



# Degraded limonoids: biologically active limonoid fragments re-enhancing interest in Meliaceae and Rutaceae sources

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**Abstract** Phytochemical studies on the roots, twigs and leaves of Meliaceae and Rutaceae family plants have revealed the presence of non-complex terpenes derived from limonoid fragmentation. The occurrence and chemical structure of these degraded limonoids isolated from 1930 to March 2022 are reported in this review. Particular attention is given to the degradation levels in these compounds and their absolute configuration to discover presumable deconstruction pathways from more complex limonoids. Plausible intermediates have been postulated for most of them that would explain their origin from limonoids. The total or semi-synthesis of the most isolated degraded limonoids or analogues remains undescribed. This review focuses on the bioactivity of these fragmented limonoids and their synthesized analogues. Based on pharmacological and agrochemical studies, degraded

limonoids appear to be excellent structural leads to consider for the total or semi-synthesis of more potent derivatives with the aim of discovering new hits and clarifying their modes of action.

**Keywords** Bioactivity · Deconstruction pathways · Degradation levels · Degraded limonoids · Meliaceae and rutaceae · Structural analogues

## Introduction

Limonoids are C-26 terpenoids (related to limonin) which may arise from the tetracyclic triterpene apoeuphol (Rao et al. 1968; Siddiqui et al. 1991). They feature a basic terpenic skeleton with 4,4,8-trimethyl-17-furyl substituents (Fig. 1). According to the connectivity of the parent core, naturally occurring limonoids are classified in ring-intact limonoids, ring-seco limonoids, highly decorated limonoids and degraded limonoids (Fu and Liu 2020). At least 35 bond patterns are observed including the following types: chukrasone, mexicanolide, havenensin, hortiolide, neotecleanin, azadirachtine, meliacarpin, andirobin, phragmalin, irobin, secomahoganin, salannin, among others (Tan and Luo 2011; Fang et al. 2011). Different cyclisation patterns of the ring backbones stand out in the basic limonoid structure (Li et al. 2016a).

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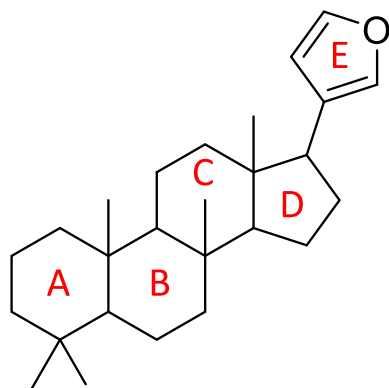
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Degraded limonoids are catabolic products resulting from the decomposition of limonoids. Several limonoid reviews have focused on the chemistry, biology and pharmacology of these natural products (Tundis et al. 2014; Lv et al. 2015a; Gualdani et al. 2016; Zhang et al. 2017; Sun et al. 2018; Shi et al. 2020). However, to the best of our knowledge, no review has fully covered the structures and bioactivities of degraded limonoids.

The number of isolated degraded limonoids has increased significantly in recent decades. In 1997, Okamura and co-workers reported that only five naturally occurring degraded limonoids were known (Okamura et al. 1997). These were fraxinellone (Pailer et al. 1965; Coggon et al. 1969), fraxinellonone (Boustie et al. 1990), isofraxinellone (Blaise and Winternitz 1985), dictamdiol (Hu et al. 1989) and calodendrolide (Cassady and Liu 1972). The number of degraded limonoids isolated from Meliaceae and Rutaceae plants increased to 12 in 2005 (Biavatti et al. 2005). Since then, that number has quadrupled.

Although simple in terms of their chemical structure, degraded limonoids have been less studied in comparison to other natural products and, in some cases, their absolute configuration incorrectly assigned. It is worth noting that the numbering of carbon atoms to describe the structures of degraded limonoids can sometimes be confusing due to the lack of consensus among authors. Most authors prefer to keep the original numbering corresponding to intact limonoids while others use the carbon atom numbering of the degraded limonoids themselves (Fig. 2). Due to these numbering discrepancies, some structures have been named in different ways depending on



**Fig. 1** Basic limonoid skeleton

the numbering criterion chosen. This is the case of dasycarpol (Yang et al. 2005), which has been named as 9 $\beta$ -hydroxyfraxinellone (D'Ambrosio and Guerriero 2002) and also as 6 $\beta$ -hydroxyfraxinellone (Zhao et al. 1997, Fig. 2b).

In this review, the original carbon numbering established for the limonoid in question is used to describe the degraded limonoid. Furthermore, the C, D and E rings belonging to the intact limonoids are re-named as A, B and C rings, respectively for the degraded limonoids (Fig. 2a).

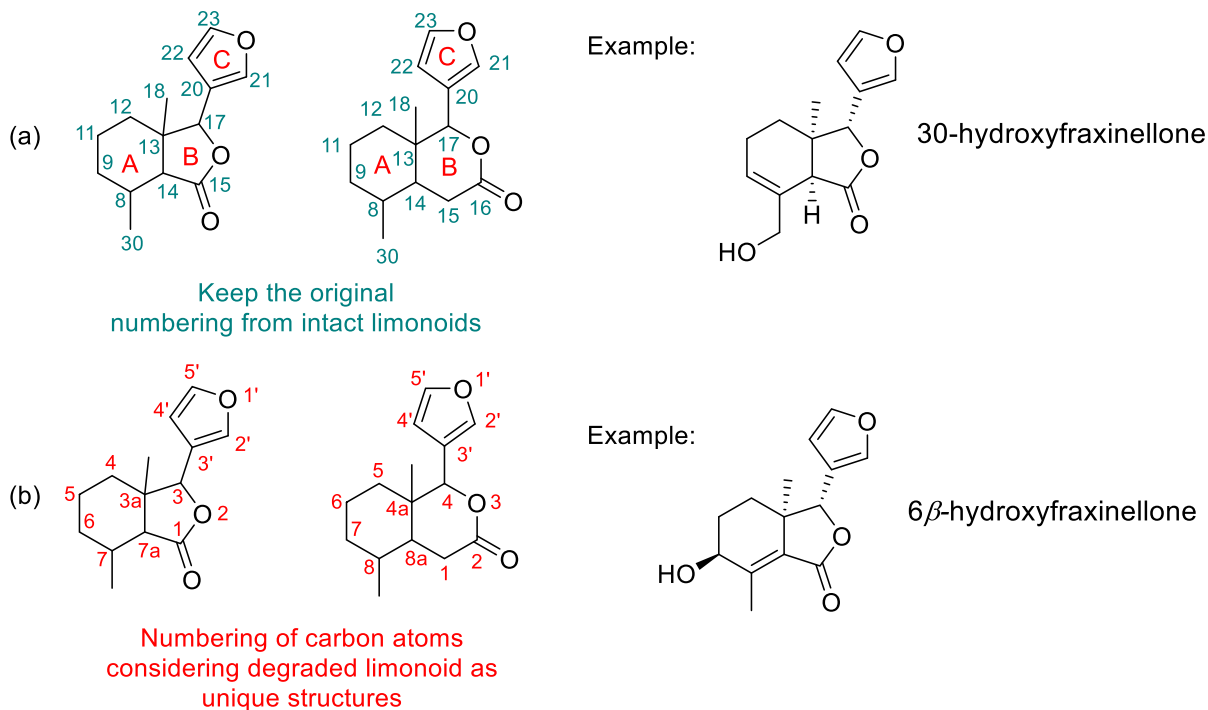
Moreover, the term degraded limonoid includes different structures with different degrees of degradation from the precursor limonoid (Fig. 3). To the best of our knowledge, no distinction is made in the literature between these levels of decomposition. In this review, we have drawn a distinction between highly-degraded and slightly-degraded limonoids. In the first group we include plant-derived products that have two or three fused-rings in their core while those tetracyclic compounds that have suffered degradation of the furan ring are referred as slightly-degraded limonoids.

Despite their much lower structural complexity and therefore easier synthetic access to these structures, very few syntheses have been described in the literature for these fascinating carbon scaffolds. Moreover, degraded limonoids are particularly unknown in terms of bioactivity as they have not been thoroughly studied. The interesting biological activities exhibited by some degraded limonoids, and their structural similarity to other more complex related natural products, could shed light on the structural features necessary for the effects observed for some of these compounds. These analyses could guide the design of a new set of biologically active molecules with promising uses in agriculture and medicine.

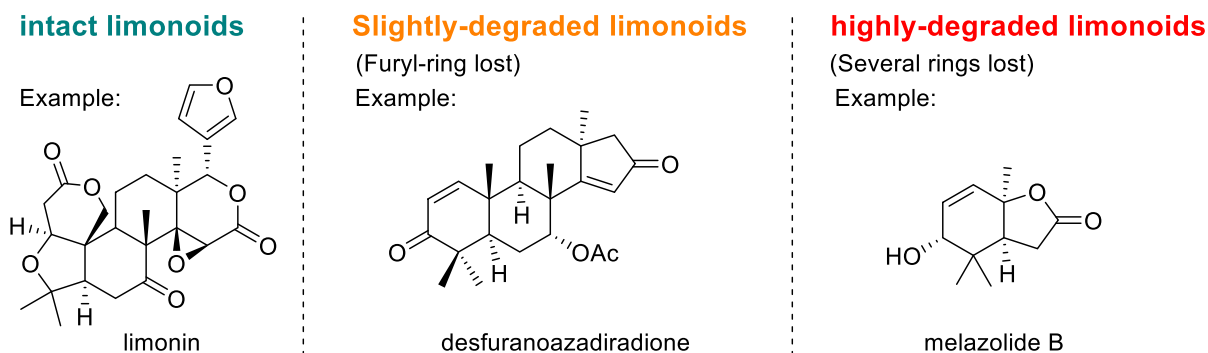
This review describes the extent to which all naturally occurring degraded limonoids discovered up to March 2022 have been studied, with emphasis on their structure, isolation, bioactivity, chemical and biological transformation and deconstruction pathways.

### Natural sources of degraded limonoids

The chief sources of limonoids are the Meliaceae and Rutaceae plant families (Da Silva et al. 1984;



**Fig. 2** Numbering systems for degraded limonoids



**Fig. 3** Different degrees of degradation in limonoids

Champagne et al. 1992; Roy and Saraf 2006; Liao et al. 2009; Fang et al. 2011; Sun et al. 2018; Sartor et al. 2019; Cui et al. 2021; Luo et al. 2022) but they also can be found very occasionally in Cneoraceae and Ptaeroxylaceae families and *Harrisonia* spp. of Simaroubaceae (Ourison et al. 1964; Connolly 1983; Da Silva et al. 1987; Tundis et al. 2014; Amit and Shailendra 2006; Tan and Luo 2011).

Limonoids from Rutaceae plants feature fewer structural changes than the ones observed in metabolites isolated from the Meliaceae family (Amit and

Shailendra 2006; Jolanta et al. 2014). Limonoids from Meliaceae are characterized by a high degree of oxidation and some feature rearrangements when compared to basic limonoid structures (Jolanta et al. 2014).

The chemical structure and occurrence of those compounds is found in Tables 1, 2, 3 and 4 and Figs. 4, 5, 6 and 7.

**Table 1** Occurrence of highly-degraded limonoids **1–23**

Name	Plant family	Natural sources	References
Calodendrolide ( <b>1</b> )	Rutaceae	<i>Calodendrum capense</i> <i>Dictamnus dasycarpus</i> <i>Euodiae fructus</i> <i>Phellodendron amurense</i> Rupr <i>Tetradium trichotomum</i>	Cassady and Liu (1972), Rajab et al. (1998), Kiprop et al. (2005) Zhao et al. (1997), Yoon et al. (2008, 2010) Yin et al. (2016) Lee et al. (2005); Kiprop et al. (2007) Quader et al. (1990)
Dictamdiol ( <b>2</b> )	Rutaceae	<i>Dictamnus dasycarpus</i> <i>Dictamnus angustifolius</i> <i>Dictamnus radialis</i> <i>Fagaropsis glabra</i>	Jiang et al. (2006); Yoon et al. (2008) Hu et al. (1989), Sun et al. (2013), Lv et al. (2015b, c) Zhao et al. (2008) Boustie et al. (1992)
Dictamdiol A ( <b>3</b> )	Rutaceae	<i>Dictamnus dasycarpus</i>	Yoon et al. (2008)
Dictamdiol B ( <b>4</b> )	Rutaceae	<i>Dictamnus dasycarpus</i>	Yoon et al. (2008)
Isodictamdiol ( <b>5</b> )	Rutaceae	<i>Dictamnus radialis</i>	Zhao et al. (2007, 2008)
Isodictamdiol A ( <b>6</b> )	Rutaceae	<i>Dictamnus angustifolius</i>	Sun et al. (2013)
Isodictamdiol C ( <b>7</b> )	Rutaceae	<i>Dictamnus dasycarpus</i>	Gao et al. (2021)
Dictamlimonol C ( <b>8</b> )	Rutaceae	<i>Dictamnus dasycarpus</i>	Chen et al. (2020)
Dictamlimonol D ( <b>9</b> )	Rutaceae	<i>Dictamnus dasycarpus</i>	Chen et al. (2020)
Dictamlimonol E ( <b>10</b> ) = 9 $\alpha$ -Methoxyl dictamdiol	Rutaceae	<i>Evodia rutaecarpa</i>	Chen et al. (2020) Qin et al. (2021)
Dasycarinone A ( <b>11</b> )	Rutaceae	<i>Dictamnus dasycarpus</i>	Gao et al. (2021)
Dictamlimonol F ( <b>12</b> )	Rutaceae	<i>Dictamnus dasycarpus</i>	Chen et al. (2020)
Dictamnusine ( <b>13</b> )	Rutaceae	<i>Dictamnus dasycarpus</i>	Yoon et al. (2008)
Fagaropsine ( <b>14</b> )	Rutaceae	<i>Fagaropsis glabra</i>	Boustie et al. (1995)
Dysodensiol A ( <b>15</b> )	Meliaceae	<i>Dysoxylum densiflorum</i>	Xie et al. (2008)
Dysodensiol B ( <b>16</b> )	Meliaceae	<i>Dysoxylum densiflorum</i>	Xie et al. (2008)
Dysodensiol C ( <b>17</b> )	Meliaceae	<i>Dysoxylum densiflorum</i>	Xie et al. (2008)
Pyroangolensolide ( <b>18</b> )	Meliaceae	<i>Melia azedarach</i>	D'Ambrosio and Guerriero (2002)
Azedaralide ( <b>19</b> )	Meliaceae	<i>Melia azedarach</i>	Nakatani et al. (1998), D'Ambrosio and Guerriero (2002), Yuan et al. (2013)
Trichiconnarin A ( <b>20</b> )	Meliaceae	<i>Trichilia connaroides</i>	Wang et al. (2008)
Trichiconnarin B ( <b>21</b> )	Meliaceae	<i>Trichilia connaroides</i>	Wang et al. (2008)
Odoratin ( <b>22</b> )	Meliaceae	<i>Cedrela odorata</i> L	Chan et al. (1966, 1972); Nogueira et al. (2020)
Siamensinolide ( <b>23</b> )	Rutaceae	<i>Chalcas siamensis</i> Tanaka	Boonyaketgoson et al. (2020)

**Table 2** Occurrence of highly-degraded limonoids **24–38**

Name	Plant family	Natural sources	References
Fraxinellone ( <b>24</b> )	Meliaceae	<i>Melia azedarach</i>	Ekong et al. (1969), Nakatani et al. (1998), D'Ambrosio and Guerriero (2002), Liu et al. (2011)
		<i>Raulinoa echinata</i>	Biavatti et al. (2005)
	Rutaceae	<i>Dictamnus dasycarpus</i>	Zhao et al. (1997), Chen et al. (2000), Yoon et al. (2008), Bai et al. (2014a, b), Dong et al. (2018a, b), Guo et al. (2018)
		<i>Dictamnus albus</i>	Thoms and Dambergis (1930), Kaku et al. (1935), Storer and Young (1973), Woo et al. (1987), Kim et al. (1997)
		<i>Dictamnus angustifolius</i>	Akhmedzhanova et al. (1978), Hu et al. (1989), Wu et al. (1998)
		<i>Fagaropsis glabra</i>	Blaise et al. (1985), Boustie et al. (1990)
	Asteraceae	<i>Pluchea indica</i>	Ruan et al. (2018)
	Ericaceae	<i>Gaultheria nummularioides</i>	Yang et al. (2007), Liu et al. (2013a)
	Ranunculaceae	<i>Pulsatilla cernua</i>	Yan et al. (2021)
	Fraxinellonone ( <b>25</b> )	Meliaceae	<i>Melia azedarach</i>
Rutaceae		<i>Dictamnus dasycarpus</i>	Du et al. (2005), Tou and Chen (2012), Bai et al. (2014a)
		<i>Dictamnus angustifolius</i>	Wu et al. (1998)
		<i>Fagaropsis glabra</i>	Boustie et al. (1990)
		<i>Raulinoa echinata</i>	Biavatti et al. (2005)
Ericaceae		<i>Gaultheria nummularioides</i>	Yang et al. (2007), Liu et al. (2013a)
9 $\beta$ -Hydroxyfraxinellone = dasycarpol ( <b>26</b> )		Meliaceae	<i>Melia azedarach</i>
	Rutaceae	<i>Dictamnus dasycarpus</i>	Zhao et al. (1997)
9 $\alpha$ -Hydroxyfraxinellone ( <b>27</b> )	Meliaceae	<i>Melia azedarach</i>	D'Ambrosio and Guerriero (2002)
30-Hydroxyfraxinellone ( <b>28</b> )	Meliaceae	<i>Melia azedarach</i>	D'Ambrosio and Guerriero (2002)
9 $\alpha$ -Hydroxyfraxinellone-9- <i>O</i> - $\beta$ -Glucoside ( <b>29</b> )	Rutaceae	<i>Dictamnus dasycarpus</i>	Tou and Chen (2012)
Dictamlimonoside B ( <b>30</b> )	Rutaceae	<i>Dictamnus dasycarpus</i>	Chen et al. (2020)
9 $\alpha$ -Hydroxy-12 $\alpha$ -Acetoxyfraxinellone ( <b>31</b> )	Meliaceae	<i>Melia azedarach</i>	D'Ambrosio and Guerriero (2002)
12 $\alpha$ -Acetoxyfraxinellone ( <b>32</b> )	Meliaceae	<i>Melia azedarach</i>	Nakatani et al. (1998)
	Rutaceae	<i>Fagaropsis glabra</i>	Blaise and Winternitz (1985)
12 $\alpha$ -Hydroxyfraxinellone ( <b>33</b> )	Meliaceae	<i>Melia azedarach</i>	D'Ambrosio and Guerriero (2002)
(-)-8,14-Epoxyfraxinellone ( <b>34</b> )	Rutaceae	<i>Raulinoa echinata</i> Cowan	Biavatti et al. (2001, 2005)

**Table 2** continued

Name	Plant family	Natural sources	References
Isofraxinellone (35)	Rutaceae	<i>Dictamnus dasycarpus</i>	Miyazawa et al. (1995)
		<i>Fagaropsis glabra</i>	Blaise and Winternitz (1985)
Dasy lactone A (36)	Rutaceae	<i>Dictamnus dasycarpus</i>	Yang et al. (2011), Chen et al. (2020)
23-Methoxydasy lactone A (37)	Rutaceae	<i>Dictamnus dasycarpus</i>	Wang et al. (2014)
Dasy lactone B (38)	Rutaceae	<i>Dictamnus dasycarpus</i>	Miyazawa et al. (1995)

**Table 3** Occurrence of highly-degraded limonoids 39–42

Name	Plant family	Natural sources	References
3-Teracryl-melazolide A (39)	Meliaceae	<i>Melia azedarach</i>	D'Ambrosio and Guerriero (2002)
3-Teracryl-melazolide B (40)	Meliaceae	<i>Melia azedarach</i>	D'Ambrosio and Guerriero (2002)
Melazolide A (41)	Meliaceae	<i>Melia azedarach</i>	D'Ambrosio and Guerriero (2002)
Melazolide B (42)	Meliaceae	<i>Melia azedarach</i>	D'Ambrosio and Guerriero (2002)

