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ACETOGENINS FROM ANNONACEAE, INHIBITORS OF MITOCHONDRIAL COMPLEX I

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Key Word Index—Annonaceae; linear and epoxy acetogenins; mono-, bis- and tri-tetrahydrofuran acetogenins; inhibitors of mitochondrial complex I.

Abstract—One-hundred and twenty-eight different linear, epoxy, mono-tetrahydrofuran, bis-tetrahydrofuran or tri-tetrahydrofuran acetogenins have been isolated from the Annonaceae. These new secondary metabolites are potent cytotoxic inhibitors of the mitochondrial NADH:ubiquinone oxidoreductase (complex I of the respiratory chain).

INTRODUCTION

Since the isolation of the first Annonaceous acetogenin, uvaricin, from *Uvaria acuminata* [1], interest in these metabolites has been growing because of their potent cytotoxic and antiparasitic activities. Nearly 150 acetogenins have been described as far as we know. The application of combined techniques has been necessary to facilitate the structural elucidation of the different parts of these complex molecules: the terminal γ-lactone subunit, the placement of the tetrahydrofuran (THF) subunit along the aliphatic chain and also the location of other functional groups along the aliphatic chain. Several strategies have also been developed to resolve the relative stereochemistry at the chiral carbons in the structures of the acetogenins. For these reasons, the elucidation of acetogenin structures has now become easier than some years ago and new structural features have been described since the last reviews of these compounds [2–6]. However, for some of them the elucidation is not yet complete or must be reconsidered according to the updated knowledge. In previous papers we have given structural considerations about mono-THF acetogenins [4] and bis-THF acetogenins [6].

The purpose of this review is to list all the Annonaceous acetogenins known up to now. The classification is made according to the structural characteristics shown in Fig. 1. Two new subgroups of acetogenins are presented, characterized by a different type of THF α-hydroxylated system: (T-E) and (T-F). Non-THF acetogenins with one (E-A), two (E-B), three epoxy groups (E-C) or with a linear alkyl chain are also included. As in our previous reviews [4, 6] we suggest, by considering the spectral data, several synonyms for compounds described as new acetogenins. Within the tables, compounds are presented according to their chronological order of discovery. If two different names were given for the same compound isolated at the same time by two different groups, the names are linked by 'or'. Names in minor characters are given when compounds have been previously described. The reliable number of acetogenins must be considered as 128 so far, four of them being linear, 12 epoxy, 51 mono-THF, 60 bis-THF and one tri-THF acetogenins (see Tables 1–9).

Table 10 summarizes the botanical sources from which new acetogenins have been isolated. Finally, the recent advances in the knowledge of their mechanism of action as inhibitors of mitochondrial NADH: ubiquinone oxidoreductase (respiratory complex I) are given [7, 8].

LINEAR AND EPOXY ACETOGENINS

These compounds belong to a class of biogenetic precursors of the THF acetogenins. Only four linear acetogenins have been isolated [9–12] (Table 1). Biomimetic synthesis of mono- and bis-THF acetogenins from bis-epoxy (**3.2** corepoxylone) [13] and tri-epoxy acetogenins (**4.1** triepoxyrollin) [14], respectively, suggest their role in the biogenetic pathway of THF acetogenins. Epoxy-acetogenins probably show different absolute configurations. The isolation of three different mono-epoxy olefinic acetogenin pre-

