

RESEARCH MONOGRAPH . COMPOUND PROFILE

Aminotadalafil

A synthetic structural analog of tadalafil in which the piperazinedione N-methyl group is replaced by a primary amine, yielding an unapproved phosphodiesterase type 5 inhibitor principally encountered as an undeclared adulterant in dietary supplements marketed for erectile dysfunction.

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AUTHOR	Kodi <i>ac</i> bio <i>l</i> abs Research
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ABSTRACT

Aminotadalafil, formally (6R,12aR)-2-amino-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione (CAS 385769-84-6), is a synthetic structural analog of tadalafil, the selective cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) inhibitor marketed as Cialis for the treatment of erectile dysfunction, pulmonary arterial hypertension, and benign prostatic hyperplasia. The single structural modification that distinguishes aminotadalafil from the parent drug is the replacement of the N-methyl substituent on the 2-position of the piperazinedione (diketopiperazine) ring with a primary amino group (NH₂), a change that alters hydrogen-bonding capacity, basicity, and physicochemical properties while preserving the core beta-carboline-fused diketopiperazine scaffold responsible for PDE5 active-site recognition. Aminotadalafil retains inhibitory activity at PDE5 and exhibits greater than 100 percent cross-reactivity with anti-tadalafil polyclonal antibodies, confirming close structural and immunochemical homology with the parent compound [1]. The compound has not undergone formal preclinical toxicology, human pharmacokinetic characterization, or clinical efficacy evaluation in any regulatory jurisdiction, and it is not approved for human use by any national medicines authority. Its principal significance in the biomedical literature arises from its repeated identification as an undeclared adulterant in dietary supplements, herbal products, and electronic cigarette liquids marketed for sexual enhancement, where it poses uncharacterized risks to consumers who are unaware of its presence and who may be concurrently taking nitrate-containing

medications or other agents that interact with the cGMP-nitric oxide signaling pathway [2, 3, 4, 5].

The analytical chemistry literature on aminotadalafil is substantial. The compound has been identified and structurally characterized by proton and carbon-13 nuclear magnetic resonance spectroscopy, electrospray ionization mass spectrometry, Fourier transform infrared spectroscopy, and ultraviolet spectrophotometry in dietary supplement matrices across multiple continents, including reports from Latin America, Asia, Europe, and North America [2, 6, 7]. Validated high-performance liquid chromatography with diode array detection (HPLC-DAD) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods permit simultaneous identification and quantification of aminotadalafil alongside other PDE5 inhibitor analogs (hydroxythiohomosildenafil, thiosildenafil, dimethylsildenafil, thiodimethylsildenafil) in complex supplement matrices [3, 8]. A dimeric interaction product of aminotadalafil has also been isolated from adulterated health food products, suggesting that the compound undergoes degradation or condensation reactions under storage conditions encountered in supplement manufacture [9].

The pharmacological characterization of aminotadalafil is limited. No peer-reviewed study has reported a direct IC₅₀ determination for aminotadalafil against recombinant human PDE5, and no selectivity panel across the eleven mammalian phosphodiesterase families has been published. The compound's activity is inferred from its structural homology to tadalafil (IC₅₀ approximately 1.8 to 5.0 nanomolar against PDE5) and from the immunochemical cross-reactivity data. Structure-activity relationship studies of the broader tadalafil analog series indicate that modifications at the 2-

position of the diketopiperazine ring modulate PDE5 affinity, and that the (6R,12aR) stereochemistry derived from L-tryptophan is essential for potent inhibition [10, 11]. Aminotadalafil preserves this stereochemistry. No human pharmacokinetic, dose-response, or safety data exist; toxicological risk assessment must therefore rely on extrapolation from tadalafil and on the general pharmacology of the PDE5 inhibitor class. This monograph reviews the chemistry, structural pharmacology, inferred pharmacokinetics, regulatory history, detection methodology, sourcing considerations, and comparative assessment of aminotadalafil against five alternative PDE5 inhibitor analogs encountered in the adulterated supplement landscape.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Preferred name: Aminotadalafil.

Common synonyms: Amino tadalafil, amino-tadalafil, 2-aminotadalafil.

Chemical Abstracts Service registry number: 385769-84-6.

PubChem compound identifier (CID): 10178467.

International Union of Pure and Applied Chemistry name: (6R,12aR)-2-amino-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione.

Development codes: None assigned. Aminotadalafil has not entered formal pharmaceutical development. The compound first appeared in the patent literature describing tadalafil structure-activity relationships and was subsequently identified in the analytical chemistry literature as a dietary supplement adulterant [10, 12].

Regulatory classification: Aminotadalafil is not a scheduled substance, not a registered pharmaceutical ingredient, and not an approved active pharmaceutical ingredient in any jurisdiction. Regulatory agencies including the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Therapeutic Goods Administration (TGA) of Australia, and the Korea Food and Drug Administration (KFDA) have identified it as an undeclared ingredient in consumer products and have issued warnings or recall orders for products found to contain it [4, 5, 13].

1.2 Structural class and chemistry

Aminotadalafil belongs to the beta-carboline-fused diketopiperazine structural class, the same chemical scaffold that underlies tadalafil. The core structure consists of a tryptoline (1,2,3,4-tetrahydro-beta-carboline) ring system fused to a 2,5-diketopiperazine (piperazine-2,5-dione) ring, with a 1,3-benzodioxol-5-yl (piperonyl) substituent at the 6-position of the tryptoline. This tricyclic fused system is the pharmacophore for PDE5 active-site binding, with the planar indole moiety oc-

cupying the hydrophobic clamp region of the PDE5 catalytic domain and the diketopiperazine carbonyl groups forming hydrogen-bond contacts with invariant glutamine residues [10, 14].

The single structural modification that distinguishes aminotadalafil from tadalafil is at the 2-position of the diketopiperazine ring: tadalafil bears an N-methyl group (NCH₃), whereas aminotadalafil bears a primary amino group (NH₂). This substitution removes one carbon atom and three hydrogen atoms from the molecular formula, introduces a hydrogen-bond donor (the NH₂ group), and increases the basicity of the 2-position nitrogen relative to the tertiary amine in tadalafil. The modification is expected to alter aqueous solubility, crystal packing, plasma protein binding, and potentially metabolic susceptibility, though none of these parameters has been experimentally determined for aminotadalafil.

Molecular formula: C₂₁H₁₈N₄O₄.

Exact mass: 390.1328 g/mol (monoisotopic).

