Nicholas D. P. Cosford, Med chem 2013, 3:4
http://dx.doi.org/10.4172/2161-0444.S1.009

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Medicinal Chemistry & Computer Aided Drug Designing

October 15-17, 2013 Hampton Inn Tropicana, Las Vegas, NV, USA

Design, synthesis and characterization of novel inhibitor of apoptosis protein (iap) antagonists

Nicholas D. P. Cosford
Burnham Medical Research Institute, USA

The inhibitor of apoptosis proteins (IAPs) are critical regulators of cell death in humans and are implicated in tumor cell survival and hence the progression of cancer. We recently reported the systematic rational design and synthesis of new monovalent Smac mimetics that bind preferentially to the BIR2 domain of the anti-apoptotic protein XIAP. Characterization of compounds *in vitro* led to the determination of key structural requirements for BIR2 binding affinity. Additional optimization led to compounds in the series with potent affinity for the BIR2 domain of XIAP and no activity at the BIR3 domain. Optimized compounds sensitized TRAIL-resistant breast cancer cells to apoptotic cell death, highlighting the value of these probe compounds as tools to investigate the biology of XIAP. More recently, we developed a novel series of highly potent, drug-like Smac mimetics that were synthesized in a highly convergent and rapid fashion (≤6 steps) using the Ugi four component reaction as the key step, thus enabling rapid lead optimization. These IAP antagonists exhibited powerful cancer cell growth inhibitory activity in multiple cell lines, including single agent toxicity at low nanomolar levels against SKOV3 human ovarian carcinoma cells. This presentation will describe the evolution and structure-activity relationships around these two novel series of compounds which display distinct biological profiles.

ncosford@sanfordburnham.org