

RESEARCH MONOGRAPH . COMPOUND PROFILE

Hydrafinil

A tricyclic fluorenol alcohol investigated by Cephalon as a next-generation wakefulness-promoting agent, distinguished from the diphenylmethylsulfinyl modafinil scaffold by higher eugeroic potency in rodent assays, weaker dopamine transporter affinity, proposed 5-HT₆ receptor antagonism, and the absence of human clinical development.

DOCUMENT	KDC-MN-1440
ISSUED	2026-05-11
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Fluorenol-class eugeroic agent with weak dopamine reuptake inhibition and putative 5-HT ₆ receptor antagonism

ABSTRACT

Hydrafinil (9H-fluoren-9-ol; 9-fluorenol; CAS 1689-64-1; molecular formula C₁₃H₁₀O; molecular weight 182.22 g/mol) is a secondary benzylic alcohol of the fluorene ring system that emerged from a Cephalon Pharmaceuticals drug discovery program seeking structural successors to the eugeroic modafinil. In the three-part structure-activity relationship series published by Dunn, Hostetler, Iqbal, and colleagues in *Bioorganic and Medicinal Chemistry Letters* in 2012, fluorenol was identified as the most efficacious wakefulness-promoting compound among more than twenty candidates evaluated in rat locomotor and electroencephalographic sleep-wake assays, producing approximately 39 percent greater wakefulness than equimolar modafinil over a four-hour observation window [1, 2, 3]. This eugeroic superiority was observed despite a substantially weaker affinity for the dopamine transporter (DAT), with a reported IC₅₀ of approximately 9 micromolar for dopamine reuptake inhibition compared to 3.7 micromolar for modafinil [4]. The dissociation between DAT affinity and eugeroic potency suggested the involvement of non-dopaminergic mechanisms; subsequent pharmacological characterization has identified 5-HT₆ serotonin receptor antagonism as a plausible contributor to the wakefulness and procognitive profile, and a free radical-mediated mechanism involving dissociative electron transfer has been proposed on the basis of computational and spectroscopic evidence [5, 6].

Cephalon elected not to advance fluorenol into clinical development, instead directing resources toward armodafinil (the R-enantiomer of modafinil), which received United States Food

and Drug Administration approval in 2007. The compound has therefore never undergone Phase 1 pharmacokinetic characterization, formal toxicology evaluation, or human clinical trials. It entered the research chemical market in the early 2010s under the trade name "hydrafenil" and has since been widely available from nootropic and chemical vendors at purities of 98 percent or greater, typically as the crystalline solid.

The pharmacokinetic profile is inferred from physicochemical properties, the Knoop et al. (2021) single-dose urinary metabolite study in three healthy volunteers, and structural analogy to related fluorene derivatives. Fluorenol is lipophilic (LogP approximately 2.4, higher than modafinil at 1.7), suggesting favorable blood-brain barrier penetration. Urinary metabolites identified by Knoop et al. include hydroxylated fluorenol conjugated as glucuronides and sulfates, indicating Phase I aromatic hydroxylation followed by Phase II conjugation as the principal elimination pathway [7]. The compound showed no affinity for cytochrome P450 2C19 in preliminary screening, distinguishing it from modafinil, which is a moderate CYP2C19 inhibitor. Formal plasma half-life, bioavailability, volume of distribution, and clearance parameters have not been determined in controlled pharmacokinetic studies.

The safety profile of hydrafenil is largely uncharacterized. No LD50 values have been established in standard toxicology models. The compound is not listed as a carcinogen by ACGIH, IARC, NTP, or California Proposition 65. Material safety data sheets note potential for skin irritation and gastrointestinal irritation on ingestion. No long-term toxicology, reproductive toxicology, or genotoxicity studies have been published. The World Anti-Doping Agency (WADA) classified hydrafenil as a non-specified stimulant

under category S6.A of the 2025 Prohibited List, effective January 1, 2025 [8]. The compound is not scheduled under the United States Controlled Substances Act, is not approved by the FDA or any other regulatory agency for any indication, and is sold exclusively as a research chemical. Investigators should treat hydrafenil as an experimental compound with a sparse evidence base and should not extrapolate clinical expectations from the preclinical eugeroic data without substantial additional characterization.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: Hydrafinil.

Systematic names: 9H-Fluoren-9-ol; 9-fluorenol; 9-hydroxyfluorene; fluoren-9-ol.

Chemical Abstracts Service registry number: 1689-64-1.

PubChem CID: 74318.

International Union of Pure and Applied Chemistry name: 9H-fluoren-9-ol. The compound is the secondary alcohol at the 9-position (bridging carbon) of the fluorene tricyclic ring system, consisting of two benzene rings fused to a central cyclopentane ring bearing the hydroxyl group.

Other identifiers: The name "hydrafinil" is a commercial designation introduced by the research chemical market and is not an International Nonproprietary Name, a United States Adopted Name, or a recognized development code. The compound is sometimes referred to simply as "fluorenol" in the pharmacology literature, though this term can refer to any hydroxylated fluorene isomer. In the Cephalon drug discovery series, the compound was identified as a lead from a broader fluorene-derived library but was not assigned a formal development code in published reports [1, 2, 3].

1.2 Structural class and chemistry

Hydrafinil is a benzylic secondary alcohol of the fluorene (9H-fluorene) ring system. The fluorene scaffold is a tricyclic aromatic hydrocarbon consisting of two benzene rings connected by a methylene bridge at the 9-position. In hydrafinil, this methylene is oxidized to a carbinol (secondary alcohol), producing the 9-fluorenol. The compound is structurally unrelated to the diphenylmethylsulfinyl scaffold of modafinil, adrafinil, and armodafinil; it lacks the sulfur atom and the amide moiety that characterize the modafinil class. The structural relationship to modafinil is therefore one of pharmacological analogy (shared eugeroic activity) rather than chemical homology.

Molecular formula: C₁₃H₁₀O.

Exact mass: 182.0732 g/mol (monoisotopic).

Molecular weight: 182.22 g/mol.

Physical properties: White to off-white crystalline solid. Insoluble in water; soluble in methanol, ethanol, dimethyl sulfoxide, acetone, and other common organic solvents. Melting point is approximately 151 to 155 degrees Celsius. The compound is stable under standard laboratory storage conditions and is not hygroscopic.

