# Pharmacological characterization of novel lead 5-HT2A receptor agonists with non-hallucinogenic potential and translational antidepressant-like profiles

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## INTRODUCTION

### TREATMENT-RESISTANT DEPRESSION (TRD)

- Impacts approximately 30% of patients with major depressive disorder.[1]
- Currently, there are limited FDA-approved treatment options.

### PSYCHEDELICS

- Chemically diverse group of 5-HT2AR agonists, such as psilocybin and LSD.
- Clinically and preclinically, they show **rapid** and **lasting antidepressant efficacy** following single dose.[2,3]
- Preclinically, antidepressant mechanisms may include promotion of **neuroplasticity.**[4, 5]

### CHALLENGES

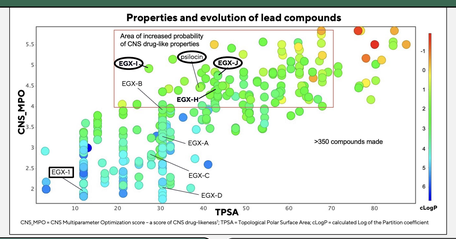
- **Hallucinatory effects** of psychedelics limit accessibility of treatment and increase health care costs.
- Concomitant **agonism of 5-HT2BR** by non-selective 5-HT2R agonists may lead to valvulopathy risk with repeated use.[6]

## APPROACH

### GOAL

Discover novel, selective, non-hallucinogenic 5-HT2AR agonists for TRD

AI/ML-driven drug design + Medicinal chemistry (SAR)




1) TARGET PHARMACOLOGY

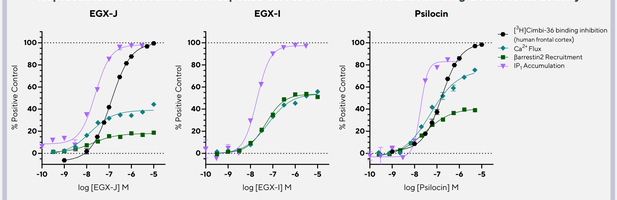
2) NON-HALLUCINOGENIC POTENTIAL

3) ANTIDEPRESSANT-LIKE ACTIVITY

4) FUNCTIONAL NEUROPLASTICITY

## 1) TARGET PHARMACOLOGY

### EGX-J and EGX-I are high affinity, potent 5-HT2AR agonists with differentiated signaling versus psilocin



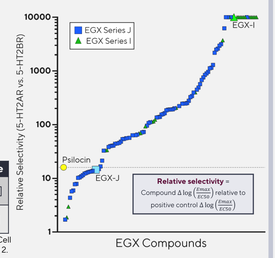

**Human 5-HT2AR *in vitro* average data**

| Assay – Readout | EGX-J | | EGX-I | Psilocin | |
|---|---|---|---|---|---|
| [³H]Cimbi-36 Binding Inhibition – Ki \| IC50 (nM) | 59 | 133 | No data | 71 | 159 |
| $Ca^{2+}$ Flux – $EC_{50}$ (nM) [$\%E_{max}$] | 14.1 [39] | | 60.9 [54] | 51.8 [75] | |
| βarrestin2 Recruitment – $EC_{50}$ (nM) [$\%E_{max}$] | 18.8 [18] | | 48.2 [54] | 27.8 [41] | |
| $IP_1$ Accumulation – $EC_{50}$ (nM) [$\%E_{max}$] | 26.5 [99] | | 19.4 [98] | 18.2 [83] | |

Human frontal cortex tissue binding: Homogenates incubated with 0.053nM [³H]Cimbi-36 and test compound for 90-mins. Inhibition of membrane-bound radioactivity was quantified via liquid scintillation. Figure depicts ΔB(nM) from vehicle, relative to 1μM 25CN-NBOH, table contains data averaged from N=4.
$Ca^{2+}$ flux FLIPR: US02-h5-HT2AR cells incubated for 2-mins with compound. Cytosolic $Ca^{2+}$ was measured in real-time using a calcium-sensitive fluorescent dye. Figure shows ΔRFU %1μM 5-HT, table contains data averaged from N=2-3.
Barrestin2 Recruitment: U2OS cells expressing ProlinkTM tagged human 5-HT2ARs incubated with compound for 30-mins. Barrestin2-GPCR interactions produce fluorescence. Figure shows ΔRFU %1μM 5-HT, table contains data from N=1.
Inositol monophosphate (IP1) accumulation: CHOK1-h5-HT2AR cells were incubated for 1hr with test compound & LiCl (blocks $IP_1$ degradation). Accumulated $IP_1$ was quantified using HTRF. Figure shows ΔRFU %1μM α-Me-5-HT, table contains data averaged from N=1-3.

