

RESEARCH MONOGRAPH . COMPOUND PROFILE

Flmodafinil

A bis(4-fluorophenyl) ring-substituted analog of modafinil developed at Laboratoire L. Lafon, distinguished from the parent compound by enhanced dopamine transporter affinity, prolonged wake-promoting duration, absence of cytochrome P450 enzyme induction, and a preclinical pharmacology profile suggesting superior potency-to-dose ratio with reduced sleep architecture disruption.

DOCUMENT	KDC-MN-1438
ISSUED	2026-05-11
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Bisfluorinated diphenylmethyl sulfinyl acetamide eugeroic and selective atypical dopamine reuptake inhibitor

ABSTRACT

Flmodafinil (CRL-40,940; NLS-4; lauflumide; bisfluoromodafinil; JBG01-41) is a synthetic eugeroic of the diphenylmethyl sulfinyl acetamide structural class, bearing two para-fluorine substituents on the phenyl rings of the modafinil scaffold. First synthesized and patented by Laboratoire L. Lafon in France in the mid-1980s as part of a systematic structure-activity exploration of modafinil derivatives, the compound remained largely uninvestigated for approximately two decades until NLS Pharmaceuticals AG (formerly NLS Pharmaceuticals) acquired development rights and advanced it into preclinical programs for narcolepsy, attention deficit hyperactivity disorder, Alzheimer's disease, idiopathic hypersomnia, and chronic fatigue syndrome. The compound acts as a selective atypical dopamine reuptake inhibitor with a binding affinity (K_i) of 4,090 nM at the dopamine transporter, approximately 12-fold selectivity over the serotonin transporter (K_i 48,700 nM), and negligible affinity for the sigma-1 receptor (K_i greater than 100,000 nM). In functional assays, flmodafinil blocks the dopamine transporter by approximately 83 percent, exceeding the inhibition produced by methylphenidate without concurrent adrenergic effects. Both the (S)-(+) enantiomer (JBG1-048, K_i 2,970 nM) and the (R)-(-) enantiomer (JBG1-049, K_i 4,830 nM) elevate extracellular dopamine in the rat nucleus accumbens to 150 to 200 percent of baseline at the highest assessed doses, with the (R)-(-) enantiomer producing a notably slower onset and longer duration of dopaminergic effect compared to (R)-modafinil. In the principal comparative preclinical study (Luca et al. 2018), NLS-4 at 64 mg/kg intraperitoneally in C57BL/6J mice induced approximately 151 minutes of additional wakefulness

compared to approximately 110 minutes for modafinil at 150 mg/kg, a 2.3-fold higher dose, establishing that flmodafinil possesses substantially greater wake-promoting potency per milligram than the parent compound. Recovery sleep following NLS-4-induced wakefulness was characterized by less non-rapid eye movement (NREM) sleep amount and attenuated delta power elevation compared to modafinil-treated animals, suggesting a qualitatively different and possibly more favorable recovery profile with reduced homeostatic sleep pressure accumulation despite longer drug-induced wakefulness. A subsequent preclinical study in a rat model of chronic severe fatigue (Konofal et al. 2023) reported that NLS-4 at 16 mg/kg produced locomotor activity restoration comparable to modafinil at 64 mg/kg, confirming a four-fold potency advantage with more sustained effects on circadian activity patterns. Unlike modafinil, flmodafinil does not induce cytochrome P450 CYP3A4 or CYP3A5 enzymes in human hepatocyte cultures, a pharmacologically significant distinction that reduces the potential for drug-drug interactions in chronic dosing regimens. The compound has not been approved for medical use in any jurisdiction. Clinical development programs initiated by NLS Pharmaceuticals for narcolepsy, ADHD, and Alzheimer's disease have been discontinued without publication of human trial data; preclinical development for chronic fatigue syndrome remains the only active program as of the most recent public disclosure. No published human clinical trial data exist for flmodafinil. The World Anti-Doping Agency has initiated investigations into urinary metabolism and detection methods for flmodafinil and its structural relative fladrafinil (CRL-40,941), confirming regulatory awareness of the compound in the context of competitive sport. This monograph reviews the chemistry, synthesis, and stereochemistry of flmodafinil; the dopamine

transporter pharmacology and enantiomer-resolved binding data; the preclinical wake-promoting and chronic fatigue evidence; the pharmacokinetic profile as characterized in animal models; sourcing and quality verification considerations for laboratory work; and a comparative assessment of five eugeroic and wakefulness-promoting alternatives against flmodafinil on five competency standards. The compound is supplied exclusively as a research-grade preparation; investigators should obtain analytical confirmation of identity, purity, and enantiomeric composition on every lot.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Proposed International Nonproprietary Name: Lauflumide (not formally assigned by the World Health Organization).

Development codes: CRL-40,940 (Laboratoire L. Lafon); NLS-4 (NLS Pharmaceuticals AG); JBG01-41 (National Institute on Drug Abuse research designation). The CRL-40,940 code is the canonical identifier in the early patent literature and in the original Lafon synthesis documentation. The NLS-4 designation appears in the preclinical pharmacology literature beginning with the Luca et al. (2018) wake-promoting study [1].

Alternative names: Bisfluoromodafinil; flmodafinil; 4,4'-difluoromodafinil.

Chemical Abstracts Service registry number: 90280-13-0.

PubChem Compound Identifier: 13271852.

International Union of Pure and Applied Chemistry name: 2-[bis(4-fluorophenyl)methylsulfinyl]acetamide. The compound is the bis(para-fluoro) ring-substituted derivative of modafinil (2-[(diphenylmethyl)sulfinyl]acetamide), differing from the parent compound solely by the addition of a fluorine atom at the para position of each phenyl ring.

1.2 Structural class and chemistry

Flmodafinil belongs to the diphenylmethyl sulfinyl acetamide structural class, a small group of synthetic eugeroics that includes modafinil (CRL-40,476), armodafinil ((R)-modafinil), adrafinil (CRL-40,028, a prodrug of modafinil), and fladrafinil (CRL-40,941, the bis(4-fluoro) analog of adrafinil). The structural class is defined by the diphenylmethyl core bearing a sulfinyl linkage to an acetamide side chain. The sulfinyl moiety confers a stereogenic center, producing a racemic mixture of (S)-(+) and (R)-(-) enantiomers unless resolved [2, 3].

Molecular formula: C₁₅H₁₃F₂NO₂S.

Exact mass: 309.0635 g/mol (monoisotopic).

Molecular weight: 309.33 g/mol.

Physical properties: White to off-white crystalline powder. Soluble in ethanol and dimethyl sulfoxide (DMSO); sparingly soluble in water. The two fluorine substituents increase the lipophilicity of the compound relative to modafinil, as reflected in a higher calculated LogP value, which is predicted to enhance blood-brain barrier penetration [1, 4]. Storage at room temperature in a dry, light-protected environment is adequate for the solid form; long-term storage at 2 to 8 degrees Celsius is recommended for research-grade material.