LogP (octanol-water partition coefficient): Approximately 2.4, higher than modafinil (approximately 1.7) and amphetamine (approximately 1.8), suggesting favorable lipophilicity for central nervous system penetration across the blood-brain barrier [4].

Stereochemistry: The 9-position of fluorenol is an sp³ carbon bearing a hydroxyl group and a hydrogen atom. In the parent compound (unsubstituted 9-fluorenol), the molecule possesses a plane of symmetry through the 9-position and the two fused rings, rendering it achiral. No stereochemical considerations apply to the unsubstituted compound. Substituted fluorenol derivatives (e.g., 9-phenyl-9-fluorenol) can be chiral, but these are distinct compounds not addressed in this monograph.

1.3 Synthesis

The standard laboratory synthesis of 9-fluorenol proceeds by sodium borohydride reduction of 9-fluorenone (9H-fluoren-9-one; CAS 486-25-9), a commercially available fluorene oxidation product. This transformation is a classical carbonyl reduction and is widely used as an instructional exercise in undergraduate organic chemistry courses [9, 10].

The procedure involves dissolving 9-fluorenone in methanol at room temperature, adding sodium borohydride (NaBH₄) in slight molar excess (typically 0.4 equivalents, as each borohydride delivers four hydride equivalents), and stirring at ambient temperature for 15 to 30 minutes. The reaction is monitored by thin-layer chromatography (8:2 hexane:ethyl acetate mobile phase). On completion, dilute hydrochloric acid is added to quench excess borohydride and to protonate the alkoxide intermediate. The product is isolated by aqueous workup and recrystallization from ethanol, ethanol-water, or ethyl acetate-hexane, yielding 9-fluorenol as white crystals. Typical yields are 85 to 95 percent. Product identity is confirmed by melt-

ing point, infrared spectroscopy (appearance of the O-H stretch at approximately 3300 cm⁻¹ and disappearance of the C=O stretch at approximately 1720 cm⁻¹), and proton nuclear magnetic resonance spectroscopy (appearance of the carbinol C-H at approximately δ 5.5 ppm).

The starting material 9-fluorenone is itself prepared by oxidation of fluorene with chromic acid, potassium permanganate, or catalytic aerobic oxidation [10]. Both 9-fluorenone and 9-fluorenol are widely available from commercial chemical suppliers (Sigma-Aldrich, TCI, Alfa Aesar, and others) at greater than 96 percent purity, typically at low cost (on the order of \$20 to \$50 per 25 grams for reagent-grade material).

Industrial-scale synthesis for the research chemical market likely follows the same borohydride reduction protocol or a catalytic hydrogenation variant, with product purified by recrystallization or column chromatography and characterized by HPLC purity analysis. The simplicity and scalability of the synthesis contribute to the low cost and wide availability of the compound.

2. Abstract

Hydrafinil (9H-fluoren-9-ol; CAS 1689-64-1) is a tricyclic benzylic alcohol that was identified in the Cephalon Pharmaceuticals eugeroic drug discovery program as the most potent wakefulness-promoting agent in a series of more than twenty fluorene-derived compounds evaluated in rat sleep-wake models [1, 2, 3]. The compound produced approximately 39 percent greater wakefulness than modafinil over a four-hour period in the principal rodent assay, despite possessing substantially lower affinity for the dopamine transporter (IC₅₀ approximately 9 micromolar versus 3.7 micromolar for modafinil) [4]. This dissociation between dopamine transporter affinity and eugeroic efficacy is the central pharmacological observation of the hydrafinil literature and has driven investigation into alternative mechanisms, including 5-HT₆ serotonin receptor antagonism and free radical-mediated dissociative electron transfer [5, 6].

Cephalon abandoned the fluorenol series in favor of armodafinil development, and hydrafinil has never been advanced to human clinical trials. The compound entered the unregulated research chemical market in the early 2010s and has been widely used in nootropic and biohacking communities on the basis of anecdotal reports of wakefulness promotion, cognitive enhancement, and shorter duration of action relative to modafinil. No controlled human efficacy or safety data exist.

The only published human pharmacological study is the Knoop et al. (2021) doping control investigation, in which three healthy male volunteers received a single 50 mg oral dose and provided urine samples over 72 hours for mass spectrometric metabolite identification [7]. The study identified the intact parent compound and multiple Phase I hydroxylated metabolites conjugated as Phase II glucuronides and sulfates. This metabolite profile confirmed oral absorption and hepatic biotransformation but did not generate formal pharmacokinetic parameters.

The World Anti-Doping Agency classified hydrafinil as a non-specified stimulant (category S6.A) on the 2025 Prohibited List [8]. The compound is not scheduled under the United States Controlled Substances Act and is not approved for any medical indication by any regulatory authority. The safety profile is essentially uncharacterized beyond material safety data sheet entries and structural class considera-

tions. Investigators should approach hydrafnil as a preclinical-stage research compound for which the evidence base consists of limited rodent pharmacology, a single human metabolite study, and no formal toxicology.

3. Discovery and Development History

3.1 Origin at Cephalon Pharmaceuticals

Hydrafinil emerged from a systematic drug discovery effort at Cephalon, Inc. (now a subsidiary of Teva Pharmaceutical Industries following the 2011 acquisition). Cephalon held the United States marketing rights to modafinil (Provigil), which had been approved by the FDA in 1998 for narcolepsy, later expanded to obstructive sleep apnea and shift work sleep disorder. Anticipating patent expiration and the entry of generic modafinil, Cephalon initiated a broad medicinal chemistry campaign to identify next-generation eugeroic compounds that might offer improved efficacy, reduced side effects, or novel intellectual property positioning.

The program was documented in a three-part publication series by Dunn, Hostetler, Iqbal, and colleagues in *Bioorganic and Medicinal Chemistry Letters* in 2012, covering the structure-activity relationships of diverse chemical scaffolds evaluated for wakefulness-promoting activity [1, 2, 3]. Part I examined diphenylmethyl derivatives related to the modafinil core. Part II expanded to heterocyclic and heteroaromatic analogs. Part III, the final installment, reported on fluorene-derived compounds and presented the key finding that 9-fluorenol (hydrafinil) was the most potent eugeroic in the entire series.

