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IDH2 Inhibitor, R140Q Somatic Mutant-Specific, AGI-6780 - CAS 1432660-47-3 - Calbiochem A cell-permeable inhibitor of isocitrate dehydrogenase 2 R140Q mutant-containing dimers. Has minimal effect on wild type dimer-catalyzed alpha-KG production.

Art. ID	SAF-5098800001
Unit	EA
Deliverydetails	No Dangerous Good /not restricted

Description

A cell-permeable urea sulfonamide that inhibits the activity of Isocitrate Dehydrogenase 2 (IDH2) R140Q mutant-containing dimers in an &alpha,-ketoglutarate/&alpha,-KG-non-competitive and NADPH-uncompetitive manner by stabilizing the mutant dimers in an inactive conformation via a high-affinity allosteric interaction at the dimer interface with a slow-binding kinetic (kon = 5.8 x 104/M/min, koff = 8.3 x 10-3/min), while displaying much reduced potency against wt IDH2 dimer-catalyzed &alpha,-KG production and little or no activity toward wt IDH1 or R132H IDH2 mutant. Selectively inhibits 2-HG production in IDH2 R140Q, but not R132H, mutant-expressing U87 cultures (IC50 in 48 h = 11 nM vs. >100 microM). AGI-6780 treatment (5 microM) of primary bone marrow cultures from AML patients with R140Q mutation is shown to reactivate the differentiation of immature AML blasts without cytotoxicity., A cell-permeable ureido-benzenesulfonamide that inhibits alpha-ketoglutarate (alpha-KG)-to-(R)-2-hydroxyglutarate (2-HG) conversion catalyzed by Isocitrate Dehydrogenase-2 (IDH2) R140Q mutant-containing dimers (IC50/preincubation time = 4 nM/16 h & 120 nM/1 h against R140Q-wt heterodimer, 23 nM/16 h & 170 nM/1 h against R140Q homodimer) in a substrate-non-competitive and NADPH-uncompetitive manner by targeting the dimer interface via a high affinity allosteric interaction with a slow-binding kinetic (kon = 5.8 x 104/M/min, koff = 8.3 x 10-3/min) and stabilizing the mutant dimers in an inactive conformation, while displaying much reduced potency against wt IDH2 dimer-catalyzed alpha-KG production (IC50/preincubation time = 190 nM/16 h & 2.7 &#181,M/1 h) and little or no activity toward LDHA, 3PGDH, GDH, G6PDH, R132H mutant or wt IDH1. Selectively inhibits 2-HG production in R140Q IDH2-expressing U87 glioblastoma & TF-1 erythroleukemia, but not R132H-expressing U87 cultures (IC50 in 48 h = 11 nM, 18 nM, and >100 &#181,M, respectively) and sensitizes R140Q IDH2-expressing TF-1 to EPO-induced erythroid differentiation. Likewise, inhibition of 2-HG production in primary bone marrow cultures from AML patients with R140Q mutation (complete inhibition with 5 &#181,M AGI-6780) is shown to reactivate the differentiation of immature AML blasts without cytotoxicity. IDH1 Inhibitor, R132 Somatic Mutant-Specific, AGI-5198 (>Cat. No. 410972) is also available.

Text/Information	Analyte/Parameter	CAS number	Concentration/Value	Unit	Method	Source
	AGI-6780	[1432660-47-3]				