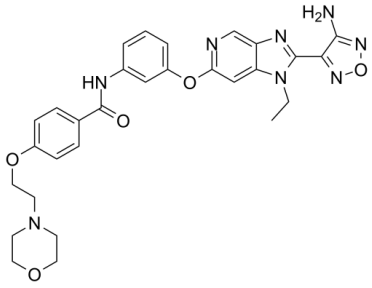
Data Sheet

Product Name:	GSK269962A
Cat. No.:	CS-2790
CAS No.:	850664-21-0
Molecular Formula:	C29H30N8O5
Molecular Weight:	570.60
Target:	ROCK
Pathway:	Cell Cycle/DNA Damage; Stem Cell/Wnt; TGF-beta/Smad
Solubility:	DMSO : ≥ 30 mg/mL (52.58 mM); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

GSK269962A is a potent **ROCK** inhibitor with **IC_{50}**s of 1.6 and 4 nM for recombinant human **ROCK1** and **ROCK2** respectively. IC50 & Target: IC50: 1.6 nM (ROCK1), 4 nM (ROCK2)[1] **In Vitro:** GSK269962A IC_{50} values of 1.6 nM toward recombinant human ROCK1. GSK269962A also exhibits more than 30-fold selectivity against a panel of serine/threonine kinases. GSK269962A induces vasorelaxation in preconstricted rat aorta with an IC_{50} of 35 nM. Both are highly potent toward human ROCK1 with IC_{50} of 1.6 nM for GSK269962A. On the other hand, GSK269962A has a significantly improved kinase selectivity profile with at least >30-fold selectivity against the panel of protein kinase tested[1]. **In Vivo:** Oral administration of GSK269965A (0.3, 1, and 3 mg/kg) induces a dose-dependent reduction in blood pressure in spontaneously hypertensive rat (SHR). The reduction of blood pressure is acute and substantial. The maximal effect on blood pressure is observed approximately 2 h after oral gavages for both compounds. Under a similar setting, oral administration of Y-27632 (10 and 30 mg/kg) also induced a dose-dependent decrease of blood pressure. For all three Rho kinase inhibitors, the reduction of blood pressure is accompanied by an acute, dose-dependent increase in heart rate, presumably due to the activation of baroreflex mechanism[1].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]The enzyme activity and kinetics of the purified ROCK1(3-543) are determined using scintillation proximity assay. In this assay, purified ROCK1 is incubated with peptide substrate (Biotin-Ahx-AKRRLSSLRA-CONH2), and ^{33}ATP and the subsequent incorporation of ^{33}P into the peptide is quantified by streptavidin bead capture. For IC_{50} determination, test compounds are dissolved at 10 mM in 100% DMSO, with subsequent serial dilution in 100% DMSO. Compounds are typically assayed over an 11-point dilution range with a concentration in the assay of 10 μM to 0.2 nM in 3-fold dilutions. For dose-response curves, data are normalized and expressed as percentage inhibition using the formula 100×[(U-C1)/(C2-C1)], where U is the unknown value, C1 is the average of the high signal (0%) control wells, and C2 is the average of the low signal (100%) control wells. Curve fitting is performed The results for each compound are recorded as pIC_{50} values[1]. **Animal Administration:** [1]Rat[1]

Male Sprague-Dawley rats (350-400g) are anesthetized with 5% isoflurane in O_2 and killed by exsanguination. Aortic rings, approximately 2 to 3 mm in length, are suspended by two 0.1-mm diameter tungsten wire hooks in 10 mL tissue baths containing Krebs of the following composition: 112 mM NaCl, 4.7 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM KH_2PO_2, 1.2 mM $MgSO_4$, 25 mM $NaHCO_3$, 11.0 mM dextrose, 0.01 mM indomethacin, and 0.01 mM L-NAME. Krebs is maintained at 37°C and aerated with 95% O_2, 5% CO_2, pH 7.4,. Changes in isometric force are measured under optimal resting tension (1 g) using FT03 force-displacement transducers coupled to model 7D polygraphs. After a 60-min equilibration period, the vessels are treated with standard concentrations of KCl (60 mM) and phenylephrine (1 μM). Cumulative concentration-response curves to phenylephrine are obtained for each tissue by dosing at 0.5-log unit intervals (1 nM to 10 μM). After several washes, each vessel is contracted to equilibrium with an EC_{80} concentration of phenylephrine, and tone is reversed by adding cumulative amounts of either GSK269962A or SB-772077-B at 0.5-log unit intervals (0.1 nM to 1 μM). Responses are expressed as percentage reversal of the tone established with phenylephrine.

References:

[1]. Doe C, et al. Novel Rho kinase inhibitors with anti-inflammatory and vasodilatory activities. J Pharmacol Exp Ther. 2007 Jan;320(1):89-98.

CAIndexNames:

Benzamide, N-[3-[[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-6-yl]oxy]phenyl]-4-[2-(4-morpholinyl)ethoxy]-

SMILES:

CCN1C2=CC(OC3=CC=CC(NC(C4=CC=C(OCCN5CCOCC5)C=C4)=O)=C3)=NC=C2N=C1C6=NON=C6N

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