3.2 Preclinical evaluation

The Cephalon series evaluated wakefulness in rat models using locomotor activity monitoring and electroencephalographic sleep-wake staging. More than twenty compounds were tested at standardized oral doses, and the fluorenol derivative was reported as 39 percent more effective than modafinil at maintaining wakefulness over a four-hour observation period [3]. The compound's superiority was notable because its affinity for the dopamine transporter was approximately 59 percent weaker than that of modafinil, challenging the prevailing hypothesis that DAT inhibition was the primary mechanism of eugeroic action for the modafinil class.

The Cephalon investigators did not publish a mechanistic characterization of the fluorenol's wakefulness-promoting activity beyond the DAT affinity measurement. The implication drawn from the data was that the eugeroic effect of 9-fluorenol in-

volved additional or alternative mechanisms to dopamine reuptake inhibition.

3.3 Discontinuation and pivot to armodafinil

For reasons not disclosed in the published literature, Cephalon did not advance 9-fluorenlol into formal preclinical development (IND-enabling toxicology, formulation development, Phase 1 clinical trials). Instead, the company directed its next-generation eugeroic efforts toward armodafinil (R-modafinil; Nuvigil), the pharmacologically active enantiomer of modafinil, which offered a longer plasma half-life, three-fold greater DAT affinity relative to S-modafinil, and a more straightforward regulatory pathway as an enantiomeric refinement of an already-approved drug [11]. Armodafinil received FDA approval in June 2007.

The decision to abandon the fluorenlol series may have reflected strategic considerations (armodafinil's simpler regulatory path), intellectual property calculations, or undisclosed preclinical findings. No published account provides the rationale.

3.4 Entry into the research chemical market

Following the publication of the Cephalon series in 2012, 9-fluorenlol attracted attention in the nootropic and biohacking communities as an unregulated alternative to prescription modafinil. The compound was marketed under the trade name "hydrafinil" by research chemical vendors beginning approximately 2013 to 2014 and has been continuously available since that time. The low cost and simple synthesis of 9-fluorenlol from commercially available 9-fluorenone contributed to broad vendor availability.

3.5 WADA classification

In September 2024, the World Anti-Doping Agency published the 2025 Prohibited List, which classified hydrafinil (fluorenlol) as a non-specified stimulant under category S6.A, effective January 1, 2025 [8]. This classification represented an elevation in regulatory scrutiny; hydrafinil had previously been monitored but not formally classified. The S6.A designation as a non-specified stimulant means that athletes cannot invoke unintentional ingestion as a mitigating factor in anti-doping violations, and the compound is prohibited both in-competition and out-of-competition.

4. Molecular Pharmacology

4.1 Dopamine reuptake inhibition

The best-characterized molecular activity of hydrafinil is weak inhibition of the dopamine transporter (DAT). The compound inhibits dopamine reuptake with an IC₅₀ of approximately 9 micromolar, compared to approximately 3.7 micromolar for modafinil [4]. This places hydrafinil's DAT potency at approximately 41 percent of modafinil's on a molar basis. The weak DAT affinity is pharmacologically significant because it implies a lower abuse and dependence liability relative to modafinil (which itself carries a lower abuse liability than classical psychostimulants such as amphetamine and methylphenidate, with DAT IC₅₀ values in the submicromolar range).

The paradox of hydrafinil pharmacology is that the compound produces greater wakefulness than modafinil in rodent assays despite weaker DAT inhibition. This observation suggests that DAT inhibition is not the sole or even the principal mechanism of hydrafinil's eugeroic activity, and that alternative pharmacological targets contribute to the wakefulness effect.

4.2 5-HT₆ serotonin receptor antagonism

The most frequently cited non-dopaminergic mechanism for hydrafinil is antagonism of the 5-HT₆ (serotonin type 6) receptor. The 5-HT₆ receptor is a G protein-coupled receptor that positively modulates adenylyl cyclase and is expressed predominantly in the central nervous system, with high density in the striatum, nucleus accumbens, hippocampus, and cortex [12]. The receptor modulates postsynaptic signaling in GABAergic medium spiny neurons and in glutamatergic cortical pyramidal cells.

Antagonism of the 5-HT₆ receptor has been demonstrated in multiple pharmacological studies to increase extracellular concentrations of acetylcholine, glutamate, dopamine, and norepinephrine in the prefrontal cortex and hippocampus [13, 14]. These neurotransmitter elevations are the mechanistic basis for the procognitive and wakefulness-promoting effects observed with selective 5-HT₆ antagonists such as SB-271046, SB-399885, and idalopirdine in rodent and primate models [14, 15].

The 5-HT6 antagonist mechanism is distinct from direct dopamine reuptake inhibition and could account for hydrafinil's eugeroic efficacy in the absence of strong DAT binding.

The binding affinity of hydrafinil at the 5-HT6 receptor has not been quantified in a published radioligand displacement assay, and the attribution of 5-HT6 antagonism to hydrafinil rests on structural analogy and indirect pharmacological evidence rather than on direct receptor-level characterization. This represents a significant gap in the compound's pharmacological profile.

4.3 Free radical mechanism

Batista et al. (2018) proposed a free radical-based mechanism for the eugeroic activity of modafinil and modafinil-like analogues, including fluorenlol, based on computational chemistry and spectroscopic evidence [6]. The proposed mechanism involves dissociative electron attachment (DEA), in which a hydrated electron attaches to the molecule and causes bond elongation or dissociation, generating radical species that may interact with neuronal signaling pathways. For modafinil, the relevant bond is the benzylic C-S bond; for fluorenlol, the analogous process would involve the benzylic C-OH bond or the aromatic ring system.

The free radical hypothesis is speculative and has not been validated by in vivo pharmacological experiments. It represents an alternative theoretical framework for understanding how structurally diverse eugeroic compounds (modafinil, adrafinil, fluorenlol, flmodafinil) might share a common downstream mechanism despite divergent primary receptor binding profiles.

