

Review

Discovery of structurally diverse and bioactive compounds from plant resources in China

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This review describes the major discoveries of structurally diverse and/or biologically significant compounds from plant resources in China, mainly from the traditional Chinese medicines (TCMs) since the establishment of our research group in 1999. In the past decade, a large array of biologically significant and novel structures has been identified from plant resources (or TCM) in our laboratory. The structural modification of several biologically important compounds led to more than 400 derivatives, some of which exhibited significantly improved activities and provided opportunities to elucidate the structure-activity relationship of the related compound class. These findings are important for drug discovery and help us understand the biological basis for the traditional applications of these plants in TCM.

Keywords: natural products; plant resources; traditional Chinese medicine; bioactive compounds; structural modification; structure-activity relationship

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Introduction

Natural products have long been used by humans, especially in the healthcare industry, providing us products from food supplements to chemical therapeutics to biological probes and beyond. Natural products from both plants and microbes have had great success in past drug discovery programs^[1, 2]. Structural novelty and biological significance are the two major innovative elements of natural products chemistry and are also key issues for drug development. The identification of natural compounds with novel structures and important biological activities, especially those possessing new carbon skeletons, has been the main challenge in the fields of natural products, organic synthesis and pharmacology. Traditional Chinese medicines (TCM) medications are proven reservoirs of novel lead structures, including the well-known examples of artemisinin (an antimalarial)^[3] and huperzine A (for AD treatment)^[4, 5]. China has rich medicinal plant resources, and approximately 11 000 species have been documented, only approximately 30% of which have been chemically studied. We therefore view TCM plants as a promising resource for lead structures that deserve further investigation. In depth chemical and pharmacological studies of TCM plants will also

provide starting points for TCM development and standardization.

In the past decade, chemical studies conducted in our research group have led to the isolation more than 2700 structurally diverse compounds from 125 plants (most with applications in TCM or folk medicine), of which 650 compounds were new structures, and 63 compounds featured unprecedented carbon skeletons or possessed unique structural motifs. The biosynthetic origins of most of these compounds with new carbon skeletons or unique structural motifs were proposed. Biological tests on these isolates via collaboration with the pharmacological research groups both in our institute and in outside organizations revealed that 182 compounds were active in the tested assays, and a number of them showed significant bioactivities associated with fatal human diseases. The structural modification of a few of the most promising bioactive compounds or drug leads produced more than 400 derivatives, 58 of which showed obviously improved activity. These studies also demonstrated the structure-activity relationship of the related compound classes. The major research findings are summarized here.

Structurally diverse and novel alkaloids

Daphniphyllum alkaloids (Figure 1): The genus *Daphniphyllum* is mainly distributed in the southern Asia, with 10 species growing in China. Some of these species have long been used

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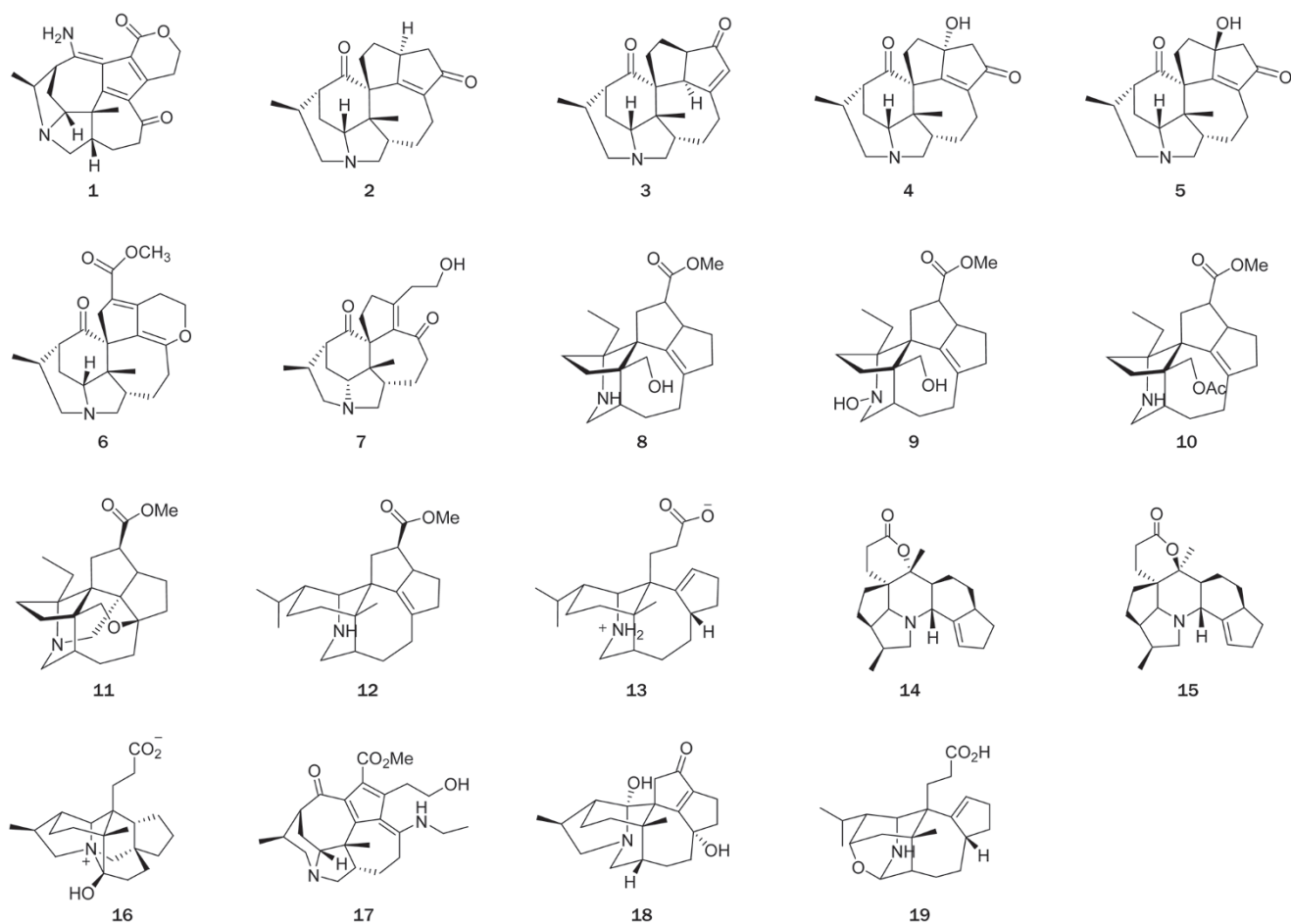


Figure 1. Alkaloids isolated from *Daphniphyllum* genus.

in TCM for the treatment of various disorders. *Daphniphyllum* alkaloids possessing highly complex and polycyclic features have been a challenging topic in natural products and organic synthesis. Since we published the first chemical studies on *D subverticillatum* in 2003, a total of 194 structurally complex alkaloids have been isolated from 9 species of *Daphniphyllum* in our research group, 72 of which were novel structures. Among the novel compounds, 14 of them had new skeletons or possessed rearranged carbon frameworks^[6–21]. Some alkaloids showed strong cytotoxic activity^[16].