**Table 4** Occurrence of degraded limonoids 43–49

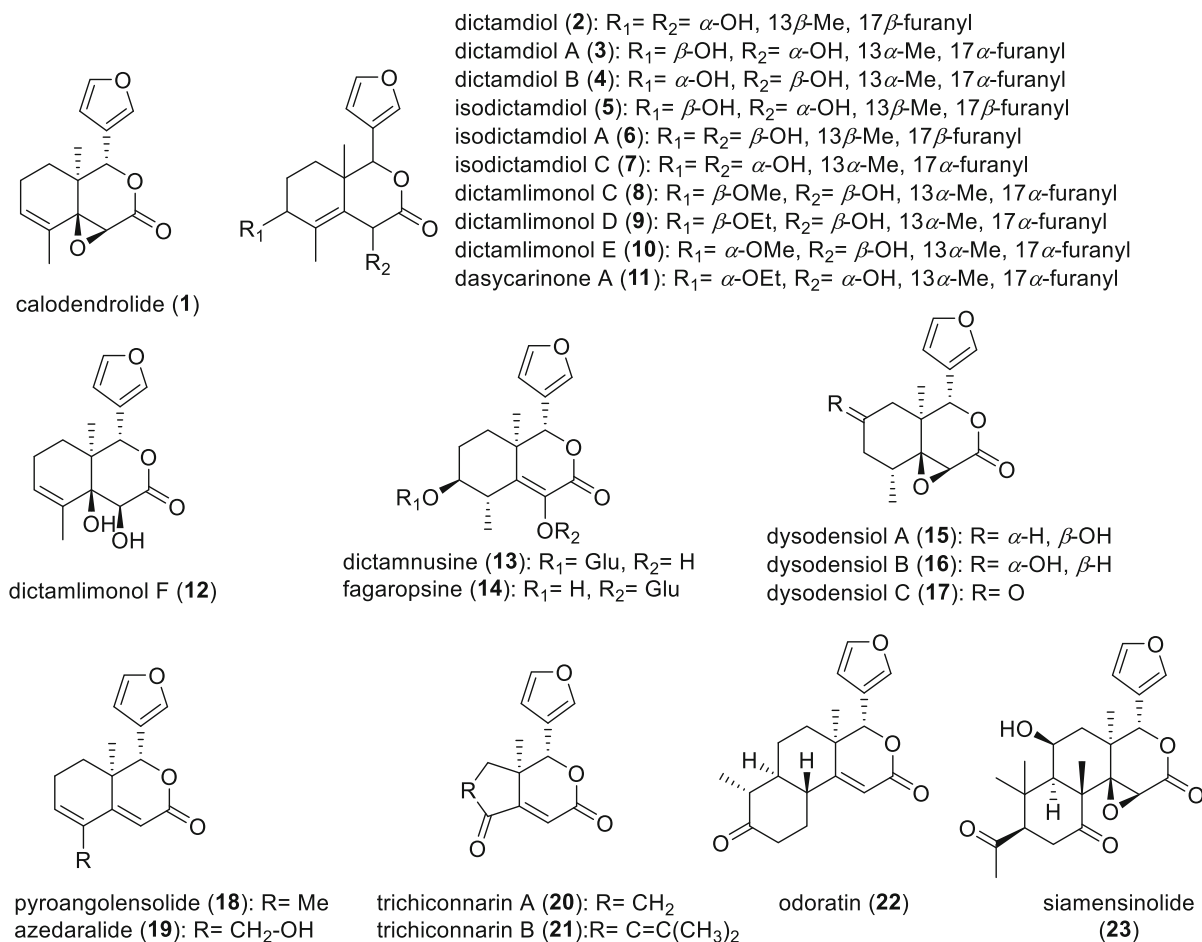
Name	Plant family	Natural sources	References
Walsunoid A (43)	Meliaceae	<i>Walsura robusta</i>	Wang et al. (2016)
Desfuranoazadiradione (44)	Meliaceae	<i>Azadirachta indica</i> A. Juss	Siddiqui et al. (1992, 2003), Akihisa et al. (2009), Kikuchi et al. (2011)
Desfurano-6'-Hydroxyazadiradione (45)	Meliaceae	<i>Azadirachta indica</i> A. Juss	Siddiqui et al. (2003)
$\alpha$ -Nimolactone (46)	Meliaceae	<i>Azadirachta indica</i> A. Juss	Siddiqui et al. (1992), Kraus et al. (1994), Tariq et al. (2004), Akihisa et al. (2009), Kikuchi et al. (2011)
$\beta$ -Nimolactone (47)	Meliaceae	<i>Azadirachta indica</i> A. Juss	Siddiqui et al. (1992), Kraus et al. (1994), Tariq et al. (2004), Akihisa et al. (2009), Kikuchi et al. (2011)
Chuktabrin L (48)	Meliaceae	<i>Chukrasia tabularis</i> A. Juss	Wang et al. (2019a)
Cipaferen R (49)	Meliaceae	<i>Cipadessa baccifera</i>	Cao et al. (2020)

Highly-degraded limonoids.

Certain degraded limonoids contain an unsaturated  $\delta$ -

Most of the highly-degraded limonoids are characterized by a fused-bicyclic substituted lactone with a

17 $\alpha$ -furyl group and a 13 $\alpha$ -methyl group at the ring junction position which could come from the C,D-rings of the precursor limonoids (Heasley 2011, Figs. 4 and 5). Based on the lactone motif size present in their structures, we have classified them into two groups:



**Fig. 4** Chemical structures of degraded limonoids **1–23**

Limonoids bearing a  $\delta$ -valero- or a  $\gamma$ -butyrolactone as a B ring. It would be reasonable to suggest a possible bio-relationship between the  $\gamma$ -butyrolactone and the  $\delta$ -valerolactone rings due to in some cases degraded limonoids bearing a  $\delta$ -valerolactone were isolated together with compounds that bear a  $\gamma$ -butyrolactone. For instance, azedaralide (**19**) which contains a  $\delta$ -valerolactone was isolated from the root bark of *Melia azedarach* together with the degraded limonoids **24**, **25** and **32**. These latter compounds bear a  $\gamma$ -butyrolactone instead (Nakatani et al. 1998). Moreover, compounds **2–4**, **7** and **11** (bearing a 6-membered lactone) were isolated from the root bark of *Dictamnus dasycarpus* along with compounds **24–26** and **35** that contain a 5-membered lactone (Gao et al. 2021). However, the bio-relationship between both lactone motif sizes remains unclear.

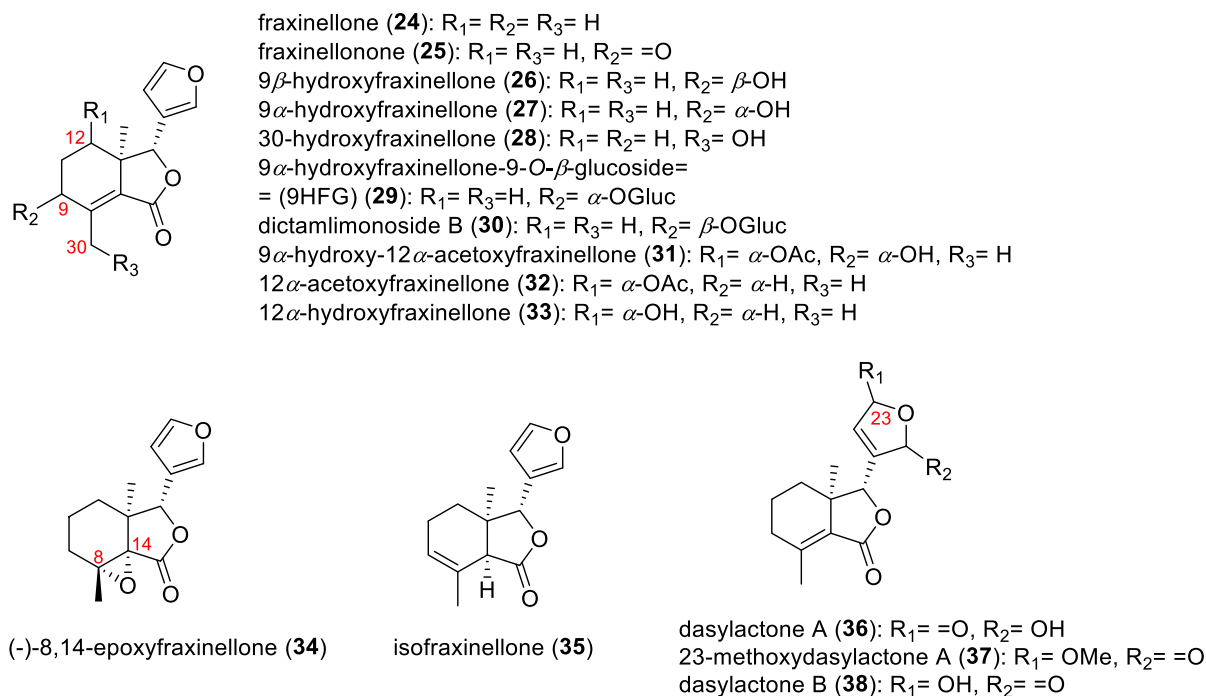
Additionally, a very small number of the highly degraded limonoids isolated (known as melazolides) keep the *gem*-dimethyl unit typically present in the A ring and have been hypothesised to derive from the left-side of the original limonoids (Fig. 6).

Degraded limonoids bearing a  $\delta$ -valerolactone as B ring

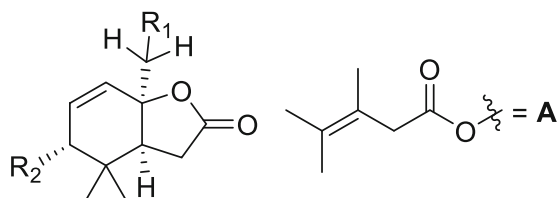
Degraded limonoids **1–23** contain a  $\delta$ -valerolactone substituted by a furyl group and a methyl group at the ring junction position and in most cases are oriented toward the same face of the molecule (Fig. 4). These compounds were isolated from both Rutaceae and Meliaceae families (Table 1).

Calodendrolide (**1**) was first isolated from seeds of *Calodendrum capense* (Cassady and Liu 1972) and was later identified in *Dictamnus dasycarpus* (Zhao





**Fig. 5** Chemical structures of degraded limonoids **24–38**

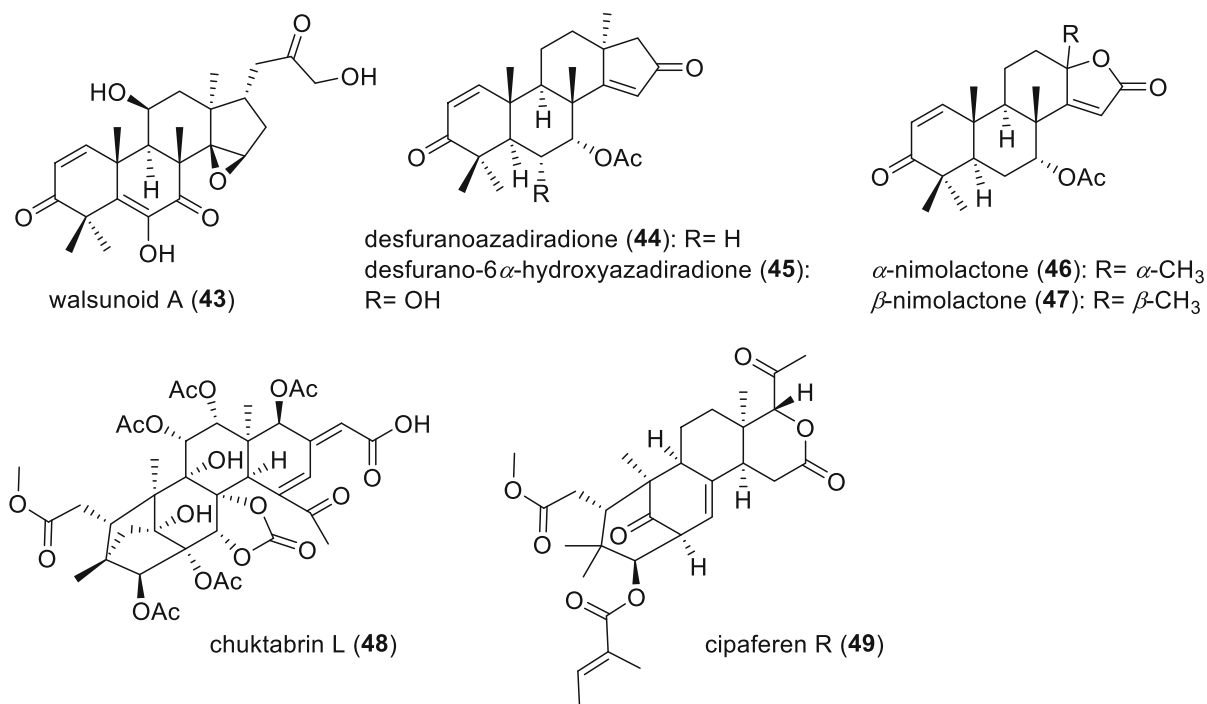


**Fig. 6** Chemical structures of melazolides **39–42**

et al. 1997; Yoon et al. 2008 and 2010), *Euodia fructus* (Yin et al. 2016), *Phellodendron amurense* Rupr. (Lee et al. 2005; Kiprop et al. 2007) and *Tetradium trichotomum* (Quader et al. 1990). Structurally, calodendrolide (**1**) is characterized by an epoxidized δ-valerolactone ring and its structure and absolute stereochemistry was confirmed by chemical transformation into pyroangolensolide (**18**) (Kiprop et al. 2007). Compounds **2–11** contain an α-hydroxy-δ-valerolactone with either a hydroxyl or ether group attached at the C-9 position and were isolated from the

genus *Dictamnus*. Dictamdiol (**2**) was described together with dictamdiols A and B (**3–4**) with α-oriented furyl and methyl groups based on biosynthetic assumptions (Hu et al. 1989; Yoon et al. 2008). However, in spite of all the limonoid precursors isolated to date feature both groups oriented toward the α-face, Zhao et al. assigned its absolute configuration as β-17-furyl-β-13-methyl by crystal X-ray diffraction (Zhao et al. 2007, 2008). Similarly, β-13-methyl and β-17-furyl configurations were established for isodictamdiol (**5**) (Zhao et al. 2007, 2008) and dictamdiol A (**6**) (Sun et al. 2013). The total synthesis of these compounds has not yet been described in the literature. Therefore, efforts toward the synthesis of these compounds it should be advisable to clarify their unusual absolute configurations. Ghao et al. isolated isodictamdiol C (**7**) from the root bark of *Dictamnus dasycarpus* (Ghao et al. 2021). The NMR data for **7** were almost identical to those of dictamdiol (**2**) (Jiang et al. 2006) but its absolute configuration was established as α-17-furyl-α-13-methyl by ECD spectrum. Dictamlimonols C–E (**8–10**) were isolated from the root bark of *Dictamnus dasycarpus* and are structurally related to **3** and **4** but bear a β- or α-oriented methoxy or ethoxy group attached at the C-9





**Fig. 7** Degraded-limonoids derived from the degradation of the furanyl side chain

position. Their absolute configurations were established by ECD experiments in combination with quantum chemical calculations (Chen et al. 2020). Although compound **10** was isolated from the root bark of the perennial herb *Dictamnus dasycarpus* and named dictamlimonol E by Chen et al. in 2020, a few months later it was described as a new degraded limonoid from the ripe fruit of *Evodia rutaecarpa* (Juss.) Benth. (Qin et al. 2021). Compound **10** was re-named 9 $\alpha$ -methoxyl dictamdiol but the two structures are identical.  $\alpha,\beta$ -Dihydroxy- $\delta$ -valerolactone dictamlimonol F (**12**) was also isolated and elucidated in that same study (Chen et al. 2020). Dasycarinone A (**11**) was isolated from the root bark of *Dictamnus dasycarpus* and it bears an extra ethoxy group in comparison to isodictamdiol C (**7**) (Ghao et al. 2021). Dictamnusine (**13**) was isolated from *D. dasycarpus* (Yoon et al. 2008) whereas fagaropsine (**14**) was identified in *Fagaropsis glabra* (Boustie et al. 1995). Both compounds share a common skeleton bearing an unsaturated  $\delta$ -valerolactone with two oxygenated functions and differentiated from the position of the D-glucose moiety attached at the C-9 or C-15 positions, respectively. Fagaropsine (**14**) differs from other reported  $\beta$ -D-limonoid glycosides in the D-ring

glycosylation pattern. Dysodensiols A-C (**15–17**) were isolated from *Dysoxylum densiflorum*, a species belonging to the Meliaceae family (Xie et al. 2008; Naini et al. 2022). They have an epoxy lactone with either a hydroxyl or keto group at C-11 and their relative configurations were deduced from ROESY experiments (Xie et al. 2008). Pyroangolensolide (**18**) and azedaralide (**19**) are unsaturated  $\delta$ -valerolactones isolated from the roots of *Melia azedarach*. The structure of pyroangolensolide (**18**) was determined long ago by NMR data and circular dichroism from pyrolysis of methyl angolensate but was not isolated from a natural source until 2002 (D'Ambrosio and Guerriero 2002). Trichiconnarins A-B (**20–21**) are rare degraded limonoids discovered in *Trichilia connaroides* bearing a contracted five-membered ring-A. This ring is believed to be an artefact produced from the isolation process by an aldol reaction of trichiconnarin A (**20**) with acetone followed by dehydration. The absolute configuration of these compounds is assumed to be the same as their biogenetic precursor trijugic C (Wang et al. 2008). Odoratin (**22**) was reported long ago from *Cedrela odorata* L. (Chan et al. 1966; Farnsworth et al. 1980; Nogueira et al. 2020) and is an extensive decomposition of the intact limonoids.

Its fused-tricyclic skeleton was established by NMR experiments and supported by a mass-spectral fragmentation pattern and is the only degraded limonoid isolated with these features. Moreover, its absolute configuration was deduced from circular dichroism and was identical to other limonoids (Dreyer 1968). The name odoratin could be a mistake since it has also been ascribed to other natural products with different structures including a flavonoid (Sun et al. 2015a; Habbu et al. 2020) and even a pseudoguaianolide (Ortega et al. 1968; Hoffmann et al. 1978). Recently, a new degraded limonoid bearing a fused-tricyclic skeleton, named siamensinolide (**23**), was isolated from the twigs of *Chalcas siamensis* Tanaka (Boonyaketguson et al. 2020).

Degraded limonoids bearing a  $\gamma$ -butyrolactone as B ring

Degraded-limonoids **24–38** contain a  $\gamma$ -butyrolactone ring belonging to a substituted bicyclooctanolide core (Fig. 5 and Table 2). Fraxinellone (**24**) and its related derivatives **25–33** have been isolated from both the Meliaceae and Rutaceae families. They have an unsaturated  $\gamma$ -butyrolactone ring in common, differing only in the substitution pattern at C-9, C-12 and C-30 positions. Furthermore, the botanical lactone fraxinellone (**24**) was encountered for the first time in *Pluchea indica*, a plant belonging to the Asteraceae family (Ruan et al. 2018). Recently, it has been also isolated from *Pulsatilla Cernua* (Thunb.) Bercht. ex J. Presl which belongs to the Ranunculaceae family. This is the first time a compound with a limonoid skeleton has been isolated from this family (Yan et al. 2021). Fraxinellone (**24**), together with fraxinellonone (**25**), have also been isolated from whole plants of *Gaultheria nummularioides* (Ericaceae family) (Yang et al. 2007; Liu et al. 2013a). Moreover, compounds **29** and **30** are two epimeric degraded limonoids bearing a  $\beta$ -D-glucose moiety at the C-9 position that were discovered from *Dictamnus dasycarpus* (Tou and Chen 2012; Chen et al. 2020). 8,14-epoxyfraxinellone (**34**) was isolated from the hexane extracts of *Raulinoa echinata* roots and its absolute configuration was confirmed by single crystal X-ray diffraction (Biavatti et al. 2005), whereas isofraxinellone (**35**) exhibited a *cis*-ring juncture and was originally identified from the trunk bark of *Fagaropsis glabra* (Blaise and Winternitz 1985) and later from the root bark of *D.*

*dasycarpus* (Miyazawa et al. 1995). Lastly, compounds **36–38** share many similarities with fraxinellone (**24**), the main difference being the presence of a substituted  $\alpha,\beta$ -unsaturated butenolide moiety instead of the furyl group. These compounds were also isolated from the root bark of *D. dasycarpus* (Miyazawa et al. 1995; Wang et al. 2014; Chen et al. 2020).

Melazolides

Melazolides **39–42** are non-furanoid compounds discovered in *Melia azedarach* roots which have been hypothesized to result from the decomposition of the right-side of the precursor limonoid (D'Ambrosio and Guerriero 2002, Fig. 6 and Table 3). Their absolute configurations were established by CD techniques.

Slightly-degraded limonoids.

Abundant and varied slight fragmentations have been observed in diverse structural type limonoids: 16-nor type limonoid backbone (Zhang et al. 2007a, 2008), 16,19-dinor degraded limonoid backbone (Liu et al. 2012) and some examples have been described where the furan ring is involved in the deconstruction of the common limonoid types (Zhang et al. 2008; Hu et al. 2013; Liu et al. 2014).

