

RESEARCH MONOGRAPH . COMPOUND PROFILE

Bemtil

A Soviet-developed 2-ethylthiobenzimidazole actoprotector that enhances physical and cognitive performance through genomic activation of protein synthesis, gluconeogenesis enzyme induction, and mitochondrial bioenergetic optimization, distinguished from classical psychostimulants by a non-exhaustive, adaptogenic mechanism that does not increase oxygen consumption or heat production.

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ABSTRACT

Bemtil (2-ethylthiobenzimidazole hydrobromide; synonyms bemethyl, metaprot, antihot) is the reference compound of the actoprotector drug class, a category of synthetic adaptogens defined by the capacity to enhance physical performance under normal and extreme conditions without increasing oxygen consumption or thermogenesis. Developed in the 1970s at the S.M. Kirov Military Medical Academy in Leningrad by Professor Vladimir Vinogradov and colleagues, bemtil was the first actoprotector to receive state registration in the Soviet Union (1983, registration number 83/654/1) and was subsequently deployed in military, aerospace, and athletic applications including cosmonaut preparation, Soviet national team conditioning for the 1980 Moscow Olympic Games, and operational support during the Afghan campaign and Chernobyl disaster response.

The molecular pharmacology of bemtil is characterized by genomic activation of RNA and protein synthesis, a property attributable to the structural similarity of the benzimidazole nucleus to the purine bases adenine and guanine. The downstream consequences of this genomic activation include induction of gluconeogenesis enzymes in liver and kidney (accelerating lactate recycling to glucose through the Cori and glucose-alanine cycles), enhanced synthesis of mitochondrial respiratory chain enzymes and structural proteins (increasing ATP production and maintaining oxidative phosphorylation coupling), and upregulation of endogenous antioxidant enzymes including superoxide dismutase, catalase, and glutathione metabolism

enzymes. The compound additionally demonstrates antihypoxic activity through maintenance of anaerobic ATP synthesis under oxygen deficit, neuroprotective activity in experimental stroke models, antimutagenic activity against alkylating agent-induced chromosomal aberrations, and immunomodulatory effects through protein synthesis-dependent augmentation of cellular immunity.

Pharmacokinetics after oral administration are characterized by rapid gastrointestinal absorption (detectable in plasma within 30 minutes), peak effect at 1 to 2 hours with duration of 4 to 6 hours, active hepatic metabolism through cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2D6, and CYP3A4, and urinary elimination predominantly as phase II conjugates. Nine metabolites have been identified in rat urine, with a benzimidazole-acetylcysteine conjugate (molecular formula $C_{12}H_{13}N_3O_3S$) representing the most abundant urinary metabolite, consistent with glutathione S-transferase-mediated detoxification. The compound exhibits tissue accumulation on prolonged dosing, with blood concentration increases observed by days 10 to 12 of continuous administration, necessitating cyclical dosing protocols (5 days on, 2 days off) in the registered prescribing information.

Clinical applications span physical performance enhancement, post-exertional recovery acceleration, treatment of asthenic disorders of diverse etiology (neurasthenia, post-infectious asthenia, postoperative asthenia), and adjunctive therapy in cerebral trauma, meningitis, encephalitis, and cerebrovascular disorders. In a comparative clinical trial of 130 patients with asthenic conditions, bemetil demonstrated superior efficacy to the nootropics piracetam and pyriditol in reducing asthenic symptoms. The compound is generally well tolerated; the

principal adverse events are gastrointestinal discomfort, headache, facial flushing, and sleep disturbance when administered in the evening. Contraindications include hypoglycemia, hepatic dysfunction, epilepsy, and pregnancy. The World Anti-Doping Agency placed bemitil on its Monitoring Program in 2018, and detection methods based on UPLC-MS/MS of the parent compound and its glucuronide conjugate in urine have been validated with detection windows extending beyond 30 days post-administration.

This monograph reviews the chemistry, synthesis, and structural pharmacology of bemitil; the genomic and metabolic mechanisms of action; the pharmacokinetic profile including biotransformation pathways; the preclinical evidence base across performance, neuroprotection, antihypoxic, and antimutagenic endpoints; the clinical evidence in asthenia, physical performance, and rehabilitation; sourcing and quality verification; reconstitution and handling; stack interactions; adverse events and safety; and a comparative assessment of five alternative performance-enhancing or adaptogenic compounds (bromantane, phenylpiracetam, rhodiola rosea extract, levamisole, and sulbutiamine) against bemitil on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Recommended name: Bemetil.

Synonyms and alternative transliterations: Bemethyl, bemithyl, bemithil, bemetil, metaprot, bemactor.

Trade names: Metaprot (Russian Federation pharmaceutical registration), Antihot (Ukraine dietary supplement certification), Bemetil (original Soviet registration).

Development origin: S.M. Kirov Military Medical Academy, Leningrad (now Saint Petersburg), USSR. The development team, led by Professor Vladimir Mikhailovich Vinogradov at the Institute of Experimental Medicine, received the USSR State Prize for the actoprotector program [1, 2].

Chemical Abstracts Service registry numbers: 14610-11-8 (free base, 2-ethylthio-1H-benzimidazole), 109628-14-0 (hydrobromide salt). The hydrobromide salt is the pharmaceutical and research form.

International Union of Pure and Applied Chemistry name: 2-(ethylsulfanyl)-1H-benzimidazole hydrobromide. The parent heterocycle is 1H-benzimidazole; the 2-position carries an ethylthio (ethylsulfanyl) substituent.

1.2 Structural class and chemistry

Bemetil is a benzimidazole derivative, a structural class that includes the antiparasitic agents albendazole and mebendazole, the proton pump inhibitor omeprazole, and the antifungal thiabendazole. The benzimidazole nucleus is a bicyclic system composed of a fused benzene and imidazole ring; the structural similarity of this nucleus to the purine bases adenine and guanine is the pharmacological basis for the genomic activation mechanism of bemetil and related actoprotectors [1, 3].

Molecular formula: C₉H₁₀N₂S (free base); C₉H₁₁BrN₂S (hydrobromide salt).

Exact mass: 178.06 g/mol (free base, monoisotopic).

Molecular weight: 178.25 g/mol (free base); 259.17 g/mol (hydrobromide salt).

SMILES: CCSc1[nH]c2ccccc2n1 (free base).

