Daphnane-Type Diterpene Orthoesters and their Biological Activities

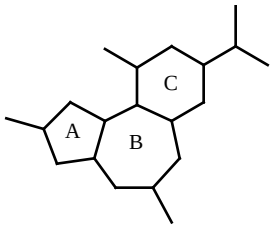
Weidong He,[1] Miroslav Cik,[2] Giovanni Appendino,[3] Luc Van Puyvelde,[1] Josée E. Leysen [2] and Norbert De Kimpe [1,*]

[1]*Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium;* [2]*Department of ReceptorPharmacology, Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium;* [3]*Dipartimento di Scienza e Tecnologia del Farmaco, Università di Torino, Via Pietro Giuria 9, I-10125 Torino, Italy*

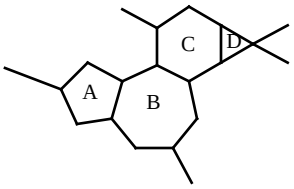
Abstract: Daphnane orthoesters are the active ingredients of plant remedies from the Western, Chinese and African traditional medicine, and have provided important tools to investigate medicinally relevant processes like tumour promotion, apoptosis, neurotrophism, and VR1 activation. The occurrence, biological activity, and molecular pharmacology of these compounds will be reviewed.

INTRODUCTION

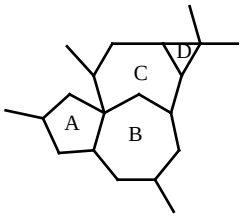
Plants from the Thymelaeaceae and the Euphorbiaceae families contain structurally unique diterpenes belonging to the tigliane, ingenane, and daphnane skeletal types. These compounds show a pleiotropic and partly overlapped pattern of biological activity, which has fuelled studies on various aspects of their chemistry, biochemistry and pharmacology. Several reviews are available [1-7] but none of them covers the development of the last two decades, which have witnessed enormous progress in the knowledge of the molecular basis underlying the biological activity of daphnanes, as well as the discovery of structural types which substantially deviate from the chemotypes described in the early studies. This review aims at filling this gap, providing a detailed list of the compounds isolated so far and an overview of their biological activity. Whenever sufficient information is available, the molecular aspects of the biological activity will be discussed.



Daphnane-type skeleton



Tigliane-type skeleton



Ingenane-type skeleton

Daphnane derivatives generally occur as ring C-orthoesters, and are more often encountered in plants from the Thymelaeaceae rather than in those from the Euphorbiaceae family [2,5]. The derivation of the daphnane skeleton from a tigliane precursor has been the subject of much speculation. A process involving opening of the tigliane cyclopropane ring via the ionization of a 16-hydroxyderivative and trapping of the 14-cation by the ester carbonyl of a 9-acyl group has been proposed [8], but attempts to mimic the process failed [8], and only compounds of the rhamnofolane type, resulting from the cleavage of the wrong cyclopropane bond, were obtained from the rearrangement of 16-hydroxytiglianes [9-10]. This failure does not disprove *per se* the plausibility of the process, but it should be pointed out that 9-esters of tiglianes are unknown, while esterification of the 13-hydroxyl is common. Thus, the intermediary of a 13,14- rather than a 9,14-dioxolanium ion seems more plausible for the cyclopropyl carbinyl rearrangement relating tiglianes and daphnanes. Formation of the orthoester moiety from 9,13-dihydroxy-14-acyl daphnanes and the reverse reaction, namely the hydrolysis of the 9,13,14-orthoester group to a 14-ester, has been reported only for compounds of the resiniferonol-type [11-13], and it is not clear if the process is possible also in other structural classes of daphnanes. The way in which the ω-1/ω carbon of a ring C orthoester group is joined to C-1 of ring A is unknown [1]. Since C-1 is the β-carbon of an enone system, a Michael addition might be involved, but the nature of the formal subterminal (terminal) anion equivalent from the acyl moiety is obscure. Furthermore, treatment of daphnane derivatives with *n*-propanethiol failed to afford any 1,2-Michael adduct, despite the high reactivity of thiols in this type of reactions [14].

*Address correspondence to this author at the Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium; Tel: +32 9 2645951; Fax: +32 9 2646243; E-mail: norbert.dekimpe@rug.ac.be

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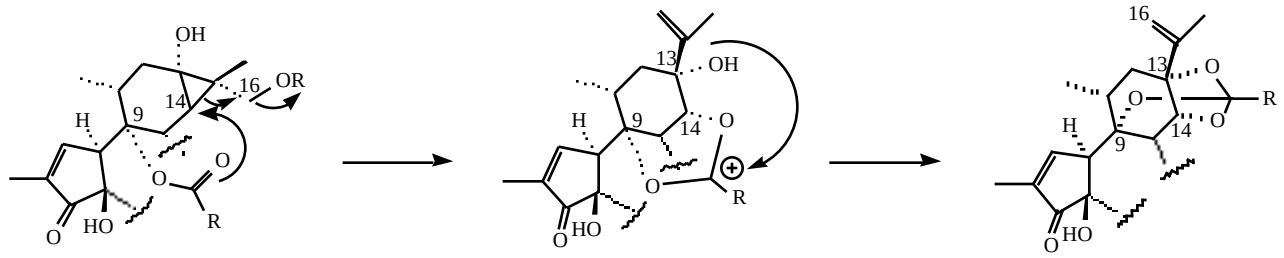
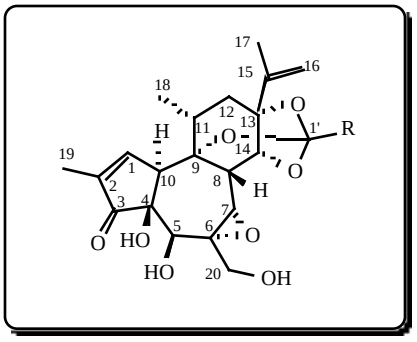


Apart for the acylation pattern, daphnane orthoesters mainly differ for the oxygenation pattern of ring C (C-12 hydroxylation or lack of it), the presence of an epoxidized or intact double bond on ring B, and for the presence of an extra alkyl group on ring A. The combination of these features, not all combinations of which co-occur, gives four major structural classes. Since biosynthetic details on the oxidative and alkylative modification of the daphnane skeleton are missing, this classification is arbitrary. Nevertheless, it makes it possible to group under the same heading compounds related in terms of occurrence and biological activity. Natural daphnanes always bear acyl group as orthoester and ester moieties. Despite the confuse redundancy of trivial names assigned the natural products, only resiniferonol among the parent polyols has been named, making it impossible a semi-systematic nomenclature.

1. DAPHNETOXIN AND ANALOGUES

Daphnetoxin (**1**) is first compound where the daphnane sekeleton was recognized. It was isolated as the poisonous principle of mezereon, a mixture of the stem bark from *Daphne mezereon, D. laureola* and *D. gnidium*. Mezereon was once an article of commerce because of its use in medicine as a cathartic as well as a counter-irritant constituent of plasters and ointments [15]. The medicinal use of mezereon caused several fatalities and is now completely obsolete [15]. Daphnetoxin was later isolated also from other *Daphne* species [16-18] . The structure of daphnetoxin was secured by an X-ray analysis of the 5,20-bisbromoacetate [15]. This evidenced differences from phorbol limited not only to ring C, but also encompassing ring B (epoxidation of the 6-double bond and hydroxylation at C-5). From a conformational standpoint, the major difference regards ring C, which is in a half-chair conformation in phorbol, but is forced into a boat geometry by the orthoesters bond typical of daphnanes [15].

