



Anticancer Extracts or Hemi-Synthesized Starting From Medicinal Herbs.

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Abstract

For much of cancer the adequate biodisponibility at the tumoral level, without over-exposure of healthy fabrics, remains a major limitation for an effective chemotherapy and not very toxic, the improvement of the specificity of action and the prevention of toxicity represent the main axes of research under full development. The greatest challenge in cancerology is to improve specificity of action of the anti-cancer drugs by detection of the cancer cells and treatment selective of these sick cells. The anti-cancer ones discovered during first decades of chemotherapy interacted mainly with the DNA or its precursors inhibiting the synthesis again material genetics, or causing irrevocable damage with the DNA itself. These last years, the discovery of new agents extended from the natural products most conventional, these substances are themselves a source for the synthesis or the hemisynthesis of other anti-cancer molecules. In this context, the objectives of our work were to give a chemical and therapeutic study of anti-cancer derived from medicinal herbs and to demonstrate the principals methods of obtaining of these anti-cancer derivatives.

Keywords: cancer, natural anticancer, synthesis, medicinal herbs.

Introduction

The DNA plays a key role in the life and the division of the cells, it constitutes the target most exploited in antitumor chemotherapy; therefore it is obvious that the sought-after goal in the use of the antitumor agents is to reach the tumoral cells in order to destroy them. All this explains the multiplicity of the research undertaken in the field of the cancerology; several processes can be used for the eradication of a tumor: the surgical exérèse, the radiotherapy and chemotherapy which are the average classics employed and intended to cause cellular death.

Progress of anticancer means allowed the emergence of different therapeutic approaches: the anticancer resulting ones from molecular biology and the anticancer ones of natural origin. Today, this therapeutic innovation has allows a better control of the side effects and toxic effects, and to note

promising results in the treatment of various types of cancers.

Anticancer extracts of Camptothécine:

Chemical structure: The compound pentacyclic comprises a cycle pyrrolo [3,4-b] quinoline (cycles A, B, C), a cycle indolizine (cycle C, D) and a d-lactonic cycle (E) with a chiral center (in C4) of configuration S, carrying a tertiary hydroxyl.

Structural modifications were carried out by substitution into 10 of (S) - camptothécine natural or of (S) - 9-hydroxycamptothécine

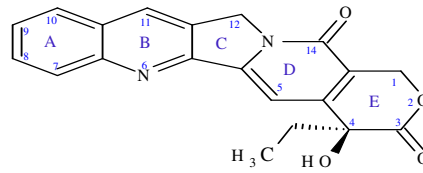


Fig.1: Chemical structure of Camptothécine.

Irinotécán, comprising OH phenolic into 9 (carbamate) and a chain ethyl in 11. The sequence pipéridinopipéridine carried by carbamic ester makes it possible to increase the hydrosolubility of éthyhydroxycamptothécine. Le

Topotécán is (+)-(4S)-10-[(diméthylamino) méthyl]-4-éthyl-4,9-dihydroxy-1H-pyranol[3',4':6,7]indolizino[1,2-b]quinoléine-3,14(4H,12H)-dione.

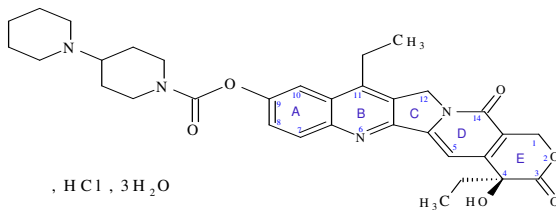


Fig. 2: Chemical structure of Irinotecan

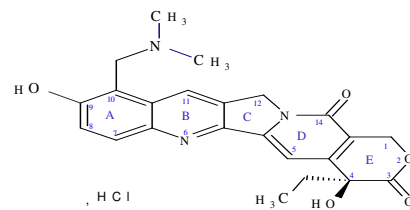


Fig.3: Chemical structure of Topotécán

- Preparation:
 The camptothécine is an alkaloid extracted for the first time from the bark from a Chinese tree, *Camptotheca acuminata*, then of a tree of t

he south of India and Taiwan, *Nothapodytes faetida*



Fig.4: Tree of *Camptotheca acuminata*

- Mode of action:
 The Camptothecin and its derivatives act on the replication of the DNA; the cut of one of the chains by a topoisomérase allows désenroulement and the relieving of the propeller of the DNA. These initial stages of the process of replication are normally followed of a welding of the chain broken with formation

of a fork of replication and a complete duplication of the molecule of DNA. The Camptothecin and its derivatives cause a stabilization of the cleavable complex normally formed between the DNA and the topoisomérase I, this action induced of the lesions simple-bit of the DNA which block the replication.

