

RESEARCH MONOGRAPH . COMPOUND PROFILE

Fladrafinil

A bis(4-fluorophenyl)-substituted analog of adrafinil developed at Laboratoire L. Lafon as a wakefulness-promoting agent with reported anti-aggressive properties in animal models, functioning as a prodrug of the dopamine transporter inhibitor flmodafinil and distinguished from its parent compound by fluorine substitution at both para-phenyl positions.

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ABSTRACT

Fladrafinil (CRL-40,941), also designated fluorafinil and bisfluoroadrafinil, is a synthetic diphenylmethylsulfinyl hydroxamic acid eugeroic compound first synthesized at Laboratoire L. Lafon in Paris in the late 1970s to early 1980s as part of the benzhydryl sulfinyl series that also produced adrafinil (CRL-40,028) and modafinil (CRL-40,476). The compound is the bis(4-fluoro) ring-substituted derivative of adrafinil and functions as a prodrug that undergoes hepatic amide hydrolysis to yield flmodafinil (CRL-40,940, bisfluoromodafinil), a selective atypical dopamine reuptake inhibitor with a reported dopamine transporter (DAT) K_i of approximately 4,090 nM and 83 percent DAT blockade in vitro [1, 2]. Fladrafinil was disclosed in a 1984 United States patent (US 4,489,095) assigned to Lafon, in which preclinical animal data demonstrated wakefulness promotion and, distinctively, anti-aggressive behavioral effects in rodent aggression paradigms at intraperitoneal doses of 16 to 1,024 mg/kg, a property not shared by the parent compound adrafinil [3]. The anti-aggressive activity, reported at potencies three to four times greater than adrafinil on a weight basis, represented the principal pharmacological distinction identified during the original Lafon screening campaign and suggested a differentiated central nervous system profile relative to the non-fluorinated congeners. Despite these early findings, fladrafinil was never advanced to formal clinical development. No peer-reviewed human pharmacokinetic, efficacy, or safety studies have been published. The compound was not registered in any jurisdiction and was not assigned an International Nonproprietary Name. The pharmacological characterization of fladrafinil therefore rests

entirely on the Lafon patent disclosures, on inference from the well-characterized pharmacology of its active metabolite flmodafinil and of the closely related modafinil and adrafinil, and on recent analytical chemistry investigations conducted under the auspices of the World Anti-Doping Agency (WADA) to establish urinary and blood detection markers for anti-doping surveillance [4, 5]. Flmodafinil itself has been characterized as a selective DAT inhibitor that blocks the dopamine transporter at 83 percent occupancy without inducing cytochrome P450 3A4 or 3A5, that maintains wakefulness over a longer timeframe than modafinil in animal models with reduced perturbation of sleep architecture, and that elevates nucleus accumbens dopamine concentrations by approximately 150 to 200 percent at peak doses [1, 2]. The active metabolite has been in preclinical development for chronic fatigue syndrome, though clinical programs for narcolepsy, attention deficit hyperactivity disorder, and Alzheimer's disease have been discontinued as of early 2024. Fladrafinil entered public awareness principally through the nootropic and dietary supplement markets beginning approximately 2015, where it is sold as a research-grade powder or capsule preparation at purities typically stated as 98 percent or greater. The compound is classified under the WADA Prohibited List as a class S6 non-specified stimulant (prohibited in-competition) and has been the subject of analytical investigations by Krug, Thevis, and colleagues at the German Sport University Cologne into its metabolism, elimination kinetics, and detection windows in urine and dried blood spots [4, 5]. This monograph reviews the chemistry, structural relationships, known and inferred pharmacology, pharmacokinetics, the absence of clinical evidence, sourcing and quality considerations, reconstitution and handling, stack interactions, adverse-event signal, and a comparative assessment

of five eugeroic and wakefulness-promoting compounds against fladrafinil on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Developmental code name: CRL-40,941 (Laboratoire L. Lafon). The CRL prefix designates the Centre de Recherche Lafon internal compound series. The compound is numbered within the same series as adrafinil (CRL-40,028), modafinil (CRL-40,476), and flmodafinil (CRL-40,940) [3].

Common names: Fladrafinil, fluorafinil, bisfluoroadrafinil.

Chemical Abstracts Service registry number: 90212-80-9.

FDA Unique Ingredient Identifier (UNII): 5RT6X0M01F.

PubChem Compound Identifier: 13316557.

International Union of Pure and Applied Chemistry name: 2-[[bis(4-fluorophenyl)methyl]sulfinyl]-N-hydroxyacetamide.

International Nonproprietary Name: None assigned. The compound was never advanced to a stage of development at which an INN application would have been submitted.

1.2 Structural class and chemistry

Fladrafinil belongs to the benzhydryl sulfinyl acetamide structural class, a small family of synthetic eugeroic compounds characterized by a diphenylmethyl (benzhydryl) group bonded through a sulfinyl linkage to an acetamide moiety. The structural class includes adrafinil (the N-hydroxy acetamide, unsubstituted phenyl rings), modafinil (the unsubstituted acetamide without the N-hydroxyl group), armodafinil (the R-enantiomer of modafinil), and flmodafinil (the bis(4-fluoro) acetamide without the N-hydroxyl group) [6, 7].

Molecular formula: C₁₅H₁₃F₂NO₃S.

Molecular weight: 325.33 g/mol.

Exact mass: 325.0584 g/mol (monoisotopic).

SMILES: ONC(=O)CS+ C(c1ccc(F)cc1)c2ccc(F)cc2.

InChIKey: VKGUUSVYPXTWMA-UHFFFAOYSA-N.

Physical properties: White to off-white crystalline powder. The compound contains one chiral center at the sulfur atom (the sulfinyl group), producing R and S enantiomers. The commercially available material is a racemic mixture with one undefined stereocenter [8]. Solubility data from published sources are limited; the compound is expected to be soluble in dimethyl sulfoxide and in polar organic solvents (methanol, ethanol) and sparingly soluble in water, consistent with the physical properties of the parent compound adrafinil.

Stereochemistry: The sulfinyl sulfur constitutes the sole stereocenter. No enantioselective synthesis or chiral resolution has been disclosed in published literature. Research-grade preparations are racemic. The relationship between enantiomeric composition and pharmacological activity has not been characterized for fladrafinil, though for modafinil the R-enantiomer (armodafinil) is pharmacologically more potent and has a longer elimination half-life than the S-enantiomer [9].

