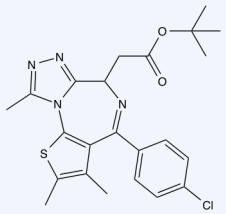
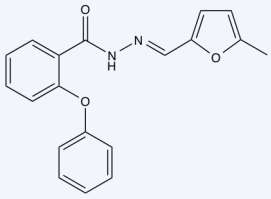
FOCUS on...

Protein-protein Interaction Inhibitors



JQ1



PNU-74654

JQ1 (+/-)

A potent BET bromodomain inhibitor. JQ1 displaces the BRD4 fusion oncoprotein from chromatin, prompting squamous differentiation and specific antiproliferative effects in BRD4-dependent cell lines and patient-derived xenograft models. This work establishes proof-of-concept for targeting protein-protein interactions of epigenetic readers[1].

10-1361 5 mg , 25 mg

Nutlin-3

MDM2 antagonist; inhibits the MDM2-p53 interaction (IC_{50} = 0.09 μM) and activates p53[2]. Displays antiproliferative activity and induces apoptosis in a variety of tumor cells.

10-1350 5 mg , 25 mg

FK506

FK-506, aka Tacrolimus, is a macrolide antibiotic with immunosuppressive properties[3]. It binds the immunophilin, FK506 binding protein (FKBP12), forming a complex which inhibits calcineurin phosphatase. It has pleiotropic effects on physiology, including inhibition of calcium dependent events, enhanced expression of TGFβ and many more.

10-1103 20 mg , 100 mg

Rapamycin

Rapamycin forms a complex with cytosolic FK-binding protein 12 (FKBP12) that binds to mTOR Complex1 (mTORC1) inhibiting the mammalian target of rapamycin (mTOR)[4]. Also binds to mTORC2 leading to decreased glucose tolerance and insensitivity to insulin.

10-1104 20 mg , 100 mg

PNU-74654

PNU-75654 disrupts the Wnt signaling pathway via inhibition of the interaction (KD_{50}= 450 nM) between β -catenin and Tcf4[5]. It was identified in a virtual and biophysical screen for compounds that bound to specific 'hot spots' of the β-catenin and Tcf4 interaction surface.

10-4519 5 mg , 25 mg

AT101 (R-(-)-Gossypol)

A small molecule mimic of the BH3 domain of cellular Bcl-2 inhibitors that interferes with the function of Bcl-2-family antiapoptotic proteins[6]. Induces apoptosis in drug-resistant multiple myeloma cell lines.

10-1165 10 mg , 50 mg

References

1. Filippakopoulos *et al.* (2010), *Selective inhibition of BET bromodomains*; Nature, **468** 1067
2. Vassilev *et al.* (2004), *In vivo activation of the p53 pathway by small-molecule antagonists of MDM2;* Science, **303** 844
3. Thomson *et al.* (1995), *Mode of action of tacrolimus (FK506): molecular and cellular mechanisms*; Ther. Drug Monit., **17** 584
4. Mita *et al.* (2003) *The molecular target of rapamycin (mTOR) as a therapeutic target against cancer;* Cancer Biol. Ther., **2(4 Suppl 1),** S169
5. Trosset *et al.* (2006) *Inhibition of protein-protein interactions: the discovery of druglike beta-catenin inhibitors by combining virtual and biophysical screening;* Proteins, **64** 60
6. Liu *et al.* (2012), *Anti-cancer drug discovery and development: Bcl-2 family small molecule inhibitors* Commun. Integr. Biol., **5** 557

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