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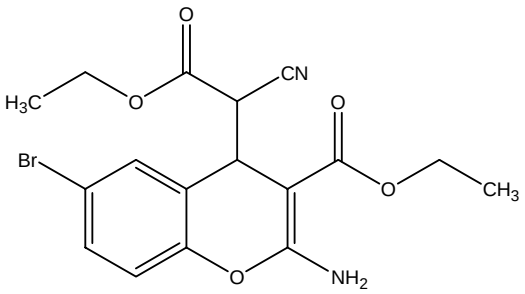
ProductInformation

HA 14-1

Product Number **H 8787**
Store at –20 °C

Cas #: 65673-63-4
Chemical Name: Ethyl [2-amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)]-4H-chromene-3-carboxylate, 2 Amino-6-bromo-α-cyano-3-(ethoxycarbonyl)-4H-1-benzopyran-4-acetic acid ethyl ester



Product Description
Molecular formula: $C_{17}H_{17}BrN_2O_5$
Molecular Weight: 409.2

HA 14-1 is a novel cell permeable, low molecular weight nonpeptide Bcl-2 ligand, which antagonizes the function of Bcl-2 and induces apoptosis.[1-5].
Bcl-2 is a potent suppressor of apoptosis originally described as the chromosomal breakpoint (t(14:18)) in B-cell lymphomas. Bcl-2 is highly overexpressed in a variety of human cancers. It belongs to a growing family of apoptosis regulators of the same name which include both anti-apoptotic (Bcl-2, Bcl-X_L) and pro-apoptotic (Bax, Bak, Bid, Bad) members. The Bcl-2 family members share Bcl-2 homology regions (BH domains) termed BH1 to BH4. BH1, BH2 and BH3 domains can interact to create a hydrophobic cleft into which the amphipathic BH3 "ligand" domain can bind. The Bcl-2 family members function through homo- or hetero-dimerization effectively titrating each other in functional concentration and acting as a rheostatic mechanism in apoptosis control. Bcl-2 family members have pore-forming capability. When homodimerized, pro-apoptotic Bcl-2 members such as BAX translocate to the mitochondrial membrane and directly mediate the release of cytochrome c and the mitochondrial permeability transition (MPT, $\Delta\psi_m$, depolarization) both being late events in mitochondrial apoptosis pathway. Bcl-2 prevents apoptotic death through protein-protein interaction with BAX and its functional removal. Hence much effort has been invested in the discovery of Bcl-2 inhibitors for their potential as cancer therapeutic agents. HA 14-1 acts by binding to the Bcl-2 surface pocket, disrupts Bax/Bcl-2 interaction, and induces apoptosis via activation of caspases.[1] In fluorescence polarization assays, HA14-1 competes against Flu-Bak-BH3 (5-carboxyfluorescein conjugated peptide derived from BH3 domain of Bak) for binding to Bcl-2 with an IC_{50} ~ 9μM. In human acute myeloid leukemia (HL-60) cells, HA 14-1 induced 100% apoptosis at 50 μM. This apoptosis is associated with the loss of the mitochondria membrane potential and proteolytic cleavage and activation of caspase 9 and caspase 3. HA14-1 induced apoptosis is also Apaf-1 dependent, consistent with a mechanism targeting the mitochondrial pathway. The compound has no effect on Apaf-1-/- mouse embryonic fibroblasts and its effect on wild type cells is abrogated by treatment with zVAD-fmk which blocks capsase activation. In addition, HA 14-1 enhances epothilone B (EpoB)-induced cell death in human breast cancer cells. [2}

BH3 domain derived peptides have been investigated and found to be effective as apoptosis inducers in cell-free systems. However, their potential use as therapeutic agent and as tools for in vivo studies of the mechanism of mitochondrial apoptosis is limited by their sensitivity to proteolysis as well as their limited ability to cross the cell membrane. HA14-1 as a small nonpeptidic inhibitor of Bcl-2 overcomes these limitations and is a unique chemical probe for elucidating the molecular mechanisms of the important and growing family of Bcl-2 apoptosis regulators.

References
1. Wang, J-L., et al., Proc. Natl. Acad. Sci., **97**, 7124-7129 (2000).
2. Yamaguchi, H., et al., Cancer Research, **62**, 466-471 (2002).
3. Milella, M., et al., Blood, **99**, 3461-3464 (2002).
4. Kessel, D., et al., Photochem Photobiol., **76**, 314-319 (2002).
5. Chen, J., et al., mol. Cancer Ther., **1**, 961-967 (2002)

KA/RP 10/03