

RESEARCH MONOGRAPH . COMPOUND PROFILE

Chlodantane

An adamantane-derived para-chlorobenzamide developed at the Zakusov State Institute of Pharmacology as a rapid-onset synthetic adaptogen, distinguished from bromantane by a benzoyl (rather than amine) linkage, broader adaptogenic activity spectrum, and more pronounced immunostimulant properties in preclinical models.

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ABSTRACT

Chlodantane (ADK-910), the para-chlorobenzoyl amide of 2-aminoadamantane, is an experimental actoprotector and synthetic adaptogen developed at the Zakusov State Institute of Pharmacology of the Russian Academy of Medical Sciences during an extensive structure-activity campaign that screened 329 novel adamantane derivatives for resistance-enhancing properties in rodent stress models [1, 2]. The compound emerged alongside bromantane (N-(2-adamantyl)-N-(para-bromophenyl)amine) as one of two lead adamantane-derived actoprotectors from the Morozov laboratory program; however, whereas bromantane proceeded to clinical registration in Russia as Ladasten for the treatment of neurasthenia, chlodantane was never advanced to human studies and remains an exclusively preclinical research compound.

Structurally, chlodantane differs from bromantane in the nature of the bond connecting the adamantane cage to the halogenated aromatic ring. Bromantane is a secondary amine (N-(2-adamantyl)-N-(4-bromophenyl)amine), whereas chlodantane is an amide (N-(2-adamantyl)-4-chlorobenzamide), a distinction that alters conformational flexibility, hydrogen-bonding capacity, metabolic susceptibility, and physicochemical behavior [1]. The chlorine-for-bromine halogen substitution is a secondary modification. These combined structural differences produce a pharmacological profile that the primary literature describes as exhibiting a broader adaptogenic activity spectrum than bromantane, with efficacy against hypoxia, hypothermia, hyperthermia, toxic chemical exposure, and other extreme

environmental stressors observable after a single administration, a property not characteristic of classical plant-derived adaptogens that typically require repeated dosing over days to weeks [2, 3].

The mechanism of action has not been fully elucidated. The available evidence, derived entirely from animal and cell-culture experiments, points to membrane stabilization as a principal contributor. Chlodantane increases the stability of cell membranes against unfavorable conditions, achieved in part through suppression of overactivated lipid peroxidation (LPO) processes [2, 3]. The adamantane cage, a rigid tricyclo[3.3.1.1(3,7)]decane skeleton with high lipophilicity, partitions into lipid bilayers and interacts with the polar headgroup region of phospholipid membranes, a property shared across the broader adamantane pharmacological class and formally characterized in molecular dynamics simulations of amantadine and memantine in model bilayers [4, 5]. The immunostimulant activity of chlodantane is reported to be more pronounced than that of bromantane, with efficacy in secondary stress-induced immunodeficiency models, though the molecular targets mediating this effect have not been identified [1, 2].

No human pharmacokinetic, efficacy, or safety data exist for chlodantane. The pharmacokinetic profile is inferred from the structurally related bromantane, which displays moderate oral bioavailability (approximately 42 percent), a plasma elimination half-life of approximately 11 hours, hepatic hydroxylation of the adamantane ring as the principal metabolic pathway, and wide tissue distribution driven by the lipophilicity of the adamantane core [6, 7]. Whether the amide bond in chlodantane introduces additional metabolic liabilities (amide hydrolysis, different ring-hydroxylation regioselectivity) relative to the amine bond in

bromantane has not been characterized. The compound is not approved for medical use in any jurisdiction and is not listed on any national pharmacopoeia. It is available as a research-grade preparation from limited specialty chemical suppliers at purities stated as greater than 98 percent. Investigators should obtain independent analytical confirmation of identity, purity, and stereochemical composition on every lot. This monograph reviews the chemistry, synthesis, and structural pharmacology of chlodantane; the available preclinical evidence for adaptogenic, actoprotective, antioxidant, and immunostimulant activity; the inferred pharmacokinetics; sourcing and quality considerations; and a comparative assessment of five actoprotector and adaptogenic candidates against chlodantane on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Proposed International Nonproprietary Name: None assigned. Chlodantane is the conventional transliteration from the Russian-language literature and is used consistently in English-language secondary sources.

Alternative transliterations and synonyms: Chlodantan (alternate transliteration); ADK-910 (development code from the Zakusov State Institute of Pharmacology); N-(2-adamantyl)-4-chlorobenzamide; N-(adamantan-2-yl)-4-chlorobenzamide; 2-(para-chlorobenzoylamino)adamantane; N-(2-adamantyl)-N-(para-chlorobenzoyl)amine.

Chemical Abstracts Service registry number: 185384-80-9.

PubChem Compound Identifier: 959689.

ChemSpider Identifier: 832832.

International Union of Pure and Applied Chemistry name: N-(adamantan-2-yl)-4-chlorobenzamide. The compound is the para-chlorobenzoyl amide of 2-aminoadamantane, placing the carbonyl of the amide bond between the adamantane nitrogen and the chlorophenyl ring.

1.2 Structural class and chemistry

Chlodantane is an adamantane derivative belonging to the N-acyladamantylamine structural subclass. The adamantane cage (tricyclo[3.3.1.1(3,7)]decane) provides a rigid, highly symmetric, and lipophilic hydrocarbon framework that is shared with several approved pharmaceutical agents including amantadine (Symmetrel; antiviral and antiparkinsonian), memantine (Namenda; NMDA receptor antagonist for Alzheimer's disease), rimantadine (Flumadine; antiviral), and vildagliptin (Galvus; DPP-4 inhibitor) [5, 8]. The adamantane scaffold confers high metabolic stability relative to open-chain alkylamines, favorable membrane partitioning, and resistance to acid-catalyzed degradation.

Molecular formula: C₁₇H₂₀ClNO.

Exact mass: 289.1233 g/mol (monoisotopic).

Molecular weight: 289.80 g/mol.

Canonical SMILES: C1C2CC3CC1CC(C2)C3NC(=O)C4=CC=C(C=C4)Cl.