Stereochemistry: Flmodafinil contains a single stereogenic center at the sulfur atom of the sulfinyl group and is supplied as a racemic mixture of (S)-(+)-flmodafinil and (R)-(-)-flmodafinil unless otherwise specified. The (S)-(+) enantiomer has been designated JBG1-048 and the (R)-(-) enantiomer JBG1-049 in the National Institute on Drug Abuse research nomenclature [5]. Enantiomer-resolved pharmacological studies demonstrate that the two enantiomers have distinguishable dopamine transporter affinities and distinct temporal profiles of dopaminergic effect in the mesolimbic system [5, 6]. Investigators acquiring research-grade flmodafinil should confirm enantiomeric composition by chiral high-performance liquid chromatography if the experimental design requires control of stereochemistry.

1.3 Synthesis

The original synthesis of flmodafinil was documented in the Lafon patent literature (Canadian Patent CA 1,199,916, issued January 1986; United States Patent US 4,489,095, issued 1984) and proceeds by adaptation of the established modafinil synthetic route [7, 8]. The general approach involves: (a) preparation of bis(4-fluorophenyl)methanol by nucleophilic addition of a 4-fluorophenyl organometallic reagent (Grignard or organolithium) to 4-fluorobenzaldehyde, followed by reduction or direct coupling; (b) conversion of the diarylmethanol to the corresponding thioether by reaction with thioglycolic acid or its ethyl ester under acid-catalyzed conditions; (c) selective oxidation of the thioether sulfide to the sulfinyl (sulfoxide) oxidation state using a controlled stoichiometry of an oxidant such as meta-chloroperoxybenzoic acid, hydrogen peroxide, or sodium periodate; and (d) conversion of the thioglycolic acid ester to the acetamide by ammonolysis or by direct coupling with ammonia. The racemic product is purified by recrystallization from

ethanol or ethyl acetate. Enantiomeric resolution, if required, is performed by chiral chromatography or by asymmetric oxidation methods. Industrial-scale synthesis has not been publicly documented; the compound is manufactured at research scale by multiple chemical suppliers at purities of 98 percent or greater by high-performance liquid chromatography. A 2013 United States patent (US 9,637,447 B2) filed by Eric Konofal and assigned to NLS Pharmaceuticals AG and Assistance Publique Hopitaux de Paris describes formulation and use claims for flmodafinil and related derivatives [9].

2. Abstract

Flmodafinil (CRL-40,940; NLS-4; lauflumide; bisfluoromodafinil) is a bisfluorinated analog of modafinil that acts as a selective atypical dopamine reuptake inhibitor with enhanced potency and duration of wake-promoting activity relative to the parent compound. The compound was first synthesized at Laboratoire L. Lafon in France in the early to mid-1980s as part of systematic structure-activity exploration of the diphenylmethyl sulfinyl acetamide scaffold that had yielded adrafinil (CRL-40,028) and modafinil (CRL-40,476) [7, 8]. Despite this early origin, flmodafinil remained essentially uninvestigated in the published scientific literature until approximately 2015, when NLS Pharmaceuticals AG initiated preclinical development programs and the compound entered the academic research literature through studies at the National Institute on Drug Abuse and at the University of Lausanne.

The principal pharmacological distinction from modafinil is the enhanced dopamine transporter (DAT) affinity and the prolonged duration of dopaminergic effect. The racemic compound binds the DAT with a K_i of 4,090 nM; the (S)-(+)-enantiomer (JBG1-048) has a K_i of 2,970 nM and the (R)-(-)-enantiomer (JBG1-049) has a K_i of 4,830 nM [5]. By comparison, armodafinil ((R)-modafinil) has a DAT K_i of 5,480 nM in the same assay system. Selectivity over the serotonin transporter is approximately 12-fold, and affinity for the sigma-1 receptor is negligible [5]. Fast-scan cyclic voltammetry and microdialysis studies in the rat nucleus accumbens shell demonstrate that both enantiomers of flmodafinil elevate extracellular dopamine to 150 to 200 percent of baseline, with the (R)-(-)-enantiomer producing a slower offset of effect compared to (R)-modafinil [5, 6].

The wake-promoting activity of flmodafinil has been characterized in two pre-clinical paradigms. In the Luca et al. (2018) study, NLS-4 at 64 mg/kg intraperitoneally in C57BL/6J mice produced approximately 151 minutes of additional wakefulness versus approximately 110 minutes for modafinil at 150 mg/kg [1]. Recovery sleep following NLS-4 treatment was characterized by reduced NREM sleep accumulation and attenuated delta power elevation relative to modafinil, suggesting less homeostatic sleep pressure despite the longer wakefulness period. In a rat model of chronic severe fatigue (presented at SLEEP 2023), NLS-4 at 16 mg/kg produced comparable locomotor restoration to modafinil at 64 mg/kg, with more sustained circadian activity normalization [10, 11].

A pharmacologically significant distinction from modafinil is that flmodafinil does not induce cytochrome P450 CYP3A4 or CYP3A5 enzymes in human hepatocyte cultures [1, 12]. Modafinil is a known inducer of CYP3A4 and produces clinically significant interactions with oral contraceptives, cyclosporine, and other CYP3A4 substrates; the absence of this induction property in flmodafinil is a potential advantage for chronic administration regimens.

No published human clinical trials exist for flmodafinil as of the monograph date. NLS Pharmaceuticals AG initiated preclinical and early clinical development programs for narcolepsy, ADHD, Alzheimer's disease, and idiopathic hypersomnia; the narcolepsy, ADHD, and Alzheimer's programs have been discontinued without publication of human data [4]. Preclinical development for chronic fatigue syndrome, including in the context of post-COVID-19 fatigue, remains active [11, 12]. The compound is not approved for medical use in any jurisdiction and is not scheduled as a controlled substance in the United States, although it falls within a regulatory gray area as an unapproved pharmaceutical compound sold for research purposes. The World Anti-Doping Agency has funded investigations into the urinary metabolism and detection of flmodafinil and fladrafinil for anti-doping surveillance purposes [13].

3. Discovery and Development History

3.1 Origin at Laboratoire L. Lafon

Flmodafinil was synthesized at Laboratoire L. Lafon in France as part of the same research program that produced adrafinil (CRL-40,028, first synthesized in 1974 and marketed as Olmifon), modafinil (CRL-40,476, the active metabolite of adrafinil and later developed as Provigil), and fladrafinil (CRL-40,941, the bis(4-fluoro) analog of adrafinil). The Lafon laboratory systematically explored halogenated derivatives of the diphenylmethyl sulfinyl acetamide scaffold to identify analogs with improved potency, bioavailability, or pharmacokinetic properties relative to modafinil [7, 8]. Flmodafinil (CRL-40,940) was patented in the mid-1980s (Canadian Patent CA 1,199,916, issued January 1986) alongside related fluorinated, chlorinated, and methylated analogs. The original patent claims covered the compound itself, its enantiomers, and its use as a psychotropic agent.

3.2 Dormancy and acquisition by NLS Pharmaceuticals

Following the acquisition of Laboratoire L. Lafon by Cephalon Inc. in 2001, and the subsequent acquisition of Cephalon by Teva Pharmaceutical Industries in 2011, commercial development priorities focused on modafinil (Provigil) and armodafinil (Nuvigil) for narcolepsy, shift-work sleep disorder, and obstructive sleep apnea. Flmodafinil was not advanced through clinical development during this period and remained essentially a patent compound without published pharmacological characterization for approximately two decades [4].

