Progress in the Chemistry of Organic Natural Products

A. Douglas Kinghorn · Heinz Falk
Simon Gibbons · Jun'ichi Kobayashi
Yoshinori Asakawa · Ji-Kai Liu *Editors*

107

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Volume 107

With contributions by

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Preface

The editors of *Progress in the Chemistry of Organic Natural Products* are pleased to announce that with the publication of Volume 107 of the book series in 2018, this marks the 80th anniversary of its founding in 1938 by Professor László Zechmeister. This monograph series was established under the title "Fortschritte der Chemie Organischer Naturstoffe", but for many years was simply known as "Zechmeister". From its inception, and continuing up to the present time, the major aim of the editors of this book series has been to convey to the reader significant new developments in the chemistry of natural product molecules from organisms. In Volume 100 of "Progress", published in 2015, a detailed profile of the coverage of the book series in the 75 years from 1938 to 2013 was provided [1].

As of Volume 107, we are delighted to welcome two highly esteemed natural product scientists as new Series Editors, namely, Professor Yoshinori Asakawa, of Tokushima Bunri University, Tokushima, Japan, and Professor Ji-Kai Liu, of South-Central University for Nationalities, Wuhan, People's Republic of China. Professor Asakawa is a world expert on the chemistry and biology of liverworts and is a distinguished and esteemed member of the natural products community who has provided three extensive monographs in the book series to date [2–4]. Professor Liu has both academic and industrial experience and is highly accomplished in the isolation chemistry, total synthesis and biosynthesis of secondary metabolites purified from higher fungi. With a colleague, he provided an excellent chapter on this topic in Volume 106 of our book series [5]. He is the founding Editor-in-Chief of the journal *Natural Products and Bioprospecting* (Springer Open journal).

The year 2018 also marks the 20th year in succession that Emeritus Professor Heinz Falk has served as Series Editor of *Progress in the Chemistry of Organic Natural Products*. He began in this capacity for Volume 75, and since then has played a major role in overseeing the many changes that have occurred, and has also ensured that the high standards established earlier for our book series have been maintained. Together with his colleague, Dr. Klaus Wolkenstein, of the Max Planck Institute for Biophysical Chemistry, Göttingen, Germany, Professor Falk

contributed an illuminating chapter on molecular fossils and biomarkers for Volume 104 of the series [6].

The first of the two chapters in Volume 107 delves into the logistics of tropical plant collecting and chemical and biological work-up in the search for new cancer chemotherapeutic agents. This was written by the Series Editor Professor Douglas Kinghorn, along with colleagues from the Ohio State University and the University of Illinois at Chicago. In the second chapter, Professor Runner Majinda, of the University of Botswana, Gaborone, Botswana, offers an updated treatise on the fascinating topic of the *Erythrina* alkaloids.

Columbus, OH — Douglas Kinghorn
Linz, Austria — Heinz Falk
London, UK — Simon Gibbons
Sapporo, Japan — Jun'ichi Kobayashi

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The Search for Anticancer Agents from Tropical Plants

Joshua M. Henkin, Yulin Ren, Djaja Djendoel Soejarto, and A. Douglas Kinghorn

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1 Introduction

There is a long and sustained history of use of secondary metabolite constituents of terrestrial and marine organisms as sources of small-molecule therapeutic agents [1–6]. Even as the end of the second decade of the twenty-first century nears, new examples of natural products and their derivatives are still being introduced into Western medicine as therapeutic agents. The screening of chemically complex natural product extracts for the discovery of new drugs in a timely manner presents a number of logistical challenges, but various modern technological approaches may be applied to enhance this process [6–9]. It is considered that when innovative methods of discovery are applied, natural products will continue to offer a vast resource to yield structurally novel compounds with promising biological activities [6–10].

