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Recent progress in the chemistry and biology of limonoids

Yuanyuan Zhang and Hui Xu *

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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] Tetranortriterpenoids 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. Limonoids are classified into different subcategories such as ring-intact limonoids, ring-*seco* limonoids, degraded limonoids, and highly oxidatively modified limonoids.[4] Limonoids exhibited a wide spectrum of biological properties including cytotoxic,[5–8] antioxidant,[9,10] antiinflammatory,[11,12] neuroprotective,[13,14] antiviral,[15] antimicrobial,[16,17] antiprotozoal,[18] antimalarial,[19–21] insect antifeedant,[22–26] and insecticidal activities.[27–29] The present review highlights the advances of limonoids in regard to isolation, total synthesis, and structural modifications with the relevant biological properties.

Research Institute of Pesticidal Design & Synthesis, College of Chemistry & Pharmacy, Northwest A&F University, Yangling 712100, Shaanxi Province, P. R. China. E-mail: orgxuhui@nwsuaf.edu.cn

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.[1] A comprehensive review of 'Meliaceous limonoids: chemistry and biological activities' has appeared in 2011.[4] Topics on the chemistry and pharmacological activities of some limonoids have also been presented.[30–35] In 2011, biosynthesis and total

Yuanyuan Zhang was born and raised in Shanxi Province, China. She received her BSc from Shanxi Agricultural University in 2015. In the same year, she joined Prof. Hui Xu's group to pursue her master studies at the College of Chemistry and Pharmacy, Northwest A&F University. Currently, she works in the semisynthesis of limonoids as insecticidal agents.

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.

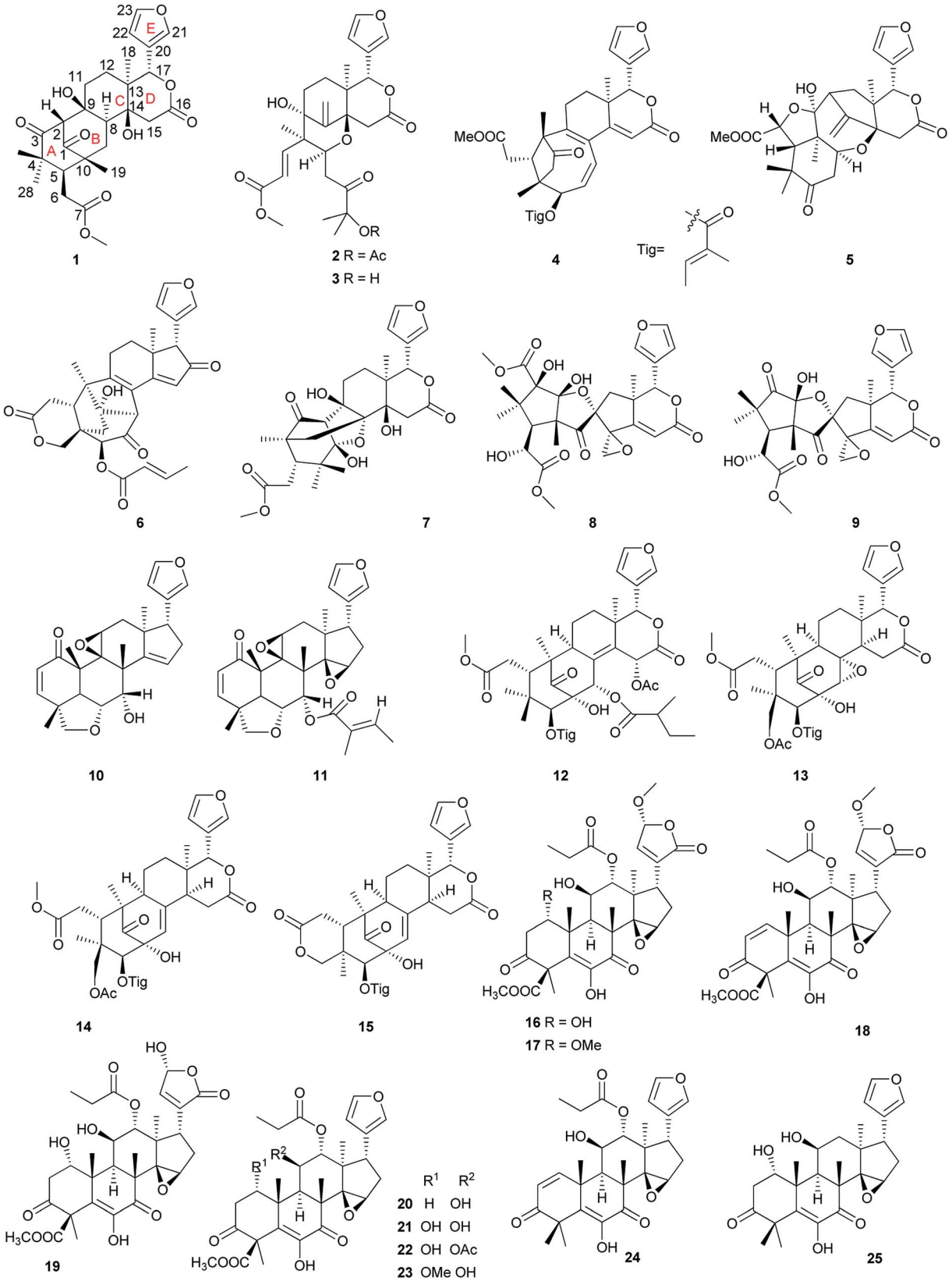

Fig. 1 Limonoids **1**–**25** from *Trichilia* genus.

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]

3. 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 CO_2 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 hydroxyazadiradione) 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

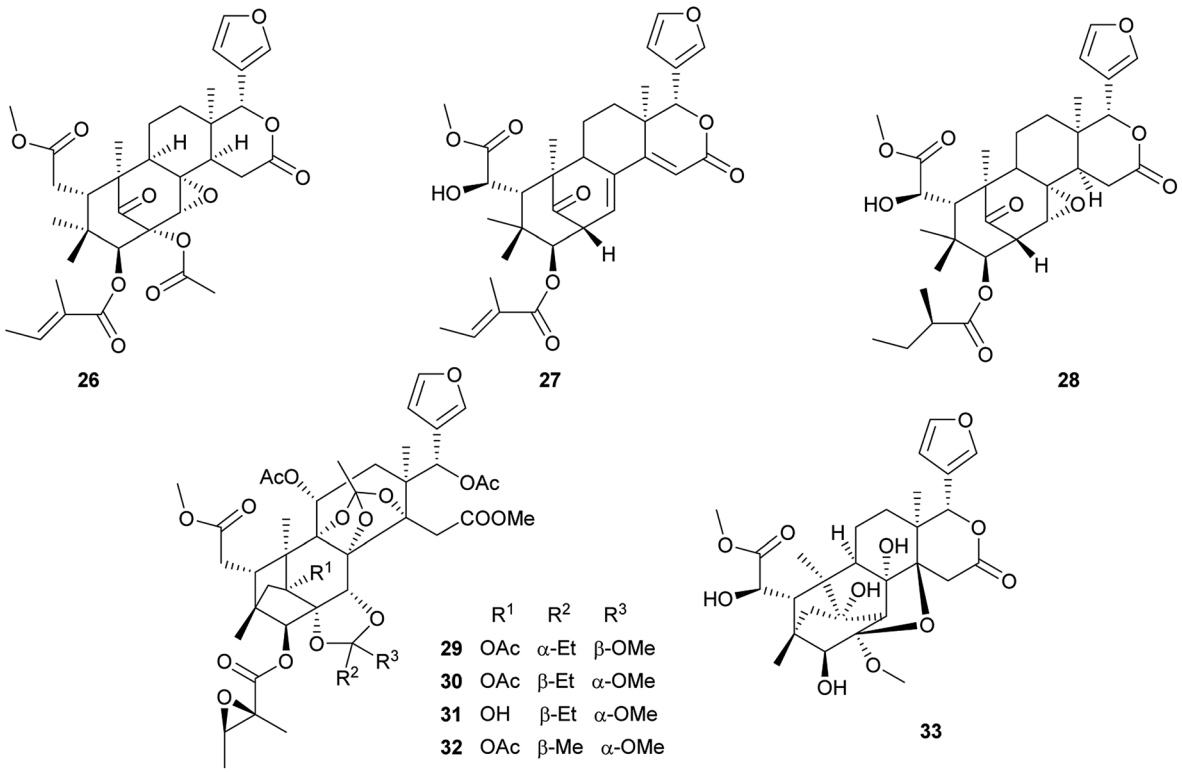

Fig. 2 Limonoids **26–33** from *Swietenia* genus.

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 μM, 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 μM. Compound **11** possessed the ability to induce

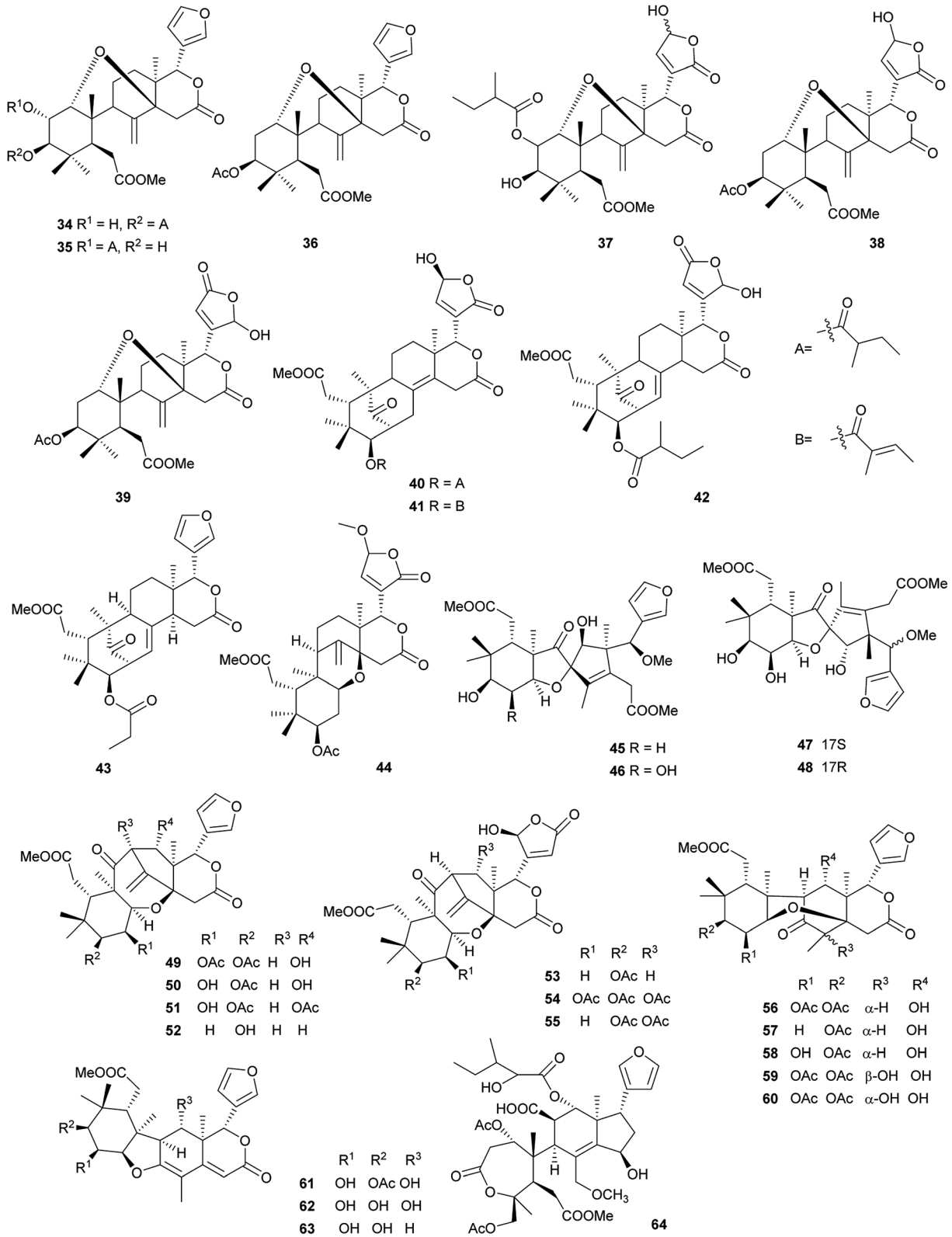

Fig. 3 Limonoids **34**–**64** from *Cipadessa* genus.