In this review, we have focused on those degraded limonoids where the main characteristic is the absence of the furanyl ring. Hence, we classified derivatives **43–49** as slightly-degraded limonoids (Fig. 7 and Table 4). These compounds have all been isolated from the Meliaceae family. Walsunoid A (**43**) is a cedrelone-type limonoid derivative isolated from the leaves of *Walsura robusta*. It has the same ring A – D pattern as 11 $\beta$ -hydroxycedrelone but the furyl group has been transformed into a 3-hydroxy-2-oxopropyl chain. The absolute configuration was assigned using the ECD technique (Wang et al. 2016). Compounds **44–45** are desfurano-azadiradione derivatives isolated from the fruit coats of *Azadirachta indica* (Siddiqui et al. 1992, 2003; Akihisa et al. 2009). Nimolactones **46–47** were isolated from the same plant and share many similarities with **44–45** but differ in the presence of an unsaturated  $\gamma$ -butyrolactone (Siddiqui et al. 1992; Kraus et al. 1994; Tariq et al. 2004; Akihisa et al. 2009; Kikuchi et al. 2011). Chuktabrin L (**48**) is the first example of a C16 degraded and C21–C15 cyclized 16-nor-phragmalin-type limonoid which was isolated from the stems of *Chukrasia tabularis* A. Juss

**Table 5** Biological activities of degraded limonoids

Natural product	Biological activity	References
Calodendrolide (1)	Antigenic effect	Yin et al. (2016)
	Fungistatic activity	Zhao et al. (1997)
	Insect-controlling activity	Kiprop et al. (2005, 2007)
	Neuroprotective activity	Yoon et al. (2008, 2010)
Dictamdiol (2)	Antiinflammatory	Gao et al. (2021)
	Antiplatelet aggregation activity	Sun et al. (2013)
Dictamdiol A (3)	Antiinflammatory	Gao et al. (2021)
	Neuroprotective activity	Yoon et al. (2008)
Dictamdiol B (4)	Antiinflammatory	Gao et al. (2021)
Isodictamdiol (5)	Antibacterial activity	Zhao et al. (2008)
Isodictamdiol A (6)	Antiplatelet aggregation activity	Sun et al. (2013)
Isodictamdiol C (7)	Antiinflammatory	Gao et al. (2021)
9 $\alpha$ -Methoxyl dictamdiol (10)	Antiinflammatory	Gao et al. (2021)
	Cytotoxic activity against tumor cell lines	Qin et al. (2021)
Dasycarinone A (11)	Antiinflammatory	Gao et al. (2021)
Dictamnusine (13)	Neuroprotective activity	Yoon et al. (2008)
Pyroangolensolide (18)	Insect-controlling activity	Kiprop et al. (2007)
Azedaralide (19)	Insect-controlling activity	Nakatani et al. (1998)
Fraxinellone (24)	Activity in liver disorders	Li et al. (2021), Sun et al. (2009)
	Antibacterial activity	Yuan et al. (2006)
	Anticancer activity	Kim et al. (1997), Yu et al. (2013, 2017), Lee et al. (2017), Xing et al. (2018), Pei et al. (2019), Bui et al. (2021), He et al. (2021)
	Antifertility activity	Woo et al. (1987)
	Antifibrotic activity	Hou et al. (2018)
	Antiinflammatory activity	Lee et al. (2009), Wu et al. (2014), Ruan et al. (2018), Jung et al. (2018), Kim et al. (2009, 2019), Chen et al. (2020), Fu et al. (2021), Gao et al. (2021)
	Antiplatelet aggregation activity	Sun et al. (2013)
	Cytotoxic activity	Woo et al. (1987), Fan et al. (2018)
	Fibroblast activator	Zheng et al. (2021)
	Fungistatic activity	Zhao et al. (1997), Yuan et al. (2006), Wang et al. (2006)
	Hepatotoxic activity	Zhou et al. (2020)
	Ichthyotoxicity	Okamura et al. (1997), Nakatani et al. (1998)
	Insect-controlling activity	Nakatani et al. (1998), Liu et al. (2002, 2008, 2009), Yuan and Wang (2006, 2012), Min et al. (2010), Lü et al. (2010, 2013), Lu et al. (2014), Lv et al. (2014, 2020), Yang et al. (2018a), Okuno et al. (2019), Lei et al. (2020)
	Neuroprotective activity	Yoon et al. (2008, 2010), Wang et al. (2014)
	Senescence inhibition	Han et al. (2018)
Th1 type cells promoter to produce IFN- $\gamma$	Lu et al. (2021)	
Vascular relaxing activity	Yu et al. (1992)	

**Table 5** continued

Natural product	Biological activity	References
Fraxinellone (25)	Antibacterial activity	Zhao et al. (2008)
	Antiinflammatory	Gao et al. (2021)
	Ichthyotoxicity	Okamura et al. (1997), Nakatani et al. (1998)
	Insect-controlling activity	Okamura et al. (1997)
9 $\beta$ -Hydroxyfraxinellone, dasycarpol (26)	Anticancer activity	Yang et al. (2005)
	Antiinflammatory	Gao et al. (2021)
	Fungistatic activity	Zhao et al. (1997)
	Neuroprotective activity	Yoon et al. (2008)
9 $\alpha$ -Hydroxyfraxinellone (27)	Activity against Brine Shrimp	Fukuyama et al. (2006)
9 $\alpha$ -Hydroxyfraxinellone-9-O- $\beta$ -glucoside (29)	Neuroprotective activity	Yoon et al. (2008)
9 $\alpha$ -Hydroxy-12 $\alpha$ -acetoxyfraxinellone (31)	Activity against Brine Shrimp	Fukuyama et al. (2006)
12 $\alpha$ -Acetoxyfraxinellone (32)	Insect-controlling activity	Nakatani et al. (1998)
12 $\alpha$ -hydroxyfraxinellone (33)	Activity against Brine Shrimp	Fukuyama et al. (2006)
(-)-8,14-Epoxyfraxinellone (34)	Antitrypanosomal activity	Biavatti et al. (2001)
Isofraxinellone (35)	Antiinflammatory activity	Gao et al. (2021)
	Antimutagenic activity	Miyazawa et al. (1995)
	Fungistatic activity	Zhao et al. (1997)
	Ichthyotoxicity	Okamura et al. (1997)
	Insect-controlling activity	Okamura et al. (1997), Okuno et al. (2019)
	Neuroprotective activity	Wang et al. (2014)
	Suppression of SOS-inducing activity	Miyazawa et al. (1995)
Dasylactone A (36)	Antiinflammatory activity	Chen et al. (2020)
Dasylactone B (38)	Antibacterial activity	Wang et al. (2014)
Desfuranoazadiradione (44)	Insect-controlling activity	Siddiqui et al. (2003)
	Melanogenesis inhibitor and chemopreventive effects	Akihisa et al. (2009)
Desfurano-6 $\alpha$ -Hydroxyazadiradione (45)	Insect-controlling activity	Siddiqui et al. (2003)
$\alpha$ -Nimolactone (46)	Antibacterial activity	Kraus et al. (1994)
	Insect-controlling activity	Kraus et al. (1994), Tariq et al. (2004)
	Melanogenesis inhibitor and chemopreventive effects	Akihisa et al. (2009)
$\beta$ -Nimolactone (47)	Antibacterial activity	Kraus et al. (1994)
	Insect-controlling activity	Kraus et al. (1994), Tariq et al. (2004)
	Melanogenesis inhibitor and chemopreventive effects	Akihisa et al. (2009)

(Wang et al. 2019a). Cipaferen R (**49**) was isolated from the twigs and leaves of *Cipadessa baccifera*. This was the first degraded limonoid featuring an acetyl group at the C-17 position (Cao et al. 2020).

Nimbidiol, nimbisonol, nimbione and nimbionone were incorrectly listed as degraded limonoids (Manosroi et al. 2014; Akihisha et al. 2021). However, all these four compounds were originally described as diterpenoids (nimbidiol is a modified diterpenoid of the abiatane skeleton (Majumder et al. 1987); nimbisonol is a tricyclic diterpenoid (Ara et al. 1990); nimbione and nimbionone are two isomeric phenolic diterpenoids (Ara et al. 1988; Siddiqui et al. 1988)).

### Biological activities of degraded limonoids

For the most part, the biological properties of degraded limonoids have not yet been described. However, several degraded limonoids such as calodendrolide (**1**), fraxinellone (**24**) and isofraxinellone (**35**) have proved to be active in diverse biological processes and this could be promising in terms of

developing new active molecules. About 43% of the degraded limonoids described in this review have either not been studied for any biological activity or their negative results have not been described. Even in spite of the promising pharmacological activities showed by some degraded limonoids only a few studies have focused on the pharmacokinetics and bioavailability of these compounds (Chen et al. 2022). The bioactivity of the degraded limonoids tested to date are listed in Table 5.

### Anticancer activity

Naturally occurring bioactive agents, including limonoids such as nimbolide, 29-deactylsendanin (A1542) and 29-isobutylsendanin (A1543), among others, are gaining in popularity over synthetic compounds in preventing and/or treating cancer (Lam et al. 1994; Tian et al. 2001; Ejaz et al. 2006; Bayazit et al. 2010; Bodduluru et al. 2014; Wang et al. 2019b; Shi et al. 2020; Yu et al. 2021). Some computational studies suggest nuclear receptors as the protein targets for limonoid-derived products (Nurlelasari et al. 2020).

**Table 6** Anticancer activities of degraded limonoids

Degraded limonoid	Cell lines	Bioactivity result/References
9 $\alpha$ -Methoxyl dictamdiol ( <b>10</b> )	HL-60 cells	<sup>a</sup> IC <sub>50</sub> = 5.8 $\mu$ M/Qin et al. (2021)
	HeLa cells	<sup>a</sup> IC <sub>50</sub> = 8.1 $\mu$ M/Qin et al. (2021)
	HepG-2 cells	<sup>a</sup> IC <sub>50</sub> > 40 $\mu$ M/Qin et al. (2021)
	A-549 cells	<sup>a</sup> IC <sub>50</sub> = 38.0 $\mu$ M/Qin et al. (2021)
	AGS cells	<sup>a</sup> IC <sub>50</sub> = 21.5 $\mu$ M/Qin et al. (2021)
	MDA-MA-468 cells	<sup>a</sup> IC <sub>50</sub> = > 40 $\mu$ M/Qin et al. (2021)
Fraxinellone ( <b>24</b> )	Cal-27 cells	<sup>a</sup> IC <sub>50</sub> = 22.4 $\mu$ g/mL/Bui et al. (2021)
	SCC-9 cells	<sup>a</sup> IC <sub>50</sub> = 43.4 $\mu$ g/mL/Bui et al. (2021)
	HOS cells	<sup>a</sup> IC <sub>50</sub> = 78.3 $\mu$ M/He et al. (2021)
	MG63 cells	<sup>a</sup> IC <sub>50</sub> = 62.9 $\mu$ M/He et al. (2021)
	A-549 cells	17.8% inhibition on PD-L1 expression at 10 $\mu$ M/Xing et al. (2018) <sup>a</sup> IC <sub>50</sub> > 100 $\mu$ g/mL/Kim et al. (1997)
	MIA PaCa-2 cells	<sup>a</sup> IC <sub>50</sub> = 100.6 $\mu$ M/Lee et al. (2017)
	TGF- $\beta$ -activated NIH3T3 cells	Reverse the increments of pSmad2/3 expression level at 20 $\times$ 10 <sup>-6</sup> M/Pei et al. (2019)
IL-13-stimulated RAW264.7 cells	Reduce to half of M2 phenotype populations in macrophages at 20 $\times$ 10 <sup>-6</sup> M/Pei et al. (2019)	
L1210 cells	<sup>a</sup> IC <sub>50</sub> = 107.3 $\mu$ M/Kim et al. (1997)	
Dasycarpol ( <b>26</b> )	A-549 cells	<sup>a</sup> IC <sub>50</sub> = 20 $\mu$ g/mL/Yang et al. (2005)

<sup>a</sup>IC<sub>50</sub> = Half-maximal inhibitory concentration

Judging from the promising results shown in some studies, degraded limonoids could possess good anticancer therapeutic potential. Their biological targets and range of activity are listed in Table 6.

9 $\alpha$ -Methoxyl dictamdiol (**10**) exhibited cytotoxic activity against the human tumor cell lines HL-60, HeLa, HepG-2, A-549, AGS and, MDA-MA-468. Compound **10** significantly inhibited selective cytotoxic activity against HL-60 ( $IC_{50} = 5.8 \mu M$ ) and HeLa cells ( $IC_{50} = 8.1 \mu M$ ) (Qin et al. 2021). In this study the compound **10** resulted to be more active than a set of limonoids including limonin and obacunone, among others which presented no cytotoxic effects against the mentioned cell lines (Qin et al. 2021). Moreover, a recent mini-review of the biological properties known for fraxinellone (**24**) includes anticancer activity (Bailly and Vergoten 2020). Fraxinellone (**24**) (together with matrine, dictamine, and maackiain) is one of the key active components of the chemopreventive agent of oral cancer antitumor B (ATB) (Bui et al. 2021). This natural product has been shown to inhibit the growth as well as the migration of osteosarcoma cells HOS and MG63. Studies show that its anti-cancer activity stems from promoting excessive autophagy flux (He et al. 2021). Fraxinellone (**24**) has also exhibited anticancer activity by inhibiting programmed cell death-ligand 1 (PD-L1) expression when it was assayed in in vivo studies (Xing et al. 2018). The PD-L1 plays a key role in tumorigenesis and compound **24** produced dose-dependent inhibition by reducing hypoxia-inducible factor-1 $\alpha$  and STAT3. This study demonstrated that fraxinellone (**24**) inhibits proliferation and angiogenesis in cancer cells. Some patented products use fraxinellone (**24**) in the preparation of antitumor drugs because this compound is considered as a tumor cell inhibitor (for example, in leukemia and pancreas cancer cells) and is used to prevent and treat these types of cancer. This natural product did not exhibit any negative effects on normal pancreatic cells (Lee et al. 2017). Another patent identifies this compound as a new antitumor drug because of its tumor suppressing effect (Yu et al. 2013; Yu and Zhu 2017). A novel strategy to treat pancreatic cancer has recently been developed involving fraxinellone-loaded CGKRK-modified nanoparticles (Frax-NP-CGKRK) that interfere with the oncogenic KRAS mutation. It was observed that fraxinellone-NP-CGKRK is able to attenuate the dense stroma barrier, reverse the activated cancer-associated

fibroblasts and enhance tumor blood perfusion (Pei et al. 2019). Cytotoxic activity against lung lymphoma L1210 cell line has also been described for compound **24** (Kim et al. 1997). Other applications have also been developed for the preparation of fraxinellone-containing antitumor drugs (Yu et al. 2013, 2017). Lastly, dasycarpol (**26**) exhibited moderate anticancer activity against lung cancer cell line A549 (Yang et al. 2005).

#### Antiinflammatory activity

Many reports have described the presence of limonoid constituents from Meliaceae and Rutaceae plants which exhibit interesting anti-inflammation activities (Mahmoud et al. 2014a, b; Mireku et al. 2014; Kelley et al. 2015; Hilmayanti et al. 2022). Consequently, interest in these natural anti-inflammatory compounds (Chen et al. 2020; Luo et al. 2020; Yang et al. 2020a, b; Shi et al. 2021) and in the preparation of derived-limonoid compounds (Jia et al. 2020) is clearly on the rise for the treatment of various human ailments. The biological targets and the level of antiinflammatory activity of degraded limonoids are listed in Table 7.

The compounds **2–4**, **7**, **11**, **24–26** and **35** were tested for anti-neuroinflammatory activities by suppressing the nitric oxide (NO) production in lipopolysaccharide (LPS) induced BV-2 cells. Fraxinellone (**24**) and isofraxinellone (**35**) exhibit similar  $IC_{50}$  values to the positive control (quercetin). Dasycarinone A (**11**), fraxinellonone (**25**) and dasycarpol (**26**) showed moderate anti-inflammatory activity ( $IC_{50}$  values: 46.9, 34.3 and 42.9  $\mu M$ , respectively) (Gao et al. 2021). In this study not only degraded limonoids but also a set of non-degraded limonoids were evaluated. Their data pointed out that obacunone-class limonoids exhibited the strongest anti-inflammatory activity among the tested limonoids, followed by fraxinellone (**24**)-class products. Dictamdiol (**2**)-class compounds showed weak activity, while the limonin-class compounds almost had no effect (Gao et al. 2021). Some other reports have described fraxinellone (**24**) as a natural anti-inflammatory. It acts as an inhibitor of inflammasomes in a mouse model. Consequently, compound **24** could lead to the suppression of inflammatory cells during acute pancreatitis by inhibition of pro-inflammatory cytokines (Kim et al. 2019). The anti-inflammatory properties of fraxinellone (**24**) are connected to down-regulations of inducible nitric oxide synthase (iNOS) and

**Table 7** Antiinflammatory activities of degraded limonoids

Degraded limonoid	Cell line/animal model	Bioactivity result/References
Dictamdiol ( <b>2</b> )	BV-2 microglial cells	<sup>a</sup> IC <sub>50</sub> > 50 μM/Gao et al. (2021)
Dictamdiol A ( <b>3</b> )	BV-2 microglial cells	<sup>a</sup> IC <sub>50</sub> > 50 μM/Gao et al. (2021)
Dictamdiol B ( <b>4</b> )	BV-2 microglial cells	<sup>a</sup> IC <sub>50</sub> > 50 μM/Gao et al. (2021)
Isodictamdiol C ( <b>7</b> )	BV-2 microglial cells	<sup>a</sup> IC <sub>50</sub> > 50 μM/Gao et al. (2021)
Dictamlimonol E ( <b>10</b> )	RAW 264.7 cells	<sup>b</sup> NRC 73.3% at 20 μM/Chen et al. (2020)
Dasycarinone A ( <b>11</b> )	BV-2 microglial cells	<sup>a</sup> IC <sub>50</sub> = 46.9 μM/Gao et al. (2021)
Fraxinellone ( <b>24</b> )	Male C57BL/6 mice	Inhibition of the pancreatic activation of multiple inflammasome molecules such as NACHT, LRR, PY-CARD, caspase-1, IL-18, and IL-1β/Kim et al. (2019)
	RAW 264.7 cells	Decreased NO production by 69% at 6.25 μM/ Kim et al. (2009) Inhibition of PGE <sub>2</sub> production at 6.25 μM/Kim et al. (2009) <sup>b</sup> NRC 52.1% at 40 μM/Ruan et al. (2018) <sup>b</sup> NRC 56.5% at 20 μM/Chen et al. (2020)
	BV-2 microglial cells	<sup>a</sup> IC <sub>50</sub> = 23.1 μM/Gao et al. (2021) Suppression JNK activation in a dose-dependent manner/Lee et al. (2009) Inhibition of dsRNA-induced iNOS expression and nitric oxide secretion in a dose-dependent manner/Lee et al. (2009) Suppression of dsRNA-induced TLR3 transcription in a dose-dependent manner/Lee et al. (2009)
	Collagen-induced arthritis in mice	Inhibition of Th17 cell differentiation at 40 μM/Jung et al. (2018)
	Peripheral blood mononuclear cells	Inhibition of osteoclast differentiation at 40 μM/Jung et al. (2018)
	<sup>c</sup> DSS-induced colitis in male C57BL/6 mice	Decrease of the colonic levels of IL-1β, IL-6, IL-18 and TNF-α in a concentration-dependent manner/Wu et al. (2014)
	lipopolysaccharide-induced <sup>d</sup> PDLSCs	Inhibition of concentration of TNF-α, IL-6 and IL-1β at 50 μM/ Fu et al. (2021) Restore the inhibitory effects of lipopolysaccharide on expression of alkaline phosphatase, Runx2, osteocalcin, bone sialoprotein, osteopontin and collagen I/ Fu et al. (2021)
	Fraxinellonone ( <b>25</b> )	BV-2 microglial cells
Dasycarpol ( <b>26</b> )	BV-2 microglial cells	<sup>a</sup> IC <sub>50</sub> = 42.9 μM/Gao et al. (2021)
Isofraxinellone ( <b>35</b> )	BV-2 microglial cells	<sup>a</sup> IC <sub>50</sub> = 20.4 μM/Gao et al. (2021)
Dasyllactone A ( <b>36</b> )	RAW 264.7 cells	<sup>b</sup> NRC 10.5% at 20 μM/Chen et al. (2020)

Percentage of control group, which was set as 100%

<sup>a</sup>IC<sub>50</sub> = Half maximal inhibitory concentration

<sup>b</sup>NRC = Nitrite relative concentration

<sup>c</sup>DSS = Dextran sulfate sodium

<sup>d</sup>PDLSC = Periodontal ligament stem cells

cyclooxygenase-2 (COX-2) due to NF-κB inhibition. Fraxinellone (**24**) also inhibits LPS-induced nitric oxide and prostaglandin E<sub>2</sub> production in RAW 264.7

cells and can reduce the LPS-induced expressions of iNOS (Kim et al. 2009). In a more recent study, fraxinellone (**24**) exhibited inhibitory activity on LPS-



**Table 8** Antifungal activities of degraded limonoids

Degraded limonoid	Fungal strains	Bioactivity result/References
Calodendrolide (1)	<i>Cladosporium cucumerinum</i>	Growth inhibition at 5 µg on TLC plates/Zhao et al. (1997)
Fraxinellone (24)	<i>Alternaria longipes</i>	<sup>a</sup> EC <sub>50</sub> = 64.2 µg/mL/Wang et al. (2006)
	<i>Cladosporium cucumerinum</i>	Growth inhibition at 5 µg on TLC plates. <sup>b</sup> MIC > 500 µg/mL/Zhao et al. (1997)
	<i>Colletrichum lagenarium &amp; verhoeven</i>	72% of inhibition rate at 50 ppm/Yuan et al. (2006)
	<i>Curvularia lunata</i>	<sup>a</sup> EC <sub>50</sub> = 123.3 µg/mL/Wang et al. (2006)
	<i>Rhizotonia cerealis van der Hoeven apud.Boerema &amp; Verhoeven</i>	100% of inhibition rate at 100 ppm/Yuan et al. (2006)
Dasycarpol (26)	<i>Cladosporium cucumerinum</i>	Growth inhibition at 5 µg on TLC plates/Zhao et al. (1997)
Isofraxinellone (35)	<i>Cladosporium cucumerinum</i>	Growth inhibition at 2 µg on TLC plates/Zhao et al. (1997)

<sup>a</sup>EC<sub>50</sub> = Half maximal effective concentration

<sup>b</sup>MIC = Minimum inhibitory concentration

**Table 9** Antibacterial activities of degraded limonoids

Degraded limonoid	Bacterial strains	Bioactivity result/References
Isodictamdiol (5)	<i>Bacillus subtilis</i>	10–12 mm inhibition zone/Zhao et al. (2008)
Fraxinellone (24)	<i>Bacillus megaterium</i>	99.8% of inhibition rate at 50 ppm/Yuan et al. (2006)
	<i>Escherichia coli</i>	100% of inhibition rate at 50 ppm/Yuan et al. (2006)
	<i>Staphylococcus aureus</i>	99.8% of inhibition rate at 50 ppm/Yuan et al. (2006)
Fraxinellonone (25)	<i>Escherichia coli</i>	10–12 mm inhibition zone/Zhao et al. (2008)
Dasyllactone B (38)	<i>Staphylococcus aureus</i>	<sup>a</sup> MIC = 160 g/mL/Wang et al. (2014)
Nimolactone A (46)	<i>Bacillus subtilis</i>	Growth inhibition at 10 µg/Kraus et al. (1994)
Nimolactone B (47)	<i>Bacillus subtilis</i>	Growth inhibition at 10 µg/Kraus et al. (1994)

<sup>a</sup>MIC = Minimum inhibitory concentration

induced NO production at 40 µM when it was assayed in RAW 264.7 macrophages (Ruan et al. 2018). Regarding viral-induced neuroinflammation, this natural compound also inhibited double-stranded RNA-induced nitric oxide synthase expression which is related to viral-infected microglia (Lee et al. 2009). Inflammatory arthritis was analysed after treatment with fraxinellone (24) in mice and a clear mitigation effect was observed. Synovial inflammation and osteoclastogenesis was reduced. This process has been associated with the inhibition of cellular differentiation and activation (Jung et al. 2018). The aftereffect of fraxinellone (24) in colonic inflammation has also been studied in in vitro assays. The use of

fraxinellone (24) in mice as animal models that mimic inflammatory bowel disease, specifically in dextran sulfate sodium-induced colitis, showed a decrease in the colonic levels of interleukin IL-1β, IL-6, IL-18 and tumor necrosis factor (TNF)-α (Wu et al. 2014). It has also recently been demonstrated that fraxinellone (24) alleviates inflammation and promotes osteogenic differentiation in lipopolysaccharide-stimulated periodontal ligament stem cells (PDLSCs) (Fu et al. 2021). Compounds 10, 24 and 36 exhibited stronger NO production inhibitory effects in RAW 264.7 cells than intact limonoid derivatives such as dictamlimonol A, dictamlimonoside B, limonin and obacunone. The levels of five proteins, specifically, TNF-α, IL-6,

iNOS, NF- $\kappa$ B, and COX-2, in LPS-stimulated RAW 264.7 cells were also evaluated for these compounds. The reduced expression of these parameters, which are directly linked to inflammation, pointed to dasylactone A (**36**) as a beneficial compound in reducing inflammation (Chen et al. 2020).