4.4 Histaminergic mechanisms

Modafinil's eugeroic effect has been partially attributed to indirect activation of histaminergic neurons in the tuberomammillary nucleus of the posterior hypothalamus, possibly through orexinergic pathway modulation [16]. Whether hydrafinil engages the same histaminergic circuitry is unknown. The hypothesis is consistent with the observed dissociation between DAT affinity and wakefulness efficacy, as histaminergic activation could produce arousal independently of dopaminergic tone. However, no direct evidence for histaminergic activity of hydrafinil has been published.

4.5 Summary of mechanistic uncertainty

The mechanism of action of hydrafinil remains incompletely characterized. The compound is a weak dopamine reuptake inhibitor, a putative 5-HT₆ receptor antagonist (by analogy, not by direct measurement), and a theoretical participant in free radical-mediated signaling. The relative contributions of these mechanisms to the observed eugeroic effect in rodents are unknown. The absence of selective receptor binding data, dose-response curves at identified targets, and mechanism-blocking experiments (e.g., co-administration with selective 5-HT₆ agonists or histamine H₁ antagonists) constitutes a fundamental limitation of the current pharmacological literature on hydrafinil.

5. Pharmacokinetics

5.1 Absorption

No formal oral bioavailability study has been conducted for hydrafinil in any species. The physicochemical properties of the compound (molecular weight 182.22, LogP approximately 2.4, no ionizable groups at physiological pH) are consistent with favorable oral absorption based on Lipinski's rule of five and the Biopharmaceutics Classification System. The high lipophilicity suggests rapid and near-complete absorption from the gastrointestinal tract.

The Knoop et al. (2021) study confirmed that a 50 mg oral dose in three healthy male volunteers produced detectable parent compound and metabolites in urine, confirming oral absorption in humans [7]. Anecdotal reports from the research chemical community describe subjective effects beginning within 15 to 45 minutes of oral ingestion, consistent with rapid absorption, though these reports lack pharmacokinetic measurement.

5.2 Distribution

Volume of distribution has not been determined. The LogP of 2.4 (higher than modafinil at 1.7 and amphetamine at 1.8) suggests substantial tissue distribution and favorable penetration of the blood-brain barrier [4]. Protein binding has not been characterized. Given the compound's molecular weight and lipophilicity, moderate-to-high protein binding (in the range of 50 to 80 percent) would be expected by analogy to structurally related aromatic alcohols.

5.3 Metabolism

The Knoop et al. (2021) urinary metabolite study provides the only published human metabolic data for hydrafinil [7]. Using gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry, the investigators identified the intact parent compound (9-fluorenol) in urine along with multiple Phase I and Phase II metabolites. The principal Phase I transformations were aromatic ring hydroxylation (mono- and di-hydroxylation of the fluorene ring system), producing

hydroxylated fluorenol derivatives. These Phase I metabolites were subsequently conjugated as glucuronides and sulfates (Phase II metabolism) for renal elimination.

The cytochrome P450 isoforms responsible for the aromatic hydroxylation have not been formally identified through recombinant enzyme or selective inhibitor studies. However, hydrafenil was reported to show no affinity for CYP2C19, distinguishing it from modafinil, which is a moderate CYP2C19 inhibitor and substrate [4]. By structural analogy to fluorene (whose bacterial and mammalian metabolism is well characterized), CYP1A2 and CYP2C9 are plausible contributors to the aromatic hydroxylation, but this remains speculative.

5.4 Elimination

The plasma elimination half-life of hydrafenil has not been measured in a formal pharmacokinetic study. Anecdotal reports and vendor literature cite a duration of subjective effect of approximately 4 to 6 hours, shorter than modafinil (12 to 15 hours) and armodafinil (15 hours), suggesting a shorter half-life [4]. The Knoop et al. (2021) study detected metabolites in urine up to 72 hours post-dose, indicating that the elimination of conjugated metabolites extends well beyond the period of apparent pharmacological activity [7].

Renal excretion of glucuronidated and sulfated metabolites is the principal elimination pathway based on the Knoop et al. urinary metabolite profile. The fraction excreted unchanged in urine has not been quantified.

5.5 Routes of administration

Oral administration is the only route documented in the published literature and in the research chemical market. The compound is supplied as a solid (powder or capsule) and is typically ingested orally. The compound is insoluble in water, precluding aqueous injection without a co-solvent system. Sublingual, intranasal, and other routes have been described anecdotally but have not been studied systematically.

5.6 Special populations

No data exist for pediatric, geriatric, hepatically impaired, renally impaired, or genetically polymorphic (CYP isoform variant) populations.

6. Preclinical Pharmacology

6.1 Rodent wakefulness assays

The principal published preclinical evidence for hydrafinil is the Cephalon three-part drug discovery series. In Part III, Dunn et al. (2012) reported that 9-fluorenonol administered orally to rats produced 39 percent greater wakefulness than modafinil at equimolar doses over a four-hour electroencephalographic recording period [3]. The wakefulness was assessed by quantification of time spent in the wake state versus slow-wave sleep and rapid eye movement sleep, as determined by standard EEG-EMG staging criteria.

The compound did not produce rebound hypersomnolence following the wakefulness period, a characteristic shared with modafinil and other eugeroic agents and distinguishing them from classical psychostimulants (amphetamine, methylphenidate), which produce sleep rebound [1].

6.2 Dopamine transporter binding

The DAT binding profile was characterized as part of the Cephalon series. The IC₅₀ for dopamine reuptake inhibition was approximately 9 micromolar, placing hydrafinil substantially below modafinil (3.7 micromolar) and far below classical stimulants (methylphenidate IC₅₀ approximately 0.02 micromolar, cocaine IC₅₀ approximately 0.3 micromolar) in potency at this target [4]. The weak DAT binding supports a lower abuse liability profile relative to both modafinil and classical stimulants, though this has not been evaluated in self-administration or conditioned place preference paradigms.

6.3 Absence of extended preclinical characterization

Beyond the wakefulness assay and DAT binding data, no published preclinical studies have characterized hydrafinil for receptor selectivity panel screening, behavioral pharmacology (anxiety, locomotor sensitization, cognitive performance), electrophysiology, neurotoxicity, acute or chronic toxicity, genotoxicity, reproductive

toxicity, or carcinogenicity. The compound was abandoned by Cephalon before IND-enabling studies were initiated, and the research chemical market has not generated systematic preclinical data.

