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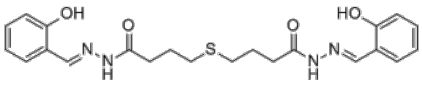
Data Sheet

Global Supplier of Chemical Probes, Inhibitors & Agonists.

Product Name	:	NRF2 inhibitor R16
Cat. No.	:	PC-21180
CAS No.	:	6325-13-9
Molecular Formula	:	$C_{22}H_{26}N_4O_4S$
Molecular Weight	:	442.53
Target	:	Keap1-Nrf2
Solubility	:	10 mM in DMSO



CAS: 6325-13-9

Biological Activity

NRF2 inhibitor R16 is a novel mutated **KEAP1** (mKEAP1)-selective **NRF2** inhibitor, binds KEAP1-mutated proteins (G333C mKEAP1, Kd=2.7 uM) and restores their interaction with NRF2, leading to proteasome-dependent NRF2 degradation.
R16 significantly inhibits G333C, G364C, or R460S KEAP1 mutants with IC50 of <10 uM in ARE-luc reporter assays.
R16 is barely active against BT-20 cells, which bear WT-KEAP1.
R16 directly binds G333C mKEAP1, with a KD of 2.7 ± 0.6 μM, with no significant interaction with WT-KEAP1.
R16 dose-dependently decreases the NRF2 level in A549, H1648, and H322 cells, but not change in transcription level.
R16 dose-dependently decreases the mRNA levels of GCLM and NQO1, which are two well-established NRF2 transcription targets.
R16 dose-dependently decreases NRF2 protein in A549ctl cells bearing the G333C mutant, but not in A549(WT-KEAP1) cells.
R16 at submicromolar concentrations selectively sensitizes KEAP1-mutated cancer cells, but not WT-KEAP1 cells, to cisplatin and gefitinib.
R16 (110 mg/kg, i.p. daily) shows in vivo efficacy and selectively sensitized A549ctl-derived xenograft to cisplatin (2 mg/kg).

References

Aboulkassim T, et al. ***Cell Rep.*** 2023 Sep 12;42(9):113104.

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