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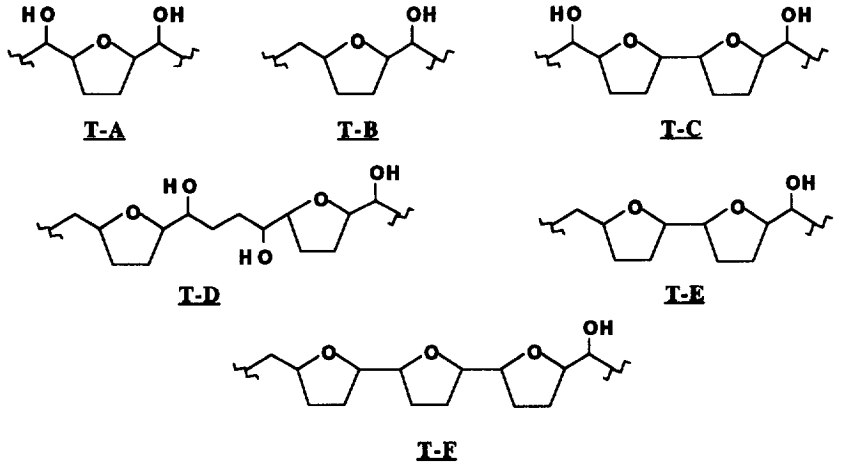
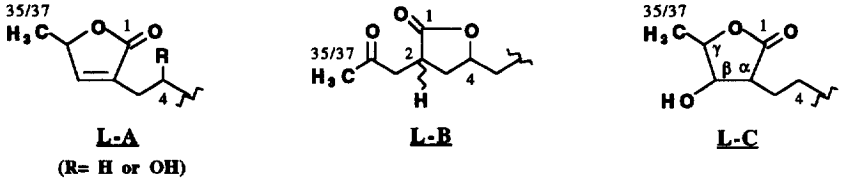
* Types of THF α-hydroxylated systems:



* Types of γ-lactone rings:



* Types of epoxy rings:

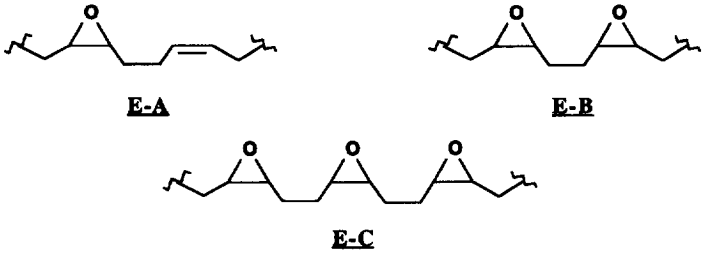


Fig. 1. Tetrahydrofuran, γ-lactone and epoxy systems in Annonaceous acetogenins.

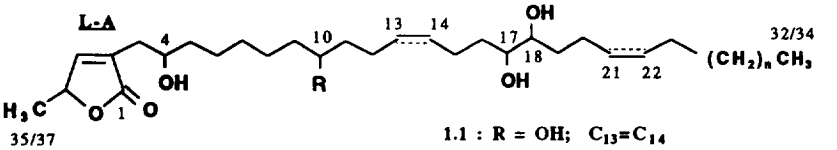
cursors from *Annona muricata* stem barks [15] and seeds [16] was published in 1993 (Table 2). Spectral data of epoxymurin-A [15] are identical to those of epomuricenin-A [16]. Acetogenins of the class of mono-epoxy olefinic are logically biogenetic precursors of bis-epoxy acetogenins [3]. Eight bis-epoxy C_{35} or C_{37} acetogenins were isolated from *Annona* and *Rollinia* seeds [13, 17–20]. The structures of epoxyrollin-A and epoxyrollin-B [21] were first described as a mixture of two questionable C_{36} and C_{38} mono-epoxy acetogenins. Examination of their NMR and mass spectrum suggested their structural revision as two C_{35} and C_{37} bis-epoxy acetogenins which were identical to dieporeticanin-1 [18] (= epoxyrollin-A) and diepomuricanin-A [17] (= epoxyrollin-B), respectively. Dieporeticenin, the only bis-epoxy olefinic acetogenin isolated, is a precursor of the tri-epoxy compounds. Diepoxymontin is an unusual adjacent bis-epoxy acetogenin [19]. Tripoxyrollin, was the first tri-epoxy acetogenin isolated from *R. membranacea* seeds [14]. Recently, trieporeticanin, from *A. reticulata* [18] has been presented as an isomer of tripoxyrollin, on the basis of its different ^{13}C NMR values at the epoxy methine carbon. Nevertheless, the chemical shifts are very similar in all carbons of both compounds (^{13}C, $\Delta_{\text{tripoxyrollin-trieporeticanin}} = -0.19$ at -0.17) [14, 18] and the difference could be due to upfield shifts of internal reference.

