-of-action precision is important.

9. Reconstitution and Handling

IDRA-21 is a crystalline solid that is insoluble in water and requires organic solvent or cosolvent systems for preparation of solutions.

Stock solution preparation for in vitro use: Dissolve in dimethyl sulfoxide (DMSO) at concentrations up to 250 mg/mL (approximately 1074 mM) with ultrasonic agitation. Stock solutions in DMSO can also be prepared at 100 mM (23.3 mg/mL) for convenient dilution into aqueous experimental buffers. The final DMSO concentration in the experimental medium should be kept below 0.1 percent (v/v) to avoid solvent effects on cellular viability and receptor function. Ethanol and methanol are alternative solvents at lower maximum concentrations.

Formulation for in vivo oral administration: For rodent studies, the compound is typically suspended in 0.5 percent methylcellulose or in a cosolvent system (10 percent DMSO, 40 percent polyethylene glycol 300, 5 percent Tween-80, 45 percent saline) to achieve working concentrations of approximately 2 mg/mL. The compound is not soluble in aqueous vehicles without cosolvents; attempts to dissolve in saline or phosphate-buffered saline will produce precipitates.

Storage conditions: Store the solid at 2 to 8 degrees Celsius for short-term use (days to weeks) or at minus 20 degrees Celsius for long-term storage (months to years). Keep in dry, dark conditions. The compound is stable at room temperature for several weeks as a solid. Stock solutions in DMSO should be stored at minus 20 degrees Celsius and are stable for at least 6 months under these conditions. Aliquoting of DMSO stock solutions for single-use is recommended to minimize freeze-thaw cycles. Aqueous dilutions should be prepared fresh for each experiment.

Light sensitivity: No specific light sensitivity has been reported, but standard practice for research compounds (storage in amber vials or foil-wrapped containers) is reasonable.

10. Stack Interaction Considerations

IDRA-21 interacts with several drug classes through its glutamatergic mechanism of action. Investigators conducting research with IDRA-21, particularly in combination with other research compounds, should consider:

Other AMPA receptor modulators: Concurrent use with other positive allosteric modulators of the AMPA receptor (aniracetam, CX516, CX614, sunifiram, piracetam at high doses) produces additive or synergistic enhancement of AMPA receptor-mediated currents. The combination may exceed the desensitization-modulation ceiling that provides the safety margin of IDRA-21 as a partial modulator, potentially producing excitotoxic calcium influx. Combination studies should employ reduced doses of each agent and should include neurotoxicity monitoring.

NMDA receptor modulators: Concurrent NMDA receptor antagonists (memantine, ketamine, phencyclidine, dizocilpine) produce additive reduction of NMDA receptor function when combined with IDRA-21, which has intrinsic NMDA receptor inhibitory activity. The combination could produce excessive glutamatergic imbalance (enhanced AMPA, reduced NMDA) with potential for psychotomimetic effects or altered seizure threshold.

GABAergic agents: The preclinical evidence for IDRA-21 was developed using alprazolam-induced cognitive impairment as the primary deficit model. IDRA-21 antagonizes benzodiazepine-induced cognitive impairment but does not antagonize the sedative or anxiolytic effects of benzodiazepines, suggesting that the interaction is at the level of cognitive circuits rather than at the level of arousal circuits [7]. Concurrent use with benzodiazepines, barbiturates, or other GABA-A receptor positive modulators may produce complex pharmacodynamic interactions.

Cholinergic agents: IDRA-21 reverses scopolamine-induced cognitive impairment, suggesting a functional interaction between glutamatergic and cholinergic cognitive circuits [4]. Concurrent acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine, huperzine A) may produce additive cognitive enhancement through parallel glutamatergic and cholinergic mechanisms. The Terry et al. (2011) study tested huperzine A and IDRA-21 in the same macaque cohort, though as separate treatment conditions rather than in combination [9].

Compounds that lower seizure threshold: AMPA receptor potentiation increases excitatory neurotransmission and could theoretically lower seizure threshold. Concurrent use with other proconvulsant agents or in individuals with seizure history warrants caution, though IDRA-21 at behaviorally active doses has not been reported to produce seizures in any published study.

Ischemia-prone conditions: Based on the Yamada et al. (1998) finding that IDRA-21 enhances ischemic neuronal injury [11], concurrent conditions or agents that increase cerebrovascular risk (uncontrolled hypertension, anticoagulant therapy, vasoconstrictors, conditions predisposing to stroke) represent a context in which AMPA receptor potentiation could exacerbate injury if an ischemic event were to occur.