1.3 Synthesis

The synthesis of fladrafinil was disclosed in the Lafon patent US 4,489,095 (1984) within a series of halogenobenzhydrylsulfinylacetohydroxamic acids [3]. The general synthetic route for the benzhydryl sulfinyl hydroxamic acid series proceeds through: (a) preparation of the bis(4-fluorophenyl)methyl thioether by nucleophilic displacement or condensation of 4,4'-difluorobenzhydrol with a thioacetamide equivalent; (b) S-oxidation of the thioether to the sulfinyl (sulfoxide) using a controlled oxidant such as meta-chloroperoxybenzoic acid, hydrogen peroxide, or sodium periodate to yield the sulfinyl intermediate; and (c) introduction of the N-hydroxy functionality on the acetamide nitrogen, either through direct hydroxamic acid formation from the corresponding ester or acid chloride with hydroxylamine, or through N-hydroxylation of the preformed acetamide [3, 10].

The fluorine atoms at both para positions of the benzhydryl moiety are introduced at the starting material stage through the use of 4-fluorobenzaldehyde or 4-fluorophenyl magnesium bromide in the construction of the bis(4-fluorophenyl)methane core. The patent describes the compound within a broader series of mono- and di-halogenated analogs (chloro, bromo, fluoro), with fladrafinil representing the bis(4-fluoro) member of the hydroxamic acid subseries.

Industrial and research-grade synthesis follows conventional sulfinyl acetamide chemistry. Purity is assessed by high-performance liquid chromatography. The compound is supplied as a racemic mixture; no enantiopure preparation has been described commercially.

2. Abstract

Fladrafinil (CRL-40,941) is a fluorinated hydroxamic acid derivative of adrafinil, synthesized at Laboratoire L. Lafon in the early 1980s as part of the benzhydryl sulfinyl series of wakefulness-promoting agents [3]. The compound functions as a prodrug that is converted by hepatic amide hydrolysis to flmodafinil (CRL-40,940), a selective atypical dopamine reuptake inhibitor. The primary pharmacological mechanism attributed to the active metabolite is competitive inhibition of the dopamine transporter (DAT), resulting in elevated extracellular dopamine concentrations in the nucleus accumbens, prefrontal cortex, and other brain regions associated with arousal, motivation, and executive function [1, 2]. Secondary downstream effects, inferred from the well-characterized pharmacology of the structurally related modafinil, include indirect modulation of noradrenergic, histaminergic, orexinergic, glutamatergic, and GABAergic neurotransmission [11, 12].

The distinguishing pharmacological feature of fladrafinil, as reported in the Lafon patent, is anti-aggressive activity in rodent behavioral paradigms at intraperitoneal doses of 16 to 1,024 mg/kg, a property not observed with adrafinil at comparable doses [3]. This anti-aggressive effect, combined with the wakefulness-promoting activity shared across the benzhydryl sulfinyl series, constituted the original pharmacological rationale for the fluorinated analog. The reported potency advantage of three to four times over adrafinil on a weight basis has not been independently confirmed in published peer-reviewed literature.

Fladrafinil has never been the subject of a human clinical trial. No human pharmacokinetic, safety, efficacy, or dose-finding data have been published. The compound was not advanced to regulatory submission in any jurisdiction and carries no approved indication. The pharmacological profile is therefore constructed entirely from: (a) the Lafon patent animal data; (b) the characterized pharmacology of the active metabolite flmodafinil; (c) the extensive clinical and preclinical literature on modafinil and adrafinil, the non-fluorinated structural congeners; and (d) recent WADA-sponsored analytical studies on metabolism and detection [4, 5].

The compound entered non-medical use through the nootropic supplement market beginning approximately 2015, where it is sold as an unregulated research chemical. It is classified as a prohibited stimulant (class S6, in-competition) on the

WADA Prohibited List [4]. This monograph documents the complete available characterization of fladrafinil, acknowledges the substantial gaps in the evidence base relative to the registered congeners modafinil and armodafinil, and provides a comparative assessment against five alternative eugeroic and wakefulness-promoting compounds.

3. Discovery and Development History

3.1 Origin at Laboratoire L. Lafon

Fladrafinil was synthesized at the Centre de Recherche of Laboratoire L. Lafon, a French pharmaceutical company based in Paris, during the late 1970s to early 1980s [3]. The compound emerged from a systematic structure-activity exploration of the benzhydryl sulfinyl series that had already produced adrafinil (CRL-40,028, synthesized 1974) and modafinil (CRL-40,476, identified as the active metabolite of adrafinil in 1976) [6, 13]. The Lafon medicinal chemistry program explored halogen substitution at the para positions of the two phenyl rings of the benzhydryl core, generating a series of mono- and di-halogenated derivatives (fluoro, chloro, bromo) in both the acetamide (modafinil-like) and the N-hydroxy acetamide (adrafinil-like) subseries.

3.2 Patent disclosure

The compound was disclosed in United States Patent 4,489,095, titled "Halogenobenzhydrylsulfinylacetohydroxamic acids," granted December 18, 1984, and assigned to Laboratoire L. Lafon [3]. The Canadian patent family member (CA 1192222A) establishes a priority date of June 4, 1982, a filing date of May 27, 1983, and a publication date of August 20, 1985. The patent describes a series of halogenated benzhydryl sulfinyl hydroxamic acids and reports pharmacological data from intraperitoneal administration in male mice and rats at doses ranging from 16 to 1,024 mg/kg in aqueous gum arabic suspension, with observations at intervals of 15 minutes to 24 hours. The key findings for fladrafinil were wakefulness promotion comparable to or exceeding adrafinil and a distinct anti-aggressive behavioral profile not present in the parent compound.

3.3 Absence of clinical development

Despite the patent disclosure, fladrafinil was not advanced to formal preclinical regulatory studies or to human clinical trials. The reasons for the decision not to develop fladrafinil are not documented in the public literature but are likely related to the concurrent and more advanced development of modafinil, which was pro-

gressing through clinical trials in France in the early to mid-1980s under the direction of neurophysiology professor Michel Jouvet [6, 13]. Modafinil received its first regulatory approval in France in 1992 (marketed as Modiodal) and was approved by the United States Food and Drug Administration in 1998 for narcolepsy. The commercial and clinical success of modafinil would have reduced the strategic incentive to develop additional members of the benzhydryl sulfinyl series, particularly those with the N-hydroxyl pharmacophore (the adrafinil and fladrafinil subseries) that adds a prodrug conversion step and the associated hepatic burden.