NLS Pharmaceuticals AG (originally NLS Pharmaceuticals Ltd.), a Swiss pharmaceutical company, subsequently acquired development rights to flmodafinil (designated NLS-4 in the company's pipeline) and initiated preclinical development programs. The company filed a new United States patent application in 2013 (published as US 2013/0295196 A1, issued as US 9,637,447 B2 on May 2, 2017), with Eric Konofal as inventor and NLS Pharmaceuticals AG and Assistance Publique Hopitaux de Paris as assignees, claiming formulations and therapeutic uses for flmodafinil and related derivatives [9].

3.3 Preclinical development programs

NLS Pharmaceuticals sponsored preclinical studies beginning approximately 2015. The principal published study is the Luca et al. (2018) characterization of NLS-4 as a wake-promoting compound in mice, published in *Frontiers in Neuroscience* [1]. Concurrent academic research at the National Institute on Drug Abuse (NIDA) investigated the dopamine transporter pharmacology and enantiomer-resolved effects of the bisfluoro modafinil analogs using voltammetry and microdialysis techniques [5, 6].

3.4 Clinical program initiation and discontinuation

NLS Pharmaceuticals disclosed clinical development intentions for multiple indications: narcolepsy, attention deficit hyperactivity disorder, Alzheimer's disease, idiopathic hypersomnia, and chronic fatigue syndrome. Phase 1 clinical studies were reportedly initiated for the Alzheimer's disease indication beginning in 2015 [4]. However, the narcolepsy, ADHD, and Alzheimer's disease programs were discontinued by late 2019 without publication of human trial results or disclosure of specific reasons for discontinuation. As of public disclosures through early 2024, the only active development program was the chronic fatigue syndrome indication, supported by preclinical studies in rat models of severe fatigue and circadian rhythm disruption [10, 11, 12].

3.5 Current status

Flmodafinil occupies an unusual position in the pharmaceutical development landscape: it is a compound with a 40-year patent history, strong preclinical pharmacological rationale, demonstrated superiority to the parent compound modafinil in animal models of wakefulness, and zero published human clinical trial data. The compound is sold commercially as a research-grade nootropic preparation and is used non-medically by an informal community of cognitive enhancement practitioners. It is not approved by the United States Food and Drug Administration, the European Medicines Agency, or any other national regulatory authority. It is not scheduled as a controlled substance in the United States (modafinil is Schedule IV), although its regulatory status is ambiguous and subject to change [4, 13].

4. Mechanism of Action

Flmodafinil is a selective atypical dopamine reuptake inhibitor. Its principal molecular activity, characterized in radioligand binding assays and in functional studies using fast-scan cyclic voltammetry and microdialysis, is inhibition of dopamine reuptake through the dopamine transporter (DAT). The compound does not produce the locomotor hyperactivity, stereotypy, or reinforcing properties characteristic of typical dopamine reuptake inhibitors such as cocaine and methylphenidate, classifying it within the "atypical" dopamine transporter inhibitor category that also includes modafinil and several modafinil-derived analogs [5, 6, 14].

4.1 Dopamine transporter binding and inhibition

The racemic compound binds the dopamine transporter with a K_i of 4,090 nM in radioligand displacement assays. Enantiomer-resolved data demonstrate that the (S)-(+ enantiomer (JBG1-048) has modestly higher affinity (K_i 2,970 nM) than the (R)-(- enantiomer (JBG1-049, K_i 4,830 nM) [5]. Both values represent improvement over armodafinil ((R)-modafinil), which has a K_i of 5,480 nM in the same assay system. Functional DAT blockade in intact neural systems has been estimated at approximately 83 percent, exceeding the blockade produced by methylphenidate at comparably active doses [1].

The "atypical" classification reflects the observation that flmodafinil, like modafinil, binds the dopamine transporter in a conformation or at a site that produces a slow onset of dopamine elevation, a moderate ceiling on maximum dopamine increase, and a prolonged duration of effect compared to cocaine-type inhibitors. The Keighron et al. (2019) voltammetry and microdialysis study in Sprague-Dawley rats demonstrated that both the (S)-(+) and (R)-(- enantiomers of flmodafinil, administered intravenously at cumulative doses of 10 to 32 mg/kg, reduced dopamine clearance rate and elevated extracellular dopamine levels in the nucleus accumbens shell [5]. The (R)-(- enantiomer (JBG1-049) exhibited a slower onset of effect compared to the other tested compounds, and (R)-modafinil effects on dopamine levels appeared to dissipate more rapidly compared to both flmodafinil enantiomers. Extracellular dopamine concentrations reached approximately 220 to 308 percent of baseline for the flmodafinil enantiomers at the highest

doses, compared to approximately 220 percent for (R)-modafinil, with the flmodafinil effect persisting beyond 60 minutes at approximately 200 percent of baseline while (R)-modafinil effects dissipated within approximately 40 minutes [5, 6].

4.2 Serotonin transporter and off-target binding

Flmodafinil has low affinity for the serotonin transporter (SERT), with a K_i of 48,700 nM, representing approximately 12-fold selectivity for the DAT over the SERT [5]. This selectivity profile is consistent with the eugeroic (wakefulness-promoting) pharmacology of the compound and distinguishes it from serotonin-norepinephrine reuptake inhibitors and from serotonergic stimulants. Affinity for the sigma-1 receptor, a target implicated in some of the non-dopaminergic effects attributed to modafinil, is negligible (K_i greater than 100,000 nM) [5]. This latter finding is pharmacologically noteworthy because modafinil itself has been reported to interact with the sigma-1 receptor at low micromolar concentrations; the absence of sigma-1 binding in flmodafinil suggests that any sigma-1-mediated contributions to modafinil pharmacology (neuroprotection, anxiolytic effects) would not be reproduced by flmodafinil.

4.3 Downstream neurochemical effects

The downstream consequences of DAT inhibition in the mesocorticolimbic dopamine system include elevated extracellular dopamine in the nucleus accumbens shell and core, ventral tegmental area projection targets, and prefrontal cortex. The dopamine elevation is proposed to underlie the wake-promoting, attention-enhancing, and motivational effects of flmodafinil [1, 5]. The absence of norepinephrine transporter (NET) inhibition at pharmacologically relevant concentrations distinguishes flmodafinil from amphetamine and from some modafinil analogs that have NET activity, and is consistent with the observation that neither NLS-4 nor modafinil induced hyperlocomotor activity, stereotypic behavior, or abnormal behavior in mice at the doses studied by Luca et al. (2018) [1].

4.4 Histaminergic and orexinergic contributions

Modafinil has been proposed to activate histaminergic neurons in the tuberomammillary nucleus and orexinergic (hypocretinergic) neurons in the lateral hypothalamus as downstream consequences of its dopaminergic action. Whether flmodafinil

engages the same downstream arousal circuitry has not been directly studied. The EEG spectral profile during NLS-4-induced wakefulness in the Luca et al. (2018) study showed increased delta power density (0.75 to 3.5 Hz) during wakefulness, a pattern that differs from the flat spectral profile observed with modafinil and that may reflect differential engagement of thalamocortical arousal circuits [1]. Direct characterization of hypothalamic neuronal activation (by c-Fos immunohistochemistry or electrophysiology) during flmodafinil-induced wakefulness has not been published.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and bioavailability

Formal pharmacokinetic studies of flmodafinil in humans have not been published. The available pharmacokinetic data derive from animal studies and from inference based on the structural relationship to modafinil. The increased lipophilicity conferred by the two para-fluorine substituents is predicted to enhance oral absorption and blood-brain barrier penetration relative to modafinil [1, 4]. In the Luca et al. (2018) mouse study, intraperitoneal administration was the route used; peak behavioral effect (maximum wakefulness suppression of sleep onset) was observed within the first hour of administration at 64 mg/kg [1].

Anecdotal reports from non-medical use suggest an onset of action of 30 to 60 minutes after oral administration and peak subjective effects at approximately 2 to 4 hours. These reports are not verified by controlled pharmacokinetic studies and should be interpreted with caution.

5.2 Distribution

Volume of distribution has not been formally characterized. The increased lipophilicity relative to modafinil (which has a volume of distribution of approximately 0.9 L/kg in humans) suggests broader tissue distribution and potentially greater central nervous system penetration [15]. The sulfinyl moiety is expected to confer moderate plasma protein binding, consistent with the approximately 60 percent protein binding reported for modafinil.

5.3 Metabolism

A critical pharmacological distinction from modafinil is the absence of cytochrome P450 enzyme induction. In human hepatocyte cultures, flmodafinil did not induce CYP3A4 or CYP3A5 [1, 12]. Modafinil is a known inducer of CYP3A4 and a modest inhibitor of CYP2C19, interactions that produce clinically significant reductions in the efficacy of oral contraceptives (ethinylestradiol), cyclosporine, triazolam, and

other CYP3A4 substrates [15]. The absence of this induction property in flmodafinil has potential clinical significance for chronic dosing regimens involving concurrent medications.

The specific metabolic pathways for flmodafinil have not been fully elucidated in published literature. By structural analogy with modafinil, the principal metabolic transformations are expected to include: (a) amide hydrolysis to the corresponding carboxylic acid (modafinilic acid analog); (b) sulfoxide reduction to the thioether or further oxidation to the sulfone; and (c) conjugation reactions (glucuronidation). The World Anti-Doping Agency investigation into flmodafinil metabolism confirmed that the compound shares metabolic pathways with modafinil and that its metabolite CRL-40,941 (fladrafinil, the hydroxamic acid prodrug form) can be detected in urine [13].

5.4 Elimination

Plasma elimination half-life estimates for flmodafinil range from 12 to 15 hours based on limited available data and extrapolation from the observed duration of wakefulness in animal studies [4]. By comparison, the half-life of modafinil in humans is approximately 12 to 15 hours for the racemic compound and 10 to 14 hours for armodafinil. The extended duration of dopaminergic effect observed in the Keighron et al. (2019) voltammetry study, where flmodafinil enantiomers maintained elevated dopamine levels beyond the time at which (R)-modafinil effects dissipated, is consistent with a moderately longer elimination half-life or with slower dissociation from the DAT binding site [5].

5.5 Routes of administration

The published preclinical studies have used intraperitoneal injection as the primary route of administration [1, 10]. Non-medical use is predominantly oral, with the compound supplied as capsules or loose powder for oral administration. No parenteral, intravenous, subcutaneous, or intranasal formulations have been developed for clinical or formal research use. For in vitro research applications, stock solutions are prepared in DMSO at concentrations of 10 to 100 mM and diluted into aqueous buffer for cell-based assays.

6. Preclinical Pharmacology

6.1 Wake-promoting activity in mice

The Luca et al. (2018) study in *Frontiers in Neuroscience* is the principal published preclinical characterization of flmodafinil as a wake-promoting agent [1]. C57BL/6J mice (adult males, 10 to 11 weeks, 22 to 26 g) were instrumented for continuous electroencephalographic (EEG) and electromyographic (EMG) recording and received intraperitoneal injections of vehicle (10 percent DMSO in saline), NLS-4 (64 mg/kg), or modafinil (150 mg/kg) at light onset. Eight mice per treatment group were recorded continuously for 24 hours.

NLS-4 at 64 mg/kg induced approximately 151 minutes of additional wakefulness above vehicle baseline, compared to approximately 110 minutes for modafinil at 150 mg/kg. Sleep latency (time to first consolidated sleep episode) was approximately 208 minutes for NLS-4 versus approximately 178 minutes for modafinil. Neither compound induced hyperlocomotor activity, stereotypic behavior, or abnormal behavior [1].

Preliminary dose-response data from the same study tested NLS-4 at 32, 64, 128, and 256 mg/kg. The 64 mg/kg dose was selected for the comparative analysis on the basis of a favorable balance between wake-promoting effect and behavioral tolerability.

6.2 Sleep architecture and recovery sleep

Recovery sleep following NLS-4-induced wakefulness differed qualitatively from recovery sleep following modafinil. Modafinil-treated mice showed significantly more NREM sleep during the recovery period compared to NLS-4-treated mice, with NREM sleep loss during the light phase of 45.04 plus or minus 19.96 minutes for modafinil versus 87.61 plus or minus 36.78 minutes for NLS-4 [1]. Despite the greater NREM loss during drug action for NLS-4, the subsequent recovery was characterized by less compensatory NREM accumulation.

Delta power (0.75 to 4 Hz), the standard electrophysiological marker of homeostatic sleep pressure, was elevated during the first 2 time intervals of recovery sleep after NLS-4 treatment compared to the first 9 intervals after modafinil treatment [1]. This attenuated delta rebound suggests that NLS-4-induced wakefulness generates less homeostatic sleep debt than modafinil-induced wakefulness of shorter duration. The authors interpreted this finding as evidence of a qualitatively different mechanism of wake promotion, potentially reflecting differential engagement of sleep-regulatory circuits.

No significant sleep rebound (compensatory hypersomnia) was observed after sleep onset for either compound. Both compounds suppressed rapid eye movement (REM) sleep during the initial hours of drug action, with recovery during the subsequent dark period.

6.3 EEG spectral characteristics

Spectral analysis of the EEG during drug-induced wakefulness revealed that NLS-4 treatment produced increased power density in the delta frequency range (0.75 to 3.5 Hz) and decreased power in the theta frequency range (6.25 to 7.25 Hz), while modafinil treatment produced no significant spectral changes relative to vehicle-induced wakefulness [1]. During recovery NREM sleep, NLS-4-treated animals showed attenuated EEG power density within slow frequencies (less than 4 Hz) compared to modafinil-treated animals. These spectral differences suggest that flmodafinil and modafinil, despite their structural similarity, engage partially distinct neural circuits or produce qualitatively different cortical arousal states.

6.4 Chronic fatigue model

A rat model of chronic severe fatigue was used to evaluate NLS-4 in comparison with modafinil, presented as an abstract at the SLEEP 2023 meeting [10]. Male Sprague-Dawley rats (7 to 8 weeks old) underwent a 7-day fatigue induction procedure, and locomotor activity was recorded for 3 days during recovery. The fatigue procedure disrupted circadian locomotor patterns, decreasing dark-phase activity and increasing light-phase activity.

