Novel 5-HT2A selective agonists with well-characterized PK profile and short duration of action

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Introduction

Psychedelic compounds have emerged as rapid-acting novel and effective treatments for a range of psychiatric disorders such as depression, PTSD, addictions, and other CNS disorders. However, their psychedelic or psychoactive effects, polypharmacology, and off-target activity create serious safety liabilities, in particular, off-target activity at the hERG channel and the 5-HT2B receptor that result in cardiac risks. Finally, very long and unpredictable in-vivo human PK/PD properties make first-generation psychedelics less than optimal as modern rapid-acting antidepressants. Bright Minds Biosciences, has developed the highly selective 5-HT2A receptor agonist, BMB-202, designed to have a short duration of action.

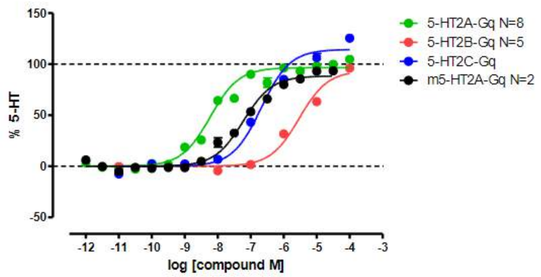
Methods

To characterize BMB-202, both in vitro and in vivo experiments have been performed, and in particular:
- 5-HT2 functional assays measuring Gq dissociation by Bioluminescence resonance energy transfer (BRET)
- Head-twitch response assay (HTR) in C57BL/6J mice.
- Novelty-induced hyperlocomotion in the open field test (OFT) in the olfactory bulbectomized (OBX) Sprague-Dawley rat model

Highly selective 5-HT$_{2A}$ receptor agonist

BMB-202 is a highly selective 5-HT2A agonist:

- Full agonist at 5-HT$_{2A}$
- 5-HT$_{2B}$ – 500-fold selectivity
- 5-HT$_{2C}$ – 36-fold selectivity

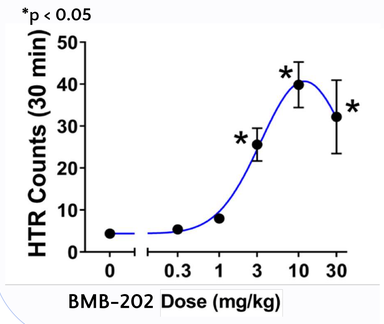


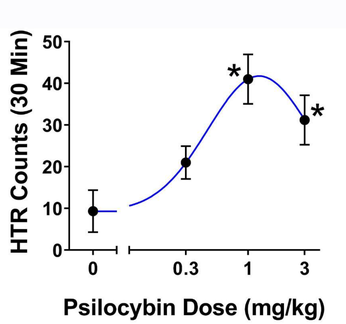
Compound	5-HT$_{2A}$ EC$_{50}$, nM (Emax, %)	5-HT$_{2B}$ EC$_{50}$, nM (Emax, %)	5-HT$_{2C}$ EC$_{50}$, nM (Emax, %)
Psilocin	8.3 (82%)	1.1 (63%)	7.8 (95%)
BMB-202	4.4 (101%)	2827 (94%)	222.5 (113%)

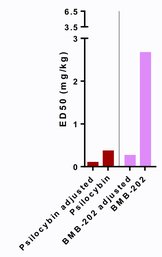
In vitro Pharmacology (John McCorvy group): Effector engagement induced by human 5-HT2A/2B/2C receptor was measured using Gq dissociation as measured by bioluminescence resonance energy transfer (BRET). Emax was defined relative to serotonin (5-HT).

HTR response

BMB-202 intraperitoneally induced the HTR with an ED50 = 2.69 mg/kg. Note the difference in human vs rodent receptor pharmacology for BMB-202





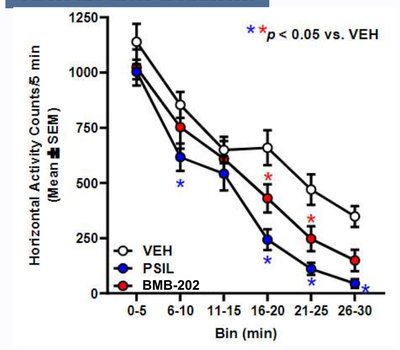


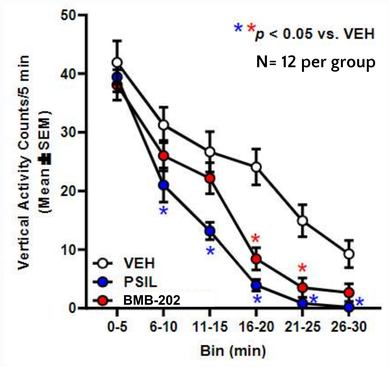
Compound ID	Human 5-HT$_{2A}$ (nM)	Mouse 5-HT$_{2A}$ (nM)
BMB-202	5.92	59.92
Psilocybin	12.61	45.18

