

Necroptosis

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 α , 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 IDO in contrast to Necrostatin-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).⁴ 7-Cl-O-Nec1 is recommended for cellular and *in vivo* use over Necrostatin-1.⁷

Product No: 10-4544 5 mg/ 25 mg/

RIPA-56

RIPA-56 is a potent (IC_{50} = 13 nM, EC_{50} = 28nM for HT-29 cells) and selective inhibitor of RIP1 kinase with significant metabolic stability. RIPA-56 showed excellent kinase selectivity and did not inhibit IDO at 200 μ M.⁸

Product No: 10-4611 10 mg/ 50 mg/

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}

Product No: 10-4861 5 mg/ 25 mg/

Dabrafenib

Dabrafenib is a clinically useful inhibitor of BRAF. It was found to selectively inhibit RIP3 (IC_{50} = 250 nM) over RIP1,2, and 5.¹¹

Product No: 10-1569 5 mg/ 25 mg/

Necrosulfonamide

Necrosulfonamide is an inhibitor (IC_{50} <200 nM) of human mixed lineage kinase domain-like protein (MLKL). Able to block necroptosis downstream of RIP3 activation.¹² MLKL is critical to the execution of necroptosis.¹³⁻¹⁵

Product No: 10-4860 5 mg/ 25 mg/

GSK2982772

Highly selective RIP1 kinase inhibitor.¹⁶

Product No: 10-4792 5 mg/ 25 mg/

CBL0137

Inhibitor of the histone chaperone FACT that activates the Z-RNA-sensor ZBP1 inducing necroptosis.¹⁷

Product No: 10-4026 5 mg/ 25 mg/

Matrine

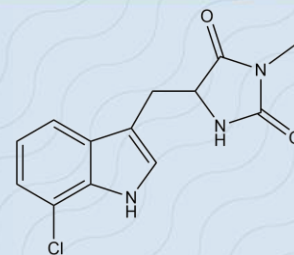
Natural product that induces RIP3-dependent necroptosis.¹⁸

Product No: 10-4612 5 mg/ 25 mg/

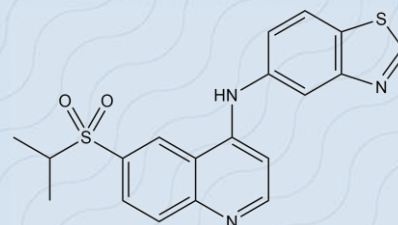
Necrostatin-34

Selective inhibitor of RIP1 kinase. It binds to a site distinct from that of 7-Cl-O-Nec1 locking the enzyme in an inactive conformation. Acts synergistically with 7-Cl-O-Nec1 to inhibit necroptosis.¹⁹

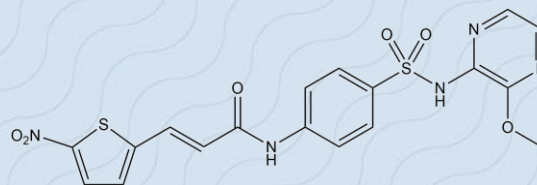
Product No: 10-4684 5 mg/ 25 mg/



7-Cl-O-Nec1



GSK872



Necrosulfonamide

REFERENCES

1. Vanden Berghe *et al.* (2014) *Nat.Rev.Mol.Cell Biol.* **15** 135
2. Weinlich *et al.* (2017) *Nat.Rev.Mol.Cell Biol.* **18** 127
3. Degtarev *et al.* (2005) *Nat.Chem.Biol.* **1** 112
4. Teng *et al.* (2010) *Bioorg.Med.Chem.Lett.* **15** 5039
5. Degtarev *et al.* (2012) *Cell Death Differ.* **20** 366
6. Takahashi *et al.* (2012) *Cell Death Dis.* **3** e437
7. Degtarev *et al.* (2013) *Nat. Chem.Biol.* **9** 192
8. Ren *et al.* (2017) *J.Med.Chem.* **60** 972
9. Kaiser *et al.* (2013) *J.Biol.Chem.* **288** 31268
10. Mandal *et al.* (2014) *Mol.Cell.* **56** 481
11. Li *et al.* (2014) *Cell Death Dis.* **5** e1278
12. Sun *et al.* (2012) *Cell* **148** 213
13. Murphy *et al.* (2013) *Immunity* **39** 443
14. Chen *et al.* (2013) *J.Biol.Chem.* **288** 16247
15. Zhao *et al.* (2012) *PNAS* **109** 5322
16. Harris *et al.* (2017) *J.Med.Chem.* **60** 1247
17. Zhang *et al.* (2022) *Nature* **606** 594
18. Xu *et al.* (2017) *Cell Death Discov.* **23** 16096
19. Meng *et al.* (2021) *Cell Discov.* **7** 41