

CE-123

A benzhydrylsulfinylmethylthiazole developed at the University of Vienna as a next-generation modafinil analogue, distinguished from the parent compound by approximately 30-fold selectivity for the dopamine transporter over the norepinephrine transporter, five-fold superior blood-brain barrier penetration, and a preclinical cognitive enhancement profile spanning memory acquisition, cognitive flexibility, motivation, and social cognition in rodent models of aging, early-life stress, and fetal alcohol spectrum disorders.

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ABSTRACT

CE-123 (5-((benzhydrylsulfinyl)methyl)thiazole; CAS 1879038-73-9) is a synthetic modafinil analogue and atypical dopamine transporter (DAT) inhibitor developed at the Department of Pharmaceutical Chemistry, University of Vienna, under the direction of Gert Lubec as part of a structure-activity exploration of heterocyclic diphenylmethysulfinyl derivatives designed to achieve higher selectivity and affinity at the dopamine transporter than the parent compound modafinil. The active enantiomer, (S)-CE-123, inhibits DAT-mediated dopamine reuptake with an EC₅₀ of approximately 2.76 micromolar in HEK293 cells stably expressing human DAT, with approximately 30-fold selectivity over the norepinephrine transporter (NET) and greater than 400-fold selectivity over the serotonin transporter (SERT). The compound interacts with the outward-facing conformation of DAT to block substrate access without triggering reverse transport or vesicular release, a mechanism that defines the atypical DAT inhibitor class and is associated with lower abuse liability than substrate-type releasers such as amphetamine. Pharmacokinetic characterization in Sprague-Dawley rats demonstrates that (S)-CE-123 achieves an unbound brain-to-plasma concentration ratio (K_{p,uu,brain}) of 0.5, compared to 0.1 for R-modafinil, indicating approximately five-fold superior blood-brain barrier penetration. Hepatic metabolism proceeds via CYP2C19, CYP3A, and CYP2B6, with a 9.3-fold faster hepatic clearance rate compared to modafinil. The principal metabolite (M1) is formed by hydroxylation of one of the aromatic rings.

The preclinical pharmacology of CE-123 spans multiple cognitive domains tested in several rodent models. In the spatial hole-board paradigm in male Sprague-Dawley rats, daily oral CE-123 at doses of 1 and 10 mg/kg improved both memory acquisition and memory retrieval, with significantly increased reference memory indices and shortened latency to find baited holes. In the attentional set-shifting task, CE-123 at 0.3 and 1.0 mg/kg increased cognitive flexibility (reduced extra-dimensional shift errors) without increasing impulsivity. In aged (26-month) Lister Hooded rats, (S)-CE-123 markedly enhanced motivation and performance in a new-to-learn operant discrimination task and in a cooperation assay of social cognition, with post-treatment proteomic analysis of prefrontal cortex synaptosomes revealing modulation of pathways involved in synaptic vesicle recycling, receptor-mediated endocytosis, and alpha-synuclein membrane localization. In a maternal separation model of early-life stress, CE-123 restored spatial memory deficits in adolescent rats with sex-dependent effects favoring females, and normalized maternal-separation-induced upregulation of DAT and dopamine D1 receptor expression in the prefrontal cortex and hippocampus. In a neonatal ethanol exposure model of fetal alcohol spectrum disorders, CE-123 at 3 and 10 mg/kg attenuated locomotor hyperactivity and ameliorated reversal learning impairment. Neurochemical microdialysis studies in freely moving rats demonstrated that (S)-CE-123 at 10 mg/kg intraperitoneally increased extracellular dopamine in the infralimbic/prelimbic cortex with a pharmacodynamic profile distinct from R-modafinil, and produced only a low and transitory dopamine increase in the nucleus accumbens shell, consistent with reduced reinforcing potential.

No human clinical trials of CE-123 have been published or registered as of the date of this monograph. The compound is not approved by any regulatory authority for human use. It is supplied as a research-grade preparation by multiple chemical vendors at greater than 98 percent purity. A process development and scale-up synthesis has been published (ACS Omega, 2023), establishing a scalable route to the (S)-enantiomer. This monograph reviews the chemistry, synthesis, and stereochemistry of CE-123; the DAT inhibitor pharmacology in molecular and functional detail; the pharmacokinetic characterization including blood-brain barrier penetration; the preclinical cognitive pharmacology across multiple behavioral paradigms and disease models; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event signal from preclinical studies; and a comparative assessment of five alternative cognitive-enhancing DAT-active compounds against CE-123 on five competency standards. The compound is strictly a research tool at this stage of development; investigators should obtain analytical confirmation of identity and purity on every lot and should not extrapolate preclinical findings to human dose-response without appropriate regulatory and ethical authorization.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Systematic name: CE-123.

Active enantiomer designation: (S)-CE-123 (the S-enantiomer at the sulfinyl stereocenter; this is the pharmacologically preferred form in all published preclinical studies from 2020 onward).

Chemical Abstracts Service registry number: 1879038-73-9 (racemate). The (S)-enantiomer is catalogued separately by vendors (MedChemExpress, TargetMol, Cayman Chemical) under supplier-specific identifiers; a distinct CAS number for the resolved (S)-enantiomer has been assigned in some databases.

UNII: 2P6T8SD99L (United States National Library of Medicine, NCATS Inxight Drugs).

International Union of Pure and Applied Chemistry name: 5-((benzhydrylsulfinyl)methyl)-1,3-thiazole. The compound is the sulfinyl (S=O) derivative of a benzhydrylthioether linked through a methylene bridge to the 5-position of a 1,3-thiazole heterocycle.

Other designations: The compound has been referenced in the primary literature as "a novel modafinil analogue" [1, 2, 3], "a novel dopamine transporter inhibitor" [4, 5], and "an atypical DAT inhibitor" [6, 7]. The "CE" prefix reflects the internal compound enumeration of the Lubec laboratory at the University of Vienna.

1.2 Structural class and chemistry

CE-123 is a diphenylmethylsulfinylmethyl heterocycle, a structural class derived from modafinil (2-(diphenylmethylsulfinyl)acetamide) by bioisosteric replacement of the acetamide group with a 1,3-thiazole ring. The structural modification was designed to enhance DAT affinity, improve selectivity over NET and SERT, increase blood-brain barrier penetration, and reduce the broad pharmacological profile (histaminergic, GABAergic, orexinergic, glutamatergic) that characterizes modafinil [1, 8].

Molecular formula: C₁₇H₁₅NO₂S₂ (racemate, free base).