Physical properties: White to off-white crystalline powder. Expected to be sparingly soluble in water owing to the high lipophilicity of the adamantane cage and the absence of ionizable groups at physiological pH (the amide nitrogen is non-basic). Soluble in dimethyl sulfoxide, methanol, and ethanol. Melting point has not been reported in the peer-reviewed literature. The compound is not classified as hazardous under Regulation (EC) No. 1272/2008 (CLP) per available vendor safety data.

Stereochemistry: The adamantane cage in chlodantane does not contain a classical stereocenter when substituted at the 2-position with a single substituent; the compound is achiral and is supplied as a single constitutional isomer. Investigators should confirm structural identity rather than enantiomeric purity, which is not applicable.

Structural comparison to bromantane: Bromantane (N-(2-adamantyl)-N-(4-bromophenyl)amine; CAS 87913-26-6; molecular formula $C_{16}H_{20}BrN$; molecular weight 306.25 g/mol) differs from chlodantane in two structural features. First, the linker between the adamantane nitrogen and the aromatic ring is a secondary amine in bromantane versus an amide (with an intervening carbonyl) in chlodantane. Second, the halogen substituent is bromine at the para position in bromantane versus chlorine in chlodantane. The amine-to-amide modification reduces conformational flexibility, introduces a hydrogen-bond acceptor (the carbonyl oxygen), and alters metabolic susceptibility by replacing a metabolically stable C-N amine bond with a potentially hydrolyzable amide bond [1, 9].

1.3 Synthesis

The synthesis of chlodantane has not been described in detail in the English-language peer-reviewed literature. The compound is a straightforward amide formed between 2-aminoadamantane and 4-chlorobenzoyl chloride, and the synthesis is expected to proceed by standard acylation chemistry. A representative route would involve: (a) preparation or procurement of 2-aminoadamantane hydrochloride (commercially available); (b) generation of the free base by treatment with aqueous sodium hydroxide or triethylamine; (c) acylation with 4-chlorobenzoyl chloride in

an inert solvent (dichloromethane, tetrahydrofuran, or toluene) in the presence of a base (triethylamine, pyridine, or N,N-diisopropylethylamine) to scavenge the liberated hydrogen chloride; and (d) purification by column chromatography, recrystallization from ethanol or ethyl acetate, or both. The product is characterized by nuclear magnetic resonance spectroscopy (^1H and ^{13}C), mass spectrometry, infrared spectroscopy (amide carbonyl stretch near 1640 cm^{-1}), and melting point determination. Yields for analogous adamantyl benzamide syntheses are typically 70 to 90 percent. An alternative approach using carbodiimide-mediated coupling of 2-aminoadamantane with 4-chlorobenzoic acid (with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and 4-dimethylaminopyridine catalysis) is equally feasible and avoids the handling of acyl chlorides.

The Morozov laboratory at the Zakusov Institute synthesized 329 adamantane derivatives in the systematic screening program that identified chlodontane and bromantane as lead compounds [1]. The specific synthetic routes, purification protocols, and analytical characterization data for chlodontane from this program were published in Russian-language journals and are not readily accessible in Western databases.

2. Abstract

Chlodantane (ADK-910) is an adamantane-derived synthetic adaptogen and actoprotector developed at the Zakusov State Institute of Pharmacology of the Russian Academy of Medical Sciences as part of a systematic program to identify compounds that enhance organism resistance to extreme environmental stressors [1, 2]. The compound is the para-chlorobenzamide of 2-aminoadamantane and is structurally related to bromantane (the para-bromophenylamino analog), which achieved clinical registration in Russia for the treatment of neurasthenia. Chlodantane itself was never advanced to human clinical trials and remains an exclusively preclinical research compound.

The pharmacological profile of chlodantane, derived entirely from animal and cell-culture experiments, is characterized by three principal properties. First, adaptogenic activity with a broader spectrum than bromantane: chlodantane protects animals against hypoxia, hypothermia, hyperthermia, toxic chemical exposure, and other extreme stressors, with effect observable after a single administration [2, 3]. Second, membrane-stabilizing and antioxidant activity: the compound increases the stability of cell membranes by suppressing overactivated lipid peroxidation (LPO), a mechanism consistent with the known interaction of adamantane derivatives with the polar headgroup region of phospholipid bilayers [4, 5]. Third, immunostimulant activity: chlodantane produces immunostimulation in secondary stress-induced immunodeficiency models, with potency reported to exceed that of bromantane [1, 2].

The mechanism of action has not been characterized at the molecular target level. Unlike bromantane, for which upregulation of tyrosine hydroxylase and aromatic L-amino acid decarboxylase in the dopamine biosynthesis pathway has been demonstrated [6, 10], no equivalent receptor-level or enzyme-level mechanism has been identified for chlodantane. The available mechanistic data are limited to the membrane stabilization and LPO suppression observations. Whether chlodantane shares the dopaminergic genomic mechanism of bromantane, or whether the amide-for-amine structural modification produces a qualitatively different pharmacological mechanism, is unknown.

No human pharmacokinetic, efficacy, or safety data exist. The compound is not approved for medical use in any jurisdiction. It is available from limited specialty chemical suppliers as a research-grade preparation. All data presented in this monograph are derived from animal experiments, cell-culture studies, and structural inference from the broader adamantane pharmacological class.

3. Discovery and Development History

3.1 Origin

Chlodantane was synthesized at the Zakusov State Institute of Pharmacology (also known as the V.V. Zakusov Research Institute of Pharmacology) of the Russian Academy of Medical Sciences in Moscow as part of a large-scale structure-activity screening program directed by I.S. Morozov and colleagues during the 1980s and 1990s [1]. The program was motivated by military and occupational interest in pharmacological agents that could enhance the physical and psychological resilience of personnel operating under extreme environmental conditions (high altitude, extreme temperature, chemical exposure, sustained physical exertion) without the exhaustive consequences of classical psychostimulants such as amphetamines [2, 3].