NLS-4 was tested at 16, 32, and 64 mg/kg, and modafinil was tested at 64 and 128 mg/kg. NLS-4 at 16 mg/kg produced comparable locomotor restoration to modafinil at 64 mg/kg, confirming the approximately four-fold potency advantage observed in

the wake-promoting study [10]. The effect of NLS-4 was reported to be more sustainable than that of modafinil, with more consistent normalization of the circadian activity pattern across the recovery period.

NLS Pharmaceuticals separately announced in October and November 2021 that preclinical studies of NLS-4 in a long-COVID fatigue model demonstrated superior motor-stimulating effects compared to modafinil at all doses tested, with the additional observation that NLS-4 at 16 mg/kg did not produce the weight loss commonly observed with conventional stimulant treatments [11, 12].

6.5 Dopamine dynamics: voltammetry and microdialysis

The Keighron et al. (2019) study in the *European Journal of Neuroscience* used fast-scan cyclic voltammetry (FSCV) and microdialysis in the nucleus accumbens shell of Sprague-Dawley rats to compare (R)-modafinil with the (S)-(+) and (R)-(-) bisfluoro analogs (JBG1-048 and JBG1-049) [5]. Cumulative intravenous doses of 10 to 32 mg/kg were administered.

All three compounds reduced dopamine clearance and elevated extracellular dopamine levels. The (R)-(-) enantiomer (JBG1-049) exhibited a notably slower onset of dopamine elevation and a more prolonged duration of effect compared to (R)-modafinil, suggesting slower association with or dissociation from the DAT binding site. Extracellular dopamine was elevated to approximately 220 to 308 percent of baseline for the flmodafinil enantiomers at the highest doses, compared to approximately 220 percent for (R)-modafinil, with the flmodafinil effect persisting beyond 60 minutes at approximately 200 percent of baseline while (R)-modafinil effects dissipated within approximately 40 minutes [5].

A related study by Keighron et al. (2019) published in *ACS Chemical Neuroscience* examined additional modafinil analogs (JJC8-016, JJC8-088, JJC8-091) in the mouse nucleus accumbens shell, establishing the broader structure-activity framework for atypical dopamine transporter inhibitors derived from the modafinil scaffold [6]. This work demonstrated that small chemical structural changes in DAT inhibitors can produce either cocaine-like or atypical behavioral profiles, with the flmodafinil analogs consistently exhibiting the atypical (non-cocaine-like) pattern.

7. Clinical Evidence Base

7.1 Absence of published human clinical data

No peer-reviewed publication of human clinical trial data for flmodafinil exists as of the monograph date. This represents the most significant limitation in the characterization of the compound and is an essential context for any research or translational consideration. All efficacy, safety, and dose-response data derive from animal studies or from inference based on the modafinil clinical record.

7.2 Disclosed clinical development programs

NLS Pharmaceuticals AG disclosed intentions to develop flmodafinil for multiple indications through regulatory filings and press releases. Phase 1 clinical studies were reportedly initiated for Alzheimer's disease beginning in 2015 [4]. Development programs for narcolepsy and ADHD were also announced. All three of these clinical programs were discontinued by late 2019, and no human trial data, interim analyses, safety summaries, or dose-finding results have been published or presented at scientific meetings.

7.3 Active preclinical development

The chronic fatigue syndrome indication, including post-COVID-19 fatigue, remains the only development program with recent activity. Preclinical data supporting this indication have been disclosed through the SLEEP 2023 conference abstract [10] and through NLS Pharmaceuticals corporate press releases describing rat fatigue model results [11, 12]. A World Intellectual Property Organization patent application (WO 2023/281095 A1) filed by NLS Pharmaceuticals claims the use of lauflumide and derivatives thereof for treating chronic fatigue syndrome and myalgic encephalomyelitis/chronic fatigue syndrome [16].

7.4 Inference from the modafinil clinical record

Given the structural and mechanistic similarity between flmodafinil and modafinil, the clinical record of modafinil provides the principal basis for pharmacological inference. Modafinil is FDA-approved for narcolepsy, shift-work sleep disorder, and obstructive sleep apnea-associated excessive sleepiness at doses of 100 to 400 mg daily. The clinical efficacy of modafinil in maintaining wakefulness, improving cognitive performance under sleep-deprivation conditions, and reducing excessive daytime sleepiness is well established across multiple randomized controlled trials [15, 17]. Whether flmodafinil would reproduce or exceed these effects in humans, at what dose, and with what safety profile are open questions that can only be resolved by human clinical studies.

8. Sourcing and Quality Verification

Flmodafinil is not available as a pharmaceutical-grade product from any regulatory-approved manufacturer. There is no pharmacopoeial monograph (United States Pharmacopeia, European Pharmacopoeia, British Pharmacopoeia, or Japanese Pharmacopoeia) for the compound. All commercially available material is research-grade, supplied by chemical research vendors and nootropic retailers.

Research-grade flmodafinil is supplied by multiple vendors (Cayman Chemical, TargetMol, Newmind, and various nootropic supply companies) at purities of 98 percent or greater by HPLC. Supply is typically in milligram to gram quantities as the racemic free base; the compound is not commonly supplied as a salt form. Pricing is variable, in the range of \$30 to \$150 per gram depending on quantity and vendor at the time of monograph preparation.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at m/z 310.07 for the protonated species)
- Nuclear magnetic resonance spectroscopy (1H and ^{19}F NMR) for structural confirmation, with the ^{19}F NMR being particularly diagnostic for confirming the presence and position of the two fluorine substituents
- Chiral HPLC for enantiomeric composition if the research application requires stereochemical control
- Residual solvent analysis by gas chromatography (common synthesis solvents: dichloromethane, ethyl acetate, ethanol, DMSO)
- Karl Fischer or loss-on-drying analysis for residual water content

The nootropic supply market for flmodafinil is less regulated than the pharmaceutical chemical supplier market, and lot-to-lot variability in purity, enantiomeric composition, and residual solvent content is expected. Investigators conducting dose-response or mechanism-of-action studies should obtain material from established

chemical suppliers (Cayman Chemical, TargetMol, or equivalent) rather than from nootropic retailers, and should confirm analytical data independently through a third-party laboratory (Janoshik Analytical or equivalent).

A specific analytical concern is the potential confusion of flmodafinil (CRL-40,940) with fladrafinil (CRL-40,941), its structural relative that bears the same bis-fluoro phenyl ring system but has an additional hydroxyl group on the nitrogen (hydroxamic acid). Gas chromatographic analysis of thermal degradation products has demonstrated the formation of 1,1,2,2-tetraphenylethane and its tetrafluoro analog as artifacts in the GC injector, complicating analytical characterization by gas chromatography and necessitating liquid chromatographic methods for definitive identification [18].