Molecular weight: 329.43 g/mol.

Exact mass: 329.0544 g/mol (monoisotopic).

Physical properties: White to off-white crystalline powder. Soluble in dimethyl sulfoxide (DMSO) and methanol; sparingly soluble in water. The compound is typically handled as a DMSO stock solution for in vitro applications and as a suspension or solution in appropriate vehicles (e.g., 0.5% methylcellulose, saline with co-solvent) for in vivo administration.

Stereochemistry: CE-123 contains a single stereocenter at the sulfinyl sulfur atom, generating two enantiomers: (S)-CE-123 and (R)-CE-123. The (S)-enantiomer is the more potent and selective DAT inhibitor and is the form used in the majority of recent pharmacological studies [6, 8]. The racemate was used in the earlier publications (2017 to 2018); subsequent work employed the resolved (S)-enantiomer following chiral HPLC separation or enantioselective synthesis. Investigators acquiring research-grade CE-123 should confirm which enantiomeric form is supplied and should verify enantiomeric purity by chiral HPLC.

1.3 Synthesis

The racemic synthesis of CE-123 proceeds through three principal stages as described by Kristofova et al. (2018) and elaborated in the ACS Omega scale-up report (2023) [1, 9].

Stage 1: Diphenylmethanol is reacted with thiourea under acidic conditions to yield a thiouronium salt intermediate ([[(diphenylmethyl)sulfanyl]methanimideamide hydrobromide]).

Stage 2: Thiazol-5-ylmethanol is converted to 5-(chloromethyl)thiazole hydrochloride by treatment with thionyl chloride.

Stage 3: The thiouronium salt is reacted under alkaline conditions with 5-(chloromethyl)thiazole hydrochloride to yield 5-((benzhydrylthio)methyl)thiazole (the thioether intermediate). This intermediate is oxidized using 30 percent hydrogen peroxide under acidic conditions (acetic acid) to yield the racemic sulfinyl product, 5-((benzhydrylsulfinyl)methyl)thiazole (CE-123).

Enantiomeric resolution of the racemate was originally achieved by chiral HPLC using a Chiralpak IA semipreparative column [1]. The ACS Omega (2023) process development report by Kalaba et al. established a scalable asymmetric synthesis or chiral resolution route to gram-scale (S)-CE-123 suitable for preclinical supply [9]. The resolved material is characterized by nuclear magnetic resonance spectroscopy (^1H and ^{13}C), mass spectrometry, optical rotation, and chiral HPLC with enantiomeric excess typically exceeding 99 percent.

2. Abstract

CE-123 (5-((benzhydrylsulfinyl)methyl)thiazole) is an atypical, selective dopamine transporter (DAT) inhibitor developed at the University of Vienna as a next-generation analogue of modafinil [1, 2]. The compound was designed through bioisosteric replacement of the modafinil acetamide with a 1,3-thiazole heterocycle to achieve enhanced DAT selectivity, improved blood-brain barrier penetration, and a cleaner pharmacological profile relative to the parent compound. The active enantiomer, (S)-CE-123, inhibits dopamine reuptake via DAT with an EC₅₀ of approximately 2.76 micromolar, with approximately 30-fold selectivity over NET and greater than 400-fold selectivity over SERT [6]. The compound interacts with the outward-facing conformation of DAT without triggering reverse transport, classifying it as an atypical (non-releasing) DAT inhibitor with theoretically lower abuse liability than substrate-type psychostimulants [4].

The preclinical cognitive enhancement profile of CE-123 is the most extensively characterized among modafinil analogues in the current literature. Daily oral administration improves memory acquisition and retrieval in the spatial hole-board task [2], increases cognitive flexibility in the attentional set-shifting task [4], enhances motivation and social cognition in aged rats [3], restores maternal-separation-induced spatial memory deficits in adolescent rats with sex-dependent efficacy [10], and ameliorates locomotor hyperactivity and reversal learning impairment in a fetal alcohol spectrum disorder model [11]. Neurochemical microdialysis demonstrates that (S)-CE-123 selectively elevates dopamine in the infralimbic/prelimbic cortex with only transient and modest dopamine elevation in the nucleus accumbens shell [6], a profile consistent with procognitive rather than reinforcing dopaminergic effects.

Pharmacokinetic studies demonstrate that (S)-CE-123 achieves an unbound brain-to-plasma ratio ($K_{p,uu,brain}$) of 0.5, approximately five-fold higher than R-modafinil (0.1), supporting superior central nervous system exposure at equivalent systemic doses [8]. Hepatic metabolism proceeds principally via CYP2C19, CYP3A, and CYP2B6, with a 9.3-fold faster clearance than modafinil [8].

No human clinical trials have been published or registered. The compound is not approved by any regulatory authority. It is available as a research-grade preparation from multiple chemical suppliers at greater than 98 percent purity. This monograph documents the full preclinical characterization of CE-123, its comparative pharmacology, and its positioning within the dopaminergic cognitive enhancement landscape.

3. Discovery and Development History

3.1 Origin and rationale

CE-123 emerged from a medicinal chemistry program at the Department of Pharmaceutical Chemistry, University of Vienna, led by Gert Lubec, during the mid-2010s. The program was motivated by the observation that modafinil, while clinically effective as a wakefulness-promoting agent and off-label cognitive enhancer, has limited selectivity for the dopamine transporter. Modafinil also engages histaminergic, GABAergic, glutamatergic, and orexinergic systems, producing a broad and sometimes unpredictable pharmacological profile that complicates mechanistic interpretation of its cognitive effects and introduces off-target adverse events at higher doses [1, 8].

The Lubec group synthesized a series of heterocyclic modafinil analogues in which the acetamide moiety was replaced with various nitrogen- and sulfur-containing heterocycles (thiazole, oxazole, imidazole, and related scaffolds). CE-123, the thiazole derivative, was selected for advancement on the basis of superior DAT affinity, high selectivity over NET and SERT, favorable oral bioavailability in rodents, and a clean safety profile in initial toxicology screening [1, 4].

3.2 Early pharmacological characterization (2017 to 2018)

The first published report on CE-123 appeared in *Frontiers in Behavioral Neuroscience* (Camats-Perna et al., 2017), demonstrating that the racemic compound improved cognitive flexibility in the attentional set-shifting task (ASST) in healthy male Sprague-Dawley rats at doses of 0.3 and 1.0 mg/kg without increasing impulsivity [4]. This was followed by a *Pharmacology Biochemistry and Behavior* report (Kristofova et al., 2018) showing that daily CE-123 improved both memory acquisition and memory retrieval in the spatial hole-board paradigm at 1 and 10 mg/kg [2]. These two reports established the basic cognitive enhancement profile and confirmed the compound's oral activity.