7. Clinical Evidence Base

7.1 Absence of clinical trials

Hydrafinil has never been evaluated in a human clinical trial, whether for safety (Phase 1), dose-finding (Phase 2), or efficacy (Phase 3). No Investigational New Drug application, Clinical Trial Application, or equivalent regulatory submission has been publicly documented for this compound.

7.2 Knoop et al. (2021) metabolite study

The only published human study involving hydrafinil administration is the Knoop et al. (2021) doping control investigation conducted at the German Sport University Cologne [7]. Three healthy male volunteers received a single oral dose of 50 mg of hydrafinil. Urine samples were collected prior to dosing and at intervals up to 72 hours post-administration. The study used gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry to identify the parent compound and Phase I/Phase II metabolites. An existing initial testing procedure based on enzymatic hydrolysis of glucuronides, liquid-liquid extraction, and trimethylsilylation proved effective for detection. The investigators also identified two out-of-competition routine doping control samples that contained hydrafinil metabolites, confirming real-world use by athletes [7].

This study was designed for analytical method development in the doping control context and did not collect pharmacokinetic parameters (plasma concentration-time curves, AUC, C_{max}, T_{max}, half-life), pharmacodynamic measurements (wakefulness, cognitive performance, subjective effects), or safety data (vital signs, electrocardiography, clinical chemistry, adverse events).

7.3 Anecdotal human evidence

A substantial body of anecdotal reports exists in online nootropic communities describing the subjective effects of hydrafinil at doses of 50 to 150 mg orally. Common reported effects include enhanced wakefulness, improved focus, reduced fatigue, and a subjective duration of approximately 4 to 6 hours. Commonly reported ad-

verse effects include headache, nausea, insomnia (when taken late in the day), and anxiety at higher doses. These reports are uncontrolled, unblinded, and subject to expectation bias, placebo effect, and confounding from concurrent substance use. They should not be interpreted as clinical evidence but are noted here as the only existing record of human pharmacological experience with the compound.

8. Sourcing and Quality Verification

Research-grade hydrafinil (9-fluorenol) is available from multiple categories of suppliers:

Chemical reagent suppliers: Sigma-Aldrich, Tokyo Chemical Industry (TCI), Alfa Aesar, Fluorochem, and other standard chemical reagent houses supply 9-fluorenol at 96 to 99 percent purity, typically in 5 to 100 gram quantities, at prices in the range of \$20 to \$80 per 25 grams. These suppliers provide certificates of analysis with HPLC purity, melting point, and spectroscopic identity confirmation. This is the highest-quality and most analytically documented source for research applications.

Research chemical vendors: Multiple nootropic and research chemical vendors (PureRawz, Science.bio (discontinued), Euro-Nootropics, and others) supply hydrafinil as capsules or powder at stated purities of 98 percent or greater. Vendor certificates of analysis vary in quality and should be independently verified.

Pharmaceutical grade: No pharmaceutical-grade product exists for hydrafinil. The compound has never been formulated as a medicine in any jurisdiction.

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

- High-performance liquid chromatography area-percent purity (target greater than 98 percent for pharmacological research)
- Mass spectrometry confirmation of molecular weight (183.08 for $[M+H]^+$ or 182.07 for $[M]$ by electron ionization)
- Melting point determination (151 to 155 degrees Celsius for pure 9-fluorenol)
- Infrared spectroscopy (O-H stretch at approximately 3300 cm^{-1} ; absence of the 9-fluorenone C=O stretch at 1720 cm^{-1} confirms complete reduction)
- Residual solvent analysis if the source is a research chemical vendor rather than a reagent-grade supplier

Third-party analytical laboratories (Janoshik Analytical, others) provide independent confirmation of vendor certificates of analysis. Given the simplicity of 9-fluorenol synthesis and the low cost of authentic material, adulteration is less of a concern for this compound than for more expensive or structurally complex research

chemicals. However, misidentification of 9-fluorenone (the ketone precursor) as 9-fluorenol (the alcohol product) is a plausible quality failure mode, and infrared spectroscopy is a rapid and definitive method for distinguishing the two.

9. Reconstitution and Handling

Hydrafinil is supplied as a white to off-white crystalline solid. The compound is stable at room temperature in dry conditions and does not require refrigerated storage, desiccation, or light protection under standard laboratory conditions. The solid is not hygroscopic and is not air-sensitive.

Solubility: The compound is insoluble in water. For in vitro research applications requiring aqueous delivery, stock solutions should be prepared in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM (approximately 1.8 to 18.2 mg/mL), then diluted into aqueous buffer at the desired final concentration. DMSO concentrations in the final assay medium should be kept below 0.1 percent (v/v) to avoid solvent-mediated cytotoxicity and pharmacological artifacts. Ethanol and methanol are also suitable solvents for stock preparation.

Oral research preparations: For oral administration in research contexts, the crystalline solid is typically weighed into gelatin capsules or dissolved in a lipophilic carrier (e.g., medium-chain triglyceride oil) for volumetric dosing. The compound is stable in capsule form at room temperature for extended periods.

Storage: Room temperature (15 to 25 degrees Celsius), dry, in a tightly sealed container. No special precautions beyond standard laboratory chemical storage are required. The compound should be stored away from strong oxidizing agents to prevent conversion to 9-fluorenone.

Stability: 9-Fluorenol can be oxidized back to 9-fluorenone under harsh conditions (strong oxidizing agents, prolonged UV exposure). Under normal storage and handling conditions, the compound is stable for at least 24 months as a dry solid. Solution stability in DMSO is at least 6 months at minus 20 degrees Celsius.

10. Stack Interactions and Combinations

Investigators combining hydrafinil with other research compounds should consider the following interaction categories:

Dopaminergic agents: Hydrafinil is a weak dopamine reuptake inhibitor. Concurrent administration with other dopamine reuptake inhibitors (modafinil, methylphenidate, bupropion) or dopamine releasers (amphetamine, methamphetamine) would produce additive dopaminergic stimulation. The combination of hydrafinil with modafinil is pharmacologically redundant at the DAT target and is not recommended. Concurrent use with strong dopaminergic agents may increase the risk of anxiety, insomnia, tachycardia, and hypertension.

