Selective 5-HT$_{2C}$ Agonists for the Treatment of Rare Epileptic Disorders

Satellite NINDS forum

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Introduction

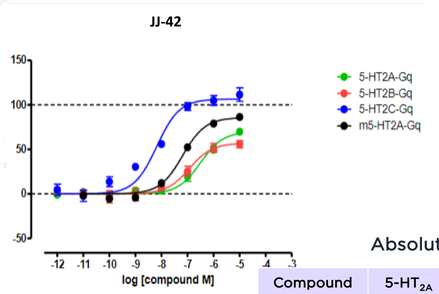
The 5-HT2C receptor, a subtype of the serotonin receptor family, plays a pivotal role in various neurological and psychiatric processes, making its agonists promising candidates for therapeutic interventions. Recent efforts have focused on developing 5-HT2C agonists for developmental and epileptic encephalopathies (DEEs). Fenfluramine, a non-selective 5-HT2C agonist, has been approved for the treatment of Dravet Syndrome and Lennox-Gastaut Syndrome, demonstrating significant efficacy in reducing seizure frequency. Fenfluramine is approved with a Black-Box-Warning and a hard dose cap due to 5HT2b mediated cardiovascular risks, necessitating regular echocardiograms during treatment.
JJ42 and BMB-101 are novel, highly selective 5-HT2C receptor agonists with minimal activity at 5-HT2A and 5-HT2B receptors, reducing liabilities linked with psychedelic effects and cardiotoxicity. Both compounds selectively activate G-protein pathways without beta-arrestin activation, making them promising candidates for chronic treatment of epileptic disorders.

Methods

JJ42 and BMB-101, 5-HT2C agonists developed by Bright Minds Biosciences underwent comprehensive preclinical development, including pharmacological profiling, receptor selectivity assays, and efficacy evaluations in seizure models. NIH, Epilepsy Therapy Screening Program (ETSP) screening was completed for JJ42 compound.

Selective 5-HT$_{2C}$ receptor agonists

BMB-101 and JJ-42 high selectivity for the 5-HT2C receptor and minimal off-target activity suggest a reduced risk of adverse effects compared to less selective agonists.

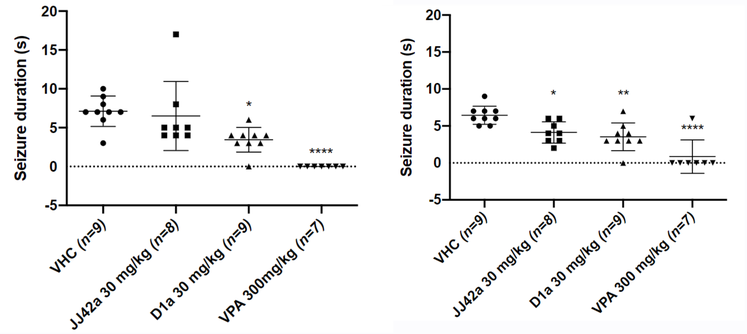


Absolute EC_{50} (nM)

Compound	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_{2C}$
BMB-101	2280	>10000	16.2
JJ42	~1000	~1000	6.6
Nor-Fenfluramine	82.8	11.6	2.5
Lorcaserin	50.1	67.4	2.4

Preclinical models

In the mouse 6-Hz (44 mA) psychomotor seizure model BMB-101 (D1a) lowered the seizure duration at 30 min (left) and 1 h (right) after injection while JJ42 lowers the seizure duration after 1 h. Valproate was used as positive control. In house model.



Behavioral antiseizure analysis of compounds JJ42a and D1a in the mouse 6-Hz (44mA) psychomotor seizure model 30 minutes (left) or 1 hour (right) after treatment. Drug-resistant psychomotor seizures were induced 30 min/1 h after i.p. injection of vehicle (VHC), positive control valproate (VPA), compound JJ42a and compound D1a, Mean seizure durations (± SD) are depicted. VHC (n=9)JJ42a 30 mg/kg (n=8)D1a 30 mg/kg (n=9)VPA 300mg/kg (n=7)***

In the Epilepsy Therapy Screening Program (ETSP), JJ42 was tested IP in the rat maximal electroshock seizure model (MES). In the initial screening assay, 30 and 50mg/kg of the test drug provided significant protection against MES-induced generalized seizures in rats. Toxicity was not observed at any doses.

JJ42 at concentration s 3, 10, and 30 mg/kg did not cause any motor impairments on rotarod, and no mortality at 72 hours was observed.

MES model – Antiseizure activity in rats (IP administration)

Dose	Test	0.25	1
		Protected/total	
10 mg/kg	MES	0/4	0/4
30 mg/kg	MES	3/4	0/4
50 mg/kg	MES	4/4	4/4
	N=4 for each dose		
10 mg/kg	TOX	0	0
30 mg/kg	TOX	0	0
50 mg/kg	TOX	0	0

JJ42 was further tested in mice and rat MES model and produced dose-dependent activity with ED50 of 23.4 mg/kg and 9.86 mg/kg correspondingly. Note that JJ42 has lower 5-HT2C activity in rodent receptors compared to human.

MES model – Antiseizure activity in rats (IP administration) at 0.5h timepoint

Dose	Protection (N=8)
5 mg/kg	1/8
15 mg/kg	6/8
30 mg/kg	8/8

MES model – Antiseizure activity in male mice (IP administration) at 0.5h timepoint

Dose	Tolerability (N=8)	Protection (N=8)
15 mg/kg	100%	1/8
22.5 mg/kg	100%	3/8
30 mg/kg	100%	7/8
45 mg/kg	100%	8/8

BMB-101 Phase 1 trial

BMB-101 has successfully completed Phase 1 studies.

Safety:
- Favorable safety & tolerability in Phase 1. All side effects were transient, no severe adverse events observed. No side-effects observed before top dose was reached.
- Side effects at top dose (2-3x of predicted therapeutic dose) as expected for the CNS drug acting at 5-HT receptors.

Target engagement:
- Transient dose-dependent prolactin release
- Central target engagement by qEEG and Potential for improved cognitive performance (increase in gamma power)

Favorable PK:
- Dose proportionality observed in SAD and MAD study. No significant food effects observed

These phase 1 results support BMB-101 further investigation in patients with epilepsy. With its high selectivity and safety profile, BMB-101 is a promising 5-HT2c agonist for the treatment of seizures in Developmental and epileptic encephalopathy (DEEs) and certain forms of generalized epilepsies. Phase II studies with BMB-101 in DEE and Absence Epilepsy will be initiated in Q4 2024.

Conclusions

- JJ42 and BMB-101 are potent and selective agonists of the 5HT2c receptor
- Both compounds produce dose-dependent activity in several preclinical seizure models as demonstrated by ETSP studies and BMB in house assays
- BMB-101 was selected as a lead candidate, that completed Phase 1 clinical trials and is progressing to Phase 2 clinical studies in absence subgroups of absence epilepsies and DEEs.

Acknowledgements

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The compounds were discovered by Alan Kozikowski group in UIC and Bryan Roth groups and licensed by Bright Minds Biosciences