Molecular weight: 390.39 g/mol.

Physical properties: White to off-white crystalline powder. Soluble in dimethyl sulfoxide; sparingly soluble in methanol and ethanol; poorly soluble in water at neutral pH. Specific optical rotation, melting point, and partition coefficient have not been reported in peer-reviewed literature. The (6R,12aR) stereochemistry is assigned by analogy to tadalafil and is confirmed by the synthetic route proceeding from L-tryptophan [10].

Stereochemistry: Aminotadalafil contains two stereocenters at C-6 and C-12a of the tryptoline-diketopiperazine fusion. The compound as encountered in adulterated products is the (6R,12aR) diastereomer, corresponding to the cis-fused ring junction that is the pharmacologically active configuration in the tadalafil series. The (6R,12aR) configuration is derived from L-tryptophan through a Pictet-Spengler condensation with piperonal (3,4-methylenedioxybenzaldehyde) followed by diketopiperazine ring closure. Structure-activity studies of the tadalafil series have established that this configuration is essential for PDE5 inhibitory potency; the corresponding trans-fused diastereomers and the enantiomeric (6S,12aS) series are substantially less active [10, 11].

1.3 Synthesis

The synthesis of aminotadalafil proceeds through the same Pictet-Spengler approach used for tadalafil and its congeners. The general route involves three stages: (a) Pictet-Spengler condensation of L-tryptophan methyl ester with piperonal to yield a tetrahydro-beta-carboline amino acid ester with the (1S,3R) relative configuration (corresponding to the (6R,12aR) numbering in the final product); (b) acylation of the secondary amine with a suitable activated amino acid derivative bearing a protected amino group at what will become the 2-position; and (c) intramolecular cyclization to form the diketopiperazine ring, followed by deprotection of the amino group to yield the free 2-amino product [10, 11, 15].

In tadalafil synthesis, the acylation step uses chloroacetyl chloride followed by reaction with methylamine to install the N-methyl group. For aminotadalafil, the corresponding step uses a protected glycine derivative (for example, N-Boc-glycine or N-Cbz-glycine) to introduce a primary amine at the 2-position, with subsequent acidolytic or hydrogenolytic deprotection. Alternative routes employing direct amination or reductive amination at the 2-position of a preformed N-unsubstituted diketopiperazine (nortadalafil) have been described in the patent literature [12, 15].

The synthesis of dimeric tadalafil analog adulterants, including products derived from aminotadalafil condensation reactions, has been independently verified and structurally revised by Lee et al. (2017), confirming the synthetic accessibility and chemical reactivity of the 2-amino functional group [16].

Research-grade aminotadalafil is supplied by multiple chemical vendors (MedChemExpress, Cayman Chemical, Sigma-Aldrich, APExBIO, LGC Standards) at stated purities of greater than 98 percent by HPLC, typically as the free base. Analytical reference standards for regulatory and forensic laboratories are supplied by LGC Standards and Cerilliant at certified purities.

2. Abstract

Aminotadalafil (CAS 385769-84-6) is a synthetic, unapproved phosphodiesterase type 5 (PDE5) inhibitor analog derived from tadalafil by replacement of the piperazinedione N-methyl substituent with a primary amino group. The compound has not undergone formal pharmaceutical development, preclinical toxicology assessment, or clinical evaluation in any jurisdiction [1, 2]. Its biomedical significance arises almost entirely from its identification as one of the most frequently encountered undeclared PDE5 inhibitor analogs in dietary supplements, herbal remedies, and novel consumer products (including electronic cigarette liquids) marketed for sexual enhancement [3, 4, 5, 6].

The analytical chemistry literature on aminotadalafil is extensive and spans multiple continents. Validated LC-MS/MS and HPLC-DAD methods have been developed for its detection and quantification in complex matrices, and it is included in the screening panels of most national regulatory laboratories tasked with supplement adulteration surveillance [3, 7, 8]. The compound has been detected in products marketed in Argentina, Brazil, South Korea, Japan, Singapore, the Netherlands, the United States, and multiple other jurisdictions, frequently in combination with other undeclared PDE5 inhibitor analogs such as hydroxythiohomosildenafil, thiosildenafil, and dimethylsildenafil [2, 3, 6, 7].

The pharmacological characterization of aminotadalafil is incomplete. No direct IC₅₀ measurement against recombinant PDE5 has been published. No selectivity profile across the phosphodiesterase family has been reported. Immunochemical cross-reactivity with anti-tadalafil polyclonal antibodies exceeds 100 percent, confirming close epitope homology [1]. Structure-activity analysis of the tadalafil dike-topiperazine series indicates that modifications at the 2-position modulate but do not abolish PDE5 affinity, and that the (6R,12aR) stereochemistry retained in aminotadalafil is the principal determinant of active-site recognition [10, 11]. Human pharmacokinetic data do not exist; inferred pharmacokinetics are extrapolated from tadalafil (CYP3A4-mediated metabolism, approximately 17.5-hour terminal half-life, approximately 80 percent oral bioavailability) with the caveat that the amino-to-methyl substitution may alter metabolic susceptibility and protein binding [17, 18].

The public health concern surrounding aminotadalafil centers on its undeclared presence in products consumed by individuals who may have contraindications to PDE5 inhibitor therapy, particularly concurrent nitrate use, where the synergistic cGMP elevation can produce life-threatening hypotension. The absence of dose standardization, purity control, and safety monitoring in adulterated products compounds this risk. Regulatory agencies have responded with product recalls, import alerts, and expanded screening programs, but the pace of novel analog appearance continues to outstrip detection capacity [4, 5, 13, 19].

3. Discovery and Development History

3.1 Origin in the tadalafil medicinal chemistry program

Aminotadalafil was first described in the patent literature associated with the structure-activity exploration of the tadalafil (IC-351) scaffold at ICOS Corporation and Eli Lilly. The discovery of tadalafil itself, reported by Daugan et al. (2003) in the *Journal of Medicinal Chemistry*, involved systematic exploration of the beta-carboline-diketopiperazine scaffold derived from Pictet-Spengler chemistry on tryptophan [10]. The medicinal chemistry program evaluated hundreds of analogs with modifications at the diketopiperazine nitrogen, at the 6-position aryl substituent, and at the tryptoline ring system. Aminotadalafil (the 2-amino analog) was among the compounds disclosed in patent filings but was not selected for development, presumably because the N-methyl analog (tadalafil) offered a superior combination of potency, selectivity, and pharmacokinetic properties for the intended clinical indications [10, 12].

3.2 Emergence as a dietary supplement adulterant

The earliest published identification of aminotadalafil in a consumer product appeared in the mid-2000s, coinciding with the broader emergence of designer PDE5 inhibitor analogs in the global supplement market. Zou et al. (2006) described the use of Fourier transform ion cyclotron resonance mass spectrometry for structure elucidation of designer drug analogs of tadalafil, vardenafil, and sildenafil in herbal and pharmaceutical matrices, establishing the analytical framework that would be applied to aminotadalafil detection [20]. By 2008, aminotadalafil had been identified in products seized in East Asia, and by 2010 its detection had been reported across multiple regulatory jurisdictions [6, 7, 21].

3.3 Proliferation and regulatory response

The Venhuis and de Kaste (2012) review, covering approximately a decade of PDE5 inhibitor analog detection in food supplements, catalogued at least 46 distinct analogs of sildenafil, tadalafil, and vardenafil that had been identified in consumer products [19]. Aminotadalafil was among the most frequently detected tadalafil

analogs. The intellectual origin of most analogs, including aminotadalafil, was traced to patent literature that described structure-activity relationships during the drug discovery process; the patents provided synthetic instructions that facilitated manufacture by clandestine or unregulated laboratories [19].

Regulatory responses have included product recalls by the FDA, KFDA, and TGA; import alerts and detention without physical examination orders for products from identified manufacturers; and the inclusion of aminotadalafil in expanded LC-MS/MS screening panels operated by national regulatory laboratories [4, 5, 13]. Despite these measures, the detection of aminotadalafil in consumer products has continued through the most recent reporting periods, reflecting the compound's synthetic accessibility and the economic incentive to adulterate sexual enhancement products with pharmacologically active ingredients [19, 22].

3.4 Current status

Aminotadalafil has not entered formal pharmaceutical development. No investigational new drug application, clinical trial authorization, or marketing authorization has been filed for this compound in any jurisdiction. Its status remains that of an unapproved pharmaceutical analog with no characterized safety profile and no legitimate therapeutic application. Research-grade material is commercially available for analytical, forensic, and in vitro pharmacological investigation.

4. Mechanism of Action

4.1 PDE5 inhibition (inferred)

The mechanism of action of aminotadalafil is inferred from its structural homology to tadalafil and from the general pharmacology of the PDE5 inhibitor class. No direct enzymological characterization of aminotadalafil against recombinant PDE5 has been published in the peer-reviewed literature.

Phosphodiesterase type 5 (PDE5) is a cGMP-specific cyclic nucleotide phosphodiesterase expressed at high density in the smooth muscle of the corpus cavernosum, in pulmonary vascular smooth muscle, and at lower density in platelets, vascular endothelium, visceral smooth muscle, and selected neuronal populations. The enzyme catalyzes the hydrolysis of cGMP to 5'-GMP, terminating the second-messenger signal initiated by nitric oxide (NO)-stimulated soluble guanylate cyclase activation. Inhibition of PDE5 elevates intracellular cGMP concentration, prolonging smooth muscle relaxation and vasodilation in tissues where the NO-cGMP pathway is active [14, 23].

Tadalafil inhibits PDE5 with an IC₅₀ of approximately 1.8 to 5.0 nanomolar against recombinant human enzyme, with greater than 700-fold selectivity over PDE1 through PDE4, PDE7 through PDE10, and approximately 40-fold selectivity over PDE11A [14, 17]. The binding mode, characterized by X-ray crystallography of the PDE5 catalytic domain with tadalafil and analogs, involves the planar indole ring system occupying the hydrophobic clamp formed by Phe820, Val782, and Leu804; the diketopiperazine carbonyls forming hydrogen bonds with the invariant Gln817; and the methylenedioxy ring of the piperonyl substituent occupying a hydrophobic pocket adjacent to the metal-binding site [14].

Aminotadalafil preserves the indole ring system, the diketopiperazine carbonyls, the piperonyl substituent, and the (6R,12aR) stereochemistry. The sole modification (NH₂ replacing NCH₃ at the 2-position) is located on the diketopiperazine ring at a position that is oriented away from the deepest contacts in the PDE5 active site but that participates in solvent-exposed interactions and potentially in secondary hydrogen-bonding contacts with the protein surface. The immunochemical cross-re-

activity of aminotadalafil with anti-tadalafil polyclonal antibodies at 105.2 percent of the tadalafil response confirms that the three-dimensional epitope presentation is closely conserved [1].

On the basis of these structural considerations, aminotadalafil is predicted to retain PDE5 inhibitory activity. The magnitude of the IC₅₀ shift relative to tadalafil cannot be precisely estimated without direct enzymological data, but the conservation of all primary pharmacophoric elements suggests that the potency is within an order of magnitude of the parent compound. Structure-activity relationship studies of related 2-position modifications (nortadalafil, chloropretadalafil, hydroxypretadalafil) indicate that this position tolerates diverse substituents with retention of PDE5 activity, though with variable effects on potency and selectivity [10, 11, 15, 24].

4.2 Selectivity considerations

Tadalafil exhibits measurable cross-reactivity with PDE11A (IC₅₀ approximately 73 nanomolar, roughly 40-fold over the PDE5 IC₅₀) [17]. PDE11A is expressed in the prostate, testis, skeletal muscle, and pituitary gland; the clinical significance of PDE11A inhibition by tadalafil has not been clearly established, though it has been investigated in the context of spermatogenesis and testicular function. Whether aminotadalafil retains, loses, or gains PDE11A cross-reactivity relative to tadalafil is unknown. The same uncertainty applies to the other phosphodiesterase isoforms (PDE1 through PDE10), for which no aminotadalafil inhibition data exist.

The Medsafe (New Zealand) classification report on PDE5 inhibitor analogs noted that some analogs are likely to be considerably more potent than the parent inhibitor and that any loss of selectivity in PDE inhibition invoked by structural modification may result in an increase in the severity of known off-target adverse effects [13]. This general caution applies to aminotadalafil in the absence of selectivity data.

4.3 Downstream pharmacology

If aminotadalafil inhibits PDE5 at pharmacologically relevant concentrations (a reasonable inference from the structural analysis), the downstream pharmacological consequences are expected to parallel those of tadalafil: elevation of intracellular cGMP in smooth muscle cells where the NO-cGMP pathway is active, resulting in

smooth muscle relaxation and vasodilation. The principal physiological consequence in erectile tissue is facilitation of penile erection in response to sexual stimulation (which provides the NO signal). The principal physiological consequence in pulmonary vasculature is reduction of pulmonary arterial pressure. Systemic vasodilation produces the characteristic adverse-event profile of the PDE5 inhibitor class: headache, flushing, nasal congestion, dyspepsia, and back pain [17, 23].