### Antimicrobial activity

Some limonoids isolated from medicinal plants have also attracted attention for their fungicidal (Adesogan and Taylor 1970; Adesisa et al. 1971; Champagne et al. 1992; Abdelgaleil et al. 2000, 2005) and bactericidal properties (Liu et al. 2013b; Zhang et al. 2007b; Rahman et al. 2009). The observed antimicrobial effects of degraded limonoids have been classified based on their antifungal or antibacterial activities (Tables 8 and 9).

**Antifungal activity:** Calodendrolide (**1**), fraxinellone (**24**), 9 $\beta$ -hydroxyfraxinellone (**26**) and isofraxinellone (**35**) exhibited fungistatic activity against the plant pathogenic fungus *Cladosporium cucumerinum*. Growth inhibition in a TLC bioassay was 5  $\mu$ g for compounds **1**, **24** and **26** and 2  $\mu$ g for compound **35**. The minimum inhibitory concentration observed for fraxinellone (**24**) was greater than 500  $\mu$ g/mL (Zhao et al. 1997). It is remarkable that in spite of degraded limonoids **1**, **24**, **26** and **35** were isolated together with five limonoid compounds (limonin, obacunone, 7 $\alpha$ -acetylobacunol, 7 $\alpha$ -acetyldihydnomilin and limonin diosphenol) from the root bark of *Dictamnus dasycarpus* Turcz, these degraded limonoids exhibited fungistatic activity against *C. cucumerinum* while limonoids resulted to be inactive even when 100  $\mu$ g were spotted on TLC plates. This fact suggests a positive response of the plants against potentially fungal attacks involving a biodegradation of limonoids into their degraded derivatives (Zhao et al. 1997). Compound **24** was also active against *Alternaria longipes* and *Curvularia lunata* (EC<sub>50</sub> values of 64.2  $\mu$ g/mL and 123.3  $\mu$ g/mL, respectively) (Wang et al. 2006). Fraxinellone (**24**) was also tested against plant diseases and its inhibition rate against *Rhizoctonia cerealis* van der Hoeven apud. Boerema & Verhoeven was 100% (at 100 ppm) and against *Colletotrichum lagenarium* & *verhoeven* was 72% (at 50 ppm) (Yuan et al. 2006). Additionally, molecular dynamics simulation identified fraxinellone (**24**) as a probable antifungal drug candidate against

*Fusarium graminearum* (Joshi et al. 2021). Cipaferen R (**49**) was inactive in antifungal assays against *Fusarium oxysporum* f. sp. cubense and *Ralstonia solanacearum* (Cao et al. 2020).

**Antibacterial activity:** isodictamdiol (**5**) exhibited weak antibacterial activity against the Gram-(+) bacteria *Bacillus subtilis* (showing a growth inhibition zone diameter of 10–12 mm) and was not active against *Staphylococcus aureus* or *Escherichia coli* (Zhao et al. 2008). However, its stereoisomer dictamdiol (**2**) was inactive against these three bacteria (Zhao et al. 2008). Fraxinellone (**24**) exhibited no antibacterial inhibition in this study while fraxinellone (**25**) exhibited weak antibacterial activity against *E. coli* (10–12 mm inhibition zone) (Zhao et al. 2008). In this antibacterial assay some intact limonoids were also evaluated. Limonin, obacunone and evodol were inactive against *B. subtilis* and *E. coli* (Zhao et al. 2008). Fraxinellone (**24**) showed antibacterial activity against *S. aureus* and *B. megaterium* with a 99.8% of inhibition rate at 50 ppm whereas 100% of inhibition rate was observed for *E. coli* (Yuan et al. 2006). Dasylactone B (**38**) was active against *S. aureus* with a MIC value of 160 g/mL (Wang et al. 2014). Nimolactones **46** and **47** exhibited antibacterial activity against *Bacillus subtilis* at doses of 10  $\mu$ g (Kraus et al. 1994).

### Insect-controlling activity

Plants have developed many defense strategies against insects producing an arsenal of phytochemical weapons resulting from the coevolution of plants and insects (Ehrlich and Raven 1964; Bentley et al. 1990). This is exemplified by the Meliaceae and Rutaceae plant families which are sources of many biopesticides including limonoids (Yang and Tang 1988; Akhtar et al. 2008; Morgan 2009). From among these active plant metabolites, the insecticidal activity of calodendrolide (**1**) and fraxinellone (**24**) has been evaluated in several insect-control studies (Lei et al. 2020). The insecticidal activities of degraded limonoids are listed in Table 10.

Calodendrolide (**1**) was active as a larvicidal compound against the dengue mosquito *Aedes aegypti* Linn showing a LC<sub>50</sub> value of 13.1  $\mu$ M, which is higher than the LC<sub>50</sub> exhibited by pyroangolensolide (**18**) (16.6  $\mu$ M) (Kiprop et al. 2005, 2007).

**Table 10** Insecticidal activities of degraded limonoids

Degraded limonoid	Insects	Bioactivity result/References
Calodendrolide (1)	Mosquito <i>Aedes aegypti</i> Linn	- Larvicidal activity ( <sup>a</sup> LC <sub>50</sub> = 13.1 μM for 2 <sup>nd</sup> -instar larvae)/Kiprop et al. (2005, 2007)
Pyroangolensolide (18)	Mosquito <i>Aedes aegypti</i> Linn	- Larvicidal activity ( <sup>a</sup> LC <sub>50</sub> = 16.6 μM for 2 <sup>nd</sup> -instar larvae)/Kiprop et al. (2007)
Azedaralide (19)	Leafworm <i>Spodoptera littoralis</i>	- Antifeedant activity (active at 500 ppm for 3 <sup>rd</sup> -instar larvae by the leaf disk method)/Nakatani et al. (1998)
Fraxinellone (24)	Armyworm <i>Mythimna separata</i>	- Ovicidal activity ( <sup>b</sup> HR = 54% for 5 mg/mL; <sup>b</sup> HR = 52% for 10 mg/mL; <sup>b</sup> HR = 48% for 20 mg/mL)/Lv et al. (2020)
	Walker	- Antifeedant activity for 3 <sup>rd</sup> -instar larvae (90.4%)/Yuan et al. (2006); Yuan and Wang (2012)
		- Mortality for 3 <sup>rd</sup> -instar larvae (95.2%)/Yuan et al. (2006); Yuan and Wang (2012)
		- Feeding deterrent activity ( <sup>a</sup> LC <sub>50</sub> = 15.95 mg/mL)/Lü et al. (2013)
		- Changes in the levels of digestive and detoxification enzymes in the 5 <sup>th</sup> instar larvae/Lv et al. (2014)
		- Structural changes in the midgut epithelium at 20 mg/mL/Min et al. (2010); Lü et al. (2010)
	Moth <i>Plutella xylostella</i>	- Feeding deterrent activity ( <sup>a</sup> LC <sub>50</sub> = 6.43 mg/mL)/Lü et al. (2013)
	Moquito <i>Culex pipiens</i>	- Feeding deterrent activity for 4 <sup>th</sup> -instar larvae (3.60 × 10 <sup>-2</sup> mg/mL)/Lü et al. (2013)
	Beetle <i>Tribolium castaneum</i>	- Antifeedant activity ( <sup>c</sup> EC <sub>50</sub> = 36.4 ppm for adults and <sup>c</sup> EC <sub>50</sub> = 29.1 ppm for larvae)/Liu et al. (2002)
	Beetle <i>Sitophilus zeamais</i>	- Antifeedant activity ( <sup>c</sup> EC <sub>50</sub> = 71.2 ppm for adults)/Liu et al. (2002)
	Moth <i>Ostrinia furnacalis</i>	- Growth inhibition (from <sup>d</sup> RGR = 0.59 mg/mg/day for 3 ppm of treatment to 0.07 mg/mg/day for 300 ppm of treatment)/Liu et al. (2008)
		- Antifeedant activity (from <sup>e</sup> RGR = 4.01 mg/mg/day for 3 ppm to 0.71 mg/mg/day for 300 ppm)/Liu et al. (2008)
	Budworm <i>Heliothis virescens</i>	- Growth inhibition (from <sup>d</sup> RGR = 0.98 mg/mg/day for 12.9 ppm of treatment to 0.12 mg/mg/day for 1293.1 ppm of treatment)/Liu et al. (2009)
		- Antifeedant activity (from <sup>e</sup> RGR = 5.88 mg/mg/day for 12.9 ppm to 1.24 mg/mg/day for 1293.1 ppm)/Liu et al. (2009)
	Cutworm <i>Agrotis ypsilon</i>	- Feeding deterrent activity for 2 <sup>nd</sup> -instar larvae ( <sup>f</sup> AFC <sub>50</sub> = 12.58 (mg/mL)/Lü et al. (2013)
	Leafworm <i>Spodoptera littoralis</i>	- Antifeedant activity (active at 500 ppm for 3 <sup>rd</sup> -instar larvae by the leaf disk method)/Nakatani et al. (1998)
	Leafworm <i>Spodoptera litura</i>	- Antifeedant activity ( <sup>g</sup> ED <sub>50</sub> = 5.06 μg/cm <sup>2</sup> )/Okuno et al. (2019)

**Table 10** continued

Degraded limonoid	Insects	Bioactivity result/References
Fraxinellonone (25)	Leafworm <i>Spodoptera exigua</i> H	- Antifeedant activity (strong activity at 1000 ppm (remainder leaf disk > 50%); moderate activity at 500 ppm (remainder leaf disk < 50%)) <sup>g</sup> Okamura et al. (1997)
12 $\alpha$ -Acetoxyfraxinellone (32)	Leafworm <i>Spodoptera littoralis</i>	- Antifeedant activity (active at 500 ppm for 3 <sup>rd</sup> -instar larvae by the leaf disk method)/Nakatani et al. (1998)
Isofraxinellone (35)	leafworm <i>Spodoptera exigua</i> H	- Antifeedant activity (moderate activity at 1000 ppm (remainder leaf disk < 50%)) <sup>g</sup> Okamura et al. (1997)
	Leafworm <i>Spodoptera litura</i>	- Antifeedant activity ( <sup>g</sup> ED <sub>50</sub> = 4.43 $\mu$ g/cm <sup>2</sup> )/Okuno et al. (2019)
Desfuranoazadiradione (44)	Mosquito <i>Anopheles stephensi</i>	- Pesticidal activity ( <sup>a</sup> LC <sub>50</sub> = 37 ppm for 4 <sup>th</sup> -instar larvae)/Siddiqui et al. (2003)
Desfurano-6 $\alpha$ -hydroxyazadiradione (45)	Mosquito <i>Anopheles stephensi</i>	- Pesticidal activity ( <sup>a</sup> LC <sub>50</sub> = 43 ppm for 4 <sup>th</sup> -instar larvae)/Siddiqui et al. (2003)
	Liston	
$\alpha$ -Nimolactone (46)	mosquito <i>Anopheles stephensi</i>	- Larvicidal activity ( <sup>a</sup> LC <sub>50</sub> = 60 ppm for 4 <sup>th</sup> -instar larvae)/Tariq et al. (2004)
	Liston	
$\beta$ -Nimolactone (47)	Beetle <i>Epilachna varivestis</i>	- Antifeedant activity ( <sup>c</sup> EC <sub>50</sub> = 80 ppm)/Kraus et al. (1994)
	mosquito <i>Anopheles stephensi</i>	- Larvicidal activity ( <sup>a</sup> LC <sub>50</sub> = 45 ppm for 4 <sup>th</sup> -instar larvae)/Tariq et al. (2004)
	Liston	
	Beetle <i>Epilachna varivestis</i>	- Antifeedant activity ( <sup>c</sup> EC <sub>50</sub> = 80 ppm)/Kraus et al. (1994)

<sup>a</sup>LC<sub>50</sub> = Half maximal lethal concentration<sup>b</sup>HR = hatching rate<sup>c</sup>EC<sub>50</sub> = Half maximal effective concentration<sup>d</sup>RGR = relative growth rate<sup>e</sup>RCR = relative consumption rate<sup>f</sup>AFC<sub>50</sub> = Median antifeedant concentration<sup>g</sup>Results for synthesized (±)-fraxinellonone or (±)-isofraxinellone

Fraxinellone (24) exhibited interesting pesticidal activities against many insects (Yang et al. 2018a). It was evaluated for its potential ovicidal activity against the insects *Mythimna separata* Walker and *Bombyx*

*mori* Linnaeus exhibiting selective activity against the eggs of *M. separata*. Eggshell size was reduced and the egg hatching inhibited. However, morphological changes were not observed in the eggshells of *B. mori*

(Lv et al. 2020). In other studies, the antifeeding and mortality rates at 72 h against third-instar armyworm *M. separata* showed by fraxinellone (**24**) were 90.4% and 95.2%, respectively (Yuan et al. 2006; Yuan and Wang 2012). Using *M. separata* as a model insect, the insecticidal mechanism of this natural product on the peritrophic membrane of sixth instar larvae in both in vitro and in vivo treatments was studied. When fraxinellone (**24**) was applied at a concentration of 20 mg/mL, a decrease in the protein content and an increase in carbohydrate content were observed when 8 mg/mL was added. In the in vivo assay, an increase in carbohydrate content was also observed at a concentration of 20 mg/mL of fraxinellone. Hence, treatments with this compound modified the carbohydrate or protein content and also altered the structure of the peritrophic membrane compared to the control group (Lu et al. 2014). Recently, study of the interactions between three kinds of DNA (armyworm, salmon sperm and calf thymus) and natural product **24** showed only weak interaction. This theoretical study supports the possible application of this compound as a pesticide (Lei et al. 2020). Studies have also been conducted to determine antifeedant and larvicidal effects against four major pests, *Mythimna separata*, *Agrotis ypsilon*, *Plutella xylostella* and *Culex pipiens pallens*. Fraxinellone (**24**) acted as a feeding deterrent against the Lepidopteran larvae *M. separata*, *A. ypsilon*, and *P. xylostella*. It also proved toxic, with LC<sub>50</sub> values of 15.95 mg/mL, against the third instar larvae of *M. separata*, 6.43 mg/mL against the second instar of *P. xylostella* and  $3.60 \times 10^{-2}$  mg/mL against the fourth instar larvae of *C. pipiens*. Pupation rate inhibition was also observed as was growth and egg hatching rate in *M. separate* (Lü et al. 2013). Fraxinellone (**24**) produces structural changes in the midgut epithelium of the lepidoptera *M. separata* Walker at a dosis of 20 mg/mL (Min et al. 2010). Compound **24** also exhibited antifeedant activity against the insects *Tribolium castaneum* and *Sitophilus zeamais* (EC<sub>50</sub> values of 36.4 and 29.1 ppm for adults and larvae of *T. castaneum*, respectively, and EC<sub>50</sub> value of 71.2 for *S. zeamais* adults) (Liu et al. 2002). When *Ostrinia furnacalis* (Asian corn borer) and *Heliothis virescens* (tobacco budworm) were fed with fraxinellone (**24**) at a concentration of 10 ppm (and above) and  $4.31 \times 10^{-5}$  mol/L (and above) respectively, growth and food consumption rate were reduced significantly (Liu et al. 2008, 2009). The

larval midguts of both insects showed reduced activity of the proteins  $\alpha$ -amilase and non-specific proteases, and showed higher activity of cytochrome P450s. Fraxinellone (**24**) acts as a digestive poison against *M. separata*, affecting the epithelium membrane in the midgut of this insect (Lü et al. 2010). It also produced changes in the levels of digestive and detoxification enzymes in 5th instar larvae of *M. separata* ( $\alpha$ -amilase activity was inhibited whereas protease activity was increased (Lv et al. 2014). It was also toxic against the black cutworm *Agrotis ypsilon* (Lü et al. 2013). Fraxinellone (**24**) also exhibited feeding deterrent activity and reduced growth rate and food consumption in *Tribolium castaneum* at a concentration of 10 ppm for both adults and larvae (Liu et al. 2002).

Fraxinellonone (**25**) exhibited moderate insect-antifeedant activity against *Spodoptera exigua* (Okamura et al. 1997) and isofraxinellone (**35**) exhibited potent antifeedant activity against larvae of *Spodoptera litura* ( $4.43 \mu\text{g}/\text{cm}^2$ ) (Okuno et al. 2019). Insect antifeedant experiments against the third-instar larvae of *Spodoptera littoralis* showed that azedaralide (**19**), fraxinellone (**24**) and 12 $\alpha$ -acetoxyfraxinellone (**32**) were active at 500 ppm ( $10 \mu\text{g}/\text{cm}^2$ ). However, fraxinellonone (**25**) did not exhibit any antifeedant activity (Nakatani et al. 1998). 8,14-Epoxy-fraxinellone (**34**) was evaluated against ant species *Atta sexdens rubropilosa* (also known as leaf-cutting ants) but was not toxic to them (Wang et al. 2016). Desfuranoadiradione (**44**) and its derivative desfurano-6  $\alpha$ -hydroxyazadiradione (**45**) was toxic against *Anopheles stephensi* Liston at 37 and 43 ppm, respectively (Siddiqui et al. 2003). Both  $\alpha$ -Nimolactone (**46**) and  $\beta$ -nimolactone (**47**) exhibited toxicity against *Anopheles stephensi* Liston, specifically against its 4<sup>th</sup>-instar larvae of the malaria vector mosquito with LC<sub>50</sub> values of 60 and 45 ppm, respectively (Siddiqui et al. 2003; Tariq et al. 2004). Nimolactones **46** and **47** exhibited moderate antifeedant activity against *Epilachna varivestis* (EC<sub>50</sub> values of 80 ppm) (Kraus et al. 1994).

#### Neuroprotective activity.

Some limonoids assayed for the treatment of neurodegenerative diseases showed notable neuroprotective activity (Abdelgaleil et al. 2000; Yoon et al. 2008; Sun et al. 2015b; Ouyang et al. 2016). Several degraded limonoids have also been evaluated for this activity. Their biological targets and the range of activity are listed in Table 11.