Serotonergic agents: If the putative 5-HT₆ antagonist mechanism is confirmed, hydrafinil could interact with other serotonergic compounds. Concurrent selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) would not produce serotonin syndrome risk through 5-HT₆ antagonism (which reduces rather than increases serotonergic signaling at that receptor), but the net effect on serotonergic tone would be complex and unpredictable. Other 5-HT₆ antagonists (idalopirdine, SB-271046 analogs) would produce additive receptor blockade.

CYP interactions: Hydrafinil does not appear to inhibit CYP2C19, distinguishing it from modafinil [4]. The potential for CYP inhibition at other isoforms has not been characterized. Investigators should consider the possibility of CYP-mediated drug-drug interactions, particularly with CYP1A2 and CYP2C9 substrates (if these are confirmed as the metabolizing enzymes), but should recognize that the interaction potential is uncharacterized.

Caffeine and methylxanthines: The combination of hydrafinil with caffeine is commonly described in anecdotal reports. The interaction is expected to be additive with respect to wakefulness and alertness, with the potential for additive adverse effects (anxiety, tachycardia, insomnia, gastrointestinal discomfort). No pharmacokinetic interaction data exist for this combination.

Racetam and cholinergic nootropics: Concurrent piracetam, aniracetam, or alpha-GPC with hydrafinil is described in nootropic communities. If hydrafinil's 5-HT6 antagonism increases cholinergic tone (by analogy to characterized 5-HT6 antagonists), the combination with exogenous cholinergic supplementation could produce additive cholinergic effects. The interaction has not been studied.

Alcohol and sedatives: Concurrent ethanol or benzodiazepine use with hydrafinil has not been studied. Eugeroic agents may partially antagonize the sedative effects of CNS depressants, potentially leading to underestimation of intoxication. This is a safety concern, not a therapeutic combination.

11. Adverse Events and Safety Signal

11.1 Absence of formal safety data

No formal safety or tolerability study has been conducted for hydrafinil in any species at any dose level. No LD50, no-observed-adverse-effect level (NOAEL), maximum tolerated dose (MTD), or dose-limiting toxicity has been established. No genotoxicity, carcinogenicity, reproductive toxicity, or chronic toxicity data exist. The safety profile is therefore entirely uncharacterized by regulatory standards.

11.2 Material safety data

Material safety data sheets for 9-fluorenol identify the following hazard statements: may cause skin irritation (H315); may cause eye irritation (H319); may be harmful if swallowed (H302). These are standard hazard classifications for organic chemical compounds and do not reflect specific toxicological findings. The compound is not classified as a carcinogen by ACGIH, IARC, NTP, or California Proposition 65 [17].

11.3 Structural class considerations

9-Fluorenol belongs to the fluorene family of polycyclic aromatic hydrocarbons. Fluorene itself is an environmental pollutant classified as a potential occupational health hazard at high chronic exposures. However, 9-fluorenol (the alcohol) differs substantially from the parent hydrocarbon in metabolic disposition and is not expected to share the same environmental toxicity profile. The hydroxylation at the 9-position renders the compound more polar and more readily conjugated for elimination.

Structurally related compounds (modafinil, armodafinil, adrafinil) have established safety profiles in humans at therapeutic doses, with principal adverse events including headache, nausea, anxiety, insomnia, and (for adrafinil) hepatotoxicity on chronic dosing [18]. Whether hydrafinil shares these adverse-event patterns is unknown. The absence of the sulfinyl and amide moieties present in the modafinil class means that direct extrapolation of the modafinil safety profile to hydrafinil is not justified.

11.4 Anecdotal adverse events

Uncontrolled reports from the research chemical community describe headache, nausea, gastrointestinal discomfort, anxiety, insomnia, and irritability at doses above 100 mg. These reports are unverifiable and may reflect impurities, co-administered substances, placebo effects, or genuine pharmacological adverse events.

11.5 Environmental toxicity

9-Fluorenone is toxic to aquatic organisms including algae, bacteria, and crustaceans. Appropriate waste disposal procedures should be followed in laboratory settings.

11.6 Regulatory status

Hydrafinil is not scheduled under the United States Controlled Substances Act. It is not approved by the FDA or any other regulatory agency for any indication. It is classified as a non-specified stimulant (S6.A) on the WADA 2025 Prohibited List [8]. Athletes subject to anti-doping regulations should not use this compound.

12. Comparative Assessment

This section presents a structured comparative assessment of five eugeroic and wakefulness-promoting compounds against hydrafnil, evaluated against five competency standards: novelty, effect size, promising potential (current development state and research trajectory), side-effect profile (clinical or preclinical), and overall validation. The five comparators were selected as the principal eugeroic or wakefulness-promoting agents with the greatest structural or pharmacological relevance to hydrafnil.

12.1 Modafinil

Mechanism: Weak dopamine reuptake inhibitor (IC₅₀ approximately 3.7 micromolar); proposed additional mechanisms include histaminergic activation, orexinergic modulation, and norepinephrine reuptake inhibition [16].

Development trajectory: Developed by Laboratoire L. Lafon in France; FDA-approved in 1998 for narcolepsy; subsequently approved for obstructive sleep apnea and shift work sleep disorder. Marketed as Provigil (Cephalon/Teva). Generic modafinil available since 2012.

Novelty: Low. Modafinil is the prototypical eugeroic and the reference standard for the class. The compound has been marketed for over 25 years.

Effect size: The registered eugeroic. In the Cephalon preclinical comparison, hydrafnil produced 39 percent greater wakefulness than modafinil in the rat assay [3]. Modafinil has extensive Phase 3 and post-marketing clinical evidence confirming efficacy for narcolepsy, obstructive sleep apnea, and shift work disorder.

Promising potential: Established. Modafinil is a globally marketed medicine with extensive clinical infrastructure. Its promising potential as a novel agent is exhausted, but its clinical positioning is secure.

Side-effect profile: Well characterized. Principal adverse events at therapeutic doses (100 to 200 mg) include headache (34 percent), nausea (11 percent), anxiety (5 percent), insomnia, dizziness, and dry mouth. Rare serious events include Stevens-

Johnson syndrome, angioedema, and multi-organ hypersensitivity. CYP2C19 inhibition produces drug-drug interactions with warfarin, clopidogrel, and proton pump inhibitors [18]. Schedule IV controlled substance in the United States.

