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Strategies for the Optimization of Natural Leads to Anticancer Drugs or Drug Candidates

Zhiyan Xiao[1,2,*], **Susan L. Morris-Natschke**[3], and **Kuo-Hsiung Lee**[3,4,*]

[1]Beijing Key Laboratory of Active Substance Discovery and Druggability Evaluation, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, China

[2]State Key Laboratory of Bioactive Substances and Functions of Natural Medicines, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, China

[3]Natural Products Research Laboratories, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599-7568, USA

[4]Chinese Medicine Research and Development Center, China Medical University and Hospital, Taichung, Taiwan

Abstract

Natural products have made significant contribution to cancer chemotherapy over the past decades and remain an indispensable source of molecular and mechanistic diversity for anticancer drug discovery. More often than not, natural products may serve as leads for further drug development rather than as effective anticancer drugs by themselves. Generally, optimization of natural leads into anticancer drugs or drug candidates should not only address drug efficacy, but also improve ADMET profiles and chemical accessibility associated with the natural leads. Optimization strategies involve direct chemical manipulation of functional groups, structure-activity relationship-directed optimization and pharmacophore-oriented molecular design based on the natural templates. Both fundamental medicinal chemistry principles (e.g., bio-isosterism) and state-of-the-art computer-aided drug design techniques (e.g., structure-based design) can be applied to facilitate optimization efforts. In this review, the strategies to optimize natural leads to anticancer drugs or drug candidates are illustrated with examples and described according to their purposes. Furthermore, successful case studies on lead optimization of bioactive compounds performed in the Natural Products Research Laboratories at UNC are highlighted.

Keywords

Natural products; Lead optimization; Anticancer Drugs

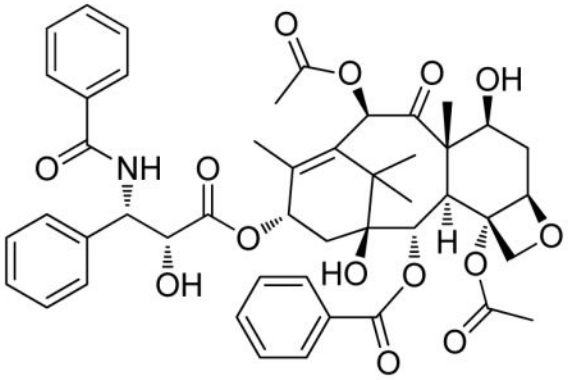
[*]To whom correspondence should be addressed. For Z.X., Tel: 86-10-63189228; Fax: 86-10-63017757; xiaoz@imm.ac.cn. For K-H Lee, Tel: 1-919-9620066; Fax: 1-919-9663893; khlee@unc.edu.

1 Introduction

Historically, natural products have played a crucial role in human's combat against diseases and have been a predominant source of early medicines.[1,2] With the advance of alternative drug discovery technologies, such as rational drug design, combinatorial chemistry, and high-throughput screening, natural products remain an essential element in modern drug discovery. As an indispensable source for lead generation and drug discovery, natural products have provided molecular diversity and structural novelty inaccessible by other means. The differences between the molecular properties of natural products and synthetic compounds were first investigated by Henkel et al, [3] and natural products were found to be significantly different from synthetic compounds. As compared to synthetic compounds, natural products generally have higher molecular weights, fewer nitrogen, halogen, or sulfur atoms, more oxygen atoms, and more sp^3-hybridized or bridgehead atoms. In addition, natural products typically have more rings and more chiral centers in their structures. Since this initial report, chemoinformatic methods have been regularly applied to analyze the molecular properties of natural products, synthetic compounds (especially those from combinatorial chemistry), and drug molecules. [4–7] The unique distribution of natural products in the chemical space was evident from these studies, and it has been gradually realized that natural products generally exhibit higher structural diversity and greater biological relevance than synthetic compounds. [4]

In recent years, many excellent review articles have highlighted the significant contributions of natural products to drug discovery. [8–13] A series of reports [14–17] emphasized the great impact of natural products on the discovery of new chemical entities (NCSs) by full analysis of the sources of all approved therapeutic agents. During the time frame from 1981 to 2010, [17] when all the approved small-molecule drugs categorized as NCEs are considered, only 36% are synthetic molecules, while the others are all originated from natural products (Table 1). [17] Although natural products play a critical role in the drug discovery of virtually all therapeutic areas, [18–20] they are particularly important for lead identification and drug discovery in oncology. As indicated in Table 1, the percentage of natural product-based molecules in anticancer drugs are significantly higher than in average drugs (79.8% for anticancer drugs approved in 1981–2010 and 74.9% for all the anticancer drugs approved worldwide). [17] The impressive role of natural products in the therapeutic area of oncology was extensively reviewed both in general [21–24] and for specific subcategories in the recent years. [25–30] In addition, two monographs have carefully elaborated the discovery and development of representative anticancer agents from natural products. [31, 32]

Furthermore, the importance of natural products in anticancer drug discovery could go beyond molecular diversity and structural novelty. The discovery of novel natural structures with significant biological relevance and the recognition of new mechanism of action thereby could pioneer innovative research fields. The potent anticancer agent paclitaxel (**1**) is an excellent example. The discovery of paclitaxel and, in particular, its novel mechanisms of action featured by tubulin-assembly promotion was a milestone and initialized a new era in anticancer drug discovery. [33, 34]



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It is worth to note that natural products are a major source of mechanistic diversity for both cytotoxic chemotherapy and molecular targeted cancer therapy. Phenotypic screening has identified numerous natural products as anticancer agents and significantly expanded the molecular diversity of anticancer drugs in the early days. With the recent advances of molecular pharmacology in cancer research, a vast diversity of molecular targets have emerged as potential intervention points to achieve specific therapeutic consequences. [35] Strikingly, target-focused approaches have revealed that natural products have great influences on many of these molecular processes and targets. As illustrated in the review by Cragg et al., [23] natural products are reported to interfere various molecular targets involved in the cell cycle and natural product-based anticancer drugs have been discovered as therapeutic agents with diverse mechanisms. The underlying molecular targets of these anticancer drugs include but not limit to tubulin, topoisomerases I and II, histone deacetylases, protein kinases, heat shock protein 90 and proteasome. These observations indicate that natural products are still a vital reservoir of molecular and mechanistic diversity for anticancer drug discovery.

2 Strategies for natural lead optimization

Although natural products have historically been a critical source for therapeutic drugs, sometimes natural molecules may suffer from insufficient efficacy, unacceptable pharmacokinetic properties, undesirable toxicity, or poor availability, which impede their direct therapeutic application. As demonstrated by data in Table 1, for all the natural product-based drugs, only a small portion are natural products per se, and the majority of these drugs are either natural product derivatives or synthetic molecules inspired by the structure or pharmacophore of natural products. Therefore, natural products often serve as lead templates and are subjected to structural optimization to generate clinically useful structures.

In general, the optimization of natural lead structures may involve efforts on three different purposes: to enhance drug efficacy, to optimize absorption, distribution, metabolism, excretion and toxicity (ADMET) profiles and to improve chemical accessibility. Traditionally, most structural optimization efforts are devoted to increasing efficacy. These

efforts can often be assisted by the application of either classic medicinal chemistry principles or modern rational drug design techniques. In recent years, it has been gradually acknowledged that poor pharmacokinetic profiles and unacceptable toxicity might be the major reasons for attritions in drug development. Therefore, optimization of ADME properties and reduction of toxicity should also be carefully considered in the lead optimization stage. For natural products, it is even more important to optimize their ADME profiles, since their structural complexity might confer unfavorable effects on their pharmacokinetic properties, such as solubility, cellular permeability, and chemical or metabolic stability. The last aspect, but probably the most practical aspect, is to improve the chemical accessibility of natural leads during structural optimization. The development of natural products into therapeutic drugs is often hampered by limited availability and synthetic intractability. Efforts to improve the chemical accessibility of natural products via rational drug design may overcome this bottleneck and eventually lead to the therapeutic application of natural product-based drugs.

Chemically, strategies for natural lead optimization can be subdivided into three progressive levels. The most straightforward approach is direct chemical manipulation of functional groups. In this approach, the natural structure can be modified by derivation or substitution of the functional groups, alteration of the ring systems, and isosteric replacement. These efforts are mainly empirical and intuition-guided, especially in the phenotypic approach. Structure-based design could assist the optimization efforts in the target-focused approach, if the structure of the biomacromolecule is available. The second approach for natural lead optimization involves the initial establishment of structure-activity relationships (SAR) and subsequent SAR-directed optimization. This approach is usually applied to natural leads with significant biological relevance, which attract extensive modification efforts. With the accumulation of chemical and biological information obtained from the first approach, meaningful SAR can be established to ensure more rational optimization of the natural leads. As indicated in Table 1, derivatives of natural products (categorized as “ND”) resulted from the afore-mentioned two approaches account for about one third of the small-molecule anticancer drugs. It is worth to note that since the basic structural cores of the natural products are generally not altered in these two approaches, therefore they mainly address efficacy and ADMET issues, while seldomly impose amelioration on the chemical accessibility of natural molecules. The last resort for natural lead optimization is pharmacophore-oriented molecular design based on the natural templates. The core structures of the natural products might be changed significantly and modern rational drug design techniques (e.g., structure-based design and scaffold hopping) can be applied to expedite the optimization efforts. SAR clues acquired in the SAR-directed approach can also facilitate the recognition of pharmacophores. This approach often intends to solve the problems associated with the chemical accessibility of the natural leads as well as to generate novel leads with intellectual properties.

In this review, we will discuss the strategies for the optimization of natural leads to anticancer drugs or drug candidates with case studies. The discussion are arranged according to the optimization purpose for natural leads. Namely, the optimization efforts to enhance drug efficacy, optimize ADMET profiles and improve chemical accessibility will be described successively. Obviously, the purposes for the structural optimization may not be

exclusive, and multi-facet improvement could be achieved simultaneously by a single structural alteration. Under such circumstances, we will categorize it according to the "main" purpose. Furthermore, the major concerns in optimization strategies vary with the different purpose involved. For example, if the drug efficacy is considered, strategies to enhance molecular interactions between the small-molecule and a specific molecular target are emphasized. When the ADME profile is aimed, strategies to modulate the physicochemical properties of the small-molecules are prioritized. While if chemical accessibility is targeted, strategies to simplify the complex natural templates are underscored. However, no matter what the purpose is, the chemical operations exploited in the optimization strategies are the same, which basically march from the empirical modification of the functional groups to the more rational SAR-directed optimization and eventually to the pharmacophore-oriented molecular design. To avoid redundancy, we will only elaborate the operations of these three progressive chemical strategies in the section on the optimization of drug efficacy. While, for the other two sections, we will only highlight the effects of structural alterations on ADMET profiles and chemical accessibility respectively. Our discussion will by no means be exhaustive; however, the main optimization strategies will be exemplified with case studies resulted in NCEs for either clinical uses or clinical trials. For the readers' reference, brief information on the clinical and investigational drugs mentioned in this review is provided in Tables 2 and 3. Furthermore, successfully examples developed in the Natural Products Research Laboratories at UNC, which have led to the development of clinical candidates, are also highlighted herein.

3 Development of anticancer drugs or drug candidates from natural leads

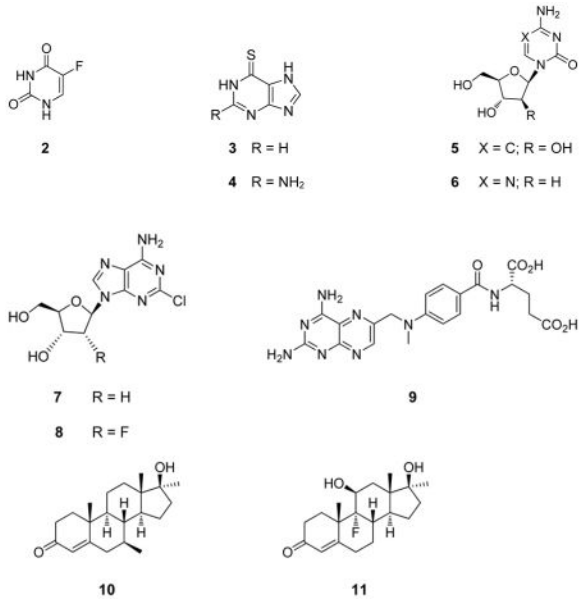
Due to their great contribution to anticancer drug discovery, natural products have been extensively investigated as potential anticancer agents in both phenotypic and target-focused approaches. Although numorous natural leads with significant biological activity have been identified, most of them are unsuitable for direct therapeutic application and structural optimization are required. In this section, we will discuss the optimization strategies to develop anticancer drugs or drug candidates from natural leads, and case studies with various optimization purposes will be covered.

3.1 Optimization of drug efficacy

The optimization of drug efficacy is conventionally the major goal for structural modification of bioactive natural products. As afore-mentioned, three different levels of chemical modification are involved in the optimization of drug efficacy. In this section, we will illustrate the effects of individual optimization approaches on the improvement of drug efficacy. However, it is worthwhile to point out that since structural alteration could lead to multi-dimentional optimization, discussion in this section may go beyond the purpose of optimizing drug efficacy.

3.1.1 Chemical manipulation of functional groups—The most straightforward approach to improve the efficacy of natural products is through appropriate chemical manipulation of the functional groups. The basic underlying principle is that similar

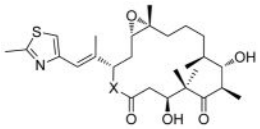
structures will present similar biological activity. In fact, early anticancer drugs classified as antimetabolites are usually generated by mimicking endogenous metabolites. The nucleotide and nucleoside analogues are particularly indicative. Fluorouracil or 5-FU (**2**) [36] is a pyrimidine analog, in which a hydrogen atom in uracil is replaced by a fluoro atom through the isosterism strategy. 5-FU irreversibly inhibits thymidylate synthase and is used in the treatment of cancer. Similarly, mercaptopurine (**3**) [37] and thioguanine (**4**) [38] were developed from hypoxanthine and guanine, respectively, through the isosterism strategy. Nucleoside mimetics can contain structural modification on either base or sugar component of the natural nucleosides. Substitution of the deoxyribose in deoxycytidine by an arabinose sugar produced cytarabine (**5**), [39] a chemotherapy agent mainly for treating acute myeloid leukemia (AML) and non-Hodgkin lymphoma. In contrast, decitabine (**6**), [40] in which the cytosine in deoxycytidine is changed to 5-aza-cytosine, is a drug for the treatment of myelodysplastic syndromes and AML. Cladribine (**7**) [41] is used to treat hairy cell leukemia (HCL) and multiple sclerosis. It contains structural alterations in both base and sugar moieties of the adenosine, and inhibits adenosine deaminase. Clofarabine (**8**) [42,43] is modified from cladribine via isosteric replacement, which makes it more stable in acidic solution and more resistant to phosphorolytic cleavage. Other endogenous substances, such as folic acid and steroids, have also served as key prototypes for early cancer chemotherapeutics. Methotrexate (**9**) [44], a folate analog, inhibits the metabolism of folic acid and is an effective chemotherapy against a variety of cancers. Calusterone (**10**) [45] and fluoxymesterone (**11**) [46] are testosterone analogs known as anabolic steroids, and are used for the treatment of cancers.



Besides endogenous “natural products”, the optimization of exogenous natural leads also involves various chemical manipulations of functional groups in the lead structures. Generally, extra chemical moieties could be grafted to the original natural structure to produce additional interaction with the macromolecule target and enhance the efficacy. Derivation, substitution as well as other modification of the functional groups is a

straightforward approach to make the prototype molecules fit the binding sites better. Isosterism is another approach to optimize efficacy, although this strategy could also be used to improve metabolic stability of natural molecules (cf. Section 3.2.3).

As a classic medicinal chemistry principle, bioisosterism is often the first resort for structural optimization. Epothilone B (**12**) is a natural microtubule–stabilizing agent isolated from *Sorangium cellulosum*. This compound and related epothilones exhibit a mode of action similar to that of paclitaxel, which kindled extensive research interest. [47] Ixabepilone (**13**) was developed from **12** by changing the ester oxygen atom to a nitrogen atom. This isosteric replacement made **13** more resistant to esterases than **12**. Ixabepilone was the most effective epothilone *in vitro* and *in vivo*, [48,49] and it was approved by the US Food and Drug Administration (FDA) in 2007 for the treatment of metastatic or locally advanced breast cancer. Similarly, hemiasterlin (**14**), a tripeptide of marine origin, was reported to be active against murine leukemia cells, [50] and was later identified as an anti-microtubule agent. [51] In the synthetic efforts to prepare **14** and its analogs, one analog, HTI-286 (**15**), [52] has been found to be more potent and more synthetically accessible than **14**. The phenyl ring could be considered as a bioisostere of the 1-methylindole moiety. Compound **15** entered clinical trials as an oncolytic drug in 2005; however, no further results have been reported after the completion of phase I trial.