### At 5-HT2BR, EGX-J shows similar agonism to psilocin, whereas EGX-I is not an agonist

- EGX-J is a 5- to 100-fold less potent agonist than reference valvulopathogen, pergolide, in human 5-HT2BR *in vitro* assays.
- Novel analogs of EGX-J & EGX-I were made, with compounds in both series exhibiting ≥10,000-fold agonist selectivity for 5-HT2AR over 5-HT2BR.

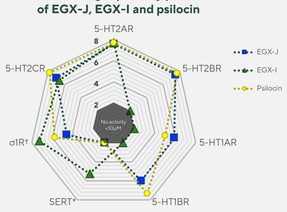



**Human 5-HT2BR *in vitro* functional activity data**

| Assay – Readout | EGX-J | EGX-I | Psilocin | Pergolide |
|---|---|---|---|---|
| $IP_1$ Accumulation $EC_{50}$ (nM) [$\%E_{max}$] | 29.3 [99] | >10,000 | 21.6 [73] | 0.30 [101] |
| CHOK1 proliferation $EC_{50}$ (nM) [$\%E_{max}$] | 43.9 [35] | >10,000 | 29.8 [15] | 7.92 [63] |

Proliferation assay: CHOK1-h5-HT2BR cells are incubated with compound for 48hr. Cell count is quantified with XTT luminescence. Figure shows ΔluminescencE %1μM 5-HT, N = 2.

### EGX-J and EGX-I show distinct profiles at additional serotonergic and plasticity-associated targets



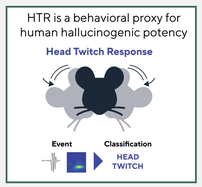

- EGX-J & EGX-I show psilocin-like 5-HT2CR agonism, which may suggest potential in substance use disorders and low addiction liability.[9]
- EGX-J's 5-HT1AR & 5-HT1BR agonism may contribute to antidepressant and anxiolytic effects.[10,11]
- EGX-I's high affinity interaction with σ1R may promote neuroplasticity and contribute to antidepressant efficacy.[12,13]

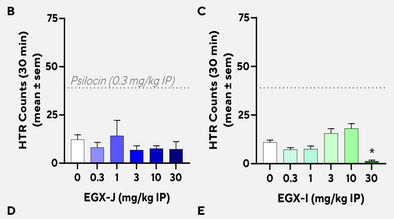
pEC50 unless otherwise stated; *pIC50, †pKi (binding affinity).
Assays: $IP_1$ = 5-HT2AR, 5-HT2BR, 5-HT2CR; GTPγS = 5-HT1AR; 5-HT1BR; monoamine uptake inhibition = SERT; [³H]Pentazocine(+) binding competition = σ1R. Psilocin σ1R data from Jain et al., 2025[14]