Daphnipaxinin (**1**)^[8], the first diamino *Daphniphyllum* alkaloid, was isolated from *D paxianum*. The structure of **1** was determined by spectroscopic methods, and its absolute configuration was assigned by CD spectrum. A series of structurally related *Daphniphyllum* alkaloids with an unusual degraded skeleton of C-22-noryuzurimine-type (**2–5**)^[15, 16] were identified from *D longeracemosum* and *D yunnanense*. Compound **4** showed strong cytotoxic activities, with IC₅₀ values of 3.0 and 0.6 μmol/L against the tumor cell lines P388 and A549, respectively^[16]. The discovery of daphnilongeranin A (**6**)^[15], the first *seco*-10,17-longistylumphylline alkaloid from *D longeracemosum*, suggested that the hypothetical biosynthetic route proposed for daphnicyclidine A should be reconsidered. The

chemical investigation of *D yunnanense* also afforded the first C22-*nor*,10,17-*seco*-yuzurimine-type alkaloid, daphniyunnine B (**7**)^[16], which represents the most degraded compound in the *Daphniphyllum* alkaloid class.

A series of *Daphniphyllum* alkaloids possessing cage-like skeletons were isolated from the seeds of *D paxianum*^[11] and *D macropodum*^[18]. Compounds **8–11** are the representatives of these cage-like *Daphniphyllum* alkaloids; in particular, paxdaphnine A (**11**) is the first identified 1,19-bisnor-*Daphniphyllum* alkaloid with a highly caged skeleton and a constrained Ring-A by the formation of C2–C8 and C1–C9 bonds, whose absolute configuration was determined by X-ray diffraction of its iodide derivative. Two structurally relevant alkaloids, paxdaphnidine A (**12**), bearing a unique pentacyclic framework, and paxdaphnidine B (**13**), possessing an uncommon tetracyclic skeleton, were isolated from the twigs and leaves of *D paxianum*^[9]. Deoxycalyciphylline B (**14**) and deoxyisocalyciphylline B (**15**) were the major alkaloids with a unique fused hexacyclic skeleton from the stem of *D subverticillatum*^[8]. Their structures were assigned based on spectroscopic methods and chemical evidence, and that of **14** was confirmed by a single crystal X-ray diffraction determination.

Recently, angustimine (**16**), featuring an unprecedented

skeleton, and angustifolimine (**17**), a rare diamino *Daphniphyllum* alkaloid, were isolated from *D angustifolium*^[6]. Calycinumines A (**18**) and B (**19**) were isolated from *D calycinum*^[7]. Compound **18** is the first example of C-22-nor yuzurimine-type alkaloid, whose structure was confirmed by a single crystal X-ray diffraction study, and calycinumine B (**19**) features an unprecedented heteroatom-containing adamantane-like motif.

C,C-linked dimeric indolizidine alkaloids (Figure 2): *Flueggea virosa* Roxb ex Willd (Euphorbiaceae) is a TCM that has been used to treat rheumatism, pruritus, cephalic eczema, leucorrhea, and injuries. Previous chemical studies on this plant identified a number of indolizidine-type alkaloids known as *Securinega* alkaloids. In our recent study of this plant, two unprecedented C,C-linked dimeric indolizidine alkaloids, flueggenines A (**20**) and B (**21**), along with their precursor (-)-norsecurinine, were isolated from the roots of *F virosa*^[22]. Their structures and absolute configurations were elucidated by extensive spectroscopic analyses. The biogenetic origin of these two compounds could be traced back to the coexisting major alkaloid (-)-norsecurinine via a self-catalyzed Baylis-Hillman reaction as the key step to achieve the dimerization.

Other structural classes of alkaloids (Figure 2): Alkaloids are a class of structurally interesting and biologically important natural products. In the past years, we examined the chemical components of eight other plant species in the families Loganiaceae, Apocynaceae, and Lycopodiaceae, and a total of 142 structurally diversified alkaloids were isolated from the genera *Gelsemium*^[23, 24], *Ervatamia*^[25, 26], *Stephania*^[27, 28], *Winchia*^[29], and *Lycopodium*^[30], of which 42 were new compounds and 5 had novel skeletons. Some alkaloids showed strong cytotoxic activities. For example, gelseganines A-D (**22–25**), a new class of monoterpene indole alkaloids that bear an *N*₄-iridoid unit, together with three new analogs (**26–29**)^[23, 24] were isolated from the stems and leaves of *Gelsemium elegans*, a well-known toxic plant in Southeast Asia. The structures of **22–29** were determined by spectroscopic analysis, single-crystal X-ray diffraction, and chemical evidence. A plausible biogenetic pathway for alkaloids **22–25** was also postulated.

Complex and novel terpenoids

Triterpenoids (limonoids) from Meliaceae plants (Figure 3): China has a rich diversity of Meliaceae. To date, 62 species and 12 varieties of 15 genera in the Meliaceae family have been documented, and these are mainly distributed in the provinces south of the Yangtze River. Plants of this family are known to metabolize abundant nortriterpenoids (limonoids) with diverse and complex structures that have been demonstrated to have a variety of important biological activities, such as antifeeding, antibacterial, anticancer and antimalarial activities.

In the past several years, our research group made tremendous efforts to explore biologically significant chemical components from the plants in the Meliaceae family, which has led to the isolation of more than 600 structurally diverse compounds from 30 plant species. Among these, 406 were new structures, and 32 possessed previously unknown skeletons.