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

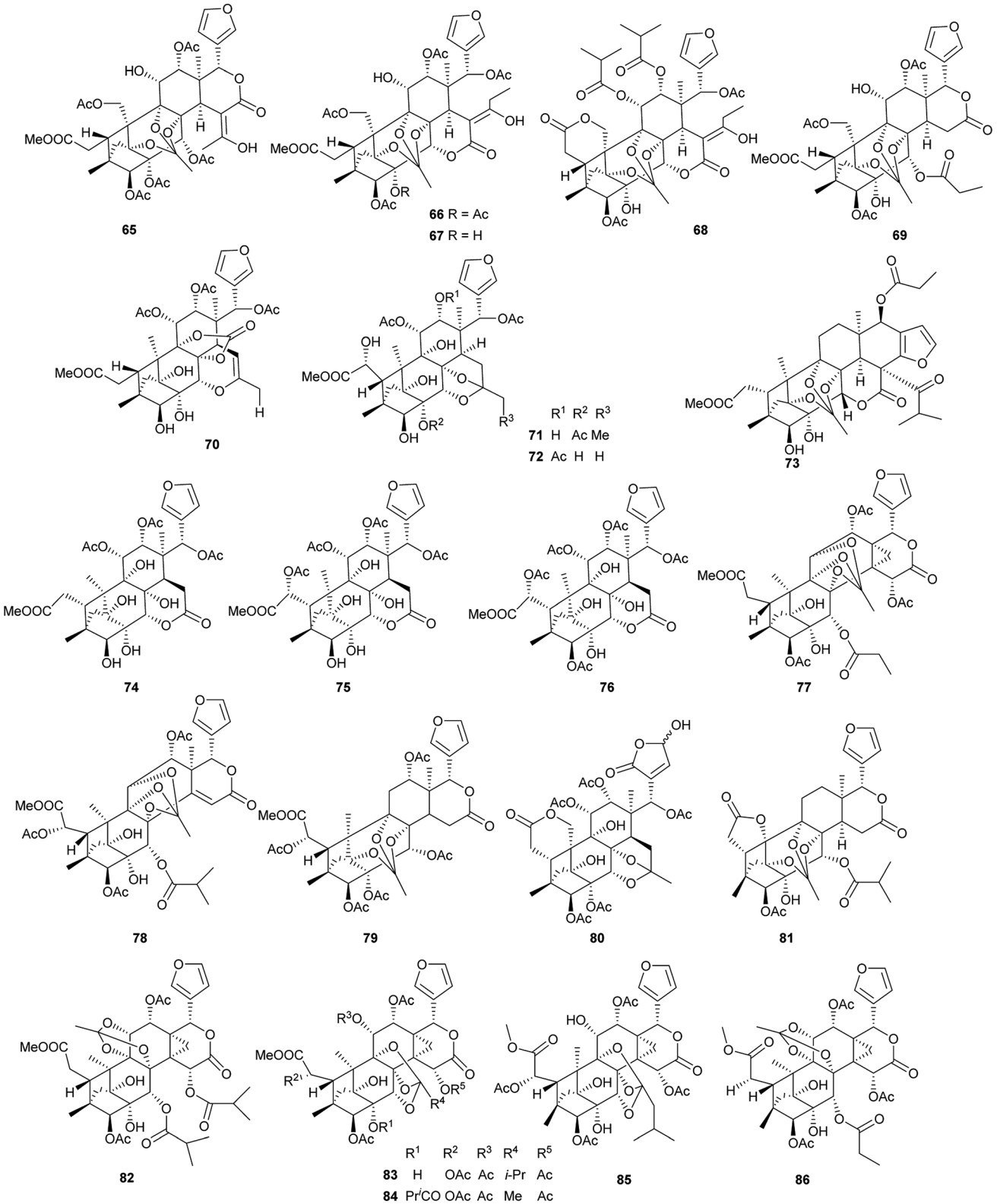

Fig. 4 Limonoids **65–86** from *Chukrasia* genus.

structure of **16** was determined by X-ray crystallographic studies. Compounds **20–25** exhibited potent or selective cytotoxic activities with IC_{50} values ranging from 1.0 to 39.6 μM 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, Bol*ivia* 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 (IC_{50}: 33.45 μM), and compound **28** exhibited significant antidengue virus 2 activity (EC_{50}: 7.2 μM).

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 A–G **49–55**,[66] cipadesin-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.[65] 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]

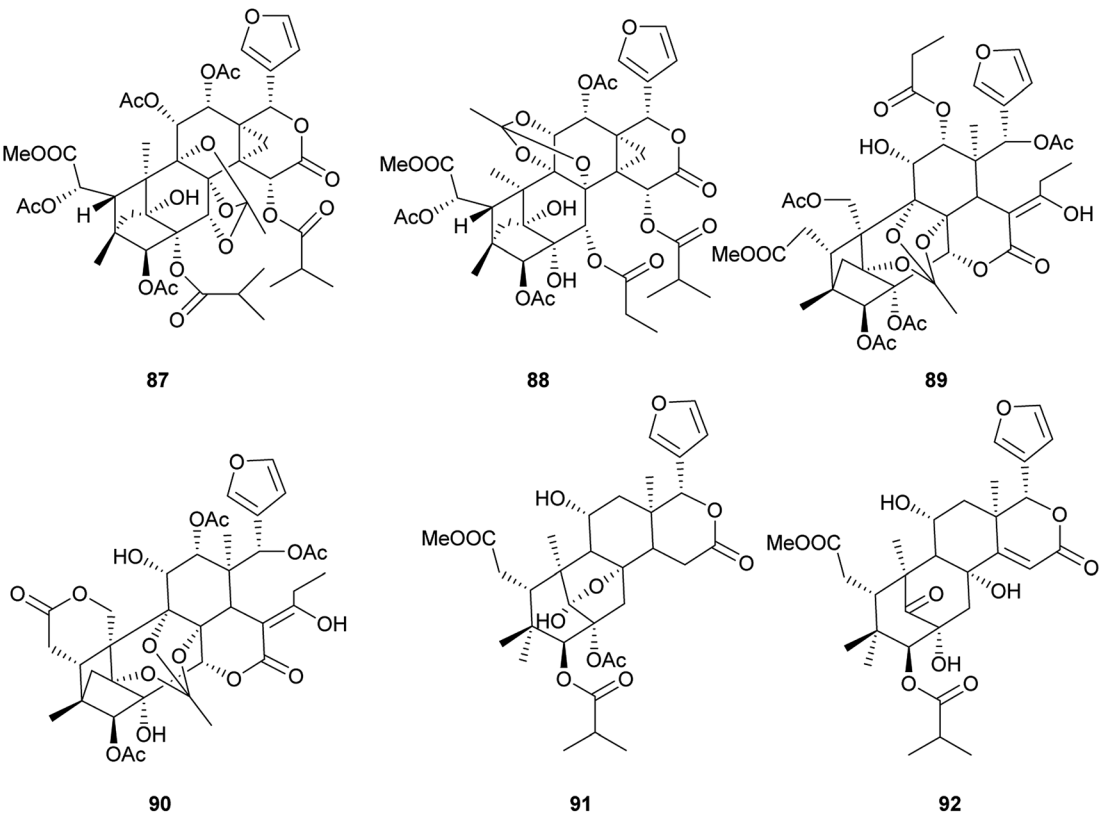

Fig. 5 Limonoids **87–92** from *Chukrasia* genus.

Compounds **81–84**, **86**, and **88** exhibited significant inhibitory activities against α-glucosidase *in vitro* with IC_{50} 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*-methyl-walsuranolide **94**, yunnanolide A **95**, yunnanol A **96**, 11β-

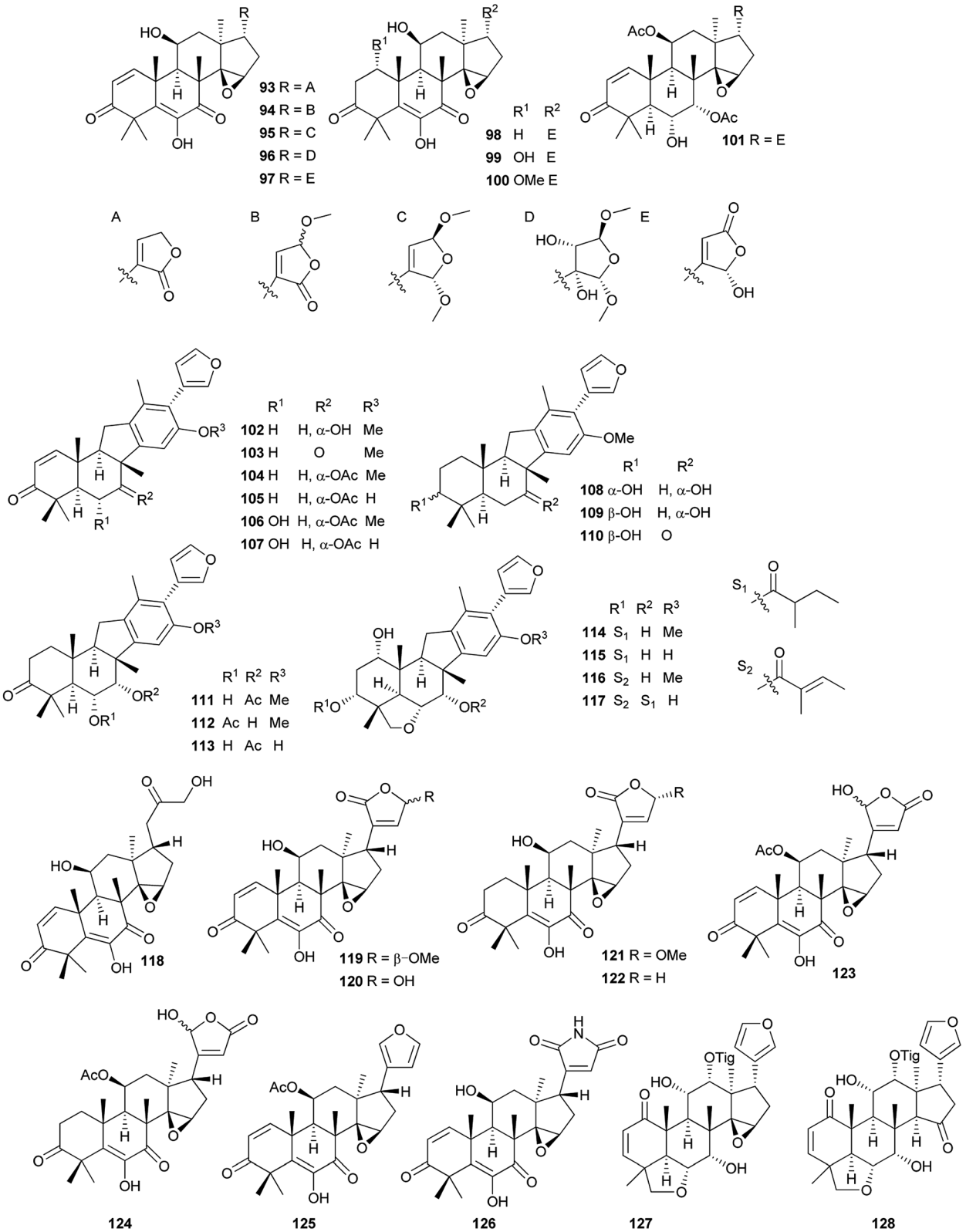

Fig. 6 Limonoids **93–128** from *Walsura* genus.

hydroxyisowalsuranolide **97**, 11β-hydroxy-1,2-dihydroisowalsuranolide **98**, 1α,11β-dihydroxy-1,2-dihydroisowalsuranolide **99**, 11β-hydroxy-1α-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.

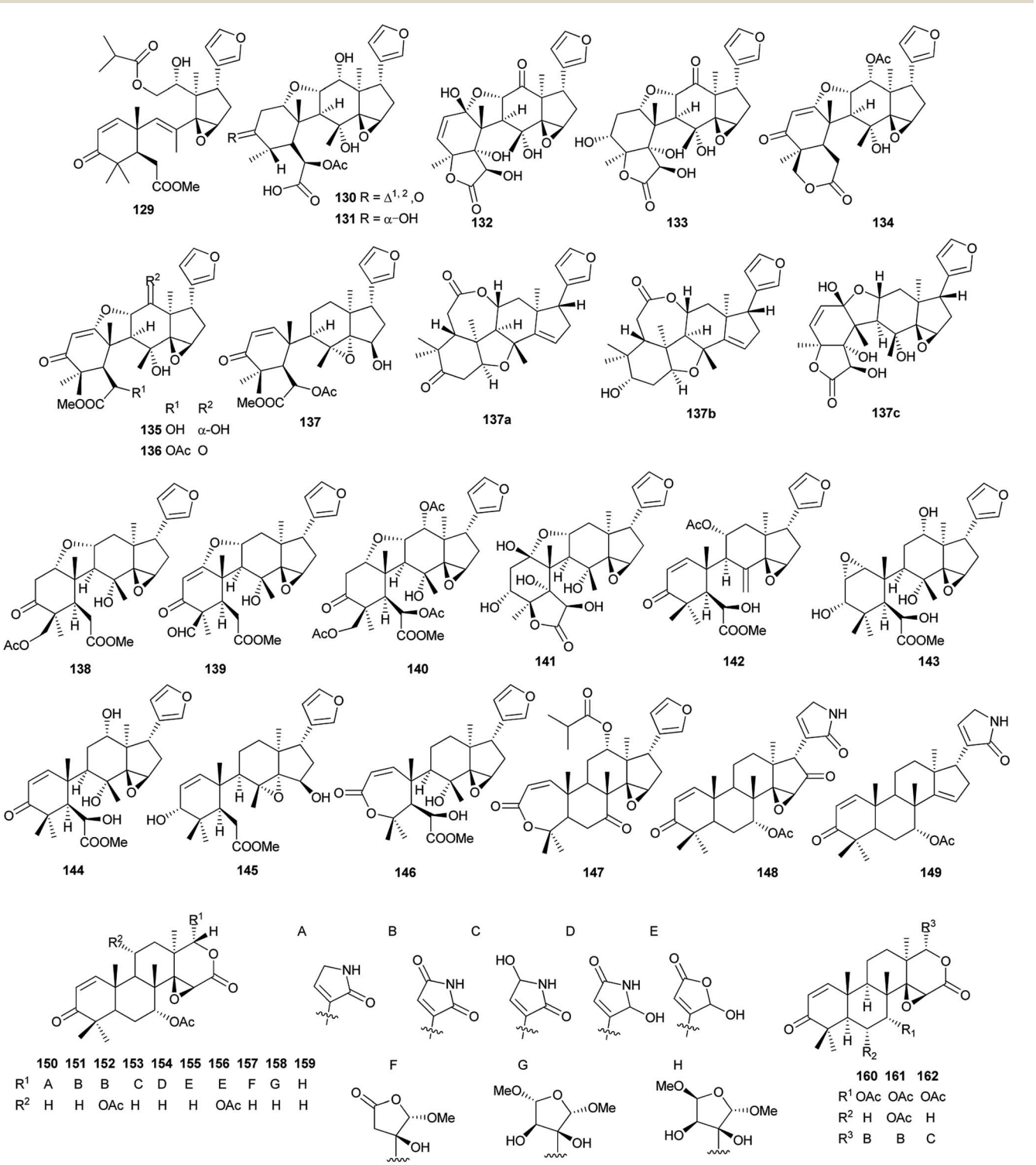

Fig. 7 Limonoids **129–162** from *Toona* genus.