InChI: InChI=1S/C9H10N2S.BrH/c1-2-12-9-10-7-5-3-4-6-8(7)11-9;/h3-6H,2H2,1H3,(H,10,11);1H

InChIKey: BKUKXOMYGPYFJJ-UHFFFAOYSA-N

Physical properties: White to off-white crystalline powder. Freely soluble in water as the hydrobromide salt. The free base is soluble in organic solvents including methanol, ethanol, and dimethyl sulfoxide. The compound is stable under standard storage conditions (room temperature, dry environment) and at refrigerated conditions (2 to 8 degrees Celsius).

Stereochemistry: Bemetil contains no stereocenters and is achiral. No enantiomeric considerations apply to sourcing or analytical verification.

1.3 Synthesis

The synthesis of 2-ethylthiobenzimidazole proceeds from commercially available starting materials through established benzimidazole chemistry. The principal route involves condensation of ortho-phenylenediamine with an appropriate sulfur-containing one-carbon electrophile. Specifically, the reaction of 1,2-diaminobenzene with diethyl dithiocarbonate or carbon disulfide followed by S-alkylation with ethyl halide produces the 2-ethylthiobenzimidazole core [4]. Alternative routes employ direct condensation with ethyl isothiocyanate or cyclization of N-(2-aminophenyl)thiourea derivatives. The hydrobromide salt is prepared by treatment of the free base with hydrobromic acid in an appropriate solvent (ethanol, diethyl ether) followed by recrystallization. The synthesis is straightforward by medicinal chemistry standards; the compound contains no stereocenters and requires no asymmetric induction or chiral resolution. Industrial production has been established in multiple post-Soviet states, with the compound manufactured as 125 mg and 250 mg oral tablets or capsules for the registered pharmaceutical presentations.

2. Abstract

Bemtil (2-ethylthiobenzimidazole hydrobromide) is the founding and reference compound of the actoprotector class, a pharmacological category defined in Soviet military pharmacology as synthetic agents that enhance physical performance without increasing oxygen consumption or heat production [1]. The actoprotector concept distinguishes these compounds from classical psychostimulants (amphetamines, methylphenidate), which produce performance gains at the cost of increased metabolic rate, oxygen debt, and subsequent exhaustion, and from natural adaptogens (ginseng, eleutherococcus, rhodiola), which produce performance effects of smaller magnitude and slower onset.

The principal pharmacological mechanism is activation of the cellular genome through structural mimicry of purine nucleotide bases, resulting in enhanced transcription and translation of specific enzyme families: gluconeogenesis enzymes in liver and kidney, mitochondrial respiratory chain enzymes and structural proteins, and endogenous antioxidant enzymes [1, 3]. The downstream metabolic consequence is accelerated lactate recycling to glucose (sustaining energy substrate availability during intense exertion), improved ATP synthesis efficiency (maintaining bioenergetic homeostasis under oxygen restriction), and reduced oxidative damage to cellular structures (providing cytoprotection under stress conditions).

In preclinical models, bemtil increases maximal work volume by approximately 33 percent and resistance to fatigue by approximately 60 percent in rodent treadmill and swimming paradigms [1]. These gains persist under hypoxic, hyperthermic, and hypothermic conditions. The compound demonstrates neuroprotective activity in middle cerebral artery occlusion models, reducing neurological deficit scores at 25 mg/kg [5]. Antimutagenic activity has been documented as a two-fold reduction in alkylating agent-induced chromosomal aberrations [1, 6].

Clinical evidence spans military operational deployment (Soviet Afghan campaign, Chernobyl disaster response), athletic performance conditioning (1980 Moscow Olympic Games preparation), treatment of asthenic disorders (superior to piracetam and pyriditol in a 130-patient comparative trial), and adjunctive therapy in neurological conditions including cerebral trauma and meningitis [1, 7, 8]. The compound received Soviet state registration in 1983 and has been registered or cer-

tified in the Russian Federation and Ukraine in various formulations. It is not approved by the United States Food and Drug Administration or the European Medicines Agency.

The World Anti-Doping Agency placed bemitil on its Monitoring Program in 2018, prompting development of validated UPLC-MS/MS detection methods for the parent compound and its glucuronide conjugate in urine with detection windows exceeding 30 days [9, 10].

3. Discovery and Development History

3.1 Origin and Soviet-era development

Bemtil was synthesized and characterized in the 1970s at the S.M. Kirov Military Medical Academy in Leningrad (now the S.M. Kirov Military Medical Academy, Saint Petersburg) under the direction of Professor Vladimir Mikhailovich Vinogradov. The development program was motivated by a military requirement for pharmacological agents that could sustain physical and cognitive performance under extreme operational conditions (prolonged marches, high-altitude deployment, hypoxic environments, sustained combat operations) without the exhaustive rebound and addiction liability associated with amphetamine-class psychostimulants [1, 2].

The actoprotector concept was defined during this development program as a distinct pharmacological class: agents that increase body stability against physical loads without increasing oxygen consumption or heat production. Bemtil was the first compound to satisfy this definition and served as the reference standard against which subsequent actoprotectors (bromantane, adamantane derivatives, ethomersol) were evaluated [1].

3.2 Military and aerospace deployment

Soviet cosmonauts were the first human recipients of bemtil in operational application. The compound was subsequently integrated into the preparation regimen for the Soviet Union's national athletic teams for the 1980 Moscow Olympic Games. By the late 1980s and early 1990s, bemtil was in use across all corps of the Soviet Armed Forces for enhancement of physical endurance, stability against hypoxia during high-altitude operations, and acceleration of recovery after sustained exertion [1, 2].

Operational deployment included support during the Soviet campaign in Afghanistan (1979 to 1989), where bemtil was provided to combat personnel for endurance maintenance during extended operations at altitude; the Chernobyl nuclear disaster (1986), where the compound was administered to emergency workers

for radiation stress mitigation and recovery support; the Armenian earthquake (1988), where bemetil was used in the medical response for treatment of post-traumatic asthenia; and railway disaster response operations [1].

3.3 Pharmaceutical registration

Bemetil received its initial state registration in the Soviet Union on May 30, 1983, under state registration number 83/654/1. The registered indications were treatment of asthenia, hypoxia-related conditions, and stress-induced fatigue. Following the dissolution of the Soviet Union in 1991, official manufacture of the original formulation was discontinued [2].

In the post-Soviet period, the compound was reintroduced under the trade name Metaprot in the Russian Federation, where it has been incorporated into military and clinical protocols. In Ukraine, the compound is certified as the dietary supplement Antihot. The finished pharmaceutical formulation has had intermittent commercial availability, though the substance persists in the Russian State Register of Medicines [2, 11].

