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Recent progress in the chemistry and biology of limonoids

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This review covers the isolation and structure determination of limonoids reported during 2014–2016 (with 363 new compounds in 68 papers), together with the relevant biological activities and source organisms. Furthermore, the total synthesis and structural modifications of limonoids and their analogs regarding the bioactivities reported during 2011–2016 have also been summarised.

1. Introduction

Limonoids, a group of highly oxygenated triterpenoids, mainly exist in the Rutaceae and Meliaceae plant families.¹ When they first attracted people's attention, limonoids were considered a major problem for the citrus juice industry due to the bitter principles through the biochemical transformation of a tasteless limonoid aglycone precursor to a bitter one.² Tetranor-triterpenoids is an alternative name for limonoids because in the process of oxidative changes of triterpenoids, the side chain is eventually oxidized to an α -substituted furyl ring by the loss of four carbon atoms.³ Basic limonoids contain the 4,4,8-trimethyl-17-furyl steroidal signature-skeleton, and all members of the family of limonoid natural products either contain this structure or are derived from such a precursor with different degrees of oxidation and skeletal rearrangement.

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Limonoids are classified into different subcategories such as ring-intact limonoids, ring-seco limonoids, degraded limonoids, and highly oxidatively modified limonoids. Limonoids exhibited a wide spectrum of biological properties including cytotoxic, antioxidant, antioxidant, antiinflammatory, neuroprotective, antioxidant, antimicrobial, antiprotozoal, antimalarial, antimicrobial, antimecrobial, antiprotozoal, antimecrobial, antiprotozoal, antimecrobial, antiprotozoal, antimecrobial, antiprotozoal, antimecrobial, antiprotozoal, antimecrobial, antiprotozoal, antiprotozoa

2. Reviews

Some excellent reviews on various aspects of limonoids studies are listed here. Overview of the distribution and chemistry of limonoids in plants kingdom was collated in 2006. A comprehensive review of 'Meliaceous limonoids: chemistry and biological activities' has appeared in 2011. Topics on the chemistry and pharmacological activities of some limonoids have also been presented. Topics In 2011, biosynthesis and total



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Prof./Dr Hui Xu was born and raised in Zhejiang Province, China. He obtained his PhD under the supervision of Prof. Yan-Guang Wang at Zhejiang University. He then joined the group of Prof. Bruno Figadere at University of Paris-Sud 11 as a postdoctoral fellow. Since 2008, he holds the position of full professor at Northwest A&F University. Up to now, he has published over 90 peer-reviewed

SCI articles. His main research interests are on the activity-guided isolation, structural modifications and structure-activity relationships (SARs) of natural bioactive products.

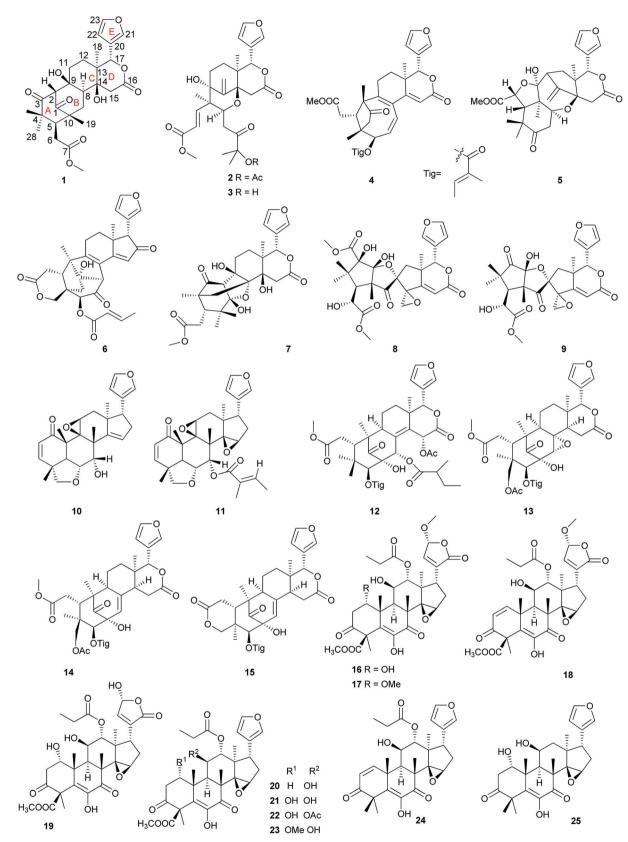


Fig. 1 Limonoids 1–25 from *Trichilia* genus.

synthesis of limonoid natural products from an organic synthesis perspective were reviewed. 36,37 On the other hand, it is noteworthy that some interesting limonoids with their relevant biological activities on annual reviews of 'Marine natural products' (covering 2011–2014)^{38–41} and 'Triterpenoids' (covering 2011–2013) have been summarised. 42–44

Phytochemistry

To efficiently extract and isolate new limonoid natural products from plants, recently, several techniques have been developed. By combination of preparative high-speed countercurrent chromatography (HSCCC) and off-line LC-ESI-MS/MS analysis, Rodríguez-Rivera et al. reported a new chromatographic technique to detect very low concentrated natural products from Citrus limetta peels; moreover, four detected limonoid glucosides such as nomilinic acid glucoside, limonin glucoside, nomilin glucoside and obacunone glucoside, were easily recovered in the fast eluting.45 Haldar et al. developed the medium pressure liquid chromatography (MPLC) and LC-ESI-MS/MS-based technique to quickly isolate, identify and obtain some basic limonoids such as azadirone, epoxyazadiradione and azadiradione from neem fruits in preparative scale.46 The LC-HRMS-guided and preparative high-performance liquid chromatography (prep-HPLC)-based protocol was efficiently performed to isolate twenty-one secondary metabolites (including one limonoid, 1-O-methylclausenolide) from the leaves and stem bark extracts of Clausena anisata. 47 Recently, supercritical CO2 extraction has been applied to obtain

limonoid extracts from the seeds of *C. aurantifolia swingle* in shorter time when compared with that of the conventional methods.⁴⁸ De Paula *et al.* reported an inexpensive and quick ultrasound-assisted extraction (UAE) and HPLC-photodiode array detector (PDA) technique to extract and determine azadirachtin from dried entire fruits of *Azadirachta indica* A. Juss (Meliaceae).⁴⁹ More recently, Rangiah *et al.* have developed an ultra high performance liquid chromatography/mass spectrometry/selected reaction monitoring (UHPLC/MS/SRM) assay for quantification of five neem metabolites (*e.g.*, azadirachtin A, nimbin, salanin, azadiradione and epoxy or hydroxy-azadiradione) from leaf extracts of Meliaceae family plants.⁵⁰

With the development of technology, during 2014–2016, a wide array of new limonoid natural products were isolated from different parts of plants. Recent advances on the isolation and structure determination of limonoids, together with their relevant biological activities are presented according to their source organisms such as Meliaceae, Rutaceae, Euphorbiaceae and Simaroubaceae families.

3.1. Meliaceae

3.1.1. Trichilia. As shown in Fig. 1, 25 new limonoids were isolated from *Trichilia* genus. For example, trichiconin A–C 1–3,⁵¹ trichiliton I 4,⁵² 12-deacetoxyltrijugin A 5,⁵² trichiconlides A 6 and B 7,⁵³ together with spirotrichilins A 8 and B 9 (ref. 54) were isolated from different parts (*e.g.*, twigs, roots and fruits) of *Trichilia connaroides*. Hypothetical biosynthetic pathways for 1–3, 6, 8 and 9 were also proposed. Rubescins D 10 and E 11 were

Fig. 2 Limonoids 26-33 from Swietenia genus.

obtained from the roots and stem barks of *T. rubescens*. ⁵⁵ Compounds 2 and 3 showed modest anti-HIV activities with EC $_{50}$ values of 5.9, and 3.6 μ M, respectively; whereas compound

6 showed a moderate inhibitory effect on lipopolysaccharide (LPS) induced nitric oxide (NO) production with an IC_{50} value of 40.5 μ M. Compound 11 possessed the ability to induce

Fig. 3 Limonoids 34–64 from Cipadessa genus.

apoptosis in hepatoma cells.⁵⁶ Ethanolic extracts of the roots of T. sinensis afforded four new limonoids, trichinenlides U-X 12-15, which showed weak acetylcholinesterase (AChE) inhibitory

activity at 50 mg mL⁻¹ (their inhibition ratios: 18.8% (12), 21.2% (13), 18.5% (14), and 23.7% (15)).57 Ten cedrelone limonoids 16-25 were isolated from the leaves of *T. Americana*. The

Fig. 4 Limonoids 65–86 from Chukrasia genus.

structure of **16** was determined by X-ray crystallographic studies. Compounds **20–25** exhibited potent or selective cytotoxic activities with $\rm IC_{50}$ values ranging from 1.0 to 39.6 μ M against five human tumor cell lines (*e.g.*, HL-60, SMMC-7721, A-549, MCF-7, and SW480).⁵⁸

3.1.2. Swietenia. Swietemacrophin **26** (ref. 59) and swielimonoids A–F **27–32** (ref. 60) (Fig. 2) were isolated from the seeds of *Swietenia macrophylla* which is a tropical timber tree natively distributed throughout tropical regions of the Americas, mainly in Mexico, Boli*via* and Central America. 2-Methoxykhayseneganin E **33** (Fig. 2) was obtained from the leaves and twigs of *S. mahagoni*. ⁶¹ Compound **26** showed potent inhibition against LPS-induced NO generation (IC₅₀: 33.45 μ M), and compound **28** exhibited significant antidengue virus 2 activity (EC₅₀: 7.2 μ M).

3.1.3. Cipadessa. As described in Fig. 3, 6 methyl angolensate type limonoids, cipaferen E–J **34–39**, and 3 mexicanolide-type limonoids, cipaferen K–M **40–42** were isolated from the seeds of *Cipadessa baccifera*. 62 3-De(2-methylbutanoyl)-3-propanoylcipadesin **43**, 63 cineracipadesin G **44**, 64 cipacinoids A–D **45–48**, 65 trijugin-type limonoids ciparasins H–O **56–63**, 66 and prieurianin-type limonoid ciparasins P **64** (ref. 66) were isolated from the fruits, branches and leaves of *C. cinerascens*. The absolute configurations of **45** and **47** were unambiguously confirmed by the solid evidence of X-ray crystallography. Interestingly, compounds **53–55** contained a rare γ -hydroxylbutenolide moiety at C-17 position. 66

Compound 37 displayed potent cytotoxic activity against B–16 with an IC $_{50}$ value of 8.51 µg mL $^{-1}$. 62 Compound 44 showed the potent antifeedant activity against fruit fly (*Drosophila melanogaster*; antifeedant index (AI) at 1 mM: 32.8%). 64 Compound 45 (IC $_{50}$: 16.7 µM) displayed moderate inhibition activity against protein tyrosine phosphatase 1B (PTP1B). 65 Compounds 50 (EC $_{50}$: 5.5 µM) and 64 (EC $_{50}$: 6.1 µM) showed significant anti-HIV activities. 66

3.1.4. Chukrasia. As shown in Fig. 4 and 5, 26 new phragmalin-type limonoids (including velutinasins A–H 65–72, ⁶⁷ velutinalide C 73, ⁶⁸ tabulalin K–M 74–76, ⁶⁹ velutabularins K–M 77–79, ⁷⁰ chukbularisins A–E 80–84, ⁷¹ tabularisins S 85 and T 86, ⁷² chuklarisin A 87 and chuklarisin B 88, ⁷³ and chukvelutilide Y 89 and Z 90 (ref. 74)), and 2 new mexicanolide-type limonoids (ivorenoid G 91 and andirolide Q 92 (ref. 74)) were isolated from the seeds, twigs, stem barks, and leaves of *Chukrasia tabularis*. The absolute configurations of 65–68 were determined by the CD exciton chirality method. Compounds 65–68, ⁶⁷ 89 and 90 (ref. 74) were a rare class of C15-acyl phragmalin-type limonoids, especially compounds 66–68 contained a δ-lactone ring formed between C-16 and C-30 positions. ⁶⁷ The steric structure of 77 was further confirmed by single crystal X-ray diffraction. ⁷⁰

Compound ⁶⁵ exhibited significant inhibition activity against LPS-induced NF-kB production. It suggested that the *ortho* ester group and/or the 2,7-dioxabicyclo[2.2.1]heptane moiety in these phragmalin limonoids were crucial for the activities.⁶⁷

Fig. 5 Limonoids 87–92 from Chukrasia genus.

Review

Compounds 81-84, 86, and 88 exhibited significant inhibitory activities against α-glucosidase in vitro with IC₅₀ values of 0.06, 0.04, 0.52, 1.09, 0.15, and 0.96 mM, respectively.71-73

3.1.5. Walsura. Nine new cedrelone limonoids 93-101 (Fig. 6), including walsuranolide B 93, 11β-hydroxy-23-O-methylwalsuranolide 94, yunnanolide A 95, yunnanol A 96, 11β-

Fig. 6 Limonoids 93-128 from Walsura genus.

hydroxyisowalsuranolide 97, 11β-hydroxy-1,2-dihydroisowalsuranolide 98, 1α ,11β-dihydroxy-1,2-dihydroisowalsuranolide 99, 11β-hydroxy-1 α -methoxy-1,2-dihydroisowalsuranolide 100 and yunnanolide B 101, were isolated from the leaves and twigs of *Walsura yunnanensis*. ⁷⁵ As shown in Fig. 6, walsucochinoids C–R 102–117 were obtained from the twigs and leaves of *W. cochinchinensis*. The steric structures of 102 and 111 were

determined by single-crystal X-ray diffraction experiments.⁷⁶ The isolation of walsunoids A-I **118–126**,⁷⁷ and walsuronoids D **127** and E **128** (ref. 78) from the leaves of *W. robusta* were reported (Fig. 6). Among them, compound **118** is a novel degradation product of cedrelone-type limonoids, and **126** is a rare cedrelone-type limonoid amide. The structure of **121** was unambiguously measured by X-ray diffraction.

Fig. 7 Limonoids 129–162 from Toona genus.

Compounds 95, 97, 127 and 128 exhibited potent cytotoxic activities against five human tumor cell lines (e.g., HL-60, SMMC-7721, A-549, MCF-7, and SW480) with IC₅₀ values in

the range of 2.2–4.5 μ M.^{75,78} Compounds **103** and **104** exhibited mild inhibitory activities against mouse and human 11 β -HSD1 with IC₅₀ values of 13.4 and 8.25 μ M, respectively.⁷⁶

Fig. 8 Limonoids 163-187 from Carapa genus.

3.1.6. Toona. As shown in Fig. 7, a 9,11-seco limonoid toonasecone A 129),⁷⁹ four B-seco-29-nor-limonoids (toonaciiatones A–D 130–133),⁸⁰ and seven B-seco-limonoids (toonaciiatones E–H 134–137)^{80a} and ciliatonoids A–C 137a–137c (ref. 80b) were isolated from the stem barks and the twigs of *Toona* (IC₅₀: 5.38 μM) and HepG2 cells (IC₅₀: 5.22 μM).⁸⁰ Compounds 141, 142 and 144–147 showed potent radical scavenging activities (DPPH IC₅₀: 51.3–104.0 μM; ABTS⁺ IC₅₀: 52.2–167.3 μM):

(IC $_{50}$: 5.38 μM) and HepG2 cells (IC $_{50}$: 5.22 μM).⁸⁰ Compounds **141**, **142** and **144–147** showed potent radical scavenging activities (DPPH IC $_{50}$: 51.3–104.0 μM; ABTS $^+$ IC $_{50}$: 52.2–167.3 μM); compounds **138–141** exhibited significant anti-inflammatory (selective inhibition of Cox-1 and Cox-2 at 100 μM: >88%), and cytotoxic activities against seven human tumor cell lines (IC $_{50}$: 2.1–14.7 μM).⁸¹ Compounds **148** (IC $_{50}$: 10.21 μM), **149** (IC $_{50}$: 20.05 μM), **153** (IC $_{50}$: 12.56 μM), **155** (IC $_{50}$: 12.56 μM) and **156** (IC $_{50}$: 20.68 μM) exhibited marked inhibitory effects on NO production in LPS-activated RAW 264.7 macrophages at nontoxic concentration.⁸²

(toonasecone A 129),⁷⁹ four B-*seco*-29-nor-limonoids (toonaciliatones A–D 130–133),⁸⁰ and seven B-*seco*-limonoids (toonaciliatones E–H 134–137)^{80α} and ciliatonoids A–C 137a–137c (ref. 80b) were isolated from the stem barks and the twigs of *Toona ciliata*. The absolute configurations of α,β-unsaturated ketone moiety of 130 and 134–136 were confirmed by CD exciton chirality method and electronic circular dichroism calculation.^{80α} Compound 137b was confirmed by single-crystal X-ray diffraction analysis.^{80b} In addition, toonasinenines A–J 138–147,⁸¹ toonasinemines A–L 148–159,⁸² and toonasins A–C 160–162 (ref. 83) were obtained from the leaves and the root barks of *T. sinensis*. It is noteworthy that compounds 148–154, and 160–162 contained the rare lactam moiety at C-17 position.^{82,83}

Fig. 9 Limonoids 188–204 from Munronia genus.

3.1.7. Carapa. As described in Fig. 8, 22 carapanolides C-X 163–184 (ref. 84–87) were isolated from the seeds of *Carapa guianasis*, a traditional medicine in Brazil and Latin American countries. The structure of 174 was unambiguously confirmed by single crystal X-ray measurements. Andirolides W-Y 185–187 (ref. 88) were obtained from the flower oil of *C. guianasis*. Their structures were elucidated on the basis of spectroscopic analyses using 1D/2D NMR spectra and FABMS. Among them, compounds 170 (IC $_{50}$: 37.4 μ M), 180 (IC $_{50}$: 22.0 μ M), and 181

(IC50: 23.3 μM) showed potent NO production inhibitory activities. 85,87

3.1.8. Munronia. As shown in Fig. 9, 17 munronins A–Q **188–204** (ref. 89 and 90) were isolated from the whole plants of *Munronia henryi*. The structure of **195** was confirmed by single-crystal X-ray diffraction analysis. Finterestingly, compound **188** contained a novel 7-oxabicyclo[2.2.1]heptane moiety at the C-11 and C-14 positions. Among them, compounds **189**, **195–199**, and **202–204** showed significant anti-TMV activity with IC₅₀

Fig. 10 Limonoids 205–230 from Khaya genus.

values in the range of 14.8– $48.3~\mu g~mL^{-1}.^{89,90}$ Compound **188** (IC₅₀ values: 0.44– $2.3~\mu M$) exhibited potent cytotoxic activities against five cancer cell lines (*e.g.*, HL-60, SMMC-7721, A-549, MCF-7, and SW480).⁸⁹

3.1.9. Khaya. As shown in Fig. 10, 14,15-didehydror-uageanin A **205**,⁹¹ 3-*O*-methylbutyrylseneganolide A **206**,⁹¹ and ivorenoids A–F **207–212** (ref. 92) were isolated from the fruits and stems of *Khaya ivorensis*. Compounds **207** and **208**

Fig. 11 Limonoids 231–255 from Xylocarpus genus.

possessed a rare rearranged skeleton and a unique γ -lactone (C-16/C-8). Additionally, khaysenelide A–F **213–218** (ref. 93) with modified furyl ring, and khasenegasins O–Z **219–230** (ref. 94)

were obtained from the stem barks and seeds of *K. senegalensis*, respectively. Compounds **213** and **215** were confirmed by single-crystal X-ray crystallography data.

Fig. 12 Limonoids 256–299 from Aphanamixis genus.

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Compounds **209** (IC₅₀: 15.3 μ M) and **212** (IC₅₀: 17.5 μ M) exhibited moderate cytotoxic activity against HL-60 cell line. Compound **230** displayed the significant neuroprotective activity against glutamate-induced injury in primary rat cerebellar granule neuronal cells with increased viability of 83.3% at 10 μ M and 80.3% at 1 μ M.

3.1.10. Xylocarpus. As depicted in Fig. 11, 3 new limonoids, 2,3-dideacetylxyloccensin S 231, 30-deacetylxyloccensin W 232 and 7-hydroxy-3-oxo-21β-methoxy-24,25,26,27-tetranortirucall-1,14-dien-23(21)-lactone 233, were isolated from the seeds of the Chinese mangrove, Xylocarpus granatum.95 With an investigation conducted on the seeds of the Trang mangrove plant X. moluccensis, two phragmalins limonoids 234 and 235,96 two mexicanolides limonoids 236 and 237,96 twelve thaixylomolins G-R 238-249, 96,97 and six trangmolins A-F 250-255 (ref. 98) were obtained. The absolute stereostructures of 246, 248 and 250 were unambiguously confirmed by X-ray crystallographic analysis. Compound 249 was the first 7-nor-limonoid with a 6oxabicyclo[3.2.1]octan-3-one motif. Compound 254 contained the first oxidative cleavage on the C2-C3 bond in limonoids. Moreover, the biosynthetic origins of 250-255 traced back to a andirobin-type limonoid with 1,2-bisketone were also proposed.98

Among them, compound **240** (IC $_{50}$: 77.1 μ M) exhibited moderate anti-H1N1 activity; 96 compound **247** showed moderate cytotoxicities against ovarian A2780 and A2780/T cells with equal IC $_{50}$ values of 37.5 μ M for each. 97

312

Fig. 14 Chisotrijugin 312 from Chisocheton genus.

3.1.11. Aphanamixis. As shown in Fig. 12, 30 new highly oxygenated prieurianin-type limonoids, zaphaprinins A–Y **256–280** (ref. 99) and aphagranols D–H **281–285**,¹⁰⁰ were isolated from the fruits of *Aphanamixis grandifolia*, which is a wild timber tree distributed mainly in the tropical and subtropical areas of South and Southeast Asia. The absolute configuration of **256** was assigned by single crystal X-ray measurements. On the other hand, 8 aphanamixoid-type aphanamixoids C–J **286–293**, and 6 prieurianin-type aphanamixoids K–P **294–299**, were obtained from *A. polystachya*.¹⁰¹

Among them, compounds **264** and **274** showed strong insecticidal activities against *Plutella xylostella*. ⁹⁹ Compounds **286**, **289** and **290** exhibited potent antifeedant activities against the generalist *Helicoverpa armigera* with EC_{50} values of 0.017, 0.008, and 0.012 μ mol cm⁻², respectively. Preliminary structure–activity relationship indicated that Δ (ref. 2 and 30)

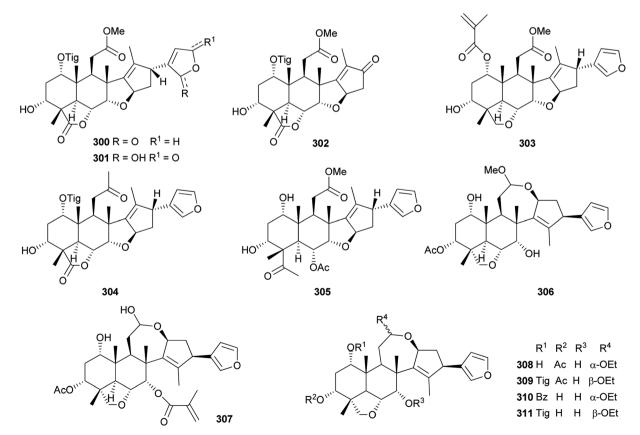


Fig. 13 Limonoids 300-311 from Melia genus.

configuration and the acetoxy substituent at C-12 position were vital to the antifeedant activity. 101

3.1.12. Melia. As described in Fig. 13, 8 new limonoids, including 3-deacetyl-28-oxosalannolactone **300**, 3-deacetyl-28-oxosalanninolide **301**, 3-deacetyl-17-defurano-17,28-dioxosalannin **302**, 3-deacetyl-4'-demethylsalannin **303**, 3-deacetyl-28-oxosalannin **304**, 1-detigloylohchinolal **305**, 3α-acetoxy-1α,7α-dihydroxy-12α-methoxynimbolinin **306**, and 3α-acetoxy-1α,12α-dihydroxy-7α-(2-methylprop-2-enoyl)nimbolinin **307**, were isolated from the leaves, fruits and stem barks of *Melia azedarach*. ¹⁰²⁻¹⁰⁴ Recently, an investigation on the fruits of *M. toosendan* resulted in four new limonoids, such as 1α ,7α-dihydroxyl-3α-acetoxyl-12α-ethoxylnimbolinin **308**, ¹⁰⁵ 1α -tigloyloxy-3α-acetoxyl-7α-hydroxyl-12β-ethoxylnimbolinin **309**, ¹⁰⁵ and 12-ethoxynimbolinins E **310** and F **311**. ¹⁰⁶

Among them, compound 300 (IC $_{50}$: 86.0 μ M) showed inhibitory effects against LPS-induced NO production in RAW 264.7 cell line; the IC $_{50}$ values of compounds 301 and 302 against the

Epstein-Barr virus early antigen (EBV-EA) were 299 and 318 molar ratio/32 pmol TPA, respectively.¹⁰² Compound **309** (MIC: $31.25 \mu g \text{ mL}^{-1}$) exhibited the potent antibiotic activity against *Porphyromonas gingivalis* ATCC 33277.¹⁰⁵

3.1.13. Chisocheton. A new 30-nor trijugin-type limonoid, chisotrijugin **312** (Fig. 14), was isolated from the bark of *Chisocheton cuminganus*.¹⁰⁷ The chemical structure of **312** was confirmed by spectroscopic techniques such as UV, IR, MS, 1D and 2D NMR.

3.1.14. Neobeguea. As described in Fig. 15, 11 new limonoids, namely, dodoguin **313**, dormir A–G **314**–**320**,¹⁰⁸ libiguins A **321**, libiguins B (a) **322** and libiguins B (b) **323**,¹⁰⁹ were isolated from the root barks of *Neobeguea mahafalensis*, a medicinal plant in Madagascar. Interestingly, compounds **318**, and **321**–**323** contained a C-16/30 δ-lactone ring, which was the first time reported in this species. Compounds **322** and **323** were existing in tautomers. Among them, compound **313** displayed sleep-inducing activity in Swiss albino mice;

Fig. 15 Limonoids 313–323 from Neobeguea genus.

and compound 322 exhibited a potent sexual enhancing activity.

3.1.15. Entandrophragma. Sixteen entangolensins A-P **324–339** (Fig. 16) were isolated from the stem barks of *Entandrophragma angolense*a, a genus of the Meliaceae family restricted to tropical Africa. Their planar structures were comprehensively characterized by HRMS and 1D/2D NMR, and the absolute configurations of most isolates were established by time-dependent density functional theory (TDDFT) calculations of the electronic circular dichroism (ECD) data. Especially compound 324 was the first natural product example of C-9/10-*seco* mexicanolide. Compounds **329** (IC₅₀: 1.75 μM) and **334**

 $(IC_{50}: 7.94~\mu M)$ exhibited significant NO inhibitory activities against LPS-activated RAW 264.7 macrophages. Furthermore, the plausible biosynthetic pathway of these compounds has been described.

Additionally, as shown in Fig. 16, entanutilin A (339a) and B (339b) were isolated from the stem barks of *Entandrophragma utile*. ^{110b} Their absolute configurations were confirmed by CD exciton chirality method.

3.2. Rutaceae

3.2.1. Hortia. As shown in Fig. 17, 3 new limonoids **340–342** were isolated from the taproots and stem of *Hortia oreadica*.¹¹¹

Fig. 16 Limonoids 324–339, 339a, and 339b from Entandrophragma genus.

3.2.2. Dictamnus. As described in Fig. 17, kihadanin C 343 with an unusual 3,4-dihydroxy-2,5-dimethoxytetrahydrofuran moiety as E ring, and 23-methoxydasylactone A 344, were isolated from the root barks of *Dictamnus dasycarpus*. ¹¹² Meanwhile, 9 dictangustones A–I 345–353, were obtained from the root barks of *D. angustifolius*. ^{113,114} Among them, compound 346 displayed significant neuroprotective activity against neuronal death induced by oxidative stress, and compound 352 exhibited potent cytotoxic activities against four cell lines (*e.g.*, Hela, A549, MCF7, and LN229) with IC₅₀ values lower than 25 μM.

3.3. Euphorbiaceae

Two highly oxygenated limonoids, such as flexuosoids A 354 and B 355 (Fig. 18), with a C-19/29 lactol bridge and heptaoxygenated substituents at C-1, C-2, C-3, C-7, C-11, C-17, and C-30 positions,

Fig. 18 Limonoids 354 and 355 from Euphorbiaceae family.

Fig. 17 Limonoids 340-353 from Rutaceae family.

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Fig. 19 Limonoids 356-358 from Simaroubaceae family.

were isolated from the roots of *Phyllanthus flexuosus*. ¹¹⁵ Compounds **354** and **355** showed antifeedant activities against the beet army worm (*Spodoptera exigua*) with EC₅₀ values of 25.1 and 17.3 μg cm⁻², respectively. In addition, compounds **354** (IC₅₀: 11.5 μ M) and **355** (IC₅₀: 8.5 μ M) displayed moderate cytotoxic activities against the ECA109 human esophagus cancer cell line.

3.4. Simaroubaceae

As shown in Fig. 19, two new 16-nor limonoids, harperspinoids A 356 and B 357, with a unique 7/5/5/6/5 ring system, were obtained from the leaves and branches of *Harrisonia perforata*.¹¹⁶ Especially the absolute structure of 356 was further confirmed by X-ray crystallographic analysis. Moreover, compound 356 exhibited the notable inhibitory activity against the 11β-HSD1 enzyme with an IC₅₀ value of 0.60 μM. The biogenetic pathway of these two compounds was also proposed. Perforanoid A 358 (Fig. 19), isolated from the leaves of *H. perforata*, showed cytotoxic activities against HEL, K562, CB3, DP17, and WM9 tumor cell lines (IC₅₀: 4.24–25.96 μM).¹¹⁷

4. Total synthesis

4.1. Cipadonoid B

In 2011, an efficient strategy for the total synthesis of cipadonoid B 359 was reported (Scheme 1). First, compound 361 was

prepared by reaction of silyl enol ether with **360**. Then, aze-daralide **363** reacted with **361** *via* the intermediate **362**, to give **359** (20% yield) by a ketal-Claisen rearrangement.¹¹⁸

4.2. Khayasin, proceranolide, and mexicanolide

Based upon cipadonoid B 359,¹¹⁸ Faber *et al.* further reported a concise and enantioselective total synthesis of proceranolide 364, khayasin 365 and mexicanolide 366 (Scheme 2). First, compound 364 was obtained from 370 by epoxidation and cyclization; then, compound 365 was afforded by acylation of 364; finally, conversion of 364 to 366 in the presence of Jones reagent was achieved.¹¹⁹

4.3. Limonin

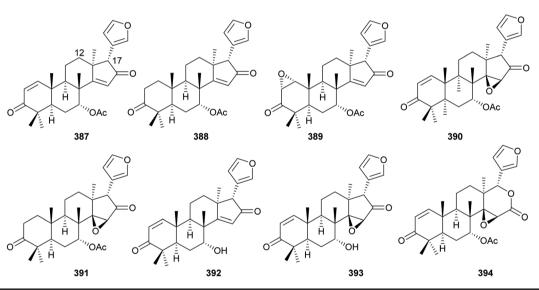
As depicted in Scheme 3, Yamashita *et al.* described the total synthesis of (\pm) -limonin 379 in 35 steps. *Via* an intermediate 372, a tandem radical cyclization of geraniol 371 gave 373 containing a BCD ring system with the C-13 α configuration. Then, the limonoid androstane framework 374 was constructed by a Robinson annulation of 373. Subsequently, compound 376 was produced by epoxidation and nitrile addition, followed by acetonitrile elimination. Through a singlet-oxygen cycloaddition and a Baeyer-Villiger oxidation, compound 378 was obtained *via* the intermediate 377. Finally, construction of target compound 379 was achieved by a Suarez reaction. ¹²⁰ This study

Scheme 1 Reagents and conditions: (a) silyl enol ether, $TiCl_4$, CH_2Cl_2 , -78 °C; (b) KH, PhH; (c) MeOTf, CH_2Cl_2 ; (d) azedaralide 363, PTSA, xylenes, 180 °C, 4 h.

Scheme 2 Reagents and conditions: (a) (i) KHMDS, THF, -78 °C, then (-)-DIP-Cl, (ii) 3-furylaldehyde, 33–44% yield, 80–90% ee; (b) (+)-DIP-Cl, DIPEA, 2-butanone, Et₂O, -78 °C, then -105 °C to -30 °C, 16 h, 47% yield, 92.5% ee; (c) TsOH, xylenes, 180 °C, 4 h; (d) 30% H₂O₂, K₂CO₃, MeOH, 0 °C to r.t., 12 h, 75%; (e) Al/Hg, EtOH/THF/H₂O/NaHCO₃, r.t., 1 h, 30%; (f) isobutyric acid, EDCI, DMAP, CH₂Cl₂, 0 °C to r.t., 4 h, 71%; (g) K₂Cr₂O₇/H₂SO₄, Me₂CO, r.t., 15 min, 68%.

Scheme 3 Reagents and conditions: (a) Mn(OAc) $_3$ ·2H $_2$ O, EtOH, r.t.; (b) Zn, AcOH, r.t.; (c) MVK, tBuOK, tBuOH, 35 °C; (d) Mel, tBuOK, tBuOH, 40 °C; (e) LiAlH $_4$, THF, 0 °C to reflux; (f) TBSCl, NaH, THF, 0 °C to r.t.; (g) Ac $_2$ O, pyridine, DMAP, CH $_2$ Cl $_2$, r.t.; (h) m-CPBA, NaHCO $_3$, CH $_2$ Cl $_2$, r.t. to -5 °C; (i) NaCN, DMSO, 120 °C; (j) Ac $_2$ O, pyridine, DMAP, CH $_2$ Cl $_2$, r.t.

Scheme 4 Reagents and conditions: (a) 2-methylpropenal (1.0 equiv.), aminonaphthol (15 mol%), 2-butyne (2.0 equiv.), Cy_2BH (2.0 equiv.), Me_2Zn (2.0 equiv.), toluene, r.t. to -78 °C then -30 °C; (b) 381 or 382, LDA, THF, -78 °C; (c) Burgess reagent.



Entry	Substrate (0.2 g/L, 8 days in <i>M881</i>)	17β-Hydroxy (%)	12β-Hydroxy (%)
1	azadiradione 387	61	38
2	1,2-dihydroazadiradione 388	59	40
3	$1,2\alpha$ -epoxyazadiradione 389	57	39
4	epoxyazadiradione 390	-	99
5	1,2-dihydroepoxyazadiradione 391	-	93
6	nimbocinol 392	71	-
7	7-deacetylepoxyazadiradione 393	-	94
8	gedunin 394	-	96

Fig. 20 Biotransformation of limonoids.

will lay the foundation for future synthesis of diverse limonoid skeletons.

4.4. Perforanoid A and 10-epi-perforanoid A

More recently, as shown in Scheme 4, Hao *et al.* developed an efficient way to total synthesis of perforancid A **358** and 10-*epi*-perforancid A **386**. The key steps were as follows: allylic alcohol **384** was enantioselectively obtained by alkenylation of 3-formylfuran **383** with 2-methylpropenal; then, Pd-catalyzed coupling of **384** with a vinyl ether gave the γ -lactone ring, with stereoselective construction of the C13 all carbon quaternary center, followed by formation of the cyclopentenone ring

by a Rh-catalyzed Pauson-Khand reaction to give **385**. Finally, reaction of **385** with **381** or **382** produced **358** (33% yield) and **386** (36% yield), respectively. Compound **358** showed potent cytotoxic activities against HEL, K562, and CB3 tumor cell lines with IC₅₀ values of 6.17, 4.24, and 3.91 μ M, respectively; in contrast, compound **386** did not display any cytotoxic activity.

Structural modifications

5.1. Biocatalytic modifications

Biotransformation is a good choice for the production of sufficient amounts of scientifically and commercially valuable

Scheme 5 Semisynthesis of libiguin A and its analogs from phragmalin. Reagents and conditions: (a) MeNHOMe·HCl, 2 M Me₃Al in Hex, CH₂Cl₂, r.t., 68%; (b) TESCl, imidazole, DMF, r.t., 79%; (c) 10 M aq. KOH, THF, r.t.; (d) EDCl, DMAP, MeOH, r.t., 63%; (e) Ac₂O, DMAP, CH₂Cl₂, r.t., 92%; (f) TFA, DMF, r.t., 78%; (g) Ac₂O or i-PrCOCl, Py, r.t.; (h) MeNHOMe·HCl, 2 M Me₃Al in Hex, CH₂Cl₂, r.t.; (i) Dess-Martin periodinane, CH₂Cl₂, r.t.; (j) TMSOTf, CH₂Cl₂, r.t.; (k) for 405, i-butyric anhydride, TMSOTf, CH₂Cl₂, r.t.

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compounds with the advantages of strict stereo- and regionselectivity, mild reaction conditions and simple operation procedure. As shown in Fig. 20, 8 limonoids including azadiradione 387, 1,2-dihydroazadiradione 388, 1,2α-epox-389, epoxyazadiradione dihydroepoxyazadiradione 391, nimbocinol 392, 7-deacetylepoxyazadiradione 393 and gedunin 394, were converted into their corresponding 12β- and/or 17β-hydroxy derivatives via fungi M881-mediated biocatalysis. Interestingly, when 14β , 15β -epoxidation was on the basic limonoid skeleton (e.g., 390, 391, 393, and 394), only 12β-hydroxy derivative was produced as the single metabolite.121

5.2. Chemical modifications

5.2.1. Phragmalin. As depicted in Scheme 5, starting from phragmalin 395 isolated from the seeds of C. tabularis, libiguin A 321 and its analogs 401, 405 and 406 were efficiently obtained by structural modification. This was based on selective aminolysis of the lactone in 395 with MeONHMe, followed by TMSOTf-promoted lactonization of the resulting Weinreb amide with the 30-OH group after protection or oxidation of the 17-OH group. 122

5.2.2. Toosendanin. Starting from toosendanin 407, we prepared a series of 28-acyloxy derivatives of toosendanin 408-434 (Scheme 6).123,124 Among them, compounds 410, 417 and 431 exhibited more potent insecticidal activity than 407 against the pre-third-instar larvae of Mythimna separata Walker in vivo at 1 mg mL⁻¹. Interestingly, it indicated that the proper length of the side chain at the 28-position of 407 was important for the insecticidal activity; however, introduction of the double bond on the side chain decreased the activity.

5.2.3. Limonin. As shown in Scheme 7, a series of limonin derivatives 436-465 were prepared by structural modifications on the A, B or D-ring of limonin 379. 125,126 It demonstrated that oxygen bridge between C-14 and C-15 positions in limonin derivatives was important for analgesic and anti-inflammatory activities. Compound 443 displayed a promising analgesic and anti-inflammatory activities with high water-solubility (14.5 mg mL^{-1}). Among 446-465, compounds 451 and 459 showed higher antimicrobial activities than 379 against 20 microorganisms.

5.2.4. Obacunone. As depicted in Scheme 8, we semisynthesized a series of obacunone (466) derivatives, including C7-oxime esters 468-491, C7-oxime sulfonate esters 492-497, and C7-esters 500-532.127-129 The structures of 480, 485, 486, 498, 499, and 518 were unambiguously determined by singlecrystal X-ray diffraction. Interestingly, when compound 466 was reduced by NaBH4, the ratio of reductive products 498 and 499 was related to the reaction mixing solvents. In addition, compounds 472, 485, 486, 490, 495, 501 and 510 (the final mortality rates (FMRs) at 1 mg mL⁻¹: 55.2-72.4%), showed more potent insecticidal activity against M. separata than their precursor 466 (FMR: 41.4%) and toosendanin (FMR: 48.3%). It demonstrated that the configuration of C7-OH of 498 (FMR: 32.1%) and 499 (FMR: 46.4%) was important for the insecticidal activity, and introduction of a chlorine atom on the phenyl ring of the substituents could improve the activity.

5.2.5. Fraxinellone. As shown in Scheme 9, to discover more potent fraxinellone (533)-based insecticidal agents, first, in the presence of selenium dioxide or chromium trioxide, we developed an efficient method for regioselectively allylic oxidation of 533 at its C-4 or C-10 position (A ring) to afford 534 and 579, respectively; then, a series of esters 559-578 and 580-596, 130 hydrazones 535-544 and 603-615, 131 and oxime esters 545-558 and 597-602,132 were smoothly prepared. On the other hand, when reduction of 533 with Red-Al reagent, we found that the kinds and the amount of the reduction products 617, 628 and 656 at the C-1 or C-8 position (B ring) were related with the molar ratio of Red-Al/533; subsequently, esters 629-655 and 657-665, were synthesized from 628 and 656, respectively.¹³³ It was noteworthy that when compound 533 reacted with different chlorination/bromination reagents,

408: Me 409: Et 410: n-propyl 411: Ph 412: PhCl(p) 413: PhCl(m) 414: PhCl(o) 415: PhOMe(p) 416: PhNO₂(p)

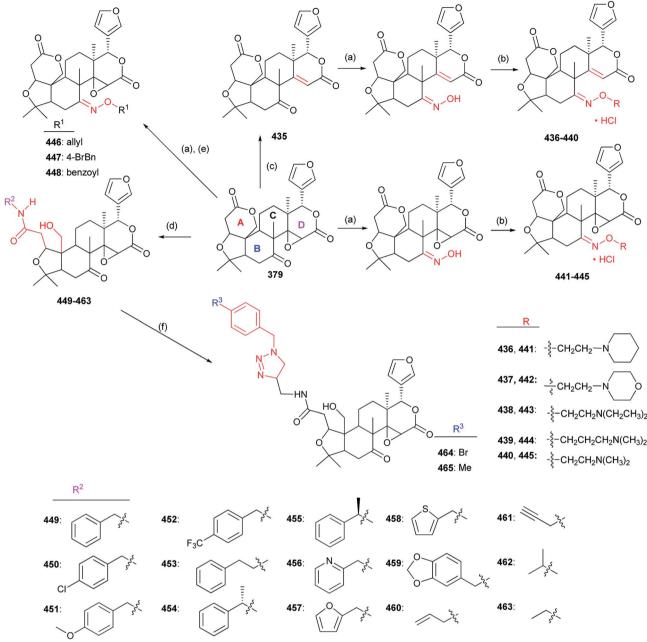
417: CH=CHPh 418: PhCH2CH2 419: CH2Ph 420: CICH2 421: CH=CH2 422: (CH3)2CH 423: C(CH3)=CH2