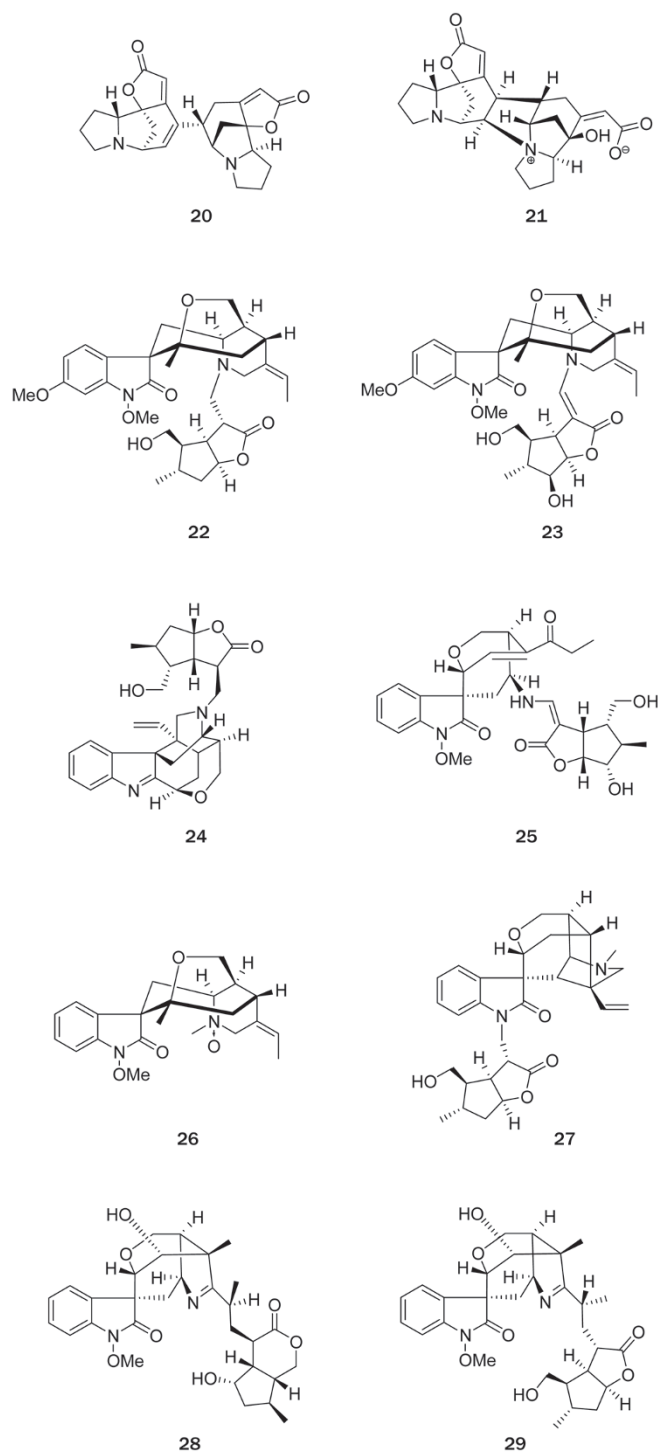


Figure 2. Dimeric indolizidine alkaloids and monoterpene indole alkaloids.

A variety of assays revealed that 50 additional compounds had important biological activities^[31–71]. Our research results supported the traditional medical applications of several plants in the Meliaceae family. This is by far the most systematic and leading chemical study on the plants of the Meliaceae family worldwide. Several representative examples are summarized

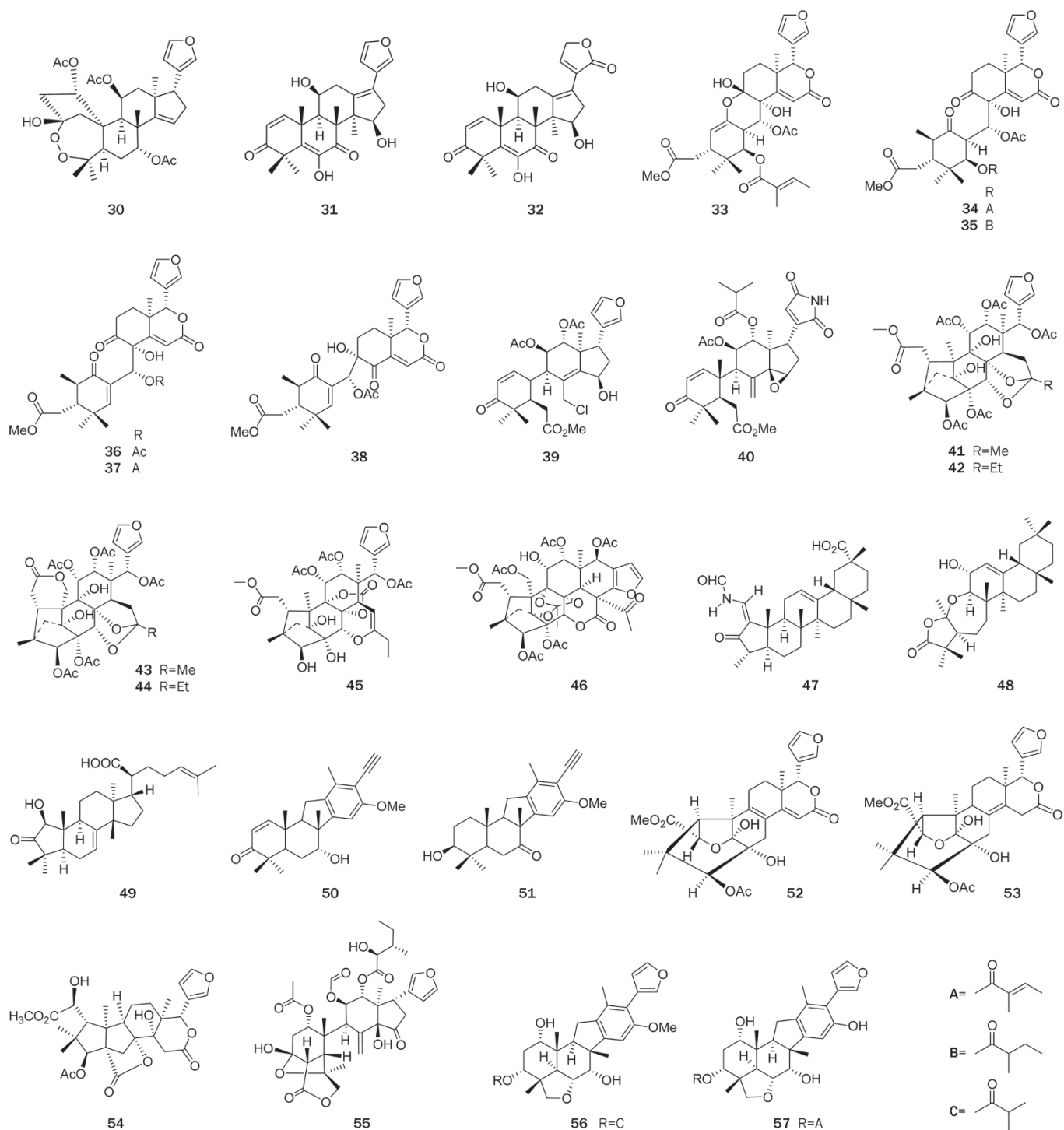


Figure 3. Triterpenoids (limonoids) isolated from Meliaceae plants.

below.