Medicinal plants have a long history of use by humans, and originally were employed as crude drugs in forms such as teas, tinctures, poultices, and powders [11, 12]. Beginning with the purification of morphine from the opium poppy at the beginning of the nineteenth century, a number of important plant-derived drugs have been obtained in pure form in the intervening period, including artemisinin, atropine, colchicine, cocaine, digoxin, galanthamine, quinine, paclitaxel, and vinblastine [11–16]. There are a large number of secondary metabolites known already from plants, with about 170,000 unique compounds of this type having been characterized [9], of which the largest groups are isoprenoids, phenolics, and terpenoids [14]. Given that a high proportion of the estimated 270,000 species of plants in existence has not yet been subjected to any phytochemical or biological activity investigation, there is a good chance that additional new lead compounds for use in drug discovery programs will continue to be elucidated for the foreseeable future.

Cancer remains a major public health problem in countries all over the world, in developed and developing countries alike. According to recent figures on global

cancer, there were over eight million deaths due to cancer in all countries in 2012, with about 65% of all deaths occurring in developing countries [16]. When the United States is taken specifically, while there has been an overall drop of about 25% in cancer mortalities over the last 20 years, still approximately 600,000 deaths from this cause are expected in 2018 [17]. As one approach to alleviating the burden of cancer, natural products have been used for many decades as cancer chemotherapeutic agents, with approximately 50% of the small-molecular-weight molecules approved for this purpose in western medicine from the 1940s to 2014 being either structurally unmodified natural products or derivatives of natural product lead compounds produced by semi-synthesis [6]. Of the anticancer compounds used clinically, these may be obtained from higher plants, terrestrial microbes, and marine organisms, with the number of such compounds available commercially continuing to expand [6, 18]. These compounds act via a wide variety of different cellular mechanisms [19].

When higher plants are considered specifically as sources of cancer chemotherapeutic agents, initial success occurred in the late 1950s and early 1960s through the isolation and development of the *Catharanthus* (vinca) alkaloids that are now known as vinblastine and vincristine [20]. The U.S. National Cancer Institute launched an extensive diverse plant collection program in the early 1960s that led to the discovery of camptothecin and taxol (later renamed paclitaxel), which together afforded four approved anticancer agents by the mid-1990s [20, 21]. A number of review articles have appeared specifically on the topic of plant-derived anticancer agents, e.g. [20–25].

2 Clinically Used Plant-derived Anticancer Agents and Compounds in Clinical Trials

2.1 Plant-derived Compounds Used Clinically as Cancer Chemotherapeutic Agents

We have previously reviewed the history of the initial discovery of the two earliest classes of plant-derived anticancer introduced clinically, namely, the vinca (*Catharanthus*) bisindole alkaloids and the podophyllotoxin lignan derivatives [25]. Currently, there are five bisindole alkaloids that are used clinically for anticancer therapy in either or both the United States and Europe, namely, the natural products vinblastine (**1**) and vincristine (**2**), and the semisynthetic derivatives vindesine (**3**), vinorelbine (**4**), and vinflunine (**5**) (Fig. 1) [26]. These compounds are used to treat a wide variety of different types of solid tumors, leukemias, and lymphomas [25, 26]. In 2012, vincristine sulfate liposome injection was approved clinically for advanced Philadelphia chromosome-negative acute lymphocytic leukemia in adults [27]. This is a cholesterol and sphingomyelin-based nanoparticle