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 IC_{50} values in the range of 2.2–4.5 μM.[75,78] Compounds **103** and **104** exhibited mild inhibitory activities against mouse and human 11β-HSD1 with IC_{50} values of 13.4 and 8.25 μM, respectively.[76]

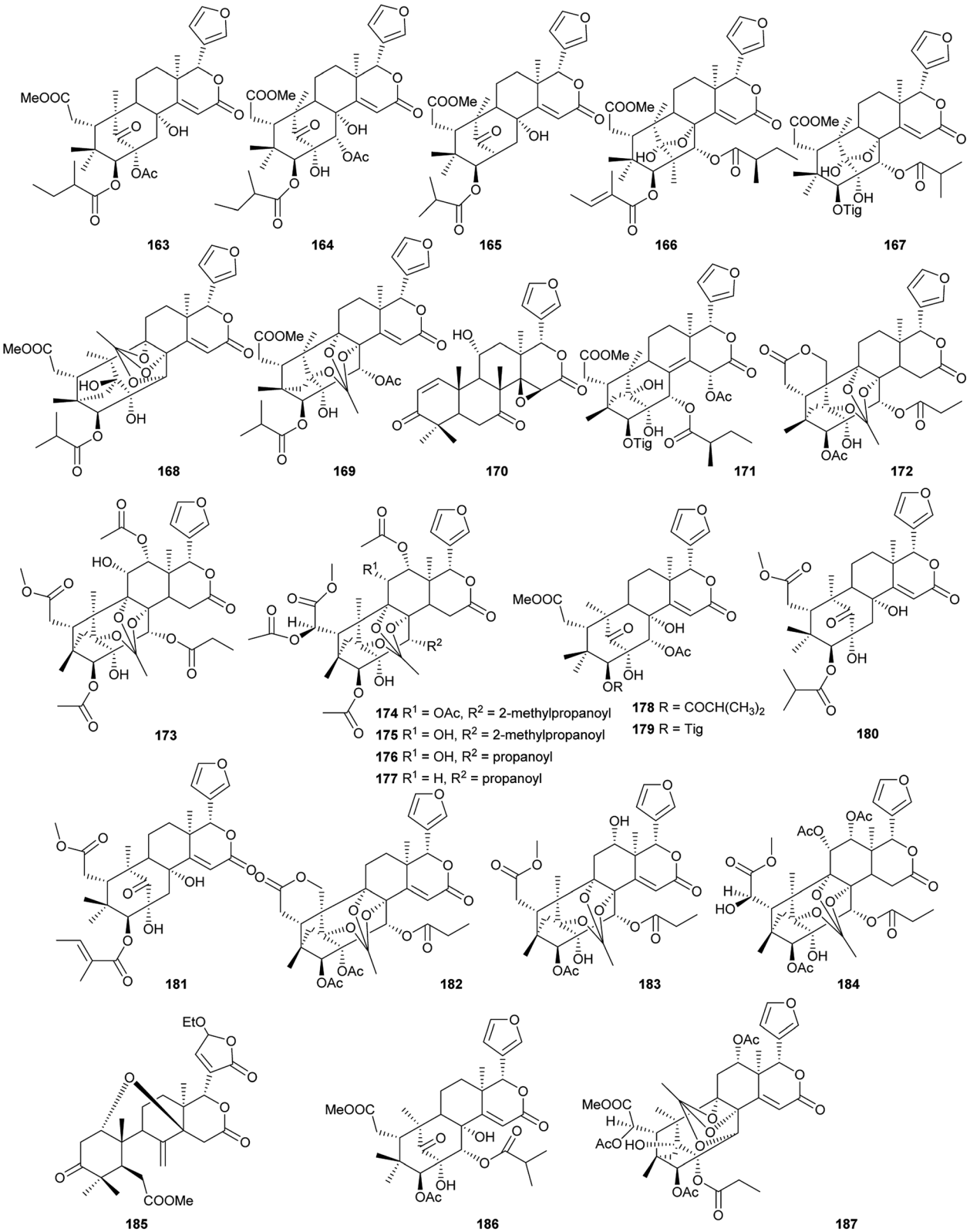

Fig. 8 Limonoids **163**–**187** from *Carapa* genus.

3.1.6. Toona. As shown in Fig. 7, a 9,11-*seco* limonoid (toonasecone A **129**),[79] four B-*seco*-29-nor-limonoids (toonaciliatones A–D **130–133**),[80] and seven B-*seco*-limonoids (toonaciliatones E–H **134–137**)[80a] and ciliatonoids A–C **137a–137c** (ref. 80*b*) 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.[80a] 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] Compound **160** was characterized by X-ray crystallographic analyses.[83]

Compound **132** exhibited modest cytotoxicity against HL-60 (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]

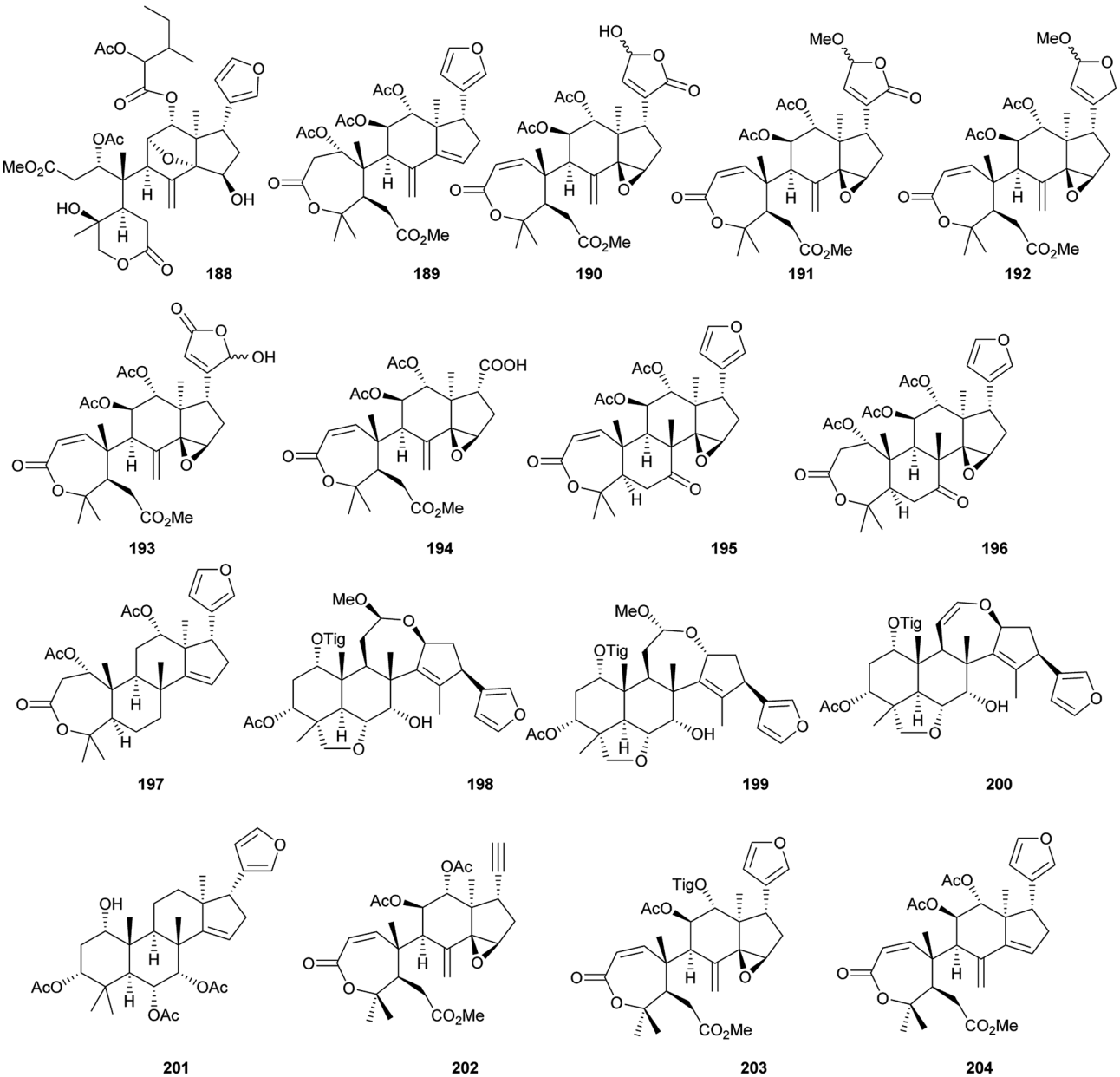

Fig. 9 Limonoids **188–204** from *Munronia* genus.

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 μM), **180** (IC_{50}: 22.0 μM), and **181** (IC_{50}: 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.[89] Interestingly, 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 IC_{50}

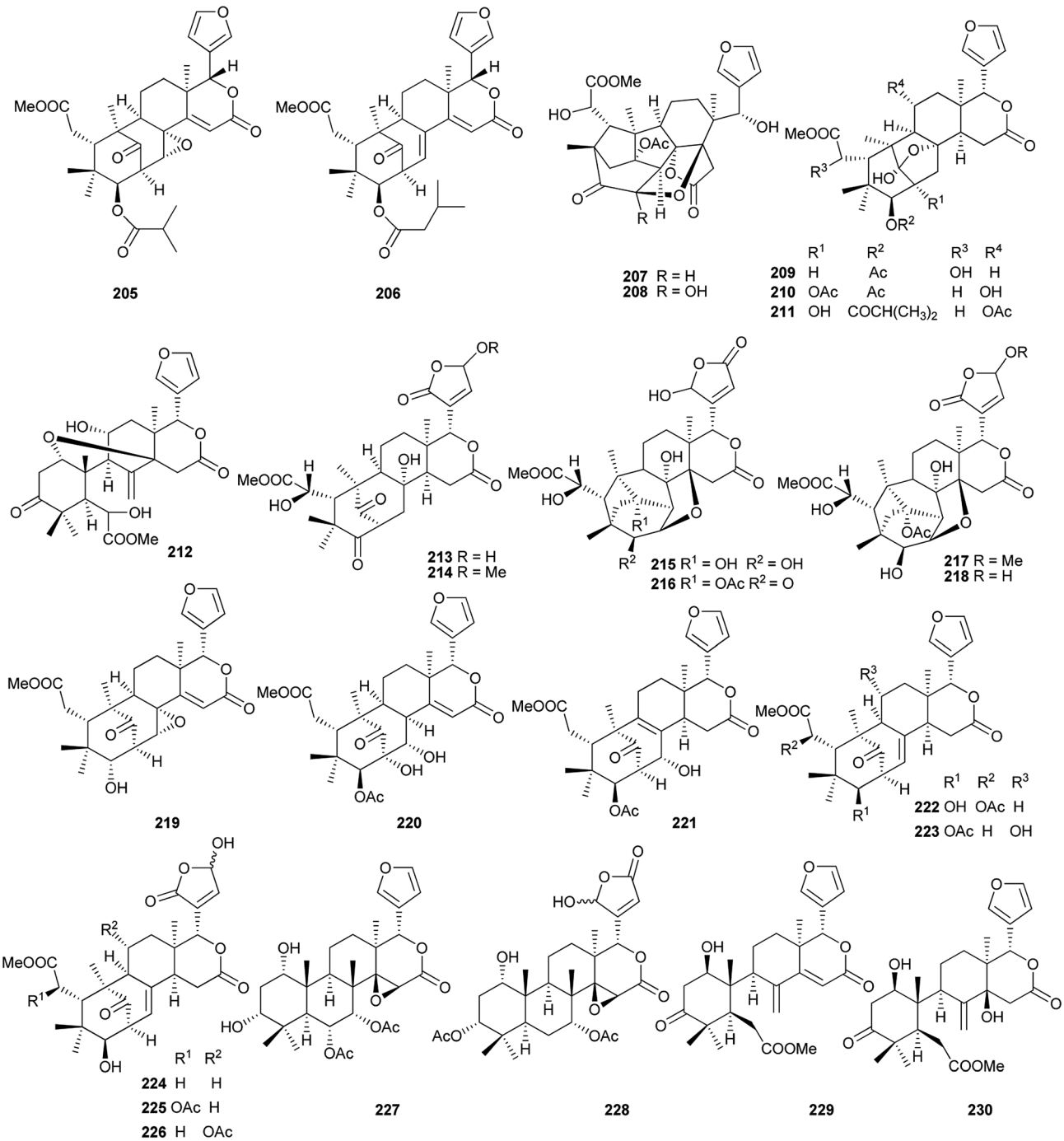

Fig. 10 Limonoids **205–230** from *Khaya* genus.

values in the range of 14.8–48.3 μg mL^{-1}.[89,90] Compound **188** (IC_{50} values: 0.44–2.3 μM) 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-didehydrorauageanin 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**

