

PHA-543613

A quinuclidine furo[2,3-c]pyridine-5-carboxamide developed at Pfizer in the mid-2000s as a brain-penetrant, orally bioavailable selective alpha-7 nicotinic full agonist with substantial preclinical pharmacology in rodent cognitive models. The principal high-potency selective alpha-7 nicotinic agonist in current research use as a tool compound, with no advancement to human clinical trials but extensive use in fundamental and combination-pharmacology studies including the recent presenilin double-knockout mouse model of Alzheimer disease and synergistic combination work with memantine in aged rats.

DOCUMENT	KDC-MN-1356
ISSUED	2026-05-10
REVISION	1.0
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PHA-543613 is a small-molecule, brain-penetrant, orally bioavailable selective full agonist of the homopentameric alpha-7 subtype of the neuronal nicotinic acetylcholine receptor, originated at Pfizer Global Research and Development in the mid-2000s as part of an alpha-7 nicotinic receptor medicinal-chemistry program for cognitive enhancement applications. The compound is a quinuclidine furo[2,3-c]pyridine-5-carboxamide, structurally related to the quinuclidine-amide alpha-7 family that includes encenicline (a quinuclidine benzothiophene-2-carboxamide) and bradanicline (a quinuclidine benzofuran-2-carboxamide), distinguished by the fused furo[2,3-c]pyridine bicyclic system in the amide-bearing aryl group. The chemistry was disclosed in the seminal Wishka et al. (2006) Journal of Medicinal Chemistry report from Pfizer, which described the structure-activity relationship study, the optimization to PHA-543613 as the lead compound, and the preliminary pharmacology supporting brain penetration, oral bioavailability, and alpha-7 selectivity [1]. The compound has not been advanced to human clinical trials; the published pharmacology is principally preclinical (rodent species). PHA-543613 binds the human alpha-7 nicotinic receptor at the orthosteric (acetylcholine) site with low-nanomolar affinity (K_i approximately 8 nanomolar at human alpha-7 expressed in heterologous systems) and acts as a full agonist with intrinsic functional activity of approximately 80 to 90 percent of the acetylcholine maximum response in *Xenopus* oocyte and cell-line expression systems, comparable to bradanicline and substantially higher than encenicline (60 to 70 percent), tropisetron (25 to 40 percent), and GTS-21 (30 to 50

percent). Selectivity over other neuronal nicotinic subtypes (alpha-4-beta-2, alpha-3-beta-4) is approximately 100-fold or greater. The compound exhibits good oral bioavailability and high brain penetration in rodent species (brain-to-plasma ratio approximately 5 to 10), supporting central nervous system pharmacology at oral doses of 0.3 to 10 milligrams per kilogram. The principal published pharmacology comprises rodent behavioral studies in scopolamine-induced cognitive impairment, MK-801-induced cognitive impairment, beta-amyloid-induced cognitive deficit (the A β 25-35 mouse model), aged-rat working memory paradigms, and the recent Hijazi et al. (2023) presenilin 1 and presenilin 2 conditional double knockout mouse model of familial Alzheimer disease [2, 3, 4]. The compound has demonstrated reversal of cognitive deficits across these models with effect sizes substantially exceeding the alpha-7 partial agonists tested in parallel comparisons (notably exceeding galantamine in head-to-head comparisons in the aged-rat model). Substantial recent work has characterized the synergistic combination of PHA-543613 with memantine (an NMDA receptor antagonist, the FDA-approved Alzheimer disease drug) in aged rats, with the combination demonstrating greater cognitive benefit than either compound as monotherapy at clinically translatable doses [4]. The combination work supports a contemporary research-clinical hypothesis that combination pharmacology of alpha-7 nicotinic full agonism (PHA-543613-class) with NMDA receptor antagonism (memantine) and acetylcholinesterase inhibition (donepezil-class) may produce cognitive benefits exceeding those achievable with monotherapy in any single mechanism class. PHA-543613 has not been licensed to a clinical-development entity for human trials as of the most recent monograph revision; the compound therefore serves as a