The critical pharmacological interaction is with organic nitrates (nitroglycerin, isosorbide mononitrate, isosorbide dinitrate) and other NO donors. Concurrent administration of a PDE5 inhibitor and an organic nitrate produces synergistic and potentially fatal hypotension through dual amplification of the cGMP signal (increased synthesis by NO-stimulated guanylate cyclase plus decreased degradation by PDE5 inhibition). This interaction is the basis for the absolute contraindication of approved PDE5 inhibitors in patients receiving nitrate therapy and is the principal acute safety concern with undeclared aminotadalafil in consumer products [17, 23].

5. Pharmacokinetics

5.1 Absence of direct data

No pharmacokinetic study of aminotadalafil has been conducted in humans or in animal models. All pharmacokinetic discussion in this section is inferred from the known pharmacokinetics of tadalafil, with qualitative adjustments for the structural modification at the 2-position of the diketopiperazine ring.

5.2 Inferred absorption

Tadalafil is well absorbed after oral administration, with an absolute bioavailability of approximately 80 percent and a time to maximum plasma concentration (Tmax) of approximately 2 hours [17, 18]. Absorption is not affected by food. The high bioavailability reflects moderate first-pass metabolism and favorable physicochemical properties (molecular weight 389.4, moderate lipophilicity, adequate aqueous solubility as the formulated product).

Aminotadalafil (molecular weight 390.4) has a similar molecular size and retains the core lipophilic scaffold. The introduction of a primary amino group at the 2-position increases hydrogen-bonding capacity and may modestly increase aqueous solubility at acidic pH (where the amino group would be partially protonated), potentially favoring gastric absorption. Conversely, the increased polarity could reduce passive membrane permeability. In the absence of experimental data, oral bioavailability is provisionally estimated as comparable to tadalafil, though this estimate carries substantial uncertainty.

5.3 Inferred distribution

Tadalafil has a steady-state volume of distribution of approximately 63 liters and is 94 percent bound to plasma proteins, predominantly albumin [17, 18]. The introduction of a primary amino group may alter protein binding through additional ionic interactions with acidic residues on albumin; however, the effect is expected to be modest given the preservation of the overall molecular topology.

5.4 Inferred metabolism

Tadalafil is predominantly metabolized by cytochrome P450 3A4 (CYP3A4), with the principal metabolic transformation being the formation of a catechol metabolite through demethylenation of the methylenedioxy ring, followed by methylation and glucuronidation to produce the methylcatechol glucuronide conjugate [17, 18]. The terminal elimination half-life of tadalafil is approximately 17.5 hours, and the mean oral clearance is approximately 2.5 liters per hour.

The CYP3A4-mediated demethylenation occurs on the piperonyl ring, remote from the 2-position modification in aminotadalafil. The principal metabolic pathway is therefore expected to be preserved. However, the primary amino group at the 2-position introduces a potential site for additional metabolic transformations, including N-acetylation (by hepatic N-acetyltransferases NAT1 and NAT2), oxidative deamination, and conjugation with glucuronic acid or sulfate. These additional metabolic routes could either accelerate or retard overall elimination depending on their kinetic contribution. In N-acetyltransferase rapid acetylators, the amino group might be efficiently acetylated to yield what would effectively be a nor-tadalafil-N-acetyl metabolite, potentially with altered pharmacological activity.

5.5 Inferred elimination

Tadalafil and its metabolites are excreted predominantly in the feces (approximately 61 percent) and urine (approximately 36 percent), with less than 0.1 percent of the administered dose recovered unchanged in urine [17]. The renal and fecal elimination proportions for aminotadalafil are unknown but are expected to be broadly similar given the preserved core structure and the predicted preservation of the CYP3A4-mediated metabolic pathway.

5.6 Drug interactions (inferred)

By analogy to tadalafil, the following drug interactions are predicted for aminotadalafil:

Strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin): predicted to substantially increase aminotadalafil exposure, as demonstrated for tadalafil where ketoconazole 400 mg daily increased tadalafil AUC by 312 percent [17].

Strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, phenobarbital): predicted to substantially decrease aminotadalafil exposure, as demonstrated for tadalafil where rifampin 600 mg daily reduced tadalafil AUC by 88 percent [17].

Organic nitrates: absolute contraindication by class mechanism, as discussed in Section 4.3.

Alpha-adrenergic antagonists: potential for additive hypotension, as documented for tadalafil with doxazosin, tamsulosin, and alfuzosin [17].

5.7 Special population considerations

No data exist for aminotadalafil in any special population (pediatric, geriatric, hepatic impairment, renal impairment, pregnancy, lactation). The compound is not approved for human use, and no dose adjustment guidance can be provided.

6. Preclinical Pharmacology

6.1 In vitro characterization

Formal in vitro pharmacological characterization of aminotadalafil is limited to immunochemical cross-reactivity studies. Amino tadalafil can be specifically detected by anti-tadalafil polyclonal antibodies, with a cross-reactivity of 105.2 percent relative to tadalafil, indicating that the antibody-binding epitope encompassing the core beta-carboline-diketopiperazine scaffold is preserved [1].

No published study has reported IC₅₀ values for aminotadalafil against recombinant PDE5, PDE1 through PDE4, PDE6 through PDE11, or any other enzyme or receptor target. No radioligand displacement, functional cGMP accumulation, or smooth muscle relaxation assay data have been published.

Diketopiperazine-based tadalafil analogs with modifications at the 2-position have been evaluated for PDE5 inhibitory activity and for anticancer activity in broader analog series. Abuo-Rahma et al. (2016) and related groups have synthesized novel tadalafil analogs and evaluated them as phosphodiesterase inhibitors and colon tumor cell growth inhibitors, demonstrating that the diketopiperazine 2-position tolerates a range of substituents while retaining measurable PDE5 activity [11, 25]. These studies did not specifically evaluate aminotadalafil but provide indirect support for the prediction that the 2-amino modification preserves PDE5 inhibition.

6.2 In vivo pharmacology

No in vivo pharmacology studies (efficacy, toxicology, or pharmacokinetics) of aminotadalafil in animal models have been published in the peer-reviewed literature. The compound has not undergone the preclinical safety assessment (acute toxicity, subchronic toxicity, genotoxicity, reproductive toxicity, carcinogenicity) required for investigational new drug applications.

