

## **INHIBITORS OF NFκB DERIVED FROM THALIDOMIDE**

Esperanza Caracache de-Blanco<sup>a</sup>, Bulbul Pandit<sup>a</sup> and Pui-Kai Li<sup>a</sup>

*<sup>a</sup>Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus Ohio 43210 USA.*

NFκB is a transcription factor that has been found to be involved in cellular alterations such as self-sufficiency in growth signals; insensitivity to growth inhibition; evasion of apoptosis; immortalization; sustained angiogenesis; and tissue invasion and metastasis. It has also been shown to be constitutively activated in some types of cancer cell. Activated NFκB has been associated with several aspects of tumorigenesis, including promoting cancer-cell proliferation, preventing apoptosis, and increasing a tumor's angiogenic and metastatic potential. Furthermore, constitutive activation of NFκB in cancer cell may be critical in their development of drug resistance to certain cytotoxicity agents. Therefore, inhibitors of NFκB activation are potential antitumor agents. In addition, they may also be potential agents to reverse chemoresistance in cancer cells.

As part of a collaborative drug design and discovery effort to search for inhibitors of NFκB, we use thalidomide as the lead structure for the design of NFκB inhibitors. Thalidomide and its analogs were tested for their potential as NFκB inhibitors using an ELISA-based assay. We demonstrated that thalidomide inhibited NFκB activation. In addition, one of the thalidomide analogs (CT-100) exhibited significant inhibitory activity of NFκB in the ELISA-based assay with an IC<sub>50</sub> value of 0.9 μM. Preliminary studies also indicated CT-100 acted in combination with cisplatin in cisplatin-resistant ovarian cancer cell lines.