9. Reconstitution and Handling

Flmodafinil is supplied as a white to off-white crystalline powder. For in vitro research applications, the compound is dissolved in DMSO to prepare stock solutions at concentrations of 10 to 100 mM. DMSO stock solutions should be aliquoted for single use and stored at minus 20 degrees Celsius; stability data for DMSO solutions have not been formally published, but the compound is expected to be stable for at least 6 months under these conditions based on the chemical stability of the sulfinyl acetamide class.

For in vivo research applications (rodent studies), the compound has been administered intraperitoneally in a vehicle of 10 percent DMSO in normal saline [1]. The 10 percent DMSO vehicle is standard for compounds with limited aqueous solubility and is tolerated at the injection volumes used in mouse and rat pharmacology studies (typically 5 to 10 mL/kg). Alternative vehicles (cyclodextrin solutions, polyethylene glycol 400, or Tween-80-based formulations) may be used if the DMSO vehicle is contraindicated for a specific experimental design.

For oral administration in animal research, the compound can be suspended in methylcellulose (0.5 percent aqueous) or dissolved in polyethylene glycol 400 for gavage dosing. Oral formulations for research use are typically prepared fresh on the day of administration.

Solid material should be stored at room temperature in a dry, light-protected environment for short-term use (weeks to months), or at 2 to 8 degrees Celsius for long-term storage (months to years). The compound should be protected from moisture; desiccant should be included in the storage container.

Handling precautions are standard for research-grade pharmaceutical chemicals: use of appropriate personal protective equipment (gloves, laboratory coat, eye protection), preparation in a chemical fume hood or with adequate ventilation, and disposal in accordance with institutional hazardous waste guidelines. No specific acute toxicity hazards beyond those expected for the general structural class have been identified, but the absence of formal toxicological evaluation mandates conservative handling practices.

10. Stack Interaction Considerations

Investigators using flmodafinil in combination with other research compounds or in experimental protocols involving concurrent pharmacological agents should consider the following interaction considerations:

CYP3A4 substrates: Unlike modafinil, flmodafinil does not induce CYP3A4 or CYP3A5 in human hepatocyte cultures [1, 12]. This represents a potentially significant advantage for combination protocols, as the drug-drug interaction risk with oral contraceptives, cyclosporine, triazolam, midazolam, and other CYP3A4 substrates is expected to be lower than with modafinil. However, the CYP inhibition profile of flmodafinil has not been comprehensively characterized; investigators should not assume the absence of all CYP-mediated interactions.

Other dopamine reuptake inhibitors: Concurrent use with methylphenidate, amphetamine, cocaine, bupropion, or other DAT inhibitors produces additive or synergistic dopamine elevation. The combination is not recommended for research protocols without specific mechanistic justification, as the additive dopaminergic load may exceed the threshold for atypical-to-typical behavioral transition (locomotor sensitization, stereotypy, reinforcement).

Modafinil and armodafinil: Concurrent use with modafinil or armodafinil is pharmacologically redundant at the DAT level. The combination has not been studied and is not recommended. Cross-tolerance between the compounds is expected given the shared mechanism.

Caffeine and other adenosine receptor antagonists: Concurrent caffeine produces additive wake-promoting effects through an independent mechanism (adenosine A2A receptor antagonism). The combination is common in non-medical use and is not expected to produce pharmacokinetic interactions but may produce additive cardiovascular stimulation (tachycardia, hypertension) and insomnia.

Serotonergic agents: Flmodafinil has low affinity for the serotonin transporter (K_i 48,700 nM) and is not expected to produce serotonergic interactions at pharmacologically relevant doses [5]. Concurrent selective serotonin reuptake inhibitors,

serotonin-norepinephrine reuptake inhibitors, or other serotonergic agents are not expected to produce pharmacodynamic interactions with flmodafinil specifically, though individual clinical monitoring is appropriate.

QT-prolonging agents: The cardiac electrophysiology of flmodafinil has not been characterized. Modafinil has not been associated with clinically significant QT prolongation at therapeutic doses, but the absence of cardiac safety data for flmodafinil mandates caution with concurrent QT-prolonging medications.

Racetams and cholinergic agents: Concurrent use with piracetam, aniracetam, or acetylcholinesterase inhibitors in cognitive enhancement research protocols produces no predicted pharmacokinetic interaction. The combination targets independent neurotransmitter systems (dopaminergic and cholinergic) and is theoretically additive for cognitive endpoints.

11. Adverse Events and Safety

11.1 Absence of formal safety data

No formal human safety data have been published for flmodafinil. The safety profile described below is derived from: (a) the animal pharmacology literature; (b) inference from the modafinil clinical safety record; and (c) uncontrolled anecdotal reports from non-medical use. This evidence base is insufficient for clinical safety conclusions and is presented for research context only.

11.2 Animal safety observations

In the Luca et al. (2018) study, neither NLS-4 nor modafinil induced hyperlocomotor activity, stereotypic behavior, or abnormal behavior in mice at the studied doses [1]. No mortality or acute toxicity was reported at doses up to 256 mg/kg intraperitoneally. NLS Pharmaceuticals reported that NLS-4 at 16 mg/kg in rats did not produce the weight loss commonly observed with amphetamine-class stimulants and modafinil at higher doses [12]. No formal acute or chronic toxicology studies have been published.

11.3 Inferred safety profile from modafinil

Modafinil has a well-characterized safety profile from decades of clinical use. The principal adverse events at approved doses (100 to 400 mg daily) include headache (34 percent in clinical trials), nausea (11 percent), nervousness (7 percent), rhinitis (7 percent), diarrhea (6 percent), anxiety (5 percent), insomnia (5 percent), and dizziness (5 percent) [15, 17]. Rare serious adverse events include Stevens-Johnson syndrome and toxic epidermal necrolysis (estimated incidence 1 to 6 per million new users), angioedema, multi-organ hypersensitivity reactions, and psychiatric events (mania, psychosis, suicidal ideation) predominantly in patients with pre-existing psychiatric conditions.

Flmodafinil may share some or all of these adverse events given its structural and mechanistic similarity to modafinil. The absence of CYP3A4 induction and the potential for different tissue distribution due to fluorine substitution may alter the

adverse-event profile, but such differences are speculative until human safety data are available.

11.4 Anecdotal reports from non-medical use

Self-reported adverse events from individuals using flmodafinil as a nootropic include headache, insomnia (particularly with late-day dosing), mild nausea, anxiety, and appetite suppression. These reports are consistent with the predicted dopaminergic mechanism and with the modafinil adverse-event profile. No severe adverse events have been publicly reported in the nootropic user community, though reporting bias is substantial and the absence of reported severe events cannot be interpreted as evidence of safety.

11.5 Abuse potential considerations

Modafinil has low abuse potential relative to classical psychostimulants and is classified as Schedule IV in the United States. Flmodafinil, as a more potent DAT inhibitor that elevates dopamine to a moderate degree (150 to 200 percent of baseline) without producing cocaine-like dopamine dynamics, is expected to have a similar or modestly higher abuse potential than modafinil [5, 6, 14]. The atypical DAT inhibitor profile (slow onset, moderate ceiling, no locomotor sensitization) is associated with lower reinforcing properties than typical DAT inhibitors. Formal abuse liability assessment in humans has not been conducted.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five eugeroic and wakefulness-promoting compounds against flmodafinil, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile (clinical or preclinical), and overall validation. The five comparators were selected as the principal alternatives in the diphenylmethyl sulfinyl acetamide class and in the broader eugeroic and atypical dopamine reuptake inhibitor space.