3.3 Enantiomeric characterization and (S)-CE-123 advancement (2019 to 2020)

Beginning in 2019, the Lubec laboratory resolved the CE-123 racemate into its (S) and (R) enantiomers by chiral HPLC and demonstrated that (S)-CE-123 was the more potent DAT inhibitor with the preferred cognitive pharmacology [6, 7]. Subsequent studies used (S)-CE-123 exclusively. The Kucerovala et al. (2019) report in *Frontiers in Pharmacology* demonstrated that (S)-CE-123 partially reversed the effort-related motivational effects of the dopamine-depleting agent tetrabenazine and increased progressive ratio responding, establishing the compound's pro-motivational profile [7]. The Nikiforuk et al. (2020) report in *Biomolecules* characterized the neurophysiological and neurochemical effects of (S)-CE-123 on the mesocorticolimbic dopamine system by in vivo microdialysis and electrophysiology in freely moving rats [6].

3.4 Disease model applications (2021 to 2024)

From 2021 onward, CE-123 was tested in multiple disease-relevant rodent models. Holzinger et al. (2021) in *Scientific Reports* reported cognitive profiling and proteomic analysis of (S)-CE-123 in experienced aged (26-month) Lister Hooded rats, demonstrating enhanced motivation, social cognition, and synaptosome-level proteomic changes in the prefrontal cortex [3]. Siwiec et al. (2021) reported that CE-123 attenuated locomotor hyperactivity and ameliorated reversal learning impairment in a neonatal ethanol exposure model of fetal alcohol spectrum disorders [11]. Gawel et al. (2022) characterized CE-123 effects on spatial memory deficits induced by maternal separation in adolescent rats, with sex-dependent effects [10]. Cieřlik et al. (2024) reported on social interaction in adolescent rats with neonatal ethanol exposure, examining the impact of sex and CE-123 [12].

3.5 Process chemistry and scale-up (2023)

The Kalaba et al. (2023) report in *ACS Omega* described the process development and scale-up of a scalable synthesis of (S)-CE-123, establishing a route suitable for multi-gram production for advanced preclinical studies and potential clinical supply [9]. This report marked a transition from the research-scale chiral HPLC resolution to a production-viable enantioselective or enrichment strategy.

3.6 Current development status

CE-123 has not entered human clinical trials as of the date of this monograph. No Investigational New Drug application or Clinical Trial Authorization is publicly recorded. The compound remains a preclinical research tool with a growing literature (approximately 15 peer-reviewed publications from 2017 to 2024) and an established position as the lead compound among modafinil analogues with enhanced DAT selectivity. The development trajectory is consistent with an academic-originated compound in the late preclinical optimization phase.

4. Mechanism of Action

4.1 Dopamine transporter inhibition

The dopamine transporter (DAT, SLC6A3) is a 12-transmembrane-domain sodium/chloride-dependent transporter expressed on dopaminergic nerve terminals in the striatum, nucleus accumbens, prefrontal cortex, and other brain regions. DAT mediates the reuptake of dopamine from the synaptic cleft into the presynaptic terminal, thereby terminating dopaminergic neurotransmission and recycling dopamine for vesicular repackaging. DAT is the primary molecular target of psychostimulants (cocaine, methylphenidate, amphetamine) and of modafinil [13, 14].

CE-123 inhibits DAT-mediated dopamine reuptake by binding to the outward-facing conformation of the transporter and preventing substrate (dopamine) access to the binding site [4, 6]. The (S)-enantiomer inhibits DAT with an EC₅₀ of approximately 2.76 micromolar in HEK293 cells stably expressing human DAT [6]. The mechanism is non-releasing: unlike amphetamine, which enters the transporter as a substrate and reverses transport to produce non-vesicular dopamine release, CE-123 binds without being translocated and does not trigger reverse transport or vesicular depletion [4]. This atypical mechanism is shared with modafinil and with the GBR series of DAT inhibitors and is associated with reduced reinforcing properties and lower abuse liability in preclinical self-administration paradigms [13].

4.2 Selectivity profile

The selectivity of (S)-CE-123 for DAT over the norepinephrine transporter (NET) and serotonin transporter (SERT) is a principal differentiating feature from modafinil. (S)-CE-123 is approximately 30-fold selective for DAT over NET and greater than 400-fold selective for DAT over SERT [6]. By comparison, modafinil has approximately 3- to 5-fold selectivity for DAT over NET and limited selectivity over SERT [8]. The enhanced selectivity of CE-123 allows more precise pharmacological attribution of cognitive effects to dopaminergic mechanisms and reduces the noradrenergic and serotonergic contributions that complicate the interpretation of modafinil studies.

The compound does not show significant affinity for monoamine receptors (dopamine D1 to D5, serotonin 5-HT1 through 5-HT3, adrenergic alpha-1 and alpha-2, histamine H1 through H3) at concentrations up to 10 micromolar in radioligand displacement assays, supporting a clean selectivity profile [4, 6].

4.3 Neurochemical effects in vivo

In vivo microdialysis in freely moving Sprague-Dawley rats (Nikiforuk et al., 2020) demonstrated that (S)-CE-123 at 10 mg/kg intraperitoneally produced a sustained increase in extracellular dopamine in the infralimbic/prelimbic cortex (medial prefrontal cortex), with a pharmacodynamic time course and magnitude distinct from R-modafinil at the same dose [6]. In the nucleus accumbens shell, the principal region mediating reward and reinforcement, (S)-CE-123 produced only a low and transitory dopamine increase, in contrast to the more sustained elevation observed with modafinil [6]. This regional selectivity of dopamine elevation (prefrontal cortex more than nucleus accumbens) is consistent with a procognitive rather than reinforcing pharmacodynamic profile and supports the hypothesis that the atypical DAT binding mode of CE-123 produces a qualitatively different dopaminergic signal than that produced by typical DAT inhibitors or by modafinil.

Electrophysiological recordings in the same report demonstrated that (S)-CE-123 altered the firing patterns of dopaminergic neurons in the ventral tegmental area (VTA), with effects on burst firing and firing rate that differed from R-modafinil [6]. The electrophysiological data support the conclusion that the compound modulates mesocorticolimbic dopaminergic circuit activity in a manner that favors cortical over limbic dopamine signaling.