The screening program synthesized and evaluated 329 novel adamantane derivatives for their effects on animal resistance to extreme stressors [1]. The adamantane scaffold was selected as the core structural motif on the basis of prior evidence that adamantane derivatives (amantadine, rimantadine) exhibited neurotropic and membrane-active properties, and on the observation that the rigid, lipophilic cage structure conferred favorable pharmacokinetic characteristics including oral bioavailability, metabolic stability, and central nervous system penetration [5, 8].

3.2 Identification of lead compounds

Two compounds emerged from the 329-compound screen as principal leads. Bromantane (N-(2-adamantyl)-N-(4-bromophenyl)amine) was identified as possessing low toxicity, high capacity to enhance physical and operant working maintenance in animals, and the ability to accelerate recovery from fatigue, hyperthermia, and hypoxia [1]. Chlodantane (N-(2-adamantyl)-4-chlorobenzamide; ADK-910) was identified as possessing the properties of a rapid-action adaptogenic agent with the capacity to enhance the resistance of animals to various physical and toxic chemical stressors [1, 2].

The Morozov et al. (1999) publication in the *Vestnik Rossiiskoi Akademii Meditsinskikh Nauk* (Bulletin of the Russian Academy of Medical Sciences) and the Morozov, Ivanova, and Lukicheva (2001) review in *Pharmaceutical Chemistry Journal* are the principal English-accessible primary sources describing the pharmacological characterization of both compounds [1, 2].

3.3 Divergent development trajectories

Bromantane was advanced through preclinical safety studies and clinical trials in Russia during the late 1990s and 2000s, culminating in registration as Ladasten (approximately 2009) for the treatment of neurasthenia at oral doses of 50 to 100 mg daily [6, 7]. The clinical program enrolled 728 patients in a 28-day treatment study and reported a Clinical Global Impression-Improvement (CGI-I) responder rate of 90.8 percent, with adverse events in only 3 percent of patients and discontinuation due to adverse events in 0.8 percent [6]. Bromantane was placed on the World Anti-Doping Agency prohibited list in 1997 following detection in Russian athletes at the 1996 Summer Olympics [6].

Chlodantane was not advanced beyond preclinical evaluation. The reasons for the decision to advance bromantane rather than chlodantane are not documented in the English-language literature. Plausible factors include the actoprotective (physical performance-enhancing) activity profile of bromantane being more directly aligned with the primary military and sports-medicine application targets; the subsequent identification of bromantane's dopaminergic genomic mechanism, which provided a clear neuropharmacological rationale for clinical development in neurasthenia; and possibly superior tolerability, pharmacokinetic, or manufacturing characteristics in bromantane. Chlodantane's characterization as an adaptogen "of the estrogen activity type" in the primary literature [2] suggests a pharmacological profile that may have been considered less therapeutically defined for conventional drug registration.

3.4 Current status

Chlodantane is not approved for medical use in any jurisdiction. It has not been studied in humans. It is not listed on any national pharmacopoeia. The compound is available as a research-grade preparation from a small number of specialty chemical suppliers (Zion Pharma, SYNTHETIKA, and others) at stated purities of greater than 98 percent [11, 12]. The compound is sold for laboratory research pur-

poses only and is explicitly not intended for human consumption per vendor documentation. No investigator-initiated clinical trials have been registered for chlordanthane in ClinicalTrials.gov or equivalent registries as of the date of this monograph.

4. Mechanism of Action

The mechanism of action of chlodontane has not been elucidated at the molecular target level. The available evidence is limited to functional observations in animal and cell-culture systems, supplemented by structural inference from the broader adamantane derivative pharmacological class. The following subsections review the characterized and inferred mechanisms.

4.1 Membrane stabilization and lipid peroxidation suppression

The principal characterized mechanism of chlodontane is stabilization of cell membranes against unfavorable conditions, achieved through suppression of overactivated lipid peroxidation (LPO) processes [2, 3]. Lipid peroxidation is a free-radical chain reaction that degrades polyunsaturated fatty acids in cell membrane phospholipids, producing malondialdehyde, 4-hydroxynonenal, and other reactive aldehyde products that compromise membrane integrity, alter membrane fluidity, and activate inflammatory signaling cascades. Under extreme physiological stress (hypoxia, hyperthermia, toxic chemical exposure), LPO is accelerated by increased production of reactive oxygen species from mitochondrial electron transport chain dysfunction, xanthine oxidase activation, and NADPH oxidase activity.

Chlodontane decreases the rate of stress-induced LPO in animal tissues [2, 3]. The molecular mechanism of this antioxidant activity has not been specified. Two non-exclusive mechanisms are plausible based on the adamantane pharmacology literature. First, direct membrane interaction: adamantane derivatives partition into lipid bilayers and localize in the polar headgroup region of phospholipid membranes, as demonstrated by molecular dynamics simulations of amantadine in dipalmitoylphosphatidylcholine (DPPC) bilayers [4]. This localization disrupts the intramolecular interactions between choline and carbonyl groups in phospholipids, altering membrane packing and fluidity. A compound positioned in the headgroup region could sterically impede the propagation of lipid peroxyl radical chain reactions across the bilayer surface. Second, indirect antioxidant enzyme induction: the structurally related actoprotector bemetil (2-ethylbenzimidazole hydrobromide) exerts its antioxidant activity through induction of protein synthesis, including up-

regulation of superoxide dismutase, catalase, and glutathione metabolism enzymes [3, 13]. Whether chlodantane shares this indirect enzyme-induction mechanism is unknown.

4.2 Immunostimulant activity

Chlodantane produces immunostimulation in animal models of secondary stress-induced immunodeficiency, with potency reported to exceed that of bromantane [1, 2]. The mechanism of the immunostimulant activity has not been characterized at the receptor or signaling-pathway level. The primary literature describes the mechanism as "membranous protective activity," suggesting that membrane stabilization in immune cells preserves receptor function, signaling competence, and proliferative capacity under stress conditions [1].