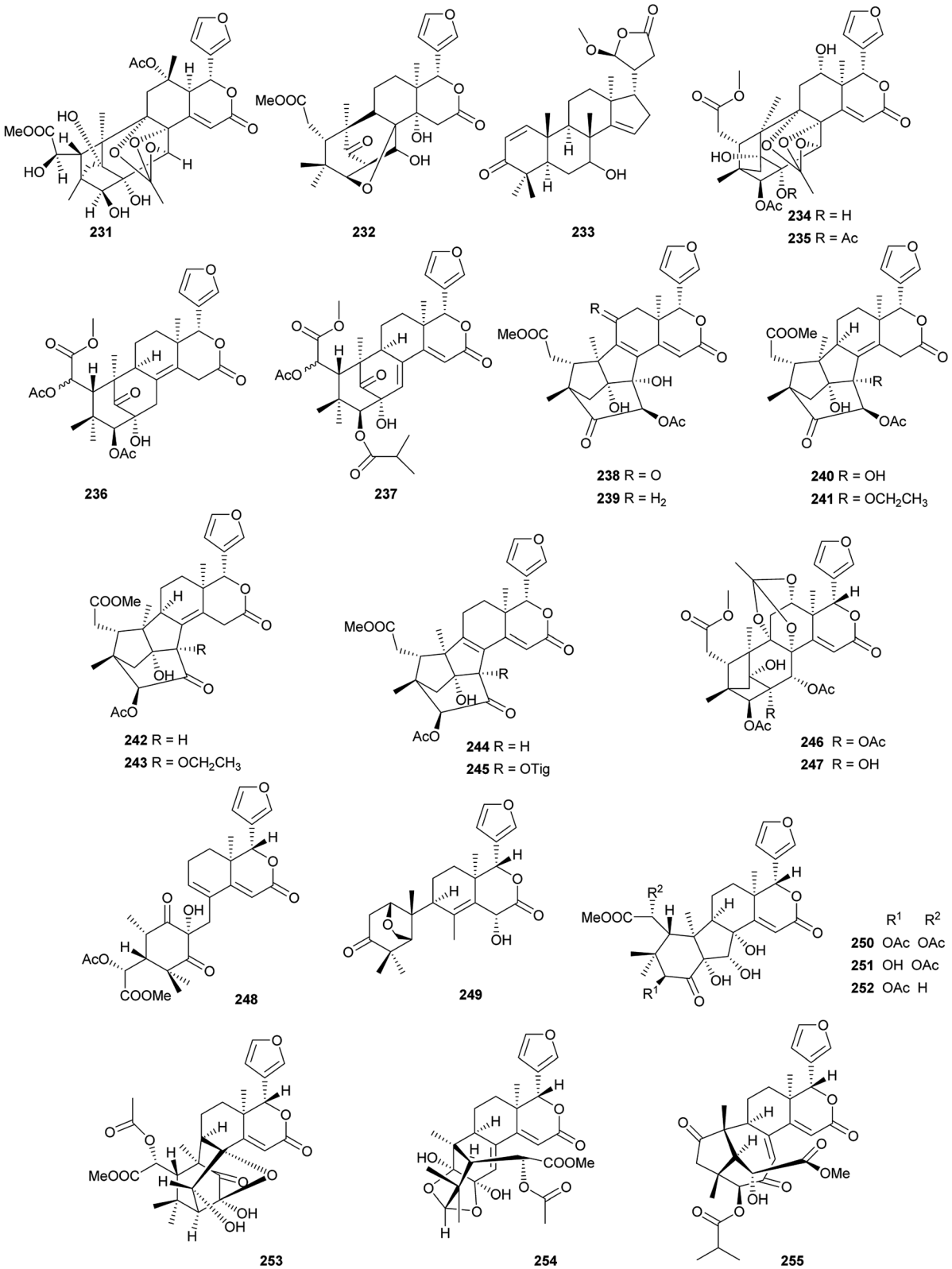

Fig. 11 Limonoids **231–255** from *Xylocarpus* genus.

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.

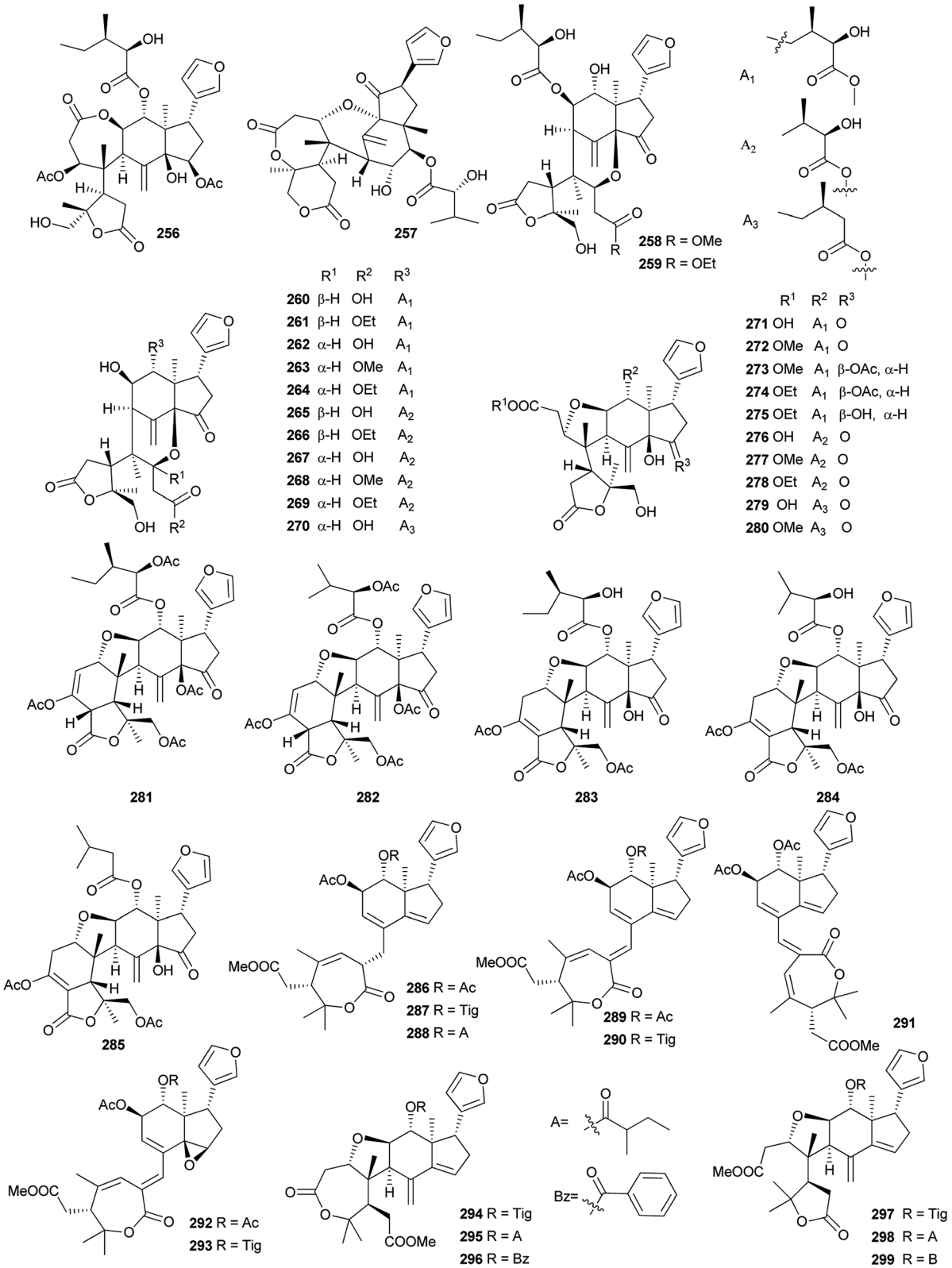

Fig. 12 Limonoids **256–299** from *Aphanamixis* genus.

Compounds **209** (IC_{50}: 15.3 μM) and **212** (IC_{50}: 17.5 μM) exhibited moderate cytotoxic activity against HL-60 cell line.[92] 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 μM and 80.3% at 1 μM.[94]

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 6-oxabicyclo[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 μM) 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 μM for each.[97]

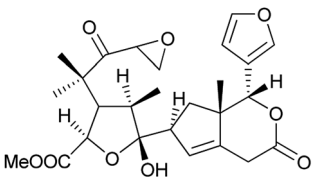

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Fig. 14 Chisotrijugin **312** from *Chisocheton* genus.

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 μmol cm^{-2}, respectively. Preliminary structure–activity relationship indicated that Δ (ref. 2 and 30)

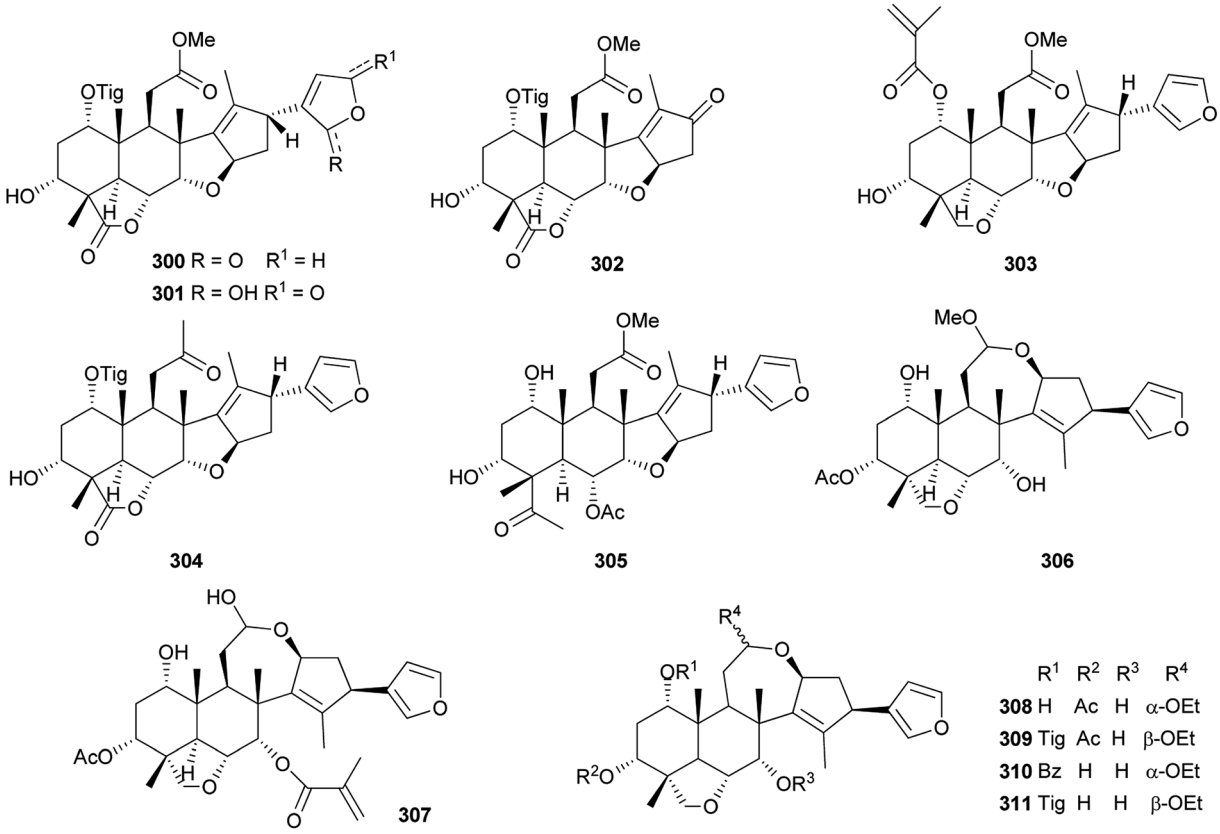


Fig. 13 Limonoids **300–311** from *Melia* genus.