6.3 Interaction products and degradation

Uchiyama et al. (2010) isolated and structurally characterized an interaction product of aminotadalafil from an illegal health food product, demonstrating that the compound undergoes chemical degradation or condensation under the uncontrolled manufacturing and storage conditions characteristic of adulterated supplements [9]. Lee et al. (2017) subsequently synthesized and structurally revised dimeric tadalafil analog adulterants, including species formed from aminotadalafil, confirming the formation of dimeric condensation products through the reactive primary amino group [16]. These degradation and interaction products have unknown pharmacological activity and represent an additional layer of safety uncertainty for consumers of adulterated products.

7. Clinical Evidence Base

7.1 Absence of clinical trials

No clinical trial of aminotadalafil has been conducted, registered, or reported. The compound has not been administered to human subjects under controlled conditions with prospective safety monitoring, efficacy assessment, or pharmacokinetic characterization. No investigational new drug application or clinical trial authorization has been filed for aminotadalafil in any jurisdiction.

7.2 Indirect human exposure data

Human exposure to aminotadalafil occurs exclusively through inadvertent consumption of adulterated dietary supplements and related products. The scale of this exposure is difficult to quantify but is inferred to be substantial on the basis of the widespread detection of aminotadalafil in products sold across multiple continents and the estimated volume of the sexual enhancement supplement market [19, 22].

Tucker et al. (2018), in a JAMA Network Open analysis of unapproved pharmaceutical ingredients in dietary supplements associated with FDA warnings, documented that PDE5 inhibitors and their analogs were the most frequently identified class of undeclared pharmaceutical ingredients in sexual enhancement supplements [4]. Aminotadalafil was among the analogs identified. In a cross-sectional survey of adulterated sexual enhancement products sold in the Sacramento area of California, 67 percent of tested products were found to be adulterated with at least one PDE5 inhibitor or analog [22].

7.3 Adverse event reports

No published case reports specifically attribute adverse events to aminotadalafil exposure as distinct from exposure to the parent compound tadalafil or to other co-present adulterants. Adverse event reports associated with adulterated sexual enhancement supplements generally describe the PDE5 inhibitor class effect profile (headache, flushing, visual disturbances, priapism) and, in serious cases, synergis-

tic hypotension with concurrent nitrate therapy [4, 5, 23]. Attribution to a specific analog is rarely possible because most adulterated products contain multiple undeclared active ingredients.

7.4 Regulatory pharmacovigilance

The FDA maintains a MedWatch database of adverse events associated with dietary supplements. PDE5 inhibitor analog-adulterated products have been the subject of multiple safety communications, though individual analog-level attribution is typically not provided in public safety alerts. The FDA, KFDA, and other regulatory agencies have issued specific warnings naming aminotadalafil as an identified adulterant [4, 5, 13].

8. Sourcing and Quality Verification

8.1 Research-grade material

Research-grade aminotadalafil is supplied by multiple chemical and pharmaceutical research suppliers, including MedChemExpress (catalog HY-13673), Cayman Chemical (catalog 20876), APExBIO, Sigma-Aldrich, LGC Standards (catalog MM1271.00), and others. Stated purities are typically greater than 98 percent by HPLC. Material is supplied as the free base in milligram quantities as a crystalline or lyophilized powder [1].

Certified reference standards for regulatory and forensic analytical work are supplied by LGC Standards and Cerilliant (a Sigma-Aldrich subsidiary), with certificates of analysis documenting identity confirmation by NMR, mass spectrometry, and HPLC purity determination.

8.2 Analytical verification

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

- High-performance liquid chromatography area-percent purity (target: greater than 98 percent)
- Electrospray ionization mass spectrometry confirmation of molecular ion ($[M+H]^+$ at m/z 391.14)
- Proton nuclear magnetic resonance spectroscopy comparison against published spectral data [2, 6]
- Chiral HPLC or optical rotation measurement to confirm the (6R,12aR) stereochemistry, particularly for lots intended for stereospecific PDE5 binding studies
- Residual solvent analysis for common synthesis solvents

8.3 Stability and storage

The solid material is stable at room temperature under dry conditions. Refrigerated storage (2 to 8 degrees Celsius) with desiccant protection is recommended for long-term archival. Solutions in dimethyl sulfoxide are stable at minus 20 degrees Celsius for at least 6 months. Aqueous solutions at neutral pH should be used within 24 hours of preparation owing to the potential for hydrolytic degradation of the diketopiperazine ring and the documented formation of dimeric interaction products from the reactive amino group [9, 16].

9. Reconstitution and Handling

Aminotadalafil is supplied as a crystalline or amorphous solid. For in vitro research applications, the compound is typically dissolved in dimethyl sulfoxide (DMSO) to prepare stock solutions at 10 to 100 millimolar concentration. The DMSO stock is then diluted into aqueous assay buffer to the desired working concentration, maintaining a final DMSO concentration of less than 0.1 percent (volume/volume) to avoid solvent effects on enzyme or cell-based assays.

For analytical reference preparation, the compound is dissolved in methanol or acetonitrile at 1 mg/mL and serially diluted for calibration curves in LC-MS/MS or HPLC-DAD assays.

Light protection is not specifically required but is reasonable practice for solutions used in spectrophotometric assays. The compound should be handled with standard laboratory precautions for pharmacologically active research chemicals: gloves, eye protection, and fume hood use during weighing and dissolution. Aminotadalafil is a pharmacologically active PDE5 inhibitor analog, and inadvertent exposure through skin contact or inhalation of powder should be minimized.

Parenteral formulations have not been developed. The compound is not approved for human use and should not be formulated for administration to human subjects outside of a properly authorized clinical investigation with appropriate regulatory and ethical oversight.

10. Stack Interactions and Combinations

10.1 Pharmacokinetic interactions

By analogy to tadalafil, the principal pharmacokinetic interaction pathway for aminotadalafil is CYP3A4-mediated metabolism. Strong CYP3A4 inhibitors (azole antifungals, macrolide antibiotics, HIV protease inhibitors, grapefruit juice in large quantities) are predicted to increase aminotadalafil exposure substantially. Strong CYP3A4 inducers (rifamycins, certain anticonvulsants, St. John's Wort) are predicted to decrease exposure [17, 18].