Bromantane similarly exhibits immunostimulant activity and has been characterized as a potential immunomodulator through indirect dopaminergic mechanisms (dopamine receptors are expressed on T cells, B cells, natural killer cells, and macrophages, and dopaminergic signaling modulates immune cell proliferation, cytokine production, and antibody secretion) [6]. Whether chlodantane shares this dopaminergic immunomodulatory pathway or operates through an independent mechanism (membrane stabilization in immune cells, direct interaction with immune cell surface receptors, modulation of stress-hormone-mediated immunosuppression) is unknown.

4.3 Adaptogenic activity and the actoprotector classification

Actoprotectors are defined as compounds that enhance body stability against physical loads without increasing oxygen consumption or heat production [3]. The actoprotector mechanism is distinguished from classical stimulant activity (amphetamines, caffeine, modafinil) by the absence of direct sympathomimetic activation, the absence of post-use exhaustion, and the preservation or reduction of physiological cost (oxygen consumption, body temperature, heart rate) during exertion [3, 14].

Chlodantane is classified as an actoprotector on the basis of its capacity to enhance animal survival and functional performance under extreme stressor paradigms (forced swimming to exhaustion, hypoxic chamber exposure, hypothermic

and hyperthermic challenge, toxic chemical exposure) [1, 2]. The effect is observable after a single administration, distinguishing chlodontane from classical plant-derived adaptogens (*Rhodiola rosea*, *Eleutherococcus senticosus*, *Panax ginseng*) that typically require multi-day loading to produce measurable effects [2, 3].

The designation of chlodontane as an adaptogen "of the estrogen activity type" in the Morozov and Ivanova (2001) review [2] is cryptic and has not been elaborated in subsequent literature. One interpretation is that the pharmacological profile of chlodontane includes membrane-protective, antioxidant, and immunomodulatory properties that overlap with the non-reproductive protective actions attributed to estrogen in certain stress models (estrogen stabilizes membranes, suppresses lipid peroxidation, and modulates immune function through estrogen receptor-independent and receptor-dependent mechanisms). Whether chlodontane interacts with estrogen receptors or estrogen-responsive signaling pathways has not been investigated.

4.4 Potential dopaminergic activity

Bromantane enhances dopamine synthesis through indirect genomic mechanisms: upregulation of tyrosine hydroxylase (TH) and aromatic L-amino acid decarboxylase (AAAD) expression, producing a 2- to 2.5-fold increase in TH expression in the rat hypothalamus 1.5 to 2 hours after administration [6, 10]. This dopaminergic mechanism is the molecular basis for bromantane's psychoactivating and anti-asthenic clinical effects and distinguishes it from direct stimulants that act on the dopamine transporter.

Whether chlodontane shares this dopaminergic genomic mechanism is unknown. The amide-for-amine structural modification in chlodontane alters the electronic properties, hydrogen-bonding capacity, and conformational flexibility of the linker region, which could affect binding to the putative intracellular receptor or signaling cascade that mediates bromantane's TH induction. The broader adaptogenic profile of chlodontane (protective against hypoxia, temperature extremes, and chemical toxins) extends beyond what would be predicted from dopaminergic enhancement alone, suggesting that additional mechanisms (membrane stabilization, antioxidant activity) contribute substantially to the observed pharmacology.

4.5 Composite pharmacology

The composite pharmacology of chlodantane is therefore: (a) membrane stabilization through direct interaction of the lipophilic adamantane cage with phospholipid bilayers; (b) antioxidant activity through suppression of lipid peroxidation, by a mechanism that may include both direct radical-chain interruption and indirect antioxidant enzyme induction; (c) immunostimulation in stress-induced immunodeficiency, possibly through membrane protection in immune cells; and (d) potential but uncharacterized effects on monoamine biosynthesis or other neurotransmitter systems. The relative contribution of each mechanism to the observed adaptogenic and actoprotective activity *in vivo* has not been determined.

5. Pharmacokinetics and Routes of Administration

5.1 General considerations

No pharmacokinetic data exist for chlodantane in any species. The following discussion is based entirely on structural inference from the pharmacokinetic profiles of bromantane and other adamantane derivatives (amantadine, memantine, rimantadine), which share the adamantane cage and display broadly similar absorption, distribution, metabolism, and elimination characteristics scaled for their respective molecular properties.

5.2 Predicted absorption

Chlodantane is expected to be absorbed from the gastrointestinal tract after oral administration. The adamantane cage confers lipophilicity (estimated LogP greater than 3), and the molecular weight (289.80 g/mol) is well within the range for passive transcellular absorption. The amide bond introduces a hydrogen-bond donor (N-H) and acceptor (C=O) that modestly reduce lipophilicity relative to the secondary amine in bromantane, potentially improving aqueous solubility at the cost of marginally lower membrane permeability. Bromantane displays a T_{max} of approximately 2.75 to 4 hours and oral bioavailability of approximately 42 percent in humans [6, 7]. Chlodantane is expected to show broadly similar absorption kinetics, though the bioavailability may differ depending on the extent of first-pass amide hydrolysis and ring hydroxylation.

5.3 Predicted distribution

The high lipophilicity of the adamantane cage predicts substantial volume of distribution, with tissue accumulation in brain lipids and adipose tissue, consistent with bromantane pharmacokinetics [6]. The compound is expected to cross the blood-brain barrier, as do all studied adamantane derivatives with molecular weight below 400 g/mol. Plasma protein binding has not been characterized but is expected to be moderate to high based on lipophilicity.

5.4 Predicted metabolism

Two principal metabolic pathways are expected. First, hydroxylation of the adamantane ring by hepatic cytochrome P450 enzymes, producing hydroxylated metabolites that are subsequently glucuronidated and excreted renally. This is the dominant metabolic pathway for bromantane (producing 6-beta-hydroxybromantane), amantadine, and memantine [6, 7, 8]. Second, hydrolysis of the amide bond by hepatic amidases or carboxylesterases, which would release 2-aminoadamantane and 4-chlorobenzoic acid. Amide hydrolysis is a metabolic pathway not available to bromantane (which contains an amine bond resistant to hydrolysis); this represents a potentially significant pharmacokinetic difference between the two compounds and could result in lower systemic exposure, shorter half-life, or a different metabolite profile for chlodantane relative to bromantane. Bromantane has a human plasma elimination half-life of approximately 11 hours [6]; chlodantane's half-life is unknown and could be shorter if amide hydrolysis is a significant metabolic pathway, or similar if ring hydroxylation dominates.

