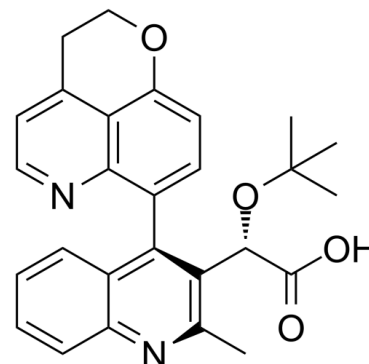


Data Sheet

Product Name:	BI 224436
Cat. No.:	CS-3472
CAS No.:	1155419-89-8
Molecular Formula:	C ₂₇ H ₂₆ N ₂ O ₄
Molecular Weight:	442.51
Target:	HIV; HIV Integrase
Pathway:	Anti-infection; Metabolic Enzyme/Protease
Solubility:	DMSO : ≥ 50 mg/mL (112.99 mM)



BIOLOGICAL ACTIVITY:

BI 224436 is a novel **HIV-1** noncatalytic site integrase inhibitor with **EC₅₀** values of less than 15 nM against different HIV-1 laboratory strains. IC₅₀ & Target: EC₅₀: 15 nM (HIV-1)^[1] **In Vitro:** BI 224436 has cellular cytotoxicity of more than 90 μM. BI 224436 has a low, 2.1-fold decrease in antiviral potency in the presence of 50% human serum. BI 224436 retains full antiviral activity against recombinant viruses encoding INSTI resistance substitutions N155S, Q148H, and E92Q. BI 224436 displays an additive effect in combination with most approved antiretrovirals, including INSTIs. BI 224436 has drug-like in vitro absorption, distribution, metabolism, and excretion (ADME) properties, including Caco-2 cell permeability, solubility, and low cytochrome P450 inhibition^[1]. **In Vivo:** BI 224436 exhibits excellent pharmacokinetic profiles in rat (clearance as a percentage of hepatic flow [CL], 0.7%; bioavailability [F], 54%), monkey (CL, 23%; F, 82%), and dog (CL, 8%; F, 81%)^[1].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: ^[1]BI 224436 is dissolved in acetonitrile-methanol (50:50, vol/vol) to achieve a concentration of 1.5 mM. Phosphate buffer (pH 7.4), cofactor, and test substance or isoform-selective inhibitors are added to 96-well plates and are prewarmed to 37°C for 10 min. Cofactor concentrations are 1.3 mM NADP, 3.3 mM glucose-6-phosphate, and 0.4 U/mL glucose-6-phosphate dehydrogenase. Reactions are initiated by the addition of prewarmed (37°C) enzyme and substrate. Reaction mixtures are incubated at 37°C and terminated by the addition of 0.038 ml of 40:40:20 (vol/vol) methanol-acetonitrile-0.5 M Tris buffer. Formation of the fluorescent metabolites is measured using a microplate spectrofluorometer at specific excitation and emission wavelengths. The IC₅₀ is determined using the 96-well 32 procedure supplied with the SAS software^[1]. **Animal Administration:** ^[1]Rats: For oral PK studies, BI 224436 is administered in a suspension of 0.5% (wt/vol) methyl cellulose (MC), 0.3% (vol/vol) Tween 80, and 1% (vol/vol) N-methyl-2-pyrrolidone (MP) in water. For i.v. dosing, BI 224436 is dissolved in 70% PEG 400–30% water (vol/vol). The appropriate amount of BI 224436 is dissolved in PEG 400 with sonication. The rats receive a single i.v. dose of 0.2 mg/kg of body weight (1 mL/kg) via the jugular vein as a bolus or received a single oral dose of 0.4 mg/kg (10 mL/kg) administered by gavage. Blood samples are obtained at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 32 h after dosing for analysis^[1].

References:

[1]. Fenwick C, et al. Preclinical profile of BI 224436, a novel HIV-1 non-catalytic-site integrase inhibitor. Antimicrob Agents Chemother. 2014 Jun;58(6):3233-44.

CAIndexNames:

3-Quinolineacetic acid, 4-(2,3-dihydropyrano[4,3,2-de]quinolin-7-yl)- α -(1,1-dimethylethoxy)-2-methyl-, (α S,4R)-

SMILES:

CC1=C([C@@H](C(O)=O)OC(C)(C)C)[C@@]([C@@]2=CC=C3C4=C2N=CC=C4CCO3)=C5C(C=CC=C5)=N1

Caution: Product has not been fully validated for medical applications. For research use only.

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