The primary amino group at the 2-position introduces a potential substrate for N-acetyltransferase (NAT1, NAT2) polymorphic metabolism, a pathway not relevant to tadalafil. If N-acetylation contributes meaningfully to aminotadalafil clearance, then NAT2 slow acetylator phenotype (approximately 50 percent of European-ancestry populations, approximately 10 to 15 percent of East Asian populations) could result in elevated aminotadalafil exposure, analogous to the well-characterized isoniazid and hydralazine acetylation polymorphisms. This interaction pathway is hypothetical and has not been experimentally evaluated.

10.2 Pharmacodynamic interactions

Organic nitrates and NO donors: Absolute contraindication by class mechanism. Concurrent administration produces synergistic and potentially fatal hypotension through dual amplification of cGMP signaling [17, 23].

Alpha-adrenergic antagonists: Additive hypotensive effect predicted, particularly with non-selective alpha-1 antagonists (doxazosin, terazosin, prazosin). Tadalafil labeling recommends caution with alpha-blockers and suggests initiation at the lowest dose [17].

Other PDE5 inhibitors: Concurrent use with sildenafil, vardenafil, avanafil, or their analogs is pharmacologically additive and increases the risk of PDE5 class adverse events (hypotension, priapism, visual disturbances). Adulterated supple-

ments frequently contain multiple PDE5 inhibitor analogs simultaneously, compounding this risk [3, 19, 22].

Antihypertensive agents: Additive blood pressure reduction predicted with all antihypertensive classes, particularly with agents that act through the NO-cGMP pathway or through vascular smooth muscle relaxation.

Riociguat and other soluble guanylate cyclase stimulators: Contraindicated by mechanism; concurrent use with PDE5 inhibitors produces excessive cGMP elevation [23].

Alcohol: Additive vasodilation and hypotensive effect; tadalafil labeling notes modest additive blood pressure reduction with alcohol consumption [17].

10.3 Research combination considerations

In research settings, aminotadalafil is used primarily as an analytical reference standard rather than as a pharmacological tool compound. Investigators conducting in vitro PDE5 inhibition studies should be aware that the reactive primary amino group may form covalent adducts with aldehyde-containing buffer components, with activated esters in assay reagents, and with itself (dimeric products) under extended incubation conditions [9, 16].

11. Adverse Events and Safety Signal

11.1 Absence of systematic safety data

No systematic safety assessment of aminotadalafil has been conducted in humans or animals. No preclinical toxicology package, no clinical safety database, and no postmarketing pharmacovigilance system exists for this compound. All safety discussion is inferred from the PDE5 inhibitor class pharmacology and from the adverse event literature associated with adulterated dietary supplements.

11.2 Inferred class adverse events

On the basis of PDE5 inhibitor class pharmacology, the following adverse events are predicted at pharmacologically active doses:

- Headache (the most common PDE5 inhibitor class effect, reported in 10 to 15 percent of tadalafil users)
- Flushing (3 to 10 percent with tadalafil)
- Dyspepsia (5 to 10 percent with tadalafil)
- Nasal congestion (2 to 5 percent with tadalafil)
- Back pain and myalgia (5 to 10 percent with tadalafil, relatively specific to the tadalafil series and attributed to PDE11A cross-reactivity)
- Dizziness (1 to 3 percent with tadalafil)
- Visual disturbances (rare with tadalafil; more common with sildenafil and vardenafil due to PDE6 cross-reactivity)

11.3 Serious safety concerns

Nitrate interaction: The synergistic hypotension produced by concurrent PDE5 inhibitor and organic nitrate use is the principal acute life-threatening risk. This interaction is pharmacologically predictable and is the basis for the absolute contraindication in approved PDE5 inhibitor labeling. Consumers of adulterated sup-

plements containing aminotadalafil are particularly vulnerable because they are unaware of PDE5 inhibitor exposure and may not inform healthcare providers of supplement use when nitrate therapy is prescribed [4, 5, 23].

Priapism: Prolonged erection (greater than 4 hours) requiring medical intervention is a rare but serious PDE5 inhibitor class effect. Risk is increased in individuals with anatomical deformation of the penis, in patients with conditions predisposing to priapism (sickle cell disease, multiple myeloma, leukemia), and potentially at supratherapeutic doses.

Cardiovascular events: Tadalafil and other approved PDE5 inhibitors carry warnings regarding use in patients with cardiovascular disease, particularly those in whom sexual activity is inadvisable. The same concerns apply to aminotadalafil, compounded by the absence of dose control in adulterated products.

Hearing loss: Sudden sensorineural hearing loss has been reported with approved PDE5 inhibitors as a rare class effect [23].

11.4 Additional risks specific to aminotadalafil

Unknown toxicology: The absence of preclinical toxicology data means that organ-specific toxicities, genotoxicity, reproductive toxicity, and carcinogenic potential have not been assessed. The amino group modification could introduce toxicological liabilities not present in tadalafil, including reactive metabolite formation or off-target receptor interactions.

Degradation products: The documented formation of dimeric and other interaction products from the reactive amino group under storage conditions introduces exposure to chemical species with completely unknown toxicological profiles [9, 16].

Dose uncertainty: Adulterated products lack dose standardization. Analytical surveys have documented wide variability in the quantity of undeclared PDE5 inhibitor analogs present in individual dosage units, ranging from subtherapeutic to supratherapeutic concentrations of the parent compound equivalents [19, 22].

Polypharmacy in adulterated products: Most adulterated sexual enhancement supplements contain multiple undeclared active ingredients (PDE5 inhibitor analogs, sibutramine, phenolphthalein, yohimbine), compounding the unpredictability of the pharmacological and toxicological response [4, 22].

12. Comparative Assessment

This section presents a structured comparative assessment of five PDE5 inhibitor analogs frequently encountered in the adulterated dietary supplement landscape, evaluated against aminotadalafil on five competency standards: structural novelty, inferred potency, detection prevalence, safety characterization, and regulatory response. The five comparators were selected as the principal tadalafil and sildenafil analogs co-detected with aminotadalafil in supplement screening programs.

12.1 Hydroxythiohomosildenafil

Structural class: Sildenafil analog with hydroxyl and thio modifications on the sulfonamide and piperazine moieties.

Structural novelty: Moderate. The compound represents a double modification of the sildenafil scaffold (thio substitution plus hydroxyl addition plus homologation), producing a structure that is not directly interconvertible with sildenafil by simple single-step chemistry. The structural distance from the parent compound is greater than that of aminotadalafil from tadalafil.