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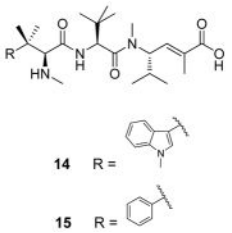
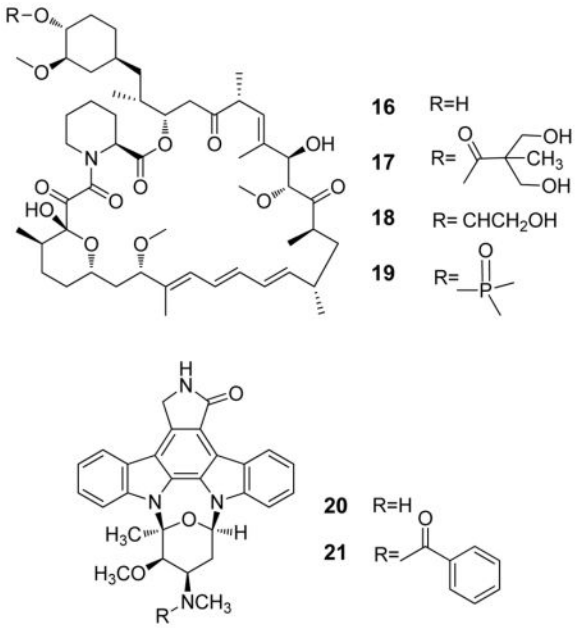
13 X = N



14 R =
15 R =

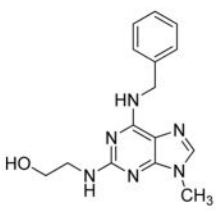
Derivation of functional groups in natural molecules is also a common strategy to improve pharmacological efficacy. Sirolimus (**16**), [53] also known as rapamycin, is a natural macrolide used as an immunosuppressant drug for preventing rejection in organ transplantation. Similar to the case of paclitaxel, the discovery of rapamycin also led to the disclosure of a novel mechanism of action, mTOR inhibition, and therefore pioneered a new era in drug discovery. As a prototype structure for mTOR inhibitors, rapamycin was later recognized for its anticancer activity. However, the therapeutic application of **16** for the treatment of cancer was hindered by its low aqueous solubility and poor chemical stability. To provide better solutions for cancer therapy, novel analogs of **16** were developed by taking advantage of a hydroxyl group in the structure. Temsirolimus (**17**) [54,55] is an ester derivative of **16**. It is a prodrug (cf. Section 3.2.5) of **16** and the first mTOR inhibitor approved for cancer therapy. Everolimus (**18**), [56] an ether derivative of **16**, was used as an immunosuppressant and cancer therapy for advanced renal carcinoma. As compared to **16**, **18** showed greater solubility and better pharmacokinetic profile, it was thereby marketed as an oral anticancer drug. Ridaforolimus (**19,** formerly known as deforolimus), a phosphinate of **16**, is an mTOR inhibitor approved as an orphan drug in 2005 for the treatment of bone sarcoma. [57] It is a non-prodrug analog of **16** with favorable pharmacokinetic properties. Staurosporine (**20**) is a bis-indole alkaloid originally isolated from the bacterium

Streptomyces staurosporeus. [58] It was later recognized as an ATP-competitive protein kinase inhibitor with strong affinity for many kinases. [59] Midostaurin (**21**, PKC412), a *N*-benzoyl derivative of **20**, (PKC412) is a multi-target protein kinase inhibitor and has been approved as an orphan drug for the treatment of acute myeloid leukemia (AML). [60]



Addition or alteration of functional groups in natural molecules may enhance the interaction with macromolecule targets and increase potency. The efficiency of this strategy was illustrated by the discovery and development of purine derivartives as cyclin-dependent kinase (CDK) inhibitors. [61] The plant hormone isopentenyladenine and another purine derivative, 6-dimethylaminopurine, were first identified as weak inhibitors of CDK1/cyclin B, which led to extensive medicinal efforts to improve their potency. [61] Olomoucine (**22**) was then identified as a CDK inhibitor with a unique selectivity profile. However, its potency against CDKs was still relatively weak and the best IC_{50} values were only at micromolar level. [62] The potency was successfully improved by incorporating additional alkyl substitutions in the molecule, and (*R*)-roscovitine (**23**) was proven to be a potent CDK inhibitor and is currenly in clinical trials for the treatment of various cancers. [63] One further example of natural product-derived CDK inhibitors is flavopiridol (**24**). This semisynthetic flavonoid is derived from rohitukine (**25**), [64] a natural chromane alkaloid first isolated from an indigenous Indian plant in 1979. SAR studies on **25** resulted in the discovery of **24**, which was identified as a potent CDK inhibitor with broad specificity. By changing the methyl group on the chromone skeleton to a bulkier *ortho*-chloro-benzene ring, flavopiridol fits better into the ATP binding site of CDKs than the parent structure and its potency was significantly enhanced. Favopiridol was later became the first CDK inhibitor to enter clinical trials, and it was also the first clinical drug targeting CDK. [65] K-252a (**26**) is an indolocarbazole structurally related to staurosporine (**20**). [66] It was isolated from microbial origin and identified as a potent inhibitor of protein kinase C. Lestaurtinib (**27**, also known as CEP-701) [67,68] is an analog of **26** with the methyl ester in **26** reduced to a hydroxymethyl

group. This analog was reported to inhibit Fms-like tyrosine kinase 3 (FLT-3) among other kinases. It was approved as an orphan drug for the treatment of acute myeloid leukemia and Philadelphia-negative classic myeloproliferative diseases. As a natural product family with extensive biological activities, flavonoids have drawn intense research interests. The isoflavone daidzein (**28**) is a key component of food and dietary supplements derived from soy. Phenoxodiol (**29**) is a synthetic analog of **28**, in which the 4*H*-chromen-4-one core in **28** was altered to 2*H*-chromene. Phenoxodiol exhibited significant antitumor activity. [69] Although its primary mode of action remains to be elucidated, **29** was investigated in clinical trials intensively. [70] Triphendiol (**30**) [71, 72] is another derivative of **29**, which incorporates a *p*-methoxy phenyl substitution and has a 2*H*-chromene rather than chromane skeleton in the structure. Triphendiol has superior anticancer activity, especially against pancreatic and bile duct cancers, and it was approved for the treatment of several solid tumors in 2008. Illudin S (**31**) [73] is a sesquiterpene toxin found in mushrooms of the genus *Omphalotus*. It belongs to the sesquiterpene family of illudins, which are generally highly toxic and not applicable for clinical use in their natural form. SAR studies on illudins resulted in the discovery of irofulven (**32**), [74,75] an analog of **31**, with improved therapeutic index. Irofulven is a DNA-alkylating agent with a unique mechanism of action. It interferes with DNA replication and targets malignant tumor cells, especially rapidly differentiating malignant cells. Irofulven was approved as a clinical drug for the treatment of renal cell carcinoma and ovarian cancer. Fumagillin (**33**) was originally isolated from the microbial organism *Aspergillus fumigatus*. It was later identified as a methionine aminopeptidase 2 (MetAP2) inhibitor, and therefore, **33** as well as its derivatives were investigated as angiogenesis inhibitors for the treatment of cancer. [76] Beloranib (**34**, CKD-732) [77,78] and PPI-2458 (**35**) [79,80] are semisynthetic derivatives of **33**, in which the tetraenoic acid moiety in **33** is replaced. These compounds were designed as MetAP2 inhibitors and were tested for the clinical treatment of cancer. With the understanding on the biological relevance of MetAP2 advanced, **34** and **35** were later investigated for the treatment of rheumatoid arthritis and obesity. Beloranib was approved for the treatment of Prader-Willi syndrome in 2013.



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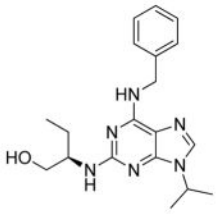

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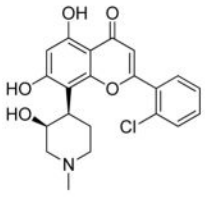

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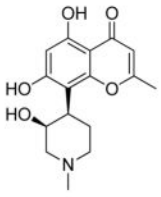

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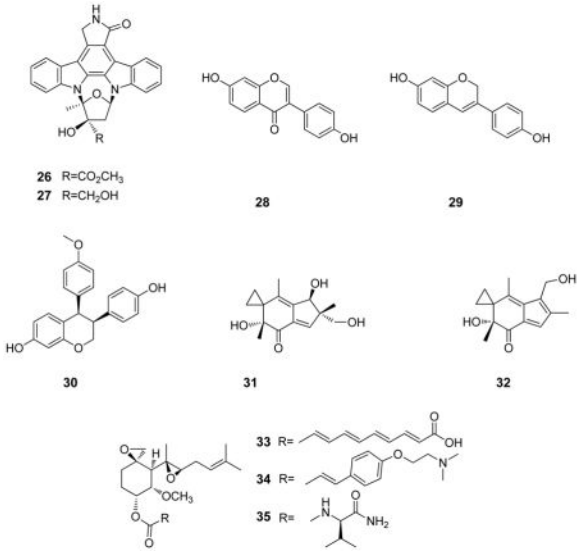
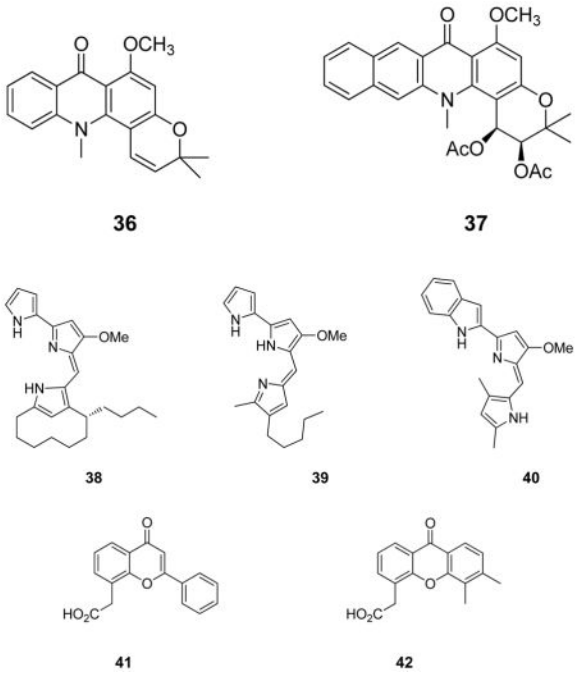
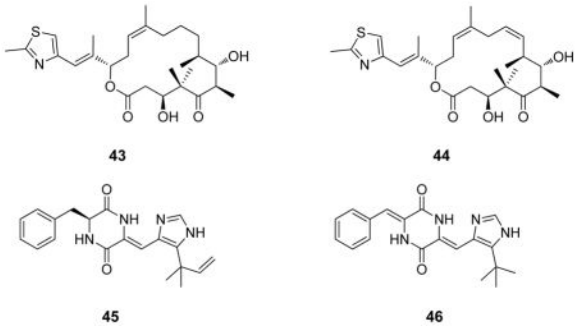


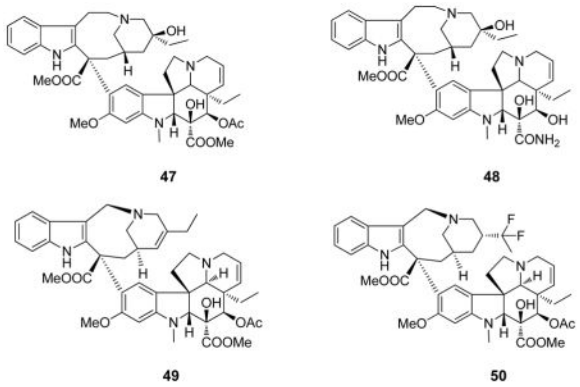
Another structural optimization strategy is to modify the ring systems in natural molecules by adding, removing, or altering ring structures so as to make the molecules in better shape complementarity with their target macromolecules. Acronycine (**36**), an alkaloid isolated from *Sarcomelicope simplicifolia*, showed broad spectrum antitumor activity. [81] However, the clinical trials on **36** as cancer chemotherapy were discontinued due to insufficient response rate and undesirable toxicities. Subsequently, the structure of **36** was modified by grafting two esters at the C1 and C2 positions of the pyran ring and extending the molecule with an extra benzene ring. A series of diester benzo[*b*]acronycine derivatives were prepared and were found to be more potent than **36**. Among them, the diacetate S23906-1 (**37**) [82] was identified as one of the most potent derivatives both *in vitro* and *in vivo*, and was investigated clinically for the treatment of cancer. Streptorubin B (**38**) and prodigiosin (**39**) are pyrrole alkaloids originated from bacteria. [83] Streptorubin B and its analogs were later revealed as small-molecule inhibitors of Bcl-2. [84,85] Extensive structural modification of **38** and **39** resulted in the discovery of obatoclax (**40,** GX15-070) [86,87] as a clinical drug for the treatment of chronic lymphocytic leukemia. As compared to **38**, the pyrrole ring in **38** is replaced by an indole moiety in **40** and the fused cyclodecane ring in **38** is simplified to two methyl groups on the pyrrole ring. Obatoclax is a more potent Bcl-2 inhibitor than **38** and binds to the hydrophobic pocket of the BH3 domain. It was also investigated in clinical trials for the treatment of various types of cancer, but there are currently no active clinical development of this drug. As mentioned previously, natural flavonoids exhibit a wide range of biological properties. In a screening program initialized by the National Cancer Institute (NCI), flavone acetic acid ester was identified as a potent antitumor agent and tested in clinical trials. Flavone-8-acetic acid (**41**) was regarded as the active form of flavone acetic acid ester and possessed unique activity and toxicity profiles, which implicated a novel mechanism of action. [88] Although **41** may represent a new chemotype of anticancer drugs, it showed low potency in human. Structural modification and SAR study on **41** resulted in the discovery of vadimezan (**42**, ASA404), which has the flavone scaffold altered to xanthenone. [89,90] Vadimezan was found to be a tumor-vascular disrupting agent and was tested clinically for the treatment of various cancers. [91,92]



Alteration of the saturation status of natural skeletons is another chemical strategy for natural lead optimization. The overall molecular conformation might be changed by either saturation or unsaturation of the skeleton. Epothilone D (**43**), a natural polyketide isolated from *Sorangium cellulosum*, is a desoxy analog of epothilone B (**12**). As revealed by the crystal structures as well as conformational analysis, the C8-C12 carbon backbone of **43** adopts a nearly anti-periplanar conformation. Accordingly, KOS-1584 (9,10-didehydroepothilone D, **44**), a highly active *trans* olefin analog of **43** with an unsaturated C9-C10 bond, is assumed to resemble the active conformation of **43**. Compound **44** is an investigational anticancer compound exhibiting improved potency and pharmacokinetic properties. [93,94] (−)-Phenylahistin (**45**) is a fungal 2,5-diketopiperazine isolated from *Aspergillus ustus*. [95] It is a microtubule binding agent cytotoxic against a number of tumor cells. [96] To optimize the biological activity of **45**, various dehydrogenated analogs were synthesized and evaluated. Plinabulin (NPI-2358, **46**) was discovered through these efforts. It is active against multidrug-resistant (MDR) tumor cell lines and entered clinical trials for the treatment of non-small cell lung cancer. [97,98]

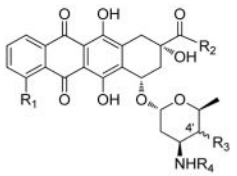


Frequently, multiple alterations of the prototype structure may be involved to finely tune the biological profiles of natural leads. Vinblastine (**47**) [99] is a natural drug from the family of vinca alkaloids and it is an anti-mitotic chemotherapy drug used for the treatment of various cancers, including Hodgkin's lymphoma, non-small cell lung cancer, breast cancer, head and neck cancer, and testicular cancer. Structural modifications of **47** have generated several new analogs with higher potency and less toxicity. Vindesine (**48**) [100,101] is one of the most impressive analogs. It only presents minor structural differences on the vindoline ring of **47**, where the methyl ester is changed to an amide group and the acetyl group is removed. However, **48** is less neurotoxic and showed no cross-resistance with vincristine. Compound **48** is used to treat different types of cancer, including leukaemia, lymphoma, melanoma, breast cancer and lung cancer. Vinorelbine (**49**) [102], the first 5′-nor semi-synthetic vinca alkaloid, is another important analog of **47**. The structural modifications in **49** include the transformation of the tryptamine moiety in **47** to gramine by reducing one carbon in the ring system and eliminating a water molecule to give a double bond in the piperidine ring. Vinorelbine exhibited better pharmacological and pharmacokinetic profiles. It is used to treat breast cancer and non-small cell lung cancer. Vinflunine (**50**) [103,104] is a novel 5′-nor vinca alkaloid with a *gem*-difluoro moiety. It showed superior *in vivo* preclinical antitumor activity and was investigated for the treatment of various solid tumors. It was approved as a clinical anticancer drug in UK in 2010 and is currently under active phase III clinical trials for the treatment of locally recurrent or metastatic Her-2 negative carcinoma of the breast in combination with capecitabine.



