LB-102, Potential Schizophrenia Treatment, Displays Polypharmacology as a Racemate—*S* Enantiomer Binds D_2 Receptors and *R* Binds 5-HT_7Receptor (P.283)

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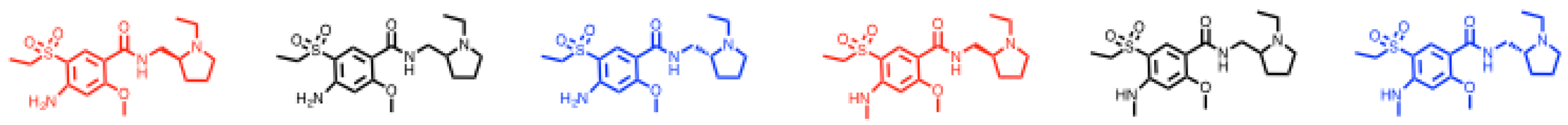
pharmaceuticals

gmatic approaches to drug discovery challenges

Introduction: Racemates are considered 2 drugs at a fixed dose combination. The EMA and FDA have a strong preference for new drugs to be developed as single enantiomers to avoid the risk of dosing a distomer (inactive enantiomer) along with its eutomer (active enantiomer) unless there is a compelling reason to use the racemic mixture. Despite an abundance of agents available for treating schizophrenia, the majority of patients respond insufficiently, frequently resulting in modest improvements of symptoms, functioning, and quality of life. Dose limiting adverse events, including peripheral off-target engagement, limit the efficacy of benzamide antipsychotics, such as amisulpride, which have poor blood-brain barrier (BBB) permeability.[1] LB Pharmaceuticals designed LB-102 to improve BBB permeability of highly polar benzamides like amisulpride. LB-102 is an *N*-methylated analogue of amisulpride (a racemic compound), while LB-103 and LB-104 are the *N*-methylated *S* and *R* enantiomers, respectively. The *S* enantiomer of amisulpride is known to be the driver of amisulpride binding to dopamine receptors:[2] binding of its enantiomers to the 5-HT_7 receptor has never been reported.

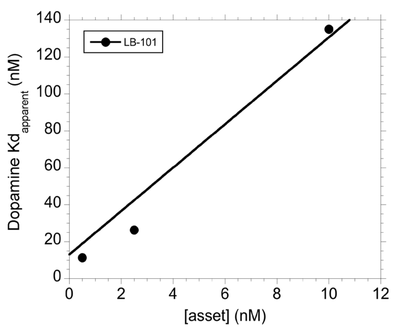
Compounds Examined



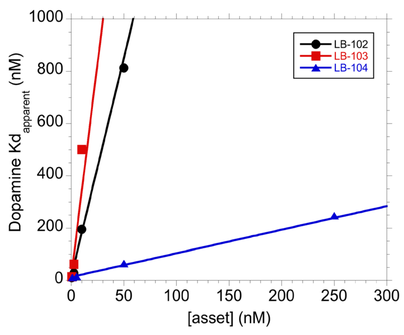
- Benzamides are dosed as racemates, antipsychotic efficacy is driven by D_2 antagonism
- $D_{2/3}$ receptors have a greater affinity for *S* than *R* enantiomers
- Amisulpride known to bind 5-HT_7 receptor; thought to be responsible for anti-depressant and anxiolytic properties[4]
- Binding of individual benzamide receptors to 5-HT_7 has not previously been reported

Results:

Dopamine D_2 inhibition

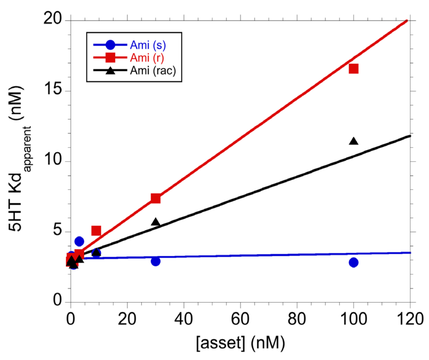


LB-101 K_i = 1.1 ± 0.12 nM

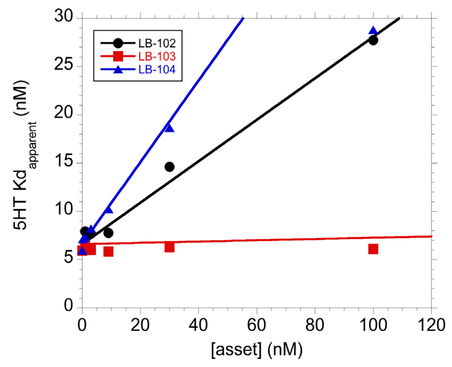


LB-102 K_i = 0.82 ± 0.02 nM
LB-103 K_i = 0.4 ± 0.04 nM
LB-104 K_i = 14.4 ± 2.2 nM

5-HT_7 inhibition

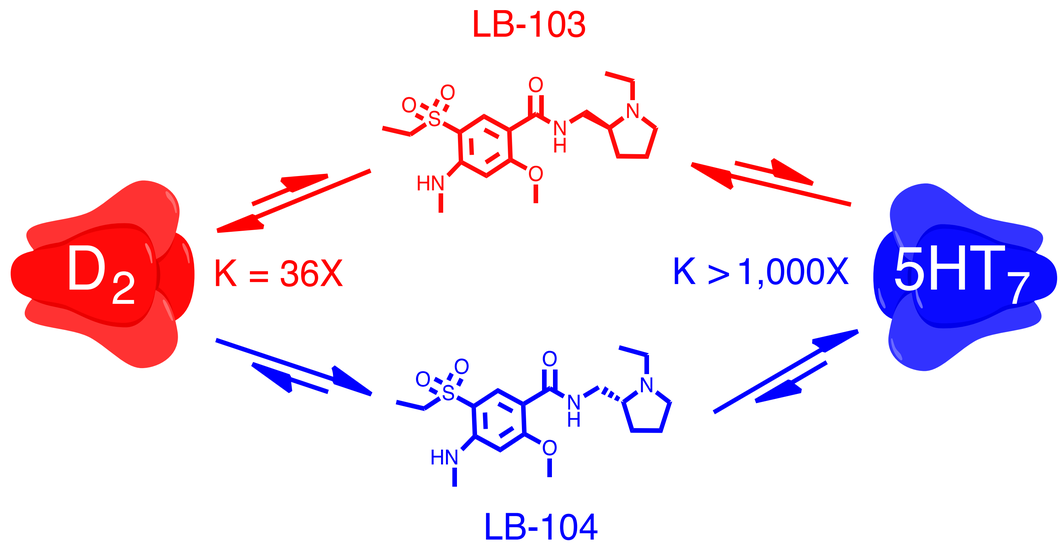


Rac amisulpride K_i = 44 nM
S amisulpride K_i = 900 ± 1300 nM
R amisulpride K_i = 21.8 ± 1.5 nM



LB-102 K_i = 31 ± 1.0 nM
LB-103 K_i > 1000 nM
LB-104 K_i = 15.6 ± 0.9 nM

- In rodent SCZ behavioural models (AIC, LMA, and NOR)[3] activity of LB-102 ~ LB-103
- LB-103 binds D_2, LB-104 binds 5-HT_7



- Same result with enantiomers of amisulpride

- $D_{2/3}$ binding to LB-103 (*S*) 36X stronger than to LB-104 (*R*)
  - Consistent with prior amisulpride data
- 5-HT_7 binding to LB-104 >1000X stronger than to LB-103
  - Consistent with amisulpride (previously unreported)

Disclosures
This work was funded by LB Pharmaceuticals. ZP and AV are employees of LB Pharmaceuticals. VG and MSH are consultants to LB Pharmaceuticals. VG, MSH, ZP, and AV are shareholders of LB Pharmaceuticals.

1 *The AAPS Journal*, **2014**, *16*, 1247–1258.
2 *Euro. J. Pharmacol.*, **2001**, *432*, 143-147.
3 *European Neuropsychopharmacology*, **2017**, *27*, S922 - S923.
4 *Psychopharmacology (Berl.)*, **2009**, *206,* 345-354.