3.4 Expansion of clinical applications

The clinical application of bemetil expanded beyond the original military and performance indications through the 1980s and 1990s into infectiology, neurology, hepatology, cardiology, pulmonology, obstetrics and gynecology, urology, dermatology, and toxicology [1]. These extensions were driven by the recognition that the protein synthesis-activating mechanism of bemetil was relevant to recovery and rehabilitation across a broad range of clinical conditions involving tissue damage, metabolic derangement, or immune dysfunction. The clinical evidence base for these extended applications is predominantly from Soviet and Russian medical literature, published in Russian-language journals with limited international accessibility [1, 12].

3.5 Anti-doping monitoring

The World Anti-Doping Agency (WADA) included bemetil in its Monitoring Program beginning in 2018 [9]. The Monitoring Program is distinct from the Prohibited List; substances on the Monitoring Program are not prohibited in sport but are monitored through doping control analysis to detect patterns of use and to gather data

that may inform future regulatory decisions. The inclusion prompted analytical chemistry research on bemitil detection, notably the Kwiatkowska et al. (2018) validation of UPLC-MS/MS methods for the parent compound and its glucuronide conjugate in urine [9].

4. Mechanism of Action

Bemtil operates through a multi-level mechanism that begins with genomic activation and cascades through transcriptional, translational, and metabolic effects. The mechanism is distinct from the receptor-mediated pharmacology characteristic of most modern drug classes and is instead a broad metabolic modulation driven by the structural relationship of the benzimidazole nucleus to endogenous purine bases.

4.1 Genomic activation and protein synthesis

The benzimidazole ring system of bemtil shares structural features with the purine bases adenine and guanine, the heterocyclic components of the nucleotides ATP, GTP, and the nucleic acids DNA and RNA [1, 3]. This structural similarity is proposed to underlie the capacity of bemtil to interact with the cellular genome and activate transcription. The specific molecular target of the genomic interaction (whether direct DNA intercalation, transcription factor modulation, or nucleotide metabolism interference) has not been fully elucidated at the molecular level, but the functional consequence is well characterized: a rapidly developing enhancement of RNA synthesis followed by protein synthesis across multiple organ systems including skeletal muscle, brain, liver, and kidney [1, 3, 13].

The protein synthesis activation is not a global, nonspecific increase in translation but is preferentially directed toward specific enzyme families with metabolic and protective functions. The principal enzyme families induced by bemtil include gluconeogenesis enzymes (phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase, glucose-6-phosphatase) in liver and kidney; mitochondrial respiratory chain enzymes (succinate dehydrogenase [Complex II], cytochrome c oxidase [Complex IV]) and mitochondrial structural proteins; endogenous antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glutathione S-transferase); and immune system proteins [1, 3, 6].

4.2 Gluconeogenesis activation and lactate recycling

The induction of gluconeogenesis enzymes in liver and kidney is the metabolic basis for the physical performance-enhancing effect of bemetil [1, 13]. During intense physical exertion, glycolytic metabolism in working muscle produces lactate as a terminal product; lactate accumulation is a principal factor limiting sustained performance. Bemetil accelerates the hepatic and renal conversion of lactate to glucose through the Cori cycle (lactate to pyruvate to oxaloacetate to phosphoenolpyruvate to glucose) and the glucose-alanine cycle (muscle alanine to hepatic pyruvate to glucose), thereby sustaining circulating glucose availability and reducing the rate of lactate accumulation in blood and tissues [1, 3].

Experimental evidence supporting this mechanism includes observations of reduced lactate levels in blood and tissues of bemetil-treated animals after exhaustive exercise, slight decreases in glycogen and creatine phosphate depletion in liver and muscle (indicating more efficient substrate utilization), accelerated recovery of metabolic parameters to baseline after cessation of exertion, and in some parameters a "super-compensation" phenomenon during the recovery phase [1].

4.3 Mitochondrial bioenergetic optimization

The enhanced synthesis of mitochondrial respiratory chain enzymes and structural proteins increases the capacity for oxidative phosphorylation and maintains the degree of coupling between electron transport and ATP synthesis [1, 3, 13]. The functional consequence is increased ATP production efficiency per unit of oxygen consumed and maintenance of bioenergetic homeostasis under conditions of restricted oxygen availability (hypoxia, ischemia). This mechanism is the molecular basis for the antihypoxic activity of bemetil and distinguishes the compound from classical psychostimulants, which increase metabolic rate and oxygen demand.

The activation of succinate dehydrogenase (Complex II of the electron transport chain, and simultaneously a tricarboxylic acid cycle enzyme) is particularly relevant, as this enzyme occupies a unique position at the intersection of the citric acid cycle and oxidative phosphorylation. Enhancement of Complex II activity by bemetil through enzyme induction (increased protein expression) should be distinguished from direct enzymatic inhibition or activation; early reports describing bemetil as a "non-competitive inhibitor" of succinate dehydrogenase may reflect concentration-dependent modulation rather than simple inhibition [1, 14].

4.4 Antioxidant enzyme induction

The upregulation of endogenous antioxidant enzymes by bemetil constitutes an indirect antioxidant mechanism distinct from the direct radical-scavenging activity of compounds such as ascorbic acid or alpha-tocopherol [1, 6]. By increasing the cellular concentration of superoxide dismutase, catalase, glutathione peroxidase, and glutathione S-transferase through transcriptional activation, bemetil enhances the endogenous capacity to neutralize reactive oxygen species and to repair oxidative damage to lipids, proteins, and nucleic acids. This enzyme-induction mechanism produces antioxidant protection that is sustained beyond the plasma residence of the parent compound, as the induced enzymes persist with their own half-lives (hours to days for most antioxidant enzymes).

4.5 Neuroprotective activity

Bemetil and its structural analog ethomersol (5-ethoxy-2-ethylthiobenzimidazole) demonstrate neuroprotective activity in experimental stroke models [5]. In a middle cerebral artery occlusion model in inbred male rats, bemetil at 25 mg/kg significantly reduced neurological deficit at 24 hours post-occlusion and improved psychofunctional state as assessed by open-field behavioral testing. The neuroprotective mechanism is attributed to the composite of antioxidant enzyme induction (reducing ischemia-reperfusion oxidative injury), mitochondrial stabilization (maintaining bioenergetic function in penumbral tissue), and potential direct neurotropic effects through modulation of ion channel function [5, 15].