**Table 11** Neuroprotective activities of degraded limonoids

Degraded limonoid	Cell line	Bioactivity result/References
Calodendrolide ( <b>1</b> )	Glutamate-induced toxicity in primary cultures of rat cortical cells	<sup>a</sup> EC <sub>50</sub> = 0.019 μM at 0.1 μM/Yoon et al. (2008, 2010)
Dictamdiol A ( <b>3</b> )	Glutamate-induced toxicity in primary cultures of rat cortical cells	<sup>a</sup> EC <sub>50</sub> = 0.068 μM at 0.1 μM/Yoon et al. (2008)
Dictamnusine ( <b>13</b> )	Glutamate-induced toxicity in primary cultures of rat cortical cells	<sup>a</sup> EC <sub>50</sub> = 0.042 μM at 0.1 μM/Yoon et al. (2008)
Fraxinellone ( <b>24</b> )	Glutamate-induced toxicity in primary cultures of rat cortical cells	<sup>a</sup> EC <sub>50</sub> = 0.022 μM at 0.1 μM/Yoon et al. (2008)
	H <sub>2</sub> O <sub>2</sub> -induced injury in SH-SY5Y cells	10.72% of increase in cell viability at 10 μM/Wang et al. (2014)
Dasycarpol ( <b>26</b> )	Glutamate-induced toxicity in primary cultures of rat cortical cells	<sup>a</sup> EC <sub>50</sub> = 0.098 μM at 0.1 μM/Yoon et al. (2008)
9α-Hydroxyfraxinellone-9-O-β-glucoside ( <b>29</b> )	Glutamate-induced toxicity in primary cultures of rat cortical cells	<sup>a</sup> EC <sub>50</sub> = 0.705 μM at 1.0 μM/Yoon et al. (2008)
Isofraxinellone ( <b>35</b> )	H <sub>2</sub> O <sub>2</sub> -induced injury in SH-SY5Y cells	12.68% of increase in cell viability at 10 μM/Wang et al. (2014)

<sup>a</sup>EC<sub>50</sub> = Half maximal effective concentration

Calodendrolide (**1**) showed promising protection against glutamate-induced neurotoxicity when assayed in primary cultures of rat cortical cells at a concentration of 0.1 μM. It exhibited an even greater neuroprotective effect than the positive control dizocipiline maleate (MK-801, a non-competitive NMDA receptor antagonist) **1** (Yoon et al. 2008). In the same toxicity assay, dictamdiol A (**3**), dictamnusine (**13**), fraxinellone (**24**) and dasycarpol (**26**) also proved active with EC<sub>50</sub> values of 0.068, 0.042, 0.022 and 0.098, respectively at 0.1 μM whereas compound **29** possessed an EC<sub>50</sub> value of 0.705 at 1.0 μM (Yoon et al. 2008). The neuroprotective mechanism involves the inhibition of calcium influx and the overproduction of reactive oxygen species and cellular nitric oxide. This all implies protection of neuronal cells against glutamate-induced oxidative stress (Yoon et al. 2010). Fraxinellone (**24**) and isofraxinellone (**35**) exhibited neuroprotective activity against H<sub>2</sub>O<sub>2</sub>-induced injury in SH-SY5Y cells (Wang et al. 2014).

#### Other biological activities

Degraded limonoids have also shown other interesting biological activities which are summarized in Table 12.

Calodendrolide (**1**) exhibited antiangiogenic activity on internode blood vessels when assayed in Zebrafish at a concentration of 20 mg/L (Yin et al. 2016). Dictamdiol (**2**), isodictamdiol A (**6**) and fraxinellone (**24**) exhibited significant inhibitory effects against adenosine diphosphate-induced blood platelet aggregation at 250 μM. Compound **6** also exhibited anti-platelet aggregation activity (Sun et al. 2013). Fraxinellone (**24**) has displayed a broad range of other bioactivities. The vasorelaxing activity of fraxinellone (**24**) was studied on rats and proved to be an effective vasorelaxant. Fraxinellone (**24**) acts as a selective blocker of voltage-dependent Ca<sup>2+</sup> channel (Yu et al. 1992). This natural product has also been added to medicines to treat allergic skin diseases as it induces Th1 type cells to produce IFN-γ (Lu et al. 2021). When fraxinellone (**24**) was administered to mice with passive skin allergy at a concentration of 100 mg/kg, the inhibition rate of skin mast cell degranulation reached 62.5% (Lu et al. 2021). Inhibitory effects on oxidative stress-senescence were also attributed to fraxinellone (**24**) where AMP-activated protein kinases seem to be involved in an autophagic mechanism associated to age-related decay (Han et al. 2018). The antifertility activity of fraxinellone (**24**) was apparently related to the inhibition of the implantation process in female Sprague–Dawley rats.



**Table 12** Other biological activities of degraded limonoids

Natural product	Biological activity	Bioactivity result/references
Calodendrolide (1)	Antigiogenic effect	Active at 20 mg/L/Yin et al. (2016)
Dictamdiol (2)	Antiplatelet aggregation activity	Active at 250 $\mu$ M/Sun et al. (2013)
Isodictamdiol A (6)	Antiplatelet aggregation activity	Active at 250 $\mu$ M/Sun et al. (2013)
Fraxinellone (24)	Activity in liver disorders	Increase of the percentage of apoptosis in <sup>a</sup> Con A-activated CD4 <sup>+</sup> T cells in vitro in a concentration-dependent manner/Sun et al. (2009)
		Induced apoptosis of activated peripheral CD4 <sup>+</sup> T cells from female C57BL/6 mice/Sun et al. (2009)
	Antifertility activity	Prevent the implantation of ova in inbred female Sprague–Dawley rats at 106 mg/kg/Woo et al. (1987)
	Antifibrotic activity	Decrease in <sup>b</sup> TAFs and stroma deposition in BPD6 tumor-bearing C57BL/6 mice at a dose of 30 mg/Kg/Hou et al. (2018)
	Antiplatelet aggregation activity	Active at 250 $\mu$ M/Sun et al. (2013)
	Cytotoxic activity	Decrease the cell viability in HepG2 cells at 200 mg/mL/Fan et al. (2018)
		<sup>c</sup> LD <sub>50</sub> = 274 mg/kg in male mice/Woo et al. (1987)
	Fibroblast activator	Inhibit the accumulation of collagen $\alpha$ 1 in the renal tissues of C57BL/6 mice/Zheng et al. (2021)
		Inhibit the activation of kidney fibroblasts by downregulating the expression of CUGBP1 in NRK-52E cells/Zheng et al. (2021)
	Hepatotoxic activity	Increase the serum <sup>d</sup> ALT and <sup>e</sup> AST activities in a dose-dependent manner in ICR mice/Zhou et al. (2020)
	Ichthyotoxicity	Active at 10 ppm against <i>Oryzias latipes</i> /Okamura et al. (1997); Nakatani et al. (1998)
	Senescence inhibition	Reduce the expression of senescence-associated-genes in NIH3T3 cells at 50–200 $\mu$ M/Han et al. (2018)
Th1 type cells promoter to produce IFN- $\gamma$	<sup>f</sup> IR = 62.5% of skin mast cell in BALB/c mice at 100 mg/kg/Lu et al. (2021)	
Vascular relaxing activity	Block of voltage-dependent Ca <sup>2+</sup> channel in rat thoracic aorta at 100 $\mu$ M/Yu et al. (1992)	
	4% contraction on wistar rat thoracic aorta caused by KCl at 500 $\mu$ M/Yu et al. (1992)	
Fraxinellonone (25)	Ichthyotoxicity	Active at 50 ppm against <i>Oryzias latipes</i> /Okamura et al. (1997); Nakatani et al. (1998)
9 $\alpha$ -Hydroxyfraxinellone (27)	Activity against Brine Shrimp	<sup>g</sup> LC <sub>50</sub> = 32.0 $\mu$ M against <i>Artemia salina</i> /Fukuyama et al. (2006)
9 $\alpha$ -Hydroxy-12 $\alpha$ -acetoxyfraxinellone (31)	Activity against Brine Shrimp	<sup>g</sup> LC <sub>50</sub> = 6.5 $\mu$ M against <i>Artemia salina</i> /Fukuyama et al. (2006)
12 $\alpha$ -Hydroxyfraxinellone (33)	Activity against Brine Shrimp	<sup>g</sup> LC <sub>50</sub> = 50.2 $\mu$ M against <i>Artemia salina</i> /Fukuyama et al. (2006)
(-)-8,14-Epoxyfraxinellone (34)	Antitrypanosomal activity	<sup>h</sup> IC <sub>50</sub> = 246.8 $\mu$ g/mL against <i>Trypanosome cruzi</i> /Biavatti et al. (2001)



**Table 12** continued

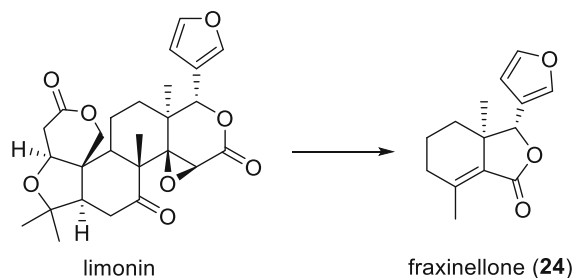
Natural product	Biological activity	Bioactivity result/references
Isofraxinellone ( <b>35</b> )	Antimutagenic activity	<sup>i</sup> ID <sub>50</sub> = 0.24 μM on furylfuramide/Miyazawa et al. (1995) <sup>i</sup> ID <sub>50</sub> = 0.30 μM on Trp-P-1/Miyazawa et al. (1995)
	Suppression of SOS-inducing activity	<sup>i</sup> ID <sub>50</sub> = 0.35 μM on furylfuramide/Miyazawa et al. (1995) <sup>i</sup> ID <sub>50</sub> = 0.50 μM on Trp-P-1/Miyazawa et al. (1995)
	Ichthyotoxicity	Moderate activity at 10 ppm/Okamura et al. (1997);
Desfuranoazadiradione ( <b>44</b> )	Melanogenesis inhibitor and chemopreventive effects	13.6% melanin content at 25 mg/mL/Akihisa et al. (2009)
α-Nimolactone ( <b>46</b> )	Melanogenesis inhibitor and chemopreventive effects	18.3% melanin content at 25 mg/mL/Akihisa et al. (2009)
β-Nimolactone ( <b>47</b> )	Melanogenesis inhibitor and chemopreventive effects	6.1% melanin content at 25 mg/mL/Akihisa et al. (2009)

<sup>a</sup>Con A = Concanavalin A<sup>b</sup>Tumor-associated fibroblasts<sup>c</sup>LD<sub>50</sub> = Half maximal lethal dose<sup>d</sup>ALT = Alanine aminotransferase<sup>e</sup>AST = Aspartate transaminase<sup>f</sup>IR = Inhibition rate<sup>g</sup>LC<sub>50</sub> = Half maximal lethal concentration<sup>h</sup>IC<sub>50</sub> = Half maximal inhibitory concentration<sup>i</sup>ID<sub>50</sub> = Half maximal infective dose

Furthermore, it also exhibited oral toxicity in female rats with a LD<sub>50</sub> value of 274 mg/kg (Woo et al. 1987). In addition to the previously described activities, compound **24** has been targeted as a potential natural product useful in the treatment of some liver disorders. Results show that fraxinellone (**24**) induces apoptosis in activated peripheral CD4<sup>+</sup> T cells and results in less CD4<sup>+</sup> activation and infiltration to the liver (Sun et al. 2009). Fraxinellone (**24**) has also been reported to be a potential hepatotoxic metabolite linked to a significant elevation of serum alanine aminotransferase and aspartate aminotransferase observed in experiments on mice (Zhou et al. 2020). On the basis of this natural compound has excellent antihepatic fibrosis activity, Li et al. recently evaluated the capacity of cyclodextrin derivatives with fraxinellone (**24**) to increase solubility and find optimal oral fraxinellone formulations for anti-fibrotic therapy (Li et al. 2021). A recent study conducted on mice showed that fraxinellone (**24**) could alleviate folic acid-induced kidney fibrosis by inhibition of the activation of kidney fibroblasts and therefore it could potentially be a candidate as a new drug to treat chronic kidney disease (Zheng et al. 2021). Fraxinellone (**24**) is one of several drugs in a nano preparation for the treatment of hepatic fibrosis

disorder (Jiang et al. 2018). The anti-fibrotic effects of a nanoemulsion formulation containing fraxinellone have recently been analysed in a tumor microenvironment (as it could stunt melanoma). Studies showed that the fraxinellone nanoemulsion combined with a tumor-specific peptide vaccine might remodel the tumor microenvironment (Hou et al. 2018). Subchronic toxicity studies using the colorimetric counting kit 8 assay (CCK-8) in HepG2 cells revealed that fraxinellone (**24**) decreased the cell viability (Fan et al. 2018). Fraxinellone (**24**) and fraxinellone (**25**) also exhibited ichthyotoxic activity against the Japanese killifish *Oryzias latipes* at 10 and 50 ppm, respectively (Nakatani et al. 1998). Okamura et al. synthesized (±)-fraxinellone ((±)-**24**) and (±)-isofraxinellone ((±)-**35**) from fraxinellone ((±)-**25**) and these related compounds were then evaluated against killifish and all exhibited high levels of ichthyotoxicity at 50 ppm at 12 h (Okamura et al. 1997). The effects of fraxinellone (**24**) and isofraxinellone (**35**) on the mutagenicity of furylfuramide and Trp-P-1 were evaluated in the umu test and Ames test (Miyazawa et al. 1995). Fraxinellone (**24**) was found to be inactive in these tests. However, isofraxinellone (**35**) suppressed the SOS-induction activity of

furylfuramide at 0.86  $\mu\text{mol/mL}$  in the umu test showing an  $\text{ID}_{50}$  value of 0.35  $\mu\text{mol/mL}$ . The  $\text{ID}_{50}$  value was 0.50  $\mu\text{mol/mL}$  when assayed with the mutagen Trp-P-1. In the Ames test using *Salmonella typhimurium* TA100, isofraxinellone (**35**) completely suppressed furylfuramide mutagenicity at 0.65  $\mu\text{mol/mL}$  ( $\text{ID}_{50}$  of 0.24  $\mu\text{mol/mL}$ ), and at 0.73  $\mu\text{mol/mL}$  with the mutagen Trp-P-1 ( $\text{ID}_{50}$  of 0.30  $\mu\text{mol/mL}$ ) (Miyazawa et al. 1995). Kinase Src is considered a target for drug development based on its established relationship with cancer and possible link to hypertension. Molecular dynamics simulation and molecular docking suggested that 9 $\alpha$ -hydroxyfraxinellone-9-*O*- $\beta$ -D-glucoside (9HFG, **29**) has stable binding affinities with Src kinase and could have an inhibitory effect against this Src kinase by competitive binding against ATP. Also, compound **29** could be a potential ligand competing for the link to kinase Src (Tou and Chen 2012). Compounds 9 $\alpha$ -hydroxyfraxinellone (**27**), 9 $\alpha$ -hydroxy-12 $\alpha$ -acetoxyfraxinellone (**31**) and 12 $\alpha$ -hydroxyfraxinellone (**33**) were 100% lethal at 100  $\mu\text{M}$  in the Brine Shrimp Lethality Test (against *Artemia salina*) (Fukuyama et al. 2006). (-)-8,14-Epoxyfraxinellone (**34**) exhibited weak activity against trypomastigote forms of *Trypanosoma cruzi*, with an  $\text{IC}_{50}$  value of 246.8  $\mu\text{g/mL}$  whereas other intact limonoid derivatives isolated from the same species such as limonin, limonexic acid, kihadalactone B and (-)-21-*O*-methyl-limonexic acid showed no activity (Biavatti et al. 2001). Desfuranoazadiradione (**44**),  $\alpha$ -nimolactone (**46**) and  $\beta$ -nimolactone (**47**) were tested on melanogenesis in B16 melanoma cells. Compounds **44** and **46** exhibited a marked inhibitory effect in this assay. Compounds **44** and **46–47** also exhibited inhibitory effects against the Epstein-Barr virus early antigen activation induced by 12-*O*-tetradecanoylphorbol-13-acetate (Akihisa et al. 2009). Chuktabin L (**48**) was evaluated for acetylcholinesterase inhibitory activity but was inactive (Wang et al.



**Scheme 2** Limonin, hypothetic precursor of fraxinellone (**24**) (Coggon et al. 1969)

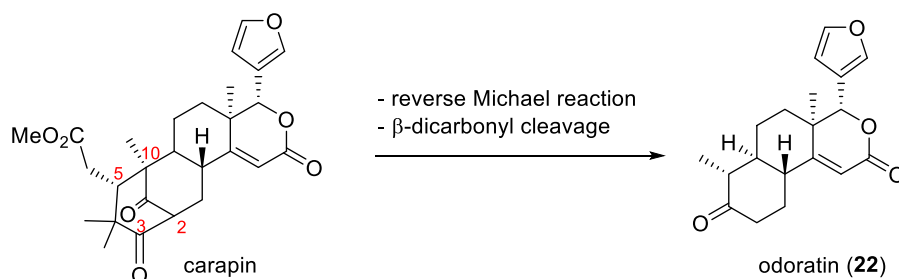
2019a). Cipaferen R (**49**) was evaluated for nematocidal activity against *Meloidogyne incognita* but was inactive (Cao et al. 2020).

### Deconstruction pathways of limonoids to degraded limonoids

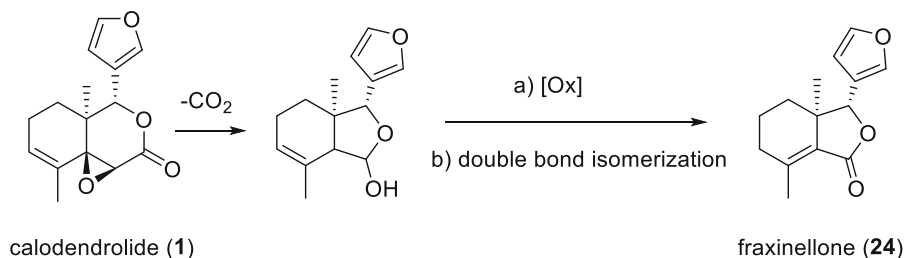
The role of these compounds in the roots, twigs and leaves of plants has not yet been clearly ascertained. Nevertheless, their origins have been postulated in some reports searching for plausible intermediates in the conversion from limonoids to degraded limonoids. Within these, some highly degraded limonoids such as fraxinellone (**24**) and its derivatives have been described as degradation products from ring-intact or seco-ring limonoids (Tan and Luo 2011). Microbial systems may have evolved to break down limonoids in the environment but this remains unclear. Potential precursors of limonoids have been considered to shed light on the routes towards the degradation products described in this review.

Chan et al. (1966, 1972) speculated that odoratin (**22**) is biogenetically related to mexicanolides and carapin which are a bicyclononanolide group of limonoids. Transformations of these bicyclononanolides involving a reverse Michael reaction and a  $\beta$ -

**Scheme 1** Hypothesized degradation route towards odoratin (**22**) (Chan et al. 1972)



**Scheme 3** Hypothesized route from calodendrolide (1) to fraxinellone (24) (Cassady and Liu 1972)



dicarbonyl cleavage could explain the C<sub>5</sub>-C<sub>10</sub> and C<sub>2</sub>-C<sub>3</sub> bonds cleavages to give odoratin (22) (Chan et al. 1972, Scheme 1).

Coggon et al. proposed that fraxinellone (24) arises from the degradation of a limonoid bitter principle, limonin (also named dictamnolactone), which is a co-metabolite in *Dictamnus albus* extracts (Coggon et al. 1969, Scheme 2).

Cassady and Liu (1972) pointed out that calodendrolide (1) appears to derive from a limonoid by the loss of A and B rings and ensuing decarboxylation to give the corresponding lactol. Oxidation and double-bond isomerization would afford fraxinellone (24) (Cassady and Liu 1972, Scheme 3). The transformation of calodendrolide (1) into fraxinellone (24) has been postulated through isofraxinellone (35) by isomerization of the double bond (Cassady and Liu 1972).

D'Ambrosio and Guerriero suggested hypothesized intermediates from limonin and andirobin-type limonoids to explain the deconstruction pathway to produce some degraded limonoids (D'Ambrosio and Guerriero 2002). Deoxyandirobin and methyl angolensate are two limonoids described as precursors of pyroangolensolide (18) and azedaralide (19) and the hypothesized **intermediate I** was postulated for the biogenesis of these compounds (Scheme 4a). In fact, limonoids methyl angolensate and 7-deacetyl-7-oxogedunin were also isolated from the root extract of *M. azedarach* as well as pyroangolensolide (18). These authors also suggested that calodendrolide (1), fraxinellone (24) and its derivatives fraxinellonone (25), 9β-hydroxyfraxinellone (26), 9α-hydroxyfraxinellone (27), 30-hydroxyfraxinellone (28) and isofraxinellone (35) are produced from the common **intermediate II** (Scheme 4b). 3-Teracrylmelazolides 39 and 40 are characterized by correspondence to the A-ring portion of an original limonoid skeleton such as deoxyandirobin or andirobin through a hypothetical **intermediate III** (Scheme 4c).

Dysodensiols A-C (15–17), isolated from *Dysoxylum densiflorum*, have also been proposed as deriving from a common B-seco-limonoid precursor (Xie et al. 2008, Scheme 5).

Trichiconnarins A and B (20 and 21) feature a contracted five-membered ring-C. Trichiconnarin A (20) has been hypothesized as a product obtained by the cleavage of the C-2 and C-8 bonds of trijugin. Several trijugins have also been isolated from *Trichilia connaroides* which have been postulated to be derivatives of trijugin C. This natural product has also been suggested to be the precursor of trichiconnarin A (Wang et al. 2008, Scheme 6). Aldol reaction of trichiconnarin A (20) with acetone and subsequent dehydration could give rise to the formation of trichiconnarin B (21) (Wang et al. 2008; Tan and Luo 2011). However, the authors did point out that trichiconnarin B (21) could be an artefact produced during the isolation process (Wang et al. 2008).