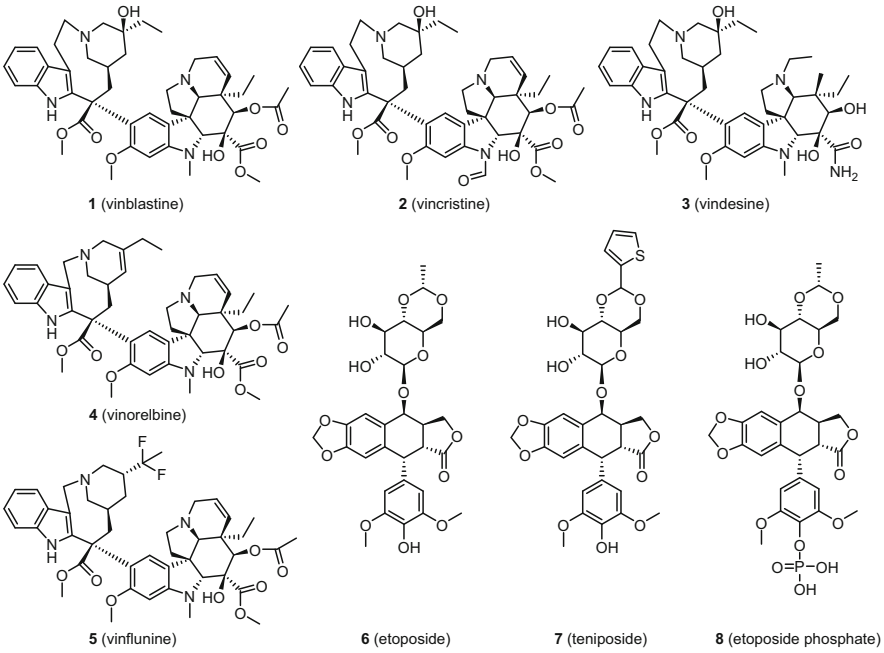

Fig. 1 Structures of clinically used bisindole alkaloid (**1**–**5**) and epipodophyllotoxin (**6**–**8**) anticancer agents

formulation that is intended to overcome dosing and pharmacokinetic limitations of unmodified vincristine sulfate [27, 28].

Summaries of the early development of the plant lignan podophyllotoxin at the U.S. National Cancer Institute as a potential anticancer agent, leading to the later introduction into therapy of the epipodophyllotoxin analogs etoposide (**6**), teniposide (**7**), and etoposide phosphate (**8**) (Fig. 1), along with their clinical uses, have been published [25, 29]. There remains a strong interest in developing new anticancer agents based on the podophyllotoxin molecule, although no new compounds of this type have been approved in recent years [29].

The seminal work of the late Monroe Wall and Mansukh Wani of the Research Triangle Institute, Research Triangle Park, NC in the discovery of the key antineoplastic compounds camptothecin and taxol (paclitaxel) has been documented by others [22, 30]. These compounds are important not only for their respective mechanisms of action but also in serving as lead compounds for a wide range of analogs with potential anticancer activity. Camptothecin has been found to stabilize the DNA-topoisomerase I complex, and while this alkaloid is not used as a drug in its natural form due to its insolubility, its derivatives topotecan (**9**) and irinotecan (**10**) (Fig. 2) both have approved clinical use, and may be used to treat a range of different types of human cancers [31]. A nanoliposomal formulation of **10**, intended to provide enhanced pharmacotherapeutic parameters compared with the parent

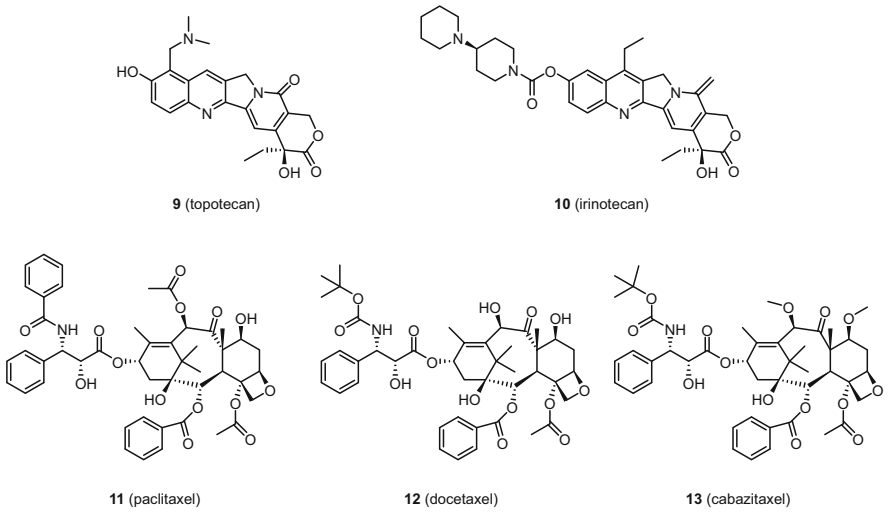

Fig. 2 Structures of clinically used camptothecin (**9** and **10**) and taxane (**11**–**13**) anticancer agents

