Receptor Selectivity Profile and Clinical Significance of Ecopipam and Relevant Metabolites, a Potential New Treatment for Tourette Syndrome

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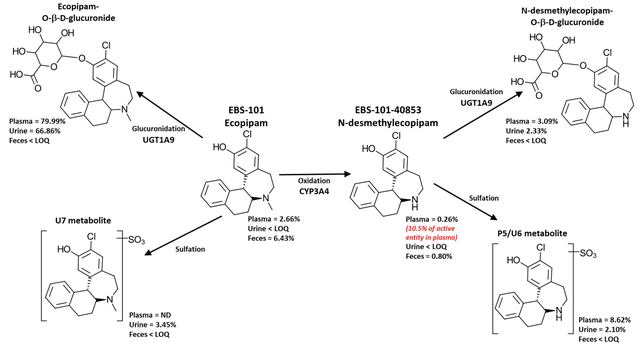
BACKGROUND

- Tourette syndrome (TS) is a childhood-onset neurodevelopmental disorder defined by motor and vocal tics lasting ≥1 year[1]
- Dopamine D2 receptor (D2R) modulators are indicated for TS but are associated with burdensome adverse effects (eg, weight gain, hyperprolactinemia, drug-induced movement disorders) believed to result from D2R blockade and off-target receptor effects[2]
- Ecopipam is a dopamine D1 receptor (D1R) antagonist in late-stage clinical development for TS[3-5]
  - Ecopipam is primarily metabolized by uridine diphosphate glucuronosyltransferase 1A9 to form ecopipam glucuronide, with a minor metabolic pathway via cytochrome P450 3A4 forming an active metabolite, EBS-101-40853, which is also glucuronidated to form EBS-101-40853 glucuronide (**Figure**)[6]

Figure. Metabolism of Ecopipam in Humans



CYP = cytochrome P450; LOQ = limit of quantitation; ND = not detectable; UGT = uridine diphosphate glucuronosyltransferase.

OBJECTIVE

- To characterize the binding selectivity of ecopipam and its metabolites across an extensive array of receptors, ion channels, enzymes, and transporters

METHODS

- In vitro assays were conducted to assess the binding profile of ecopipam and 3 metabolites
  - A panel of 98 targets was screened for >50% inhibition at 10-μM concentrations of ecopipam, EBS-101-40853, ecopipam glucuronide, and EBS-101-40853 glucuronide
  - A subsequent study determined the half-maximal inhibitory concentration (IC_{50}) for each analyte at the D1R; dopamine D2 short (D2SR) and long (D2LR) receptors; dopamine D3 (D3R), D4 (D4R), and D5 (D5R) receptors; human ether-a-go-go-related gene (hERG) receptor; and each receptor that exhibited >50% inhibition during the initial screenings
  - Clinically relevant binding was inferred from the ratio of IC_{50} to free-fraction maximum plasma concentration (free C_{max}) for each analyte under ecopipam steady-state dosing for TS (1.8 mg/kg/day; weight-based)
    - IC_{50}:free C_{max} <10× (10-fold "safety margin") was considered clinically relevant; if the ratio exceeded 10× but remained below 15×, then a potential effect on receptor binding could not be ruled out

RESULTS

Table. Receptor IC_{50} and IC_{50}:Free C_{max} for Ecopipam and Its Metabolites

Receptor	Ecopipam		EBS-101-40853		Ecopipam glucuronide		EBS-101-40853 glucuronide	
	IC_{50}, nM	IC_{50}:free C_{max}	IC_{50}, nM	IC_{50}:free C_{max}	IC_{50}, nM	IC_{50}:free C_{max}	IC_{50}, nM	IC_{50}:free C_{max}
D1	2.4	0.27	15.1	4.8	435	0.07	2660	17.0
D2S	332	38.7	1194	378	>100,000	15.2	>100,000	652
D2L	514	60.0	1565	495	89,221	13.6	>100,000	652
D3	2367	276	4802	1520	>100,000	15.2	>100,000	652
D4	3473	405	14,160	4481	>100,000	15.2	>100,000	652
D5	5.13	0.60	38.7	12.3	1175	0.18	>10,000	65
hERG	>10,000	1166	23,076	7303	409,895	62.0	>100,000	652
5-HT1A	99.4	11.6	28.0	8.9	NR	NR	NR	NR
Alpha-2A	990	115	1967	622	NR	NR	NR	NR
5-HT2B	2421	282	4053	1283	NR	NR	NR	NR
5-HT2A	264	30.8	6399	2025	NR	NR	NR	NR
H1	206	24.0	1262	399	NR	NR	NR	NR
Mu-opioid	2883	336	3939	1247	NR	NR	NR	NR
Alpha-1A	4247	495	1996	632	NR	NR	NR	NR
DAT	NR	NR	1012	320	NR	NR	NR	NR
5-HT2C	618	72	NR	NR	NR	NR	NR	NR
Alpha-2B	4256	496	1728	547	NR	NR	NR	NR
Alpha-1D	1723	201	2522	798	NR	NR	NR	NR
Alpha-2C	116	13.5	405	128	NR	NR	NR	NR
Alpha-1B	3740	436	NR	NR	NR	NR	NR	NR
Sigma-1	2672	311	NR	NR	NR	NR	NR	NR
Cav1.2	671	78.0	2540	804	NR	NR	NR	NR
5-HT7	NR	NR	8553	2707	NR	NR	NR	NR

Blue shading indicates clinically relevant binding at dopamine receptors using IC_{50}:free C_{max} <10.