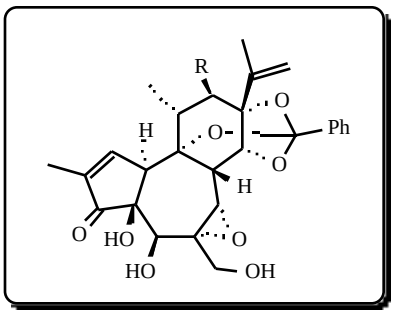


daphnetoxin (**1**)	R= C_6H_5
huratoxin (**2**)	R= $(CH=CH)_2(CH_2)_8CH_3$
excoecariatoxin (**3**)	R= $(CH=CH)_2(CH_2)_4CH_3$
simplexin (**4**)	R= C_9H_{19}
pimelea factor P_4 (**5**)	R= $C_{13}H_{27}$

Analogues of daphnetoxin where the orthobenzoate is replaced by aliphatic acids are know from plants of the Euphorbiaceae family. Thus, huratoxin (**2**) from *Hura crepitans* [19] has a bis-dehydromiristoyl orthoester group, and shows an extraordinary piscicidal activity, outperforming rotenone in killie-fish (*Oryzias laptipes*) by a factor of ten [19]. Interestingly, peracetylation abolished ichtyotoxicity, suggesting that either or both the hydroxyls on ring B are essential for activity [19]. Analogues with shorter orthoester group also show a diminished piscicidal activity [20-24], as exemplified by excoecariatoxin (**3**) from *Excoecaria* spp. (Euphorbiaceae). Huratoxin and related aliphatic orthoesters are among the few daphnanes isolated from plants belonging to both the Euphorbiaceae and the Thymelaeaceae families (25-29) (Table **1**, Fig **1**). Among their analogues, simplexin (**4**) and the Pimelea factor P_4 (**5**), isolated from various *Pimelea* spp. [25,30-31] are of particular toxicological relevance, being implicated in St. George's disease, a cardiopulmonary syndrome affecting livestock in Australia and New Zealand caused by the consumption of various *Pimelea* species [25,30,32-33]. Mellerin (**35**) was isolated from the leaves of *Neoboutonia melleri* (Euphorbiaceae) [28], and synaptolepis factor K_8 (**25**) was found in the roots of *Synaptolepis* spp. (Thymelaeaceae) as a weak irritant to the mouse ear [26]. From *Baliospermum montanum* [34] as well as from *Cunuria spruceana* [35], *Gnidia kraussiana* [36] and *Diarthron vericulosum* [29], montanin (**38**) revealed to have antileukaemia, anticancer and piscicidal activities. As a 5-deoxy isomer of simplexin, daphnopsis factor R_4 (**16**) was found in the roots of *Daphnopsis racemosa* and demonstrated weaker irritancy than simplexin [37]. Detailed structure-activity studies on daphnetoxin derivatives have not been carried out. The scanty data available point to an important role for the 5-hydroxyl, as also evidenced in other phorboids [37].

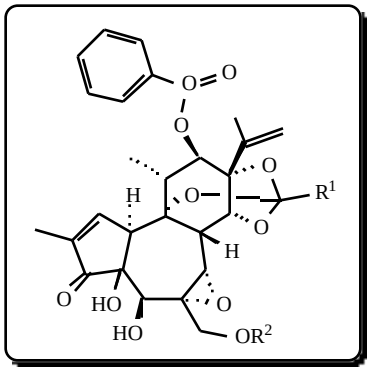
Further daphnetoxin-analogues were isolated from various plants belonging to the *Excoecaria*, *Wikstroemia* and *Synaptolepsis* species [22-24,26,29,38-43,80]. The strong irritant and tumor promoting activity of synaptolepsis factor K_7 (**23**) is worth mention [26]. This compound is also a very potent neurotrophic agent [44], and show nM-level anticancer activity in human leukaemia cells [45].

2. 12-HYDROXYDAPHNETOXIN AND ANALOGUES



mezerein (**6**)	R = $OCO(CH=CH)_2C_6H_5$
gnididin (**7**)	R = $OCO(CH=CH)_2(CH_2)_4CH_3$
gniditrin (**8**)	R = $OCO(CH=CH)_3(CH_2)_2CH_3$
gnidicin (**9**)	R = $OCOCH=CHC_6H_5$
12-hydroxydaphnetoxin (**10**)	R = OH
genkwadaphnin (**11**)	R = $OCOC_6H_5$

Mezerein (**6**) is the archetypal 12-acyloxyderivative of daphnetoxin, and was first isolated from the bark and the seeds of *D. mezereum* [15,17,46-48], a plant firmly enshrined in the Greek and Roman medicinal tradition as a treatment of various cancerous conditions [49]. It was also isolated as the poisonous principle of *Lasiosiphon burchellii* (Thymelaeaceae), a South African plant involved in livestock poisoning [16]. Mezerein is lethal to guinea pigs within a few hours at 5 mg/kg [16] and shows significant inhibitory activity against P-388 and L-1210 leukaemia in mice at dosages of 50 µg/kg [46]. The absolute configuration was established by an X-ray analysis in 1975 [50]. Mezerein is a powerful sensitizer of cancer cells to P-glycoprotein (Pgp) substrates, an activity unrelated to the activation of protein kinases but seemingly mediated by direct interaction with Pgp [51]. Mezerein analogues with a modified 12-acyl moiety occur in *Gnidia lamprantha* (Thymelaeaceae, compounds **7**-**9**). Compared to phorbol esters, mezerein derivatives show a stronger cytotoxicity and an attenuated co-cancerogenic activity [50], making them attractive leads in cancer research. Remarkably, the parent compound (12-hydroxydaphnetoxin (**10**)) is devoid of cytotoxic [52] and tumor promoting activity [16,50], while esterification of the 12-hydroxyl re-establish biological activity [52]. The rather broad tolerance of acyl group at C-12 suggests that this moiety essentially acts as an activity modulator, presumably involved in cell penetration but not directly in binding [29,52]. A structure-activity study showed that the acyl moiety at C-12, 5,20-diol system, and the double bond on ring A are all important for the activity, while the 15-double bond is not [14].



	R^1	R^2
gnidilatin (**12**)	C_9H_{19}	H
gnidilatidin (**13**)	$(CH=CH)_2(CH_2)_4CH_3$	H
gnidilatin-20-palmitate (**14**)	C_9H_{19}	$CO(CH_2)_{14}CH_3$
gnidilatidin-20-palmitate (**15**)	$(CH=CH)_2(CH_2)_4CH_3$	$CO(CH_2)_{14}CH_3$

Analogues of mezerein modified on both the 12-acyl and the orthoester moiety are known (**12-15**). Among them, gnidiladin (**13**), also known as odoracin [53] and yuanhuacine [54-55], show nematicidal [53] and antifertility properties [18,56]. Related compounds isolated from *D. genkwa* (Yuan Hua of the traditional Chinese medicine) [54,57-62,81] and *D. tangutica* [18] were studied in China as abortifacients [56,63]. Structure-activity studies showed that esterification of the 20-hydroxyl with fatty acids led to a substantial retention of activity with an overall decrease of toxicity, while formation of an acetonide between the 5- and 20-hydroxyl was detrimental for the activity [56], as also noticed in the cytotoxicity studies [14]. Saturation of the 1,2-double has been reported to occur in the natural products yuanhuatine (**52**) and yuanhuapine (**53**) from *D. genkwa,* which showed a decreased but still significant level of abortifacient activity compared to their unsaturated analogues [56,64-65].