compound, was approved recently by the U.S. Food and Drug Administration (FDA) for use in combination chemotherapy for gemitabine-resistant metastatic pancreatic cancer [28, 32].

Paclitaxel (**11**) (Fig. 2), a nitrogen-containing diterpenoid used clinically in its native form, has become a major resource in cancer chemotherapy [33], and its cellular mechanism action was shown by Susan Band Horwitz and her co-workers to involve the promotion and stabilization of tubulin polymerization and the inhibition of microtubule depolymerization, producing cell cycle arrest [34]. Two semi-synthetic analogs of paclitaxel are also currently used in oncology, namely, docetaxel (**12**) (Fig. 2), developed by the late Pierre Potier and colleagues in France [33], and cabazitaxel (**13**) (Fig. 2) [33, 35]. The latter compound was approved for patients with hormone-refractory prostate cancer showing resistance to treatment with docetaxel [35]. Due to the poor water solubility of paclitaxel and other disadvantages as an anticancer agent, some new polymer formulations have been developed. A nanoparticle albumen-bound form with the tradename Abraxane® that can be used as an injectable suspension gained marketing approval by FDA initially over a decade ago, and was later approved for advanced forms of breast cancer, non-small cell lung cancer, and pancreatic cancer [28]. A micellar form of paclitaxel (Genoxol®-PM), consisting of polyethylene glycol and poly(DL-lactic acid), has been FDA-approved for use in patients with breast cancer [28, 36]. According to Cragg et al., in 2013 there were several thousand clinical trials ongoing at that time on the already approved taxane derivatives [37].

In 2014, the plant alkaloid derivative omacetaxine mepesuccinate (**14**) (Fig. 3) was given full FDA approval, having earlier been granted accelerated approval for the treatment of adults with certain forms of chronic myeloid leukemia that are resistant or show intolerance to selected tyrosine kinase inhibitors [38, 39]. This

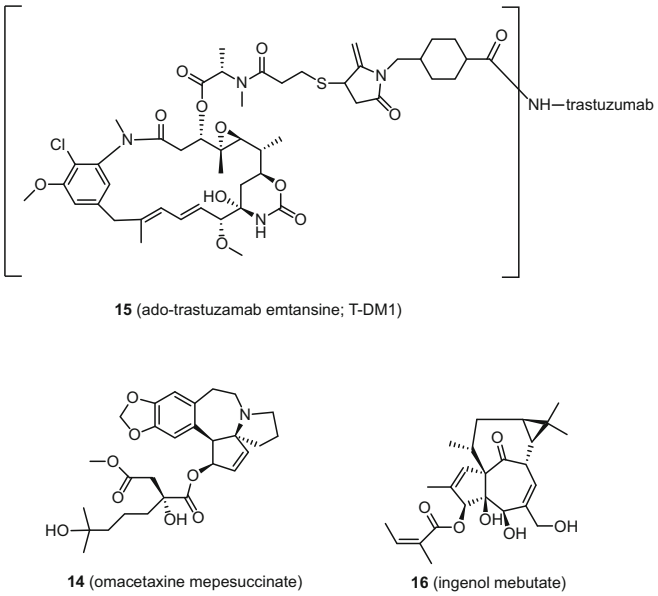

Fig. 3 Structures of omecetaxine mepesuccinate (**14**), ado-tratuzamab emrtansine (**15**), and ingenol mebutate (**16**)