12.1 Modafinil (CRL-40,476; Provigil)

Mechanism: Atypical dopamine reuptake inhibitor. DAT Ki approximately 2,280 to 6,400 nM depending on the assay system and enantiomer. Additional reported activities at the sigma-1 receptor, orexin system, and histaminergic arousal nuclei [15, 17].

Development and regulatory status: Approved by the United States FDA in 1998 for narcolepsy; subsequently approved for shift-work sleep disorder and obstructive sleep apnea-associated excessive sleepiness. Registered as a controlled substance (Schedule IV) in the United States and in most jurisdictions where it is approved. The most extensively studied eugeroic compound in clinical medicine, with thousands of published clinical studies.

Novelty: Low. Modafinil is the reference compound for the structural class and the wake-promoting mechanism.

Effect size: Substantial and well established. In narcolepsy, modafinil produces significant improvements in Maintenance of Wakefulness Test and Epworth Sleepiness Scale scores. In healthy volunteers under sleep deprivation, cognitive performance is significantly maintained [15, 17].

Promising potential: High, as a registered and widely prescribed pharmaceutical. Research potential is mature; the compound is a standard comparator for all new eugeroic candidates.

Side-effect profile: Well characterized. Headache, nausea, insomnia, and anxiety are common. Rare Stevens-Johnson syndrome and multi-organ hypersensitivity reactions. CYP3A4 induction produces clinically significant drug interactions [15].

Overall validation: Very high. The most comprehensively validated eugeroic compound in clinical medicine.

Comparison to flmodafinil: Flmodafinil offers superior per-milligram potency in preclinical wake-promoting studies (approximately 2 to 4-fold), longer duration of dopaminergic effect, a recovery sleep profile suggesting less homeostatic sleep debt, and absence of CYP3A4 induction. Modafinil has the decisive advantage of extensive human clinical data, regulatory approval, and decades of post-marketing safety surveillance. Flmodafinil is the structurally optimized analog with superior preclinical pharmacology but zero clinical validation.

12.2 Armodafinil (Nuvigil)

Mechanism: (R)-enantiomer of modafinil. DAT K_i approximately 5,480 nM. The same atypical DAT inhibitor mechanism as racemic modafinil, with a longer plasma half-life (10 to 14 hours) owing to slower metabolic clearance of the (R)-enantiomer [15].

Development and regulatory status: Approved by the United States FDA in 2007 for the same indications as modafinil. Marketed by Cephalon (Teva) as a next-generation alternative to modafinil with more sustained plasma levels through the afternoon dosing window.

Novelty: Low. An enantiomeric variant of the reference compound.

Effect size: Comparable to modafinil in clinical trials. Some evidence of superior maintenance of late-day wakefulness attributable to the longer half-life of the (R)-enantiomer.

Promising potential: High as a registered pharmaceutical. Similar clinical utility to modafinil.

Side-effect profile: Similar to modafinil. Also induces CYP3A4 and shares the modafinil drug interaction profile.

Overall validation: High. Approved pharmaceutical with substantial clinical data.

Comparison to flmodafinil: Flmodafinil has higher DAT affinity than armodafinil (Ki 4,090 versus 5,480 nM for the racemic compound versus armodafinil), longer duration of dopaminergic effect in voltammetry studies, and absence of CYP enzyme induction. Armodafinil has the advantage of full regulatory approval and human clinical validation.

12.3 Adrafinil (CRL-40,028; Olmifon)

Mechanism: Prodrug of modafinil. Converted in the liver to modafinil by amide hydrolysis. No intrinsic activity at the DAT; all pharmacological effects are mediated through the active metabolite modafinil [19].

Development and regulatory status: Developed by Laboratoire L. Lafon and marketed in France as Olmifon for geriatric excessive sleepiness. Marketing authorization voluntarily withdrawn in 2011 by the manufacturer (Cephalon France). Not approved in the United States. Currently sold as a research-grade and nootropic compound.

Novelty: Low. A prodrug of the reference compound, with an additional metabolic activation step.

Effect size: Lower on a per-milligram basis than modafinil due to incomplete conversion (approximately 300 mg adrafinil yields modafinil-equivalent exposure to approximately 100 to 150 mg modafinil). Onset of effect is delayed by 45 to 60 minutes relative to modafinil.

Promising potential: Low. Marketing authorization withdrawn. No active clinical development.

Side-effect profile: Similar to modafinil with the addition of hepatotoxicity concerns from the hepatic activation step. Elevated liver enzymes have been reported with chronic use, a concern not shared by modafinil or flmodafinil [19].

Overall validation: Moderate historically; low in current practice. The compound is of primarily historical interest as the original eugeroic that led to the discovery of modafinil.

Comparison to flmodafinil: Flmodafinil is superior on every measured pharmacological parameter: higher potency, direct activity (not a prodrug), absence of the hepatotoxicity concern, and absence of CYP induction. Adrafinil's only advantage is

longer commercial history and historical availability.

12.4 Fladrafinil (CRL-40,941)

Mechanism: The bis(4-fluoro) analog of adrafinil. A prodrug that is expected to be converted to flmodafinil (CRL-40,940) by hepatic amide hydrolysis, analogous to the adrafinil-to-modafinil conversion. DAT Ki approximately 230 nM (substantially higher affinity than flmodafinil), though this high affinity may reflect the parent compound rather than the active metabolite [20].

Development and regulatory status: Not approved in any jurisdiction. Sold as a research-grade and nootropic compound. No clinical development programs have been disclosed.

Novelty: Low. A prodrug variant within the same structural series.

Effect size: Limited published preclinical data. Reported to be 3 to 4 times more potent than adrafinil in producing anti-aggressive effects in animals, but this endpoint is distinct from wake-promoting activity [20].

Promising potential: Low. No active clinical development. The compound is primarily of interest as a structural relative and potential metabolic precursor of flmodafinil.

Side-effect profile: Unknown. No formal safety data. As a prodrug requiring hepatic conversion, the same hepatotoxicity concerns that apply to adrafinil may apply to fladrafinil.

Overall validation: Low. Minimal published pharmacological data; no clinical data.

Comparison to flmodafinil: Flmodafinil is the predicted active metabolite of fladrafinil, analogous to the modafinil-adrafinil relationship. Flmodafinil has the advantage of direct activity, published preclinical characterization, and an identified development sponsor. Fladrafinil has the advantage of reported high DAT affinity in binding assays, though the interpretation is complicated by the prodrug relationship.

12.5 Solriamfetol (JZP-110; Sunosi)

Mechanism: Dopamine and norepinephrine reuptake inhibitor. Unlike the modafinil class, solriamfetol inhibits both the DAT and the norepinephrine transporter (NET), placing it mechanistically between the atypical DAT inhibitors and the classical psychostimulants [21].

Development and regulatory status: Approved by the United States FDA in 2019 for excessive daytime sleepiness in narcolepsy and obstructive sleep apnea. Marketed by Jazz Pharmaceuticals as Sunosi at doses of 75 to 150 mg daily. The most recently approved eugeroic compound.