Considerable attention has been given to the cinnamoyl analogue of mezerein, known under the trivial names of gnidicin and thymeleatoxin (**9**). This compound was reported as a selective activator of the PKC isoforms α, β_1 and γ. However, later studies showed that, disappointingly, gnidicin (**9**) does not show more isoform selectivity than phorbol esters [66].

12β-Acetoxyhuratoxin (**31**), a constituent of *Stellera chamaejasme* [67], *Wikstroemia retusa* [68] and *Synaptolepsis kirkii* [45], exhibits termite-killing activity [69], while kirkinine (**51**) and related compounds from the roots of *Synaptolepsis kirkii* show strong neurotrophic activity, promoting neuronal survival at an EC_{50} value of about 50 nM which is comparable to that of NGF (nerve growth factor) [70]. Further derivatives of 12-hydroxydaphnetoxin are listed in Table **1** and Fig. (**1**). Among these, maprouneacin (**54**) from the African plant *Maprounea africana* Muell-Arg. shows a particular interest, not only for its structure, which features an α-oriented 12-oxygen function and oxygenation of C-18, but also for its remarkable *in vivo* anti-diabetic activity [71]. The molecular mechanism of this activity is unknown, and worth pursuing in the light of the social relevance of diabetes.

3. ALKYLDAPHNANES

With one notable exception, these compounds have so far been isolated only in plants from the Thymelaeaceae family. Their hallmark is the two-fold merging of a carboxylic acid moiety and the terpenoid core via an orthoester bond and a carbon-carbon link. This motif is *per se* not unprecedented within the *Euphorbia* diterpenoids, but, apart form the 1-

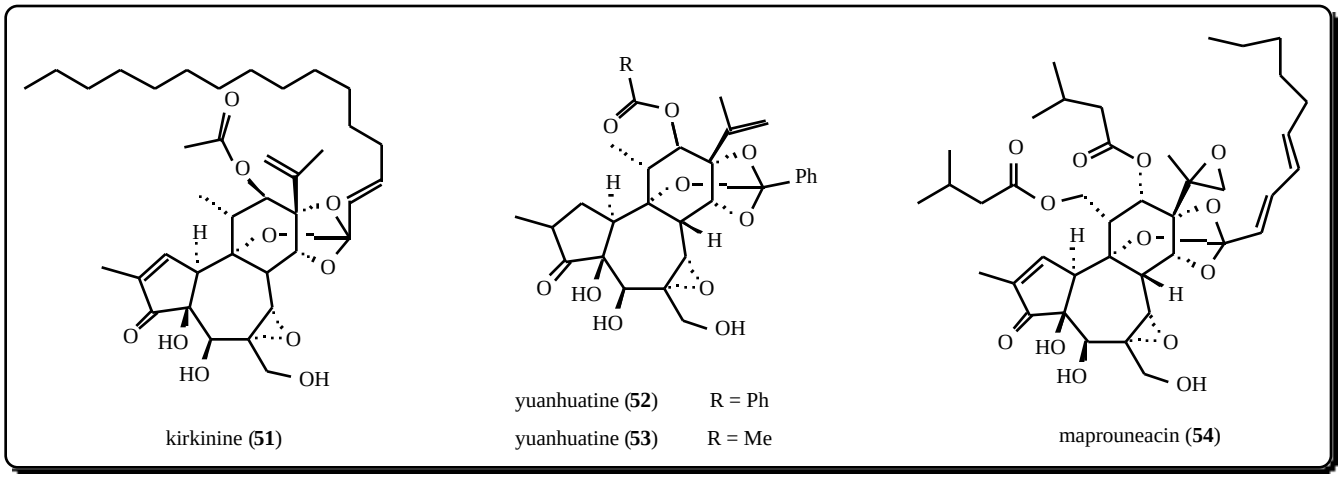


Table 1. Overview of Naturally Occurring Daphnetoxin- and 12-Hydroxydaphnetoxin-Type Diterpene Orthoesters Reported up to Date (Structures of the Compounds Listed in this Table Correspond to Fig. (1)) with their Physiological Activities

		Formula	Activity [a]										Plant	
Natural product	**No.**	**MW**	**I**	**L**	**T**	**A**	**C**	**P**	**D**	**N**	**S**	**Plant**	**family [b]**	**Literature**
Daphnetoxin	**1**	$C_{27}H_{30}O_8$										*Daphne mezereum* L.	T	[17]
		482							x			*Daphne giraldii* Nitsche	T	[15-16]
						n						*Daphne tangutica* Maxim	T	[57]
Huratoxin	**2**	$C_{34}H_{48}O_8$						x				*Hura crepitans* L.	E	[19-20]
		584										*Wikstroemia monticola* Skotsberg	T	[42]
												Diarthron vesiculosum Mey.	T	[29]
								x				*Stellera chamaejasme* L.	T	[67]
												Pimelea simplex F. Muell.	T	[32,72]
											x	*Wikstroemia retusa* A. Gray	T	[43,68-69,80]
								x				*Excoecaria agallocha* L.	E	[20]
Daphne factor F_1			x									*Daphne feddei* Lévl.	T	[73]
Hippomane factor M_1			x									*Hippomane mancinella* L.	E	[38,41]
Excoecariatoxin	**3**	$C_{30}H_{40}O_8$										*Daphne tangutica* Maxim	T	[18]
		528										*Gnidia kraussiana* Meisn.	T	[36]
												Wikstroemia monticola Skotsberg	T	[42]
												Diathron vesiculosum Mey.	T	[29]
											x	*Lasiosiphon kraussianus* Meisn.	T	[74]
Excoecaria factor A_3			x					x				*Excoecaria agallocha* L.	E	[20,22-23]
Excoecaria factor B_3												*Excoecaria bicolour* Zoll. ex. Hassk.	E	[24]
Ricinodendron factor Heu1												*Ricinodendron heudelotii* Baill.	E	[24]
Sapium factor G_4												*Sapium grahamii* Prein.	E	[24]
Synaptolepis factor K_5			x									*Synaptolepis kirkii* Oliv.	T	[26]

(Table 1). contd….