MONO-THF ACETOGENINS

Since our first review of mono-THF acetogenins in

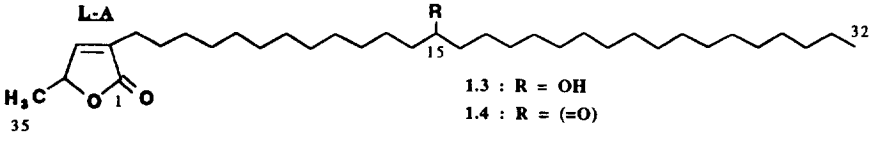
Table 1. Acetogenins without tetrahydrofuran rings: linear acetogenins

	Hydroxyl positions	Relative configuration*	Molecular formula	M^+	Annonaceae species† [reference]
		I—*Linear acetogenins*			
1—Hydroxylated and ketonic linear acetogenins, 'giganin type':					
1.1 Giganin (C_{13}=C_{14})	4,10,17,18	*c-th*	$C_{35}H_{64}O_6$	580	*G. giganteus* [9]
1.2 Venezenin (C_{21}=C_{22})	4,17,18 (CO, 10)	*th-c*	$C_{37}H_{66}O_6$	606	*X. aromatica* [10]



1.1 : R = OH; C_{13}=C_{14}
1.2 : R = (=O); C_{21}=C_{22}

1.3 Reticulatamol	15	—	$C_{35}H_{66}O_3$	534	*A. reticulata* [11]
1.4 Reticulatamone	(CO, 15)	—	$C_{35}H_{64}O_3$	532	*A. reticulata* [12]



1.3 : R = OH
1.4 : R = (=O)

th: threo; c: cis.
†*G: Goniothalamus; X: Xylopia; A: Annona.*

1991 [4], which listed 18 compounds, 33 other new structures have been reported. Mono-THF acetogenins are classified here in four subtypes (Tables 3–5).

(i) Mono-THF α,α'-dihydroxylated type is the most important subclass of the mono-THF acetogenins (Table 3), which include 34 dihydroxylated, trihydroxylated, tetrahydroxylated or pentahydroxylated acetogenins. A number of these compounds are characterized by the presence of a double bond in the alkyl chain (giganenin type: **6.4**). Mono-THF olefinic acetogenins (gonionenin: **7.13**; and gigantetronenin: **9.4**) were oxidized to adjacent or nonadjacent bis-THF acetogenins [38] by biomimetic pathways. All the mono-THF α,α'-dihydroxylated acetogenins have the relative configurations *threo/trans/threo* (annonacin type: **7.1**) or *threo/trans/erythro* (annonacin-A type: **7.4**).

(ii) Mono-THF α-monohydroxylated type (Table 4) is a new subclass of acetogenins (gigantetrocin-A type: **9.1**) [45]. Densicomacins-1 and 2 were first isolated as a mixture of two stereoisomers. NMR, mass spectra and relative configuration of densicomacin-2 are identical to those of gigantetrocin-A [42, 45].

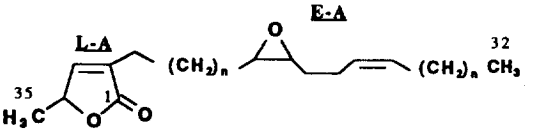
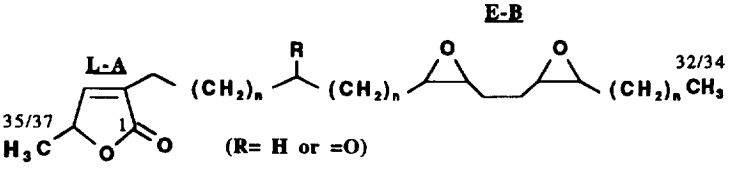
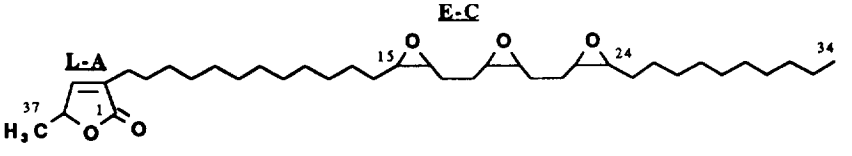
(iii) Iso-acetogenin mono-THF type (see Table 5, and see also Table 8) showed double signals in their ^1H and ^{13}C NMR spectra, which suggests that they are mixtures of C-2/C-4 *cis* and *trans* diastereoisomers, typically observed for all iso-acetogenins [5]. Isolation from some *Annona* species of classical 4-hydroxy-acetogenins (L-A, Fig. 1) and also iso-acetogenins (L-B, Fig. 1) revealed that isomers are artefacts of the extraction procedure, obtained by translactonization of 4-hydroxy-acetogenins, through an effect of alkaloids (basic medium) existing in the crude material and/or by an effect of alcohol extraction [52].