4.4 Downstream cognitive mechanisms

The procognitive effects of CE-123 are attributable to enhanced dopaminergic tone in the prefrontal cortex and hippocampus, where dopamine acts through D1 and D2 receptor families to modulate working memory, cognitive flexibility, motivation, and attention [3, 4]. Proteomic analysis of prefrontal cortex synaptosomes in aged rats treated with (S)-CE-123 revealed modulation of pathways involved in synaptic vesicle recycling (clathrin-mediated endocytosis, synaptic vesicle protein turnover), receptor-mediated endocytosis, and alpha-synuclein membrane localization [3]. These proteomic changes suggest that the compound produces durable

synaptic remodeling beyond the acute pharmacodynamic effects on extracellular dopamine, potentially contributing to the sustained cognitive improvement observed with repeated dosing.

In the maternal separation model, CE-123 normalized the stress-induced upregulation of DAT and D1 receptor expression in the hippocampus and prefrontal cortex [10]. The normalization of DAT expression is particularly notable because maternal separation produces a compensatory DAT upregulation that accelerates dopamine clearance and reduces tonic dopaminergic signaling; CE-123 treatment both directly inhibits DAT function and reverses the expression-level upregulation, producing a dual mechanism of dopaminergic restoration.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and bioavailability

CE-123 is orally bioavailable in rodents, as confirmed by the cognitive enhancement observed in multiple studies using oral (per os, gavage) administration at doses of 0.3 to 10 mg/kg [2, 4]. Quantitative oral bioavailability has been characterized in the Sanna et al. (2023) pharmacokinetic study, which compared intravenous and oral routes in Sprague-Dawley rats [8]. The compound achieves adequate systemic exposure for central nervous system effects at the studied oral doses, though precise oral bioavailability percentages have not been reported in a peer-reviewed publication accessible at the time of this monograph.

5.2 Distribution and blood-brain barrier penetration

The blood-brain barrier penetration of (S)-CE-123 is a principal pharmacokinetic advantage over modafinil. The Sanna et al. (2023) study used the combination of plasma and brain microdialysis (for unbound interstitial fluid concentrations) and total brain homogenate analysis to determine that (S)-CE-123 achieves an unbound brain-to-plasma concentration ratio ($K_{p,uu,brain}$) of approximately 0.5, compared to approximately 0.1 for R-modafinil [8]. This five-fold superiority in brain penetration means that, at equivalent plasma exposures, (S)-CE-123 achieves five-fold higher unbound drug concentrations in the brain interstitial fluid, the pharmacologically relevant compartment for DAT engagement.

The compound primarily localizes in the brain interstitial space, with membrane distribution patterns distinct from modafinil [8]. This intracellular-versus-extracellular partitioning difference is pharmacologically meaningful because the DAT protein is an integral membrane protein with its substrate-binding site accessible from the extracellular (synaptic cleft) face, favoring an extracellularly localized compound.

5.3 Metabolism

Hepatic metabolism of (S)-CE-123 proceeds principally through cytochrome P450 enzymes CYP2C19, CYP3A4, and CYP2B6, as determined by human liver microsome incubation studies [8]. The primary metabolite (designated M1) is formed by hydroxylation of one of the aromatic (phenyl) rings of the benzhydryl group. The rate of hepatic metabolism is 9.3-fold faster than that of modafinil under identical microsomal incubation conditions [8], indicating a shorter predicted plasma half-life in humans and potentially requiring more frequent dosing or sustained-release formulation for clinical translation.

The CYP enzyme profile has implications for drug-drug interactions: CYP2C19 polymorphism (poor metabolizers at approximately 2 to 5 percent frequency in European-ancestry populations and approximately 15 to 20 percent in East Asian populations) could substantially alter (S)-CE-123 exposure. Concurrent CYP3A4 inhibitors or inducers would additionally modulate plasma levels. These interactions have not been characterized *in vivo*.

5.4 Elimination

Elimination kinetics have been characterized in the rat. Specific plasma half-life values and clearance rates are reported in the Sanna et al. (2023) study [8]. The rapid hepatic metabolism relative to modafinil predicts a shorter elimination half-life. Urinary and biliary excretion pathways for the metabolites have not been separately characterized.

5.5 Routes of administration

Two principal routes have been used in published preclinical studies:

Oral (gavage): The most common route for cognitive behavioral studies. Doses of 0.3 to 10 mg/kg have been used, with the compound administered as a suspension in 0.5 percent methylcellulose or as a solution in appropriate vehicles (saline with DMSO or PEG co-solvent) [2, 4, 10, 11].

Intraperitoneal injection: Used in neurochemical (microdialysis) and electrophysiological studies. The standard dose for microdialysis studies is 10 mg/kg, administered as a solution in saline with DMSO co-solvent (typically 5 to 10 percent DMSO final concentration) [6].

No intravenous, subcutaneous, or intracerebroventricular administration data have been published in the behavioral pharmacology literature, though intravenous dosing was used in the formal pharmacokinetic study for bioavailability determination [8].

6. Preclinical Pharmacology

6.1 Cognitive flexibility

The Camats-Perna et al. (2017) report in *Frontiers in Behavioral Neuroscience* was the first published evaluation of CE-123 cognitive effects [4]. Male Sprague-Dawley rats were tested in the attentional set-shifting task (ASST), a rodent analogue of the Wisconsin Card Sort Test that evaluates the ability to shift attention between perceptual dimensions. CE-123 (racemate) at 0.3 and 1.0 mg/kg administered orally after attentional set acquisition significantly reduced the number of trials required for the extra-dimensional shift (EDS) compared to vehicle-treated controls, indicating enhanced cognitive flexibility [4]. Importantly, CE-123 did not increase impulsivity as measured by premature responses or perseverative errors, a favorable dissociation from the psychostimulant class in which cognitive enhancement and impulsivity typically co-occur.

6.2 Spatial memory acquisition and retrieval

The Kristofova et al. (2018) report in *Pharmacology Biochemistry and Behavior* evaluated CE-123 in the spatial hole-board task, a paradigm in which rats learn to identify and remember the locations of baited holes in a 4x4 grid over repeated daily trials [2]. CE-123 (racemate) at 1 and 10 mg/kg administered orally as a daily single dose significantly improved reference memory indices (the ratio of first visits to baited holes relative to total first visits) and shortened the latency to locate all baited holes, demonstrating enhancement of both memory acquisition (learning) and memory retrieval (recall of previously learned spatial information) [2]. The effect was dose-dependent and was observed without significant effects on locomotor activity or anxiety-related behavior, supporting a specific cognitive enhancement rather than a non-specific arousal effect.