		Formula	Activity [a]										Plant	
Natural product	**No.**	**MW**	**I**	**L**	**T**	**A**	**C**	**P**	**D**	**N**	**S**	**Plant**	**family [b]**	**Literature**
Pimelea factor P_1	**4**	$C_{30}H_{44}O_8$	x									*Pimelea prostrata* Willd.	T	[25,27]
Daphnopsis factor R_3		532	x									*Daphnopsis racemosa* Griseb.	T	[37]
Wikstrotoxin D											x	*Wikstroemia monticola* Skotsberg	T	[42]
												Lasiosiphon kraussianus Meisn.	T	[74]
Pimelea factor S_8												*Pimelea simplex* F. Muell.	T	[75]
Simplexin				x								*Pimelea prostrata* Willd.	T	[76]
												Excoecaria bicolour Zoll. ex. Hassk.	E	[24]
												Daphne giraldii Nitsche	T	[77]
												Diarthron vesiculosum Mey.	T	[29]
								x				*Stellera chamaejasme* L.	T	[67]
									x			*Pimelea simplex* F. Muell.	T	[72,78]
			x	x	x				x			*Pimelea simplex/trichostachya* Form B.	T	[32]
Pimelea factor P_4	**5**	$C_{34}H_{52}O_8$	x									*Pimelea prostrata / simplex*	T	[25,27]
		588												
Mezerein	**6**	$C_{38}H_{38}O_{10}$		x			x					*Daphne mezereum* L.	T	[17,46-48,
		654												50,52,79]
Gnididin	**7**	$C_{37}H_{44}O_{10}$		x				x				*Gnidia lamprantha* Gilg.	T	[36,52]
		648												
Gniditrin	**8**	$C_{37}H_{42}O_{10}$		x				x	x			*Gnidia lamprantha* Gilg.	T	[52]
		646										*Daphne tangutica* Maxim	T	[18,57]
					x			x				*Daphne odora* Thunb.	T	[82]
												Daphne tangutica Maxim	T	[83]
												Thymelaea hirsuta L.	T	[84]
Daphne factor P_1												*Daphne papyrecea* Wall.	T	[85]
Gnidicin	**9**	$C_{36}H_{36}O_{10}$										*Gnidia lamprantha* Gilg.	T	[52]
		628										*Lasiosiphon burchellii* Meisn.	T	[16]
												Ginidia kraussiana Meisn.	T	[36]
Thymeleatoxin (A)			x									*Thymelaea hirsuta* L.	T	[84,86-87]
Tanguticafine												*Daphne tangutica* Maxim	T	[57]
12-Hydroxydaphnetoxin	**10**	$C_{27}H_{30}O_9$										*Daphne mezereum* L.	T	[17]
		498										*Lasiosiphon burchellii* Meisn.	T	[16]
												Daphne giraldii Nitsche	T	[15]
												Thymelaea hirsuta L	T	[84]
12-Benzoxydaphnetoxin	**11**	$C_{34}H_{34}O_{10}$		x								*Daphne genkwa* Sieb. et Zucc.	T	[58,62]
		602										*Lasiosiphon burchellii* Meisn.	T	[16]
Genkwadaphnin				x								*Daphne genkwa* Sieb. et Zucc.	T	[88-89]
												Peddiea africana / volkensii	T	[39]

(Table 1). contd….

		Formula	Activity [a]										Plant	
Natural product	**No.**	**MW**	**I**	**L**	**T**	**A**	**C**	**P**	**D**	**N**	**S**	**Plant**	**family [b]**	**Literature**
												Thymelaea hirsuta L.	T	[84]
Daphne factor F_2												*Daphne feddei* Lévl.	T	[73]
Gnidilatin	**12**	$C_{37}H_{48}O_{10}$		x								*Gnidia latifolia* Gilg.	T	[81]
		652										*Gnidia kraussiana* Meisn.	T	[36]
Gnidilatidin	**13**	$C_{37}H_{44}O_{10}$		x								*Gnidia latifolia* Gilg.	T	[57]
Yuanhuacine		648	x			x		x				*Daphne genkwa* Sieb. et Zucc.	T	[54-55,57]
												Excoecaria bicolour Zoll. ex. Hassk.	E	[24]
Ordoracin				x								*Daphne genkwa* Sieb. et Zucc.	T	[89]
												Daphne odora Thunb.	T	[82]
Stillingia factor S_6												*Stillingia sylvatica* L.	E	[90]
Gnidilatin-20-palmitate	**14**	$C_{53}H_{78}O_{11}$		x								*Gnidia latifolia* Gilg.	T	[57]
		890												
Gnidilatidin-20-palmitate	**15**	$C_{53}H_{74}O_{11}$		x								*Gnidia latifolia* Gilg.	T	[57]
		886												
Daphnopsis factor R_4	**16**	$C_{30}H_{44}O_7$										*Daphnopsis racemosa* Grisseb.	T	[37]
		516												
Excoecaria factor O_2	**17**	$C_{28}H_{36}O_8$										*Excoecaria oppositifolia* Griff.	E	[23-24,40]
		500												
Excoecaria factor A_2	**18**	$C_{36}H_{48}O_8$	x									*Excoecaria agallocha* L.	E	[22-23]
Excoecaria factor B_2		608	x									*Excoecaria bicolour* Zoll. ex. Hassk.	E	[24]
Hippomane factor M_2	**19**	$C_{36}H_{50}O_8$	x									*Hippomane mancinella* L.	E	[38,41]
Excoecaria factor B_1		610										*Excoecaria bicolour* Zoll. ex. Hassk.	E	[24]
Heudelotii factor Heu2												*Ricinodendron heudelotii* Baill.	E	[24]
Grahamii factor G_2												*Sapium grahamii* Prein.	E	[24]
Excoecaria factor A_1			x									*Excoecaria agallocha* L.	E	[24]
Excoecaria factor O_3 / A_7	**20**	$C_{36}H_{48}O_9$										*Excoecaria oppositifolia* Griff.	E	[40]
Excoecaria factor B_6		624										*Excoecaria bicolour* Zoll. ex. Hassk.	E	[24]
Excoecaria factor A_6	**21**	$C_{36}H_{50}O_9$				x						*Excoecaria agallocha* L.	E	[22]
Excoecaria factor B_5		626				x						*Excoecaria bicolour* Zoll. ex. Hassk.	E	[24]
Excoecaria factor O_1	**22**	$C_{30}H_{38}O_8$										*Excoecaria oppositifolia* Griff.	E	[40]
		526	n									*Excoecaria oppositifolia* Griff.	E	[23]
Excoecaria factor B_4												*Excoecaria bicolour* Zoll. ex. Hassk.	E	[23-24]
Sapium factor G_5												*Sapium grahamii* Prein.	E	[24]
Peddiea factor V_1			x									*Peddiea volkensii* Gilg.	T	[39]
Synaptolepis factor K_7	**23**	$C_{36}H_{54}O_8$	x		x							*Synaptolepis kirkii / retusa*	T	[26]
		614		x						x		*Synaptolepis kirkii* Oliv.	T	[44]

(Table 1). contd….