11. Adverse Events and Safety

11.1 Preclinical safety under normal physiological conditions

Under normal (non-ischemic) physiological conditions, IDRA-21 has a favorable preclinical safety profile. In the Impagnatiello et al. (1997) study, the compound was completely devoid of neurotoxicity at concentrations up to 100 micromolar in cultured cerebellar granule neurons in the presence of AMPA, whereas cyclothiazide produced severe neurotoxicity at 5 to 25 micromolar [5]. The margin between cognitive-enhancing doses (1 to 3 micromol/kg in rats, approximately 0.23 to 0.7 mg/kg) and the absence of in vitro neurotoxicity at 100 micromolar is several orders of magnitude.

In all published behavioral studies in rats, patas monkeys, rhesus monkeys, and macaques, IDRA-21 at cognitive-enhancing doses did not produce observable adverse behavioral effects, motor impairment, sedation, or behavioral stimulation [4, 7, 8, 9]. No formal toxicology studies (maximum tolerated dose, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive toxicity) have been published.

11.2 Ischemic injury potentiation

The principal identified safety concern is the enhancement of ischemic neuronal injury. Yamada et al. (1998) demonstrated in an in vivo rat model that oral IDRA-21 at 12 and 24 mg/kg increases CA1 hippocampal neuron loss following 10 minutes of global ischemia, and in cultured hippocampal neurons that glutamate plus IDRA-21 produces AMPA receptor-dependent cell death [11]. The doses that enhanced ischemic injury (12 to 24 mg/kg) are approximately 17- to 34-fold higher than the maximum cognitive-enhancing dose range in rats (approximately 0.7 mg/kg), providing some margin, but the finding is mechanistically concerning because the AMPA receptor potentiation mechanism that produces cognitive enhancement is the same mechanism that exacerbates excitotoxic injury under pathological glutamate release conditions.

11.3 Theoretical risks

Several theoretical risks are inherent to the AMPA receptor positive modulator class and apply to IDRA-21:

- Seizure facilitation through excessive excitatory neurotransmission (not observed at behaviorally active doses, but a dose-limiting concern for more potent modulators in the class)
- Excitotoxic neurodegeneration under conditions of pathological glutamate release (confirmed in the ischemia model)
- Tolerance development through homeostatic downregulation of AMPA receptor expression or sensitivity with chronic dosing (not studied for IDRA-21)
- Withdrawal hyperexcitability following chronic administration and abrupt discontinuation (not studied for IDRA-21)

11.4 Human safety data

No human safety data exist. All safety assessments are derived from preclinical studies.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five AMPA receptor positive allosteric modulators against IDRA-21, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal AMPA receptor modulators with substantive preclinical or clinical pharmacology programs in cognitive applications.

12.1 Aniracetam (Ro 13-5057)

Mechanism: Positive allosteric modulator of AMPA receptors. Slows both deactivation and desensitization of the receptor channel. Also possesses weak activity at metabotropic glutamate receptors and cholinergic muscarinic receptors. Classified as a low-impact (type I) AMPA receptor modulator [13, 14].

Development trajectory: Developed by Hoffmann-La Roche. Approved as a prescription medicine for cognitive impairment in Japan and several European countries. Not approved in the United States. Has been in clinical use for age-related cognitive decline since the early 1990s.

Novelty: Low. Aniracetam was the first identified AMPA receptor positive modulator and is the historical reference compound for the class. The pyrrolidinone scaffold is well characterized.

Effect size: Modest. In the Thompson et al. (1995) patas monkey study, aniracetam at 30 mg/kg orally antagonized alprazolam-induced learning deficits but was approximately 10-fold less potent than IDRA-21 in the same paradigm [7]. Human clinical data from the approved indication show modest improvements in cognitive assessment batteries.

Promising potential: Low to moderate. The compound is clinically available in some jurisdictions but has not achieved regulatory approval in the United States. The short duration of action (plasma half-life of approximately 35 minutes in humans owing to rapid pyrrolidone hydrolysis) limits practical utility.

Side-effect profile: Generally well tolerated. Principal adverse events are gastrointestinal discomfort, headache, and anxiety at higher doses. No neurotoxicity concerns at therapeutic doses.

Overall validation: Moderate. Clinical registration in multiple jurisdictions provides the highest level of clinical validation among the comparators. Modest effect sizes limit enthusiasm.

Comparison to IDRA-21: IDRA-21 is 10- to 30-fold more potent than aniracetam in preclinical cognitive models and has a substantially longer duration of effect (up to 48 hours in primates versus minutes for aniracetam). IDRA-21 lacks the clinical validation (registered indication, human safety data) that aniracetam possesses. The two compounds share the AMPA receptor desensitization-modulatory mechanism but differ in potency, duration, and clinical development status.