Inferred potency: No published IC₅₀ data. Inferred PDE5 inhibitory activity from sildenafil structural homology. The thio modification at the sulfonamide may alter selectivity between PDE5 and PDE6.

Detection prevalence: High. Hydroxythiohomosildenafil is among the most frequently co-detected PDE5 inhibitor analogs in screening studies alongside aminotadalafil [3, 8].

Safety characterization: No preclinical or clinical safety data. Risk profile inferred from PDE5 inhibitor class pharmacology with additional uncertainty from the thio and hydroxyl modifications.

Regulatory response: Included in FDA, KFDA, and TGA screening panels. Subject to product recalls and import alerts [4, 5].

Comparison to aminotadalafil: Both compounds are frequently co-detected in the same adulterated products. Hydroxythiohomosildenafil is derived from the sildenafil scaffold (pyrazolopyrimidine) rather than the tadalafil scaffold (beta-carboline-diketopiperazine), producing a structurally distinct pharmacophore. Neither compound has published IC50 data. Both carry equivalent levels of safety uncertainty.

12.2 Thiosildenafil

Structural class: Sildenafil analog with a sulfur atom replacing the oxygen in the sulfonamide carbonyl.

Structural novelty: Low. The single thio-for-oxo substitution is a minimal structural modification.

Inferred potency: Thiosildenafil has been reported to inhibit PDE5 with potency comparable to sildenafil in at least one published assessment. The thio modification is a bioisosteric replacement that generally preserves target binding.

Detection prevalence: High. Among the most commonly identified PDE5 inhibitor analogs globally [3, 8, 19].

Safety characterization: Minimal. No systematic preclinical or clinical data. The thio modification introduces a potential for different metabolic activation pathways.

Regulatory response: Included in standard screening panels across multiple jurisdictions [4, 5, 13].

Comparison to aminotadalafil: Thiosildenafil is sildenafil-derived and therefore inhibits PDE5 through a different structural class than aminotadalafil. Both are commonly detected adulterants. Thiosildenafil may have slightly better-characterized potency owing to the minimal nature of the structural modification and the direct bioisosteric relationship with sildenafil.

12.3 Nortadalafil (Demethyltadalafil)

Structural class: Tadalafil analog with the N-methyl group at the 2-position of the diketopiperazine replaced by hydrogen (NH).

Structural novelty: Low. The demethylation at the 2-position is a minimal structural modification and is, in fact, the expected Phase I metabolic product of tadalafil.

Inferred potency: Nortadalafil retains PDE5 inhibitory activity. The demethylation removes a hydrophobic contact but does not introduce new functionality. Potency is inferred to be modestly reduced relative to tadalafil.

Detection prevalence: Moderate. Nortadalafil is detected in adulterated products but less frequently than aminotadalafil or the sildenafil analogs [19, 24].

Safety characterization: Minimal. As a Phase I metabolite of tadalafil, nortadalafil has been characterized in metabolic studies but not in independent safety evaluation.

Regulatory response: Included in screening panels in some jurisdictions [13, 19].

Comparison to aminotadalafil: Nortadalafil and aminotadalafil are closely related; both are 2-position modifications of tadalafil. Nortadalafil replaces NCH₃ with NH; aminotadalafil replaces NCH₃ with NNH₂. Aminotadalafil has the additional amino hydrogen-bond donor that nortadalafil lacks. Both are expected to retain PDE5 activity. Aminotadalafil has the unique reactivity of the primary amino group that produces the dimeric interaction products not observed with nortadalafil.

12.4 Chloropretadalafil

Structural class: Tadalafil analog with a chloro substituent on the piperonyl ring and modifications to the diketopiperazine nitrogen.

Structural novelty: Moderate. The chloro substitution on the aromatic ring modifies the electronic and steric properties of the piperonyl pharmacophore.

Inferred potency: No published IC₅₀ data. The chloro substitution is expected to modulate aromatic ring electron density and potentially alter the hydrophobic contacts in the PDE5 active-site pocket.

Detection prevalence: Low to moderate. Chloropretadalafil has been detected in products subject to FDA recalls [5, 24].

Safety characterization: No preclinical or clinical data. The chloro substituent introduces a potential metabolic liability (reductive dehalogenation, reactive metabolite formation).

Regulatory response: Named in specific FDA recall communications [5].

Comparison to aminotadalafil: Chloropretadalafil modifies a different region of the tadalafil scaffold (the piperonyl aromatic ring rather than the diketopiperazine nitrogen). The two compounds represent orthogonal structure-activity probes of the tadalafil pharmacophore. Aminotadalafil is more frequently detected in global surveillance.

12.5 Dimethylsildenafil (Homosildenafil)

Structural class: Sildenafil analog with additional methyl groups on the piperazine nitrogen, extending the side chain.

Structural novelty: Low. The homologation of the piperazine N-methyl to N,N-dimethyl is a minimal modification.

Inferred potency: Dimethylsildenafil has been reported to retain PDE5 inhibitory activity. The extended alkyl chain modestly alters the steric environment near the solvent-exposed face of the sildenafil binding pose.

Detection prevalence: High. Among the most commonly detected sildenafil analogs in dietary supplement screening [3, 8, 19].

Safety characterization: No systematic safety data. Risk profile inferred from sildenafil class pharmacology.

Regulatory response: Included in standard screening panels. Subject to product recalls [4, 5].

Comparison to aminotadalafil: Both are frequently co-detected adulterants representing modifications to different parent PDE5 inhibitor scaffolds. Both lack systematic safety data. Both are synthetically accessible from patent-disclosed intermediates.

12.6 Comparator summary

The five comparator analogs and aminotadalafil share a common profile: they are unapproved PDE5 inhibitor analogs derived from patent literature, synthesized for illicit incorporation into dietary supplements, lacking systematic pharmacological and toxicological characterization, and presenting unquantified safety risks to consumers. The principal differentiating features are structural class (tadalafil-derived versus sildenafil-derived), frequency of detection in global surveillance, and the specific chemical reactivity introduced by the structural modification.

Aminotadalafil occupies a position of moderate structural novelty (single-atom substitution with the addition of a reactive functional group), high detection prevalence, and average safety uncertainty within this comparator group. Its unique feature is the reactive primary amino group, which produces documented dimeric interaction products of unknown toxicological significance. Among the tadalafil analogs in the panel, aminotadalafil is more frequently detected than nortadalafil or chloropretadalafil, reflecting either greater synthetic accessibility, greater commercial availability of starting materials, or preferential selection by manufacturers of adulterated products.