5.5 Predicted elimination

Renal excretion of hydroxylated and glucuronidated metabolites is the expected principal elimination pathway, consistent with the broader adamantane class. Biliary excretion may contribute a minor fraction. The high lipophilicity of the parent compound disfavors direct renal clearance of unchanged drug.

5.6 Routes of administration

The only route of administration described in the available literature (vendor documentation) is oral, at a reported research dose of approximately 50 mg once daily [11]. Sublingual administration has also been mentioned in informal user reports [11]. No intravenous, intramuscular, or subcutaneous formulations have been described. The compound's limited aqueous solubility would require solubilization in dimethyl sulfoxide or cyclodextrin-based vehicles for parenteral research applications.

6. Preclinical Pharmacology

6.1 Adaptogenic activity in acute stressor models

The Morozov laboratory characterized chlodontane in multiple acute stressor paradigms in rodents [1, 2]. The compound enhanced animal survival and functional performance under the following conditions:

Hypoxia: Animals treated with chlodontane demonstrated increased survival time under conditions of normobaric or hypobaric hypoxia compared to untreated controls. The adaptogenic effect against hypoxia was observable after a single administration, contrasting with plant-derived adaptogens that require multi-day loading [2, 3].

Hypothermia and hyperthermia: Chlodontane protected animals against both low and high temperature extremes, maintaining core body temperature homeostasis and extending survival time under forced exposure conditions [2].

Toxic chemical exposure: Chlodontane enhanced resistance to various toxic chemical stressors, though the specific toxicants, doses, and effect magnitudes have not been described in the English-language literature [1, 2].

Physical exhaustion: As an actoprotector, chlodontane enhanced physical working capacity in forced swimming and related endurance paradigms, though quantitative data on swimming time extension, weight-loaded swimming, or treadmill performance are not available in English-language publications [1, 3].

6.2 Comparison to bromantane in preclinical models

The primary literature consistently characterizes chlodontane as having a broader activity spectrum than bromantane [2, 3]. Bromantane was characterized principally for its actoprotective properties (enhancement of physical and operant working capacity, acceleration of recovery from fatigue) and its dopaminergic mechanism [6, 10]. Chlodontane extended the activity profile to include protective efficacy against a wider range of environmental stressors (hypoxia, temperature extremes, toxic chemicals) and more pronounced immunostimulant activity [1, 2]. The

broader activity spectrum is consistent with a mechanism that includes membrane stabilization and antioxidant activity (which protect against a general range of stressors) in addition to any neurotransmitter-specific effects.

6.3 Immunostimulant activity

Chlodantane produced immunostimulation in models of secondary stress-induced immunodeficiency, with the immunostimulant potency exceeding that of bromantane [1, 2]. The specific immunological endpoints (T-cell proliferation, antibody titers, natural killer cell activity, cytokine production, phagocytic index) and the specific stress models (restraint stress, forced swimming, cold exposure) used to characterize this activity have not been detailed in accessible publications. The mechanism was described as "membranous protective activity," suggesting that membrane stabilization in immune cells preserves immunocompetence under stress conditions [1].

6.4 Lipid peroxidation suppression

Chlodantane decreased the rate of stress-induced lipid peroxidation in animal tissues [2, 3]. The specific biomarkers measured (malondialdehyde, thiobarbituric acid reactive substances, 4-hydroxynonenal, isoprostanes), the tissues assayed, and the dose-response relationships have not been reported in accessible publications. The antioxidant activity is consistent with the membrane-stabilizing mechanism and with the broader literature on adamantane derivative interactions with phospholipid bilayers [4, 5].

6.5 Toxicity

Formal toxicology data for chlodantane are not available in the English-language literature. Bromantane, the structurally closest characterized analog, displays low toxicity: the LD50 in rodents is high (specific values vary by route and species), adverse events in the 728-patient clinical program were reported at only 3 percent, and the compound produced no serious adverse events at registered doses of 50 to 100 mg daily [6]. The toxicity profile of chlodantane is expected to be broadly similar based on structural analogy, but this inference has not been validated experimentally.

7. Clinical Evidence Base

No clinical evidence exists for chlodantane. The compound has not been administered to humans in any context (healthy volunteer pharmacokinetic studies, Phase 1 safety studies, Phase 2 or Phase 3 efficacy trials, compassionate use, or off-label administration). All pharmacological data are derived from animal and cell-culture experiments conducted at the Zakusov State Institute of Pharmacology and reported in Russian-language publications with limited English-language review coverage [1, 2, 3].

The absence of clinical data represents the principal limitation of chlodantane as a research compound. The structurally related bromantane has produced a modest but clinically meaningful evidence base (728-patient neurasthenia trial, 90.8 percent CGI-I responder rate, 3 percent adverse-event rate) [6], providing proof-of-concept that the adamantane-derived actoprotector class can produce clinically measurable effects at tolerable doses. Whether the broader adaptogenic activity spectrum and enhanced immunostimulant potency of chlodantane relative to bromantane would translate to clinically relevant advantages in human subjects is entirely speculative in the absence of human data.

Investigators considering chlodantane for human research should note that: (a) no established human dose exists; (b) no human pharmacokinetic parameters have been determined; (c) no human safety profile has been established; (d) the reported research dose of 50 mg daily in vendor documentation [11] is not derived from human dose-finding studies and should not be interpreted as a validated starting dose for clinical investigation; and (e) the compound would require full preclinical toxicology, pharmacokinetic, and safety pharmacology characterization before any regulatory authority would authorize first-in-human administration.

8. Sourcing and Quality Verification

Chlodantane is not available as a pharmaceutical-grade preparation from any registered pharmaceutical manufacturer. No national pharmacopoeia includes a monograph for chlodantane. The compound is available exclusively as a research-grade preparation from a small number of specialty chemical suppliers.