research tool rather than as a clinical candidate. Research-grade PHA-543613 is widely available from chemical suppliers at moderate cost and is one of the most extensively used alpha-7 nicotinic receptor agonist tool compounds in contemporary fundamental pharmacology research. This monograph reviews the chemistry, synthesis, and stereochemistry of PHA-543613; the receptor pharmacology in molecular and electrophysiological detail; the preclinical pharmacokinetic record in rodent species; the comprehensive preclinical pharmacology across cognitive enhancement, neuroprotection, and combination pharmacology applications; sourcing, reconstitution, and stock-interaction considerations; the safety record (preclinical only); and a structured comparative assessment of five alpha-7 nicotinic acetylcholine receptor candidates against PHA-543613 on the five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Names: PHA-543613. The compound has not received an International Nonproprietary Name owing to the absence of clinical development; the name "PHA-543613" is the Pfizer development code that has persisted as the working designation for the compound in the research literature and supplier catalogs.

Trade names: None.

Chemical Abstracts Service registry numbers: 478149-53-0 (free base), 478148-58-2 (dihydrochloride), 1586767-92-1 (hydrochloride salt).

International Union of Pure and Applied Chemistry name: N-[(3R)-1-azabicyclo[2.2.2]octan-3-yl]furo[2,3-c]pyridine-5-carboxamide.

1.2 Structural class and chemistry

PHA-543613 is a quinuclidine furo[2,3-c]pyridine-5-carboxamide. The structural class is the quinuclidine-amide medicinal-chemistry family that includes encenicline (a quinuclidine benzothiophene-2-carboxamide) and bradanicline (a quinuclidine benzofuran-2-carboxamide bearing an additional 2-(pyridin-3-ylmethyl) substituent on the quinuclidine). Within the family, PHA-543613 is distinguished by:

- The furo[2,3-c]pyridine bicyclic heterocycle in place of the benzothiophene (encenicline) or benzofuran (bradanicline)
- The 5-carboxamide linkage position on the heterocycle (versus 2-carboxamide in encenicline and bradanicline)
- An unsubstituted (R)-quinuclidine in place of the substituted bradanicline quinuclidine

The furo[2,3-c]pyridine heterocycle introduces a pyridine nitrogen into the aryl portion of the molecule that is positioned to interact with the alpha-7 receptor binding pocket in a manner that supports full-agonist intrinsic activity at the receptor. The (R)-stereochemistry at the quinuclidine 3-position is the active configuration; the (S)-enantiomer has substantially reduced affinity.

Molecular formula: C₁₅H₁₇N₃O₂ (free base); C₁₅H₁₈Cl₁N₃O₂ (hydrochloride); C₁₅H₁₉Cl₂N₃O₂ (dihydrochloride).

Exact mass: 271.13 g/mol (free base, monoisotopic).

Molecular weight: 271.32 g/mol (free base); 307.78 g/mol (hydrochloride); 344.24 g/mol (dihydrochloride).

Physical properties: White to off-white crystalline solid as the hydrochloride or dihydrochloride salt. Soluble in water (as the salt forms), methanol, dimethyl sulfoxide; sparingly soluble in apolar solvents. Stable at room temperature in dry conditions.

Stereochemistry: PHA-543613 contains a single stereocenter at carbon 3 of the quinuclidine ring. The active form is the (R) enantiomer; the (S) enantiomer has substantially reduced α -7 nicotinic affinity and is sometimes used as a research control compound. Investigators acquiring research-grade PHA-543613 should confirm enantiomeric purity by chiral high-performance liquid chromatography against an (R)-reference standard.

1.3 Synthesis

The published synthesis of PHA-543613 (Wishka et al. 2006) proceeds through synthesis of furo[2,3-c]pyridine-5-carboxylic acid (prepared by oxidation of the corresponding aldehyde or by hydrolysis of the methyl ester), synthesis of (R)-3-aminoquinuclidine (the chiral amine partner, available commercially as the dihydrochloride salt or prepared by enzymatic resolution), and amide coupling of the two fragments using standard peptide-coupling reagents [1]. Recrystallization purification of the free base, conversion to the hydrochloride or dihydrochloride salt by addition of stoichiometric hydrogen chloride. The synthesis is similar in operational complexity to encenicline (single stereocenter) and substantially less complex than bradanicline (two stereocenters).

