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New agents for the treatment of leukemia: discovery of DMAPT (LC-1)

Acute myeloid leukemia (AML) is a relatively rare cancer with approximately 13,000 new cases diagnosed and approximately 9000 deaths per year in the United States [1]. AML is a potentially curable cancer; however, only about 40% of patients under age 60 and about 15% of patients over age 60 are cancer free four years after treatment. Although the prognosis is significantly better in patients under age 60, overall, treatment for AML remains an area of high unmet medical need. Inhibition of the NF-κB transcription factor complex leads to downregulation of certain antiapoptotic genes thereby promoting apoptosis. A recent report details the discovery of a novel NF-κB inhibitor DMAPT (LC-1, **1**, Fig. 1), a compound reported to be in phase I clinical trials in the United Kingdom for the treatment of AML [2].

The naturally occurring agent parthenolide (PTL, **2**, Fig. 1) has been identified as a promising inhibitor of NF-κB. Treatment with parthenolide at 10 μM concentration led to 84% cell death and LD_{50} of 1.4 μM, in a cell culture assay of primary AML cells. The main limitation of parthenolide as a clinical agent, however, is its low serum solubility (0.169 μmole/mL). SAR studies of parthenolide demonstrated that various structural modifications including reduction of the exocyclic alkene, epoxidation of the endocyclic alkene, or oxidation of the allylic methyl group resulted in loss of activity. By contrast, conjugate addition of aliphatic amines to the exocyclic alkene produced adducts which retained potency and were also water soluble, as their corresponding ammonium salts, overcoming the primary limitation of parthenolide. A screen of 31 aliphatic amines yielded the dimethyl analog DMAPT (LC-1, **1**) as an optimized analog. In the primary AML cell-line assay, treatment with DMAPT at 10 μM led to 93% cell death and LD_{50} of 1.7 μM.

In vivo studies of DMAPT demonstrated an oral bioavailability of 70% in the rat; with the main metabolite resulting from mono *N*-demethylation. It has been reported that aminoparthenolide derivatives, such as DMAPT, can undergo retro-Michael additions to regenerate the parent, parthenolide. However, stability assays of DMAPT in the AML cell culture media displayed <3% degradation of DMAPT to parthenolide over 24 hours. Furthermore, only very low levels of parthenolide were detected in plasma after eight hours following oral dosing in the rat. Because of its favorable profile, DMAPT is currently being evaluated in combination with other chemotherapeutics for the treatment of primary AML in the United Kingdom.

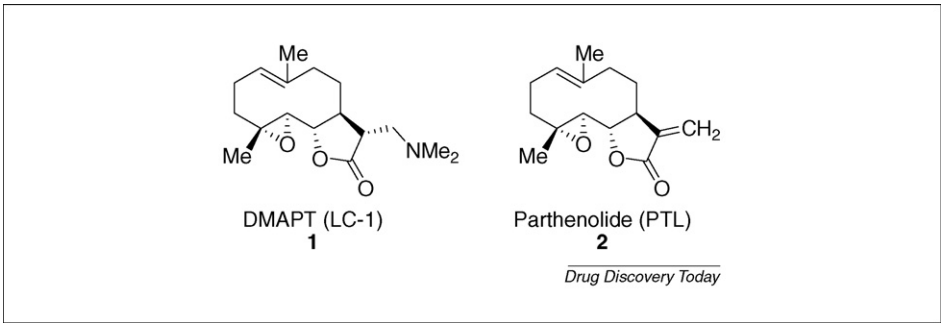

FIGURE 1

Structures of DMAPT (LC-1) **1** and parthenolide (PTK) **2**.

1 American Cancer Society website: www.cancer.org

2 Crooks, P.A. *et al.* (2009) Aminoparthenolides as novel anti-leukemic agents: discovery of the NF-κB inhibitor, DMAPT (LC-1). *Bioorg. Med. Chem. Lett.* 19, 4346–4349

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