Walsuronoid A (**30**)^[39], a limonoid featuring an unprecedented 3,4-peroxide-bridged *A-seco* skeleton, together with walsuronoids B (**31**) and C (**32**), possessing a rare 18(13→14)-abeo-limonoid skeleton, was isolated from *Walsura robusta*. Their structures were elucidated by spectroscopic analysis and chemical correlation, and that of **30** was con-

firmed by single-crystal X-ray diffraction. Compounds **31** and **32** showed antimalarial activities, which well matched the traditional application of this plant as a treatment for malaria.

Compounds **33**–**38** are 9,10-seco-tetranortriterpenoids that were discovered in the seeds of the Chinese marine mangrove plant *Xylocarpus granatum*^[42, 63]. Xylogranatin A (**33**) featured a unique 1,9-oxygen bridge, whose structure was confirmed by

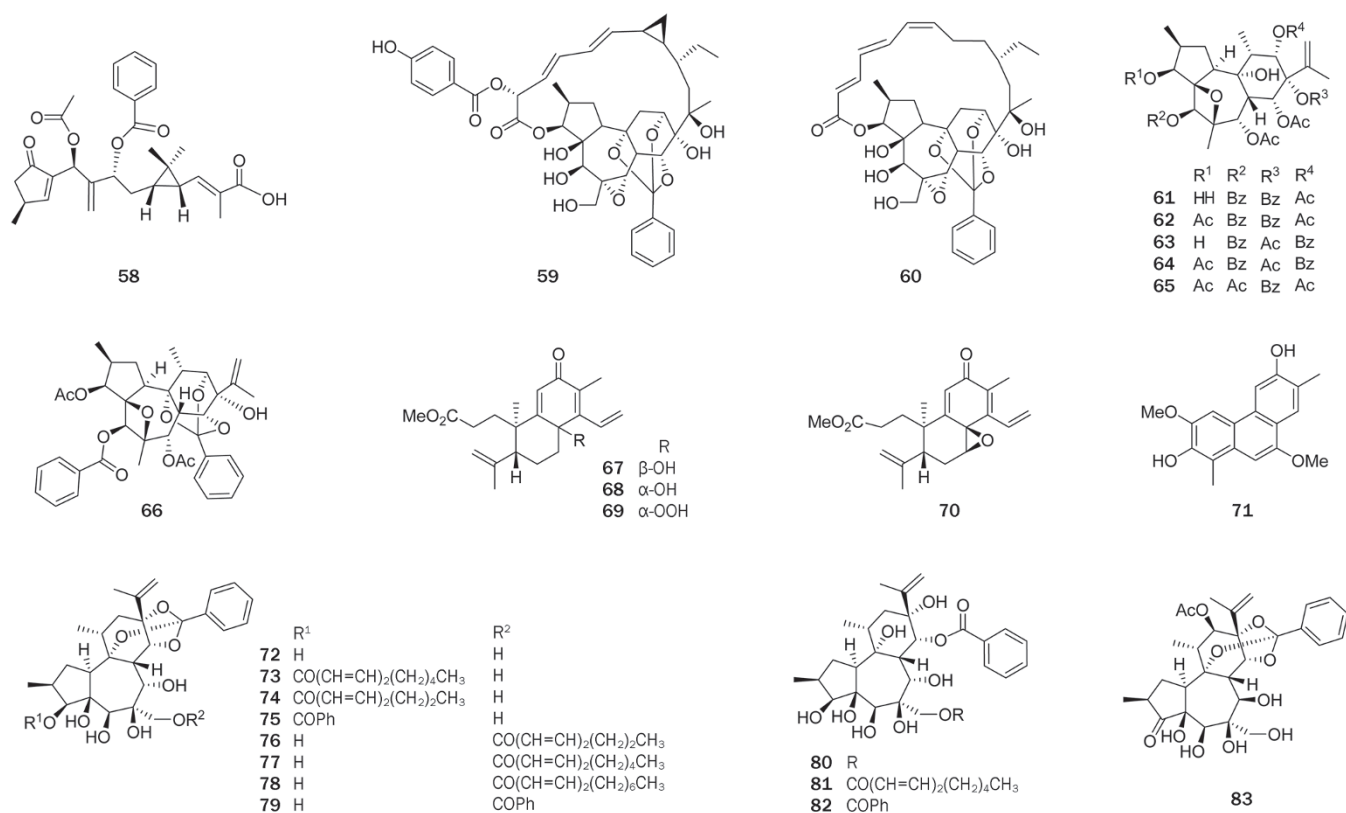


Figure 4. Structurally interesting and biologically important diterpenoids.

single-crystal X-ray diffraction, and xylogranatin D (**38**) furnished a novel skeleton via C-30–C-9 linkage that was postulated to arise from **36** via an γ -hydroxyl ketone rearrangement, and this pathway was chemically mimicked. Compounds **33–38** were cytotoxic to the tumor cell lines P388 and A549, with IC₅₀ values ranging from 6.3 to 15.7 μ mol/L.

Turrappubesins A (**39**) and B (**40**)^[41], two tetranortriterpenoids representing the first examples of halogenated and maleimide-bearing limonoids, respectively, were isolated from the twigs and leaves of *Turraea pubescens*. Their absolute configurations were determined by X-ray crystallography (**39**) and by CD analysis of a dihydrogenated derivative (**40**).

Four 16-norphragmalin-type limonoids, chuktabularins A–D (**41–44**)^[40], featuring unprecedented carbon skeletons of a biosynthetically extended C2 or C3 unit at C-15 forming a unique 2,7-dioxabicyclo[2.2.1]heptane moiety, and two limonoids, chuktabrin A (**45**), with the unique 1,3-dioxolan-2-one and 3,4-dihydro-2H-pyran motifs, and chuktabrin B (**46**)^[37] possessing an unprecedented polycyclic skeleton, were isolated from *Chukrasia tabularis*. Their structures were elucidated by spectroscopic analyses and single crystal X-ray diffraction.

The chemical investigations of *Dysoxylum hainanense* revealed a series of ring A modified triterpenoids among which dysoxyhainanin A (**47**)^[38] possessed a unique 1,3-cyclo-2,3-*seco* A ring with a formamido-containing appendage, dysoxyhainanin B (**48**)^[38] featured an unprecedented 1,2-dinor-3,10:9,10-*bisseco* skeleton, and dysoxyhainic acid A (**49**)^[52] had

an unprecedented 2-nor-1,3-cyclotirucallane skeleton. Four compounds, dysoxyhainanin A (**47**) and dysoxyhainic acids B–C, showed significant activities against four gram-positive bacteria, *Staphylococcus aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *Micrococcus luteus* ATCC 9341, and *Bacillus subtilis* CMCC 63501, with MICs in the range of 6.25–50 μ g/mL.

Walsucochins A (**50**) and B (**51**), with a novel carbon skeleton, were isolated from *Walsura cochinchinensis*^[36]. Their structures, including absolute configuration, were elucidated by spectral methods. Both compounds significantly attenuated H₂O₂-induced damage in PC12 cells in a dose-dependent manner at dosages of 1, 5, and 10 μ mol/L.

