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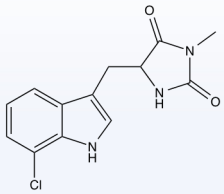
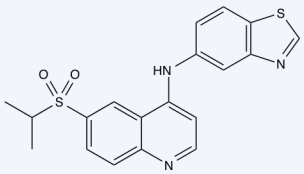
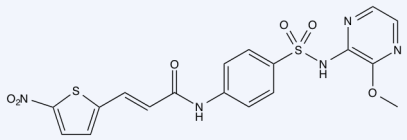
# Necroptosis



7-Cl-O-Nec1



GSK872



Necrosulfonamide

Necroptosis is a caspase-independent form of programmed cell death. It is involved in the pathology of many diseases involving cell death and inflammation. Necroptosis can be triggered by myriad signals including TNF$\alpha$, TRAIL, TWEAK, genotoxic stress, PAMPS (pathogen-associated molecular patterns), and caspase 8 inhibition. The necroptotic signaling pathway begins with activation of Receptor-Interacting Protein 1(RIP1) kinase. In the absence of caspase 8 signaling, RIPK1 and RIPK3 form the necrosome (or complex IIb). This complex recruits mixed-lineage kinase domain-like protein (MLKL), which is phosphorylated by RIPK3. MLKL translocates to the plasma and cytoplasmic membranes starting the necroptotic process.[1,2]

## 7-Cl-O-Nec1

Necrostatin-1 analogue with superior potency ($IC_{50}$ = 206nM vs 494nM), selectivity and metabolic stability in blocking RIP1.[3,4] 7-Cl-O-Nec1 shows no off-target inhibition of indolamine-2,3-deoxygenase (IDO) in contrast to Necrostatin-1 (Nec-1).[5,6] 7-Cl-O-Nec1 showed higher activity in inhibiting necroptosis in Jurkat cells than Necrostatin-1 ($EC_{50}$ = 210 nM vs. $EC_{50}$ = 490 nM), no non-specific cytotoxicity at high concentrations (100 µM) and reasonable pharmacokinetic characteristics when used in mice.[4] 7-Cl-O-Nec1 is recommended for cellular and *in vivo* use over Necrostatin-1.[7]

10-4544 5 mg / $50.00, 25 mg / $185.00

## RIPA-56

RIPA-56 is a potent ($IC_{50}$ = 13 nM, $EC_{50}$ = 28nM for HT-29 cells) and selective inhibitor of Receptor-Interacting Protein 1 (RIP1) kinase with significant metabolic stability ($t_{1/2}$ = 128min human liver microsomal stability assay). RIPA-56 showed excellent kinase selectivity and did not inhibit IDO at 200 µM.[8]

10-4611 10 mg / $40.00, 50 mg / $135.00

## GSK872

GSK872 is a potent ($IC_{50}$ = 1.3 nM) and selective inhibitor of Receptor-Interacting Protein 3 (RIP3). It is able to block virus-induced and TLR3-induced necrosis.[9,10]

10-4861 5 mg / $70.00, 25 mg / $275.00

## Dabrafenib

Dabrafenib is a clinically useful inhibitor of BRAF. It was recently found to selectively inhibit RIP3 ($IC_{50}$ = 250 nM) over RIP1,2, and 5.[11]

10-1569 5 mg / $34.00, 25 mg / $150.00

## Necrosulfonamide

Necrosulfonamide is an inhibitor ($IC_{50}$ <200 nM) of human mixed lineage kinase domain-like protein (MLKL). It is able to block necroptosis downstream of RIP3 activation.[12] MLKL has been found to be critical to the execution of necroptosis.[13-15]

10-4860 5 mg / $40.00, 25 mg / $160.00

## References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