(iv) β-Hydroxy-acetogenins (Table 5) are a new type of acetogenin isolated only from *A. cherimolia* seed [51] and characterized by the presence of a β-hydroxyl saturated γ-lactone moiety (L-C, Fig. 1).

BIS-THF ACETOGENINS

In 1993 we reported the classification and the structural revisions of the first 31 bis-THF acetogenins [6] from Annonaceae. Since that review, 29 new acetogenins have been isolated. So far, 33 adjacent, 11 non-adjacent, 13 iso- and three β-hydroxy bis-THF different acetogenins have been reported. Some similar bis-THF acetogenins have been claimed as new products, but they are identical to previously known compounds (Tables 6–8). Purpureacin-2 (**13.7**, Table 6) is a new adjacent bis-THF acetogenin whose relative stereochemical configuration has not been yet reported. Here, we propose that it has the most common relative configuration, *threo/trans/threo/trans/erythro*, established by the ^1H- and ^{13}C-NMR values of bis-THF, α,α'-dihydroxylated system. All adjacent bis-THF show seven different relative stereochemical relationships across the bis-THF skeleton, belonging to T-C type (Fig. 1), *threo/trans/threo/trans/erythro*, *threo/trans/threo/trans/threo*, *threo/cis/threo/cis/erythro*, *threo/trans/erythro/trans/threo*, *erythro/trans/threo/trans/threo* and *threo/cis/threo/cis/threo*, and T-E

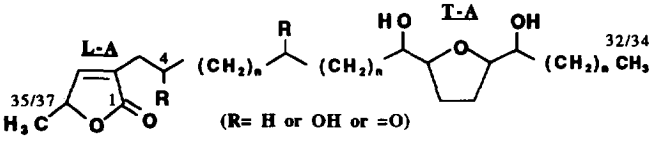
Table 2. Acetogenins without tetrahydrofuran rings: epoxy-acetogenins

	Olefinic position	Epoxy positions	Molecular formula	M^+	Annonaceae species* [reference]
		II—*Epoxy-acetogenins*			
2—Mono-epoxy olefinic, 'epoxymurin-A type':					
					
2.1 Epoxymurin-A or epomuricenin-A	C_{19}=C_{20}	15,16	$C_{35}H_{62}O_3$	530	*A. muricata* [15] *A. muricata* [16]
2.2 Epoxymurin-B	C_{15}=C_{16}	19,20	$C_{35}H_{62}O_3$	530	*A. muricata* [15]
2.3 Epomuricenin-B	C_{17}=C_{18}	13,14	$C_{35}H_{62}O_3$	530	*A. muricata* [16]
3—Bis-epoxy, 'diepomuricanin-A type':					
					