A chemical study of the stems of *Khaya senegalensis* led to the isolation of two limonoids, namely khayalenoids A (**52**) and B (**53**)^[35], with an unprecedented 8-oxa-tricyclo[4.3.2.0^{2,7}]undecane motif in the nortriterpenoid core. Their structures, with absolute configuration, were determined by spectroscopy, X-ray crystallography, and CD analysis. Recently, another limonoid with an unprecedented carbon skeleton, grandifotane A (**54**), was isolated from the stem bark of *K. grandifoliola*^[34]. The absolute configuration of **54** was determined by spectroscopy, X-ray crystallography, and ECD calculations. A biogenetic route for grandifotane A (**54**) synthesis from a mexicanolide-type limonoid precursor, involving an enzymatic Baeyer-Villiger oxidation as the key step, was proposed.

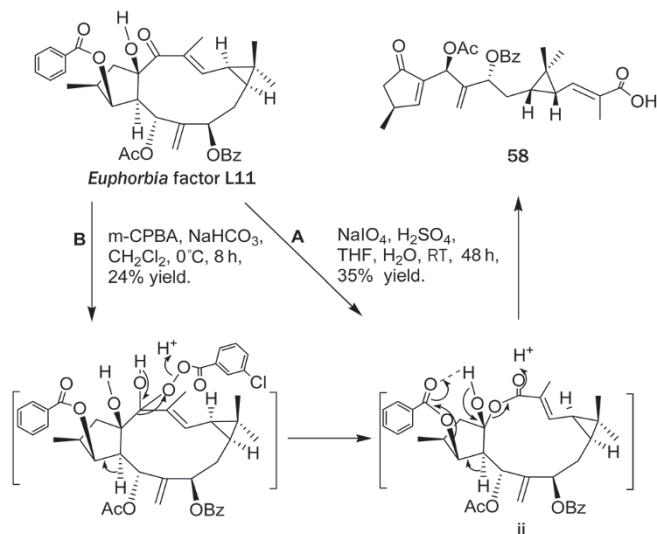
Aphanamolide A (**55**)^[33], featuring an unprecedented carbon skeleton with a C-3–C-6 bond, was isolated from the seeds of

Aphanamixis polystachya. Its structure was established using spectroscopic methods.

Walsucochinoids A (**56**) and B (**57**)^[32], two rearranged limonoids possessing an unprecedented carbon framework, were isolated from *Walsura cochinchinensis*. Their absolute configurations were assigned based on a detailed examination of spectroscopic data, single crystal X-ray diffraction analysis, and CD experiments.

Diterpenoids (Figure 4): Diterpenoids are a class of structurally interesting and biologically important natural products that are found in many TCM plants, and some were even proven to be the active ingredients in their respective plants. More than 260 diterpenoids were obtained by our research group in the past years from the *Euphorbia*^[72], *Trigonostemon*^[73-79], *Daphne*^[80], *Pseudolarix*^[81, 82], *Siegesbeckia*^[83], *Sapium*^[84], and *Larix*^[85] genera. Among them, 122 were new compounds, and 4 possessed novel carbon scaffolds. Biological tests demonstrated that 49 compounds exhibited important biological activities in a variety of bioassays, some of which demonstrated the biological basis of the traditional applications of those plants in TCM medication.

Diterpenoids from the Euphorbiaceae family: Lathyranic acid A (**58**)^[72], the first *seco*-lathyrane diterpenoid with a new skeleton was isolated from the seeds of *Euphorbia lathyris*. Its structure was elucidated by spectroscopic analysis and chemical transformation. Lathyranic acid A was proposed to be biosynthetically produced from the co-existing diterpenoid *Euphorbia* factor L11 with an enzymatic Baeyer-Villiger oxidation as the key and the committed step, and its chemical synthesis was achieved (Scheme 1).



Scheme 1. Chemical transformations from *Euphorbia* factor L11 to **58**.

Two highly modified daphnane-type diterpenoids, trigochilides A (**59**) and B (**60**), together with six highly oxygenated diterpenes, trigochinins A-I (**61-66**)^[73-75], were isolated

from the twigs and leaves of *Trigonostemon chinensis* Merr collected from Yunnan Province. Trigochilides A (**59**) and B (**60**) contain 12-carbon-containing polyketide appendages, which are linked to the diterpenoid core at C-16 by a C-bond and form a macrolactone between C-1' and C-3, while trigochinins A-I (**61-66**) share a rare 4,6-oxetane moiety. Their structures were elucidated by spectroscopic analysis, X-ray crystallography, and CD analysis. Compounds **64** and **65** showed potent cytotoxic activities against HL-60 tumor cell lines with IC₅₀ values of 8.1 and 6.4 μmol/L, respectively. Compound **66** significantly inhibited MET tyrosine kinase activity (IC₅₀=1.95 μmol/L). Trigonochinines A-E (**66-71**)^[79], five antibacterial diterpenoids, were isolated from the aerial parts of this plant collected from Hainan Province. Compounds **67-70** possess a rare 3,4-*secocleistanthanic* skeleton, and compound **71** is a highly aromatized tetranorditerpene. Compounds **67-71** were tested for antimicrobial activity against 11 microorganisms *in vitro*. All compounds tested were active against *Helicobacter pylori*-SS1, with MICs of 12.5-25 μg/mL, and compounds **67-70** also significantly inhibited the growth of the drug (metronidazole)-resistant strain *H. pylori*-ATCC 43504, with MICs of ca 50 μg/mL. Compounds **69** and **71** also exhibited selective activities against the gram-positive bacteria *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228, and *Micrococcus luteus* ATCC 9341 with MICs in the range of 6.25-50 μg/mL.

Twelve new highly oxygenated daphnane-type diterpenoids, genkwanines A-L (**72-83**)^[80], were isolated from the bud of *Daphne genkwa*, a well-known TCM. These compounds showed very potent cytotoxic activities against two tumor cell lines, P388 and A549, with IC₅₀ levels of 0.15-8.40 μmol/L. Most interestingly, three of the compounds, **75**, **78**, and **81**, and two known compounds, yuanhuacine and yuanhuadine, strongly inhibited the endothelial cell line HMEC at the IC₅₀ levels of 2.90-15.0 μmol/L.