4.6 Antimutagenic activity

Bemetil produces a two-fold decrease in chromosomal aberrations induced by alkylating agents in experimental systems [1, 6]. The antimutagenic mechanism is proposed to operate through enhanced DNA repair enzyme expression (a consequence of the protein synthesis-activating effect) and through antioxidant protection of genomic DNA from oxidative mutagenesis. Protective effects against radiation-induced chromosomal aberrations have also been reported, consistent with deployment during the Chernobyl disaster response [1].

4.7 Immunomodulatory activity

The protein synthesis-dependent mechanism of bemetil extends to immune system proteins, producing immunomodulatory effects characterized as augmentation of cellular immune function [1, 3, 13]. The clinical consequence is accelerated recovery from infections and enhanced resistance to infectious challenge under conditions of physical stress and exhaustion, both of which are associated with transient immunosuppression. The immunomodulatory effect is consistent with the clinical deployment of bemetil in post-infectious asthenia and in the support of military personnel under operational stress.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Bemtil is well absorbed from the gastrointestinal tract after oral administration [13]. The compound is detectable in plasma within 30 minutes of a single oral dose. The maximum pharmacological effect is achieved at 1 to 2 hours post-dose and persists for 4 to 6 hours. Absorption is accelerated by carbohydrate-rich food; the prescribing information recommends administration after meals with a diet rich in carbohydrates during treatment [13].

Specific values for oral bioavailability have not been published in the accessible literature. The rapid plasma appearance (30 minutes) and the clinical efficacy at oral doses suggest substantial bioavailability, though first-pass hepatic metabolism is expected to reduce systemic exposure relative to the administered dose.

5.2 Distribution

Bemtil penetrates the blood-brain barrier, a property consistent with its central nervous system effects (nootropic activity, neuroprotection, psychostimulating activity in open-field behavioral models) [1, 2]. The volume of distribution has not been quantified in published human pharmacokinetic studies. Animal data indicate a polymodal distribution pattern in healthy volunteers, suggesting heterogeneous tissue partitioning [1].

In rat studies, long-term administration produced a 1.38-fold increase in drug concentration in the brain and a 1.68-fold increase in skeletal muscles, indicating preferential accumulation in metabolically active tissues that are the principal targets of the compound's pharmacological action [2]. Plasma protein binding has not been formally characterized in the accessible literature.

5.3 Metabolism

Bemtil undergoes active biotransformation in the liver [13]. The compound is metabolized through both Phase I oxidative reactions (cytochrome P450-mediated) and Phase II conjugation reactions.

The Kuzivanova et al. (2021) study identified nine metabolites with six molecular formulas in rat urine using LC-MS/HRMS [10]. The major metabolic pathways are:

Phase I (CYP450-mediated oxidation): Sulfoxide formation at the ethylthio sulfur atom (producing hydroxylated bemethyl metabolites M2a/M2b, molecular formula C₉H₁₀N₂O₂S); further oxidation to sulfone metabolites (M3a/M3b, molecular formula C₉H₁₀N₂O₃S); and oxidative dealkylation producing 2-thiobenzimidazole (M1a/M1b, molecular formula C₇H₆N₂S), which exists as thione-thiol tautomers in a 60:1 ratio [10]. The CYP isoforms involved include CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CYP3A4 [10, 13].

Phase II (conjugation): Glutathione S-transferase (GST)-mediated conjugation of the sulfoxide/sulfone metabolites produces a benzimidazole-acetylcysteine conjugate (M5, molecular formula C₁₂H₁₃N₃O₃S) through a sequential pathway involving glutathione conjugation, gamma-glutamyltransferase cleavage, cysteine-glycine dipeptidase cleavage, and N-acetyltransferase acetylation [10]. This mercapturic acid pathway product is the most abundant urinary metabolite, indicating that glutathione conjugation is the primary detoxification route. Additional Phase II reactions include sulfation (producing M4, molecular formula C₉H₁₀N₂O₄S₂) and glucuronidation (producing M6, molecular formula C₁₅H₁₈N₂O₇S) of hydroxylated metabolites [10].

The benzimidazole core remains intact across all identified metabolites; no ring-opening products have been detected [10].

5.4 Elimination

Elimination is predominantly renal, with metabolites excreted in urine [1, 13]. The unchanged parent compound represents only approximately 0.56 percent of total urinary excretion, consistent with extensive hepatic metabolism [10]. The plasma elimination half-life has not been precisely quantified in published studies, but the duration of pharmacological effect (4 to 6 hours after a single dose) and the drug ac-

cumulation observed on prolonged dosing suggest a functional half-life in the range of several hours, with the potential for tissue accumulation extending the effective duration.

5.5 Accumulation

A distinctive pharmacokinetic feature of bemitil is its tendency to accumulate on prolonged dosing. During extended therapy, especially at higher doses, blood concentrations increase progressively, with measurable accumulation by days 10 to 12 of continuous administration [13]. This accumulation is the pharmacokinetic basis for the recommended cyclical dosing protocol of 5 days on, 2 days off, which allows partial washout and prevents excessive tissue concentrations [13]. The accumulation mechanism is attributed to the combination of tissue partitioning (preferential accumulation in brain and skeletal muscle), possible autoinhibition of metabolizing enzymes, and the slow elimination of tissue-bound drug.

5.6 Routes of administration

The compound is administered orally in all registered and researched applications. The pharmaceutical presentations are 125 mg and 250 mg tablets or capsules. No parenteral formulations are described in the accessible literature. The oral route is appropriate given the rapid and substantial gastrointestinal absorption and the sustained duration of effect.

5.7 Special populations

Pharmacokinetic data in special populations are limited. The prescribing information specifies weight-based dose adjustment for individuals over 80 kg (maximum 1000 mg daily, divided as 500 mg morning and 500 mg after lunch) [13]. Contraindications include hepatic dysfunction (which would be expected to impair metabolism and increase accumulation), hypoglycemia (consistent with the gluconeogenesis-modulating mechanism), and pregnancy and lactation [13]. Pediatric pharmacokinetic data are not available; the compound is not approved for use in children.

6. Clinical Evidence Base

6.1 Physical performance enhancement

The primary clinical application of bemetil is enhancement of physical performance under normal and extreme conditions. Preclinical data demonstrate increases in maximal work volume of approximately 33 percent and increases in resistance to fatigue of approximately 60 percent in rodent treadmill and swimming paradigms [1]. These effects are preserved under hypoxic, hyperthermic, and hypothermic conditions, distinguishing bemetil from psychostimulants whose performance gains diminish or reverse under environmental stress.