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 μM) 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 μg 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;

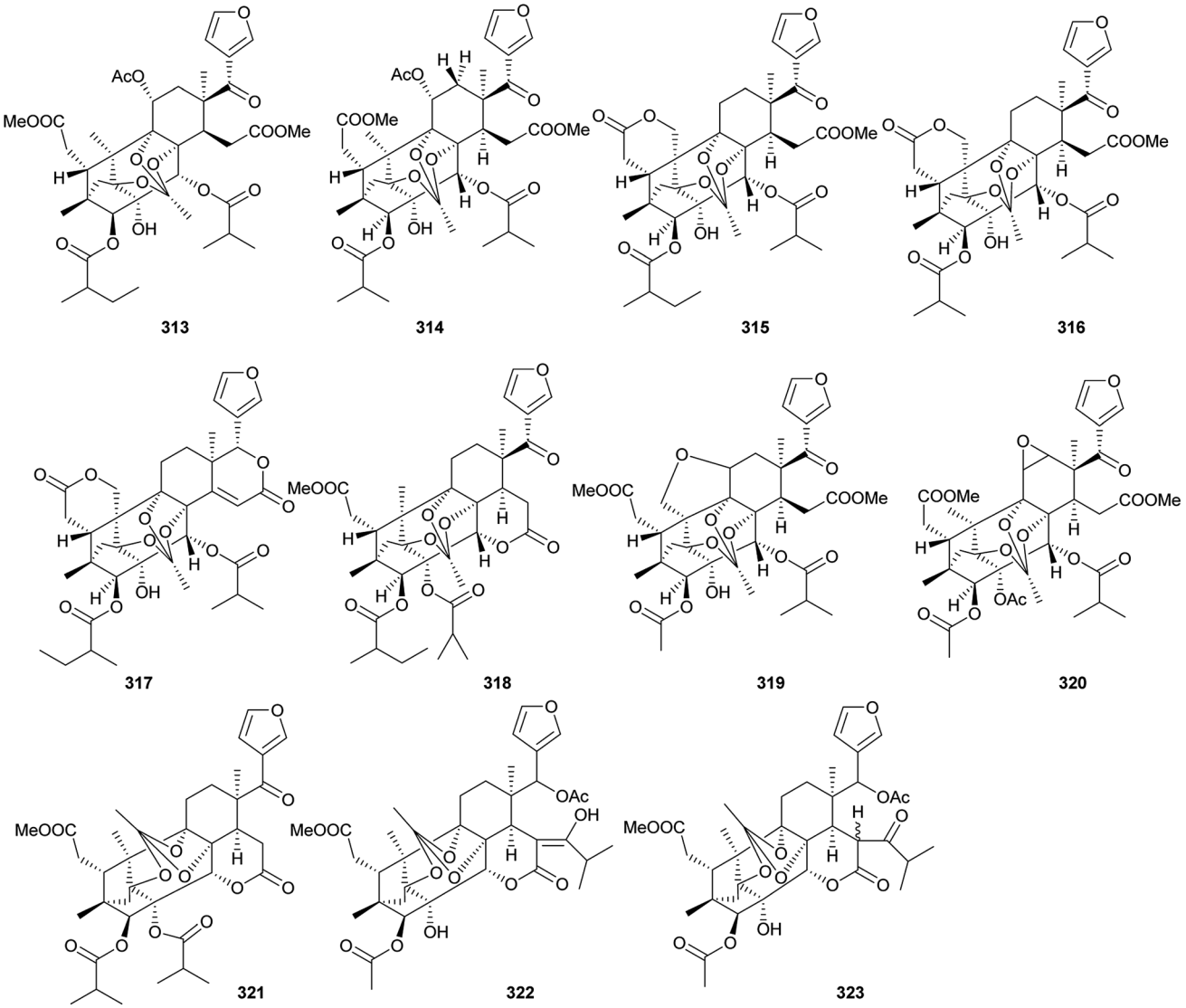


Fig. 15 Limonoids **313–323** from *Neobeguea* genus.

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.[110a] 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** (IC_{50}: 1.75 μM) and **334** (IC_{50}: 7.94 μM) 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]

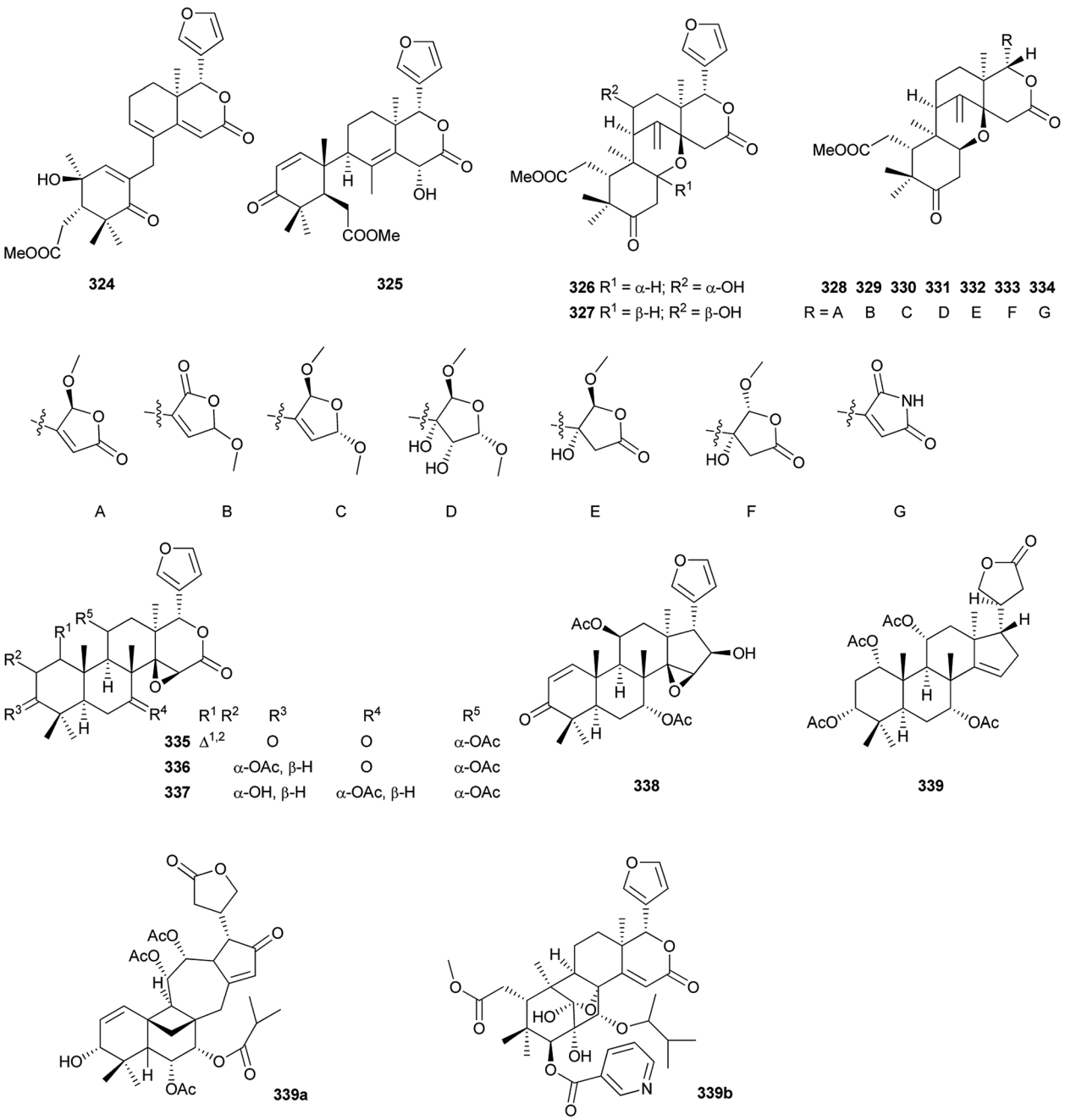
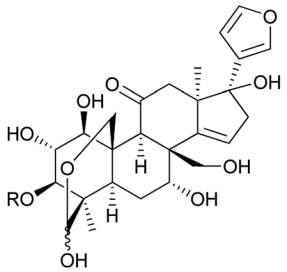


Fig. 16 Limonoids **324–339**, **339a**, and **339b** from *Entandrophragma* genus.

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 IC_{50} values lower than 25 μM.

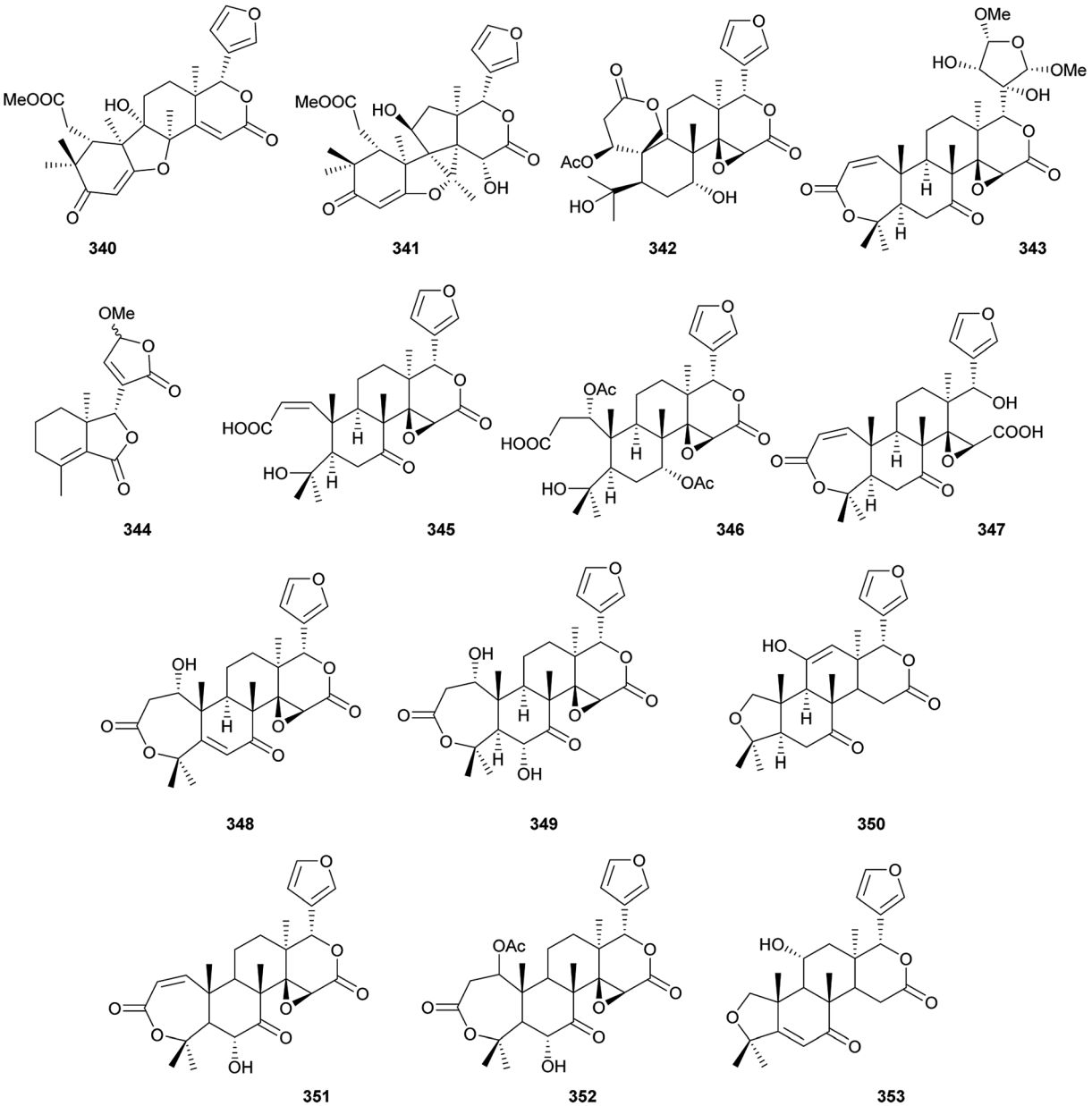
3.3. Euphorbiaceae

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,



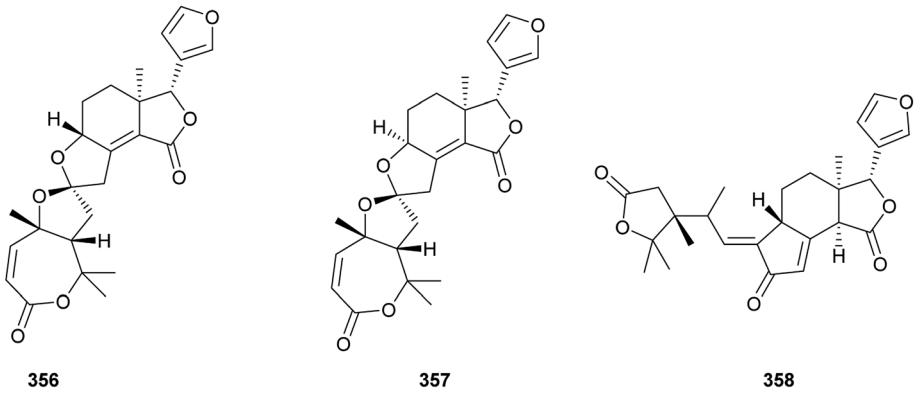
354 R = H
355 R = Ac

Fig. 18 Limonoids **354** and **355** from Euphorbiaceae family.



340 **341** **342** **343**
344 **345** **346** **347**
348 **349** **350**
351 **352** **353**

Fig. 17 Limonoids **340–353** from Rutaceae family.



