

Anti-diabetic/obesity agents

Technology Overview

- Anti-diabetic agent: Non systemic approach of GPR119 agonist
- Anti-obesity agent: TAZ modulator

Core Technologies

- Non-systemic GPR119 agonist (small molecule)
 - KRI60209: lead compound, good in vitro potency, in vivo acute efficacy non-systemic property, druggability, toxicity profile
- TAZ modulator (small molecule)
 - KR64105: lead compound, good in vitro anti-adipogenic effect, drugability, in vivo efficacy

Application Area and Advantages

- Non-systemic GPR119 agonist : anti-diabetes
- TAZ modulator: anti obesity/diabetes

Accomplishments

- Strong IP Portfolios
- Looking for licensing & collaborative research opportunities

Non systemic GPR119 strategy

Diagram illustrating the non-systemic GPR119 strategy. A compound acts on GPR119 in various tissues (Heart, Liver, Intestine, Pancreas, Muscle, Adipose tissue) leading to multiple physiological effects: Cardioprotection, Cardiac function, Glucose production, Insulin sensitivity, Beta-cell proliferation, Beta-cell apoptosis, and GLP-1 release. The compound is administered at > 500 mg/Kg.

Scaffold 1

KR-code	In vitro activity (EC50 value)	Liver Microsomal Stability (% remaining after 30 min)	CYP (5 subtypes) % inh at 10 μM	hERG (binding)
KRI60209	14 nM	Human 99%	1A2= 8.2 %, 2C9 = 56.2 % 2C19 = 0.0 % 2D6 = 0.5 %, 3A4 = 0.0 %	21.3% inhibition at 10 μM
Stability (37°C, 24 hr, Water)	Solubility (equilibrium)	PAMPA Permeability	LD50 in ICR mice	
99 %	20μM in FaSSIF (simulated intestinal fluid in fed state)	5.12± 0.157 (grade - low) Suitable for non systemic approach	> 500 mg/Kg	

OGTT (normal mice)

OGTT (normal mice) AUC (0-120 min) (mg/dl·min)

Vehicle	Januvia	Metformin	KR64105
~35000	~35000	~35000	~35000

OGTT (TallyHo mice)

OGTT (TallyHo mice) AUC (0-120 min) (mg/dl·min)

Vehicle	Januvia	Metformin	KR64105
~40000	~30000	~30000	~20000

In vivo PK in rat

Parameter	T _{1/2} (h)	AUC (0-120 min) (μg·h/ml)	V _d (L)	V _d /V _{ss}	F (%)
T _{1/2} (h)	1.13 ± 0.57	-	-	-	-
C _{max} (μg/ml)	-	0.028 ± 0.017	-	-	-
T _{max} (h)	4.22 ± 0.5	4.65 ± 2.7	-	-	-
AUC (0-120 min)	7.01 ± 1.37	0.134 ± 0.076	-	-	-
AUC _{0-∞} (μg·h/ml)	7.15 ± 1.35	0.135 ± 0.078	-	-	-
V _d (L)	0.089 ± 0.095	-	-	-	-
V _d /V _{ss}	1.05 ± 1.43	-	-	-	-
F (%)	-	1.05	-	-	-

TAZ: Transcriptional Co-Aktivator with PDZ-Binding Motif

Original articles: *Science 2005, 309, 1074; Brit J Pharmacol 2012, 165, 1584*

The transcriptional co-activator with PDZ-binding motif (TAZ) is characterized as a transcriptional modulator of mesenchymal stem cell differentiation into osteoblasts and adipocytes. Increased TAZ activity in the nucleus suppresses adipocyte development.

Small molecule TAZ modulator could be an anti-obesity drug candidate

TAZ modulator KR64105 (In vitro, in vivo efficacy)

structure	In vitro activity Anti-adipogenic effect 3T3BL1	Liver microsomal stability 30 min incub.	hERG (Patch clamp)	Permeability (PAMPA)
active	>99.9 (h) 86 (m)	-	IC ₅₀ = 79 μM	4.42±0.243 (medium)
Cytotoxicity (EC ₅₀ (μM))	Micronucleus, Chromosomal aberration	PK (10 mpk, rat)	In vivo efficacy (long term, DIO) 50 mpk, B/F ⁺	In vivo efficacy (long term, DIO) 50 mpk
NH 3T3 = 35.6 Vero = 34.6 HFL-1 = 76.2 CHO-K1 = 38.9	negative	AUC 2.36 (ug·h/ml) CL 0.09 (L·h/g) F = 52 %	Weight gain reduction (> 10%)	OGTT (IT) ITT (AUC reduction)

O in vivo long term study 50 mpk, 10 weeks in DIO model

Weight (g) OGTT (mg/dl) ITT (mg/dl)

ND	HF	HF+TM	HF+KR64105	HF+TT	HF+T8
~30	~35	~35	~30	~30	~30
~25	~30	~30	~25	~25	~25
~20	~25	~25	~20	~20	~20