JOURNAL OF NATURAL PRODUCTS

BOOK REVIEW

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Review of The Epothilones: An Outstanding Family of Anti-Tumor Agents. From Soil to the Clinic

The Epothilones: An Outstanding Family of Anti-Tumor Agents. From Soil to the Clinic. Edited by A. D. Kinghorn, H. Falk, and J. Kobayashi. Progress in the Chemistry of Organic Natural Products, Vol. 90. SpringerWien: NewYork, NY, USA. 2009. x + 260 pp. 9.4 × 6.2 in. $249.00. ISBN 978-3-211-78206-4 (hardcover), 978-3-211-99928-8 (paper).

There are many twists and turns in the path of a drug candidate on its way from the lab to the clinic, and these are not always evident from a reading of the primary scientific literature. Coupled with the many years the process takes, it can be difficult to achieve any sort of perspective. Book-length, multiauthor reviews such as this example thus play an important role, integrating the many events, blind alleys, and successes that make up the complete story. This is particularly true for natural products, where the final clinical indication is not always clear at the outset.

The epothilones were initially isolated from the slime mold *Sorangium cellulosum* as antifungal compounds by the Reichenbach group at the German Centre for Biotechnology. While their cytotoxic properties were noted early on, this was considered more a limitation to antifungal use in human medicine or in crop protection than as an invitation to cancer drug development. Testing in the U.S. National Cancer Institute 60-cell screen did not engender immediate interest. What moved the epothilones forward as cancer drug candidates was their rediscovery in a Merck screening program for compounds that could stabilize microtubules in a manner similar to Taxol. Notably, however, a similar Upjohn screening program turned up no meaningful hits.

Thereafter, the epothilones developed momentum, and this volume does a fine job of describing the details. An initial chapter by Gerhard Höfle covers much of the early history, while Rolf Müller describes the extensive work in Braunschweig and at Kosan and Novartis to elucidate the epothilone biosynthesis gene clusters and their functions. The largest single chapter is a review of the total synthesis of epothilones, in which many prominent synthesis groups participated. At least 16 approaches to the total synthesis of the major epothilones have appeared! Despite the fine science developed for biosynthesis and total synthesis, at this time the most practical strategy for sourcing the compounds has turned out to be semisynthesis, and a chapter by Karl-Heinz Altmann describes many synthetic modifications of the epothilone skeleton. A further chapter by the same author treats structure−activity studies and preclinical pharmacology separately from the earlier chapter. Finally, Altmann is called on again to describe clinical studies with various epothilones.

At this time, ixabepilone (BMS) is the sole drug to have reached the market; however, sagopilone (Bayer) is currently in phase II clinical trials. Other analogues such as patupilone and ABJ-879 failed in clinical trials, and their development has not been pursued.

The volume is a fine addition to the literature and should be informative to anyone interested in the historical trajectory of successful cancer drug development from natural products. Despite the high list price of both the hardback and paperback editions, it is readily available through Internet booksellers at a more modest cost.

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10.1021/np200131z

Published: March 02, 2011