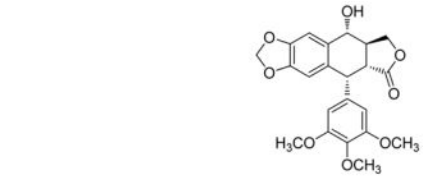
Doxorubicin (**51**) belongs to the family of anthracycline aminoglycosides. It was originally obtained by fermentation of *Streptomyces* strains and was isolated together with the major fermentation product daunorubicin (**52**). [105] The discovery of **51** and **52** provides an important chemotype for anticancer drugs. Doxorubicin is a topoisomerase II inhibitor used widely for cancer chemotherapy. However, problems of drug resistance and cardiotoxicity associated with **51** stimulated extensive structural modification. Such efforts revealed that minor structural changes in **51** could result in significant changes in biological effects, particularly the antitumor spectra and toxicity profiles. Several new anthracyclines with either altered aglycone or sugar moieties were discovered. Epirubicin (**53**) [106] is a diastereomer of **51**, and it differs from **51** only in the chirality of the 4′ carbon. Epirubicin showed better therapeutic profiles than **51**, and the minor change in stereochemistry resulted in faster elimination and, therefore, reduced toxicity. The efficacy of anthracyclines could be

improved by increasing molecular lipophilicity and thereby facilitating cellular uptake. Pirarubicin (**54**) [107] is a 4′-*O*-tetrahydropyranyl derivative of **51**. It interacts with topoisomerase II like the parent structure **51**, but is less cardiotoxic and also exhibits activity against some **51**-resistant cell lines. Valrubicin (**55**), [108] an *N*-trifluoroacetyl-14-valerate derivative of **51**, is used to treat bladder cancer, and idarubicin (**56**) [109] is a 4-demethoxy derivative of **52** used against acute myelogenous leukemia. The structures of **54**–**56** are characterized by their higher lipophilicity, which is responsible for their increased potency and decreased cardiotoxicity.

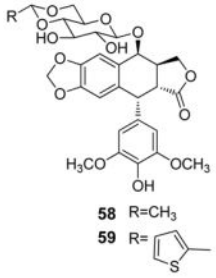


	R_1	R_2	R_3	R_4
51	OCH_3	CH_2OH	β-OH	H
52	OCH_3	CH_3	β-OH	H
53	OCH_3	CH_2OH	α-OH	H
54	OCH_3	CH_2OH	β-*O*-tetrahydropyranyl	H
55	OCH_3	$CH_2OCO(CH_2)_3CH_3$	β-OH	H
56	H	CH_3	β-OH	CF_3CO

Derivation of functional groups in a natural molecule may also cause a shift in the mechanism of action. The structural modification of the natural lignan podophyllotoxin (**57**) serves as a good example. Podophyllotoxin was originally discovered as a cytotoxic agent inhibiting the assembly of the mitotic spindle. [110] Although unacceptable side effects, particularly gastrointestinal toxicity, associated with **57** prevented its clinical use as cancer therapy, extensive structural modification efforts on this natural chemotype eventually led to the discovery of etoposide (**58**) and teniposide (**59**). [111,112] Interestingly, instead of inhibiting the assembly of microtubules, **58** and **59** exert their cytotoxicity by inducing DNA breaks mediated by topoisomerase II. The successful marketing of **58** and **59** has prompted further structural modification of **57**. Tafluposide (**60**) [113] is a fluorinated phosphate of **58**, which uniquely acts as a dual inhibitor of topoisomerases I and II. Tafluposide demonstrated high *in vivo* antitumor activity with a superior therapeutic spectrum and has been advanced to clinical trials. These **57**-derived anticancer drugs exhibited divergent molecular mechanisms, different antitumor spectra, and distinct therapeutic profiles.

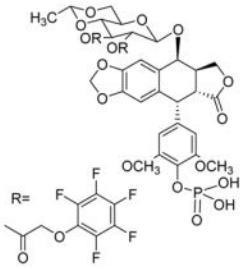


57



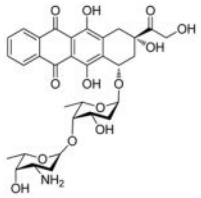
58 R=CH_3

59 R=

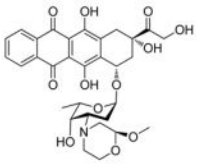


60

As mentioned earlier, the natural product doxorubicin (**51**) is a topoisomerase II inhibitor. Sabarubicin (**61**), a disaccharide analog of **51**, exhibits superior antitumor efficacy and is used for the treatment of small cell lung cancer (SCLC). The unique antitumor profiles of **61** could result from activation of p53-independent apoptosis. [114] Nemorubicin (**62**) is another derivative of **51**, which has the 3′-NH_2 group in **51** replaced with a 3′-methoxymorpholinyl group. This substitution increases the lipophilicity of the molecule and improves cellular permeability. Nemorubicin differs significantly from **51** in terms of antitumor, metabolic, and toxicity profiles. Its mechanism of action involves the nucleotide excision repair (NER) pathway, as well as topoisomerase I inhibition. [115] Both **61** and **62** were approved as anticancer drugs in European Union.



61



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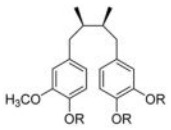


63 R=H

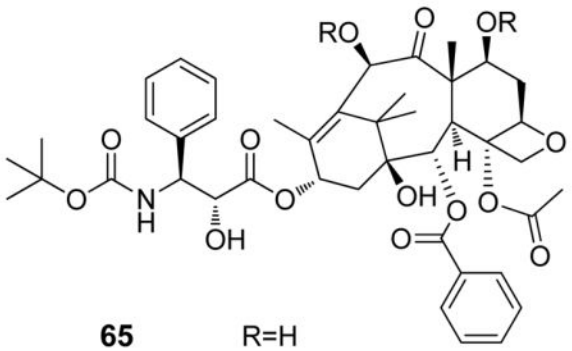
64 R=CH_3

Structural modification of a natural molecule can also lead to new therapeutic applications. The naturally occurring lignan meso-nordihydroguaiaretic acid (**63**) and other nordihydroguaiaretic acid (NDGA) derivatives were initially investigated as transcription inhibitors with effects against various viral infections. [116–119] However, a semi-synthetic NGDA derivative, terameprocol (**64**), was unexpectedly found to be a novel site-specific transcription inhibitor affecting the cell cycle and thereby exhibiting tumoricidal activity *in vivo*. Terameprocol was studied for the clinical treatment of cancers. [120,121]

3.1.2 Structure-activity relationship-directed optimization—For many natural products with novel structure and unique mechanism of action, the prototype molecule will

be subjected to extensive structural modification and conclusive SAR correlations can be established based on the resulting data, which can guide further optimization of the natural structures. Many examples are present in the literature, and SAR discussions on major classes of clinically useful anticancer natural products as well as their application in structural optimization are elucidated in many monographs, such as those cited herein. [31,32] Thus, our coverage of SAR-directed optimization in this section is intended to be selective rather than comprehensive. Tubulin-interactive natural products are of great research interest and have produced many therapeutic agents. [29,122] The microtubule-targeting natural products, paclitaxel, epothilones, and dolastatins will be briefly discussed as the most illustrative examples to highlight the importance of SAR study in structural optimization.

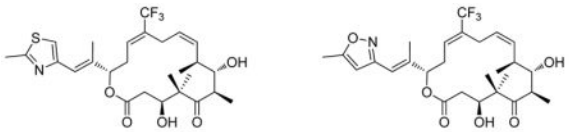
As mentioned earlier, the discovery of paclitaxel (**1**) initialized a new era in anticancer drug research. The recogition of its unique mechanism of action not only stimulated extensive structural modification and SAR study on this prototype molecule, but also prompted the search for new microtubule binding agents. Despite its high efficacy, **1** suffers from poor solubility and high toxicity, therefore, numerous **1**-analogs have been synthesized to overcome these drawbacks and SAR has been thoroughly studied. [123,124] Major structural components required for antitumor activity include the diterpene taxane core, the phenylisoserine side chain at C13 position, the *N*-acyl group at the 3′ position of the side chain, and the oxetane ring incorporating C4, C5 and C20. Structural modifications of functional groups on both the taxane core and the C13 side chain have been examined for their effects on antitumor activity, and the key SAR correlations for cytotoxic taxoids are summarized in Figure 1. [124] Based on these SAR clues, several new analogs with improved therapeutic profiles have been developed. [125] Docetaxel (**65**) is a **1**-analog used for the treatment of breast, ovarian, prostate and non-small cell lung cancers. Structurally, it differs from **1** only at the C10 and C3′ positions. Such structural alterations increase the water solubility of **65**. [126] Cabazitaxel (**66**) is a semisynthetic dimethoxy derivative of **65**. The modification of the C7 and C10 hydroxyls to dimethoxy groups might alter the P-glycoprotein (P-gp) affinity, and thereby, overcome the drug resistance problem associated with **65**. Cabazitaxel was approved for the treatment of hormone-refractory prostate cancer in 2010. [127] Although many other taxoids also entered clinical trials and currently there are still literally thousands of clinical trials ongoing, no more new taxoids have been marketed since the approval of cabazitaxel. The emergence of novel non-taxane tubulin interactive agents, such as epothilones, could further toughen the competition in this field. Recent reviews have underscored future efforts on both “synthetic repurposing” of this compound class [128] and the search for simplified molecules based on the pharmacophore of paclitaxel [129].



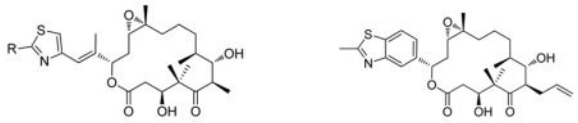
65 R=H
66 R=CH_3

The epothilones are polyketide macrolactones of bacterial origin, and they represent another important family of natural product-derived microtubule-stabilizing anticancer agents. Although they share the same binding site and exhibit similar biological effects as paclitaxel (**1**), the epothilones showed better efficacy and milder adverse effects than **1** in early trials. [27,130] Extensive structural modifications on this chemical family have revealed some SAR features (Figure 2). [27,131,132] Basically, the 16-membered macrocycle and the configuration of the seven chiral centers are essential for biological activity. However, alteration, addition and reduction of various functionalities in the prototype molecule epothilone B (**12**) could be readily accommodated (Figure 2).[131] Guided by such SAR, several new epothilone analogs have been developed for therapeutic uses or clinical trials. Ixabepilone (**13**) was obtained by isosteric replacement of the lactone moiety in **12** with a lactam. This structural alteration slightly reduced cytotoxic and tubulin binding activities, while it improved the resistance to esterase cleavage and expanded the therapeutic window. Ixabepilone was approved for use in the treatment of breast cancer in 2007. [133] As demonstrated by the efficient microtubule stabilization and potent antiproliferative activity of epothilone D (**43**), the epothilone C12–C13 epoxide moiety is not an absolute requirement for bioactivity, and it can be changed to a double bond. Further incorporation of a *trans* double bond between C9 and C10 or C10 and C11 can also improve the antitumor activity. KOS-1584 (**44**) is a (*E*)-9,10-dehydro derivative of **43**. KOS-1584 exhibited enhanced *in vivo* potency and was tested in clinic. [134] This SAR feature also led to the discovery of the C26-fluorinated analog fludelone (**67**), which has proved to be a potent antitumor agent *in vivo*. [135] To further improve potency, another epothilone congener iso-fludelone (**68**) was prepared by substituting the thiazole moiety in **67** with an iso-oxazole group. Iso-fludelone showed excellent biological stability, water solubility, and potency as compared with other epothilones. [136] This new analog has recently entered Phase I clinical study in patients with advanced solid tumors. [137] Modifications of the C20 methyl on the thiazole ring of **12** to small or moderate size substituents were generally well tolerated. Two new analogs, BMS-310705 (**69**) and ABJ879 (**70**), were developed for clinical trials by following this SAR observation. BMS-310705 contains an amino group at C21 of **12**, which increases chemical stability and water solubility. [138] ABJ879 is a 20-desmethyl-20-methylsulfanyl derivative of **12**, and it is more potent than **12** against human tumor cell lines. [139] The side chain at C15 and the methyl at C6 of **12** were also modified to improve the multi-drug resistant profiles and antitumor efficacy. Sagopilone (**71,** ZK-EPO) is a

lipophilic analog of **12**, in which the thiazole ring is changed to a benzothiazole ring and the C6 methyl is replaced by propenyl. This compound not only showed significant antitumor activity and efficacy, but also was distinguished from other epothilones by its capability to cross blood-brain barrier and the lack of recognition by efflux mechanisms. [140] A comparison of data from preclinical and phase I clinical studies on seven epothilone analogs was reported. [141] Currently, there are still three epothilones, epothilone B (**12**, phase II), isofludelone (**68**, phase I) and sagopilone (**71**, phase II) under active clinical trials.

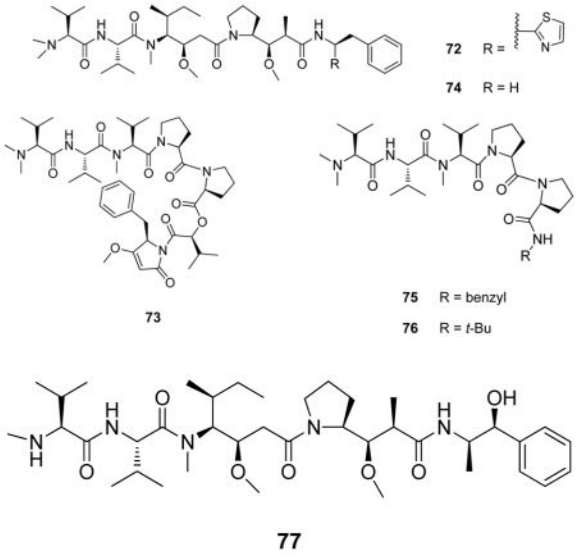


67 **68**



69 R=CH_2NH_2
70 R=SCH_3 **71**

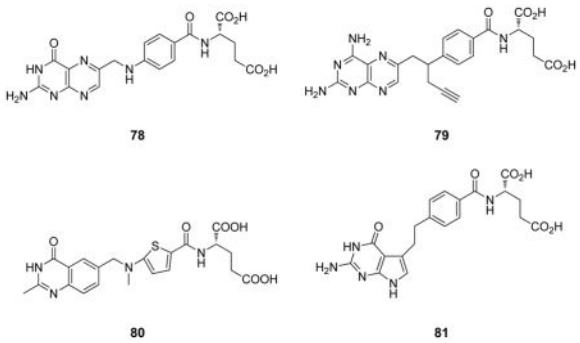
Dolastatins are a series of antineoplastic peptides of marine origin. Dolastatin 10 (**72**), the most potent compound in this structural family, showed subnanomolar inhibitory activity against murine P388 lymphocytic leukemia. [142] It was identified as an antimitotic agent binding at the vinca alkaloid site, and was tested in clinical trials. [143] Although the clinical studies were terminated due to an unacceptable toxicity profile, its high *in vitro* activity and novel mode of action promoted extensive structural modification studies on **72** as well as another structurally related natural depsipeptide, dolastatin 15 (**73**),[144] to retain anticancer activity and reduce toxicity. The effects of structural modifications on **72** and **73** are briefly summarized in Figure 3, and the SAR studies resulted in the discovery of several synthetic analogs as potent anticancer agents for clinical trials. [145] Soblidotin (**74**) [146] is an analog of **72** with the thiazole ring removed. Cematodin (**75**) [147] and synthadotin (**76**) [148] are synthetic analogs of **73**. In these compounds, the unique 2-hydroxyisovaleric acid–dolapyrrolidone (Hiva–Dpy2) terminal moieties in **73** have been changed to benzylamino and *tert*-butylamino groups, respectively. Analogs **74–76** exhibited potent antimitotic activity with significant antiproliferative and preclinical antitumor effects. They were investigated in clinic for the treatment of various cancers, but failed to reach market as anticancer chemotherapy. However, another **72**-analog, monomethyl auristatin E (MMAE, **77**), was chemically conjugated to a chimeric anti-CD30 antibody to provide the antibody-drug conjugate (ADC) brentuximab vedotin, which was approved for treatment of relapsed Hodgkin lymphoma and systemic anaplastic large cell lymphoma. [149]



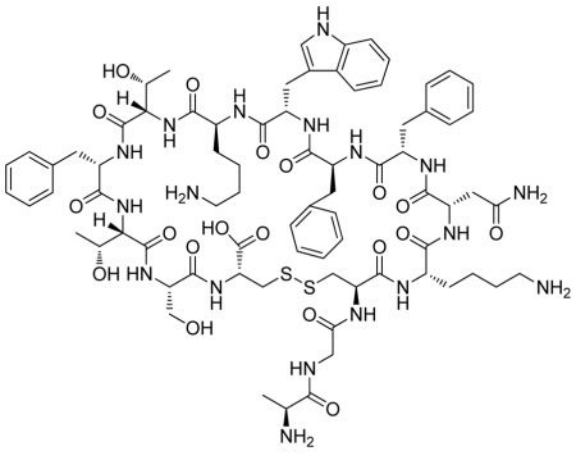
3.1.3 Pharmacophore-oriented molecular design—A further strategy to optimize natural leads is to design and synthesize natural product mimetics based on pharmacophores of the natural leads. In this approach, the key pharmacophoric features of the natural leads are first identified. Then, novel structures with scaffolds different from those of the natural leads are designed, while the pharmacophoric features are retained. Compared with the previous two strategies, this approach has the obvious advantages of enhanced structural novelty and potentially better chemical accessibility. In a broader view, this strategy can be termed as a pharmacophore-oriented molecular design. As illustrated in Table 1, the number of NCEs derived from this approach (S*, S*/NM and S/NM) is comparable to that of natural product-derivatives (ND), and account for another one third of small-molecule anticancer drugs.