		Formula	Activity [a]										Plant	
Natural product	**No.**	**MW**	**I**	**L**	**T**	**A**	**C**	**P**	**D**	**N**	**S**	**Plant**	**family [b]**	**Literature**
Synaptolepis factor K_6	**24**	$C_{35}H_{50}O_8$	x									*Synaptolepis kirkii* Oliv.	T	[26]
Wikstrotoxin A		598										*Wikstroemia monticola* Skotsberg	T	[42]
Wikstroelides A				x								*Wikstroemia retusa* A. Gray	T	[43,80]
Synaptolepis factor K_8	**25**	$C_{36}H_{56}O_8$	x									*Synaptolepis kirkii / retusa*	T	[26]
		616												
Synaptolepis factor K'_7	**26**	$C_{52}H_{84}O_9$										*Synaptolepis kirkii* Oliv.	T	[26]
		852												
Synaptolepis factor K_3	**27**	$C_{32}H_{40}O_{10}$	n									*Synaptolepis kirkii* Oliv.	T	[26]
Peddiea factor V_2		584	n									*Peddiea volkensii* Gilg.	T	[39]
Synaptolepis factor K_4	**28**	$C_{32}H_{42}O_{10}$										*Synaptolepis kirkii* Oliv.	T	[26]
Yuanhuadine		586	x			x						*Daphne genkwa* Sieb. et Zucc.	T	[57-61]
Synaptolepis factor K'_3	**29**	$C_{48}H_{70}O_{11}$	n									*Synaptolepis kirkii* Oliv.	T	[26]
		822												
Synaptolepis factor K'_4	**30**	$C_{48}H_{72}O_{11}$	n									*Synaptolepis kirkii* Oliv.	T	[26]
		824												
Synaptolepis factor R_3	**31**	$C_{36}H_{50}O_{10}$	x									*Synaptolepis retusa* H.H.W.	T	[26]
Subtoxin A		642										*Pimelea simplex/trichostachya* Form B.	T	[32]
Wikstroelides L (2'E,4'Z)												*Wikstroemia retusa* A. Gray	T	[80]
12β-Acetoxyhuratoxin								x				*Stellera chamaejasme* L.	T	[67]
											x	*Wikstroemia retusa* A. Gray	T	[68-69]
Peddiea factor A_1	**32**	$C_{30}H_{38}O_9$	n									*Peddiea africana* Harv.	T	[39]
		542												
Yuanhuafine	**33**	$C_{29}H_{32}O_{10}$				x						*Daphne genkwa* Sieb. et Zucc.	T	[58,62]
		540												
Tanguticacine	**34**	$C_{53}H_{72}O_{11}$										*Daphne tangutica* Maxim	T	[18]
		884				x						*Daphne genkwa* Sieb. et Zucc.	T	[57]
Mellerin B	**35**	$C_{28}H_{40}O_8$										*Neoboutonia melleri* Meull-Arg.	E	[28]
		504												
Gnidiglaucin	**36**	$C_{32}H_{46}O_{10}$		n								*Ginidia glaucus* Fres.	T	[57]
		590												
Wikstrotoxin B	**37**	$C_{32}H_{44}O_8$										*Diarthron vesiculosum* Mey.	T	[29]
		556										*Wikstroemia monticola* Skotsberg	T	[42]
Montanin	**38**	$C_{32}H_{48}O_8$										*Diarthron vesiculosum* Mey.	T	[29]
		560		x			x		x			*Baliospermum montanum* Muell-Arg.	E	[34]
								x				*Cunuria spruceana* Baillon	E	[35]
												Gnidia kraussiana Meisn.	T	[36]

(Table 1). contd….

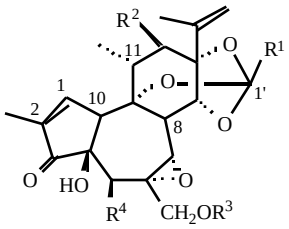
		Formula	Activity [a]										Plant	
Natural product	**No.**	**MW**	**I**	**L**	**T**	**A**	**C**	**P**	**D**	**N**	**S**	**Plant**	**family [b]**	**Literature**
Stillingia factor S_1	**39**	$C_{38}H_{48}O_{11}$	x									*Stillingia sylvatica* L.	E	[90]
		680												
Stillingia factor S_2	**40**	$C_{52}H_{74}O_{12}$	x									*Stillingia sylvatica* L.	E	[90]
		890												
Stillingia factor S_3	**41**	$C_{52}H_{72}O_{12}$	x									*Stillingia sylvatica* L.	E	[90]
		902												
Stillingia factor S_4	**42**	$C_{54}H_{78}O_{12}$	x									*Stillingia sylvatica* L.	E	[90]
		918												
Stillingia factor S_5	**43**	$C_{55}H_{76}O_{12}$	x									*Stillingia sylvatica* L.	E	[90]
		930												
Wikstroelides H	**44**	$C_{34}H_{46}O_{10}$										*Wikstroemia retusa* A. Gray	T	[80]
		614												
Wikstroelides B	**45**	$C_{37}H_{52}O_{10}$										*Wikstroemia retusa* A. Gray	T	[43,68,80]
		656									x	*Wikstroemia retusa* A. Gray	T	[69]
Wikstroelides C	**46**	$C_{51}H_{76}O_{11}$										*Wikstroemia retusa* A. Gray	T	[43,80]
		864												
Wikstroelides I	**47**	$C_{52}H_{78}O_{11}$										*Wikstroemia retusa* A. Gray	T	[80]
		878												
12-*O*-Heptadecenoy-daphnetoxin	**48**	$C_{44}H_{60}O_{10}$ 748	x									*Thymelaea hirsuta* L.	T	[84-85]
12-*O*-Butenyl-daphnetoxin	**49**	$C_{31}H_{34}O_{10}$										*Thymelaea hirsuta* L.	T	[84-85]
		566												
12-Hydroxydaphnetoxin-5,12,20-triacetate	**50**	$C_{33}H_{36}O_{12}$ 624	x									*Thymelaea hirsuta* L.	T	[84-85]
Kirkinine	**51**	$C_{38}H_{56}O_{10}$		x						x		*Synaptolepis kirkii* Oliv.	T	[70]
		672												

[a] Activities: **I**; irritant; **L**: antileukaemia; **T**: tumour-promoting; **A**: abortion (birth and fertility regulation); **C**: anticancer; **P**: piscicidal; **D**: toxicity; **N**: neurotrophic; **S**: insecticidal; **x**: active; **n**: inactive. [b] E: Euphorbiaceae, T: Thymelaeaceae

alkyldaphnanes, it is limited to acetyl residues, as in terracinolides from *Euphorbia terracina* L. [91]. From a structural standpoint, the occasional reduction of the 3-ketogroup is also noteworthy, and reminiscent of ingenane derivatives.

The archetypal 1-alkyldaphnane is gnidimacrin (**55a**), a constituent of *Gnidia subcordata*, where it occurs with its 20-palmitate analogue (**55b**). Neither compound show a significant antileukaemic activity, and their structure was eventually resolved by X-ray analysis of the 20-*p*-iodobenzoate of **55a** [92]. Analogues of gnidimacrin have been isolated from plants belonging to the *Pimelea, Daphnopsis* and *Gnidia* genera. As with gnidiladin (**13**), a confusing proliferation of trivial names exists for linifolin B **(55c**), reflecting its isolation from different plant sources (*P. prostrata* [27,76,93], *P. linifolia*, *P. ligustrina* [94], *Daphnopsis racemosa* [37,93], *Gnidia kraussiana* [36]).

The biological activity of kirkinine B from *Synaptolepis kirkii* [45] and reidiocide A (**57**) from *Trigonostemom reidioides* Graib (Euphorbiaceae) [95] is most remarkable. The former has a NGF-like activity not unlike that shown by the synaptolepsis factor K_7 (**23**) and kirkinine (**51**) [70],

