• 综　述 •　　• 特邀稿件 •

# 苦毒烷型萜类化合物及其生物活性的研究进展 *

杨田融，杨雅琳，许　敏△
（昆明理工大学生命科学与技术学院制药工程中心，云南 昆明 650500）

**摘要**：苦豆烷型萜类化合物是一类独特的天然产物，具有高度密集的多环结构和连续的手性中心。苦毒烷型萜类化合物具有倍半萜、降二萜和倍半萜生物碱的骨架类型，是中药的主要功效成分之一，主要分布在苦皮桐科、兰科、防己科、叶下珠科和马桑科等中药民族药中。例如石斛、马桑、木奶果等均富含苦毒烷型萜类化合物。该类化合物具有 6,5-双环骨架的母核，通常发生氧化和骨架重排，从而产生结构多样的衍生物，例如具有络合或桥连 γ-内酯的苦毒烷型类倍半萜和具有螺 γ-内酯的苦毒烷型类降二萜。部分苦毒烷型类分子具有高度复杂的四环或五环环系结构，多达 12 个手性中心。苦毒烷型类化合物不仅用于治疗神经系统、癌症和免疫系统疾病，而且是神经系统疾病研究的工具分子，因此备受关注。近年来，大量具有显著生物活性的苦毒烷型类化合物不断被报道。迄今为止，已经有文献对苦毒烷型类生物碱和苦毒烷型类倍半萜的合成进行了综述，该文主要详细总结了天然苦毒烷型萜类化合物的结构。同时，对该类分子的分布和生物活性也进行概述。

**关键词**：萜类化合物；苦毒烷型倍半萜；苦毒烷型降二萜；石斛；马桑；木奶果
**中图分类号**：R284.3　　**文献标志码**：A　　**文章编号**：1000－2723(2022)05－0092－13
**DOI**：10.19288/j.cnki.issn.1000-2723.2022.05.018

## Recently Advances in Chemical Structures and Biological Activities of Picrotoxane Terpenoids

YANG Tianrong, YANG Yalin, XU Min
(Center for Pharmaceutical Sciences, Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, China)

**ABSTRACT**: Picrotoxane terpenoids are a unique class of natural products that have the features of a highly crowded polycyclic structure and continuous chiral centres. And it is a group of sesquiterpenes, nor-diterpenes and sesquiterpene alkaloids, which are one of the major active constituents of traditional Chinese medicine. These compounds were usually found in herbs from the Picrodendraceae, Orchidaceae, Menispermaceae, Phyllanthaceae and Coriariaceae families, e.g., *Dendrobium nobile*, *Bccaurea ramiflora*, and *Coriaria nepalensis*. A variety of oxidations and skeletal rearrangements occurring in the basic 6/5 dicyclic skeleton led to various picrotoxane derivatives. Picrotoxane sesquiterpenes are featured with the fused or the bridged γ-lactone and picrotoxane nor-diterpenes in spiro γ-lactone. In some case, they are bearing with highly complex tetra, or pentacyclic structures and up to 12 stereogenic centers. The picrotoxanes not only have been used in the treatment of neurological disorder, cancer and immune system diseases, but also in the indispensable neuropharmacological tool molecules. The diverse structures and biological activities of picrotoxanes have attracted considerable attention. Recently, a number of novel picrotoxanes with significant activities have been reported continuously. Until now, picrotoxane alkaloids and the synthesis of picrotoxane sesquiterpenes had been reviewed. Herein, this review mainly surveyed recently advances in chemical structures and biological activities of picrotoxane terpenoids.

**KEY WORDS**: terpenoids; picrotoxane sesquiterpenes; picrotoxane nor-diterpenes; *Dendrobium nobile*; *Bccaurea ramiflora*; *Coriaria nepalensis*.

**收稿日期**：2022－10－10
* **基金项目**：云南省创新研究团队项目；Ronald J Q A M 院士工作站(2019IC003)
**第一作者简介**：杨田融(1996-)，男，在读博士研究生，研究方向：天然产物化学。
△通信作者：许敏，E-mail: xumin@kust.edu.cn

Picrotoxanes are a group of alkaloids, sesquiterpenes, and nor-diterpenes featuring 6/5 dicyclic ring skeleton. A variety of oxidation and skeletal rearrangement occurring in the basic 6/5 dicyclic ring led to various picrotoxane derivatives, e.g., picrotoxane sesquiterpenes with the fused or the bridged γ-lactone and picrotoxane nor-diterpenes with spiro-γ-lactone. They are bearing with highly complex tracyclic, or pentacyclic structures. And some structures have up to 12 stereogenic centers. In addition, lactone functionalities are opened formally to alcohols and in some case glycosylated.

Picrotoxanes are mainly reported to exist in the Picrodendraceae, Orchidaceae, Menispermaceae, Phyllanthaceae and Coriariaceae families. Among them, picrotoxane terpenoids are mainly distributed in a variety of Traditional Chinese Medicines (TCMs), e.g., *Dendrobium findlayanum*[1], *D. nobile*[2], *D. amoenum*[3], *D. aduncum*[4] and *D. williamsonii*[5]. A few picrotoxane terpenoids are also found in ethnomedicines, e.g., *Bcaurea ramiflora*[6], *Coriaria nepalensis*[7], *Picrodendron baccatum*[8], *Hyaenanche globosa*[9] and *Celaenodendron mexicana*[10], *Maesobotrya floribunda*[11], *Austrobuxus swanii*[12], *A. carunculatus*[13] and *Anamirta cocculus*[14]. It is noted that a small number of picrotoxane sesquiterpenes from honey were reported occasionally[15-16]. Picrotoxanes are mostly crystals or white powders, and a small amount of them are oily substance[17-19]. For example, the coriaria oil extracted from seed of *C. nepalensis* contained 0.24% picrotoxane sesquiterpenes[19]. The picrotoxanes are the indispensable neuropharmacological tool molecules as the antagonist of aminobutyric acid (GABA) receptors and ligand gated chloride channels[20-21]. They also showed potent biological activities such as anti-tumor[22], insecticidal[21,23], immunoregulation[24] and antibacterial[25] activities, which have been used in the treatment of neurological disorder[20], cancer[22] and immune system diseases[24].

In recent years, a number of novel picrotoxanes with significant biological activities have been continuously reported such as picrotoxanes from *Dendrobium* spp. Until now, picrotoxane alkaloids[26-30] and the synthesis of picrotoxane terpenoids[31-32] had been summarized. Herein, this review mainly surveyed recently advances in chemical structures and biological activities of picrotoxane terpenoids.

## 1　Picrotoxane terpenoid derivatives

Picrotoxane terpenoids are a group of sesquiterpenes and nor-diterpenes bearing with high complex tetracyclic, or pentacyclic structures and up to 12 stereogenic centers. A variety of oxidation, skeletal rearrangement and and heterozygosis occurring in the basic 6/5 dicyclic ring led to various derivatives, e.g., picrotoxane sesquiterpenes with the fused or the bridged γ-lactone and picrotoxane nor-diterpenes with spiro-γ-lactone. In addition, lactone functionalities are reduced formally to alcohols and in some case glycosylated. Plaus biostnthetic pathways of picrotoxane terpenoids are shown in Figure 1.

1.1　*Picrotoxane sesquiterpenes with the γ-lactone and the bridged γ-lactone*　These are a group of sesquiterpenes with 6/5 dicyclic skeleton with a bridged γ-lactone. They are distributed in *C. nepalensis*, *C. japonica*, *D. nobile*, *D. amoenum*, *D. findlayanum*, *P. baccatum*, and a few in *B. ramiflora* and *A. carunculatus*. Their structures were shown in Fig. 2, and their names and the related plant sources were organized in Table 1.

In general, a variety of oxidation occurring at C2, 3, 7, 8, 9, 10, 12, 13 or/and 14 leads to the hydroxyl group positioned in the 6/5 dicyclic skeleton. In some case, the hydroxyl group at C2, 7, 8, 10 or 13 is glycosylated, e.g. compounds **37-48**. It is noted that the oxidation occurring at C10 led to the formation of aldehyde or carboxyl group, e.g. corialactone C (**16**) and dendromoniliside B (**45**)[7]. The hydroxyl functionalities are reduced formally to terminal olefin positioned between C9 and C10, e.g. compounds **18**[7], **19**[33], **47** and **48**[34]. In addition, most epoxides of picrotoxane sesquiterpenes have been reported. They feature in the fused oxirane at C9 (10) and C7 (8), e.g. compounds **20-34**. They mainly exist in the stem and bark

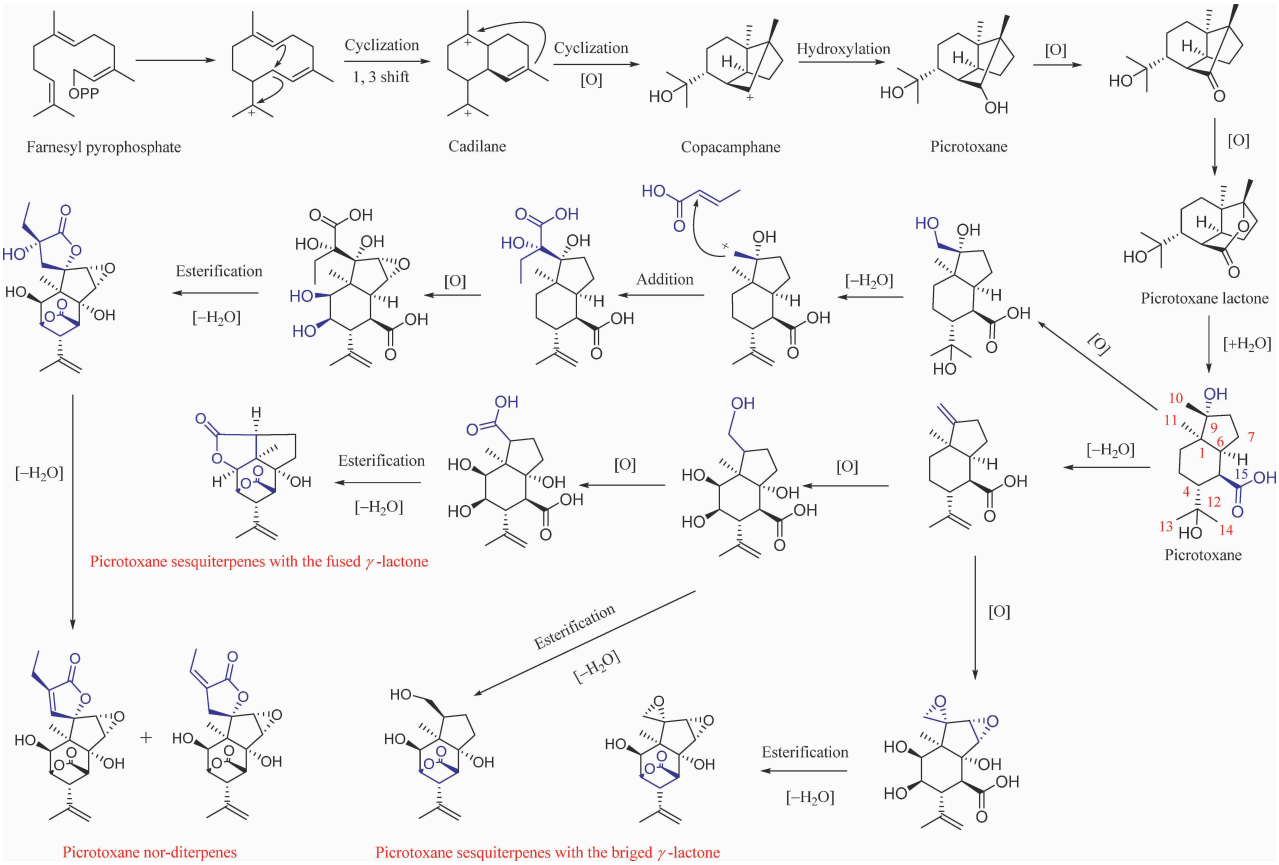



**Fig. 1 Biosynthesis of picrotoxane terpenoids**

**Tab. 1 Picrotoxane sesquiterpenes with the bridged γ–lactone and their plant sources**

| No. | Compounds | Plant sources | Parts of plants | Families | Ref. |
|---|---|---|---|---|---|
| **1** | Dendrobiumane B | *D. nobile* | Stem | Orchidaceae | [2] |
| **2** | (+)–(1R,2S,3R,4S,5R,6S,9R)–2,1,12–trihydroxypicrotoxane–3(15)–lactone | *D. nobile* | Stem | Orchidaceae | [22] |
| **3** | Dendronobilin B | *D. nobile* | Stem | Orchidaceae | [22, 35] |
| **4** | Dendronobilin L | *D. nobile* | Stem | Orchidaceae | [24, 36] |
| **5** | Dendronobilin D | *D. nobile* | Stem | Orchidaceae | [35] |
| **6** | Dendronobilin E | *D. nobile* | Stem | Orchidaceae | [35] |
| **7** | Dendronobilin M | *D. nobile* | Stem | Orchidaceae | [36] |
| **8** | Amoenin | *D. amoenum* | Whole plant | Orchidaceae | [37] |
| **9** | Dendronobilin F | *D. nobile* | Stem | Orchidaceae | [35] |
| **10** | Crystallinin | *D. findlayanum* | Whole plant | Orchidaceae | [1] |
| **11** | Dendrobiumane C | *D. nobile* | Stem | Orchidaceae | [2] |
| **12** | Corialactone B | *C. nepalensis* | Root | Coriariaceae | [7] |
| **13** | Flakinin B | *D. nobile* | Whole plant | Coriariaceae | [36] |
| **14** | Picrodendrin α | *P. baccatum* | Leaf & bark | Picrodendraceae | [38] |
| **15** | Picrodendrin β | *P. baccatum* | Leaf & bark | Picrodendraceae | [38] |
| **16** | Corialactone C | *C. nepalensis* | Root | Coriariaceae | [7] |

**Continuation Tab.1**

| No. | Compounds | Plant sources | Parts of plants | Families | Ref. |
|---|---|---|---|---|---|
| **17** | Dendrobiumane D | *D. nobile* | Stem | Orchidaceae | [2] |
| **18** | Corialactone D | *C. nepalensis* | Root | Coriariaceae | [7] |
| **19** | Nobilomethylene | *D. nobile* | Stem | Orchidaceae | [33] |
| **20** | Picrodendrin R | *P. baccatum* | Stem | Picrodendraceae | [8] |
| **21** | Picrodendrin D | *P. baccatum* | Stem | Picrodendraceae | [8] |
| **22** | Isohyenanchin | *P. baccatum* | Bark | Picrodendraceae | [17] |
| | Hydroxycoriatin | *C. nepalensis* | Root | Coriariaceae | [7] |
| **23** | Picrodendrin C | *P. baccatum* | Bark | Picrodendraceae | [17, 39] |
| **24** | Coriatin | *C. nepalensis* | Aerial part | Coriariaceae | [40] |
| | | *C. nepalensis* | Root | Coriariaceae | [7] |
| **25** | Picrodendrin J | *P. baccatum* | Leaf & bark | Picrodendraceae | [39] |
| **26** | Corialactone A | *C. nepalensis* | Root | Coriariaceae | [7] |
| **27** | Dihydrocoriamyrtin | *C. nepalensis* | Root | Coriariaceae | [7] |
| **28** | Dihydrotutin | *C. nepalensis* | Root | Coriariaceae | [7] |
| | | *P. baccatum* | Bark | Picrodendraceae | [8] |
| **29** | Coriamyrtin | *C. nepalensis* | Root | Coriariaceae | [7] |
| **30** | Tutin | *C. nepalensis* | Root | Coriariaceae | [7] |
| | | *A. carunculatus* | Fruit | Picrodendraceae | [13] |
| **31** | Austrobuxusin E | *A. carunculatus* | Fruit | Picrodendraceae | [13] |
| **32** | Picrodendrin I | *P. baccatum* | Bark | Picrodendraceae | [41] |
| **33** | Apotutin | *C. nepalensis* | Root | Coriariaceae | [40] |
| **34** | Coriarin | *C. japonica* | Berry | Coriariaceae | [42] |
| **35** | Dendroterpene E | *D. nobile* | Stem | Orchidaceae | [43] |
| **36** | Dendronobilin A | *D. nobile* | Stem | Orchidaceae | [44] |
| **37** | Dendromoniliside A | *D. moniliforme* | Stem | Coriariaceae | [24] |
| **38** | Dendronobilin G | *D. nobile* | Stem | Coriariaceae | [41, 45] |
| **39** | Dendromoniliside D | *D. nobile* | Stem | Coriariaceae | [45] |
| | | *D. moniliforme* | Stem | Coriariaceae | [24] |
| **40** | Ramifloside | *B. ramiflora* | Berry | Phyllanthaceae | [6] |
| **41** | Dendroside F | *D. nobile* | Stem | Coriariaceae | [41, 44] |
| **42** | Dendroside G | *D. nobile* | Stem | Coriariaceae | [41] |
| **43** | Picrodendrioside A | *D. nobile* | Stem | Coriariaceae | [41] |
| **44** | Dendrobinoside A | *D. nobile* | Stem | Coriariaceae | [45] |
| **45** | Dendromoniliside B | *D. moniliforme* | Stem | Coriariaceae | [24] |
| **46** | Dendromoniliside C | *D. moniliforme* | Stem | Coriariaceae | [24] |
| **47** | Nepalactone A | *C. nepalensis* | Root & bark | Coriariaceae | [34] |
| **48** | Nepalactone B | *C. nepalensis* | Root & bark | Coriariaceae | [34] |

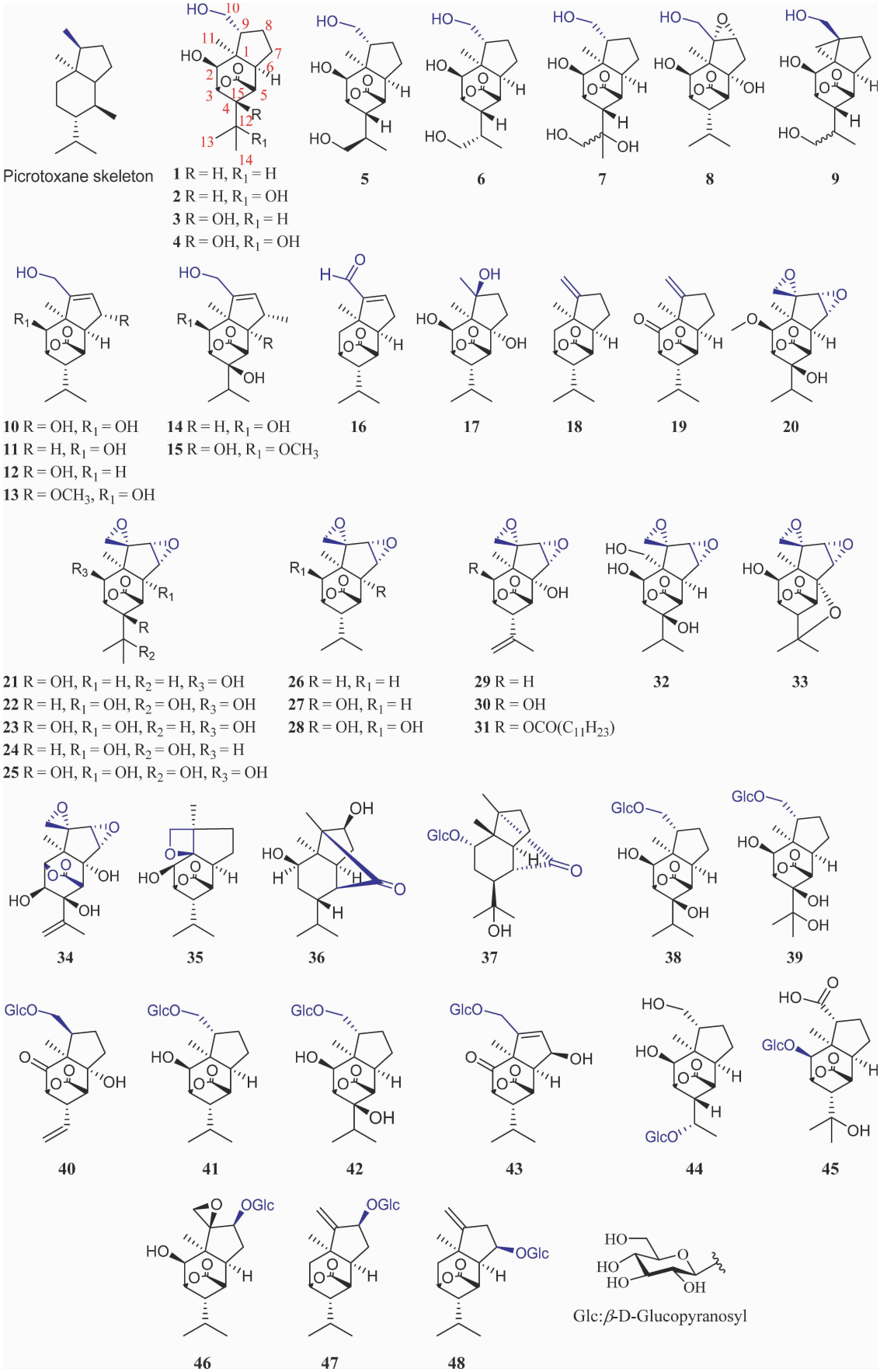



**Fig. 2 Structures of picrotoxane sesquiterpenes with the bridged γ–lactone**

of *P. baccatum*, as well as the root and aerial parts of *C. nepalensis*.

1.2　*Picrotoxane sesquiterpenes with the fused γ–lactone*　These are a group of sesquiterpenes with 6/5 dicyclic skeleton with a fused γ–lactone. Most of the sesquiterpenes feature in the fused γ–lactone at C1 (2, 9) except for a bridged γ–lactone at C3 (5). Their structures were shown in Fig. 3, their names and the related plant sources were organized in Table 2.

Similar to the picrotoxane sesquiterpenes with the bridged γ–lactone, these compounds are hydroxy lated at C9 and most of them are fused with oxirane at C7(8) or C8(9). It is noted that some of them are bearing with an additional fused γ–lactone at C5 (6, 7) without the bridged γ–lactone at C3 (5). For example, compounds **66**[41] and **68**[45] fused a γ–lactone at C5 (6, 7), and compound **65** fused at C4 (5, 12)[1]. Sometimes, the bridged γ–lactone at C3 (5) is opened, and in the same case further methyl esterification, e.g. compounds **67**[14] and **69**[7]. Compared with the picrotoxane sesquiterpenes with only bridged γ–lactone, there are few reports of sesquiterpenes with the fused γ–lactone. They were mainly distributed in stem of *D. nobile*, whole portion of *D. amoenum*, *D. williamsonii* and *D. findlayanum*, and are the characteristic compounds of *Dendrobium* spp. A few of them were distributed in the berry of *B. ramiflora*, the root of *C. nepalensis*, the leaf of *P. baccatum*, the berry of *M. floribunda* and *M. coccus*.

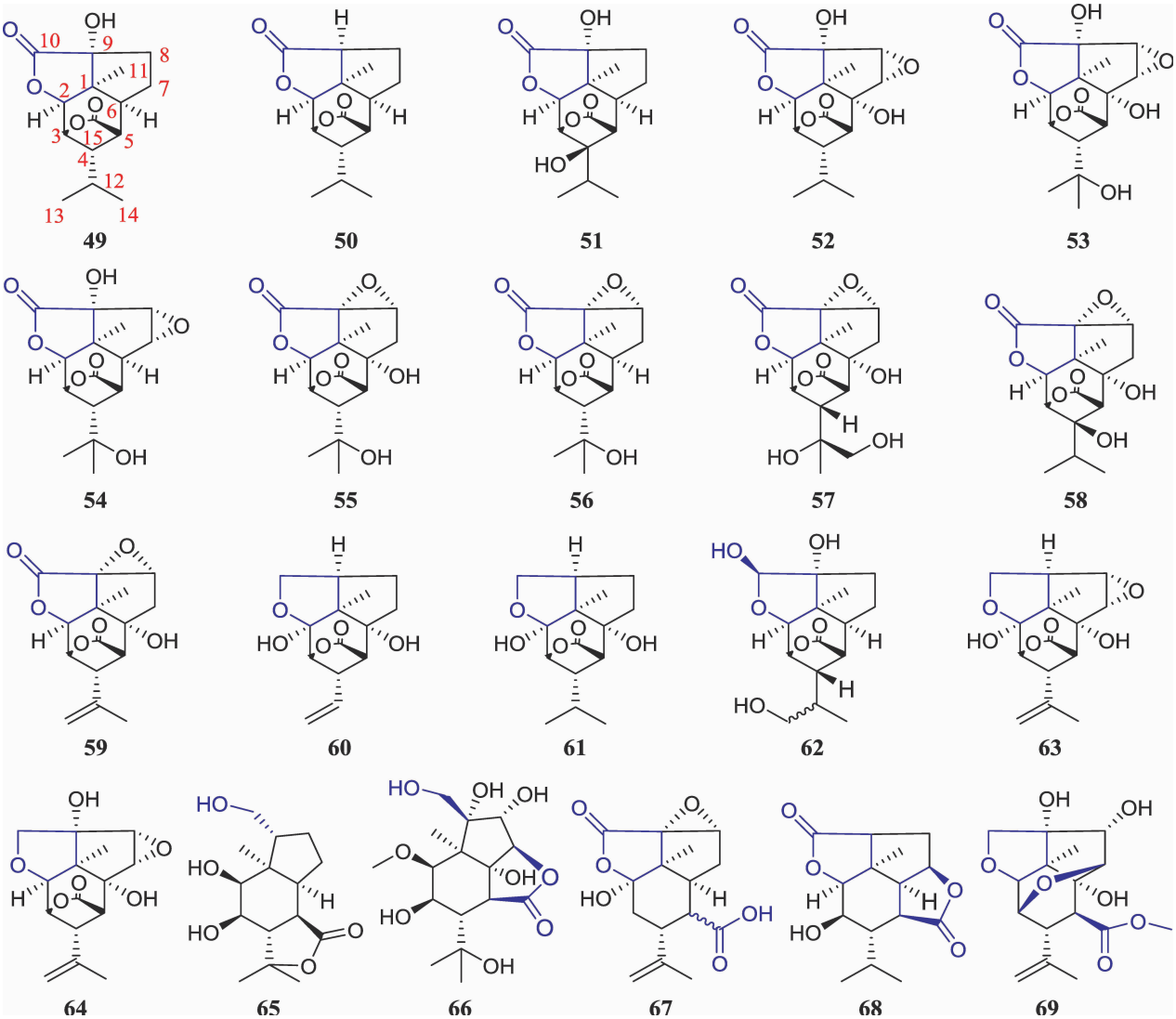


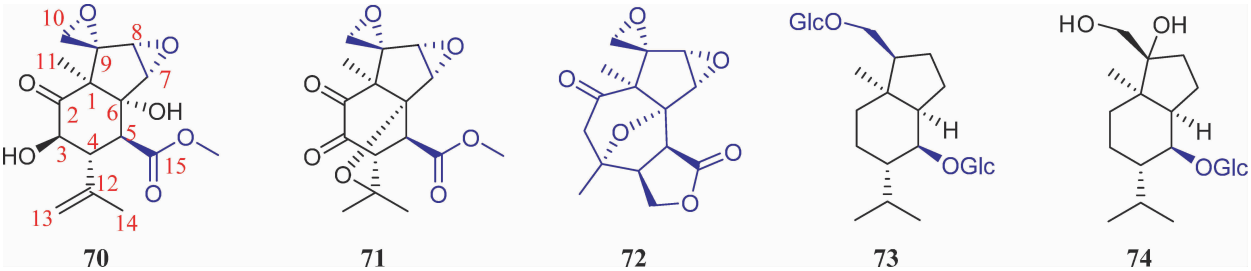

**Fig. 3　Structures of picrotoxane sesquiterpenes with the fused γ–lactone**

**Tab. 2 Picrotoxane sesquiterpenes with the fused γ–lactone and their plant sources**

| No. | Compounds | Plant sources | Parts of plants | Families | Ref. |
|---|---|---|---|---|---|
| **49** | Dendroterpene D | *D. nobile* | Stem | Coriariaceae | [46] |
| **50** | Dendroterpene C | *D. nobile* | Stem | Coriariaceae | [46] |
| **51** | Amotin | *D. amoenum* | Whole plant | Coriariaceae | [37] |
| **52** | Dendrobiumane E | *D. nobile* | Stem | Coriariaceae | [2] |
| **53** | Dendrowillins A | *D. williamsonii* | Whole plant | Coriariaceae | [5] |
| **54** | Dendrowillins B | *D. williamsonii* | Whole plant | Coriariaceae | [5] |
| **55** | (–)–Picrotin | *D. williamsonii* | Whole plant | Coriariaceae | [5] |
| **56** | α–Dihydropicrotoxinin | *D. williamsonii* | Whole plant | Coriariaceae | [5] |
| **57** | Dihydroxy–picrotoxinin | *M. cocculus* | Seed | Menispermaceae | [14] |
| **58** | Aduncin | *D. aduncum* | Whole plant | Coriariaceae | [4] |
| **59** | Picrotoxinin | *M. cocculus* | Seed | Menispermaceae | [14] |
| **60** | Sapidolide A | *B. ramiflora* | Berry | Phyllanthaceae | [6] |
| | | *B. sapida* | Seed | Phyllanthaceae | [25] |
| **61** | Picrotoximaesin | *B. ramiflora* | Berry | Phyllanthaceae | [6] |
| | | *M. Floribunda* | Berry | Gramineae | [11] |
| **62** | Dendronobilin C | *D. nobile* | Stem | Coriariaceae | [35] |
| **63** | Asteromurin A | *M. Floribunda* | Berry | Gramineae | [11] |
| **64** | Corianin | *C. nepalensis* | Root | Coriariaceae | [7] |
| **65** | Findlayanin | *D. findlayanum* | Whole plant | Orchidaceae | [1] |
| | | *D. nobile* | Stem | Coriariaceae | [22] |
| **66** | Picrodendrin Z | *P. baccatum* | Leaf & bark | Picrodendraceae | [38] |
| **67** | Picrotoxic acid | *M. cocculus* | Seed | Menispermaceae | [14] |
| **68** | Flakinin A | *D. nobile* | Whole plant | Coriariaceae | [36] |
| **69** | Corianol | *C. nepalensis* | Root | Coriariaceae | [7] |

1.3 *Picrotoxane sesquiterpenes without the γ–lactone*

Lactone functionalities of these picrotoxane sesquiterpenes are reduced formally to carbonyl and in some case glycosylated. For example, the bridged–lactone at C3 (5) of compounds **70** and **71** is opened, and they distributed in *C. nepalensis*. It is noted that corianlactone (**72**) derived from coriatone (**71**) is the only one picrotoxane sesquiterpene with 5/7 dicyclic skeleton [18]. In addition, dendronobilosides A (**73**) and B (**74**) without γ–lactone were isolated from *D. nobile*, but there were glycosylated at C5 and C10. Compound **73** is the only picrotoxine sesquiterpene with two glycosyl units[47]. Their structures were shown in Figure 4, and their names and the related plant sources were organized in Table 3.




**70** **71** **72** **73** **74**

**Fig. 4 Structures of picrotoxane sesquiterpenes without the γ–lactone**

**Tab. 3　Picrotoxane sesquiterpenes without the γ-lactone and their plant sources**

| No. | Compounds | Plant sources | Parts of plants | Source families | Ref. |
|---|---|---|---|---|---|
| **70** | Coriantone | *C. nepalensis* | Root | Coriariaceae | [7] |
| **71** | Coriatone | *C. nepalensis* | Aerial part | Coriariaceae | [18] |
| **72** | Corianlactone | *C. nepalensis* | Aerial part | Coriariaceae | [18] |
| **73** | Dendronobiloside A | *D. nobile* | Stem | Coriariaceae | [47] |
| **74** | Dendronobiloside B | *D. nobile* | Stem | Coriariaceae | [47] |

1.4　*Picrotoxane nor-diterpenes*　These compounds sometimes possess a unique carbon skeleton containing a spiro-γ-lactone positioned at C13 except for a bridged-lactone at C3 (5, 15)[13]. The physical state of these compounds are mostly prismatic crystal and white powder [24, 35], and they are one of the characteristic chemical constituents of *P. baccatum* and *A. swanii*. Their structures were shown in Figure 5, and their names and the related plant sources were organized in Table 4.

In same case, an isopropyl moiety or isopropenyl functionality was linked with C16. Similar to picrotoxane sesquiterpenes, a variety of oxidation occurring at C2, 4, 6, 11, 12, or/and 13 led to the various hydroxyl groups and in some case methylated. In addition, most epoxides of picrotoxane nor-diterpenes have been reported. They feature in the fused oxirane at C11 (12). Few of them bear an oxygen bridge at C2 (14), e.g. compound **96** [12]. It is noted that the rearrange occurs at isopropyl moiety at C16 letting to a methyl linked with C16 and or carboxyl group positioned at C17, e.g. compound **90** [9]. Some picrotoxane nor-diterpenes formed an ester at C18 with long alkane chain, e.g. compounds **101-107** [13]. Picrodendrin X (**109**) is fused a γ-lactone at C5 (6, 11), but picrodendrin Y (**110**) fused at C4 (5, 8)[38].

## 2　Bioactivity of picrotoxane terpenoids

2.1　*Neuroprotective effects*　Picrotoxane terpenoids were ligand gated chloride channels and ionic GABA receptor antagonists[20-21]. The tutin (**30**) from the parasitism of mulberry has been used to treat schizophrenia. Tutin (**30**) with an isopropyl moiety at C4 had more antagonistic effect on GABA than that of with hydroxyisopropyl group[50]. In addition, the compounds **1a-1e** (Figure 6) were the synthetic derivatives of nepalactone A (**47**), which showed better neurotrophic activity than that of compound **47** [45, 50-51]. Compared with 21.11% ± 1.62% for 10 ng/mL NGF (Nerve growth factor) alone, compound **1c** at a concentration of 10 μM increased the numbers of neurite-bearing cells by 27.81% ± 1.48% . The neurotrophic activities of the compound **1a** decreased due to the glycolation at C8.

2.2　*Cytotoxic effects*　Dendronobilin B (**3**) promoted the proliferation of intersegmental vessel (ISV) and endothelial cells with a dose-dependent manner on the recovery of ISV deletion induced by sunitinib. Dendronobilin B (**3**) repaired ISV injury in Tg zebrafish embryos induced by sunitinib by promoting the proliferation of ISV endothelial cells [22]. Austrobuxusin E (**31**), austrobuxusin L (**100**) and austrobuxusin F (**101**) showed different antiproliferative effects against U87-MG glioblastoma, HCT116 colon, and A549 cells. Importantly, austrobuxusin L (**100**) and austrobuxusin F (**101**) showed $IC_{50}$ values of 5.8 ± 0.5 μM for the A549 cells and 0.7 ± 0.1 μM for the U87-MG cell line, respectively. Among them, picrotoxane nor-diterpenes bearing an acyl chain at C2 exhibited potential antitumor effects[13].

2.3　*Insecticidal effects*　Coriamyrtin (**29**) had obvious antifeedant behavior, which could delay the pupation time of *Plutella xylostella* and inhibit the development of *P. xylostella*[52]. The structure activity of relationships (SARs) suggested that the double bond of C12/13 and hydroxyl group at C2 may be a key active

**Tab.4 Picrotoxane nor-diterpenes with spiro γ-lactone and their plant sources**

| No. | Compounds | Plant sources | Parts of plants | Families | Ref. |
|---|---|---|---|---|---|
| **75** | Picrodendrin K | *P. baccatum* | Stem | Picrodendraceae | [8] |
| **76** | Picrodendrin L | *P. baccatum* | Stem | Picrodendraceae | [8] |
| **77** | Picrodendrin F | *P. baccatum* | Stem | Picrodendraceae | [8] |
| **78** | Picrodendrin M | *P. baccatum* | Stem | Picrodendraceae | [8] |
| **79** | Picrodendrin Q | *P. baccatum* | Stem | Picrodendraceae | [8] |
| **80** | Picrodendrin N | *P. baccatum* | Stem | Picrodendraceae | [8] |
| **81** | Picrodendrin A | *P. baccatum* | Stem | Picrodendraceae | [8, 39] |
| **82** | Picrodendrin O | *P. baccatum* | Stem | Picrodendraceae | [8] |
| **83** | Picrodendrin E | *P. baccatum* | Stem | Picrodendraceae | [8] |
| **84** | Picrodendrin P | *P. baccatum* | Stem | Picrodendraceae | [8] |
| | | *P. baccatum* | Bark | Picrodendraceae | [48] |
| **85** | Picrodendrin S | *P. baccatum* | Bark | Picrodendraceae | [48] |
| **86** | Picrodendrin U | *P. baccatum* | Bark | Picrodendraceae | [49] |
| **87** | Picrodendrin B | *P. baccatum* | Bark | Picrodendraceae | [39] |
| **88** | Picrodendrin T | *P. baccatum* | Bark | Picrodendraceae | [48] |
| **89** | Lambicin | *H. globosa* | Fruit | Picrodendraceae | [9] |
| **90** | Capenicin | *H. globosa* | Fruit | Picrodendraceae | [9] |
| **91** | Celaenodendrolide I | *C. mexicana* | Stem & bark | Picrodendraceae | [10] |
| **92** | Pretoxin | *H. globosa* | Fruit | Picrodendraceae | [9] |
| **93** | Austrobuxusin A | *A. swanii* | Leaf | Picrodendraceae | [12] |
| **94** | Austrobuxusin B | *A. swanii* | Leaf | Picrodendraceae | [12] |
| **95** | Austrobuxusin C | *A. swanii* | Leaf | Picrodendraceae | [12] |
| **96** | Austrobuxusin D | *A. swanii* | Leaf | Picrodendraceae | [12] |
| **97** | Austrobuxusin M | *A. swanii* | Leaf | Picrodendraceae | [12] |
| **98** | 16-Epi-austrobuxusin B | *A. carunculatus* | Fruit | Picrodendraceae | [13] |
| **99** | Austrobuxusin K | *A. carunculatus* | Fruit | Picrodendraceae | [13] |
| **100** | Austrobuxusin L | *A. carunculatus* | Fruit | Picrodendraceae | [13] |
| **101** | Austrobuxusin F | *A. carunculatus* | Fruit | Picrodendraceae | [13] |
| **102** | Austrobuxusin G | *A. carunculatus* | Fruit | Picrodendraceae | [13] |
| **103** | Austrobuxusin H | *A. carunculatus* | Fruit | Picrodendraceae | [13] |
| **104** | 16-Epi-austrobuxusin H | *A. carunculatus* | Fruit | Picrodendraceae | [13] |
| **105** | 16-Epi-austrobuxusin G | *A. carunculatus* | Fruit | Picrodendraceae | [13] |
| **106** | Austrobuxusin I | *A. carunculatus* | Fruit | Picrodendraceae | [13] |
| **107** | Austrobuxusin J | *A. carunculatus* | Fruit | Picrodendraceae | [13] |
| **108** | Picrodendrin G | *P. baccatum* | Bark | Picrodendraceae | [39] |
| **109** | Picrodendrin X | *P. baccatum* | Leaf & bark | Picrodendraceae | [38] |
| **110** | Picrodendrin Y | *P. baccatum* | Leaf & bark | Picrodendraceae | [38] |

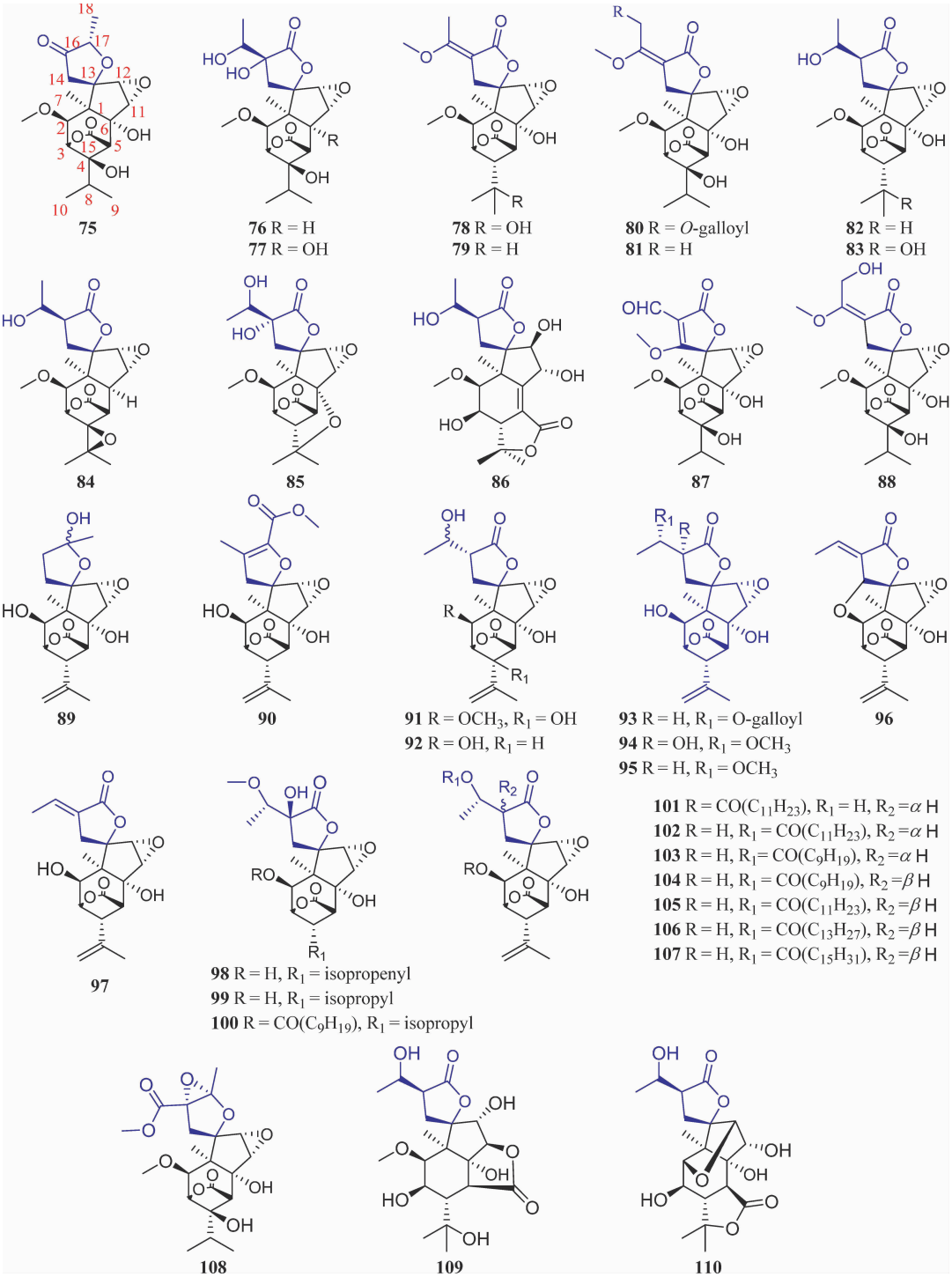



**Fig. 5　Structures of picrotoxane nor-diterpenes with spiro γ-lactone**

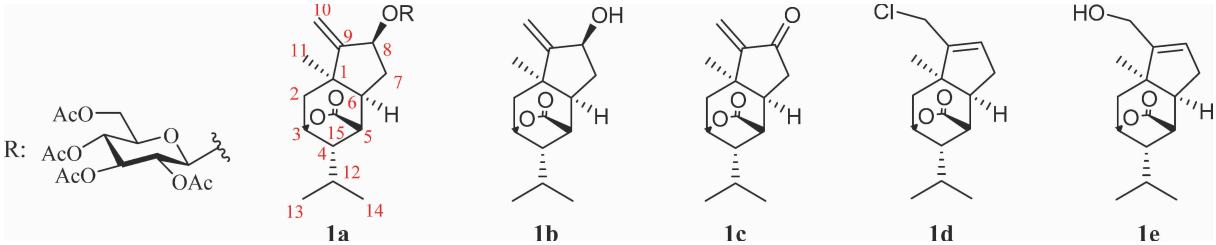



**Fig. 6　Structures of synthetic picrotoxane sesquiterpenes 1a–1e**

group. Picrodendrin Q (**79**) showed a potent inhibition in the development of *Musca domestica* L. with an $IC_{50}$ value of 22 nM. The presence or absence of the C4, C8-dihydroxyl groups and electronegativity of the 16-carbon atom were important determinants of the potency of nor-diterpenes in inhibiting *M. domestica*[21].