2. Abstract

PHA-543613 is a small-molecule, brain-penetrant, orally bioavailable selective full agonist of the alpha-7 subtype of the neuronal nicotinic acetylcholine receptor, originated at Pfizer Global Research and Development in the mid-2000s. The chemistry was disclosed in the Wishka et al. (2006) Journal of Medicinal Chemistry report describing the structure-activity relationship study and the optimization to PHA-543613 as the lead compound from a quinuclidine-amide series [1]. The compound has not been advanced to human clinical trials; the published pharmacology is principally preclinical in rodent species.

The compound binds the human alpha-7 nicotinic receptor at the orthosteric site with a K_i of approximately 8 nanomolar in heterologous expression systems and acts as a full agonist with intrinsic functional activity of approximately 80 to 90 percent of the acetylcholine maximum response in *Xenopus* oocyte and HEK293 cell-line systems [1, 5]. The functional intrinsic activity profile places PHA-543613 alongside bradanicline in the high-efficacy stratum of alpha-7 nicotinic full agonists, substantially above the partial agonists encenicline (60-70 percent), tropisetron (25-40 percent), and GTS-21 (30-50 percent). Selectivity over other neuronal nicotinic subtypes (alpha-4-beta-2, alpha-3-beta-4, alpha-3-beta-2) is approximately 100-fold or greater; selectivity over the muscle-type alpha-1 nicotinic receptor and over the related Cys-loop receptors (5-HT₃, GABA-A) is similar.

Pharmacokinetics in rodent species (mouse, rat) support oral bioavailability of approximately 50 to 70 percent and brain penetration with brain-to-plasma ratio of approximately 5 to 10. Plasma elimination half-life in rats is approximately 1 to 3 hours, supporting twice-daily or three-times-daily dosing in rodent behavioral studies. Metabolism is hepatic; the principal metabolic pathways have not been fully characterized.

The principal published preclinical pharmacology comprises:

- Reversal of scopolamine-induced cognitive impairment in rat spontaneous alternation (T-maze) and novel object recognition paradigms at 0.3 to 3 milligrams per kilogram subcutaneous or intraperitoneal [1]
- Partial reversal of MK-801-induced cognitive impairment with an inverted-U dose-response (the partial reversal indicates that the alpha-7 nicotinic mecha-

nism contributes to but does not fully account for the cognitive deficit produced by NMDA receptor antagonism)

- Reversal of beta-amyloid (A β 25-35) induced cognitive deficits in mouse object recognition memory at 1 to 3 milligrams per kilogram [3]
- Reversal of recognition memory impairment in aged rats, with PHA-543613 effect superior to galantamine in head-to-head comparisons at clinically translatable doses
- Synergistic combination with memantine in aged rats: the combination produced cognitive benefits superior to either compound as monotherapy [4]
- Memory rescue in presenilin 1 and presenilin 2 conditional double knockout mice (Hijazi et al. 2023), a familial Alzheimer disease model, supporting application to genetic Alzheimer disease forms [2]

The combination work with memantine is the principal contemporary scientific contribution of PHA-543613. The synergy supports a research-clinical hypothesis that alpha-7 nicotinic full agonism plus NMDA receptor antagonism may produce cognitive benefits exceeding those achievable with monotherapy in either mechanism class. The hypothesis has not been tested in human clinical trials with PHA-543613 (which has not been advanced to clinical development) or with the structurally related bradanicline or encenicline.

The compound is not in active clinical development; Pfizer has not advanced PHA-543613 to human trials, and the compound has not been licensed to another commercial development entity for clinical work as of the most recent monograph revision. The compound therefore serves as a research tool rather than as a clinical candidate. Research-grade PHA-543613 (greater than 98 percent purity) is widely available from multiple chemical suppliers at moderate cost (\$150 to \$400 per gram of the hydrochloride salt) and is one of the most extensively used alpha-7 nicotinic receptor agonist tool compounds in fundamental pharmacology research.

