Epothilones as lead structures for new anticancer drugs – pharmacology, fermentation, and structure-activity-relationships

By Karl-Heinz Altmann¹ and Klaus Memmert²

¹Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, Swiss Federal Institute of Technology (ETH) Zürich, Switzerland
<karl-heinz.altmann@pharma.ethz.ch>

²Novartis Institute for Biomedical Research Basel, Switzerland
Abstract

Epothilones (Epo’s) A and B are naturally occurring microtubule-stabilizers, which inhibit the growth of human cancer cells \textit{in vitro} at low nM or sub-nM concentrations. In contrast to taxol (paclitaxel, Taxol®) epothilones are also active against different types of multidrug-resistant cancer cell lines \textit{in vitro} and against multidrug-resistant tumors \textit{in vivo}. Their attractive preclinical profile has made epothilones important lead structures in the search for improved cytotoxic anticancer drugs and Epo B (EPO906, patupilone) is currently undergoing Phase III clinical trials. Numerous synthetic and semisynthetic analogs have been prepared since the absolute stereochemistry of epothilones was first disclosed in mid-1996 and their \textit{in vitro} biological activity has been determined. Apart from generating a wealth of SAR information, these efforts have led to the identification of at least six compounds (in addition to Epo B), which are currently at various stages of clinical evaluation in humans. The most advanced of these compounds, Epo B lactam BMS-247550 (ixabepilone), has recently obtained FDA approval for the treatment of metastatic and advanced breast cancer. This chapter will first provide a summary of the basic features of the biological profile of Epo B \textit{in vitro} and \textit{in vivo}. This will be followed by a review of the processes that have been developed for the fermentative production of Epo B. The main part of the chapter will focus on the most relevant aspects of the epothilone SAR with regard to effects on tubulin polymerization, \textit{in vitro} antiproliferative activity, and \textit{in vivo} antitumor activity. Particular emphasis will be placed on work conducted in the authors’ own laboratories, but data from other groups will also be included. In a final section, the current status of those epothilone analogs undergoing clinical development will be briefly discussed.

1 Introduction

Cancer represents one of the most severe health problems worldwide, with a total of 1,399,790 new cancer cases and 564,830 deaths from cancer expected in 2006 in the US alone [1]. Substantial progress in our ability to treat this deadly disease (or, more accurately, this heterogeneous group of diseases) will critically depend on the discovery of new anticancer drugs and the development of more effective clinical treatment strategies. Much of the recent research in these areas has focused on cancer-specific mechanisms and the corresponding molecular targets, which may be addressed either by small molecules or, increasingly so, by therapeutic antibodies [2–5]. However, in spite of impressive advances in the development of signal transduction kinase inhibitors for cancer treatment [2, 3] or receptor- or ligand-directed antibodies [4, 5], the search for improved cytotoxic agents (acting on ubiquitous targets such as DNA or tubulin) still constitutes an important part of modern anticancer drug discovery. As the major types of solid human tumors (breast, lung, prostate, and colon), which represent the vast majority of cancer cases today, are multi-causal