3.4 Lafon acquisition and subsequent history

Laboratoire L. Lafon was acquired by Cephalon, Inc. in 2001. Cephalon was subsequently acquired by Teva Pharmaceutical Industries in 2011. Neither Cephalon nor Teva pursued development of fladrafinil. The compound remained dormant in the patent literature until its emergence in the nootropic research chemical market approximately 2015, driven by consumer interest in eugeroic compounds beyond modafinil and adrafinil.

3.5 WADA classification and analytical investigation

Fladrafinil (along with flmodafinil) was added to the WADA Prohibited List under class S6.A (non-specified stimulants), prohibited in-competition [4]. This classification reflects the structural and pharmacological relationship to modafinil, which has been a WADA-prohibited stimulant since 2004. Analytical investigations by Krug, Toma, Thomas, and Thevis at the German Sport University Cologne, presented at the 43rd Cologne Workshop on Dope Analysis (2025), characterized the metabolism and elimination of flmodafinil and fladrafinil in urine and dried blood spots, establishing detection windows and urinary biomarkers for routine anti-doping surveillance [4, 5].

4. Mechanism of Action

4.1 Prodrug conversion

Fladrafinil is a prodrug. Following oral administration, the compound undergoes hepatic hydrolysis of the N-hydroxy bond on the acetamide nitrogen, converting the hydroxamic acid to the corresponding amide, flmodafinil (CRL-40,940) [2, 3]. This biotransformation is analogous to the conversion of adrafinil to modafinil, in which the N-hydroxyl group of adrafinil is cleaved to yield the active metabolite modafinil [6, 14]. The hydrolysis is mediated by hepatic amidases and is the rate-limiting step in the onset of pharmacological activity, introducing a delay between oral administration and the attainment of active metabolite plasma concentrations.

A parallel metabolic pathway, also analogous to adrafinil metabolism, converts a fraction of fladrafinil directly to the inactive modafinilic acid derivative (bisfluoromodafinilic acid) without passage through flmodafinil, reducing the net yield of the active metabolite [14]. The relative contributions of the active (hydroxamic acid to amide) and inactive (hydroxamic acid to acid) pathways have not been quantified for fladrafinil in published studies.

4.2 Dopamine transporter inhibition

The principal pharmacological mechanism of flmodafinil, the active metabolite, is inhibition of the dopamine transporter (DAT). Flmodafinil binds the DAT with a K_i of approximately 4,090 nM and achieves 83 percent transporter blockade in vitro, a degree of inhibition greater than that reported for methylphenidate without the concomitant adrenergic effects associated with that compound [1, 2]. The DAT inhibition elevates extracellular dopamine concentrations in the nucleus accumbens shell, the prefrontal cortex, and other dopaminergic projection targets, producing the wakefulness-promoting, attention-enhancing, and motivation-supporting effects characteristic of the eugeroic class [11, 15].

The selectivity profile of flmodafinil favors dopamine over serotonin reuptake inhibition. The serotonin transporter (SERT) K_i is approximately 48,700 nM, representing 12-fold lower affinity than for the DAT [1]. Affinity for the sigma-1 receptor is negligible (K_i greater than 100,000 nM), distinguishing flmodafinil from

modafinil, which has measurable sigma-1 receptor binding [1]. The selectivity for DAT over other monoamine transporters and over non-monoamine targets classifies flmodafinil as a selective atypical dopamine reuptake inhibitor.

4.3 Downstream neurotransmitter modulation

By analogy with the well-characterized pharmacology of modafinil, the elevated dopamine concentrations resulting from DAT inhibition by flmodafinil are expected to activate both D1 and D2 dopamine receptors in the cortex, striatum, and hypothalamus, producing downstream effects on multiple neurotransmitter systems [11, 12, 15]:

(a) Noradrenergic activation through alpha-1 adrenergic receptor engagement in the locus coeruleus and cortical projection areas, contributing to arousal and attention.

(b) Histaminergic activation through indirect stimulation of tuberomammillary nucleus histamine neurons, contributing to cortical desynchronization and sustained wakefulness.

(c) Orexinergic engagement through indirect activation of lateral hypothalamic orexin (hypocretin) neurons via glutamatergic inputs, supporting sleep-wake boundary stabilization.

(d) Glutamatergic enhancement and GABAergic reduction in cortical and thalamic circuits, shifting the excitation-inhibition balance toward cortical activation [12].

These downstream mechanisms have been characterized for modafinil through electrophysiological, microdialysis, and knockout-mouse studies; they are inferred for flmodafinil (and by extension for fladrafinil as a prodrug of flmodafinil) on the basis of the shared DAT inhibition mechanism and the overlapping behavioral pharmacology in animal wakefulness models [11, 12].

4.4 Anti-aggressive activity

The anti-aggressive behavioral effect reported in the Lafon patent is the principal pharmacological distinction between fladrafinil and adrafinil [3]. In resident-intruder and isolation-induced aggression paradigms in male mice, fladrafinil at intraperitoneal doses of 64 to 256 mg/kg produced significant reductions in aggressive

behaviors (biting, chasing, attack latency) relative to vehicle controls, at potencies reported as three to four times greater than adrafinil on a weight basis. Adrafinil at equivalent doses did not produce comparable anti-aggressive effects. The mechanism underlying this differential activity has not been elucidated. Possible contributors include: (a) direct or indirect serotonergic modulation by the fluorinated metabolite that is absent in the non-fluorinated series; (b) altered receptor selectivity profile at the DAT or at secondary targets introduced by the para-fluoro substituents; or (c) pharmacokinetic differences in brain distribution or metabolite profile. The anti-aggressive effect has not been replicated in independent published studies.

4.5 Absence of direct receptor binding data for fladrafinil

No published study has characterized the binding affinity of fladrafinil itself (as distinct from its active metabolite flmodafinil) at any receptor, transporter, or enzyme target. The pharmacological activity of the parent compound prior to metabolic conversion is unknown. It is possible that fladrafinil has direct pharmacological activity at one or more central nervous system targets in addition to its prodrug function, but this has not been investigated.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

No formal pharmacokinetic study of fladrafinil in humans or animals has been published in the peer-reviewed literature. The compound is reported to be rapidly absorbed after oral administration, consistent with the physicochemical properties of the benzhydryl sulfinyl class (moderate molecular weight, moderate lipophilicity) [3, 14]. By analogy with adrafinil, oral bioavailability is expected to be moderate but reduced relative to the active metabolite due to first-pass hepatic conversion through both the active (to flmodaflinil) and inactive (to bisfluoromodaflinilic acid) pathways.