Kinase inhibitors binding at the ATP site constitute a prominent example of pharmacophore-oriented molecular design based on endogenous substances. Most kinase inhibitors could be regarded as ATP mimetics with the pharmacophoric features preserved (e.g., hydrogen bond forming atoms interacting with the hinge region of the ATP site), but the basic skeleton (e.g., the hydrophobic core) altered to improve structural novelty and chemical accessibility. The discovery and development of antimetabolites as anticancer drugs is another example of pharmacophore-oriented molecular design in the area of cancer chemotherapy. Folic acid (**78**) is an endogenous substance essential for numerous body functions, particularly for cells and tissues that divide rapidly. Therefore, antifolates with structural similarity to folic acid can interfere with folate metabolism and be used to treat cancer. Methotrexate (MTX, **9**) [44] is a folate analog widely used as an effective therapeutic agent against many solid tumors. However, in spite of the development of new drug delivery systems to improve the distribution of MTX,[150] the poor pharmacokinetics and narrow safety margin of the drug limit its therapeutic application. Therefore, novel folate analogs are being actively sought as better therapeutic drugs. Pralatrexate (**79**) is a derivative of 10-deazaaminopterin, an isosteric congener of MTX. It selectively inhibits cancerous cells that express reduced folate carrier type 1 (RFC-1), a plasma membrane transporter responsible for cellular uptake of

folate. Pralatrexate was approved as the first drug for relapsed or refractory peripheral T-cell lymphoma (PTCL). [151] In addition to **79**, other folate analogs have been discovered through pharmacophore-oriented molecular design, in which glutamate, the key pharmacophoric feature in **78**, is retained, while the aromatic pteridine ring and the *para*-aminobenzoic acid moieties are altered to other scaffolds. Raltitrexed (**80**) [152] is a thymidylate synthase inhibitor used in cancer chemotherapy. **80** differs from the prototype molecule **78** in both the pteridine and benzene rings. Similarly, pemetrexed (**81**) is also a folate analog with the pteridine and benzene rings in **78** altered. Pemetrexed inhibits three enzymes that use folate derivatives as substrates, namely thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT). It has been developed as a multi-targeted anti-folate for the treatment of a variety of cancers. [153]



The pharmacophore-oriented molecular design strategy was also applied to design synthetic analogs of endogenous hormones. The tetradecapeptide somatostatin ($SRIF_{14}$, **82**) is a cyclic peptide hormone that regulates the endocrine system and affects neurotransmission as well as cell proliferation. The potential medicinal applications of **82** make it an attractive template for peptidomimetic drug design. The residues Phe^{7}-Trp^{8}-Lys^{9}-Thr^{10} were identified as the pharmacophore of $SRIF_{14}$. [154] Two truncated peptide analogs of **82**, octreotide (**83**) and lanreotide (**84**), were designed accordingly, in which the pharmacophoric residues were either maintained (for **83**) or slightly modified (for **84**). Both octreotide and lanreotide are long-acting analogs of **82**, and are used for the treatment of neuroendocrine tumors. [155,156]



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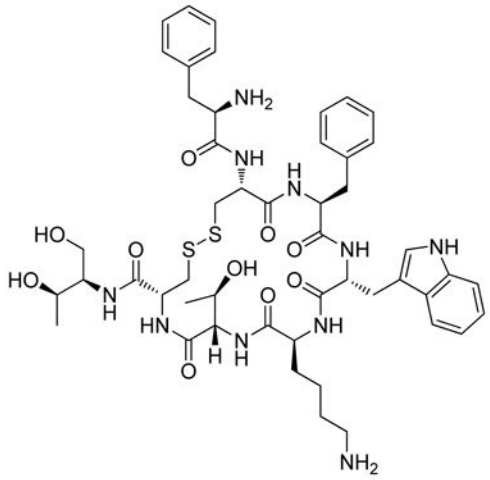

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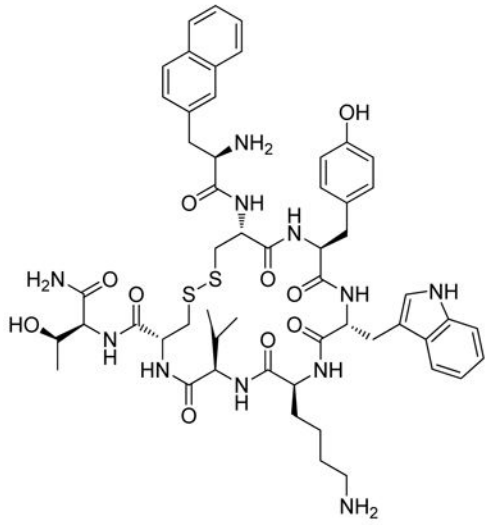
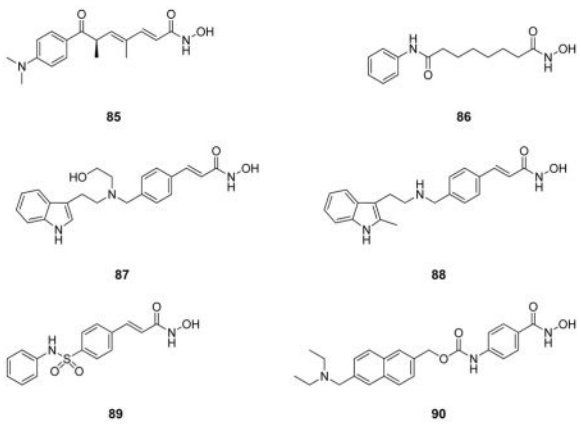
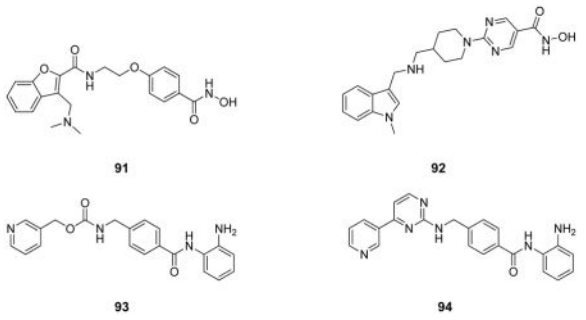


84

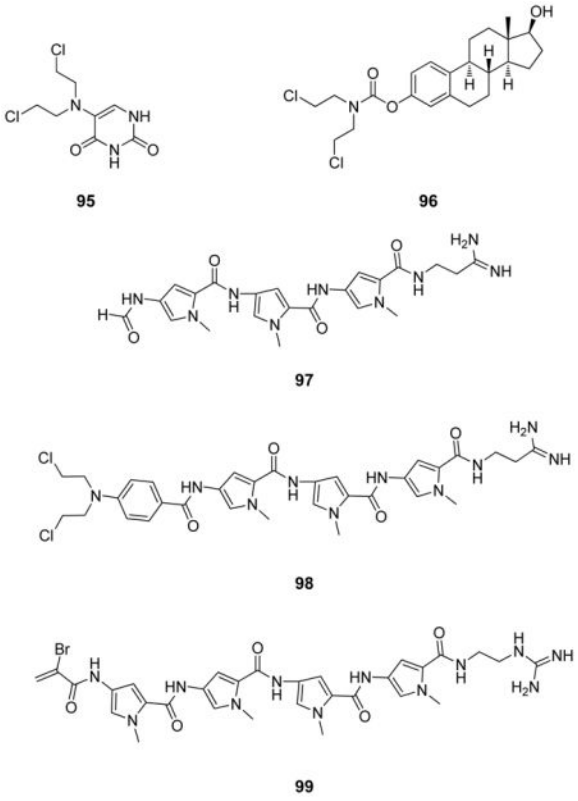
The development of histone deacetylase inhibitors as anticancer drugs is another good example for pharmacophore-oriented drug design based on natural leads. Trichostatin A (TSA, **85**) is a *Streptomyces* product with significant *in vivo* effects on cell proliferation and differentiation. It was identified as a potent and selective inhibitor against mammalian histone deacetylase (HDAC). [157] The hydroxamate group in TSA was regarded as a pharmacophoric feature for HDAC inhibition. Vorinostat (suberoylanilide hydroxamic acid, SAHA, **86**) [158] is a simplified analog of **85** in which the hydroxamate moiety was retained, while the conjugated *trans* double bonds as well as the chiral center were eliminated. Vorinostat was the first HDAC inhibitor approved by the FDA for the treatment of cutaneous T cell lymphoma (CTCL). The resolution of the structures formed by **85** or **86** complexed with an HDAC homologue revealed the interaction mode of these HDAC inhibitors, and suggested a three-part pharmacophore: a zinc-binding moiety, a hydrophobic linker, and a surface recognition group (Figure 4). [159] The hydroxamate group and the

substituted aromatic ring serve as the zinc-binding moiety and the surface recognition group, respectively, which are crucial for high-affinity to HDAC. In contrast, the hydrophobic linker plays an important role to appropriately position the former two moieties, while variation in the linker could also affect the inhibitory activity. Identification of this pharmacophore facilitated further molecular design of HDAC inhibitors. Several cinnamic hydroxamates that meet the pharmacophoric structural requirements have been successfully developed into investigational drugs. Dacinostat (LAQ-824, **87**) [160,161] and panobinostat (LBH-589, **88**) [162] are two HDAC inhibitors tested in clinical trials. In both molecules, the hydroxamate moiety was kept, a styrene group was incorporated as the hydrophobic linker, and a tryptamine-containing fragment was designed for surface recognition. Belinostat (PXD101, **89**) [163] is another cinnamic hydroxamate analog, in which an *N*-phenyl sulfonamide group is featured as the recognition cap group. Belinostat has been approved recently for the treatment of relapsed or refractory peripheral T-cell lymphoma. Givinostat (ITF2357, **90**) [164] and abexinostat (PCI-24781, **91**) [165] represent a new generation of HDAC inhibitors, and they are currently under active clinical trials. Structurally, they are benzoic hydroxamates with either a carbamate or an ether linkage extending the hydrophobic linker to the recognition cap groups. Tertiary amines are added to the recognition moieties to improve solubility. Quisinostat (JNJ-26481585, **92**) [166] is closely related to **90** and **91**, in which the benzene ring in **91** was changed to a pyrimidine ring, the aromatic benzofuran ring was changed to indole, and the ether linkage was replaced by a pyridine ring. *o*-Phenylenediamine is another effective zinc-binding group in addition to hydroxamate. Therefore, benzamide derivatives with *o*-phenylenediamine as the zinc-binding group have been designed as HDAC inhibitors, and two of them, entinostat (MS-275, **93**) [167] and mocetinostat (MGCD0103, **94**), [168] are being investigated in clinical trials as oral anticancer drugs.





The pharmacophore-oriented molecular design strategy can also involve the hybridization or merging of pharmacophores from distinct chemical classes of anticancer-agents to generate new chemotypes. Uramustine (uracil mustard, **95**) is a hybrid structure of nitrogen mustard and uracil. [169] It is a DNA alkylating agent and works by damaging DNA, primarily in cancer cells that preferentially take up the compound due to its structural similarity to uracil. Uramustine is a chemotherapeutic drug used for lymphatic malignancies such as non-Hodgkin's lymphoma, and was later withdrawn. [170] Similarly, estramustine (**96**) is a hybrid structure of estradiol and nitrogen mustard combined through a carbamate linkage, giving the compound both alkylating capability and estrogen-induced specificity. Estramustine is marketed as a chemotherapy agent for the treatment of prostate cancer. [171] Distamycin A (**97**) is a naturally occurring antibiotic isolated from cultures of *Streptomyces distallicus*. [172] It is a prototype of the polyamide minor groove binder (MGB) with a strong preference for AT rich sequences. When the pyrrole-amide skeleton of **97** is linked to other DNA interactive agents, it can serve as a DNA sequence selective vehicle and improve the cytotoxicity as well as therapeutic index of the hybrid molecule. The use of **97** in the design of hybrid molecules as potential antitumor agents with alkylating functions has been previously reviewed. [173] Tallimustine (**98**) was designed by combining the key DNA-interacting components of **97** and the alkylating agent nitrogen mustard. [174] Brostallicin (**99**) was designed by adding a latent alkylating functional group, a α,β-unsaturated bromoamide, to the pyrrole-amide skeleton of **97**. The α-bromoacrylic moiety could be activated to an alkylating agent by Michael addition to the glutathione in tumor cells. [175] Both **98** and **99** have been tested in clinical trials for the treatment of a variety of cancers, and **99** is still under active development.

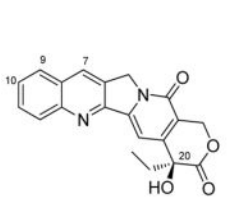


3.2 Optimization of ADMET profiles

Although the structural optimization of natural products has conventionally been dominated by efforts to improve efficacy, attempts to address poor pharmacokinetic profiles and unacceptable toxicity have been gradually emphasized. Efforts to increase the bioactivity of natural leads generally involve the refinement of structural details in the prototype molecule to enhance specific interaction with a certain macromolecule. However, the ADME profile of a molecule is often associated with molecular properties of the entire molecule. Consequently, structural modifications to tune the ADME profiles usually involve chemical modifications that can improve the physico-chemical properties of the molecule, which are often introduced at sites that can tolerate structural alteration. Toxicity is more complicated. Except for structural alerts or toxicophores, which are well-defined structural motifs with increased incidence of adverse outcomes, overall molecular properties, particularly lipophilicity, can also contribute to drug accumulation and thereby affect the toxicity of the drug. General approaches to improve solubility, enhance cellular permeability, increase chemical or metabolic stability, and decrease toxicity will be discussed with illustrative examples in this section. The prodrug approach, which is an important approach in medicinal chemistry to address the ADME and toxicity issues, will be discussed separately.

3.2.1 Approaches to improve solubility—Poor solubility, especially the lack of water-solubility, is frequently a hurdle in developing natural products into therapeutic drugs, and it can present a huge challenge to the formulation and administration of drugs. The most straightforward approach to improve water-solubility is to intentionally incorporate

hydrophilic groups into the natural leads. The development of camptothecin (CPT, **100**) analogs as effective anticancer drugs is a good example of this approach. CPT is a cytotoxic alkaloid isolated from the bark and stems of *Camptotheca acuminata*. [176] CPT inhibits the DNA enzyme topoisomerase I. It showed remarkable anticancer activity in preliminary clinical trials. However, adverse drug reaction and low solubility are major disadvantages of this natural lead, which limits its therapeutic application. The SAR studies on CPT analogs indicated that the conjugated fused ABCD rings, the lactone E ring, the hydroxyl and the (*S*)-configuration at C-20 are essential for cytotoxic activity. However, positions 7, 9, and 10 can tolerate structural alterations. [177] Accordingly, several water-soluble CPT analogs were developed with hydrophilic fragments incorporated at these positions. Topotecan (**101**) [178] is a water-soluble derivative of CPT with hydroxy and dimethylaminomethyl groups present at C10 and C7, respectively. Topotecan is used in the form of its hydrochloride salt to treat ovarian, cervical, and small cell lung cancers. Belotecan (**102**) [179] is another water-soluble CPT analog bearing an isopropylaminoethyl moiety at position 7. It is in clinical use for the treatment of ovarian and small cell lung cancers. Other water-soluble CPT analogs, such as exatecan (**103**), [180] lurtotecan (**104**), [181] and namitecan (**105**), [182] are all featured by the inclusion of aliphatic amino substitution at the C7 position, although structural alteration at other positions may also exist. Furthermore, the prodrug approach has also been successfully exploited to improve water-solubility of CPT derivatives and has led to the development of the clinical drug irinotecan (cf. Section 3.2.5).