356 357 358

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 EC_{50} values of 25.1 and 17.3 μg cm^{-2}, respectively. In addition, compounds **354** (IC_{50}: 11.5 μM) and **355** (IC_{50}: 8.5 μM) 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 IC_{50} 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 (IC_{50}: 4.24–25.96 μM).[117]

4. Total synthesis

4.1. Cipadonoid B

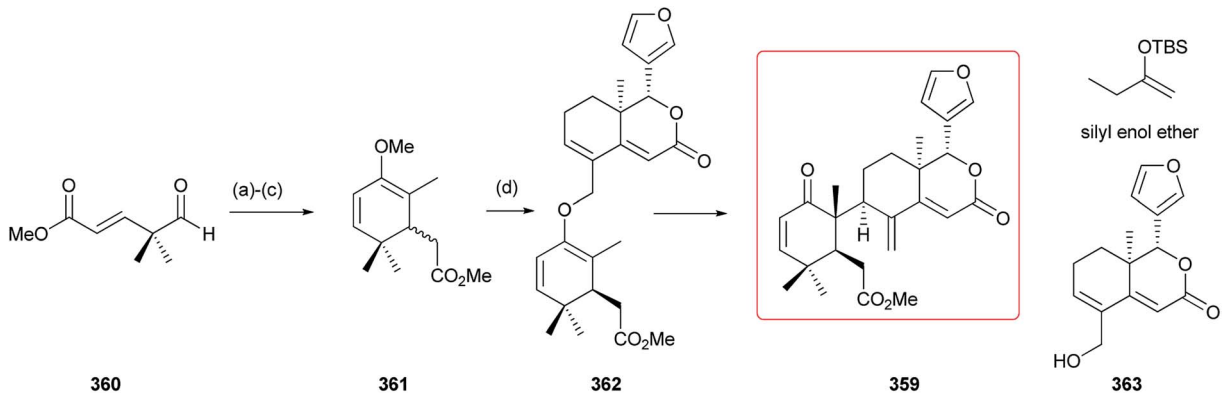
In 2011, an efficient strategy for the total synthesis of cipadonoid B **359** was reported (Scheme 1). First, compound **361** was prepared by reaction of silyl enol ether with **360.** Then, azedaralide **363** reacted with **361** *via* the intermediate **362**, to give **359** (20% yield) by a ketal-Claisen 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]

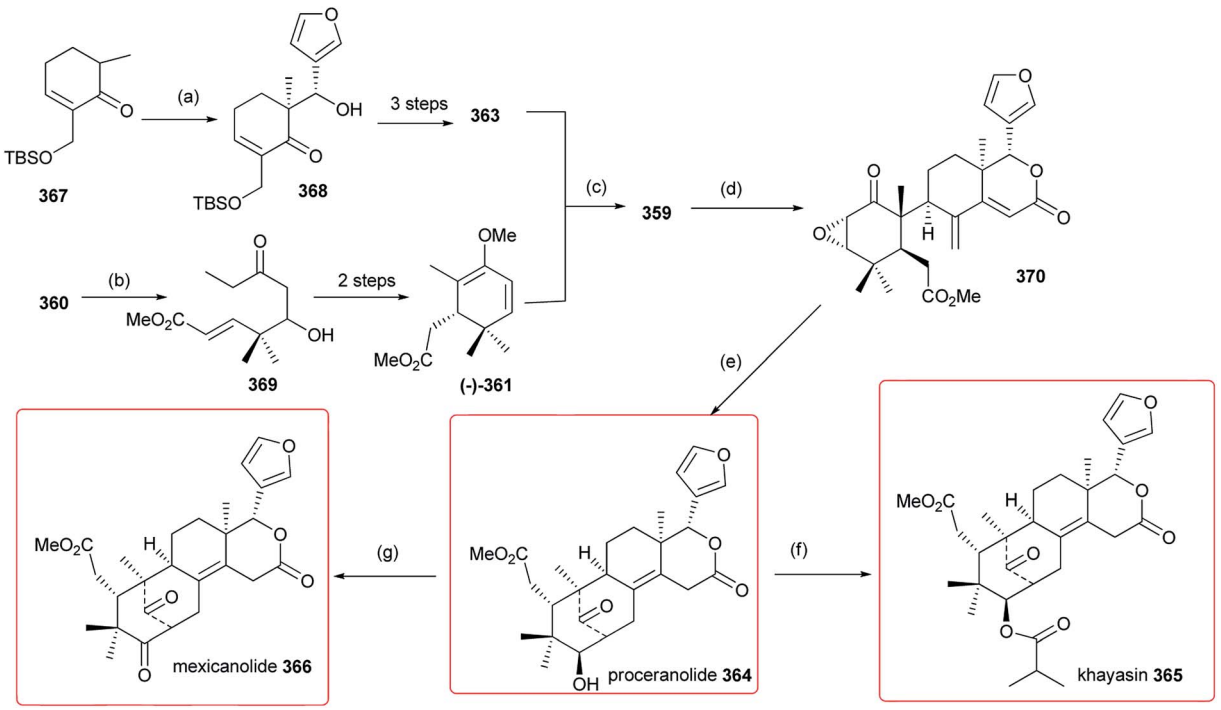
4.3. Limonin

As depicted in Scheme 3, Yamashita *et al.* described the total synthesis of (±)-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-13α 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

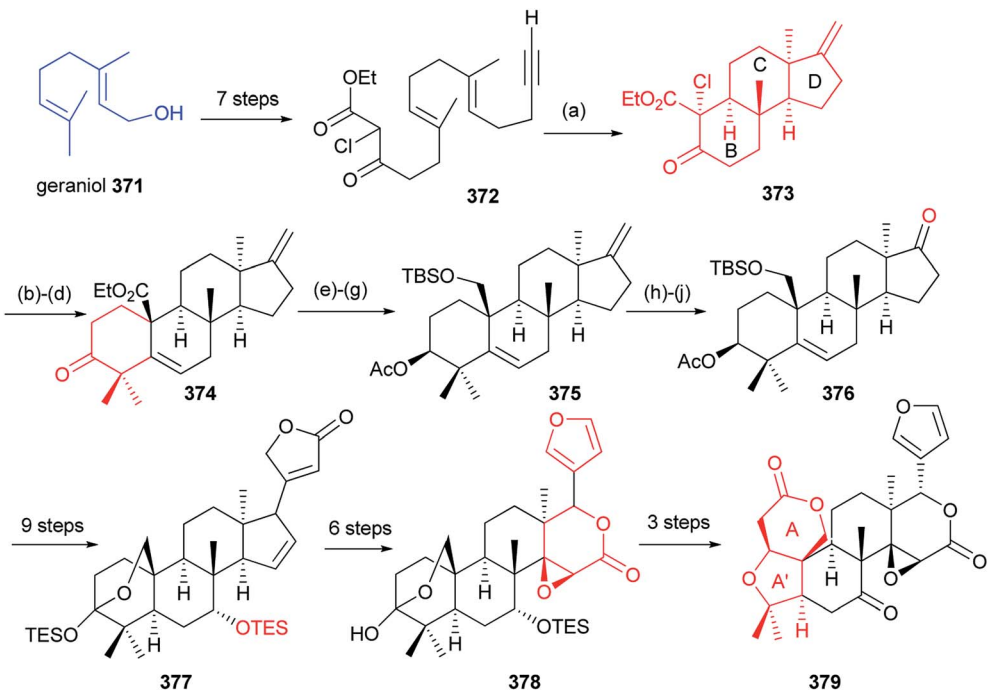


360 361 362 359 363

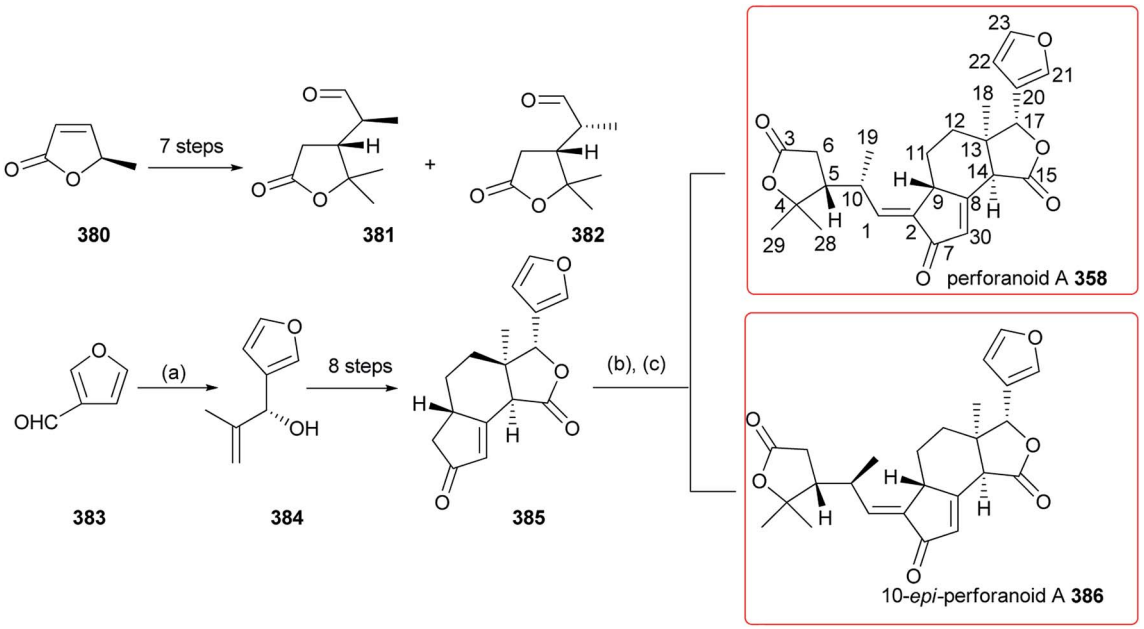
Scheme 1 Reagents and conditions: (a) silyl enol ether, $TiCl_4$, CH_2Cl_2, −78 °C; (b) KH, PhH; (c) MeOTf, CH_2Cl_2; (d) azedaralide **363**, PTSA, xylenes, 180 °C, 4 h.



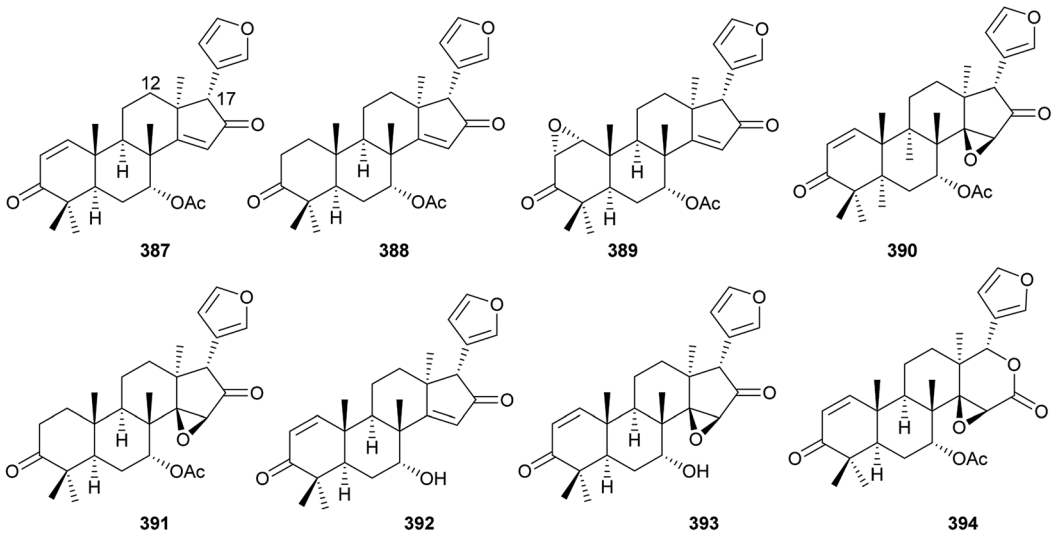
Scheme 2 Reagents and conditions: (a) (i) KHMDS, THF, −78 °C, then (−)-DIP-Cl, (ii) 3-furylaldehyde, 33–44% yield, 80–90% ee; (b) (+)-DIP-Cl, DIPEA, 2-butanone, Et_2O, −78 °C, then −105 °C to −30 °C, 16 h, 47% yield, 92.5% ee; (c) TsOH, xylenes, 180 °C, 4 h; (d) 30% H_2O_2, K_2CO_3, MeOH, 0 °C to r.t., 12 h, 75%; (e) Al/Hg, EtOH/THF/H_2O/$NaHCO_3$, r.t., 1 h, 30%; (f) isobutyric acid, EDCI, DMAP, CH_2Cl_2, 0 °C to r.t., 4 h, 71%; (g) $K_2Cr_2O_7$/H_2SO_4, Me_2CO, r.t., 15 min, 68%.



Scheme 3 Reagents and conditions: (a) $Mn(OAc)_3 \cdot 2H_2O$, EtOH, r.t.; (b) Zn, AcOH, r.t.; (c) MVK, *t*BuOK, *t*BuOH, 35 °C; (d) MeI, *t*BuOK, *t*BuOH, 40 °C; (e) $LiAlH_4$, THF, 0 °C to reflux; (f) TBSCl, NaH, THF, 0 °C to r.t.; (g) Ac_2O, pyridine, DMAP, CH_2Cl_2, r.t.; (h) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, −20 °C to −5 °C; (i) NaCN, DMSO, 120 °C; (j) Ac_2O, pyridine, DMAP, CH_2Cl_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 *M881*)	17β-Hydroxy (%)	12β-Hydroxy (%)
1	azadiradione **387**	61	38
2	1,2-dihydroazadiradione **388**	59	40
3	1,2α-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.

