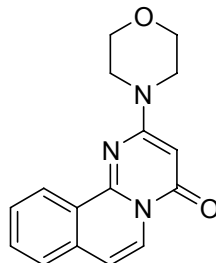


2-(4-Morpholinyl)-4H-Pyrimido[2,1-a]isoquinolin-4-one (Compound 401) - a synthetic inhibitor of DNA-dependent protein kinase (DNA-PK); inhibitor of mammalian target of rapamycin signalling



Chemical Formula: C₁₆H₁₅N₃O₂
Molecular Weight: 281.31

- Ref. 1: Ballou et al. **Inhibition of Mammalian Target of Rapamycin Signaling by 2-(Morpholin-1-yl)pyrimido[2,1-a]isoquinolin-4-one.** *Journal of Biological Chemistry* (2007), 282, 24463-24470
Signalling through the mammalian target of rapamycin (mTOR) is hyperactivated in many human tumors, including hamartomas associated with tuberous sclerosis complex (TSC). Several small molecules such as LY294002 inhibit mTOR kinase activity, but they also inhibit phosphatidylinositol 3-kinase (PI3K) at similar concns. **Compound 401** is a synthetic inhibitor of DNA-dependent protein kinase (DNA-PK) that also targets mTOR but not PI3K in vitro (Griffin, R. J., Fontana, G., Golding, B. T., Guiard, S., Hardcastle, I. R., Leahy, J. J., Martin, N., Richardson, C., Rigoreau, L., Stockley, M., and Smith, G. C. (2005) *J. Med. Chem.* 48, 569-585). **Compound 401** was used to test the cellular effect of mTOR inhibition without the complicating side effects on PI3K. Treatment of cells with 401 blocked the phosphorylation of sites modified by mTOR-Raptor and mTOR-Rictor complexes (ribosomal protein S6 kinase 1 Thr389 and Akt Ser473, resp.). By contrast, there was no direct inhibition of Akt Thr308 phosphorylation, which is dependent on PI3K. Similar effects were also observed in cells that lack DNA-PK. The proliferation of TSC1^{-/-} fibroblasts was inhibited in the presence of 401, but TSC1^{+/+} cells were resistant. In contrast to rapamycin, long-term treatment of TSC1^{-/-} cells with 401 did not up-regulate phospho-Akt Ser473. Because increased Akt activity promotes survival, this may explain why the level of apoptosis was increased in the presence of 401 but not rapamycin. These results suggest that mTOR kinase inhibitors might be more effective than rapamycins in controlling the growth of TSC hamartomas and other tumors that depend on elevated mTOR activity.
- Ref. 2: Griffin et al. **Selective benzopyranone and pyrimido[2,1-a]isoquinolin-4-one inhibitors of DNA-dependent protein kinase: Synthesis, structure-activity studies, and radiosensitization of a human tumor cell line in vitro.** *Journal of Medicinal Chemistry* (2005), 48, 569-585
A diverse range of chromen-2-ones, chromen-4-ones, and pyrimidoisoquinolin-4-ones was synthesized and evaluated for inhibitory activity against the DNA repair enzyme DNA-dependent protein kinase (DNA-PK), with a view to elucidating structure-activity relationships for potency and kinase selectivity. DNA-PK inhibitory activity varied widely over the series of compounds

evaluated (IC_{50} values ranged from 0.19 to >10 mM), with excellent activity being observed for the 7,8-benzochromen-4-one and pyrimido[2,1-*a*]isoquinolin-4-one templates. By contrast, inhibitors based on the benzochromen-2-one (coumarin) or 2-aryl-7,8-benzochromen-4-one (flavone) scaffolds were less potent. Crucially, these studies revealed a very constrained structure-activity relationship at the 2-position of the benzopyranone and pyrimido[2,1-*a*]isoquinolin-4-one pharmacophore, with only a 2-morpholino or 2-(2'-methylmorpholino) group being tolerated at this position. More detailed biological studies conducted with the most potent inhibitor NU7163 (IC_{50} = 0.19 mM) demonstrated ATP-competitive DNA-PK inhibition, with a K_i value of 24 nM, and NU7163 exhibited selectivity for DNA-PK compared with the related enzymes ATM, ATR, mTOR, and PI 3-K (p110alpha). NU7163 sensitized the HeLa human tumor cell line to the cytotoxic effects of ionizing radiation in vitro, a dose modification factor of 2.3 at 10% survival being observed with an inhibitor concentration of 5 mM. This study identified these structural classes as novel DNA-PK inhibitors and delineated initial structure-activity relationships against DNA-PK.

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7070707024	168425-64-7	1 mg 5 mg 25 mg 1 gram	In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR