CHEMICAL REVIEWS

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# Meliaceous Limonoids: Chemistry and Biological Activities

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## 1. BACKGROUND AND INTRODUCTION

The word "limonoids" originated from the bitterness of lemon or other citrus fruit. Structurally, limonoids are formed by loss of four terminal carbons of the side chain in the apotirucallane or apoeuphane skeleton and then cyclized to form the 17$\beta$-furan ring, and thus limonoids are also known as tetranortriterpenoids. Limonoids in the plant kingdom occur mainly in the Meliaceae and Rutaceae families and less frequently in the Cneoraceae.[1] With 50 genera and more than 1400 species, Meliaceae are distributed in tropical and subtropical regions throughout the world.[2] As the characteristic natural products of the Meliaceae, limonoids have attracted considerable interest within the chemical and biological research communities. The neem tree (*Azadirachta indica*), one of the most famous limonoid producing plants in Meliaceae, has long been recognized as a source of environment-friendly biopesticide. Azadirachtin (**292**), a complex limonoid from neem seed kernel, is the main component responsible for the toxic effects on insects. The commercial application of the limonoids in the agricultural industry has enjoyed significant growth in recent decades. Commercial neem products (seed kernel extract of *A. indica*), such as Margosan-O, Azitin, Turplex, and Align were granted approval for pest control usage in the United States by the EPA.[3−5] Furthermore, *A. indica* was also introduced and has been planted on a large scale in Yunnan province, P. R. China since the 2000s (Figure 1). Three commercial limonoids products (extracts of *A. indica, Melia toosendan*, and *M. azedarach*), known as biorational insecticides, were also granted approval in China for insect control on organic vegetable plantings. In a pharmaceutical application from China, a formulation with toosendanin, a limonoid from *M. toosendan* that displays dramatic antibotulismic effects, was developed as a commercial product from TCM (Traditional Chinese Medicine), where it has been used as an anthelmintic vermifuge against ascarids for a long time.[6]

Some mini-reviews related to limonoids from Meliaceae have been presented since 1966. For example, the chemistry,[7−13]

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biosynthesis,[1,13−15] and biological activities[16−18] of meliaceous limonoids were summarized in different years. It is noteworthy that some reviews emphasize the well-known azadirachtin (**292**) and aspects of its chemistry,[19−22] synthesis,[23,24] and bioactivities including antifeedant activity,[25−27] insecticidal activity,[25] and insect-growth-regulating activity,[25,28,29] as well as its environmental behavior,[19] and its physiological behavior properties.[30,31] In addition, the toxicity characteristics of azadirachtin and the mechanisms of its insecticidal action[32−35] were also reviewed. Reviews on the chemistry and biological activities of limonoids from *Azadirachta indica*,[36−43] *Melia azedarach*, and *M. toosendan*[37,44−47] have been presented. Moreover, some other reviews related to meliaceous limonoids have also been published, such as those on the chemistry of cedrelone (**81**),[48] the biological activity of gedunin (**416**),[49] and the occurrence, biosynthesis, biological activity, and NMR spectroscopy of D and B,D-ring seco-limonoids from Meliaceae.[50] However, none of them gave general insight into the chemistry and biological activities of meliaceous limonoids.

During our investigations on the biologically active constituents of Meliaceae, we noticed confusion and ambiguity about limonoids in the literature. (i) Some limonoids structures were


**Figure 1.** *Azadirachta indica* at Yuanmou county, Yunnan Province, P. R. China. (A) Neem seedlings were bred on a large scale. (B) Neem trees were cultivated at both sides of the road. (C) Four-year-old neem trees produced plenty of fruit. Photographs courtesy of Dr. Yanping Zhang.

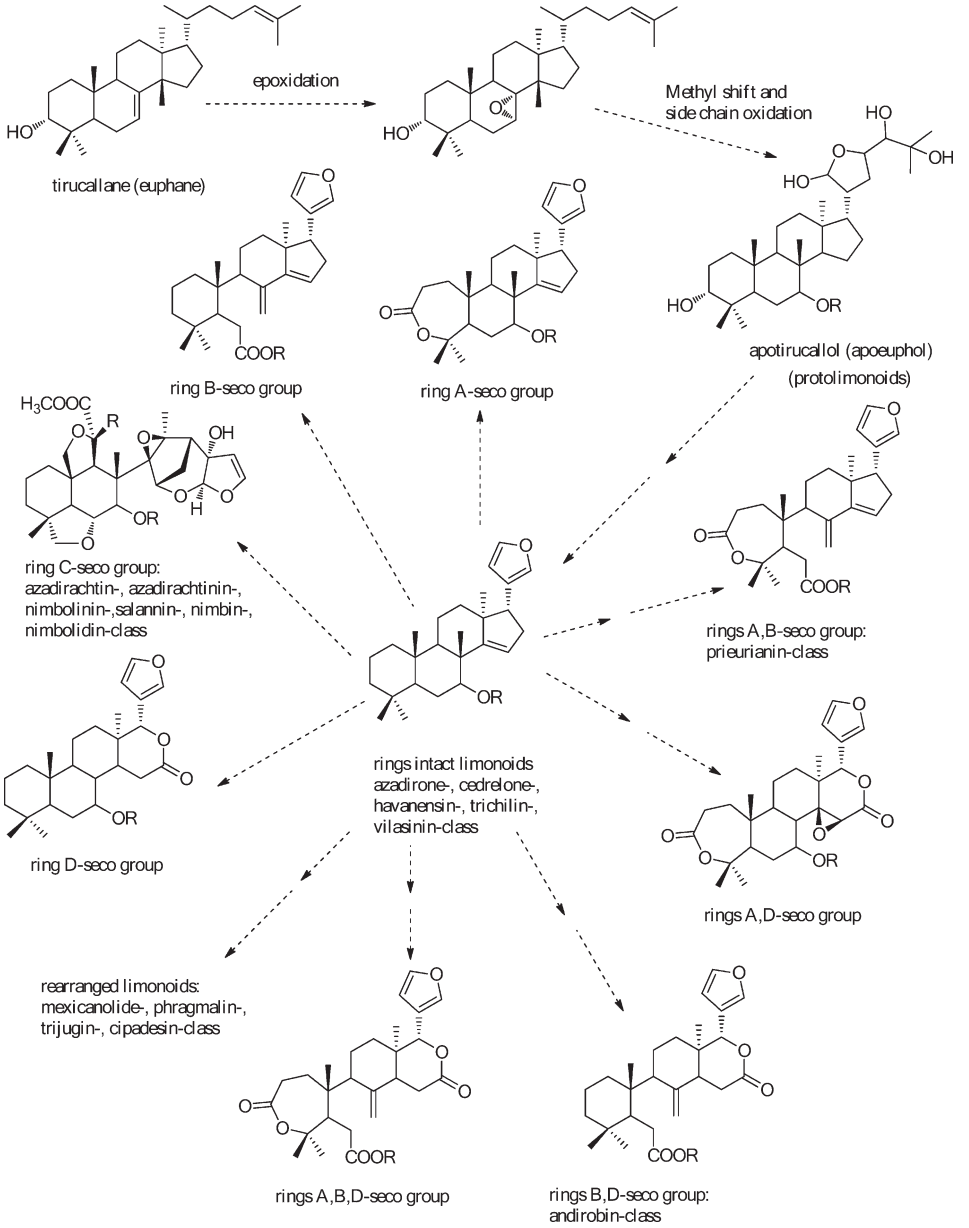


**Figure 2.** Proposed major biosynthesis routes and classification of meliaceous limonoids.


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**Table 1. Structures and Sources of Azadirone-Class Limonoids 1−80**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **1** | azadirone | $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = Ac$ | *Azadirachta indica*;[57−59,80−83] *Entandrophragma delevoyi*;[75] *Melia toosendan*;[76,84,85] *Trichilia havanensis*;[86] *Turraea robusta*;[87] *Khaya anthotheca*[60] |
| **2** | 7-deacetoxy-7-hydroxyazadirone | $R_1 = R_2 = R_3 = R_4 = R_5 = H$ | *Walsura piscidia*[88] |
| **3** | 11$\alpha$-acetoxyazadirone | $R_1 = R_4 = R_5 = H$; $R_2 = Ac$, $R_3 = \alpha$-OAc | *Khaya anthotheca*[60] |
| **4** | 11$\beta$-acetoxyazadirone | $R_1 = R_4 = R_5 = H$; $R_2 = Ac$, $R_3 = \beta$-OAc | *K. anthotheca*[60,89] |
| **5** | 12$\alpha$-acetoxy-7-deacetylazadirone | $R_1 = R_2 = R_3 = R_5 = H$; $R_4 = OAc$ | *Turraesa cornucopia*[90] |
| **6** | chisosiamensin | $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = Ac$; $\Delta^{5,6}$ | *Chisocheton siamensis*[91] |
| **7** | nimonol (nimocinol) | $R_1 = \alpha$-OH; $R_2 = Ac$; $R_3 = R_4 = R_5 = H$ | *Azadirachta indica*[61,62,64,92] |
| **8** | 6$\alpha$-*O*-acetyl-7-deacetylnimocinol | $R_1 = \alpha$-OAc; $R_2 = R_3 = R_4 = R_5 = H$ | *A. indica*[93] |
| **9** | 6$\alpha$-acetoxyazadirone (paniculatin) | $R_1 = \alpha$-OAc; $R_2 = Ac$; $R_3 = R_4 = R_5 = H$ | *Chisocheton paniculatus*;[69,94−96] *Entandrophragma delevoyi*[75] |
| **10** | nimocin | $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = Bz$ | *Azadirachta indica*[80] |
| **11** | dysobinin | $R_1 = \beta$-OAc; $R_2 = Ac$; $R_3 = R_4 = R_5 = H$ | *Dysoxylum binetariferum*;[66] *Chisocheton siamensis*[91,97] |
| **12** | azadiradione | $R_1 = R_3 = R_4 = H$; $R_2 = Ac$; $R_5 = O$ | *C. siamensis*;[91,97] *Cedrela odorata*;[98] *Quivisia papinae*;[99] *Lansium domesticum*;[100] *Azadirachta indica*[57,58,70,80−82,101−108] |
| **13** | nimbocinol (7-deacetylazadiradione) | $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = O$ | *A. indica*[101,109,110] |
| **14** | 7-desacetyl-7-benzoylazadiradione (7-benzoylnimbocinol) | $R_1 = R_3 = R_4 = H$; $R_2 = Bz$; $R_5 = O$ | *A. indica*[68,70] |
| **15** | 7-deacetyl-7-angeloyl-6$\alpha$-hydroxyazadiradione | $R_1 = \alpha$-OH; $R_2 = Ang$; $R_3 = R_4 = H$; $R_5 = O$ | *Quivisa papinae*[99] |
| **16** | 6$\alpha$-hydroxyazadiradione | $R_1 = \alpha$-OH; $R_2 = Ac$; $R_3 = R_4 = H$; $R_5 = O$ | *Q. papinae*[99] |
| **17** | 6$\alpha$-acetoxy-16-oxoazadirone (mahonin) | $R_1 = \alpha$-OAc; $R_2 = Ac$; $R_3 = R_4 = H$; $R_5 = O$ | *Chisocheton paniculatus*;[69] *Swietenia mahagoni*[71,111,112] |
| **18** | 17$\beta$-hydroxyazadiradione | $R_1 = H$; $R_2 = Ac$ | *Carapa guianensis*;[113] *Azadirachta indica*[70,81,103,104,109,114−116] |
| **19** | 7-deacetyl-17$\beta$-hydroxyazadiradione | $R_1 = R_2 = H$ | *A. indica*[101,107] |
| **20** | 6$\alpha$-acetoxy-17$\beta$-hydroxyazadiradione | $R_1 = OAc$; $R_2 = Ac$ | *Chisocheton paniculatus*[94,117] |
| **21** | 7-benzoyl-17-hydroxynimbocinol | $R_1 = H$; $R_2 = Bz$ | *Azadirachta indica*[70] |
| **22** | 15-hydroxyazadiradione | | *A. indica*[70] |
| **23** | 7-acetyl-16,17-dehydro-16-hydroxyneotrichilenone | | *A. indica*[70] |
| **24** | isonimolide | $R_1 = OCH_3$; $R_2 = Ac$; $R_3 = R_4 = R_5 = H$; $R_6 = OH$; $R_7 = O$ | *A. indica*[118] |
| **25** | isolimbolide | $R_1 = R_5 = H$; $R_2 = Ac$; $R_3 = OAc$; $R_4 = R_6 = OH$; $R_7 = O$ | *A. indica*[118] |
| **26** | nimocinolide | $R_1 = R_7 = OH$; $R_2 = Ac$; $R_3 = R_4 = R_5 = H$; $R_6 = O$ | *A. indica*[80] |
| **27** | 23-*O*-methylnimocinolide | $R_1 = OH$; $R_2 = Ac$; $R_3 = R_4 = R_5 = H$; $R_6 = O$; $R_7 = OCH_3$ | *A. indica*[119] |
| **28** | 7-*O*-deacetyl-23-*O*-methyl-7$\alpha$-*O*-senecioylnimocinolide | $R_1 = OH$; $R_2 = Sen$; $R_3 = R_4 = R_5 = H$; $R_6 = O$; $R_7 = OCH_3$ | *A. indica*[119,120] |
| **29** | isonimocinolide | $R_1 = R_6 = OH$; $R_2 = Ac$; $R_3 = R_4 = R_5 = H$; $R_7 = O$ | *A. indica*[80,118] |


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**Table 1. Continued**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **30** | nimbocinolide | $R_1 = R_5 = H$; $R_2 = Ac$; $R_3 = OiBu(OH)$; $R_4 = R_7 = OH$; $R_6 = O$ | *A. indica*[121] |
| **31** | isonimbocinolide | $R_1 = R_5 = H$; $R_2 = Ac$; $R_3 = OiBu(OH)$; $R_4 = R_6 = OH$; $R_7 = O$ | *A. indica*[122] |
| **32** | meliacinanhydride | $R_1 = OH$; $R_2 = Ac$; $R_3 = OCH_3$; $R_4 = OAc$; $R_5 = H$; $R_6 = R_7 = O$ | *A. indica*[92] |
| **33** | 22,23-dihydronimocinol | $R_1 = OH$; $R_2 = Ac$; $R_3 = R_4 = R_5 = R_6 = R_7 = H$; 22,23-dihydro; $\Delta^{20,21}$ | *A. indica*[120] |
| **34** | azadironolide | $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = Ac$; $R_6 = O$; $R_7 = OH$ | *A. indica*[123] |
| **35** | *O*-methylazadironolide | $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = Ac$; $R_6 = O$; $R_7 = OCH_3$ | *A. indica*[124] |
| **36** | 12$\alpha$-acetoxyazadironolide | $R_1 = R_3 = R_5 = H$; $R_2 = Ac$; $R_4 = OAc$; $R_6 = O$; $R_7 = OH$ | *Turraea parvifolia*[125] |
| **37** | 23-deoxyazadironolide | $R_1 = R_3 = R_4 = R_5 = R_6 = H$; $R_2 = Ac$; $R_7 = O$ | *Azadirachta indica*[70] |
| **38** | isoazadironolide | $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = Ac$; $R_6 = OH$; $R_7 = O$ | *A. indica*;[123] *Turraea pubescens*[126] |
| **39** | azadiradionolide | $R_1 = R_3 = R_4 = R_7 = H$; $R_2 = Ac$; $R_5 = R_6 = O$ | *Azadirachta indica*[70,123,127] |
| **40** | salimuzzalin | $R_1 = R_2 = R_3 = R_4 = R_5 = H$; $R_6 = R_7 = OAc$ | *A. indica*[128] |
| **41** | turraparvin A | $R_1 = R_2 = R_3 = R_5 = H$; $R_4 = OAc$; $R_6 = O$; $R_7 = OH$ | *Turraea parvifolia*[125] |
| **42** | turraparvin B | $R_1 = R_2 = R_3 = R_5 = H$; $R_4 = OAc$; $R_6 = OH$; $R_7 = O$ | *T. parvifolia*[125] |
| **43** | turraparvin C | $R_1 = R_3 = R_5 = H$; $R_2 = Ac$; $R_4 = OAc$; $R_6 = OH$; $R_7 = O$ | *T. parvifolia*[125] |
| **44** | | $R_1 = OAc$; $R_2 = Ac$; $R_3 = R_4 = R_5 = H$; $R_6 = OH$; $R_7 = O$ | *Chisocheton paniculatus*[117] |
| **45** | 7$\alpha$,23-dihydroxy-3-oxo-24,25,26,27-tetranortirucall-1,14,20(22)-trien-21,23-olide | $R_1 = R_2 = R_3 = R_4 = R_5 = H$; $R_6 = O$; $R_7 = OH$ | *Trichilia estipulata*[129] |
| **46** | limocin A | $R_1 = R_4 = H$; $R_2 = Ac$; $R_3 = \alpha$-$OCH_3$ | *Azadirachta indica*[79] |
| **47** | limocin B | $R_1 = R_3 = H$; $R_2 = Ac$; $R_4 = OCH_3$ | *A. indica*[79] |
| **48** | 23-desmethyl limocin B | $R_1 = R_4 = H$; $R_2 = Ac$; $R_4 = OH$ | *A. indica*[130] |
| **49** | limocin C | $R_1 = R_4 = H$; $R_2 = Ac$; $R_3 = OCH_2CH_3$ | *A. indica*[127] |
| **50** | limocin D | $R_1 = R_3 = H$; $R_2 = Ac$; $R_4 = OCH_2CH_3$ | *A. indica*[127] |
| **51** | limocin E | $R_1 = R_3 = H$; $R_2 = Ac$; $R_4 = \alpha$-$OCH_3$ | *A. indica*[70] |
| **52** | 23-*epi*limocin E | $R_1 = R_3 = H$; $R_2 = Ac$; $R_4 = \beta$-$OCH_3$ | *A. indica*[70] |
| **53** | | $R_1 = R_2 = R_3 = H$; $R_4 = O$ | *Chisocheton microcarpus*[131] |
| **54** | | $R_1 = OAc$; $R_2 = Ac$; $R_3 = H$; $R_4 = O$ | *C. paniculatus*[117] |
| **55** | | $R_1 = OAc$; $R_2 = Ac$; $R_3 = H$; $R_4 = OH$ | *C. paniculatus*[117] |
| **56** | 20,21,22,23-tetrahydro-23-oxoazadirone | $R_1 = R_3 = H$; $R_2 = Ac$; $R_4 = O$ | *C. microcarpus*;[131] *Cedrela odorata*;[98] *C. fissilis*;[132] *Azadirachta indica*[70] |
| **57** | meliatoosenin A | $R_1 = R_3 = H$; $R_2 = R_4 = O$ | *Melia toosendan*[133] |
| **58** | meliatoosenin B | $R_1 = R_2 = R_3 = H$; $R_4 = O$; 1,2-dihydro | *M. toosendan*[133] |
| **59** | isonimolicinolide | | *Azadirachta indica*[72] |
| **60** | nimbinin (epoxyazadiradione) | $R_1 = R_3 = R_4 = H$; $R_2 = Ac$; $R_5 = O$ | *A. indica*;[57,58,70,73,78,80−82,103−106,115,134−136] *Carapa guianensis*;[137] *Entandrophragma delevoyi*;[75] *Chisocheton siamensis*[91] |
| **61** | 7-desacetyl-7-benzoylepoxyazadiradione | $R_1 = R_3 = R_4 = H$; $R_2 = Bz$; $R_5 = O$ | *Azadirachta indica*[68,70] |
| **62** | 6$\alpha$-acetoxyepoxyazadiradione | $R_1 = OAc$; $R_2 = Ac$; $R_3 = R_4 = H$; $R_5 = O$ | *Carapa guianensis*;[137] *Chisocheton siamensis*[91,138] |
| **63** | 14,15-epoxynimonol | $R_1 = OH$; $R_2 = Ac$; $R_3 = R_4 = R_5 = H$ | *Azadirachta indica*[139] |


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**Table 1. Continued**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **64** | trichilenone acetate (14$\beta$,15$\beta$-epoxyazadirone; acetyltrichilenone) | $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = Ac$ | *Melia toosendan*;[76,84] *Azadirachta indica*;[124] *Trichilia havanensis*;[74] *Entandrophragma delevoyi*[75] |
| **65** | 6$\alpha$-acetoxy-14$\beta$,15$\beta$-epoxyazadirone | $R_1 = OAc$; $R_2 = Ac$; $R_3 = R_4 = R_5 = H$ | *E. delevoyi*;[75] *Toona ciliata*;[140] *Chisocheton paniculatus*[94] |
| **66** | heudelottin C | $R_1 = R_5 = H$; $R_2$ = iVal(OH); $R_3 = OH$; $R_4$ = *O*-2-acetoxy-3-methylpentanoyl | *Trichilia heudelottii*[77] |
| **67** | heudelottin E | $R_1 = R_5 = H$; $R_2$ = iVal(OH); $R_3 = OCHO$; $R_4$ = *O*-2-hydroxy-3-methylpentanoyl | *T. heudelottii*[77,141] |
| **68** | heudelottin F | $R_1 = R_5 = H$; $R_2$ = iVal(OH); $R_3 = OCHO$; $R_4$ = *O*-2-acetoxy-3-methylpentanoyl | *T. heudelottii*[77] |
| **69** | 6-acetoxy-7$\alpha$-hydroxy-3-oxo-14$\beta$,15$\beta$-epoxymeliace-1,5-diene | $R_1 = OAc$; $R_2 = R_3 = R_4 = R_5 = H$; $\Delta^{5,6}$ | *Melia azedarach*[142] |
| **70** | 7-acetoxyneotrichilenone | $R_1 = R_3 = H$; $R_2 = Ac$ | *Azadirachta indica*[68] |
| **71** | 12$\alpha$-acetoxyneotrichilenone | $R_1 = R_2 = H$; $R_3 = OAc$; | *Turraea floribunda*[143] |
| **72** | walsurin | $R_1 = O$; $R_2 = R_3 = H$ | *Walsura yunnanensis*[144] |
| **73** | toonaciliatone A | $R_1 = OH$; $R_2 = R_3 = H$ | *Toona ciliata*[145] |
| **74** | 7-deacetyl-21-hydroxyneotrichilenonelide | $R_1 = OH$; $R_2 = O$ | *Trichilia estipulata*[129] |
| **75** | 7-deacetyl-23-hydroxyneotrichilenonelide | $R_1 = O$; $R_2 = OH$ | *T. estipulata*[129] |
| **76** | 17-*epi*nimbocinol | $R_1 = R_2 = H$ | *Azadirachta indica*[110,146] |
| **77** | 17-*epi*azadiradione | $R_1 = Ac$; $R_2 = H$ | *A. indica*[70,103,104,114] |
| **78** | 17-*epi*-17-hydroxyazadiradione | $R_1 = Ac$; $R_2 = OH$ | *A. indica*[70,107] |
| **79** | vepinin | | *A. indica*[78] |
| **80** | limocinin | | *A. indica*[79] |

assigned incorrectly because of the lack of the advanced spectral methods, such as 2D-NMR, HRMS, in the early time. For example, even though azadirachtin (**292**) was found early in 1968,[51] its structure was revised several times before the final unambiguous assignment was made in 1986.[52] (ii) On one hand, some limonoids were given the same nomenclature but had different structures, such as cipadesin D being used for both compound **578**[53] and **1038**[54] even though they were ascribed to different classes. On the other hand, some limonoids have the same structure but different names. Taking compound **805** as an example, it was first reported as 8,30-epoxy swietenine acetate in 1983[55] and subsequently mistaken as swietemahonin F in 1990.[56]

This review is an extensive coverage of all naturally occurring limonoids from Meliaceae discovered in the last six decades (from 1942 to June 30, 2010) along with their various bioactivities. The distribution, chemotaxonomy significance, synthesis, and biological activity of meliaceous limonoids are summarized. In the cases where sufficient information is available, the structure–activity relationship (SAR) and the mode of action of the active limonoids have been presented. Furthermore, we try to clarify the confusing trivial names in meliaceous limonoid investigations. However, limonoids whose names were not proposed by their discoverers (**44**, **53**–**55**, **119**, **125**-**127**, **231**, **457**, **511**, **563**, **602**, **607**, and **844**) were presented only with numbers in the tables.

## 2. MELIACEOUS LIMONOIDS AND THEIR SOURCES

Limonoids are supposed to arise from $\Delta^7$-tirucallol (20*S*) or $\Delta^7$-euphol (20*R*). The $\Delta^7$-bond is epoxidized and is then opened inducing a Wagner–Meerwein shift of Me-14 to C-8, which leads to the formation of the OH-7 and the introduction of a double bond at C-14/15. This scheme account for both the ubiquitous presence of oxygen at C-7 and the correct stereochemistry of the C-30 methyl group. Subsequently the side chain is cyclized with the loss of four carbons to form the 17 $\beta$-furan ring. That the latter step is accomplished after the formation of the 4,4,8-trimethyl-steroid skeleton is indicated by the occurrence of several protolimonoids. Followed formation of the basic limonoid skeleton, a variety of oxidations and skeletal rearrangements can occur and lead to various classes of limonoids (Figure 2),[17] which will be discussed in detail in this review.

### 2.1. Ring Intact Limonoids

**2.1.1. Azadirone-Class.** Azadirone-type limonoids are characteristic of 3-oxo-$\Delta^{1,2}$ and C-7 oxygenation. In their $^1$H NMR spectroscopy, the chemical shifts of H-1 and H-2 were $\delta$ 7.0–7.2 and 5.7–6.0, respectively, which showed the coupling constant of ~10 Hz. In their $^{13}$C NMR spectroscopy, the $\alpha,\beta$-unsaturated ketone system exhibited signals of $\delta$ = 156–160 (C-1), 124–127 (C-2), and 202–205 (C-3), respectively. The signal of H-7 ($\delta$ 5.2–5.4) might shift by 0.1–0.2 ppm and the signal of C-7 (~$\delta$ 70–75) shifts to 75–83 ppm if C-6 is oxygenated.

Azadirone (**1**) was first isolated from oil of *Azadirachta indica* in 1967,[57] and its structure was later elucidated in 1971.[58] It was also obtained from a rare stem exudation of *A. indica*, together with nimbin (**391**) and gedunin (**416**).[59] The interrelationship between azadirone (**1**), azadiradione (**12**), and nimbinin (**60**) was analyzed in terms of a possible chemical degradation through a stepwise oxidation and transformation in nature.[58] The relative stereochemistry of 11$\alpha$- and 11$\beta$-acetoxyazadirone (**3** and **4**) was assigned from the downfield shift of the angular methyl groups at C-8 and C-10, in which the shifts in the 11$\beta$-isomer were more strongly influenced by the acetate function.[60]

The structure corresponding to **7** was assigned to be nimonol[61,62] and confirmed by crystal analysis[63] despite once having been mistaken to be nimocinol.[64] Photooxygenation of nimonol (**7**) yielded a novel product, 14,15,20,21-diepoxy-23-nimonolactone, and involved interesting Diels–Alder and ene


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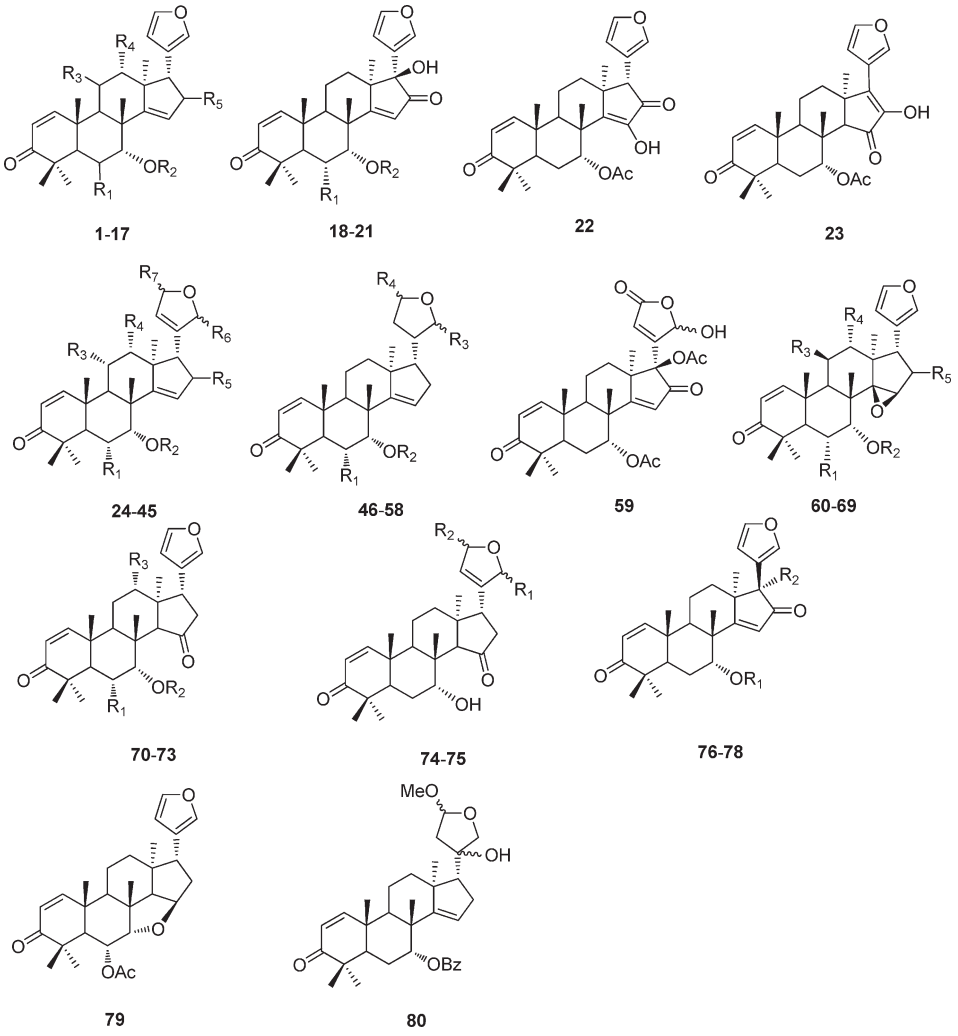


**Figure 3.** Structures of azadirone-class limonoids **1**−**80**.

reactions. This was the first example of the photolysis of intact limonoids in the absence of a sensitizer and of the epoxidation of the D-ring with an $\alpha$ stereochemistry under photolysis.[65] The structure of dysobinin (**11**) was elucidated on the basis of chemical evidence[66] and then confirmed by X-ray diffraction.[67] 7-Desacetyl-7-benzoylazadiradione (**14**)[68] and 6$\alpha$-acetoxy-16-oxoazadirone (**17**)[69] were mistaken for 7-benzoylnimbocinol[70] and mahonin,[71] respectively. Isonimolicinolide (**59**), the first limonoid with an acetoxy function at C-17, might be regarded as a possible intermediate in the biosyntheses of 17$\beta$-hydroxyazadiradione (**18**) and nimolicinol (**451**).[72] Compound **60** was obtained and named as epoxyazadiradione[57] and nimbinin[73] by two separate research groups in 1967. The structure corresponding to **64** was first named as trichilenone acetate early in 1973,[74] and mistaken for 14$\beta$,15$\beta$-epoxyazadirone in 1994[75] and acetyltrichilenone in 1995,[76] when it was isolated from different plants. Heudelottins E and F (**67** and **68**) were of interest because they were the simplest limonoids containing the 11$\beta$-formyloxy-12$\alpha$-(2-hydroxy-3-methylvaleryloxy) system, which had been found very commonly in the complex A,B-seco limonoids of prieurianin class.[77] Three 17-*epi* isomers **76**-**78** obtained from *A. indica* were rare in limonoids from Meliaceae. Vepinin (**79**)[78] and limocinin (**80**),[79] two unique compounds from *A. indica*, were distinguished by the 7$\alpha$,15$\beta$-epoxy ring of the former and the −OH substitution at C-20 of the latter.

**2.1.2. Cedrelone-Class.** The cedrelone-class limonoids are characterized as the 5,6-enol-7-one derivatives. The $^{13}$C NMR spectra showed signals of $\delta$ = 132−135 (C-5), 140−143 (C-6), and 196−199 (C-7). The UV spectra showed the absorption at 277 nm (in EtOH) from the diosphenol chromophore.

The molecular formula of cedrelone (**81**), the principal constituent of *Cedrela toona*, was first assigned as $C_{25}H_{30}O_5$,[147] and later was revised to be $C_{26}H_{30}O_5$ based on chemical and mass spectroscopic work.[148−151] Its structure was finally confirmed by X-ray diffraction.[152] Furthermore, the X-ray study of cedrelone iodoacetate proved its biosynthetic relationship to limonin.[148,153] On the basis of the HMBC and DEPT experiments, the signals for C-9, -11, -12, -17, -21, -23, and -28 of **81** were reassigned.[154] The chemistry of **81** was reviewed in some detail by Govindachari in 1968.[48] The structure of one of the photooxidation product of **81**, in particular the product with epoxy lactone, was established by NMR data and confirmed by X-ray crystallography.[155]

In the course of model experiments with anthothecol (**84**) aimed at structural correlation with 11$\beta$-acetoxyazadirone (**4**), a Zn−Cu couple was found in the meliacin series to be a


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**Table 2. Structures and Sources of Cedrelone-Class Limonoids 81−105**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **81** | cedrelone | $R_1 = R_2 = H$ | *Cedrela toona*;[147,158−160] *Toona ciliata*;[154,161] *T. australis*;[162] *Khaya anthotheca*;[163,164] *Trichilia catigua*;[165] *Walsura yunnanensis*[144] |
| **82** | 11$\beta$-hydroxycedrelone | $R_1 = \beta$-OH; $R_2 = H$ | *W. yunnanensis*[144] |
| **83** | 11$\beta$,12$\alpha$-diacetoxycedrelone | $R_1 = \beta$-OAc; $R_2 = \alpha$-OAc | *Turraea holstii*[143] |
| **84** | anthothecol | $R_1 = \alpha$-OAc; $R_2 = H$ | *Khaya anthotheca*[60,89,163,164,166−168] |
| **85** | deacetylanthothecol | $R_1 = \alpha$-OH; $R_2 = H$ | *K. anthotheca*[89,163] |
| **86** | 23-hydroxycedrelonelide (walsuranolide) | $R_1 = H$; $R_2 = O$; $R_3 = OH$ | *Toona ciliata*;[154] *Walsura yunnanensis*[144] |
| **87** | 11$\beta$-acetoxywalsuranolide | $R_1 = OAc$; $R_2 = O$; $R_3 = OH$ | *W. yunnanensis*[144] |
| **88** | 20,22-dihydro-22,23-epoxywalsuranolide | $R_1 = H$; $R_2 = O$; 20,22-dihydro; 22,23-epoxy | *W. yunnanensis*[144] |
| **89** | 21-hydroxycedrelonelide (isowalsuranolide) | $R_1 = H$; $R_2 = OH$; $R_3 = O$ | *W. yunnanensis*;[144] *Toona ciliata*[154] |
| **90** | 1,2-dihydrocedrelone | R = H | *Cedrela toona*[158] |
| **91** | 11$\beta$-hydroxydihydrocedrelone | R = $\beta$-OH | *Walsura yunnanensis*[144] |
| **92** | 11$\beta$-acetoxydihydrocedrelone | R = $\beta$-OAc | *W. yunnanensis*[144] |
| **93** | 1$\alpha$,11:14$\beta$,15$\beta$-diepoxy-6-hydroxymeliaca-5,9,20,22-tetraene-3,7-dione | | *Khaya anthothea*[60] |
| **94** | hirtin | $R_1$ = Ac; $R_2$ = propanoyl | *Trichilia hirta*;[169,170] *T. pallida*[171] |
| **95** | deacetylhirtin | $R_1 = H$; $R_2$ = propanoyl | *T. hirta*;[169] *T. pallida*[171] |
| **96** | methyl 6-hydroxy-11$\beta$-acetoxy-12$\alpha$-(2-methylpropanoyloxy)-3,7-dioxo-14$\beta$,15$\beta$-epoxy-1,5-meliacadien-29-oate | $R_1$ = Ac; $R_2$ = iBu | *T. pallida*[171] |
| **97** | methyl 6,11$\beta$-dihydroxy-12$\alpha$-(2-methylpropanoyloxy)-3,7-dioxo-14$\beta$,15$\beta$-epoxy-1,5-meliacadien-29-oate | $R_1 = H$; $R_2$ = iBu | *T. pallida*[171] |
| **98** | methyl 6-hydroxy-11$\beta$-acetoxy-12$\alpha$-(2-methylbutanoyloxy)-3,7-dioxo-14$\beta$,15$\beta$-epoxy-1,5-meliacadien-29-oate | $R_1$ = Ac; $R_2$ = Piv | *T. pallida*[171] |
| **99** | methyl 11$\beta$-acetoxy-6-hydroxy-12$\alpha$-(2-methylpropionyloxy)-3,7-dioxo-1,5,14,20,22-meliacapentaen-29-oate | | *T. hirta*[172] |
| **100** | methyl 11$\beta$-acetoxy-6,23-dihydroxy-12$\alpha$-(2-methylpropionyloxy)-3,7,21-trioxo-1,5,14,20,22-meliacatetraen-29-oate | | *T. hirta*[172] |
| **101** | azecin 3 | $R_1$ = $\alpha$-L-Rha-(1→4)-$\beta$-D-Glc-(1→6)-$\beta$-D-Glc; $R_2 = H$ | *Melia azedarach*[173] |
| **102** | 6,11-diacetoxy-7-oxo-14$\beta$,15$\beta$-epoxymeliacin-1,5-diene-3-*O*-$\beta$-D-glucopyranoside | $R_1$ = $\beta$-D-Glc; $R_2$ = OAc | *M. azedarach*[174] |
| **103** | 6-acetoxy-3$\beta$-hydroxy-7-oxo-14$\beta$,15$\beta$-epoxymeliac-1,5-diene-3-*O*-$\beta$-D-xylopyranoside | $R_1$ = $\beta$-D-Xyl; $R_2 = H$ | *M. azedarach*[175] |
| **104** | 6-acetoxy-11$\alpha$-hydroxy-7-oxo-14$\beta$,15$\beta$-epoxymeliacin-1,5-diene-3-*O*-$\alpha$-L-rhamnpyranoside | $R_1$ = $\alpha$-L-Rha; $R_2$ = OH | *M. azedarach*[176] |
| **105** | 6-acetoxy-3$\beta$-hydroxy-7-oxo-14$\beta$,15$\beta$-epoxymeliac-1,5-diene-3-*O*-$\beta$-D-glucuronopyranoside | $R_1$ = $\beta$-D-glucuronic acid; $R_2 = H$ | *M. azedarach*[142] |

convenient and superior reagent for the reduction of epoxides to olefins, $\alpha,\beta$-unsaturated ketones to saturated ketones, and ketols and their acetates to ketones.[89] Burke et al. presented the chemical correlation of **84** with hirtin (**94**), which differ in oxidation status at C-29.[156] Walsuranolide and isowalsuranolide reported by Luo et al. in 2000[144] were actually 23-hydroxycedrelonelide (**86**) and 21-hydroxycedrelonelide (**89**) isolated in 1994,[154] respectively, whose structures were introduced incorrectly as 30-nor (C-8 Methyl) derivatives by Chemical Abstracts (*CA*, 1994). In the crystal structure which was established for 1,2-dihydrocedrelone (**90**), the rings A, B, C, and D adopted sofa, half-chair, twist and envelope conformations, respectively.[157] In 1$\alpha$,11:14$\beta$,15$\beta$-diepoxy-6-hydroxymeliaca-5,9,20,22-tetraene-3,7-dione (**93**), an unusual compound with a 1,11-ether and a 9,11-double bond, the enol ether group of was stable to both acid and base. This unreactivity was probably because of steric hindrance to attack on the enol system.[60]

**2.1.3. Havanensin-Class.** The havanensin-class limonoids bear oxygenic substituent at C-1, C-3, and C-7, and the degree of oxidation at C-28 varies from methyl to carboxyl. Under mildly acid conditions, the first stage of the ring-opening of havanensin (**106**) gives a 15-hydroxy-14-carbonium ion, which then either undergoes Wagner−Meerwein rearrangement or loses a proton to give a 15-ketone enolate and involves participation of the oxygenated function at C-7.[177] Grandifolione (**112**) was the first natural representative of a stage regarded as intermediate in the in vivo transformation of apo-euphol (or apo-tirucallol) into the typical pentenolide system found in limonoids.[178]


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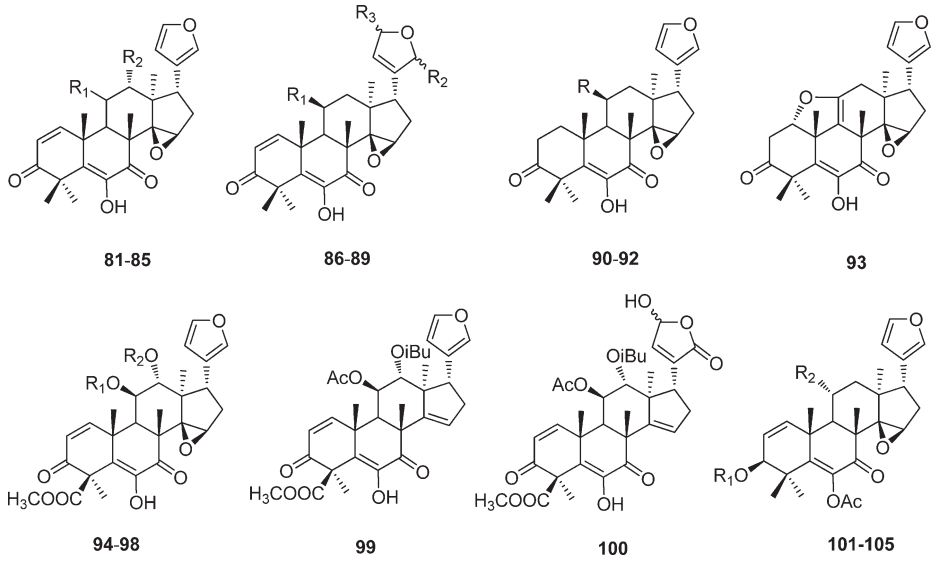


**Figure 4.** Structures of cedrelone-class limonoids **81**−**105**.

14,15-Deoxyhavanensin 3,7-diacetate (**114**) and deoxyhavanensin triacetate (**115**) isolated from the unripened seeds of *Trichilia havanensin* revealed a lower degree of oxidation of the limonoid skeleton and could be viewed as the biosynthetic precursors of the limonoids isolated from the mature seeds.[86] Sendanal (**122**) was of biosynthetic interest from the viewpoint that it was closely related to a precursor of the 14,15-epoxy-12-hydroxy moiety, which could yield limonoids of the nimbin class through a Grob fragmentation followed by formation of an ether ring between the C-7 and C-15 hydroxyl groups via an $S_N1$ mechanism. The co-occurrence of **122** and ohchinal (**343**) in the same tree provided a piece of evidence for such pathway.[179] Unfortunately, limonoids **131**−**134** isolated by Torto et al. were named mistakenly as 28-nor-4$\alpha$-carbomethoxy derivatives of havanensin (**106**). However, C-28 of **131**−**134** was present and so numbered in the original paper, and **131** was confirmed by X-ray diffraction.[180]

**2.1.4. Trichilin-Class.** The trichilin-class limonoids mostly originated from genera *Melia* and *Trichilia* (Table 4), and contained the C-19/29 lactol bridge and the 14,15-epoxide moieties except in compounds **172**−**185**. The $^{13}$C NMR spectral assignments for trichilin A (**135**) were revised based on 2D-NMR data in 1998.[192] Treatment of **135** with zinc borohydride in 2-propanol led to acyl migration in ring A and gave its 1,2-diacetyl and 1,3-diacetyl isomers.[193] Trichilin D (**141**) from *Trichilia roka*, first assigned in 1981,[194] was subsequently obtained from *Melia azedarach* and mistaken for meliatoxin $A_1$ in 1983.[195] The structure of aphanastatin (**142**), along with amoorastatin (**165**) and 12$\alpha$-hydroxyamoorastatin (**166**) isolated from *Aphanamixis grandifolia*, has been determined from three-dimensional X-ray diffraction data.[196,197] The absolute configuration of sendanin (**156**) was proposed based on CD data,[198] and the structure was confirmed by crystallographic means.[199] As concerns biosynthesis, it should be noted that all trichilins isolated from the root bark of *Trichilia roka* were oxidized at the C-2 positon,[194,200] while **156** obtained from the fruit of *T. roka* was not oxidized at C-2.[198] The structure of **156** could not be studied directly because it had been isolated from *Melia azedarach* only after acetylation of the crude limonoid fraction. Therefore the structure of its natural −OH precursor was studied and it was determined from the chemical and spectral data obtained that **156** derived from that precursor should be an epimer mixture of the hemiacetal.[201] The structure of 28-deacetylsendanin referred to in some literature[202−204] should in fact be 29-deacetylsendanin (**157**),[205] which was isolated as a 5:3 mixture of epimer with respect to C-29.[206] In fact, the structure of compound 29-isobutylsendanin[205] obtained from *Melia azedarach* in 1995 was the same as 12-*O*-acetylazedarachin B (**161**)[207] found in 1994 in the same species. Meliartenin (**164**) was shown to be a mixture of two interchangeable isomers.[208] Huang et al. mistook compound **166** as 12-deacetyltoosendanin[209] when citing its origin, in which it was in fact named as 12$\alpha$-hydroxyamoorastatin.[210] The structure of toosendanin[211,212] and 12$\alpha$-acetoxyamoorastatin[213,214] was in fact proved to be identical with that of chuanliansu (**167**), which was first assigned in 1975[215] and subsequently corrected in 1980.[216] Based on the observation of a significant difference in the chemical shift between 3$\alpha$-deacetylamoorastatin (**168**, $\delta$ C-9: 39.5) and 9$\beta$-amoorastatin (**169**, $\delta$ C-9: 48.2), Vardamides et al. proposed the stereochemistry of H-9 as $\beta$ in **169**.[217] The biosynthetic formation of 7,14-epoxyazedarachin B (**183**) could presumably be explained by an intramolecular nucleophilic attack of the hydroxyl group on the C-14 position of the epoxide ring, and in contrast a preferable alternative route led to neoazedarachin B (**181**) with a 1,2-hydrogen shift.[218] As for the structure of toosendanal (**185**), it contained one more lactol bridge at C-1/29 in addition to the C-19/29 ether bridge.[211]

**2.1.5. Vilasinin-Class.** The vilasinin-class limonoids characterized by a 6$\alpha$,28-ether bridge were proposed as biosynthetic precursor of ring C cleaved salannin-type limonoids,[237,238] which were formed through a Grob type olefin-forming fragmentation of a 12-hydroxy-14,15-epoxyvilasinin-class compound and subsequent ether ring formation between C-7 and C-15 hydroxyl groups to yield nimbolidins and salannins.[239] The occurrence of nimbolins A and B (**202** and **366**) in both *Melia azedarach* and *Azadirachta indica* further underlined the close relationship between the two species.[240] Munronolide 21-*O*-$\beta$-D-glucopyranoside (**213**), from *Munronia henryi*, was the first limonoid with a D-glucose moiety attached to the C-21 position.[241] Malleastrones A-C (**227**−**229**) possessed a rare skeleton with an acetyl group at C-6 and the C-6/29 ether bridge. Of these, the structure of **227** was confirmed by X-ray diffraction.[242]


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**Table 3. Structures and Sources of Havanensin-Class Limonoids 106−134**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **106** | havanensin | $R_1 = R_2 = R_3 = R_4 = H$ | *Trichilia havanensis*;[181] *Khaya anthotheca*[163] |
| **107** | 3,7-di-*O*-acetylhavanensin | $R_1 = R_4 = H$; $R_2 = R_3 = Ac$ | *K. anthotheca*;[163] *Trichilia havanensis*[74,181] |
| **108** | 1,7-di-*O*-acetylhavanensin | $R_1 = R_3 = Ac$; $R_2 = R_4 = H$ | *T. havanensis*;[74,181] *Khaya anthotheca*[163] |
| **109** | havanensin triacetate | $R_1 = R_2 = R_3 = Ac$; $R_4 = H$ | *K. anthotheca*;[163] *Trichilia havanensis*[74,86,181] |
| **110** | trifolin | $R_1 = Ac$; $R_2 = H$; $R_3 = iVal(OH)$; $R_4 = O$ | *T. trifolia*[182] |
| **111** | khayanthone | $R_1 = R_2 = R_3 = Ac$; $R_4 = O$ | *Khaya anthotheca*;[163,164,183] *K. nyasica*[184] |
| **112** | grandifolione | $R_1 = R_2 = Ac$; $R_3 = H$; $R_4 = O$ | *K. grandifolia*[164,178,185] |
| **113** | 1$\alpha$-methoxy-1,2-dihydroepoxyazadiradione | | *Azadirachta indica*[68] |
| **114** | 14,15-deoxyhavanensin 3,7-diacetate | $R_1 = R_4 = R_5 = H$; $R_2 = R_3 = Ac$ | *Khaya anthotheca*;[163] *Chisocheton paniculatus*[117] |
| **115** | deoxyhavanensin triacetate | $R_1 = R_2 = R_3 = Ac$; $R_4 = R_5 = H$; | *Trichilia havanensis*[86] |
| **116** | 14,15-deoxyhavanensin 1,7-diacetate | $R_1 = R_3 = Ac$; $R_2 = R_4 = R_5 = H$ | *T. havanensis*;[86] *Melia toosendan*[186] |
| **117** | 1$\alpha$,12$\alpha$-diacetoxy-7-deacetyl-1,2-dihydro-3$\alpha$-hydroxyazadirone | $R_1 = Ac$; $R_4 = OAc$; $R_2 = R_3 = R_5 = H$ | *Turraea cornucopia*[90] |
| **118** | deoxykhayanthone | $R_1 = R_2 = R_3 = Ac$; $R_4 = H$; $R_5 = O$ | *Khaya nyasica*[184] |
| **119** | | $R_1 = R_2 = Ac$; $R_3 = OH$; 20,22-didehydro | *Trichilia havanensis*[86] |
| **120** | melianin C | $R_1 = Ac$; $R_2 = Bz$; $R_3 = H$ | *Melia volkensii*[187] |
| **121** | toosendone | | *M. toosendan*[186] |
| **122** | sendanal | | *M. azedarach*[179] |
| **123** | 1$\alpha$,7$\alpha$,11$\beta$-triacetoxy-4$\alpha$-carbomethoxy-12$\alpha$-(2-methylpropanoyloxy)-14$\beta$,15$\beta$-epoxyhavanensin | $R_1 = R_3 = Ac$; $R_2 = H$; $R_4 = iBu$ | *Turraea floribunda*[188] |
| **124** | 1$\alpha$,7$\alpha$,11$\beta$-triacetoxy-4$\alpha$-carbomethoxy-12$\alpha$-(2-methylbutanoyloxy)-14$\beta$,15$\beta$-epoxyhavanensin | $R_1 = R_3 = Ac$; $R_2 = H$; $R_4 = Piv$ | *T. floribunda*[188] |
| **125** | | $R_1 = R_4 = Ac$; $R_2 = R_3 = H$ | *T. floribunda*[189] |
| **126** | | $R_1 = R_4 = Ac$; $R_2 = H$; $R_3 = iBu$ | *T. floribunda*[189] |
| **127** | | $R_1 = H$; $R_2 = R_4 = Ac$; $R_3 = iBu$ | *T. floribunda*[189] |
| **128** | 11$\beta$-acetoxy-3,7-diacetyl-4$\alpha$-carbomethoxy-12$\alpha$-isobutyryloxy-28-nor-1-tigloyl-havanensin | $R_1 = Tig$; $R_2 = R_3 = Ac$; $R_4 = iBu$ | *T. floribunda*[190] |
| **129** | nilotin | $R_1 = R_2 = R_3 = Ac$; $R_4 = Tig$ | *T. nilotica*[191] |
| **130** | 1$\alpha$,11$\beta$-diacetoxy-4$\alpha$-carbomethoxy-7$\alpha$-hydroxy-12$\alpha$-(2-methylpropanoyloxy)-15-oxohavanensin | | *T. floribunda*[188] |
| **131** | 28-nor-4$\alpha$-carbomethoxy-11$\beta$-acetoxy-12$\alpha$-(2-methylbutanoyloxy)-14,15-deoxyhavanensin-1,7-diacetate | $R_1 = R_2 = Ac$ | *T. floribunda*[180] |
| **132** | 28-nor-4$\alpha$-carbomethoxy-11$\beta$-hydroxy-12$\alpha$-(2-methylbutanoyloxy)-14,15-deoxyhavanensin-1-acetate | $R_1 = R_2 = H$ | *T. floribunda*[180] |
| **133** | 28-nor-4$\alpha$-carbomethoxy-11$\beta$-acetoxy-12$\alpha$-(2-methylbutanoyloxy)-14,15-deoxyhavanensin-1-acetate | $R_1 = H$; $R_2 = Ac$ | *T. floribunda*[180] |
| **134** | 28-nor-4$\alpha$-carbomethoxy-7-deoxy-7-oxo-11$\beta$-acetoxy-12$\alpha$-(2-methylbutanoyloxy)-14,15-deoxyhavanensin-1-acetate | | *T. floribunda*[180] |

**2.1.6. Others.** The characterization of the epoxides 1$\alpha$,2$\alpha$-epoxy-17$\beta$-hydroxyazadiradione (**248**) and 1$\alpha$,2$\alpha$-epoxynimolicinol (**453**) in *Azadirachta indica* oil was of biosynthetic significance, as they might be considered as intermediates between A-ring 3-oxo-$\Delta^{1,2}$ and 1,3-diols among the *A. indica* limonoids.[115]

## 2.2. Ring-seco Limonoids

**2.2.1. Demolition of a Single Ring.** *2.2.1.1. Ring A-seco Group.* The cleavage of C-3/4 and then formation of a 3,4-lactone mostly occurred in the ring A-seco group, and usually led to either the $\Delta^{1,2}$ system or 1$\alpha$-acetyl substitution (Figure 9). Dregeanas 3−5 (**256**, **261**, and **260**) were considered as intermediates between the intact limonoids such as heudelottins C, E, and F (**66**-**68**) and the complex compounds of the prieurianin-class.[274] Kihadalactone A obtained from *Aphanamixis polystacha* in 1999[275] was in fact identical with carapolide I (**257**) obtained from *Carapa grandiflora* in 1994.[276] In addition, **257** was of interest because the complex rohitukin limonoids could arise from compounds of this relatively simple type by oxidation of ring B and the $\Delta^{14}$-double bond.[275]

*2.2.1.2. Ring B-seco Group.* Up to now, the limonoids of ring B-seco (C-7/8) from Meliaceae were found only in the *Turraea* and *Toona* genera (Table 8). The substituents at C-11 in turraflorins A−C (**266**, **267**, and **283**), first isolated from *Turraea floribunda*,[284] were revised to be $\beta$-oriented[143] and the complete assignment of the NMR spectra of **266** and **267** were presented.[285] The structure of 6-acetoxytoonacilin (**269**), the first B-seco


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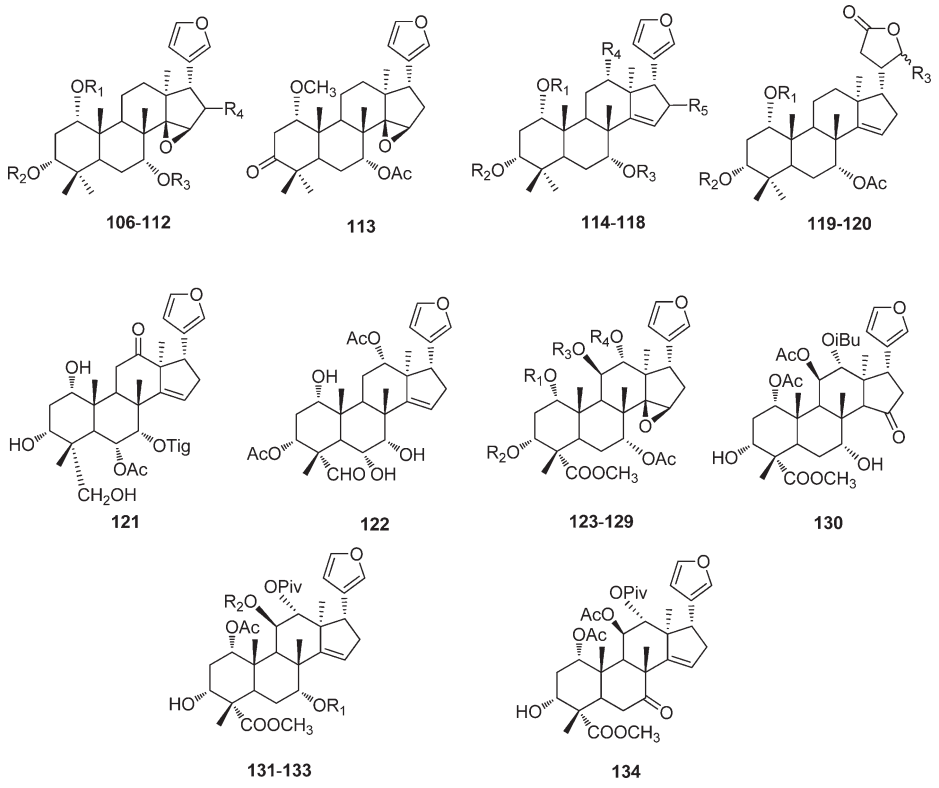


**Figure 5.** Structures of havanensin-class limonoids **106**−**134**.

limonoid with an intact A ring related to cedrelone (**81**), was confirmed by X-ray analysis.[286] The absolute configurations of turrapubesins D−G (**275**−**278**) were established by correlating their CD spectra to that of turrapubesin B (**1153**),[59] a model compound whose absolute configuration was assigned by CD analysis of its dihydrogenated derivatives.[266] Unlike the limonoids **266**−**286**, all of which have a $\Delta^{8,30}$ exocyclic double bond, turrapubesins A (**290**) and C (**291**) both have a $\Delta^{8,14}$ double bond, and the latter also has a 1,30-oxygen bridge. Wang et al. presented the first report on the determination of the absolute configuration of **290** by chlorine-based X-ray crystallography[287] and proposed a plausible biosynthetic pathway to **291** starting from the precursor 11-*epi*toonacilin (**271**).[126]

*2.2.1.3. Ring C-seco Group. 2.2.1.3.1. Azadirachtin/Meliacarpin-Class.* The ring C-seco limonoids originated mainly from the *Azadirachta* and *Melia* genera (Table 9). Deciphering the structure of the very potent biopesticide azadirachtin (**292**), first isolated from *Azadirachta indica* (syn. *Melia azadirachta*),[51] also called azadirachtin A according to Rembold,[35] was a long journey. Butterworth et al. presented the correct formula of **292** as $C_{35}H_{44}O_{16}$[293] and delineated important structural features.[294] Based on the NMR study including the NOE experiments, the structure of **292** was proposed[295,296] and subsequently revised.[297,298] The final and unambiguous determination did not arrive until 1986 based on the X-ray crystallographic analysis of its derivatives,[52,257] and thus reassignments of its NMR data have been proposed by several research groups.[299−301] Crystalline **292** was obtained in 1994 and its crystal parameters were measured by X-ray diffraction.[302,303] Then its absolute configuration was finally determined by high field NMR application of the Mosher method.[304] To determine the properties of **292**, it was converted to the natural product 22,23-dihydro-23$\beta$-methoxyazadirachtin (**303**) via selective bromomethoxylation of the C-22,23 enol ether double bond and tri-n-butyltin hydride reduction.[305] A wonderful review of the chemistry of **292** was presented by Ley et al.,[21] and a methodology of structure determination was also developed taking **292** as an example.[306] The structure of 3-tigloylazadirachtol (**296**),[307] once incorrectly assigned as deacetylazadirachtinol,[308] was also called azadirachtin B.[309] Azaidrachtin F and 11-hydroxyazadirachtin B, both reported in 1996 by two different research groups, had the same structure as **300**.[130,310] The spectral data of azadirachtin D (**309**), which was identical with 1-tigloyl-3-acetyl-11-hydroxy-4$\beta$-methylmeliacarpin isolated in 1992,[311] were introduced by Govindachari in the same year.[312] Unlike most azadirachtin/meliacarpin-class limonoids, azadirachtin G (**305**) and 13,14-desepoxyazadirachtin A (**306**) had a double bond at C-13/14 instead of an epoxy moiety. 1,3-Diacetyl-11,19-deoxa-11-oxo-meliacarpin (**311**) from *Azadirachta indica* was considered to be a possible intermediate in the biosynthesis of **292**.[313]

*2.2.1.3.2. Azadirachtinin/Meliacarpinin-Class.* It was thought that an intramolecular $S_N2$ nucleophilic reaction resulted in the formation of 7$\alpha$,13$\beta$-ether bridge moiety in azadirachtin/meliacarpin-class limonoids. 1-Cinnamoyl-3-acetyl-11-methoxymeliacarpinin (**327**) reported in 1994[339] was cited as meliacarpinin A by Zhou et al. in 1997.[214] It was odd that Nakatani et al. reported 1-deoxy-3-tigloyl-11-methoxymeliacarpinin (**328**)[340] in 1993 and 1-acetyl-3-tigloyl-11-methoxymeliacarpinin (**329**)[219] in 1994, but then presented these two compounds as meliacarpins B and C in 1995,[341] respectively. The structure **330** had been variously assigned to meliacarpinin D[341] and, in 1995, to 1-tigloyl-3-acetyl-11-methoxymeliacarpinin,[205] while **331** was reported as meliacarpinin E[342] in 1996 and was in fact the 3-tigloyl-11-methoxymeliacarpinin reported in 1993.[206]


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**Table 4. Structures and Sources of Trichilin-Class Limonoids 135−185**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **135** | trichilin A | $R_1 = R_4 = H$; $R_2 = OAc$; $R_3 = Ac$; $R_5 = O$; $R_6 = \beta$-OH; $R_7 = Piv$ | *Trichilia emetica*;[192] *T. roka*[194] |
| **136** | 7-acetyltrichilin A | $R_1 = H$; $R_2 = OAc$; $R_3 = R_4 = Ac$; $R_5 = O$; $R_6 = \beta$-OH; $R_7 = Piv$ | *T. roka*[200] |
| **137** | trichilin B | $R_1 = R_4 = H$; $R_2 = OAc$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OH; $R_7 = Piv$ | *T. roka*;[194] *Melia azedarach*;[206,207,209,219,220] *M. toosendan*[85,214] |
| **138** | 12-*O*-acetyltrichilin B | $R_1 = R_4 = H$; $R_2 = OAc$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OAc; $R_7 = Piv$ | *M. azedarach*;[206,207,209,219,220] *M. toosendan*[214] |
| **139** | 1,12-diacetyltrichilin B | $R_1 = R_3 = Ac$; $R_2 = OAc$; $R_4 = H$; $R_5 = O$; $R_6 = \alpha$-OAc; $R_7 = Piv$ | *M. azedarach*[206,207,209,219−221] |
| **140** | trichilin C | $R_1 = R_4 = H$; $R_2 = OAc$; $R_3 = Ac$; $R_5 = OH$; $R_6 = O$; $R_7 = Piv$ | *Trichilia roka*[194] |
| **141** | trichilin D (meliatoxin $A_1$) | $R_1 = R_4 = R_6 = H$; $R_2 = OAc$; $R_3 = Ac$; $R_5 = O$; $R_7 = Piv$ | *T. roka*;[194] *Melia azedarach*[195,206,207,209,219−222] |
| **142** | aphanastatin | $R_1 = R_3 = Ac$; $R_2 = OH$; $R_4 = H$; $R_5 = O$; $R_6 = \alpha$-OH; $R_7 = Piv$ | *M. azedarach*;[209,219] *Aphanamixis grandiflora*;[196] *Trichilia roka*[194] |
| **143** | trichilin F | $R_1 = Ac$; $R_2 = OAc$; $R_3 = R_4 = H$; $R_5 = O$; $R_6 = \beta$-OH; $R_7 = Piv$ | *T. roka*[194,223] |
| **144** | trichilin G | $R_1 = R_4 = H$; $R_2 = OH$; $R_3 = Ac$; $R_5 = O$; $R_6 = \beta$-OH; $R_7 = Piv$ | *T. roka*[223] |
| **145** | trichilin H | $R_1 = R_4 = H$; $R_2 = OAc$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OAc; $R_7 = iBu$ | *Melia azedarach*;[206,207,209,219−221] *M. toosendan*[85,211,224] |
| **146** | 1-acetyltrichilin H | $R_1 = R_3 = Ac$; $R_2 = OAc$; $R_4 = H$; $R_5 = O$; $R_6 = \alpha$-OAc; $R_7 = iBu$ | *M. azedarach*;[221,225] *M. toosendan*[85] |
| **147** | 1-acetyl-2-deacetyltrichilin H | $R_1 = R_3 = Ac$; $R_2 = OH$; $R_4 = H$; $R_5 = O$; $R_6 = \alpha$-OAc; $R_7 = iBu$ | *M. azedarach*[221] |
| **148** | 3-deacetyltrichilin H | $R_1 = R_3 = R_4 = H$; $R_2 = OAc$; $R_5 = O$; $R_6 = \alpha$-OAc; $R_7 = iBu$ | *M. azedarach*[221] |
| **149** | 1-acetyl-3-deacetyltrichilin H | $R_1 = Ac$; $R_2 = OAc$; $R_3 = R_4 = H$; $R_5 = O$; $R_6 = \alpha$-OAc; $R_7 = iBu$ | *M. azedarach*[221] |
| **150** | 12-*O*-deacetyltrichilin H | $R_1 = R_4 = H$; $R_2 = OAc$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OH; $R_7 = iBu$ | *M. azedarach*[226] |
| **151** | trichilin I | $R_1 = R_4 = H$; $R_2 = OH$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OAc; $R_7 =$Piv | *M. toosendan*[85,209,224,227] |
| **152** | 12-deaceyltrichilin I | $R_1 = R_4 = H$; $R_2 = OH$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OH; $R_7 = Piv$ | *M. azedarach*[221] |
| **153** | trichilin J | $R_1 = R_4 = R_6 = H$; $R_2 = OH$; $R_3 = Ac$; $R_5 = O$; $R_7 = Piv$ | *M. toosendan*[85,209,224,227] |
| **154** | trichilin K | $R_1 = R_4 = R_6 = H$; $R_2 = OH$; $R_3 = Ac$; $R_5 = O$; $R_7 = iBu$ | *M. toosendan*[85,224] |
| **155** | trichilin L | $R_1 = R_3 = R_4 = R_6 = H$; $R_2 = OAc$; $R_5 = O$; $R_7 = Piv$ | *M. toosendan*[85,224] |
| **156** | sendanin | $R_1 = R_2 = R_4 = H$; $R_3 = R_7 = Ac$; $R_5 = O$; $R_6 = \alpha$-OAc; | *M. azedarach*;[199] *Trichilia roka*[198] |
| **157** | 29-deacetylsendanin | $R_1 = R_2 = R_4 = R_7 = H$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OAc; | *Melia azedarach*;[205] *M. toosendan*[202−204] |
| **158** | azedarachin A | $R_1 = R_2 = R_4 = H$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OH; $R_7 = Piv$ | *M. azedarach*;[206,207,209,219] *M. toosendan*[85,224] |
| **159** | 12-O-acetylazedarachin A | $R_1 = R_2 = R_4 = H$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OAc; $R_7 = Piv$ | *M. azedarach*;[205,207,209,219] *M. toosendan*[85,133] |
| **160** | azedarachin B | $R_1 = R_2 = R_4 = H$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OH; $R_7 = iBu$ | *M. azedarach*;[205,206,218] *M. toosendan*[85,214] |
| **161** | 12-*O*-acetylazedarachin B (29-isobutylsendanin) | $R_1 = R_2 = R_4 = H$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OAc; $R_7 = iBu$ | *M. azedarach*;[207,209,219] *M. toosendan*[224] |


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**Table 4. Continued**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **162** | azedarachin C | $R_1 = R_2 = R_4 = R_6 = H$; $R_3 = Ac$; $R_5 = O$; $R_7 = iBu$ | *M. azedarach*[206,209,228] |
| **163** | meliatoxin $A_2$ | $R_1 = R_4 = R_6 = H$; $R_2 = OAc$; $R_3 = Ac$; $R_5 = O$; $R_7 = iBu$ | *M. azedarach*[195,206,207,219,220,222] |
| **164** | meliartenin | $R_1 = R_2 = R_4 = R_7 = H$; $R_3 = Ac$; $R_5 = OH$; $R_6 = O$ | *M. azedarach*[208] |
| **165** | amoorastatin | $R_1 = R_2 = R_4 = R_6 = R_7 = H$; $R_3 = Ac$; $R_5 = O$ | *Pterohrachis zenkeri*;[217] *Aphanamixis grandiflora*[229] |
| **166** | 12$\alpha$-hydroxyamoorastatin (12-deacetyltoosendanin) | $R_1 = R_2 = R_4 = R_7 = H$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OH | *A. grandiflora*;[210] *Melia toosendan*;[85,133,214] *M. azedarach*[201,205,209,213,230] |
| **167** | chuanliansu (toosendanin; 12$\alpha$-acetoxyamoorastatin) | $R_1 = R_2 = R_4 = R_7 = H$; $R_3 = Ac$; $R_5 = O$; $R_6 = \alpha$-OAc | *M. toosendan*;[85,133,211,212,214] *M. azedarach*[209,213,230] |
| **168** | 3$\alpha$-deacetylamoorastatin | $R_1 = R_2 = R_3 = R_4 = R_6 = R_7 = H$; $R_5 = O$ | *Pterohrachis zenkeri*[217] |
| **169** | 9$\beta$-amoorastatin | $R_1 = R_2 = R_4 = R_6 = R_7 = H$; $R_3 = Ac$; $R_5 = O$; 9$\beta$-H | *P. zenkeri*[217] |
| **170** | meliatoosenin D | $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = O$ $R_6 = \alpha$-OAc; $R_7 = OH$ | *Melia toosendan*[133] |
| **171** | meliatoosenin C | | *M. toosendan*[133] |
| **172** | amoorastatone | $R_1 = \alpha$-OH; $R_2 = R_4 = R_5 = H$; $R_3 = \alpha$-OAc | *Aphanamixis grandiflora*;[210] *Melia azedarach*[230] |
| **173** | 12$\alpha$-hydroxyamoorastatone | $R_1 = \alpha$-OH; $R_2 = R_5 = H$; $R_3 = \alpha$-OAc; $R_4 = OH$ | *M. azedarach*;[213,230−232] *M. toosendan*[85,133,225] |
| **174** | 29-[(2-methylbutanoyl)oxy]-2$\alpha$-hydroxyamoorastatone | $R_1 = \alpha$-OH; $R_2 = OH$; $R_3 = \alpha$-OAc; $R_4 = H$; $R_5 = Piv$ | *M. toosendan*[233] |
| **175** | 1,3-*epi*-29-[(2-methylbutanoyl)oxy]-2$\alpha$-hydroxyamoorastatone | $R_1 = \beta$-OH; $R_2 = OH$; $R_3 = \beta$-OAc; $R_4 = H$; $R_5 = Piv$ | *M. toosendan*[233] |
| **176** | 1,3-*epi*-29-[(2-methylpropanoyl)oxy]-2$\alpha$-hydroxyamoorastatone | $R_1 = \beta$-OH; $R_2 = OH$; $R_3 = \beta$-OAc; $R_4 = H$; $R_5 = i$Bu | *M. toosendan*[233] |
| **177** | meliatoxin $B_1$ | $R_1 = \alpha$-OH; $R_2 = OAc$; $R_3 = \alpha$-OAc; $R_4 = H$; $R_5 = Piv$ | *M. azedarach*[195,211,221,222] |
| **178** | meliatoxin $B_2$ | $R_1 = \alpha$-OH; $R_2 = OAc$; $R_3 = \alpha$-OAc; $R_4 = H$; $R_5 = iBu$ | *M. azedarach*[195,222] |
| **179** | isochuanliansu (isotoosendanin) | $R_1 = \alpha$-OH; $R_2 = R_5 = H$; $R_3 = \alpha$-OAc; $R_4 = OAc$ | *M. azedarach*;[230,234] *M. toosendan*[85,225,234,235] |
| **180** | neoazedarachin A | $R_1 = \alpha$-OH; $R_2 = H$; $R_3 = \alpha$-OAc; $R_4 = OH$; $R_5 = Piv$ | *M. toosendan*[85,225] |
| **181** | neoazedarachin B | $R_1 = \alpha$-OH; $R_2 = H$; $R_3 = \alpha$-OAc; $R_4 = OH$; $R_5 = iBu$ | *M. toosendan*[85,218,225] |
| **182** | neoazedarachin D | $R_1 = \alpha$-OH; $R_2 = H$; $R_3 = \alpha$-OAc; $R_4 = OH$; $R_5 = CH_3$ | *M. toosendan*[225] |
| **183** | 7,14-epoxyazedarachin B | | *M. azedarach*[218] |
| **184** | azadirachtanin | | *Azadirachta indica*[236] |
| **185** | toosendanal | | *Melia toosendan*[211] |

*2.2.1.3.3. Salannin-Class.* The structures of salannin (**332**) and 3-deacetylsalannin (**333**), in which many of the conformations were similar to those of in azadirachtins, were confirmed by X-ray diffraction analysis.[347] Photooxidation of **332** and nimbin (**391**) by UV light in the presence of oxygen led to more polar unstable intermediates that rearranged on silica gel to two final products in which the furan ring had been oxidized to isomeric hydroxybutenolides.[348] The photooxidation products of **332**, salanninolide (**349**), and its isomer isosalanninolide (**348**) were also isolated as natural products from *Azadirachta indica*.[317,318] The molecules of 2′,3′-dehydrosalannol (**338**) were linked into chains by intermolecular O−H···O hydrogen bonds.[349] The biosynthetic pathway to nimbolide (**345**) from [2-$^{14}$C,(4*R*)4-$^{3}H_1$]-mevalonic acid lactone was confirmed by feeding experiments.[350−354] The isomer of **345** was unexpectedly produced when it was treated with boron trifluoride etherate and tetrabutyl ammonium bromide.[355] Salannolide[356] and compositolide[253] were both obtained in 1984 by two research groups, and had the same structure as **348**. In addition, it was mistaken for isosalanninolide by Jarvis et al. in 1999.[317]


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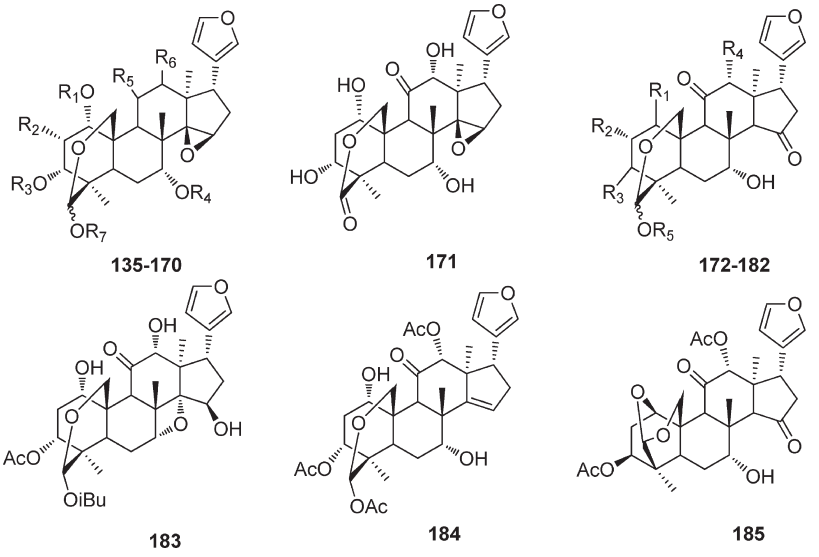


**Figure 6.** Structures of trichilin-class limonoids **135**−**185**.

*2.2.1.3.4. Nimbolinin-Class.* It seems that melianolide (**389**) was situated in a position to link ring C-seco limonoids such as nimbolinin B (**358**) to azadirachtinin-class limonoids.[361] The biosynthetic routes from ohchinolide A (**371**) to salannal (**396**) and further to salannin (**332**) involving Grob type olefin formation and subsequent ether ring formation were presented.[361] Zhang et al. proposed 12-ethoxynimbolinins A−D[186] for the structure of **357**, **361**, **385**, and **388** based on comparison of the skeleton with the virtual compound nimbonlinin, which was a presumed intermediate in the biosynthetic pathway to more highly rearranged limonoids not yet isolated as a natural product. However, 12-ethoxynimbolinins A−D were not simple ethoxyl derivatives of nimbolinin A−D (**355**, **358**, **363**, and **364**), which might cause misunderstanding and confusion.[212]

*2.2.1.3.5. Nimbin-Class.* The structure of nimbin (**391**), the major crystal bitter constituent of *Azadirachta indica*, was characterized by chemical means[392−401] and spectroscopic analysis.[402] The assignment of the absolute configuration in **391** was determined by making certain biosynthetic assumptions[403] and using information from the ORD study of pyronimbic acid.[404] The NMR spetral data of **391**, 6-deacetylnimbin (**392**), nimbanal (**393**), and nimbolide (**345**) were subsequently partially reassigned in 1990.[377] Ohchinolal (**396**), obtained from *Melia azedarach* early in 1983,[370] was isolated from the same species and renamed as salannal by Nakatani et al. in 1995.[360] 3-*O*-Acetylohchinolal (**399**) was considered to be one of the biosynthetic precursors to the ring C-seco limonoids with C-6/28 and C-7/15 ether linkages, such as are found in salannin (**332**) and ohchinin (**340**).[84]

*2.2.1.3.6. Nimbolidin-Class.* Walsogyne (**414**), with a C-11/14 ether bridge, might be derived through keto−enol isomerization of the aldehyde at C-9 followed by formation of a tetrahydrofuran-2-ol.[412] 7$\alpha$-Acetyl-15$\beta$-methoxy-29-methylene-7,15-deoxonimbolide (**415**) should be named as 7$\alpha$-acetyl-15$\beta$-methoxy-28a-methylene-7,15-deoxonimbolide based on its skeleton numbering, and the source of C-28a was not biosynthetically available.[411]

*2.2.1.4. Ring D-seco Group.* Limonoids in this group with a $\delta$-lactone in ring D derived from azadirone class via ring expansion by a Baeyer−Villiger type reaction.[413] Gedunin (**416**), the representative compound of this class, was obtained from various species (Table 15). For **416** the MS[135,414] and NMR spectral data[415] presented were used for its characterization, and its constitution and relative stereochemistry were deduced from the dihydrogedun-3$\beta$-yl iodoacetate[416] derivative and confirmed by X-ray diffraction analysis.[417] Moreover, reactions of **416** were described and explained by a structure similar to that proved for limonin.[418] The crystal structure of 6$\alpha$-acetoxygedunin (**418**) was determined by X-ray analysis.[419] The $^1$H NMR data of 7-deacetylgedunin (**421**) had not been completely assigned until 2006[113] although it was isolated from *Azadirachta indica* in 1967.[57] Cespedes et al. presented the isolation of the epimeric mixture of photogedunin (**433**) and the formation and phytosynthetic activities of its acetates.[420] The chemical conversion of **416** and khivorin (**434**) to deacetoxy-7-oxoisogedunin confirmed the structure of **434**.[421] The crystal packing of 3$\alpha$,7$\alpha$-dideacetylkhirorin (**440**) was stabilized by both intra- and intermolecular hydrogen bonds, whose six-membered rings showed chair, boat and half-chair conformations while the furan ring was planar.[422] Biosynthetically, formation of mahmoodin (**454**), the first limonoid with a C-17 ethylene glycol side chain, might be considered as being from isonimolicinolide (**59**) through oxidation of ring D to a $\delta$-lactone, as is observed in the case of the epoxyazadiradione-gedunin conversion, followed by transformation of the acetyl group to an ethylene glycol group.[81]

**2.2.2. Demolition of Two Rings.** *2.2.2.1. Rings A,B-seco Group. 2.2.2.1.1. Prieurianin-Class.* The complex prieurianin-class limonoids were depicted as arising from cleavages of C-3/4 and C-7/8 and the formation of 3(4)-lactone or 7(4)-lactone, with the substitution of a formyloxy or acetoxy group at C-11 (Figure 18 and Table 16). Prieurianin (**458**), first isolated from *Trichilia prieuriana*, is the representative compound of this class,[168] but the presence of multiple conformational isomers at room temperature caused its $^1$H NMR peaks to be poorly resolved so that its structure remained obscure. However, the $^1$H NMR spectrum was well resolved when the sample was heated to ~67 °C so that at that temperature it was possible to perform a detailed analysis and make proton assignments.[481] Similarly, its $^{13}$C NMR spectrum should be measured at 50 °C to avoid broad or missing peaks which occur in measurements made at 33 °C. Finally, the structure of **458** was unambiguously confirmed


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**Table 5. Structures and Sources of Vilasinin-Class Limonoids 186−229**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **186** | vilasinin | $R_1 = R_2 = R_3 = R_4 = H$ | *Azadirachta indica*[238] |
| **187** | 1$\alpha$-acetyl-3$\alpha$-propionylvilasinin | $R_1$ = Ac; $R_2$ = propanoyl; $R_3 = R_4 = H$ | *Turraea wakefieldii*;[188] *T. parvifolia*[243] |
| **188** | 1$\alpha$,3$\alpha$-diacety-7$\alpha$-tigloylvilasinin | $R_1 = R_2$ = Ac; $R_3$ = Tig; $R_4 = H$ | *T. parvifolia*[243] |
| **189** | 1$\alpha$,3$\alpha$-diacetylvilasinin | $R_1 = R_2$ = Ac; $R_3 = R_4 = H$ | *T. parvifolia*;[243] *T. holstii*;[143] *Chisocheton paniculatus*;[117] *Malleastrum antsingyense*;[244] *Melia volkensii*;[187] *Azadirachta indica*[245] |
| **190** | 1,3-diacetyl-7-tigloyl-12$\alpha$-hydroxyvilasinin | $R_1 = R_2$ = Ac; $R_3$ = Tig; $R_4$ = OH | *A. indica*;[130] *Malleaxtrum antsingyense*[244] |
| **191** | trichilinin | $R_1 = R_3 = H$; $R_2$ = Ac; $R_4$ = OAc | *Trichilia roka*[237] |
| **192** | 1-cinnamoyltrichilinin | $R_1$ = Cin; $R_2$ = Ac; $R_3 = H$; $R_4$ = OAc | *Melia volkensii*;[246] *M. toosendan*[186,212] |
| **193** | 1-tigloyltrichilinin | $R_1$ = Tig; $R_2$ = Ac; $R_3 = H$; $R_4$ = OAc | *M. volkensii*[246] |
| **194** | 1-acetyltrichilinin | $R_1 = R_2$ = Ac; $R_3 = H$; $R_4$ = OAc | *M. volkensii*;[246] *M. toosendan*[186] |
| **195** | trichilinin B | $R_1$ = Tig; $R_2$ = Ac; $R_3 = H$; $R_4$ = OAc | *M. toosendan*[85,186,239] |
| **196** | trichilinin C | $R_1$ = Ac; $R_2$ = Tig; $R_3 = R_4 = H$ | *M. toosendan*[85,239] |
| **197** | trichilinin D | $R_1$ = Cin; $R_2 = R_3 = H$; $R_4$ = OAc | *M. toosendan*[85,212,247] |
| **198** | trichilinin E | $R_1$ = Bz; $R_2 = R_3 = H$; $R_4$ = OAc | *M. toosendan*[85,212,247] |
| **199** | meliavolkinin | $R_1$ = Bz; $R_2$ = Ac; $R_3 = R_4 = H$ | *M. volkensii*[187] |
| **200** | meliavolkin | $R_1$ = Cin; $R_2$ = Ac; $R_3 = R_4 = H$ | *M. volkensii*[248] |
| **201** | nimbidinin | $R_1 = R_2 = R_3 = H$; $R_4$ = O | *Azadirachta indica*[249,250] |
| **202** | nimbolin A | $R_1 = R_2$ = Ac; $R_3$ = Cin; $R_4 = H$ | *A. indica*;[240] *Melia azedarach*;[240,251] *M. birmanica*[252] |
| **203** | compositin | $R_1 = R_3$ = Tig; $R_2 = R_4 = H$ | *M. dubia*[253] |
| **204** | compositin acetate | $R_1 = R_3$ = Tig; $R_2$ = OAc; $R_4 = H$ | *M. composita*[254] |
| **205** | dysoxylin A | $R_1$ = Ac; $R_2 = R_5 = H$; $R_3$ = Tig; $R_4$ = OAc; $R_6$ = O; 20,22-dihydro | *Dysoxylum gaudichaudianum*[255] |
| **206** | dysoxylin B | $R_1$ = Ac; $R_2 = R_5 = H$; $R_3$ = Bz; $R_4$ = OAc; $R_6$ = O; 20,22-dihydro | *D. gaudichaudianum*[255] |
| **207** | dysoxylin C | $R_1$ = Ac; $R_2 = R_5 = H$; $R_3$ = Piv; $R_4$ = OAc; $R_6$ = O; 20,22-dihydro | *D. gaudichaudianum*[255] |
| **208** | dysoxylin D | $R_1$ = Ac; $R_2 = R_5 = H$; $R_3$ = 3,4-dimethylpent-2-enoyl; $R_4$ = OAc; $R_6$ = O; 20,22-dihydro | *D. gaudichaudianum*[255] |
| **209** | azadirachtolide | $R_1$ = Sen; $R_2$ = Ac; $R_3 = R_4 = R_5 = H$; $R_6$ = O | *Azadirachta indica*[256] |
| **210** | deoxyazadirachtolide | $R_1$ = Sen; $R_2$ = Ac; $R_3 = R_4 = R_5 = R_6 = H$ | *A. indica*[256] |
| **211** | 3-acetoxy-7-tigloylvilasinin lactone | $R_1 = R_4 = R_5 = H$; $R_2$ = Ac; $R_3$ = Tig; $R_6$ = O | *A. indica*[70,257] |
| **212** | munronolide | $R_1 = R_2$ = Ac; $R_3 = R_4 = H$; $R_5$ = OH; $R_6$ = O; $\Delta^{20,22}$ | *Munronia henryi*[241] |
| **213** | munronolide 21-*O*-$\beta$-D-glucopyranoside | $R_1 = R_2$ = Ac; $R_3 = R_4 = H$; $R_5 = \beta$-D-glc; $R_6$ = O; $\Delta^{20,22}$ | *M. henryi*[241] |
| **214** | neem A | $R_1 = R_2 = R_3 = R_4 = R_5 = H$; $R_6$ = O | *Azadirachta indica*[258] |
| **215** | neem B | $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$ | *A. indica*[258] |
| **216** | munronin G | | *Munronia delavayi*[259] |
| **217** | limbocinin | $R_1 = R_2 = H$ | *Azadirachta indica*[260] |
| **218** | limbocidin | $R_1 = R_2$ = OH | *A. indica*[260] |
| **219** | TS1 | $R_1$ = OH; $R_2 = H$; 9$\beta$,11$\beta$-epoxy; 14$\beta$,15$\beta$-epoxy | *Trichilia rubescens*[261] |
| **220** | TS2 | $R_1$ = OCOC($CH_3$)=$CH_2$; $R_2 = H$; 9$\beta$,11$\beta$-epoxy; 14$\beta$,15$\beta$-epoxy | *T. rubescens*[261] |
| **221** | TS3 | $R_1 = R_2 = H$; 9$\beta$,11$\beta$-epoxy; 14$\beta$,15$\beta$-epoxy; $\Delta^{6,7}$ | *T. rubescens*[261] |
| **222** | ceramicine B | $R_1 = R_2 = H$; $\Delta^{14,15}$ | *Chisocheton cermicus*[262] |
| **223** | ceramicine C | $R_1 = H$; $R_2$ = methylacryl; $\Delta^{14,15}$ | *C. cermicus*[262] |
| **224** | ceramicine D | $R_1 = R_2 = H$ | *C. cermicus*[262] |
| **225** | trichirubine B | $R_1$ = OBz; $R_2$ = OH; 9$\beta$,11$\beta$-epoxy | *Trichilia rubescens*[263] |
| **226** | trichirubine A | | *T. rubescens*[263] |
| **227** | malleastrone A | $R_1 = H$; $R_2 = CH_3$; $\Delta^{1,2}$ | a *Malleastrum* sp.[242] |
| **228** | malleastrone B | $R_1 = H$; $R_2 = CH_2CH_3$; $\Delta^{1,2}$ | a *Malleastrum* sp.[242] |
| **229** | malleastrone C | $R_1$ = OH; $R_2 = CH_3$ | a *Malleastrum* sp.[242] |


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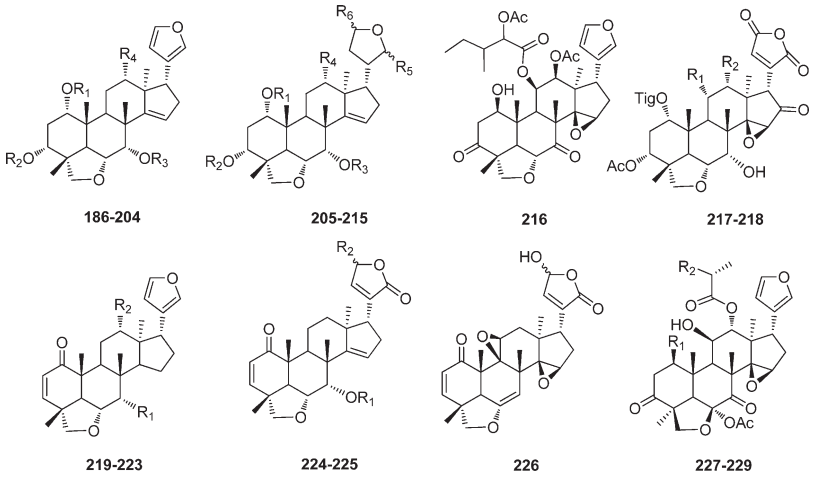


**Figure 7.** Structures of vilasinin-class limonoids **186**−**229**.

**Table 6. Other Structures and Sources of Rings Intact Limonoids 230−248**

| no. | compounds | substitution groups | sources |
|---|---|---|---|
| **230** | neeflone | | *Azadirachta indica*[264] |
| **231** | | | *Cedrela odorata*[265] |
| **232** | 11$\beta$-acetoxy-7$\alpha$-acetyl-12$\alpha$-hydroxy-1,2-dihydroneotrichilenone | $R_1$ = Ac, $R_2$ = $\beta$-OAc; $R_3$ = OH | *Turraea floribunda*[143] |
| **233** | 12$\alpha$-acetoxy-7-acetyl-1,2-dihydroneotrichilenone | $R_1$ = Ac, $R_2$ = H; $R_3$ = OAc | *T. floribunda*[143] |
| **234** | 12$\alpha$-acetoxy-1,2-dihydroneotrichilenone | $R_1$ = $R_2$ = H; $R_3$ = OAc | *T. floribunda*[143] |
| **235** | turranolide | R = H | *T. robusta*[87] |
| **236** | lenticellatumin | R = OH | *Dysoxylum lenticellatum*[266] |
| **237** | 1,2-dihydroazadirone | $R_1$ = O; $R_2$ = $R_4$ = H; $R_3$ = Ac | *Turraea robusta*[87] |
| **238** | 12$\alpha$-acetoxy-1,2-dihydroazadirone | $R_1$ = O; $R_2$ = H; $R_3$ = Ac; $R_4$ = OAc | *T. parvifolia*[243] |
| **239** | 1,2-dihydro-6$\alpha$-acetoxyazadirone | $R_1$ = O; $R_2$ = OAc; $R_3$ = Ac; $R_4$ = H | *Chisocheton paniculatus*[267] |
| **240** | mzikonone | $R_1$ = O; $R_2$ = $R_3$ = H; $R_4$ = OAc | *Turraea robusta*;[87,268] *T. parvifolia*;[243] *T. cornucopia*[90] |
| **241** | mzikonol | $R_1$ = OH; $R_2$ = $R_3$ = H; $R_4$ = OAc | *T. robusta*[87] |
| **242** | meldenindiol | $R_1$ = O; $R_2$ = OH; $R_3$ = $R_4$ = H | *Azadirachta indica*[269] |
| **243** | meldenin | $R_1$ = Ac; $R_2$ = H | *A. indica*;[134,270,271] *Melia azedarach*[176] |
| **244** | isomeldenin | $R_1$ = H; $R_2$ = Ac | *Azadirachta indica*[62,92,270,271] |
| **245** | meliatetraolenone | | *A. indica*[272] |
| **246** | 1$\beta$,2$\beta$;21,23-diepoxy-7$\alpha$-hydroxy-24,25,26,27-tetranor-apotirucalla-14,20,22-trien-3-one | | *Trichilia havanensis*[273] |
| **247** | 1$\beta$,2$\beta$-diepoxyazadiradione | | *Azadirachta indica*[68] |
| **248** | 1$\alpha$,2$\alpha$-epoxy-17$\beta$-hydroxyazadiradione | | *A. indica*[115] |

by X-ray analysis of prieurianin 2′-*p*-bromobenzenesulphonate,[481,482] and the stereochemical ambiguities remaining for C-1, C-4 and C-14 were resolved.[481] Just as for **458**, spectral measurements of epoxyprieurianin (**464**),[454] dysoxylumins A-C (**465**−**467**),[483] and rohitukas 1, 2, 4, and 7−9 (**490**, **491**, **459**, **483**, **469**, and **484**)[484] were performed at 60 °C to obviate the difficulties caused by restricted rotation around the C-9/10 bond at lower temperatures. The isolation of these compounds was impeded, just as was previously experienced for rohitukas and prieurianin, by difficulties such as a mild alkaline hydrolysis causing opening of the ring A-lactone, followed by a variety of further changes, which produced a complex mixture of products difficult to resolve.[484]

Some complicated prieurianin-class structures were revised with the development of new structure determination techniques. The $^{13}$C NMR data of Tr-B (**479**) were analyzed[192] and subsequently reassigned for the formate, acetyl, methylene groups and for two quaternary carbons.[485] X-ray crystallography showed that rohituka 7 (**483**) bore the 15$\beta$-substituent,[486] as opposed to the original assignment.[484] The assigned structure of dregeanin with ring A as a seven-membered lactone[487] was revised by comparison of the spectroscopy data with those of prieurianin derivatives to contain instead an eight-membered lactone ring as is shown in **488**.[488] Cipadessalide (**489**), the first prieurianin-class compound isolated from *Cipadessa* plants, was the first example of a limonoid with an oxygen bridge between C-1 and C-30. Moreover, a biosynthetic relationship between **489** and mombasol (**471**) was proposed.[282] MacLachlan et al. revised the seven membered 3(4)-lactone ring in rohitukas 1, 2 (**490**, **491**)[484] and D-5 (**493**)[489] as five membered 7(4)-lactone rings and expressed doubt as to whether they were true natural products.[490]


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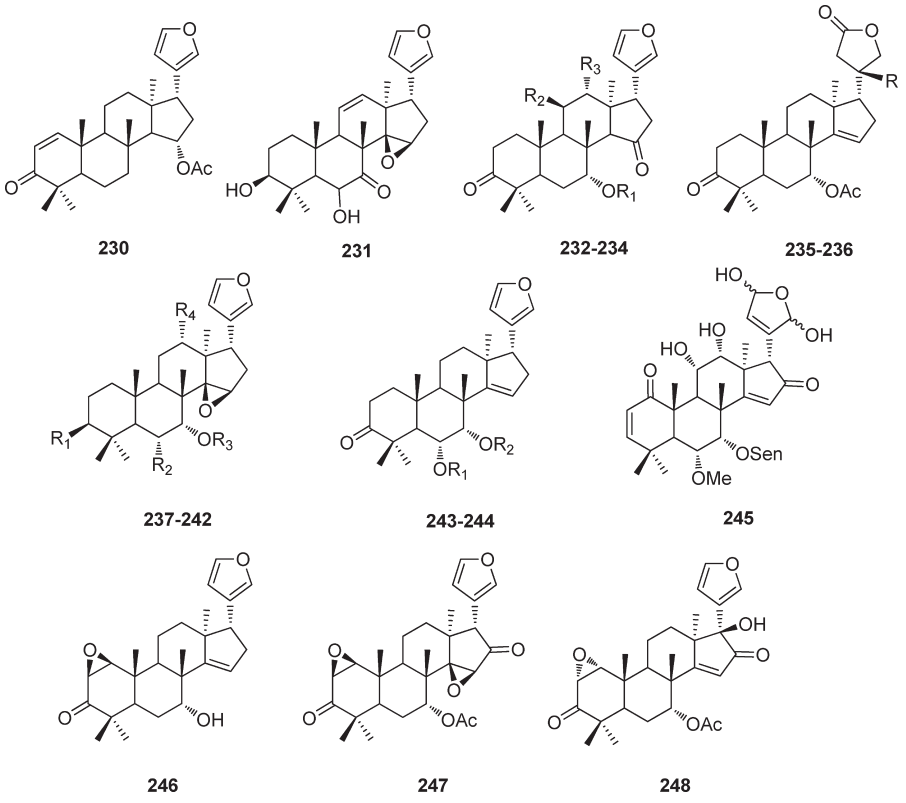


**Figure 8.** Other structures of rings intact limonoids **230**−**248**.

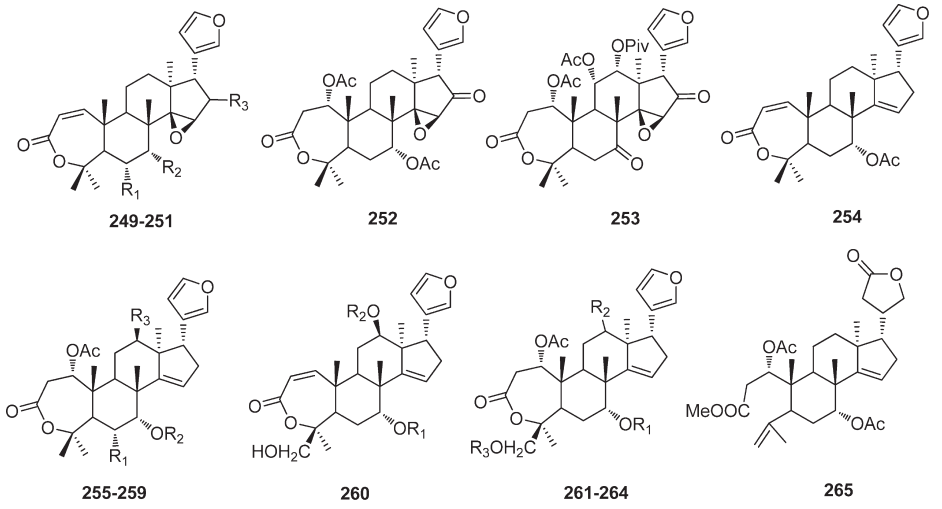


**Figure 9.** Structures of ring A-seco limonoids **249**−**265**.

*2.2.2.1.2. Others.* All of **494**−**497** contain 3-oxo-$\Delta^{1,2}$ system and 3(4)-lactone groups, with toonaciliatin E and H (**494** and **495**) having an 8$\alpha$,14$\alpha$-epoxide, while toonaciliatin I (**496**) and surenolactone (**497**) have a 14$\beta$,15$\beta$-epoxide bridge. The co-occurrence of **494**−**496** in *Toona ciliata* suggested that **494** and **495** might derive from **496** through an acid-catalyzed intramolecular rearrangement followed by an oxidation and acetylation of **495** to produce **494**.[290] Zhang et al. demonstrated that the $^{13}$C NMR data previously reported for rohituka 3 (**507**)[192] agreed instead with the structure for rohituka 15 (**516**).[485] For rohituka 14 (**510**) a complete reassignment of the previously reported assignment[275] of the ester carbons (C-1′, C-3) and quaternary carbons (C-10, C-14) was presented.[485] Limonoids **514**−**517** are characterized by the 1$\alpha$,14$\beta$-ether linkage, $\Delta^{8,30}$ system and 15-oxo groups. Although previously reported differently,[503] the C-1 substituent in polystachin (**517**) has been reassigned as $\alpha$.[275] Rubrins A-G (**518**−**524**), isolated from *Trichilia rubra* in 1994, possessed the C-3/29 cyclic hemi *ortho* ester structure, which alleviated the steric congestion of groups in the vicinity of the C-9, C-10 bond and thus eliminated the broadening of their $^{1}$H NMR peaks.[504] Among them, the structures of rubrins C and E (**520** and **522**) were identical to


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**Table 7. Structures and Sources of Ring A-seco Limonoids 249−265**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **249** | evodulone | $R_1$ = H, $R_2$ = OAc; $R_3$ = O | *Carapa procera*;[277] *C. grandiflora*[276] |
| **250** | surenin | $R_1$ = $R_2$ = OAc, $R_3$ = H | *Toona sureni*[278] |
| **251** | surenone | $R_1$ = OH; $R_2$ = O, $R_3$ = H | *T. sureni*[278] |
| **252** | carapolide H | | *Carapa grandiflora*[276] |
| **253** | amotsangin G | | *Amoora tsangii*[279] |
| **254** | proceranone | | *Carapa procera*[280] |
| **255** | rubralin C | $R_1$ = H; $R_2$ = Tig, $R_3$ = OAc | *Trichilia rubra*[281] |
| **256** | dregeana 3 | $R_1$ = H; $R_2$ = Ac, $R_3$ = O-(2-acetoxy-3-methylpentanoxy) | *T. dregeana*[274] |
| **257** | carapolide I (kihadalactone A) | $R_1$ = $R_3$ = H; $R_2$ = Ac | *Carapa grandiflora*;[276] *Aphanamixis ploystacha*[275] |
| **258** | delevoyin B | $R_1$ = OAc; $R_2$ = Ac; $R_3$ = H | *Entandrophragma delevoyi*[75] |
| **259** | quivisianthone | $R_1$ = OH; $R_2$ = Ang; $R_3$ = H | *Quivisia papinae*[99] |
| **260** | dregeana 5 | $R_1$ = iVal(OH); $R_2$ = 2-acetoxypivaloyl | *Trichilia dregeana*[274] |
| **261** | dregeana 4 | $R_1$ = iBu(OH); $R_2$ = $\beta$-O-(2-acetoxypivaloyl); $R_3$= H | *T. dregeana*;[274] *T. emetica*[192] |
| **262** | rubralin A | $R_1$ = $R_3$ = 2-hydroxy-3-methylpentanoyl; $R_2$ = $\alpha$-OAc | *T. rubra*[281] |
| **263** | rubralin B | $R_1$ = iVal(OH); $R_2$ = $\alpha$-OAc; $R_3$ = 2-hydroxy-3-methylpentanoyl | *T. rubra*[281] |
| **264** | rubralin D | $R_1$ = iVal(OH); $R_2$ = $\alpha$-OAc; $R_3$ = 2,3-dihydroxy-3-methylvaleroyl | *Cipadessa baccifera*[282] |
| **265** | nymania 2 | | *Nymania capensis*[283] |

**Table 8. Structures and Sources of Ring B-seco Limonoids 266−291**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **266** | turraflorin A | R = Ac | *Turraea floribunda*[284,285] |
| **267** | turraflorin B | R = H | *T. floribunda*[284,285] |
| **268** | toonacilin | $R_1$ = H; $R_2$ = $\alpha$-OAc; $R_3$ = OAc | *Toona ciliata*[140,161,286,288,289] |
| **269** | 6-acetoxytoonacilin | $R_1$ = $R_3$ = OAc; $R_2$ = $\alpha$-OAc | *T. ciliata*[286,288,289] |
| **270** | 12-deacetoxytoonacilin | $R_1$ = $R_3$ = H; $R_2$ = $\alpha$-OAc | *T. ciliata*[140] |
| **271** | 11-*epi*-toonacilin | $R_1$ = H; $R_2$ = $\beta$-OAc; $R_3$ = OAc | *Turraea floribunda*[143] |
| **272** | turraflorin D | $R_1$ = Ac; $R_2$ = O; $R_3$ = OH | *T. floribunda*[285] |
| **273** | turraflorin E | $R_1$ = Ac; $R_2$ = OH; $R_3$ = O | *T. floribunda*;[285] *T. pubescens*[126] |
| **274** | turraflorin F | $R_1$ = $R_3$ = H; $R_2$ = O | *T. floribunda*[285] |
| **275** | turrapubesin D | $R_1$ = $\beta$-OAc; $R_2$ = $COCH_2Ph$; $R_3$ = O; $R_4$ = OH | *T. pubescens*[126] |
| **276** | turrapubesin E | $R_1$ = $\beta$-OAc; $R_2$ = $COCH_2Ph$; $R_3$ = OH; $R_4$ = O | *T. pubescens*[126] |
| **277** | turrapubesin F | $R_1$ = $\beta$-OAc; $R_2$ = iBu; $R_3$ = OH; $R_4$ = O | *T. pubescens*[126] |
| **278** | turrapubesin G | $R_1$ = $\beta$-OAc; $R_2$ = Piv; $R_3$ = OH; $R_4$ = O | *T. pubescens*[126] |
| **279** | 21-(*R*,*S*)-hydroxytoonacilide | $R_1$ = $\alpha$-OAc; $R_2$ = Ac; $R_3$ = OH; $R_4$ = O | *Toona ciliata*[288,289] |
| **280** | 23-(*R*,*S*)-hydroxytoonacilide | $R_1$ = $\alpha$-OAc; $R_2$ = Ac; $R_3$ = O; $R_4$ = OH | *T. ciliata*[154,288,289] |
| **281** | 11-*epi*-21-hydroxytoonacilide | $R_1$ = $\beta$-OAc; $R_2$ = Ac; $R_3$ = OH; $R_4$ = O | *Turraea parvifolia*[125] |
| **282** | 11-*epi*-23-hydroxytoonacilide | $R_1$ = $\beta$-OAc; $R_2$ = Ac; $R_3$ = O; $R_4$ = OH | *T. parvifolia*[125] |
| **283** | turraflorin C | $R_1$ = Ac; $R_2$ = OAc | *T. floribunda*[284] |
| **284** | turraflorin H | $R_1$ = $R_2$ = H | *T. floribunda*[285] |
| **285** | turraflorin I | | *T. floribunda*[285] |
| **286** | turraflorin G | | *T. floribunda*[285] |
| **287** | toonaciliatin B | | *Toona ciliata*[290] |
| **288** | toonaciliatin C | | *T. ciliata*[290,291] |
| **289** | toonafolin | | *T. ciliata*[292] |
| **290** | turrapubesin A | | *Turraea pubescens*[287] |
| **291** | turrapubesin C | | *T. pubescens*[126] |

those of hispidin A isolated from *T. hispida* in 1981[501] and nymania 1 isolated from *T. emetica* in 1998,[192] respectively. Unlike the rohitukas 6, 3, 5, 13, 14 (**505**, **507**−**510**), **511**, dysoxylumolide A (**512**), and dysoxylumic acid (**506**), toonaciliatin D (**513**) was deduced on the basis of its NOESY spectrum to have 1$\beta$-substituent.[290]

*2.2.2.2. Rings A,D-seco Group.* Rings A,D-seco limonoids found in Meliaceae, most of which belong to the obacunol-class, were found only in the *Toona*, *Cedrela*, and *Dysoxylum* genera (Table 18). Except for dysoxylumolide C (**554**) and odoralide (**555**), they were characterized by a 3(4)-lactone with an epoxidized $\delta$-lactonic D ring.[510] The biosynthesis of the


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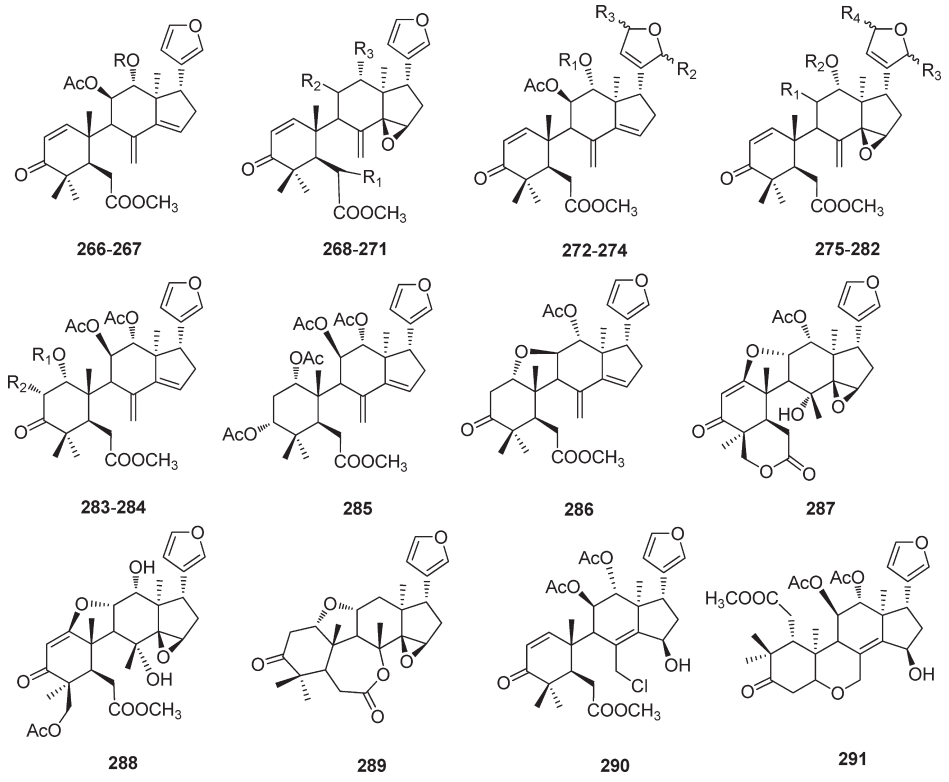


**Figure 10.** Structures of ring B-seco limonoids **266**−**291**.

limonoids with an epoxy-lactone ring D proceeded through a 14,15-unsaturated meliacane, which was successively oxidized to a 14(15)-en-16-one, to a 14,15-epoxy-16-one, and finally to the lactone.[77] The structures of the three limonoids 11-oxo-7$\alpha$-obacunol (**532**), 11-oxo-7$\alpha$-obacunyl acetate (**533**), and 11-oxocneorin G (**548**), all of which contain the rare 11-ketone functionality, were confirmed by X-ray analysis.[511] Of the seven kihadanin A and B derivatives obtained from *Trichilia elegans* ssp. *elegans*, the structure of 7-deoxo-7$\alpha$-acetoxykihadanin A (**539**) was confirmed by X-ray crystallographic analysis.[512] 7-Deoxo-7$\alpha$-hydroxykihadanin A (**538**) and 7-deoxo-7$\beta$-hydroxykihadanins A and B (**540** and **544**) were isolated after acetylation procedures as their mono- and/or diacetate derivatives.[512] Moreover, limonoids **540** and **544**, together with 7-deoxo-7$\beta$-acetoxykihadanins A and B (**541** and **545**), were the first reported natural occurrence of C-7$\beta$-substituted limonoids without any oxygenated function at C-6.[512] Ng et al. reported the crystal structure of 7$\alpha$-acetoxydihydronomilin (**546**)[513] and subsequently pointed out that it originated from *Xylocarpus granatum* rather than *Uncaria gambier*.[514]

*2.2.2.3. Rings B,D-seco Group. 2.2.2.3.1. Andirobin-Class.* Andirobin-class limonoids are characterized as the cleavages of C-7/8 and C-16/17 and the formation of $\Delta^{8,30}$ exocyclic double bond and $\delta$-lactonic D ring. The chemical correlations of gedunin (**416**) with **556** and with methyl angolensate (**568**) supported the structures previously proposed for **556** and **568**.[523] Methyl angolensate (**568**) was distributed widely, especially in the genus *Khaya* (Table 19). Its structure was proposed on the basis of chemical and spectroscopic evidence[524−526] and confirmed by X-ray crystallographic analysis.[527] The partial synthesis of **568** from 7-deacetoxy-7-oxokhivorin (**441**) has proved that the configuration of the etheroxygen attached to C-1 was $\alpha$.[528,529] Compound **568** might arise by a Bayer−Villiger type peroxide oxidation of a 7-oxo compound or an earlier intermediate in the biosynthesis.[530] The unusual chemical shift of the acetate methyl group ($\delta_H$ 1.55) in methyl 6,12$\alpha$-diacetoxyangolensate (**571**) was caused by the shielding effect of the furan ring.[531] Both sandoricin (**573**) and its 6-hydroxy derivative **574** were determined by NMR, mass spectra, and X-ray analysis.[532] It is worth noting that the two compounds **578**[53] and **1038**[54] were reported separately by two research groups in 2007, and both compounds were named as cipadesin D, but different skeletons were ascribed to them.

