

**B14** The biological activities of new polyamine derivatives as potential therapeutic agents

**P. Kong Thoo Lin<sup>1</sup>, A.M. Dance<sup>1</sup>, C. Bestwisck<sup>2</sup>, L. Milne<sup>2</sup>**

*<sup>1</sup>The Robert Gordon University, School of Life Sciences, St. Andrew Street, Aberdeen, UK, <sup>2</sup>The Rowett Research Institute, Greenburn Road, Aberdeen, UK*

A number of polyamine derivatives have demonstrated potential as therapeutic agents. For example, 1,12-bisethylspermine, bisnaphthalimide (elinafide) are currently in phase I pre-clinical trials for the treatment of certain cancers. Here the biological activities of two new groups of polyamine derivatives, namely the oxa-polyamines and the bisnaphthalimides are presented. The most active compounds in the oxa-polyamine and bisnaphthalimido series, possessed an IC<sub>50</sub> of 2.93  $\mu$ M and 1.38  $\mu$ M respectively against MCF7 cells after 48h exposure. The SAR of each group of compounds will be discussed.

Bisnaphthalimido compounds are well known DNA binding agents. The DNA binding properties with our series of bisnaphthalimido compounds was studied with T<sub>m</sub> (oC) measurement of DNA duplex, ethidium bromide displacement using fluorimetric method and DNA gel retardation assay.

In HL-60 promyelocytic leukaemia cells, oxa-polyamine and bisnaphthalimido treatment resulted in a decline in cell proliferation and viability. With oxa-polyamine, changes in viability were accompanied by DNA fragmentation typical of apoptosis but the rapidity of membrane damage suggested a principally non-apoptotic mode of cell death. In contrast, cell death induced by the bisnaphthalimido series was characterized by elevated caspase-3 activity, exposure of phosphatidylserine exclusive from membrane damage, increased DNA instability and, ultimately DNA fragmentation. Thus the principal cytotoxic members of the bisnaphthalimido series appear to induce apoptosis.