This monograph reviews the chemistry, synthesis, and stereochemistry of PHA-543613; the receptor pharmacology in detail; the preclinical pharmacokinetic record; the comprehensive preclinical pharmacology across cognitive enhancement, neuroprotection, and combination-pharmacology applications; sourcing, reconstitution, and stack-interaction considerations; the safety record from rodent toxicology; and a structured comparative assessment of five alpha-7 nicotinic acetylcholine receptor candidates against PHA-543613 on the five competency standards.

3. Discovery and Development History

3.1 Origin at Pfizer

The PHA-543613 chemistry program was developed at Pfizer Global Research and Development as part of a broader exploration of alpha-7 nicotinic receptor agonists for cognitive enhancement applications. The Pfizer alpha-7 nicotinic program was a multi-year effort that produced PHA-543613 alongside several other compounds in related quinuclidine-amide and other chemical classes. The Wishka et al. (2006) report consolidates the structure-activity relationship study leading to the selection of PHA-543613 as the lead compound from this series [1]. The compound was selected on the basis of high alpha-7 selectivity, full-agonist functional intrinsic activity, brain penetration, and oral bioavailability in rodent species.

3.2 Preclinical pharmacology development

Following the Wishka et al. 2006 disclosure, the compound has been extensively characterized in preclinical pharmacology studies by multiple independent academic and commercial laboratories. The principal preclinical pharmacology accumulated through approximately 2008 to 2025 includes:

- Cognitive enhancement in scopolamine-induced amnesia paradigms (rat T-maze spontaneous alternation, novel object recognition)
- Partial reversal of MK-801-induced cognitive deficits (NMDA antagonist amnesia model)
- Reversal of beta-amyloid (A β 25-35) induced cognitive deficits in mouse object recognition (the A β 25-35 fragment is a research-grade truncated amyloid that produces cognitive deficits when injected intracerebroventricularly, modeling some aspects of Alzheimer disease) [3]
- Reversal of recognition memory deficits in aged rats with effect superior to galantamine in head-to-head comparisons
- Synergistic combination with memantine in aged rats producing superior cognitive benefits to monotherapy [4]
- Reversal of memory deficits in presenilin 1 and presenilin 2 conditional double knockout mice (a genetic Alzheimer disease model) by Hijazi et al. (2023)

[2]

- Neuroprotective effects in rat hippocampal excitotoxicity models
- Anti-inflammatory effects in rodent sepsis models

The cumulative preclinical literature is substantial and supports the alpha-7 nicotinic full agonist mechanism as a robust cognitive enhancement and neuroprotective concept in rodent models.

3.3 Absence of clinical development

PHA-543613 has not been advanced to human clinical trials. The reasons for the absence of clinical development have not been formally disclosed by Pfizer; candidate explanations from the contemporary literature include:

- Pfizer's broader alpha-7 nicotinic strategy may have focused on different lead compounds within the program
- The clinical development decisions in the broader alpha-7 receptor agonist class (encenicline Phase 3 termination, bradanicline Phase 2 confirmatory failure) may have created a less attractive commercial environment for additional alpha-7 candidates after approximately 2016
- Specific intellectual-property, regulatory, or commercial considerations that would preclude or disincentivize clinical development of PHA-543613 specifically

The compound has not been licensed to another commercial development entity for clinical work. The research-tool status is the principal contemporary positioning of PHA-543613.

3.4 Recent research expansion

Substantial research with PHA-543613 has continued in the 2020s, including:

- The Hijazi et al. (2023) demonstration of memory rescue in presenilin 1 and presenilin 2 conditional double knockout mice [2]
- The Kaur et al. (2025) demonstration of synergistic combination with memantine in aged rats [4]
- Additional preclinical work on combination with selected acetylcholinesterase inhibitors and other cognitive enhancement compounds

The continued research interest reflects the value of PHA-543613 as a tool compound for the alpha-7 nicotinic full agonist mechanism and the broader research strategy of combination pharmacology for Alzheimer disease.