Sesquiterpenoids: Sesquiterpenoids are the major components of many TCM plants, and they have a broad spectrum of biological activities including antiinflammatory, antiparasitic, antitumor, and anti-HIV properties. More than 18 TCM plants in the families of Chloranthaceae (four genera, *Chloranthus*, *Sarcandra*, and *Hedyosmum*)^[86-95] and Compositae (five genera, *Eupatorium*^[96, 97], *Vernonia*^[98], *Siegesbeckia*, *Saussurea*, and *Parasenecio*)^[96-101], and a fungus (*Lactarius piperatus*)^[102], have been investigated in our laboratory, which led to the identification more than 280 compounds. Among them, 126 were new compounds, and 8 possessed new carbon skeletons. Biological activity screening revealed that 28 isolates showed important biological activities in a number of tested bioassays, and some of the results were consistent with the traditional applications of these plants in TCM.

Mono- and dimeric sesquiterpenoids (Figure 5): The Chloranthaceae family has 16 species and 5 variants belonging to three genera, *Chloranthus*, *Sarcandra* and *Hedyosmum*, in China. Most plants in this family have been applied in TCM and/or Chinese folk medicine for a variety of indications. Chemical studies of seven species in the Chloranthaceae family con-

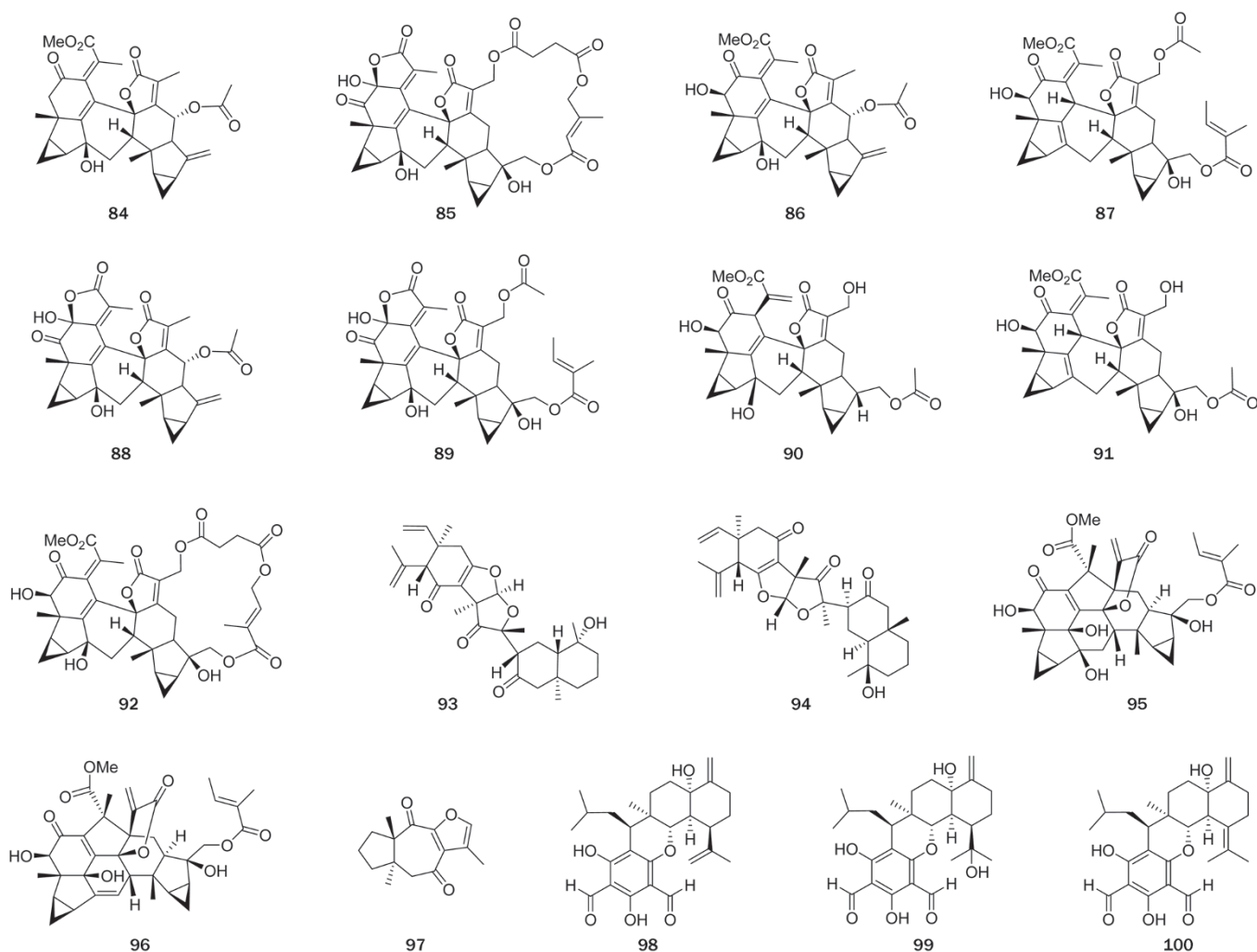


Figure 5. Structurally complex sesquiterpenoids.

ducted in our research group identified 42 new mono- and dimeric sesquiterpenoids, of which the sesquiterpenoid dimers are particularly interesting, especially 4 of these dimers, which possessed unprecedented carbon skeletons.

Chlorahololides A-F (**84-89**)^[87, 88], six highly complex sesquiterpenoid dimers, were isolated from whole *C holostegius*. Their structures and absolute configurations were established by spectroscopy, X-ray crystallography and CD analysis. Chlorahololides A-F (**84-89**) exhibited potent and selective inhibition of the delayed rectifier (I_K) K^+ current, with IC_{50} values of 10.9 ± 12.3 , 18.6 ± 2.5 , 3.6 ± 10.1 , 2.7 ± 0.3 , 27.5 ± 5.1 , and 57.5 ± 6.1 $\mu\text{mol/L}$, respectively. It is noteworthy that the activities of chlorahololides A-F (**84-89**) are 18- to 388-fold more potent than the positive control tetraethylammonium chloride ($IC_{50} = 1.05 \pm 0.21$ mmol/L), a classical blocker of the delayed rectifier K^+ current. Three more sesquiterpenoid dimers, multistalides A-B and chloramultilide A (**90-92**), were isolated from whole *C multistachys*^[90, 91]. Serratustones A (**93**) and B (**94**), which share an unprecedented carbon skeleton representing a novel dimerization of an elemene and a eudesmane

sesquiterpenoid, were isolated from *C serratus*^[86]. Two novel lindenane-type sesquiterpenoid dimers, sarcanolides A (**95**) and B (**96**), featuring an unprecedented carbon framework via the formation of C-11-C-7' bond, were isolated from whole *S hainanensis*^[92]. The structures of compounds **93-96**, including the absolute configuration were fully determined by spectroscopy, X-ray crystallography, and CD analysis in combination with ECD calculation. A number of novel sesquiterpenoids were also isolated from plants in the Chloranthaceae family; eg, hlorantene A (**97**) isolated from *C serratus* possessed a unique C-4 to C-10 linkage^[89].