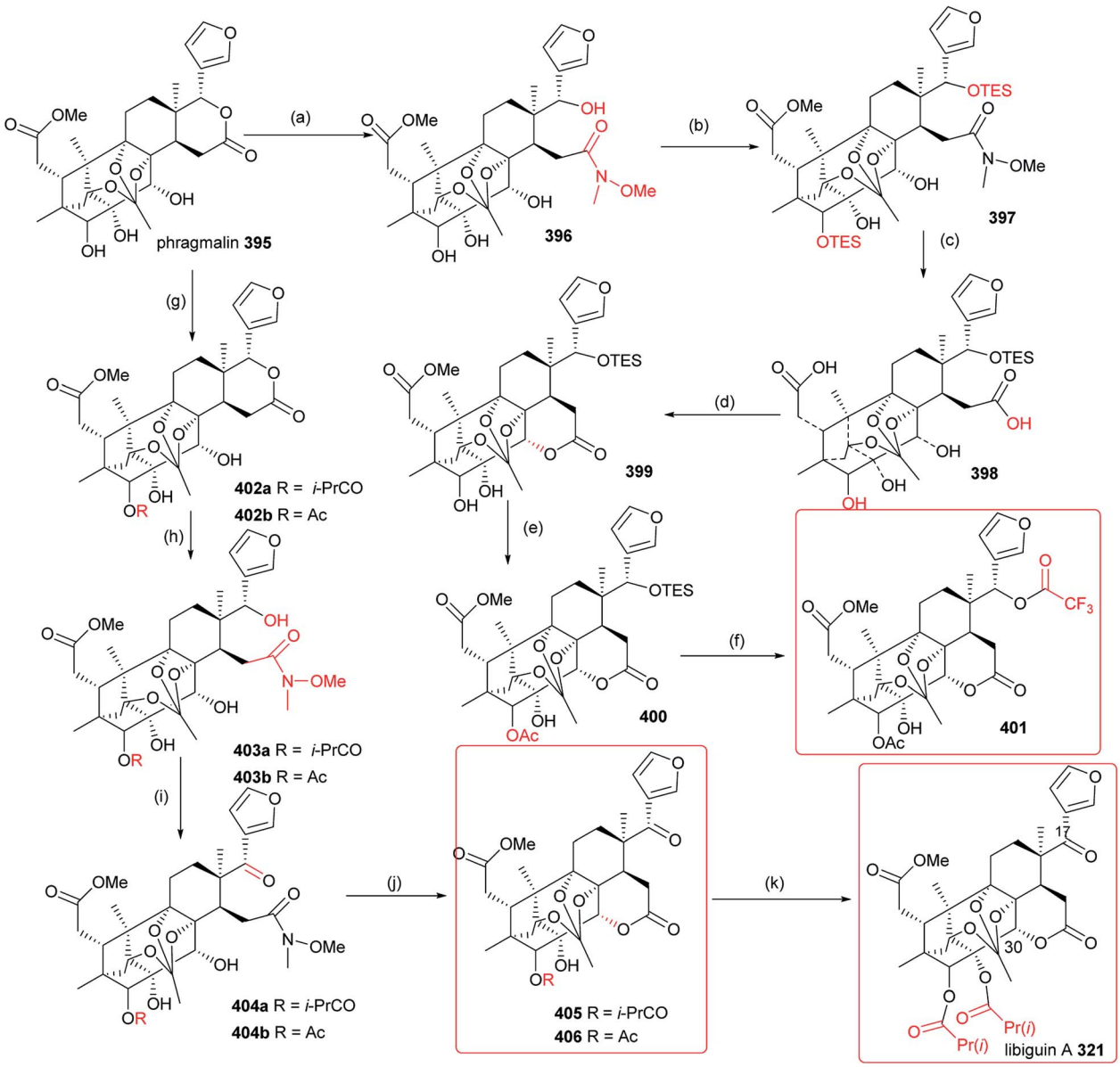
4.4. Perforanoid A and 10-*epi*-perforanoid A

More recently, as shown in Scheme 4, Hao *et al.* developed an efficient way to total synthesis of perforanoid A **358** and 10-*epi*-perforanoid 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.[117] Compound **358** showed potent cytotoxic activities against HEL, K562, and CB3 tumor cell lines with IC_{50} values of 6.17, 4.24, and 3.91 μM, respectively; in contrast, compound **386** did not display any cytotoxic activity.

5. 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 Me_3Al in Hex, CH_2Cl_2, r.t., 68%; (b) TESCl, imidazole, DMF, r.t.,79%; (c) 10 M aq. KOH, THF, r.t.; (d) EDCI, DMAP, MeOH, r.t., 63%; (e) Ac_2O, DMAP, CH_2Cl_2, r.t., 92%; (f) TFA, DMF, r.t., 78%; (g) Ac_2O or i-PrCOCl, Py, r.t.; (h) MeNHOMe·HCl, 2 M Me_3Al in Hex, CH_2Cl_2, r.t.; (i) Dess-Martin periodinane, CH_2Cl_2, r.t.; (j) TMSOTf, CH_2Cl_2, r.t.; (k) for **405**, i-butyric anhydride, TMSOTf, CH_2Cl_2, r.t.

compounds with the advantages of strict stereo- and region-selectivity, mild reaction conditions and simple operation procedure. As shown in Fig. 20, 8 limonoids including azadiradione **387**, 1,2-dihydroazadiradione **388**, 1,2α-epoxyazadiradione **389**, epoxyazadiradione **390**, 1,2-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

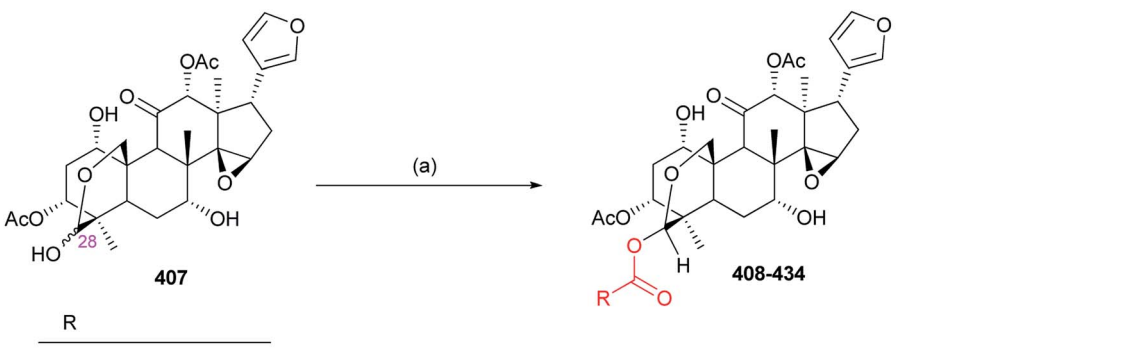
5.2.1. Phragmalin. As depicted in Scheme 5, starting from phragmalin **395** isolated from the seeds of *C. tabularis*, libiguin A **321** and its analogs **401**, **405** and **406** were efficiently obtained by structural modification. This was based on selective aminolysis of the lactone in **395** 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.

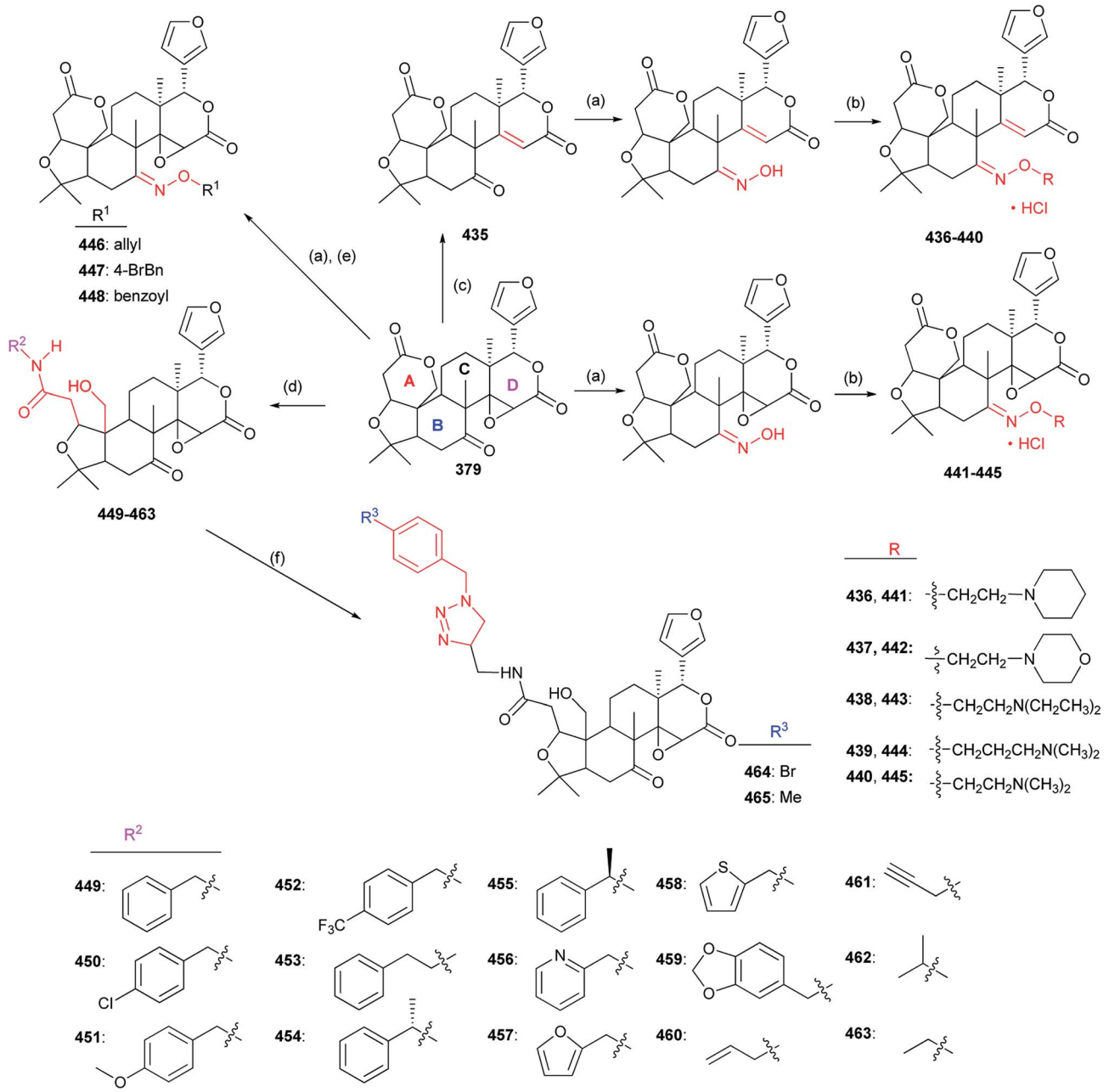
5.2.4. Obacunone. As depicted in Scheme 8, we semi-synthesized a series of obacunone (**466**) derivatives, including C7-oxime esters **468–491**, C7-oxime sulfonate esters **492–497**, and C7-esters **500–532**.[127–129] The structures of **480**, **485**, **486**, **498**, **499**, and **518** were unambiguously determined by single-crystal X-ray diffraction. Interestingly, when compound **466** was reduced by $NaBH_4$, 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**: $PhNO_2$(*p*)
417: CH=CHPh **418**: $PhCH_2CH_2$ **419**: CH_2Ph **420**: $ClCH_2$ **421**: $CH=CH_2$ **422**: $(CH_3)_2CH$ **423**: $C(CH_3)=CH_2$
424: $CH_3(CH_2)_3$ **425**: $(CH_3)_2CHCH_2$ **426**: $CH_3(CH_2)_4$ **427**: $CH=CHCH=CHCH_3$ **428**: $CH_3(CH_2)_5$ **429**: $CH_3(CH_2)_6$
430: $CH_3(CH_2)_9$ **431**: $CH_3(CH_2)_{10}$ **432**: (*Z*)-$CH_3(CH_2)_7CH=CH(CH_2)_7$ **433**: $CH_3(CH_2)_7OCO(CH_2)_6$ **434**: $CH_3(CH_2)_7OCO(CH_2)_8$

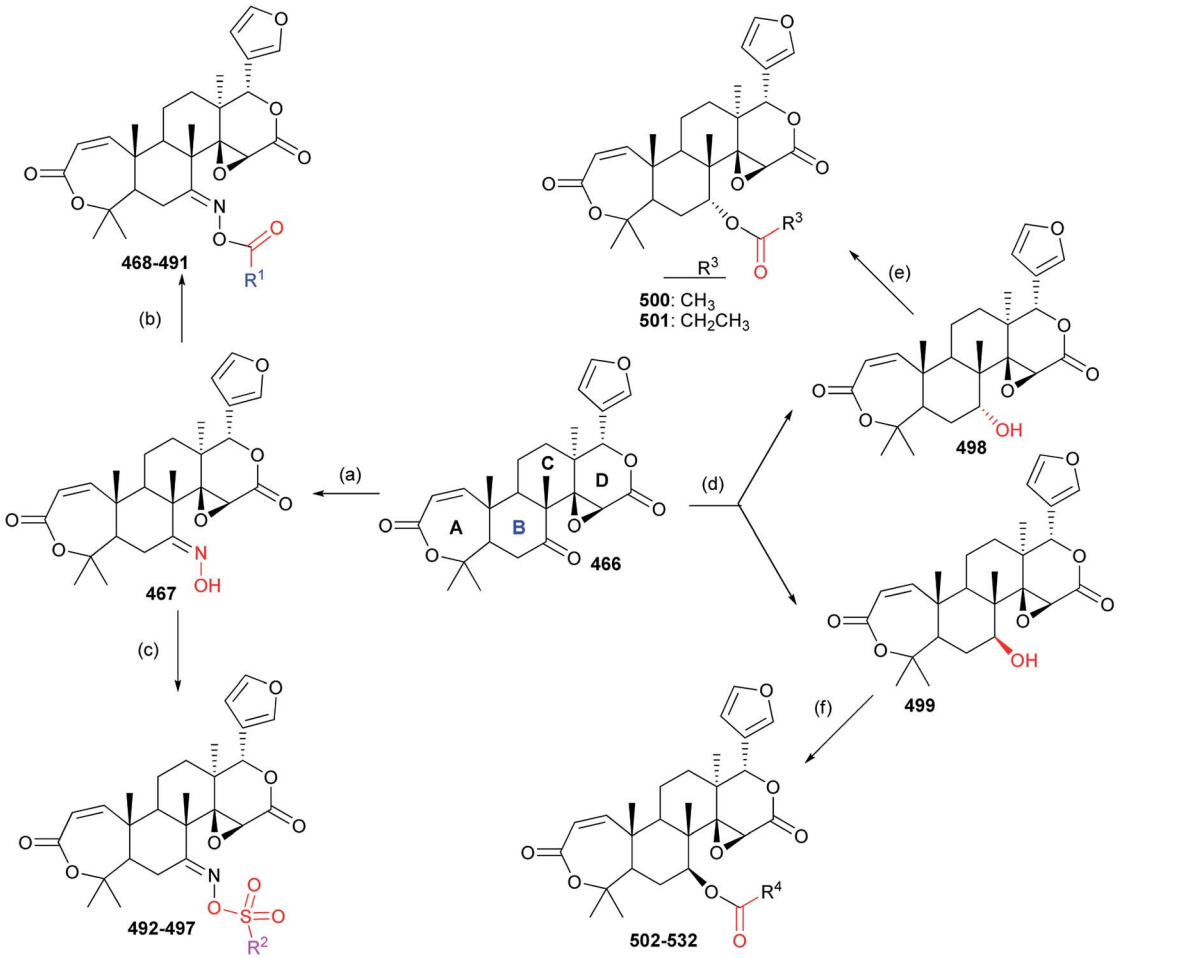
Scheme 6 Semisynthesis of a series of 28-acyloxytoosendanin derivatives. Reagents and conditions: (a) $(RCO)_2O$/NaOAc/acetone/reflux, 10–20 h; or RCO_2H/DIC/DMAP/CH_2Cl_2/r.t., 6–12 h, 14–88%.