4. Mechanism of Action

4.1 Alpha-7 nicotinic acetylcholine receptor full agonism

PHA-543613 binds the alpha-7 nicotinic receptor at the orthosteric (acetylcholine) site with a K_i of approximately 8 nanomolar at human alpha-7 expressed in HEK293 cells and at rat alpha-7 in brain membranes. Functional activity in *Xenopus* oocyte and cell-line expression systems is full-agonist intrinsic activity of approximately 80 to 90 percent of the maximum acetylcholine response, with functional EC_{50} in the low-micromolar range [1, 5]. The full-agonist intrinsic activity is comparable to bradanicline at the same receptor and substantially higher than the partial agonist class.

4.2 Selectivity profile

Selectivity over alpha-4-beta-2 is approximately 100-fold or greater; over alpha-3-beta-4 and alpha-3-beta-2, similar; over the muscle-type alpha-1 nicotinic receptor, approximately 1000-fold; over 5-HT₃ and GABA-A Cys-loop receptors, similar. The high selectivity profile is comparable to bradanicline and encenicline and substantially exceeds GTS-21.

4.3 Brain penetration

Brain-to-plasma ratio in rodent species is approximately 5 to 10 [1]. The high brain penetration is supported by the moderate lipophilicity of the quinuclidine-amide scaffold and by the absence of strong P-glycoprotein efflux. Brain exposure substantially exceeds plasma at oral or intraperitoneal doses, supporting central nervous system pharmacology at the doses studied in rodent behavioral models.

4.4 Downstream signaling

Activation of alpha-7 nicotinic receptors by PHA-543613 produces the standard alpha-7 receptor signaling consequences: calcium-dependent activation of calcium/calmodulin-dependent protein kinase II, ERK1/2 mitogen-activated protein kinase pathway activation, transcriptional upregulation of brain-derived neu-

retrophic factor and nerve growth factor, modulation of glutamate release from cortical and hippocampal presynaptic terminals, and activation of the cholinergic anti-inflammatory pathway in macrophages [6, 7].

4.5 Composite pharmacology

The composite pharmacology of PHA-543613 at the studied research doses produces brain concentrations consistent with substantial alpha-7 receptor occupancy and sustained channel activation. The full-agonist intrinsic activity supports near-maximum channel currents at occupied receptors, distinguishing the in vivo pharmacology from the partial-agonist class which produces partial channel currents at the same receptor occupancy.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption (rodent species)

PHA-543613 is well absorbed from the gastrointestinal tract in rodent species after oral administration. Oral bioavailability in rats is approximately 50 to 70 percent of the intravenous reference dose [1]. Time to peak plasma concentration is approximately 0.5 to 1 hour after oral dosing in fasted rats.

5.2 Distribution

Plasma protein binding has not been precisely characterized in published material. Volume of distribution and brain penetration are favorable; brain-to-plasma ratio is approximately 5 to 10 in rats and mice [1].

5.3 Metabolism

PHA-543613 is metabolized hepatically; the principal cytochrome P450 isoforms involved have not been fully characterized. The compound is not anticipated to be a major CYP2D6 substrate based on the chemical structure.

5.4 Elimination

Plasma elimination half-life in rats is approximately 1 to 3 hours, supporting twice-daily or three-times-daily dosing in rodent behavioral studies. The relatively short half-life is a notable feature of PHA-543613 versus the longer-acting encenicline (50 to 60 hours in humans). Half-life in humans has not been characterized owing to the absence of clinical development.

5.5 Routes of administration

Oral, subcutaneous, and intraperitoneal administration are all used in rodent pre-clinical studies. Specific dose ranges in published studies are: oral 0.3 to 10 milligrams per kilogram; subcutaneous 0.3 to 3 milligrams per kilogram; intraperitoneal 0.3 to 3 milligrams per kilogram. Intravenous administration has been used in pharmacokinetic studies.

6. Clinical Evidence Base

6.1 Absence of human clinical trials

PHA-543613 has not been advanced to human clinical trials. No published human pharmacokinetic or efficacy data are available.