The WADA-sponsored analytical studies by Krug, Thevis, and colleagues reported that after oral administration of fladrafinil, a slight temporal offset was observed before peak plasma concentrations of flmodaflinil were reached, consistent with the prodrug conversion step [4, 5]. Analyte quantities were considerably lower in blood (dried blood spots) than in urine, indicating extensive metabolic processing and renal elimination of metabolites.

5.2 Distribution

No distribution data specific to fladrafinil have been published. By analogy with modafinil, the active metabolite flmodaflinil is expected to have moderate protein binding (modafinil protein binding is approximately 60 percent, predominantly to albumin), moderate volume of distribution, and adequate blood-brain barrier penetration to produce central effects [16].

5.3 Metabolism

Fladrafinil undergoes hepatic metabolism through at least two principal pathways:

(a) Amide hydrolysis of the N-hydroxyl bond, yielding flmodafinil (CRL-40,940, the active metabolite). This pathway is analogous to the conversion of adrafinil to modafinil and is the pharmacologically productive route [2, 14].

(b) Oxidative cleavage or hydrolysis to bisfluoromodafinilic acid, the inactive carboxylic acid metabolite. This pathway is analogous to the direct conversion of adrafinil to modafinilic acid and represents a pharmacological dead end [14].

Flmodafinil itself is subsequently metabolized, presumably through pathways analogous to those of modafinil: amide hydrolysis to bisfluoromodafinilic acid and sulfone formation to bisfluoromodafinil sulfone [16]. A notable pharmacological distinction of flmodafinil relative to modafinil is the absence of cytochrome P450 3A4 and 3A5 enzyme induction, a property that reduces the potential for metabolic drug-drug interactions [1, 2].

The specific cytochrome P450 isoforms responsible for the hepatic biotransformation of fladrafinil and flmodafinil have not been fully characterized. For modafinil, the principal metabolizing enzymes are CYP3A4 and CYP2C9, with minor contributions from other CYP isoforms [16, 17]. The fluorine substitution may alter the CYP isoform selectivity and the rate of metabolism, but this has not been experimentally determined for the fluorinated series.

5.4 Elimination

Elimination is expected to be predominantly renal, through excretion of the inactive acid metabolite and conjugated metabolites, consistent with the elimination profile of adrafinil and modafinil [14, 16]. The WADA analytical studies reported relatively long detection windows for both the intact drug and its metabolites in urine, necessitating careful interpretation of adverse analytical findings given the in-competition-only prohibition status [4, 5].

5.5 Half-life

No formal half-life determination has been published for fladrafinil. Nootropic community sources report an estimated half-life of approximately 12 to 16 hours, though this figure lacks published pharmacokinetic validation. By comparison, modafinil has an elimination half-life of approximately 12 to 15 hours (R-enan-

tiomer) and 4 to 5 hours (S-enantiomer); adrafinil, as a prodrug, has an effective duration of action limited by the rate of metabolic conversion rather than by the half-life of the parent compound [9, 16].

5.6 Routes of administration

Oral administration is the only route described in the Lafon patent (intraperitoneal injection was used in the animal studies) and the only route used in the nootropic supplement context. No parenteral, intravenous, or other formulations have been developed or characterized.

6. Preclinical Pharmacology

6.1 Lafon patent animal data

The preclinical pharmacological data on fladrafinil originate solely from the animal assays disclosed in the Lafon patent (US 4,489,095; CA 1192222A) [3]. Male mice and rats were administered fladrafinil by intraperitoneal injection at doses ranging from 16 mg/kg to 1,024 mg/kg, suspended in aqueous gum arabic solution. Behavioral observations were conducted at intervals of 15 minutes to 24 hours following administration. The compound produced dose-dependent wakefulness promotion, characterized by increased locomotor activity, reduced sleep time, and sustained arousal in dark-phase (normal sleep period) assessments. The wakefulness-promoting effect was comparable to or greater than adrafinil at equivalent intraperitoneal doses.

6.2 Anti-aggressive behavioral profile

The anti-aggressive activity was assessed in standard rodent aggression paradigms, including the resident-intruder test and isolation-induced aggression models [3]. Fladrafinil reduced aggression measures at doses three to four times lower than those required for adrafinil to produce any measurable anti-aggressive effect. Adrafinil itself did not produce statistically significant anti-aggressive effects at the doses tested. This differential activity was the primary novel finding of the patent and the principal basis for the compound's inclusion in the patent claims as a distinct entity from adrafinil.

6.3 Absence of independent replication

No independent laboratory has published a replication or extension of the Lafon patent animal data. The anti-aggressive effect, the potency comparison with adrafinil, and the dose-response relationship for wakefulness promotion have not been confirmed through peer-reviewed research. The absence of independent replication is a significant limitation of the preclinical evidence base.

6.4 Inferred preclinical pharmacology from flmodafinil

The active metabolite flmodafinil has been characterized in animal wakefulness models. In comparative studies with modafinil, flmodafinil maintained wakefulness over a significantly longer timeframe than modafinil in rodents, with reduced perturbation of sleep architecture (less disturbance of non-rapid-eye-movement and rapid-eye-movement sleep structure during recovery sleep) [1, 2]. Flmodafinil elevated nucleus accumbens dopamine concentrations by approximately 150 to 200 percent at peak doses, a magnitude substantially lower than that produced by amphetamine or cocaine, consistent with the atypical stimulant profile of the eugeroic class [1]. Neither compound produced sleep rebound. These findings, while applicable to the active metabolite rather than to fladrafinil directly, support the inference that fladrafinil (through conversion to flmodafinil) would produce a wakefulness-promoting effect in preclinical models.

7. Clinical Evidence Base

7.1 Absence of clinical data

Fladrafinil has never been the subject of a human clinical trial. No Phase 1, Phase 2, or Phase 3 studies have been conducted or registered. No human pharmacokinetic data have been published. No human safety data exist beyond spontaneous adverse-event reports from uncontrolled nootropic supplement use. The compound has no approved indication in any jurisdiction worldwide [8].

This absence of clinical evidence is the single most important limitation of fladrafinil relative to the registered congeners modafinil and armodafinil, which have been evaluated in thousands of patients across dozens of randomized controlled trials for narcolepsy, obstructive sleep apnea, shift work sleep disorder, and off-label cognitive applications [16, 18, 19].

7.2 Inferred clinical pharmacology from modafinil

The clinical pharmacology of fladrafinil can be inferred, with appropriate caution, from the established modafinil evidence base. Modafinil at 200 to 400 mg daily produces robust wakefulness promotion in narcolepsy (maintained wakefulness test improvement of approximately 2 to 3 minutes, clinically significant by regulatory standards), reduces excessive daytime sleepiness in obstructive sleep apnea and shift work sleep disorder, and produces modest cognitive enhancement effects in healthy adults (overall standardized mean difference approximately 0.12, with larger effects on complex decision-making and planning tasks) [16, 18, 19, 20]. Whether fladrafinil reproduces these effects in humans, and at what dose, is unknown.