Phloroglucinol-coupled sesquiterpenoids (Figure 5): *Eucalyptus globulus* Labill, a tall timber tree, grows widely in the southern part of China. Its fruits and leaves have been used as a Chinese folk medicine to treat flu, dysentery, eczema, and scald. A large number of phloroglucinol-coupled sesquiterpenoids and other classes of phloroglucinol-coupled compounds were isolated from *E globulus* and other species in the *Eucalyptus* genus. Of these, eucalyptals A-C (**98-100**)^[94], with a novel 3,5-diformyl-isopentyl phloroglucinol-coupled cadinane

carbon framework, were isolated from the fruits of *E globulus*. Their structures were elucidated by spectroscopic analysis, and that of **98** was confirmed by single-crystal X-ray diffraction. Compounds **98–100** showed selective activity against HL-60, with IC₅₀ values of 1.7, 6.8, and 17 μmol/L, respectively.

Miscellaneous

In addition to our particular interests in natural alkaloids and terpenoids (tri, di, and sesquiterpenoids), we isolated more than 300 phenolics and prenylated polyketides from approximately 20 TCM or herb plants. Among them, approximately 60 were new compounds, and 6 had new carbon skeletons (Figure 6). In particular, 48 of these compounds showed significant biological activities in a variety of bioassays and provided a scientific foundation for the use of a number of traditional Chinese herbs^[103–114].

A series of phenolic compounds were isolated from the ethanolic extract of whole *Sarcostemma acidum*. Sacidumlignan D (**101**)^[108] was found to have an unprecedented rearranged tetrahydrofuran lignan skeleton. Psoracorylifols A–E (**102–106**)^[105] represented five novel compounds from buguzhi, a well-known TCM made from the seeds of *Psoralea corylifolia*. The structure of **102** was confirmed by single-crystal X-ray diffraction. Psoracorylifols D and E (**105** and **106**) exhibit an unprecedented carbon skeleton. A plausible biogenetic origin of psoracorylifols A–E (**102–106**) was also postulated. Psoracorylifols A–E (**102–106**) showed significant inhibition against two strains of *H pylori* (SS1 and ATCC 43504), with

MICs of 12.5–25 μg/mL, respectively. Notably, the activity of psoracorylifols A–E (**102–106**) are 5–10 times stronger than that of metronidazole against *H pylori* ATCC 43504, a drug (metronidazole)-resistant strain; metronidazole is a critical ingredient in combination therapies of *H pylori* infection. The chemical investigation of the seeds of *Psoralea corylifolia* also revealed a number of prenylflavonoids, among which the two new compounds, corylifols A and B (**107** and **108**)^[107], significantly inhibited two hospital pathogenic gram-positive bacteria, *S aureus* ATCC 25923 (MICs: 0.147 and 0.037 mmol/L) and *S epidermidis* ATCC 12228 (MICs: 0.147 and 0.037 mmol/L) *in vitro*. Cinnacassides A–E (**109–113**)^[103] are five novel glycosides with a unique geranylphenylacetate aglycone carbon skeleton from a common TCM (Rougui) based on the stem bark of *Cinnamomum cassia*. Each of the cinnacassides A–D (**109–113**) possessed one of the four stereoisomers of the aglycone. Their structures were established by extensive spectroscopic analysis and chemical and chiroptical methods. Plausible biosynthetic routes for **109–113** were also proposed.

Harrisetones A–E (**114–118**), five novel prenylated polyketides with a rare spirocyclic hydroperoxypolyketide-derived skeleton, along with the new hydroperoxypolyketide harrisonol A (**119**), were isolated from *Harrisonia perforate*^[104]. Their structures were extensively elucidated through spectroscopic analysis and CD spectra. The origins of compounds **114–118** could be traced back to harrisonol A (**119**). Harrisonone A and C and harrisonol A (**114**, **116**, and **119**) exhibited significant cytotoxic activity against P388 tumor cells, with IC₅₀ values of 1.56, 2.35, and 0.27 μmol/L, respectively. Har-

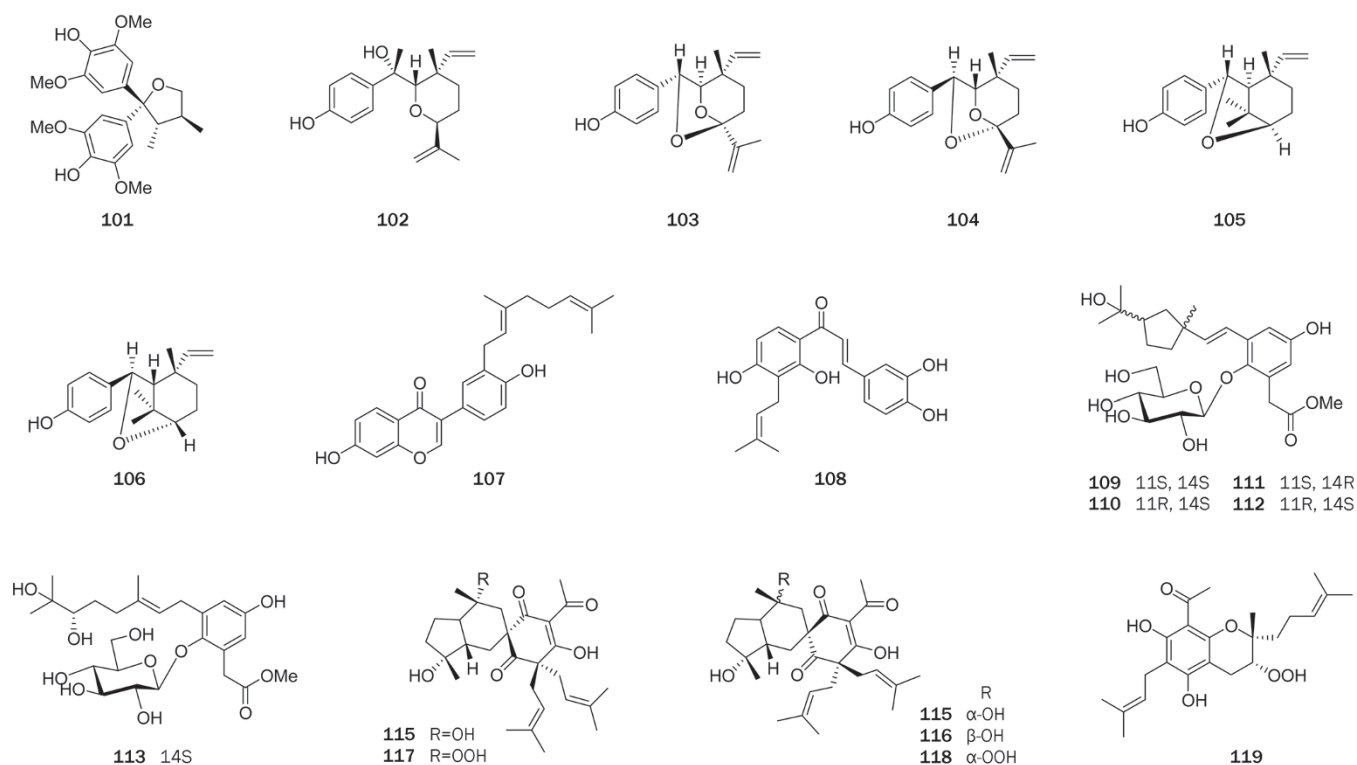


Figure 6. Phenolics and prenylated polyketides.

