

RESEARCH MONOGRAPH . COMPOUND PROFILE

TAK-653 (NBI-1065845)

A low-impairment AMPA receptor potentiator advanced through Phase 2 in treatment-resistant depression by Takeda and Neurocrine, distinguished from earlier ampakines by minimal receptor desensitization.

DOCUMENT	KDC-MN-1327
ISSUED	2026-05-10
REVISION	1.0
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COMPOUND CLASS	Non-desensitizing AMPA receptor positive allosteric modulator

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ABSTRACT

TAK-653 (also designated NBI-1065845; emraclidine has the same NBI prefix, distinct compound; CAS 1626387-80-1; molecular formula C₁₉H₂₁F₃N₄O₃S; molecular weight 442.46) is a small-molecule non-desensitizing positive allosteric modulator of AMPA-class glutamate receptors developed by Takeda and out-licensed to Neurocrine Biosciences for clinical development in treatment-resistant depression. The compound was selected from a structural class designed to achieve allosteric AMPA potentiation without the receptor desensitization characteristic of earlier ampakines (CX-516, CX-546), which limited potency and produced cognitive impairment at higher doses. TAK-653 binds at an allosteric site distinct from the glutamate-binding domain, slowing AMPA receptor deactivation and increasing the integrated current produced by physiological glutamate transients without persistent receptor activation in the absence of glutamate; this profile produces synaptic potentiation under physiological signaling without the off-target excitotoxicity concerns of full agonists or strongly desensitizing modulators. Phase 1 imaging studies report dose-dependent BOLD signal modulation in cortical regions consistent with AMPA potentiation. The compound was advanced through Phase 2 in treatment-resistant depression by Neurocrine; published Phase 2a results from 2023 reported numerical separation from placebo on Hamilton Depression Rating Scale change at week 4 with improvement maintained through week 8, with a favorable safety profile (no seizures, no notable sedation, no dose-limiting cognitive impairment). The compound has not yet received regulatory approval as of the most recent monograph revision.

Distinguishing features versus other AMPA modulators are the absence of receptor desensitization, the minimal impairment profile at antidepressant doses, and the rapid-onset depression treatment positioning targeting the same therapeutic niche as ketamine and esketamine.

1. Compound Identification

TAK-653 (NBI-1065845) is described as non-desensitizing ampa receptor positive allosteric modulator. A low-impairment AMPA receptor potentiator advanced through Phase 2 in treatment-resistant depression by Takeda and Neurocrine, distinguished from earlier ampakines by minimal receptor desensitization.

1.1 Class summary

Non-desensitizing AMPA receptor positive allosteric modulator

1.2 Subtitle

A low-impairment AMPA receptor potentiator advanced through Phase 2 in treatment-resistant depression by Takeda and Neurocrine, distinguished from earlier ampakines by minimal receptor desensitization.

2. Abstract

TAK-653 (also designated NBI-1065845; emraclidine has the same NBI prefix, distinct compound; CAS 1626387-80-1; molecular formula C₁₉H₂₁F₃N₄O₃S; molecular weight 442.46) is a small-molecule non-desensitizing positive allosteric modulator of AMPA-class glutamate receptors developed by Takeda and out-licensed to Neurocrine Biosciences for clinical development in treatment-resistant depression. The compound was selected from a structural class designed to achieve allosteric AMPA potentiation without the receptor desensitization characteristic of earlier ampakines (CX-516, CX-546), which limited potency and produced cognitive impairment at higher doses. TAK-653 binds at an allosteric site distinct from the glutamate-binding domain, slowing AMPA receptor deactivation and increasing the integrated current produced by physiological glutamate transients without persistent receptor activation in the absence of glutamate; this profile produces synaptic potentiation under physiological signaling without the off-target excitotoxicity concerns of full agonists or strongly desensitizing modulators. Phase 1 imaging studies report dose-dependent BOLD signal modulation in cortical regions consistent with AMPA potentiation. The compound was advanced through Phase 2 in treatment-resistant depression by Neurocrine; published Phase 2a results from 2023 reported numerical separation from placebo on Hamilton Depression Rating Scale change at week 4 with improvement maintained through week 8, with a favorable safety profile (no seizures, no notable sedation, no dose-limiting cognitive impairment). The compound has not yet received regulatory approval as of the most recent monograph revision. Distinguishing features versus other AMPA modulators are the absence of receptor desensitization, the minimal impairment profile at antidepressant doses, and the rapid-onset depression treatment positioning targeting the same therapeutic niche as ketamine and esketamine.

3. Mechanism of Action

Allosteric AMPA receptor potentiation at a non-desensitizing binding site. Slows deactivation of physiological AMPA currents without persistent receptor activation. Synaptic potentiation downstream of glutamate signaling.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

Phase 2 dosing 6 mg and 35 mg per oral administration once daily. Research literature reports up to 70 mg single dose.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Suzuki M, et al. TAK-653: a novel AMPA receptor potentiator with antidepressant-like activity. J Pharmacol Exp Ther 2021.
2. Hara H, et al. Pharmacological characterization of TAK-653, a non-desensitizing AMPA potentiator. Neuropharmacology 2021.
3. Neurocrine Biosciences. Phase 2a study of NBI-1065845 in treatment-resistant depression. Press release 2023.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.