2.4 *Immunomodulatory effects* Dendromoniliside C (**46**) stimulated the proliferation of B cells and inhibited the proliferation of T cells[24], and dendroside F (**41**) significantly stimulated the proliferation of mouse T or B lymphocytes.

2.5 *Antifungal effects* Picrotoximaesin (**61**), ramifloside (**40**) and sapidolide A (**60**) exhibited weak antibacterial activities against *Colletotrichum gloeosporioides*, and showed strong activity against C. gloeosporioides with minimum inhibitory concentrations (MICs) of 12.5, 12.5 and 50 μg/mL[6]. It was speculated that the double bond between C-12 and C-13 is the key unit for the strong antibacterial ability of compounds **40** and **60**.

2.6 *Anti-α-glucosidase effects* Using acarbose as positive control ($IC_{50}$ = 0.72 mM), dendroterpene C (**50**) manifested inhibitory activity on α-glucosidase with $IC_{50}$ value of 0.97 mM. However, dendroterpene D (**49**) had no effect on α-glucosidase ($IC_{50}$ > 1 mM), indicating that the activity decreased due to the hydroxyl group at C-9[46].

## 3 Conclusion

Picrotoxin, the first picrotoxine terpenoid, was isolated in 1811 shortly after isolation of morphine in 1806, which signified the start of plant secondary products research. Due to complex structures and potential activities, a number of novel picrotoxanes with significant biological activities have been reported continuously. Picrotoxanes bearing with unique skeleton are one of the main active components in TCMs and herbs. Interestingly, some picrotoxanes has certain therapeutic effects on neurological disorder, e.g. schizophrenia. These active natural products will be potent tool molecules for investigating on target identification and mechanism of action for complex brain diseases. Chemical proteomics is one of new approaches for identifying targets by active natural product probes, especially affinity -based protein profiling (ABPP). Thus, it will be an interesting research work to use active picrotoxine terpenoid as probe to reveal new drug target and its mechanism, especially druggable target of neurological disorder.

**References:**

[1] QIN X D, QU Y, NING L, et al. A new picrotoxane-type sesquiterpene from *Dendrobium findlayanum* [J]. J Asian Nat Prod Res, 2011, 13(11): 1047-1050.

[2] ZHAO W, YE Q, DAI J, et al. Allo-aromadendrane- and picrotoxane-type sesquiterpenes from *Dendrobium moniliforme*[J]. Planta Med, 2003, 69(12): 1136-1140.

[3] DAHMEN J, LEANDER K. Amotin and amoenin, two sesquiterpenes of picrotoxane group from *Dendrobium amoenum*[J]. Phytochemistry, 1978, 17(11): 1949-1952.

[4] GAWELL L, LEANDER K. The constitution of aduncin, a sesquiterpene related to picrotoxinin, found in *Dendrobium aduncum* [J]. Phytochemistry, 1976, 15 (12): 1991 - 1992.

[5] YANG M, CHEN L J, ZHANG Y, et al. Two new picrotoxane-type sesquiterpenoid lactones from *Dendrobium williamsonii*[J]. J Asian Nat Prod Res, 2019, 21(2): 129-133.

[6] PAN Z H, NING D S, HUANG S S, et al. A new picrotoxane sesquiterpene from the berries of *Baccaurea ramiflora* with antifungal activity against *Colletotrichum gloeosporioides*[J]. Nat Prod Res, 2015, 29(14): 1323-1327.

[7] ZHAO F, LIU Y B, MA S G, et al. New sesquiterpenes from the roots of *Coriaria nepalensis* [J]. Tetrahedron, 2012, 68(31): 6204-6210.

[8] SUZUKI Y, KOIKE K, OHMOTO T. Eight picrotoxane terpenoids, picrodendrins K-R, from *Picrodendron baccatum*[J]. Phytochemistry, 1992, 31(6): 2059-2064.

[9] CORBELLA A, JOMMI G, RINDONE B, et al. Structure of pretoxin and lambicin [J]. Tetrahedron, 1969, 25 (19): 4835-4841.

[10] CASTAÑEDA P, BAHENA A, GARCÍA E, et al. Secondary metabolites from the stem bark of *Celaenodendron mexicanum*[J]. J Nat Prod, 2004, 56(9): 1575-1579.

[11] TANE P, AYAFOR J F, FARRUGIA L, et al. Picrotoximaesin, a novel picrotoxane sesquiterpenoid from the berries of *Maesobotrya floribunda* [J]. Nat Prod Lett, 1996, 9(1): 39–45.

[12] DEMIRKIRAN O, CAMPITELLI M, WANG C, et al. New picrotoxane terpenoids, austrobuxusins A–D, from the australian endemic plant *Austrobuxus swanii* [J]. Tetrahedron, 2016, 72(51): 8400–8405.

[13] OLIVON F, RETAILLEAU P, DESRAT S, et al. Isolation of picrotoxanes from *Austrobuxus carunculatus* using taxonomy–based molecular networking[J]. J Nat Prod, 2020, 83(10): 3069–3079.

[14] AGARWAL S K, SINGH S S, VERMA S, et al. Two picrotoxin derivatives from *Anamirta cocculus* [J]. Phytochemistry, 1999, 50(8): 1365–1368.

[15] LARSEN L, JOYCE N I, SANSOM C E, et al. Sweet poisons: honeys contaminated with glycosides of the neurotoxin tutin[J]. J Nat Prod, 2015, 78(6): 1363–1369.

[16] WATKINS O C, JOYCE N I, GOULD N, et al. Glycosides of the neurotoxin tutin in toxic honeys are from *Coriaria arborea* phloem sap, not insect metabolism[J]. J Nat Prod, 2018, 81(4): 1116–1120.

[17] OHMOTO T, KOIKE K, FUKUDA H, et al. Studies on the constituents of picrodendron baccatum growing in indonesia. II. Structures of two new sesquiterpene lactones, picrodendrins C and D [J]. Chem Pharm Bull, 1989, 37 (11): 2988–2990.

[18] SHEN Y H, LI S H, LI R T, et al. Coriatone and corianlactone, two novel sesquiterpenes from *Coriaria nepalensis*[J]. Org Lett, 2004, 6(10): 1593–1595.

[19] ZHANG Y, WANG G, LI L, et al. GC–MS analysis of volatile oils of *Coriaria sinica* (masang) maxim[J]. Zhengzhou Daxue Xuebao (Lixueban), 2004, 36(3): 73–75.

[20] OZOE Y, HASEGAWA H, MOCHIDA K, et al. Picrodendrins, a new group of picrotoxane terpenoids: structure–activity profile of action at the $GABA_A$ receptor–coupled picrotoxinin binding site in rat brain [J]. Biosci Biotechnol Biochem, 1994, 58(8): 1506–1507.