12.2 CX516 (Ampalex)

Mechanism: Benzamide-type positive allosteric modulator of AMPA receptors. Low-impact (type I) modulator that primarily slows receptor deactivation. Developed by Cortex Pharmaceuticals (later RespireRx Pharmaceuticals) [15, 16].

Development trajectory: Advanced through Phase 2 clinical trials in schizophrenia cognitive impairment and Alzheimer's disease. The Goff et al. (2001) randomized controlled trial in 19 schizophrenia patients receiving clozapine reported improvement on a brief cognitive battery at 900 mg three times daily for 4 weeks, but the Goff et al. (2008) larger trial (105 patients) of adjunctive CX516 at 900 mg three times daily with atypical antipsychotics showed no significant cognitive benefit [15, 16]. Development was deprioritized following the negative Phase 2 results.

Novelty: Low. First-generation ampakine with well-characterized pharmacology and structural biology.

Effect size: Small to absent. Phase 2 cognitive trials produced inconsistent results. The compound has low potency relative to second-generation modulators and a very short half-life (approximately 15 minutes in humans), limiting the achievable receptor occupancy.

Promising potential: Low. Development is essentially discontinued. The compound serves as a reference first-generation ampakine in the research literature.

Side-effect profile: Generally well tolerated at studied doses. No serious adverse events reported. The short half-life and low potency limit both efficacy and toxicity.

Overall validation: Low to moderate. The compound advanced through Phase 2 but produced negative efficacy results. The clinical pharmacology literature is substantial.

Comparison to IDRA-21: IDRA-21 is substantially more potent than CX516 in pre-clinical cognitive models and has a much longer duration of effect. CX516 has the advantage of human clinical data (though negative), providing pharmacokinetic and tolerability information that IDRA-21 lacks entirely. The clinical failure of CX516 has been attributed in part to insufficient potency and duration rather than to a failure of the AMPA receptor modulation mechanism.

12.3 CX614

Mechanism: Conformationally rigid tetracyclic benzoxazinone positive allosteric modulator of AMPA receptors. Developed by Cortex Pharmaceuticals as a second-generation ampakine with improved potency and metabolic stability relative to CX516 [14, 17].

Development trajectory: Extensively characterized in preclinical studies. CX614 is approximately 50-fold more potent than CX516 and has improved oral bioavailability. Published preclinical data include enhancement of long-term potentiation in hippocampal slices, improvement of cognitive performance in rodent models, and upregulation of brain-derived neurotrophic factor expression. The compound has not been advanced to human clinical trials in published form.

Novelty: Moderate. The rigid benzoxazinone scaffold represents a second-generation medicinal chemistry approach to the ampakine class with improved drug-like properties.

Effect size: Substantial in preclinical models. Effect sizes in hippocampal slice long-term potentiation and rodent cognitive paradigms are consistently larger than CX516.

Promising potential: Low to moderate. The compound remains a preclinical research tool without published human clinical data.

Side-effect profile: Preclinical only. Higher potency relative to CX516 raises theoretical concerns about excitotoxicity at higher doses, though no neurotoxicity has been reported at behaviorally active doses in published studies.

Overall validation: Low to moderate. Extensive preclinical characterization but no clinical validation.

Comparison to IDRA-21: CX614 and IDRA-21 are both second-generation AMPA receptor modulators with improved potency relative to first-generation compounds (aniracetam, CX516). IDRA-21 has the advantage of primate behavioral data (patas monkeys, rhesus monkeys, macaques) that CX614 lacks in published form. Both compounds lack human clinical data. IDRA-21 has been characterized as a partial modulator with demonstrated absence of neurotoxicity, a safety feature that has not been as explicitly demonstrated for CX614.

12.4 Sunifiram (DM-235)

Mechanism: Piperazine-derived AMPA receptor positive allosteric modulator. Acts at a binding site distinct from the cyclothiazide/benzothiadiazine site, occupying the more superficial subsites of the AMPA receptor dimer interface. Also reported to enhance NMDA receptor-mediated currents through protein kinase C activation and to increase acetylcholine release in the prefrontal cortex [18, 19].

Development trajectory: Developed at the University of Firenze. Preclinical characterization in rodent cognitive models has shown cognitive enhancement at doses of 0.001 to 1 mg/kg, making it one of the most potent nootropic compounds in the literature on a weight basis. The compound has not been advanced to formal human clinical trials. It has appeared on the unregulated nootropic market, raising concerns about safety and misuse [19].