424: CH₃(CH₂)₃ 425: (CH₃)₂CHCH₂ 426: CH₃(CH₂)₄ 427: CH=CHCH=CHCH₃ 428: CH₃(CH₂)₅ 429: CH₃(CH₂)₆

430: CH₃(CH₂)₉ 431: CH₃(CH₂)₁₀ 432: (Z)-CH₃(CH₂)₇CH=CH(CH₂)₇ 433: CH₃(CH₂)₇OCO(CH₂)₆ 434: CH₃(CH₂)₇OCO(CH₂)₈

Scheme 6 Semisynthesis of a series of 28-acyloxytoosendanin derivatives. Reagents and conditions: (a) (RCO)₂O/NaOAc/acetone/reflux, 10-20 h; or RCO₂H/DIC/DMAP/CH₂Cl₂/r.t., 6-12 h, 14-88%

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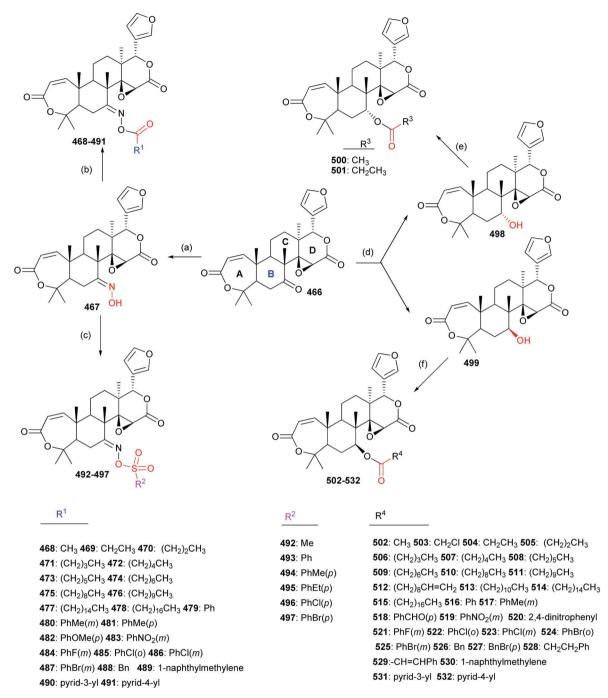
Scheme 7 Semisynthesis of limonin derivatives. Reagents and conditions: (a) NH2OH·HCl, pyridine, EtOH, reflux; (b) (i) RCl, NaOH, TBAB, dry THF, 80 °C; (ii) HCl, dry ether, CH₂Cl₂; (c) HI, HOAc; (d) condition (i): abs. EtOH, appropriate amine, montmorillonite K-10, microwaveassisted; condition (ii): abs. EtOH, appropriate amine, montmorillonite K-10, reflux; condition (iii): CH₂Cl₂, appropriate amine, montmorillonite K-10, ultrasonic bath; (e) R¹Br or R¹Cl, NaH, DMF, 0 °C to r.t.; (f) for 461, sodium ascorbate, Cu(OAc)₂.H₂O, THF: H₂O (1:1), 1-(azidomethylene)-4-bromobenzene or 1-(azidomethylene)-4-methylbenzene, r.t., 10 h.

some unexpected furyl-ring (C ring) halogenation products 623-627 were obtained. Moreover, their possible reaction mechanism was also proposed.134 Especially, 20 steric structures of compounds 534, 539, 544, 553, 566, 601, 611, 617, 620-628, 659, 660 and 663, were unambiguously established by X-ray analysis. Among them, compounds 534, 535, 557, 566, 575, 578, 579, 596, 598, 602, 606, 617, 620, 622, 627, 652, 653 and 665 (FMRs: 51.7-73.3%) displayed

more promising insecticidal activity than toosendanin (FMR: 48.3%).

The structure-activity relationships demonstrated introduction of the carbonyl or oxime group on the C-4 position of 533 generally resulted in more promising derivatives than those containing a carbonyl or oxime one at the C-10 position; introduction of the heterocyclic fragments at C-4 or C-10 position of 533 was necessary for the insecticidal activity;

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Scheme 8 Semisynthesis of B-ring modified obacunone derivatives. Reagents and conditions: (a) NH₂OH·HCl/EtOH/Py, 60 °C, 2 h, 93%; (b) $R^1CO_2H/DCC/DMAP$, CH_2Cl_2 , r.t., 5–20 h, 64–97%; (c) R^2SO_2Cl/Et_3N , CH_2Cl_2 , r.t., 14–30 h, 54–89%; (d) NaBH₄; (e) $(R^3CO)_2O$, reflux, 2 or 4 h; (f) $R^4CO_2H/DCC/DMAP$, CH_2Cl_2 , r.t., 6–24 h, 40–97%.

the lactone (B ring) of 533 was important for the insecticidal activity; the double bond at the C-2 position of 533 was not necessary for the insecticidal activity; substitution of the oxygen atom on the carbonyl group of 533 by the sulfur one did not improve the insecticidal activity; introduction of the acyl group on the C ring of 533 could lead to more potent compounds than those containing the halogen atom at the same position. $^{130-134}$

6. Biological activities of the most active limonoids

Due to exhibiting a large number of biological properties, currently, limonoids and their analogs have received much research attention in the medicinal and agricultural fields. Additionally, the most active limonoids and

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535,603: COPh **536**,604: COPhNO₂(p) **537**,605: COPhCl(m) **538**,606: 4-pyridylcarbonyl **539**,607: 3-thienylcarbonyl **540**,608: COCH₂CN **541**,609: Ph **542**,610: PhNO₂(p) **543**,611: PhNO₂(o) **544**,612: 2,3,5,6-tetrafluorophenyl **613**: COPhOMe(p) **614**: COPhMe(m) **615**: 2,4-dinitrophenyl R¹

545, **597**: CH₃ **546**, **598**: CH₂CH₃ **547**: CH₂CH₂CH₃ **548**: (CH₂)₃CH₃ **549**, **599**: Ph **550**, **600**: PhMe(m) **551**: PhMe(p) **552**: PhOMe(p) **553**, **601**: PhCl(m) **554**: PhCl(o) **555**, **602**: PhNO₂(p) **556**: PhNO₂(m) **557**: PhF(m)

559, 580: CH₃CH₂ 560, 581: CH₃(CH₂)₆ 561, 582: CH₃(CH₂)₉ 562, 583: CH₂Ph 563, 584: 1-naphthylmethylene 564, 585: Ph 565, 586: PhMe(*p*) 566, 587: PhF(*p*) 567, 588: PhF(*m*) 568, 589: PhCl(*p*) 569, 590: PhBr(*m*) 570, 591: PhBr(*p*) 571, 592: PhNO₂(*m*) 572, 593: PhNO₂(*p*) 573, 594: PhNC(*p*) 574, 595: pyrid-3-yl 575, 596: pyrid-4-yl 576: fur-2-yl 577: quinolin-8-yloxymethylene 578: 8-methoxyquinolin-2-yl

R³
629, 642, 657: CH₂Ph 630, 643: CH₂PhF(*p*) 631, 644: CH₂PhCl(*p*) 632, 645: CH₂PhBr(*p*) 633, 646, 658: 1-naphthylmethylene
634, 647, 659: Ph 635, 648, 660: PhMe(*p*) 636, 649, 661: PhOMe(*p*) 637, 650, 662: PhCN(*p*) 638, 651, 663: PhF(*p*) 639, 652, 664: PhBr(*p*)
640, 653: fur-2-yl 641, 654: thien-2-yl 655: pyrid-4-yl 665: PhCl(*p*)