6.3 Motivation and social cognition in aged rats

The Holzinger et al. (2021) report in *Scientific Reports* evaluated (S)-CE-123 in a cohort of 27 experienced aged male Lister Hooded rats (26 months old) that had previously learned multiple cognitive tasks [3]. (S)-CE-123 markedly enhanced motiva-

tion as measured by superior performance in a new-to-learn operant discrimination task (increased response rates, reduced omissions) and enhanced social cognition in a cooperation assay requiring coordinated lever-pressing with a conspecific partner [3]. The compound also mildly increased impulsivity in this aged cohort, a finding that the authors interpreted as potentially reflecting a restoration of dopaminergic tone from a hypo-dopaminergic aged baseline.

Post-treatment proteomic analysis of prefrontal cortex synaptosomes using label-free quantification revealed that (S)-CE-123 modulated the expression of proteins involved in synaptic vesicle recycling (including clathrin heavy chain, dynamin, and synaptojanin), receptor-mediated endocytosis, and alpha-synuclein membrane localization [3]. These proteomic changes provide a molecular basis for the sustained cognitive improvements observed with CE-123 treatment and suggest that the compound produces synaptic-level remodeling in the aged prefrontal cortex.

6.4 Maternal separation stress model

The Gawel et al. (2022) report in the International Journal of Molecular Sciences evaluated CE-123 in adolescent rats exposed to maternal separation (a model of early-life stress that produces lasting cognitive, emotional, and neurochemical alterations relevant to depression, anxiety, and cognitive impairment) [10]. Maternal separation impaired acquisition of spatial learning and memory in the Morris water maze, with a more severe effect in females. CE-123 restored spatial memory performance in both sexes, with effects more pronounced in females [10].

At the molecular level, maternal separation induced upregulation of DAT and D1 receptor expression in the prefrontal cortex and hippocampus; CE-123 treatment normalized these expression changes. The expression of RIT2, a protein involved in DAT endocytic trafficking, was decreased by maternal separation in the hippocampus for both sexes and in the prefrontal cortex for females only; the sex-dependent pattern of RIT2 changes may partially explain the sex-dependent efficacy of CE-123 [10].

6.5 Fetal alcohol spectrum disorder model

The Siwiec et al. (2021) report evaluated CE-123 in a neonatal ethanol exposure model of fetal alcohol spectrum disorders (FASD) [11]. Rats exposed to ethanol on postnatal days 4 to 9 developed locomotor hyperactivity and cognitive inflexibility (impaired reversal learning in a T-maze) in adolescence. CE-123 at 3 mg/kg attenuated the locomotor hyperactivity, and at 10 mg/kg ameliorated the reversal learning deficit [11]. The reversal learning improvement is consistent with the cognitive flexibility enhancement observed in the ASST study in healthy rats and supports the hypothesis that CE-123 acts through a general mechanism of prefrontal dopaminergic optimization that is beneficial across cognitive domains.

The Cieslik et al. (2024) study further examined social interaction in adolescent rats with neonatal ethanol exposure, finding that male and female rats exhibited sex- and age-dependent deficits in social novelty discrimination that were partially modulated by CE-123 treatment [12].

6.6 Neurochemical and electrophysiological characterization

The Nikiforuk et al. (2020) study provides the most detailed neurochemical and electrophysiological characterization of (S)-CE-123 [6]. Key findings from in vivo microdialysis in freely moving Sprague-Dawley rats:

(S)-CE-123 at 10 mg/kg intraperitoneally produced a sustained (approximately 2 to 3 hour) increase in extracellular dopamine in the infralimbic/prelimbic cortex (medial prefrontal cortex). The magnitude and time course of this increase differed from R-modafinil at the same dose, with CE-123 producing a more rapid onset and a different plateau pattern [6].

In the nucleus accumbens shell, (S)-CE-123 produced only a low and transitory dopamine increase, whereas R-modafinil produced a more sustained elevation [6]. This regional selectivity (prefrontal more than accumbens) is a favorable pharmacodynamic feature for a cognitive enhancer, as accumbens dopamine elevation is the primary neurochemical correlate of the reinforcing and addictive properties of psychostimulants.

Electrophysiological recordings from ventral tegmental area dopaminergic neurons demonstrated that (S)-CE-123 altered burst firing patterns with a profile distinct from R-modafinil, consistent with differential modulation of the mesocortical versus mesolimbic dopaminergic pathways [6].

6.7 Behavioral safety profile

Across all published studies, CE-123 at the effective cognitive doses (0.3 to 10 mg/kg) did not produce hyperlocomotion, stereotypy, or anxiety-like behavior in open-field and elevated plus maze assessments [2, 4, 6, 10, 11]. Chronic treatment at both low (1 mg/kg) and high (10 mg/kg) doses did not induce behavioral sensitization (a marker of abuse potential) or pro-psychotic-like effects such as disruption of prepulse inhibition of the acoustic startle reflex [3, 6]. Working memory and behavioral flexibility were preserved or enhanced, not impaired, at all studied doses.

7. Clinical Evidence Base

No human clinical trials of CE-123 have been published, registered in ClinicalTrials.gov, or announced by any sponsor as of the date of this monograph. The compound has not received any regulatory approval for human use. The absence of clinical data is a principal limitation of the current evidence base.

The compound's positioning as a potential clinical candidate for cognitive enhancement in conditions such as attention-deficit/hyperactivity disorder (ADHD), age-related cognitive decline, fetal alcohol spectrum disorders, or other dopamine-sensitive cognitive impairments is based entirely on preclinical evidence. Translation to human studies would require completion of formal Good Laboratory Practice toxicology studies, formulation development, and regulatory authorization.

The closest clinical precedent is modafinil itself, which is approved for narcolepsy, shift work sleep disorder, and obstructive sleep apnea-associated excessive daytime sleepiness, and has been extensively studied off-label for cognitive enhancement. The CE-123 preclinical data suggest potential advantages over modafinil in DAT selectivity and brain penetration, but these advantages have not been validated in human pharmacokinetic or efficacy studies.

8. Sourcing and Quality Verification

Research-grade CE-123 (both racemate and (S)-enantiomer) is supplied by multiple chemical research vendors:

Vendors supplying (S)-CE-123: MedChemExpress (catalog HY-136862), TargetMol, Cayman Chemical, Tocris (where available). Purity typically stated as greater than 98 percent by HPLC. Supply is in milligram quantities (1 mg to 25 mg vials) as lyophilized powder or crystalline solid.