Known suppliers (as of the date of this monograph): Zion Pharma (marketed as Chlodantan; powder formulation; 1 g and 5 g quantities; reported purity greater than 98 percent) [11]; SYNTHETIKA (powder formulation; Poland-based supplier) [12]. Availability is intermittent; both suppliers have reported stock-out periods. Additional suppliers may offer the compound under the ADK-910 development code or under the IUPAC name.

Pricing: Approximately 14 to 50 euros per gram at the time of monograph preparation, depending on supplier and quantity [11, 12]. The pricing is consistent with small-scale custom synthesis rather than industrial manufacturing.

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

- High-performance liquid chromatography area-percent purity (target: greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (289.12 +/- 0.01 for the protonated molecular ion [M+H]⁺ at m/z 290.13)
- Nuclear magnetic resonance spectroscopy (1H and 13C) for structural confirmation, with particular attention to the amide carbonyl carbon resonance (expected near 165 to 170 ppm in 13C NMR) and the adamantane ring proton multiplet pattern
- Infrared spectroscopy for the amide carbonyl stretch (expected near 1640 cm⁻¹) as a rapid identity confirmation
- Residual solvent analysis (gas chromatography of common synthesis solvents: dichloromethane, ethyl acetate, dimethylformamide)
- Karl Fischer or loss-on-drying analysis for residual water

Third-party analytical laboratories (Janoshik Analytical and others) provide independent confirmation of vendor certificates of analysis. The research-grade chlordantane market is very small and not well established; lot-to-lot variability is expected and on-receipt analytical confirmation is strongly recommended for any quantitative investigation.

9. Reconstitution and Handling

Chlodantane is supplied as a white to off-white crystalline powder. The compound is expected to be sparingly soluble in water owing to the lipophilic adamantane cage. For research applications, stock solutions are typically prepared in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM, with subsequent dilution into aqueous buffers or cell culture media to the desired working concentration. The final DMSO concentration in biological assays should be kept below 0.1 to 0.5 percent (v/v) to avoid solvent cytotoxicity.

For oral administration in animal studies, the compound can be suspended in aqueous vehicles containing carboxymethylcellulose (0.5 percent w/v) and polysorbate 80 (0.1 percent v/v), or dissolved in polyethylene glycol 400 or cyclodextrin-based formulations. Dissolution in corn oil or sesame oil is an alternative vehicle for lipophilic compounds in rodent oral gavage studies.

Storage of the solid should be at room temperature or at 2 to 8 degrees Celsius in a dry, sealed container protected from light. Stability of the solid under these conditions is expected to be at least 24 months based on the chemical stability of the adamantane scaffold and the amide bond, though formal stability studies have not been published.

DMSO stock solutions should be aliquoted for single-use and stored at -20 degrees Celsius. Freeze-thaw stability has not been characterized for chlodantane; limiting freeze-thaw cycles to fewer than 3 is prudent until stability data are available.

For sublingual administration in research contexts (as mentioned in informal user reports), the powder is placed under the tongue at the reported dose of approximately 50 mg [11]. This route has not been validated pharmacokinetically and mild oral irritation (headache, gum irritation) has been reported anecdotally [11].

10. Stack Interaction Considerations

The drug-drug interaction profile of chlodantane has not been characterized. The following considerations are based on structural inference from the adamantane derivative class and from the limited mechanistic information available.

Cytochrome P450 interactions: Bromantane induces hepatic CYP450 enzymes [6]. If chlodantane shares this CYP-inducing property, concurrent administration with CYP450 substrates (including many pharmaceutical agents) could alter the metabolism and plasma concentrations of co-administered drugs. Conversely, strong CYP inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin) could increase chlodantane exposure if ring hydroxylation by CYP enzymes is a significant metabolic pathway.

Other actoprotectors: Concurrent administration with bromantane, bemtil, or ethomorsol has not been studied. Additive or synergistic effects on membrane stabilization, antioxidant activity, or immunomodulation are plausible but uncharacterized. The combination is unlikely to produce pharmacokinetic interactions unless CYP induction by one agent affects the metabolism of the other.

Classical adaptogens: Concurrent administration with plant-derived adaptogens (*Rhodiola rosea*, *Eleutherococcus senticosus*, *Panax ginseng*, *Schisandra chinensis*) has not been studied. Mechanistic complementarity is plausible (plant adaptogens modulate the hypothalamic-pituitary-adrenal axis and heat shock protein expression, while chlodantane stabilizes membranes and suppresses lipid peroxidation), but no data exist to support or contradict additive benefit.

Stimulants: Bromantane potentiates amphetamine-induced stereotypies in animal models [6], suggesting pharmacodynamic interaction with dopaminergic stimulants. If chlodantane shares dopaminergic activity, caution is warranted with concurrent stimulant use (amphetamines, methylphenidate, modafinil, caffeine at high doses).

Antioxidants: Concurrent administration with exogenous antioxidants (N-acetylcysteine, alpha-lipoic acid, vitamin C, vitamin E) could produce additive antioxidant effects. Whether this additivity is beneficial or whether it could overshoot an-

tioxidant capacity and impair physiological redox signaling (which requires basal reactive oxygen species for normal cell function) is unknown.

Immunomodulators: Given the immunostimulant activity of chlodontane, concurrent administration with immunosuppressive agents (cyclosporine, tacrolimus, mycophenolate, corticosteroids) could produce opposing effects on immune function. Concurrent use with other immunostimulants could produce additive immunostimulation with unknown safety consequences.

Amidase substrates: If hepatic amide hydrolysis is a significant metabolic pathway for chlodontane, concurrent administration with other amidase substrates or inhibitors could alter chlodontane metabolism.

Investigators conducting research with chlodontane in combination with other compounds should approach all combinations as pharmacologically uncharacterized and should monitor for unexpected pharmacodynamic and pharmacokinetic interactions.

11. Adverse Events and Safety

11.1 Preclinical safety

Formal preclinical toxicology data for chlodantane are not available in the English-language literature. The compound is not classified as hazardous under Regulation (EC) No. 1272/2008 (CLP) per available vendor safety data [12], though this classification reflects the absence of submitted hazard data rather than the confirmation of safety.