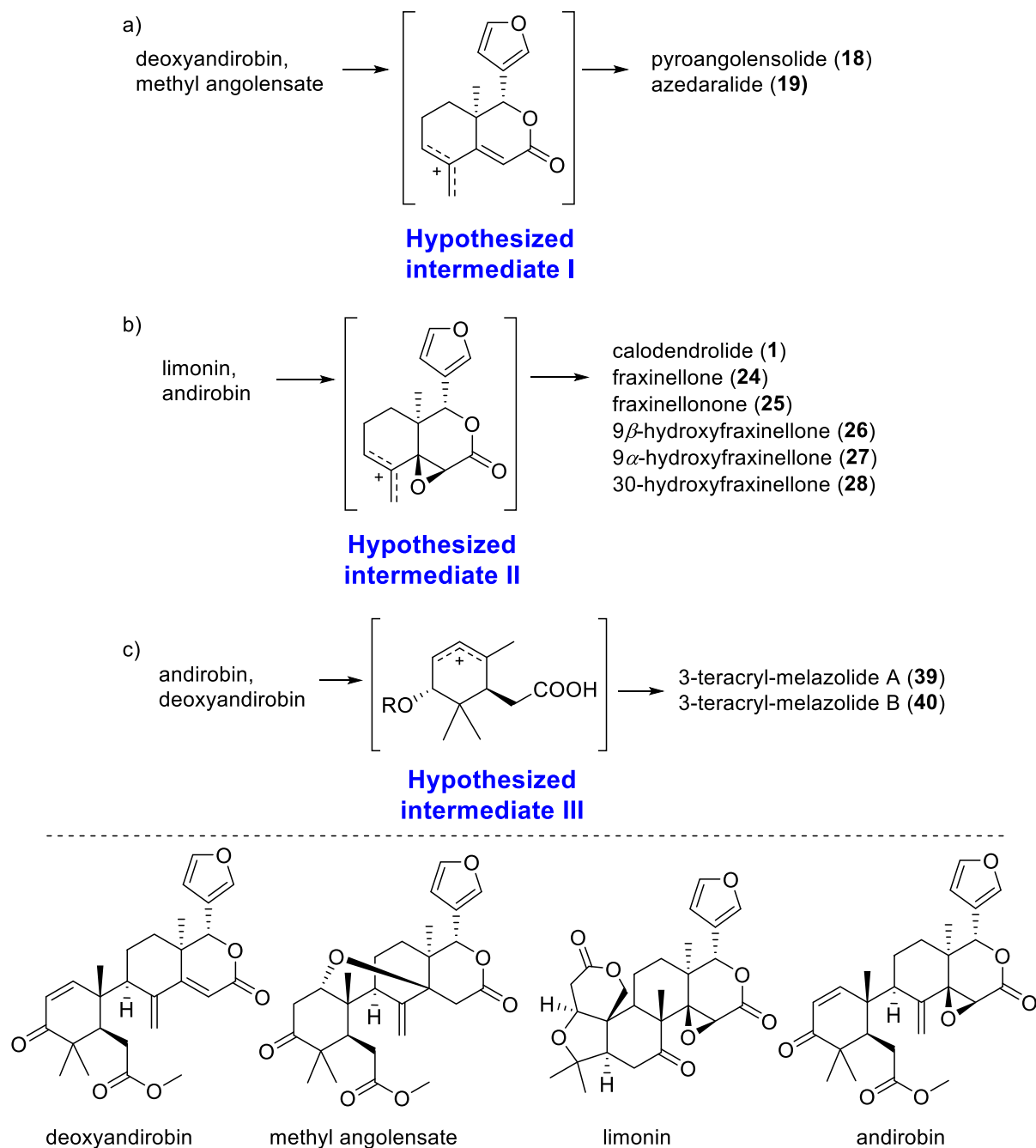
Walsunoid A (43) is considered to be a degradation product of cedrelone-type limonoids. A furanyl transformation mechanism underlines walsunoid A (43) formation (Wang et al. 2016, Scheme 7).

A biosynthetic pathway starting from phragmalin-type limonoids as precursors was proposed by Wang et al. to explain the formation of chuktabin L (48) (Wang et al. 2019a, Scheme 8).

Lastly, in a more recent work, Bailly and Vergoten (2020) proposed that degraded limonoids like calodendrolide (1) and fraxinellone (24) could derive from tetra or pentacyclic limonoids such obacunone, kihadanins A-D or limonin (Bailly and Vergoten 2020, Scheme 9).

### Syntheses of degraded limonoids and analogues

Structurally complex natural limonoids as well as their analogues have been a profitable source to identify new bioactive agents (Furiassi et al. 2021; Mulani

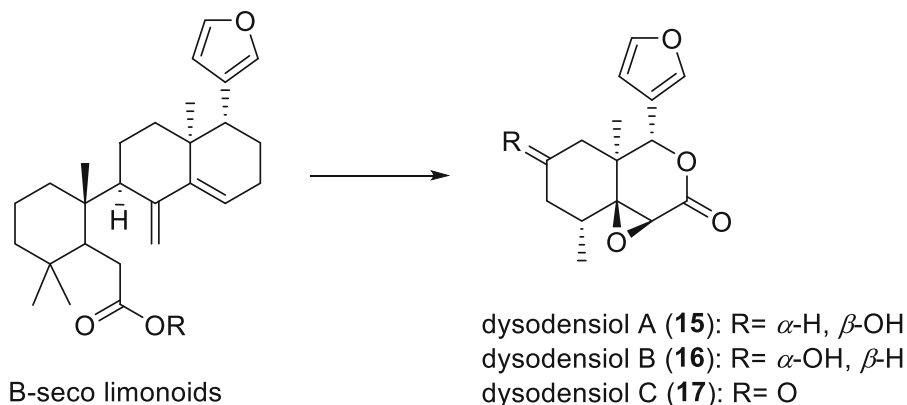


**Scheme 4** Hypothesized intermediates I–III leading to some degraded limonoids (D'Ambrosio and Guerriero 2002)

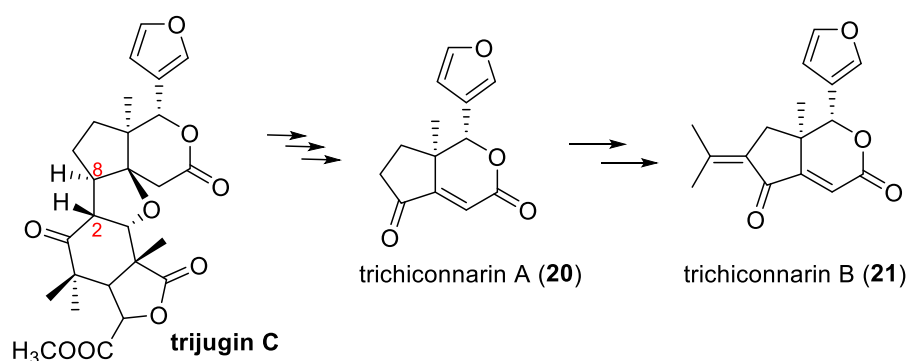
et al. 2022; Sun et al. 2022). However, degraded limonoids are also interesting biologically active entities that have attracted the attention of some chemists because they can be used as valuable building blocks for the total synthesis of intact limonoids. In 2011, Heasley published an excellent

review on progress made in limonoid synthesis including degraded limonoids. At that time, only total or formal syntheses had been performed on calodendrolide (1), pyroangolensolide (18), azedaralide (19), fraxinellone (24), fraxinellonone (25) and isofraxinellone (35) (Fukuyama et al. 1972, 1973; Drewes et al.

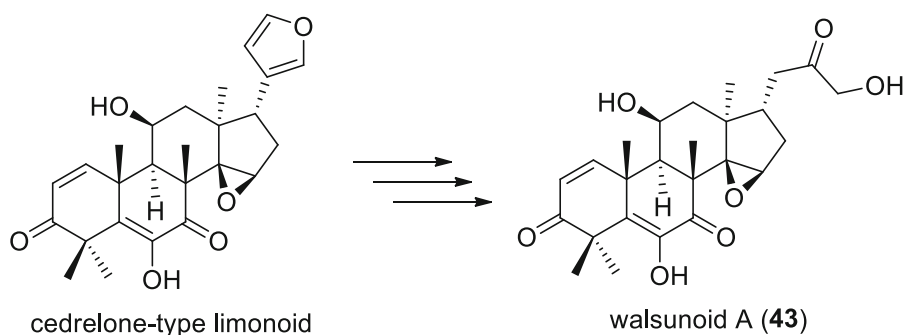
**Scheme 5** Plausible precursors of dysodensiols **15–17** (Xie et al. 2008)



**Scheme 6** Trijugin C, precursor of trichiconnarins A and B (Wang et al. 2008)



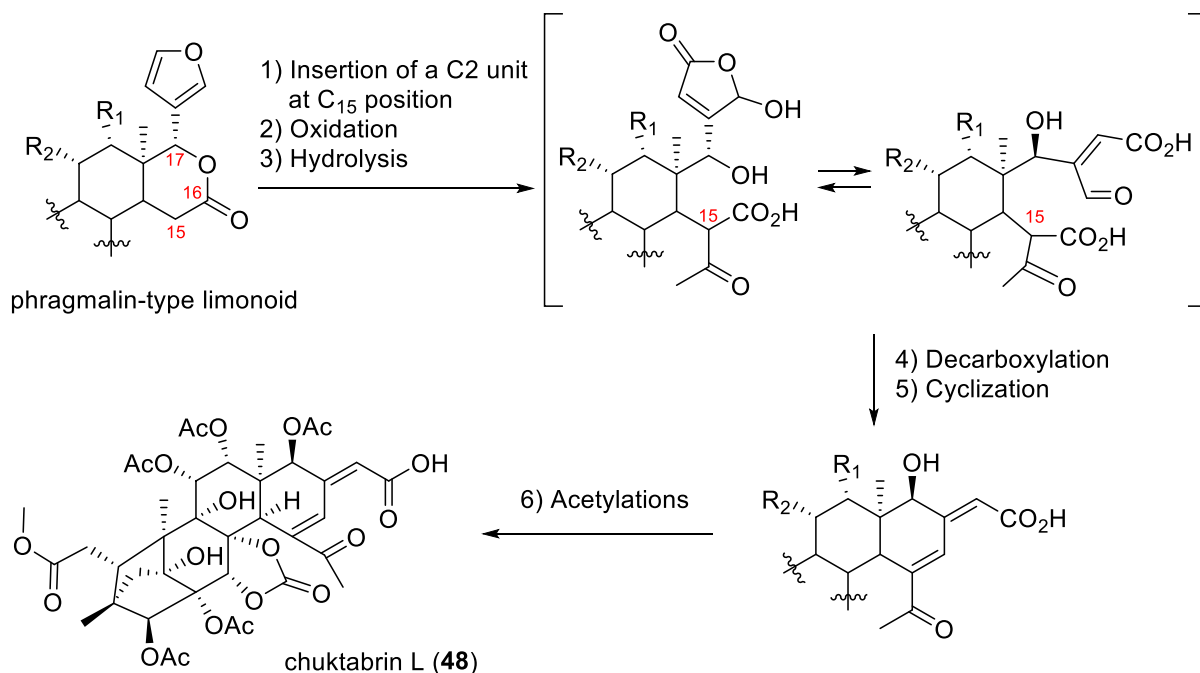
**Scheme 7** Walsunoid A (**43**) from cedrelone-type precursors (Wang et al. 2016)



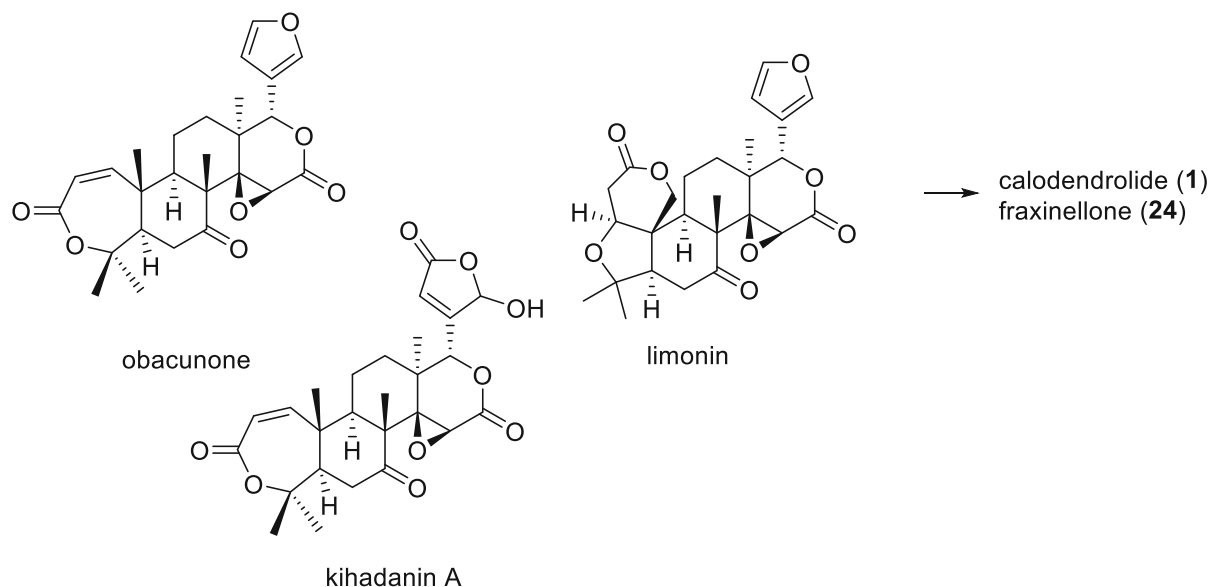
1985; Tokoroyama et al. 1990; Fernández-Mateos et al. 1991; Rajab et al. 1994; Okamura et al. 1997; Trudeau et al. 2005; Baker et al. 2006).

A year later, Guo et al. developed a stereoselective method to synthesize 9 $\alpha$ -hydroxyfraxinellone (**27**) from fraxinellonone (**25**) (Guo et al. 2012a). It is worth mentioning that the authors named this molecule 4 $\alpha$ -hydroxyfraxinellone because they used different carbon atom numbering for fraxinellone (C-9 re-named as C-4). Consequently, they described **27** as 4 $\alpha$ -hydroxyfraxinellone (Scheme 10).

A new review summarizing the main efforts made to synthesize limonoids was published by Fu and Liu (2020). They highlight the total enantioselective syntheses of these compounds covering from January 2011 to March 2020. Surprisingly, no new degraded limonoid syntheses were reported in this review. Recently, the total synthesis of (-)-melazolidine B (**42**) was reported through a six-step sequence involving a preparation of a keto-lactone intermediate **50** derived from  $\alpha$ -ionone. Chemoselective dehydrogenation of **50**, epoxidation and Wharton reduction afforded (-)-



**Scheme 8** Plausible biosynthetic route for chuktabrin L (**48**) (Wang et al. 2019a)

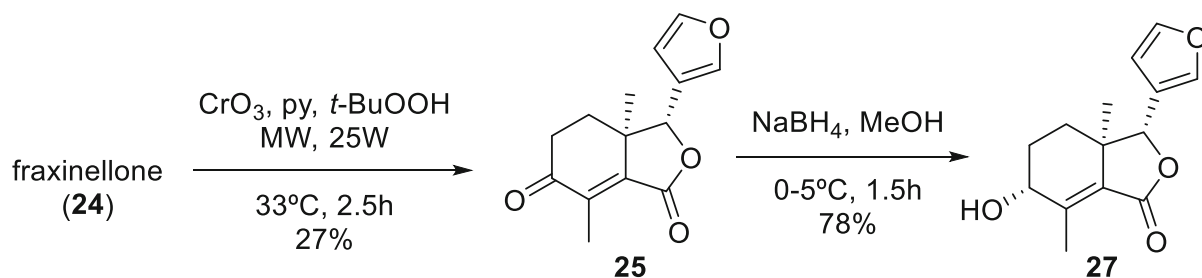


**Scheme 9** Hypothesized precursors leading to calodendrolide (**1**) and fraxinellone (**24**) (Bailly and Vergoten 2020)

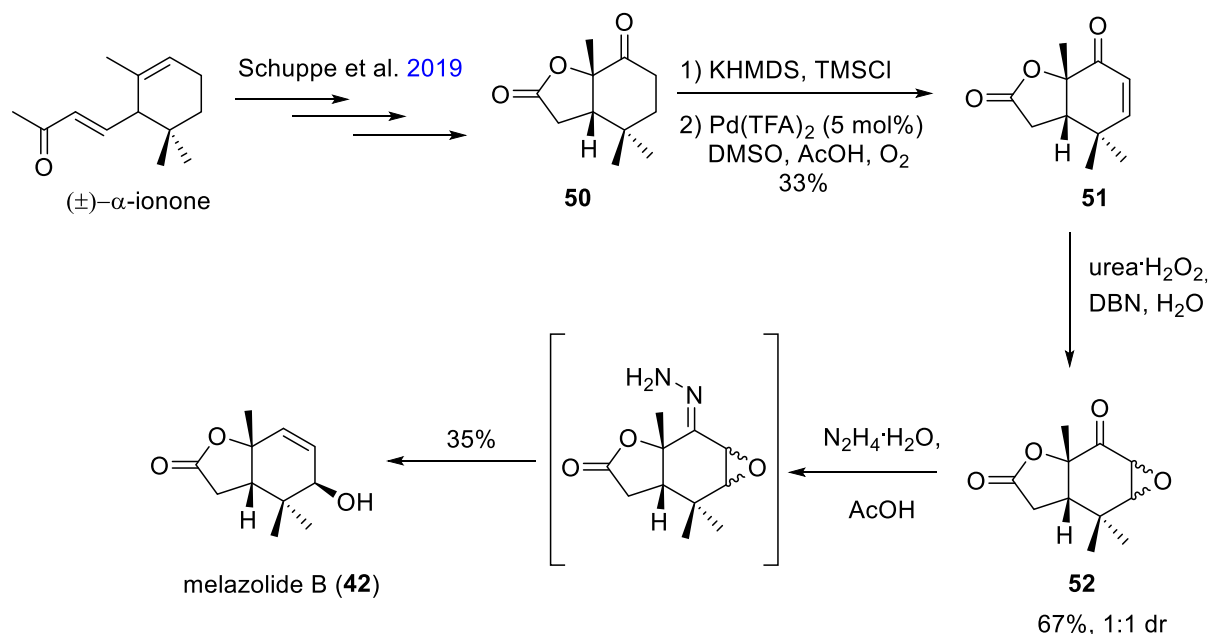
melazolid B (**42**) (Scheme 11). The synthesis of C3-*epi*-melazolid B was also achieved by a similar synthetic route from compound **50** (Liu et al. 2022).

To the best of our knowledge, no total synthesis or semi-synthesis of the remainder of degraded limonoids listed in the present review has been performed.

