
Contents

Acknowledgements	ix
Foreword	xi
Chapter 1. Co-constructing the Past for a History of the Chemistry of Natural Substances	1
1.1. A convergence.	1
1.2. “A small world”.	5
1.3. Incomplete sources on the history of the chemistry of natural substances?	11
1.4. An original way of telling the history of chemistry: “a <i>compagnonnage</i> ”	16
Chapter 2. The <i>Institut de chimie des substances naturelles</i> of the CNRS (1955–2000): Emblematic of an Evolving Area of Research?	25
2.1. Research in France and the CNRS: ambivalent sentiments?	25
2.1.1. From the creation of the CNRS in 1939 to its first reorganization in 1959.	25
2.1.2. From pragmatism to 1979 reform	31
2.1.3. From the “ <i>Assises de la recherche</i> ” of 1981–1982 to the 2000s.	32
2.2. Chemistry at the CNRS	35
2.3 The ICSN: a place for discovery (from 1955 to the 2000s)	43

2.4. “Science is a social and political act”: Pierre Potier (1934–2006)	65
2.4.1. Learning from research	66
2.4.2. Research is a resource	70
2.4.3. Intuition and daring in service of a cause: the discoveries of Navelbine® and Taxotere®	73
Chapter 3. From <i>Catharanthus roseus</i> Alkaloids to the Discovery of Vinorelbine (Navelbine®)	87
3.1. <i>Catharanthus roseus</i> : botany, herbaria, empirical medicine	88
3.1.1. Creation of the genus <i>Catharanthus</i>	89
3.1.2. The earliest samples and herbaria of <i>C. roseus</i>	90
3.1.3. From the use of <i>C. roseus</i> in popular medicine for its antidiabetic properties to the discovery of cytotoxic properties.	92
3.2. Bisindolic alkaloids of <i>Catharanthus roseus</i> (1950s–60s).	98
3.2.1. From the first chemical studies to the structural characterization of vinblastine and vincristine	98
3.2.2. Vinblastine and vincristine: the first plant-based anti-cancer medications.	101
3.3. Studies conducted at the ICSN: modified Polonovski reaction and chemical studies of <i>Catharanthus</i> (1960s–1970s).	102
3.3.1. The modified Polonovski reaction or Polonovski-Potier reaction.	103
3.3.2. First chemical studies of <i>Catharanthus</i> species at the ICSN	109
3.4. Studies conducted at the ICSN: semisynthesis of alkaloids such as vinblastine – biological activity and biosynthesis (1970s–1980s)	112
3.4.1. State of the art: first semisynthesis leading to analogs of vinblastine with “unnatural” 18’R configuration	114
3.4.2. First semisynthesis of anhydrovinblastine – an analog of vinblastine with the natural configuration (18’S)	115
3.4.3. Mechanism of anhydrovinblastine formation	118

3.4.4. Determination of the configuration at C-18 (18'S versus 18'R): electronic circular dichroism.	121
3.4.5. Antitumoral activity and evaluation with the tubulin test	122
3.4.6. Biosynthesis of bisindolic alkaloids: anhydrovinblastine is a natural product	126
3.5. From anhydrovinblastine to leurosine, leurosidine, vinblastine and the discovery of vinorelbine	131
3.5.1. Transformation of anhydrovinblastine into leurosine, leurosidine and vinblastine	132
3.5.2. Discovery of 7'-nor-anhydrovinblastine or navelbine and first pharmacological and clinical results.	134
3.5.3 The search for a new process to synthesize 7'-nor-anhydrovinblastine (vinorelbine)	144

Chapter 4. From the Pacific Yew (<i>Taxus brevifolia</i>) to the English Yew (<i>Taxus baccata</i>): Steps Towards the Discovery of Docetaxel (Taxotere®)	151
4.1. The common yew, <i>Taxus baccata</i>	152
4.1.1. Yews, botanics and toxicity	152
4.1.2. First phytochemical studies of the common yew (<i>T. baccata</i>) and other species of <i>Taxus</i>	155
4.2. From the Pacific yew, <i>Taxus</i> <i>brevifolia</i> , to Taxol®, an anti-cancer molecule with a new mechanism of action.	159
4.2.1. Discovery of taxol, cytotoxic diterpene isolated from the Pacific yew	159
4.2.2. Taxol: a new mechanism of action and difficulties encountered during its development	162
4.3. Phytochemical studies carried out at the ICSN: discovery of 10-deacetylbaccatin III in the natural state (1980s)	166
4.3.1. Extraction and purification of <i>T. baccata</i> , monitoring the activity on tubulin.	167
4.3.2. Isolation of 10-deacetylbaccatin III	169
4.3.3. Isolation of other taxanes and biological activity on tubulin	173

4.3.4. Study of the pharmacological properties of taxol at the ICSN and at the <i>Faculté de Pharmacie</i> in Grenoble	176
4.4. Steps toward the first semisynthesis of 10-deacetyltaxol, of taxol and discovery of a highly active analog by the aminohydroxylation reaction.	177
4.4.1. Chemical studies of 10-deacetylbaccatin III	178
4.4.2. Studies on the esterification of 7, 10-ditroc-10-deacetylbaccatin III. Semisynthesis of cinnamic ester of 10-deacetylbaccatin III	182
4.4.3. Functionalization of the cinnamic ester double bond: discovery of a compound (Oxy 1) more active than taxol	185
4.4.4. First semisynthesis of 10-deacetyltaxol and taxol	194
4.4.5. Earliest pharmacological studies of Oxy 1 (56 976 R.P.)	197
4.5. Second semisynthesis of taxol by a convergent process	198
4.5.1. First convergent semisynthesis of taxol	199
4.5.2. Other convergent semisynthesis and semisynthetic version of taxol approved by the FDA.	201
4.6. A step toward the development of 56 976 R.P., which was to become Taxotere®	202
4.6.1. Large-scale extraction and purification of 10-deacetylbaccatin III	203
4.6.2. Steps toward the convergent synthesis of 56 976 R.P.	205
4.6.3. From pharmacological and clinical properties to market authorization for Taxotere® (56 976 R.P.)	209
Conclusion	213
Bibliography	217
Index	245