# Cognitive effects of individual enantiomers of LB-102

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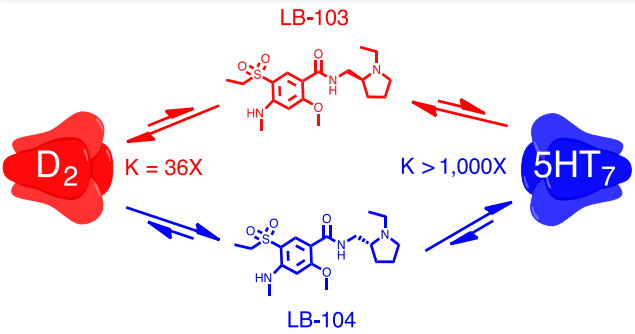
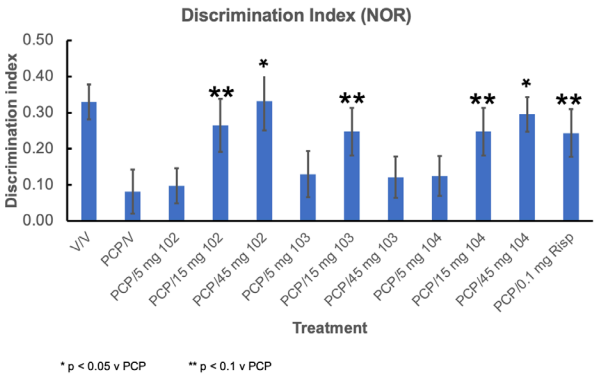
**Introduction:** LB-102 is a novel, racemic, benzamide known to inhibit both dopamine $D_{2/3}$, and 5-$HT_7$ receptors designed to treat schizophrenia. Modulation of 5-$HT_7$ has been implicated as affecting cognition and overall well-being and may contribute to improvements in bipolar depression and cognitive impairment associated with schizophrenia. Previous work with LB-102[1] demonstrated that the *R* enantiomer (LB-104) showed a preference for 5-$HT_7$ binding ($K_i$ v. $D_{2/3}$ = 14.4 nM, $K_i$ v. 5-$HT_7$ = 15.6 nM) over the *S* enantiomer (LB-103) binding ($K_i$ v. $D_{2/3}$ = 0.4 nM, $K_i$ v. 5-$HT_7$ = >1000 nM). To establish if the differential binding profiles of the individual enantiomers of LB-102 had effects on behavior in rats, two common tests of cognition/negative symptoms, Novel Object Recognition (NOR) and Social Interaction (SI) were carried out in the sub-chronic phencyclidine model (scPCP) with each enantiomer along with the racemic mixture.



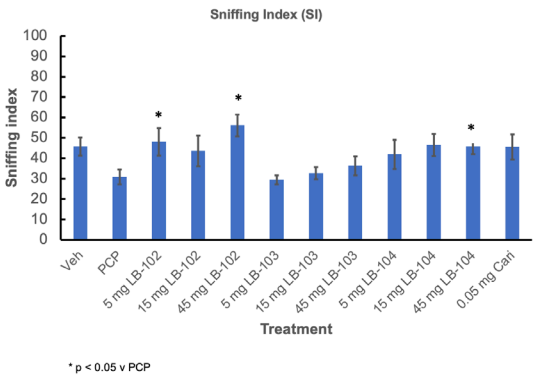

- **NOR** Object exploration data from a scPCP NOR study in rats (2 mg/kg i.p. twice daily followed by 7 days drug free (n = 12/grp) measured 60-180 min post drug. Rats were dosed with 5, 15, or 45 mg/kg LB-102, LB-103, or LB-104 PO.
- **SI** Sniffing index data from a sub-chronic PCP SI study in rats (2 mg/kg i.p. twice daily followed by 7 days drug free (n = 12/grp) measured 60-180 min post drug. Rats were dosed with 5, 15, or 45 mg/kg LB-102, LB-103, or LB-104 PO.
- **Plasma PK in rats:** PK samples were taken from rats (n = 3/grp) at 0.0416, 0.083, 0.166, 0.333, 0.5, 1, 2, 4, 8 and 16 hours after oral dosing and analyzed by HPLC to determine if $T_{max}$ for either enantiomer was different from the other.

## Results:



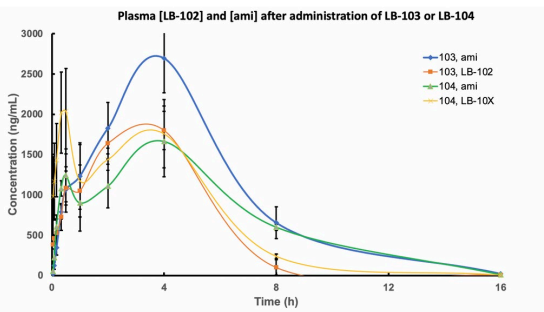

* p < 0.05 v PCP ** p < 0.1 v PCP

- 45 mg/kg LB-102 and LB-104 had p < 0.05 v 45 mg/kg LB-103




* p < 0.05 v PCP

- LB-102 = LB-104 at all doses (p > 0.1), LB-104 > LB-103 (p < 0.05) at 15 and 45 mg/kg
- LB-102 > LB-103 at all doses (p < 0.05) at 5 and 45 mg/kg (p < 0.1) at 15 mg/kg




- Plasma PK profile LB-102 and amisulpride in rats (n = 3) after administration of a single 100 mg/kg oral dose of either LB-103 or LB-104

- In two models of cognition LB-102 (racemic) was equivalent to LB-104 (*R* enantiomer) in the scPCP model
- LB-102 and LB-104 were superior to LB-103 (*S* enantiomer) at certain doses
- These results suggest that the increased affinity of LB-104 for 5-$HT_7$ manifests in behavioral assays but that the magnitude is subtle enough that 2X greater $K_i$ is not noticeable
- A relative decrease in dopamine binding with LB-104 may improve tolerability, though interrogating safety in animal studies can be challenging

**Disclosures**
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1 V. Grattan, A. R. Vaino, Z. Prensky, and M. S. Hixon, "Antipsychotic benzamides amisulpride and LB-102 display polypharmacy as racemates, S enantiomers engage receptors $D_2$ and $D_3$, while R enantiomers engage 5-$HT_7$", ACS *Omega,* **2019**, *4*, 14151–14154