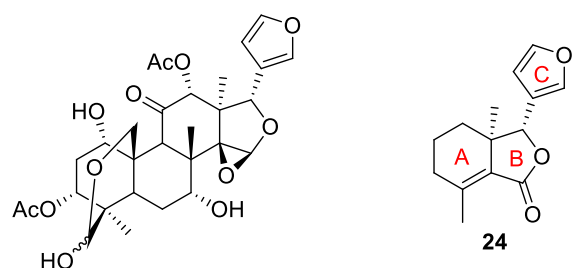
A simple approach to a set of degraded limonoids analogs has been carried out for the antibacterial (Ferrera-Suanzes et al. 2020) and antifeedant (Bentley et al. 1990) evaluation. In fact, two simplified models based on the C and D rings of limonin showed a higher antifeedant activity against *L. decemlineata* Larvae



**Scheme 10** Synthesis of 9 $\alpha$ -hydroxyfraxinellone (27) (Guo et al. 2012a)



**Scheme 11** Synthetic route for the synthesis of (-)-melazolide B (42)



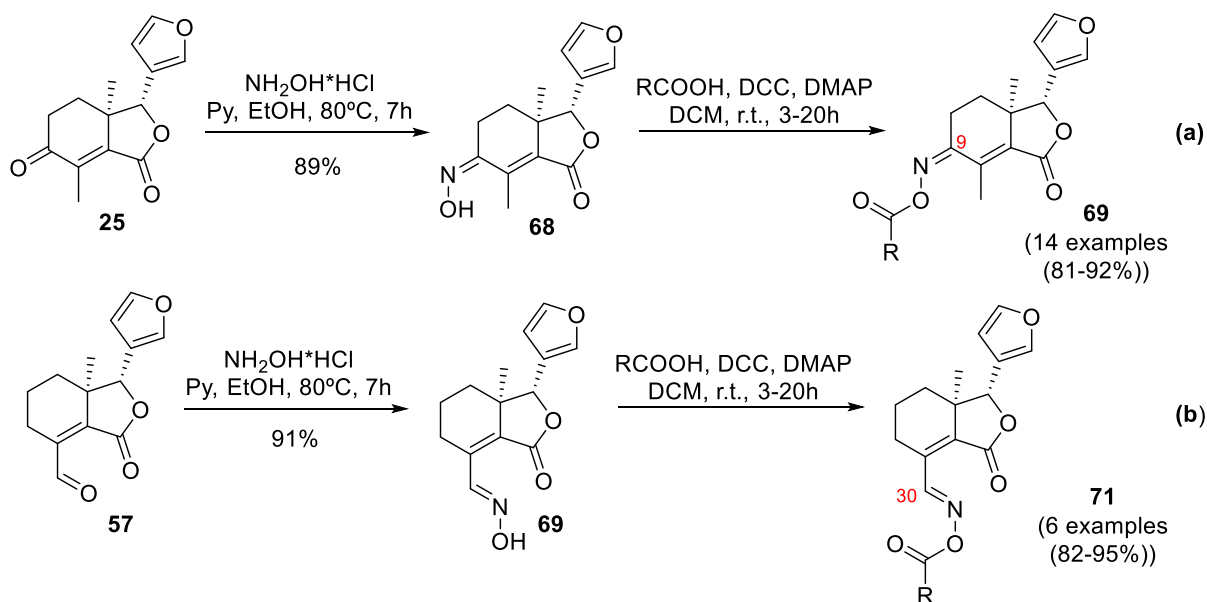
**Fig. 8** Chemical structure of toosendanin (left) and A, B and, C-rings of fraxinellone 24 (right)

than limonin (Bentley et al. 1990). Additionally, the number of fraxinellone (24)-based molecules synthesized in the last decade for the purpose of obtaining new natural products-based pesticides is remarkable. In fact, fraxinellone (24) has been used as a platform

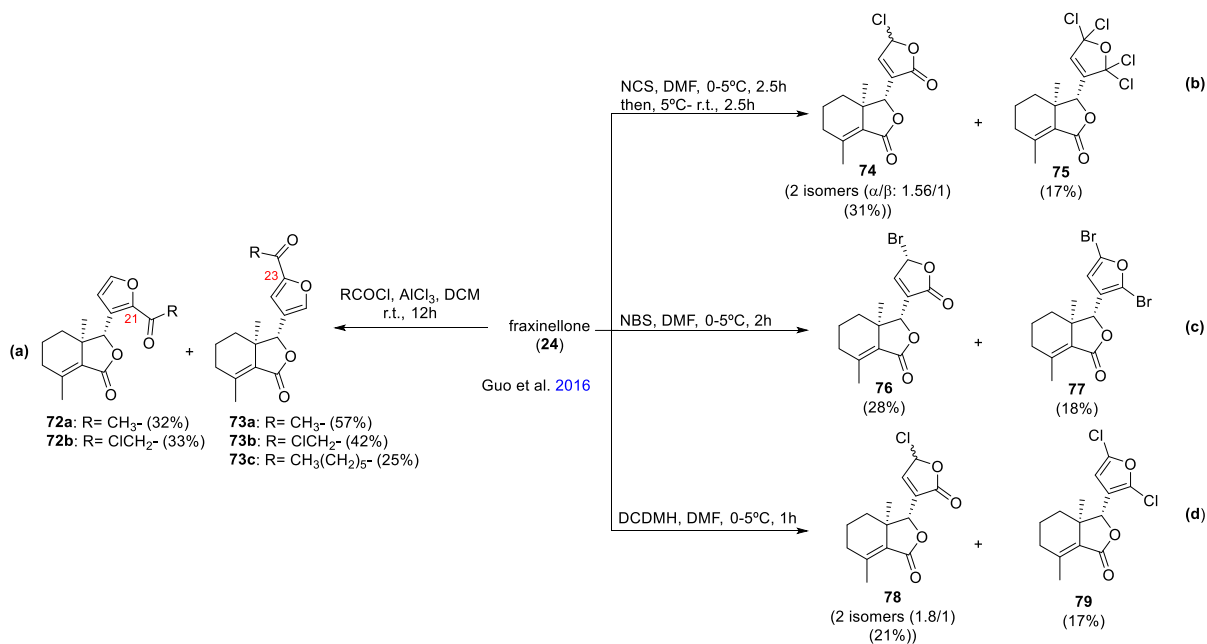
where numerous structural modifications have been performed for evaluation as potentially more potent insecticides than traditional ones such as toosendanin (a natural limonoid which is a well-known digestive tract parasiticide (Shi et al. 2007) with a notable growth inhibition effect and potent antifeedant activity against armyworm *M. separata* Walker and other insects (Shi et al. 1986; Chen et al. 1995)) (Fig. 8).

A small number of these chemical structures of the synthetic fraxinellone analogues were listed in a recent mini review by Bailly and Vergoten in June 2020, but that review did not include the preparation or the insecticidal activity range of values of all the most potent derivatives. In order to list all the semi-syntheses and clarify structure–activity relationships,





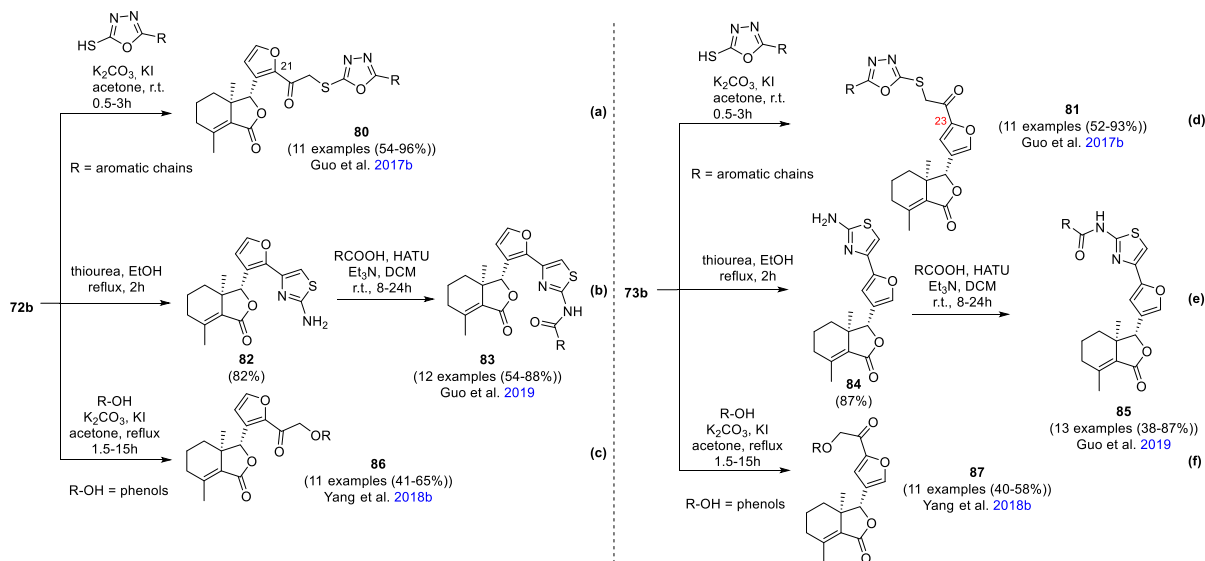
**Scheme 14** Synthesis of esters of fraxinellone C9/C30 oxime (Li et al. 2016b)



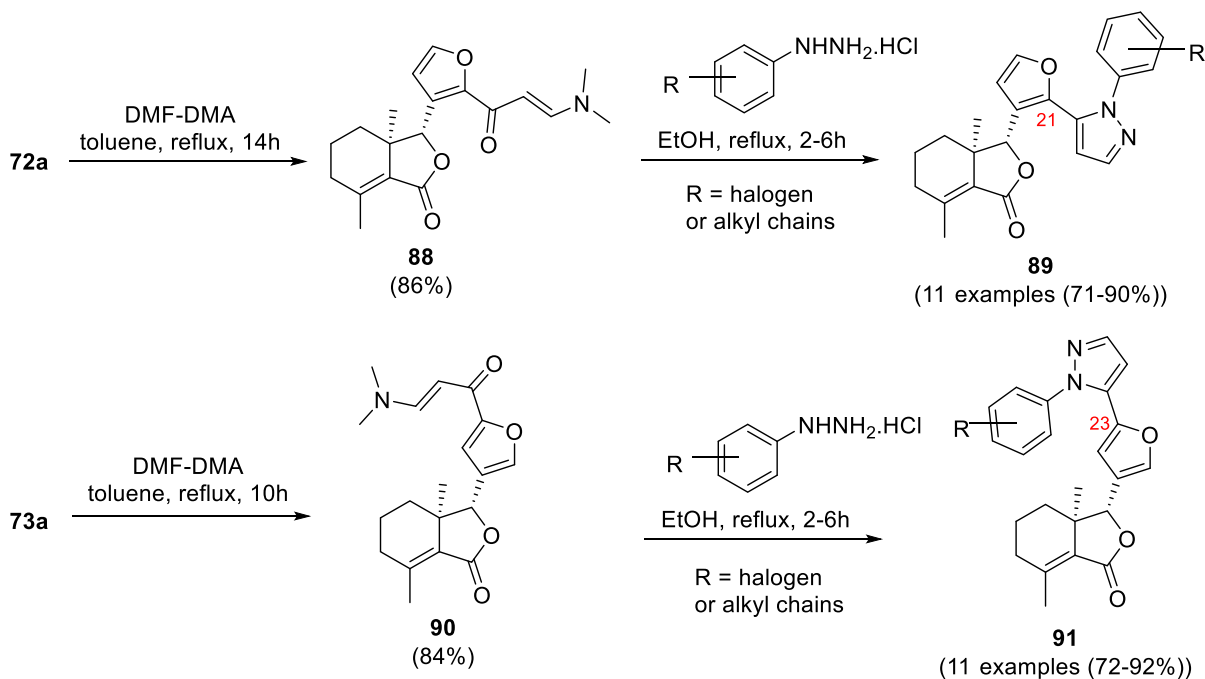
**Scheme 15** Halogenation and acylation reactions on the furyl-ring of fraxinellone (Guo et al. 2016)

in this review we present the structural modifications that have been performed in the A or B rings (Schemes 14, 15 and 16) and in the C-ring of fraxinellone (Schemes 17, 18, 19, 20 and 21), and a thorough analysis of the growth inhibition activity of the most active derivatives in terms of mortality rates versus the

mortality rates observed in the control toosendanin and the precursor **24** (Table 13).



**Scheme 16** Synthesis of fraxinellone-based thioether derivatives (containing 1,3,4-oxadiazole moiety) and *N*-(1,3-thiazol-2-yl)carboxamides (Guo et al. 2017b and 2019, respectively) and ethers from C-ring based acylation derivatives (Yang et al. 2018b)

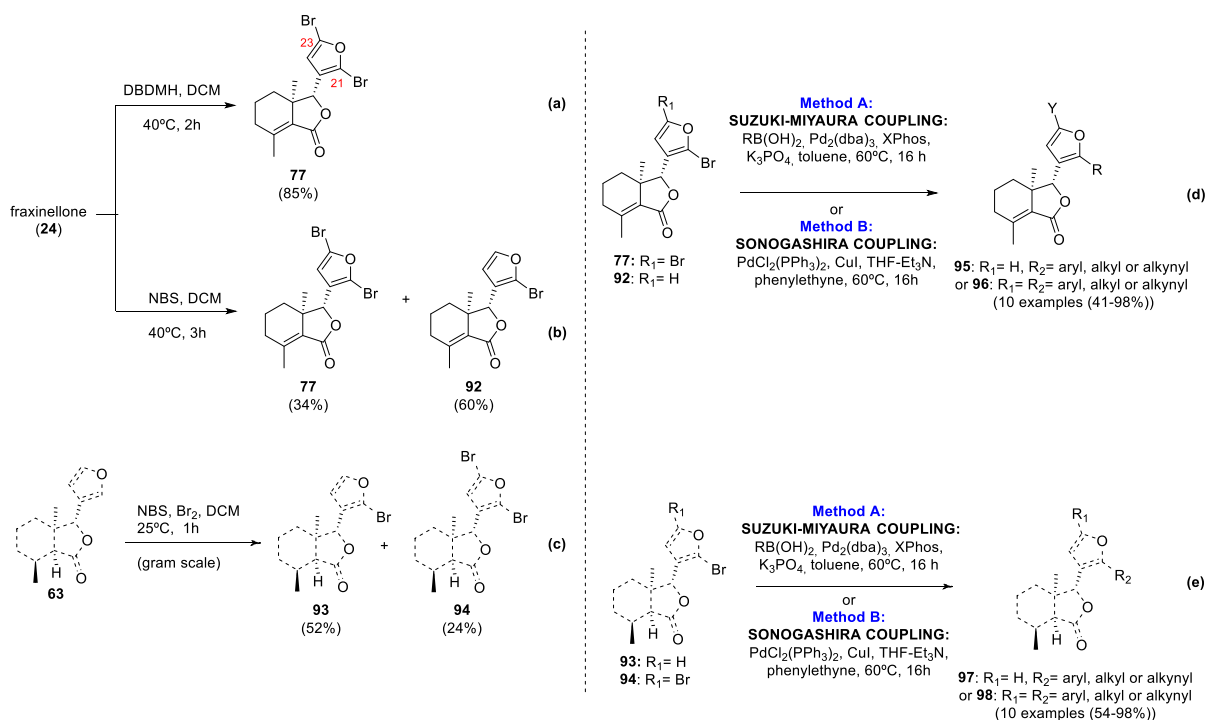


**Scheme 17** Synthesis of *N*-phenylpyrazole ring derivatives (Yang et al. 2018a)

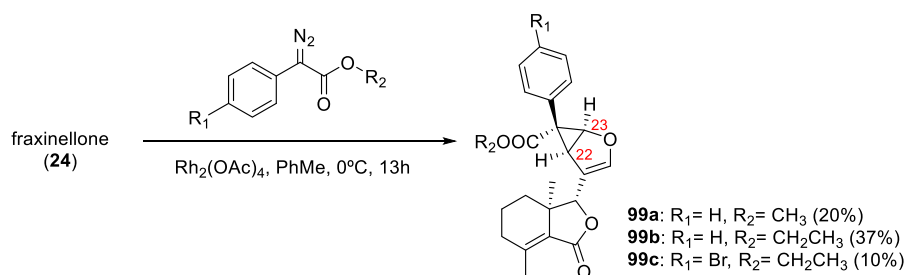
Structural modifications of A or B-rings of fraxinellone

Guo et al. studied the allylic oxidation of fraxinellone (**24**) (Guo et al. 2012a, b) and obtained either natural

product **25** or compound **57** depending on the reaction conditions used (Scheme 12). Then, reduction of the generated carbonyl group at C-9 or C-30 and subsequent Steglich esterification afforded compounds **55** or **59**, respectively (Guo et al. 2012a, Scheme 12b, d).



**Scheme 18** Furan-site bromination and subsequent transformations (Dong et al. 2018a, b)



**Scheme 19** Cyclopropanation of the furyl-ring of fraxinellone (Yang et al. 2020a, b)

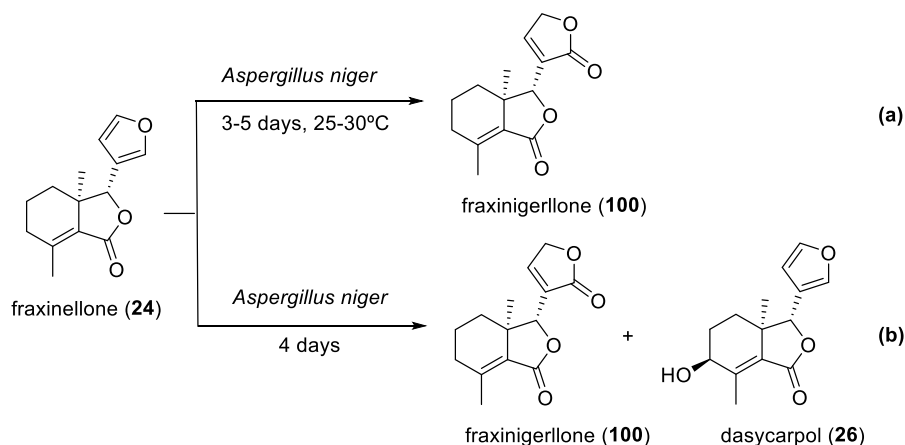
Fraxinellone-based hydrazones modified at C-9 or C-30 were also prepared by Guo et al. (Guo et al. 2012b, Scheme 12c, e). Some years later Guo et al. reported the preparation of the N-phenylpyrazole derivatives **54** (Guo et al. 2017a, Scheme 12a).

Guo et al. (2013) performed the reduction of fraxinellone (**24**) using sodium bis(2-methoxyethoxy) aluminium hydride (Red-Al) at low temperature which gave the mixture of compounds **61–63** (Scheme 13a). Esterification of **61** and **62** enabled the authors to prepare analogues **64–66** (Scheme 13b, c). Thionation of the carbonyl group from the lactone of **24** gave rise to thiocarbonyl derivative **67** in moderate reaction yield (Scheme 13d).

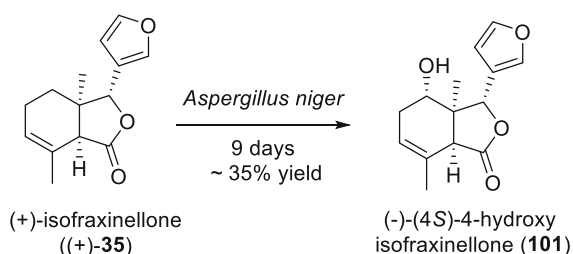
Analogues **25** and **57** were converted into the corresponding oximes at C-9 and C-30 positions (**69** and **71**) through a two-step reaction sequence, respectively, in high reaction yields (Li et al. 2016b, Scheme 14).

Structural modifications of the C-ring of fraxinellone.

Among the modifications of fraxinellone (**24**), transformations on the furan ring are abundant (Guo et al. 2016, 2017b, 2018; Dong et al. 2018a, b; Yang et al. 2018a, b, Schemes 15–19). The Friedel–Crafts acylation of the fraxinellone C-ring was performed by Guo et al. in low to moderate reaction yields (Guo et al. 2016, Scheme 15a). Moreover, they converted



**Scheme 20** Biotransformations of fraxinellone (24) by *A. niger* ((a) microbial study described by Zhang et al. 2005; (b) microbial study described by Yang et al. 2005)



**Scheme 21** Biotransformation of isofraxinellone (35) (Miyazawa et al. 2009; Okuno et al. 2019)

fraxinellone (24) into their mono-, di- and tetra-halogenated analogues (Scheme 15b, c, d).

The acyl derivatives of fraxinellone **72b** and **73b** were also treated with 2-mercapto-5-aryl-1,3,4-oxadiazoles to afford a set of thioethers **80** and **81** (Guo et al. 2017b, Scheme 16a, d). Analogues **72b** and **73b** were also transformed to obtain carboxamides **83** and **85** through a two-step reaction sequence (Guo et al. 2017b, Scheme 16b, e). Aryloxy groups were added to the furan ring by reaction with phenols (Yang et al. 2018b, Scheme 16c, f).

Starting from compounds **72a** and **73a**, Yang et al. prepared two series of N-phenylpyrazole derivatives (**89** and **91**) characterised by halogen atoms (F, Cl or Br) on the phenyl group (Yang et al. 2018a, Scheme 17).

Guo et al. described the furyl-ring bromination of fraxinellone (24) getting the dibrominated derivative in only 18% reaction yield (Guo et al. 2016, Scheme 15c). Later, Dong et al. optimized the reaction yield of this transformation (up to 85%) using 1,3-

dibromo-5,5-dimethylhydantoin (DBDMH) as the brominating reagent and a higher reaction temperature (Dong et al. 2018a, b, Scheme 18a). This latter compound was also obtained together with the C-21 monobrominated derivative when N-bromosuccinimide was used (Scheme 18b). Compound **63** was also transformed into the mono- and di-brominated furyl derivatives **93** and **94** (Scheme 18c). All these products were coupled to organoboron species or terminal alkynes through Suzuyi-Miyaura or Sonogashira couplings respectively, to get the new carbon-carbon single bonds containing derivatives **95–98** (Scheme 18d, e).

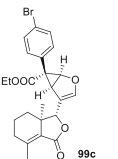
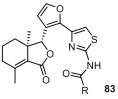

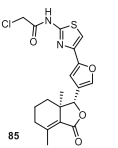
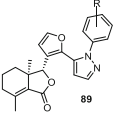
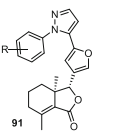
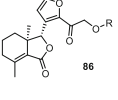


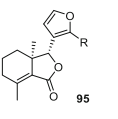



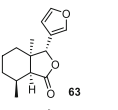
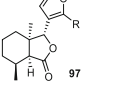

Monocyclopropanated derivatives of fraxinellone (24) were formed through the [2 + 1] addition between the C22-C23 double bond of the furyl-ring of fraxinellone and a set of  $\alpha$ -carbonyldiazoesters (Yang et al. 2020a, b, Scheme 19).

#### Insecticidal activity of semi-synthesized fraxinellone analogues

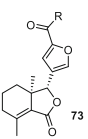
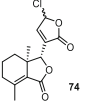
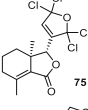
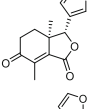
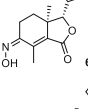
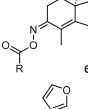


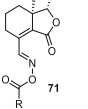


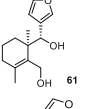
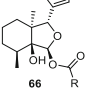



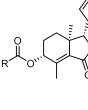



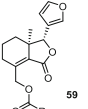

The previously mentioned fraxinellone-based analogues were assayed as insecticidal agents against lepidopteran insect pests (*Mythimna separata* Walker and/or *Plutella xylostella* Linnaeus). Those that exhibited stronger growth inhibition activity than their parental counterpart **24** and toosendanin (**T**) are listed in Table 13.