7.3 Inferred clinical pharmacology from flmodafinil

Flmodafinil, the active metabolite of fladrafinil, has been in preclinical development but has not produced published human trial results. As of early 2024, flmodafinil was in preclinical stage for chronic fatigue syndrome; clinical programs for narcolepsy, attention deficit hyperactivity disorder, and Alzheimer's disease had

been discontinued [1]. The absence of human data for both the prodrug and the active metabolite places fladrafinil in a distinctly lower evidence tier than modafinil and armodafinil.

7.4 Anti-doping surveillance data

The WADA analytical studies represent the closest available approximation to human pharmacokinetic data for fladrafinil, though these studies were designed for detection methodology rather than for clinical pharmacological characterization [4, 5]. The studies confirmed that fladrafinil is converted to flmodafinil in vivo (human subjects), that both the parent compound and metabolites are detectable in urine and dried blood spots, and that the detection window is relatively long. Quantitative pharmacokinetic parameters (C_{max} , T_{max} , AUC, half-life) from these studies have not been published in peer-reviewed form as of monograph preparation.

8. Sourcing and Quality Verification

Research-grade fladrafinil is supplied by multiple chemical and research compound vendors (MedChemExpress, BenchChem, Cayman Chemical, various nootropic-oriented suppliers) at stated purities of 98 percent or greater by HPLC [8, 21]. The compound is typically supplied as a white to off-white powder in the racemic form as the free compound (not as a salt). Pricing varies substantially across vendors and is generally in the range of \$15 to \$80 per gram for research quantities.

No pharmaceutical-grade fladrafinil exists. The compound has never been manufactured to Good Manufacturing Practice standards, has never been included in a pharmacopoeial monograph, and has no reference standard in the United States Pharmacopeia, European Pharmacopoeia, or Japanese Pharmacopoeia.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (326.0663 for the protonated molecule $[M+H]^+$ from the monoisotopic mass of 325.0584)
- Nuclear magnetic resonance spectroscopy (1H and ^{19}F NMR) for structural confirmation, with the ^{19}F NMR particularly diagnostic for the para-fluoro substituents
- Differential scanning calorimetry or melting point determination for solid-state characterization
- Residual solvent analysis by gas chromatography

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) provide independent verification of vendor certificates of analysis. Given the absence of pharmacopoeial standards, on-receipt analytical confirmation is particularly important for any investigation where dose-response precision or mechanistic interpretation depends on compound identity and purity.

Investigators should be aware that the fladrafinil supply chain is unregulated and that vendor certificates of analysis may not be reliable. Batch-to-batch variability in purity, enantiomeric composition, and residual solvent content should be expected and tested.

9. Reconstitution and Handling

Fladrafinil is supplied as a solid powder and is administered orally in the nootropic context, typically in gelatin capsules or dissolved in a liquid vehicle. For in vitro research applications, the compound is dissolved in dimethyl sulfoxide (DMSO) to prepare stock solutions at concentrations of 10 to 100 mM, consistent with standard practice for sulfinyl acetamide compounds. Aqueous solubility is limited; for cell-based or tissue-based assays requiring aqueous stock solutions, the compound should be dissolved first in DMSO and then diluted into the assay medium, maintaining a final DMSO concentration below 0.1 percent to avoid solvent-mediated cytotoxicity.

Storage of the solid compound should be at room temperature in a dry environment, protected from moisture. Refrigerated storage (2 to 8 degrees Celsius) in a desiccated container is appropriate for long-term archival. DMSO stock solutions should be aliquoted for single-use and stored at negative 20 degrees Celsius; stability under freeze-thaw cycling has not been formally characterized for fladrafinil, and investigators should minimize freeze-thaw cycles.

No parenteral formulations have been developed. The compound is not supplied in ampoule, vial, or lyophilized injectable form. Any parenteral research application would require formulation development including solubility optimization, sterile filtration, and stability testing.

10. Stack Interactions and Combinations

Fladrafinil interacts with several drug classes through its prodrug metabolism and through the pharmacological activity of its active metabolite flmodafinil. Investigators and individuals using the compound should consider the following interactions:

Hepatic metabolism interactions: Fladrafinil requires hepatic conversion to the active metabolite flmodafinil. Compounds that inhibit or induce the hepatic amidases or cytochrome P450 enzymes involved in this conversion will alter the rate and extent of active metabolite formation. Unlike modafinil, flmodafinil does not induce CYP3A4 or CYP3A5, which reduces one major category of drug-drug interaction risk relative to the non-fluorinated congeners [1, 2]. However, the specific CYP isoforms involved in fladrafinil metabolism have not been characterized, and interactions with CYP inhibitors and inducers cannot be excluded.

Other eugeroic compounds: Concurrent administration of fladrafinil with modafinil, armodafinil, adrafinil, or flmodafinil is pharmacologically redundant and produces additive DAT inhibition. The combination increases the risk of dopaminergic overstimulation (anxiety, insomnia, tachycardia) without a characterized benefit. The combination is not recommended.

Dopaminergic agents: Concurrent use with other dopamine reuptake inhibitors (methylphenidate, bupropion), dopamine releasers (amphetamines), or direct dopamine agonists (pramipexole, ropinirole) produces additive or synergistic dopaminergic activation. The combination increases the risk of insomnia, anxiety, agitation, and cardiovascular stimulation.

Caffeine and other xanthines: Concurrent caffeine use is common in the nootropic context. The combination produces additive wakefulness promotion through complementary mechanisms (DAT inhibition plus adenosine receptor antagonism) and additive cardiovascular stimulation (tachycardia, hypertension). The interaction is not pharmacokinetically mediated but is pharmacodynamically relevant.

Serotonergic agents: The low SERT affinity of flmodafinil (K_i approximately 48,700 nM) suggests minimal direct serotonergic interaction [1]. However, elevated dopaminergic tone can indirectly modulate serotonin release, and concurrent use with serotonin reuptake inhibitors (SSRIs, SNRIs) should be approached with awareness of the potential for altered mood, sleep, and appetite effects.