The effect develops progressively during the first 3 to 5 days of course administration and is maintained at steady intensity for the remainder of the treatment period [1, 13]. This temporal profile is consistent with the protein synthesis-dependent mechanism, as induction of new enzyme protein requires transcriptional and translational time.

Human evidence for physical performance enhancement derives primarily from Soviet military and athletic programs. Documentation of the preparation of the Soviet national team for the 1980 Moscow Olympic Games reports the use of bemetil in conditioning regimens, though controlled trial data from these programs have not been published in the international peer-reviewed literature [1, 2]. Military operational data from the Afghan campaign and disaster response deployments document sustained endurance on prolonged marches, enhanced stability to altitude-related hypoxia, and accelerated recovery after sustained physical exertion [1].

6.2 Asthenic disorders

The treatment of asthenic disorders of diverse etiology represents the principal registered clinical indication for bemetil. In a clinical trial of 130 patients with asthenic conditions associated with borderline neuropsychiatric disturbances, bemetil demonstrated superior efficacy compared to the nootropic drugs piracetam and pyriditol in reducing asthenic symptoms [7, 8]. The trial design compared the clini-

copharmacological action of bemtil with established nootropic agents in patients with neurasthenia, somatogenic asthenia, post-infectious asthenia, and postoperative asthenia.

The registered indications for the Metaprot formulation include asthenic disorders of various etiology (neurasthenia, somatic diseases, post-infectious and post-intoxication states, pre-operative and postoperative periods), consistent with the broad protein synthesis-activating and recovery-accelerating mechanism [13].

6.3 Neurological applications

Bemtil is indicated as adjunctive therapy in complex treatment of cerebral trauma, meningitis, encephalitis, cerebrovascular disorders, and cognitive disorders [13]. The evidence base for these applications derives from Soviet and Russian clinical practice rather than from randomized controlled trials meeting current international regulatory standards. The neuroprotective mechanism (antioxidant enzyme induction, mitochondrial stabilization, potential neurotropic effects) provides a rational pharmacological basis for these applications [5, 15].

The neuroprotective activity has been characterized in preclinical models. In a middle cerebral artery occlusion model, bemtil at 25 mg/kg significantly reduced neurological deficit and improved motor activity in open-field testing, effects attributed to free radical scavenging, augmentation of endogenous antioxidant proteins (glutathione S-transferase, reduced glutathione), and amelioration of lipid peroxidation [5].

6.4 Extreme environment adaptation

The adaptogenic properties of bemtil support its use in facilitating human adaptation to extreme environmental conditions including high altitude (hypoxic stress), heat (hyperthermic stress), cold (hypothermic stress), and radiation exposure [1, 2]. The mechanism of environmental adaptation is the composite of enhanced mitochondrial bioenergetics (maintaining ATP synthesis under oxygen restriction), antioxidant enzyme induction (protecting against oxidative stress amplified by environmental extremes), and gluconeogenesis activation (sustaining energy substrate availability). Evidence derives primarily from military operational deployment and cosmonaut preparation programs.

6.5 Extended clinical applications

The clinical application of bemitil has been extended to multiple medical specialties in Soviet and Russian medical practice, including infectiology (post-infectious asthenia and immunomodulatory support), hepatology (hepatoprotective effects through the closely related analog ethomersol), cardiology (adjunctive therapy in ischemic conditions), pulmonology (antihypoxic support in respiratory insufficiency), and dermatology [1]. The evidence base for most extended applications is limited to case series and open-label studies in the Russian-language literature.

7. Preclinical Pharmacology

7.1 Physical performance models

In rodent exercise models, bemetil produces consistent and reproducible increases in physical performance parameters. Swimming endurance in mice is increased by approximately 60 percent, and maximal work volume on forced treadmill protocols is increased by approximately 33 percent [1]. These gains occur without proportional increases in oxygen consumption or heat production, confirming the actoprotector mechanism and distinguishing the compound from classical psychostimulants. The performance enhancement is preserved under conditions of environmental stress including reduced atmospheric oxygen (simulated altitude), elevated ambient temperature, and reduced ambient temperature [1].

7.2 Metabolic effects

Bemetil-treated animals show characteristic metabolic alterations during and after exhaustive exercise: slight decreases in hepatic and muscular glycogen and creatine phosphate depletion (indicating more efficient substrate utilization), reduced blood glucose decrements during exercise, reduced lactate accumulation in blood and tissues, lower increases in heat production and oxygen consumption, and accelerated restoration of metabolic parameters during recovery, with some parameters showing super-compensation above baseline [1].

7.3 Neuroprotection

In the middle cerebral artery occlusion model in inbred male rats, bemetil at 25 mg/kg administered before occlusion significantly reduced neurological deficit scores at 24 hours and improved psychofunctional state as measured by open-field behavioral testing (increased motor activity, reduced anxiety-related behaviors) [5]. The related benzimidazole derivative ethomersol (5-ethoxy-2-ethylthiobenzimidazole) showed comparable neuroprotective activity in the same model, suggesting that the benzimidazole-ethylthio pharmacophore is the structural determinant of neuroprotection [5].

7.4 Antimutagenic activity

Bemtil produces a two-fold reduction in chromosomal aberrations induced by alkylating agents in rodent bone marrow cytogenetic assays [1, 6]. The protective effect extends to radiation-induced chromosomal damage. The antimutagenic mechanism is attributed to enhanced DNA repair enzyme expression and to antioxidant protection of genomic DNA, both consequences of the protein synthesis-activating mechanism.

7.5 Open-field behavioral effects

In open-field behavioral testing in rats, bemtil and the parent benzimidazole heterocycle produce psychostimulating effects characterized by increased motor activity and exploratory behavior [16]. These effects are consistent with central nervous system penetration and with the nootropic and antiasthenic clinical effects.

8. Sourcing and Quality Verification

Pharmaceutical-grade bemetil (Metaprot brand, 125 mg or 250 mg tablets/capsules) represents the highest quality source for research applications. Pharmaceutical sourcing is limited to jurisdictions where the compound is registered or certified (Russian Federation as a prescription medicine, Ukraine as the dietary supplement Antihot). Availability has been intermittent since the dissolution of the Soviet Union.

Research-grade bemetil is supplied by multiple chemical and pharmaceutical research suppliers as the hydrobromide salt at purities of 98 percent or greater by HPLC. The free base (CAS 14610-11-8) is also available from some suppliers. Supply is in milligram to gram quantities.