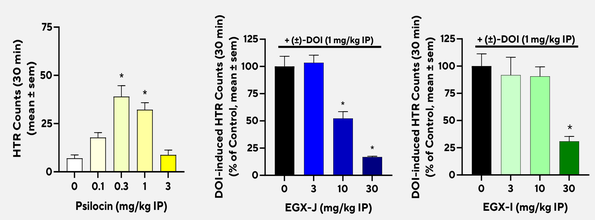
## 2) NON-HALLUCINOGENIC POTENTIAL

### EGX-J and EGX-I do not induce Head Twitch Response (HTR) and attenuate DOI-induced HTR

HTR is a behavioral proxy for human hallucinogenic potency



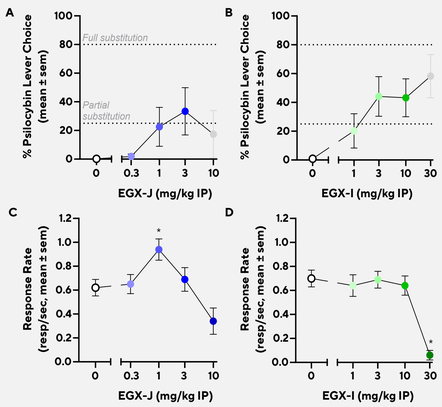




Male C57BL/6 mice implanted with cranium-attached magnets were administered test compounds, placed individually in a glass cylinder surrounded by a magnetometer, and the HTR was measured for 30 min. Psilocin, a known hallucinogen, significantly induced HTR (A). Neither EGX-J (B) nor EGX-I (C) up to 30 mg/kg induced HTR, suggesting a lack of hallucinogenic potential. Moreover, compound pretreatment reduced HTR induced by a known hallucinogen, DOI, in a dose-dependent manner (D, E). These data are indicative of 5-HT2A receptor interactions *in vivo*. n=4–12 mice/condition.

### EGX-J and EGX-I do not fully substitute for psilocybin's discriminative stimulus effects

Psilocybin-appropriate responding (Left lever press rewarded by food)

Saline-appropriate responding (Right lever press rewarded by food)

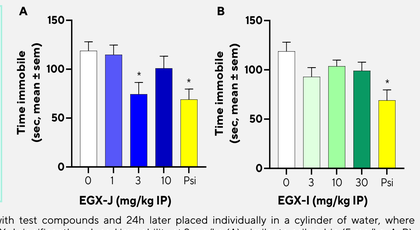



Food-restricted male SD rats trained to discriminate psilocybin (0.5 mg/kg SC) were administered EGX compounds and placed individually in operant chambers. During test sessions, every 10th response on either lever resulted in food pellet delivery. The percentage of psilocybin-appropriate lever presses was assessed for 30 min or until 50 pellets were delivered. Neither EGX-J (A) nor EGX-I (B) fully substituted for psilocybin's discriminative stimulus effects, suggesting a lack of hallucinogen-like subjective effects. Compounds were tested up to behaviorally-active doses (C, D). n=5–15 rats/condition.

## 3) ANTIDEPRESSANT-LIKE ACTIVITY

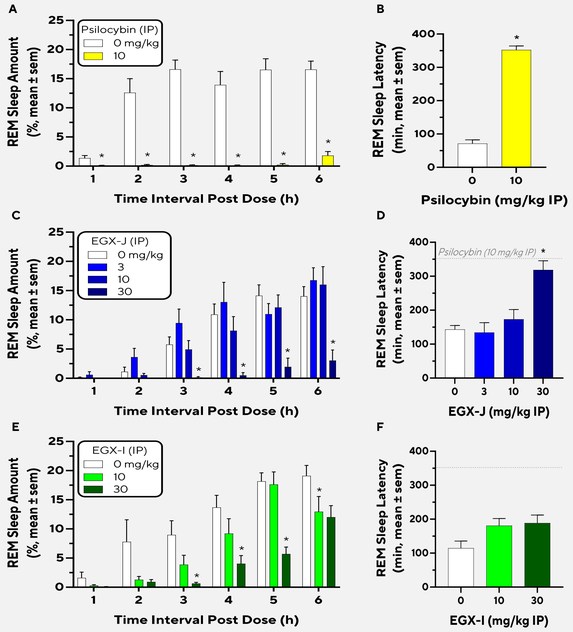
### EGX-J attenuates immobility in the mouse Forced Swim Test (FST) at 24h post single administration

FST measures immobility behavior observed following an inability to escape from a cylinder of water




Male C57BL/6 mice were injected with test compounds and 24h later placed individually in a cylinder of water, where immobility was analyzed for 4 min. EGX-J significantly reduced immobility at 3 mg/kg (A), similar to psilocybin (5 mg/kg, A, B), indicative of persistent antidepressant-like effects. In contrast, EGX-I (3-30 mg/kg) did not significantly reduce immobility 24h after dosing (B). n=14 mice/condition.