○

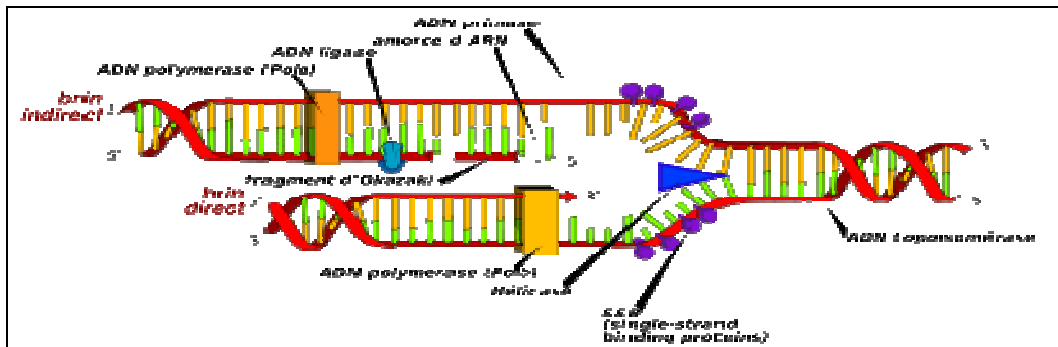


Fig.5: Site of action of Irinotecan and Topotecan.

○ Therapeutic use: Irinotecan is used for treatment of colorectal cancers metastatic after failure of a former

treatment by the 5-fluorouracile, while Topotecan is used for treatment of cancer of the repeating ovary.

▪ **Anticancer synthesized starting from Podophyllotoxine:**

○ Chemical structure:

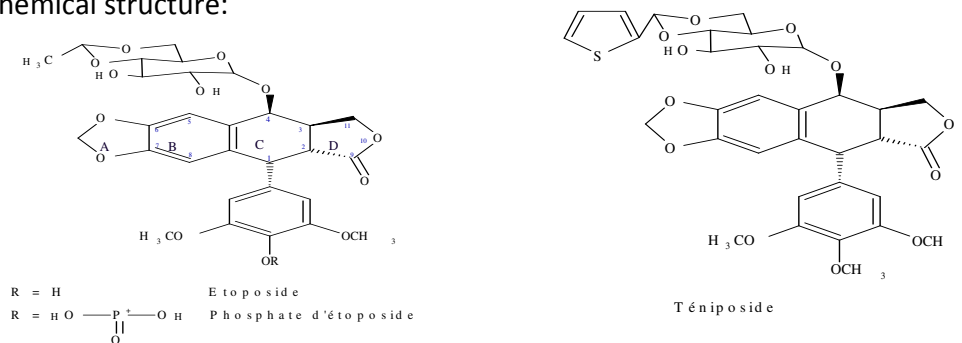
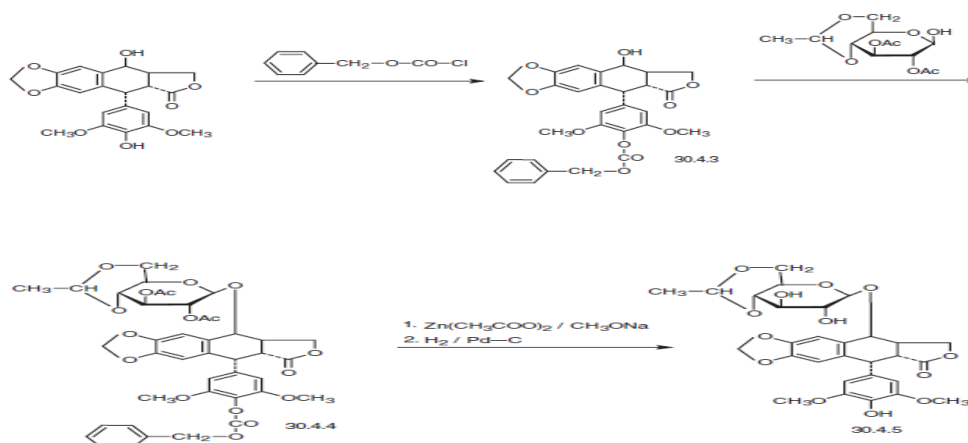