[21] OZOE Y, AKAMATSU M, HIGATA T, et al. Picrodendrin and related terpenoid antagonists reveal structural differences between ionotropic GABA receptors of mammals and insects[J]. Bioorg Med Chem, 1998, 6(4): 481–492.

[22] MENG C W, HE Y L, PENG C, et al. Picrotoxane sesquiterpenoids from the stems of *Dendrobium nobile* and their absolute configurations and angiogenesis effect [J]. Fitoterapia, 2017, 121: 206–211.

[23] SCHMIDT T J, GURRATH M, OZOE Y. Structure–activity relationships of seco–prezizaane and picrotoxane/picrodendrane terpenoids by quasar receptor–surface modeling[J]. Bioorg Med Chem, 2004, 12(15): 4159–4167.

[24] ZHAO C, LIU Q, HALAWEISH F, et al. Copacamphane, picrotoxane, and alloaromadendrane sesquiterpene glycosides and phenolic glycosides from *Dendrobium moniliforme*[J]. J Nat Prod, 2003, 66(8): 1140–1143.

[25] BORDOLOI M, BARUA N C, MOHAN S, et al. Sapidolide A: an unprecedented spherical carbocyclic lactone from *Baccaurea sapida* seed kernels: is it a meroisoprenoid?[J]. Tetrahedron Lett, 1996, 37(37): 6791–6792.

[26] YAMADA K, SUZUKI M, HAYAKAWA Y, et al. Total synthesis of dl–dendrobine[J]. J Am Chem Soc, 1972, 94 (23): 8278–8280.

[27] GUO L, FREY W, PLIETKER B. Catalytic enantioselective total synthesis of the picrotoxane alkaloids (–)–dendrobine, (–)–mubironine b, and (–)–dendroxine [J]. Org Lett, 2018, 20(14): 4328–4331.

[28] KENDE A S, BENTLEY T J, MADER R A, et al. A simple total synthesis of (plus or minus)–dendrobine [J]. J Am Chem Soc, 1974, 96 (13): 4332–4334.

[29] MARQUéS–LóPEZ E, CHRISTMANN M. $\beta$–lactones through catalytic asymmetric heterodimerization of ketenes [J]. Angew Chem Int Edit, 2012, 51(35): 8696–8698.

[30] LEE Y, ROCHETTE E M, KIM J, et al. An asymmetric pathway to dendrobine by a transition–metal–catalyzed cascade process[J]. Angew Chem Int Edit, 2017, 56 (40): 12250–12254.

[31] OHMOTO T. Studies on the constituents and biological activities of Simaroubaceous plants[J]. Yakugaku Zasshi, 1995, 115(4): 261–279.

[32] GOSSINGER E. Picrotoxanes [J]. Fortschr Chem Org Naturst, 2010, 93: 71–210.

[33] OKAMOTO T, NATSUME M, ONAKA T, et al. Further studies on the alkaloidal constituents of *Dendrobium nobile* (Orchidaceae)–structure determination of 4–hydroxy–dendroxine and nobilomethylene[J]. Chem Pharm Bull, 1972, 20(2): 418–421.

[34] WANG Y Y, TIAN J M, ZHANG C C, et al. Picrotoxane sesquiterpene glycosides and a coumarin derivative from *Coriaria nepalensis* and their neurotrophic activity[J]. Molecules, 2016, 21(10): 1344.

[35] ZHANG X, TU F J, YU H Y, et al. Copacamphane, picrotoxane and cyclocopacamphane sesquiterpenes from *Dendrobium nobile* [J]. Chem Pharm Bull , 2008, 56(6): 854–857.

[36] MORITA H, FUJIWARA M, YOSHIDA N, et al. New picrotoxinin –type and dendrobine –type sesquiterpenoids from *Dendrobium snowflake* 'red star' [J]. Tetrahedron, 2000, 56(32): 5801–5805.

[37] DAHMEN J, LEANDER K. Amotin and amoenin, two sesquiterpenes of the picrotoxane group from *Dendrobium amoenum*[J]. Phytochemistry, 1978, 17 (11): 1949–1952.

[38] SUZUKI Y, KOIKE K, NAGAHISA M, et al. New picrotoxane terpenoids from *Picrodendron baccatum*[J]. Tetrahedron, 2003, 59(32): 6019–6025.

[39] KOIKE K, FUKUDA H, MITSUNAGA K, et al. Picrodendrins B, G and J, new picrotoxane terpenoids from *Picrodendron baccatum* [J]. Chem Pharm Bull, 1991, 39 (4): 934–936.

[40] WEI H, ZENG F, LU M, et al. Studies on chemical constituents from the root of *Coriaria nepalensis* wall (*Coriaria sinica* Maxim)[J]. Yaoxue Xuebao, 1998, 33(9): 688–692.

[41] YE Q, QIN G, ZHAO W. Immunomodulatory sesquiterpene glycosides from *Dendrobium nobile*[J]. Phytochemistry, 2002, 61(8): 885–890.

[42] KINOSHITA T, ITAKI N, HIKITA M, et al. The isolation and structure elucidation of a new sesquiterpene lactone from the poisonous plant *Coriaria japonica* (Coriariaceae) [J]. Chem Pharm Bull, 2006, 53(8): 1040–1042.

[43] WANG P, CHEN X, CAI C H, et al. A new picrotoxane–type sesquiterpene from *Dendrobium nobile* lindl [J]. Nat Prod Res, 2020, 36(8): 2112–2117.

[44] ZHANG X, LIU H W, GAO H, et al. Nine new sesquiterpenes from *Dendrobium nobile*[J]. Helv Chim Acta, 2007, 90(12): 2386–2394.

[45] THANH N T V, LY G T P, TRAM L H, et al. A new picrotoxane sesquiterpene glucoside from *Dendrobium nobile*[J]. Nat Prod Commun, 2017, 12(12): 1825–1826.

[46] WANG P, CHEN X, WANG H, et al. Four new picrotoxane–type sesquiterpenes from *Dendrobium nobile* lindl [J]. Front Chem, 2019, 7: 812.

[47] YE Q, ZHAO W. New alloaromadendrane, cadinene and cyclocopacamphane type sesquiterpene derivatives and bibenzyls from *Dendrobium nobile*[J]. Planta Med, 2002, 68(8): 723–729.

[48] KOIKE K, SUZUKI Y, OHMOTO T. Picrotoxane terpenoids, picrodendrins S and T, from *Picrodendron baccatum*[J]. Phytochemistry, 1994, 35(3): 701–704.

[49] NAGAHISA M, KOIKE K, NARITA M, et al. Novel picrotoxene norditerpene lactones from *Picrodendron baccatum*[J]. Tetrahedron, 1994, 50(37): 10859–10866.

[50] ZHANG C C, YIN X, CAO C Y, et al. Chemical constituents from *Hericium erinaceus* and their ability to stimulate NGF–mediated neurite outgrowth on PC12 cells [J]. Bioorg Med Chem Lett, 2015, 25(22): 5078–5082.

[51] SHI X W, LIU L, GAO J M, et al. Cyathane diterpenes from Chinese mushroom *Sarcodon scabrosus* and their neurite outgrowth –promoting activity [J]. Eur J Med Chem, 2011, 46(7): 3112–3117.

[52] ZHANG Y, ZHU X, AI G, et al. Extraction and separation of lactones in seeds of *Coriaria sinica* maxim. and their activities[J]. Zhongcaoyao, 2007, 38(5): 678–680.