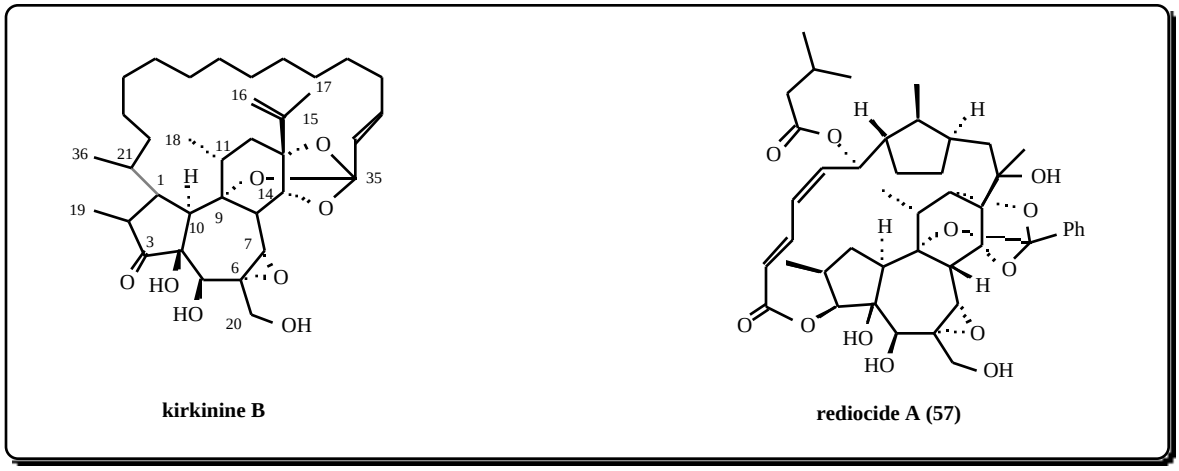


	R[1]	**R[2]**	**R[3]**	**R[4]**
1	C_6H_5	H	H	OH
2	$(CH=CH)_2(CH_2)_8CH_3$	H	H	OH
3	$(CH=CH)_2(CH_2)_4CH_3$	H	H	OH
4	C_9H_{19}	H	H	OH
5	$C_{13}H_{27}$	H	H	OH
6	C_6H_5	$OCO\text{-}(CH=CH)_2C_6H_5$	H	OH
7	C_6H_5	$OCO\text{-}(CH=CH)_2(CH_2)_4\text{-}CH_3$	H	OH
8	C_6H_5	$OCO\text{-}(CH=CH)_3(CH_2)_2\text{-}CH_3$	H	OH
9	C_6H_5	$OCOCH=CHC_6H_5$	H	OH
10	C_6H_5	OH	H	OH
11	C_6H_5	$OCOC_6H_5$	H	OH
12	C_9H_{19}	$OCOC_6H_5$	H	OH
13	$(CH=CH)_2(CH_2)_4CH_3$	$OCOC_6H_5$	H	OH
14	C_9H_{19}	$OCOC_6H_5$	$CO(CH_2)_{14}CH_3$	OH
15	$(CH=CH)_2(CH_2)_4CH_3$	$OCOC_6H_5$	$CO(CH_2)_{14}CH_3$	OH
16	$(CH_2)_8CH_3$	H	H	H
17	$(CH=CH)_2(CH_2)_2CH_3$	H	H	OH
18	$(CH=CH)_2(CH_2)_6CH_3$	H	H	OH
19	$(CH=CH)_3(CH_2)_8CH_3$	H	H	OH
20	$(CH=CH)_4(CH_2)_6CH_3$	OH	H	OH
21	$(CH=CH)_3(CH_2)_8CH_3$	OH	H	OH
22	$(CH=CH)_3(CH_2)_2CH_3$	H	H	OH
23	$CH=CH(CH_2)_{12}CH_3$	H	H	OH
24	$(CH=CH)_2(CH_2)_9CH_3$	H	H	OH
25	$(CH_2)_{14}CH_3$	H	H	OH
26	$CH=CH(CH_2)_{12}CH_3$	H	$CO(CH_2)_{14}CH_3$	OH
27	$(CH=CH)_3(CH_2)_2CH_3$	$OCOCH_3$	H	OH
28	$(CH=CH)_2(CH_2)_4CH_3$	$OCOCH_3$	H	OH
29	$(CH=CH)_3(CH_2)_2CH_3$	$OCOCH_3$	$CO(CH_2)_{14}CH_3$	OH
30	$(CH=CH)_2(CH_2)_4CH_3$	$OCOCH_3$	$CO(CH_2)_{14}CH_3$	OH
31	$(CH=CH)_2(CH_2)_8CH_3$	$OCOCH_3$	H	OH
32	$(CH=CH)_3(CH_2)_2CH_3$	OH	H	OH

(Fig. 1) contd….

33	C_6H_5	$OCOCH_3$	H	OH
34	C_6H_5	$OCO(CH=CH)_3CH_2CH_3$	$CO(CH_2)_{14}CH_3$	OH
35	C_7H_{15}	H	H	OH
36	C_9H_{19}	$OCOC_6H_5$	H	OH
37	$(CH=CH)_2(CH_2)_8CH_3$	H	H	OH
38	$C_{11}H_{23}$	H	H	OH
39	$(CH=CH)_2(CH_2)_2CH_3$	$OCO(CH=CH)_3(CH_2)_3OH$	H	OH
40	$(CH=CH)_2(CH_2)_2CH_3$	$OCO(CH=CH)_3(CH_2)_3OCOC_{13}H_{27}$	H	OH
41	$(CH=CH)_2(CH_2)_2CH_3$	$OCO(CH=CH)_3(CH_2)_3OCOCH=CHC_{12}H_{25}$	H	OH
42	$(CH=CH)_2(CH_2)_4CH_3$	$OCO(CH=CH)_3(CH_2)_3OCOC_{13}H_{27}$	H	OH
43	$(CH=CH)_2(CH_2)_4CH_3$	$OCO(CH=CH)_3(CH_2)_3OCOCH=CHC_{12}H_{25}$	H	OH
44	$(CH=CH)_2(CH_2)_6CH_3$	$OCOCH_3$	H	OH
45	$(CH=CH)_2(CH_2)_9CH_3$	$OCOCH_3$	H	OH
46	$(CH=CH)_2(CH_2)_8CH_3$	$OCOCH_3$	$CO(CH_2)_{14}CH_3$	OH
47	$(CH=CH)_2(CH_2)_9CH_3$	$OCOCH_3$	$CO(CH_2)_{14}CH_3$	OH
48	C_6H_5	$OCOCH=CH(CH_2)_{13}CH_3$	H	OH
49	C_6H_5	$OCOCH=CHCH_3$	H	OH
50	C_6H_5	$OCOCH_3$	$COCH_3$	$OCOCH_3$
51	$CH=CH(CH_2)_{12}CH_3$	$OCOCH_3$	$CO(CH_2)_{14}CH_3$	OH

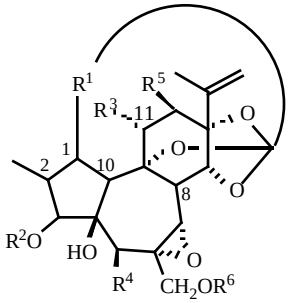
Fig. (1). Structures of known daphnetoxin- and 12-hydroxydaphnetoxin-type diterpene orthoesters.



while the latter displays exceedingly high insecticidal properties, with a sub-nM activity against flea larvae. The insecticidal properties have been shown not to be mediated by activation of PKC [95]. Reidiocide A is also exceptional in having a 9,12,14-orthoester moiety instead of the usual 9,13,14 arrangement for this group, and in having the 3-hydroxyl and the 17-methyl involved in the two-fold merging of the acyl moiety and the diterpenoid skeleton.