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 (179.06 for the protonated free base $[M+H]^+$, or 259.17 for the hydrobromide salt)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) to confirm the benzimidazole-ethylthio structural assignment and to exclude positional isomers
- Residual solvent analysis by gas chromatography for common synthesis solvents
- Bromide content determination for the hydrobromide salt (stoichiometric bromide content is 30.8 percent by weight)
- Karl Fischer or loss-on-drying analysis for residual water

The achiral nature of bemetil simplifies analytical verification relative to chiral compounds; no chiral HPLC or polarimetry is required. Third-party analytical confirmation of vendor certificates of analysis is appropriate for any investigation where dose-response precision is important.

9. Reconstitution and Handling

Bemtil hydrobromide is freely soluble in water at room temperature. For research applications requiring solution preparation, the compound is reconstituted in aqueous media (normal saline, phosphate-buffered saline, water for injection) or in dimethyl sulfoxide for in vitro applications where higher concentrations are required.

Storage of solid material: Room temperature (15 to 25 degrees Celsius), protected from moisture, in sealed containers. The compound is stable under these conditions for the shelf life specified by the manufacturer (typically 2 to 3 years from date of manufacture). Refrigerated storage (2 to 8 degrees Celsius) is acceptable and may extend stability.

Storage of solutions: Aqueous solutions should be prepared fresh for each experimental session or stored at 2 to 8 degrees Celsius for no more than 7 to 14 days. Dimethyl sulfoxide stock solutions are more stable and may be stored at minus 20 degrees Celsius for several months. Freeze-thaw cycling should be minimized; aliquoting of stock solutions for single use is recommended.

Dosing considerations for animal research: A published application protocol for mice specifies oral gavage administration at doses of 25 to 50 mg/kg in aqueous vehicle [5, 17]. The Kuzivanova et al. (2021) biotransformation study administered a single oral dose of 330 mg/kg in male Wistar rats (300 plus or minus 30 g body weight) [10]. Investigators should adjust doses according to interspecies allometric scaling for the target species.

Handling precautions: The compound is a research chemical and should be handled with standard laboratory precautions including gloves, eye protection, and use in a ventilated area. The hydrobromide salt contains bromide; investigators with bromide sensitivity or working in bromide-restricted environments should consider the free base form.

10. Stack Interactions and Combinations

Bemtil interacts with several drug classes through its hepatic CYP450-mediated metabolism and through its broad metabolic modulation mechanism. The prescribing information for the Metaprot formulation specifies the following interactions [13]:

CYP450 inhibitors: Inhibitors of CYP1A2, CYP2C9, CYP2D6, and CYP3A4 (for example, cimetidine) may increase bemtil blood concentration by reducing hepatic clearance. The breadth of CYP isoform involvement (four principal isoforms identified) means that a wide range of pharmaceutical agents could potentially elevate bemtil exposure. Strong inhibitors of any of these isoforms should be considered for dose adjustment or increased monitoring when co-administered with bemtil.

Metabolic and neuroprotective agents: Bemtil enhances the positive effects of metabolic drugs (including inosine), neuroprotective drugs (including piracetam), antihypoxic agents (including trimetazidine), potassium and magnesium aspartate, glutamic acid, vitamins (including alpha-tocopherol), and antianginal agents (nitrates, beta-blockers) [13]. These synergistic interactions are consistent with the mechanism of bemtil, which augments endogenous metabolic and protective pathways that overlap with the targets of these co-administered agents.

Hypoglycemic agents: The gluconeogenesis-activating mechanism of bemtil would be expected to partially antagonize the effects of hypoglycemic agents (insulin, sulfonylureas, metformin) by increasing hepatic glucose output. Conversely, the gluconeogenesis activation could exacerbate hypoglycemia risk in fasting individuals or in those with impaired glycogen reserves, which is the basis for the hypoglycemia contraindication [13].

Psychostimulants: The combination of bemtil with classical psychostimulants (amphetamines, methylphenidate, modafinil) has not been formally characterized but would be expected to produce additive or synergistic performance-enhancing effects with the potential for excessive sympathetic activation and cardiovascular stress. The combination is not recommended.

Evening administration: Bemetil should not be taken in the evening due to the risk of sleep disturbance [13]. The psychoactivating properties of the compound, including affective irritability and reduced sleep quality, are dose-dependent and time-of-day-dependent.

Diet: A carbohydrate-rich diet is recommended during bemetil treatment to support the gluconeogenesis substrate pool and to accelerate gastrointestinal absorption [13].

11. Adverse Events and Safety

11.1 Common adverse events

The adverse event profile of bemetil is generally mild and self-limiting [1, 13]. The principal reported adverse events are:

- Gastrointestinal: discomfort in the stomach and liver region, rarely nausea and vomiting. Gastrointestinal symptoms are more common when the compound is taken on an empty stomach and are reduced by post-meal administration [1, 13].
- Central nervous system: headache [13].
- Allergic: facial flushing, rhinitis [13].
- Psychoactivation: affective irritability, reduced sleep quality, reduced sleep duration. These effects are dose-dependent and are the basis for the recommendation against evening administration [1].

Additional effects reported in some users include reduced appetite with weight loss and increased libido [1].

11.2 Overdose

Overdose symptoms include irritability and sleep disturbance [13]. Treatment is gastric lavage, activated charcoal, and symptomatic therapy as indicated. No lethal overdose cases have been reported in the accessible literature.

11.3 Contraindications

The following contraindications are specified in the Metaprot prescribing information [13]:

- Hypoglycemia (risk of exacerbating glucose depletion through altered gluconeogenesis regulation)
- Liver dysfunction (impaired hepatic metabolism would increase accumulation and toxicity risk)

- Epilepsy
- Hypertension
- Glaucoma
- Ischemic heart disease
- Arrhythmias
- Lactase deficiency, lactose intolerance, glucose-galactose malabsorption (formulation-related)
- Pregnancy and lactation
- Pediatric age
- Hypersensitivity to the drug or to bromide (the hydrobromide salt contains bromide, which may produce allergic reactions in sensitive individuals)

11.4 Long-term safety

Long-term safety data are limited. The cyclical dosing protocol (5 days on, 2 days off) is designed to prevent excessive tissue accumulation and to mitigate the potential for cumulative toxicity [13]. The compound has been in clinical and military use since 1983 without reports of severe or life-threatening adverse events in the accessible literature; however, the predominantly Russian-language evidence base and the military context of early deployment limit the completeness of the available safety record by international pharmacovigilance standards.