*2.2.2.3.2. Others.* Secomahoganin (**596**), in which ring C had a skew-boat conformation, was formed by oxidative cleavage of the C-6/7 bond in the normal tetranortriterpene nucleus and was an interesting compound from a biosynthetic viewpoint.[71] Cedrelanolide I (**599**), for which the structure was established by spectroscopic methods and X-ray diffraction analysis, might be biosynthetically derived from a methyl angolensate type of precursor.[570] However, Cespedes et al. cited it as cedrelanolide.[571] The structure of swiemahogin A (**600**), confirmed by single-crystal X-ray diffraction, incorporated a rare five-membered $\gamma$-lactone fused to the C-ring at C-8 and C-14, where the six-membered $\delta$-lactone in the D-ring was destroyed.[572]

**2.2.3. Demolition of Three Rings (Rings A,B,D-seco Group).** Methyl ivorensate (**601**), the first A,B,D-seco limonoid obtained from plants of family Meliaceae, was structurally related to methyl angolensate (**568**) since treatment of **568** with perbenzoic acid produced a moderate yield of the corresponding lactone **601**.[576] A detailed analysis of the NMR data of **601** was presented but some assignments were interchanged.[446]

## 2.3. Rearranged Limonoids

**2.3.1. 1,*n*-Linkage Group.** It is interesting that the carapolide-class compounds **607**−**613** were found only in genus


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**Table 9. Structures and Sources of Azadirachtin/Meliacarpin Limonoids 292−315**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **292** | azadirachtin (azadirachtin A) | $R_1$ = Tig; $R_2$ = Ac; $R_3$ = OH | *Melia azedarach*;[314] *Azadirachta indica*;[51,293,295,300,315−321] *A. excelsa*[322] |
| **293** | 3-deacetyl-11-desoxyazadirachtin | $R_1$ = Tig; $R_2$ = $R_3$ = H | *A. indica*[257] |
| **294** | 3-deacetyl-3-cinnamoylazadirachtin | $R_1$ = Tig; $R_2$ = Cin; $R_3$ = OH | *A. indica*[300] |
| **295** | azadirachtol | $R_1$ = $R_2$ = $R_3$ = H | *A. indica*;[323] *A. excelsa*[324] |
| **296** | 3-tigloylazadirachtol (azadirachtin B, deacetylazadirachtinol) | $R_1$ = $R_3$ = H; $R_2$ = Tig | *A. indica*;[70,300,309,316,317,319,325,326] *A. excelsa*[324] |
| **297** | 1-tigloyl-3-acetylazadirachtol | $R_1$ = Tig; $R_2$ = Ac; $R_3$ = H | *A. excelsa*;[322] *A. siamensis*[327] |
| **298** | 3$\alpha$-acetoxy-1$\alpha$-hydroxyazadirachtol | $R_1$ = $R_3$ = H; $R_2$ = Ac | *A. indica*[328] |
| **299** | azadirachtin E | $R_1$ = H; $R_2$ = Ac; $R_3$ = OH | *A. indica*[35] |
| **300** | azadirachtin F (11-hydroxyazadirachtin B) | $R_1$ = H; $R_2$ = Tig; $R_3$ = OH | *A. indica*[130,310] |
| **301** | azadirachtin O | $R_1$ = iVal; $R_2$ = Ac; $R_3$ = H | *A. excelsa*[324] |
| **302** | azadirachtin Q | $R_1$ = $R_2$ = Ac; $R_3$ = H | *A. excelsa*[324] |
| **303** | 22,23-dihydro-23$\beta$-methoxyazadirachtin (vepaol) | R = $\beta$-$OCH_3$ | *A. indica*[70,298,300,325] |
| **304** | isovepaol(23-*epi*-vepaol) | R = $\alpha$-$OCH_3$ | *A. indica*[70,325] |
| **305** | azadirachtin G | | *A. indica*[35] |
| **306** | 13,14-desepoxyazadirachtin A | | *A. indica*[329] |
| **307** | azadirachtin K | | *A. indica*[102] |
| **308** | 1-cinnamoylmelianolone | | *Melia azedarach*[330−332] |
| **309** | azadirachtin D (1-tigloyl-3-acetyl-11-hydroxy-4$\beta$-methylmeliacarpin) | $R_1$ = OH; $R_2$ = $COOCH_3$ | *Azadirachta indica*[311,317,319,333,334] |
| **310** | 11-*epi*-azadirachtin D | $R_1$ = $COOCH_3$; $R_2$ = OH | *A. indica*[70,335] |
| **311** | 1,3,-diacetyl-11,19-deoxa-11-oxomeliacarpin | | *A. indica*[313] |
| **312** | 1-cinnamoyl-3,11-dihydroxymeliacarpin | R = H | *Melia azedarach*[331,336,337] |
| **313** | 1,3-dicinnamoyl-11-hydroxymeliacarpin | R = Cin | *M. azedarach*[338] |
| **314** | 1-cinnamoyl-3-acetyl-11-hydroxymeliacarpin | R = Ac | *M. azedarach*[338] |
| **315** | 1-cinnamoyl-3-methacrylyl-11-hydroxymeliacarpin | R = methacrylyl | *M. azedarach*[338] |

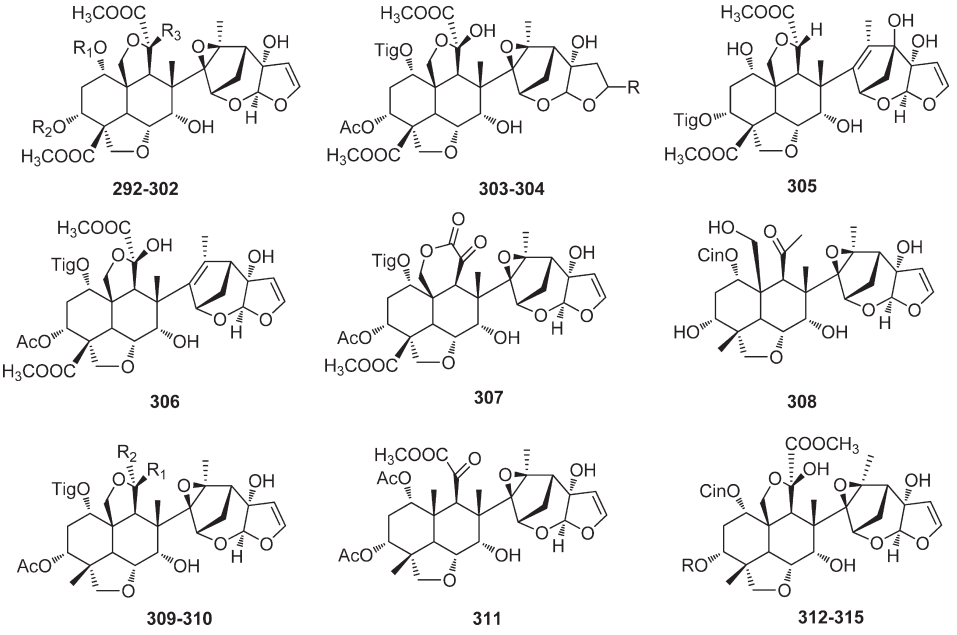


**Figure 11.** Structures of azadirachtin/meliacarpin-class limonoids **292**−**315**.

*carapa*, the dukunolide-class limonoids **614**−**620** originated in genus *Lansium*, the neotecleanin-class compounds **621**−**625** came from genus *Turraea* (Table 22). A possible biosynthetic pathway leading to the carapolides from carapolide G (**613**) as


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**Table 10. Structures and Sources of Azadiracthinin/Meliacarpinin Limonoids 316−331**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **316** | 3-tigloylazadiracthinin | $R_1 = R_3 = H$; $R_2$ = Tig | *Azadirachta indica*[325] |
| **317** | 1-tigloyl-3-acetylazadirachtinin | $R_1$ = Tig; $R_2$ = Ac; $R_3 = H$ | *A. indica*[130,325] |
| **318** | 1-tigloyl-3-acetyl-11-methoxyazadirachtinin | $R_1$ = Tig; $R_2$ = Ac; $R_3 = CH_3$ | *A. indica*[70,300] |
| **319** | azadirachtin N | | *A. indica*[343] |
| **320** | 3,20-diacetyl-11-methoxymeliacarpinin | $R_1 = H$; $R_2 = R_3$ = Ac | *Melia azedarach*[344] |
| **321** | 1-tigloyl-3,20-diacetyl-11-methoxymeliacarpinin | $R_1$ = OTig; $R_2 = R_3$ = Ac | *M. azedarach*;[345] *M. toosendan*[133] |
| **322** | 3-tigloyl-1,20-diacetyl-11-methoxymeliacarpinin | $R_1$ = OAc; $R_2$ = Tig; $R_3$ = Ac | *M. azedarach*;[345] *M. toosendan*[133] |
| **323** | 1-cinnamoyl-3-hydroxy-11-methoxymeliacarpinin | $R_1$ = OCin; $R_2 = R_3 = H$ | *M. azedarach*[345] |
| **324** | 1-deoxy-3-methacrylyl-11-methoxymeliacarpinin | $R_1 = R_3 = H$; $R_2$ = methacrylyl | *M. azedarach*[345] |
| **325** | 1-(2-methylpropanoyl)-3-acetyl-11-methoxymeliacarpinin | $R_1$ = OiBu; $R_2$ = Ac; $R_3 = H$ | *M. azedarach*[346] |
| **326** | 1-methacrylyl-3-acetyl-11-methoxymeliacrpinin | $R_1$ = methacrylate; $R_2$ = Ac; $R_3 = H$ | *M. azedarach*[346] |
| **327** | 1-cinnamoyl-3-acetyl-11-methoxymeliacarpinin (meliacarpinin A) | $R_1$ = OCin; $R_2$ = Ac; $R_3 = H$ | *M. azedarach*;[206,209,339,345] *M. toosendan*[85,133,214] |
| **328** | 1-deoxy-3-tigloyl-11-methoxymeliacarpinin (meliacarpinin B) | $R_1 = R_3 = H$; $R_2$ = Tig | *M. azedarach*[209,219,340,341] |
| **329** | 1-acetyl-3-tigloyl-11-methoxymeliacarpinin (meliacarpinin C) | $R_1$ = OAc; $R_2$ = Tig; $R_3 = H$ | *M. azedarach*;[205,219,341] *M. toosendan*[85,214] |
| **330** | 1-tigloyl-3-acetyl-11-methoxymeliacarpinin (meliacarpinin D) | $R_1$ = OTig; $R_2$ = Ac; $R_3 = H$ | *M. azedarach*;[205,219,341,346] *M. toosendan*[85,214] |
| **331** | 3-tigloyl-11-methoxymeliacarpinin (meliacarpinin E) | $R_1$ = OH; $R_2$ = Tig; $R_3 = H$ | *M. azedarach*[206,342] |

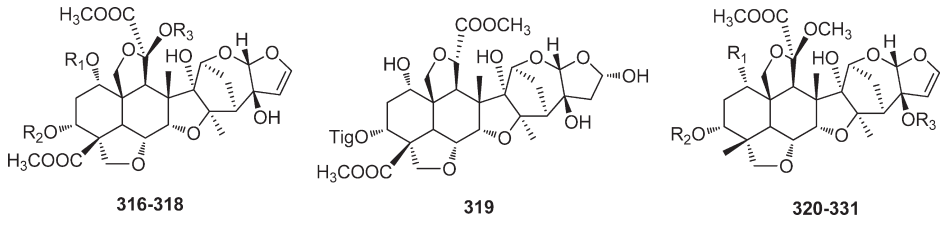


**Figure 12.** Structures of azadirachtinin/meliacarpinin-class limonoids **316**−**331**.

the progenitor was proposed.[276] The structures of dukunolides A−C (**614**−**616**) including their absolute configurations were established by X-ray analysis and chemical correlation.[577] The biosynthesis of **614** was recognized by considering the intermediary mexicanolide or its analogs.[578] Neotecleanins **621**−**625**, the first natural occurrence of limonoids with a five-membered-ring A-seco structure, might serve as intermediates in the pathway to the formation of tecleanin and related compounds.[579]

**2.3.2. 2,30-linkage Group.** *2.3.2.1. Mexicanolide-Class.* Mexicanolide (**626**), first isolated as the main constituent of *Carapa procera*,[167] was proved to be the "substance B" from *Cedrela odorata* by analysis of its spectral data.[459,585] Its structure, including the absolute configuration, was assigned on the basis of its NMR spectral data,[586] chemical reaction,[587] and CD data,[588] and was confirmed by its crystallographic analysis.[589] The structure of **632** was assigned as 6-deoxyswietenolide early in 1968,[533] but Sondengam et al. named it as proceranolide when they isolated it in 1980.[590] As for 2′*R*- and 2′*S*-methylbutanoylproceranolide (**633** and **634**), the considerable steric interaction between the 2-methylbutanoyl group and the limonoid core made one stable conformation dominant in solution. Furthermore, a general rule for the determination of the absolute configurations of 2*R*- and 2*S*-methylbutanoyl at C-3 of a limonoid in a mixture was proposed based on the $^1$H NMR conformational analysis.[591] The structure of swietenolide (**638**) was elucidated on the basis of evidence from chemical properties[592−594] and spectroscopic data.[594] The crystal structure analysis of diacetylswietenolide (**647**) was provided by Goh et al.[595] One of the double bond of fissinolide (**648**) was first assigned as C-8/14 in 1966[596] and then was revised to be angustinolide, in which the double bond was assigned as C-8/9,[597,598] to better fit its origin, but finally the original structure based on the spectroscopic and chemical properties was preferred.[599,600] Subsequently, the $^{13}$C NMR signals of fissinolide were reassigned in 1998,[601] and the structures of the "grandifoliolin" isolated in 1967[602] and the "3$\beta$-acetoxymexicanolide" obtained in 1999 were shown to be **648**.[603] Gan et al. mistakenly cited khayasin (**652**) as 3$\beta$-isobutyryloxymexicanolide.[591] In terms of biosynthetic pathway, xyloccensin N (**669**) was a possible intermediate on the route to xyloccensin M (**771**), and they were once isolated from the same plant simultaneously as a pair of isomers of mexicanolides.[604,605] The structure of swietenine (**677**) was elucidated on the basis of chemical[606,607] and spectroscopic evidence,[608,609] and confirmed by X-ray analysis of the *p*-iodobenzoate of detigloylswietenine[610,611] and swietenine itself.[612] The structure of the 3$\beta$-hydroxymexicanolide ($\Delta^{8,30}$ instead of $\Delta^{8,14}$) reported by Govindachari et al. in 1997[468] was in fact identical with 6-deoxydestigloylsweietenine (**684**), which was reported in 1967.[464] 2-Hydroxy-6-deoxyswietenine (**690**) was obtained early in 1988,[613] and was mistakenly reported as methyl 3$\beta$-tigloyloxy-2-hydroxy-1-oxo-meliac-8(30)-enate ten years later.[614] The structure of febrigugin (**694**), first obtained from *Soymida febrifuga*[615] and identical with 6-deoxyswietenine from *Swietenia mahagoni*,[616] was incorrectly assigned,[290] and its spectroscopic data were revised.[617] The absolute configurations of **694** and cipadesin (**703**) were determined by spectroscopic and X-ray methods.[618] The mixture of methyl 2-hydroxy-3$\beta$-isobutyroxymeliac-8(30)-enate (**699**) and its 3$\beta$-tiglate derivative,


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**Table 11. Structures and Sources of Salannin-Class Limonoids 332−352**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **332** | salannin | $R_1$ = Tig; $R_2$ = OAc; $R_3$ = $CH_3$ | *Azadirachta indica*;[102,104,106,107,295,316,317,357] *Melia dubia*;[358] *M. azedarach*;[142,176,219,342,359−361] *M. volkensii*;[362] *M. toosendan*[84,239,363] |
| **333** | 3-deacetylsalannin | $R_1$ = Tig; $R_2$ = OH; $R_3$ = $CH_3$ | *M. azedarach*;[342,361,364] *Azadirachta indica*[103,104,245,316,317] |
| **334** | 1-detigloyl-1-isobutylsalannin | $R_1$ = iBu; $R_2$ = OAc; $R_3$ = $CH_3$ | *Melia volkensii*[365] |
| **335** | 2′,3′-dihydrosalannin | $R_1$ = dihydrotigloyl; $R_2$ = OAc; $R_3$ = $CH_3$ | *M. volkensii*[365] |
| **336** | salannol | $R_1$ = iVal; $R_2$ = OH; $R_3$ = $CH_3$ | *Azadirachta indica*[245,366] |
| **337** | salannol acetate | $R_1$ = iVal; $R_2$ = OAc; $R_3$ = $CH_3$ | *A. indica*[366,367] |
| **338** | 2′,3′-dehydrosalannol | $R_1$ = Sen; $R_2$ = OH; $R_3$ = $CH_3$ | *A. indica*[368] |
| **339** | 3-deoxymethylnimbidate | $R_1$ = $R_2$ = H; $R_3$ = $CH_3$ | *A. excelsa*[369] |
| **340** | ohchinin | $R_1$ = Cin; $R_2$ = OH; $R_3$ = $CH_3$ | *Melia azedarach*[370] |
| **341** | ohchinin acetate (ohchinin-3-acetate) | $R_1$ = Cin; $R_2$ = OAc; $R_3$ = $CH_3$ | *M. azedarach*;[364] *M. volkensii*[246] |
| **342** | nimbidic acid | $R_1$ = $R_3$ = H; $R_2$ = OH | *Azadirachta indica*[249,250] |
| **343** | ohchinal | R = Bz | *Melia azedarach*[364] |
| **344** | 1-*O*-tigloyl-1-*O*-debenzoylohchinal | R = Tig | *M. toosendan*[235,371] |
| **345** | nimbolide | R = O; $\Delta^{2,3}$ | *Azadirachta indica*;[102,355,372−376] *A. excelsa*[369] |
| **346** | 28-deoxonimbolide | R = H; $\Delta^{2,3}$ | *A. indica*;[373,374,377] *A. excelsa*;[369] *Owenia cepiodora*[378] |
| **347** | 2,3-dihydronimbolide | R = O | *Azadirachta excelsa*[369] |
| **348** | salannolide (compositolide, isosalanninolide) | $R_1$ = OTig; $R_2$ = OAc; $R_3$ = O; $R_4$ = OH | *A. indica*;[317,325,356] *Melia dubia*[253] |
| **349** | salanninolide | $R_1$ = OTig; $R_2$ = OAc; $R_3$ = OH; $R_4$ = O | *Azadirachta indica*[317,318] |
| **350** | isoazadirolide | $R_1$ = OSen; $R_2$ = $R_3$ = OH; $R_4$ = O | *A. indica*[379] |
| **351** | margosinolide | $R_1$ = H; $R_2$ = $R_3$= O; $R_4$ = OH; $\Delta^{1,2}$ | *A. indica*[380] |
| **352** | isomargosinolide | $R_1$ = H; $R_2$ = $R_4$ = O; $R_3$ = OH; $\Delta^{1,2}$ | *A. indica*[380] |

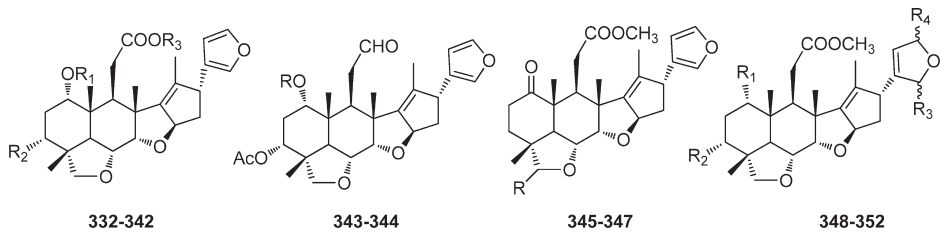


**Figure 13.** Structures of salannin-class limonoids **332**−**352**.

which showed a mass peak at 556 with a less intense companion at 568, was very difficult to separate.[619] The $\Delta^{8,9}$ double bond in angustidienolide[597] was revised to be $\Delta^{8,30}$ on the basis of chemical and spectroscopic evidence,[162,600] and then 2$\alpha$-hydroxyangustidienolide was correspondingly shown as **722**. Unfortunately, methyl 3$\beta$-acetoxy-6-hydroxy-1-oxomeliac-14-enoate (**743**) reported in 1998[601] was wrongly cited as 3$\beta$-acetoxy-3-deoxo-6*R*-hydroxycarapin by Tchimene et al. in 2005.[552] The structures of utilins B (**749**) and C (**755**) from the barks of *Entandrophragma utile*, were assigned on the basis of extensive NMR experiments and then confirmed by single crystal X-ray measurements.[620,621] The discovery of khayalenoids A-D (**751**-**754**) provided examples of limonoids containing the 8-oxa-tricyclo[4.3.2.0$^{2,7}$]undecane motif.[622,623] The mixture having xyloccensins X (**758**) and Y (**759**) with interchangeable substitutions of isobutyl and isopropyl group between the C-3 and C-30 positions was unequivocally assigned through the HMBC spectrum.[624] The spectroscopic properties of xyloccensin F (**768**) assigned by Connolly et al.[625] were revised on the basis of extensive NMR analysis.[626] Although the structure of xyloccensin K (**788**) was elucidated by X-ray crystallography, its NMR data corroborated and later clarified its structure as featuring a tetrahydrofuran subunit with oxygen bridging from C-3 to C-8.[113,627,628] Unfortunately, the structure of **793** was first named as humilinolide A in 1993[629] and was mistakenly documented as methyl 3$\beta$-isobutyryloxy-2,6-dihydroxy-8$\alpha$,30$\alpha$-epoxy-1-oxo-meliacate by Kojima et al. in 1998,[614] however, methyl 3$\beta$-tigloyloxy-2-hydroxy-8$\alpha$,30$\alpha$-epoxy-1-oxo-meliacate (**797**) reported by him in 1998[614] was renamed as 2-hydroxyswietemahonolide in 2004 by another research group.[630] In addition, the same incidents occurred to **805**, which was first named as 8,30-epoxy swietenine acetate in 1983[55] and subsequently reported mistakenly as swietemahonin F in 1990 by Kadota et al.[56] It was noteworthy to point out that two compounds, **815**[617] and **1051**,[631] were isolated in 2005 by two research groups independently, and they were both named as cipadesin A though different skeletons were ascribed to them. Granaxylocarpin B and xylocarpin H, both of which were isolated from *Xylocarpus granatum* by two research groups in 2007, had the same structure as **822**.[632,633] Xylocarponoid A (**825**),


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**Table 12. Structures and Sources of Nimbolinin-Class Limonoids 353−390**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **353** | 1α-tigloyloxy-3α-acetoxyl-7α-hydroxyl-12α-ethoxyl nimbolinin | $R_1$ = Tig; $R_2$ = H; $R_3$ = $OCH_2CH_3$ | *Melia toosedan*[381] |
| **354** | 1α-benzoyloxy-3α-acetoxyl-7α-hydroxyl-12α-ethoxyl nimbolinin | $R_1$ = Bz; $R_2$ = H; $R_3$ = $OCH_2CH_3$ | *M. toosedan*[381] |
| **355** | nimbolinin A | $R_1$ = Ac; $R_2$ = Bz; $R_3$ = OH | *M. toosendan*[85,212] |
| **356** | 1-deacetylnimbolinin A | $R_1$ = H; $R_2$ = Bz; $R_3$ = OH | *M. azedarach*;[382] *M. toosendan*[85,247] |
| **357** | 12-ethoxynimbolinin A | $R_1$ = 2′-methylacryl; $R_2$ = H; $R_3$ = $OCH_2CH_3$ | *M. toosendan*[186] |
| **358** | nimbolinin B | $R_1$ = Ac; $R_2$ = Tig; $R_3$ = OH | *M. toosendan*;[212,247] *M. azedarach*;[342,360,361,382] *Turraea robusta*[87] |
| **359** | 1-deacetylnimbolinin B | $R_1$ = H; $R_2$ = Tig; $R_3$ = OH | *Melia toosendan*[85,247] |
| **360** | 12-*O*-methylnimbolinin B | $R_1$ = H; $R_2$ = Tig; $R_3$ = $OCH_3$ | *M. toosendan*;[186] *Turraea holstii*[143] |
| **361** | 12-ethoxynimbolinin B | $R_1$ = Cin; $R_2$ = H; $R_3$ = $OCH_2CH_3$ | *Melia toosendan*[186] |
| **362** | 12-*O*-ethyl-1-deacetylnimbolinin B | $R_1$ = H; $R_2$ = Tig; $R_3$ = $OCH_2CH_3$ | *M. toosendan*[371] |
| **363** | nimbolinin C | $R_1$ = Cin; $R_2$ = H; $R_3$ = $OCH_3$ | *M. toosendan*[212] |
| **364** | nimbolinin D | $R_1$ = H; $R_2$ = Bz; $R_3$ = $OCH_3$ | *M. toosendan*[212] |
| **365** | nimbolicin | $R_1$ = methylacryl; $R_2$ = Cin; $R_3$ = OH | *Azadirachta indica*[383] |
| **366** | nimbolin B | $R_1$ = Ac; $R_2$ =Cin; $R_3$ = OH | *A. indica*;[240,383] *Melia azedarach*;[240] *M. volkensii*[384] |
| **367** | nimbilin | $R_1$ = Ang; $R_2$ = Cin; $R_3$ = OH | *Azadirachta indica*[385] |
| **368** | heudebolin | $R_1$ = $R_2$ = Ac; $R_3$ = OH | *Trichilia heudelotii*[386] |
| **369** | volkensin | $R_1$ = Tig; $R_2$ = H; $R_3$ = OH | *Melia volensii*[362] |
| **370** | 12-*O*-methylvolkensin | $R_1$ = Tig; $R_2$ = H; $R_3$ = $OCH_3$ | *M. toosendan*[211] |
| **371** | ohchinolide A | $R_1$ = Ac; $R_2$ = Bz; $R_3$ = O | *M. azedarach*[382,387−389] |
| **372** | 1-*O*-deacetylohchinolide A | $R_1$ = H; $R_2$ = Bz; $R_3$ = O | *M. azedarach*[387] |
| **373** | 1-*O*-deacetyl-1-*O*-tigloylohchinolide A | $R_1$ = Tig; $R_2$ = Bz; $R_3$ = O | *M. azedarach*[387] |
| **374** | ohchinolide B | $R_1$ = Ac; $R_2$ = Tig; $R_3$ = O | *M. azedarach*;[382,387,389] *M. toosendan*;[85] *Azadirachta indica*[102] |
| **375** | 1-*O*-deacetylohchinolide B | $R_1$ = H; $R_2$ = Tig; $R_3$ = O | *Melia azedarach*[387] |
| **376** | 1-*O*-deacetyl-1-*O*-tigloylohchinolide B | $R_1$ = $R_2$ = Tig; $R_3$ = O | *M. azedarach*[387] |
| **377** | 1-*O*-deacetyl-1-*O*-benzoylohchinolide B | $R_1$ = Bz; $R_2$ = Tig; $R_3$ = O | *M. azedarach*[387] |
| **378** | chisonimbolinin A | $R_1$ = $R_2$ = Ac; $R_3$ = $OCH_3$ | *Chisocheton paniculatus*[390] |
| **379** | chisonimbolinin B | $R_1$ = H; $R_2$ = Ac; $R_3$ = $OCH_3$ | *C. paniculatus*[390] |
| **380** | chisonimbolinin C | $R_1$ = H; $R_2$ = Tig; $R_3$ = $OCH_3$ | *C. paniculatus*[390] |
| **381** | chisonimbolinin D | $R_1$ = H; $R_2$ = Ac; $R_3$ = OH | *C. paniculatus*[390] |
| **382** | chisonimbolinin E | $R_1$ = H; $R_2$ = Ac; $R_3$ = $OCH_2CH_3$ | *C. paniculatus*[390] |
| **383** | chisonimbolinin F | $R_1$ = $R_3$ = H; $R_2$ = Ac | *C. paniculatus*[390] |
| **384** | chisonimbolinin G | $R_1$ = $R_2$ = Ac; $R_3$ = H | *C. paniculatus*[390] |
| **385** | 12-ethoxynimbolinin C | | *Melia toosendan*[186] |
| **386** | ohchinolide C | R = iBu | *M. toosendan*[84,85] |
| **387** | azecin 2 | R = H | *M. azedarach*[173] |
| **388** | 12-ethoxynimbolinin D | | *M. toosendan*[186] |
| **389** | melianolide | | *M. azedarach*[361] |
| **390** | 17-*epi*-12-dehydroxyheudebolin | | *Turreanthus africanus*[391] |

containing a $C_{28}$ limonoid skeleton, may originate from xylogranatin C (**823**) by an aldol condensation followed by intramolecular hemiacetal formation.[634] In addition, its ring cleavage isomer (xylocarponoid B) was formed gradually in $CDCl_3$ during the NMR experiments and finally reached equilibrium at an A: B ratio of 4:1.[634] Compound **829**, possessing a highly oxidized heptacyclic A,B,D-seco limonoid with an 8α,30α-epoxy ring and 1,29-oxygen bridge, was patented as xylolactone[635] and then was named xyloccensin L[636] in *Tetrahedron Letters* in 2004 by Wu et al. The structure of xylogranatin A (**832**), featuring a 1,9-oxygen bridge, was confimed by X-ray diffraction analysis.[637] The hypothetical biosynthetic route and chemical correlations of **832** and xylogranatin D (**833**) were postulated in 2006,[637] and **833**, the sole limonoid with a C-9/30 linkage, was apparently considered to be an artifact.[638] Unfortunately, the trivial names "xylogranatin A−D" were also proposed for the compounds **737** and **762−764** isolated in 2006.[639] Xylogranatins I-Q (**834-842**) all contained a central furan core, and they were derivated from the key biosynthetic intermediates xylogranatins C and R (**823** and **843**).[638] The possible biosynthetic pathway of grandifotane A (**845**) was postulated, in which an intermediate was formed from a mexicanolide-type limonoid by an enzymatic Baeyer−Villiger oxidation. Then, the intermediate might undergo serials of reactions to keep the required stereochemistry for **845**.[640]


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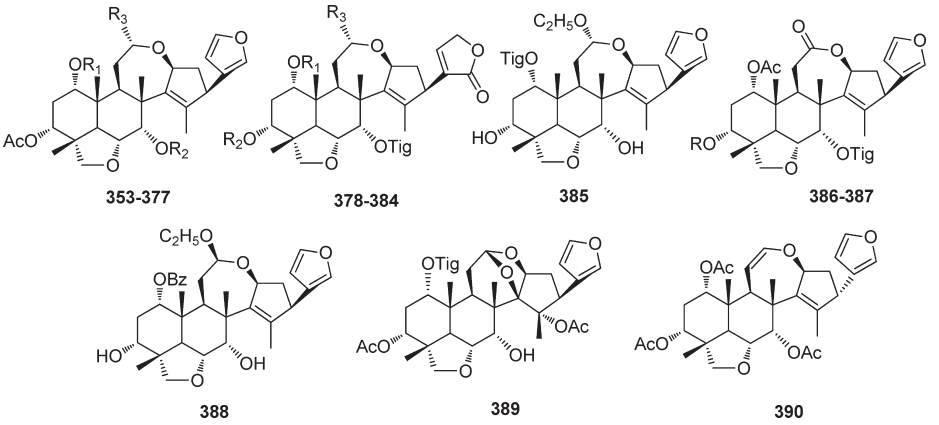


**Figure 14.** Structures of nimbolinin-class limonoids **353**−**390**.

**Table 13. Structures and Sources of Nimbin-Class Limonoids 391−404**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **391** | nimbin | $R_1$ = $COOCH_3$; $R_2$ = Ac | *Azadirachta indica*[59,70,81,102−106,115,136,317,325,357,405−407] |
| **392** | 6-deacetylnimbin | $R_1$ = $COOCH_3$; $R_2$ = H | *A. indica*[70,81,102−104,106,317,325,407,408] |
| **393** | nimbanal | $R_1$ = CHO; $R_2$ = Ac | *A. indica*[367] |
| **394** | 6-deacetylnimbanal | $R_1$ = CHO; $R_2$ = H | *A. indica*[377] |
| **395** | nimbinol | $R_1$ = $CH_2OH$; $R_2$ = Ac | *A. indica*[377] |
| **396** | ohchinolal (salannal) | $R_1$ = Tig; $R_2$ = H | *Melia azedarach*[342,360,370,387] |
| **397** | 1-*O*-detigloyl-1-*O*-benzoylohchinolal | $R_1$ = Bz; $R_2$ = H | *M. azedarach*[387] |
| **398** | 1-*O*-detigloyl-1-*O*-cinnamoylohchinolal | $R_1$ = Cin; $R_2$ = H | *M. azedarach*[387] |
| **399** | 3-*O*-acetylohchinolal | $R_1$ = Tig; $R_2$ = Ac | *M. toosendan*[84,85] |
| **400** | desacetylnimbinolide | $R_1$ = H; $R_2$ = O; $R_3$ = OH | *Azadirachta indica*[408] |
| **401** | isonimbinolide | $R_1$ = Ac; $R_2$ = OH; $R_3$ = O | *A. indica*[409] |
| **402** | desacetylisonimbinolide | $R_1$ = H; $R_2$ = OH; $R_3$ = O | *A. indica*[408] |
| **403** | 4-*epi*-nimbin | | *A. indica*[410] |
| **404** | 7$\alpha$-hydroxy-15$\beta$-hydroxy-7,15-deoxo nimbin | | *A. indica*[411] |

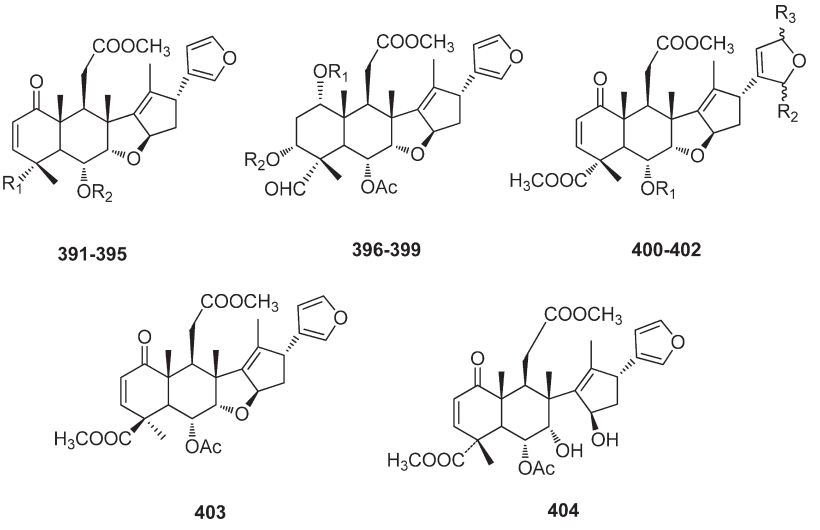


**Figure 15.** Structures of nimbin-class limonoids **391**−**404**.

*2.3.2.2. Phragmalin-Class. 2.3.2.2.1. Phragmalin-ortho Esters.* Phragmalin-class limonoids possessed characteristic rings of A and B tricyclo[3.3.$1^{2,10}$.$1^{1,4}$]decane or tricyclo[4.2.$1^{10,30}$.$1^{1,4}$]-decane, and most of them also bore an ortho ester group. Up to now, four subtypes of phragmalin orthoesters have been reported, which were classified into 1,8,9- (−-**910**), 8,9,11- (**911**−**916**),


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**Table 14. Structures and Sources of Nimbolidin-class 405−415**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **405** | nimbolidin A | $R_1 = R_3 = Ac$; $R_2 = Bz$ | *Melia azedarach*[382] |
| **406** | 15-*O*-deacetyl-15-*O*-methylnimbolidin A | $R_1 = Ac$; $R_2 = Bz$; $R_3 = CH_3$ | *M. azedarach*[226] |
| **407** | nimbolidin B | $R_1 = R_3 = Ac$; $R_2 = Tig$ | *M. azedarach*;[342,361,382] *M. toosendan*[209,363] |
| **408** | 15-*O*-deacetylnimbolidin B | $R_1 = Ac$; $R_2 = Tig$; $R_3 = H$ | *M. azedarach*[226] |
| **409** | 15-*O*-deacetyl-15-*O*-methylnimbolidin B | $R_1 = Ac$; $R_2 = Tig$; $R_3 = CH_3$ | *M. azedarach*[226] |
| **410** | nimbolidin C | $R_1 = R_3 = Ac$; $R_2 = iBu$ | *M. toosendan*[85,363] |
| **411** | nimbolidin D | $R_1 = R_2 = Tig$; $R_3 = Ac$ | *M. toosendan*[85,363] |
| **412** | nimbolidin E | $R_1 = Tig$; $R_2 = iBu$; $R_3 = Ac$ | *M. toosendan*[85,363] |
| **413** | nimbolidin F | $R_1 = Piv$; $R_2 = Tig$; $R_3 = Ac$ | *M. toosendan*[84,85] |
| **414** | walsogyne A | | *Walsura chrysogyne*[412] |
| **415** | 7$\alpha$-acetyl-15$\beta$-methoxy-29- methylene-7,15-deoxonimbolide | | *Azadirachta indica*[411] |

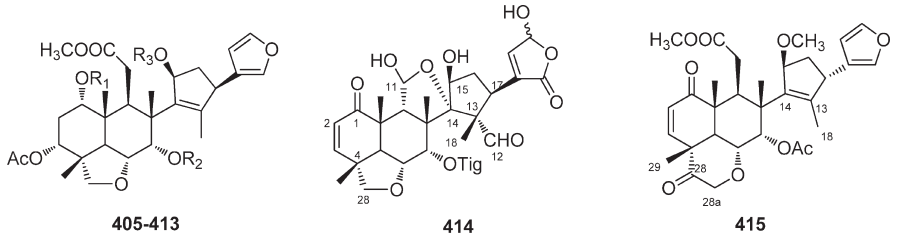


**Figure 16.** Structures of nimbolidin-class **405**−**415**.

8,9,14- (**917**−**930**), and 8,9,30-phragmalin orthoesters (**931**−**962**) according to the position of the *ortho*-acetate group. The structure of phragmalin (**846**) was proposed on the basis of chemical and spectroscopic evidence[689] and then determined by means of an X-ray study of its iodoacetate.[690] The distribution of phragmalins and mexicanolides in the stem barks, fruits, and seeds of the Chinese mangrove plant *Xylocarpus granatum* was discussed, and the conclusion was reached that the high concentration of phragmalin orthoesters in the stem barks of *Xylocarpus* plants might serve as an important chemical defense aginst invasion by pests or microorganisms.[633] A biosynthetic route to **846** which could explain why 1,29-cycloswietenan derivatives were hydroxylated at C-8 and C-9 was presented.[683] The structure of **850** was assigned as xyloccensin E early in 1976,[625] and was obtained and then reported as phragmalin 2,3,30-triacetate in 1992.[162] The substance 'bussein' obtained from *Entandrophraga bussei*,[424,530] was shown to be a mixture of busseins A (**865**) and B (**866**), whose structures were first assigned on the basis of spectroscopic properties and chemical reactions[691] and then were subsequently modified.[692,693] The $^1$H NMR-based conformational analysis on the epimeric compounds swietenitins A and B (**897** and **898**) provided a general approach to determining the absolute configuration of the 2,3-epoxy-2-methylbutyryloxy unit borne at C-3 by a large group of the phragmalin-orthoester limnoids.[456] The structure of pseudrelone B (**903**) from *Pseudocedrela kotschyii*[694] was revised to have C-11/19 instead of C-11/18 ether bridge based on the X-ray analysis of its triacetate.[695] It was suggested on the basis of a plausible proposed biosynthetic origin that chukvelutilides A-F (**904**−**909**), which have a C-16/30 lactone ring, also have a three- or four-carbon enolized acyl substituent at C-15.[696] Chuktabrin B (**910**) had a polycyclic skeleton containing a 4,5,6,7-tetrahydrobenzofuran formed via a cyclization reaction between C-15 and C-21, a $\delta$-lactone furnished between C-16 and C-30, and a biosynthetically extended C2 unit at C-15.[697] The structure of utilin (**920**), possessing the 1,29-cycloswietenan skeleton, was confirmed by X-ray analysis, and its absolute configuration was established by chemical methods.[698] The structure of xyloccensin O (**948**), the first example of an 8,9,30-phragmalin orthoester limonoid, was confirmed by X-ray crystallographic analysis, and a biosynthetic pathway to it from mexicanolide was proposed.[699] The structures of some xyloccensins from *Xylocarpus granatum* were not in accord with the nomenclatures used by different research groups, which led to great confusion. On one hand, the structures of xyloccensins Q (**950**), R (**951**), and V (**955**) obtained by Wu et al.[639,659,700] were identical to xyloccensins R, Q, and T reported by Cui et al.,[701] respectively. On the other hand, both **954**[659,700] and **987**[701] were named xyloccensin U.

*2.3.2.2.2. Polyoxyphragmalins.* Unfortunately, in 2010, two separate groups selected the trivial names moluccensins H−J to apply to six compounds (**963**−**968**) with the same skeleton but different substitutions, which caused each trivial name to correspond to two different structures (Figure 27 and Table 25). In fact, the structures of xylocarpins A (**981**) and D (**984**) obtained from *Xylocarpus granatum* and elucidated in 2007,[633] were the same as granaxylocarpins E and D, respectively, obtained from the same species in the same year.[632] The structure of xyloccensin U, isolated from *X. granatum*,[701] was revised to be **987** by analysis of its HMBC data and analogous comparison.[632,633] From a biosynthetic perspective, atomasins such as atomasins A and B (**974** and **975**) from *Entandrophragma candollei*[719] and 8,9-dihydroxy phragmalins, such as tabulalides A and B (**995** and **996**) from *Chukrasia tabularis*,[706] were the precursor of the phragmalin orthoesters. The extensive spectroscopic analyses including MS, NMR, and single crystal X-ray diffraction experiments suggested that methyl l$\alpha$-acetoxy-6,8$\alpha$,14$\beta$,30$\beta$-tetrahydroxy-3-oxo-[3.3.1$^{10,2}$.1$^{1,4}$]-tricyclomeliac-7-oate (**992**)[720] and methyl l$\alpha$,6,8$\alpha$,14$\beta$,30$\beta$-pentahydroxy-3-oxo-[3.3.1$^{10,2}$.1$^{1,4}$]-tricyclomeliac-7-oate (**991**)[721] were, in fact, khayanolide E (**1007**)


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**Table 15. Structures and Sources of Ring D-seco Limonoids 416−457**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **416** | gedunin | $R_1 = R_3 = H$; $R_2 = OAc$ | *Entandrophragma angolense*;[423] *E. delevoyi*;[424,425] *Xylocarpus granatum*;[49,424,426,427] *X. obovatus*;[428] *Azadirachta indica*;[57−59,70,80−82,103,104,107,115,240,429] *Trichilia trifolia*;[182] *Cabralea eichleriana*;[430] *Melia azedarach*;[240,251] *Cedrela fissilis*;[113,132] *C. odorata*;[98,431,432] *C. sinensis*;[433] *Guarea grandiflora*;[434,435] *Khaya grandifoliola*;[436] *Chisocheton paniculatus*;[117] *Carapa guianensis*[113,437] |
| **417** | 6$\alpha$-hydroxygedunin | $R_1 = \alpha$-OH; $R_2 = OAc$; $R_3 = H$ | *C. guianensis*[137] |
| **418** | 6$\alpha$-acetoxygedunin | $R_1 = \alpha$-OAc; $R_2 = OAc$; $R_3 = H$ | *C. guianensis*;[113,137,437,438] *Cedrela fissilis*;[113] *Chisocheton paniculatus*;[94,117] *Swietenia mahagoni*;[112] *Guarea grandiflora*;[434] *Aglaia elaeagnoidea*[419] |
| **419** | 6$\alpha$,11$\beta$-diacetoxygedunin | $R_1 = \alpha$-OAc; $R_2 = OAc$; $R_3 = \beta$-OAc | *A. elaeagnoidea*;[439] *Carapa guianensis*;[438,440] *C. granatum*[441] |
| **420** | 6$\beta$-hydroxygedunin | $R_1 = \beta$-OH; $R_2 = OAc$; $R_3 = H$ | *Azadirachta indica*[442] |
| **421** | 7-deacetylgedunin | $R_1 = R_3 = H$; $R_2 = OH$ | *A. indica*;[57,70,103,104] *Cedrela fissilis*;[113] *C. odorata*;[98] *C. sinensis*;[433] *Pseudocedrela kotschyi*;[443,444] *Trichilia trifolia*;[182] *Swietenia aubrevilleana*;[445] *Khaya ivorensis*;[446,447] *K. grandifoliola*;[164] *Cabralea eichleriana*;[430] *Carapa guianensis*;[437] *Xylocarpus granatum*[448] |
| **422** | 7-desacetyl-7-benzoylgedunin | $R_1 = R_3 = H$; $R_2 = Bz$ | *Azadirachta indica*[68,70] |
| **423** | 7-deacetoxy-7-oxogedunin | $R_1 = R_3 = H$; $R_2 = O$ | *Carapa guianensis*;[113,137,437,449,450] *Pseudocedrela kotschyii*;[443,444] *Khaya senagalensis*;[164,451] *K. ivorensis*;[446,447] *Melia azedarach*;[251,452] *Trichilia schomburgkii*;[453] *Guarea grandiflora*;[434,435] *G. guidona*;[454] *Cabralea eichleriana*;[430] *Xylocarpus granatum*;[448,455] *X. moluccensis*;[162] *Swietenia macrophylla*;[445,456] *S. mahagoni*;[112,457,458] *Cedrela fissilis*;[113,132] *C. odorata*[98,167,459] |
| **424** | 7-deacetoxy-7$\alpha$,11$\beta$-dihydroxygedunin | $R_1 = H$; $R_2 = OH$; $R_3 = \beta$-OH | *C. sinensis*[433] |
| **425** | 7-deacetoxy-7$\alpha$,11$\alpha$-dihydroxygedunin | $R_1 = H$; $R_2 = OH$; $R_3 = \alpha$-OH | *C. sinensis*[433] |
| **426** | 11$\alpha$-hydroxygedunin | $R_1 = H$; $R_2 = OAc$; $R_3 = \alpha$-OH | *C. sinensis*[433] |
| **427** | 11$\beta$-hydroxygedunin | $R_1 = H$; $R_2 = OAc$; $R_3 = \beta$-OH | *C. sinensis*[433] |
| **428** | 11$\beta$-acetoxygedunin | $R_1 = H$; $R_2 = OAc$; $R_3 = \beta$-OAc | *Carapa guianensis*;[440] *Entandrophragma delevoyi*[425] |
| **429** | 11-oxogedunin | $R_1 = H$; $R_2 = OAc$; $R_3 = O$ | *Cedrela sinensis*[433] |
| **430** | 7$\alpha$-acetoxy-14$\beta$,15$\beta$-epoxygedunan-1-ene-3-*O*-$\beta$-D-glucopyranoside | R = $\beta$-D-Glc | *Melia azedarach*[460] |
| **431** | azecin 4 | R = $\beta$-D-Ara | *M. azedarach*[173] |
| **432** | 7-deacetoxy-7-hydroxyphotogedunin | R = H | *Cabralea eichleriana*[430] |
| **433** | photogedunin | R = Ac | *Cedrela fissilis*;[113] *C. salvadorensis*;[413,420] *C. dugessi*;[413] *C. odorata*;[461] *C. ciliolata*;[462] *Xylocarpus granatum*[427] |
| **434** | khivorin | $R_1 = R_2 = R_3 = OAc$; $R_4 = H$ | *Khaya ivorensis*;[446,463] *K. anthotheca*;[163,183] *K. grandifolia*;[164,167] *K. senegalensis*;[451,464−466] *K. nyasica*;[184] *Swietenia mahagoni*[458] |
| **435** | 1-deacetylkhivorin | $R_1 = OH$; $R_2 = R_3 = OAc$ $R_4 = H$ | *S. mahagoni*;[458] *Khaya grandifoliola*[436] |
| **436** | 3-deacetylkhivorin | $R_1 = R_3 = OAc$; $R_2 = OH$; $R_4 = H$ | *K. senegalensis*;[464−468] *K. anthotheca*;[163,183] *K. nyasica*;[184] *K. madagascariensis*;[164,469] *K. ivorensis*;[447] *Swietenia mahagoni*[458] |
| **437** | 7-deacetylkhivorin | $R_1 = R_2 = OAc$; $R_3 = OH$; $R_4 = H$ | *S. mahagoni*;[458] *Khaya grandifoliola*[436] |



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**Table 15. Continued**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **438** | 1,3,7-trideacetylkhivorin | $R_1 = R_2 = R_3 = OH$; $R_4 = H$ | *K. ivorensis*;[447] *K. senegalensis*;[470,471] *Swietenia mahagoni*[458] |
| **439** | 3-deacetyl-7-oxokhivorin | $R_1 = OAc$; $R_2 = OH$; $R_3 = O$; $R_4 = H$ | *Khaya senegalensis*[465,466,468,472] |
| **440** | 3$\alpha$,7$\alpha$-dideacetylkhivorin | $R_1 = OAc$; $R_2 = R_3 = OH$; $R_4 = H$ | *K. senegalensis*;[164,422,467,468,470,473] *K. ivorensis*;[447] *Swietenia mahagoni*[458] |
| **441** | 7-deacetoxy-7-oxokhivorin | $R_1 = R_2 = OAc$; $R_3 = O$; $R_4 = H$ | *Khaya senegalensis*[164,167,451,464,465] |
| **442** | 11$\beta$-acetoxykhivorin | $R_1 = R_2 = R_3 = R_4 = OAc$ | *K. madagascariensis*;[469,474] *K. nyasica*[164,184] |
| **443** | dihydrogedunin | $R_1 = R_4 = H$; $R_2 = O$; $R_3 = OAc$ | *Guarea thompsonii*[167,475] |
| **444** | 7-oxodeacetoxydihydro-$\alpha$-gedunol | $R_1 = R_4 = H$; $R_2 = OH$; $R_3 = O$ | *G. thompsonii*[475] |
| **445** | 1$\alpha$-hydroxy-1,2-dihydrogedunin | $R_1 = OH$; $R_2 = O$; $R_3 = OAc$; $R_4 = H$ | *Xylocarpus granatum*[49] |
| **446** | 1$\alpha$-methoxy-1,2-dihydrogedunin | $R_1 = OCH_3$; $R_2 = O$; $R_3 = OAc$; $R_4 = H$ | *Cedrela odorata*[98] |
| **447** | nyasin | $R_1 = R_2 = R_3 = OAc$; $R_4 = OH$ | *Khaya nyasica*[184,476,477] |
| **448** | 1,2-dihydro-3$\beta$-hydroxy-7-deacetoxy-7-oxogedunin | | *Cedrela fissilis*;[113] *C. guianesnsis*[113] |
| **449** | azadirinin | | *Azadirachta indica*[478] |
| **450** | 3,7-dideacetyl-6$\alpha$-hydroxykhivorin | | *Khaya senegalensis*[466] |
| **451** | nimolicinol | R = Ac; $\Delta^{1,2}$ | *Azadirachta indica*[70,115,479] |
| **452** | 7-deacetynimolicinol | R = H; $\Delta^{1,2}$ | *A. indica*[115] |
| **453** | 1$\alpha$,2$\alpha$-epoxynimolicinol | R = Ac; 1,2-epoxy | *A. indica*[115] |
| **454** | mahmoodin | | *A. indica*[81] |
| **455** | piscidofuran | | *Walsura piscidia*[88] |
| **456** | meliacinol | | *Azadirachta indica*[93] |
| **457** | | | *Melia azedarach*[480] |

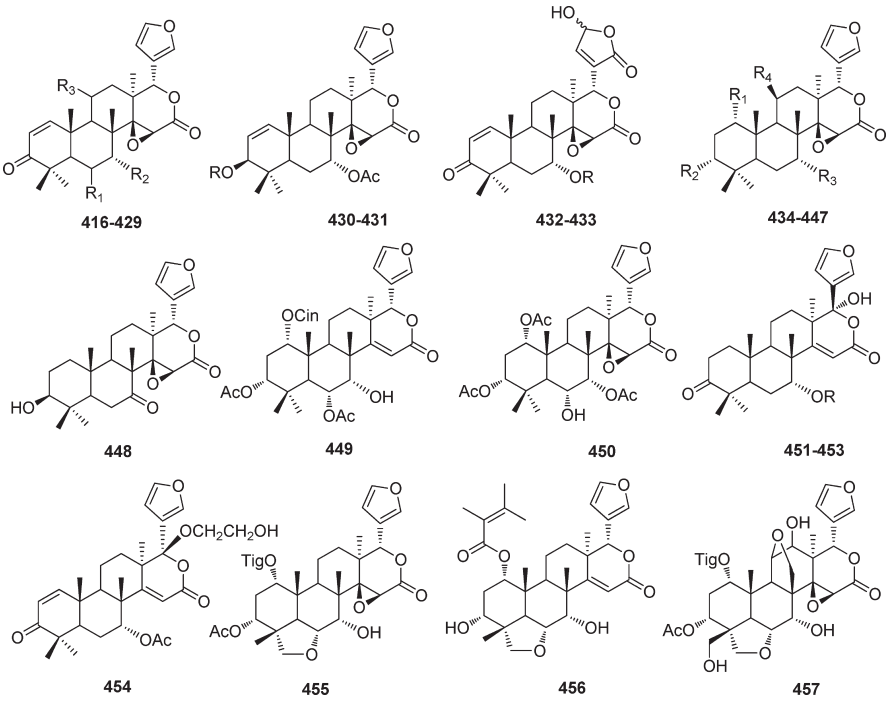


**Figure 17.** Structures of ring D-seco limonoids **416**−**457**.

and 1-*O*-deacetylkhayanolide E (**1008**) respectively.[722] Swiemahogin B (**993**) was an example of incorporating a rare five-membered $\gamma$−lactone fused to the C-ring at C-8 and C-14 and in which the six-membered $\delta$-lactone in the D-ring was destroyed.[572] The biosynthesis of trichiliton A (**997**), bearing a bicyclo[5.2.1$^{4,10}$]decane motif, involved an alternative new route from mexicanolide to phragmalin.[651] Khayalactone (**998**) could arise from a 1,2,3,8-tetrahydroxylated precursor by cleavage of the


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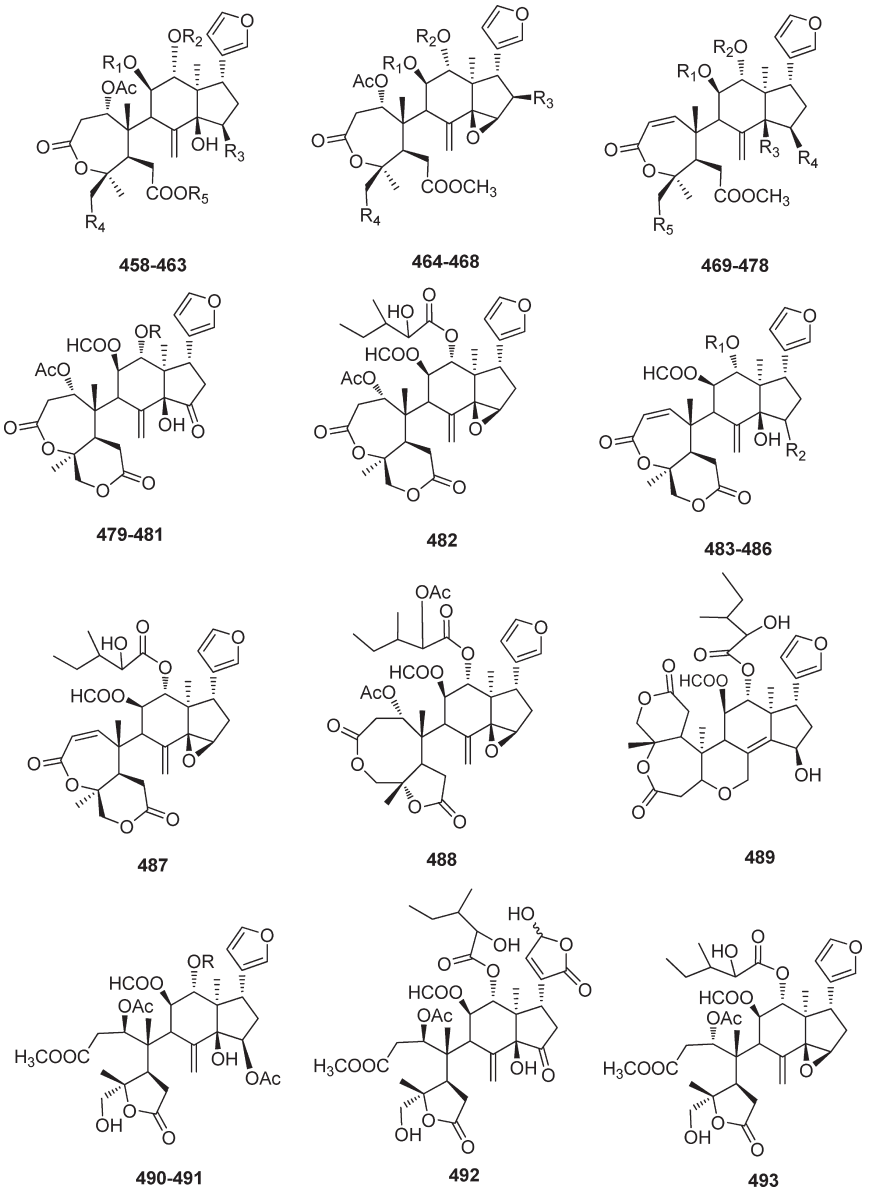


**Figure 18.** Structures of prieurianin-class limonoids **458**−**493**.

1,2-diol followed by formation of the hemiketal by addition of the 8-hydroxyl group to the newly formed 1-carbonyl group.[553,680] The absolute configuration of khayanolide A (**1002**) was established by X-ray analysis and a CD study.[548,549] In biosynthetic terms, a pinacol−pinacolone rearrangement of a 2,3,30-trihydroxyl-1,29-cyclomeliacate precursor is possible, resulting in a 2-oxo-tricyclo-[4,2,$1^{10,30}$.$1^{1,4}$]-decane, and subsequently reduction or addition of an hydroxyl group at C-14 to the ketone and *O*-2-methylation may then led to the limonoids **1013** and **1015**, respectively,[720] which gives a further enlargement of the biosynthetic mexicanolide pathways.[721] In addition, a possible biosynthetic pathway leading to the formation of khayanolides from mexicanolide was proposed.[549] On the basis the extensive spectroscopic analyses including MS, NMR, and single crystal X-ray diffraction experiments, Zhang et al. proposed that methyl l$\alpha$,2$\beta$,3$\alpha$,6,8$\alpha$,14$\beta$-hexahydroxy-[4.2.$1^{10,30}$.$1^{1,4}$]-tricyclomeliac-7-oate (**1014**) and methyl l$\alpha$-acetoxy-2$\beta$,3$\alpha$,6,8$\alpha$,14$\beta$-pentahydroxy-[4.2.$1^{10,30}$.$1^{1,4}$]-tricyclomeliac-7-oate (**1015**)[721] were, in fact, khayanolide B (**1004**) and 1-*O*-acetylkhayanolide B (**1005**),[722] respectively.

**2.3.3. 8,11-Linkage Limonoids (Trijugin-Class).** Trijugin-class limonoids with contracted ring C were postulated to be produced biosynthetically *via* a pinacol−pinacolone rearrangement of a methyl 9, 11-dihydroxyangolensate.[563,565,729] Capensolactones 2 and 3 (**1034** and **1022**) were isolated as a mixture with their ester moieties interchanged at C-2$\alpha$ and C-3$\alpha$.[730] Trichilin B (**1043**), featuring a 9,17-oxygen bridge and a highly rearranged ring system, along with the biosynthetically correlated trichilin A (**1036**), was isolated from *Trichilia connaroides*.[731] Unfortunately, the two trivial names were previously assigned to intact limonoids **137** and **135**, respectively.[194,732]

**2.3.4. 10,11-Linkage Limonoids (Cipadesin-Class).** The rings A and C of cipadesin-class limonoids were joined via C-10/11, and among these limonoids the structure of cipadesin C (**1044**) was confirmed by X-ray crystallographic analysis.[631] Two compounds found in *Cipadesa cinerascens*, **1039**[54,563] and **1045**,[53]


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**Table 16. Structures and Sources of Prieurianin-Class Limonoids 458−493**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **458** | prieurianin | $R_1$ = formacyl; $R_2$ = 2-hydroxy-3-methylpentanoyl; $R_3$ = O; $R_4$ = OAc; $R_5$ = $CH_3$ | *Trichilia prieuriana*;[168] *Guarea guidona*;[454] *Nymania capensis*;[283] *Turraea obtusifolia*;[189] *Entandrophragma candolei*[491] |
| **459** | rohituka 4 | $R_1$ = formacyl; $R_2$ = iVal; $R_3$ = O; $R_4$ = OAc; $R_5$ = $CH_3$ | *Aphanamixis polystacha*[484] |
| **460** | dregeana 2 | $R_1$ = $R_2$ = Ac; $R_3$ = O; $R_4$ = H; $R_5$ = $CH_3$ | *Trichilia dregeana*[274] |
| **461** | trichavensin | $R_1$ = formacyl; $R_2$ = 2-hydroxy-3-methylpentanoyl; $R_3$ = OAc; $R_4$ = pivalyloxy; $R_5$ = $CH_3$ | *T. havanensis*[492] |
| **462** | Tr-A | $R_1$ = formacyl; $R_2$ = 2-hydroxy-3-methylpentanoyl; $R_3$ = OAc; $R_4$ = OH; $R_5$ = $CH_2CH_3$ | *T. roka*[493] |
| **463** | Tr-C | $R_1$ = formacyl; $R_2$ = 2-hydroxy-3-methylpentanoyl; $R_3$ = OAc; $R_4$ = OH; $R_5$ = $CH_3$ | *T. roka*[493] |
| **464** | expoxyprieurianin | $R_1$ = formacyl; $R_2$ = 2-hydroxy-3-methylpentanoyl; $R_3$ = H; $R_4$ = OAc | *Guarea guidona*;[454] *Entandrophragma candolei*[494] |
| **465** | dysoxylumin A | $R_1$ = formacyl; $R_2$ = iVal(OH); $R_3$ = OPiv; $R_4$ = OAc | *Dysoxylum hainanense*[483] |
| **466** | dysoxylumin B | $R_1$ = formacyl; $R_2$ = iVal(OH); $R_3$ = iVal(OAc); $R_4$ = OAc | *D. hainanense*[483] |
| **467** | dysoxylumin C | $R_1$ = formacyl; $R_2$ = iVal(OH); $R_3$ = OiVal(OH); $R_4$ = OAc | *D. hainanense*;[483] *D. lenticellatum*[266] |
| **468** | nymania 4 | $R_1$ = $R_2$ = Ac; $R_3$ = $R_4$ = H | *Nymania capensis*[283] |
| **469** | rohituka 8 | $R_1$ = formacyl; $R_2$ = iVal; $R_3$ = OH; $R_4$ = OAc; $R_5$ = OAc | *Aphanamixis polystacha*[484] |
| **470** | mombasone | $R_1$ = formacyl; $R_2$ = 2-oxo-3-methylpentanoyl; $R_3R_4$ = O; $R_5$ = OAc | *Turraea mombasana*[495] |
| **471** | mombasol | $R_1$ = formacyl; $R_2$ = 2-hydroxy-3-methylpentanoyl; $R_3R_4$ = O; $R_5$ = OAc | *T. mombasana*;[495] *Guarea guidona*[496] |
| **472** | amotsangin A | $R_1$ = Ac; $R_2$ = Piv; $R_3R_4$ = O; $R_5$ = H | *Amoora tsangii*[279] |
| **473** | amotsangin B | $R_1$ = Ac; $R_2$ = iBu; $R_3R_4$ = O; $R_5$ = H | *A. tsangii*[279] |
| **474** | amotsangin C | $R_1$ = Ac; $R_2$ = 2-hydroxy-3-methylpentanoyl; $R_3R_4$ = O; $R_5$ = H | *A. tsangii*[279] |
| **475** | amotsangin D | $R_1$ = Ac; $R_2$ = propanoyl; $R_3R_4$ = O; $R_5$ = H | *A. tsangii*[279] |
| **476** | amotsangin E | $R_1$ = Ac; $R_2$ = Bz; $R_3R_4$ = O; $R_5$ = H | *A. tsangii*[279] |
| **477** | amotsangin F | $R_1$ = formacyl; $R_2$ = Bz; $R_3R_4$ = O; $R_5$ = H | *A. tsangii*[279] |
| **478** | nymania 3 | $R_1$ = $R_2$ = Ac; $R_3R_4$ = O; $R_5$ = H | *Dysoxylum malabaricum*;[497] *Nymania capensis*[283] |
| **479** | Tr-B | R = 2-hydroxy-3-methylpentanoyl | *Trichilia roka*;[493] *T. emetica*;[192] *Apanamixis ploystacha*[485] |
| **480** | rohitukin | R = iVal | *A. ploystacha*;[484,487] *Turraea obtusifolia*[498] |
| **481** | 2′-hydroxyrohitukin | R = iVal(OH) | *Guarea cedrata*[499] |
| **482** | guarea B | | *G. multiflora*;[500] *G. thompsonii*[489] |
| **483** | rohituka 7 | $R_1$ = 2-hydroxy-3-methylpentanoyl; $R_2$ = $\beta$-OAc | *Aphanamixis polystacha*[275,484,485] |
| **484** | rohituka 9 | $R_1$ = iVal; $R_2$ = $\beta$-OAc | *A. polystacha*[275,484] |
| **485** | hispidin B | $R_1$ = 2-hydroxy-3-methylpentanoyl; $R_2$ = $\alpha$-OTig | *Trichilia hispida*[501] |
| **486** | hispidin C | $R_1$ = 2-hydroxy-3-methylpentanoyl; $R_2$ = $\alpha$-OAc | *T. hispida*[501] |
| **487** | D-4 | | *T. prieuriana*[489] |
| **488** | dregeanin | | *T. dreageana*;[487] *T. heudelottii*[77] |
| **489** | cipadessalide | | *Cipadessa baccifera*[282] |
| **490** | rohituka 1 | R = iVal | *Aphanamixis polystacha*[484] |
| **491** | rohituka 2 | R = 2-hydroxy-3-methylpentanoyl | *A. polystacha*[484] |
| **492** | gaudichaudysolin A | | *Dysoxylum gaudichaudianum*[502] |
| **493** | D-5 | | *Trichilia prieuriana*[489] |

had both been given the trivial name cipadesin E. Fang et al. postulated that cipadonoids C−G (**1046**−**1050**) might be biosynthetically derived from the methyl angolensate-class limonoid via a pinacol rearrangement, which was confirmed by a computational study at the DFT level with a B3LYP/6-31G basis set as well as by chemical transformation. In addition, the presence of a $\Delta^{8,30}$ double bond in the methyl angolensate precursor led to trijugin-class limonoids while its absence led to cipadesin-class limonoid.[544]

**2.3.5. Other Linkages Group.** The structure of walsuronoid A (**1054**), featuring a 3,4-peroxide bridge A-seco skeleton and a C-3/19 linkage bridge, was confirmed by single-crystal X-ray diffraction.[739] The hypothetical biosynthesis route from 11$\beta$-hydroxycedrelone (**82**) to walsuronoids B (**1058**) and C (**1059**), which have the 18 (13→14) abeo limonoid skeletons, and the chemical correlations between them were proposed.[739] The structure of delevoyin C (**1060**), possessing a cyclobutanyl ring incorporating C-19 and a cycloheptanyl ring C including C-30,


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Table 17. Other Structures and Sources of Rings A,B-seco Limonoids 494−524

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| 494 | toonaciliatin E | R = OAc | *Toona ciliata*[290] |
| 495 | toonaciliatin H | R = H | *T. ciliata*[290] |
| 496 | toonaciliatin I | | *T. ciliata*[290] |
| 497 | surenolactone | | *T. sureni*[505] |
| 498 | munronin A | $R_1$ = O; $R_2$ = OH | *Munronia henryi*[506] |
| 499 | munronin B | $R_1$ = OH; $R_2$ = O | *M. henryi*[506] |
| 500 | munronin C | $R_1$ = O; $R_2$ = H | *M. henryi*[506] |
| 501 | dysoxylumolide B | R = 2-hydroxy-3-methylpentanoyl | *Dysoxylum hainanense*[507] |
| 502 | dysoxylumic acid D | R = 2-hydroxy-3-methylpentanoyl | *D. hainanense*[507] |
| 503 | dysoxylumic acid A | | *D. hainanense*[507] |
| 504 | dysoxylumic acid B | | *D. hainanense*[507] |
| 505 | rohituka 6 | | *Aphanamixis polystacha*[484] |
| 506 | dysoxylumic acid C | | *Dysoxylum hainanense*[507] |
| 507 | rohituka 3 | $R_1$ = 2-hydroxy-3-methylpentanoyl; $R_2$ = OH; $R_3$ = O; $R_4$ = H | *Trichilia emetica*;[192] *Aphanamixis polystacha*[484,485] |
| 508 | rohituka 5 | $R_1$ = 2-hydroxy-3-methylpentanoyl; $R_2$ = OH; $R_3$ =OAc; $R_4$ = H | *A. polystacha*[484,485] |
| 509 | rohituka 13 | $R_1$ = iVal; $R_2$ = OH; $R_3$ =OAc; $R_4$ = H | *A. polystacha*[275] |
| 510 | rohituka 14 | $R_1$ = iVal; $R_2$ = OH; $R_3$ =O; $R_4$ = H | *A. polystacha*[275,485] |
| 511 | | $R_1$ = formacyl; $R_2R_3$ = O; $R_4$ = H | *Trichilia prieuriana*[489] |
| 512 | dysoxylumolide A | $R_1$ = iVal(OH); $R_2R_3$ = O; $R_4$ = OiVal(OH) | *Dysoxylum hainanense*[507] |
| 513 | toonaciliatin D | | *Toona ciliata*[290] |
| 514 | dregeana 1 | $R_1$ = formacyl; $R_2$ = 2-hydroxy-3-methylpentanoyl | *Trichilia dregeana*;[274] *Aphanamixis polystachya*[485,508] |
| 515 | rohituka 12 | $R_1$ = H; $R_2$ = iVal | *A. polystacha*[275] |
| 516 | rohituka 15 | $R_1$ = H; $R_2$ = 2-hydroxy-3-methylpentanoyl | *A. polystacha*[485,508] |
| 517 | polystachin | $R_1$ = formacyl; $R_2$ = iVal | *A. polystacha*[275,503] |
| 518 | rubrin A | $R_1$ = OH; $R_2$ = OPiv | *Trichilia rubra*[504] |
| 519 | rubrin B | $R_1$ = OH; $R_2$ = OiBu | *T. rubra*[504] |
| 520 | hispidin A (rubrin C) | $R_1$ = OH; $R_2$ = OTig | *T. hispida*;[501] *T. rubra*[504] |
| 521 | rubrin D | $R_1$ = OH; $R_2$ = propanoylate | *T. rubra*[504] |
| 522 | rubrin E (nymania 1) | $R_1$ = OH; $R_2$ = O | *T. rubra*;[504] *T. emetica*;[192] *T. obtusifolia*[509] |
| 523 | rubrin F | $R_1$ = O; $R_2$ = OAc | *T. rubra*[504] |
| 524 | rubrin G | $R_1$ = OH; $R_2$ = OAc | *T. rubra*[504] |

was suggested by the LSD (Logic for Structure Determination) program.[425] The absolute configurations of cipadonoid A (**1061**), which featured a tetrahydropyranyl ring B and characterized by a C-30 exomethylene group inserted between C-8 and C-10,[740] was revised to be 1*S*,3*R*,5*S*,8*S*,10*R*,13*S*,14*R*,17*R*.[741]

## 2.4. Limonoids Derivatives

**2.4.1. Pentanortriterpenoids, Hexanortriterpenoids, Heptanortriterpenoids, Octanortriterpenoids, and Enneanortriterpenoids Derivatives.** A possible degradation pathway for 2-oxo-deacetyl salannin (**1063**), the sole C-2 degraded limonoid, was not proposed or hypothesized.[411] Azadirachtin L, obtained by Kanokmedhakul et al. in 2005,[324] was in fact reported as marrangin (**1067**) early in 1993.[746] The structure of **1068** was assigned as 11$\alpha$-hydroxy-12-norazadirachtin[747] in 1994, but Ramji et al. isolated and mistook it as 11-*epi*azadirachtin H[748] in 1996, and Kanokmedhakul et al. isolated and named it as 11$\alpha$-azadirachtin H in 2005.[324] 11-*epi*azadirachtin I (**1070**) was characterized by both NMR and X-ray crystallography techniques.[749] Chuktabularins A−D (**1074**, **1096**, **1078**, and **1089**) are four 16-norphragmalin-class limonoids with a biosynthetically extended C2 or C3 unit at C-15 forming a unique 2,7-dioxabicycl[2.2.1]heptane moiety. Moreover, a plausible biosynthetic origin of chuktabularins A−D was also postulated.[750] The structure of chuktabrin A (**1097**), featuring motifs of a 1,3-dioxolan-2-one and a 3,4-dihydro-2*H*-pyran formed *via* an ether bond between C-30 and C-1 in the biosynthetically extended C3 unit at C-15, was confirmed by X-ray diffraction.[697] The co-occurrence of limonoids and norlimonoids in *Toona ciliata* together with the possible mechanisms of conversion suggested a biosynthetic map that encompassed the pathways for all limonoids started from the common precursor 14,15-deoxyhavanensin.[290]

In biosynthetic terms, carapolide A (**1115**) could be derived from a spiro-precursor through pathway involving a retro-prins reaction, cleavage and protonation.[581] A limonoid belonging to the 1,8,9-orthoesters phragmalin-class might biosynthetically undergo insertion of an isobutyryl group from C-30 to C-15 through a Claisen reaction, cleavage of the C-16/17 $\delta$-lactone, and then decarboxylation and de-*ortho*-acetation to form another intermediate, which, after a series of ketal formations and esterifications, gives chukvelutins A−C (**1086**−**1088**).[751] Similarly, chuktabularins E−T (**1090**−**1095**, **1075**, **1079**−**1085**, **1076**, **1077**) possessed a biosynthetically extended propionyl or acetyl group at C-15 and a characteristic ketal moiety between the limonoid skeleton and the acyl substituent at C-15.[752] Ceramicine A (**1118**) could be transformed from limonoids skeleton via oxidation at C-28 and C-29 followed


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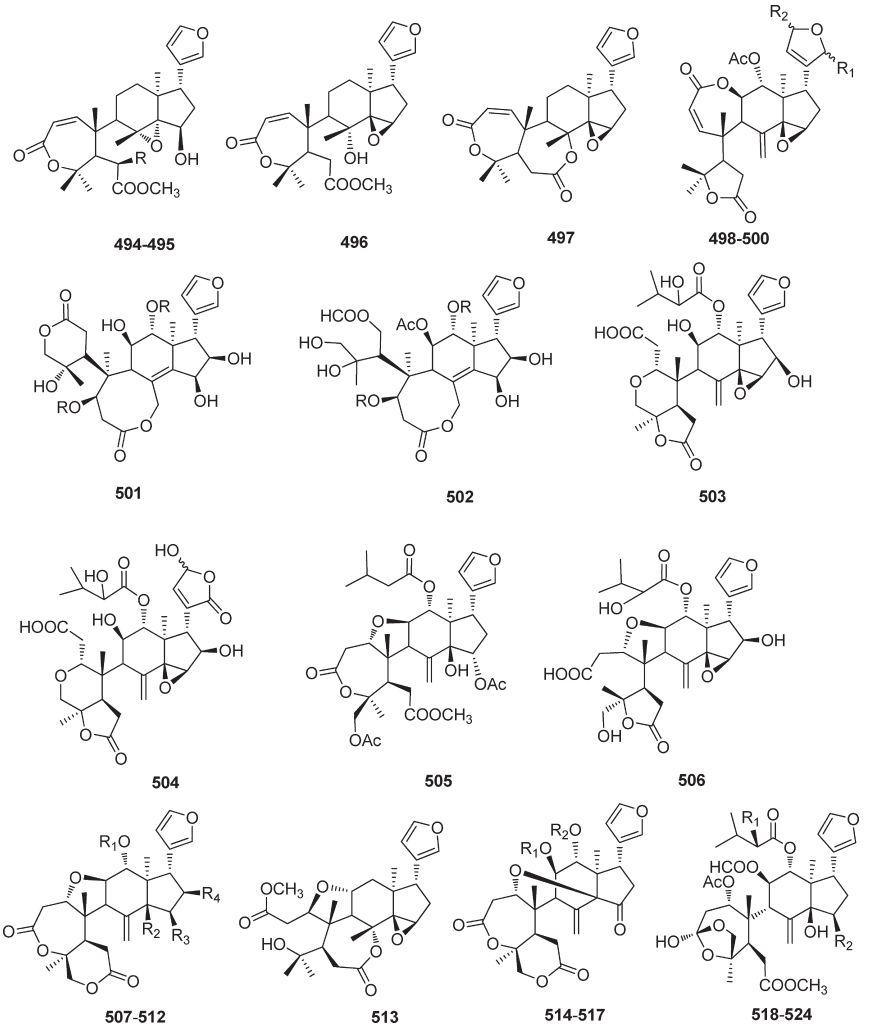


**Figure 19.** Other structures of rings A,B-seco limonoids **494**−**524**.

by decarboxylation.[412] Two degraded limonoids, assigned as 7$\alpha$-acetoxy-4,4,8-trimethyl-5$\alpha$-(13$\alpha$Me)-17-oxa-androsta-1,14-dien-3,16-dione (**1130**) and 7$\alpha$-acetoxy-4,4,8-trimethyl-5$\alpha$-17-oxa-androsta-1,14-dien-3,16-dione (**1131**) in 1992,[753] were isolated and reported as 13$\alpha$-nimolactone and 13$\beta$-nimolactone in 1994,[107] respectively.

**2.4.2. Simple Degraded Derivatives.** Trichiconnarins A and B (**1139** and **1140**) are degraded limonoids with a contracted five-membered ring-C. Of these, **1139** is likely to be the degradation products of trijugin C (**1111**) by cleavage of the C-2 and C-8 bonds, and **1140** is then derived from reaction of **1139** with acetone through an aldol reaction followed by dehydration.[573] X-ray analysis of 9$\beta$-bromofraxinellone has defined the absolute stereochemistry of fraxinellone (**1142**).[763]

**2.4.3. N-Containing Derivatives.** Microbes, such as endophytic fungi, may contribute to the biosynthesis of turrapubesin B (**1153**), which contains a maleimide ring.[287] Wu et al. proposed a new biosynthetic pathway with xylogranatin R (**843**) as a key intermediate to reach the limonoids xylogranatins F−H (**1156**−**1158**), which bear a novel skeleton with a pyridine ring.[638] Cui et al. suggested that granatoine (**1159**) could be biosynthetically derived from the precursor 9,10-seco-mexicanolide xylogranatin C (**823**) via a pathway in which the pyridine ring would be formed through ring condensation and dehydroxylation while the $\gamma$-lactone would be formed by esterification between C-7 and C-10.[726]

## 3. CHEMOTAXONOMIC SIGNIFICANCE OF MELIACEOUS LIMONOIDS

As one of many types of natural products in plants, the limonoids were significant chemotaxonomic markers of Meliaceae, Rutaceae, and Simarubaceae. A wonderful review presented in 1983 treated the chemotaxonomic significance of limonoids in Meliaeae and discussed the biosynthesis, distribution, and systematic significance of limonoids in the Meliaceae, Cneoraceae, and allied taxa.[15] Up until the present, the chemotaxonomy significances of limonoids for Meliaceae focused mainly on the subfamily Swietenioideae and Melioideae.

Different research groups have proposed the chemotaxonomic significance of genera *Khaya*, *Soymida*, *Neobeguea*, *Swietenia*, *Toona*, and *Cedrela* of subfamily Swietenioideae. The western and eastern forms of *Khaya anthotheca* were different chemically in that the western variety gave no ring D-expanded meliacins, in contrast to the other species.[164] The timber of *Soymida febrifuga* contained no detectable level of limonoids and the bark contained ~0.1% methyl angolensate (**568**). These results showed that *Soymida* was closely related to the African genus *Khaya*.[767]


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**Table 18. Structures and Sources of Rings A,D-seco Limonoids 525−555**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **525** | obacunol | $R_1 = R_2 = R_3 = R_4 = H$ | *Lovoa trichiliodes*;[515] *Trichilia trifolia*[182] |
| **526** | 6$\alpha$-acetoxyobacunol acetate | $R_1 = \alpha$-OAc; $R_2$ = Ac; $R_3 = R_4 = H$ | *Dysoxylum spectabile*;[516] *D. richii*;[517] *D. muelleri*;[518] *Cedrela sinensis*[519] |
| **527** | 11$\beta$-acetoxyobacunyl acetate | $R_1 = R_4 = H$; $R_2$ = Ac; $R_3 = \beta$-OAc | *C. odorata*[510] |
| **528** | 11$\beta$-acetoxyobacunol | $R_1 = R_2 = R_4 = H$; $R_3 = \beta$-OAc | *C. odorata*[510] |
| **529** | 6$\beta$-acetoxyobacunol | $R_1 = \beta$-OAc; $R_2 = R_3 = R_4 = H$ | *Trichilia trifolia*[182] |
| **530** | dysoxylone | $R_1$ = O; $R_2$ = iVal(OH); $R_3 = R_4 = H$ | *Dysoxylum richii*[517] |
| **531** | 11$\beta$-hydroxy-7$\alpha$-obacunyl acetate | $R_1 = R_4 = H$; $R_2$ = Ac; $R_3 = \beta$-OH | *Cedrela sinensis*[511] |
| **532** | 11-oxo-7$\alpha$-obacunol | $R_1 = R_2 = R_4 = H$; $R_3$ = O | *C. sinensis*[511] |
| **533** | 11-oxo-7$\alpha$-obacunyl acetate | $R_1 = R_4 = H$; $R_2$ = Ac; $R_3$ = O | *C. sinensis*[511] |
| **534** | 7$\alpha$-obacunyl acetate | $R_1 = R_3 = R_4 = H$; $R_2$ = Ac | *C. sinensis*[519] |
| **535** | perforin A | $R_1 = R_3 = \alpha$-OAc; $R_2$ = Ac; $R_4 = \beta$-OAc | *Toona ciliata*[145] |
| **536** | 11$\beta$-acetoxyobacunone | | *Trichilia elegans*[165] |
| **537** | kihadanin A | $R_1 = R_3$ = O; $R_2$ = OH | *T. elegans* ssp. *elegans*[520] |
| **538** | 7-deoxo-7$\alpha$-hydroxykihadanin A | $R_1 = \alpha$-OH; $R_2$ = OH; $R_3$ = O | *T. elegans* ssp. *elegans*[512] |
| **539** | 7-deoxo-7$\alpha$-acetoxykihadanin A | $R_1 = \alpha$-OAc; $R_2$ = OH; $R_3$ = O | *T. elegans* ssp. *elegans*[512,520] |
| **540** | 7-deoxo-7$\beta$-hydroxykihadanin A | $R_1 = \beta$-OH; $R_2$ = OH; $R_3$ = O | *T. elegans* ssp. *elegans*[512] |
| **541** | 7-deoxo-7$\beta$-acetoxykihadanin A | $R_1 = \beta$-OAc; $R_2$ = OH; $R_3$ = O | *T. elegans* ssp. *elegans*[512] |
| **542** | kihadanin B | $R_1 = R_2$ = O; $R_3$ = OH | *T. elegans* ssp. *elegans*[520] |
| **543** | 7-deoxo-7$\alpha$-acetoxykihadanin B | $R_1 = \alpha$-OAc; $R_2$ = O; $R_3$ = OH | *T. elegans* ssp. *elegans*[520] |
| **544** | 7-deoxo-7$\beta$-hydroxykihadanin B | $R_1 = \beta$-OH; $R_2$ = O; $R_3$ = OH | *T. elegans* ssp. *elegans*[512] |
| **545** | 7-deoxo-7$\beta$-acetoxykihadanin B | $R_1 = \beta$-OAc; $R_2$ = O; $R_3$ = OH | *T. elegans* ssp. *elegans*[512] |
| **546** | 7$\alpha$-acetoxydihydronomilin | R = H | *Xylocarpus granatum*;[513,514] *Cedrela sinensis*;[519] *C. odorata*[510] |
| **547** | 11$\beta$-hydroxyceorin G | R = OH | *C. sinensis*[511] |
| **548** | 11-oxocneorin G | R = O | *C. sinensis*[511] |
| **549** | 7$\alpha$,11$\beta$-diacetoxydihydronomilin | R = OAc | *C. mexicana*;[521] *C. odorata*[510] |
| **550** | cedrellin | | *C. sinensis*[519] |
| **551** | 11$\beta$,19-diacetoxy-1-deacetyl-1-epidihydronomilin | | *C. odorata*[510] |
| **552** | dysoxylin | R = H | *Dysoxylum richii*[517,522] |
| **553** | tigloyldysoxylin | R = Tig | *D. richii*[517] |
| **554** | dysoxylumolide C | | *D. hainanense*[507] |
| **555** | odoralide | | *Cedrela odorata*[510] |

Zhang et al. concluded that the configuration at C-6 of mexicanolides, phragmalins, and khayanolides from *Khaya senegalensis* had a 6*S* configuration while those from *Swietenia* species had a 6*R* configuration, and then pointed out this difference implies a significant chemotaxonomy difference between the African mahogany genus *Khaya* and the genuine mahogany genus *Swietenia*.[722] Six phragmalin-class limonoids from *Swietenia macrophylla* showed significant chemotaxonomic evidence in favor of linking this speices with *S. mahagoni*.[716] Furthermore, Wu et al. described the distribution of kinds of phragmalin orthoesters in Xylocarpeae and Swietenieae and pointed out that the two tribes were closely related subfamilies in Meliaceae.[659] The chemotaxonomic significances of limonoids in *Toona* and *Cedrela* were hot topics for years. Agostinho et al. objected to the affiliation of *Toona* to Swietenioideae by the occurrence of the meliacin butenolides in both *Toona* and *Trichilia*.[154] In addition, Neto and da Silva et al. pointed out that *Toona* differed notably from other genera of Swietenioideae by the absence of the mexicanolide-class limonoids and the presence of limonoids rather typical of Melioideae, and thus showed a less pronounced relationship to the Swietenioideae.[161,768] Neto et al. pointed out that the ring B-seco limonoids of *Toona* could be considered the biosynthetic precursors of the mexicanolide-class limonoids which were common in *Cedrela*, suggesting a direct derivation of *Cedrela* from *Toona*-like ancestors.[140] Yet Liao et al. supported *Toona* as a separate subfamily because of the biosynthetic relationship between the limonoids from *Toona ciliata* and the occurrence of mexicanolide-class limonoids in this speices.[290]

The chemotaxonomic significance of limonoids for genera *Ekebergia*, *Nymania*, *Trichilia*, *Turraea*, *Astrotrichilia*, *Dysoxylum*, *Malleastrum*, and *Cipadessa* ascribed to subfamily Melioideae were also investigated extensively. The limonoids of *Ekebergia* were not far removed from the general pattern found in *Trichileae*, in which highly oxidized ring B fissioned limonoids appeared to be the most common terpenoid constituents.[567] Since trijugin-class limonoids were obtained both from *Heynea trijuga* and *Ekebergia terophylla*, the possible relationship between *Ekebergia* and *Heynea* was proposed.[565] Because of the structural relation between astrotrichilin (**566**) and ekebergin (**588**), Mulholland et al. proposed a relationship between *Astrotrichilia* and *Ekebergia*,[543] which disagreed with Pennington's viewpoint.[769] Chemically, *Ekebergia* itself was rather distinct and not closely related to *Trichilia* so that it seemed possible that both *Quivisianthe* and *Ekebergia* occupy positions on the fringes


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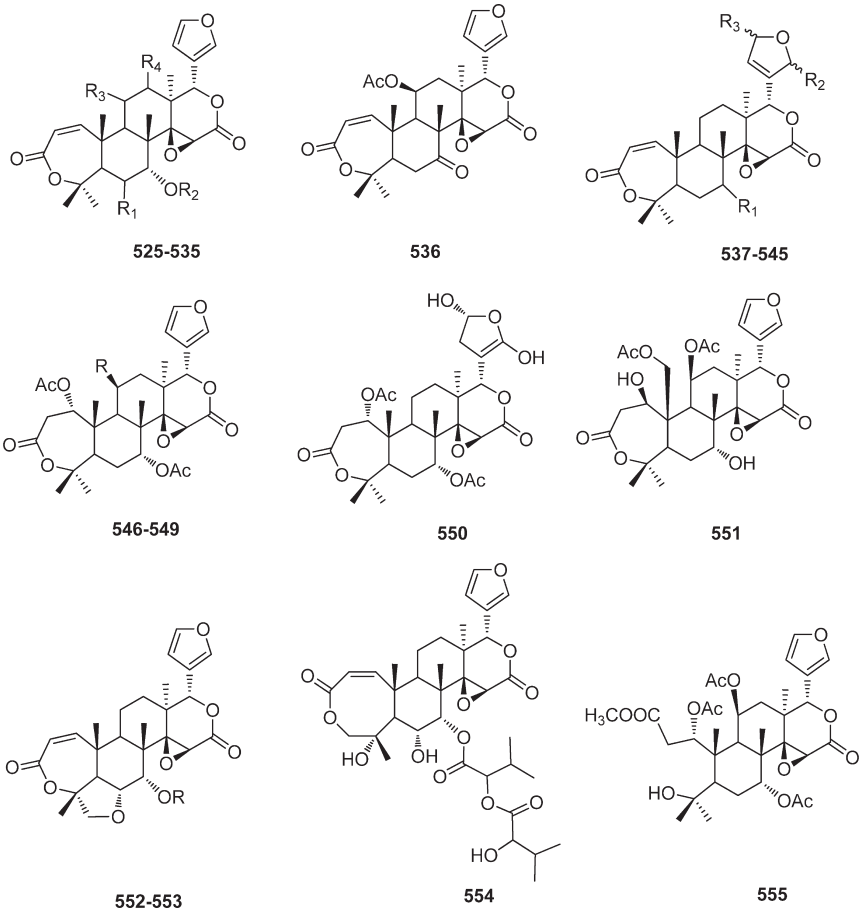


**Figure 20.** Structures of rings A,D-seco limonoids **525**−**555**.

of the main groups of the Meliaceae, perhaps without especially close relation to any other genera.[613] The limonoids from *Nymania* were typical of those from species of the genera *Guarea*, *Trichilia*, and *Aphanamixis*, which strongly supported the placing of *Nymania* in the subfamily Melioideae.[283] The chemotaxonomic link between the genera *Nymania* and *Turraea* was established based on the occurrence of nymania-1 (**522**) in both *Nymania capensis* and *Turraea obtusifolia*.[509] Three limonoids from *Turraea obtusifolia* are structurally similar to hirtin (**94**) and havanensin (**106**) and thus represent intermediates or byways on the route to the more characteristic prieurianin group, and they are consistent with the close taxonomic relationship of *Turraea* and *Nymania*.[189] In contrast to the other species of *Trichilia*, *T. connaroides* contains the andirobin, mexicanolide and trijugin class limonoids, which could be used as a chemical marker to differentiate this species from the other species in the same genus.[573] Mzikonone (**240**), the principal limonoid of *Turraea robusta*, was much less oxidized than the havanensin-class limonoids from *T. obtusifolia* and the prieurianin-class from *T. floribunda*,[189] which suggested that caution needed to be exercised in defining the oxidation pattern of limonoids as taxonomic markers for the genus *Turraea*.[268] The limonoids from *Turraea parvifolia* of the Turraeeae tribe were typical of those from the genera *Melia* and *Azadirachta* of the Melioideae which suggests their close chemotaxonomic relationship.[243] Dysodensiols A-C (**1135**−**1137**) from *Dysoxylum densiflorum*, which are likely biotransformed products from a common precursor of a B-seco-limonoid, supported the proposition that it would be preferred to include the genus *Dysoxylum* in the subfamily Melioideae.[764] The distribution of methyl ivorensate-like limonoids with A,B-seco and D carbocyclic rings **601**−**606** indicated the chemosystematic relevance between the genera *Khaya*,[446,576] and *Soymida*[538] of the subfamily Swietenioideae and the genera *Dysoxylum*,[516] and *Trichilia*[520] of the Melioideae. The isolation of 1$\alpha$,3$\alpha$-diacetylvilasinin (**189**) and 1,3-diacetyl-7-tigloyl-12$\alpha$-hydroxyvilasinin (**190**) from *Malleastrum antsingyense* supported the placement of *Malleastrum* in the subfamily Melioideae although no prieurianin or evodulone-class limonoids were found.[244] The mexicanolide-class limonoids found in *Cipadessa fruticosa*[617] along with the andirobin- and trijugin-class limonoids from *C. cinerascens*[563,647] provided firm support for including *Cipadessa* in Trichilieae, which is in agreement with Pennington's viewpoint.[769]

## 4. SYNTHESIS OF MELIACEOUS LIMONOIDS

Because of the important biological activities and the high structural complexity, the limonoids of Meliaceae have attracted considerable attention from the organic synthesis community, which has focused particularly on the total synthesis of the well-known azadirachtin (**292**).

The potent antifeedant activity of **292** against various insect coupled with its remarkable selectivity and nontoxicicity toward mammalian organisms made it an attractive candidate as a natural pesticide. Enormous efforts directed toward the total synthesis of


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**Table 19. Structures and Sources of Andirobin-Class Limonoids 556−594**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **556** | andirobin | R = O | *Carapa guianensis*;[137,437,449,450] *Cedrela odorata*;[533] *Swietenia macrophylla*[445] |
| **557** | amoorinin | R = OH | *Amoora rohituka*[534,535] |
| **558** | amoorinin-3-*O*-$\alpha$-L-rhamnopyranosyl-(1→6)-$\beta$-D-glucopyranoside | R = 3-*O*-$\alpha$-L-Rha-(1→6)-$\beta$-D-Glc | *Aphanamixis polystachya*[536] |
| **559** | deoxyandirobin | R = H; $\Delta^{1,2}$ | *Soymida febrifuga*;[537] *Khaya grandifoliola*[164] |
| **560** | swietmanin J | R = OH | *Swietenia mahagoni*[458] |
| **561** | domesticulide A | R = H | *Lansium domesticum*[100] |
| **562** | domesticulide B | R = Ac | *L. domesticum*[100] |
| **563** | | | *Soymida febrifuga*[538] |
| **564** | dihydroamoorinin | R = OH | *Aphanamixis polystachya*[539] |
| **565** | aphanamixinin | R = O | *A. polystachya*[536,540−542] |
| **566** | astrotrichilin | R = cinnamate/nicotinate ester | *Astrotrichilia asterotricha*[543] |
| **567** | cipadonoid B | | *Cipadessa cinerascens*[544] |
| **568** | methyl angolensate | $R_1$ = O; $R_2$ = $R_3$ = $R_4$ = H | *Entandrophragma angolense*;[423,545] *E. macrophyllum*;[530] *Guarea thompsonii*;[475] *Soymida febrifuga*;[537,546] *Khaya senegalensis*;[451,464,547−551] *K. anthotheca*;[552] *K. grandifoliola*;[164,436,553] *K. ivorensis*;[446,447,554] *Cedrela odorata*;[98,168] *C. fissilis*;[132] *Lansium domesticum*;[100] *Swietenia mahagoni*;[112,458,555] *Ruagea glabra*;[556] *Carapa guianensis*;[113,137,437] *Cabralea eichleriana*;[430] *Neobeguea mahafalensis*;[557] *Melia azedarach*;[452] *Trichilia catigua*;[165] *Xylocarpus granatum*;[448] *X. moluccensis*[558] |
| **569** | methyl 6-hydroxyangolensate | $R_1$ = O; $R_2$ = OH; $R_3$ = $R_4$ = H | *Khaya senegalensis*;[451,467,468,472,547−550,559] *K. anthotheca*;[552] *K. ivorensis*;[446,447,554] *K. grandifoliola*;[164,436,553,560] *Swietenia mahagoni*;[457,458,555] *S. aubrevilleana*;[445] *Lansium domesticum*[100] |
| **570** | methyl 6-acetoxyangolensate | $R_1$ = O; $R_2$ = OAc; $R_3$ = $R_4$ = H | *L. domesticum*;[100] *Khaya grandifoliola*;[560,561] *K. senegalensis*[451,547,549,550,559] |
| **571** | methyl 6,12$\alpha$-diacetoxyangolensate | $R_1$ = O; $R_2$ = $R_3$ = OAc; $R_4$ = H | *Guarea thompsonii*[531] |
| **572** | azecin 1 | $R_1$ = OAc; $R_2$ = H; $R_3$ = OAc; $R_4$ = *O*-L-rha (1→6)- $\beta$-D-glc | *Melia azedarach*[173] |
| **573** | sandoricin | $R_1$ = OAc; $R_2$ = H; $R_3$ = OAc; $R_4$ = OH | *Sandoricum koetjape*[532] |
| **574** | 6-hydroxysandoricin | $R_1$ = OAc; $R_2$ = $R_4$ = OH; $R_3$ = OAc | *S. koetjape*[532] |
| **575** | [2$\alpha$-(2-methylbutanoyl)oxy]sandoricin | $R_1$ = $\alpha$-Opiv; $R_2$ = OAc; $R_3$ = OH | *S. koetjape*[562] |
| **576** | [2$\alpha$-(2-methylpropanoyl)oxy]sandoricin | $R_1$ = $\alpha$-OiBu; $R_2$ = OAc; $R_3$ = OH | *S. koetjape*[562] |
| **577** | methyl 2$\beta$,3$\beta$-diacetoxy-3-deoxoangolensate | $R_1$ = $\beta$-OAc; $R_2$ = $R_3$ = H | *Cipadessa cinerascens*[563] |
| **578** | cipadesin D | $R_1$ = H; $R_2$ = OH; $R_3$ = $\beta$-OAc | *C. cinerascens*[53] |
| **579** | cipadesin F | $R_1$ = OAc; $R_2$ = OH; $R_3$ = H | *C. cinerascens*[54] |
| **580** | cineracipadesin B | $R_1$ = OAc; $R_2$ = OH; $R_3$ = $\alpha$-OH | *C. cinerascens*[563] |
| **581** | cineracipadesin C | $R_1$ = H; $R_2$ = OH; $R_3$ = O | *C. cinerascens*[563] |
| **582** | cineracipadesin D | $R_1$ = $R_2$ = H; $R_3$ = $\alpha$-OAc | *C. cinerascens*[563] |
| **583** | cineracipadesin E | $R_1$ = OAc; $R_2$ = OH; $R_3$ = $\alpha$-OAc | *C. cinerascens*[563,564] |
| **584** | E.P.1 | $R_1$ = OAc; $R_2$ = $R_3$ = H | *Ekebergia pterophylla*[565,566] |
| **585** | E.P.2 | $R_1$ = H; $R_2$ = Ac; $R_3$ = OAc | *E. pterophylla*[566] |
| **586** | E.P.3 | $R_1$ = $R_3$ = OAc; $R_2$ = H | *E. pterophylla*[565,566] |
| **587** | E.P.6 | $R_1$ = OTig; $R_2$ = H; $R_3$ = OH | *E. pterophylla*[565] |
| **588** | ekebergin | $R_1$ = O*i*Val; $R_2$ = H; $R_3$ =OAc | *E. capensis*[567] |
| **589** | domesticulide C | $R_1$ = OAc; $R_2$ = O; $R_3$ = OH | *Lansium domesticum*[100] |
| **590** | domesticulide D | $R_1$ = OAc; $R_2$ = OH; $R_3$ = O | *L. domesticum*[100] |
| **591** | moluccensin N | $R_1$ = H; $R_2$ = O; $R_3$ = OH | *Xylocarpus moluccensis*[568] |
| **592** | moluccensin O | $R_1$ = H; $R_2$ = OH; $R_3$ = O | *X. moluccensis*[568] |
| **593** | sandoripin A | R = Piv | *Sandoricum koetjape*[569] |
| **594** | sandoripin B | R = iBu | *S. koetjape*[569] |


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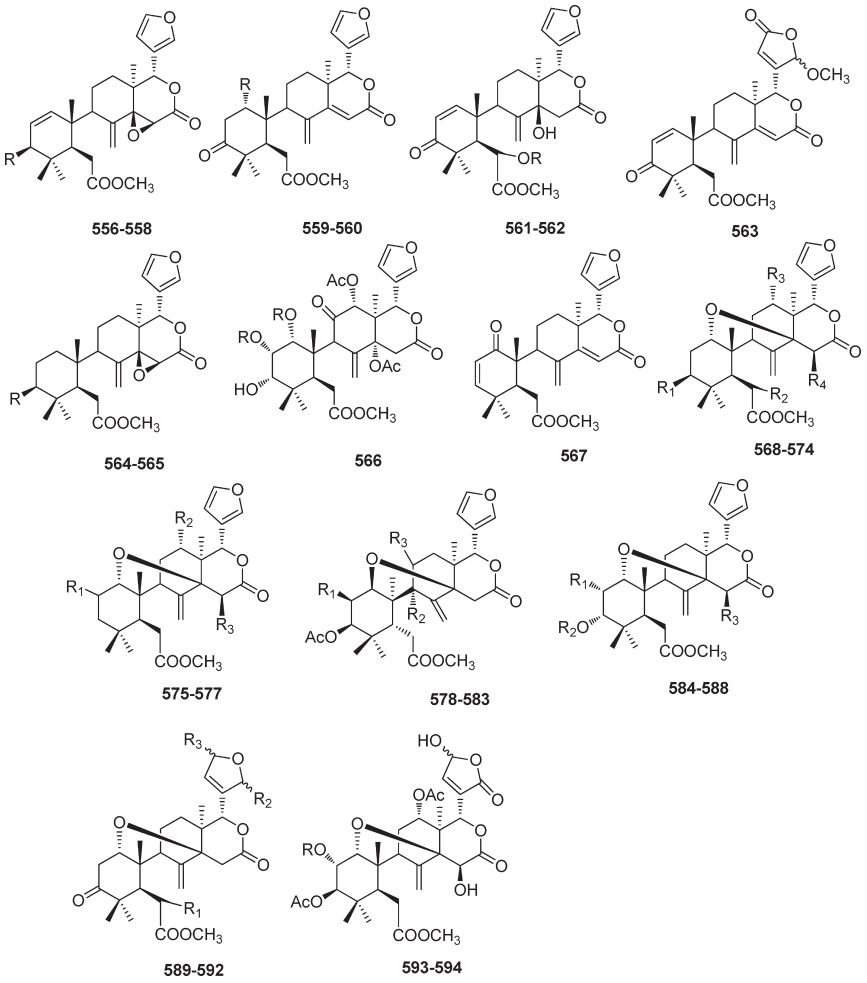


**Figure 21.** Structures of andirobin-class limonoids **556**−**594**.

**Table 20. Other Structures and Sources of Rings B,D-seco Limonoids 595−600**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **595** | methyl 8$\alpha$-hydroxy-8,30-dihydroangolensate | | *Trichilia connaroides*[573] |
| **596** | secomahoganin | R = Ac | *Entandrophragma angolense*;[545] *Swietenia mahagoni*;[71,111,112] *S. macrophylla*[456] |
| **597** | deacetylsecomahoganin | R = H | *S. mahagoni*[457] |
| **598** | khayanoside | R = $\beta$-D-glucopyranoside | *Khaya senegalensis*;[550,574,575] *K. ivorensis*[554] |
| **599** | cedrelanolide I | | *Cedrela salvadorensis*[570,571] |
| **600** | swiemahogin A | | *Swietenia mahagoni*;[572] *Khaya ivorensis*[554] |

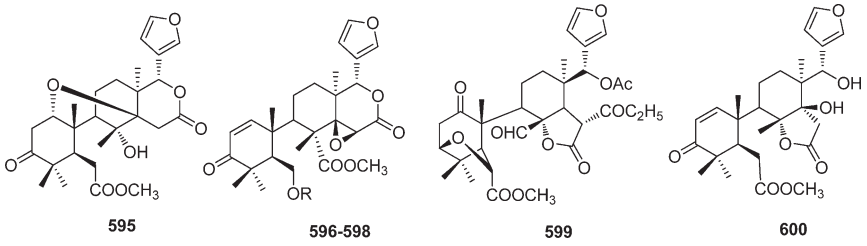


**Figure 22.** Other structures of rings B,D-seco limonoids **595**−**600**.

**292** have been continuing for more than twenty years in several research groups. This was undoubtedly due to its complex molecular architecture, which comprised sixteen contiguous stereogenic centers, seven of which were tetrasubstituted carbon atoms, and a diverse array of oxygenated functionalities in addition to a rigid conformation imposed by intramolecular


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**Table 21. Structures and Sources of Rings A,B,D-seco Limonoids 601−606**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **601** | methyl ivorensate | | *Khaya ivorensis*;[446,576] *Dysoxylum spectabile*[516] |
| **602** | | | *Soymida febrifuga*[538] |
| **603** | elegantin A | $R_1$ = O; $R_2$ = OH | *Trichilia elegans* ssp. *elegans*[520] |
| **604** | elegantin B | $R_1$ = OH; $R_2$ = O | *T. elegans* ssp. *elegans*[520] |
| **605** | 1,2-dihydro-l$\alpha$-acetoxyelegantin A | $R_1$ = O; $R_2$ = OH | *T. elegans* ssp. *elegans*[520] |
| **606** | 1,2-dihydro-l$\alpha$-acetoxyelegantin B | $R_1$ = OH; $R_2$ = O | *T. elegans* ssp. *elegans*[520] |

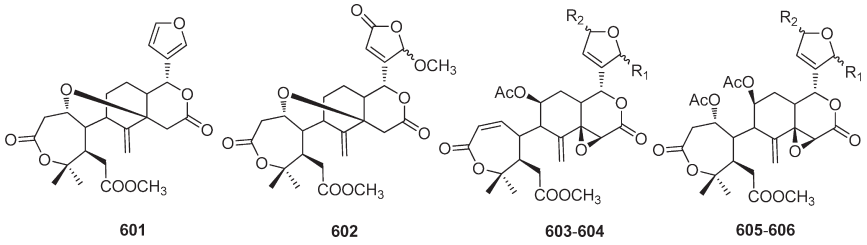


**Figure 23.** Structures of rings A,B,D-seco limonoids **601**−**606**.

**Table 22. Structures and Sources of 1,*n*-Linkage Rearranged Limonoids 607−625**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **607** | | | *Carapa procera*[580] |
| **608** | carapolide B | | *C. procera*[581] |
| **609** | carapolide C | | *C. procera*;[581] *C. grandiflora*[276] |
| **610** | carapolide D | $R_1R_2$ = $CH_2$ | *C. grandiflora*[276,582] |
| **611** | carapolide E | $R_1$ = $CH_3$; $R_2$ = OH | *C. grandiflora*[276,582] |
| **612** | carapolide F | R = OH | *C. grandiflora*[276,582] |
| **613** | carapolide G | R = H | *C. grandiflora*[276] |
| **614** | dukunolide A | $R_1$ = $R_2$ = $\alpha$-OH; $R_3$ = H; 5,6-epoxy; $\Delta^{8,9}$ | *Lansium domesticum*[577,578] |
| **615** | dukunolide B | $R_1$ = $R_2$ = $\alpha$-OH; $R_3$ = H; 5,6; 8,9-diepoxy | *L. domesticum*[100,577] |
| **616** | dukunolide C | $R_1$ = $R_2$ = $\alpha$-OH; $R_3$ = OAc; 5,6-epoxy; $\Delta^{8,9}$ | *L. domesticum*[100,577] |
| **617** | dukunolide D | $R_1$ = $R_2$ = $\alpha$-OH; $R_3$ = H; $\Delta^{8,9}$ | *L. domesticum*[100,583] |
| **618** | dukunolide E | $R_1$ = $R_2$ = $\alpha$-OH; $R_3$ = H; 8,9-epoxy | *L. domesticum*[583] |
| **619** | dukunolide F | $R_1$ = $R_2$ = $\beta$-OH; $R_3$ = H; 8,9-epoxy | *L. domesticum*[583] |
| **620** | seco-dukunolide F | | *L. domesticum*[584] |
| **621** | 7$\alpha$, 12$\alpha$-diacetoxy-11$\beta$-hydroxyneotecleanin | $R_1$ = OAc; $R_2$ = H | *Turraea wakefieldii*[579] |
| **622** | 11$\beta$, 12$\alpha$-diacetoxyneotecleanin | $R_1$ = O; $R_2$ = Ac | *T. wakefieldii*[579] |
| **623** | 11$\beta$, 12$\alpha$-diacetoxy-14$\beta$,15$\beta$-epoxyneotecleanin | $R_1$ = O; $R_2$ = Ac | *T. wakefieldii*[579] |
| **624** | 7$\alpha$,12$\alpha$-diacetoxy-14$\beta$,15$\beta$-epoxy-11$\beta$-hydroxyneotecleanin | $R_1$ = OAc; $R_2$ = H | *T. wakefieldii*[579] |
| **625** | 11$\beta$, 12$\alpha$-diacetoxy-1-deoxo-14$\beta$, 15$\beta$-epoxy-3$\beta$-hydroxy-2-oxo-neotecleanin | | *T. wakefieldii*[579] |

hydrogen bonding. Furthermore its sensitivity to acid and base together with its photoinstability made it particularly prone to rearrangement, thereby frustrating many synthesis plans.[770] The strategy applied to the total synthesis of **292**, called "relay route" or "relay synthesis", consisted of attempting to degrade **292** to a specific potential synthetic intermediate and then transform this back into the natural product. For example, one application of this strategy involved the degradation of the enol double bond to give an advanced intermediate and development of methods to convert this intermediate back into the natural product by reintroduction of the enol double bond using an acetal exchange process. In addition, the strategy focused on a convergent approach, which would bring together a decalin fragment with a hydroxydihydrofuran acetal portion (Scheme 1).[771]

The strategy in the formation of the decalin unit of **292** included two different ways. One is the employment of a silyl group to control the stereoselectivity of several key steps and to introduce C-3 hydroxyl functionality in decalin motif,[772−774] and another is the cleavage of C8−C14 bond via a base-mediated retro-Aldol reaction of natural product **292**, in which macrocyclic carbonate is a key intermediate.[774−776] The degradation of **292** to the demethylated decalin and the subsequent remethylation to the protected fragment has been presented. This not only connected the total synthesis and the degradation route of **292**,


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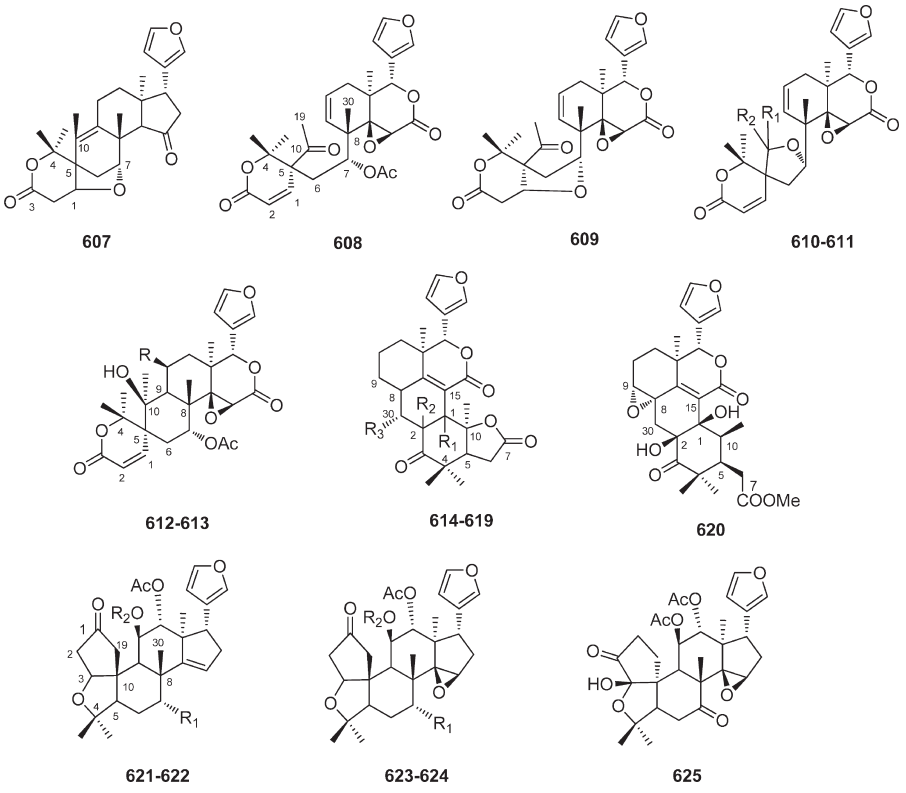


**Figure 24.** Structures of 1,*n*-linkage rearranged limonoids **607**−**625**.

### Table 23. Structures and Sources of Mexicanolide-Class Limonoids 626−845

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **626** | mexicanolide | $R_1 = R_3 = H$; $R_2 = O$ | *Carapa procera*;[167] *Cedrela mexicana*;[587] *C. odorata*;[533,641] *C. fissilis*;[642] *Khaya senagalensis*;[451,467,603] *K. ivorensis*;[446] *K. grandifoliola*;[164] *Neobeguea mahafalensis*;[557] *Cipadessa fruticosa*;[617,643] *Swietenia mahagoni*;[458] *Xylocarpus granatum*[448] |
| **627** | 2$\alpha$-hydroxymexicanolide | $R_1 = OH$; $R_2 = O$; $R_3 = H$ | *Khaya senegalensis*[467,603] |
| **628** | 2$\alpha$,3$\beta$-dihydroxy-3-deoxymexicanolide | $R_1 = R_2 = OH$; $R_3 = H$ | *K. senegalensis*[467,468,603] *Swietenia mahagoni*[458] |
| **629** | 3$\beta$-hydroxy-3-deoxymexicanolide | $R_1 = R_3 = H$; $R_2 = OH$ | *Khaya senegalensis*;[467,603] *Cabralea eichleriana*[644] |
| **630** | 6-hydroxymexicanolide | $R_1 = H$; $R_2 = O$; $R_3 = OH$ | *Cedrela odorata*;[533] *Khaya senegalensis*;[164] *Lansium domesticum*[100,645] |
| **631** | 6-acetoxymexicanolide | $R_1 = H$; $R_2 = O$; $R_3 = OAc$ | *L. domesticum*[100] |
| **632** | 6-deoxyswietenolide (proceranolide) | $R_1 = R_3 = H$; $R_2 = OH$ | *Carapa procera*;[590] *Swietenia macrophylla*;[445] *S. mahagoni*;[112] *Cedrela odorata*;[533] *Quivisia papinae*;[646] *Xylocarpus granatum*[448,633] |
| **633** | 2′*R*-methylbutanoylproceranolide | $R_1 = R_3 = H$; $R_2$ = 2′R-OPiv | *Cipadessa baccifera*;[591] *C. cinerascens*[647] |
| **634** | 2′*S*-methylbutanoylproceranolide | $R_1 = R_3 = H$; $R_2$ = 2′S-OPiv | *C. baccifera*;[591] *C. cinerascens*;[647] *Xylocarpus moluccensis*[558] |
| **635** | proceranolide butanoate | $R_1 = R_3 = H$; $R_2 = OBu$ | *Khaya ivorensis*[648] |
| **636** | 2-hydroxy-3-*O*-isobutyrylproceranolide | $R_1 = OH$; $R_2$ = OiBu; $R_3 = H$ | *Swietenia mahagoni*[458] |
| **637** | 2-hydroxy-3-*O*-benzoylproceranolide | $R_1 = OH$; $R_2$ = OBz; $R_3 = H$ | *S. mahagoni*[458] |
| **638** | swietenolide | $R_1 = H$; $R_2 = R_3 = OH$ | *S. mahagoni*;[112,603,649] *S. macrophylla*;[55,445] *Khaya grandifoliola*;[436] *Cedrela odorata*;[510] *Quivisia papinae*[646] |
| **639** | 2$\alpha$-hydroxyswietenolide | $R_1 = R_2 = R_3 = OH$ | *Q. papinae*[646] |
| **640** | 2-hydroxy-3-*O*-tigloyl-6-*O*-acetylswietenolide | $R_1 = OH$; $R_2$ = OTig; $R_3$ = OAc | *Trichilia connaroides*[650] |