Scheme 7 Semisynthesis of limonin derivatives. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, pyridine, EtOH, reflux; (b) (i) RCl, NaOH, TBAB, dry THF, 80 °C; (ii) HCl, dry ether, CH_2Cl_2; (c) HI, HOAc; (d) condition (i): abs. EtOH, appropriate amine, montmorillonite K-10, microwave-assisted; condition (ii): abs. EtOH, appropriate amine, montmorillonite K-10, reflux; condition (iii): CH_2Cl_2, appropriate amine, montmorillonite K-10, ultrasonic bath; (e) R^1Br or R^1Cl, NaH, DMF, 0 °C to r.t.; (f) for **461**, sodium ascorbate, $Cu(OAc)_2.H_2O$, THF : H_2O (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;



R^1

468: CH_3 **469**: CH_2CH_3 **470**: $(CH_2)_2CH_3$
471: $(CH_2)_3CH_3$ **472**: $(CH_2)_4CH_3$
473: $(CH_2)_5CH_3$ **474**: $(CH_2)_6CH_3$
475: $(CH_2)_8CH_3$ **476**: $(CH_2)_9CH_3$
477: $(CH_2)_{14}CH_3$ **478**: $(CH_2)_{16}CH_3$ **479**: Ph
480: PhMe(*m*) **481**: PhMe(*p*)
482: PhOMe(*p*) **483**: $PhNO_2$(*m*)
484: PhF(*m*) **485**: PhCl(*o*) **486**: PhCl(*m*)
487: PhBr(*m*) **488**: Bn **489**: 1-naphthylmethylene
490: pyrid-3-yl **491**: pyrid-4-yl

R^2

492: Me
493: Ph
494: PhMe(*p*)
495: PhEt(*p*)
496: PhCl(*p*)
497: PhBr(*p*)

R^4

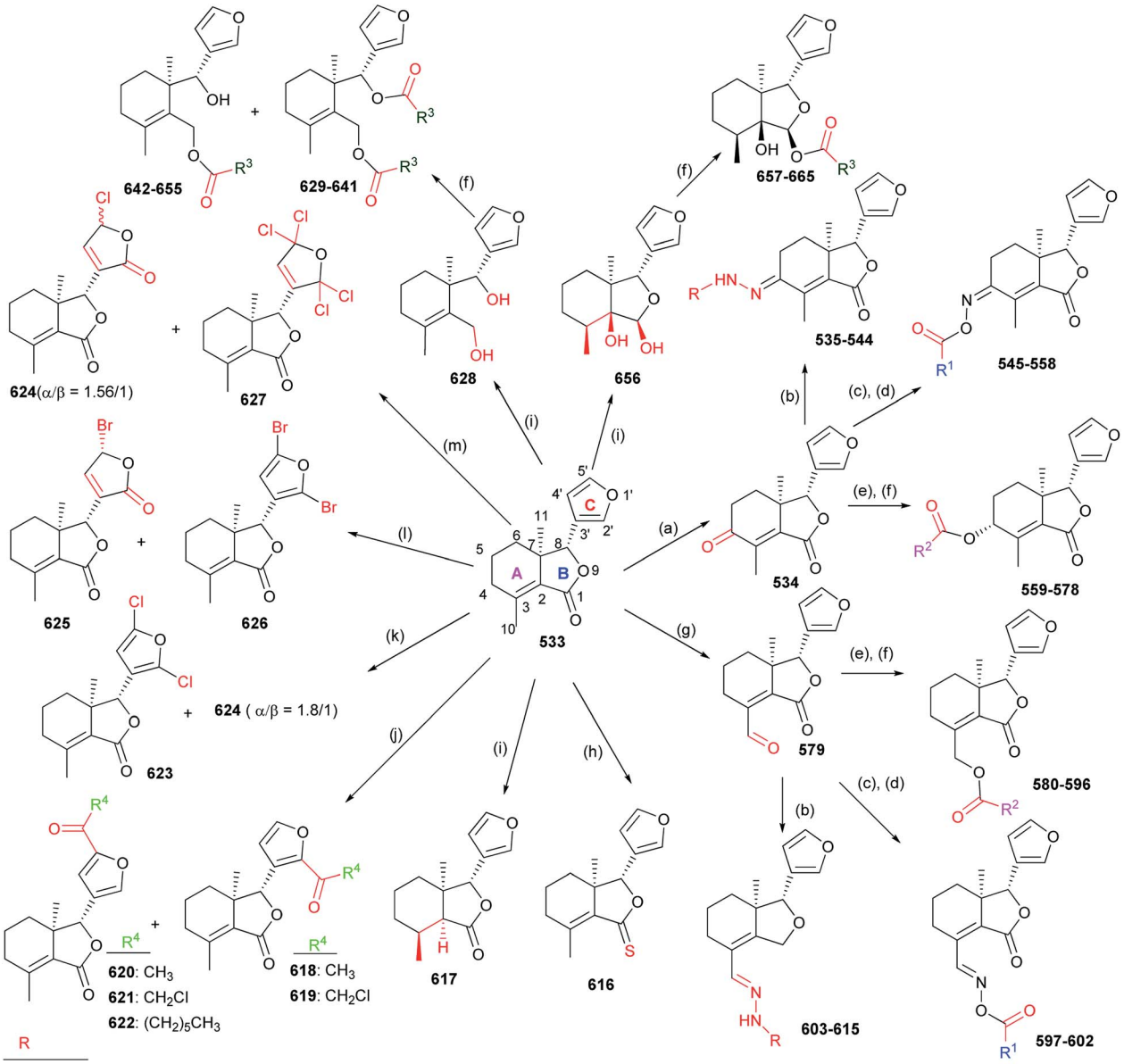
502: CH_3 **503**: CH_2Cl **504**: CH_2CH_3 **505**: $(CH_2)_2CH_3$
506: $(CH_2)_3CH_3$ **507**: $(CH_2)_4CH_3$ **508**: $(CH_2)_5CH_3$
509: $(CH_2)_6CH_3$ **510**: $(CH_2)_8CH_3$ **511**: $(CH_2)_9CH_3$
512: $(CH_2)_8CH{=}CH_2$ **513**: $(CH_2)_{10}CH_3$ **514**: $(CH_2)_{14}CH_3$
515: $(CH_2)_{16}CH_3$ **516**: Ph **517**: PhMe(*m*)
518: PhCHO(*p*) **519**: $PhNO_2$(*m*) **520**: 2,4-dinitrophenyl
521: PhF(*m*) **522**: PhCl(*o*) **523**: PhCl(*m*) **524**: PhBr(*o*)
525: PhBr(*m*) **526**: Bn **527**: BnBr(*p*) **528**: CH_2CH_2Ph
529:-CH=CHPh **530**: 1-naphthylmethylene
531: pyrid-3-yl **532**: pyrid-4-yl

Scheme 8 Semisynthesis of B-ring modified obacunone derivatives. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$/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) $NaBH_4$; (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



R

535,**603**: COPh **536**,**604**: COPhNO$_2$(*p*) **537**,**605**: COPhCl(*m*) **538**,**606**: 4-pyridylcarbonyl **539**,**607**: 3-thienylcarbonyl **540**,**608**: COCH$_2$CN **541**,**609**: Ph **542**,**610**: PhNO$_2$(*p*) **543**,**611**: PhNO$_2$(*o*) **544**,**612**: 2,3,5,6-tetrafluorophenyl **613**: COPhOMe(*p*) **614**: COPhMe(*m*) **615**: 2,4-dinitrophenyl

R^1

545, **597**: CH$_3$ **546**, **598**: CH$_2$CH$_3$ **547**: CH$_2$CH$_2$CH$_3$ **548**: (CH$_2$)$_3$CH$_3$ **549**, **599**: Ph **550**, **600**: PhMe(*m*) **551**: PhMe(*p*) **552**: PhOMe(*p*) **553**, **601**: PhCl(*m*) **554**: PhCl(*o*) **555**, **602**: PhNO$_2$(*p*) **556**: PhNO$_2$(*m*) **557**: PhF(*p*) **558**: PhF(*m*)

R^2

559, **580**: CH$_3$CH$_2$ **560**, **581**: CH$_3$(CH$_2$)$_6$ **561**, **582**: CH$_3$(CH$_2$)$_9$ **562**, **583**: CH$_2$Ph **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**: PhNO$_2$(*m*) **572**, **593**: PhNO$_2$(*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

R^3

629, **642**, **657**: CH$_2$Ph **630**, **643**: CH$_2$PhF(*p*) **631**, **644**: CH$_2$PhCl(*p*) **632**, **645**: CH$_2$PhBr(*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) Red-Al, THF-PhMe, −78–10 °C, 24 h; (j) R^4COCl, $AlCl_3$, r.t., 5–12 h; (k) 2.2 equiv. DCDMH, DMF, 0–5 °C, 1 h; (l) 2.2 equiv. NBS, DMF, 0–5 °C, 2 h; (m) 2.2 equiv. NCS, DMF, 0–5 °C, 2.5 h, then 5 °C – r.t., 2.5 h.

Table 1 14 most active limonoids against human cancer cell lines

Compounds	Cells	IC_{50} (μM)
1,2-Dihydrodeacetylhirtin **20** (ref. 58)	HL-60	4.9
	SMMC-7721	3.1
	A-549	2.9
	MCF-7	9.8
	SW480	9.0
1α-Hydroxy-1,2-dihydrodeacetylhirtin **21** (ref. 58)	HL-60	3.1
	SMMC-7721	1.0
	A-549	1.1
	MCF-7	1.0
	SW480	1.6
1α-Methoxy-1,2-dihydrodeacetylhirtin **23** (ref. 58)	HL-60	5.3
	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
Yunnanolide A **95** (ref. 75)	HL-60	3.6
	SMMC-7721	2.4
	A-549	3.7
	MCF-7	4.2
	SW480	3.5
	BEAS-2B	5.0
11β-Hydroxyisowalsuranolide **97** (ref. 75)	HL-60	3.1
	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
	SMMC-7721	3.1
	A-549	4.1
	MCF-7	3.1
	SW480	2.8
Walsuronoids E **128** (ref. 78)	HL-60	3.3
	SMMC-7721	4.1
	A-549	4.4
	MCF-7	4.4
	SW480	4.5
Toonaciliatones C **132** (ref. 80)	HL-60	5.38
	HepG2	5.22
Toonasinenines B **139** (ref. 81)	A-549	5.7
	CHG-5	5.0
	HCT15	5.7
	HeLa	6.2
	HepG2	5.5
	MDA-MB-231	6.0
	SGC-7901	6.0
Toonasinenines C **140** (ref. 81)	A-549	9.7
	CHG-5	8.3
	HepG2	9.1
	MDA-MB-231	9.4
	SGC-7901	9.4
Toonasinenines D **141** (ref. 81)	A-549	2.3
	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	1.5
	SW480	0.86
Perforanoid A **358** (ref. 117)	HEL	6.17
	K562	4.24
	CB3	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** (ref. 64)	*Drosophila melanogaster*	AI[a] = 32.8% at 1 mM (nicotine: AI = 28.5% at 1 mM)
Aphanamixoids C **286** (ref. 101)	*Helicoverpa armigera*	EC_{50}[b] = 9.27 μg cm^{-2}
Aphanamixoids F **289** (ref. 101)		EC_{50} = 4.28 μg cm^{-2}
Aphanamixoids G **290** (ref. 101)		EC_{50} = 6.82 μg cm^{-2} (neem oil: EC_{50} = 2.62 μg cm^{-2})
Flexuosoids A **354** (ref. 115)	*Spodoptera exigua*	ED_{50}[c] = 25.1 μg cm^{-2}
Flexuosoids B **355** (ref. 115)		ED_{50} = 17.3 μg cm^{-2}
410 (ref. 123)	Pre-third-instar larvae of *Mythimna separata*	73.1% toosendanin: 50.0%
417 (ref. 123)		61.5%
431 (ref. 124)	Pre-third-instar larvae of *M. separata*	63.0%
472 (ref. 127)	Pre-third-instar larvae of *M. separata*	62.1%
485 (ref. 127)		72.4%
486 (ref. 127)		65.5%
490 (ref. 127)		62.1%
566 (ref. 131)	Pre-third-instar larvae of *M. separata*	63.0%
575 (ref. 131)		66.7%
578 (ref. 131)		63.0%
534 (ref. 132)	Pre-third-instar larvae of *M. separata*	73.3%
552 (ref. 132)		70.0%
558 (ref. 132)		73.3%
597 (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 of *M. separata*	76.9%
536 (ref. 130)		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)		61.5%
662 (ref. 133)	Pre-third-instar larvae of *M. separata*	65.5%

[a] Antifeedant index: AI. [b] EC_{50} value: the effective concentration for 50% feeding reduction. [c] ED_{50} value: the effective dosage for 50% feeding reduction.

7. 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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