11.5 Pregnancy and lactation

The compound is contraindicated in pregnancy and lactation [13]. Teratogenicity and reproductive toxicity data have not been published in the accessible international literature.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative performance-enhancing, adaptogenic, or actoprotector compounds against bemtil, evaluated against five competency standards: novelty, effect size, promising potential (current regulatory and research trajectory), side-effect profile, and overall validation. The five comparators were selected to span the pharmacological space relevant to bemtil's applications: physical performance enhancement, adaptogenic and antihypoxic activity, and nootropic or antiasthenic effects.

12.1 Bromantane (Ladasten)

Mechanism: Adamantane-derivative actoprotector. N-(2-adamantyl)-N-(para-bromophenyl)amine. The mechanism involves upregulation of tyrosine hydroxylase and aromatic L-amino acid decarboxylase, increasing dopamine synthesis through a non-releasing, non-reuptake-inhibiting mechanism [1, 18]. Additional anxiolytic activity is attributed to enhancement of GABAergic transmission. Bromantane is structurally and mechanistically distinct from bemtil; it is an adamantane derivative rather than a benzimidazole derivative, and its primary mechanism operates through dopaminergic rather than genomic protein-synthesis pathways.

Development trajectory: Developed in Russia as the second actoprotector after bemtil. Registered in the Russian Federation under the trade name Ladasten for the treatment of asthenic disorders with anxiolytic properties [18]. Bromantane is the only actoprotector besides bemtil to have achieved pharmaceutical registration. It was identified as a substance of doping concern after detection in multiple athletes at the 1996 Atlanta Olympic Games and was subsequently added to the WADA Prohibited List [18].

Novelty: Moderate. The dopaminergic actoprotector mechanism is distinct from both the bemtil protein-synthesis mechanism and from classical psychostimulant mechanisms. The dual actoprotector-anxiolytic profile is unique.

Effect size: Comparable to or modestly greater than bemetil in physical performance enhancement in preclinical models, with additional anxiolytic effects not observed with bemetil. The more pronounced and prolonged stimulant activity of bromantane relative to bemetil has been noted in comparative preclinical studies [1].

Promising potential: Low to moderate. Pharmaceutical registration in Russia is maintained (Ladasten), but international regulatory interest is absent. The compound is on the WADA Prohibited List, limiting research applications in sport contexts.

Side-effect profile: Generally well tolerated. The principal adverse events are similar to bemetil (gastrointestinal discomfort, headache). The dopaminergic mechanism introduces a theoretical risk of psychomotor agitation that is absent from the bemetil profile.

Overall validation: Moderate. The compound has pharmaceutical registration, a distinct mechanism, and a substantial Russian-language evidence base. International validation is limited.

Comparison to bemetil: Bromantane offers more pronounced stimulant and anxiolytic effects but operates through a fundamentally different mechanism (dopaminergic vs. genomic protein synthesis). Bemetil has the advantages of a longer track record (registered 1983 vs. later for bromantane), a broader range of clinical applications (neurological, immunomodulatory), and absence from the WADA Prohibited List (bemetil is on the Monitoring Program only). The two compounds are the only registered actoprotectors and represent complementary approaches within the class.

12.2 Phenylpiracetam (Fonturacetam, Phenotropil)

Mechanism: 4-phenyl derivative of piracetam, a racetam-class nootropic. The mechanism involves modulation of AMPA and NMDA glutamate receptor function, enhancement of dopaminergic and noradrenergic neurotransmission, and cold-resistance effects [19]. The compound combines nootropic (cognitive enhancement) and psychostimulant (physical performance) properties.

Development trajectory: Developed in Russia at the Institute of Biomedical Problems of the Russian Academy of Sciences, originally for cosmonaut cognitive support during extended space missions. Registered in the Russian Federation un-

der the trade name Phenotropil for cognitive and asthenic disorders. Added to the WADA Prohibited List in 2017 as a non-specified stimulant [19].

Novelty: Moderate. The racetam scaffold is well established; the phenyl substitution provides the additional psychostimulant and cold-resistance properties that distinguish phenylpiracetam from the parent piracetam.

Effect size: Cognitive enhancement effects are comparable to or greater than piracetam; physical performance effects are modest relative to dedicated actoprotectors. The cognitive domain is the principal strength.

Promising potential: Low. The compound is on the WADA Prohibited List. Russian pharmaceutical registration has been intermittent owing to manufacturing and regulatory issues.

Side-effect profile: Generally well tolerated. Insomnia and psychomotor agitation at higher doses. Tolerance development on chronic use has been reported anecdotally.

Overall validation: Moderate. Substantial Russian-language clinical literature in cognitive and asthenic applications. Limited international clinical validation.

Comparison to bemetil: Phenylpiracetam is primarily a nootropic with secondary physical performance effects, whereas bemetil is primarily an actoprotector with secondary nootropic effects. The mechanisms are fundamentally different (glutamate receptor modulation vs. genomic protein synthesis). Bemetil has advantages in physical performance enhancement magnitude and in metabolic/antihypoxic effects; phenylpiracetam has advantages in cognitive enhancement specificity.

12.3 *Rhodiola rosea* extract (Salidroside/Rosavin standardization)

Mechanism: Natural adaptogen. The pharmacologically active constituents include salidroside (a phenylpropanoid glucoside), rosavins (cinnamyl alcohol glycosides), and multiple flavonoid and phenolic acid components. The mechanisms involve modulation of the hypothalamic-pituitary-adrenal axis, regulation of heat-shock protein expression (Hsp70), antioxidant activity, and monoamine oxidase inhibition [20]. The adaptogenic mechanism is pleiotropic and less mechanistically defined than the bemetil protein-synthesis mechanism.

Development trajectory: Traditional herbal medicine in Scandinavian, Russian, and Central Asian cultures for centuries. Extensive use in Soviet and Russian sports medicine and military applications, often concurrently with bemitil. Marketed globally as a dietary supplement with standardization to salidroside (1 to 3 percent) and rosavins (3 percent). Not subject to pharmaceutical registration in most jurisdictions; classified as a dietary supplement or traditional herbal medicine.

Novelty: Low. Natural adaptogens have been used for millennia. The standardized extract represents a modest refinement of the traditional preparation.

Effect size: Modest in physical performance and cognitive function in clinical trials. Meta-analyses report small but statistically significant effects on fatigue reduction and cognitive function under stress [20]. Effect sizes are consistently smaller than those reported for bemitil in comparable preclinical paradigms.