3.1 Diepomuricanin-A =epoxyrollin-B	—	15,16,19,20	$C_{35}H_{62}O_4$	546	*A. muricata* [17] *A. muricata* [21]
3.2 Corepoxylone	(C=O, 10)	15,16,19,20	$C_{35}H_{60}O_5$	560	*A. muricata* [13]
3.3 Dieporeticanin-1 =epoxyrollin-A	—	17,18,21,22	$C_{37}H_{66}O_4$	574	*A. reticulata* [18] *A. muricata* [21]
3.4. Dieporeticanin-2	—	19,20,23,24	$C_{37}H_{66}O_4$	574	*A. reticulata* [18]
3.5 Dieporeticenin	C_{23}=C_{24}	15,16,19,20	$C_{37}H_{64}O_4$	572	*A reticulata* [18]
3.6 Diepoxymontin	—	11,12,13,14	$C_{35}H_{62}O_4$	546	*A. montana* [19]
3.7 Diepomuricanin-B	—	17,18,21,22	$C_{35}H_{62}O_4$	546	*R. membranacea* [20]
3.8 Diepoxyrollin	—	15,16,19,20	$C_{37}H_{66}O_4$	574	*R. membranacea* [20]
4—Tri-epoxy, 'tripoxyrollin type'					
					
4.1 Tripoxyrollin =trieporeticanin	—	15,16,19,20,23,24	$C_{37}H_{64}O_5$	588	*R. membranacea* [14] *A. reticulata* [18]

**A: Annona; R: Rollinia.*

type (Fig. 1), *trans/threo/trans/threo*. Relative stereochemical configuration of the non-adjacent bis-THF bullatalicin (**16.3**, Table 7) isolated from *A. bullata*, was predicted on the basis of the ^{13}C NMR values [6, 84] as *erythro-threo/trans/threo*. Recently, relative configuration of bullatalicin was revised as being *threo-threo/trans/erythro* [85], which is identical to cherimolin-1, a non-adjacent bis-THF acetogenin isolated from *A. cherimolia* seeds [82, 83]. Cherimolin-1 (or bullatalicin) and cherimolin-2 (or bullatanocin) [83, 85] are the most frequently non-adjacent bis-THF acetogenins isolated from *Annona* species: *A. cherimolia*, *A. bullata*, *A. squamosa*, *A. purpurea* and *A. crassiflora* (see **16.3** and **16.4**, Table 7). Squamostatin-A [91], was considered in our previous review [6] as an epimer of almunequin [83] on the basis of the different chemical shifts in the ^{13}C NMR spectrum, at C_{20} and C_{23} given by the authors (THF carbons: δ 82.2 and δ 82.4 for squamostatin-A; δ 83.2 and δ 82.1 for almunequin). Nevertheless, in 1994 the same authors have redescribed the ^{13}C NMR spectral data for this non-adjacent bis-THF acetogenin in a way that makes it completely identical (C_{20} is now δ 83.2!) to almunequin (see **17.1**, Table 7). Squamostatin-B [87], recently described as a new acetogenin, is very similar to the previously characterized cherimolin-1 (**16.3**).

Table 3. Mono-THF α,α'-dihydroxylated γ-lactone acetogenins

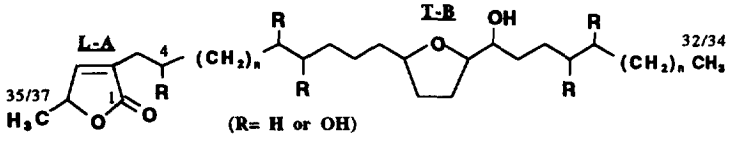
		Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species† [reference]
III—*Mono-THF α,α'-dihydroxylated acetogenins*						
						
