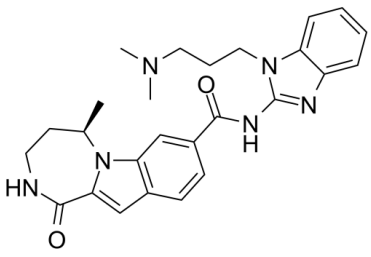
Data Sheet

Product Name:	BIX 02565
Cat. No.:	CS-1659
CAS No.:	1311367-27-7
Molecular Formula:	C26H30N6O2
Molecular Weight:	458.56
Target:	Ribosomal S6 Kinase (RSK)
Pathway:	MAPK/ERK Pathway
Solubility:	DMSO : 20.75 mg/mL (45.25 mM; Need ultrasonic and warming)



BIOLOGICAL ACTIVITY:

BIX 02565 is a potent ribosomal S6 kinase 2 (**RSK2**) inhibitor with **IC_{50}** of 1.1 nM. IC50 & Target: IC50: 1.1 nM (RSK2)[1] **In Vitro:** BIX 02565, a potent RSK2 inhibitor (IC_{50}=1.1 nM) targets for the treatment of heart failure secondary to myocardial infarction through indirect NHE inhibition[1]. BIX 02565, a second Rsk inhibitor, protects enzyme active sites from reaction with biotinylated nucleotide acyl phosphates[2]. **In Vivo:** In telemetry-instrumented rats, BIX 02565 (30, 100, and 300 mg/kg p.o. QD for 4 days) elicits concentration-dependent decreases in MAP after each dose (to -39±4 mm Hg on day 4 at T_{max}). BIX 02565 produces concentration-dependent relaxation ex vivo in the phenylephrine-constricted rat aortic ring at concentrations above 0.03 μM with a calculated EC_{50} of 3.1 μM. Subsequently, BIX 02565 is infused in the anesthetized rat in a low-dose (0.1, 0.3, and 1.0 mg/kg per 20 min) and high-dose (1.0, 3.0, and 10.0 mg/kg per 20 min) series of continuous infusions to test the effect of compound on hemodynamics in vivo[1].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]Radioligand binding studies are performed at MDS Pharma Services. Mean percentage inhibition of specific binding or activity is shown for each assay tested, and in selected assays (for BIX 02565) when inhibition of adrenergic binding generally exceeded 50%, an IC_{50} is determined by a nonlinear least-squares regression analysis. In brief, human RSK2 protein is used to measure kinase activity utilizing Kinase GloPlus that uses a luciferin-luciferase based detection reagent to quantify residual ATP. The relative light unit signal is measured on an LJL Analyst in luminescence mode using 384 aperture; relative light unit signals are converted to percentage of control; the IC_{50} is fitted to a standard four-parameter logistic equation[1]. **Animal Administration:** BIX 02565 is prepared in DMSO and diluted with saline or PBS[1].[1]Rat[1]

Mean arterial pressure is assessed in conscious, freely moving male Sprague-Dawley rats (n=6/group) instrumented with telemetry transmitters. BIX 02565 (30, 100, and 300 mg/kg p.o. QD) is administered as a solution (10 mL/kg) in a 20% hydroxy-propyl-β-cyclodextran vehicle. Mean arterial pressure is reported from 2 h before (baseline) and 90 h after the first dose; compound is administered at 0, 24, 48, and 72 h. A blood sample is collected from satellite rats (n=3/group) at 1-h after dose (T_{max}) on days 1 and 4 for analysis of plasma drug concentrations by mass spectrometry.

References:

[1]. Fryer RM, et al. Mitigation of off-target adrenergic binding and effects on cardiovascular function in the discovery of novel ribosomal S6 kinase 2 inhibitors. Journal of Pharmacology and Experimental Therapeutics (2012), 340(3), 492-500.

[2]. Edgar AJ, et al. A combination of SILAC and nucleotide acyl phosphate labelling reveals unexpected targets of the Rsk inhibitor BI-D1870. Biosci Rep. 2013 Dec 17.

CAIndexNames:

1H-[1,4]Diazepino[1,2-a]indole-8-carboxamide, N-[1-[3-(dimethylamino)propyl]-1H-benzimidazol-2-yl]-2,3,4,5-tetrahydro-5-methyl-1-oxo-, (5R)-

SMILES:

O=C(C1=CC2=C(C=C1)C=C3N2[C@H](C)CCNC3=O)NC4=NC5=CC=CC=C5N4CCCN(C)C

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