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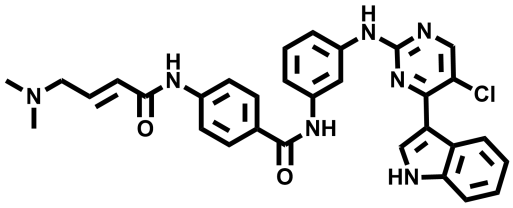
Covalent CDK7 Inhibitor THZ1

Chemical Name: (E)-N-(3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)phenyl)-4-(4-(dimethylamino)but-2-enamido)benzamide



Molecular Weight:	566.05
Formula:	$C_{31}H_{28}ClN_7O_2$
Purity:	≥98%
CAS#:	
Solubility:	DMSO up to 50 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

THZ1 is a novel potent, selective and cell permeable irreversible CDK7 inhibitor with an IC_{50} ~3.2 nM. It has the unprecedented ability to target a remote cysteine residue located outside of the canonical kinase domain, providing an unanticipated means of achieving selectivity for CDK7. Cancer cell line profiling indicates that a subset of cancer cell lines, including human T-cell acute lymphoblastic leukaemia (T-ALL), have exceptional sensitivity to THZ1. It strongly reduces the proliferation and cell viability of T-ALL cell lines. Genome-wide analysis in Jurkat T-ALL cells shows that THZ1 disproportionally affects transcription of RUNX1 and suggests that sensitivity to THZ1 may be due to vulnerability conferred by the RUNX1 super-enhancer and the key role of RUNX1 in the core transcriptional regulatory circuitry in these tumor cells. THZ1 exhibited efficacy in a bioluminescent xenografted mouse model using the human T-ALL cell line KOPTK1. Pharmacological modulation of CDK7 kinase activity by using THZ1 may thus provide an approach to identify and treat tumor types that are dependent on transcription for maintenance of the oncogenic state.

How to Use:

In vitro: THZ1 was used at 0.25-2.5 μM final concentration in various in vitro assays.

In vivo: THZ1 was dosed to the KOPTK1 T-ALL human xenograft mice via IV injection in the lateral tail vein at 10 mg/kg once or twice per day in a volume of 3.3 μL/g. Formulation is 10% DMSO in D5W.

Reference:

1. Kwiatkowski N, et al. Targeting transcription regulation in cancer with a covalent CDK7 inhibitor. (2014) Nature. 511(7511):616-20.