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**Table 23. Continued**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **641** | 2-hydroxy-3-tigloyl-6-deoxyswietenolide | $R_1$ = OH; $R_2$ = OTig; $R_3$ = H | *Capuronianthus mahafalensis*;[613] *Trichilia connaroides*;[651] *Swietenia mahagoni*[458] |
| **642** | 2-hydroxy-3-*O*-tigloylswietenolide | $R_1$ = $R_3$ = OH; $R_2$ = OTig | *S. mahagoni*[457,649] |
| **643** | 3-acetylswietenolide | $R_1$ = H; $R_2$ = OAc; $R_3$ = OH | *S. mahagoni*;[112,652] *Khaya ivorensis*;[447] *K. senegalensis*[623] |
| **644** | 3-tigloylswietenolide | $R_1$ = H; $R_2$ = OTig; $R_3$ = OH | *Swietenia mahagoni*;[112,603] *S. macrophylla*[55,653] |
| **645** | 6-acetylswietenolide | $R_1$ = H; $R_2$ = OH; $R_3$ = OAc | *S. mahagoni*;[112] *S. macrophylla*;[445] *Khaya grandifoliola*[436] |
| **646** | 6-acetyl-3-tigloylswietenolide | $R_1$ = H; $R_2$ = OTig; $R_3$ = OAc | *Swietenia mahagoni*;[112,603] *S. macrophylla*[653] |
| **647** | diacetylswietenolide | $R_1$ = H; $R_2$ = $R_3$ = OAc | *S. macrophylla*;[55,445,653,654] *S. mahagoni*;[112,603] *Khaya ivorensis*;[446] *K. senegalensis*[623] |
| **648** | fissinolide (grandifoliolin, angustinolide, 3$\beta$-acetoxymexicanolide) | $R_1$ = $R_3$ = H; $R_2$ = OAc | *K. nyasica*;[164,184] *K. senegalensis*;[601,603,623] *K. grandifoliola*;[602] *K. madagascariensis*;[469] *Cedrela fissilis*;[596] *Cabralea eichleriana*;[430,644] *Swietenia mahagoni*[458] |
| **649** | 2-hydroxyfissinolide | $R_1$ = OH; $R_2$ = OAc; $R_3$ = H | *S. mahagoni*;[458] *Khaya ivorensis*;[164,446] *K. senegalensis*[623] |
| **650** | 2,6-dihydroxyfissinolide | $R_1$ = $R_3$ = OH; $R_2$ = OAc | *K. senegalensis*[601,623] |
| **651** | 3$\beta$-deacetylfissinolide | $R_1$ = $R_3$ = H; $R_2$ = OH | *Cabralea eichleriana*;[430] *Cedrela odorata*[98] |
| **652** | khayasin (3$\beta$-isobutyryloxymexicanolide) | $R_1$ = $R_3$ = H; $R_2$ = OiBu | *C. odorata*;[641] *Neobeguea mahafalensis*;[557] *Cipadessa baccifera*;[591] *Xylocarpus moluccensis*;[558] *Khaya senegalensis*;[451,655] *K. grandifoliola*[164] |
| **653** | 2-hydroxykhayasin | $R_1$ = OH; $R_2$ = OiBu; $R_3$ = H | *K. madagascariensis*[164] |
| **654** | khayasin B | $R_1$ = $R_3$ = H; $R_2$ = OBz | *K. senegalensis*[451] |
| **655** | khayasin T | $R_1$ = $R_3$ = H; $R_2$ = OTig | *K. senegalensis*;[451] *Cipadessa fruticosa*;[617,656] *C. baccifera*;[591,657] *C. cinerascens*;[647] *Xylocarpus granatum*;[426,633] *X. moluccensis*;[558] *Toona ciliata*;[290] *Swietenia macrophylla*;[445,653] *S. mahagoni*[112,458] |
| **656** | augustineolide | $R_1$ = Tig; $R_2$ = OH; $R_3$ = OAc; $R_4$ = OiBu | *S. macrophylla*[445] |
| **657** | swietmanin E | $R_1$ = Tig; $R_2$ = $R_4$ = H; $R_3$ = OH | *S. mahagoni*[458] |
| **658** | swietmanin F | $R_1$ = Ac; $R_2$ = $R_4$ = H; $R_3$ = OH | *S. mahagoni*;[458] *Khaya senegalensis*[623] |
| **659** | khayalenoid G | $R_1$ = Ac; $R_2$ = OAc; $R_3$ = OH; $R_4$ = H | *K. senegalensis*[623] |
| **660** | khayalenoid H | $R_1$ = Ac; $R_2$ = OAc; $R_3$ = $R_4$ = H | *K. senegalensis*[623] |
| **661** | khayalenoid I | $R_1$ = Ac; $R_2$ = $R_3$ = $R_4$ = H; 11$\alpha$-OAc | *K. senegalensis*[623] |
| **662** | cabralin | $R_1$ = OAc; $R_2$ = H; $R_3$ = O; $R_4$ = OH | *Cabralea eichleriana*[430] |
| **663** | isocabralin | $R_1$ = OAc; $R_2$ = H; $R_3$ = OH; $R_4$ = O | *C. eichleriana*[430] |
| **664** | domesticulide E | $R_1$ = $R_3$ = O; $R_2$ = $R_4$ = OH | *Lansium domesticum*[100] |
| **665** | 2-hydroxy-8(14)-dihydrofissinolide | $R_1$ = $R_2$ = OH; $R_3$ = $R_4$ = H | *Khaya madagascariensis*[164] |
| **666** | methyl 3$\beta$-acetoxy-2-hydroxy-1-oxomeliacate | $R_1$ = OH; $R_2$ = OAc; $R_3$ = $R_4$ = H | *K. madagascariensis*[469] |
| **667** | dihydrokhayasin | $R_1$ = $R_3$ = $R_4$ = H; $R_2$ = OiBu | *K. anthotheca*;[163] *K. madagascariensis*[164] |
| **668** | khayanone | $R_1$ = H; $R_2$ = O; $R_3$ = OH; $R_4$ = $\beta$-OH | *K. senegalensis*[470,550,559,575,623,658] |
| **669** | xyloccensin N | $R_1$ = $R_3$ = H; $R_2$ = OAc; $R_4$ = OH | *Xylocarpus granatum*[604,659] |
| **670** | 3-deacetylxyloccensin N | $R_1$ = $R_3$ = H; $R_2$ = $R_4$ = OH | *X. granatum*[605] |
| **671** | xylocarpin B | $R_1$ = $R_3$ = H; $R_2$ = OTig; $R_4$ = OH | *X. granatum*[660] |
| **672** | angolensin A | $R_1$ = $R_3$ = $R_4$ = H; $R_2$ = OTig; $\Delta^{14,15}$ | *Entandrophragma angolense*[545] |
| **673** | angolensin C | $R_1$ = H; $R_2$ = O; $R_3$ = $\alpha$-OAc; $R_4$ = OH | *E. angolense*[545] |
| **674** | 8$\beta$,14$\alpha$-dihydroxyswietenolide | $R_1$ = $R_4$ = H; $R_2$ = OH; $R_3$ = $\beta$-OH | *Cedrela odorata*[510] |
| **675** | granatumin D | $R_1$ = $R_3$ = $R_4$ = H; $R_2$ = OTig | *Xylocarpus granatum*[426] |
| **676** | 3$\beta$-hydroxyisomexicanolide | | *Cedrela fissilis*[642] |
| **677** | swietenine | $R_1$ = H; $R_2$ = OTig; $R_3$ = OH | *Swietenia macrophylla*;[55,445,612,653,661,662] *S. mahagoni*;[112,603,663] *Khaya ivorensis*[447] |
| **678** | swietenine B | $R_1$ = H; $R_2$ = propanate; $R_3$ = OH | *Swietenia mahagoni*[112] |
| **679** | swietenine C | $R_1$ = H; $R_2$ = OiBu; $R_3$ = OH | *S. mahagoni*;[112] *S. macrophylla*;[614] *S. humilis*[434] |
| **680** | swietenine D | $R_1$ = H; $R_2$ = methacrylyl; $R_3$ = OH | *S. mahagoni*[112] |
| **681** | swietenine E | $R_1$ = H; $R_2$ = OPiv; $R_3$ = OH | *S. mahagoni*[112] |


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**Table 23. Continued**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **682** | swietenine F | $R_1$ = H; $R_2$ = OBz; $R_3$ = OH | *S. mahagoni*[112] |
| **683** | sweitenine acetate | $R_1$ = H; $R_2$ = OTig; $R_3$ = OAc | *S. mahagoni*;[112] *S. macrophylla*[55,653] |
| **684** | 6-deoxydestigloylswietenine (3$\beta$-hydroxymexicanolide, $\Delta^{8,30}$) | $R_1$ = $R_3$ = H; $R_2$ = OH | *Khaya senegalensis*[451,464,467,468] |
| **685** | 6-deoxydestigloylswietenine acetate | $R_1$ = $R_3$ = H; $R_2$ = OAc | *K. senegalensis*;[451,464,466] *Xylocarpus granatum*[162] |
| **686** | 3-*O*-detigloyl-3-*O*-acetylswietenine | $R_1$ = H; $R_2$ = OAc; $R_3$ = OH | *Khaya ivorensis*[447] |
| **687** | 6-acetylswietenine | $R_1$ = H; $R_2$ = OTig; $R_3$ = OAc | *Swietenia mahagoni*[603] |
| **688** | 6-*O*-acetyl-2-hydroxyswietenine | $R_1$ = OH; $R_2$ = OTig; $R_3$ = OAc | *S. mahagoni*[630] |
| **689** | 2-hydroxyswietenine | $R_1$ = $R_3$ = OH; $R_2$ = OTig | *S. mahagoni*;[559,630,663,664] *S. macrophylla*[445] |
| **690** | 2-hydroxy-6-deoxyswietenine (methyl 3$\beta$-tigloyloxy-2-hydroxy-1-oxo-meliac-8(30)-enate) | $R_1$ = OH; $R_2$ = OTig; $R_3$ = H | *S. macrophylla*;[614] *Capuronianthus mahafalensis*[613] |
| **691** | 6-dexoxyswietenine isobutyrate | $R_1$ = $R_3$ = H; $R_2$ = OiBu | *Khaya nyasica*[164] |
| **692** | 2-hydroxydestigloyl-6-deoxyswientenine acetate | $R_1$ = OH; $R_2$ = OAc; $R_3$ = H | *Xylocarpus molluccensis*[162] |
| **693** | 12$\beta$-hydroxy-6-deoxy-destigloylswientenine diacetate | $R_1$ = $R_3$ = H; $R_2$ = OAc; 12$\beta$- OAc | *Khaya senegalensis*[451] |
| **694** | febrifugin (6-desoxyswietenine) | $R_1$ = $R_3$ = H; $R_2$ = OTig | *Soymida febrifuga*;[615] *Cedrela odorata*;[98] *Cipadessa baccifera*;[591,618,657] *C. fruticosa*;[617,643,656] *C. cinerascens*;[647] *Toona ciliata*;[290] *Xylocarpus granatum*;[426] *Swietenia mahagoni*;[603,616] *S. macrophylla*[445,653] |
| **695** | humilinolide C | $R_1$ = OAc; $R_2$= OTig; $R_3$ = H | *S. humilis*[434,629,665] |
| **696** | 6-acetoxyhumilinolide C | $R_1$ = $R_3$ = OAc; $R_2$ = OTig | *S. aubrevilleana*[445] |
| **697** | humilinolide D | $R_1$ = OH; $R_2$ = OAc; $R_3$ = OAc | *S. humilis*[434,629,665] |
| **698** | humilinolide E | $R_1$ = OH; $R_2$ = OTig; $R_3$ = OAc | *S. humilis*[434] |
| **699** | methyl-2-hydroxy-3$\beta$-isobutyroxy-1-oxomeliac-8(30)-enate | $R_1$ = OH; $R_2$ = OiBu; $R_3$ = H | *S. humilis*[434,619] |
| **700** | methyl-2-hydroxy-3$\beta$-tigloyloxy-1-oxomeliac-8(30)-enate | $R_1$ = OH; $R_2$ = OTig; $R_3$ = H | *S. humilis*[434] |
| **701** | methyl 3$\beta$-tigloyloxy-2,6-dihydroxy-1-oxo-meliac-8(30)-enate | $R_1$ = OH; $R_2$ = OTig; $R_3$ = $\beta$-OH | *S. macrophylla*[614] |
| **702** | methyl 3$\beta$-isobutyryloxy-1-oxomeliac-8(30)-enate | $R_1$ = $R_3$ = H; $R_2$ = OiBu | *Carapa procera*;[666] *Khaya nyasica*;[184] *Cipadessa baccifera*[591] |
| **703** | cipadesin | $R_1$ = $R_3$ = H; $R_2$ = OPiv | *C. baccifera*;[618,657] *C. fruticosa*[617,643,656] |
| **704** | 2′*R*-cipadesin | $R_1$ = $R_3$ = H; $R_2$ = 2′R-OPiv | *C. baccifera*[591] |
| **705** | 2′*S*-cipadesin | $R_1$ = $R_3$ = H; $R_2$ = 2′S- =OPiv | *C. baccifera*[591] |
| **706** | ruageanin D | $R_1$ = OH; $R_2$ = OAc; $R_3$ = H | *Ruagea glabra*[556] |
| **707** | 6-epidestigloylswietenine diacetate | $R_1$ = H; $R_2$ = OAc; $R_3$ = OAc | *Khaya senegalensis*[464] |
| **708** | khayalenoid E | $R_1$ = H; $R_2$ = O; $R_3$ = OAc | *K. senegalensis*[623] |
| **709** | swietmanin A | $R_1$ = $R_3$ = H; $R_2$ = OiBu; 11$\alpha$-OAc | *Swietenia mahagoni*[458] |
| **710** | swietmanin B | $R_1$ = $R_3$ = H; $R_2$ = OAc; 11$\alpha$-OAc | *S. mahagoni*[458] |
| **711** | swietmanin C | $R_1$ = $R_3$ = H; $R_2$ = OH; 11$\alpha$-OAc | *S. mahagoni*[458] |
| **712** | swietmanin D | $R_1$ = $R_2$ = OAc; $R_3$ = H; 11$\alpha$-OAc | *S. mahagoni*[458] |
| **713** | 11$\alpha$-acetoxy-2$\alpha$-hydroxy-6-deoxy-destigloylswietenine acetate | $R_1$ = OH; $R_2$ = OAc; $R_3$ =H; 11$\alpha$-OAc | *Khaya ivorensis*[554] |
| **714** | erythrocarpine B | R = Bz | *Chisocheton erythrocarpus*[667] |
| **715** | erythrocarpine C | R = Cin | *C. erythrocarpus*[667] |
| **716** | febrifugin A | $R_1$ = O; $R_2$ = OH | *Cipadessa fruticosa*;[617,656] *Xylocarpus granatum*[426,633] |
| **717** | granatumin E | $R_1$ = OH; $R_2$ = H | *X. granatum*[426] |
| **718** | dehydrocarapin | R = O | *Cedrela odorata*[500] |
| **719** | xylomexicanolide B | R = OiBu | *Xylocarpus moluccensis*[558] |
| **720** | mahagonin | | *Swietenia mahagoni*[668] |
| **721** | angustidienolide | $R_1$ = $R_3$ = H; $R_2$ = Ac | *Cedrela augustifolia*[597] |


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**Table 23. Continued**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **722** | 2$\alpha$-hydroxyangustidienolide | $R_1$ = OH; $R_2$ = Ac; $R_3$ = H | *C. augustifolia*[597] |
| **723** | seneganolide A | $R_1$ = $R_2$ = $R_3$ = H | *Swietenia mahagoni*;[458] *Khaya senegalensis*[472] |
| **724** | 2-hydroxyseneganolide A | $R_1$ = OH; $R_2$ = $R_3$ = H | *K. senegalensis*[472] |
| **725** | 2-acetoxyseneganolide A | $R_1$ = OAc; $R_2$ = $R_3$ = H | *K. senegalensis*[472] |
| **726** | tigloylseneganolide A | $R_1$ = $R_3$ = H; $R_2$ = Tig | *Cipadessa baccifera*;[591] *Xylocarpus granatum*[426] |
| **727** | erythrocarpine A | $R_1$ = $R_3$ = H; $R_2$ = Bz | *Chisocheton erythrocarpus*[667] |
| **728** | granatumin A | $R_1$ = $R_3$ = H; $R_2$ = methylacryl | *Xylocarpus granatum*[426] |
| **729** | granatumin B | $R_1$ = $R_3$ = H; $R_2$ = Piv | *X. granatum*[426] |
| **730** | swietmanin G | $R_1$ = OH; $R_2$ = iBu; $R_3$ = H | *Swietenia mahagoni*[458] |
| **731** | swietmanin H | $R_1$ = OH; $R_2$ = Ac; $R_3$ = H | *S. mahagoni*[458] |
| **732** | swietmanin I | $R_1$ = OH; $R_2$ = Tig; $R_3$ = H | *S. mahagoni*[458] |
| **733** | xylomexicanolide A | $R_1$ = $R_3$ = H; $R_2$ = iBu | *Xylocarpus moluccensis*[558] |
| **734** | khayalenoid F | $R_1$ = OH; $R_2$ = Ac; $R_3$ = S-OAc | *Khaya senegalensis*[623] |
| **735** | quivisianolide B | $R_1$ = OH; $R_2$ = Ang; $\Delta^{9,11}$ | *Quivisia papinae*[646] |
| **736** | granatumin C | $R_1$ = H; $R_2$ = Tig; $\Delta^{14,15}$ | *Xylocarpus granatum*[426] |
| **737** | xylogranatin A | $R_1$ = $R_3$ = $R_5$ = H; $R_2$ = OTig; $R_4$ = $\alpha$-OH | *X. granatum*[633,639] |
| **738** | 30$\alpha$-hydroxylxylogranatin A | $R_1$ = $R_3$ = H; $R_2$ = OTig; $R_4$ = $R_5$ = $\alpha$-OH | *X. granatum*[669] |
| **739** | carapin | $R_1$ = $R_3$ = $R_5$ = H; $R_2$ = O; $R_4$ = $\beta$-H | *Carapa procera*[670] |
| **740** | 3$\beta$-hydroxy-3-deoxycarapin | $R_1$ = $R_3$ = $R_5$ = H; $R_2$ = OH; $R_4$ = $\beta$-H | *Khaya senegalensis*;[467] *Entandrophragma angolense*[545] |
| **741** | methyl-3$\beta$-acetoxy-1-oxomeliac-14(15)-enate (3$\beta$-acetoxycarapin) | $R_1$ = $R_3$ = $R_5$ = H; $R_2$ = OAc; $R_4$ = $\beta$-H | *Khaya nyasica*;[184] *Toona ciliata*;[145] *Cedrela fissilis*[132,671] |
| **742** | 6-hydroxycarapin | $R_1$ = $R_5$ = H; $R_2$ = O; $R_3$ = OH; $R_4$ = $\beta$-H | *C. glaziovii*[672] |
| **743** | methyl 3$\beta$-acetoxy-6-hydroxy-1-oxomeliac-14-enoate (3$\beta$-acetoxy-3-deoxo-6R-hydroxycarapin) | $R_1$ = $R_5$ = H; $R_2$ = OAc; $R_3$ = OH; $R_4$ = $\beta$-H | *Khaya anthotheca*;[552] *K. senegalensis*[601] |
| **744** | 8$\alpha$-hydroxycarapin | $R_1$ = $R_3$ = $R_5$ = H; $R_2$ = O; $R_4$ = $\alpha$-OH | *Swietenia mahagoni*[458] |
| **745** | 6*R*,8$\alpha$-dihydroxycarapin | $R_1$ = $R_5$ = H; $R_2$ = O; $R_3$ = $R_4$ = $\alpha$-OH | *Khaya anthotheca*[552] |
| **746** | 3$\beta$,6-dihydroxydihydrocarapin | $R_1$ = $R_5$ = H; $R_2$ = OH; $R_3$ = $\beta$-OH; $R_4$ = $\beta$-H | *Swietenia macrophylla*;[445] *Cedrela odorata*[510] |
| **747** | xyloccensin $X_1$ | $R_1$ = $R_5$ = H; $R_2$ = OH; $R_3$ = $\beta$-OAc; $R_4$ = $\alpha$-OH | *Xylocarpus granatum*[673] |
| **748** | xyloccensin $X_2$ | $R_1$ = $R_3$ = $R_5$ = H; $R_2$ = OH; $R_4$ = $\alpha$-OH | *X. granatum*[673] |
| **749** | utilin B | $R_1$ = OH; $R_2$ = $R_5$ = OAc; $R_3$ = H; $R_4$ = $\alpha$-OiBu | *Entandrophragma utile*[491,620,674] |
| **750** | xylomexicanin B | $R_1$ = $R_3$ = $R_5$ = H; $R_2$ = OPiv; $R_4$ = $\alpha$-OH | *Xylocarpus granatum*[675] |
| **751** | khayalenoid A | R = H; $\Delta^{8,9}$; $\Delta^{14,15}$ | *Khaya senegalensis*[622] |
| **752** | khayalenoid B | R = H; $\Delta^{8,14}$ | *K. senegalensis*[622] |
| **753** | khayalenoid C | R = OH; $\Delta^{8,14}$ | *K. senegalensis*[623] |
| **754** | khayalenoid D | R = H; $\Delta^{8,30}$ | *K. senegalensis*[623] |
| **755** | utilin C | $R_1$ = $\alpha$-OH; $R_2$ = OAc; $R_3$ = H; $R_4$ = OiBu | *Entandrophragma utile*[491,621,674] |
| **756** | xyloccensin A | $R_1$ = $R_3$ = H; $R_2$ = $R_4$ = OiVal | *Xylocarpus moluccensis*[625] |
| **757** | xyloccensin D | $R_1$ = $\alpha$-OH; $R_2$ = $R_4$ = OiBu; $R_3$ = H | *X. moluccensis*[625] |
| **758** | xyloccensin X | $R_1$ = $\alpha$-OH; $R_2$ = OPiv; $R_3$ = H; $R_4$ = OiBu | *X. molluccensis*[624] |
| **759** | xyloccensin Y | $R_1$= $\alpha$-OH; $R_2$= OiBu; $R_3$= H; $R_4$= OPiv | *X. molluccensis*[624] |
| **760** | xylocarpin F | $R_1$ = $\beta$-H; $R_2$ = $R_4$ = OAc; $R_3$ = H | *X. granatum*[633] |
| **761** | xylocarpin G | $R_1$ = $\beta$-H; $R_2$ = OAc; $R_3$ = H; $R_4$ = OTig | *X. granatum*[633] |
| **762** | xylogranatin B | $R_1$ = $\beta$-H; $R_2$ = OTig; $R_3$ = H; $R_4$ = OAc | *X. granatum*[639] |
| **763** | xylogranatin C | $R_1$ = $\beta$-H; $R_2$ = OPiv; $R_3$ = H; $R_4$ = OAc | *X. granatum*[633,639] |
| **764** | xylogranatin D | $R_1$ = $\beta$-H; $R_2$ = OiBu; $R_3$ = H; $R_4$ = OAc | *X. granatum*[639] |
| **765** | xylogranatin S | $R_1$ = $\beta$-H; $R_2$ = OAc; $R_3$ = H; $R_4$ = OPiv | *X. granatum*[676] |
| **766** | angolensin B | $R_1$ = $\alpha$-OH; $R_2$ = OTig; $R_3$ = OAc; $R_4$ = OiBu | *Entandrophragma angolense*[545] |
| **767** | xyloccensin B | $R_1$ = $R_3$ = H; $R_2$ = $R_4$ = OiBu | *Xylocarpus moluccensis*[625] |
| **768** | xyloccensin F | $R_1$ = OH; $R_2$ = $R_4$ = OiBu; $R_3$ = H | *X. moluccensis*[625] |
| **769** | xyloccensin I | $R_1$ = OH; $R_2$ = OAc; $R_3$ = H; $R_4$ = OPiv | *X. granatum*;[626] *X. moluccensis*[626] |


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**Table 23. Continued**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **770** | xyloccensin J | $R_1$ = OH; $R_2$ = OAc; $R_3$ = H; $R_4$ = OiBu | *X. granatum*;[626] *X. moluccensis*[626] |
| **771** | xyloccensin M | $R_1 = R_3 = R_4$ = H; $R_2$ = OAc | *X. granatum*[604,659,677] |
| **772** | 3-deacetylxyloccensin M | $R_1 = R_3 = R_4$ = H; $R_2$ = OH | *X. granatum*[605] |
| **773** | xylocarpin A | $R_1 = R_3 = R_4$ = H; $R_2$ = OTig | *X. granatum*[660] |
| **774** | khayalactol | $R_1 = R_3$ = OH; $R_2$ = O; $R_4$ = H | *Khaya ivorensis*;[554] *K. senegalensis*[547,550,559,575,678] |
| **775** | grandifolide A | $R_1 = R_3$ = OH; $R_2$ = OAc; $R_4$ = H | *K. grandifoliola*[679] |
| **776** | xylocarpin J | | *Xylocarpus granatum*[677] |
| **777** | seneganolide | $R_1 = R_3$ = H; $R_2$ = O | *Khaya ivorensis*;[554] *K. senegalensis*[549−551,559] |
| **778** | 2-hydroxyseneganolide | $R_1$ = OH; $R_2$ = O; $R_3$ = H | *K. senegalensis*[550,559,658] |
| **779** | anthothecanolide | $R_1 = R_2 = R_3$ = OH | *K. grandifoliola*;[679] *K. anthotheca*[552] |
| **780** | 3-*O*-acetylanthothecanolide | $R_1 = R_3$ = OH; $R_2$ = OAc | *K. grandifoliola*;[679] *K. anthotheca*[552] |
| **781** | 2,3-di-*O*-acetylanthothecanolide | $R_1 = R_2$ = OAc; $R_3$ = OH | *K. anthotheca*[552] |
| **782** | 1$\alpha$,8$\alpha$-oxido-3$\beta$-acetoxy-2$\alpha$-acylperoxy-1$\alpha$,14$\alpha$-dihydroxy[3,3,1$^{10,2}$]-bicyclomeliac-7,19-olide | $R_1$ = OOAc; $R_2$ = OAc; $R_3$ = OH | *K. anthotheca*[680] |
| **783** | 3,8-hemiketalcarapin | | *Swietenia mahagoni*[458] |
| **784** | cedrodorin | $R_1$ = OH; $R_2 = R_3$ = H | *Cedrela odorata*[510,681] |
| **785** | 6-acetoxycedrodorin | $R_1$ = OAc; $R_2 = R_3$ = H | *C. odorata*;[681] *Xylocarpus granatum*[627,628,659] |
| **786** | 6-deoxy-9$\alpha$-hydroxycedrodorin | $R_1 = R_3$ = H; $R_2$ = OH | *Cedrela odorata*[681] |
| **787** | 9$\alpha$-hydroxycedrodorin | $R_1 = R_2$ = OH; $R_3$ = H | *C. odorata*[681] |
| **788** | xyloccensin K | $R_1 = R_2 = R_3$ = H | *C. guianensis*;[113] *C. odorata*;[510] *Entandrophragma angolense*;[545] *Xylocarpus granatum*[448,627,628,633,659,682] |
| **789** | xyloccensin W | $R_1 = R_2$ = H; $R_3$ = OAc | *X. granatum*[628,659] |
| **790** | xyloccensin G | R = OPiv | *X. moluccensis*[683] |
| **791** | xyloccensin H | $R_1$ = H | *X. moluccensis*[683] |
| **792** | swietemahonolide | $R_1 = R_3$ = H; $R_2$ = Tig | *X. granatum*;[426] *Cipadessa fruticosa*;[671] *C. baccifera*;[591] *C. cinerascens*;[647] *Switenia mahagoni*[56,112] |
| **793** | humilinolide A (methyl 3$\beta$-isobutyryloxy-2,6-dihydroxy-8$\alpha$,30$\alpha$-epoxy-1-oxo-meliacate) | $R_1 = R_3$ = OH; $R_2$ = iBu | *S. humilis*;[434,629,665,684] *S. macrophylla*[614] |
| **794** | humilinolide B | $R_1$ = OH; $R_2$ = iBu; $R_3$ = OAc | *S. humilis*[434,629,665] |
| **795** | humilinolide F | $R_1 = R_3$ = OAc; $R_2$ = Tig | *S. humilis*[434] |
| **796** | methyl 3$\beta$-acetoxy-2,6-dihydroxy-8$\alpha$,30$\alpha$-epoxy-1-oxo- meliacate | $R_1 = R_3$ = OH; $R_2$ = Ac | *S. macrophylla*[614] |
| **797** | methyl 3$\beta$-tigloyloxy-2-hydroxy-8$\alpha$,30$\alpha$-epoxy-1-oxo- meliacate (2-hydroxyswietemahonolide) | $R_1$ = OH; $R_2$ = Tig; $R_3$ = H | *S. macrophylla*;[614,653] *S. mahagoni*;[630] *Khaya senegalensis*[559] |
| **798** | methyl 2-hydroxy-3$\beta$-isobutyoyl-8$\alpha$,30$\alpha$-epoxy-1-oxo- meliacate | $R_1$ = OH; $R_2$ = iBu; $R_3$ = H | *Swietenia humilis*[619] |
| **799** | xylocarpin | $R_1 = R_3$ = H; $R_2$ = Ac | *Xylocarpus granatum*;[162,685] *Ruagea glabra*[556] |
| **800** | swietemahonin A | $R_1$ = H; $R_2$ = propanoyl; $R_3$ = OH | *Switenia mahagoni*[56,112,652] |
| **801** | swietemahonin B | $R_1$ = H; $R_2$ = propanoyl; $R_3$ = OAc | *S. mahagoni*[56,112] |
| **802** | swietemahonin C | $R_1$ = H; $R_2$ = iBu; $R_3$ = OAc | *S. mahagoni*;[56,112] *S. humilis*[434] |
| **803** | swietemahonin D | $R_1$ = H; $R_2$ = Ac; $R_3$ = OH | *S. mahagoni*[56,112] |
| **804** | swietemahonin E | $R_1$ = H; $R_2$ = Tig; $R_3$ = OH | *S. mahagoni*;[56,112,652] *S. macrophylla*[445,653] |
| **805** | 8,30-epoxy swietenine acetate (swietemahonin F) | $R_1$ = H; $R_2$ = Tig; $R_3$ = OAc | *S. mahagoni*;[56,112] *S. macrophylla*[55,445] |
| **806** | swietemahonin G | $R_1 = R_3$ = OH; $R_2$ = Tig | *S. mahagoni*;[56,112,457,559,630] *S. macrophylla*[445] |
| **807** | 6-*O*-acetylswietemahonin G | $R_1$ = OH; $R_2$ = Tig; $R_3$ = OAc | *S. mahagoni*;[559,630] *S. macrophylla*[653] |
| **808** | ruageanin A | $R_1 = R_3$ = H; $R_2$ = iBu | *Cipadessa baccifera*;[591] *C. fruticosa*;[617,647,656] *Ruagea glabra*[556] |
| **809** | ruageanin B | $R_1$ = OH; $R_2$ = Tig; $R_3$ = H | *R. glabra*[556] |
| **810** | 3-angeloyl-3-detigloylruageanin B | $R_1$ = OH; $R_2$ = Ang; $R_3$ = H | *Quivisia papinae*[646] |


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**Table 23. Continued**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **811** | ruageanin C | $R_1$ = OH; $R_2$ = Ac; $R_3$ = H | *Ruagea glabra*[556] |
| **812** | humilin B | $R_1$ = H; $R_2$ = iBu; $R_3$ = OH | *Swietenia humilis*;[434] *Xylocarpus moluccensis*[162] |
| **813** | 2′*R*-cipadesin A | $R_1$ = $R_3$ = H; $R_2$ = 2′R-pivalyoyl | *Cipadessa baccifera*;[591] *C. cinerascens*[647] |
| **814** | 2′*S*-cipadesin A | $R_1$ = $R_3$ = H; $R_2$ = 2′S-pivalyoyl | *C. baccifera*[591] |
| **815** | cipadesin A | $R_1$ = $R_3$ = H; $R_2$ = Piv | *C. fruticosa*;[617,643,656] *C. cinerascens*[647] |
| **816** | cineracipadesin A | $R_1$ = H; $R_2$ = Piv | *C. cinerascens*[563] |
| **817** | quivisianolide A | $R_1$ = OH; $R_2$ = Ang | *Quivisia papinae*[646] |
| **818** | quivisianone | | *Q. papinae*[646] |
| **819** | granaxylocarpin A | $R_1$ = OPiv; $R_2$ = Ac | *Xylocarpus granatum*[632] |
| **820** | xylogranatin B | $R_1$ = OTig; $R_2$ = Ac | *X. granatum*[637] |
| **821** | xylomexicanin A | $R_1$ = H; $R_2$ = *i*Bu; $\Delta^{2,3}$ | *X. granatum*[675] |
| **822** | granaxylocarpin B (xylocarpin H) | $R_1$ = H; $R_2$ = Tig; $\Delta^{2,3}$ | *X. granatum*[632,633] |
| **823** | xylogranatin C | $R_1$ = H; $R_2$ = Ac; $\Delta^{2,3}$ | *X. granatum*[448,637,638] |
| **824** | ecuadorin | | *Guarea kunthiana*[686] |
| **825** | xylocarpanoid A | | *Xylocarpus granatum*[634] |
| **826** | xylogranatin E | | *X. granatum*[687] |
| **827** | erythrocarpine D | $R_1$ = Cin; $R_2$ = H; $\Delta^{8,30}$, $\Delta^{14,15}$ | *Chisocheton erythrocarpus*[667] |
| **828** | erythrocarpine E | $R_1$ = Cin; $R_2$ = OH; $\Delta^{8,30}$ | *C. erythrocarpus*[667] |
| **829** | xylolactone (xyloccensin L) | $R_1$ = Tig; $R_2$ = H; 8,30-epoxy | *Xylocarpus granatum*[635,636,659] |
| **830** | granaxylocarpin C | $R_1$ = Tig; $R_2$ = OH; 8,30-epoxy | *X. granatum*[632] |
| **831** | grandifolin | | *Khaya grandifoliola*[561] |
| **832** | xylogranatin A | | *Xylocarpus granatum*[637] |
| **833** | xylogranatin D | | *X. granatum*[637,638] |
| **834** | xylogranatin I | $R_1$ = $R_2$ = H | *X. granatum*[638] |
| **835** | xylogranatin J | $R_1$ = $R_2$ = $CH_3$ | *X. granatum*[638] |
| **836** | xylogranatin K | $R_1$ = H; $R_2$ = $CH_3$ | *X. granatum*[638] |
| **837** | xylogranatin L | $R_1$ = H; $R_2$ = $CH_2CH_3$ | *X. granatum*[638] |
| **838** | xylogranatin M | $R_1$ = $CH_3$; $R_2$ = Ac | *X. granatum*[638] |
| **839** | xylogranatin N | $R_1$ = H; $R_2$ = 2′*S*-methylbutyroyl | *X. granatum*[638] |
| **840** | xylogranatin O | $R_1$ = H; $R_2$ = Tig | *X. granatum*[638] |
| **841** | xylogranatin P | $R_1$ = H; $R_2$ = *i*Bu | *X. granatum*[638] |
| **842** | xylogranatin Q | | *X. granatum*[638] |
| **843** | xylogranatin R | | *X. granatum*[638] |
| **844** | | | *Khaya ivorensis*[688] |
| **845** | grandifotane A | | *K. grandifoliola*[640] |

but also gave ready access to the demethylated decalin with the hydroxydihydrofuran acetal unit (right-hand side of the molecule as drawn) and the synthesis of important model compounds.[777] Several research groups have proposed the construction of a highly functionalized tricyclic *trans*-decalin system by IMDA (intramolecular Diels−Alder) cycloaddition.[778−784] In addition, the tetracyclic decalin portion was synthesized in an optically pure form *via* reduction of a silyloxyfuran derivative, and the key reactions involved the CBS (Corey-Bakshi-Shibata) asymmetric reduction of a ketone and an IMDA reaction.[785,786] The development of a strategy for the functionalization of the decalin portion based on the thermal Claisen rearrangement represented significant progress toward the total synthesis of **292**.[787] For a more advanced decalin system, both the total synthesis and semisynthesis with efficient and stereoselective construction of the ABCD rings,[788] ABC rings,[789] AB rings,[790] and B-ring,[791] all with full functionality, were reported.

For biological evaluation and a total synthesis study directed toward azadirachtin (**292**), the hydroxyfuran acetal functional group related to **292** have been prepared[792−796] using some reactions which involved an enantioselective route.[797,798] An extensive body of work has been completed on the preparation of models for the decalin portion of **292** and has led to the design of an effective route to the fragment methyl (3*SR**,3a*R**,6a*R**,10a*R**)-3-hydroxy-5-oxoperhydronaphtho[1,8*a*-*c*]furan-3-carboxylate, containing some of the functionality required for antifeedant activity.[799] A model substance for **292**, 9-hydroxy-dihydrofuro-2,3-tetrahydropyran, was synthesized by a route in which the key step involved cyclization of hydroxyl-dialdehyde precursors, acetylation and pyrolysis.[800] A tricyclic lactone derived from D-galactal via tin hydride mediated transannular radical cyclization was easily converted into an advanced precursor of the tricyclic dihydrofuran portion of **292**.[801] The Diels−Alder adduct formed using Evans' chiral Cu-bisoxazoline complex catalyst was easily converted to the tricyclic dihydrofuran moiety via $SmI_2$ reductive cleavage and selective functionalization.[802] Furthermore, a synthesis route to mimics of **292** containing the hydrotetrahydrofurancarboxylate hemiketal functional moiety was developed.[803,804] A key tricyclic acetal intermediate has been prepared in optically pure form in 12 steps from the known (-)-3-endobromotricyclo-[3.2.0.0$^{2,7}$]heptan-6-one.[805]


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The extreme steric congestion at the C8−C14 bond has resulted in the failure of many attempted coupling strategies. The convergent synthetic approach toward **292** and functionalized analogs was based on the construction of the C8−C14 bond through a diastereoselective Claisen rearrangement,[806−809] or through a transition metal chemistry strategy,[810] or through an intramolecular radical reaction followed by a cation-induced rupture of an initially formed bridge.[811,812] Finally, Ley placed particular emphasis on the key coupling of a left-hand decalin fragment with a right-hand hydroxydihydrofuran acetal unit via a Claisen rearrangement reaction of an intermediate propargylic enol ether.[23]

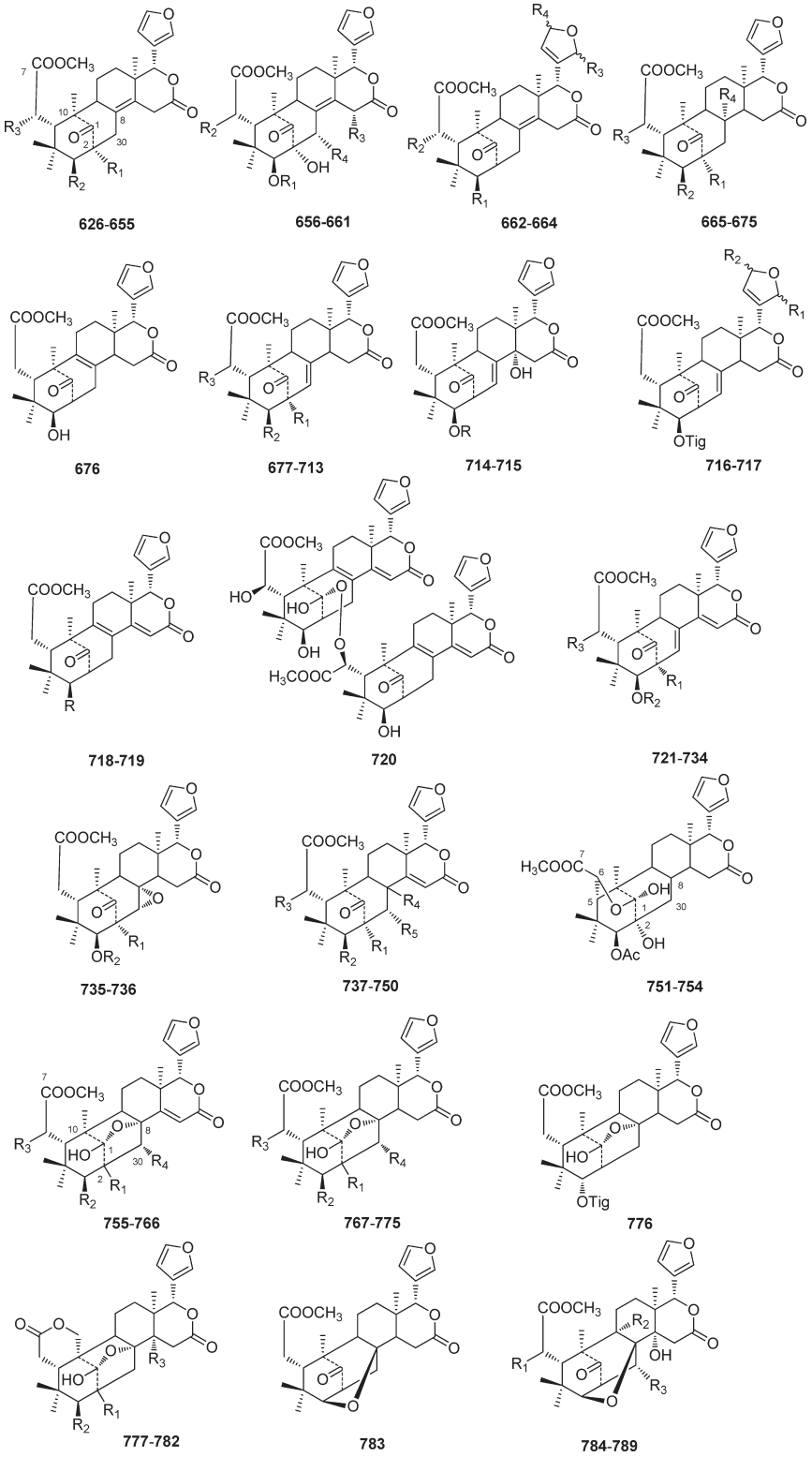


**Figure 25.** Continued


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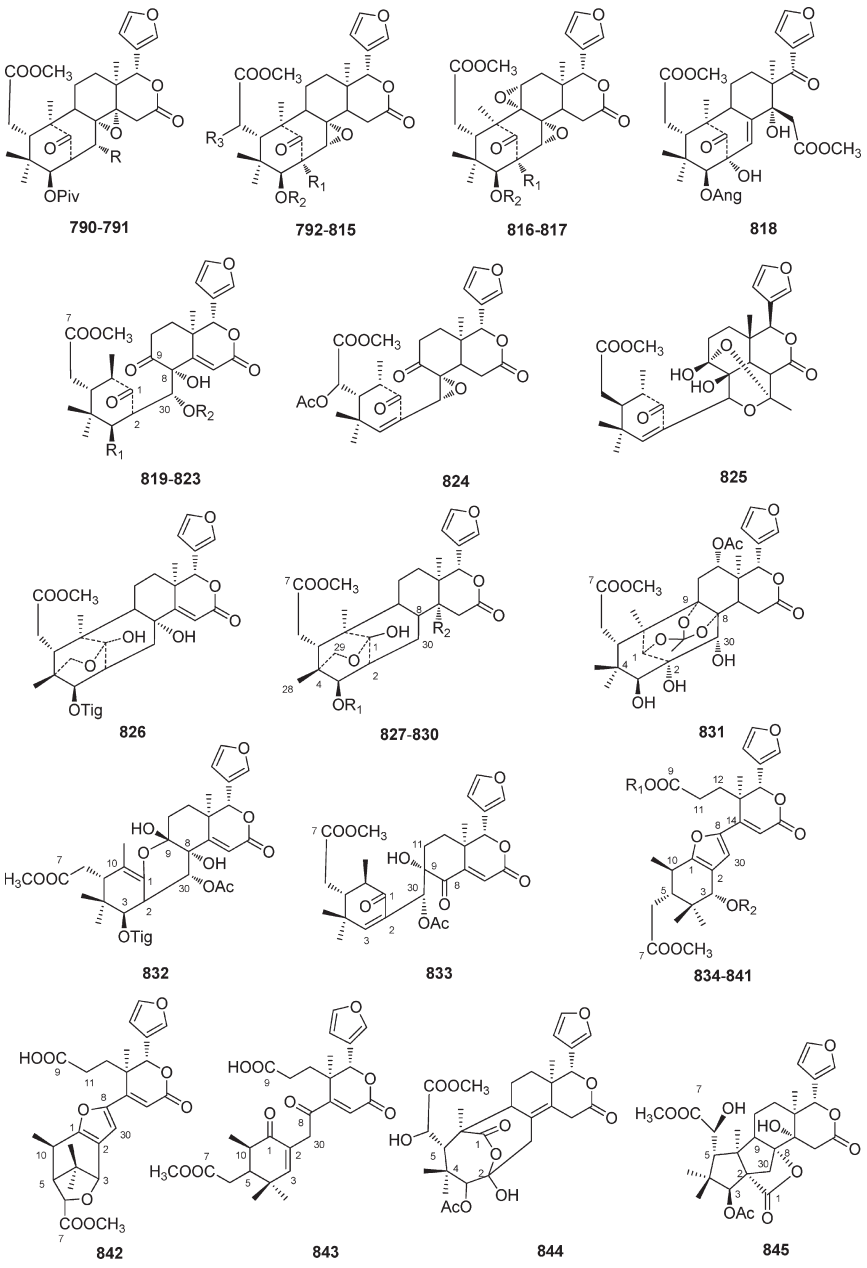


**Figure 25.** Structures of mexicanolide-class limonoids **626**−**845**.

After a long journey of 22 years, the total synthesis of **292** was finally completed. It could be produced from the key intermediate through a series of selective transformations.[770,813] Jauch summarized the retrosynthetic analysis, the key Ireland-Claisen rearrangement, radical cyclization, epoxidation, and completion of the total synthesis of **292** through relay synthesis, which contained 71 steps with a total yield of 0.00015%, and commented this work was a real highlight of organic chemistry.[814] In addition, Devakumar et al. summarized the decalin scaffold synthesis, pyran fragment construction, and the 'last summit' of the total synthesis of **292**, and called it a chemical odyssey.[24]

Azadirachtin (**292**), along with another four limonoids vepaol (**303**), isovepaol (**304**), 3-desacetylazadirachtin, and 1-tigloyl-3-acetyl-11-methoxyazadirachtinin (**318**), was synthesized from a common intermediate, and the judicious choice of transacetalization conditions allowed efficient access to both the azadirachtin and the azadirachtinin skeleton (Scheme 2).[815]

The conversion of **292** derivatives to the corresponding azadirachtinin skeletons could be achieved in high yield under mild conditions (Scheme 3).[816] Dinitrophenylamino, dansyl, and biotin groups were covalently attached to several derivatives of **292** via a linker group to give fluorescent or immunogenic compounds that generally retain the biological properties of **292**, which were potential tools for the determination of the mechanisms of **292** in living systems.[817]

Some derivatives related to naturally occurring limonoids were prepared for the purpose of either biological activity evaluation or reaction mechanistic investigation. On the basis


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**Table 24. Structures and Sources of Phragmalin-*ortho* Ester Limonoids 846−962**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **846** | phragmalin | $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$ | *Entandrophragma caudatum*;[689] *Khaya senegalensis*[559] |
| **847** | 12-acetoxyphragmalin | $R_1 = R_2 = R_3 = R_5 = R_6 = H$; $R_4 = OAc$ | *Chukrasia tabularis*[702] |
| **848** | phragmalin 3,30-di-isobutyrate | $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = R_6 =$ iBu | *C. tabularis*;[702] *Entandrophragma caudatum*[703] |
| **849** | phragmalin 3,30-diacetate | $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = R_6 = Ac$ | *Xylocarpus moluccensis*[162] |
| **850** | xyloccensin E (phragmalin 2,3,30-triacetate) | $R_1 = R_2 = R_6 = Ac$; $R_3 = R_4 = R_5 = H$ | *X. moluccensis*[162,625] |
| **851** | 12-acetoxyphragmalin 3,30-di-isobutyrate | $R_1 = R_3 = R_5 = H$; $R_2 = R_6 =$ iBu; $R_4 = OAc$ | *Chukrasia tabularis*[702] |
| **852** | phragmalin 3-isobutyrate 30-propionate | $R_1 = R_3 = R_4 = R_5 = H$; $R_2 =$ iBu; $R_6 =$ propanoyl | *C. tabularis*;[702] *Entandrophragma caudatum*[703] |
| **853** | 12-acetoxyphragmalin 3-isobutyrate 30-propionate | $R_1 = R_3 = R_5 = H$; $R_2 =$ iBu; $R_4 = OAc$; $R_6 =$ propanoyl | *E. caudatum*;[703] *Chukrasia tabularis*[702] |
| **854** | leandreanin C | $R_1 = R_2 = R_6 = Ac$; $R_3 = R_4 = H$; $R_5 =$ OAc | *Neobeguea leandreana*[704] |
| **855** | 14,15-dihydroepoxyfebrinin B | $R_1 = R_6 = Ac$; $R_2 =$ epoxytigloyl; $R_3 = R_4 = R_5 = H$ | *Soymida febrifuga*[705] |
| **856** | tabulalide C | $R_1 = R_2 = R_6 = H$; $R_3 = OH$; $R_4 = R_5 = OAc$ | *Chukrasia tabularis*[706] |
| **857** | tabulalide D | $R_1 = R_6 = H$; $R_2 = Ac$; $R_3 = OH$; $R_4 = R_5 = OAc$ | *C. tabularis*[559,706] |
| **858** | 2-*O*-acetyltabulalide D | $R_1 = R_2 = Ac$; $R_3 = OH$; $R_4 = R_5 = OAc$ $R_6 = H$ | *C. tabularis*[559] |
| **859** | tabularisin N | $R_1 = H$; $R_2 = R_6 = Ac$; $R_3 = OH$; $R_4 = R_5 = OAc$ | *C. tabularis*[707] |
| **860** | febrinin A | $R_1 = Ac$; $R_2 =$ Tig; $R_3 = R_4 = R_5 = H$; $R_6 =$ propanoyl; $\Delta^{14,15}$ | *Soymida febrifuga*[708] |
| **861** | febrinin B | $R_1 = R_6 = Ac$; $R_2 =$ Tig; $R_3 = R_4 = R_5 = H$; $\Delta^{14,15}$ | *S. febrifuga*[708] |
| **862** | epoxyfebrinin B | $R_1 = R_6 = Ac$; $R_2 =$ epoxytigloyl; $R_3 = R_4 = R_5 = H$; $\Delta^{14,15}$ | *S. febrifuga*[705] |
| **863** | xylocarpin I | | *Xylocarpus granatum*[633] |
| **864** | neobeguin | $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = R_6 = Ac$; $R_7 = CH_3$ | *Neobeguea mahafalensis*[709] |
| **865** | bussein A | $R_1 = R_3 = H$; $R_2 =$ Piv; $R_4 = R_5 = OAc$; $R_6 = Ac$; $R_7 = CH_3$ | *Entandrophragma bussei*[424,691,693] |
| **866** | bussein B | $R_1 = R_3 = H$; $R_2 =$ iBu; $R_4 = R_5 = OAc$; $R_6 = Ac$; $R_7 = CH_3$ | *E. bussei*[424,691,693] |
| **867** | bussein C | $R_1 = R_3 = R_7 = H$; $R_2 =$ Piv; $R_4 = R_5 = OAc$; $R_6 = Ac$ | *E. bussei*[693] |
| **868** | bussein D | $R_1 = R_3 = H$; $R_2 =$ epoxytigloyl; $R_4 = R_5 = OAc$; $R_6 = Ac$; $R_7 = CH_3$ | *E. bussei*[693] |
| **869** | bussein E | $R_1 = R_3 = H$; $R_2 =$ Tig; $R_4 = R_5 = OAc$; $R_6 = Ac$; $R_7 = CH_3$ | *E. bussei*[693] |
| **870** | bussein F | $R_1 = R_3 = R_7 = H$; $R_2 =$ iBu; $R_4 = R_5 = OAc$; $R_6 = Ac$ | *E. bussei*[693] |
| **871** | bussein G | $R_1 = R_3 = H$; $R_2 = 2'$-hydroxypivalyloyl; $R_4 = R_5 = OAc$; $R_6 = Ac$; $R_7 = CH_3$ | *E. bussei*[693] |
| **872** | bussein H | $R_1 = R_3 = H$; $R_2 = R_6 = Ac$; $R_4 = R_5 = OAc$; $R_7 = CH_3$ | *E. bussei*[693] |
| **873** | bussein J | $R_1 = R_3 = H$; $R_2 =$ Piv; $R_4 = OH$; $R_5 = OAc$; $R_6 = Ac$; $R_7 = CH_3$ | *E. bussei*[693] |
| **874** | bussein K | $R_1 = R_3 = H$; $R_2 =$ iBu; $R_4 = OH$; $R_5 = OAc$; $R_6 = Ac$; $R_7 = CH_3$ | *E. bussei*[693] |
| **875** | bussein L | $R_1 = R_3 = H$; $R_2 =$ iBu(OH); $R_4 = R_5 = OAc$; $R_6 = Ac$; $R_7 = CH_3$ | *E. bussei*[693] |
| **876** | bussein M | $R_1 = R_3 = H$; $R_2 = 2',3'$-dihydroxypivalyloyl; $R_4 = R_5 = OAc$; $R_6 = Ac$; $R_7 = CH_3$ | *E. bussei*[693] |
| **877** | spicata 2 | $R_1 = R_3 = H$; $R_2 =$ Piv; $R_4 =$ OiBu; $R_5 = OAc$; $R_6 = Ac$; $R_7 = CH_3$ | *E. spicatum*[710] |
| **878** | tabularisin P | $R_1 = R_4 = R_6 = R_7 = H$; $R_2 =$ iBu; $R_3 = R_5 = OAc$ | *Chukrasia tabularis*[707] |
| **879** | chukrasin A | $R_1 = H$; $R_2 = Ac$; $R_3 = OH$; $R_4 = OAc/OiBu$; $R_5 =$ OiBu; $R_6 = Ac/iBu$; $R_7 = CH_3$ | *C. tabularis*[711] |
| **880** | chukrasin B | $R_1 = R_3 = H$; $R_2 = Ac$; $R_4 = R_5 =$ OiBu; $R_6 =$ iBu; $R_7 = CH_3$ | *C. tabularis*[711] |