Hepatotoxic agents: Adrafinil (the non-fluorinated parent compound) has been associated with elevated liver enzymes on prolonged use, a concern attributed to the hepatic metabolic burden of the N-hydroxyl cleavage and potentially to the generation of reactive hydroxylamine intermediates [14, 22]. Whether fladrafinil carries a similar hepatotoxic potential is unknown. Concurrent use with other hepatotoxic compounds (acetaminophen at high doses, certain statins, azole antifungals) should be considered for potential additive hepatic burden.

Oral contraceptives and CYP-sensitive medications: Modafinil induces CYP3A4 and can reduce the efficacy of oral contraceptives and other CYP3A4 substrates [16, 17]. Flmodafinil reportedly does not induce CYP3A4 or CYP3A5 [1, 2], which, if confirmed in human pharmacokinetic studies, would represent a clinically meaningful advantage. However, this property has not been verified in formal drug-drug interaction studies.

11. Adverse Events and Safety

11.1 Absence of formal safety data

No formal safety data exist for fladrafinil. The compound has not been evaluated in preclinical toxicology studies (acute toxicity, subchronic toxicity, genotoxicity, carcinogenicity, reproductive toxicity) beyond the limited observations in the Lafon patent [3]. No human safety data from controlled studies exist. The adverse-event profile is therefore constructed from: (a) the known safety profile of modafinil and armodafinil; (b) theoretical concerns arising from the prodrug metabolism and the hydroxamic acid pharmacophore; and (c) anecdotal reports from uncontrolled nootropic use.

11.2 Inferred adverse events from modafinil

The adverse-event profile of modafinil at registered doses (200 to 400 mg daily) provides the closest available approximation to the expected adverse-event profile of fladrafinil through its active metabolite. Common adverse events for modafinil include [16, 23]:

- Headache (34 percent in clinical trials, the most common adverse event)
- Nausea (11 percent)
- Nervousness (7 percent)
- Rhinitis (7 percent)
- Insomnia (5 percent)
- Anxiety (5 percent)
- Dizziness (5 percent)
- Diarrhea (6 percent)
- Back pain (6 percent)
- Dyspepsia (5 percent)

Serious adverse events for modafinil include rare severe cutaneous reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms) reported in 6 cases between 1998 and 2007,

typically occurring within 1 to 5 weeks of treatment initiation [23, 24]. Cardiovascular events (hypertension, tachycardia, chest pain, arrhythmias) have been reported in association with sympathetic nervous system activation [23].

11.3 Hepatotoxicity concern

Adrafinil, the non-fluorinated analog sharing the N-hydroxyl acetamide pharmacophore with fladrafinil, has been associated with elevated hepatic transaminases on prolonged use [14, 22]. This concern is attributed to the metabolic processing of the hydroxamic acid group, which may generate reactive intermediates during the amidase-mediated cleavage. Modafinil, which lacks the N-hydroxyl group, does not carry this hepatotoxic signal (zero cases attributed to modafinil in 899 cases of drug-induced liver injury in a US prospective study between 2004 and 2013) [22]. Fladrafinil, as a hydroxamic acid like adrafinil, may share the hepatotoxic potential. Investigators and users should consider periodic monitoring of hepatic transaminases during extended use.

11.4 Theoretical concerns from fluorine substitution

The para-fluoro substituents on both phenyl rings alter the electronic properties of the benzhydryl core. While fluorine substitution is a common medicinal chemistry strategy to improve metabolic stability and lipophilicity, the specific effects of the fluorine atoms on the toxicological profile of fladrafinil and its metabolites have not been characterized. The generation of fluorinated metabolites during hepatic biotransformation is a theoretical concern that has not been addressed experimentally.

11.5 Abuse potential

Modafinil has demonstrated abuse potential in preclinical and clinical studies, though substantially lower than that of classical psychostimulants (amphetamines, cocaine) [16]. Modafinil is classified as a Schedule IV controlled substance in the United States. Fladrafinil, as a prodrug of an atypical dopamine reuptake inhibitor, carries a similar theoretical abuse potential. The compound is not scheduled in most jurisdictions, though its WADA classification as a prohibited stimulant reflects the performance-enhancing potential [4].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five eugeroic and wakefulness-promoting compounds against fladrafinil, evaluated on five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The five comparators were selected as the principal compounds with substantive pharmacological data in the wakefulness-promoting and cognitive-enhancement space that share mechanistic or structural relationships with fladrafinil.

12.1 Modafinil (CRL-40,476, Provigil)

Mechanism: Weak, selective dopamine transporter inhibitor with downstream noradrenergic, histaminergic, orexinergic, glutamatergic, and GABAergic modulation. Active compound (not a prodrug). Racemic mixture of R- and S-enantiomers [11, 15, 16].

Development trajectory: Synthesized at Laboratoire L. Lafon in 1976 as the active metabolite of adrafinil. Approved in France in 1992, in the United States in 1998 for narcolepsy, and subsequently for shift work sleep disorder and obstructive sleep apnea (2003). Marketed globally as Provigil (Cephalon/Teva) and in extensive generic competition. The most extensively studied eugeroic compound in clinical medicine [6, 13, 16].

Novelty: Low relative to fladrafinil. The two compounds share the benzhydryl sulfinyl core mechanism; modafinil is the non-fluorinated, non-hydroxamic acid congener. The mechanism is thoroughly characterized.

Effect size: Robust for wakefulness promotion in narcolepsy and sleep disorders. Modest for cognitive enhancement in healthy adults (SMD approximately 0.12 overall, with larger effects on complex tasks) [19, 20]. The clinical evidence base is the largest of any eugeroic compound, with thousands of patients across dozens of randomized trials.

Promising potential: High. Modafinil is an established, registered medicine with well-characterized clinical pharmacology and broad off-label use for cognitive enhancement, fatigue, and attention support [16, 18].

Side-effect profile: Well characterized. Common adverse events (headache, nausea, insomnia) are mild to moderate. Rare serious adverse events (Stevens-Johnson syndrome, cardiovascular stimulation) are documented. Abuse potential is low (Schedule IV) [16, 23].

Overall validation: Very high. The compound has the highest level of clinical validation of any eugeroic agent, supported by regulatory approval in multiple jurisdictions, extensive randomized trial data, and decades of postmarketing surveillance.

Comparison to fladrafinil: Modafinil is superior to fladrafinil on every dimension of clinical evidence, safety characterization, and regulatory validation. Fladrafinil's theoretical advantage is the fluorine substitution, which may confer improved metabolic stability and reduced CYP enzyme induction (through the active metabolite flmodafinil), and the reported anti-aggressive activity. Neither advantage has been validated in human studies. Modafinil is the clear reference standard against which fladrafinil should be evaluated.

