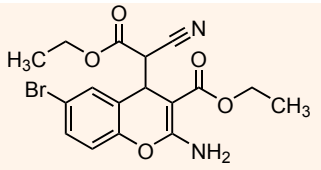
New Product Highlights

HA 14-1: A cell-permeable, nonpeptide apoptosis inducer and Bcl-2 antagonist

Bcl-2 is a potent suppressor of apoptosis originally described as the chromosomal breakpoint (t(14:18)) in B-cell lymphomas and is highly overexpressed in a variety of human cancers. It belongs to a growing family of apoptosis regulators that include both anti-apoptotic **Bcl-2** (Prod. No. B 1182) and **Bcl-X_L** (Prod. Nos. B 0934 and B 8056)) and pro-apoptotic (Bax, Bak, **Bid** (Prod. No. B 8181) and **Bad** (Prod. No. B 1682)) members. 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. When homo-dimerized, pro-apoptotic Bcl-2 members such as Bax translocate to the mitochondrial membrane and directly mediate cytochrome c release and mitochondrial permeability transition (MPT, $\Delta\psi m$, depolarization), both late events in the 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 search for Bcl-2 inhibitors as potential cancer therapeutic agents. **HA 14-1** (Prod. No. H 8787) is a novel cell-permeable, nonpeptide Bcl-2 ligand that antagonizes the function of Bcl-2 and induces apoptosis [1-5]. HA 14-1 acts by binding to the Bcl-2 surface pocket, thus disrupting Bax/Bcl-2 interaction, and inducing apoptosis via activation of caspases [1]. In fluorescence polarization assays, HA 14-1 competes with Flu-Bak-BH3 (5-carboxyfluorescein-conjugated peptide derived from the BH3 domain of Bak) for binding to Bcl-2 displaying an IC_{50} value of 9 µM. Using human acute myeloid leukemia (HL-60) cells, HA 14-1 (50 µM) effectively induced apoptosis associated with the loss of the mitochondrial membrane potential and activation of caspase 9 and caspase 3.

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 agents 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. HA 14-1, as a small nonpeptide inhibitor of Bcl-2, overcomes these limitations and is therefore a unique chemical probe for elucidating the molecular mechanisms associated with the important and growing family of Bcl-2 apoptosis regulators.



HA 14-1
(Prod. No. H 8787)

References
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2. Yamaguchi, H., et al., *Cancer Res.*, **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).
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Related Products

B1809	**Monoclonal Anti-Bcl2α,** Clone 10C4 (mouse)
B9429	**Monoclonal Anti-Bcl-X_L**, Clone 2H12 (mouse)
B8554	**Monoclonal Anti-Bax**, Clone 2D2 (mouse)
B3170	**Monoclonal Anti-Bcl-2**, Clone Bcl-2-100 (mouse)
B9804	**Monoclonal Anti-Bcl-2**, Clone 10C4 (mouse)
C5723	**Anti-Cytochrome C** (rabbit)
B5897	**Anti-Bak** (rabbit)
B8429	**Anti-Bax**, Clone 6A7 (mouse)
B9054	**Anti-Bax**, Clone 5B7 (mouse)

Antibodies to Multi-Drug Resistance Associated Proteins (MRPs)

Many cancer cells treated with chemotherapy agents develop multi-drug resistance (MDR). As a result, several different proteins are upregulated in the resistant cells. These proteins include P-glycoprotein (PgP/P-170/MDR1) - an efflux pump, lung resistance-related protein (LRP) - a major vault protein, topoisomerase II, glutathione S-transferase, and multi-drug resistance associated protein (MRP), another efflux pump [1].

Multi-drug resistance proteins (MRPs) belong to the ABC (ATP-binding cassette) superfamily of transporter proteins that share a common molecular architecture. These transporters are able to transfer a wide range of different drugs out of cells [2,3]. The MRP subfamily of ABC transporters consists of seven members of which six are able to traffic amphipathic anions. MRP1, MRP2 and MRP3 have similar structures and the ability to transport glutathione and glucuronate conjugates. MRP4 and MRP5 share more structural similarity with each other than with MRP1, MRP2 and MRP3. MRP4 and MRP5 also have the ability to transport cyclic nucleotides [4].

Sigma-RBI is pleased to offer several antibodies to human MRPs that may be used to study the role of these proteins in the multi-drug resistance process.

Antibodies

M 9067	**Monoclonal Anti-MRP1,** Clone QCRL-1 (mouse)
M 9192	**Monoclonal Anti-MRP1,** Clone QCRL-4 (mouse)
M 6565	**Monoclonal Anti-MRP1,** Clone P2A8/6 (mouse)
M 8316	**Anti-MRP2** (rabbit)
M 6567	**Monoclonal Anti-MRP3,** Clone M3II-21 (mouse)
M 6067	**Monoclonal Anti-MRP5,** Clone M5I-1 (mouse)
M 6442	**Monoclonal Anti-MRP5,** Clone M5II-54 (mouse)

References
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2. Gottesman, M.M., et al., *Ann. Rev. Biochem.*, **62**, 385-427 (1993).
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