Novelty: Moderate. The dual DAT/NET mechanism distinguishes solriamfetol from the modafinil class and provides a differentiated pharmacological profile.

Effect size: Substantial in clinical trials. In narcolepsy (Phase 3 TONES studies), solriamfetol 150 mg produced significant improvements in Maintenance of Wakefulness Test and Epworth Sleepiness Scale scores, with effect sizes comparable to or exceeding modafinil in indirect comparisons [21].

Promising potential: High. Approved, marketed, and in active clinical use.

Side-effect profile: Headache (12 to 16 percent), nausea (6 to 8 percent), decreased appetite (6 to 9 percent), insomnia (4 to 6 percent), and anxiety (2 to 5 percent). Cardiovascular effects (blood pressure increase, heart rate increase) are more prominent than with modafinil, reflecting the noradrenergic contribution. Abuse potential assessment (human abuse potential studies) demonstrated lower subjective effects than amphetamine but higher than placebo; classified as Schedule IV [21].

Overall validation: High. Approved pharmaceutical with robust Phase 3 clinical data.

Comparison to flmodafinil: Solriamfetol has the decisive advantage of FDA approval, human clinical data, and a characterized safety profile. Flmodafinil has the potential advantage of dopamine-selective activity without noradrenergic effects (potentially fewer cardiovascular adverse events), absence of CYP enzyme induction, and the preclinical evidence of reduced homeostatic sleep debt. Solriamfetol represents the current clinical standard for a recently developed eugeroic; flmodafinil represents an untested preclinical candidate with an attractive pharmacological profile.

12.6 Comparator summary

The five comparators span the spectrum from the reference compound (modafinil) through enantiomeric variants (armodafinil), prodrugs (adrafenil, fladrafenil), and a mechanistically distinct recent entrant (solriamfetol). Flmodafinil occupies a unique position: it is the structurally optimized bisfluorinated analog of the reference compound, with demonstrated superior preclinical potency, a favorable recovery sleep profile, and absence of CYP enzyme induction. Its principal limitation, and it is a decisive one, is the complete absence of published human clinical data. No claim of clinical superiority can be made in the absence of human studies; the preclinical pharmacology supports the hypothesis of an improved therapeutic profile but does not confirm it.

For research applications, flmodafinil offers the investigator a more potent, longer-acting dopamine reuptake inhibitor than modafinil with potentially fewer drug-drug interaction concerns. For clinical or translational applications, modafinil, armodafinil, and solriamfetol remain the only validated options. The discontinuation of most clinical development programs for flmodafinil raises the question of whether undisclosed safety, efficacy, or commercial viability concerns contributed to the decision; this question is unanswerable from public information and should be considered by investigators evaluating the compound for research use.

13. References

1. Luca G, Bandarabadi M, Konofal E, Lecendreux M, Ferrie L, Figadere B, Tafti M. Lauflumide (NLS-4) is a new potent wake-promoting compound. *Front Neurosci.* 2018;12:519.
2. Baselt RC. Disposition of toxic drugs and chemicals in man. 12th ed. Seal Beach: Biomedical Publications; 2020.
3. Zolkowska D, Jain R, Ganti V, et al. Novel and high affinity 2-[(diphenylmethyl)sulfinyl]acetamide (modafinil) analogues as atypical dopamine transporter inhibitors. *J Med Chem.* 2009;52(24):7968-7980.
4. Flmodafinil. Wikipedia. Accessed May 2026.
5. Keighron JD, Giancola JB, Shaffer RJ, DeMarco EM, Bhimani R, Tanda G. Distinct effects of (R)-modafinil and its (R)- and (S)-fluoro-analogs on mesolimbic extracellular dopamine assessed by voltammetry and microdialysis in rats. *Eur J Neurosci.* 2019;50(3):2045-2053.
6. Keighron JD, Quarterman JC, Bhimani R, Tanda G. Effects of (R)-modafinil and modafinil analogues on dopamine dynamics assessed by voltammetry and microdialysis in the mouse nucleus accumbens shell. *ACS Chem Neurosci.* 2019;10(4):2012-2021.
7. Lafon L. Halogenated derivatives of modafinil. Canadian Patent CA 1,199,916. January 28, 1986.
8. Lafon L. Halogenated benzhydrylsulfinylacetamide derivatives. United States Patent US 4,489,095. December 18, 1984.
9. Konofal E. Compositions and methods for treating excessive sleepiness. United States Patent US 9,637,447 B2. May 2, 2017. Filed November 7, 2013. Assignees: NLS Pharmaceuticals AG; Assistance Publique Hopitaux de Paris.
10. Konofal E, Lecendreux M, et al. Effects of NLS-4 (Lauflumide) and modafinil in a rat model of circadian rhythm and chronic severe fatigue. *Sleep.* 2023;46(Suppl 1):A11.

11. NLS Pharmaceuticals. Announces preclinical data demonstrating the potential of NLS-4 (Lauflumide) to treat chronic fatigue associated with long-COVID. Press release. October 14, 2021.
12. NLS Pharmaceuticals. Announces preclinical results confirming the potential benefit and safety profile of NLS-4 for circadian rhythm dysregulation and chronic fatigue syndrome in long-Covid model. Press release. November 30, 2021.
13. World Anti-Doping Agency. Investigations into the metabolism and elimination of flmodafinil and fladrafinil as well as their prevalence in elite sports. WADA Scientific Research. 2022.
14. Tanda G, Newman AH, Bhimani R, et al. Translating the atypical dopamine uptake inhibitor hypothesis toward therapeutics for treatment of psychostimulant use disorders. *Neuropsychopharmacology*. 2019;44(8):1435-1444.
15. Robertson P, Hellriegel ET. Clinical pharmacokinetic profile of modafinil. *Clin Pharmacokinet*. 2003;42(2):123-137.
16. NLS Pharmaceuticals AG. Lauflumide and derivatives thereof for treating chronic fatigue syndrome and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). World Intellectual Property Organization Patent WO 2023/281095 A1. January 12, 2023.
17. Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. *Neuropsychopharmacology*. 2008;33(7):1477-1502.
18. Cowan DA, Kapur BM, Nair N. Outsmarted by nootropics? An investigation into the thermal degradation of modafinil, modafinic acid, adrafinil, CRL-40,940 and CRL-40,941 in the GC injector: formation of 1,1,2,2-tetraphenylethane and its tetra fluoro analog. *Drug Test Anal*. 2017;9(3):518-522.
19. Milgram NW, Callahan H, Siwak C. Adrafinil: a novel vigilance promoting agent. *CNS Drug Rev*. 1999;5(3):193-212.
20. Fladrafinil. Wikipedia. Accessed May 2026.
21. Thorpy MJ, Shapiro C, Mayer G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. *Ann Neurol*. 2019;85(3):359-370.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. No human clinical trial data have been published for flmodafinil; all efficacy and safety characterizations derive from animal studies or inference from the modafinil clinical record. The compound is not approved for medical use in any jurisdiction. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Investigators should obtain analytical confirmation of identity, purity, and enantiomeric composition on every research-grade lot.