Fig.6: Chemical structure of Etoposide and Teniposide

○ Chemical synthesis:

Podophyllotoxine is one of the components of podophylline extracts alcoholic coniferous tree from the roots and the rhizomes of various species of podophylle: Podophyllum peltatum .The chemical synthesis of Etoposide is done by use of

Epipodophyllotoxine like a raw material, the chemical synthesis of Teniposide is carried out by substitution of methy group of Etoposide by a thiophene group.



Etoposide

Fig.7: Chemical synthesis of Etoposide.

- Relation structure-activity:
- ✓ Influence of the nature of the chain in position 4: simple glycosylée chain: D-glucose in position 4 of podophyllotoxine increases the hydrosolubility, the replacement of a β, D-glucose by β.D galactopyranose decreases the activity in vivo and in vitro, it is with the steric obstruction, which prevented the connection with report- isomérase II. The best results have summers obtained after condensation with the ethanal which make Etoposide or condensation by 2-thiénylcarboxaldéhyde which make Téniposide.
- ✓ Influence of the modification of the cycle lactone: Trans stereophony- isomerism is fundamental for the stabilization of the cleavable complex with the topo-isomérase II, the complexes cis are inactive. The replacement of lactone by a lactam of the Etoposide increases the activity of 10%, the reduction of lactonic group(CO) in (CH₂) decreases the cytotoxicity on various tumoral lines. The opening of the cycle lactone of Etoposide and Teniposide leads to the inactive acid cis- hydroxy.
- **Anticancer extracts of Taxane :**
- Chemical structure: Structure complexes class of Taxane.
- ✓ Influence of the modification of cycle a: The grouping méthylendioxy of cycle A is essential for the activity, its replacement by 2groupings methoxyl, hydroxyl or by a fonction thiocarbonyle led to molecules of low toxicity in vitro, inactive on L1210 in vivo.
- ✓ Influence of the nature of the substituents of the cycle E: Derivatives 4'-demethylated are slightly more active that the not demethylated compounds, the cytotoxic activity of the inhibitors of the topoisomérase II seems dependent the presence of hydroxyl into 4'.
- Mode of action: Inhibition of report-isomérase II, enzyme allowing the transcription and the replication of the DNA, the blocking of the cellular division is carried out at a stage earlier than for the poisons of the spindle.
- Therapeutic use : Etoposide is used for treatment of disease of Hodgkin and lymphomas not Hodgkin, solid tumors, acute myeloid and lymphoblastic leukemia, while Teniposide is used for treatment of cancers of the testicule, the bronchi with small cells, breast cancer.

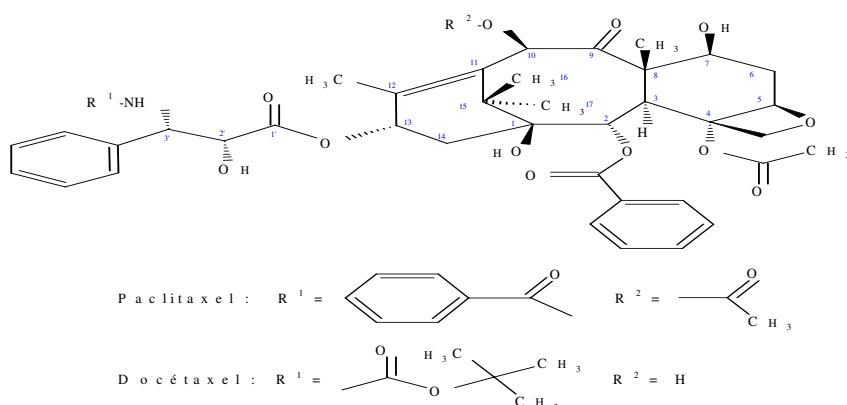


Fig.8: Chemical structure of Paclitaxel and Docetaxel.