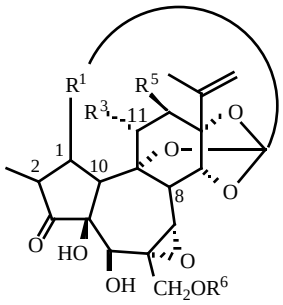
4. RESINIFERONOIDS

In these compounds, the A/B ring system has the functionalization pattern of phorbol. Resiniferonoids have a very narrow distribution, limited to three succulent African Euphorbias, two of which (*E. poissonii* Pax and *E. unispina* N.E.Br.) are so closely related to be considered by some authors as a single taxonomic unit [12,100]. Resiniferatoxin



55

	R^1 (C_1-R^1-)	R^2	R^3	R^4	R^5	R^6
55a	$CH(CH_3)(CH_2)_6CH(OH)$	COC_6H_5	$CH_2OCOC_6H_5$	OH	H	H
55b	$CH(CH_3)(CH_2)_6CH(OH)$	COC_6H_5	$CH_2OCOC_6H_5$	OH	H	$CO(CH_2)_{14}CH_3$
55c	$CH(CH_3)(CH_2)_7$	COC_6H_5	CH_3	OH	H	H
55d	$CH(CH_3)(CH_2)_7$	COC_6H_5	CH_3	OH	$OCOCH_3$	H
55e	$CH(CH_3)(CH_2)_7$	COC_6H_5	CH_3	H	H	H
55f	$CH(CH_3)(CH_2)_6CH(OH)$	H	$CH_2OCOC_6H_5$	OH	H	H
55g	$CH(CH_3)(CH_2)_6CH(OH)$	COC_6H_5	CH_3	OH	H	H
55h	$CH(CH_3)(CH_2)_6CH(OAc)$	COC_6H_5	CH_3	OH	H	H
55i	$CH(CH_3)(CH_2)_6CH(CH_3)$	H	$CH_2OCOC_6H_5$	OH	H	H



56

	R^1 (C_1-R^1-)	R^3	R^5	R^6
56a	$CH(CH_3)(CH_2)_7$	CH_3	H	H
56b	$CH(CH_3)(CH_2)_6$-$CH(OCOC_6H_5)$	CH_3	H	H
56c	$C_{13}H_{26}CH{=}CH$	CH_3	H	H
56d	$CH(CH_3)(CH_2)_{11}$-$CH{=}CH$	CH_3	H	H
56e	$CH(CH_3)(CH_2)_{11}$-$CH{=}CH$	CH_3	$OCOCH_3$	H
56f	$CH(CH_3)(CH_2)_{11}$-$CH{=}CH$	CH_3	H	$CO(CH_2)_{14}CH_3$
56g	$C(OH)(CH_3)(CH_2)_{11}CH{=}CH$	CH_3	H	H
56h	$CH(\alpha CH_3)(CH_2)_7$	$CH_2OCOC_6H_5$	H	H
56i	$CH(\alpha CH_3)(CH_2)_7$	$CH_2OCOC_6H_5$	H	$CO(CH_2)_{14}CH_3$
56j	$CH(CH_3)(CH_2)_7$	$CH_2OCOC_6H_5$	H	$CO(CH_2)_{14}CH_3$
56k	$C(CH_3)(CH_2)_7$	$CH_2OCOC_6H_5$	H	H

Fig. (2). Structures of known 1-alkyldaphnane diterpene orthoesters (continued).

Table 2. Overview of Naturally Occurring 1-Alkyldaphnane Diterpene Orthoesters in the Thymelaeaceae up to Date (Structures of the Compounds Illustrated in this Table Correspond to Fig. (2)) with their Physiological Activities

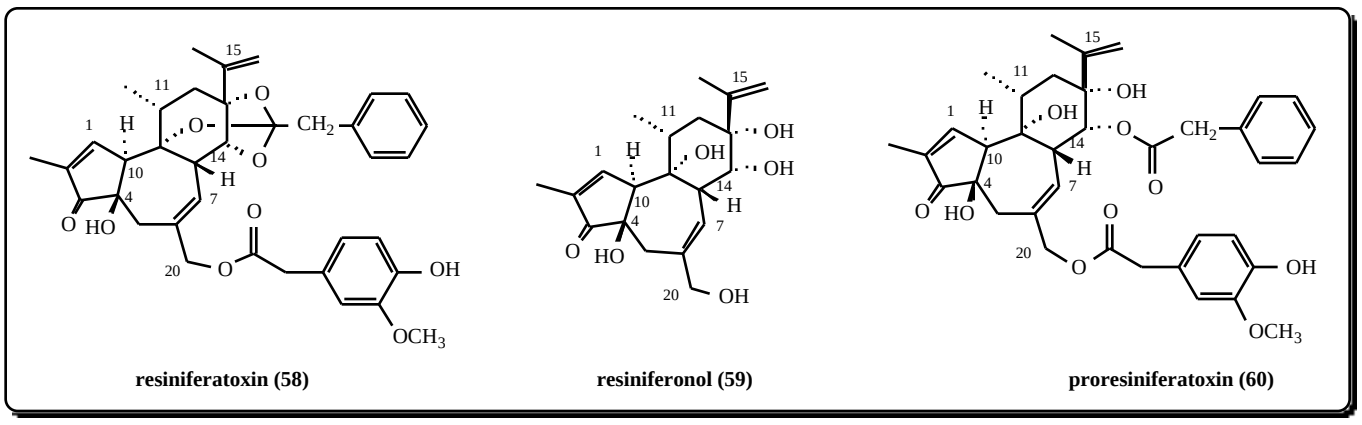
		Formula	Activity [a]							
Natural product	**Structure**	**MW**	**I**	**L**	**T**	**P**	**S**	**N**	**Plant**	**Literature**
Gnidimacrin	**55a**	$C_{44}H_{54}O_{12}$		x		x			*Gnidia subcordata* Engl.	[92,81]
		758							*Pimelea prostrata* Willd.	[76]
									Daphnopsis racemosa Grisseb.	[37]
				x					*Stellera chamaejasme* L.	[96-97]
Gnidimacrin-20-palmitate	**55b**	$C_{60}H_{84}O_{13}$		x					*Gnidia subcordata* Engl.	[92]
		1012								
Pimelea factor P_2	**55c**	$C_{37}H_{50}O_9$	x	x					*Pimelea prostrata* Willd.	[27,76,93]
		638							*Gnidia kraussiana* Meisn.	[36]
				x					*Wikstroemia retusa* A. Gray	[43,49,80]
							x		*Wikstroemia retusa* A. Gray	[69]
						x			*Stellera chamaejasme* L.	[67]
				x					*Stellera chamaejasme* L.	[97]
Daphnopsis factor R_1			x		x				*Daphnopsis racemosa* Grisseb.	[37,93]
Linifolin B				x		x			*Pimelea linifolia / ligustrina* Labill.	[94]
Gnilatimacrin									*Gnidia subcordata* Engl.	[92]
Linimacrin B									*Pimelea linifolia / ligustrina* Labill.	[94]
Pimelea factor P_3	21β-Me		x						*Pimelea prostrata* Willd.	[27]
Pimelea factor P_3									*Stellera chamaejasme* L.	[67]
Daphnopsis factor R_5			x		x				*Daphnopsis racemosa* Grisseb.	[37]
Linifolin A	**55d**	$C_{39}H_{52}O_{11}$		x		x			*Pimelea linifolia* Sm.	[94]
Linimacrin A		696							*Pimelea linifolia / ligustrina* Labill.	[94]
Daphnopsis factor R_6	**55e**	$C_{37}H_{50}O_8$	x						*Daphnopsis racemosa* Grisseb.	[37]
Daphnopsis factor R_7	21β-Me	622	x						*Daphnopsis racemosa* Grisseb.	[37]
Stelleramacrin	**55f**	$C_{37}H_{50}O_{11}$		x					*Stellera chamaejasme* L.	[97]
		670								
Kraussianin	**55g**	$C_{37}H_{50}O_{10}$		x					*Gnidia kraussiana* Meisn.	[36]
Linimacrin C	21β-Me	654							*Pimelea linifolia / ligustrina* Labill.	[94]
Dircin	**55h**	$C_{39}H_{52}O_{11}$		x					*Dirca occidentalis* A. Gray	[98]
		696								
Stelleramacrin A	**55I**	$C_{38}H_{52}O_{10}$		x					*Stellera chamaejasme* L.	[99]
		668								
Pimelea factor S_7	**56a**	$C_{30}H_{44}O_8$	x						*Pimelea prostrata* Willd.	[93]
Pimelea factor S_7		532	x		x				*Pimelea simplex* F. Muell.	[75,78]
Wikstroelides E				x					*Wikstroemia retusa* A. Gray	[80]
							x		*Wikstroemia retusa* A. Gray	[69]
Pimelea factor S_6	21β-Me		x						*Pimelea simplex* F. Muell.	[75]