6.2 Preclinical cognitive enhancement

The compound has been extensively characterized in rodent cognitive models:

- **Scopolamine-induced amnesia (rat T-maze and novel object recognition):** Dose-dependent reversal at 0.3 to 3 milligrams per kilogram [1]
- **MK-801-induced amnesia:** Partial reversal with inverted-U dose-response, suggesting that alpha-7 nicotinic activation contributes to but does not fully restore cognition in the NMDA antagonist amnesia model
- **Beta-amyloid (A β 25-35) induced cognitive deficit:** Reversal of object recognition memory impairment in mouse models at 1 to 3 milligrams per kilogram [3]
- **Aged-rat recognition memory:** Reversal of age-related decline at clinically translatable doses, with effect superior to galantamine in head-to-head comparisons
- **Presenilin 1/presenilin 2 conditional double knockout mice (familial Alzheimer disease model):** Memory rescue at 1 to 3 milligrams per kilogram [2]

6.3 Combination pharmacology

The synergistic combination of PHA-543613 with memantine in aged rats is the principal contemporary research finding for the compound. The Kaur et al. (2025) study demonstrated that PHA-543613 (1 milligram per kilogram subcutaneous) combined with memantine (5 milligrams per kilogram subcutaneous) produced cognitive benefits superior to either compound as monotherapy at the same doses

[4]. The synergy supports a research-clinical hypothesis that combination pharmacology of alpha-7 nicotinic full agonism with NMDA receptor antagonism may produce superior cognitive benefits to monotherapy.

6.4 Other preclinical applications

- Neuroprotection in rodent excitotoxicity models
- Anti-inflammatory effects in rodent sepsis models
- Sensorimotor gating in rodent prepulse inhibition models (relevance to schizophrenia)

7. Reported Research Dose Ranges

7.1 Approved doses

None. PHA-543613 has not been advanced to clinical development.

7.2 Investigational doses (preclinical)

For research applications using PHA-543613 as an alpha-7 nicotinic receptor full agonist tool compound:

- **In vitro concentrations:** 0.1 to 10 micromolar in heterologous expression systems and primary neuronal culture
- **Rodent oral doses:** 0.3 to 10 milligrams per kilogram, typically as twice-daily administration
- **Rodent subcutaneous doses:** 0.3 to 3 milligrams per kilogram, typically as single-dose pre-task administration
- **Rodent intraperitoneal doses:** 0.3 to 3 milligrams per kilogram

The dose ranges have been validated across multiple independent laboratories and across multiple cognitive behavioral paradigms.

8. Sourcing and Quality Verification

PHA-543613 has not been advanced to clinical development and is not available as a pharmaceutical-grade preparation. Research-grade PHA-543613 (greater than 98 percent purity) is widely supplied by multiple chemical suppliers (Sigma-Aldrich, Tocris/Bio-Techne, Cayman Chemical, MedChemExpress, MedKoo Biosciences, BocSci, Santa Cruz Biotechnology, Merck Millipore/Calbiochem, others) at moderate prices, typically \$150 to \$400 per gram of the hydrochloride or dihydrochloride salt 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 (272.14 ± 0.01 for the protonated free base $[M+H]^+$)
- Chiral HPLC or polarimetry to confirm enantiomeric purity (greater than 99 percent enantiomeric excess of the (R)-enantiomer)
- Karl Fischer or loss-on-drying analysis for residual water in the salt form
- Residual solvent analysis

9. Reconstitution and Handling

PHA-543613 hydrochloride and dihydrochloride are freely soluble in water. For research applications, the compound is supplied as a crystalline powder and is reconstituted as needed. Stock solutions are typically prepared at 10 to 50 millimolar concentrations in water or in dimethyl sulfoxide for in vitro work. For in vivo work, aqueous solutions in normal saline at 0.1 to 1 milligrams per milliliter are appropriate for the typical rodent dosing.

Refrigerated storage of the solid is appropriate; the compound is stable at room temperature in dry conditions and at refrigerated conditions in solution for at least 30 days. The compound is photo-stable under typical laboratory lighting.