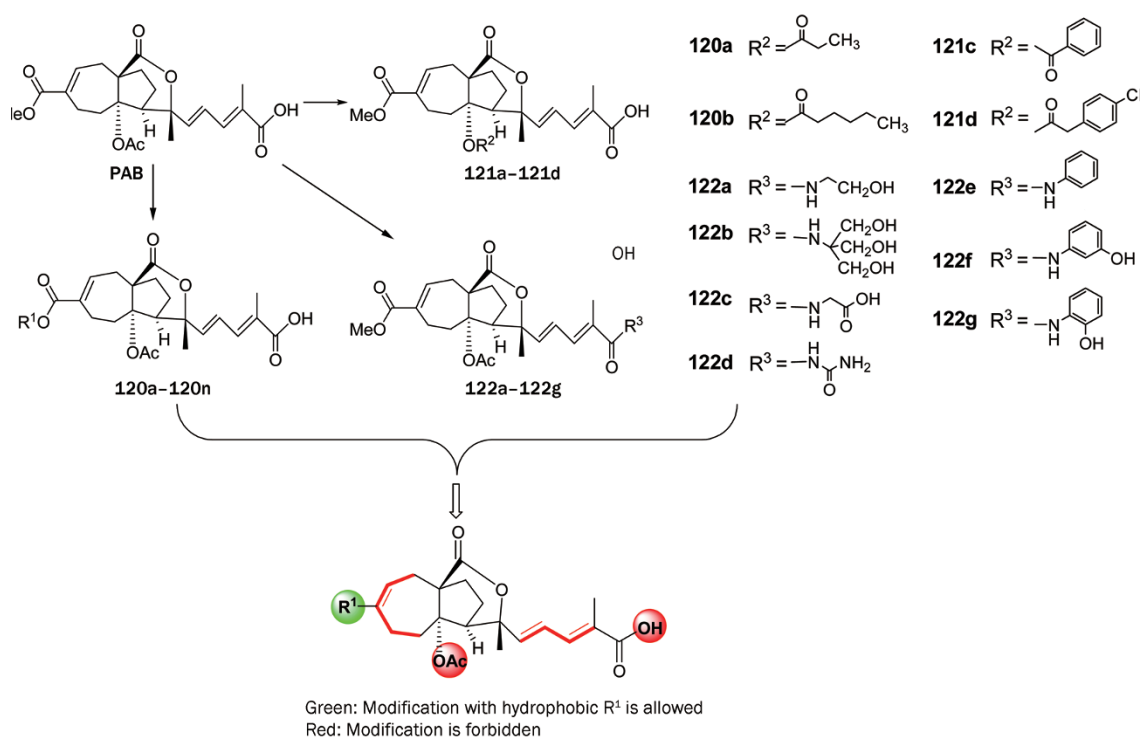
risotone A (**114**) and harrisonol A (**119**) also showed moderate activity against A549 tumor cells, with IC_{50} values of 24.5 and 26.6 $\mu\text{mol/L}$, respectively.

Structural modifications and structure-activity relationship studies

In our search for bioactive natural products^[13, 16, 22, 24, 25, 29, 33, 36, 38, 39, 41, 42, 44–46, 51–53, 58, 63, 68, 70, 73–81, 85, 87–88, 93, 95–98, 103–109, 115–120], a large number of compounds were found to exhibit a variety of biological activities, and 11 compounds with particularly promising potential were selected for structure optimization and structure-activity relationship studies. As a result, over 400 new derivatives were obtained. Among these derivatives, 58 showed significantly improved activities, which provided opportunities to explore the structure-activity relationship of the related compound class^[121–125]. As an example, we will discuss the structure optimization and structure-activity relationship study of the antiangiogenesis pseudolaric acid B (PAB)^[121]. PAB is the major active component of a well-known TCM (Tujinpi), the root bark of *Pseudolarix kaempferi*, which has traditional applications as an antifungal and abortifacient for use in the early stage of pregnancy. PAB also showed strong cytotoxic activity. In our collaboration study, this compound was found for the first time to have strong antiangiogenic activity with a unique mode of antitumor action^[118–120]. A structural modification of PAB was thus conducted, and more than 40 derivatives were prepared in the first round. Antitumor assays showed that nine derivatives in the series **120a–120n** showed significantly improved activities, while those in the **121a–121d** and **122a–122g** series were inactive.

Observation of the structures of PAB and its derivatives revealed a clear antitumor structure activity relationship (Scheme 2)^[121]: (1) All of the active PAB compounds tested in our study (**120a–120n**) have amphipathic properties and possess a hydrophobic domain of a constrained-rings system and a hydrophilic domain consisting of a side chain possessing an conjugated double bond and a terminal carboxylic acid. (2) A hydrophobic group R^1 at C-7 and a Δ^7 double bond are necessary for the anticancer activity, and the bulk and steric factor of R^1 also seem relevant to the activity. (3) The chain length and/or the conjugated double bonds in the side chain are essential for the anticancer activity. (4) Any structural changes in the seven-membered ring, eg, Δ^7 double bond migration and oxygenation at C-7 or C-8, will render the analogs inactive. (5) The C-4 acetoxy group is crucial for the activity and its removal or replacement with a bulk acyloxy group significantly attenuated the activity. (6) The free carboxylic acid group in the terminus of the side chain is necessary for the anticancer activity, while acylation or amidation of this group with either a hydrophilic or a hydrophobic group is detrimental to the activity.

PAB is also a strong antifungal agent. The anticancer SAR of the aforementioned PAB analogs is very similar to the antifungal SAR reported by our group^[81], except for the difference in the modification of the R^1 group. The modification of the R^1 group of PAB showed a particularly exciting result with respect to anticancer activity. Meanwhile, in an antifungal assay, all of the structurally modified PAB analogs showed attenuated activities or were completely inactive^[81]. Our studies suggest that PAB is very promising as an anticancer drug



Scheme 2. Preparation of PAB derivatives and structure activity relationship study.

lead but limited as an antifungal lead due to its loss of activity upon modification and strong cytotoxic side effects.

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