(Table 2). contd….

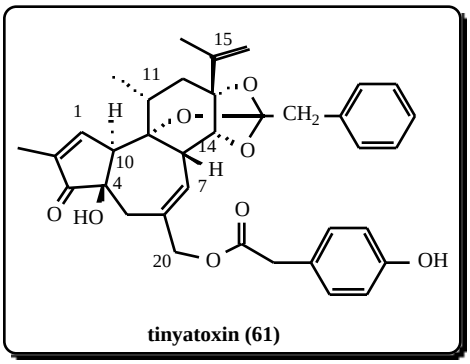
		Formula	Activity [a]							
Natural product	**Structure**	**MW**	**I**	**L**	**T**	**P**	**S**	**N**	**Plant**	**Literature**
Pimelea factor P_6	**56b**	$C_{37}H_{48}O_{10}$	x						*Pimelea prostrata* Willd.	[27,93]
		652							*Pimelea prostrata* Willd.	[27]
Synaptolepis factor K_1	**56c**	$C_{36}H_{54}O_8$	x						*Synaptolepis spp.*	[93]
Synaptolepis factor K_1	**56d**	$C_{36}H_{54}O_8$	x		x				*Synaptolepis kirkii / retusa*	[26]
Kirkinine B	$\Delta^{33,34}$-*trans*	614		x				x	*Synaptolepis kirkii* Oliv.	[45]
Synaptolepis factor K_2	**56e**	$C_{38}H_{56}O_{10}$	x		x				*Synaptolepis kirkii* Oliv.	[26]
		672								
Synaptolepis factor K_1'	**56f**	$C_{52}H_{84}O_9$	x						*Synaptolepis kirkii* Oliv.	[26]
		852								
Synaptolepis factor R_4	**56g**	$C_{36}H_{54}O_9$	x						*Synaptolepis retusa* H.H.W.	[26]
		630								
Wikstroelides F	**56h**	$C_{37}H_{48}O_{10}$					x		*Wikstroemia retusa* A. Gray	[69]
		652							*Wikstroemia retusa* A. Gray	[43]
Wikstroelides G	**56i**	$C_{53}H_{78}O_{11}$					x		*Wikstroemia retusa* A. Gray	[69]
		890							*Wikstroemia retusa* A. Gray	[43]
Wikstroelides K	**56j**	$C_{53}H_{78}O_{11}$							*Wikstroemia retusa* A. Gray	[80]
		890								
Wikstroelides O	**56k**	$C_{37}H_{48}O_{10}$							*Wikstroemia retusa* A. Gray	[80]
		652								

[a] Activities: **I**; irritant; **L**: antileukaemia; **T**: tumour-promoting; **P**: piscicidal; **S**: insecticidal; **N**: neurotrophic; **x**: active;

(RTX, **58**) is the best known resiniferonoid. It was first isolated from Euphorbium, the dried latex of *E. resinifera* Berg., one of the oldest drug of the Western medicinal tradition [11,101]. Resiniferonoids are the daphnanes which have elicited more interest within the biomedical community. All resiniferonoids isolated so far are closely related to resiniferatoxin and contain acyl groups possessing an aromatic ring. Remarkably, the one at C-20 is phenolic (homovanillic acid in RTX (**58**) and *p*-hydroxyphenylacetic acid in tinyatoxin (**61**) [12]). Acylation of the 20-hydroxyl is rare within the other classes of daphnanes, and generally limited to long-chain acyl residues. Proresiniferatoxin (**60**) co-occur with RTX [11-12] , and could be turned into RTX by mild acidic treatment. The reverse reaction is also easy, while basic hydrolysis of proresiniferatoxin (**60**) afforded the parent polyol resiniferonol (**59**) [13]. Proresiniferatoxin is the only natural daphnane lacking the ring C orthoester group isolated so far. It is not clear if it is a natural product or an



resiniferatoxin (58) **resiniferonol (59)** **proresiniferatoxin (60)**



tinyatoxin (61)

artefact, but its isolation shows that the presence of a phorbol-like A/B ring system somewhat makes the orthoester linkage more prone to acidic hydrolysis.

RTX was discovered because of its extraordinary activity in the mouse ear erythema assay, where it outperforms TPA, the most potent phorbol ester, by a factor of 10^2-10^3 [11-12]. In certain assays of vanilloid activity, it also outperforms capsaicin, the hot principle of chilli, by a factor of 10^4 [101], and no compound approaching the activity level of RTX in these assays is known. RTX has played a pivotal role in the characterization of VR1, a receptor protein for a series of structurally diverse pungent compounds commonly referred to as vanilloids [102]. Its pharmacology and the rationale for its current pharmaceutical development to treat bladder hyperreflexia and diabetic neuropathy have been discussed in a major review on vanilloids [102]. Modification of the natural leads as well as the synthesis of phorbol-RTX hybrids has been reported [13,103-104], affording interesting probes to investigate the pharmacology of VR1 as well as the vanilloid-induced apoptosis [105]. The total synthesis of RTX has been reported by Wender [106], and no other daphnane has so far surrended to total synthesis.

RTX was reported to selectively activate PKC-α in a DAG-like manner [66]. Interestingly, also tionyatoxin (**61**) behaves as a PKC-α selective activator, but with a different and so far unclear mechanism [66].

CLOSING REMARKS

Daphnane orthoesters have provided important tools to investigated medicinally relevant processes like tumour promotion, apoptosis, neurotrophism, and VR1 activation. However, the therapeutic exploitation of these compounds has so far lagged behind their application in basic research. One of the major reasons for this gap is the unavailability of daphnane orthoesters in amounts sufficient to sustain a significant medicinal chemistry effort. Complex mixtures of daphnane orthoesters occur as minor or trace components in several plants, but no commercial source is available in sizable amounts. On the other hand, the horticultural relevance of several Thymelaeaceae and Euphorbiaceae should spur investigations aimed at the discovery of species and/or varieties amenable to medicinal exploitation for the production of crude daphnane mixtures. Attempt to use tigliane derivatives as daphane surrogates have been reported [103-104,107-108], and a total synthesis of RTX, currently the "hottest" member of the daphnane family, has also been accomplished [106]. These achievements bode well for the ultimate pharmaceutical exploitation of the wealth of basic information which has been unravelled thanks to the unique pharmacological properties of daphnane orthoesters.

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