Scheme 9 Semisynthesis of fraxinellone derivatives. Reagents and conditions: (a) CrO_3 , Py, t-BuOOH, MW, 25 W, 25 h, 33 °C; (b) HOAc, hydrazides or hydrazines, reflux, 5-48 h; (c) $NH_2OH \cdot HCl$, EtOH, Py, 80 °C; (d) R^1CO_2H , DCC, DMAP, CH_2Cl_2 , r.t.; (e) $NaBH_4$, MeOH, 0-5 °C, 1.5 h; (f) R^2/R^3CO_2H , DIC, DMAP, r.t.; (g) SeO_2 , MW, 150 W, 2.5 h, 110 °C; (h) Lawessson's reagent, toluene, reflux, 12 h; (i) R^4COCl , R^4COCl ,

Table 1 14 most active limonoids against human cancer cell lines

Compounds	Cells	IC ₅₀ (μM)
1,2-Dihydrodeacetylhirtin 20	HL-60	4.9
(ref. 58)	SMMC-7721	3.1
,	A-549	2.9
	MCF-7	9.8
	SW480	9.0
α-Hydroxy-1,2-dihydrodeacetylhirtin 21	HL-60	3.1
ref. 58)	SMMC-7721	1.0
101. 30)	A-549	1.1
	MCF-7	
		1.0
	SW480	1.6
α-Methoxy-1,2-dihydrodeacetylhirtin 23	HL-60	5.3
ref. 58)	SMMC-7721	3.7
	A-549	5.2
	SMMC-7721	5.3
	A-549	6.4
Cipaferen E 37 (ref. 62)	B-16	8.51
runnanolide A 95 (ref. 75)	HL-60	3.6
,	SMMC-7721	2.4
	A-549	3.7
	MCF-7	4.2
	SW480	3.5
140 H	BEAS-2B	5.0
11β-Hydroxyisowalsuranolide 97	HL-60	3.1
ref. 75)	SMMC-7721	2.2
	A-549	2.6
	MCF-7	3.9
	SW480	2.4
	BEAS-2B	9.4
Walsuronoids D 127 (ref. 78)	HL-60	2.7
(1 1 2)	SMMC-7721	3.1
	A-549	4.1
	MCF-7	3.1
Walan and Ha P 420 (m. f. 70)	SW480	2.8
Valsuronoids E 128 (ref. 78)	HL-60	3.3
	SMMC-7721	4.1
	A-549	4.4
	MCF-7	4.4
	SW480	4.5
Coonaciliatones C 132 (ref. 80)	HL-60	5.38
, ,	HepG2	5.22
Coonasinenines B 139 (ref. 81)	A-549	5.7
roomasmenmes B 103 (rem 01)	CHG-5	5.0
	HCT15	5.7
	HeLa	6.2
	HepG2	5.5
	MDA-MB-231	6.0
	SGC-7901	6.0
Coonasinenines C 140 (ref. 81)	A-549	9.7
	CHG-5	8.3
	HepG2	9.1
	MDA-MB-231	9.4
	SGC-7901	9.4
oonasinenines D 141 (ref. 81)	A-549	2.3
oomonicimes D 141 (ici. 01)	CHG-5	2.8
	HCT15	2.6
	HeLa	2.9
	HepG2	3.0
	MDA-MB-231	2.7
	SGC-7901	2.1
Munronins A 188 (ref. 89)	HL-60	0.44
,	SMMC-7721	2.3
	A-549	1.6
	MCF-7	1.0

MCF-7

SW480

1.5

0.86

Table 1 (Contd.)

Compounds	Cells	IC_{50} (μM)
Perforanoid A 358 (ref. 117)	HEL K562 CB3	6.17 4.24 3.91

their analogs in each series against human cancer cell lines and insect pests were summarized in Tables 1 and 2, respectively.

 Table 2
 33 most active limonoids and their analogs as insecticidal agents

Compounds	Insect pests	FMRs (at 1 mg mL ⁻¹)
Cineracipadesin G 44	Drosophila	$AI^a = 32.8\%$ at 1 mM
(ref. 64)	melanogaster	(nicotine: AI =
,	· ·	28.5% at 1 mM)
Aphanamixoids C 286 (ref. 101)	Helicoverpa armigera	$EC_{50}^{\ \ b} = 9.27 \ \mu g \ cm^{-2}$
Aphanamixoids F 289 (ref. 101)		$EC_{50} = 4.28 \ \mu g \ cm^{-2}$
Aphanamixoids G 290		$EC_{50} = 6.82 \ \mu g \ cm^{-2}$
(ref. 101)		(neem oil: $EC_{50} =$
		2.62 μg cm ⁻²)
Flexuosoids A 354 (ref. 115)	Spodoptera exigua	$ED_{50}^{\ c} = 25.1 \ \mu g \ cm^{-2}$
Flexuosoids B 355		$ED_{50} = 17.3 \ \mu g \ cm^{-2}$
(ref. 115)		2250 — 17.0 pg cm
410 (ref. 123)	Pre-third-instar larvae	73.1% toosendanin:
110 (1011 120)	of Mythimna separata	50.0%
417 (ref. 123)	J	61.5%
431 (ref. 124)	Pre-third-instar larvae	63.0%
,	of M. separata	
472 (ref. 127)	Pre-third-instar larvae	62.1%
485 (ref. 127)	of M. separata	72.4%
486 (ref. 127)	•	65.5%
490 (ref. 127)		62.1%
566 (ref. 131)	Pre-third-instar larvae	63.0%
575 (ref. 131)	of M. separata	66.7%
578 (ref. 131)		63.0%
534 (ref. 132)	Pre-third-instar larvae	73.3%
552 (ref. 132)	of M. separata	70.0%
558 (ref. 132)		73.3%
59 7 (ref. 132)		66.7%
598 (ref. 132)		70.0%
600 (ref. 132)		66.7%
602 (ref. 132)		70.0%
535 (ref. 130)	Pre-third-instar larvae	76.9%
536 (ref. 130)	of M. separata	65.4%
537 (ref. 130)		69.2%
540 (ref. 130)		61.5%
603 (ref. 130)		65.4%
604 (ref. 130)		61.5%
606 (ref. 130)		73.1%
608 (ref. 130)		69.2%
612 (ref. 130)	Pre-third-instar larvae	61.5% 65.5%
662 (ref. 133)		

 $[^]a$ Antifeedant index: AI. b EC₅₀ value: the effective concentration for 50% feeding reduction. c ED₅₀ value: the effective dosage for 50% feeding reduction.

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Conclusions

However, the availability of limonoids is very limited from natural resources because of intensive collection of plants from the wild and long plant growth period. Although total chemical synthesis of limonoids remains a challenge of significant novelty and interest, it is not a practical option from a commercial point of view. Consequently, sustainable biotechnology and tissue culture techniques may be extensively exploited to enhance production of limonoids to meet the increasing demands. Additionally, to improve the water solubility and bioactivities, structural modifications of limonoids should be further strengthened.

In the present review, we summarised 363 new limonoid natural products isolated from plants during 2014-2016, together with their relevant biological activities and source organisms. Moreover, we highlighted recent developments in the total synthesis, and structural modifications of limonoids and their analogs regarding their bioactivities during 2011-2016. We hope that this review can provide necessary information for synthetic, medicinal and pesticidal chemistry, and phytochemistry researchers who are interested in the chemistry and biology of limonoids.

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