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**Table 24. Continued**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **881** | chukrasin C | $R_1 = R_3 = H$; $R_2 = Ac$; $R_4 = OAc/OiBu$; $R_5 = OiBu$; $R_6 = Ac/iBu$; $R_7 = CH_3$ | *C. tabularis*[711] |
| **882** | chukrasin D | $R_1 = R_2 = Ac$; $R_3 = H$; $R_4 = OAc/OiBu$; $R_5 = OiBu$; $R_6 = Ac/iBu$; $R_7 = CH_3$ | *C. tabularis*[711] |
| **883** | chukrasin E | $R_1 = R_2 = Ac$; $R_3 = H$; $R_4 = R_5 = OiBu$; $R_6 = iBu$; $R_7 = CH_3$ | *C. tabularis*[711] |
| **884** | tabularisin O | | *C. tabularis*[707] |
| **885** | leandreanin A | $R_1 = H$; $R_2 = OAc$; $R_3 = O$; $R_4 = Ac$ | *Neobeguea leandreana*[704] |
| **886** | leandreanin B | $R_1 = R_4 = Ac$; $R_2 = OAc$; $R_3 = O$ | *N. leandreana*[704] |
| **887** | kotschyin B | $R_1 = Ac$; $R_2 = H$; $R_3 = OAc$; $R_4 = iBu$ | *Pseudocedrela kotschyii*[443] |
| **888** | kotschyin C | $R_1 = Ac$; $R_2 = OAc$; $R_3 = O$; $R_4 = iBu$ | *P. kotschyii*[443] |
| **889** | swietenialide D | $R_1 = H$; $R_2 = 2'\beta,3'\beta$-epoxytigloyl; $R_3 = OH$; $R_4 =$ propanoyl | *Swietenia mahagoni*;[664] *S. macrophylla*[456] |
| **890** | 2-acetoxyswietenialide D | $R_1 = Ac$; $R_2 = 2'\beta,3'\beta$-epoxytigloyl; $R_3 = OH$; $R_4 =$ propanoyl | *S. macrophylla*[456] |
| **891** | 2,11-diacetoxyswietenialide D | $R_1 = Ac$; $R_2 = 2'\beta,3'\beta$-epoxytigloyl; $R_3 = OAc$; $R_4 =$ propanoyl | *S. macrophylla*[456] |
| **892** | 11-deoxyswietenialide D | $R_1 = R_3 = H$; $R_2 = 2'\beta,3'\beta$-epoxytigloyl; $R_4 =$ propanoyl | *S. macrophylla*[456] |
| **893** | swietenitin G | $R_1 = R_4 = Ac$; $R_2 = 2'\beta,3'\beta$-epoxytigloyl; $R_3 = OH$ | *S. macrophylla*[456] |
| **894** | swietenitin H | $R_1 = Ac$; $R_2 =$ Tig; $R_3 = OAc$; $R_4 =$ propanoyl | *S. macrophylla*[456] |
| **895** | swietenialide E | | *S. mahagoni*[664] |
| **896** | kotschyin A | $R_1 = R_2 = Ac$; $R_3 = iBu$ | *Pseudocedrela kotschyii*[443] |
| **897** | swietenitin A | $R_1 = R_3 = Ac$; $R_2 = 2'\beta,3'\beta$-epoxytigloyl | *S. macrophylla*[456] |
| **898** | swietenitin B | $R_1 = R_3 = Ac$; $R_2 = 2'\alpha,3'\alpha$-epoxytigloyl | *S. macrophylla*[456] |
| **899** | swietenitin C | $R_1 = Ac$; $R_2 = 2'\beta,3'\beta$-epoxytigloyl; $R_3 =$ propanoyl | *S. macrophylla*[456] |
| **900** | swietenitin D | $R_1 = H$; $R_2 = 2'\beta,3'\beta$-epoxytigloyl; $R_3 =$ propanoyl | *S. macrophylla*[456] |
| **901** | swietenitin E | $R_1 = Ac$; $R_2 =$ Tig; $R_3 =$ propanoyl | *S. macrophylla*[456] |
| **902** | swietenitin F | $R_1 = H$; $R_2 =$ Tig; $R_3 = iBu$ | *S. macrophylla*[456] |
| **903** | pseudrelone B | | *Pseudocedrela kotschyii*[694] |
| **904** | chukvelutilide A | $R_1 = R_2 = H$ | *Chukrasia tabularis*[696] |
| **905** | chukvelutilide B | $R_1 = Ac$; $R_2 = H$ | *C. tabularis*[696] |
| **906** | chukvelutilide C | $R_1 = H$; $R_2 = CH_3$ | *C. tabularis*[696] |
| **907** | chukvelutilide D | $R_1 = Ac$; $R_2 = CH_3$ | *C. tabularis*[696] |
| **908** | chukvelutilide E | $R_1 = R_2 = Ac$; $R_3 = H$ | *C. tabularis*[696] |
| **909** | chukvelutilide F | $R_1 = H$; $R_2 = iBu$; $R_3 = CH_3$ | *C. tabularis*[696] |
| **910** | chuktabrin B | | *C. tabularis*[697] |
| **911** | tabularisin A | $R_1 = OAc$; $R_2 = Ac$ | *C. tabularis*[707,712,713] |
| **912** | tabularisin B | $R_1 = OAc$; $R_2 = H$ | *C. tabularis*[707,712,713] |
| **913** | tabularisin E | $R_1 = H$; $R_2 = Ac$ | *C. tabularis*[707,712] |
| **914** | tabularisin F | $R_1 = R_2 = H$ | *C. tabularis*[707,712] |
| **915** | tabularisin J | $R_1 = OH$; $R_2 = Ac$ | *C. tabularis*[707] |
| **916** | tabularisin K | $R_1 = OH$; $R_2 = H$ | *C. tabularis*[707] |
| **917** | candollein | $R_1 = H$; $R_2 = iBu$ | *Entandrophragma candollei*;[530] *E. cylindricum*[714] |
| **918** | $\beta$-dihydroentandrophragmin | $R_1 = OH$; $R_2 = iBu$ | *E. cylindricum*[714] |
| **919** | entandrophragmin | R = iBu | *E. cylindricum*;[168,423,530,714] *E. bussei*;[424,530] *E. spicatum*;[530,710] *E. caudatum*[530] |
| **920** | utilin | R = Ac | *E. utile*[168,423,530] |
| **921** | swietenialide A | $R_1 = H$; $R_2 =$ Tig; $R_3 = CH_3$ | *Swietenia mahagoni*[664] |
| **922** | swietenialide B | $R_1 = H$; $R_2 =$ Tig; $R_3 = CH_2CH_3$ | *S. mahagoni*[664] |
| **923** | swietenialide C | $R_1 = H$; $R_2 = 2'\beta,3'\beta$-epoxytigloyl; $R_3 = CH_3$ | *S. mahagoni*[664] |
| **924** | swietenitin I | $R_1 = H$; $R_2 = 2'\beta$, $3'\beta$-epoxytigloyl; $R_3 = CH_2CH_3$ | *S. macrophylla*[456] |


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**Table 24. Continued**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **925** | swietenitin J | $R_1$ = Ac; $R_2$ = 2′$\beta$, 3′$\beta$-epoxytigloyl; $R_3$ = $CH_2CH_3$ | *S. macrophylla*[456] |
| **926** | swietenitin K | $R_1$ = Ac; $R_2$ = Tig; $R_3$ = $CH_2CH_3$ | *S. macrophylla*[456] |
| **927** | procerin | $R_1$ = propanoyl; $R_2$ = H; $R_3$ = OAc; $R_4$ = Ac | *Carapa procera*[580,715] |
| **928** | swietenitin L | $R_1$ = 2′$\beta$, 3′$\beta$-epoxytigloyl; $R_2$ = OH; $R_3$ = H; $R_4$ = proanoyl | *Swietenia macrophylla*[456] |
| **929** | swietenitin M | $R_1$ = 2′$\beta$, 3′$\beta$-epoxytigloyl; $R_2$ = OAc; $R_3$ = H; $R_4$ = proanoyl | *S. macrophylla*[456] |
| **930** | febrinolide | | *Soymida febrifuga*[705] |
| **931** | swietephragmin A | $R_1$ = Ac; $R_2$ = Tig; $R_3$ = $R_4$ = H; $R_5$ = $CH(CH_3)_2$ | *Swietenia mahagoni*[457] |
| **932** | swietephragmin B | $R_1$ = Ac; $R_2$ = Tig; $R_3$ = $R_4$ = H; $R_5$ = $CH(CH_3)CH_2CH_3$ | *S. mahagoni*[457] |
| **933** | swietephragmin C | $R_1$ = $R_3$ = $R_4$ = H; $R_2$ = Tig; $R_5$ = $CH(CH_3)CH_2CH_3$ | *S. mahagoni*[457] |
| **934** | 12$\alpha$-acetoxyswietephragmin C | $R_1$ = $R_3$ = H; $R_2$ = Tig; $R_4$ = OAc; $R_5$ = $CH(CH_3)CH_2CH_3$ | *S. macrophylla*[716] |
| **935** | 3$\beta$-*O*-destigloyl-3$\beta$-*O*-benzoyl-12$\alpha$-acetoxyswietephragmin C | $R_1$ = $R_3$ = H; $R_2$ = Bz; $R_4$ = OAc; $R_5$ = $CH(CH_3)CH_2CH_3$ | *S. macrophylla*[716] |
| **936** | swietephragmin D | $R_1$ = $R_3$ = $R_4$ = H; $R_2$ = Tig; $R_5$ = $CH(CH_3)_2$ | *S. mahagoni*[457] |
| **937** | 12$\alpha$-acetoxyswietephragmin D | $R_1$ = $R_3$ = H; $R_2$ = Tig; $R_4$ = OAc; $R_5$ = $CH(CH_3)_2$ | *S. macrophylla*[716] |
| **938** | 3$\beta$-*O*-destigloyl-3$\beta$-*O*-benzoyl-12$\alpha$-acetoxyswietephragmin D | $R_1$ = $R_3$ = H; $R_2$ = Bz; $R_4$ = OAc; $R_5$ = $CH(CH_3)_2$ | *S. macrophylla*[716] |
| **939** | swietephragmin E | $R_1$ = $R_4$ = H; $R_2$ = Tig; $R_3$ = OH; $R_5$ = $CH(CH_3)CH_2CH_3$ | *S. mahagoni*[457] |
| **940** | 6-*O*-acetylswietephragmin E | $R_1$ = $R_4$ = H; $R_2$ = Tig; $R_3$ = OAc; $R_5$ = $CH(CH_3)CH_2CH_3$ | *S. macrophylla*[716] |
| **941** | 3$\beta$-*O*-destigloyl-3$\beta$-*O*-benzoyl-6-*O*-acetylswietephragmin E | $R_1$ = $R_4$ = H; $R_2$ = Bz; $R_3$ = OAc; $R_5$ = $CH(CH_3)CH_2CH_3$ | *S. macrophylla*[716] |
| **942** | 6-*O*-acetyl-3′-demethylswietenphragmin E | $R_1$ = $R_4$ = H; $R_2$ = Tig; $R_3$ = OAc; $R_5$ = $CH(CH_3)_2$ | *S. macrophylla*[653] |
| **943** | swietephragmin F | $R_1$ = $R_3$ = $R_4$ = H; $R_2$ = Tig; $R_5$ = $CH_2CH_3$ | *S. mahagoni*[457] |
| **944** | swietephragmin G | $R_1$ = $R_3$ = $R_4$ = H; $R_2$ = Tig; $R_5$ = $CH_3$ | *S. mahagoni*[457] |
| **945** | swietephragmin H | $R_1$ = Ac; $R_2$ = Tig; $R_3$ = $R_4$ = H; $R_5$ = $CH_2CH_3$ | *S. macrophylla*[717] |
| **946** | swietephragmin I | $R_1$ = Ac; $R_2$ = Tig; $R_3$ = $R_4$ = H; $R_5$ = $CH_3$ | *S. macrophylla*[717] |
| **947** | swietephragmin J | $R_1$ = Ac; $R_2$ = Tig; $R_3$ = H; $R_4$ = OH; $R_5$ = $CH_2CH_3$ | *S. macrophylla*[717] |
| **948** | xyloccensin O | $R_1$ = H; $R_2$ = OAc | *Xylocarpus granatum*[448,659,699,718] |
| **949** | xyloccensin P | $R_1$ = $R_2$ = OAc | *X. granatum*[448,633,639,659,699,718] |
| **950** | xyloccensin Q (xyloccensin R) | $R_1$ = OH; $R_2$ = OAc | *X. granatum*[639,659,700,701,718] |
| **951** | xyloccensin R (xyloccensin Q) | $R_1$ = $R_2$ = OH | *X. granatum*[659,700,701] |
| **952** | xyloccensin S | $R_1$ = OAc; $R_2$ = OH | *X. granatum*[659,700,701] |
| **953** | xyloccensin T | $R_1$ = H; $R_2$ = OH | *X. granatum*[659,700] |
| **954** | xyloccensin U | $R_1$ = OH; $R_2$ = H | *X. granatum*[659,700] |
| **955** | xyloccensin V (xyloccensin T) | $R_1$ = OAc; $R_2$ = H | *X. granatum*[659,700,701] |
| **956** | tabularisin C | $R_1$ = OAc; $R_2$ = H; $R_3$ = $R_4$ = Ac | *Chukrasia tabularis*[707,712,713] |
| **957** | tabularisin D | $R_1$ = $R_2$ = $R_4$ = H; $R_3$ = Ac | *C. tabularis*[713] |
| **958** | tabularisin G | $R_1$ = $R_2$ = H; $R_3$ = $R_4$ = Ac | *C. tabularis*[707,712] |
| **959** | tabularisin H | $R_1$ = OAc; $R_2$ = H; $R_3$ = Ac; $R_4$ = iBu | *C. tabularis*[707,712] |
| **960** | tabularisin I | $R_1$ = OAc; $R_2$ = $R_3$ = H; $R_4$ = iBu | *C. tabularis*[707,712] |
| **961** | tabularisin L | $R_1$ = OAc; $R_2$ = $R_3$ = H; $R_4$ = Ac | *C. tabularis*[707] |
| **962** | tabularisin M | $R_1$ = OAc; $R_2$ = $R_4$ = Ac; $R_3$ = H | *C. tabularis*[707] |

of an intramolecular cyclopropanation of a diazo ketone and subsequent selective cleavage of a cyclopropyl ketone, a stereoselective synthesis of a model compound for azadiradione (**12**) was accomplished starting from $\alpha$-cyclocitral in 12 steps with 15% overall


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yield.[818] Early in 1989, Corey reported the synthesis of **12** from *trans,trans*-farnesol stereoselectively.[819] Sastry et al. prepared a series of nimbolide (**345**) derivatives modified on the lactone ring under catalyst-free conditions, and pointed out that the position and nature of the substituent seemed to be crucial for the cytotoxic activity.[820] The brief and stereoselective synthesis of havanensin-class limonoid models was based on a radical domino reaction converting an epoxyketone to a bicyclic hydroxyketone, and was

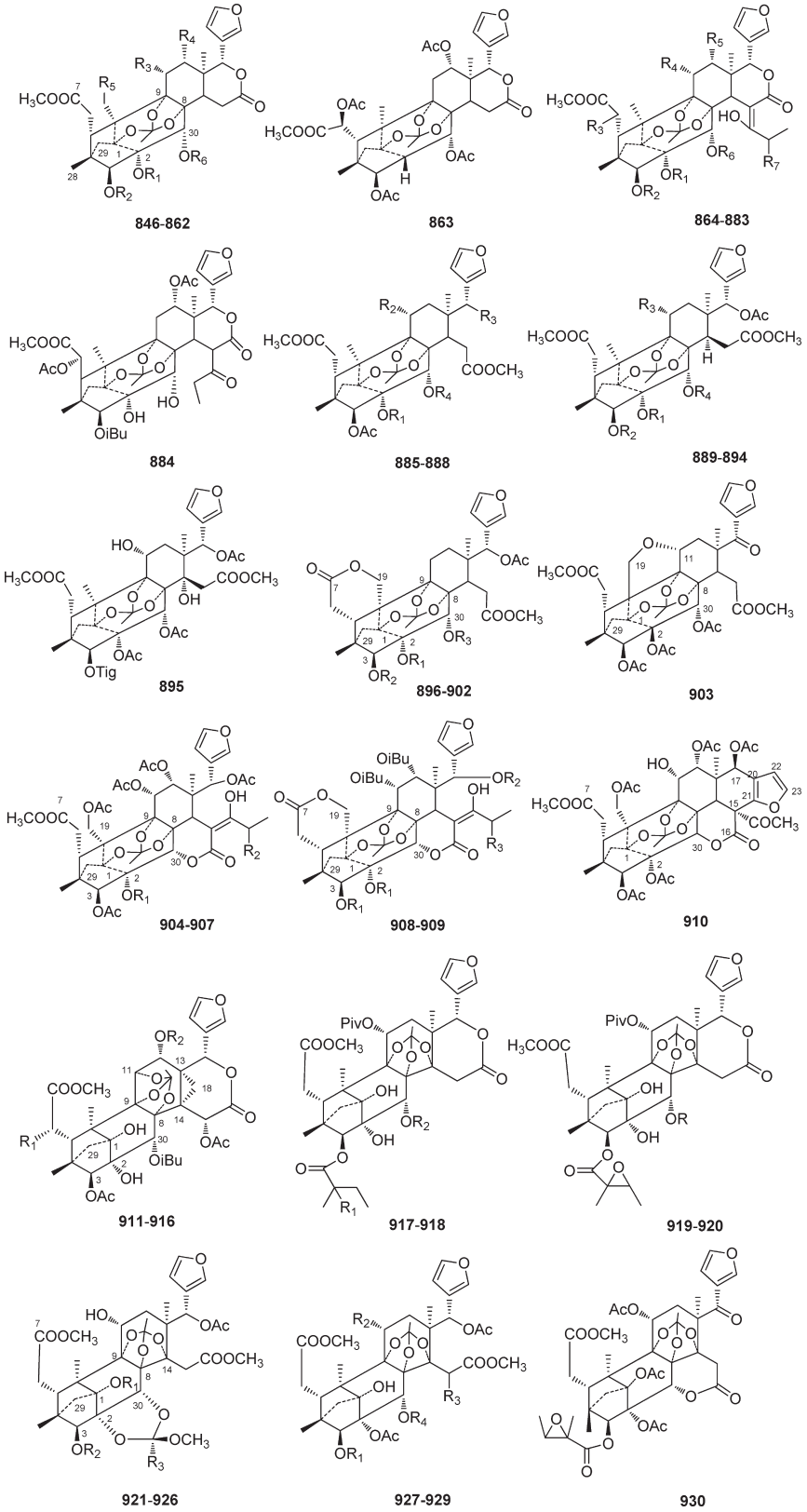


**Figure 26.** Continued


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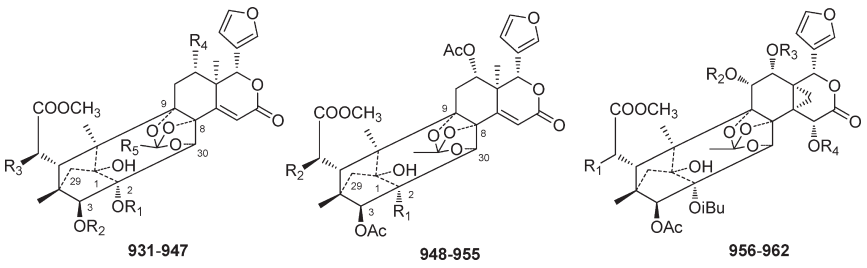


**Figure 26.** Structures of phragmalin-*ortho* ester limonoids **846**−**962**.

achieved in six steps overall from simple cyclohexenones (Scheme 4).[821]

A possible key intermediate in the biosynthesis of the ring D-seco limonoids was synthesized by the conversion of the side-chain of turraeanthin, a protolimonoid in *Turraeanthus africanus*, into a $\beta$-substituted furan in two steps with considerable yield.[822,823] The tactics of the synthesis of fraxinellone (**1142**) included reaction of 6-formyl-2,6-dimethyl-cyclohex-2-enecarboxylates with furyllithium followed by double-bond isomerization with base,[824,825] and conversion from fraxinellonone (**1141**) in short steps.[826] After formation of the five-membered lactone, an aldol reaction and olefin metathesis established the bicyclic ring system, in which the catalytic diastereoselective Oshima−Utimoto reaction was employed as key step (Scheme 5).[827] The short and stereocontrolled simple synthetic approach to the limonoids system was presented in 1987 by Corey et al., which introduced a high susceptibility for $\alpha$-oxygenated, $\alpha$-stannylated allylic systems to undergo free radical attack at the $\gamma$-carbon.[828]

Chemical transformation was considered to be an efficient method in structure elucidation and revision. A direct relationship between the melianes and meliacins (limonoids) was established through opening the 7$\alpha$,8$\alpha$-epoxide ring of a melianone derivative.[829] Swietenine (**677**) was converted into diacetylswietenolide (**647**), two compouds which differed mainly in the position of the double bond, in seven steps via 14$\alpha$-hydroxyswietenine and the $\Delta^{8,30}$, $\Delta^{14,15}$ diene intermediates.[830] Khayanthone (**111**) was converted into khivorin (**434**) by oxidation with alkaline hydrogen peroxide followed by reacetylation.[831] The preparations of methyl angolensate (**568**) and andirobin (**556**) from 7-deacetoxy-7-oxokhivorin (**441**)[529] substantiated the suggestion that the characteristic bicycle[3.3.1]nonane ring system of the swietenine group was formed from the normal tetracyclic triterpene nucleus by oxidative cleavage of ring B followed by intramolecular Michael addition of a C-2 carbanion to the diene lactone system.[609] Mexicanolide (**626**) was prepared from 7-deacetoxy-7-oxokhivorin (**441**) via a diene-lactone intermediate, which subsequently underwent intramolecular Michael addition by alkaline hydrolysis.[832−834] E.P.1 (**584**) has been partially synthesized from gedunin (**416**), by a synthesis in which the key stage involved the Baeyer−Villiger oxidation of the 7-oxo group to a lactone.[835] **416** was transformed along an unambiguous route into 6$\beta$-hydroxygedunin (**420**) and the chemical and spectroscopy properties of the acetate of this product were different from the natural 6$\alpha$-acetoxygedunin (**418**).[836] An investigation was made of the oxidation of **626** and related compounds with a view to the partial preparation of the 1,8-hemiacetal bridge characteristic of the limonoids such as xyloccensin A (**756**) which originated from *Xylocarpus molccensis*.[837]

Besides chemical conversion, structural modification using biocatalysts was also documented. *Nocardia* sp. quantitatively converted salannin (**332**) and 3-deacetylsalannin (**333**) into 3-deacetoxy-1-de[(E)-2-methylbut-2-enoloxy]salannin-1-en-3-one, a potentially bioactive compound with an $\alpha$,$\beta$-unsaturated ketone moiety in ring A.[838]

## 5. BIOLOGICAL ACTIVITIES OF MELIACEOUS LIMONOIDS

Meliaceous limonoids have been gaining global acceptance in agricultural applications and in contemporary medicine for their myriad but discrete properties. The need to protect our food supply from phytophagous insect attack using ecologically acceptable methods has led to a growing interest in behavior modifying chemicals from natural sources. For example, considering azadirachtin (**292**), we see that its potent activity against a broad range of insect species combined with its remarkable nontoxicity toward mammalian organism made **292** an attractive candidate as a natural pesticide.[839] Miscellaneous activities of meliaceous limonoids have been investigated and some wonderful general reviews,[840−842] and specific reviews on insect growth regulating activity,[843] insecticidal activity,[34,844] and the cytotoxic activity against the P388 cell line[845] have been presented in the past decades. In addition, the biological activities of limonoids from *Melia azedarach*,[37,44−47] *M. toosendan*,[47,85] and *Azadirachta indica*,[3,29,35−37,39,41−43,846] including especially the activities[19,26−28,30,847] and commercial application of **292**,[848] have been reviewed. Furthermore, the modes and toxicity characteristics of the biological action of **292** were presented.[32,33] For example, Mordue et al. proved that the mode of **292** involved (i) effects on deterrent and other chemoreceptors resulting in antifeedancy (ii) effects on ecdysteroid and juvenile hormone titers through a blockage of morphogenetic peptide hormone release, and (iii) direct effects on most other tissues studied resulting in an overall loss of fitness of the insect.[25] The biological activity of ring D and rings B,D-seco limonoids of Meliaceae,[50] and of gedunin (**416**) have also been summarized recently.[49] Furthermore, the activities of natural limonoids from plants have been presented including the meliaceous limonoids as one of their discussion topics.[10,16−18]

In addition, the toxicity evaluation of meliaceous limonoids has been reported occasionally. Among the six limonoids from *Melia azedarach*, azedarachin B (**160**) showed remarkable BST (brine shrimp lethality test) activity with an $LC_{50}$ value of 0.0098 $\mu$M.[218] 1-Methacrylyl-3-acetyl-11-methoxymeliacarpinin (**326**) exhibited significant lethal activity with an $IC_{50}$ value of 19 $\mu$g/mL in the BST test.[346] The highest dose of azadirachtin (**292**), 1500 mg/kg, was well tolerated by rats of both sexes thus could be used as a basal dose for the determination of the


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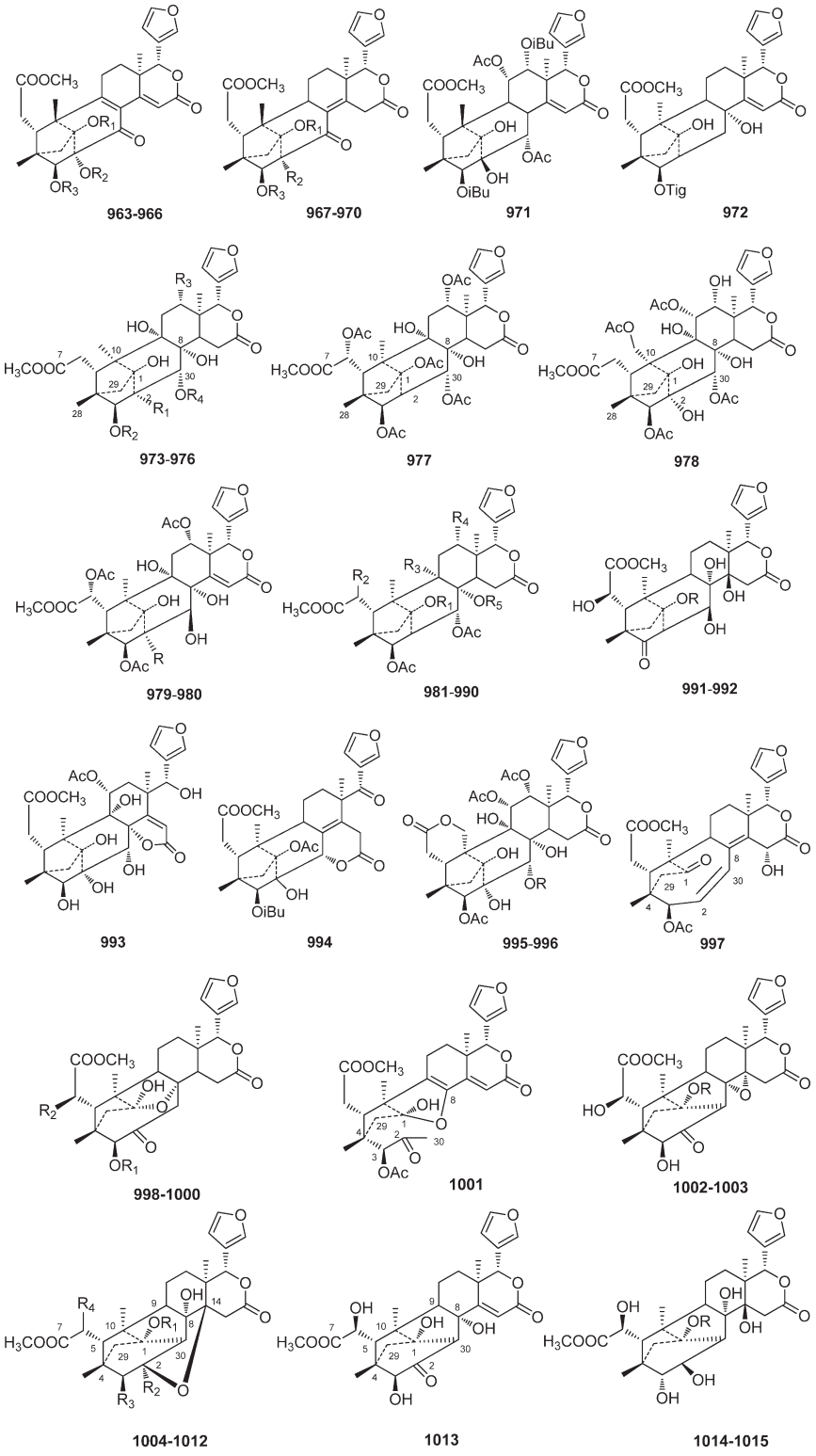


**Figure 27.** Structures of polyoxyphragmalin limonoids **963**−**1015**.

NOEL (no-observed-effect level) of **292** to calculate its safety margin.[849] Nimbolide (**345**) was proved to be toxic to mice only when given i.p. and i.v., and less toxic to rats and hamsters, and it was supposed that when given i.v., the possible cause of death induced by it was a sudden hypotensive shock.[850] Azedaralide (**1138**), fraxinellonone (**1141**) and 12$\alpha$-acetoxyfraxinellone (**1147**) showed ichthyotoxic activity at a concentration of 50 ppm, while fraxinellone (**1142**) required only 10 ppm.[230]

## 5.1. Biological Activities in Agricultural Use

**5.1.1. Insects Antifeeding Activity.** Insect antifeedant activity, the most potent activity of limonoids, has been extensively


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Table 25. Structures and Sources of Polyoxyphragmalin Limonoids 963−1015

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **963** | moluccensin H | $R_1 = R_2 = H$; $R_3 = Ac$ | *Xylocarpus moluccensis*[723] |
| **964** | moluccensin H | $R_1 = Piv$; $R_2 = H$; $R_3 = iBu$ | *X. moluccensis*[568] |
| **965** | moluccensin I | $R_1 = iBu$; $R_2 = H$; $R_3 = Piv$ | *X. moluccensis*[568] |
| **966** | moluccensin J | $R_1 = Piv$; $R_2 = iBu$; $R_3 = H$ | *X. moluccensis*[568] |
| **967** | moluccensin I | $R_1 = H$; $R_2 = OCH_3$; $R_3 = Ac$ | *X. moluccensis*[723] |
| **968** | moluccensin J | $R_1 = R_2 = H$; $R_3 = Ac$ | *X. moluccensis*[723] |
| **969** | moluccensin K | $R_1 = H$; $R_2 = Piv$; $R_3 = iBu$ | *X. moluccensis*[568] |
| **970** | moluccensin L | $R_1 = R_3 = Piv$; $R_2 = H$ | *X. moluccensis*[568] |
| **971** | tabularin | | *Chukrasia tabularis*[724] |
| **972** | xylogranatin $E_2$ | | *Xylocarpus granatum*[669] |
| **973** | tabulalin | $R_1 = R_3 = OH$; $R_2 = Ac$; $R_4 = H$; $\Delta^{14,15}$ | *Chukrasia tabularis*[706] |
| **974** | atomasin A | $R_1 = OAc$; $R_2 = Ac$; $R_3 = H$; $R_4 = iBu$ | *Entandrophragma candollei*[719,725] |
| **975** | atomasin B | $R_1 = OAc$; $R_2 = Ac$; $R_3 = H$; $R_4 = propanoyl$ | *E. candollei*[719,725] |
| **976** | swietemacrophine | $R_1 = OH$; $R_2 = R_4 = Tig$; $R_3 = OAc$ | *Swietenia macrophylla*[717] |
| **977** | xylocarpin K | | *Xylocarpus granatum*[677] |
| **978** | tabulalide E | | *Chukrasia tabularis*[706] |
| **979** | granatumin F | R = H | *Xylocarpus granatum*[426] |
| **980** | granatumin G | R = OH | *X. granatum*[426] |
| **981** | xylocarpin A (granaxylocarpin E) | $R_1 = Ac$; $R_2 = OAc$; $R_3 = R_4 = R_5 = H$ | *X. granatum*[632,633] |
| **982** | xylocarpin B | $R_1 = Ac$; $R_2 = R_3 = R_4 = R_5 = H$ | *X. granatum*[633] |
| **983** | xylocarpin C | $R_1 = R_2 = R_3 = R_5 = H$; $R_4 = OAc$ | *X. granatum*[633] |
| **984** | xylocarpin D (granaxylocarpin D) | $R_1 = Ac$; $R_2 = OH$; $R_3 = R_5 = H$; $R_4 = OAc$ | *X. granatum*[632,633] |
| **985** | xylocarpin E | $R_1 = Ac$; $R_2 = OAc$; $R_3 = R_5 = H$; $R_4 = OH$ | *X. granatum*[633] |

investigated with respect to many kinds of insects. For example, a number of evaluations of the well-known azadirachtin (**292**) were carried out, and some nice reviews described its antifeedancy against miscellaneous insects in detail.[25−27] In addition, some antifeeding data of **292** are summarized in Table 32. With as l ittle as 0.2 ppm of **292** incorporated into the diet of *Spodoptera frugiperda*, it showed antifeedant effects on first instar larvae and inhibited the molting of the nymphs to the adult stage when it was applied topically with 0.01 $\mu$g to newly molted fifth instar nymphs of *Oncopeltus fasciatus*.[851] **292** also elicited dose-dependent neural and antifeedant behavioral responses in *S. littoralis*, *Schistocerca gregaria*, and *Locusta migratoria* when it was used to investigate the mechanism of its effects on the feeding behavior of these three species.[26] The pathological effects of **292** on *S. gregaria* and *L. migratoria* were closely linked to a loss of feeding, with injections of 5, 10, and 15 $\mu$g/g causing an increasingly rapid onset of the effects associated with an increasingly reduced food intake.[852] In greenhouse and seedbed tests, the feeding deterrence provided by **292** against the striped *Acalymma vittatum* was not as great as by carbaryl.[853] Exposure of **292** to sunlight caused a rapid decrease in antifeedant potency against newly emerged first-instar (0.046 mg) of *Spodoptera frugiperda*, and acetone solutions of **292** exposed for seven days gave more than a 50% reduction in activity.[854] Interestingly, *Crocidolomia binotalis* was capable of detoxifying the antifeedancy of **292** to a limited extent at the cost of poor weight gain and disruption in larval and pupal development.[855] Feeding behavior of four slug species of *Deroceras reticulatum*, *Arion distinctus*, *Agriolimax caruanae*, and *Maximus* sp., as detected by the amount of leaf eaten compared to the controls, was not affected by the presence of **292** at those concentrations (<500 ppm) which deterred from feeding in *Rhopalosiphum padi* and *Sitobion avenae*.[856]

Using *Pericallia ricini* in dual choice bioassay, nymania 3 (**478**) was an effective antifeedant at concentrations of 1−10 $\mu$g/cm$^2$ leaf, which is half as active as **292**.[497] Salannin (**332**) was less active than **292** in feeding suppression against the larvae of *Spodoptera littoralis* and *Earias insulana*.[857] **292** was more potent as an antifeedant and growth inhibitor than any of five limonoids 17$\beta$-hydroxyazadiradione (**18**), salannin (**332**), 6-deacetylnimbin (**392**), gedunin (**416**), and 7-deacetylgedunin (**421**) against *Helicoverpa armigera*,[858] and produced almost 100% larval mortality at 1 ppm concentration.[859] At 4 $\mu$g/cm$^2$ and 1 $\mu$g/cm$^2$, the isomeric mixture of meliartenin (**164**) was active as **292** in strongly inhibiting the larval feeding of *Epilachna paenulata* and *S. eridania*.[208] 1-Tigloyl-3-acetylazadirachtol (**297**) and marrangin (**1067**) were reported as being more potent than **292** in the 24 h dual choice antifeedant test against *E. varivestis* (Table 33).[322] Similarly, the crop protection against *Schistocerca gregaria* afforded by **292** resulted from both antifeedancy and toxicity, whereas 3-tigloylazadirachtol (**296**) was more effective by direct toxicity after significant ingestion.[860] *Cnaphalocrocis medinalis* larvae which were chronically exposed to any of 17$\beta$-hydroxyazadiradione (**18**), **292**, salannin (**332**), deacetylnimbin (**392**), gedunin (**416**), or 7-deacetylgedunin (**421**), showed a reduction in weight of 59−89% and exhibited a significant reduction in activities of acid phosphatases (ACP), alkaline phosphatases (ALP), and adenosine triphosphatases (ATPase). These results indicate that neem limonoids affected gut enzyme activities.[861,862]

The five limonoids 17$\beta$-hydroxyazadiradione (**18**), salannin (**332**), 6-deacetylnimbin (**392**), gedunin (**416**), and 7-deacetylgedunin (**421**) affected feeding, development and reproduction in *Helicoverpa armigera*, and the reduced nutritional efficiency and fecundity were recorded as the consequence of postingested


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**Table 26. Structures and Sources of 8,11-Linkage Limonoids (Trijugin-Class) 1016−1043**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **1016** | trijugin A | $R_1$ = H; $R_2$ = O; $R_3$ = $\beta$-OH; $R_4$ = OAc | *Heynea trijuga*[729] |
| **1017** | trijugin G | $R_1$ = O; $R_2$ = OPiv; $R_3$ = $\beta$-OH; $R_4$ = H | *Trichilia connaroides*[573] |
| **1018** | voamatin A | $R_1$ = OH; $R_2$ = OCin; $R_3$ = $\alpha$-OH; $R_4$ = H | *Astrotrichilia voamatata*[733] |
| **1019** | voamatin B | $R_1$ = OH; $R_2$ = OCin; $R_3$ = $\beta$-OH; $R_4$ = H | *A. voamatata*[733] |
| **1020** | trijugin B | R = H | *Heynea trijuga*[729] |
| **1021** | trijugin B acetate | R = Ac | *H. trijuga*[734] |
| **1022** | capensolactone 3 | $R_1$/ $R_2$ = ONic/OiBu; $R_3$ = H; $R_4$ = $R_5$ = OAc | *Ekebergia capensis*[730] |
| **1023** | cipatrijugin A | $R_1$ = $R_3$ = $R_4$ = $R_5$ = H; $R_2$ = OAc | *Cipadessa cinerascens*[544,735] |
| **1024** | cipatrijugin B | $R_1$ = $R_4$ = $R_5$ = H; $R_2$ = OAc; $R_3$ = OH | *C. cinerascens*[563,735] |
| **1025** | cipatrijugin C | $R_1$ = $R_4$ = $R_5$ = H; $R_2$ = $R_3$ = OAc | *C. cinerascens*[563,735] |
| **1026** | cipatrijugin D | $R_1$ = $R_3$ = $R_5$ = H; $R_2$ = $R_4$ = OAc | *C. cinerascens*[563,735] |
| **1027** | sandrapin A | $R_1$ = $R_2$ = $R_5$ = OAc; $R_3$ = H; $R_4$ = OH | *Sandoricum koetjape*[736,737] |
| **1028** | sandrapin B | $R_1$ = OPiv; $R_2$ = $R_5$ = OAc; $R_3$ = H; $R_4$ = OH | *S. koetjape*[736,737] |
| **1029** | sandrapin C | $R_1$ = OiBu; $R_2$ = $R_5$ = OAc; $R_3$ = H; $R_4$ = OH | *S. koetjape*[736,737] |
| **1030** | sandrapin D | $R_1$ = OTig; $R_2$ = $R_5$ = OAc; $R_3$ = H; $R_4$= OH | *S. koetjape*[737,738] |
| **1031** | sandrapin E | $R_1$ = methacrylate; $R_2$ = $R_5$ = OAc; $R_3$ = H; $R_4$ = OH | *S. koetjape*[737,738] |
| **1032** | E.P.4 | $R_1$ = $R_4$ = OAc; $R_2$ = OAng; $R_3$ = $R_5$ = H | *Ekebergia pterophylla*[565] |
| **1033** | capensolactone 1 | $R_1$ = iBu; $R_2$ = $R_4$ = H; $R_3$ = OH | *E. capensis*[730] |
| **1034** | capensolactone 2 | $R_1$/ $R_2$ = Nic/Piv; $R_3$ = OH; $R_4$ = Ac | *E. capensis*[730] |
| **1035** | E.P.5 | $R_1$ = $R_2$ = $R_4$ = Ac; $R_3$ = H | *E. pterophylla*[565] |
| **1036** | trichilin A | | *Trichilia connaroides*[731] |
| **1037** | trijugin H | | *T. connaroides*[573] |
| **1038** | cipadesin D | $R_1$ = $R_3$ = H; $R_2$ = OAc | *Cipadessa cinerascens*[54,544,564] |
| **1039** | cipadesin E | $R_1$ = OH; $R_2$ = $R_3$ = H | *C. cinerascens*[54,563] |
| **1040** | cineracipadesin F | $R_1$ = OAc; $R_2$ = $R_3$ = H | *C. cinerascens*[563] |
| **1041** | cipadesin H | $R_1$ = $R_2$ = $R_3$ = H | *C. cinerascens*[564] |
| **1042** | cipadesin I | $R_1$ = H; $R_2$ = $R_3$ = OAc | *C. cinerascens*[564] |
| **1043** | trichilin B | | *Trichilia connaroides*[731] |

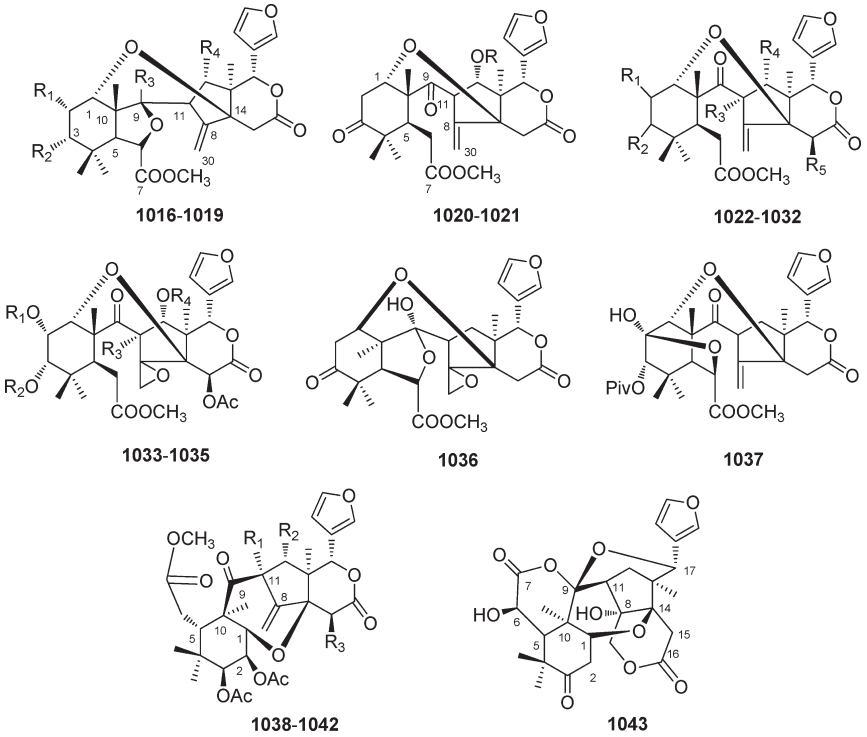


**Figure 28.** Structures of 8,11-linkage limonoids (trijugin-class) **1016−1043**.


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Table 27. Structures and Sources of 10,11-Linkage Limonoids (Cipadesin-Class) 1044−1053

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **1044** | cipadesin C | $R_1$ = OAc; $R_2$ = H; $R_3$ = OH | *Cipadessa cinerascens*[564,631] |
| **1045** | cipadesin E | $R_1$ = $R_2$ = H; $R_3$ = OH | *C. cinerascens*[53] |
| **1046** | cipadonoid C | $R_1$ = $R_2$ = $R_3$ = H | *C. cinerascens*[544] |
| **1047** | cipadonoid D | $R_1$ = $R_2$ = H; $R_3$ = OAc | *C. cinerascens*[544] |
| **1048** | cipadonoid E | $R_1$ = H; $R_2$ = $R_3$ = OAc | *C. cinerascens*[544] |
| **1049** | cipadonoid F | $R_1$ = H; $R_2$ = OAc; $R_3$ = $\alpha$-$CH_3$ | *C. cinerascens*[544] |
| **1050** | cipadonoid G | $R_1$ = H; $R_2$ = OAc; $R_3$ = $\alpha$-$CH_3$; 11$\alpha$-OH | *C. cinerascens*[544] |
| **1051** | cipadesin A | $R_1$ = $R_2$ = OAc; $R_3$ = $\beta$-$CH_3$ | *C. cinerascens*[563,631,735] |
| **1052** | cipadesin B | $R_1$ = OAc; $R_2$ = H; $R_3$ = $\beta$-$CH_3$ | *C. cinerascens*;[631] *C. fruticosa*[563,564,671] |
| **1053** | cipadesin G | $R_1$ = $R_2$ = H; $R_3$ = $\beta$-$CH_3$ | *C. cinerascens*[564] |

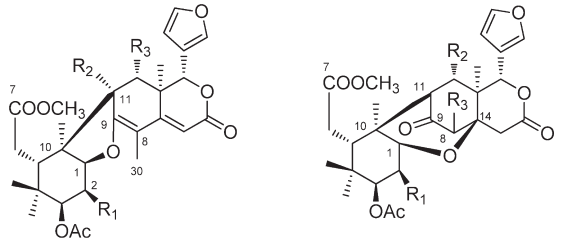


**Figure 29.** Structures of 10,11-linkage limonoids (cipadesin-class) **1044**−**1053**.

toxic effects of these compounds.[863] Both azecins 1 and 3 (**572** and **101**) were effective antifeedants when incorporated into the fourth-instar larvae of *Spodoptera litura* and third-instar larvae of *Henosepilachna vigintioctopunctata*, as was evidenced by the reduced growth rate, increased time of pupation, and even significant mortality.[173] Of the five limonoids **94**−**98** from *Trichilia pallida*, methyl 6,11$\beta$-dihydroxy-12$\alpha$-(2-methylpropanoyloxy)-3,7-dioxo-14$\beta$,15$\beta$-epoxy-1,5-meliacadien-29-oate (**97**) showed the greatest activity in tests against the larvae of *S. littoralis*, *S. exigua*, *Heliothis virescens*, and *Helicoverpa armigera* with feeding index (FI) values varing from 40 to 49.[171] In the antifeeding percentage test against *S. littoralis*, khayalactol (**774**) showed the highest potential with 83.8% at 1000 $\mu$g/mL, followed by 1-*O*-acetylkhayanolide A (**1003**) with 58.3% at 500 $\mu$g/mL, khayanolide D (**1006**) with 55.8 at 200 $\mu$g/mL and finally **1003** with 31.4% at 100 $\mu$g/mL.[550] The growth inhibitory activities after 7 days and antifeedant activities of **774**, khayanolide A (**1002**), khayanolide B (**1004**), and 1-*O*-acetylkhayanolide B (**1005**) were evaluated against *S. littoralis*. Among these, **1004** was the most active antifeedant with an $EC_{50}$ value of 6.96 mg/kg for growth inhibitory activity and 2.19 mg/kg for antifeedancy.[678] Xylogranatins F, G, and R (**1156**, **1157**, and **843**) exhibited marked antifeedant activity against the third-instar larvae of *Mythimnaseparate* at a concentration of 1 mg/mL. Among these, **1157** was the most potent with AFC50 (concentration for 50% antifeedant activity) values of 0.31 and 0.30 mg/mL at exposure times of 24 and 48 h, respectively.[638]

Modes of action other than their useful antifeedant activity were also investigated for limonoids. Chuanliansu (**167**) stimulated a deterrent receptor cell located in the medical maxillary sensillum styloconicum, and inhibited responses of both the sugar and glucosinolate receptor cell which are localized in the lateral sensillum styloconicum.[864,865] In other experiments, when *Pieris brassicae* fed on its natural foodplant, the deterrent effect of **167** and salannin (**332**) were mediated solely via the medial deterrent receptor, whereas inhibitory effects on the sugar and glucosinolate receptors did not play a significant role.[866] Investigation of the bioefficacy and mode of action of some salannin-class limonoids and their role in a multicomponent system against lepidopteran larvae led to the conclusion that nonazadirachtin limonoids having structural similarities and explicitly similar modes of action have no potentiating effect in any combination.[366] Ortego et al. concluded that the effects of azadirone (**1**) and the mixture of 3,7-di-*O*-acetylhavanensin (**107**) and 1,7-di-*O*-acetylhavanensin (**108**) on digestive proteases and detoxication enzymes in the larval midgut of *Leptinotarsa decemlineata* larvae reflected their postulated mode of action.[867] Salannin (**332**) and nimbinene (**1099**) showed no toxicity-mediated effects on *Spodoptera litura* larvae, and the antifeedant activity was a result of the effects on other chemoreceptors.[868] Potentiation among nonazadirachtin limonoids having two explicitly different modes of action, such as feeding deterrence and physiological toxicity, might be playing a significant role in the potentiation effect.[442]

From studies in which the *Spodoptera* species insects were frequently used, the $EC_{50}$ (50% effective concentration), $ED_{50}$ (50% effective dosage), MAC (minimum antifeedant concentration), $PC_{50}$ (50% protective concentration), $PC_{95}$ (95% protective concentration), AR (antifeedant rate), $FI_{50}$ (50% feeding inhibition), and AI (antifeedant index, mean ± SEM) values of antifeedant activity of meliaceous limonoids were summarized in detail (Tables 33 and 34). Unfortunately, some limonoids were declared to show antifeedant activity against

Table 28. Sources of Rearranged Limonoids with Other Linkage 1054−1062

| no. | compounds | sources |
|---|---|---|
| **1054** | walsuronoid A | *Walsura robusta*[739] |
| **1055** | 4$\alpha$,6$\alpha$-dihydroxy-A-homoazadirone | *Azadirachta indica*[742] |
| **1056** | spirosendan | *Melia toosendan*[85,247,743] |
| **1057** | volkensinin | *M. volkensii*[744] |
| **1058** | walsuronoid B | *Walsura robusta*[739] |
| **1059** | walsuronoid C | *W. robusta*[739] |
| **1060** | delevoyin C | *Entandrophragma delevoyi*[425] |
| **1061** | cipadonoid A | *Cipadessa cinerascens*[740,741] |
| **1062** | cumindysoside B | *Dysoxylum cumingianum*[745] |


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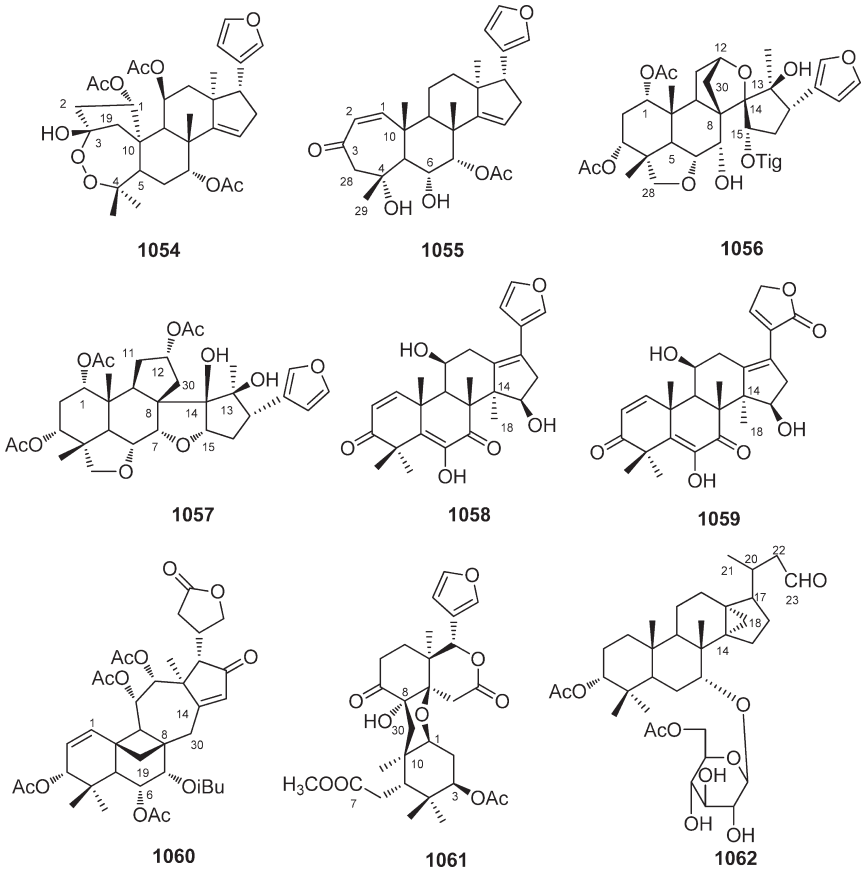


**Figure 30.** Structures of rearranged limonoids with other linkages **1054**−**1062**.

different insects, but no data had been presented in the original paper. These limonoids were 7-acetyltrichilin A (**136**),[200] 1$\alpha$,3$\alpha$-diacetylvilasinin (**189**),[245] toonacilin (**268**) and 6-acetoxytoonacilin (**269**),[286,289] 21-(*R*,*S*)-hydroxytoonacilide (**279**) and 23-(*R*,*S*)-hydroxytoonacilide (**280**),[288] salannin (**332**),[853] 3-deacetylsalannin (**333**) and salannol (**336**),[245] 2′,3′-dehydrosalannol (**338**),[349] munronins A−E (**498**−**500**, **1151**, **1116**),[506] methyl 3$\beta$-isobutyrloxy-1-oxomeliac-8(30)-enate (**702**),[666] salannolactam-(23) (**1154**), and salannolactam-(21) (**1155**).[766] In addition, azadirachtol (**295**) was reported to exhibit higher antifeedant activity than azadirachtin (**292**), but supporting data was lacking for this claim.[323] Negatively, nimbinin (**60**), 17-*epi*azadiradione (**77**), and nimbin (**391**) were inactive against *Reticulitermes speratus* and the $PC_{95}$ values were beyond the bioassay limits.[103]

As for structure−activity relationship of the insect antifeedant activity, Govindachari et al. pointed out that the C-seco limonoids were the most effective compounds while the intact limonoids were the least effective.[869] Similarly, antifeedant activity tests showed that azadirachtin-class C-seco limonoids were the most potent ones, followed by the 12$\alpha$-OH compounds of the trichilin-class and azedarachins containing a 14,15-epoxide combined with either a C-19/29 acetal bridge or a C-11/19 acetal bridge.[85,209,341] Suresh et al. concluded that the most active among the fifty-six limonoids were the C-ring modified limonoids of the azadirachtin-class followed by the intact apo-euphol types having a 14,15-epoxide and either a C-19/28 lactol bridge or a cyclohexenone A ring.[870] Another supporting example is provided by azedarachins and trichilins showing the most antifeedant activity against the larvae of *Spodoptera eridania* at a concentration of 200−400 ppm, followed by nimbolidins at 500 ppm and trichilinins at 1000 ppm.[239]

Ley et al. pointed out that the potent antifeedant activity of the derivatives of azadirachtin (**292**) with C-7 $\beta$-OH were significantly less active than its $\alpha$-epimer.[871] Mordue et al. proposed that the C-7, C-11, C-22, and C-23 positions of the carbon ring were key positions for bioactivity where substitution significantly influences the potency of **292**.[872] Furthermore, it was possible to draw some general conclusions that hydrogenation of the C-22/23 enol ether double bond did not significantly diminish activity of either the azadirachtin or 11-deoxy series, and that both the bulky substituents at C-22 and increasingly larger groups at C-23 caused a considerable drop in antifeedancy.[873,874] For example, both **292** and 22,23-dihyro-23$\beta$-methoxyazadirachtin (**303**) were potent antifeedant against *S. littoralis* and *Heliothis virescens*, whereas the latter, which had greater steric bulk at C-23, had weaker activity.[305] The nature of the substituents at C-1 and C-3 of the decalin ring of azadirachtins affected the antifeedancy of the compounds, as did the additional substituents to C-22/23.[875] In addition, Yamasaki et al. suggested that the hydroxyl groups on **292** were essential for maximum activity and that the molecule must also have a lipophilic region.[876] Methylation of the hydroxyl substitutions on the azadirachtins molecule resulted in a decrease in antifeedant activity, as did the addition of bulky groups to the dihydrofuran ring.[877] On the basis of the antifeedant potency of several limonoids from *Azadirachta indica*, it could be suggested that the furan ring, the $\alpha,\beta$-unsaturated ketone, and the hydroxyl group each played an important role in determining the activity.[103]