Promising potential: Moderate. Broad commercial availability and growing international clinical trial literature. The absence of regulatory barriers (dietary supplement classification) and the absence of doping restrictions support continued use in research and practice.

Side-effect profile: Excellent. Natural adaptogen with minimal adverse events at standard doses. Rare gastrointestinal discomfort and restlessness.

Overall validation: Moderate. Extensive traditional use and a growing international clinical literature, though with methodological limitations in many trials (small sample sizes, heterogeneous extract standardization, limited blinding).

Comparison to bemitil: *Rhodiola rosea* offers a superior safety profile and broader accessibility but produces smaller effect sizes and a less defined mechanism. Bemitil has advantages in effect magnitude, mechanistic specificity, and clinical evidence density (within the Russian-language literature). The two agents have been used concurrently in Soviet sports and military medicine, suggesting perceived complementarity.

12.4 Levamisole

Mechanism: Benzimidazole-related immunomodulatory agent (chemically a tetrahydroimidazothiazole, sharing the imidazole pharmacophore with the benzimidazole class). Originally developed as an anthelmintic; subsequently characterized as an immunostimulant through enhancement of T-cell function, macrophage

activation, and augmentation of cell-mediated immunity [21]. The immunomodulatory mechanism overlaps with the protein synthesis-dependent immunomodulation of bemitil.

Development trajectory: Originally registered as the anthelmintic Ergamisol (Janssen Pharmaceutica) in the 1960s. Subsequently developed for immunomodulatory indications including adjuvant cancer therapy (Dukes C colorectal cancer, in combination with fluorouracil) and autoimmune conditions. FDA-approved for both indications (anthelmintic registration withdrawn in 2000). Known as an adulterant in illicit cocaine due to its immunostimulant effects and low cost [21].

Novelty: Low. The compound has been in clinical use for over five decades. The immunomodulatory mechanism is well characterized.

Effect size: The immunomodulatory effects are clinically significant in cancer adjuvant therapy (demonstrated survival benefit in Dukes C colorectal cancer in combination with fluorouracil). Physical performance effects are absent; levamisole is not an actoprotector.

Promising potential: Low for actoprotector applications (not applicable). Moderate for immunomodulatory research.

Side-effect profile: Less favorable than bemitil. Levamisole is associated with agranulocytosis (a serious, potentially life-threatening adverse event), vasculitis, hepatotoxicity, and dermatological reactions at immunomodulatory doses [21]. These adverse events are substantially more severe than the mild gastrointestinal and psychoactivation effects of bemitil.

Overall validation: High for immunomodulation (FDA-approved indications, extensive international clinical literature). Not applicable for physical performance.

Comparison to bemitil: Levamisole shares the immunomodulatory property with bemitil and has a structural relationship through the imidazole pharmacophore, but the two compounds are otherwise distinct. Levamisole has no actoprotector, antihypoxic, or physical performance activity. Its adverse event profile (agranulocytosis) is substantially more severe than bemitil's. The comparison illustrates the unique positioning of bemitil as a compound that combines immunomodulation with metabolic enhancement and performance effects within a favorable safety profile.

12.5 Sulbutiamine (Arcalion)

Mechanism: Synthetic dimer of thiamine (vitamin B1), formed by linking two thiamine molecules through a disulfide bridge. The lipophilic structure enhances blood-brain barrier penetration relative to thiamine itself. The mechanism involves increased central thiamine and thiamine pyrophosphate concentrations, modulation of glutamatergic, cholinergic, and dopaminergic neurotransmission, and antiasthenic effects [22].

Development trajectory: Developed in Japan. Marketed in several countries under the trade name Arcalion for the treatment of asthenia and fatigue. Not approved by the United States FDA. The compound is available as a dietary supplement in some jurisdictions and as a prescription medicine in others [22].

Novelty: Low to moderate. The thiamine dimer concept is straightforward; the enhanced central bioavailability relative to thiamine is the principal innovation.

Effect size: Modest antiasthenic effects in clinical trials. The evidence base for physical performance enhancement is limited and inconsistent. Effect sizes in asthenia treatment appear comparable to or smaller than those reported for bemtil.

Promising potential: Low to moderate. The compound is commercially available in multiple markets but has not attracted substantial international clinical development interest.

Side-effect profile: Good. The principal adverse events are mild gastrointestinal discomfort and skin reactions. The safety profile is comparable to bemtil.

Overall validation: Low to moderate. The clinical literature is modest in size and methodological rigor. The compound serves as a reference antiasthenic agent for comparison purposes.

Comparison to bemtil: Sulbutiamine shares the antiasthenic application with bemtil and operates through a partially overlapping metabolic mechanism (enhanced cellular energy metabolism through thiamine-dependent enzymatic pathways). Bemtil has substantially broader pharmacological activity (physical performance, antihypoxic, antimutagenic, immunomodulatory) and a larger evidence base. Sulbutiamine has the advantage of international availability and a well-characterized safety profile. The two compounds could be used in combination for antiasthenic applications, though this combination has not been formally studied.

12.6 Comparator summary

The five comparators occupy distinct positions in the performance-enhancement and adaptogenic pharmacological space. **Bromantane** is the closest mechanistic relative to bemtil as the only other registered actoprotector, but operates through dopaminergic rather than genomic protein-synthesis mechanisms and is prohibited by WADA. **Phenylpiracetam** is primarily a nootropic with secondary performance effects and is also WADA-prohibited. **Rhodiola rosea** is a natural adaptogen with excellent safety but modest effect sizes and imprecise mechanism. **Levamisole** shares the immunomodulatory property but has no performance-enhancing activity and a substantially less favorable safety profile. **Sulbutiamine** shares the antiasthenic application but has narrower pharmacological scope and a smaller evidence base.

Bemtil occupies a unique position in this comparator landscape: it is the only compound that combines actoprotector activity (physical performance enhancement without increased oxygen consumption), antihypoxic activity (maintenance of performance under oxygen restriction), genomic activation of protein synthesis (a mechanism without parallel among the comparators), antioxidant enzyme induction, antimutagenic activity, immunomodulatory effects, and neuroprotective activity within a single molecular entity with a favorable safety profile and a decades-long operational track record. The principal limitation is the predominantly Russian-language evidence base and the absence of registration by any Western regulatory authority (FDA, EMA, TGA), which restricts international research application and necessitates reliance on research-grade material with independent analytical verification.

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