Highly Soluble TRPV4 Antagonists for Oral & IV Delivery

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All studies were conducted in accordance With the GSK policy on the Care, Welfare And Treatment of Laboratory Animals and were reviewed by the Institutional Animal Care and Use Committee either At GSK or by the ethical review process at the Institution where the work was performed.

TRPV4

Transient Receptor Potential Vanilloid-4 Sensory Protein

- Non-selective (Na^+ , Ca^{2+}) ion channel
- Responsive to pressure, heat, osmolarity pH and endogenous ligands
- Regulates alveolar-septal barrier permeability
- Potential for CHF & respiratory indications

Lawhorn, *Bioorg. Med. Chem. Lett.* **2020**
<https://doi.org/10.1016/j.bmcl.2020.127022>

TRPV4 and Heart Failure

Effects of TRPV4 Activation in Pulmonary Vasculature

Congestive Heart Failure

- #1 cause of hospitalization in elderly
- Disrupted lung / vasculature barrier
- Pulmonary congestion
- Shortness of breath

TRPV4

- Responsive to vasculature pressure
- Regulates endothelial cell permeability
- Agonists cause lung edema & death
- Antagonists prevent HF-induced lung edema in animal models

GSK TRPV4 Program

Seeking Backup Candidate from a Novel Chemotype

GSK2798745

- First-in-class TRPV4 Ion Channel Inhibitor
- Entered Phase 2 in 2018
- Heart Failure & Respiratory indications

Brooks, *ACS Med Chem Lett.* **2019**, *10*, 1228

2nd Generation Drug Candidate

- Novel chemotype
- Drug-like properties
- Specificity for TRPV4

Sulfonamide TRPV4 Antagonists

Poor Solubility - An Unintended Consequence of LLE Optimization

- Goal of LLE (LipE) optimization: identify compounds with drug-like properties
- Optimization of LLE via entropic effects can produce agents with poor solubility

Origin of Poor Solubility

Excessive stability of crystalline material

Poor solubility resulting from

- Reduced entropy of solvation
- High crystal lattice energy
- Extended ring stacking within crystal
- Stabilizing hydrogen bond network

Small Molecule X-ray Crystal Structure

Oral Bioavailability of Suspension Doses

Poor solubility limits dose escalation required for safety studies

Rat Oral Bioavailability

Optical
Microscopy
(solid)

crystalline

amorphous

Dose Suspension
Partly crystalline

Strategies to Improve Solubility

Reducing Conformational Bias

$IC_{50} = 34 \text{ nM}$
ChromLogD = 3.4
FaSSIF = 26 $\mu\text{g/mL}$

Conformational
Relaxation

$IC_{50} = 3800 \text{ nM}$
ChromLogD = 3.1
FaSSIF > 1000 $\mu\text{g/mL}$

$IC_{50} = 190 \text{ nM}$
ChromLogD = 3.5
FaSSIF = 130 $\mu\text{g/mL}$

Rigid

trans-diaxial

Flexible Templates

equatorial XAr

- Crystalline stability arises from strong conformational bias of trans-pyrrolidine diol

Strategies to Improve Solubility

Solubilizing Prodrug

7d Rat Safety Findings for Prodrug

- Kidney stones & dilated tubules
- Liver hypertrophy, $\uparrow$ billirubin, $\uparrow$ ALP

Obstructive liver & kidney effects may be caused by crystallization of parent *in vivo*

Strategies to Improve Solubility

Charged, Stable Analogues

$IC_{50} = 34 \text{ nM}$
ChromLogD = 3.4
FaSSIF = 26 $\mu\text{g/mL}$

Introduce Stable
Charged Group

$IC_{50} = 12 \text{ nM}$
ChromLogD = 2.5
FaSSIF > 1000 $\mu\text{g/mL}$

$IC_{50} = 3.5 \text{ nM}$
ChromLogD = 4.0
FaSSIF = 78 $\mu\text{g/mL}$

Safety Risks

hERG = 20 μM
Cyp3A4 = 12 μM
CAD-likeness = 51

hERG = 3 μM
Cyp3A4 = 1.6 μM
CAD-likeness = 61

- Solubility of amino alcohol template is governed by lipophilicity, unlike the trans-diol core
- Controlling lipophilicity is critical to attenuate off-target activities of the basic amines

GSK3527497 – A Highly Soluble TRPV4 Candidate

Novel chemotype – suitable for oral and iv delivery

GSK3527497

Pharmacokinetics

Species	Rat	Dog
CL (ml/min/kg)	45	5.9
Vdss (L/kg)	6.7	5.9
MRT (hr)	2.5	17
Oral F (%)	26	84
PPB (% free)	14	32
Proj. Human Dose	150 mg bid	10 mg qd

Pharmacology & Safety

- Prevents lung edema due to TRPV4 activation
- Ames-negative
- 84% Oral F @ 100 mg/kg
- Suitable safety profile in rodents & non-rodents
- Novel drug candidate

Key Lessons

- Entropically-driven LLE optimization identifies selective leads, with poor solubility
- In extreme cases, poorly soluble compounds may crystallize *in vivo* causing toxicity
- Entropically-optimized templates with solubilizing amino groups have drug-like properties

Synthesis of GSK3527497

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