OBX model

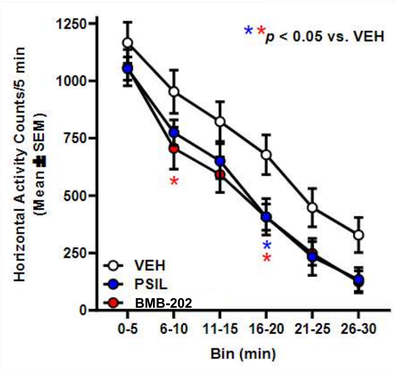
Similar to psilocybin, BMB-202 i.p. reduced vertical and horizontal novelty-induced hyperlocomotion in the OFT, 72 hours and 2 weeks after treatment, suggestive long lasting effects and needs for less frequent dosing

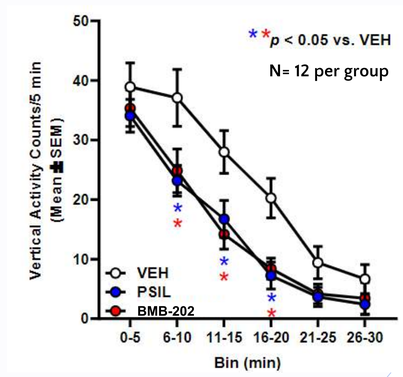
72 hours after treatment





2 weeks after treatment





About Bright Minds Biosciences

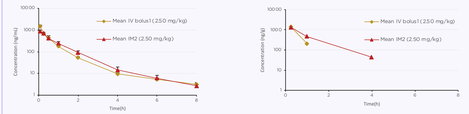
Bright Minds Biosciences is a clinical-stage biotech company developing highly selective 5-HT$_2$ agonists with improved therapeutic profiles for for treatment of neurological and psychiatric disorders

Portfolio of 5-HT$_2$ agonists without 5-HT$_{2B}$ activity

Lead	Features	Research	Ph-1	Ph-2	Indications
5-HT$_{2C}$ agonists for CNS disorders					
BMB-101	• Selective and biased 2C agonist, low 5-HT$_{2A/2B}$ • Biased agonism with minimal arrestin recruitment • Suitable for chronic dosing	Clinical Studies – Phase 2			Rare epilepsies
BMB-xxx	• Selective 5-HT$_{2C}$ agonist compound • Biased agonist	ADME/PK profiling			Obesity and feeding behaviour
Non-hallucinogenic psychoplastogens					
BMB-201	• Promotes neuroplasticity • Low or absent psychedelic activity • Devoid of 5-HT$_{2B}$ activity	IND-enabling studies			Treatment-resistant depression
5-HT$_{2A}$ agonists for the treatment of depression					
BMB-202	• Selective 5-HT$_{2A}$ "Fast-On-Fast-Off" compound • High C_{max} and short plasma half-life • 2-fold more potent than psilocin at 5-HT$_{2A}$	IND-enabling tox			Depression (Fast-onset)
BMB-xxx	• Mixed 5-HT$_{2A/2C}$ compound • 10-fold more potent than psilocin at 5-HT$_{2A}$	ADMEPK profiling			Neurology / Neuropsychiatric Indication

Additional profiling data

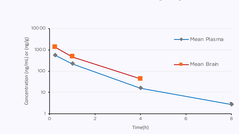
BMB-202 Pharmacokinetic Profile in SD Rats in brain and plasma after IV and IM administration



Plasma

BRAIN

Mean BMB-202 PK profile in plasma and Brain: SD Rats intramuscular (2.5 mg/kg, solution dose)



The key profiling findings are summarized below:

- Low hERG safety risk (EC50 = 2.9 uM, 659x vs 5-HT2A)
- Low off-target liability (Eurofins panel 44 and functional follow-up)
- Ames negative
- 91-94% PPB in human, dog and monkey plasma, 84.5% PPB in mouse plasma; Comparable brain binding in mouse (3.5%) and human (4%).
- Short half-life in mice, rats and dogs (0.6-0.7 h) with IV and IM administration. Fast metabolic clearance consistent with 1st pass elimination
- Allometric model with SC administration projects short human half-life (less than 2 hours) relative to psilocybin

Conclusions

BMB-202 is a potent and selective 5-HT$_{2A}$ receptor agonist, that demonstrates effects similar to psilocybin in vitro and in vivo. Contrary to psilocybin it does not have significant off-target activity at any other receptors. The shorter half-life and fast metabolic clearance of BMB-202 make it a more suitable candidate for use in clinical settings. Future clinical studies are warranted for this type of drug to assess the efficacy and durability of this molecule.

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