Cephalotaxus alkaloid was first isolated from a Chinese plant as homoharringtonine by Richard Powell and the late Cecil Smith and their colleagues from the USDA laboratory at Peoria, Illinois in 1970 [40], and a review of the early relevant chemical work performed has been published [41]. Mechanistically, **14** interferes with protein biosynthesis in the cancer cell by binding to the A-cleft of ribosomes [42]. Omacetaxine mepesuccinate (**14**) is of importance in being the first member of an entirely new structural class of plant-derived anticancer agents utilized for cancer treatment, and also in being the initial protein translation inhibitor approved by the U.S. FDA for this purpose [42].

Two further compounds are considered relevant for inclusion in this section, namely, ado-trastuzamab emtansine (T-DM1) (**15**) (Fig. 3) and ingenol mebutate (**16**) (Fig. 3). In 1972, the lead compound maytansine, a chlorinated ansamycin derivative, was reported by the late S. Morris Kupchan and associates as an anti-leukemic constituent of the East African plant, *Maytenus ovatus* [43, 44]. Excellent review contributions on the development of the maytansinoids have appeared in the literature [44, 45], and it is now considered that such compounds are actually of microbial endophyte origin rather than being biosynthesized by plants [46]. Ado-trastuzamab emtansine (**15**), an antibody-drug conjugate [47], was registered for the chemotherapy of patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer [48]. In turn, ingenol mebutate (ingenol-3-angelate) (**16**) was approved by the FDA in 2012 as a topical treatment for actinic keratosis, which is a skin ailment that can lead to the formation of

squamous cell carcinoma [49]. The history of the development of this compound as a biologically active constituent of the plant *Euphorbia peplus* was described in a recent volume of this book series [50].

2.2 *Examples of Derivatives of Plant Secondary Metabolites Undergoing Clinical Trials as Potential Anticancer Agents*

As may be expected, there is a considerable interest in finding new anticancer agents of plant origin to supplement those used already clinically. Accordingly, there are a large number of such compounds undergoing clinical trials (e.g. [8, 9, 24, 37, 51]). In the following paragraphs, 11 anticancer leads of plant origin that are in current clinical trials have been selected as representative examples, including several derivatives of camptothecin and paclitaxel.

As mentioned earlier, the naturally occurring pentacyclic quinoline alkaloid, camptothecin, is the parent compound of topotecan (**9**) and irinotecan (**10**) (Fig. 2) [31, 51]. Structure-activity relationship studies have shown that the (20*S*)-hydroxy group, the pyridone (D-ring) and lactone (E-ring) units, and a planar A, B, C, D, and E ring system are essential for camptothecin to mediate its cytotoxicity. Also, an increase of water solubility and substitution at the C-7, C-9, C-10, and/or the C-11 position can increase the resultant cytotoxic activity of camptothecin, but substitution at the C- and D-rings reduces the potency [31, 51, 52]. Following these observations, several derivatives showing an improved efficacy, including exatecan (**17**) and afeletecan (**18**) (Fig. 4), have been prepared and evaluated in cancer clinical trials.

Exatecan (**17**), used as its mesylate salt (DX-8951f), is a water-soluble synthetic derivative of camptothecin, with potentially enhanced therapeutic parameters, when compared with topotecan (**9**) or irinotecan (**10**) (Fig. 2). The safety, dosing limits, and pharmacokinetics of **17** were evaluated in several phase I clinical trials [53]. In a phase II study, exatecan mesylate showed a modest activity against metastatic gastric cancer, and was considered worthy of further development [54]. However, in a randomized phase III study, **17** plus gemcitabine were not found to be superior to gemcitabine alone in the first-line treatment of advanced pancreatic cancer, hence, further work has been discontinued [31, 55]. Recently, a new antibody-drug conjugate (ADC) comprising an anti-HER2 antibody, a cleavable peptide linker, and an exatecan-derived topoisomerase inhibitor (DXd), namely, DS-8201a, has been developed. It has a higher drug-to-antibody-ratio than that of T-DM1 (**15**) (Fig. 3), a HER2-targeting ADC comprising the antibody trastuzumab and maytansine, and is effective against cancers with low HER2 expression. Also, DS-8201a was found to inhibit T-DM1-resistant cancer cell growth, and it appears promising to overcome HER2-positive gastric cancer T-DM1 resistance [56]. Afeletecan (BAY 38-3441) (**18**), a 20-*O*-linked CPT glycoconjugate, is a camptothecin prodrug. It showed improved