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**Table 29. Sturctures and Sources of Pentanortriterpenoids 1063−1114, Hexanortriterpenoids 1115−1118, Hepanortriterpenoids 1119−1126, Octanortriterpenoids 1127−1129, and Enneanortriterpenoids 1130−1131**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **1063** | 2-oxo-deacetyl salannin | | *Azadirachta indica*[411] |
| **1064** | voamatin C | R = palmityl | *Astrotrichilia voamatata*[754] |
| **1065** | voamatin D | R = Cin | *A. voamatata*[754] |
| **1066** | 11$\beta$-azadirachtin H | $R_1$ = Tig; $R_2$ = OH; $R_3$ = H; $R_4$ = $COOCH_3$ | *Azadirachta indica*;[312,319,755] *A. excelsa*[324] |
| **1067** | marrangin (azadirachtin L) | $R_1$ = Tig; $R_2$ = H; $R_3$ = OAc; $R_4$ = $COOCH_3$ | *A. excelsa*[322,324,746] |
| **1068** | 11$\alpha$-hydroxy-12-norazadirachtin (11-*epi*-azadirachtin H, 11$\alpha$- azadirachtin H) | $R_1$ = Tig; $R_2$ = H; $R_3$ = OH; $R_4$ = $COOCH_3$ | *A. indica*;[343,747,748,756] *A. excelsa*[324] |
| **1069** | azadirachtin I | $R_1$ = Tig; $R_2$ = OH; $R_3$ = H; $R_4$ = $CH_3$ | *A. indica*[312,317,319] |
| **1070** | 11-*epi*-azadirachtin I | $R_1$ = Tig; $R_2$ = H; $R_3$ = OH; $R_4$ = $CH_3$ | *A. indica*[749] |
| **1071** | azadirachtin M | $R_1$ = Tig; $R_2$ = H; $R_3$ = OH; $R_4$ = $CH_2OH$ | *A. indica*;[343] *A. excelsa*[324] |
| **1072** | azadirachtin P | $R_1$ = *i*Val; $R_2$ = H; $R_3$ = OH; $R_4$ = $COOCH_3$ | *A. excelsa*[324] |
| **1073** | moluccensin M | | *Xylocarpus moluccensis*[568] |
| **1074** | chuktabularin A | $R_1$ = $R_3$ = Ac; $R_2$ = H | *Chukrasia tabularis*[750,752] |
| **1075** | chuktabularin K | $R_1$ = $R_3$ = Ac; $R_2$ = OAc | *C. tabularis*[752] |
| **1076** | chuktabularin S | $R_1$ = $R_2$ = H; $R_3$ = Ac | *C. tabularis*[752] |
| **1077** | chuktabularin T | $R_1$ = Ac; $R_2$ = $R_3$ = H | *C. tabularis*[752] |
| **1078** | chuktabularin C | $R_1$ = $R_3$ = Ac; $R_2$ = $R_4$ = $R_5$ = H | *C. tabularis*[750,752] |
| **1079** | chuktabularin L | $R_1$ = $R_2$ = $R_5$ = H; $R_3$ = Ac; $R_4$ = OAc | *C. tabularis*[752] |
| **1080** | chuktabularin M | $R_1$ = $R_3$ = Ac; $R_2$ = $R_5$ = H; $R_4$ = OAc | *C. tabularis*[752] |
| **1081** | chuktabularin N | $R_1$ = Ac; $R_2$ = $R_5$ = H; $R_3$ = propanoyl; $R_4$ = OAc | *C. tabularis*[752] |
| **1082** | chuktabularin O | $R_1$ = Ac; $R_2$ = $R_5$ = H; $R_3$ = iBu; $R_4$ = OAc | *C. tabularis*[752] |
| **1083** | chuktabularin P | $R_1$ = $R_3$ = Ac; $R_2$ = OH; $R_4$ = $R_5$ = H | *C. tabularis*[752] |
| **1084** | chuktabularin Q | $R_1$ = $R_3$ = Ac; $R_2$ = OAc; $R_4$ = $R_5$ = H | *C. tabularis*[752] |
| **1085** | chuktabularin R | $R_1$ = $R_2$ = $R_4$ = $R_5$ = H; $R_3$ = Ac | *C. tabularis*[752] |
| **1086** | chukvelutin A | $R_1$ = $R_4$ = H; $R_2$ = OAc; $R_3$ = Ac; $R_5$ = $CH_3$ | *C. tabularis*[751] |
| **1087** | chukvelutin B | $R_1$ = $R_3$ = Ac; $R_2$ = OAc; $R_4$ = H; $R_5$ = $CH_3$ | *C. tabularis*[751] |
| **1088** | chukvelutin C | $R_1$ = $R_2$ = $R_3$ = $R_4$ = Ac; $R_5$ = $CH_3$ | *C. tabularis*[751] |
| **1089** | chuktabularin D | $R_1$ = $R_2$ = $R_3$ = $R_4$ = Ac; $R_5$ = H | *C. tabularis*[750,752] |
| **1090** | chuktabularin E | $R_1$ = $R_5$ = H; $R_2$ = $R_3$ = $R_4$ = Ac | *C. tabularis*[752] |
| **1091** | chuktabularin F | $R_1$ = $R_2$ = $R_3$ = Ac; $R_4$ = propanoyl; $R_5$ = H | *C. tabularis*[752] |
| **1092** | chuktabularin G | $R_1$ = $R_2$ = $R_3$ = Ac; $R_4$ = iBu; $R_5$ = H | *C. tabularis*[752] |
| **1093** | chuktabularin H | $R_1$ = $R_2$ = $R_5$ = H; $R_3$ = $R_4$ =Ac | *C. tabularis*[752] |
| **1094** | chuktabularin I | $R_1$ = $R_2$ = Ac; $R_3$ = $R_4$ = $R_5$ = H | *C. tabularis*[752] |
| **1095** | chuktabularin J | $R_1$ = $R_3$ = $R_4$ = $R_5$ = H; $R_2$ = Ac | *C. tabularis*[752] |
| **1096** | chuktabularin B | | *C. tabularis*[750,752] |
| **1097** | chuktabrin A | | *C. tabularis*[697] |
| **1098** | 21,24,25,26,27-pentanor-15,22-oxo-7$\alpha$,23-dihydroxy-apotirucalla(eupha)-1-en-3-one | | *Trichilia estipulata*[757] |
| **1099** | nimbinene | R = Ac | *Azadirachta indica*[758] |
| **1100** | 6-deacetylnimbinene | R = H | *A. indica*[758] |
| **1101** | nimbandiol | R = H | *A. indica*[103,104,270,758] |
| **1102** | 6-acetylnimbandiol | R = Ac | *A. indica*[316,758] |
| **1103** | 5$\alpha$,6$\beta$,8$\alpha$-trihydroxy-28-norisotoonafolin | $R_1$ = O; $R_2$ = H | *Toona ciliata*[161,290,291] |
| **1104** | 5$\alpha$,6$\beta$,8$\alpha$,12$\alpha$-tetrahdroxy-28-norisotoonafolin | $R_1$ = O; $R_2$ = OH | *T. ciliata*[161] |
| **1105** | toonaciliatin A | $R_1$ = O; $R_2$ = OH, $\Delta^{1,2}$ | *T. ciliata*[290] |
| **1106** | toonaciliatin F | $R_1$ = $R_2$ = OH | *T. ciliata*[290] |
| **1107** | toonaciliatin G | $R_1$ = OH; $R_2$ = H | *T. ciliata*[290] |
| **1108** | toonaciliatin H | $R_1$ = Ac; $R_2$ = OH | *T. ciliata*[291] |
| **1109** | toonaciliatin I | $R_1$ = Ac; $R_2$ = O | *T. ciliata*[291] |
| **1110** | toonaciliatin J | $R_1$ = $R_2$ = OH | *T. ciliata*[291] |
| **1111** | trijugin C | $R_1$ = $R_2$ = H | *Trichilia connaroides*[573,651,759] |


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Table 29. Continued

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| 1112 | trijugin D | $R_1$ = Ac; $R_2$ = H | *T.connaroides*[573] |
| 1113 | trijugin E | $R_1$ = Ac; $R_2$ = OH | *T. connaroides*[573] |
| 1114 | trijugin F | | *T. connaroides*[573] |
| 1115 | carapolide A | | *Carapa procera*[581] |
| 1116 | munronin E | | *Munronia henryi*[506] |
| 1117 | nimolicinoic acid | | *Azadirachta indica*[72] |
| 1118 | ceramicine A | | *Chisocheton ceramicus*[262,412] |
| 1119 | entilin A | $R_1$ = $R_2$ = H | *Entandrophragma utile*[491,760] |
| 1120 | entilin B | $R_1$ = H; $R_2$ = Ac | *E. utile*[491,760] |
| 1121 | entilin C | $R_1$ = $CH_3$; $R_2$ = H | *E. utile*[761] |
| 1122 | entilin D | | *E. utile*[491,762] |
| 1123 | munronin F | | *Munronia henryi*[506] |
| 1124 | turrapubesic acid A | R = Ac | *Turraea pubescens*[126] |
| 1125 | turrapubesic acid B | R = iBu | *T. pubescens*[126] |
| 1126 | turrapubesic acid C | R = Piv | *T.pubescens*[126] |
| 1127 | azadironol | | *Azadirachta indica*[128] |
| 1128 | desfurano-6$\alpha$-hydroxyazadiradione | R = OH | *A. indica*[120] |
| 1129 | desfurano-azadiradione | R = H | *A. indica*[70,753] |
| 1130 | 7$\alpha$-acetoxy-4,4,8-trimethyl-5$\alpha$-(13$\alpha$Me)-17-oxa-androsta-1, 14-dien-3,16-dione (13$\alpha$-nimolactone) | R = $\alpha$-$CH_3$ | *A. indica*[70,107,753] |
| 1131 | 7$\alpha$-acetoxy-4,4,8-trimethyl-5$\alpha$-17-oxa-androsta-1,14-dien-3, 16-dione (13$\beta$-nimolactone) | R = $\beta$-$CH_3$ | *A. indica*[70,107,753] |

When trichilin-class limonoids are tested against *Spodoptera eridania*, there is a remarkably clear-cut structure activity relationship in which the 12$\alpha$-OH function was the most potent, followed by 12$\beta$-OH, 12-desoxy, and 12$\alpha$-acetoxy groups, in oder of decreasing potency.[194,224] Similar results indicated that the 12-OH functionality could be necessary for maximum activity in trichilin-class limonoids, and it appeared from the variable activities of meliatoxins $A_1$ and $A_2$ that even the epoxide function on ring D had an important role to play.[878] Zhou et al. also concluded that isomerization of the D-ring epoxide to a 15-keto and acetylation of the 12- and 29-OH groups of trichilin-class limonoids reduced the antifeedant activity, but the side-chain change at C-29 did not influence their activity.[225] The highly oxygenated 1-*O*-acetylkhayanolide A (**1003**) was the most active antifeedant among the six limonoids from *Khaya senegalensis*. This finding was in agreement with the observation that the role played by increasing oxygenation in limonoids is to increase their biological activity.[550] The introduction of the *O*-acetyl group of xylogranatin F (**1156**) at C-3 enhanced the antifeedant rate significantly (16 to 25%).[638] Hydrogenation of the furan ring, replacement of the acetoxyl group with methoxyl group, and saponification of the methyl ester at C-11 all increased the antifeedant activity of salannin (**332**) against *Leptinotarsa decemlineata*. Modification of the tigloyl group also changed this activity.[879]

**5.1.2. Insects Growth Regulatory Activity.** Besides the well-known antifeedant activity, azadirachtin (**292**) also showed strong insect growth regulating activity against many insects. Since **292** did not reduce feeding in *Pieris brassicae* pupae, the growth retardation and deformities were the direct effect of **292** and not due to lack of food.[889] Nutritional analyses revealed that the insect growth inhibitory and antifeedant effects were independent of each other and relative to the level of treatment with **292**.[884] Furthermore, 48 h feeding of **292** on foliage treated at 5−10 ppm appeared to be sufficient for growth disruption of *Spodoptera litura* at early instars age, and no juvenilizing effect was observed.[890] Injection of **292** at higher concentration caused metabolic defects including weight reduction and metamorphosis inhibition in last larval instars of *Epilachna varivestis*.[891] In addition, prolonged development, wing deformities, unplasticization of wing lobes, development of wingless adults, and larval mortality were the characteristic features of **292** on various stages of *Dysdercus koenigii*.[892]

The insect growth regulating activity of azadirachtin (**292**) focused its effects mainly on the molt of insects. Feeding on azadirachtin-sprayed creeping bentgrass caused molting disorders and death of early instar *Agrotis ipsilon* and slowed feeding and stunted the growth of late instars.[893] **292** caused significant reduction in feeding activity at 2.5 g/L, prolonged the period for molting to nymphal stage, and caused 60% reduction in moltability.[894] Gaaboub et al. investigated the molting inhibition of **292** against *Musca autumnalis*, which involved delayed lethal action, adult emergence, and pupae or adults size.[895] The $ED_{50}$ values for molting inhibition by injected **292** were in the range of 10−25 ng/larvae for fourth-instar larvae of ten insect species of *Triatoma*, *Rhodnius* and *Panstrongylus*.[896] In addition, **292** inhibited cold-induced supernumerary molt of last-instar *Galleria mellonella* and induced disturbances in larval and pupal ecdysis as well as in the metamorphic process, thus resulting in the formation of various intermediates.[897] Feeding inhibition is an indirect effect on *Rhodnius prolixus* due to an interference of **292** with the endocrine system rather than through the inhibition of chemoreceptors.[887] Although injection **292** elicited feeding inhibition, molt inhibition against *Locusta migratoria* was due to interference with the endocrine system rather than to the altered feeding behavior.[898]

Azadirachtin (**292**) inhibited the release of ecdysone from blowfly larval and pupal brain-ring gland complexes (BRGC)


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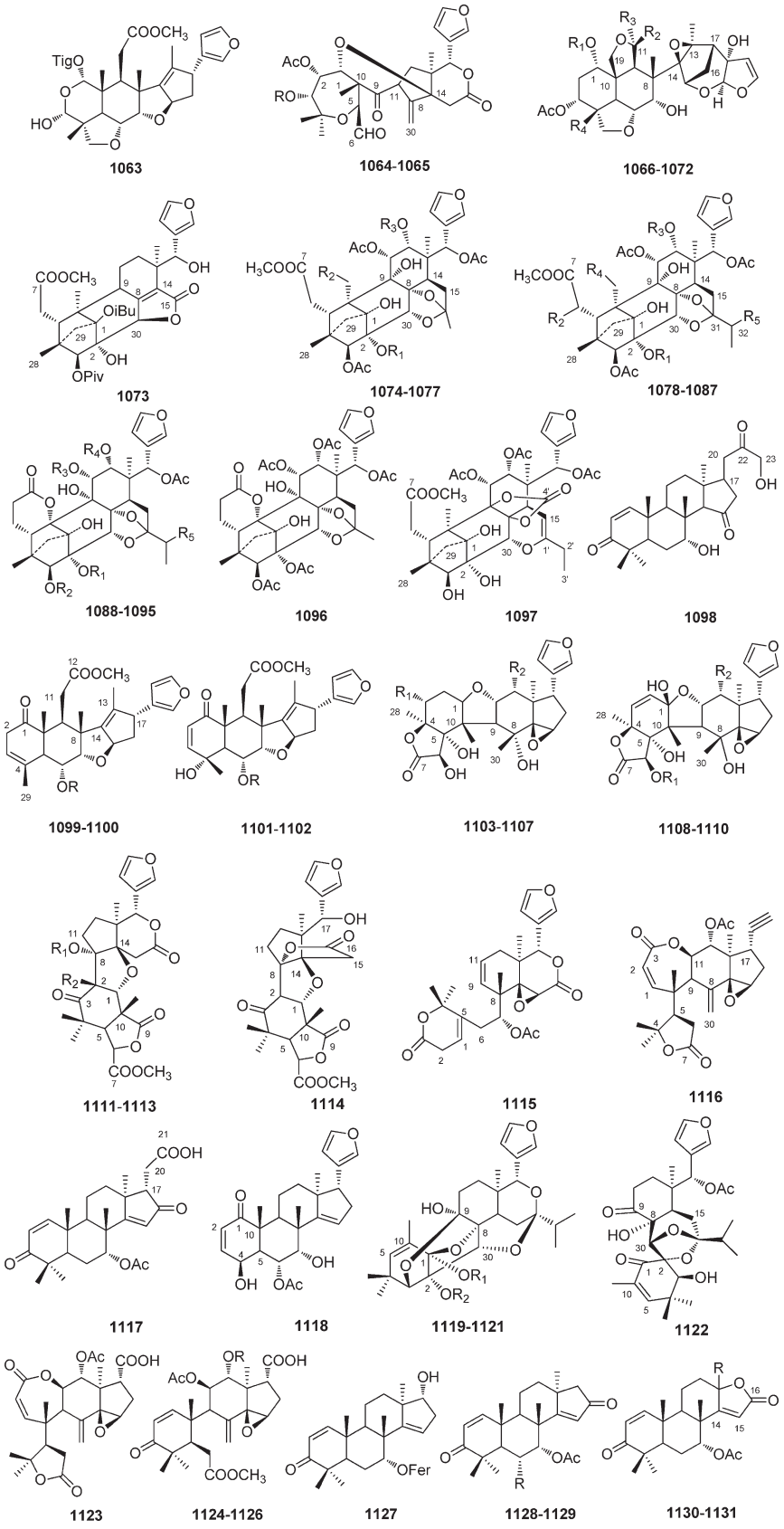


**Figure 31.** Structures of pentanortriterpenoids **1063**−**1114**, hexanortriterpenoids **1115**−**1118**, and hepanortriterpenoids **1119**−**1126**, octanortriterpenoids **1127**−**1129**, and enneanortriterpenoids **1130**−**1131**.


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**Table 30. Structures and Sources of Simple Degraded Limonoids 1132−1149**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **1132** | melazolide A | $R_1$ = OH; $R_2$ = H | *Melia azedarach*[452] |
| **1133** | 3-teracrylmelazolide A | $R_1$ = OH; $R_2$ = teracryl | *M. azedarach*[452] |
| **1134** | 3-teracrylmelazolide B | $R_1$ = H; $R_2$ = teracryl | *M. azedarach*[452] |
| **1135** | dysodensiol A | R = $\beta$-OH | *Dysoxylum densiforum*[764] |
| **1136** | dysodensiol B | R = $\alpha$-OH | *D. densiforum*[764] |
| **1137** | dysodensiol C | R = O | *D. densiforum*[764] |
| **1138** | azedaralide | | *Melia azedarach*[230] |
| **1139** | trichiconnarin A | | *Trichilia connaroides*[573] |
| **1140** | trichiconnarin B | | *T. connaroides*[573] |
| **1141** | fraxinellonone | $R_1$ = O; $R_2$ = H | *Melia azedarach*[206,230] |
| **1142** | fraxinellone | $R_1$ = $R_2$ = H | *M. azedarach*[230,240,251,452] |
| **1143** | 9$\alpha$-acetoxyfraxinellone | $R_1$ = $\alpha$-OAc; $R_2$ = H | *M. azedarach*[206] |
| **1144** | 9$\alpha$-hydroxy-12$\alpha$-acetoxyfraxinellone | $R_1$ = $\alpha$-OH; $R_2$ = OAc | *M. azedarach*[218] |
| **1145** | 9$\alpha$-hydroxyfraxinellone | $R_1$ = $\alpha$-OH; $R_2$ = H | *M. azedarach*[218,452] |
| **1146** | 9$\beta$-hydroxyfraxinellone | $R_1$ = $\beta$-OH; $R_2$ = H | *M. azedarach*[452] |
| **1147** | 12$\alpha$-acetoxyfraxinellone | $R_1$ = H; $R_2$ = OAc | *M. azedarach*[230] |
| **1148** | 12$\alpha$-hydroxyfraxinellone | $R_1$ = H; $R_2$ = OH | *M. azedarach*[218] |
| **1149** | 30-hydroxyfraxinellone | | *M. azedarach*[452] |

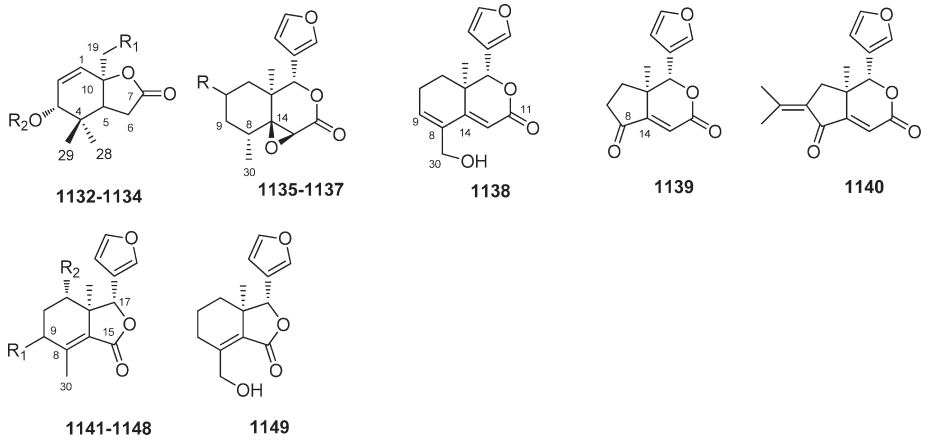


**Figure 32.** Structures of simple degraded limonoids **1132−1149**.

**Table 31. Structures and Sources of N-Containing Limonoids 1150−1159**

| no. | compounds | substitution groups and others | sources |
|---|---|---|---|
| **1150** | turraparvin D | | *Turraea parvifolia*[125] |
| **1151** | munronin D | R = H | *Munronia henryi*[506] |
| **1152** | munroniamide | R = $CO(CH_2)_2NHNH_2$ | *M. henryi*[765] |
| **1153** | turrapubesin B | | *Turraea pubescens*[287] |
| **1154** | salannolactam-(23) | $R_1$ = H; $R_2$ = O | *Azadirachta indica*[766] |
| **1155** | salannolactam-(21) | $R_1$ = O; $R_2$ = H | *A. indica*[766] |
| **1156** | xylogranatin F | R = H; $\Delta^{14,15}$ | *Xylocarpus granatum*[638] |
| **1157** | xylogranatin G | R = Ac; $\Delta^{14,15}$ | *X. granatum*[638] |
| **1158** | xylogranatin H | R = H | *X. granatum*[638] |
| **1159** | granatoine | | *X. granatum*[726] |

without affecting its biosynthesis.[899] The induction of a supernumerary larval molt with moderate doses of the ecdysteroid agonist (RH-2485) and the synergistic potentiation of this effect by **292** were observed.[900] Depending on the timing of injection with **292**, the ecdysteroid levels of *Locusta migratoria* could be drastically reduced, or delayed, or extended, or unaffected.[901] Josephrajkumar et al. found that when applied at $ED_{50}$ doses, **292** significantly depleted the content and altered the profile of


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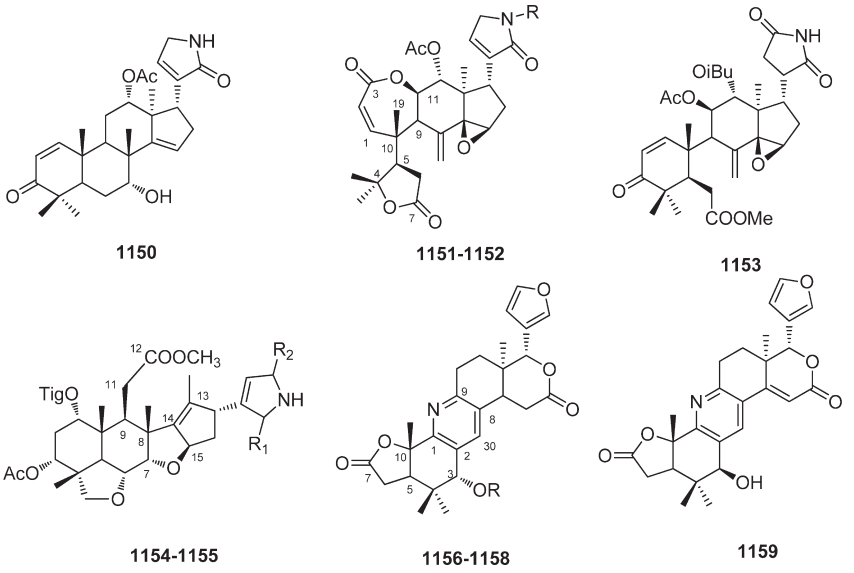
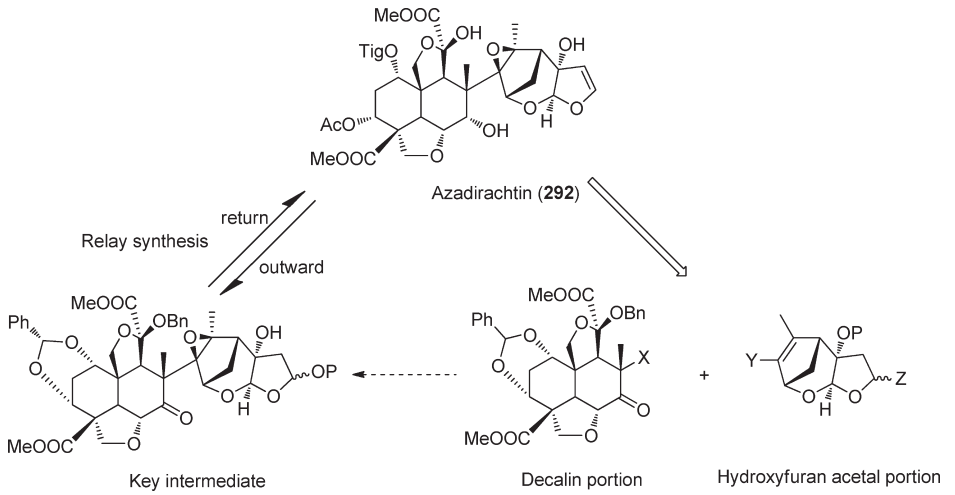



**Figure 33.** Structures of N-containing limonoids **1150**−**1159**.

**Scheme 1. Strategy for the Synthesis of Azadirachtin (292)**




ecdysteroids at crucial stages. This involved modification of the ecdysteroid titer and then in turn led to changes in lysosomal enzyme activity causing overt morphological abnormalities during the metamorphic molt.[902] It seemed likely that pupation in azadirachtin-treated *Manduca sexta* was inhibited by a disturbed ecdysteroid regulation shortly before pupal ecdysis, and **292** was able to inhibit development even when individuals performed a complete molt after the treatment.[903] In addition, low doses of **292** injected into newly molted last-instar larvae of *Oncopeltus fasciatus* prolonged the intermolt stage, apparently due to a delayed ecdysteroid peak.[904] In preventing normal development of final-instar larvae of *Heliothis virescens*, **292** apparently reduced molting hormone titers by reducing prothoracicotropic hormone (PTTH) titers and the receptivity of prothoracic glands to produce ecdysone *via* stimulation by PTTH.[905] Remold et al. suggested that **292** might influence the release of trophic hormones from the corpus cardiacum leading to alterations in timing and titer of morphogenetic hormone pools.[906] The strong effect of **292** on larval-pupal and pupal-adult of *Epilachna varivestis* was interpreted as an interference with molting hormone pools.[907] It was reported that **292** induced disturbances in larval and pupal ecdysis, decreased cold-induced elevation of juvenile hormone titers in the larval body, and might have an effect on the prothoracicotropic function of the brain.[897] A brain factor, possibly the prothoracicotropic hormone that stimulates ecdysteroid production on the prothoracic glands, might act directly or indirectly on both the midgut cell organization and the intestinal microenvironment, interfering in the trypanosome survival and infection of the vector *Rhodnius prolixus*.[908] Remold established a precise correlation between administered dose, resulting effects, and retention of **292**, and concluded that azadirachtin shifted and decreased the ecdysterone, juvenile hormone, and vitellogenin peaks concomitantly.[909] The $LC_{50}$ values of **292** against ecdysone 20-monooxygenase activity ranged from $10^{-4}$ M for *Drosophila melanogaster* to $4 \times 10^{-4}$ for *Manduca sexta*.[910]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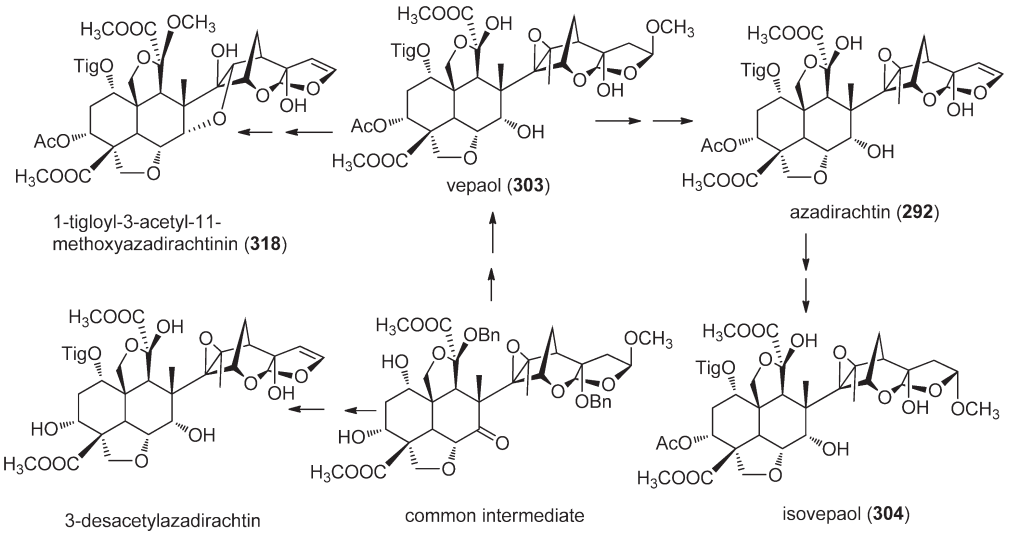
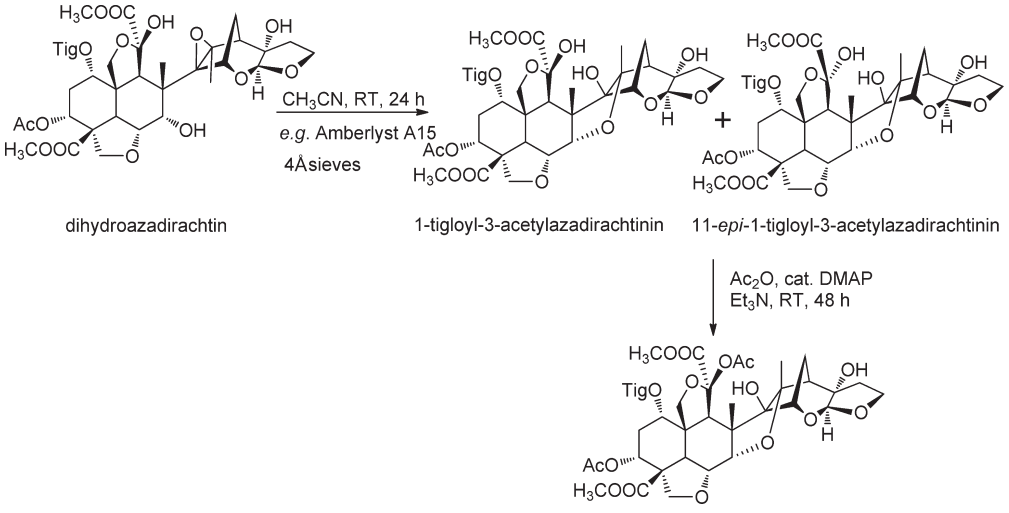
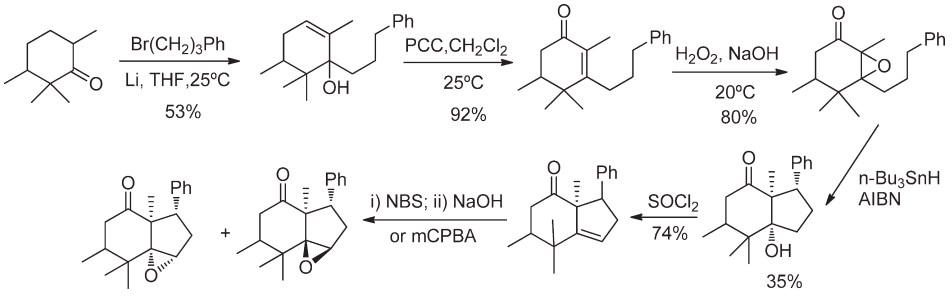
**Scheme 2. Synthesis of Azadirachtin and Azadirachtinin Skeleton from a Common Intermediate**




**Scheme 3. Chemical Conversion from Azadirachtin Skeleton to Azadirachtinin Skeleton**




**Scheme 4. Strategy of Synthesis of 12-Oxo-14,15-epoxy Havanensin Derivatives**




Exposure to **292** reduced the fertility and fecundity of adult *Myzus persicae, Nasonovia ribisnigri, Chaetosiphon fragaefolii* in a linear, concentration-dependent manner.[911] Injection of **292** into newly hatched adults of *Oncopeltus fasciatus* affected the longevity, fecundity, and hatchability of eggs from treated parents, and there were marked differences between males and females.[912] Most of the *Locusta migratoryia* treated with **292** had no oviposition, and radioimmunoassay showed quantatively that only traces of ecdysteroids were present in their ovaries.[913] In addition, feeding adult *Epilachna varivestis* with **292** for first five days after molting decreased its reproduction, increased mortality, and delayed the onset of the oviposition.[914] Moreover, **292**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**Scheme 5. Synthesis of Fraxinellone (1142) Using Stereoselective Oshima-Utimoto Reaction**

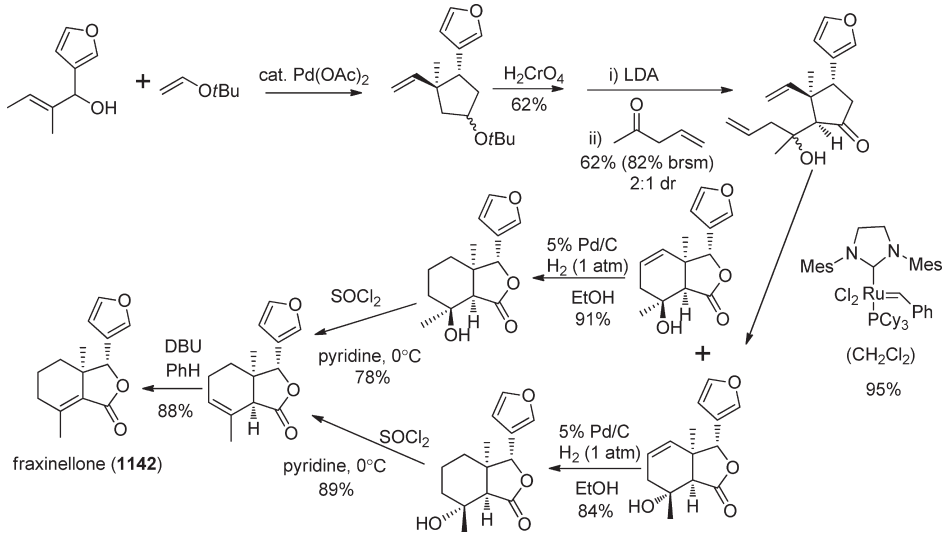


**Table 32. Antifeedancy of Azadirachtin (292) against Insects**

| insects | antifeedancy |
|---|---|
| *Epilachna varivesti* | $EC_{50}$ = 13 ppm;[322] $EC_{100}$ = 120 ppm[322] |
| *E. paenulata* | $ED_{50}$ = 0.72 $\mu g/cm^2$, $LD_{50}$ = 1.24 $\mu g/cm^2$ (96 h)[880] |
| *Helicoverpa armigera* | $EC_{50}$ = 0.26 ppm (for neonates), 0.4 ppm (for 3rd instar larvae)[494] |
| *Locusta migratoria* | MIC = 25 ppm[881] |
| *L. migratoria* | $ED_{50}$ = 3 ppm[882] |
| *Ostrinia nubilalis* | $PC_{50}$ = 3.5 ppm (for neonate larvae), 24 ppm (for 3rd-instar larvae)[883] |
| *Peridroma saucia* | $EC_{50}$ = 0.26 ppm[884] |
| *Pieris rapae* | AR = 100 (1000 ppm)[507] |
| *Phyllotreta striolata* | MIC = 10 ppm[885] |
| *Reticulitermes speratus* | $PC_{95}$ = 65.293[886] |
| *Rhodnius prolixus* | $ED_{50}$ = 25.0 $\mu g/mL$[887,888] |
| *Schistocerca gregaria* | $ED_{50}$ = 0.001 ppm[882] |
| *Spodoptera littoralis* | AI = 98.8 ± 1.11 (1 ppm), 100.0 ± 0.00 (10 ppm);[792] 99 ± 1.1(1 ppm)[305] |

delayed the release of one or more factors from the head that regulate oogenesis in *Aedes aegypti*.[915] Ovarian development was severely reduced in azadirachtin-injected females, and the vitellogenesis was rescuable by juvenile hormone treatment.[916] Both 20-hydroxyecdysone and **292** caused inhibition of vitellogenesis and ultrastructural damages in corpus allatum cells. Interestingly, some ultrastructural modifications were specific to each molecule, suggesting that they would act via different mechanisms.[917] The vitellogenesis inhibition produced by **292** in *Labidura riparia* consisted of direct cytotoxic effects as well as a generalized disruption of endocrine and neuroendocrine functions.[918] Spermiogenesis of *Mamestra brassicae* occurred in Grace's medium when the testis sheath was also present, but even in the presence of both ruptured testis and 20-hydroxyecdysone, 3 ppm of **292** caused degenerated spermatocysts.[919] Nisbet et al. reported that **292** bound preferentially to sites on the organelles associated with maturing *Schistocerca gregaria* sperm tails, and that **292** at concentrations of $10^{-4}$ M and above caused a time-dependent reduction in the motility of eupyrene sperm bundles liberated from the accessory glands of mature male *S. gregaria*.[920] Subrahmanyam et al. pointed out that **292** delayed the synthesis and release of neurosecretion from the A-type median neurosecretory cells of *S. gregaria*, thereby affecting the ovarian development.[921]

Administration of a physiological dose of **292** into female *Locusta migratoria* by injection led neither to starvation (though food consumption was reduced) nor to a qualitative change in the neurosecretory proteins of the corpus cardiacum.[922] However, the neurosecretory system was accompanied by an unusually high accumulation of paraldehyde fuchsin (PAF)-stainable neurosecretory material in the brain fibers and in the storage lobes of the corpus cardiacum.[923] The morphological and biochemical effects induced by **292** suggested a widespread blockade of factors presumably located in the central nervous system.[924] **292** stimulated a specific deterrent neuron in the lepidopterous species tested and inhibited the firing of neurons with signal phagostimulants in another test.[925]

Experiments in vivo and in vitro proposed by Mordue et al. demonstrated that treatment with **292** resulted in a significant growth reduction in the rate of passage of food through the gut, and in gut motility of *Locusta migratoria*.[926] Furthermore, azadirachtin (**292**) directly or indirectly inhibited the reduction


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**Table 33. Antifeedancy of Meliaceous Limonoids**

| compounds | insects and antifeedancy |
|---|---|
| azadirone (**1**) | *Leptinotarsa decemlineata*, AI = 11.6 ± 6.3 (100 ppm), 22.4 ± 7.4 (300 ppm), 26.9 ± 5.1 (500 ppm)[273] |
| azadiradione (**12**) | *Reticulitermes speratus*, $PC_{95}$ = 827.5 μg/disk;[103] *Heliothis virescens*, $EC_{50}$= 560 ppm[101] |
| 7-deacetylazadiradione (**13**) | *H. virescens*, $EC_{50}$ = 1600 ppm[101] |
| 17β-hydroxyazadiradione (**18**) | *Reticulitermes speratus*, $PC_{95}$ = 235.6 μg/disk[103] |
| 7-deacetyl-17β-hydroxyazadiradione (**19**) | *Heliothis virescens*, $EC_{50}$ = 240 ppm[101] |
| nilotin (**129**) | *Leptinotarsa decemlineata*, $ED_{50}$ = 7 μg/mL[191] |
| 12α-hydroxyamoorastatin (**166**) | *Epilachna paenulata*, $ED_{50}$ = 0.80 μg/cm$^2$ (in choice assay); $LD_{50}$ = 0.76 μg/cm$^2$ (in no-choice assay)[880] |
| chuanliansu (**167**) | *Helicoverpa armigera*, $EC_{50}$ = 26.8 ppm; $FI_{50}$ = 56.6 ppm (for third-instar larvae)[865]<br>*Epilachna paenulata*, $ED_{50}$ = 3.69 μg/cm$^2$[880] |
| 1β,2β;21,23-diepoxy-7α-hydroxy-24,25,26,27-tetranor-apotirucalla-14,20,22-trien-3-one (**246**) | *Leptinotarsa decemlineata*, AI = 10.8 ± 4.5 (100 ppm), 21.4 ± 2.6 (300 ppm), 24.9 ± 3.7 (500 ppm)[273] |
| 3-tigloylazadirachtol (**296**) | *Epilachna varivesti*, $EC_{50}$ = 30 ppm;[322] $EC_{100}$ = 150 ppm[322]<br>*Schistocerca gregaria*, $ED_{50}$ = 80 μg/l[872]<br>*Locusta migratoria*, $ED_{50}$ = 12 mg/L[872] |
| 1-tigloyl-3-acetylazadirachtol (**297**) | *Epilachna varivesti*, $EC_{50}$ = 6 ppm;[322] $EC_{100}$ = 50 ppm[322] |
| salannin (**332**) | *Spodoptera frugiperda*, $ED_{50}$ = 13 μg/cm$^2$;[362] *Reticulitermes speratus*, $PC_{95}$ = 203.3 μg/disk[103] |
| 3-deacetylsalannin (**333**) | *R. speratus*, $PC_{95}$ = 1373.1 μg/disk[103] |
| nimbolide (**345**) | *Epilachna varivesti*, $EC_{50}$ = 90 ppm;[322] $EC_{100}$ > 500 ppm[322] |
| volkensin (**369**) | *Spodoptera frugiperda*, $ED_{50}$ = 3.5 μg/cm$^2$[362] |
| 6-deacetylnimbin (**392**) | *Reticulitermes speratus*, $PC_{95}$ = 1581.2 μg/disk[103] |
| gedunin (**416**) | *R. speratus*, $PC_{95}$ = 218.4 μg/disk[103] |
| 7-deacetylgedunin (**421**) | *R. speratus*, $PC_{95}$ = 113.7 μg/disk[103] |
| prieurianin (**458**) | *Helicoverpa armigera*, $EC_{50}$ = 18.8 ppm (for neonates), $EC_{50}$ = 92.2 ppm (for 3rd instar larvae)[494] |
| epoxyprieurianin (**464**) | *H. armigera*, $EC_{50}$ = 3.2 ppm (for neonates), $EC_{50}$ = 55.7 ppm (for 3rd instar larvae)[494] |
| dysoxylumin A (**465**) | *Pieris rapae*, AR = 73.8 (1000 ppm)[507] |
| dysoxylumin B (**466**) | *P. rapae*, AR = 77.4 (1000 ppm)[507] |
| dysoxylumin C (**467**) | *P. rapae*, AR = 74.9 (1000 ppm)[507] |
| dysoxylumolide B (**501**) | *P. rapae*, AR = 28.3 (1000 ppm)[507] |
| dysoxylumic acid D (**502**) | *P. rapae*, AR = 29.5 (1000 ppm)[507] |
| dysoxylumic acid A (**503**) | *P. rapae*, AR = 78.7 (1000 ppm)[507] |
| dysoxylumic acid B (**504**) | *P. rapae*, AR = 64.1(1000 ppm)[507] |
| dysoxylumic acid C (**506**) | *P. rapae*, AR = 59.4 (1000 ppm)[507] |
| dysoxylumolide A (**512**) | *P. rapae*, AR = 27.9 (1000 ppm)[507] |
| dysoxylumolide C (**554**) | *P. rapae*, AR = 22.4 (1000 ppm)[507] |
| methyl angolensate (**568**) | *Spodoptera frugiperda*, AI = 66.4 ± 10.63 (1000 ppm)[556] |
| swietenolide (**638**) | *S. frugiperda*, AI = 94.1 ± 2.90 (1000 ppm)[445] |
| 6-acetylswietenolide (**645**) | *S. frugiperda*, AI = 72.2 ± 19.60 (1000 ppm)[445] |
| diacetylswietenolide (**647**) | *S. frugiperda*, AI = 72.0 ± 9.38(1000 ppm)[445] |
| xylocarpin (**799**) | *S. frugiperda*, AI = 77.8 ± 6.90 (1000 ppm)[556] |
| swietemahonin F (**805**) | *S. frugiperda*, AI = 70.2 ± 8.90 (1000 ppm)[445] |
| ruageanin A (**808**) | *S. frugiperda*, AI = 72.6 ± 19.60 (1000 ppm)[556] |
| ruageanin B (**809**) | *S. frugiperda*, AI = 86.3 ± 6.41(1000 ppm)[556] |
| khayanolide A (**1002**) | *S. littoralis*, $EC_{50}$ = 11.18 mg/kg[678] |
| khayanolide B (**1004**) | *S. littoralis*, $EC_{50}$ = 2.19 mg/kg[678] |
| 1-*O*-acetylkhayanolide B (**1005**) | *S. littoralis*, $EC_{50}$ = 2.66 mg/kg[678] |
| marrangin (**1067**) | *Epilachna varivesti*, $EC_{50}$ = 6 ppm;[322] $EC_{100}$ = 50 ppm[322] |
| nimbandiol (**1101**) | *Reticulitermes speratus*, $PC_{95}$ = 245.4 μg/disk[103] |
| munroniamide (**1152**) | *Pieris brassicae*, AR = 27.6 (1000 ppm)[765] |

of trypsin by the enzyme-secreting cells of the midgut wall and consequently resulted in the increased costs and reduced rate of growth.[927] When *Spodoptera litura* larvae were fed a diet of castor leaves treated with **292**, gut enzyme-acid phosphatases, alkaline


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**Table 34. MAC Values (ppm) of Antifeedancy of Meliaceous Limonoids**

| compounds | insects | MAC values |
|---|---|---|
| trichilin B (**137**) | *Spodoptera exigua*;[207,220,341] *S. littoralis*[214] | 200 |
| 12-*O*-acetyltrichilin B (**138**) | *S. exigua*[220,341] | 400 |
| 1,12-diacetyltrichilin B (**139**) | *S. exigua*[207,220,341] | |
| trichilin D (**141**) | *S. exigua*[207,220] | |
| aphanastatin (**142**) | *S. exigua* and *S. eridania*[341] | 200 |
| trichilin F (**143**) | *S. littoralis*[223] | 300 |
| trichilin G (**144**) | *S. littoralis*[223] | |
| trichilin H (**145**) | *S. exigua*;[207,220,227,341] *S. eridania*[224] | 400 |
| 1-acetyltrichilin H (**146**) | *S. littoralis*[225] | |
| trichilin I (**151**) | *S. exigua*;[220,227,341] *S. eridania*[224] | |
| trichilin J (**153**) | *S. exigua*;[220,227,341] *S. eridania*[224] | |
| trichilin K (**154**) | *S. eridani*[224] | |
| trichilin L (**155**) | *S. eridani*[224] | |
| sendanin (**156**) | *S. littoralis*[214] | |
| azedarachin A (**158**) | *S. exigua*;[207,227,341] *S. eridania*[224,341] | 200 |
| 12-*O*-acetylazedarachin A (**159**) | *S. exigua*;[207,341] *S. eridania*[341] | |
| | *S. littoralis*[214] | 400 |
| azedarachin B (**160**) | *S. littoralis*[214,225] | 200 |
| 12-*O*-acetylazedarachin B (**161**) | *S. eridani*;[224] *S. exigua*[207,227] | 400 |
| azedarachin C (**162**) | *S. exigua*[228,341] | |
| meliatoxin $A_2$ (**163**) | *S. litura*[878] | 300 |
| | *S. exigua*;[207,341] *S. eridania*[341] | 400 |
| 12$\alpha$-hydroxyamoorastatin (**166**) | *S. littoralis*[214] | 150 |
| toosendanin (**167**) | *S. littoralis*[212] | 200 |
| | *S. littoralis*[214] | 300 |
| 12$\alpha$-hydroxyamoorastatone (**173**) | *S. littoralis*[225] | 250 |
| isochuanliansu (**179**) | *S. littoralis*[214] | 400 |
| | *S. littoralis*[225] | 300 |
| neoazedarachins A, B, D (**180**−**182**) | *S. littoralis*[225] | 400 |
| 1-cinnamoyltrichilinin (**192**) | *S. littoralis*[212] | 1000 |
| trichilinin B (**195**) | *S. eridania*[239] | |
| trichilinin C (**196**) | *S. eridania*[239] | |
| trichilinin D (**197**) | *S. littoralis*[212,247] | |
| trichilinin E (**198**) | *S. littoralis*[212,247] | |
| meliacarpinin A (**327**) | *S. exigua*;[341] *S. littoralis*[214] | 50 |
| meliacarpinin B (**328**) | *S. exigua*[340] | 150 |
| | *S. exigua* and *S. eridania*[341] | 50 |
| meliacarpinin C (**329**) | *S. exigua* and *S. eridania*,[341] *S. littoralis*[214] | 50 |
| meliacarpinin D (**330**) | *S. exigua* and *S. eridania*,[341] *S. littoralis*[214] | |
| meliacarpinin E (**331**) | *S. eridania*[342] | |
| salannin (**332**) | *S. exigua*;[341] *S. eridania*[84,239,341,342,363] | 1000 |
| 3-deacetylsalannin (**333**) | *S. eridania*[342] | |
| nimbolinin A (**355**) | *S. littoralis*[212] | |
| 1-deacetylnimbolinin A (**356**) | *S. littoralis*[247] | |
| nimbolinin B (**358**) | *S. exigua*;[341] *S. eridania*[341,342] | |
| | *S. littoralis*[247] | |
| nimbolinin C (**363**) | *S. littoralis*[212] | |
| nimbolinin D (**364**) | *S. littoralis*[212] | |
| ohchinolide C (**386**) | *S. eridania*[84] | |
| 3-*O*-acetylohchinolal (**399**) | *S. eridania*[84] | |
| nimbolidin B (**407**) | *S. eridania*[247,342] | 1000 |
| | *S. eridania*[363] | 500 |
| nimbolidins C-E (**410**−**412**) | *S. eridania*[363] | 500 |
| nimbolidin F (**413**) | *S. eridania*[84] | |


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**Table 34. Continued**

| compounds | insects | MAC values |
|---|---|---|
| Trs A-C (**462**, **479**, **463**) | *Ajrotis sejetum Denis*[493] | 200 |
| methyl angolensate (**568**) | *Spodoptera littoralis*[547−549,551] | 500 |
| methyl 6-hydroxyangolensate (**569**) | *S. littorali*[547−549] | |
| methyl 6-acetoyxangolensate (**570**) | *S. littoralis*[547,549] | |
| sandoricin (**573**) and 6-hydroxysandoricin (**574**) | *S. frugiperda*[532] | 25 |
| | *Ostrinia nubilalis*[532] | 200 |
| khayanoside (**598**) | *Spodoptera littoralis*[574] | 1000 |
| proceranolide butanoate (**635**) | *Agrotis segetum*[648] | 100 |
| khayanone (**668**) | *Spodoptera littoralis*[658] | 300 |
| angolensins A-C (**672**, **766**, and **673**) | *S. littoralis*[545] | 1000 |
| 8$\beta$,14$\alpha$-dihydroxyswietenolide (**674**) | *S. littoralis*[510] | 500 |
| khayalactol (**774**) | *S. littoralis*[547] | 300 |
| seneganolide (**777**) | *S. littoralis*[547,549,551] | |
| 2-hydroxyseneganolide (**778**) | *S. littoralis*[559,658] | 200 |
| 2-hydroxyswietemahonolide (**797**) | *S. littoralis*[630] | 500 |
| swietemahonin G (**806**) | *S. littoralis*[630] | 300 |
| 6-*O*-acetylswietemahonin G (**807**) | *S. littoralis*[630] | 500 |
| xyloccensin L (**829**) | *Piece brassicae*[635] | 1000 |
| tabulalide D (**857**) | *Spodoptera littoralis*[706] | 500 |
| swietenialides A−E (**921**−**923**, **889**, **895**) | *S. littoralis*[664] | 1000 |
| xyloccensins P, Q (**949**, **950**) | *Mythimna separata*[700] | 500 |
| tabulalin (**973**) | *Spodoptera littoralis*[706] | |
| tabulalides A, B, E (**995**, **996**, and **978**) | *S. littoralis*[706] | 1000 |
| khayanolide A (**1002**) | *S. littoralis*[547−549] | 300 |
| 1-*O*-acetylkhayanolide A (**1003**) | *S. littoralis*[559,658] | 100 |
| khayanolide B (**1004**) | *S. littoralis*[547−549] | 1000 |
| 1-*O*-acetylkhayanolide B (**1005**) | *S. littoralis*[547] | 300 |
| khayanolide D (**1006**) | *S. littoralis*[559] | 200 |
| | *S. littoralis*[574] | 1000 |
| khayanolide E (**1007**) | *S. littoralis*[574] | 100 |
| khayanolide C (**1013**) | *S. littoralis*[549] | 500 |
| spirosendan (**1056**) | *S. littoralis*[247] | 1000 |
| azedararide (**1138**) | *S. littoralis*[230] | 500 |
| fraxinellone (**1142**) | *S. littoralis*[230] | |
| 12$\alpha$-acetoxyfraxinellone (**1147**) | *S. littorali*[230] | |

phosphatases, adenosine triphosphatases, and lactate dehydrogenase decreased.[928]

Using *Drosophila melanogaster* as model system, the insect cellular cytoskeletal $\beta$-actin was found to be the probable target of azadirachtin (**292**).[929,930] Azadirachtin (**292**), salannin (**332**), nimbin (**391**), and 6-deacetylnimbin (**392**) inhibited the ecdysone 20-monooxygenase (E-20-M) activity against *Aedes aegypti*, *Drosophila melanogaster*, and *Manduca sexta* in a dose-dependent fashion. Based on the dose reponse as well as the 50% inhibition ($I_{50}$) value, **332** was found to be the most effective whereas **391** was the least effective.[931] The effects of 17$\beta$-hydroxyazadiradione (**18**), **292**, **332**, 3-deacetylnimbin (**333**), gedunin (**416**), and 7-deacetylgedunin(**421**) on enzyme lactate dehydrogenase (LDH) activity of *Cnaphalocrocis medinalis* larvae were investigated with clear dose−response dependency manner. Among these compounds, **292** is most potent in all experiments with $EC_{50}$ values at least 0.043, 0.057, and 0.063 ppm for third, fourth and fifth instars, respectively.[932,933] Azadirachtin B (**296**) was 2.5-fold less active than azadiracthin (**292**) as an insect growth inhibitor but comparably effective in ecdysis inhibition.[316,843] Surprisingly, salannin (**332**) was comparable to **292** in growth-regulatory activity against *Spodoptera litura*, *Pericallia ricini*, and *Oxya fuscovittata*.[934]

Nimocinolide (**26**) and isonimocinolide (**29**) affected fecundity in *Musca domestica* at doses of 100−500 ppm and showed mutagenic properties in *Aedes aegypti* producing intermediates.[80] Nutritional analyses revealed that both growth inhibition and reduced consumption of cedrelone (**81**) were a consequence of postingestive malaise rather than a peripherally mediated antifeedant effect.[935] The feeding experiments showed the $ED_{50}$ values of sendanin (**156**) for growth inhibition against *Pectinophora gossypiella*, *Heliothis zea*, *H. virescens*, and *Spodoptera frugiperda* ranged from 9 to 60 ppm, with *P. gossypiella* being the most sensitive and *Heliothis* complex the least.[198] When incorporated into artificial diets of neonates at 50 ppm, humilinolides A−D (**793**, **794**, **695**, and **697**) caused larval mortality, as well as growth reduction and increased the development time of survivors in a concentration-dependent manner. In addition, **695** at


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**Table 35. Insects Growth Regulatory Activity of Meliaceous Limonoids**

| compounds | insects and efficacy |
|---|---|
| hirtin (**94**) | *Peridroma saucia*, $EC_{50}$ = 13 ppm[170] |
| toosendanin (**167**) | *Spodoptera frugiperda*, $LC_{50}$ = 7.0 ppm[413] |
| azadirachtin (**292**) | *Heliothis zea* and *H. virescens*, $ED_{50}$ = 0.7 ppm; *Spodoptera frugiperda*, *Pectinophora gossypiella*, $ED_{50}$ = 0.4 ppm[936] |
| | *Rhodnius prolixus*, $ED_{50}$ = 0.04 $\mu$g/mL[888] |
| | *Helicoverpa armigera*, $EC_{50}$ = 0.26 ppm; *Spodoptera litura*, $EC_{50}$ = 0.21 ppm[442] |
| azadirachtin B (**296**) | *Rhodnius prolixus*, $ED_{50}$ = 0.015 $\mu$g/mL[888] |
| salannin (**332**) | *Helicoverpa armigera*, $EC_{50}$ = 74.5 ppm,[442] $EC_{50}$ = 86.5 ppm, $EC_{95}$ = 187.4 ppm[366] |
| | *Spodoptera litura*, $EC_{50}$ = 72.0 ppm[442] |
| | *S. litura*, $EC_{50}$ = 87.7 ppm, $EC_{95}$ = 197.3 ppm and $FI_{50}$ = 2.8 $\mu$g/cm[2366] |
| salannol (**336**) | *S. litura*, $EC_{50}$ = 77.4 ppm, $EC_{95}$ = 220.8 ppm, and $FI_{50}$ = 2.3 $\mu$g/cm[2366] |
| | *Helicoverpa armigera*, $EC_{50}$ = 79.7 ppm, $EC_{95}$ = 219.7 ppm[366] |
| salannol acetate (**337**) | *H. armigera*, $EC_{50}$ = 64.2 ppm, $EC_{95}$ = 166.9 ppm[366] |
| | *Spodoptera litura*, $EC_{50}$ = 65.6 ppm, $EC_{95}$ = 169.1 ppm, and $FI_{50}$ = 2.0 $\mu$g/cm[2366] |
| gedunin (**416**) | *Spodoptera litura*, $EC_{50}$ = 40.4 ppm[442] |
| | *S. frugiperda*, $LC_{50}$ = 39.0 ppm[413] |
| | *Helicoverpa armigera*, $EC_{50}$ = 50.8 ppm[442] |
| 6$\beta$-hydroxygedunin (**420**) | *H. armigera*, $EC_{50}$ = 24.2 ppm; *Spodoptera litura*, $EC_{50}$ = 21.5 ppm[442] |
| photogedunin (**433**) | *S. frugiperda*, $LC_{50}$ = 10.0 ppm[413] |
| prieurianin (**458**) | *Drosophila melanogaster*, $ED_{50}$ = $10^{-5}$ M[498] |
| rohitukin (**480**) | *D. melanogaster*, $ED_{50}$ = 1.25 × $10^{-4}$ M[498] |
| khayalactol (**774**) | *Spodoptera littoralis*, $EC_{50}$ = 11.48 mg/kg[678] |
| khayanolide A (**1002**) | *S. littoralis*, $EC_{50}$ = 14.65 mg/kg[678] |
| khayanolide B (**1004**) | *S. littoralis*, $EC_{50}$ = 6.96 mg/kg[678] |
| 1-*O*-acetylkhayanolide B (**1005**) | *S. littoralis*, $EC_{50}$ = 16.75 mg/kg[678] |
| nimbinene (**1099**) | *S. litura*, $EC_{50}$ = 404.5 ppm; *Helicoverpa armigera*, $EC_{50}$ = 394.1 ppm[442] |

5 ppm also reduced growth and survivorship of *Ostrinia nubilalis*.[665]

The $EC_{50}$ values of 7-deacetyl-17$\beta$-hydroxyazadiradione (**19**), azadiradione (**12**), and nimbocinol (**13**) against *Heliothis virescens* were 240, 560, and 1600 ppm, respectively, which suggested that the insect growth regulating activity was reduced by a hydroxyl group at C-7 but increased by a hydroxyl group at C-17.[101] Siddiqui et al. proposed that the senecioyloxy substituent at C-7 in 7-*O*-deacetyl-23-*O*-methyl-7$\alpha$-*O*-senecioylnimocinolide (**28**) resulted in a significant increase of insect growth regulating activity against *Aedes aegypti*.[119]