11.2 Inferred safety from the adamantane class

The adamantane derivative class has a generally favorable safety profile at therapeutic doses. Amantadine (100 to 300 mg daily) produces insomnia, dizziness, nausea, and livedo reticularis as the principal dose-limiting adverse events. Memantine (5 to 20 mg daily) is well tolerated with headache, dizziness, and constipation as the principal adverse events. Bromantane (50 to 100 mg daily in the 728-patient neurostenia trial) produced adverse events in only 3 percent of patients, with no serious adverse events and discontinuation due to adverse events in only 0.8 percent [6]. The tolerability of the adamantane class at therapeutic doses is high, and this inference provides a preliminary (but unvalidated) expectation that chlodantane at comparable doses might be similarly tolerable.

11.3 Potential safety concerns

Several potential safety concerns can be identified on the basis of the pharmacological profile:

Amide hydrolysis products: If hepatic amidases cleave the chlodantane amide bond, the hydrolysis products are 2-aminoadamantane and 4-chlorobenzoic acid. 2-Aminoadamantane is pharmacologically active (it is structurally related to amantadine) and could produce independent neurological effects at sufficient concentrations. 4-Chlorobenzoic acid is a common industrial chemical with low acute toxicity but uncertain chronic safety at pharmacologically relevant exposures.

Immunostimulation: The enhanced immunostimulant activity of chlodontane relative to bromantane could be a liability in individuals with autoimmune conditions, chronic inflammatory states, or transplant immunosuppression regimens.

Unknown reproductive and developmental toxicity: No reproductive or developmental toxicity studies have been conducted.

Unknown genotoxicity and carcinogenicity: No genotoxicity (Ames test, micronucleus assay) or carcinogenicity studies have been reported.

11.4 Anecdotal reports

Informal user reports (from vendor product pages and online forums) describe mild headaches and gum irritation with sublingual administration as the most commonly mentioned adverse effects [11]. These reports are not systematically collected, are subject to reporting bias and placebo effects, and should not be interpreted as a safety profile.

11.5 Safety summary

The safety profile of chlodontane is unknown. No formal toxicology, safety pharmacology, or human safety data exist. Investigators should treat the compound as pharmacologically uncharacterized from a safety perspective, should conduct appropriate preclinical toxicology before any animal research program, and should recognize that the research dose reported in vendor documentation is not derived from dose-finding safety studies.

12. Comparative Assessment

This section presents a structured comparative assessment of five actoprotector, adaptogen, or adamantane-derived research compounds against chlodantane, evaluated against five competency standards: novelty, effect size, promising potential (current research and development state), side-effect profile (clinical or preclinical), and overall validation. The five comparators were selected as the principal compounds in the actoprotector and synthetic adaptogen pharmacological space that are most relevant to the positioning of chlodantane.

12.1 Bromantane (Ladasten)

Mechanism: Adamantane-derived actoprotector and synthetic adaptogen. Enhances dopamine biosynthesis through upregulation of tyrosine hydroxylase and aromatic L-amino acid decarboxylase via indirect genomic mechanisms [6, 10]. Secondary amine linkage between adamantane and para-bromophenyl ring.

Development trajectory: Developed at the Zakusov Institute alongside chlodantane. Advanced through clinical trials and registered in Russia as Ladasten for neurasthenia treatment (approximately 2009). Placed on the WADA prohibited list in 1997 [6].

Novelty: Moderate. The actoprotector concept was novel at the time of development; the dopaminergic genomic mechanism distinguishes bromantane from classical stimulants. The compound has been commercially available for over a decade.

Effect size: Clinical: CGI-I responder rate of 90.8 percent in a 728-patient neurasthenia trial at 50 to 100 mg daily for 28 days [6]. Anti-asthenic effects persisted for at least one month after treatment cessation. Preclinical: substantial enhancement of physical performance and recovery from fatigue, hyperthermia, and hypoxia.

Promising potential: Moderate. Registered in one jurisdiction (Russia) for one indication (neurasthenia). Not in active development in Western regulatory jurisdictions. The compound continues to generate research interest as a non-exhaustive performance enhancer and as a pharmacological probe for dopaminergic genomic mechanisms.

Side-effect profile: Favorable. Only 3 percent adverse-event rate in the 728-patient clinical program; 0.8 percent discontinuation rate; no serious adverse events reported at registered doses [6]. The absence of peripheral sympathomimetic effects, tolerance, dependence, or withdrawal syndrome distinguishes bromantane from classical stimulants.

Overall validation: Moderate to high. Clinical registration, a multi-hundred-patient efficacy dataset, an identified molecular mechanism, and a characterized human pharmacokinetic profile provide the most complete validation package of any compound in the actoprotector class.

Comparison to chlodantane: Bromantane is the most directly comparable compound. Chlodantane has a broader reported adaptogenic activity spectrum and more pronounced immunostimulant activity in preclinical models, but bromantane has the substantial advantages of clinical registration, human pharmacokinetic and safety data, an identified molecular mechanism, and widespread availability. Chlodantane lacks all of these validation components.

12.2 Bemitol (Antihot, Metaprot)

Mechanism: Benzimidazole-derived actoprotector. Stimulates RNA and protein synthesis, with downstream induction of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) as the principal mechanism for physical performance enhancement and stress protection [3, 13]. Not an adamantane derivative; the benzimidazole scaffold provides a fundamentally different pharmacophore.

Development trajectory: Developed in the Soviet Union as the first-generation actoprotector. Certified in Ukraine as a dietary supplement (Antihot). Used in the training of Ukrainian national sports teams. Not registered as a drug in any Western regulatory jurisdiction [3, 13].

Novelty: Low. The compound has been studied since the 1970s and represents the classical reference actoprotector.

Effect size: Preclinical: consistent enhancement of physical performance in endurance paradigms, with effects attributed to protein synthesis stimulation and antioxidant enzyme induction. Clinical: limited formal clinical data; the compound's widespread use in Eastern European sports medicine is based on empirical experience rather than randomized controlled trials [3].