Cav1.2 = voltage-dependent L-type calcium channel alpha-1C subunit; DAT = dopamine transporter; D1 = dopamine D1; D2L = dopamine D2 long; D2S = dopamine D2 short; D3 = dopamine D3; D4 = dopamine D4; D5 = dopamine D5; H1 = histamine 1; hERG = human ether-a-go-go-related gene; IC_{50} = half-maximal inhibitory concentration; IC_{50}:free C_{max} = ratio of IC_{50} to free-fraction maximum plasma concentration for each analyte after steady-state dosing with ecopipam, 1.8 mg/kg/day; NR = no relevant inhibition; 5-HT1A = serotonin 1A; 5-HT2A = serotonin 2A; 5-HT2B = serotonin 2B; 5-HT2C = serotonin 2C; 5-HT7 = serotonin 7.

D1Rs and D5Rs

- Ecopipam and its major metabolite (ecopipam glucuronide) demonstrated selectivity for D1Rs and D5Rs (**Table**). Although ecopipam glucuronide is much less potent than ecopipam at the D1R and D5R (0.540% and 0.437%, respectively), plasma concentrations are ~50× higher than for ecopipam.[7] Therefore, ecopipam glucuronide may contribute to efficacy
  - The minor metabolite of ecopipam (EBS-101-40853) demonstrated selectivity for D1Rs and D5Rs. The potencies of antagonism at the human D1R and D5R, relative to ecopipam, were 15.6% and 13.3%, respectively. EBS-101-40853 accounts for 10.5% of the exposure to ecopipam.[6] Therefore, EBS-101-40853 is unlikely to substantially contribute to efficacy. EBS-101-40853 also had the potential to bind serotonin 1A (5-HT1A) receptors (IC_{50}:free C_{max}, 8.9)
  - EBS-101-40853 glucuronide: not active at any dopamine receptor subtypes

Other

- IC_{50}:free C_{max} for hERG was lowest for ecopipam glucuronide (IC_{50}:free C_{max}, 62.0) and high for ecopipam, EBS-101-40853, and EBS-101-40853 glucuronide (IC_{50}:free C_{max} range, 652 to 7303), suggesting any risk of QT prolongation is due to ecopipam glucuronide
- Using IC_{50}:free brain concentration ratio of 40:1 for ecopipam (assuming brain:plasma ratio ≤8 for ecopipam), there is potential for ecopipam to bind to D2SRs and 5-HT1A, histamine 1, and alpha-2C receptors
- Using IC_{50}:free brain concentration ratio of 125:1 for EBS-101-40853 (assuming brain:plasma ratio ≤25 for EBS-101-40853), there is potential for EBS-101-40853 to bind to D5Rs and 5-HT1A receptors at clinically relevant concentrations
- Because ecopipam glucuronide has a blood:brain penetration ≤14% that of ecopipam,[8] no additional receptors met the criteria for clinically relevant brain concentrations, unless the IC_{50}:free brain concentration ratio reaches 13:1 to 15:1, in which case activity of ecopipam glucuronide at the D2SR, D2LR, D3R, and D4R cannot be ruled out

CONCLUSIONS

- Ecopipam demonstrated selectivity for D1Rs over 98 off-target receptors, ion channels, enzymes, and transporters
- The major metabolite (ecopipam glucuronide) is much less potent than ecopipam at human D1Rs and D5Rs (0.540% and 0.437%, respectively), but concentrations are ~50× higher than ecopipam; thus, there is the potential for ecopipam glucuronide to contribute some efficacy
- The minor metabolite (EBS-101-40853) is less potent than ecopipam at human D1Rs and D5Rs (15.6% and 13.3%, respectively) and only accounts for 10.5% of the exposure to ecopipam; thus, EBS-101-40853 does not substantially contribute to efficacy
- EBS-101-40853 glucuronide does not bind to D1Rs at clinically relevant concentrations
- These data are consistent with the clinical profile of ecopipam in children, adolescents, and adults with TS[3-5]
- As a selective D1R antagonist, ecopipam has the potential to improve tic severity while avoiding some of the adverse effects commonly associated with approved D2R modulators

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DISCLOSURES:

SPW and TMC are employees of Paragon Biosciences, LLC, which has controlling equity interest in Emalex Biosciences, Inc.; additionally, they have personal equity interest in Emalex Biosciences, Inc.

VDS is a paid consultant for Emalex Biosciences, Inc.

GBK is an employee of and has personal equity interest in Emalex Biosciences, Inc.