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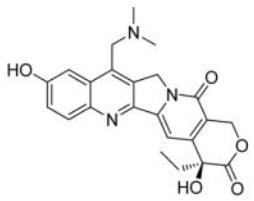

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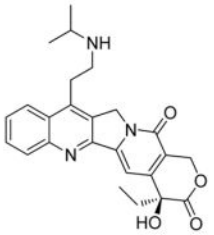

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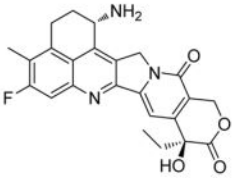

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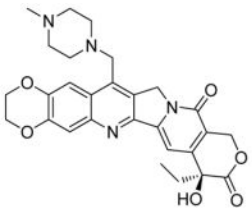

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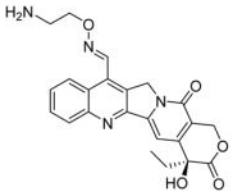
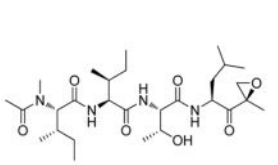


105

The bacterial natural product epoxomicin (**106**) was identified as an inhibitor of the chymotrypsin-like activity of the 20S proteasome. [183] To improve proteasome inhibitory activity, a series of epoxyketone derivatives were synthesized and evaluated. YU-101 (**107**), which is a tetrapeptide slightly different from **106**, was discovered as a more potent proteasome inhibitor than the natural compound. [184] YU-101 was further modified by adding a morpholino substitution on the acetyl group of its *N*-terminus. This modification was intended to improve the ADME properties, especially water-solubility, and eventually led to the discovery of carfilzomib (**108**). Carfilzomib was approved as a therapeutic drug for the treatment of multiple myeloma in 2012. [185] The interesting story on the discovery and development of **108** from the natural lead **106** has been recently described. [186]



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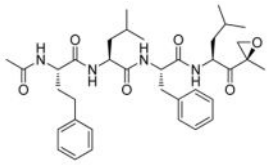

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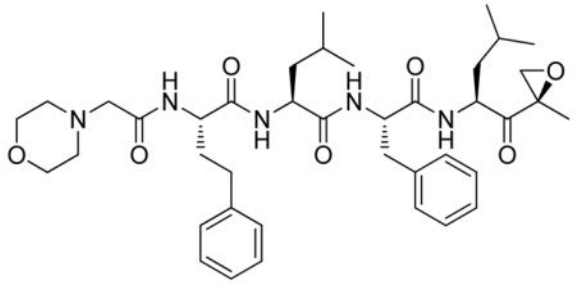
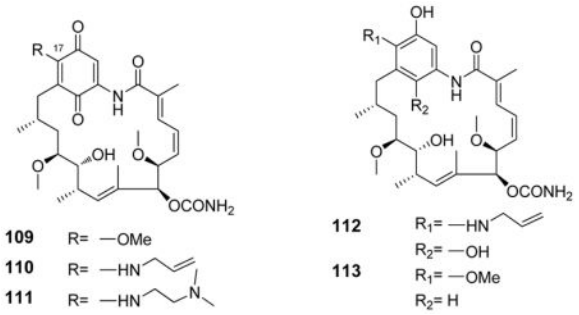
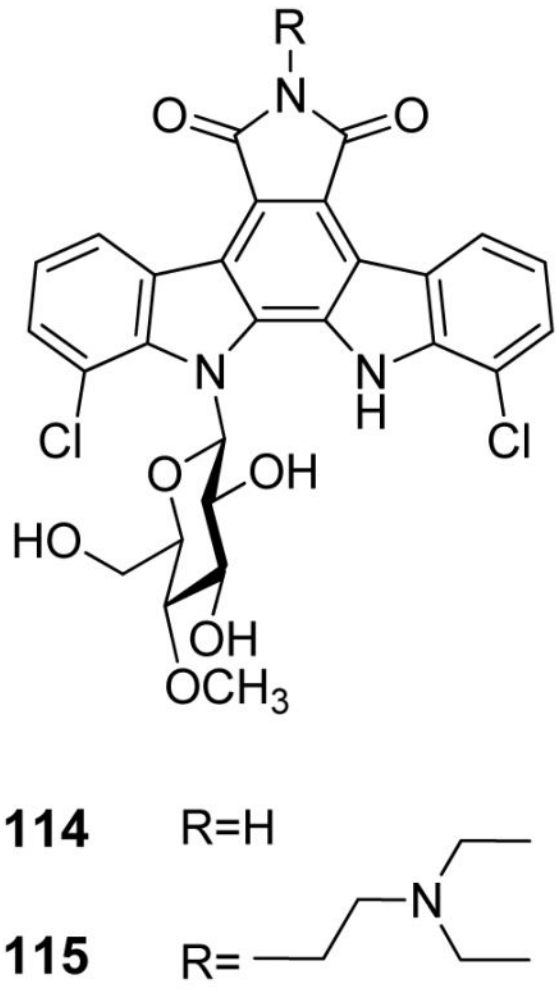


108

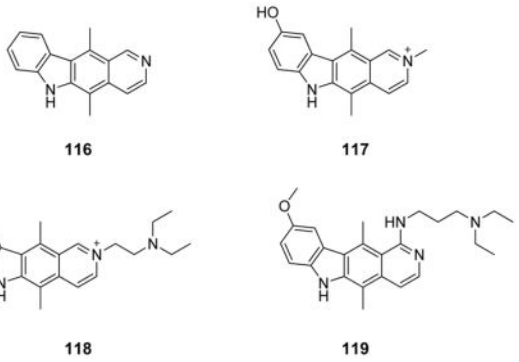
Geldanamycin (GM, **109**) is a benzoquinone ansamycin antibiotic first isolated from a strain of *Streptomyces hygroscopicus*. It inhibits the function of heat shock protein 90 (Hsp90) by binding to its ADP/ATP-binding pocket. [187] Although the clinical trials of **109** were discontinued due to hepatotoxicity and poor solubility, SAR and X-ray crystal studies suggested that structural alterations at the C17 position of **109** would be well tolerated. [188] Therefore, several **109**-analogs with various substitutions at C17 were subsequently developed and tested in clinical trials. Tanespimycin (17-AAG, **110**) is a 17-allylamino-GM developed by Bristol-Myers Squibb, [189] which was approved for the treatment of multiple myeloma in 2004. However, further clinical trials of **110** were impeded by the major obstacle of poor solubility. Later structural optimization of **109** focused mainly on improving water-solubility through C17 modification. Alvespimycin (17-DMAG, **111**) [190] is a water-soluble **109**-derivative with dimethylaminoethylamino substitution at C17. Its hydrochloride salt was tested for the treatment of advanced solid tumors. The realization that reduction of the *p*-benzoquinone skeleton in **109** to a hydroquinone would make the C17 amino group sufficiently basic to form stable salts prompted the conversion of **110** to its hydroquinone congener retaspimycin (**112**). [191] This compound is a water-soluble analog of **109** and also structurally related to the hydroquinone natural product reblastatin (**113**). [192]



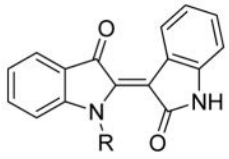
Rebeccamycin (**114**) is a natural bis-indole alkaloid originated from bacteria. [193] While it is structurally similar to staurosporine (**20**), **114** did not inhibit protein kinases. Instead, it was a weak topoisomerase I inhibitor. [194] Becatecarin (**115**) is a semisynthetic water-soluble derivative of **114** with a diethylaminoethyl substituent on the imide nitrogen. Becatecarin showed dual inhibition of topoisomerases I and II, and was approved for the treatment of bile duct tumors. [195]



Ellipticine (**116**) is a natural alkaloid isolated from the plant family Apocynaceae. This planar heterocyclic structure showed high antineoplastic activity and it acts through DNA intercalation and topoisomerase II inhibition. [196] However, water insolubility hampered its progression to clinical trials. Accordingly, a number of water soluble derivatives with either a quaternary ammonium ion at N-2 or an amino-alkyl substituent at C-1 have been designed to overcome this problem. Elliptinium (**117**) is a 2-methyl-9-hydroxyl derivative of **116** with improved water-solubility. [197] It was used for the treatment of metastatic breast cancer. Similarly, datelliptium (**118**), an ellipticine derivative bearing a diethylaminoethyl substituent at N-2, was tested clinically as the water soluble hydrochloride salt. [198] Retelliptine (**119**) contains a diethyl-aminopropylamino substituent at the C-1 position and this compound reached clinical investigation in the form of a water-soluble dihydrochloride salt. [199]



Indirubin (**120**) is the active ingredient of the traditional Chinese prescription Danggui Longhui Wan. As a bis-indole natural product isolated from *Indigo naturalis* (leaves of *Indigofera tinctoria* or *baphicacanthus cusia*), **120** was found to be effective against chronic myelogenous leukemia. [200] However, the poor solubility of **120** resulted in low bioavailability when administered orally. [201] The introduction of a methyl group on one amide nitrogen of **120** led to the discovery of meisoindigo (**121**), an analog with higher antineoplastic activity and better absorption properties. [202] The presence of the methyl group in **121** decreases the possibility of intra-molecular hydrogen bonding and increases water-solubility, which contributes to the improved pharmacokinetic profiles of **121**.

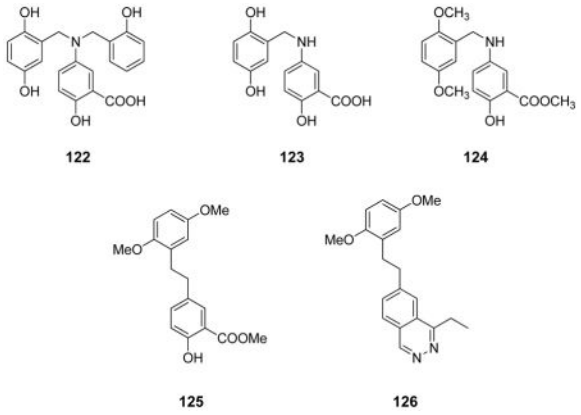


120 R = H

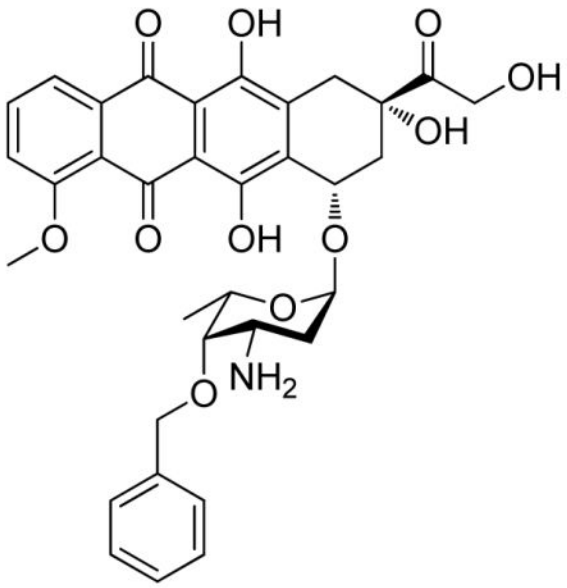
121 **R** = CH_3

3.2.2 Approaches to enhance cellular permeability—The poor cellular permeability of some natural leads could cause insufficient exposure to macromolecule targets, and thereby, failure to achieve cellular as well as *in vivo* activity. To increase cellular permeability, the overall lipophilicity of the entire molecule must be modulated by either eliminating polar, hydrophilic moieties or adding lipophilic fragments.

Lavendustin A (**122**) is a microbial secondary metabolite. It showed potent inhibition against the epidermal growth factor receptor (EGFR) tyrosine kinase in cell-free extracts, but not in intact cells. [203] The discrepancy was attributed to poor cellular permeability resulting from the multiple polar groups and high polar surface area of **122**. [204] Medicinal chemistry efforts to improve cellular penetration and antiproliferative activity of **122** were initiated. [205] The partial structure **123** was prepared, in which the *o*-cresol moiety was removed to decrease polarity, however, it was still inactive in cells. Further esterification of the carboxylic acid and *O*-methylation of the 2,5-dihydroxyphenyl moiety in **123** produced compound **124**, which did exhibit antiproliferative activity in the micromolar range. Substantial increases in cellular activity were achieved by replacing the nitrogen in **124** with a carbon atom to further increase lipophilicity and cellular penetration. The resulting structure SDZ-LAP-977 (**125**) exhibited high antiproliferative activity against tumor and keratinocyte cell lines. [206] Based on the fact that the hydroxyl and carbonyl of the methyl salicylate portion in **125** could form a pseudo six-membered ring through intra-molecular hydrogen bonding, this portion of the molecule was changed to 4-ethylquinazoline, which further decreased polarity. Interestingly, the resultant compound SDZ-LAV-694 (**126**) was inactive against the EGF-R tyrosine kinase. Instead, it blocks the cell cycle in mitosis and inhibits tubulin polymerization by binding to the colchicine binding site on tubulin. Compound **126** was a potent tubulin inhibitor with a nanomolar IC_{50} value. The optimization of **125** to **126** is also a good example of scaffold hopping (cf. Section 3.3.3). Both **125** and **126** have been tested in clinical trials. [206,207]



Structural optimization to enhance cellular permeability could also facilitate penetration through the blood-brain barrier (BBB). Berubicin (**127**) is a 4′-*O*-benzylated doxorubicin (**51**) analog designed to circumvent drug resistance. However, the presence of an additional benzyl group also allowed **127** to penetrate the BBB, which distinguished this compound from other anthracycline derivatives and made it applicable for the treatment of brain tumors. [208]



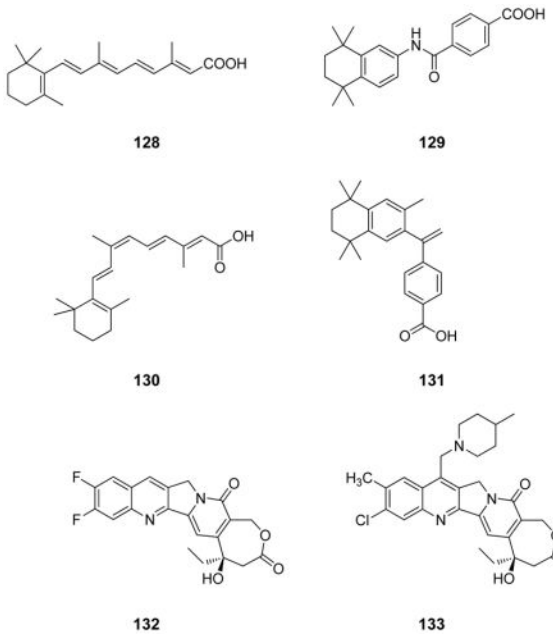
127

3.2.3 Approaches to increase chemical or metabolic stability—A lack of chemical or metabolic stability can present severe challenges for the development of natural leads into therapeutic drugs. The all-*trans*-retinoic acid (ATRA, **128**) is a therapeutic drug mainly used for the treatment of acute promyelocytic leukemia. However, this agent is chemically unstable at room temperature, especially in the presence of UV light, air, and oxidizing agents. ATRA acts as a retinoic acid receptor (RAR) agonist, and the pharmacophore for RAR agonists comprises a hydrophobic tail and a polar end. Accordingly, tamibarotene (**129**) was designed by incorporating a tetramethyltetralin group as a hydrophobic tail. This compound was a potent and orally active RAR agonist with significantly improved chemical stability as compared to **128**, and has been successfully developed as an anti-leukemia drug. [209] Similarly, 9-*cis*-retinoic acid (**130**) is also an antineoplastic agent with poor chemical stability. Its tetramethyltetralin analog, bexarotene (**131**), [210] was approved as an oral antineoplastic agent for the treatment of cutaneous T cell lymphoma.

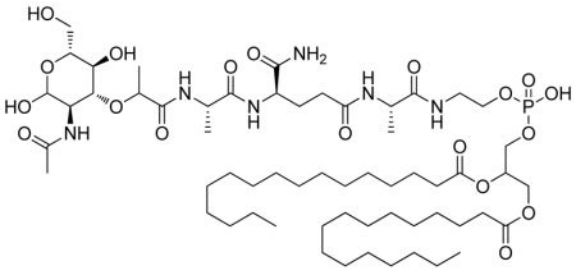
Isosteric replacement is also a strategy to improve metabolic stability of natural leads. As mentioned earlier in Section 3.1.1, substituting the ester oxygen in epothilone B (**12**) with a nitrogen atom produced ixabepilone (**13**). Compound **13** is more resistant to cellular esterases than **12** and, consequently, has better metabolic stability, as well as higher efficacy. [49] Such a subtle change also granted intellectual property status to **13** and made it possible for Bristol-Myers Squibb to develop it as a new chemical entity.