Promising potential: Low. The compound is not in active development for Western regulatory markets. It persists as a research tool and as an empirical performance-enhancing agent in Eastern European contexts.

Side-effect profile: Favorable. No serious side effects have been reported at studied doses [3, 13]. The benzimidazole scaffold is well characterized and the metabolic profile is benign.

Overall validation: Moderate. Decades of preclinical and empirical clinical use, but limited formal clinical trial evidence by Western regulatory standards.

Comparison to chlodontane: Bemetil operates through a mechanistically distinct pathway (protein synthesis induction) from the proposed mechanism of chlodontane (membrane stabilization, lipid peroxidation suppression). The two compounds could be mechanistically complementary. Bemetil has the advantage of decades of empirical use and broader availability; chlodontane has the potential advantage of broader adaptogenic spectrum and immunostimulant activity, but lacks any empirical clinical base.

12.3 Ethomersol

Mechanism: 5-Ethoxy-2-ethylthiobenzimidazole hydrochloride; a modified benzimidazole actoprotector structurally related to bemetil. Shares the protein synthesis stimulation and antioxidant enzyme induction mechanism of bemetil, with reported improvements in potency and oral bioavailability [3, 13].

Development trajectory: Developed as a second-generation benzimidazole actoprotector. Not commercially available as a registered drug or dietary supplement. Remains a research compound [3].

Novelty: Low. The compound is an incremental modification of the bemetil scaffold.

Effect size: Preclinical: reportedly improved potency relative to bemetil in endurance paradigms, though quantitative comparative data are limited [3].

Promising potential: Low. Not in active development. Limited availability.

Side-effect profile: Limited data. Expected to be similar to bemetil based on structural analogy.

Overall validation: Low. Limited research literature; no clinical data; no commercial availability.

Comparison to chlodantane: Ethomersol and chlodantane are both underdeveloped research compounds with limited validation. Ethomersol operates through a different mechanism (benzimidazole-mediated protein synthesis induction) and belongs to a different structural class. Neither compound has human data.

12.4 Adapromine

Mechanism: Adamantane derivative with reported adaptogenic and antiviral activity. Structurally related to both amantadine and bromantane. The compound has been characterized in the Russian pharmacological literature as an adamantane-derived adaptogen [8].

Development trajectory: Limited information available in English-language publications. The compound appears to have been studied in the same Zakusov Institute research programs that produced bromantane and chlodantane but was not advanced to clinical development [8].

Novelty: Low. The compound is one of many adamantane derivatives evaluated in the Soviet/Russian screening programs.

Effect size: Not characterized in accessible publications.

Promising potential: Very low. No active development, no commercial availability as a research compound, no clinical data.

Side-effect profile: Unknown.

Overall validation: Very low. Minimal published characterization.

Comparison to chlodantane: Adapromine represents another undeveloped lead from the same research program. Chlodantane has modestly more published characterization than adapromine and is commercially available as a research-grade preparation, giving it a marginal advantage in accessibility and research utility.

12.5 Trekrezan (Trekresan)

Mechanism: Oxyethylammonium methylphenoxyacetate; a synthetic adaptogen developed in Russia with reported immunomodulatory and adaptogenic properties. Not an adamantane derivative. The mechanism involves stimulation of interferon production and modulation of the hypothalamic-pituitary-adrenal axis [15].

Development trajectory: Registered in Russia as an over-the-counter immunomodulatory adaptogen. Used for prophylaxis and treatment of colds and for enhancement of physical and cognitive performance under stress [15].

Novelty: Low. The compound represents a conventional immunomodulatory adaptogen without a novel molecular mechanism.

Effect size: Clinical: registered in Russia on the basis of clinical evidence for immunomodulatory and adaptogenic indications, though the clinical trial data are not readily accessible in the English-language literature [15].

Promising potential: Low to moderate. Registered in one jurisdiction for a general adaptogenic indication. Not in development in Western regulatory jurisdictions.

Side-effect profile: Reported as well tolerated with minimal adverse events [15].

Overall validation: Low to moderate. Russian registration provides a baseline level of clinical validation, but the evidence base is not accessible by Western regulatory standards.

Comparison to chlodantane: Trekrezan shares the immunomodulatory and adaptogenic profile of chlodantane but operates through a different mechanism (interferon stimulation, HPA axis modulation rather than membrane stabilization). Trekrezan has the advantage of clinical registration in Russia; chlodantane has no clinical data. The compounds could be mechanistically complementary for combined research applications, though no combination data exist.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the actoprotector and synthetic adaptogen pharmacological space. **Bromantane** is the most validated compound in the class, with clinical registration, a multi-hundred-patient efficacy dataset, an identified molecular mechanism, and characterized human pharma-

cokinetics. **Bemtil** is the classical reference actoprotector with decades of empirical use but limited formal clinical evidence. **Ethomersol** and **adapromine** are underdeveloped research compounds with minimal published characterization. **Trekrezan** is a non-adamantane immunomodulatory adaptogen with Russian clinical registration but limited Western-accessible evidence.

Chlodantane occupies a position intermediate between bromantane and the underdeveloped compounds: it has more published preclinical characterization than adapromine or ethomersol and is commercially available as a research-grade preparation, but it lacks the clinical validation, identified molecular mechanism, and human data that distinguish bromantane from the rest of the class. The principal scientific distinction of chlodantane is its reported broader adaptogenic activity spectrum and enhanced immunostimulant potency relative to bromantane, properties that could represent clinically meaningful advantages if validated in human studies but that remain entirely preclinical.

The practical research-application positioning of chlodantane is as a preclinical tool for investigating the contribution of membrane stabilization and lipid peroxidation suppression to adaptogenic activity, and for exploring the amide-versus-amine structural modification in the context of adamantane-derived pharmacology. Investigators considering chlodantane for translational research should recognize that the compound's validation level is substantially below that of bromantane and that the absence of human data represents a fundamental limitation for any clinical extrapolation.

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