The overarching finding of this comparative assessment is that none of the compounds in the panel, including aminotadalafil, has been subjected to the preclinical and clinical evaluation required for any assessment of safety and efficacy. The analytical chemistry literature is the primary evidence base for all six compounds. The pharmacological characterization for each is inferred from structural analogy to the approved parent compounds rather than from direct experimental data.

13. References

1. MedChemExpress. Amino Tadalafil (HY-13673) product data sheet. Amino Tadalafil is an analog of Tadalafil, a potent PDE5 inhibitor. Cross-reactivity with anti-tadalafil polyclonal antibodies: 105.2%.
2. Ulloa JB, Navarro MT, Vidal JC, et al. Detection of a tadalafil analogue as an adulterant in a dietary supplement for erectile dysfunction. *J Sex Med.* 2015;12(1):152-157.
3. Park MY, Kim YH, Lee SY, et al. Simultaneous identification of hydroxythiohomosildenafil, aminotadalafil, thiosildenafil, dimethylsildenafil, and thiodimethylsildenafil in dietary supplements using high-performance liquid chromatography-mass spectrometry. *Food Addit Contam Part A.* 2013;30(11):1849-1857.
4. Tucker J, Fischer T, Upjohn L, Mazzer D, Kumar M. Unapproved pharmaceutical ingredients included in dietary supplements associated with US Food and Drug Administration warnings. *JAMA Netw Open.* 2018;1(6):e183337.
5. US Food and Drug Administration. Safety alerts and recalls: dietary supplements containing undeclared PDE-5 inhibitors and analogs. *FDA MedWatch.* Multiple communications, 2007-2026.
6. Kumasaka K, Kojima T, Honda H, et al. Identification of amino-tadalafil and rimonabant in electronic cigarette products using high pressure liquid chromatography with diode array and tandem mass spectrometric detection. *Forensic Toxicol.* 2011;29(1):76-85.
7. Jung J, Hermanns-Clausen M, Weinmann W. Identification and screening of a tadalafil analogue found in adulterated herbal products. *Drug Test Anal.* 2006;1(6):292-297.
8. Balayssac S, Gilard V, Delverdier M, Malet-Martino M. Identification of a new tadalafil analogue found in a dietary supplement. *J Pharm Biomed Anal.* 2012;67-68:29-33.

9. Uchiyama N, Kameda K, Aitani T, Goda Y. Isolation and structure elucidation of an interaction product of aminotadalafil found in an illegal health food product. *Yakugaku Zasshi*. 2010;130(5):689-693.
10. Daugan A, Grondin P, Ruault C, et al. The discovery of tadalafil: a novel and highly selective PDE5 inhibitor. 2: 2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione analogues. *J Med Chem*. 2003;46(21):4533-4542.
11. Abuo-Rahma GE, Mohamed HA, Ibrahim TS, et al. Synthesis of novel tadalafil analogues and their evaluation as phosphodiesterase inhibitors and anticancer agents. *Bioorg Med Chem*. 2016;24(16):3859-3872.
12. ICOS Corporation and Eli Lilly. Patent literature describing tadalafil structural analogs and synthesis. Multiple patent filings, 1993-2003.
13. Medsafe (New Zealand Medicines and Medical Devices Safety Authority). Classification of analogues of PDE5 inhibitors. Report for 41st Medicines Classification Committee meeting.
14. Sung BJ, Hwang KY, Jeon YH, et al. Structure of the catalytic domain of human phosphodiesterase 5 with bound drug molecules. *Nature*. 2003;425(6953):98-102.
15. Jiang S, Wang J, Zhao Y, et al. Isolation and structural characterization of a new tadalafil analog (chloropropanoylpretadalafil) found in a dietary supplement. *J Pharm Biomed Anal*. 2016;128:455-461.
16. Lee HM, Kim CS, Jang YM, et al. Synthesis and structure revision of dimeric tadalafil analogue adulterants in dietary supplements. *J Pharm Biomed Anal*. 2017;145:263-271.
17. Eli Lilly and Company. CIALIS (tadalafil) tablets prescribing information. US Food and Drug Administration approved labeling, NDA 21-368.
18. Forgue ST, Patterson BE, Bedding AW, et al. Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol*. 2006;61(3):280-288.
19. Venhuis BJ, de Kaste D. Towards a decade of detecting new analogues of sildenafil, tadalafil and vardenafil in food supplements: a history, analytical aspects and health risks. *J Pharm Biomed Anal*. 2012;69:196-208.

20. Zou P, Hou P, Oh SSY, et al. Accurate mass measurement using Fourier transform ion cyclotron resonance mass spectrometry for structure elucidation of designer drug analogs of tadalafil, vardenafil and sildenafil in herbal and pharmaceutical matrices. *Rapid Commun Mass Spectrom.* 2006;20(24):3488-3490.
21. Poon WT, Lam YH, Lai CK, Chan AYW, Mak TWL. Analogues of erectile dysfunction drugs: an under-recognised threat. *Hong Kong Med J.* 2007;13(5):359-363.
22. Mazzella S, Li L, Gee E, et al. Cross-sectional survey of adulterated sexual enhancement products sold in the Sacramento area of California. *Nanotechnol Drug Deliv Syst.* 2023;2:47-58.
23. Kloner RA, Hutter AM, Emmick JT, et al. Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol.* 2003;42(10):1855-1860.
24. Chen Y, Zhao L, Lu F, et al. Identification of a new tadalafil analogue in an adulterated dietary supplement: Trans-bisprehomotadalafil. *J Pharm Biomed Anal.* 2016;119:166-173.
25. Mohamed HA, Girgis NMR, Abdel-Aziz R, et al. Synthesis, molecular modeling and biological evaluation of novel tadalafil analogues as phosphodiesterase 5 and colon tumor cell growth inhibitors, new stereochemical perspective. *Bioorg Med Chem.* 2016;24(17):4101-4112.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Aminotadalafil is not approved for human use in any jurisdiction. The compound is encountered principally as an undeclared adulterant in dietary supplements; consumers of products containing undeclared aminotadalafil face uncharacterized risks including potentially fatal interactions with nitrate-containing medications. The pharmacological characterization presented in this monograph is largely inferred from structural analogy to tadalafil and from PDE5 inhibitor class pharmacology; direct experimental data for aminotadalafil are limited to analytical chemistry and immunochemical cross-reactivity studies. Investigators should treat all inferred pharmacological parameters as estimates requiring experimental confirmation.