Overall validation: Very high. The most extensively validated eugeroic compound.

Comparison to hydrafinil: Hydrafinil produced greater wakefulness than modafinil in one published rodent assay but has no human clinical data, no formal safety evaluation, and no regulatory approval. Modafinil is the clear choice for any application requiring clinical evidence, regulatory compliance, or established safety. Hydrafinil's potential advantages (shorter duration, weaker DAT affinity suggesting lower abuse liability, absence of CYP2C19 inhibition) are theoretical and unconfirmed in humans.

12.2 Armodafinil

Mechanism: R-enantiomer of modafinil; weak dopamine reuptake inhibitor with three-fold greater DAT affinity and three-fold slower metabolism than S-modafinil [11].

Development trajectory: FDA-approved June 2007 for narcolepsy, obstructive sleep apnea, and shift work disorder. Marketed as Nuvigil (Cephalon/Teva).

Novelty: Low. Armodafinil is an enantiomeric refinement of modafinil, not a novel mechanism.

Effect size: Comparable to modafinil per milligram at lower doses (150 mg armodafinil approximates 200 mg modafinil). Longer duration of action owing to slower R-enantiomer metabolism.

Promising potential: Established. Generic armodafinil is available.

Side-effect profile: Similar to modafinil with comparable adverse-event rates. Same CYP interaction profile.

Overall validation: Very high.

Comparison to hydrafinil: Armodafinil was the compound Cephalon chose to develop instead of hydrafinil. The choice reflected a lower-risk regulatory pathway and a clinically validated mechanism. Hydrafinil's theoretical advantages (novel

mechanism, potentially shorter duration) remain unvalidated.

12.3 Adrafinil

Mechanism: Prodrug of modafinil. Hepatic metabolism (via CYP3A4 and other enzymes) converts adrafinil to modafinil and to the inactive metabolite modafinilic acid [19].

Development trajectory: Developed by Laboratoire L. Lafon in France in the 1970s. Marketed as Olmifon in France for narcolepsy and age-related cognitive decline. Withdrawn from the French market in 2011. Not FDA-approved.

Novelty: Low. The active metabolite is modafinil.

Effect size: Comparable to modafinil after metabolic conversion, but delayed onset (30 to 60 minutes to modafinil generation) and lower bioavailability of the active metabolite compared to direct modafinil administration.

Promising potential: Low. The compound has been withdrawn from its only marketed jurisdiction and is pharmacologically inferior to direct modafinil administration.

Side-effect profile: The prodrug metabolism generates modafinilic acid, which has been associated with hepatotoxicity on chronic dosing [19]. Liver function monitoring was recommended during marketed use. This hepatotoxic liability is not shared by modafinil or armodafinil.

Overall validation: Low to moderate. Historical use in France provides some clinical evidence, but the compound has been superseded.

Comparison to hydrafinil: Both compounds are unregulated research chemicals (in the United States) that have been used as alternatives to prescription modafinil. Adrafinil has the advantage of producing a known active metabolite (modafinil) with extensive clinical data. Hydrafinil's mechanism is less well understood but does not carry the hepatotoxicity concern associated with adrafinil's metabolic pathway.

12.4 Flmodafinil (CRL-40,940)

Mechanism: Bisfluorinated modafinil analog. Dopamine reuptake inhibitor with reported higher potency than modafinil at the DAT. Does not induce cytochrome P450 enzymes [20].

Development trajectory: Developed at Laboratoire L. Lafon. Patent literature describes longer wakefulness duration than modafinil in rodent assays with less perturbation of sleep architecture. The compound has not completed clinical trials and is not approved in any jurisdiction. Available as a research chemical.

Novelty: Low to moderate. The compound is a fluorinated modification of the modafinil scaffold, representing incremental medicinal chemistry rather than a novel pharmacological mechanism.

Effect size: Reported in patent literature as maintaining wakefulness over a significantly longer timeframe than modafinil in rodent assays [20]. Formal effect-size comparisons with statistical power have not been published in peer-reviewed literature.

Promising potential: Low to moderate. The compound is not in active clinical development and is sold as a research chemical.

Side-effect profile: No formal human safety data. The absence of CYP enzyme induction is a theoretical advantage over modafinil for drug-drug interaction risk.

Overall validation: Low. Patent literature and preclinical data only; no peer-reviewed clinical evidence.

Comparison to hydrafinil: Both compounds are unregulated modafinil-adjacent research chemicals with preclinical evidence of eugeroic activity but no clinical validation. Flmodafinil retains the modafinil sulfoxide scaffold and is therefore more likely to share modafinil's mechanism of action. Hydrafinil represents a structurally distinct scaffold with a potentially different mechanism. Neither compound has clinical evidence supporting use.

12.5 Pitolisant

Mechanism: Selective histamine H3 receptor inverse agonist/antagonist. Increases histamine release in the tuberomammillary nucleus by blocking autoreceptor-mediated feedback inhibition, producing wakefulness through the histaminergic

arousal system [21].

Development trajectory: Developed by Bioprojet. FDA-approved August 2019 (Wakix) for excessive daytime sleepiness in narcolepsy. EMA-approved 2016. Subsequently approved for cataplexy associated with narcolepsy.

Novelty: High. Pitolisant is the first and only histamine-based eugeroic approved for clinical use, representing a mechanistically distinct approach to wakefulness promotion compared to the dopaminergic modafinil class.

Effect size: Phase 3 trials (HARMONY I, HARMONY Ibis, HARMONY CTP) demonstrated significant reduction in Epworth Sleepiness Scale scores compared to placebo [21]. The effect size is generally comparable to modafinil in head-to-head comparisons, with some trials showing non-inferiority.

Promising potential: High. Pitolisant is an actively marketed medicine with expanding indications and a growing clinical evidence base.

Side-effect profile: Well characterized. Principal adverse events include headache (14.7 percent), insomnia (6.4 percent), nausea (5.6 percent), and anxiety. QT prolongation has been reported at supratherapeutic doses. CYP2D6 and CYP3A4 interactions are clinically relevant [21].

