

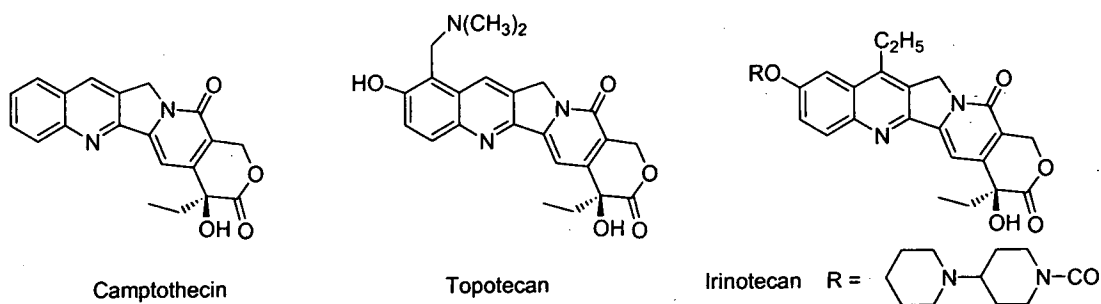
Research Progress on Camptothecin Analogues as Topoisomerase Inhibitors

Sabrina Dallavalle

Dipartimento di Scienze Molecolari Agroalimentari, Università di Milano,
Via Celoria 2, 20133 Milano, Italy
E-mail: Sabrina.dallavalle@unimi.it

Natural products, with their tremendous structural diversity, are an important source of new biologically active compounds. Many useful drugs are of natural origin, or are obtained by skilful modification of natural substances. Various important anti-cancer agents like vincristine, vinblastin, paclitaxel and podophyllotoxin have been isolated from various plant sources.

Camptothecin (CPT), a pentacyclic alkaloid first isolated by Wall et al. in 1966 from the Chinese tree *Camptotheca acuminata*,¹ was found to possess an interesting antitumor activity. Late in 1985, it was reported by Liu et al. that the cytotoxic activity of CPT was attributed to a novel mechanism of action involving the nuclear enzyme classified as type I DNA topoisomerase.² Topoisomerase I is an ubiquitous enzyme that plays an important role in DNA replication, transcription, recombination and repair. Thus, inhibition of topoisomerase I has important consequences for chemotherapeutic treatment of tumors.



Camptothecin has a broad spectrum of anticancer activities, however its low solubility in water, the lactone ring instability and high toxicity, including myelosuppression, vomiting, diarrhoea and serious hemorrhagic cystitis, severely limited its clinical use. These adverse effects led to a growing interest in the development of CPT analogues that exhibit less severe drawbacks, while maintaining their therapeutic activity.

Fifty years after its discovery, extensive efforts continue to be made in the medicinal chemistry of camptothecin. Thousands of CPT analogues have been prepared and structure-activity relationship studies have been developed. Some analogues are in various stages of preclinical and clinical development; two of them, topotecan and irinotecan, have successfully entered the market and are used as topoisomerase I poisons in clinical practice.³

Besides structural modification, the establishment of new drug delivery systems has recently become a hot topic in the CPT research. Progresses in the delivery systems, in controlled

release systems and targeting delivery systems of camptothecins are the great challenge of the last decade.

The main focus of this presentation will be on the development of CPT derivatives over the years (including those from our own research) and the potential and future development trends of the newly discovered anticancer compounds.

References

1. Wall, M.E.; Wani, M.C.; Cooke, C.E.; Palmer, K.T.; McPhail, A.T.; Sim, G.A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.
2. Hsiang, Y.-H.; Hertzberg, R.; Hecht, S.M.; Liu, L.F. *J. Biol. Chem.* **1985**, *260*, 14873.
3. Dallavalle S.; Merlini, L. in "Modern Alkaloids"; E. Fattorusso, O. Tagliatella Eds.; Wiley-VCH: Weinheim, **2008**, pp. 503-520.