The lactone ring in camptothecin (CPT, **100**) is susceptible to hydrolysis, which is potentiated by the electron-withdrawing effect of the hydroxyl at C20. Hence, homocamptothecin (hCPT) derivatives with an extra methylene unit between C20 and C21,

which expands the six-membered lactone ring to a seven-membered ring, were designed to improve plasma stability. Two of these compounds, diflomotecan (**132**) and elomotecan (**133**), reached clinical trials. Diflomotecan, a 10,11-difluoro-hCPT, was the first hCPT tested in clinical studies. It is a potent topo I inhibitor with high oral bioavailability, but in contrast to other topoisomerase I inhibitors, it did not cause severe gastrointestinal toxicity. [211] Elomotecan is an hCPT derivative, which inhibits both topoisomerases I and II. [212] It exhibited potent antiproliferative effects against a panel of tumor cell lines, including drug-resistant lines, and also showed high *in vivo* efficiency in tumor xenograft studies. [213]



Mifamurtide (**134**) is a synthetic lipophilic analog of muramyl dipeptide (MDP, **135**), [214] the smallest naturally-occurring immune stimulatory component of cell walls from *Mycobacterium* species. When conjugated with alanyl-2-aminoethyl-2,3-dipalmitoylglycerylphosphoric acid, mifamurtide exhibited similar immune-stimulatory effects as natural MDP, but has the advantage of a longer half-life in plasma. The phospholipid side chain of **134** makes it accumulate in the lipid bilayer of the liposomes. Liposome-entrapped **134** is designed for *in vivo* targeted delivery to macrophages and stimulates them to kill various tumor cells. Mifamurtide was approved as a drug against osteosarcoma, a kind of bone cancer mainly affecting children and young adults. [215,216]



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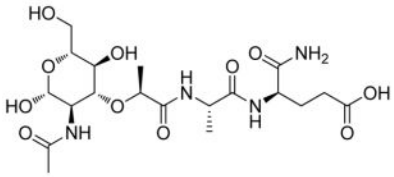

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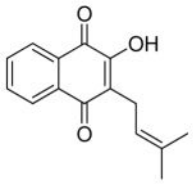
3.2.4 Approaches to decrease toxicity—Unacceptable toxicity is another problem that impedes the development of natural products into therapeutic drugs. Two sources of toxicity are generally involved: off-target effects and the so-called idiosyncratic drug reactions. The first type of toxicity generally requires structural optimization to improve a compound's specificity, which usually relates to structural alteration in certain molecular areas of the prototype molecules. This issue can generally be addressed in the optimization efforts to improve efficacy, as illustrated by many examples in Section 3.1. The second source of toxicity usually involves nonspecific adverse effects caused by unpredictable stimulation of endogenous biomolecules. Such toxicity is usually caused by structural alerts with either inherent or metabolic chemical reactivity. [217] Two alternative approaches are usually taken to overcome toxicity caused by structural alerts. Firstly, the toxicity could be reduced by increasing potency or local accumulation so as to decrease exposure duration of the drug. Secondly, it is possible to avoid toxicity by modifying the structural alerts.

The development of doxorubicin (**51**) analogs as new therapeutic drugs with less cardiotoxicity is a good example for reducing toxicity by increasing local accumulation and potency. As mentioned earlier in Section 3.1.1, pirarubicin (**54**), valrubicin (**55**) and idarubicin (**56**) are all highly lipophilic analogs of **51**. Such a change in molecular property allows the compounds to accumulate more readily in the nuclei, and therefore, increases potency as well as decreases cardiotoxicity.

The natural product β-lapachol (**136**) is a relatively simple naphthoquinone with significant antitumor activity. The naphthoquinone skeleton is generally considered as a structural alert, since it is a reactive electrophile susceptible to endogenous nucleophiles. β-Lapachol was advanced to clinical status by NCI in the 1970s, but was later withdrawn due to unacceptable toxicity. [218] β-Lapachone (**137**) is a structurally related *o*-naphthoquinone and can be obtained by treating **136** with sulfuric acid. The intra-molecular cyclization reduces the susceptibility to nucleophilic attack due to decreased electrophilicity and increased steric

effects. β-Lapachone showed strong anticancer activity both *in vitro* and *in vivo*, and was tested in clinical trials for advanced solid tumors. [219] Although there is no further report on the clinical development of β-lapachone as an anticancer drug, it is currently being investigated as a potential therapy for the treatment of non-alcoholic fatty liver disease (information from Thomson Reuters Integrity).



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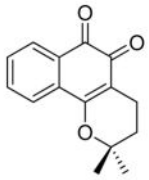

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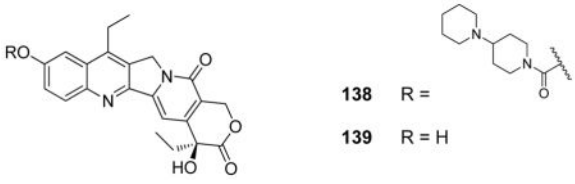
3.2.5 Prodrug approaches—By definition, a prodrug is an inactive molecule that can be converted to its active form through *in vivo* metabolic processes. The prodrug approach is often used to improve ADME properties, especially oral bioavailability. It can also reduce adverse effects, facilitate formulation efforts, and even improve the taste of intended drugs. The prodrug approach is an important strategy in developing natural leads into therapeutic anticancer drugs. This approach is used most frequently to enhance oral bioavailability, improve metabolic stability, or facilitate target delivery. A "straightforward" design of prodrugs takes advantage of ubiquitous enzymes, such as esterases or amidases, while a "smart" design involves cleavage reactions only induced by enzymes unique to the target tissue or even cascade enzymatic reactions. [220]

In the field of natural products, a prodrug approach is most frequently applied to improve solubility and enhance oral bioavailability. As mentioned in Section 3.2.1, the clinical application of camptothecin (CPT, **100**) was hampered by low solubility. Irinotecan (**138**) is a water-soluble prodrug of CPT with a bispiperidine functionality incorporated at C10 via a carbamate linkage. Enzymatic cleavage of the C10 side chain by carboxylesterases mainly in the liver affords the active metabolite SN-38 (**139**), which is 1000-fold more potent as a topoisomerase I inhibitor and also more cytotoxic than **138**. Irinotecan was approved for the treatment of cancer, especially colon cancer. [221, 222]

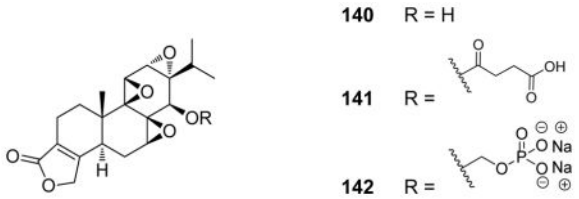


138 R =

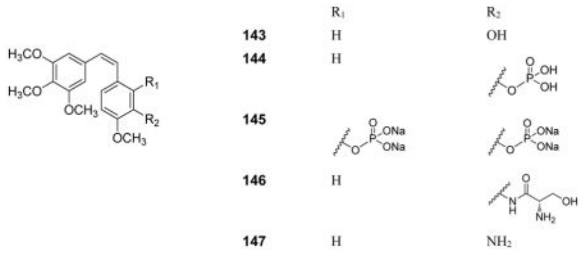
139 R = H

Triptolide (**140**) is a diterpenoid epoxide isolated from *Tripterygium wilfordii*. It demonstrated a unique bioactivity spectrum and was evaluated clinically in China for the treatment of rheumatoid arthritis and leukemia. However, its poor water solubility and severe toxicity limited its therapeutic application. [223] Omtriptolide (PG-490-88Na, **141**), 14-succinyl triptolide sodium salt, is a prodrug designed to improve water solubility. It is highly water soluble and can be converted into **140** *in vivo*. It entered phase I clinical trials to treat

solid tumors, but was later discontinued due to a similar toxicity profile to **140**. Minnelide (**142**), another water-soluble prodrug of **140**, bears an *O*-methyl phosphate disodium salt on the C-14β hydroxyl of **140**. It was investigated mainly for potential treatment of pancreatic cancer and gastrointestinal tumors. [224]



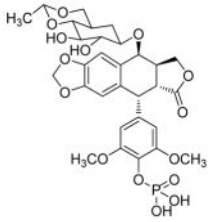
Combretastatins are a family of natural phenols isolated from *Combretum caffrum*. Combretastatin A-4 (CA-4, **143**), [225] the most potent naturally occurring combretastatin known, is a strong vascular disrupting agent, binds at the colchicine site of β-tubulin, and shows significant cytotoxicity against human cancer cell lines. Structurally, CA-4 is a stilbenoid with two substituted aromatic rings linked by an ethene bridge, which is a relatively rigid structure with poor water solubility. To overcome the solubility problem, prodrugs based on **143** and its analogs have been designed and investigated. Combretastatin A-4 phosphate (CA-4P, **144**) is a water-soluble phosphate prodrug of **143**. It can be converted to its active metabolite **143** by phosphatases, and acts as a vascular disrupting agent and significantly reduces the blood flow to tumor cells. [226] Similarly, combretastatin A-1 diphosphate (CA-1P, **145**) is a phosphate prodrug of CA-1. [227] Ombrabulin (AVE8062, **146**) is another combretastatin prodrug, which has a serine conjugated with the synthetic CA-4 analog RPR-258063 (**147**) through an amide linkage to improve water-solubility. Ombrabulin can be rapidly converted into its active metabolite **147** *in vivo*, and exerts its antitumor effect by disrupting the formation of blood vessels needed for tumor growth. Ombrabulin is being investigated clinically for the treatment of soft tissue sarcoma. [228]



Etopophos (etoposide phosphate, **148**) is a water-soluble prodrug developed to overcome the poor water solubility of etoposide (**58**). Etopophos can be efficiently converted *in vivo* by endogenous phosphatase to the active drug **58**, and exhibits pharmacological and pharmacokinetic profiles similar to those of **58**. Notably, the prodrug approach increased the *in vivo* bioavailability from 0.04% to over 50%, and also resulted in more predictable oral bioavailability. [111]

F14512 (**149**) is a water-soluble derivative of epipodophyllotoxin, the synthetic precursor of **58**. It is a prodrug designed for targeted delivery. The spermine moiety present in the side chain facilitates selective uptake of **149** by tumor cells via the polyamine transport system,

which is generally over-activated in tumor cells. F14512 has been characterized as a potent drug candidate and is currently in Phase I clinical trials. [229]



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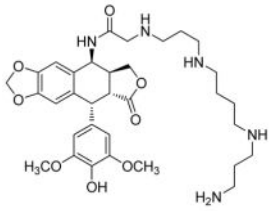

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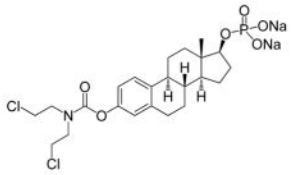
Estramustine phosphate (estramustine phosphate sodium, **150**) is an oral oncolytic drug used for the treatment of advanced prostatic carcinoma. It is a prodrug of estramustine (**151**), which can be prepared directly from estradiol with a carbamate ester linkage to nor-nitrogen mustard. Estramustine phosphate can be readily metabolized to estramustine and a closely related structure, estromustine *in vivo*, and exert its cytotoxic activity as a microtubule inhibitor. [230,231]



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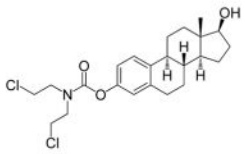

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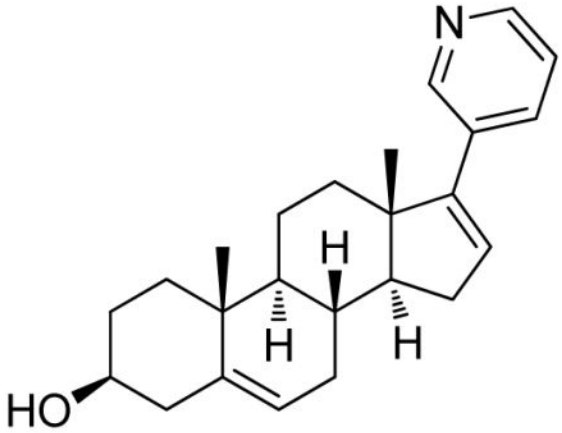
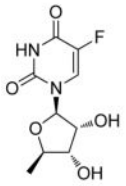
Abiraterone (**152**) is a derivative of steroidal progesterone featured by a 3-pyridyl substituent at C-17 and a $\Delta^{16,17}$ double bond. It is a potent and selective cytochrome P450 17α-hydroxylase-17,20-lyase (CYP17A1) inhibitor and inhibits CYP17A1 in an irreversible manner via a covalent binding mechanism. However, **152** has very poor bioavailability and is susceptible to hydrolysis; thus, it was marketed as an acetate prodrug, which is orally active and also less susceptible to hydrolysis than **152**. As an innovative drug, **152**-acetate was used for castration-resistant prostate cancer. [232]



152

As mentioned earlier, 5-fluorouracil (5-FU, **2**) is an anti-metabolite designed from uracil by isomeric replacement. A critical limitation of **2** is its rapid degradation and inactivation by dihydropyrimidine dehydrogenase (DPD) *in vivo*. To overcome the metabolic instability of **2**, a series of prodrugs was developed by making use of thymidine phosphorylase (TP), an enzyme highly expressed in tumor issues. Doxifluridine (5′-DFUR, **153**) is an oral prodrug designed for this purpose. 5′-DFUR circumvents the degradation by DPD in the gut wall, and is converted into **2** by TP in tumor tissue. Since **2** is produced *in situ* in tumor tissue, **153** could be considered as a target delivery device to deliver **2** selectively to tumor tissue. [233] Capecitabine (**154**) is a novel carbamate derivative of **153** rationally designed to generate **2** preferentially in tumors. It is metabolized to **153** by carboxyl esterases and is further enzymatically converted to **2** in tumor tissue. Capecitabine has even higher tumor-selectivity than **153** and is an oral chemotherapeutic agent used in the treatment of metastatic breast and colorectal cancers. [234]



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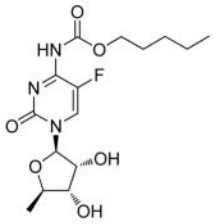

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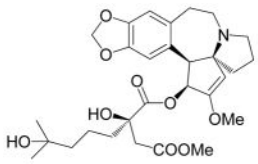
3.3 Improving chemical accessibility

Besides efficacy and ADMET profiles, another bottleneck in developing natural products into therapeutic drugs is chemical accessibility. Many natural products have only limited supply from nature, and the situation can be even worse under the pressure of environmental protection issues. On the other hand, although total synthesis can be an alternative way to produce natural products, it is more likely to be an academic triumph rather than an

alternative source for drug supply, due to the complexity of many natural structures. Biosynthetic technology could be a potential solution. However, it still faces severe technical challenges before it is truly applicable on industrial scales. It is worth to note that semi-synthesis from reproducible natural precursors is a practical strategy to solve the chemical accessibility problem. This has been vividly demonstrated by the successful example of paclitaxel (**1**), which can be obtained in large-scale though semi-synthesis from 10-deacetylbaccatin III (10-DAB), a synthetic precursor of paclitaxel abundant in yew needles. [124] Another example is omacetaxine mepesuccinate (homoharringtonine, **155**), a protein synthesis inhibitor approved by FDA for the treatment of chronic myeloid leukemia (CML) in 2012. **155** was isolated from the whole plant of *Cephalotaxus harringtonia*. [235] As a natural ester of cephalotaxine (**156**), **155** is now manufactured by direct esterification of cephalotaxine, which is extracted from dry leaves of *Cephalotaxus* species and serves as a reproducible natural precursor of **155**. [236]



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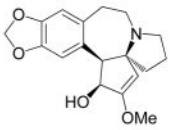

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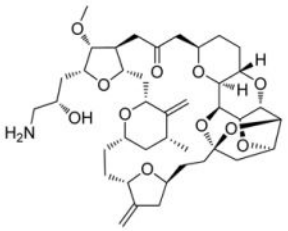
The preparation of simplified analogs based on complex natural structures represents a rational way to improve the chemical accessibility of natural products. As illustrated by the example of morphine alkaloids, simplified analogs of morphine, including morphinanes, benzomorphanes, phenylpiperidines, and even methadone, all retain analgesic activity, while they have significantly decreased structural complexity and improved chemical accessibility. Chemically, the strategies to make simplified analogs of a natural product include dissection of the complex natural template, elimination of redundant chiral centers, and pharmacophore-oriented scaffold hopping.