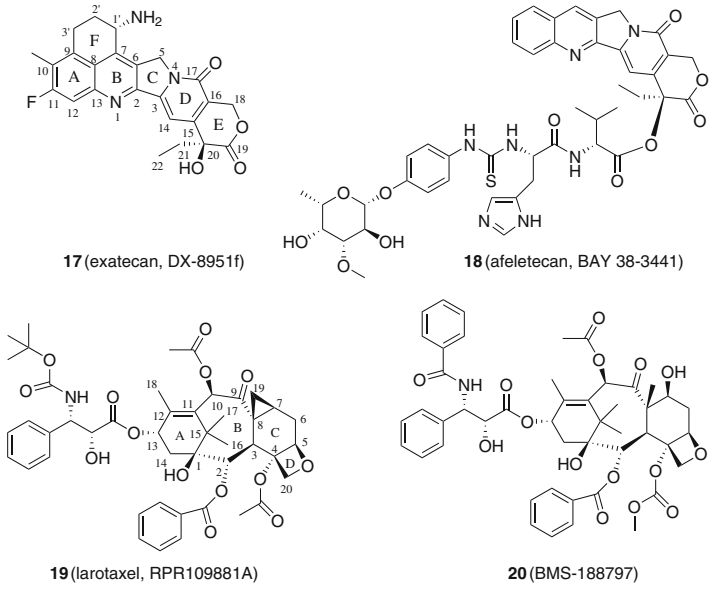

Fig. 4 Structures of some camptothecin and paclitaxel derivatives **17**–**20** that have reached cancer clinical trials

anticancer activity and has been selected for evaluation in cancer clinical trials [57, 58]. A phase I study for the treatment of a wide variety of malignancies showed that **18** was tolerated [59], indicating that glycoconjugation is supportive of effective drug delivery. Other camptothecin derivatives that were undergoing oncology clinical trials recently included AR-67, cositecan, CZ48, diflomotecan, DRF-1042, elomotecan, gimatecan, lurtotecan, and namitecan, with several other camptothecin conjugates also being in clinical trials [8, 31, 58].

Paclitaxel (**11**) (Fig. 2) is one of the most important natural product anticancer drugs that is used in its native chemical form, as it occurs in the producing organism. Structure-activity relationship studies have shown that the taxane (A, B, C, and D) ring system (both its constitution and conformation) and the C-13 side chain are essential, with the C-2 benzyl and C-4 acetyl groups being critical, for **11** to bind to tubulin and to mediate its cytotoxicity. In addition, the substituents at the C-1, C-4, C-7, C-9, C-10, and C-14 positions can be modified to improve its cytotoxic potency [60]. Based on these conclusions, two promising leads, larotaxel (RPR 109881A) (**19**) and BMS-188797 (**20**) (Fig. 4), were produced through changing the C-7 and C-13 side chains and modification of the C-4 substituent of **11**, respectively. However, it should be pointed out that these are only two examples of over 20 paclitaxel derivatives that were in various stages of clinical trial recently [8, 33, 37].

Larotaxel (RPR 109881A) (**19**) is a semi-synthetic taxane analogue, which showed a broad spectrum of cytotoxicity and more potent activity than docetaxel (**12**) against murine P388 leukemia cells, and also effectiveness toward multidrug-resistant (MDR) cancer cell lines. Phase I and II studies showed that this agent has a