Overall validation: High. FDA-approved, EMA-approved, with robust Phase 3 evidence.

Comparison to hydrafinil: Pitolisant represents the strongest mechanistic contrast with hydrafinil in this comparator panel. If hydrafinil's eugeroic mechanism involves histaminergic activation (as hypothesized but unconfirmed), pitolisant provides a validated example of the histamine-based wakefulness approach. Pitolisant has the decisive advantage of clinical validation, regulatory approval, and an established safety profile. Hydrafinil has no clinical evidence and an uncharacterized safety profile.

12.6 Comparator summary

The five comparators occupy distinct positions in the eugeroic pharmacology landscape. **Modafinil** and **armodafinil** are the established reference standards with extensive clinical validation. **Adrafinil** is a superseded prodrug with hepatotoxicity

concerns. **Flmodafinil** is a structurally related research chemical with similar regulatory and evidentiary limitations to hydrafinil. **Pitolisant** represents the only non-dopaminergic, histamine-based eugeroic with clinical approval.

Hydrafinil occupies the least validated position among these comparators. Its distinguishing characteristics are: (a) the highest eugeroic efficacy in one published rodent assay, (b) the weakest DAT affinity among the dopaminergic comparators (suggesting lower abuse liability), (c) the absence of CYP2C19 inhibition, (d) a potentially novel mechanism involving 5-HT₆ antagonism, and (e) a shorter apparent duration of action. All of these characteristics are derived from limited preclinical data and have not been confirmed in human studies. The principal practical limitation is the complete absence of clinical safety and efficacy data, which precludes evidence-based comparison on any clinical endpoint.

Investigators considering hydrafinil for research applications should recognize that modafinil, armodafinil, and pitolisant provide clinically validated alternatives with established safety profiles, dose-response relationships, and pharmacokinetic parameters. Hydrafinil may be of interest as a research tool for exploring non-DAT mechanisms of wakefulness promotion and as a comparator in structure-activity relationship studies, but it is not a validated alternative to any approved eugeroic.

13. References

1. Dunn D, Hostetler G, Iqbal M, et al. Wake-promoting agents: search for next generation modafinil: part I. *Bioorg Med Chem Lett*. 2012;22(6):2312-2314.
2. Dunn D, Hostetler G, Iqbal M, et al. Wake-promoting agents: search for next generation modafinil: part II. *Bioorg Med Chem Lett*. 2012;22(6):2315-2317.
3. Dunn D, Hostetler G, Iqbal M, et al. Wake promoting agents: search for next generation modafinil, lessons learned: part III. *Bioorg Med Chem Lett*. 2012;22(11):3751-3753.
4. PubChem Compound Summary for CID 74318, Fluoren-9-ol. National Center for Biotechnology Information. Accessed 2026.
5. Heal DJ, Smith SL, Gosden J, Nutt DJ. Amphetamine, past and present: a pharmacological and clinical perspective. *J Psychopharmacol*. 2013;27(6):479-496.
6. Batista VS. Modafinil and modafinil analogues: free radical mechanism of the eugeroic and cognitive enhancement effect. *HAL Archives-Ouvertes*. 2018; hal-01933737.
7. Knoop A, Fusshöller G, Krug O, et al. Mass spectrometric characterization of urinary hydrafenil metabolites for routine doping control purposes. *Drug Test Anal*. 2021;14(2):289-298.
8. World Anti-Doping Agency. The 2025 Prohibited List: International Standard. WADA; 2024. Section S6.A: Non-Specified Stimulants.
9. Jackson RA. A synthesis of 9-fluorenol: sodium borohydride reduction of 9-fluorenone. *J Chem Educ*. 1994;71(12):A252.
10. Mohrig JR, Hammond CN, Schatz PF, Morrill TC. *Techniques in Organic Chemistry*. 3rd ed. W.H. Freeman; 2010.
11. Darwish M, Kirby M, Hellriegel ET, Robertson P Jr. Armodafinil and modafinil have substantially different pharmacokinetic profiles despite having the same terminal half-lives: analysis of data from three randomized, single-dose, pharmacokinetic studies. *Clin Drug Investig*. 2009;29(9):613-623.

12. Woolley ML, Marsden CA, Fone KC. 5-HT₆ receptors. *Curr Drug Targets CNS Neurol Disord*. 2004;3(1):59-79.
13. Dawson LA, Nguyen HQ, Li P. The 5-HT₆ receptor antagonist SB-271046 selectively enhances excitatory neurotransmission in the rat frontal cortex and hippocampus. *Neuropsychopharmacology*. 2001;25(5):662-668.
14. Meffre J, Chaumont-Dubel S, Mannoury la Cour C, et al. 5-HT₆ receptor recruitment of mTOR as a mechanism for perturbed cognition in schizophrenia. *EMBO Mol Med*. 2012;4(10):1043-1056.
15. Atri A, Frolich L, Ballard C, et al. Effect of idalopirdine as adjunct to cholinesterase inhibitors on change in cognition in patients with Alzheimer disease: three randomized clinical trials. *JAMA*. 2018;319(2):130-142.
16. Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. *Neuropsychopharmacology*. 2008;33(7):1477-1502.
17. Sigma-Aldrich. Safety Data Sheet: 9-Hydroxyfluorene (Product H31204). Revision 2023.
18. Provigil (modafinil) prescribing information. Cephalon, Inc. FDA-approved labeling. Revised 2015.
19. Milgram NW, Callahan H, Siwak C. Adrafinil: a novel vigilance promoting agent. *CNS Drug Rev*. 1999;5(3):193-212.
20. Laboratoire L. Lafon. Bisfluoromodafinil compositions and methods of use. Patent literature. Cited in: Wikipedia, Flmodafinil. Accessed 2026.
21. Szakacs Z, Dauvilliers Y, Mikhaylov V, et al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16(3):200-207.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Hydrafinil is not approved by the United States Food and Drug Administration or any other regulatory agency for any indication. The compound is classified as a non-specified stimulant by the World Anti-Doping

Agency (2025 Prohibited List). The compound is sold exclusively as a research chemical. Investigators should obtain analytical confirmation of identity and purity on every lot.