Vendors supplying racemic CE-123: Sigma-Aldrich (where available), Alkonchem (1 g and 5 g quantities at greater than 98 percent purity), and several research chemical vendors. The racemic material is generally less expensive per milligram than the resolved enantiomer.

Vendor certificates of analysis typically report HPLC purity, mass spectrometry confirmation, and (for the resolved enantiomer) chiral HPLC enantiomeric excess. Investigators should independently confirm:

- HPLC area-percent purity (greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at m/z 330.06 for $C_{17}H_{15}NO_2S_2$)
- Chiral HPLC confirmation of enantiomeric purity for (S)-CE-123 (greater than 99 percent enantiomeric excess)
- Residual solvent analysis (the synthesis involves dichloromethane, methanol, acetic acid, and hydrogen peroxide)
- Karl Fischer or loss-on-drying moisture determination

Third-party analytical confirmation (Janoshik Analytical or equivalent) is advisable for high-stakes dose-response studies, as the compound is relatively new to the research-grade chemical market and lot-to-lot variability data are limited. The racemate is the less expensive option for mechanistic studies where enantiospecificity is not critical; the (S)-enantiomer should be used for studies requiring pharmacological consistency with the recent literature.

9. Reconstitution and Handling

CE-123 (both racemate and (S)-enantiomer) is supplied as a white to off-white powder. The compound has limited aqueous solubility and requires co-solvent systems for solution preparation.

For in vitro applications: Stock solutions are typically prepared at 10 to 50 mM in DMSO. The compound is stable in DMSO at room temperature for at least 24 hours and at minus 20 degrees Celsius for extended storage (months). Aliquoting is recommended to avoid repeated freeze-thaw cycles. Working concentrations for cell-based assays (uptake inhibition, electrophysiology) are in the low-micromolar range (0.1 to 30 micromolar), achieved by serial dilution of the DMSO stock into assay buffer with a final DMSO concentration not exceeding 0.1 to 0.5 percent.

For in vivo oral administration: The compound is typically suspended in 0.5 percent methylcellulose in water or dissolved in a co-solvent vehicle (e.g., 5 percent DMSO, 10 percent PEG-400, 85 percent saline) and administered by oral gavage. Suspension homogeneity should be confirmed by visual inspection and by brief sonication immediately before dosing. Preparation fresh daily is recommended; stability data for the oral suspension formulation are not published.

For in vivo intraperitoneal administration: The compound is dissolved in a vehicle containing 5 to 10 percent DMSO in sterile saline. The solution should be prepared fresh, sterile-filtered (0.22 micrometer) for aseptic applications, and used within 24 hours.

Storage: Solid material should be stored at minus 20 degrees Celsius, protected from light and moisture, under desiccant. DMSO stock solutions should be stored at minus 20 degrees Celsius in sealed vials. The compound is not reported to be hygroscopic but standard small-molecule handling precautions apply.

10. Stack Interactions and Combinations

CE-123 interacts with several drug classes through its DAT inhibitor mechanism and its CYP-mediated metabolism. Investigators conducting research with CE-123, especially in combination with other compounds, should consider:

CYP2C19 inhibitors: Strong inhibitors (omeprazole, esomeprazole, fluvoxamine, fluconazole, ticlopidine) can substantially elevate (S)-CE-123 exposure by reducing its principal hepatic clearance pathway. Concurrent use may require dose reduction to avoid supratherapeutic brain concentrations. CYP2C19 polymorphism (poor metabolizers) produces the same effect endogenously.

CYP3A4 inhibitors and inducers: CYP3A4 is a secondary metabolic pathway for CE-123. Strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin) may modestly increase exposure. CYP3A4 inducers (rifampin, carbamazepine, phenytoin, St. John's wort) may reduce exposure.

Other DAT inhibitors: Concurrent administration with methylphenidate, modafinil, bupropion, or cocaine would produce additive DAT occupancy and potentially excessive dopaminergic stimulation in cortical and striatal regions. The combination has not been studied but is pharmacologically predictable to increase both cognitive and adverse effects.

Dopamine releasers: Concurrent administration with amphetamine or methamphetamine would combine DAT blockade with reverse transport, producing a complex and potentially unpredictable dopaminergic signal. The combination is not recommended and has not been studied.

Dopamine receptor antagonists: Concurrent administration with antipsychotics (haloperidol, risperidone, olanzapine, clozapine) would partially or completely antagonize the downstream effects of CE-123-mediated dopamine elevation. This interaction is relevant for studies in schizophrenia models where antipsychotic co-administration is present. The Nikiforuk et al. (2020) study notes that the neurochemical effects of (S)-CE-123 should be interpreted in the context of concurrent dopaminergic medications [6].

Serotonergic and noradrenergic agents: Given the high selectivity of CE-123 for DAT over NET and SERT (greater than 30-fold and greater than 400-fold, respectively), pharmacokinetic interactions via transporter competition are unlikely at therapeutic doses. However, CYP-mediated metabolic interactions remain relevant for SSRIs (which inhibit CYP2C19 and CYP3A4 variably), SNRIs, and tricyclic antidepressants.

Cholinesterase inhibitors: Concurrent donepezil, rivastigmine, or galantamine would produce complementary cholinergic-plus-dopaminergic cognitive enhancement. The combination has not been studied but is a plausible preclinical research paradigm for multi-mechanism cognitive enhancement in aging or Alzheimer's models.

11. Adverse Events and Safety Signal

11.1 Preclinical behavioral safety

Across all published studies, CE-123 at effective cognitive doses (0.3 to 10 mg/kg) has not produced the following adverse behavioral signals:

- Hyperlocomotion or locomotor sensitization (a preclinical marker of psychostimulant abuse potential) [2, 4, 6]
- Stereotypic behavior (repetitive movements indicative of excessive striatal dopamine) [6]
- Anxiogenic effects in the elevated plus maze or open field [2, 4]
- Disruption of prepulse inhibition (a marker of sensorimotor gating relevant to psychosis) [6]
- Impairment of working memory or behavioral flexibility at any tested dose [3, 4]

The mild increase in impulsivity observed in aged rats at the highest dose [3] may reflect age-related hypo-dopaminergia rather than a true adverse signal, as the same effect was not observed in young healthy rats.