3.3.1 Dissection of complex natural templates—Complex natural structures are usually secondary metabolites produced during the evolution of an organism, and are intended for self-defense of the organism rather than as medicines for humans. Therefore, it is possible that not all of the structural features in a natural molecule are required for bioactivity, and structural redundancy may exist. Intense efforts have been devoted to reduce the structural complexity of natural products through truncation by organic synthesis, and some studies have successfully produced anticancer drugs with improved chemical accessibility. [237] The most telling example for this approach is the development of the anticancer drug eribulin (**157**) from the natural product halichondrin B (**158**).

Halichondrin B (**158**), a polyether macrolide isolated from the marine sponge *Halichondra okadai*, exhibited potent anticancer activity against murine cancer cells both in culture and *in vivo*. [238] Compound **158** was identified as a tubulin-targeted mitotic inhibitor by analyzing its cytotoxicity data against 60 different human tumor cell lines. [239] It attracted much attention due to its intriguing structural architecture and extraordinary antitumor activity. In spite of its structural complexity and the presence of 32 chiral centers, its first

total synthesis was achieved in 1992. [240] When synthetic **158** and several intermediates were tested for antitumor activity, intermediate **159** with only the right half of **158** showed *in vitro* activity identical to that of **158**, however, it showed no *in vivo* efficacy. This exciting discovery eventually led to the discovery and development of the structurally simplified and pharmaceutically optimized analog eribulin (**157**). [241,242] Compounds **157** and **158** exhibited comparable *in vitro* and *in vivo* activities, but due to the absence of an ester linkage, **157** showed improved metabolic stability. More notably, its significantly simplified structure made large-scale synthesis possible, and adequate supplies could be provided by chemical synthesis. Eribulin mesylate was approved for the treatment of refractory metastatic breast cancer in 2010. The synthesis of halichondrins and the case history for the development of eribulin mesylate have been nicely reviewed. [243,244]



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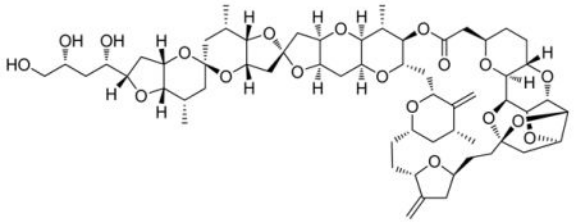

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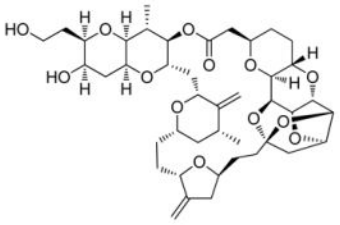

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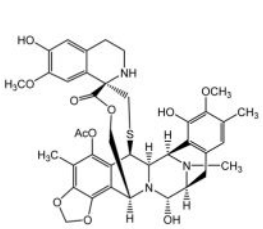
Trabectedin (ecteinascidin 743 or ET-743, **160**) was identified as an antitumor component from the sea squirt *Ecteinascidia turbinata*. It has a unique molecular architecture characterized by the presence of three tetrahydroisoquinoline moieties and one of them connected with the other two through a ten-membered lactone ring incorporating a cysteine residue. [245] Trabectidin has been approved in Europe as Yondelis for the treatment of soft tissue sarcoma and ovarian cancer. Due to its scarcity in nature, total synthesis of trabectedin was attempted and was first achieved in 1996. [246] Although the total synthesis failed to provide an adequate supply of **160**, it led to the discovery of simplified analogs with *in vitro* potency and mode of action similar to those of **160**. The simplified structure phthalascidin

(PT-650, **161**) is characterized by the elimination of one tetrahydroisoquinoline moiety and the bridging lactone ring of **160** as well as the addition of a phthalimide side chain. Phthalascidin showed significant antiproliferative activity, even in camptothecin- and etoposide-resistant cells, and was more readily synthesized and more chemically stable than **160**. [247] Compounds **160** and **161** can be obtained efficiently through a semisynthetic process starting from cyanosafracin B (**162**), a fermentation product from *Pseudomonas fluorescens*. [248] Zalypsis (**163**) is a synthetic simplified dimeric isoquinoline alkaloid structurally related to **160**, **161** and several other tetrahydroisoquinoline marine products, such as jorumycin from *Jorunna funebris*, and renieramycins from sponges and tunicates. Again, the lactone ring is absent and a substituted *trans*-cinnamamide side chain is present. Zalypsis showed potent cytotoxic activity against a 24-cell line panel, and could form covalent bonds with guanines in the DNA double helix. [249] It is currently under active phase II clinical trials for various cancers, including cervical cancer, metastatic endometrial cancer and bladder cancer.



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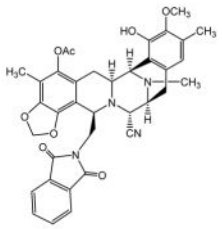

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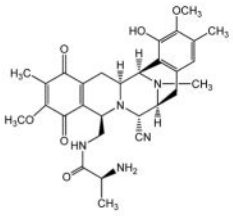

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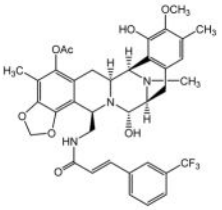

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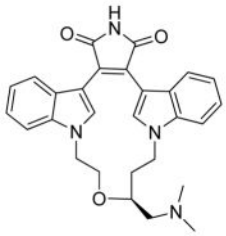
3.3.2 Diminishing stereogenic centers—The presence of multiple stereogenic centers is a key feature of many natural products and is also a major challenge in the total synthesis of natural products. Therefore, an important way to improve chemical accessibility is to reduce the number of chiral centers in the natural prototype molecule. The bis-indole alkaloid staurosporine (**20**) is a potent protein kinase C (PKC) inhibitor of bacterial origin. Although its lack of specificity has precluded the clinical use of **20**, it still serves as a critical prototype structure and a valuable research tool, especially for anticancer drug discovery. Macrocyclic [250] and acyclic derivatives [251] were designed and synthesized as simplified analogs of **20** to improve PKC isozyme selectivity and increase the pharmacological benefits. Ruboxistaurin (LY333531, **164**) is a bisindolylmaleimide macrocycle structure, in which the aminosugar moiety in **20** is replaced with a 14-membered *N*-*N*' bridged macrocyclic ether and the number of chiral centers is reduced from four to one. Enzastaurin (**165**) is an acyclic derivative of **20**. It is an achiral molecule with all four chiral centers in the natural structure eliminated. Both **164** and **165** showed significant selectivity for PKCβ

and also exhibited kinase selectivity for PKC in comparison to other ATP-dependent kinases. [250,251] Ruboxistaurin is an investigational drug for diabetic peripheral retinopathy sponsored by Eli Lilly. Enzastaurin has been tested in the clinic as an oral small molecule for the treatment of cancer, either as stand-alone therapy or in combination with traditional cancer therapies. [252]



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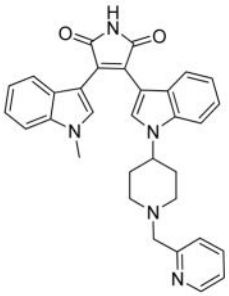

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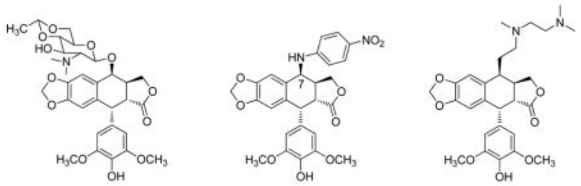
3.3.3 Scaffold hopping—The concept of scaffold hopping was first introduced in 1999 as a technique to identify different molecular backbones with similar biological activities. [253] Virtually, scaffold hopping is a technique to identify novel bioactive chemotypes by modifying the central core structure of known active compounds. Even before the introduction of the concept, the scaffold hopping strategy has been widely applied to discover novel lead structures with better therapeutic profiles based on known active molecules. Theoretically, scaffold hopping can be an effective approach to improve efficacy and pharmacokinetic properties as well as chemical accessibility. The application and classification of scaffold hopping strategies in drug discovery have been recently reviewed. [254,255] Usually, functional or topological pharmacophores are identified and maintained during the operation of scaffold hopping. Therefore, the case studies cited in Section 3.1.3 could also serve as examples for scaffold hopping. Scaffold hopping is less frequently applied in the optimization of natural leads than in synthetic molecules. This is probably because the scarcity of chemical and biological information on natural leads makes it difficult for efficient detection of pharmacophores. We will only highlight a few examples using the scaffold hopping strategy intently to improve chemical accessibility. However, it is worth noting that the application of scaffold hopping could be an important trend in the field of natural product-based drug discovery. Octreotide (**83**) and lanreotide (**84**) are simplified analogs of the tetradecapeptide somatostatin ($SRIF_{14}$, **82**). The pharmacophoric residues Phe^{7}-Trp^{8}-Lys^{9}-Thr^{10} were preserved and the cyclic peptide backbone $SRIF_{14}$ was truncated to improve chemical accessibility. Both **83** and **84** are long-acting analogs of **82** and are used for the treatment of neuroendocrine tumors. [155,156] Trichostatin A (TSA, **85**) is a selective inhibitor of mammalian histone deacetylase (HDAC). In the simplified analog vorinostat (SAHA, **86**), the hydroxamate pharmacophore is preserved, but the natural linker moiety containing conjugated *trans* double bonds and a chiral center has been changed to a simple linear alkyl chain. [158] The compound resulting from this scaffold hopping was more chemically accessible and retained the HDAC inhibition of the natural compound.

4 Highlights of natural product research in NPRL

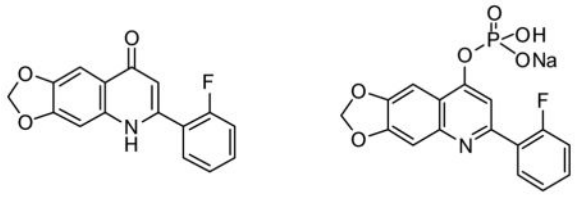
The Natural Products Research Laboratories (NPRL) at the University of North Carolina at Chapel Hill have been engaged in the discovery and development of natural product-derived chemotherapeutic agents based on medicinal chemistry approaches since 1971, and have discovered several thousands of bioactive natural products and their synthetic derivatives/analogs. Several reviews have featured major achievements in natural products-based drug discovery, particularly research performed in the NPRL on the discovery of novel anticancer drugs. [256–259] We will highlight herein only the case studies that successfully led to the discovery and development of anticancer drug candidates.

As mentioned earlier, the structural modification of the natural lignan podophyllotoxin (**57**) successfully led to the discovery of three therapeutic drugs, etoposide (**58**), teniposide (**59**), and etopophos (**148**). However, the therapeutic application of these drugs is often hampered by problems such as poor water-solubility, acquired drug resistance, and metabolic inactivation. In extensive efforts to overcome the above problems, several novel podophyllotoxin analogs, NK 611 (**166**), GL-331 (**167**), and TOP-53 (**168**), were discovered and reached clinical trials. [260] Among them, GL-331 was initially discovered by the NPRL and investigated in clinical trials by Genelabs Technologies, Inc. In an effort to improve the antitumor profile, especially to overcome multidrug resistance, various aniline substitutions were introduced at the C7 position of 4′-demethyl-epipodophyllotoxin and a series of novel 4β-arylamino derivatives with superior DNA topo II inhibitory activity were identified. [261] GL-331 was one of the most potent topo II inhibitors in this series. As compared to **58**, GL-331 is a DNA topo II inhibitor with superior activity both *in vitro* and *in vivo*. It also overcame multidrug resistance in many cell lines, and showed toxicological and pharmacokinetic profiles similar to those of **58**. In addition, formulated GL-331 has desirable stability and biocompatibility. After being tested in phase I clinical trials at M. D. Anderson Cancer Center, GL-331 was progressed to phase II clinical trials against small cell lung cancers. However, currently, there is no active development of this compound (information from Thomson Reuters Integrity).



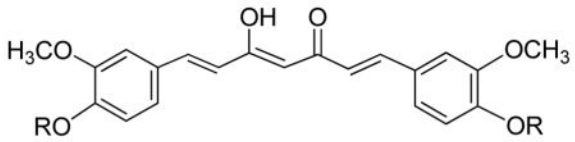
The fluorinated 2-phenyl-4-quinolone derivative **169** was originally developed as an antimitotic agent bearing the (methylenedioxy)benzene moiety, which is a common motif in natural antimitotic agents, such as cornigerine, podophyllotoxin (**57**), steganacin, and combretastatin A-2. [262] Compound **169** showed potent cytotoxicity against the NCI's 60 human tumor cell lines (HTCL) panel with an average logGI_{50} value of -6.47. It is also a potent inhibitor of tubulin polymerization with an IC_{50} value of 0.85 μM. This compound exhibited good *in vivo* activity against OVCAR-3 ovarian cell line, and prolonged the life span of treated mice by 130%. [263] Compound **169** was later found to inhibit hepatocyte

growth factor-induced invasion of SK-Hep-1 human hepatocellular carcinoma cells at micromolar concentrations by suppressing matrix metalloproteinase-9 expression, and was regarded as a potential therapeutic agent against tumor invasion. [264] Unfortunately, compound **169** is poorly water soluble, and thus, the monosodium phosphate salt of **169** (**170**) was developed as a prodrug of **169**. Compound **170** was rapidly converted into **169** following iv and po administration and exhibited excellent antitumor activity in the SKOV-3 xenograft nude mice model. Due to its superior pharmacological profiles, compound **170** is highly promising for development as an anticancer candidate and is licensed to Effpha Corporation of Taiwan for further investigation in clinical trials. [265]



169 **170**

Curcumin (**171**) is a yellow diarylheptanoid isolated from *Curcuma longa* (Zingiberaceae). Based on this natural chemotype, a number of synthetic curcumin analogs have been synthesized and evaluated as anticancer agents by the NPRL. [266–269] Some analogs were identified as potent androgen receptor antagonists with strong cytotoxic activity against prostate cancer cells as well as other tumor cell lines. Among them, JC-9 (**172**), a curcumin analog with high efficacy *in vitro* and *in vivo*, was licensed to Androscience Corporation, San Diego, CA for further preclinical and clinical studies. So far, JC-9 succeeded in Phase II clinical trials for treating acne in August 2012, and clinical trials for treating prostate cancer are being planned.



171 R = H
172 R = CH_3

5 Conclusions

Natural products have historically been and will continue to be a precious source for anticancer drug discovery. Sometimes, the natural products themselves are used directly as therapeutic drugs, but more often, they need careful structural optimization to improve their efficacy, pharmacokinetic and safety profiles, as well as chemical accessibility. We have reviewed herein the general strategies for the evolution of natural leads into anticancer drug candidates or therapeutic drugs. It is also important to be aware of the benefits brought to natural product-based drug discovery by the development of new concepts and technologies, especially the strategy of diverted total synthesis [270] to efficiently prepare natural product-

inspired chemical libraries as well as the application of chemoinformatic tools [271,272] to extract useful information for natural product-based drug discovery.

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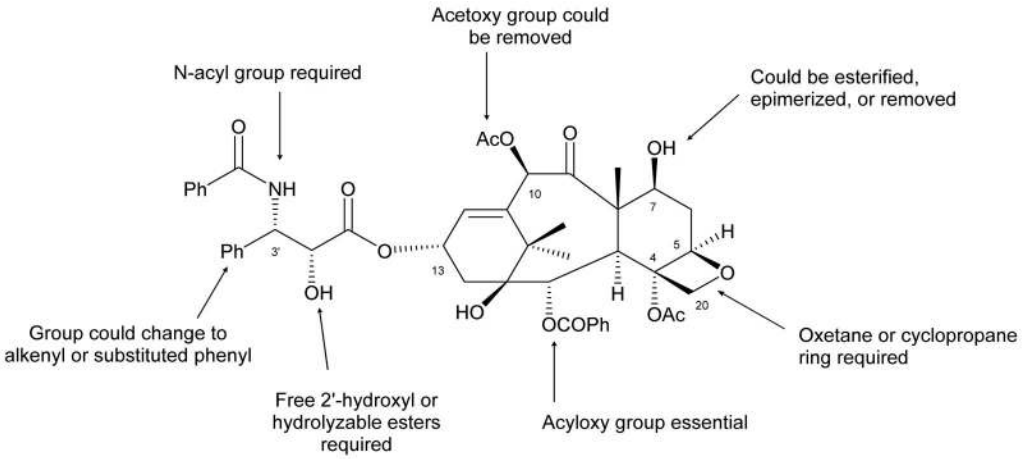

Figure 1.
Summary of key SAR for taxoid analogs (modified from ref. 124).