- Relation structure-activity: complex of the class of the taxane whose activity depends on the presence of a skeleton taxane of the type polyoxygéné methanobenzocyclodecene, coupled cycle oxétane in position 4 and 5 and one site chain carrying the function ester out of carbon 13.
- Preparation: Paclitaxel was isolated from the barks of the Yew of the pacific (*Taxus*

brevifolia). Currently, these derivatives are obtained by hemisynthesis starting from the baccatine III or the 10-désacétylbaccatine III after extraction of the needles of the yew of various origins (*Taxus baccata*) more available than the barks necessary to the extraction.

The paclitaxel is the derivative of the yew of the Pacific whereas the Docetaxel is the derivative of the European yew.

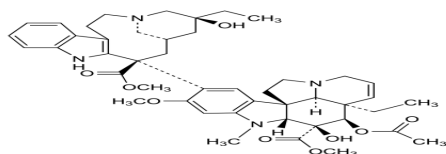


Fig.9: Yew of the pacific (*Taxus brevifolia*).

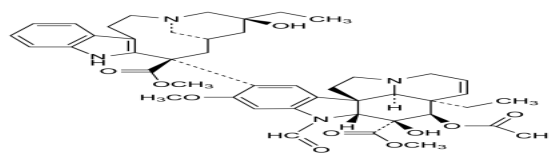
- Mode of action: Block the cellular replication by inhibiting the depolymerisation of the tubuline and by increasing its polymerization, which would make it possible to decrease the resistance of certain cancers the other anti-cancer ones.
- Therapeutic use: Paclitaxel is used for treatment of ovarian cancers metastases, in the event of failure

of derived from platinum, while Docetaxel is used for treatment of breast cancer metastases in the patients pretreated with the anthracyclines.

- **Anticancer Alkaloids of the Periwinkle:**
- Chemical Structure: dimerous alkaloids indolic, comprising fragment velbénamine and a fragment vindoline.



Vinblastine



Vincristine

Fig.10: Chemical structure of Alkaloids of Periwinkle.

○ Mode of action: They act by connection with dimerous tubuline by inhibiting Polymerization, the assembly of the microtubules is blocked and consequently the cellular division.

○ Preparation: Drugs extracted from the plant Periwinkle of Madagasca, *Cataranthus roseus*, this plant belonged to the family of Apocynacées.

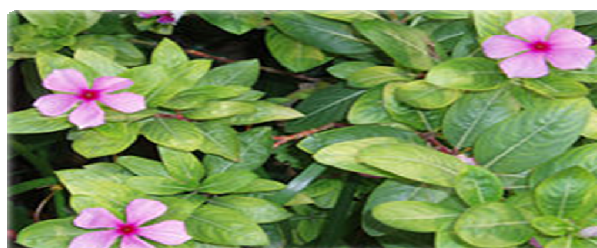


Fig.11: Periwinkle of Madagasca (*Cataranthus roseus*)

○ Therapeutic use: Vinblastine is used for treatment of disease of Hodgkin, lymphomas not Hodgkin, breast cancers, cancer of the ovary, cancer of the testicle, syndrome of Kaposi, choriocarcinomas, while Vincristine is used for treatment of leukemia acute, disease of Hodgkin, lymphoma not Hodgkin, neuroblastoma, tumor of Wilms, sarcoma of Ewing.

Conclusion:

Significant number of anticancer drugs available with various mechanisms of action and multiple possible therapeutic methods; used only or in combination according to the histological type, of the stage and the condition of the patient. Choice of the therapeutic strategies is based on a primary empirical advance, the evolution towards a greater specificity and a less great toxicity is based on elements of natural origin.

The contribution of recent discovered the 25 last years results in new specific drugs of cancer (more than 100),for a great part; those are of natural origin, they are especially active in partnership with the cytotoxic classics of chemical origin. Large field of investigation remains open in biological and botanical fields, little explored in associations of targeted drugs, ignored by pharmaceutical industry.

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