11.2 Abuse liability considerations

The atypical DAT inhibitor mechanism (outward-facing conformation binding, non-releasing) and the regional selectivity of dopamine elevation (prefrontal cortex more than nucleus accumbens) are pharmacological predictors of reduced abuse liability [4, 6, 13]. The low and transitory dopamine increase in the nucleus accumbens shell, the principal reward-circuit node, contrasts sharply with the sustained accumbens dopamine elevation produced by cocaine, amphetamine, and even modafinil. However, formal self-administration, conditioned place preference, and drug discrimination studies have not been published for CE-123.

11.3 General toxicology

No Good Laboratory Practice toxicology studies have been published. The published behavioral pharmacology studies report that CE-123 was well tolerated at all tested doses (up to 10 mg/kg orally and intraperitoneally) in Sprague-Dawley, Wistar, and Lister Hooded rats across multiple age groups (adolescent, adult, and aged) without reported mortality, weight loss, or clinical signs of toxicity [2, 3, 4, 6, 10, 11].

11.4 Predicted human adverse events

In the absence of human safety data, the predicted adverse-event profile is extrapolated from the DAT inhibitor pharmacology and from the known adverse events of modafinil:

- Insomnia (dopaminergic wakefulness-promoting effect)
- Headache (common to dopaminergic and many CNS-active agents)
- Nausea (dopaminergic stimulation of the area postrema)
- Anxiety or restlessness at supratherapeutic doses (excessive prefrontal dopaminergic activation)
- Potential for cardiovascular effects (tachycardia, blood pressure elevation) at high doses

These predictions are speculative and have not been confirmed in human subjects. The 9.3-fold faster hepatic metabolism compared to modafinil may mitigate duration of adverse effects but could also produce pharmacologically active metabolites that have not been characterized.

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative cognitive-enhancing compounds with dopaminergic activity against CE-123, evaluated on five competency standards: novelty, effect size, promising potential (current development state and trajectory), side-effect profile (clinical or preclinical), and overall validation. The five comparators were selected as the principal DAT-active or dopaminergic cognitive enhancers with substantive pharmacological literature, prioritizing compounds that share CE-123's positioning as dopaminergic cognitive enhancers.

12.1 Modafinil (2-(diphenylmethylsulfinyl)acetamide)

Mechanism: Atypical DAT inhibitor with additional activity at histamine, GABA, glutamate, orexin, and norepinephrine systems. The multi-target pharmacology is both a clinical strength (broad wakefulness promotion) and a mechanistic liability (difficulty attributing cognitive effects to specific receptor targets) [14].

Development trajectory: Approved by the FDA for narcolepsy (1998), shift work sleep disorder (2003), and obstructive sleep apnea-associated excessive daytime sleepiness. Extensively studied off-label for cognitive enhancement in ADHD, depression-associated cognitive impairment, military fatigue, and age-related cognitive decline. Generic availability worldwide.

Novelty: Low. Modafinil is the oldest compound in this class and the structural parent of CE-123. Its pharmacology has been studied for over 30 years.

Effect size: Moderate. Meta-analyses of modafinil cognitive effects in healthy subjects report small to moderate effect sizes on attention, executive function, and working memory (Cohen's d approximately 0.2 to 0.5), with effects more robust under conditions of sleep deprivation than in rested states [14].

Promising potential: Moderate. The compound is clinically established but is unlikely to produce new cognitive indications at this stage of its lifecycle. Patent expiry limits commercial interest in new indication development.

Side-effect profile: Well characterized. Principal adverse events are headache (34 percent), nausea (11 percent), anxiety, insomnia, and rare serious skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis). The FDA issued a warning regarding serious skin reactions in 2007. The compound is a Schedule IV controlled substance in the United States reflecting low but non-zero abuse potential [14].

Overall validation: High. Modafinil has the most extensive clinical validation of any compound in this comparator panel, including multiple approved indications and extensive off-label cognitive enhancement data.

Comparison to CE-123: CE-123 was designed to improve upon modafinil in three specific dimensions: DAT selectivity (approximately 30-fold versus 3-fold over NET), blood-brain barrier penetration ($K_{p,uu,brain}$ 0.5 versus 0.1), and pharmacological cleanliness (absence of histaminergic, GABAergic, and orexinergic activities). CE-123 achieves all three preclinical goals. The trade-off is the complete absence of human safety and efficacy data, the 9.3-fold faster hepatic metabolism (which may necessitate more frequent dosing), and the lack of a clinical development pathway.

12.2 Methylphenidate (methyl phenyl(piperidin-2-yl)acetate)

Mechanism: DAT and NET inhibitor (typical, non-releasing). Methylphenidate blocks dopamine and norepinephrine reuptake with approximately equal affinity, producing sustained elevations of both catecholamines in the prefrontal cortex and striatum [15].

Development trajectory: Approved for ADHD (1955, Ritalin) and narcolepsy. One of the most prescribed psychostimulants worldwide, with extensive generic and extended-release formulation availability.

Novelty: Very low. Methylphenidate has been in clinical use for over 70 years.

Effect size: Moderate to large in ADHD populations (Cohen's d approximately 0.5 to 0.8 on ADHD symptom scales). In healthy subjects, cognitive effects are modest and task-dependent, with improved attention and working memory but inconsistent effects on higher-order cognition [15].

Promising potential: Low for new indications. The compound is mature and well understood. New formulation variants (extended-release, transdermal) continue to be developed.

Side-effect profile: Well characterized. Principal adverse events are appetite suppression, insomnia, nervousness, tachycardia, and blood pressure elevation. Growth suppression in children on chronic therapy is a concern. The compound is a Schedule II controlled substance with documented abuse potential, particularly the immediate-release formulation [15].

Overall validation: Very high. Methylphenidate has the longest and most extensive clinical validation of any dopaminergic cognitive enhancer.

Comparison to CE-123: CE-123 has substantially higher DAT selectivity over NET (approximately 30-fold versus approximately 1-fold) and an atypical binding mechanism that predicts lower abuse liability. The regional selectivity of dopamine elevation (prefrontal more than accumbens for CE-123 versus more diffuse for methylphenidate) is a further differentiating feature. However, methylphenidate has decades of clinical safety and efficacy data that CE-123 entirely lacks. The comparison is primarily useful for mechanistic distinction rather than practical clinical alternatives.

12.3 Atomoxetine (N-methyl-3-phenyl-3-(o-tolyloxy)propan-1-amine)

Mechanism: Selective NET inhibitor. Atomoxetine has negligible DAT affinity and produces cognitive effects primarily through noradrenergic enhancement of prefrontal cortex function, with secondary dopaminergic effects in the prefrontal cortex (where NET, not DAT, is the primary dopamine clearance mechanism) [16].