Novelty: Moderate. The piperazine scaffold and the protein kinase C-dependent mechanism of NMDA receptor potentiation distinguish sunifiram from the benzothiadiazine and benzamide AMPA modulator classes.

Effect size: Substantial in rodent models at very low doses. The extremely high potency raises both efficacy and safety questions.

Promising potential: Low. No formal clinical development. Unregulated market presence without quality control or safety monitoring.

Side-effect profile: Limited formal safety data. The very high potency and the combined AMPA/NMDA receptor potentiation through protein kinase C create theoretical excitotoxicity concerns that have not been adequately addressed in published studies.

Overall validation: Low. Preclinical data only, with no formal toxicology or clinical development.

Comparison to IDRA-21: Sunifiram is more potent than IDRA-21 on a weight basis in rodent models. IDRA-21 has the advantage of explicit safety characterization (partial modulator mechanism, demonstrated absence of neurotoxicity at pharmacologically active doses, primate behavioral data). The lack of safety characterization for sunifiram, combined with its appearance on the unregulated market, makes it a less well-validated research tool than IDRA-21.

12.5 Piracetam

Mechanism: Weak positive allosteric modulator of AMPA receptors, binding at the superficial B/B' subsites of the AMPA receptor dimer interface rather than the deep C/C' subsites occupied by cyclothiazide and the benzothiadiazines [20]. Also modulates membrane fluidity and has weak effects on multiple neurotransmitter systems. Classified as a nootropic with a very broad and weak pharmacological profile.

Development trajectory: Developed by UCB Pharma in the 1960s. The oldest compound in the racetam class. Approved as a medicine for cognitive impairment in multiple European and Asian jurisdictions. Not approved in the United States. Decades of clinical use and an extensive safety database.

Novelty: Low. The oldest nootropic compound in clinical use.

Effect size: Small. Clinical trials in various cognitive impairment populations have shown modest and inconsistent benefits. The compound has very low potency at the AMPA receptor.

Promising potential: Low. The compound is well established but has not demonstrated robust efficacy in modern randomized controlled trials.

Side-effect profile: Excellent. Decades of clinical use have established piracetam as one of the safest compounds in clinical pharmacology. Adverse events are rare and mild (headache, gastrointestinal discomfort, insomnia).

Overall validation: Moderate. Extensive clinical use and safety database. Modest efficacy limits clinical enthusiasm.

Comparison to IDRA-21: IDRA-21 is orders of magnitude more potent than piracetam at the AMPA receptor and produces substantially larger cognitive effects in preclinical models. Piracetam has the advantage of decades of human clinical use and an unmatched safety database. The two compounds occupy opposite ends of the potency-safety spectrum within the AMPA receptor modulator class: piracetam is safe and weak; IDRA-21 is potent and preclinically characterized but clinically untested.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the AMPA receptor positive modulator pharmacology space. **Aniracetam** is the historical reference compound with clinical registration in selected jurisdictions, moderate efficacy, and short duration of action. **CX516** represents the first clinical development attempt for an ampakine in cognitive impairment and failed at Phase 2 due to insufficient potency and duration. **CX614** is a more potent second-generation preclinical tool compound without clinical data. **Sunifiram** is the most potent comparator on a weight basis but lacks formal safety characterization and has appeared on unregulated markets. **Piracetam** is the oldest and safest comparator with the weakest efficacy at the AMPA receptor.

IDRA-21 occupies a distinctive position in this landscape. It is the only compound with explicit characterization as a partial modulator with demonstrated absence of neurotoxicity at pharmacologically active concentrations, the only compound with behavioral data in three primate species (patas monkeys, rhesus monkeys, macaques), and the compound with the longest documented duration of cognitive enhancement in primates (48 hours after a single dose). Its principal limitation is the complete absence of human clinical data, a limitation shared with CX614 and sunifiram but not with aniracetam, CX516, or piracetam.

The practical question for investigators is whether the potency, duration, partial-modulator safety profile, and primate evidence base of IDRA-21 outweigh the absence of human data and the discontinued commercial development. For preclinical AMPA receptor pharmacology research, IDRA-21 is among the best-character-

ized tool compounds available. For any consideration of human translation, the complete absence of Phase 1 data represents a fundamental gap that would need to be addressed before clinical application.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. IDRA-21 is not approved by any regulatory authority for therapeutic use in any jurisdiction. No human clinical trials have been conducted. The compound is available as a research-grade chemical only; investigators should obtain analytical confirmation of identity and purity on every lot.