**5.1.3. Insecticidal Activity.** The insecticidal activities of azadirachtin-like compounds were listed in detail by Govindachari et al. in 1998.[937] We now summarize the insecticidal efficacy of limonoids in Table 36. The $LC_{50}$ values of **292** against the second-instar nymphs of nine species of aphids ranged from 2.4 ppm for *Myzus persicae* on pepper to 635.0 ppm for *Chaetosiphon fragaefolii* on strawberry.[938] Contact and dipping $LC_{50}$ values of **292** against larvae of *Hyalomma dromedarii* were >20.3 $\mu$g/cm$^2$ and >2.5 g/L, respectively.[894] Arnason et al. proved that **292** was an effective botanical insecticide for control of *Ostrinia nubilalis* at 10 ppm.[883] In addition, **292** was efficacious against *Haematobia irritans*, *Stomoxys calcitrans*, and *Musca domestica* and also had potential for *H. irritans* control.[939] It was announced that **292** in ppm concentrations inhibited proliferation and monolayer formation of *Spodoptera frugiperda* (Sf9) insect cells in monolayer culture.[831,940] However, Cohen et al. stated that **292** was not cytotoxic against Sf9 cell lines.[941] The evidence presented by Salehzadeh et al. suggested that in insect cells **292** acted similarly to the antimitotic plant metabolite colchicine, namely, by interfering with the polymerization of tubulin.[942]

Swietenin C (**679**), humilinolide E (**698**), methyl-2-hydroxy-3$\beta$-isobutyroxy-1-oxomeliac-8(30)-enate (**699**), and humilin B (**812**) reduced survivorships at various stages against *Ostrinia nubilalis*, while 6$\alpha$-acetoxygedunin (**418**) reduced growth at the test concentration of 50 ppm.[434] Khayasin (**652**) exhibited marked insecticidal activity against the fifth larvae of *Brontispa longissima* at a concentration of 10 mg/L.[558] Among khayasin T (**655**), febrifugin (**694**), cipadesin (**703**), ruageanin A (**808**), cipadesin A (**815**), and febrifugin A (**716**), the last showed the hightest insecticidal activity at 50.0 mg/kg against *Spodoptera frugiperda*, comparable to that of the positive control-gedunin (**416**).[656] Moluccensins H and I (**964** and **965**) showed moderate insecticidal activity against the fifth instar larvae of *Brontispa longissima* at a concentration of 100 mg/L, whereas moluccensins J−L (**966**, **969**, **970**) exhibited no activity.[568] Preliminary studies showed that the limonoids and triterpenoids in *Cedrela fissilis* and *C. fruticosa* were promising in controlling leaf-cutting ants *Atta sexdens rubropilosa*,[671] and subsequent research revealed that the toxicity for the ants seemed not to be related only to the presence of the limonoids.[113] Neither **53** nor 20,21,22,23-tetrahydro-23-oxoazadirone (**56**) showed insecticidal activity against *Peridroma saucia*.[131] In addition, meliacinol (**456**) did not show insecticidal activity against *Aedes aegypti* at up to 100 ppm.[93]

Quantitative molecular calculations of the structure−activity relationship indicated that the insecticidal activity of azadirachtins was directly proportional to the polarity of ring A, the steric requirements of the substituents at C-7, and the rotations around the single bond between C-8 and C-14.[943] The potent larvicidal activity of gedunin (**416**) indicated that the epoxidation and expansion of ring D had a favorable effect on this activity, as was


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**Table 36. Insecticidal Efficacy of Meliaceous Limonoids**

| compounds | insects and efficacy |
|---|---|
| nimocinol (**7**) | *Aedes aegypti*, $LC_{50}$ = 21 ppm[93] |
| 6α-*O*-acetyl-7-deacetylnimocinol (**8**) | *A. aegypti*, $LC_{50}$ = 83 ppm[93] |
| 23-*O*-methylnimocinolide (**27**) | *A. aegypti*, $LC_{50}$ = 53 ppm[119] |
| 7-*O*-deacetyl-23-*O*-methyl-7α-*O*-senecioylnimocinolide (**28**) | *A. aegypti*, $LC_{50}$ = 2.14 ppm[119] |
| 22,23-dihydronimocinol (**33**) | *Anopheles stephensi*, $LC_{50}$ = 60 ppm[120] |
| 1α,7α,11β-triacetoxy-4α-carbomethoxy-12α-(2-methylpropanoyloxy)-14β,15β-epoxyhavanensin (**123**) | *A. gambiae*, $LD_{50}$ = 4.0 ppm[188] |
| 1α,11β-diacetoxy-4α-carbomethoxy-7α-hydroxy-12α-(2-methylpropanoyloxy)-15-oxohavanensin (**130**) | *A. gambiae*, $LD_{50}$ = 3.6 ppm[188] |
| 1α-acetyl-3α-propionylvilasinin (**187**) | *A. gambiae*, $LD_{50}$ = 7.1 ppm[188] |
| meliatetraolenone (**245**) | *A. stephensi*, $LC_{50}$ = 16 ppm[272] |
| azadirachtin (**292**) | *A. gambiae*, $LD_{50}$ = 57.1 ppm[188] *Plutella xylostella*, $LD_{50}$ = 7.04 (24 h); 4.12 (48 h); 1.28 (72 h); 0.87 (96 h) μg/g[324] *Spodoptera littoralis*, $LC_{50}$ = 0.32 ppm, $EC_{50}$ = 0.11 ppm[338] |
| azadirachtol (**295**) | *Plutella xylostella*, $LD_{50}$ = 4.88 (24 h); 3.28 (48 h); 2.35 (72 h); 1.78 (96 h) μg/g[324] |
| azadirachtin B (**296**) | *P. xylostella*, $LD_{50}$ = 4.85 (24 h); 2.26 (48 h); 1.56 (72 h); 1.06 (96 h) μg/g[324] |
| azadirachtin O (**301**) | *P. xylostella*, $LD_{50}$ = 3.92 (24 h); 1.92 (48 h); 1.19 (72 h); 0.79 (96 h) μg/g[324] |
| azadirachtin Q (**302**) | *P. xylostella*, $LD_{50}$ = 5.95 (24 h); 1.89 (48 h); 1.40 (72 h); 1.10 (96 h) μg/g[324] |
| 1,3-dicinnamoyl-11-hydroxymeliacarpin (**313**) | *Spodoptera littoralis*, $LC_{50}$ = 2.36 ppm, $EC_{50}$ = 0.57 ppm[338] |
| 1-cinnamoyl-3-acetyl-11-hydroxymeliacarpin (**314**) | *S. littoralis*, $LC_{50}$ = 0.48 ppm[338] |
| 1-cinnamoyl-3-methacrylyl-11-hydroxymeliacarpin (**315**) | *S. littoralis*, $LC_{50}$ = 1.19 ppm, $EC_{50}$ = 0.57 ppm[338] |
| 7α,12α-diacetyoxy-11β-hydroxyneotecleanin (**621**) | *Anopheles gambiae*, $LD_{50}$ = 7.83 ppm[579] |
| 11β,12α-diacetoxyneotecleanin (**622**) | *A. gambiae*, $LD_{50}$ = 7.07 ppm[579] |
| 11β,12α-diacetoxy-14β,15β-epoxyneotecleanin (**623**) | *A. gambiae*, $LD_{50}$ = 7.05 ppm[579] |
| azadirachtin L (**1067**) | *Plutella xylostella*, $LD_{50}$ = 10.27 (24 h); 7.89 (48 h); 5.39 (72 h); 1.92 (96 h) μg/g[324] |
| 11α-azadirachtin H (**1068**) | *P. xylostella*, $LD_{50}$ = 5.75 (24 h); 4.20 (48 h); 1.38 (72 h); 0.75 (96 h) μg/g[324] |
| azadirachtin M (**1071**) | *P. xylostella*, $LD_{50}$ = 8.46 (24 h); 4.84 (48 h); 4.23 (72 h); 1.30 (96 h) μg/g[324] |
| azadirachtin P (**1072**) | *P. xylostella*, $LD_{50}$ = 2.19 (24 h); 1.73 (48 h); 1.19 (72 h); 0.79 (96 h) μg/g[324] |
| desfurano-6α-hydroxyazadiradione (**1128**) | *Anopheles stephensi*, $LC_{50}$ = 43 ppm[120] |

also the case for the C═C bond in the ring A in nimbocinol (**13**) and nimolicinol (**451**).[944]

**5.1.4. Antiphytopathogen Activity.** Interestingly, pure azadiradione (**12**), epoxyazadiradione (**60**), salannin (**332**), and nimbin (**391**) did not have appreciable antifungal activity. However, when these limonoids were mixed and bioassayed, they showed antifungal activity against *Drechslera oryzae*, *Alternaria tenuis*, and *Fusarium oxysporum* f. sp. *vasinfectum*, indicating possible additive/synergistic effects.[105] Among azadiradione (**12**), cedrelone (**81**), and several derivatives of **81**, the most effective in reducing rust pustule emergence was **81** itself, which gave emergence reductions of 98.4% and 93.4% at concentrations of 1 μg/cm$^2$ and 10 μg/cm$^2$, repectively.[945] The results obtained by Kraus et al. showed that nimbolide (**345**) inhibited *Bacillus subtilis* even at a concentration of 0.5 μg/spot.[322] Nimbin (**391**) inhibited the growth of potato virus X *in vitro* by <50% at a concentration of 1000 ppm.[946] Ten limonoids from *Khaya ivorensis* were tested antifungal activity against *Botrytis cinerea*, and among these 1,3,7-trideacetylkhivorin (**438**) and **568** showed the highest activity, while 7-deacetylgedunin (**421**) had the lowest activity.[447] With the exception of *Penicillium expansum*, 3α,7α-dideacetylkhivorin (**440**) showed stronger antimicrobial activity than methyl 6-hydroxyangolensate (**569**) against all of the fungi tested (*Aspergillus niger*, *Monilinia fructicola*, *Botrytis cinerea*, *Geotrichum candidum*, *Colletotrichum acutatum*, *Penicillium expansum*, *P. italicum*, *Glomerella cingulata*, and *Phytophthora citrophthora*).[447] Among the microbial species tested (*Bacillus subtilis*, *Aspergillus fumigatus*, *A. niger*, and *Alternaria alternata*), methyl angolensate (**568**) exhibited the maximum zone of inhibition (17.3 mm) against *A. niger*.[947] mexicanolide (**626**), 2α,3β-dihydroxy-3-deoxymexicanolide (**628**), 3β-hydroxy-3-deoxymexicanolide (**629**), 6-acetyl-3-tigloylswitenolide (**646**), and 6-acetylswietenine (**687**) effectively reduced the number of rust pustules on detached groundnut leaves.[603] 2-Acetoxyseneganolide (**725**) at concentrations of 1000 and 1500 ppm showed inhibitions against *B. cinerea* growth of 61.50% and 68.33%, respectively, which differ only insignificantly from the inhibitions yielded by methyl 6-hydroxyangolensate (**569**) at 1500 ppm (65.33%) and seneganolide A (**723**) at 1000 ppm (60.83%).[472] 1,2-Dihydro-6α-acetoxyazadirone (**239**) showed strong inhibitory properties against the pathogenic fungi *Curvularia verruciformis*, *Dreschlera oryzae*, and *Alternaria solani*, but no related data were presented in the original paper.[267] 6-Acetoxy-7α-hydroxy-3-oxo-14β,15β-epoxymeliac-1,5-diene (**69**) exhibited strong antibacterial activity against *Bacillus antimacis*, *B. pumilus*, and *B. subtilis*, but no data were provided in the original paper.[142]

**5.1.5. Others.** Cherry found that **292** did not cause mortality, antifeeding responses, or change the growth rate of *Melanotus communis* wireworms; however, azadirachtin-treated soil was repellent to the wireworms.[948] 7-Deacetoxy-7-oxogedunin (**423**) acted as an inhibitor of photophosphorylation in spinach thylakoids since it inhibited ATP synthesis and phosphorylating electron flows by 88 and 83%, respectively, at a concentration


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**Table 37. Cytotoxic Activity of Meliaceous Limonoids against Tumor Cell Lines**

| compounds | cells | activity |
|---|---|---|
| dysobinin (**11**) | KB | $IC_{50}$ = 3.17 $\mu$g/mL[97] |
| | NCI-H187 | $IC_{50}$ = 1.67 $\mu$g/mL[97] |
| | MCF7 | $IC_{50}$ = 2.15 $\mu$g/mL[97] |
| azadiradione (**12**) | KB | $IC_{50}$ = 9.38 $\mu$g/mL[97] |
| | NCI-H187 | $IC_{50}$ = 6.44 $\mu$g/mL[97] |
| | MCF7 | $IC_{50}$ = 7.13 $\mu$g/mL[97] |
| mahonin (**17**) | NCI-H187 | $IC_{50}$ = 15.61 $\mu$g/mL[97] |
| | MCF7 | $IC_{50}$ = 18.42 $\mu$g/mL[97] |
| epoxyazadiradione (nimbinin) (**60**) | GPK | $ED_{50}$ = 7.13 $\mu$g/mL[500] |
| | KB | $IC_{50}$ = 12.87 $\mu$g/mL[97] |
| | NCI-H187 | $IC_{50}$ = 7.54 $\mu$g/mL[97] |
| | MCF7 | $IC_{50}$ = 4.68 $\mu$g/mL[97] |
| | N1 × $10^{-115}$ | $IC_{50}$ = 23 $\mu$M[941] |
| | 143B.TK | $IC_{50}$ = 24 $\mu$M[941] |
| anthothecol (**84**) | P388 | $ED_{50}$ = 1.2 $\mu$g/mL[210] |
| 1,12-diacetyltrichilin B (**139**) | P388 | $IC_{50}$ = 0.46 $\mu$g/mL[221] |
| trichilin D (**141**) | P388 | $IC_{50}$ = 0.055 $\mu$g/mL[221] |
| trichilin H (**145**) | P388 | $IC_{50}$ = 0.16 $\mu$g/mL[221] |
| | KB | $IC_{50}$ = 0.11 $\mu$g/mL[211] |
| 1-acetyltrichilin H (**146**) | P388 | $IC_{50}$ = 0.47 $\mu$g/mL[221] |
| 1-acetyl-2-deacetyltrichilin H (**147**) | P388 | $IC_{50}$ = 0.66 $\mu$g/mL[221] |
| 3-deacetyltrichilin H (**148**) | P388 | $IC_{50}$ = 0.045 $\mu$g/mL[221] |
| 1-acetyl-3-deacetyltrichilin H (**149**) | P388 | $IC_{50}$ = 0.40 $\mu$g/mL[221] |
| 12-*O*-deacetyltrichilin H (**150**) | HeLa S3 | $IC_{50}$ = 0.48 $\mu$M[226] |
| 12-deacetyltrichilin I (**152**) | P388 | $IC_{50}$ = 0.011 $\mu$g/mL[221] |
| sendanin (**156**) | P388 | $IC_{50}$ = 0.078 $\mu$g/mL;[205] $ED_{50}$ = 0.01 $\mu$g/mL[210] |
| | N1 × $10^{-115}$ | $IC_{50}$ = 133 $\mu$M[941] |
| | 143B.TK | $IC_{50}$ = 89 $\mu$M[941] |
| 29-deacetylsendanin (**157**) | Hepa1c1c7 | $GI_{50}$ = 0.238 $\mu$g/mL[202] |
| | HepG2 | $GI_{50}$ = 0.805 $\mu$g/mL[202] |
| | P388 | $IC_{50}$ = 0.026 $\mu$g/mL[205] |
| 29-isobutylsendanin (**161**) | P388 | $IC_{50}$ = 0.034 $\mu$g/mL[205] |
| 12$\alpha$-hydroxyamoorastatin (**166**) | P388 | $ED_{50}$ = 0.002 $\mu$g/mL;[210] $IC_{50}$ = 0.090 $\mu$g/mL[205] |
| toosendanin (**167**) | KB | $IC_{50}$ = 3.82 $\mu$g/mL[211] |
| | PC3 | $IC_{50}$ = 1.2 × $10^{-7}$ M (120 h)[960] |
| | BEL7404 | $IC_{50}$ = 2.6 × $10^{-8}$ M (96 h)[960] |
| | SH-SY5Y | $IC_{50}$ = 1.5 × $10^{-7}$ M (96 h)[960] |
| | U251 | $IC_{50}$ = 3.3 × $10^{-8}$ M (96 h)[960] |
| | HL-60 | $IC_{50}$ = 6.1 × $10^{-9}$ M (96 h)[960] |
| | U937 | $IC_{50}$ = 5.4 × $10^{-9}$ M (72 h)[960] |
| amoorastatone (**172**) | P388 | $ED_{50}$ = 30 $\mu$g/mL[210] |
| meliatoxin $B_1$ (**177**) | P388 | $IC_{50}$ = 5.4 $\mu$g/mL[221] |
| | KB | $IC_{50}$ >10 $\mu$g/mL[211] |
| toosendanal (**185**) | KB | $IC_{50}$ >10 $\mu$g/mL[211] |
| meliavolkin (**200**) | A-549 | $ED_{50}$ = 0.57 $\mu$g/mL[248] |
| | MCF-7 | $ED_{50}$ = 0.26 $\mu$g/mL[248] |
| | HT-29 | $ED_{50}$ = 0.12 $\mu$g/mL[248] |
| malleastrone A (**227**) | A2780 | $IC_{50}$ = 0.49 $\mu$M[242] |
| | MDA-MB-435 | $IC_{50}$ = 0.41 $\mu$M[242] |
| | HT-29 | $IC_{50}$ = 0.24 $\mu$M[242] |
| | H552-T1 | $IC_{50}$ = 0.24 $\mu$M[242] |
| | U937 | $IC_{50}$ = 0.20 $\mu$M[242] |
| malleastrone B (**228**) | A2780 | $IC_{50}$ = 0.63 $\mu$M[242] |
| | MDA-MB-435 | $IC_{50}$ = 0.34 $\mu$M[242] |


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**Table 37. Continued**

| compounds | cells | activity |
|---|---|---|
| | HT-29 | $IC_{50}$ = 0.22 $\mu$M[242] |
| | H552-T1 | $IC_{50}$ = 0.23 $\mu$M[242] |
| | U937 | $IC_{50}$ = 0.19 $\mu$M[242] |
| malleastrone C (**229**) | A2780 | $IC_{50}$ = 18 $\mu$M[242] |
| turrapubesin A (**290**) | P388 | $IC_{50}$ = 12.14 $\mu$M[287] |
| 1-tigloyl-3-acetyl-11-methoxymeliacarpinin (**318**) | P388 | $IC_{50}$ = 3.2 $\mu$g/mL[205] |
| 1-tigloyl-3,20-diacetyl-11-methoxymeliacarpinin (**321**) | P388 | $IC_{50}$ = 100 $\mu$g/mL[345] |
| 3-tigloyl-1,20-diacetyl-11-methoxymeliacarpinin (**322**) | P388 | $IC_{50}$ = 48 $\mu$g/mL[345] |
| 1-cinnamoyl-3-hydroxy-11-methoxymeliacarpinin (**323**) | P388 | $IC_{50}$ = 1.5 $\mu$g/mL[345] |
| 1-deoxy-3-methacrylyl-11-methoxymeliacarpinin (**324**) | P388 | $IC_{50}$ = 47 $\mu$g/mL[345] |
| 1-cinnamoyl-3-acetyl-11-methoyxmeliacarpinin (**327**) | P388 | $IC_{50}$ = 10.5 $\mu$g/mL[345] |
| 1-acetyl-3-tigloyl-11-methoxymeliacarpinin (**329**) | P388 | $IC_{50}$ = 3.3 $\mu$g/mL[205] |
| nimbolide (**345**) | GPK | $ED_{50}$ = 10.14 $\mu$g/mL[500] |
| | N1 × $10^{-115}$ | $IC_{50}$ = 1.5 $\mu$g/mL;[961] 5.2 $\mu$M[941] |
| | 143B.TK | $IC_{50}$ = 4.3 $\mu$M[941] |
| | BC-1 | $ED_{50}$ = 0.39 $\mu$g/mL;[373] 3.1 $\mu$g/mL[369] |
| | COL-2 | $ED_{50}$ = 0.41 $\mu$g/mL;[373] 4.2 $\mu$g/mL[369] |
| | HT-1080 | $ED_{50}$ = 0.31 $\mu$g/mL[373] |
| | LU-1 | $ED_{50}$ = 0.42 $\mu$g/mL;[373] 3.3 $\mu$g/mL[369] |
| | MEL-2 | $ED_{50}$ = 0.53 $\mu$g/mL[373] |
| | KB | $ED_{50}$ = 0.25 $\mu$g/mL;[373] 1.7 $\mu$g/mL[369] |
| | P388 | $ED_{50}$ = 0.065 $\mu$g/mL[373] |
| | LNCaP | $ED_{50}$ = 0.9 $\mu$g/mL[369] |
| 28-deoxonimbolide (**346**) | BC-1 | $ED_{50}$ = 1.34 $\mu$g/mL;[373] 3.2 $\mu$g/mL[369] |
| | COL-2 | $ED_{50}$ = 1.81 $\mu$g/mL;[373] 9.0 $\mu$g/mL[369] |
| | HT-1080 | $ED_{50}$ = 1.04 $\mu$g/mL[373] |
| | LU-1 | $ED_{50}$ = 0.84 $\mu$g/mL;[373] 8.5 $\mu$g/mL[369] |
| | MEL-2 | $ED_{50}$ = 2.05 $\mu$g/mL[373] |
| | KB | $ED_{50}$ = 1.30 $\mu$g/mL;[373] 4.1 $\mu$g/mL[369] |
| | P388 | $ED_{50}$ = 0.66 $\mu$g/mL[373] |
| | LNCaP | $ED_{50}$ = 1.9 $\mu$g/mL[369] |
| 12-*O*-methylvolkensin (**370**) | KB | $IC_{50}$ = 8.72 $\mu$g/mL[211] |
| 1-*O*-deacetylohchinolide A (**372**) | HeLa S3 | $IC_{50}$ = 2.40 $\mu$M[387] |
| 1-*O*-deacetyl-1-*O*-tigloylohchinolide A (**373**) | HeLa S3 | $IC_{50}$ = 29.7 $\mu$M[387] |
| ohchinolide B (**374**) | HeLa S3 | $IC_{50}$ = 40.5 $\mu$M[387] |
| 1-*O*-deacetylohchinolide B (**375**) | HeLa S3 | $IC_{50}$ = 0.10 $\mu$M[387] |
| 1-*O*-deacetyl-1-*O*-tigloylohchinolide B (**376**) | HeLa S3 | $IC_{50}$ = 33.8 $\mu$M[387] |
| 1-*O*-deacetyl-1-*O*-benzoylohchinolide B (**377**) | HeLa S3 | $IC_{50}$ = 33.0 $\mu$M[387] |
| chisonimbolinin C (**380**) | HeLa | $IC_{50}$ = 13 $\mu$M[390] |
| chisonimbolinin D (**381**) | HeLa | $IC_{50}$ = 32 $\mu$M[390] |
| 15-*O*-deacetyl-15-*O*-methylnimbolindin A (**406**) | HeLa S3 | $IC_{50}$ = 37.4 $\mu$M[226] |
| 15-*O*-deacetylnimbolindin B (**408**) | HeLa S3 | $IC_{50}$ = 0.10 $\mu$M[226] |
| 15-*O*-deacetyl-15-*O*-methylnimbolindin B (**409**) | HeLa S3 | $IC_{50}$ = 28.3 $\mu$M[226] |
| walsogyne A (**414**) | P388 | $IC_{50}$ = 5 $\mu$g/mL[412] |
| gedunin (**416**) | CaCo-2 | $IC_{50}$ = 16.83 $\mu$M[49] |
| | GPK | $ED_{50}$ = 275.10 $\mu$g/mL[500] |
| | P388 | $IC_{50}$ = 3.3 $\mu$g/mL[433] |
| 7-deacetylgedunin (**421**) | CHAGO | $IC_{50}$ = 16.00 $\mu$M[448] |
| | Hep-G2 | $IC_{50}$ = 10.26 $\mu$M[448] |
| | P388 | $IC_{50}$ = 4.5 $\mu$g/mL[433] |
| 7-deacetoxy-7-oxogedunin (**423**) | Hep-G2 | $IC_{50}$ = 16.17 $\mu$M[448] |
| 7-deacetoxy-7$\alpha$,11$\beta$-dihydroxygedunin (**424**) | P388 | $IC_{50}$ = 7.8 $\mu$g/mL[433] |
| 11$\alpha$-hydroxygedunin (**426**) | P388 | $IC_{50}$ = 71 $\mu$g/mL[433] |
| 11$\beta$-hydroxygedunin (**427**) | P388 | $IC_{50}$ = 5.4 $\mu$g/mL[433] |
| 11-oxogedunin (**429**) | P388 | $IC_{50}$ = 3.0 $\mu$g/mL[433] |


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**Table 37. Continued**

| compounds | cells | activity |
|---|---|---|
| 3$\alpha$,7$\alpha$-diacetylkhivorin (**440**) | Caco-2 | $IC_{50}$ = 35 ppm[473] |
| | SiHa | $IC_{50}$ = 54 ppm[473] |
| | MCF-7 | $IC_{50}$ = 69 ppm[473] |
| humilinolide C (**695**) | A-549 | $ED_{50}$ = 37.7 $\mu$g/mL[665] |
| | MCF-7 | $ED_{50}$ = 94.1 $\mu$g/mL[665] |
| humilinolide D (**697**) | A-549 | $ED_{50}$ = 60.6 $\mu$g/mL[665] |
| | MCF-7 | $ED_{50}$ = 65.0 $\mu$g/mL[665] |
| | HT-29 | $ED_{50}$ = 53.6 $\mu$g/mL[665] |
| erythrocarpine B (**714**) | P388 | $IC_{50}$ = 6.0 $\mu$g/mL[667] |
| erythrocarpine C (**715**) | P388 | $IC_{50}$ = 9.9 $\mu$g/mL[667] |
| erythrocarpine A (**727**) | P388 | $IC_{50}$ = 2.0 $\mu$g/mL[667] |
| xylogranatin B (**762**) | P388 | $IC_{50}$ = 8.9 $\mu$M[637] |
| | A549 | $IC_{50}$ = 11.3 $\mu$M[637] |
| xylogranatin C (**763**) | P388 | $IC_{50}$ = 6.3 $\mu$M[637] |
| xylogranatin D (**764**) | P388 | $IC_{50}$ = 14.6 $\mu$M[637] |
| xyloccensin M (**771**) | HCT-8 | $IC_{50}$ = 14.77 $\mu$M[677] |
| | Bel-7402 | $IC_{50}$ = 12.81 $\mu$M[677] |
| | BGC-283 | $IC_{50}$ = 8.90 $\mu$M[677] |
| | A549 | $IC_{50}$ = 18.55 $\mu$M[677] |
| | A2780 | $IC_{50}$ = 16.60 $\mu$M[677] |
| xylocarpin J (**776**) | HCT-8 | $IC_{50}$ = 7.75 $\mu$M[677] |
| | Bel-7402 | $IC_{50}$ = 8.22 $\mu$M[677] |
| | BGC-283 | $IC_{50}$ = 8.38 $\mu$M[677] |
| | A549 | $IC_{50}$ = 5.35 $\mu$M[677] |
| | A2780 | $IC_{50}$ = 4.77 $\mu$M[677] |
| humilinolide A (**793**) | A-549 | $ED_{50}$ = 64.4 $\mu$g/mL[665] |
| | MCF-7 | $ED_{50}$ = 79.5 $\mu$g/mL[665] |
| | HT-29 | $ED_{50}$ = 59.6 $\mu$g/mL[665] |
| humilinolide B (**794**) | HT-29 | $ED_{50}$ = 81.1 $\mu$g/mL[665] |
| granaxylocarpin A (**819**) | P388 | $IC_{50}$ = 9.3 $\mu$M[632] |
| xylomexicanin A (**821**) | KT | $IC_{50}$ = 4.59 $\mu$M[675] |
| granaxylocarpin B (**822**) | P388 | $IC_{50}$ = 4.9 $\mu$M[632] |
| xylogranatin C (**823**) | CHAGO | $IC_{50}$ = 9.16 $\mu$M[448] |
| erythrocarpine D (**827**) | P388 | $IC_{50}$ = 10.0 $\mu$g/mL[667] |
| erythrocarpine E (**828**) | P388 | $IC_{50}$ = 16.0 $\mu$g/mL[667] |
| xylogranatin A (**832**) | A549 | $IC_{50}$ = 15.7 $\mu$M[637] |
| xyloccensin Y (**988**) | HCT-8 | $IC_{50}$ = 10.43 $\mu$M[677] |
| | Bel-7402 | $IC_{50}$ = 13.55 $\mu$M[677] |
| | BGC-283 | $IC_{50}$ = 9.87 $\mu$M[677] |
| | A549 | $IC_{50}$ = 16.23 $\mu$M[677] |
| | A2780 | $IC_{50}$ = 11.64 $\mu$M[677] |
| ceramicine A (**1118**) | P388 | $IC_{50}$ = 15 $\mu$g/mL[412] |

of 300 $\mu$M.[435] The epimeric mixture of photogedunin (**433**)[462] and cedrelanolide I (**599**)[571] partially inhibited photophosphorylation, $H^+$ uptake, and noncyclic electron flow, and then **599** interfered with monocot preemergence properties, mainly energy metabolism of the seeds at the level of respiration.[571] In addition, an epimeric mixture of photogedunin inhibited seed germination, seedling growth, and root and hypocotyl/coleoptyle growth in all species assayed.[949] Humilinolides A (**793**) and C (**695**) inhibited the radicle growth of *Echinochloa crus-galli* with $IC_{50}$ values of 99.06 $\mu$g/mL and 163.0 $\mu$g/mL, respectively. In addition, *Amaranthus hypochondriacus* was less sensitive to **793** and **695** with $IC_{50}$ values of 199.0 $\mu$g/mL and 215.8 $\mu$g/mL, respectively, in contrast to no inhibition of humilinolides B (**794**) and D (**697**) at the tested concentration.[629]

## 5.2. Biological Activities in Medicinal Use

**5.2.1. Antineoplastic Activity.** Most limonoids showed their antineoplastic activity as cytotoxicity with the $IC_{50}$ values listed in Table 37. The cytotoxicity of ten limonoids from *Turrea pubescens* was evaluated. Of these limonoids, isoazadironolide (**38**) and turrapubesin E (**276**) exhibited moderate activities against the P388 cell line, with the $IC_{50}$ values of 16.0 and 12.3 $\mu$M, respectively, and none of them were active against the A549 cells.[126] Among the eight human cancer cell lines M14,


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**Table 38. Inactive Meliaceous Limonoids against Tumor Cell Lines**

| compounds | cell lines |
|---|---|
| mahonin (**17**) | KB[97] |
| 6$\alpha$-acetoxyepoxyazadiradione (**62**) | KB, NCI-H187, MCF7[97] |
| toonaciliatone A (**73**), perforin A (**535**), and methyl 3$\beta$-acetoxy-1-oxomelic-14(15)-enate (**741**) | SMMC-7721, HL-60, A549, SK-BR-3, PANC-1[145] |
| 3-deoxymethylnimbidate (**339**), 2,3-dihydronimbolide (**347**) | ASK[369] |
| ohchinolide A (**371**), 1-*O*-detigloyl-1-*O*-benzoylohchinolal (**397**), 1-*O*-detigloyl-1-*O*-cinnamoylohchinolal (**398**), ohchinolal (**556**) | HeLa S3[387] |
| chisonimbolinins A−G (**378**−**384**) | HeLa, SMMC-7721[390] |
| 7-deacetoxy-7$\alpha$,11$\alpha$-dihydroxygedunin (**425**) | P388[433] |
| rohitukin (**480**) | P388[210] |
| gaudichaudysolin A (**492**) | HL-60, RPMI8226, NCI-H226, HCT116, MCF7[502] |
| cipadonoids B−G (**567**, **1046**−**1050**) | P388[544] |
| methyl angolensate (**568**), mexicanolide (**626**), proceranolide (**632**), xyloccensins K (**788**), O (**948**), P (**949**) | CHAGO, SW-620, KATO-3, BT-474, Hep-G2[448] |
| methyl 2$\beta$,3$\beta$-diacetoxy-3-deoxoangolensate (**577**), cineracipadesins A−F (**816**, **580**−**583**, **1040**) | P-388[563] |
| humilinolide C (**695**) | HT-29[665] |
| xylomexicanin B (**750**) | HeLa, HEC-1, SHIN3, HOC-2, HAC-2, HLE, U251-SP, T-98,MM1-CB, HMV-1, KT[675] |
| xylogranatin S (**765**) | HeLa, HLE, MDA-MB-231, SW-620[676] |
| humilinolide B (**794**) | A549, MCF-7[665] |
| granaxylocarpins A and B (**819** and **840**) | A549[632] |
| xylomexicanin A (**821**) | HeLa, HEC-1, SHIN3, HOC-2, HAC-2, HLE, U251-SP, T-98,MM1-CB, HMV-1[675] |
| xylocarpanoid A (**825**) | MDAMB-21, SW-620[634] |
| granaxylocarpins C−E (**830**, **984**, and **981**) | P388, A549[632] |
| moluccensins H−J (**963**, **967**, and **968**) | BT474, CHAGO, Hep-G2, KATO-3, SW-620[723] |
| trichiliton A (**997**) | HL-60, SMMC-7721, A-549, SK-BR-3[651] |
| cipatrijugins A−D (**1023**−**1026**), cipadesin A (**1051**) | A549, K562[735] |
| trichilins A and B (**1036** and **1043**) | HL-60, BEL7402, Hela, MCF-7[731] |
| cipadonoid F (**1049**) | HT29, HCT116, SW480, MDA-MB-231, MDA-MB-468, MCF-7, SMMC-7721, BEL-7402, MKN28, MKN45, SGF-7901, KB, RH30, SK-OV-3, Hela, HL-60, K562, K562/A02[544] |

NCI-H23, SF-539, PC-3, SW620, KM12, UO-31, and ACHN, the most sensitive cells according to the dose−response profiles to 29-deacetylsendanin (**157**) were SF-539 and PC-3 which had $GI_{50}$ (growth inhibition of 50%) values of less than 0.010 $\mu$g/mL.[203] 12$\alpha$-Hydroxyamoorastatin (**166**), 12$\alpha$-acetoxyamoorastatin (**167**), and 12$\alpha$-hydroxyamoorastatone (**173**) were all significantly cytotoxic to the human tumor cell lines of A-549, SK-OV-3, SK-MEL-2, XF-498, and HCT-15. Of these compounds, **167** was the most active with $ED_{50}$ values from 0.7 to 40 ng/mL.[213] In the human glioblastoma cell lines of G-28, G-112, and G-60, azadiracthin (**292**) induced a significant suppression of the binucleation index of 11, 8, and 24% respectively.[950] In comparison with azadirachtin (**292**), nimbolide (**345**) was found to be a more potent antiproliferative and apoptosis-inducing agent and offered promise as a candidate agent in multitargeted prevention and treatment of cancer.[951,952] The cellular and molecular mechanism by which **292** and **345** act against the HeLa cell line was investigated, and it was concluded that both compounds simultaneously arrest the cell cycle and target multiple molecules involved in mitochondrial apoptosis, and thus offer immense potential as anticancer therapeutic drugs.[953] Treatment with nimbolide (**345**) resulted in dose and time-dependent inhibition of growth of BeWo cells,[954,955] HL-60, U937, THP-1 and B16,[956] suggesting that **345** has immense potential in cancer prevention and therapy based on its antiproliferative and apoptosis inducing effects. The nimbolide-induced growth inhibition and cell cycle arrest of HT-29 were not associated with cellular differentiation, but instead with the time-dependent up-regulation of p21, cyclin D2, Chk2.[957] Methyl angolensate (**568**) inhibited growth of T-cell leukemia and chronic myelogenous leukemia cells in a time- and dose-dependent manner, which involved the induction of apoptosis by triggering the intrinsic pathway.[958]

Nimbolin B (**366**) was moderately active in the brine shrimp lethality test, and it was significantly cytotoxic against HT-29 with an $ED_{50}$ value of $<10^{-3}$ $\mu$g/mL.[384] Volkensinin (**1057**) showed weak bioactivity in BST with an $LC_{50}$ value of 57 $\mu$g/mL, and it was generally but weakly cytotoxic against six human tumor cell lines, giving $ED_{50}$ values of 27.90, 28.35, 33.56, 29.56, 8.43, and 28.51 $\mu$g/mL against A-498, PC-3, PACA-2, A-549, MCF-7, and HT-29, respectively.[744] Gedunin (**416**) showed anticancer activity via inhibition of the 90 kDa heat shock protein (Hsp90) folding machinery and caused the degradation of Hsp90-dependent client proteins similarly to other Hsp90 inhibitors.[959] Nymania 1 (**522**) showed reproducible, significant, and selective activity against the DNA repair-deficient RS322YK yeast strain, whereas Tr-B (**479**) exhibited moderate but selective activity, suggesting that they might have cytotoxic activity mediated by a DNA-damaging mechanism.[192]

Aphanastatin (**142**), together with amoorastatin (**165**) and 12$\alpha$-hydroxyamoorastatin (**166**), was reported as showing


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significant antineoplastic activity, but no data were provided.[197] On the negative side, many limonoids were found to be inactive against specific tumor cell lines. These results are listed in Table 38 in detail.

The presence of both a C-19/28 lactol and a C-14/15-epoxide group was found to be especially important for pronounced inhibition of the P-388 lymphocytic leukemia system in vitro cell line, and substitution of an A-ring $\alpha,\beta$-unsaturated ketone (3-oxo-1-ene) for the lactol led to diminished activity, while reduction of the olefin caused complete loss of activity.[845] Most trichilin-class limonoids with a C-14/15-epoxide and a C-19/28 acetal bridge exhibited strong cytotoxicity against P388 cells.[196,205,213,221,226,433] Similarly, trichilin H (**145**) and toosendanin (**167**), which have C-14/15 epoxide moieties, showed highly cytotoxicity against KB cell, whereas toosendanal (**185**) and meliatoxin $B_1$ (**177**), possessing C-15 keto structure, did not show any significant level of cytotoxicity.[211] The $ED_{50}$ values of 12$\alpha$-hydroxyamoorastatin (**166**) (0.002 $\mu$g/mL) and amoorastatone (**172**) (30 $\mu$g/mL) further supported the supposition that the C-14$\beta$/15$\beta$ epoxy was a definite requirement for growth inhibition of P388 cell lines.[210] The cytotoxic activity against P388 cells of the five melicarpinin derivatives (**321**−**324** and **327**) with a C-3 acetate was decreased, and with a C-20 acetate it was almost zero.[345] The more pronounced cell growth inhibitory activity of the structurally simpler amoorastatin (**165**) as compared to aphanastatin (**142**) suggested that the 1$\alpha$-acetoxy, 2$\alpha$,12$\alpha$-dihydroxy, and 28-methylbutyryl groups of **142** were unnecessary and indeed might even lessen inhibition of neoplastic (P388) cell growth.[229] In addition, the $\alpha,\beta$-unsaturated enone moiety or its equivalent conjugated system in the A-ring, the C-7 acetyloxy/chloroacetyloxy or keto group on the B-ring, and the furan moiety were the structural requirements for the high activity of azadirone (**1**), which was a potent cytotoxic agent with good in vitro and in vivo activity.[83]

**5.2.2. Antimicrobial Activity.** Among the five limonoids dysobinin (**11**), azadiradione (**12**), mahonin (**17**), epoxyazadiradione (**60**), and 6$\alpha$-acetoxyepoxyazadiradione (**62**), only **12** exhibited a strong antibacterial effect against *Mycobacterium tuberculosis*, giving a MIC of 6.25 $\mu$g/mL.[97] 6-Acetoxy-11$\alpha$-hydroxy-7-oxo-14$\beta$,15$\beta$-epoxymeliacin-1,5-diene-3-*O*-$\alpha$-L-rhamnopyranoside (**104**) had more positive antibacterial activity than streptomycin at the concentrations tested against *Vibrio cholerae*, *Klebsiella pneumoniae*, *Salmonella typhimurium*, and *Escherichia coli*.[176] 1-Cinnamoyltrichilinin (**192**), trichilinin B (**195**), and 12-ethoxynimbolinin C (**385**) exhibited significant antibacterial activity against *Porphyromonas gingivalis* ATCC 33 277, with MIC values of 15.6, 31.5, and 31.3 $\mu$g/mL, respectively.[186] No mutagenicity of nimbolide (**345**) was detected by Ames' test using both TA98 and TA100 tested strains. However, at 0.875 mg/disk it exhibited antibacterial activity against the three strains *Staphylococcus aureus*, *S. coagulase* (+), and *S. coagulsae* (-) out of a total of 3/17 strains.[962] The results obtained by Kraus et al. showed that **345** inhibited *Pseudomonas stutzeri* even at a concentration of 0.5 $\mu$g/spot.[322] 3$\alpha$,7$\alpha$-Dideacetylkhivorin (**440**) showed stronger antimicrobial activity than methyl 6-hydroxyangolensate (**569**) against *Rhizopus stolonifer*.[447] Methyl angolensate (**568**) displayed growth inhibition against *Proteus vulgaris* with an inhibition zone of 14.1 mm, followed by *Klebsiella pneumoniae* with 13.5 mm, *Staphylococcus aureus* with 13.3 mm, *Escherichia coli* with 12.8 mm, and *Salmonella typhimurium* with 12.0 mm.[947] As swietenolide (**638**) and 2-hydroxy-3-*O*-tigloylswietenolide (**642**) have the same skeleton, and show promising antibacterial activity against all the eight tested multiple-drug-resistant (MDR) bacterial strains tested, this limonoid skeleton may be useful as a template for the synthesis of more potent structural analogs.[649] 2-Hydroxy-3-*O*-isobutyrylproceranolide (**636**) and 2-hydroxyfissinolide (**649**) exhibited antimicrobial activity against *Micrococcus luteus* ATCC 9341 with MIC values of 50 and 12.5 $\mu$g/mL, respectively.[458] Moluccensins H−J (**963**, **967**, and **970**) were tested for antibacterial properties against *Staphylococcus aureus*, *S. hominis*, *S. epidermidis*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, and *Salmonella typhimurium*, but only **967** displayed weak activity against *S. hominis* and *E. faecalis* with a MIC at 256 $\mu$g/mL.[723] 6-Acetoxy-7$\alpha$-hydroxy-3-oxo-14$\beta$,15$\beta$-epoxymeliac-1,5-diene (**69**) exhibited strong antibacterial activity against *Salmonella paratyphi* and *Vibrio cholerae* but no data were provided in the original paper.[142]

Neither xyloccensin I (**769**) nor xyloccensin J (**770**) was active in a broad screening effort which included assays for antimicrobial, antiviral, anthelmintic, and antikinase responses.[626] The six limonoids grandifolide A (**775**), anthothecanolide (**779**), 3-*O*-acetylanthothecanolide (**780**), 6*S*-hydroxykhayalactone (**999**), khayanolide A (**1002**), and deacetylkhayanolide E (**1008**), were all inactive in an antimicrobial assay against *Escherichia coli*, *Staphylococcus aureus*, *S. epidermidis*, and *Candida albicans* with MIC values of greater than 50 $\mu$g/mL.[679]

The antiviral activity of limonoids was also investigated. 29-Deacetylsendanin (**157**) showed antiviral activity by inhibiting the replication of HSV-1, reducing the synthesis of HSV-1 TK, and leading to the formation of defective nucleocapsids.[963] Dysoxylins A−D (**205**−**208**) showed anti-RSV (respiratory syncytial virus) activities with the $EC_{50}$ values in the range of 1.0−4.0 $\mu$g/mL in cytopathic effect inhibition and plaque reduction assays.[255] 1-Cinnamoyl-3,11-dihydroxymeliacarpin (**312**) displayed a potent antiviral action affecting both DNA and RNA viruses by the same mechanism of action, and also comprised an additional biological property consisting of altering the NF-$\kappa$B pathway, which suggested an eventual role as an anti-inflammatory agent.[337] In addition, **312** showed $IC_{50}$ values of 6 $\mu$M and 20 $\mu$M for vesicular stomatitis (VSV) and herpes simplex (HSV-1) viruses, respectively.[336] **312** exerted its antiviral action on the endocytic and exocytic pathways of VSV by pre- and post-treatment, respectively.[964] In addition to its antiviral effect, **312** would be acting as an immunomodulating candidate, which would be responsible for the improvement of murine HSK already reported.[965] The delay on glycoprotein transport caused by **312** would account for the strong inhibition on virus multiplication without interfering with the bioactivity of cellular glycoproteins.[966] Besides, for 6-*O*-acetyl-2-hydroxyswietenine (**688**), 2-hydroxyswietenine (**689**), 2-hydroxyswietemahonolide (**797**), swietemahonin G (**806**), and 6-*O*-acetylswietemahonin G (**807**), their antiviral activity against HIV-1 replication was tested by their inhibition of virus-induced cytopathicity in MT-4 cells, and none of them showed activity at 100 $\mu$g/mL.[630]

**5.2.3. Antiprotozoal Activity.** Omar et al. reviewed the traditionally used antimalarials from *Azadirachta indica*, *Lansium domesticum*, and *Cedrela odorata*, and presented the improvement of the activity in vivo of gedunin (**416**).[967] Gedunin (**416**) has been proved to be the most active limonoid according to miscellaneous antimalarial tests up to now. It had $IC_{50}$ values against *Plasmodium falciparum* of 3.1 and 0.14 $\mu$M using [$^3$H]-hypoxanthine and 48 h culture assays, respectively.[968] Its antimalarial activity was qualitatively assessed in vitro with an $IC_{50}$ of


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~1 $\mu$M after 48 h exposure (0.3 $\mu$M after 96 h), which is roughly equivalent to quinine.[429] Among the 27 limonoids tested, **416** showed the most potent activity against *P. falciparum* with an $IC_{50}$ value of 0.72 $\mu$g/mL, but it did not inhibit *P. berghei* in a 4-day test in mice at doses of 90 mg/kg/day.[500] The five limonoids, gedunin (**416**), 1-deacetylkhivorin (**435**), 7-deacetylkhivorin (**437**), methyl angolensate (**568**), and 6-acetylswietenolide (**645**) showed antimalarial activity with $IC_{50}$ values between 1.25 and 9.63 $\mu$g/mL, among which the most active, **416**, had an additive effect with chloroquine.[436] When orally administered at 50 mg/kg/d for 4 days, **416** suppressed the parasitemia level by 44%, and synergism with the cytochrome P450 inhibitor dillapiol or addition of a stable methoxy group at the C-7 position increased its antimalarial activity.[969]

Among the four limonoids nimocinol (**7**), meldenin (**243**), isomeldenin (**244**), and nimbandiol (**1101**), **243** was the most active with $IC_{50}$ value of 5.23 $\mu$g/mL against a chloroquine-resistant *Plasmodium falciparum* strain.[270] All limonoids of dysobinin (**11**), azadiradione (**12**), mahonin (**17**), epoxyazadiradione (**60**), and 6$\alpha$-acetoxyepoxyazadiradione (**62**) had an inhibitory effect against *P. falciparum* with $IC_{50}$ values ranging from 2.06 to 6.31 $\mu$g/mL.[97] Azadiradione (**12**), domesticulides B−D (**562**, **589**, and **590**), methyl angolensate (**568**), methyl 6-acetoxyangolensate (**570**), dukunolide C (**616**), and 6-acetoxymexicanolide (**631**) showed antimalarial activities against *P. falciparum* with $IC_{50}$ values of 2.4−9.7 $\mu$g/mL, and among these **589** was the most active.[100] Anthotechol (**84**) showed potent antimalarial activity against *P. falciparum* with $IC_{50}$ values of 1.4 and 0.17 $\mu$M as measured by two different assays.[968] Ceramicine B (**222**) had potent in vitro antiplasmodial activity against *P. falciparum* 3D7 with an $IC_{50}$ value of 0.23 $\mu$g/mL, while ceramicines C and D (**223** and **224**) exhibited moderate activity with $IC_{50}$ values of 2.38 $\mu$g/mL and 2.15 $\mu$g/mL, respectively.[262] Trichirubine A (**226**) had significant antimalarial activity against *P. falciparum* with an $IC_{50}$ value of 0.3 $\mu$g/mL.[263] A single dose of **292** was sufficient to give the insect host-*Rhodnius prolixus*, a permanent resistance against its reinfection with *Trypanosoma cruzi* and to block the ecdysis for a long time.[970] Fifth-instar larvae of *Rhodnius prolixus*, *Triatoma infestans*, and *Dipetalogaster maximus* infected with different clone/strains of *Trypanosoma cruzi* displayed drastic inhibition of trypanosome development when treated with **292**, which might act directly on gut physiology and/or indirectly through the neurosecretory system.[971] Jones et al. demonstrated blockage of the development of the motile male malarial gamete by azadirachtin (**292**), and changes in the hemiacetal group at C-11 in the molecule resulted in a loss of activity.[972] In addition, **292** disrupted formation of organized microtubule arrays during microgametogenesis of *P. berghei* and specifically disrupted the patterning of microtubules into more complex structures, such as mitotic spindles and axonemes.[973] Nimbolide (**345**) inhibited *P. falciparum* in culture with moderate potency, giving an $EC_{50}$ of 0.95 mg/mL.[974] 7-Deacetylgedunin (**421**) and 7-deacetoxy-7-oxogedunin (**423**) exhibited good antiprotozoal activity against *Trypanosoma brucei rhodesiense*, *T. cruzi*, *Plasmodium falciparum*, and *Leishmania donovani*, suggesting a lack of specificity for a protozoal target.[443] Among mexicanolide (**626**), febrifugin (**694**), cipadesin (**703**), and cipadesin A (**815**), the last, with an $IC_{50}$ value of 136.1 $\mu$M, showed more appreciable trypanocidal activity against *Trypanosoma cruzi*.[643] Fissinolide (**648**) was slightly active against chloroquine resistant strains of *P. falciparum* ($IC_{50}$ 48 ± 3 $\mu$M) and promastigotes of *Leishmania major* ($IC_{50}$ 69 ± 13 $\mu$M), and 2,6-dihydroxyfissinolide (**668**) had an $IC_{50}$ of 0.12 ± 0.08 mM against *P. falciparum* and an $IC_{50}$ of greater than 0.20 mM against *L. major*.[601] Walsuronoids A and B (**1054** and **1058**) showed 40% inhibition of *P. falciparum* at a concentration of 40 $\mu$M.[739]

The in vitro trypanocidal activity of six mexicanolide- and gedunin-class limonoids on trypomastigote forms of *Trypanosoma cruzi* was less than the activity of oleanane- and tirucallane-type triterpenes.[132] Ceramicines B−D (**222**−**224**), which contain a tetrahydrofuran ring, showed potent antiplasmodial activity, whereas ceramicine A (**1118**) without the tetrahydrofuran ring exhibited relatively weak activity.[262] From the data obtained with the modified furan moieties of gedunin (**416**), it seemed that this section of the molecule was less important for antimalarial activity than the $\alpha,\beta$-unsaturated ketone in ring A and the 7-acetate function in ring B.[432]A comparison of the activities of methyl angolensate (**568**) and methyl 6-hydroxyangolensate (**569**) suggested that the addition of a hydroxyl group at C-6 decreased the antimalarial activity considerably.[100]

**5.2.4. Others.** Dysobinin (**11**) showed general CNS-depressant action and mild anti-inflammatory activity.[66] All of azadiradione (**12**), 7-acetyl-16,17-dehydro-16-hydroxyneotrichilenone (**23**), epoxyazadiradione (**60**), 17-*epi*-17-hydroxyazadiradione (**78**), 7-deacetylgedunin (**421**), and nimolicinol (**451**) exhibited marked anti-inflammatory activity ($ID_{50}$ values 0.09−0.26 mg/ear) against TPA-induced inflammation.[70] 6$\alpha$-Acetoxyepoxyazadiradione (**62**), gedunin (**416**), 6$\alpha$-acetoxygedunin (**418**), 7-deacetoxy-7-oxogedunin (**423**), andirobin (**556**), and methyl angolensate (**568**) of *Carapa guianensis* oil were responsible for the antiedematogenic and analgesic effects which were dependent on blockade of signaling mechanisms triggered by histamine, bradykinin, and PAF.[975] In addition, these limonoids inhibited zymosan-induced arthritis in mice *via* the impairment of TNF-$\alpha$, IL-1$\beta$, and CXCL8/IL-8 generation, as well as the NF-$\kappa$B signaling pathway.[976] Isochuanliansu (**179**) and 1-*O*-tigloyl-1-*O*-debenzoylohchinal (**344**) were the active constituents contributing to the anti-inflammatory and analgesic effects of the fruit of *Melia toosendan*.[235] The data provided by Thoh et al. suggested that azadirachtin (**292**) modulated cell surface TNFRs thereby decreasing TNF-induced biological responses, which might be beneficial for anti-inflammatory therapy.[977] Among the eleven limonoids isolated from *Swietenia macrophylla*, 6-*O*-acetylswietemahonin G (**807**) showed the most effective anti-inflammatory activity ($IC_{50}$ = 27.6 ± 1.7 $\mu$M) against fMLP-induced superoxide anion generation.[653]

Toosendanin (**167**), which itself was not able to form ion channels in lipid bilayers, increased $Ca^{2+}$ conductance related to the intrinsic channel activity.[978] **167** not only had different effects on various subtypes of calcium channels,[979] but also had an inhibitory effect on the inward rectifier potassium channel in an excised inside-out patch of the neuron under a symmetrical 150 mM $K^+$ condition.[980] It inhibited the activity of small-conductance calcium-activated potassium channels by significant concentration-dependent reduction of the open probability and open frequency, and these effects were partially reversible.[981] Moreover, **167** did not selectively affect acetylcholine release, but probably acted on a common mechanism responsible for transmitter release at different synapses by interfering with the proteins involved in fusion and resulting in diffusion of the vesicular contents into the cytoplasm and blockade of normal exocytosis.[982]


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Salannin (**332**) showed a significant protective activity on aspirin induced gastric lesions at oral doses of 10, 20, and 50 mg/kg. At 0.5 and 0.25% concentrations, **332** also showed spermicidal activity against human spermatozoa.[983] $H^+$ $K^+$-ATPase activity in vitro was significantly inhibited by gedunin (**416**) and photogedunin (**433**) with $IC_{50}$ values of 58.86 and 66.54 $\mu$g/mL, respectively, confirming their antisecretory activity as compared to the $IC_{50}$ value of omeprazole (30.24 $\mu$g/mL).[427] Methyl angolensate (**568**) produced its antiulcer activity by inhibition of gastric acid secretion,[984] exerted significant spasmolytic activity through concentration dependent inhibition of smooth muscle and reduced the propulsive action of the gastrointestinal tract in mice,[985] reduced spontaneous motor activity in mice, prolonged the duration of pentobarbital sleeping time, and attenuated amphetamine-induced stereotype behavior in rats.[986]

Among the limonoids tested (swietenolide (**638**), 3-acetylswietenolide (**643**), swietenine (**677**), swietemahonin A (**800**), and swietemahonin E (**804**)), when the final concentration of PAF and sample were $7.5 \times 10^{-8}$ M and 100 $\mu$g/mL, respectively, **800** showed the strongest anti-PAF activity with an inhibition of 97.4% against rabbit platelet aggregation.[652] In another test, **800** showed an $IC_{50}$ value of 40.3 $\mu$g/mL against PAF-induced aggregation of rabbit platelets in vitro, comparable to that of swietemahonin D (**803**).[987]

Penido et al. demonstrated that in mice the inhibition of allergic eosinophilia by 6$\alpha$-acetoxyepoxyazadiradione (**62**), gedunin (**416**), 6$\alpha$-acetyoxygedunin (**418**), 7-deacetoxy-7-oxogedunin (**423**), andirobin (**556**), and methyl angolensate (**568**) was correlated with the inhibition of CCL11/eotaxin and IL-5 generation through impairment of the NF-$\kappa$B signaling pathway.[988] 29-Deacetylsendanin (**157**) was found to promote slightly the drug metabolizing enzyme activities and decreased serum transaminase activities, which were elevated by $CCl_4$ intoxication.[204] TS3 (**221**) increased chloride conductance in epithelial cells to an extent comparable to genistein, a known cystic fibrosis transmembrane conductance regulator.[261] In a similar bioassay, rubralins A and B (**262** and **263**) showed moderate inhibitory activity with $IC_{50}$ values of 30−50 $\mu$M.[281] Rubrins A−G (**518**-**524**), with the hemi ortho ester A-ring moiety which is crucial to potency, showed potent inhibitory activity in the LFA-1:ICAM-1 mediated cell adhesion assay with $IC_{50}$ values of 10−25 nM.[504] Oral administration of swietenine (**677**) at 25 and 50 mg/kg body weight per day to diabetic rats was found to possess significant dose dependent hypoglycemic and hypolipidemic activity in type 2 diabetic rats.[662] The contractile response induced by humilinolide A (**793**) could be mediated by estrogens, probably by occupancy of some receptors in myometrial plasma membranes to induce uterotonic response, which might be estrogen-dependent.[684] Owing to the low DPPH free radical scavenging activity of swietephragmins H and I (**945** and **946**), the $IC_{50}$ values could not be determined in the study proposed by Tan et al.[717] In comparison with pentoxifylline as a standard, the antisickling activity of methyl 1$\alpha$, 2$\beta$,3$\alpha$,6,8$\alpha$,14$\beta$-hexahydroxy-[4,2,$1^{10,30}$,$1^{1,4}$]tricyclomeliac-7-oate (**1014**) was much higher at any concentration and incubation condition without altering significantly the corpuscular indices.[728]

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