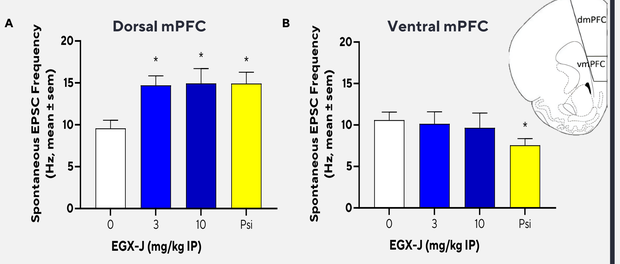
### EGX-J and EGX-I show translational antidepressant-like REM sleep suppression in Wistar Kyoto rats




Translational antidepressant potential was tested in male Wistar Kyoto rats, a TRD model that exhibits depression-like phenotypes, including increased rapid eye movement (REM) sleep. REM sleep was measured by chronically implanted EEG and EMG electrodes for 6 hours following administration of compounds. EGX-J and EGX-I (10-30 mg/kg) suppressed REM sleep by significantly reducing REM sleep amount (C, E), mimicking the effects of psilocybin (A). Additionally, EGX-J significantly increased REM sleep latency (D), similar to psilocybin (B). n=8 rats/condition.

## 4) FUNCTIONAL NEUROPLASTICITY

### EGX-J increases mPFC pyramidal neuron activity ex vivo in rats at 24h post single administration




Female SD rats were injected with test compounds, sacrificed 24h later and brain slices were prepared for electrophysiological recording of layer V medial prefrontal cortex (mPFC) pyramidal neuron activity. EGX-J significantly increased spontaneous excitatory post synaptic currents (EPSC) in dorsal (A) but not ventral (B) mPFC, distinct from psilocybin (3 mg/kg), which significantly increased EPSCs in dorsal (A) and decreased EPSCs in ventral mPFC (B). These data indicate persistent changes in mPFC synaptic activity, which may be relevant to lasting antidepressant-like behavioral effects. n=20-35 neurons/condition.

## SUMMARY

**EGX-J and EGX-I are promising lead compounds for discovery of novel non-hallucinogenic 5-HT2AR agonist antidepressants that may exhibit durable efficacy and potential for flexible dosing options in a broad patient population.**

In vitro and in vivo data indicate that EGX-J and EGX-I exhibit pharmacological profiles that are distinct but overlapping with each other and psilocybin/psilocin.

In vitro, EGX-J and EGX-I are potent 5-HT2AR agonists with EGX-I showing complete selectivity over 5-HT2BR, suggesting improved cardiac safety. Both compounds interact with additional depression and plasticity-associated targets.

In vivo, EGX-J and EGX-I demonstrate non-hallucinogenic potential and translational antidepressant-like activity, similar to psilocybin. EGX-J shows psilocybin-like persistent increases in dorsal mPFC excitatory neurotransmission that may be relevant to lasting antidepressant-like behavioral effects.[3,5]

### Next Steps

Ongoing lead optimization continues in an effort to identify promising development candidates with high 5-HT2AR selectivity and oral bioavailability, while maintaining a non-hallucinogenic profile and translational antidepressant-like efficacy.

For informational purposes only. Not an offer or solicitation of an offer to purchase or sell securities.

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1) Voineskos, D., et al. (2020). Neuropsych Dis Treat, 16, 221–234. 2). Goodwin, G. M., et al. (2022). N Engl J Med, 387, 1637–1648. 3). Hibicke, M., et al. (2020). ACS Chem Neurosci, 11, 864–871. 4). Zhao, X., et al. (2024). J Psychopharmacol, 38(5), 489–499. 5). Shao, L. X., et al. (2021). Neuron, 109(16), 2535–2544. 6). Papoian, T., et al. (2017). Toxicologic Pathology, 45(3), 381–388. 7). Wager, T. T., et al. (2016). ACS Chem Neurosci, 7(6), 767–775. 8). Ubhayarathna, M., et al. (2023). BJP, 181(22), 4414–4429. 9). Canal, C. E., & Murnane, K. S. (2017). J Psychopharmacol, 31(1), 127–143. 10). Kaufman, J., et al. (2016). Eur Neuropsychopharmacol, 26(3), 397–410. 11). Fleury, J., & Nautiyal, K. M. (2025). bioRxiv preprint. 12). Morales-Garcia, J. A., et al. (2020). Translational Psychiatry, 10, 311. 13). Ma, H., et al. (2024). Acta Pharmacol Sin, 45(4), 704–713. 14). Jain, M. K., et al. (2025). Neuron, S0896-6273(25)00470-2.