12.2 Armodafinil (R-modafinil, Nuvigil)

Mechanism: R-enantiomer of modafinil. Identical mechanism (DAT inhibition) but with longer elimination half-life (12 to 15 hours vs. 4 to 5 hours for the S-enantiomer), producing higher plasma concentrations at later time points and more sustained wakefulness promotion [9, 25].

Development trajectory: Developed by Cephalon as the enantiopure successor to modafinil. Approved by the FDA in 2007 for narcolepsy, shift work sleep disorder, and obstructive sleep apnea. Marketed as Nuvigil. Now in generic competition [25].

Novelty: Low. The compound is the isolated active enantiomer of modafinil with no novel mechanism.

Effect size: Comparable to modafinil in head-to-head trials, with pharmacokinetic advantages (higher late-day plasma concentrations, reduced dosing variability) [9, 25].

Promising potential: High. Registered medicine with established clinical use.

Side-effect profile: Similar to modafinil. Common adverse events include headache, nausea, and insomnia. The enantiopure formulation may produce a modestly different adverse-event profile than the racemate in individual patients [25].

Overall validation: Very high. Supported by regulatory approval, randomized trial data, and postmarketing surveillance.

Comparison to fladrafinil: Armodafinil shares with modafinil the comprehensive advantage over fladrafinil in clinical evidence, safety data, and regulatory status. The pharmacokinetic advantage of the enantiopure R-form (longer half-life, more sustained effect) is a further distinction that fladrafinil, as a racemic prodrug, does not offer.

12.3 Adrafinil (CRL-40,028, Olmifon)

Mechanism: Prodrug of modafinil. N-hydroxy acetamide that is cleaved hepatically to yield modafinil (the active metabolite) and modafinilic acid (the inactive metabolite). Identical prodrug concept to fladrafinil but without the fluorine substitution [6, 14].

Development trajectory: Synthesized at Laboratoire L. Lafon in 1974. Marketed briefly in France as Olmifon for the treatment of inattention and drowsiness in the elderly. Withdrawn from the French market in 2011. Not approved in the United States or in other major jurisdictions [14].

Novelty: Low relative to fladrafinil. The two compounds share the hydroxamic acid prodrug strategy; adrafinil is the direct non-fluorinated parent compound.

Effect size: Modest. Comparable to modafinil through the prodrug mechanism, but with lower effective bioavailability due to the competing inactive metabolic pathway to modafinilic acid [14].

Promising potential: Low. The compound was withdrawn from its only registered market. It persists as a research compound and as an unregulated nootropic supplement.

Side-effect profile: Similar to modafinil for common adverse events, with the additional concern of hepatotoxicity on prolonged use attributable to the N-hydroxyl pharmacophore and hepatic metabolic burden [14, 22].

Overall validation: Low to moderate. Limited clinical trial data. Regulatory approval was brief and followed by withdrawal.

Comparison to fladrafinil: Adrafinil is the closest structural and pharmacological analog of fladrafinil. Both are hydroxamic acid prodrugs that yield fluorinated and non-fluorinated modafinil derivatives, respectively. Fladrafinil's theoretical advantages over adrafinil are the fluorine substitution (potentially improved potency and metabolic stability), the reported anti-aggressive activity, and the active metabolite's lack of CYP3A4/3A5 induction. Adrafinil has the advantage of having been (briefly) marketed with at least some clinical characterization. Neither compound has a strong evidence base by modern standards.

12.4 Flmodafinil (CRL-40,940, bisfluoromodafinil, lauflumide)

Mechanism: Selective atypical dopamine reuptake inhibitor. DAT Ki approximately 4,090 nM, 83 percent DAT blockade. Does not induce CYP3A4 or CYP3A5. The direct active metabolite of fladrafinil [1, 2].

Development trajectory: Patented in 2013. Preclinical development by NLS Pharmaceuticals for chronic fatigue syndrome. Clinical programs for narcolepsy, ADHD, and Alzheimer's disease were initiated but discontinued as of early 2024. No published human clinical trial results [1, 2].

Novelty: Moderate. The CYP non-induction property and the improved DAT selectivity relative to modafinil represent meaningful pharmacological refinements.

Effect size: Preclinical only. Animal studies show longer wakefulness duration than modafinil with reduced sleep architecture perturbation [1]. No human efficacy data.

Promising potential: Low to moderate. Preclinical development continues for chronic fatigue syndrome, but major indications have been discontinued. The compound is available as a research chemical.

Side-effect profile: Preclinical only. No human safety data. The absence of CYP3A4 induction is theoretically advantageous for drug interaction safety [1, 2].

Overall validation: Low. Exclusively preclinical data. No regulatory approval.

Comparison to fladrafinil: Flmodafinil is the active metabolite of fladrafinil and represents what fladrafinil becomes after hepatic conversion. Direct administration of flmodafinil eliminates the prodrug conversion step, avoids the hepatic burden associated with the hydroxamic acid pharmacophore, and provides more predictable pharmacokinetics. For research applications requiring the active eugeroic effect, flmodafinil is pharmacologically preferable to fladrafinil. Fladrafinil's only potential advantage over flmodafinil is if the parent compound itself has direct pharmacological activity (such as the reported anti-aggressive effect) that is not reproduced by the metabolite alone.

12.5 Hydrafinil (9-fluorenonol, fluorenonol)

Mechanism: Weak dopamine reuptake inhibitor (IC₅₀ approximately 9 micromolar, 59 percent weaker than modafinil at IC₅₀ approximately 3.7 micromolar) with reported serotonin 5-HT₆ receptor antagonism. Structurally unrelated to the benzhydryl sulfinyl series; the compound is a fluorene-derived alcohol [26, 27].

Development trajectory: Identified through Cephalon research (2011 to 2012) as a metabolite of a fluorene-derived series. Never advanced to clinical development. Sold as an unregulated research chemical and nootropic supplement [26, 27].

Novelty: Moderate. The 5-HT₆ antagonism mechanism is distinct from the pure DAT inhibition of the benzhydryl sulfinyl series and may provide complementary cognitive enhancement through acetylcholine and glutamate release [27].

Effect size: Preclinical only. The Cephalon study reported 39 percent greater wakefulness promotion than modafinil over a 4-hour period in rats [26]. No human efficacy data.

Promising potential: Low. No clinical development. No regulatory pathway. Available only as an unregulated research chemical.

Side-effect profile: Unknown. No human safety data. The weaker DAT inhibition relative to modafinil may predict a lower stimulant-type adverse-event burden, but this is speculative.

Overall validation: Very low. A single preclinical series from Cephalon and no subsequent development.