Development trajectory: Approved for ADHD (2002, Strattera). The first non-stimulant ADHD medication. Available as generic.

Novelty: Low. Atomoxetine has been in clinical use for over 20 years.

Effect size: Moderate in ADHD populations (Cohen's d approximately 0.4 to 0.6 on ADHD symptom scales). Effects are slower in onset than stimulants (weeks versus hours), reflecting the chronic noradrenergic mechanism.

Promising potential: Low for new indications. The compound is mature.

Side-effect profile: Nausea, decreased appetite, dry mouth, insomnia, and rare hepatotoxicity. Not a controlled substance; minimal abuse potential. Better cardiovascular safety profile than methylphenidate [16].

Overall validation: High. Atomoxetine has a robust clinical evidence base for ADHD and is well characterized pharmacologically.

Comparison to CE-123: CE-123 and atomoxetine operate through complementary monoamine mechanisms (DAT versus NET). The combination of DAT-selective (CE-123) and NET-selective (atomoxetine) inhibition would theoretically produce a broader dopaminergic/noradrenergic cognitive enhancement, though this combination has not been studied. CE-123's DAT selectivity over NET is the mirror image of atomoxetine's NET selectivity over DAT, making the two compounds mechanistically orthogonal comparators.

12.4 GBR 12909 (vanoxerine; 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine)

Mechanism: Highly selective, atypical DAT inhibitor. GBR 12909 binds DAT with high affinity and very high selectivity over NET and SERT (greater than 100-fold). Like CE-123, it interacts with the outward-facing conformation of DAT and does not produce substrate-type reverse transport [13].

Development trajectory: Extensively studied as a preclinical tool compound for dopamine pharmacology since the 1980s. Entered early clinical development as a potential treatment for cocaine addiction (the DAT blockade hypothesis of cocaine antagonism) but was discontinued due to QT prolongation in Phase 1 studies [13].

Novelty: Low to moderate. GBR 12909 is the historical reference compound for the atypical selective DAT inhibitor class.

Effect size: Substantial in preclinical models of cocaine self-administration and dopaminergic cognitive paradigms. No clinical efficacy data.

Promising potential: Very low. Clinical development was terminated due to cardiac safety signals.

Side-effect profile: QT interval prolongation (the primary reason for clinical discontinuation). Other adverse events not well characterized in humans due to limited clinical exposure [13].

Overall validation: Moderate as a research tool; low as a clinical candidate.

Comparison to CE-123: GBR 12909 is the closest mechanistic comparator to CE-123 in the atypical selective DAT inhibitor class. CE-123 has the advantage of a more modern structure-activity relationship foundation, better-characterized blood-brain barrier penetration, the absence (so far) of cardiac safety signals, and a more extensive cognitive behavioral pharmacology dataset. GBR 12909 has the advantage of a longer history as a reference pharmacological tool and more extensive in vitro mechanistic characterization.

12.5 JJC8-091 (modafinil analogue with modified sulfinyl stereochemistry)

Mechanism: Atypical DAT inhibitor from the modafinil analogue class. JJC8-091 is a structural congener of modafinil with modifications designed to enhance DAT selectivity and reduce reinforcing properties [13].

Development trajectory: Preclinical research compound studied primarily in cocaine addiction models by the Newman and Bhatt laboratories at NIDA/NIH. Demonstrated to produce sustained DAT occupancy without locomotor stimulation or reinforcement in self-administration paradigms in squirrel monkeys and rats [13].

Novelty: Moderate. The compound represents the same medicinal chemistry strategy as CE-123 (modafinil analogue optimization) but from an independent laboratory with different structural modifications.

Effect size: Demonstrated in preclinical cocaine self-administration and reinstatement paradigms. Cognitive enhancement data are more limited than for CE-123.

Promising potential: Low to moderate. The compound is in preclinical development for cocaine use disorder rather than cognitive enhancement.

Side-effect profile: Preclinical only. No cardiac, behavioral, or general toxicology safety signals reported.

Overall validation: Low. Limited published data outside cocaine addiction models.

Comparison to CE-123: JJC8-091 and CE-123 are structurally related modafinil analogues developed independently for enhanced DAT selectivity, but with different therapeutic goals (cocaine addiction versus cognitive enhancement). CE-123 has a substantially more extensive cognitive behavioral pharmacology dataset. JJC8-091 has more extensive cocaine self-administration data and primate pharmacology. The two compounds are complementary research tools for understanding the atypical DAT inhibitor mechanism across different behavioral domains.

12.6 Comparator summary

The five compounds occupy distinct positions in the dopaminergic cognitive enhancement landscape. **Modafinil** is the structural parent of CE-123 with extensive clinical validation but limited DAT selectivity and a broad, sometimes unpredictable pharmacological profile. **Methylphenidate** is the most clinically validated dopaminergic cognitive enhancer with high efficacy in ADHD but limited DAT selectivity and documented abuse potential. **Atomoxetine** operates through the complementary noradrenergic mechanism with good safety but a different cognitive enhancement profile. **GBR 12909** is the historical reference atypical selective DAT inhibitor but was eliminated from clinical development by cardiac toxicity. **JJC8-091** is a structural congener from an independent program targeting cocaine addiction rather than cognition.

CE-123 occupies a unique position in this comparator landscape: it is the only compound specifically designed for cognitive enhancement with optimized DAT selectivity, superior blood-brain barrier penetration relative to its parent compound, and an extensive preclinical cognitive pharmacology dataset spanning multiple cognitive domains (flexibility, memory acquisition, memory retrieval, motivation, social cognition) and multiple disease models (aging, early-life stress, fetal alcohol spectrum disorders). Its principal limitation is the complete absence of human clinical data. Among the comparators evaluated, only modafinil, methylphenidate, and atomoxetine have established clinical evidence bases; CE-123 has the most focused preclinical cognitive dataset but the least clinical validation.

The combination of enhanced DAT selectivity (30-fold over NET), superior brain penetration ($K_{p,uu,brain}$ 0.5 versus 0.1 for modafinil), atypical binding mechanism (non-releasing), favorable regional selectivity of dopamine elevation (prefrontal more than accumbens), clean behavioral safety profile (no hyperlocomotion, no sensitization, no sensorimotor gating disruption), and cognitive enhancement

across multiple domains and disease models supports the positioning of CE-123 as the most promising next-generation atypical DAT inhibitor for cognitive applications in the current preclinical pipeline. Translation to human research requires formal toxicology, formulation development, and regulatory authorization that have not yet been initiated.

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