Antifungal studies carried out by Zhao et al. showed that the furyl-ring in degraded limonoids seemed to be crucial for the growth inhibition effect

**Table 13** Growth inhibition activity of selected semi synthesized fraxinellone derivatives against lepidopteran pests

Entry	Compound	MR	MR for 24 and toosendanin (T)	References
1		MR = 37.5% (35 days) <sup>a</sup>	MR ( <b>24</b> ) = 17.4% (35 days) <sup>a</sup> MR ( <b>T</b> ) = 33.3% (35 days) <sup>a</sup>	Yang et al. (2020a, b)
2		R:  ; MR = 75.9% (35 days) <sup>a</sup> R: -CH <sub>2</sub> Cl; MR = 58.6% (35 days) <sup>a</sup> R: -CH <sub>2</sub> Cl; MR = 69.0% (35 days) <sup>b</sup>	MR ( <b>24</b> ) = 44.8% (35 days) <sup>a</sup> MR ( <b>T</b> ) = 48.3% (35 days) <sup>a</sup> MR ( <b>24</b> ) = 41.4% (35 days) <sup>b</sup>	Guo et al. (2019)
3		MR = 65.5% (35 days) <sup>b</sup>	MR ( <b>T</b> ) = 48.3% (35 days) <sup>b</sup>	
4		R: 2-Cl, 4-F; MR = 82.8% (33 days) <sup>a</sup> R: 2-F, 4-Br; MR = 75.9% (33 days) <sup>a</sup> R: 2-Cl, 4-Cl; MR = 69.0% (33 days) <sup>a</sup> R: 2-Cl, 5-F; MR = 58.6% (33 days) <sup>a</sup> R: 2-Cl, 4-F; MR = 66.7% (3 days) <sup>b</sup> R: 2-F, 4-Br; MR = 63.3% (3 days) <sup>b</sup>	MR ( <b>24</b> ) = 48.3% (33 days) <sup>a</sup> MR ( <b>T</b> ) = 55.2% (33 days) <sup>a</sup> MR ( <b>24</b> ) = 26.7% (3 days) <sup>b</sup> MR ( <b>T</b> ) = 50.0% (3 days) <sup>b</sup>	Yang et al. (2018a)
5		R: 2-Cl, 4-F; MR = 75.9% (33 days) <sup>a</sup> R: 2-F, 4-Br; MR = 72.4% (33 days) <sup>a</sup> R: 2-Cl, 4-Cl; MR = 69.0% (33 days) <sup>a</sup> R: 2-F, 4-Br; MR = 60.0% (3 days) <sup>b</sup>		
6		R:  ; MR = 64.3% (35 days) <sup>a</sup> R:  ; MR = 60.7% (35 days) <sup>a</sup>	MR ( <b>24</b> ) = 42.9% (35 days) <sup>a</sup> MR ( <b>T</b> ) = 46.4% (35 days) <sup>a</sup>	Yang et al. (2018b)
7		R =  ; MR = 52.7% (35 days) <sup>a</sup> R =  ; MR = 45.5% (35 days) <sup>a</sup> R =  ; MR = 39.4% (35 days) <sup>a</sup>	MR ( <b>24</b> ) = 17.4% (35 days) <sup>a</sup> MR ( <b>T</b> ) = 39.0% (35 days) <sup>a</sup>	Dong et al. (2018a, b)
8		MR = 71.4% (35 days) <sup>a</sup>		
9		R =  ; MR = 45.0% (35 days) <sup>a</sup> R = -(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub> ; MR = 40.8% (35 days) <sup>a</sup>		

**Table 13** continued

Entry	Compound	MR	MR for 24 and toosendanin (T)	References
10		R: CH <sub>3</sub> ; MR = 57.1% (35 days) <sup>a</sup> R: CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> ; MR = 53.6% (35 days) <sup>a</sup>	MR ( <b>24</b> ) = 42.9% (35 days) <sup>a</sup> MR ( <b>T</b> ) = 46.4% (35 days) <sup>a</sup>	Guo et al. (2016)
11		MR = 50.9% (35 days) <sup>a</sup>		
12		MR = 51.9% (35 days) <sup>a</sup>		
13		MR = 73.3% (33 days) <sup>a</sup>	MR ( <b>24</b> ) = 56.7% (33 days) <sup>a</sup>	Li et al. (2016b)
14		MR = 70.0% (33 days) <sup>a</sup>		
15		R:  ; MR = 73.3% (33 days) <sup>a</sup> R:  ; MR = 60.0% (33 days) <sup>a</sup>	MR ( <b>T</b> ) = 56.7% (33 days) <sup>a</sup>	
16		R: CH <sub>3</sub> CH <sub>2</sub> -; MR = 70.0% (33 days) <sup>a</sup> R:  ; MR = 70.0% (33 days) <sup>a</sup> R: CH <sub>3</sub> ; MR = 66.7% (33 days) <sup>a</sup> R:  ; MR = 66.7% (33 days) <sup>a</sup>		
17		MR = 58.6% (35 days) <sup>a</sup>	MR ( <b>24</b> ) = 41.4% (35 days) <sup>a</sup> MR ( <b>T</b> ) = 48.3% (35 days) <sup>a</sup>	Guo et al. (2013)
18		R:  ; MR = 65.5% (35 days) <sup>a</sup> R:  ; MR = 58.6% (35 days) <sup>a</sup> R:  ; MR = 51.7% (35 days) <sup>a</sup>		
19		R:  ; MR = 63.0% (35 days) <sup>a</sup> R:  ; MR = 66.7% (35 days) <sup>a</sup> R:  ; MR = 63.0% (35 days) <sup>a</sup>	MR ( <b>24</b> ) = 44.4% (35 days) <sup>a</sup> MR ( <b>T</b> ) = 48.1% (35 days) <sup>a</sup>	Guo et al. (2012a)
20		R:  (35 days) <sup>a</sup>		

**Table 13** continued

Entry	Compound	MR	MR for 24 and toosendanin (T)	References
21		R: ; MR = 76.9% (35 days) <sup>a</sup> MR = 69.2% (35 days) <sup>a</sup> R: ; MR = 65.4% (35 days) <sup>a</sup> R: ; MR = 61.5% (35 days) <sup>a</sup>	MR ( <b>24</b> ) = 53.8% (35 days) <sup>a</sup> MR ( <b>T</b> ) = 53.8% (35 days) <sup>a</sup>	Guo et al. (2012b)
22		R: ; MR = 73.1% (35 days) <sup>a</sup> R: ; MR = 65.4% (35 days) <sup>a</sup> R: ; MR = 62.9% (35 days) <sup>a</sup> R: ; MR = 61.5% (35 days) <sup>a</sup> R: ; MR = 61.5% (35 days) <sup>a</sup>		

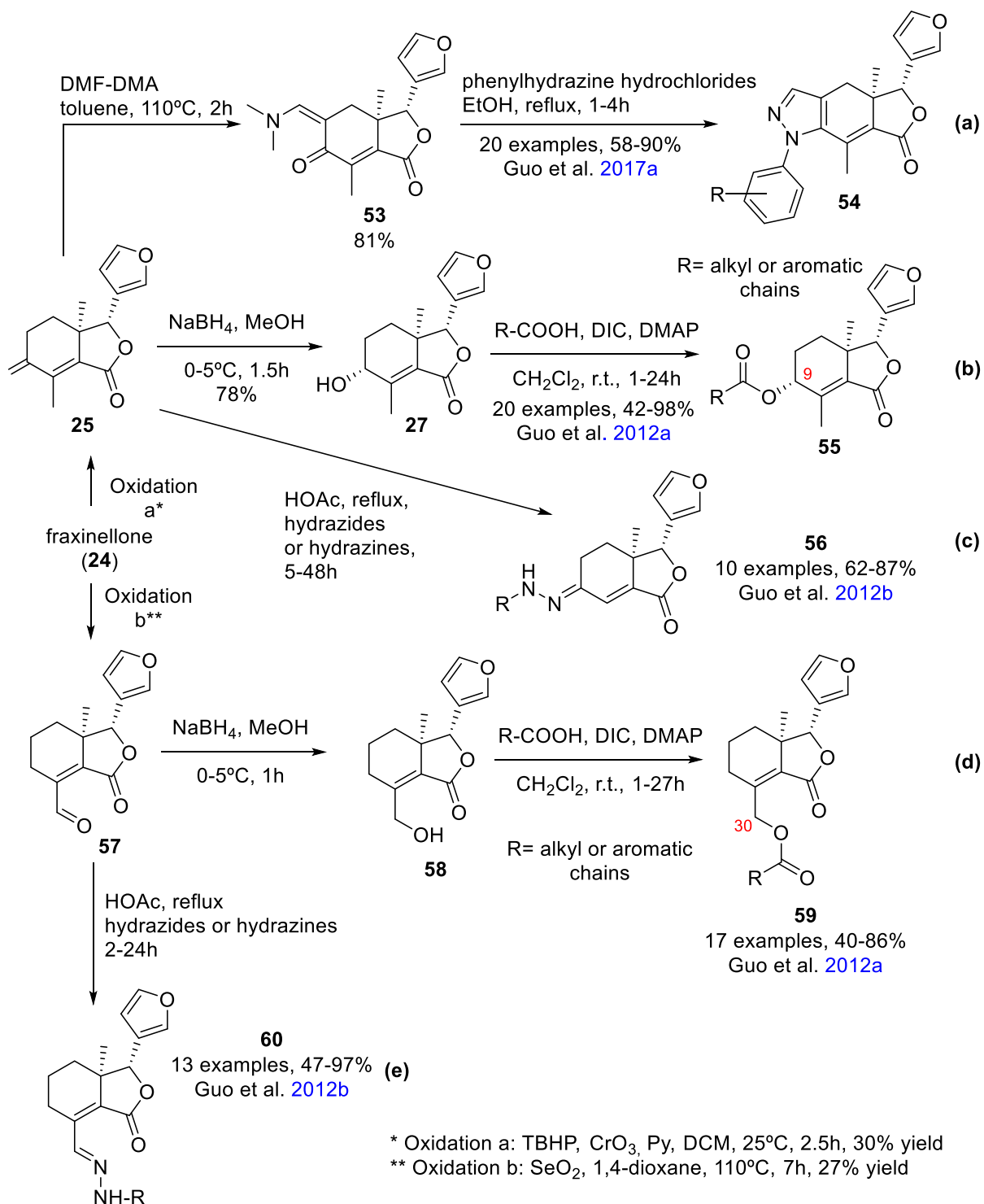
<sup>a</sup>Mortality rate values (MR) for insecticidal activity of compounds against pre-third-instar larvae of *M. separata* Walker fed with leaves treated with a concentration of 1 mg mL<sup>-1</sup>

<sup>b</sup>Mortality rate values (MR) for insecticidal activity of compounds against second-instar larvae of *P. xylostella* Linnaeus fed with leaves treated with a concentration of 250 µg mL<sup>-1</sup>

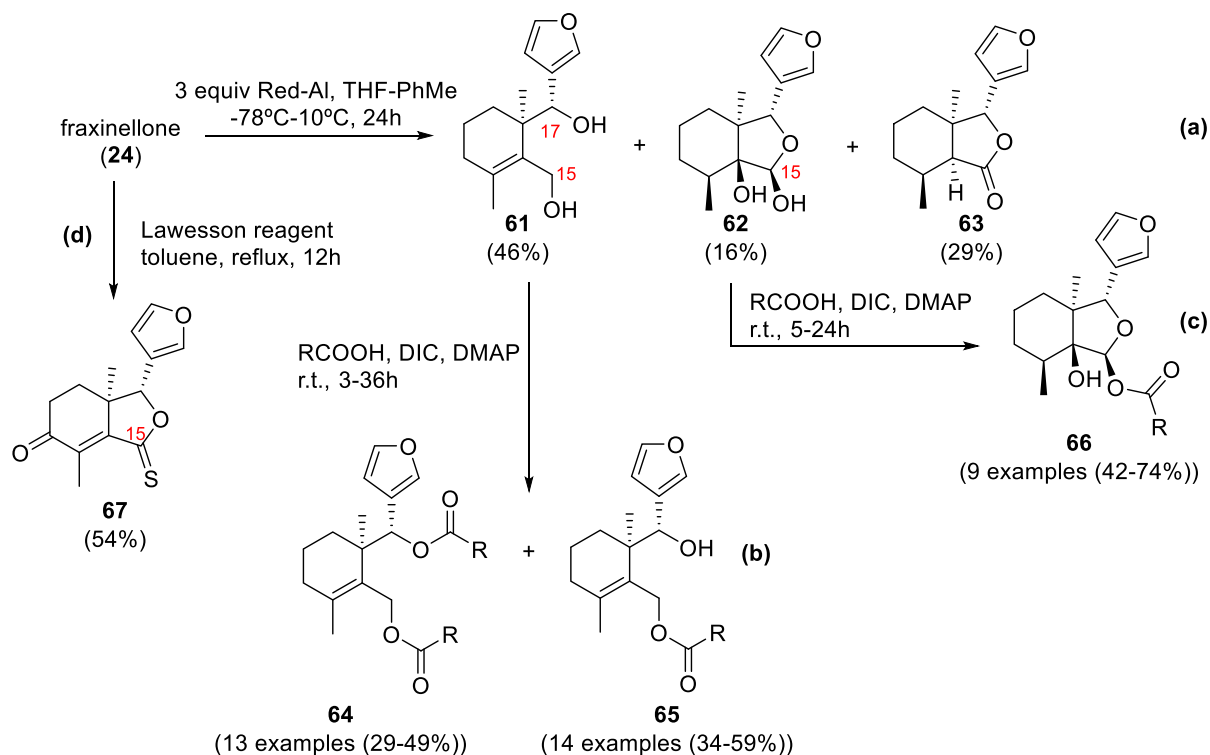
(Zhao et al. 1997). Three cyclopropyl analogues at C-22/C-23 positions (compounds **99a-c**) with an aromatic substituent were prepared by Yang et al. (2020a, b). Compound **99c**, with a bromine atom on the aryl side chain, was the most active product (Table 13, entry 1). Mode of action has yet to be described but data suggest that this analogue might affect the insect molting hormone based on larval malformations of the oriental armyworm. Among the twenty-five *N*-(1,3-thiazol-2-yl) carboxamide derivatives synthesized, it is remarkable those bulkier products that contain a -CH<sub>2</sub>Cl side chain in the carboxamide unit (compounds **83** and **84**) (Guo et al. 2019). When the carboxamide motif was introduced at C-21 position, the reaction product became more active than **24** and toosendanin against both *M. separata* and *P. xylostella* showing with mortality rate percentages (MR (%)) of 58.6% and 69.0%, respectively (Table 13, entry 2). Replacement of the -CH<sub>2</sub>Cl by a *p*-nitrophenyl group led to the most active one of all against the armyworm with a mortality rate of 75.9%, but was less active than the precursor and toosendanin against *P. xylostella* (Table 13, entry 2). The presence of the -CH<sub>2</sub>Cl unit in the analogue

modified **85** at C-23 gave a stronger insecticidal agent against *P. xylostella* but lower activity against *M. separata* in comparison to fraxinellone (**24**) and toosendanin (Table 13, entry 3). When an *N*-phenylpyrazole unit is introduced at C-21 or C-23 of the furan-site of fraxinellone (**89** and **91**), an increase in mortality rate is observed if the phenyl group contains a halogen atom both at the ortho- and para- positions (Yang et al. 2018a, Table 13, entries 4 and 5). The most active compounds of this series were those that possess a chlorine atom in the ortho position and a fluorine atom in the para position of the phenyl group (MR = 82.8% and 75.9% for the C-21 and C-23 substituted analogues, respectively, versus 55.2% for toosendanin when the growth of *M. separata* was evaluated). The introduction of other bulky chains such as aryloxy or aryl groups on the furan ring at C-21 also gave promising insecticidal compounds **86** and **95** against the armyworm (Yang et al. 2018b, Table 13, entries 6 and 7). Reduction of the double bond of the A-ring of fraxinellone afforded compound **61** that exhibited a fourfold increase in growth inhibition of *M. separata* compared to **24** (MR = 71.4% versus 17.4%) (Dong et al. 2018a, b, Table 13, entry 8).





**Scheme 12** Transformations of A and/or B rings of fraxinellone (Guo et al. 2012a, b, 2017a)



**Scheme 13** Syntheses of fraxinellone-based esters modified at C-15 or C-17. (Guo et al. 2013)

However, if this latter molecule is coupled to an alkyl chain on the C-21 of the C-ring, a dramatic decrease in the inhibition rate is observed (Table 13, entry 9). The acyl derivative **73** (Table 13, entry 10) and chlorinated analogues **74–75** (Guo et al. 2016, Table 13, entries 11–12) led only to slightly higher mortality rates. Transformations on the A-ring of fraxinellone at C-9 or C-30 in terms of oxidation on the C-9 allylic position, transformation in an oxime or related esters of C9/C30 oximes or the introduction of bulky motifs (aromatic-ring containing esters or hydrazones at C-9/C-30) gave a set of higher potency natural-product-based derivatives (Table 13, entries 13–16 (Li et al. 2016b), entries 19–22 (Guo et al. 2012a, b)). Zhao et al. (1997) also indicated that the lactone group in limonoids did not appear to be critical for antifungal effects. Modifications of the B-ring to give compounds **61** and **63** did not result in significantly more potent insecticidal compounds (Guo et al. 2013, Table 13, entries 17–18) which is consistent with the Zhao's assessment.

All these structural changes should be taken into account for further chemical modifications with a view

to identifying promising insecticidal candidates. However, it is noteworthy a clear lack of consistency in the insecticidal data for the control compounds fraxinellone (**24**) and toosendanin (**T**). For example, it is described mortality rate values of 17.4% (Table 13, entries 1 and 7), around 42–45% (Table 13, entries 2–3, 6, 10–12) or even upper than 50% (Table 13, entries 21 and 22) when fraxinellone (**24**) was assayed against pre-third-instar larvae of *M. separata* Walker in the same concentration and 35-days assay. Some discrepancies in the mortality rate percentages are also observed for toosendanin (**T**). Variability in the data are also observed in the experiments against *P. xylostella* Linnaeus. For this reason, it would be inappropriate to conclude which of these fraxinellone (**24**)-analogues could be the most active of all of them.

### Biotransformations of degraded limonoids

It is well known that conventional synthetic tools are tedious at times. Biotransformation of natural products could save time or eliminate undesired effects such as

the sensitivity of some functional groups in the presence of specific reagents or steric hindrance. However, the literature contains only a few reports of biotransformation of limonoids highlighting hydroxylation on different carbons of the basic limonoid skeleton (Haldar et al. 2013, 2015) or rare modifications of the furan moiety (Haldar et al. 2014) among others (Madyastha and Venkatakrishnan 2000).

Only a handful of degraded limonoid biotransformations have been reported. In all of them, fraxinellone (**24**) or isofraxinellone (**35**) were modified using the fungi *Aspergillus niger* (Yang et al. 2005; Zhang et al. 2005).

A fermentation culture of *A. niger* to which fraxinellone (**24**) was added led to the isolation and purification of a new compound known as fraxinigerllone (**100**) (Scheme 20a). This compound also exhibits antitumor activity (Zhang et al. 2005). In other microbial transformation studies, fraxinellone (**24**) was modified by *Aspergillus niger* (AS 3.421) and dasycarpol (9 $\beta$ -hydroxyfraxinellone, **26**) giving rise to fraxinigerllone (**100**) as the biotransformation product (Yang et al. 2005, Scheme 20b). In this study, dasycarpol (**26**) and fraxinigerllone (**100**) were also evaluated against EC9706 and A549 cell lines. Both products exhibited moderate cytotoxicity against the A549 cell line. Dasycarpol (**26**) showed an LC<sub>50</sub> value of 20  $\mu\text{g}/\text{mL}$  while fraxinigerllone (**100**) showed an inhibition rate of 32% at a concentration of 87  $\mu\text{g}/\text{mL}$ .

The cytotoxic activities of 1–3 were tested in vitro against EC9706 and A549 cell lines.

The bioconversion of (+)-isofraxinellone ((+)-**35**) was achieved through incubation with the fungi *Aspergillus niger* leading to (4*S*)-4-hydroxyisofraxinellone (**101**) (Miyazawa et al. 2009; Okuno et al. 2019; Scheme 21). Both the starting material ((+)-**35**) and the biotransformation product **101** exhibited antifeedant activity against *Spodoptera litura*, with ED<sub>50</sub> values of 3.91 and 4.43  $\mu\text{g}/\text{cm}^2$ , respectively.

## Conclusions and future outlook

In summary, this comprehensive review covered the isolation of slightly- and highly-degraded limonoids for the first time. From 1930 to March 2022, 49 degraded limonoids were reported, mostly from Meliaceae and Rutaceae plants.

Although common hypothesized intermediates have been postulated to explain the fragmentation routes towards degraded limonoids from more complex limonoid precursors, in-depth knowledge about how limonoid biodegradation occurs in the environment remain unavailable. Surprisingly, in most cases the furanyl ring remains intact in the decomposition pathways in both Meliaceae and Rutaceae families. In this review, the bioactivities of the isolated degraded limonoids were also enhanced in search of insecticidal, anticancer, anti-inflammatory, antimicrobial and neuroprotective activity. Nevertheless, approximately 43% of these compounds have not been tested in any biological evaluation to date or have turned out to be inactive. The most degraded limonoids have yet to be synthesized and their preparation could shed light on some stereochemical discrepancies. Moreover, chemical or microbial transformations could lead to new limonoid-derived analogues which could then be explored for potential biological activities. That is why we believe that these compounds could display yet to be discovered and potentially excellent pharmacological activities, which would spark more interest in them, prompt further studies and get more chemists interested in the total or semi syntheses of degraded limonoids. We anticipate that these compounds, and their more potent analogues, which to date remain under-explored, could be used in the study of protein-natural product interactions with the aim of designing new agrochemicals and therapeutic agents.

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## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

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