Comparison to fladrafinil: Hydrafinil shares with fladrafinil the status of an unregulated, clinically uncharacterized eugeroic research compound. Both lack human trial data. Hydrafinil has the potential mechanistic advantage of 5-HT₆ antagonism but the pharmacological disadvantage of weaker DAT inhibition. Fladrafinil has the advantage of structural relationship to the well-characterized modafinil series and the availability of the active metabolite pharmacology. Neither compound has sufficient evidence to support a clinical recommendation over modafinil or armodafinil.

12.6 Comparator summary

The five comparators span the spectrum of eugeroic compound development from registered medicines (modafinil, armodafinil) through withdrawn products (adrafinil) to preclinical or undeveloped research compounds (flmodafinil, hydrafinil). Fladrafinil occupies the lowest validation tier along with hydrafinil: both are unregistered, clinically untested research chemicals sold in the nootropic supplement market without regulatory oversight.

Modafinil and **armodafinil** are the clear reference standards, with extensive clinical evidence, regulatory approval, well-characterized safety profiles, and predictable pharmacokinetics. Any investigator or user considering fladrafinil for wakefulness promotion or cognitive enhancement should recognize that modafinil and armodafinil offer the same fundamental mechanism with incomparably greater evidence and safety characterization.

Adrafinil is the direct non-fluorinated parent compound of fladrafinil and serves as the closest structural comparator. Its withdrawal from the French market and its hepatotoxicity concern are relevant considerations that may apply equally to fladrafinil given the shared hydroxamic acid pharmacophore.

Flmodafinil is the active metabolite of fladrafinil and is pharmacologically preferable for research applications that seek the eugeroic effect without the pro-drug conversion overhead and hepatic burden.

Hydrafinil is mechanistically distinct and equally uncharacterized, serving as a reminder that the eugeroic research compound space contains multiple agents of uncertain safety and efficacy.

The principal research interest in fladrafinil, if any, lies in the reported anti-aggressive activity that distinguishes it from the other members of the benzhydryl sulfinyl series. If this activity is confirmed through independent replication in modern behavioral paradigms, it would represent a genuinely novel pharmacological property within the eugeroic class. Absent such confirmation, fladrafinil offers no characterized advantage over modafinil, armodafinil, or direct administration of flmodafinil.

13. References

1. Flmodafinil pharmacological characterization. DAT Ki, SERT Ki, sigma-1 receptor affinity, and CYP non-induction properties derived from NLS Pharmaceuticals preclinical data and receptor binding studies, referenced through secondary literature and patent filings, 2013 to 2024.
2. NLS Pharmaceuticals. Preclinical development program for flmodafinil (CRL-40,940, NLS-4). Data referenced through regulatory filings and secondary literature, 2015 to 2024.
3. Lafon L (assignee). Halogenobenzhydrylsulfinylacetohydroxamic acids. US Patent 4,489,095. December 18, 1984. Canadian family member CA 1192222A, priority date June 4, 1982.
4. Krug O, Toma F, Thomas A, Thevis M. Investigations into the metabolism and elimination of flmodafinil and fladrafinil in urine and blood (DBS). Proceedings of the 43rd Cologne Workshop on Dope Analysis. German Sport University Cologne. 2025.
5. World Anti-Doping Agency. Prohibited List, Class S6: Stimulants. WADA; 2026 edition.
6. Jouvet M, Bastuji H. Modafinil: its discovery, the early European and North American studies, and clinical use in narcolepsy and idiopathic hypersomnia. *Sleep Med.* 2018;49:69-72.
7. List of modafinil analogues and derivatives. Structural relationships within the benzhydryl sulfinyl series. Referenced through published medicinal chemistry reviews.
8. National Center for Advancing Translational Sciences (NCATS). NCATS Inxight Drugs: Fladrafinil (UNII 5RT6X0M01F). National Institutes of Health.
9. 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.

10. Lafon L (assignee). General synthetic methods for benzhydryl sulfinyl compounds. Patent family CA 1192222A and US 4,489,095. 1982-1984.
11. Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. *Neuropsychopharmacology*. 2008;33(7):1477-1502.
12. Gerrard P, Malcolm R. Mechanisms of modafinil: a review of current research. *Neuropsychiatr Dis Treat*. 2007;3(3):349-364.
13. Milgram NW, Callahan H, Siwak C. Adrafinil: a novel vigilance promoting agent. *CNS Drug Rev*. 1999;5(3):193-212.
14. Ballas CA, Kim D, Baldassano CF, Hoeh N. Adrafinil: psychostimulant and purported nootropic. *Am J Psychiatry Resid J*. 2021;17(1):4-6.
15. Volkow ND, Fowler JS, Logan J, et al. Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. *JAMA*. 2009;301(11):1148-1154.
16. Robertson P Jr, Hellriegel ET. Clinical pharmacokinetic profile of modafinil. *Clin Pharmacokinet*. 2003;42(2):123-137.
17. Robertson P, Hellriegel ET, Arora S, Nelson M. Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. *Clin Pharmacol Ther*. 2002;71(1):46-56.
18. Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. *J Clin Psychiatry*. 2006;67(4):554-566.
19. Battleday RM, Brem AK. Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: a systematic review. *Eur Neuropsychopharmacol*. 2015;25(11):1865-1881.
20. Kredlow MA, Keshishian A, Oppenheimer S, Otto MW. How effective are pharmaceuticals for cognitive enhancement in healthy adults? A series of meta-analyses of cognitive performance during acute administration of modafinil, methylphenidate and d-amphetamine. *Eur Neuropsychopharmacol*. 2020;38:40-62.
21. BenchChem. Fladrafinil (CRL-40,941) product information. Product B104434. Research chemical specifications.

22. Modafinil. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. National Institute of Diabetes and Digestive and Kidney Diseases. Updated 2020.
23. Provigil (modafinil) prescribing information. Cephalon/Teva Pharmaceutical Industries. US Food and Drug Administration approved labeling. Revised 2010.
24. US Food and Drug Administration. MedWatch Safety Alert: Modafinil (marketed as Provigil). Reports of severe cutaneous adverse reactions. 2007.
25. Garnock-Jones KP, Dhillon S, Scott LJ. Armodafinil. CNS Drugs. 2009;23(9):793-803.
26. Cephalon, Inc. Fluorene-derived wakefulness-promoting compounds. Research publications 2011-2012. Referenced through secondary literature.
27. Fluorenol pharmacological characterization. DAT IC50 and 5-HT6 receptor antagonism data derived from Cephalon research program, referenced through secondary literature.

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