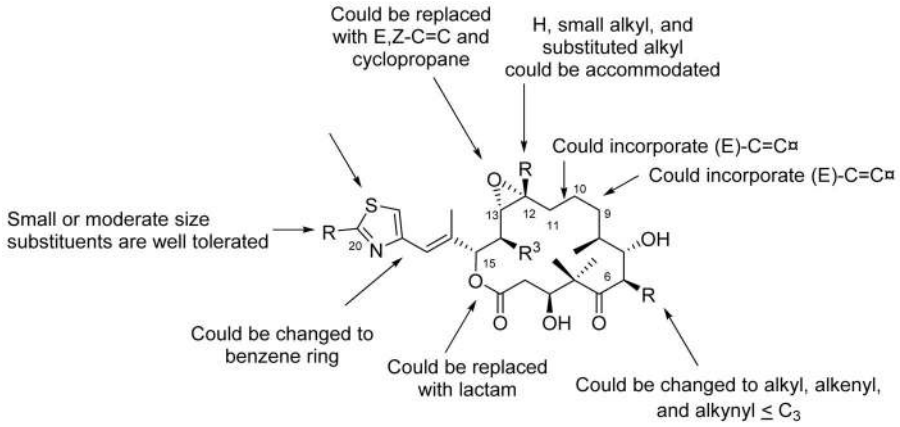

Figure 2.
Summary of key SAR for epothilone analogs (modified from ref. 131).

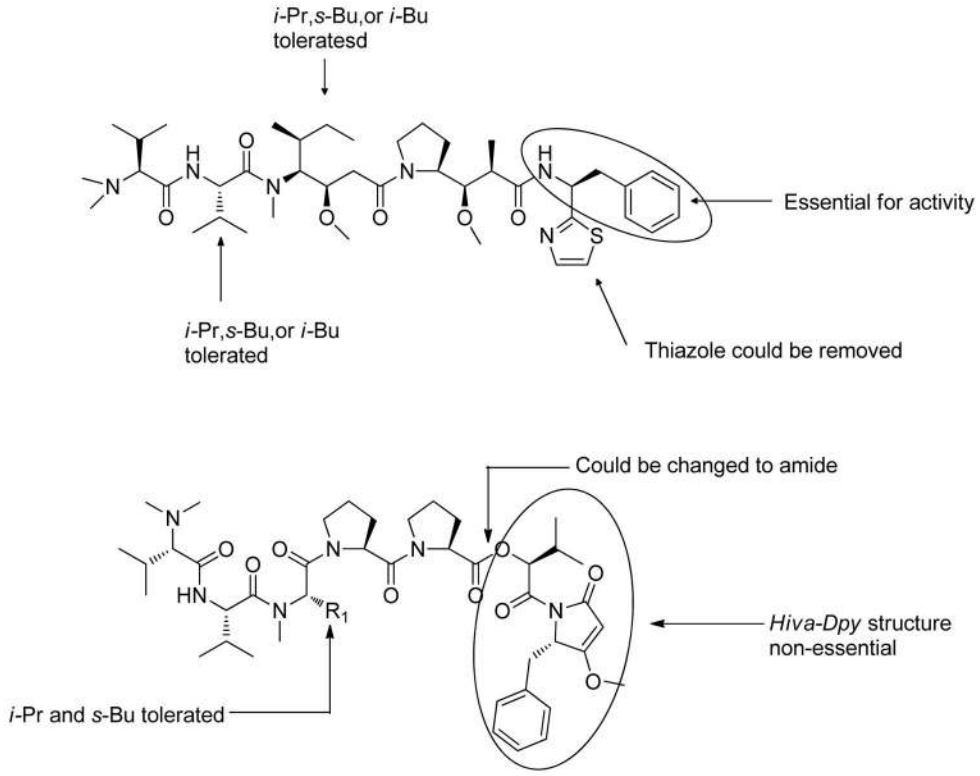

Figure 3.
Summary of key SAR for dolastatins analogs (modified from ref. 145).

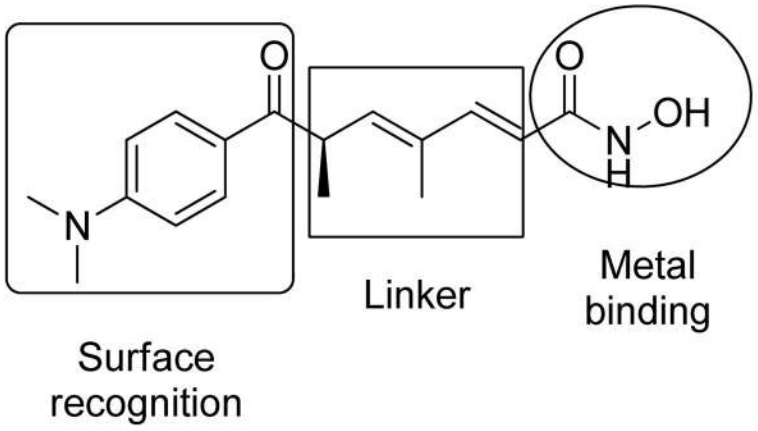

Figure 4.
TSA and its pharmacohporic features

Table 1

Source of approved small-molecule drugs categorized as NCEs

	All drugs, 1981–2010	Anticancer drugs, 1981–2010	All anticancer drugs
N	5.5% (59)[#]	11.1% (11)	15.4% (27)
ND	27.9% (299)	32.3% (32)	32.6% (57)
NB	0.5% (5)	1.0% (1)	0.6% (1)
S*	5.1% (55)	11.1% (11)	11.4% (20)
S*/NM	11.4% (122)	8.1% (8)	4.6% (8)
S	36.0% (387)	20.2% (20)	25.1% (44)
S/NM	13.6% (146)	16.2% (16)	10.3% (18)
Total	100.0% (1073)	100.0% (99)	100.0% (175)

[#] percentage (number)

"N": Natural product; "ND": Derived from a natural product; "NB" Natural product "botanical" ;"S*": Synthetic drug with a pharmacophore from a natural product; "NM": Natural product mimic; "S": Totally synthetic drug. For detailed definition of the categories, please refer to reference 17.

Table 2

Clinical anticancer drugs optimized from natural leads

Clinical drug	Lead compound	Year first introduced *	Section cited
fluorouracil (**2**)	uracil	1962	3.1.1
mercaptopurine (**3**)	hypoxanthine	1955	3.1.1
thioguanine (**4**)	guanine	1966	3.1.1
cytarabine (**5**)	deoxycytidine	1969	3.1.1
decitabine (**6**)	deoxycytidine	2006	3.1.1
cladribine (**7**)	adenosine	1993	3.1.1
clofarabine (**8**)	adenosine	2005	3.1.1
methotrexate (**9**)	folic acid (**78**)	1954	3.1.1
calusterone (**10**)	testosterone	1973 #	3.1.1
fluoxymesterone (**11**)	testosterone	pre-1970 #	3.1.1
ixabepilone (**13**)	epothilone B (**12**)	2007	3.1.1
temsirolimus (**17**)	rapamycin (**16**)	2004	3.1.1
everolimus (**18**)	rapamycin (**16**)	2009	3.1.1
ridaforolimus (**19**)	rapamycin (**16**)	2005	3.1.1
midostaurin (**21**)	staurosporine (**20**)	2004	3.1.1
flavopiridol (**24**)	rohitukine (**25**)	2007	3.1.1
lestaurtinib (**27**)	K-252a (**26**)	2006	3.1.1
triphendiol (**30**)	daidzein (**28**)	2008	3.1.1
irofulven (**32**)	illudin S (**31**)	1999	3.1.1
obatoclax (**40**)	streptorubin B (**38**)	2004	3.1.1
vindesine (**48**)	vinblastine (**47**)	1979	3.1.1
vinorelbine (**49**)	vinblastine (**47**)	1989	3.1.1
vinflunine (**50**)	vinblastine (**47**)	2010	3.1.1
epirubicin (**53**)	doxorubicin (**51**)	1984	3.1.1
pirarubicin (**54**)	doxorubicin (**51**)	1988	3.1.1
valrubicin (**55**)	doxorubicin (**51**)	1994	3.1.1
idarubicin (**56**)	daunorubicin (**52**)	1990	3.1.1
etoposide (**58**)	podophyllotoxin (**57**)	1980	3.1.1
teniposide (**59**)	podophyllotoxin (**57**)	1967	3.1.1
sabarubicin (**61**)	doxorubicin (**51**)	2004	3.1.1
nemorubicin (**62**)	doxorubicin (**51**)	2005	3.1.1
docetaxel (**65**)	paclitaxel (**1**)	1995	3.1.2
cabazitaxel (**66**)	paclitaxel (**1**)	2010	3.1.2
pralatrexate (**79**)	folic acid (**78**)	2006	3.1.3
raltitrexed (**80**)	folic acid (**78**)	1996	3.1.3
pemetrexed (**81**)	folic acid (**78**)	2004	3.1.3
octreotide (**83**)	somatostatin (**82**)	1988	3.1.3
lanreotide (**84**)	somatostatin (**82**)	1994	3.1.3

Clinical drug	Lead compound	Year first introduced *	Section cited
vorinostat (**86**)	trichostatin A (**85**)	2006	3.1.3
belinostat (**89**)	trichostatin A (**85**)	2014	3.1.3
estramustine (**96**)	estradiol	1980	3.1.3
topotecan (**101**)	camptothecin (**100**)	1996	3.2.1
belotecan (**102**)	camptothecin (**100**)	2004	3.2.1
carfilzomib (**108**)	epoxomicin (**106**)	2012	3.2.1
tanespimycin (**110**)	geldanamycin (**109**)	2004	3.2.1
becatecarin (**115**)	rebeccamycin (**114**)	2004	3.2.1
elliptinium (**117**)	ellipticine (**116**)	1983	3.2.1
berubicin (**127**)	doxorubicin (**51**)	1995	3.2.2
tamibarotene (**129**)	all-*trans*-retinoic acid (**128**)	2005	3.2.3
bexarotene (**131**)	9-*cis*-retinoic acid (**130**)	2000	3.2.3
mifamurtide (**134**)	muramyl dipeptide (**135**)	2010	3.2.3
irinotecan (**138**)	camptothecin (**100**)	1994	3.2.5
combretastatin A-1 diphosphate (**145**)	combretastatin A-1	2012	3.2.5
etopophos (**148**)	podophyllotoxin (**57**)	1996	3.2.5
estramustine phosphate (**150**)	estradiol	1980	3.2.5
abiraterone (**152**) acetate	abiraterone (**152**)	2011	3.2.5
doxifluridine (**153**)	fluorouracil (**2**)	1987	3.2.5
capecitabine (**154**)	fluorouracil (**2**)	1998	3.2.5
eribulin (**157**) mesylate	halichondrin B (**158**)	2010	3.3.1
enzastaurin (**165**)	staurosporine (**20**)	2005	3.3.2

* Data from Thomson Reuters Integrity. It indicates the year, in which the drug was first introduced as a clinical anticancer drug.

Information from reference 17.

Table 3

Investigational anticancer drugs optimized from natural leads

Investigational drug	Lead compound	Mechanism of action	Highest Phase *	Current status *	Section cited
HTI-286 (**15**)	hemiasterlin (**14**)	tubulin polymerization inhibitor	I	no active development	3.1.1
(*R*)-roscovitine (**23**)	olomoucine (**22**)	CDK inhibitor	II	under active development	3.1.1
phenoxodiol (**29**)	daidzein (**28**)	BIRC4 expression inhibitor tumor NADH oxidase (tNOX) inhibitor sphingosine kinase inhibitor	III	no active development	3.1.1
beloranib (**34**)	fumagillin (**33**)	methionine aminopeptidase-2 (MetAP2) inhibitor	I	no active development	3.1.1
PPI-2458 (**35**)	fumagillin (**33**)	methionine aminopeptidase-2 (MetAP2) inhibitor	I	no active development	3.1.1
diacetate S23906-1 (**37**)	acronycine (**36**)	DNA alkylating drug	-[$]	discontinued	3.1.1
vadimezan (**42**)	flavone-8-acetic acid (**41**)	vascular disrupting agent	III	discontinued	3.1.1
KOS-1584 (**44**)	epothilone D (**43**)	microtubule-stabilizing agent	II	no active development	3.1.1
plinabulin (**46**)	(−)-Phenylahistin (**45**)	tubulin polymerization inhibitor	II	no active development	3.1.1
tafluposide (**60**)	podophyllotoxin (**57**)	DNA topoisomerase I & II Inhibitor	I	no active development	3.1.1
terameprocol (**64**)	meso-nordihydroguaiaretic acid (**63**)	tat inhibitor; antimitotic drug	II	no active development	3.1.1
iso-fludelone (**68**)	epothilone D (**43**)	microtubule-stabilizing agent	I	under active development[#]	3.1.2
BMS-310705 (**69**)	epothilone B (**12**)	microtubule-stabilizing agent	I	no active development	3.1.2
ABJ879 (**70**)	epothilone B (**12**)	microtubule-stabilizing agent	I	discontinued	3.1.2
sagopilone (**71**)	epothilone B (**12**)	microtubule-stabilizing agent	II	under active development	3.1.2
soblidotin (**74**)	dolastatin 10 (**72**)	tubulin polymerization inhibitor	II	no active development	3.1.2
cematodin (**75**)	dolastatin 15 (**73**)	tubulin polymerization inhibitor	-	discontinued	3.1.2
synthadotin (**76**)	dolastatin 15 (**73**)	tubulin polymerization inhibitor	I	discontinued	3.1.2
dacinostat (**87**)	trichostatin A (**85**)	histone deacetylase (HDAC) inhibitor	-	discontinued	3.1.3
panobinostat (**88**)	trichostatin A (**85**)	histone deacetylase (HDAC) inhibitor	III	under active development	3.1.3
givinostat (**90**)	trichostatin A (**85**)	histone deacetylase (HDAC) inhibitor	II	under active development	3.1.3
abexinostat (**91**)	trichostatin A (**85**)	histone deacetylase (HDAC) inhibitor	II	under active development	3.1.3
quisinostat (**92**)	trichostatin A (**85**)	histone deacetylase 1 (HDAC 1) inhibitor	II	under active development	3.1.3
entinostat (**93**)	trichostatin A (**85**)	histone deacetylase (HDAC) inhibitor	III	under active development	3.1.3
mocetinostat (**94**)	trichostatin A (**85**)	histone deacetylase (HDAC) inhibitor	II	under active development	3.1.3
tallimustine (**98**)	distamycin A (**97**)	DNA-damaging drug	II	no active development	3.1.3
brostallicin (**99**)	distamycin A (**97**)	apoptosis inducers	II	under active development	3.1.3

Investigational drug	Lead compound	Mechanism of action	Highest Phase *	Current status *	Section cited
exatecan (**103**)	camptothecin (**100**)	DNA topoisomerase I inhibitor	III	no active development	3.2.1
lurtotecan (**104**)	camptothecin (**100**)	DNA topoisomerase I inhibitor	II	no active development	3.2.1
namitecan (**105**)	camptothecin (**100**)	DNA topoisomerase I inhibitor	I	under active development	3.2.1
alvespimycin (**111**)	geldanamycin (**109**)	heat shock protein 90 (Hap90) inhibitor	II	discontinued	3.2.1
retaspimycin (**112**)	geldanamycin (**109**) reblastatin (**113**)	heat shock protein 90 (Hap90) inhibitor	II	discontinued	3.2.1
datelliptium (**118**)	ellipticine (**116**)	DNA-intercalating drug DNA topoisomerase II inhibitor	III	no active development	3.2.1
retelliptine (**119**)	ellipticine (**116**)	DNA-intercalating drug DNA topoisomerase II inhibitor	II	no active development	3.2.1
meisoindigo (**121**)	indirubin (**120**)	signal transduction modulator STAT-3 inhibitor	II	under active development	3.2.1
SDZ-LAP-977 (**125**)	lavendustin A (**122**)	tyrosine kinase inhibitor	II	no active development	3.2.2
SDZ-LAV-694 (**126**)	lavendustin A (**122**)	antimitotic drug	I	under active development	3.2.2
diflomotecan (**132**)	camptothecin (**100**)	DNA topoisomerase I inhibitor	II	under active development	3.2.3
elomotecan (**133**)	camptothecin (**100**)	DNA topoisomerases I & II inhibitor	I	under active development	3.2.3
β-lapachone (**137**)	β-lapachol (**136**)	-	II	no active development	3.2.4
omtriptolide (**141**)	triptolide (**140**)	-	I	under active development	3.2.5
minnelide (**142**)	triptolide (**140**)	heat shock protein 70 inhibitor angiogenesis inhibitor	I	under active development	3.2.5
combretastatin A-4 phosphate (**144**)	combretastatin A-4 (**143**)	vascular disrupting agent	III	under active development	3.2.5
ombrabulin (**146**)	combretastatin A-4 (**143**)	vascular disrupting agent	III	discontinued	3.2.5
F14512 (**149**)	podophyllotoxin (**57**)	DNA topoisomerase II inhibitor	I	under active development	3.2.5
zalypsis (**163**)	trabectedin (**160**)	-	II	under active development	3.3.1

*Data from Thomson Reuters Integrity (updated by September 2014).

#Data from clinicaltrials.gov

-$Information unavailable