10. Stack Interaction Considerations

PHA-543613 has been extensively studied in combination pharmacology. Investigators should consider:

Memantine: Synergistic combination demonstrated in aged rats (Kaur et al. 2025) [4]. Combination produces cognitive benefits superior to monotherapy at clinically translatable doses. The combination is supported by complementary mechanisms (alpha-7 nicotinic activation augments cholinergic signaling; memantine NMDA antagonism reduces excitotoxic glutamatergic signaling). The combination is the principal contemporary research-clinical hypothesis for combination pharmacology in Alzheimer disease.

Acetylcholinesterase inhibitors: Concurrent administration with donepezil, galantamine, or rivastigmine produces additive cholinergic activity. Galantamine (which has its own modest alpha-7 nicotinic positive allosteric modulator activity in addition to the acetylcholinesterase inhibition) is a particularly interesting combination partner.

Other alpha-7 nicotinic agonists or PAMs: Concurrent administration with other alpha-7 candidates (tropisetron, encenicline, bradanicline, GTS-21, AVL-3288) produces additive effects at the alpha-7 receptor. Combination with AVL-3288 (Type I PAM) is theoretically attractive: PHA-543613 provides direct full-agonist activation; AVL-3288 augments endogenous acetylcholine signaling at the same receptor through allosteric modulation. The combination could produce greater functional response than either compound alone at lower individual-component doses.

Beta-amyloid: PHA-543613 reverses beta-amyloid-induced cognitive deficits, suggesting possible mechanism of disease modification beyond symptomatic cognitive enhancement. The compound has not been characterized as binding to amyloid beta directly (in contrast to tropisetron, which binds to APP ectodomain).

11. Adverse Events and Safety

11.1 Preclinical safety

PHA-543613 has been characterized in rodent toxicology studies. The compound is well tolerated at the studied behavioral pharmacology doses (0.3 to 10 milligrams per kilogram in rats and mice). No specific toxicities have been reported in published material at the doses used in cognitive behavioral studies.

11.2 Absence of human safety data

The compound has not been advanced to human clinical trials; no human safety data are available.

11.3 Class considerations

The alpha-7 nicotinic receptor agonist class has shown a heterogeneous safety profile across compounds. Encenicline produced severe gastrointestinal toxicity at Phase 3 clinical doses (the September 2015 FDA clinical hold trigger); bradanicline did not produce comparable toxicity at Phase 2 clinical doses; tropisetron has been used clinically at registered doses without comparable toxicity. The mechanism of the differential class safety is incompletely characterized. Whether PHA-543613, if advanced to clinical development, would produce encenicline-class gastrointestinal toxicity, bradanicline-class acceptable safety, or some intermediate profile cannot be predicted from preclinical data alone.

12. Comparable Compounds Assessment

Five alpha-7 nicotinic acetylcholine receptor candidates are evaluated against PHA-543613 on the five competency standards.

12.1 Tropisetron

Mechanism: Multi-target ligand (5-HT₃ antagonist plus alpha-7 partial agonist plus APP ectodomain binding). Alpha-7 intrinsic activity 25-40 percent.

Novelty: Moderate.

Effect size: Modest in cognitive endpoints; strong in fibromyalgia.

Promising potential: Moderate. Registered antiemetic and fibromyalgia indications.

Side-effect profile: Well characterized.

Overall validation: Moderate to high.

Comparison to PHA-543613: Tropisetron and PHA-543613 are highly distinct in clinical positioning (tropisetron registered, PHA-543613 preclinical only), in alpha-7 intrinsic activity (tropisetron partial, PHA-543613 full), and in pharmacological breadth (tropisetron multi-target, PHA-543613 selective alpha-7). PHA-543613 serves as a fundamental research tool; tropisetron has clinical applications.

12.2 Encenicline

Mechanism: Selective alpha-7 partial agonist (60-70 percent intrinsic activity).

Novelty: Moderate.

Effect size: Phase 2 cognitive signals; Phase 3 missed primary endpoints.

Promising potential: Low. Development terminated.

Side-effect profile: Phase 3 severe gastrointestinal toxicity.

Overall validation: Moderate. Phase 3 advancement.

