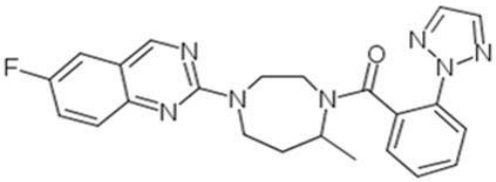
Compound Information Sheet

DORA-12



Formula: $C_{23}H_{22}FN_7O$ (free base)
MW: 431.476
FW: 431.476
Batch: -003

In Vitro Inhibition / Binding

Species	Receptor	Kb	Ki
mouse	OX1R	21 nM	1.9 nM
mouse	OX2R	18 nM	0.37 nM
rat	OX1R	50 nM	2.1 nM
rat	OX2R	25 nM	0.45 nM
human	OX1R	46 nM	1.8 nM
human	OX2R	19 nM	0.2 nM

Solubility in select solvents

Solvent	Solubility (mg/ml)
10% TWEEN 80	8.395
FaSSIF (Intestinal mimic)	0.17
SGF (gastric mimic)	1.68
100% PEG400	94.68
30% CAPTISOL	13.8
20% TPGS	15.3

Rat Pharmacokinetic Properties

Free Fraction: 3% (rat)
CSF/plasma ratio: 0.02-0.03
brain/plasma ratio: 0.4-0.6
Clearance: 33 ml/min/kg (10 mg/kg in 20% VitE TPGS, p.o.)
Oral Bioavailability: 47% (10 mg/kg in 20% VitE TPGS, p.o.)

Mouse Plasma levels following oral administration

(all oral dosing in 20% VitE TPGS; dose volume: 6.67 ml/kg)

	30 mg/kg		100 mg/kg	
Time (hr)	Plasma (uM)	CSF (uM)	Plasma (uM)	CSF (uM)
0.5	1.6	0.013	36.5	0.278
1	1.7	0.009	41.4	0.162
2	0.31	BLQ	31	0.136
4	0.026	BLQ	2.63	BLQ

References:

Compound identification, in vitro characterization and specificity (compound 10): Cox CD, et al. 2010. Discovery of the dual orexin receptor antagonist [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (MK-4305) for the treatment of insomnia. *J Med Chem.* 53(14):5320-32.

In vivo Sleep effects in mice are selective for OX1/2R: Gotter AL, et al. 2012. International Union of Basic and Clinical Pharmacology. LXXXVI. Orexin receptor function, nomenclature and pharmacology. *Pharmacol Rev.* 64(3):389-420.

Rat sleep efficacy vs OX2R occupancy: Gotter et al. 2013. The duration of sleep promoting efficacy by dual orexin receptor antagonists is dependent upon receptor occupancy threshold. *BMC Neuroscience* 14:90.

Preclinical sleep architecture: Gotter et al., 2014. Differential sleep-promoting effects of dual orexin receptor antagonists and GABAA receptor modulators. BMC Neuroscience 14:90. *BMC Neuroscience* 15:109.

Lack of effects on motor coordination: Ramirez et al., Dual orexin antagonists show distinct effects on locomotor performance, ethanol interaction and sleep architecture relative to gamma-aminobutyric acid-A receptor modulators. 2013. Front Neurosci 7:254.