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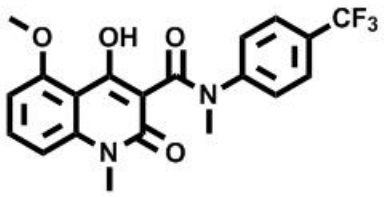
Allosteric HDAC4 Inhibitor – Tasquinimod

Chemical Name: 4-hydroxy-5-methoxy-N,1-dimethyl-2-oxo-N-(4-(trifluoromethyl)phenyl)-1,2-dihydroquinoline-3-carboxamide



Molecular Weight:	406.36
Formula:	$C_{20}H_{17}F_3N_2O_4$
Purity:	≥98%
CAS#:	254964-60-8
Solubility:	DMSO up to 100 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

Tasquinimod (ABR-215050) is a potent and selective allosteric HDAC4 inhibitor. It allosterically binds (Kd 10-30 nmol/L) to the regulatory Zn(2+) binding domain of HDAC4 that locks the protein in a conformation preventing HDAC4/N-CoR/HDAC3 complex formation. This binding inhibited colocalization of N-CoR/HDAC3, thereby inhibiting deacetylation of histones and HDAC4 client transcription factors, such as HIF-1α, which are bound at promoter/enhancers where epigenetic reprogramming is required for cancer cell survival and angiogenic response. In vivo Tasquinimod was effective as a monotherapeutic agent against human prostate, breast, bladder, and colon tumor xenografts by oral dosing. Tasquinimod also targets infiltrating myeloid cells, and modulates local tumour immunity by blocking the interaction between S100A9 and its ligands receptor of advanced glycation end products and Toll-like receptor 4. Currently it is in phase III clinical trials to treat advanced tumors.

How to Use:

In vitro: Tasquinimod was used at 1-10 μM final concentration in various in vitro assays.

In vivo: Tasquinimod was dosed to mice bearing PC-82 , CWR-22Rv1, LAPC-4, or LNCaP prostate cancer xenografts orally at 30 mg/Kg once per day.

Reference:

1. Raymond E, et al. Mechanisms of action of tasquinimod on the tumour microenvironment. (2014) Cancer Chemother Pharmacol. 73(1):1-8.
2. Isaacs JT, et al. Tasquinimod Is an Allosteric Modulator of HDAC4 survival signaling within the compromised cancer microenvironment. (2013) Cancer Res. 73(4):1386-99.
3. Isaacs JT, et al. Identification of ABR-215050 as lead second generation quinoline-3-carboxamide anti-angiogenic agent for the treatment of prostate cancer. (2006) Prostate. 66(16):1768-78.