Comparison to PHA-543613: Encenicline and PHA-543613 are structurally related quinuclidine-amides differing in the aryl heterocycle and intrinsic activity. PHA-543613 has higher alpha-7 functional intrinsic activity than encenicline. Encenicline's Phase 3 termination is the principal scientific event for the alpha-7 nicotinic agonist class; PHA-543613 was not advanced to clinical trials and therefore did not produce a clinical readout.

12.3 Bradanicline

Mechanism: Selective alpha-7 full agonist (80-90 percent intrinsic activity, comparable to PHA-543613).

Novelty: Low.

Effect size: Phase 2 mixed.

Promising potential: Low for cognition; ongoing for Tourette syndrome.

Side-effect profile: Well tolerated.

Overall validation: Low to moderate.

Comparison to PHA-543613: Bradanicline and PHA-543613 are the closest comparators in the panel: both are quinuclidine-amide selective alpha-7 full agonists with comparable functional intrinsic activity. The principal differentiator is clinical development (bradanicline Phase 2; PHA-543613 preclinical only). The bradanicline Phase 2 confirmatory failure on cognitive endpoints provides a partial preview of what PHA-543613 clinical development might encounter at similar doses; the synergistic combination of PHA-543613 with memantine, demonstrated in preclinical work, has not been tested with bradanicline in similar preclinical paradigms.

12.4 AVL-3288

Mechanism: Type I PAM at alpha-7 (allosteric, mechanistically distinct from PHA-543613).

Novelty: High.

Effect size: Phase 1b modest exploratory.

Promising potential: Moderate. Novel mechanism.

Side-effect profile: Phase 1 favorable.

Overall validation: Low to moderate.

Comparison to PHA-543613: AVL-3288 (allosteric PAM) and PHA-543613 (orthosteric full agonist) are mechanistically complementary for the alpha-7 receptor target. Combination of the two would test whether PAM augmentation of full-agonist signaling produces additional benefit beyond either alone. The combination has not been characterized in published research and is a productive line of investigation for fundamental alpha-7 nicotinic mechanism studies.

12.5 GTS-21 (DMXBA)

Mechanism: Orthosteric alpha-7 partial agonist (30-50 percent intrinsic activity); also alpha-4-beta-2 cross-reactivity.

Novelty: Low.

Effect size: Modest in early Phase 2; non-significant in larger Phase 2.

Promising potential: Low.

Side-effect profile: Well tolerated.

Overall validation: Moderate. Long clinical history.

Comparison to PHA-543613: GTS-21 is the historical reference compound that predates PHA-543613. GTS-21's lower selectivity (alpha-4-beta-2 cross-reactivity) and lower intrinsic activity (partial agonist) are the principal differentiators from PHA-543613. The mixed clinical results of GTS-21 do not provide direct prediction for PHA-543613 outcomes; PHA-543613 has not been advanced to clinical trials.

12.6 Comparator summary

PHA-543613 is the principal high-potency selective alpha-7 nicotinic full agonist in current research use as a tool compound. The compound's preclinical pharmacology is extensive and demonstrates robust cognitive enhancement effects in rodent models, particularly in beta-amyloid-induced cognitive deficits, in aged-rat recognition memory, and in the Hijazi et al. (2023) presenilin double knockout familial

Alzheimer disease model. The synergistic combination with memantine in aged rats is the principal contemporary research-clinical hypothesis for combination pharmacology in Alzheimer disease and supports continued investigation of the alpha-7 nicotinic mechanism in conjunction with NMDA receptor antagonism. PHA-543613 has not been advanced to human clinical trials; its principal contribution to the alpha-7 nicotinic receptor agonist field is as a research tool and as the most extensively characterized selective alpha-7 full agonist for fundamental and combination-pharmacology studies. The encenicline Phase 3 termination and the bradanicline Phase 2 confirmatory failure have made the alpha-7 orthosteric full agonist class a less attractive standalone clinical-development strategy; PHA-543613's continued utility lies in research applications and in supporting the combination-pharmacology hypothesis that may yet produce a successful clinical strategy through partnership with NMDA antagonism, acetylcholinesterase inhibition, or alpha-7 PAM modulation.

13. References

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