5—*Dihydroxylated, 'uvariamicin-I type'*:						
5.1	*Uvariamicin-I*	15,20	*th/t/th*	$C_{37}H_{68}O_5$	592	*U. narum* [22]
5.2	Uvariamicin-II or reticulatacin	17,22	*th/t/th*	$C_{37}H_{68}O_5$	592	*U. narum* [22] *A. reticulata* [23]
5.3	Uvariamicin-III	19,24	*th/t/th*	$C_{37}H_{68}O_5$	592	*U. narum* [22]
5.4	Solamin	15,20	*th/t/th*	$C_{35}H_{64}O_5$	564	*A. muricata* [4]
5.5	Uvariamicin-IV	13,18	*th/t/th*	$C_{37}H_{68}O_5$	592	*A. bullata* [24]
5.6	Bullatencin (C_{23}=C_{24})	15,20	*th/t/th*	$C_{37}H_{66}O_5$	590	*A. bullata* [24]
5.7	Reticulatain-1	17,22	*th/t/er*	$C_{37}H_{68}O_5$	592	*A. reticulata* [12]
5.8	Reticulatain-2	19,24	*th/t/er*	$C_{37}H_{68}O_5$	592	*A. reticulata* [12]
6—Trihydroxylated and dihydroxylated ketonic, 'murisolin type':						
6.1	Murisolin	4,15,20	*th/t/th*	$C_{35}H_{64}O_6$	580	*A. muricata* [25]
6.2	Corossolin	10,15,20	*th/t/th*	$C_{35}H_{64}O_6$	580	*A. muricata* [26]
6.3	Corossolone	15,20 (CO, 10)	*th/t/th*	$C_{35}H_{62}O_6$	578	*A. muricata* [26]
6.4	Giganenin (C_9=C_{10})	13,18,21	*th/t/th*	$C_{37}H_{66}O_6$	606	*G. giganteus* [27]
7—Tetrahydroxylated and trihydroxylated ketonic, 'annonacin type':						
7.1	Annonacin	4,10,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. densicoma* [28]
7.2	Goniothalamicin	4,10,13,18	*th/t/th*	$C_{35}H_{64}O_7$	596	*G. giganteus* [29]
7.3	Annonacinone	4,15,20 (CO, 10)	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. densicoma* [30]
7.4	Annonacin-A	4,10,15,20	*th/t/er*	$C_{35}H_{64}O_7$	596	*A. squamosa* [31]
7.5	Annomontacin	4,10,17,22	*th/t/th*	$C_{37}H_{68}O_7$	624	*A. montana* [32]
7.6	Annoreticuin	4,9,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. reticulata* [33]
7.7	Annoreticuinone	4,15,20 (CO, 9)	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. reticulata* [34]
7.8	Xylopianin	4,8,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*X. aromatica* [35]
7.9	Xylopiacin	4,8,15,20	*th/t/th*	$C_{37}H_{68}O_7$	624	*X. aromatica* [35]
7.10	Xylomaticin	4,10,15,20	*th/t/th*	$C_{37}H_{68}O_7$	624	*X. aromatica* [35]
7.11	Reticulacinone	4,15,20 (CO, 11)	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. reticulata* [36]
7.12	Squamosten-A (C_{23}=C_{24})	4,12,15,20	*th/t/th*	$C_{37}H_{66}O_7$	622	*A. squamosa* [37]
7.13	Gonionenin (C_{21}=C_{22})	4,10,13,18	*th/t/th*	$C_{37}H_{66}O_7$	622	*G. giganteus* [38]
7.14	Xylopien (C_{23}=C_{24})	4,8,15,20	*th/t/th*	$C_{37}H_{66}O_7$	622	*X. aromatica* [39]
7.15	Xylomatenin (C_{23}=C_{24}) or annogalene	4,10,15,20	*th/t/th*	$C_{37}H_{66}O_7$	622	*X. aromatica* [39] *A. senegalensis* [40]
7.16	Annosenegalin	4,10,15,20	*th/t/er*	$C_{37}H_{68}O_7$	624	*A. senegalensis* [40]
8—Pentahydroxylated and tetrahydroxylated ketonic, 'annomonicin type':						
8.1	Annomonicin	4,8,13,15,20	*th/t/th*	$C_{35}H_{64}O_8$	612	*A. montana* [41]
8.2	Montanacin	4,8,13,19,24	*th/t/th*	$C_{37}H_{68}O_8$	640	*A. montana* [41]
8.3	8-Hydroxyannonacin	4,8,10,15,20	*th/t/th*	$C_{35}H_{64}O_8$	612	*A. densicoma* [42]
8.4	Annomuricin-A	4,10,11,15,20	*th-th/t/er*	$C_{35}H_{64}O_8$	612	*A. muricata* [43]
8.5	Annomuricin-B	4,10,11,15,20	*er-th/t/er*	$C_{35}H_{64}O_8$	612	*A. muricata* [43]
8.6	Muricatin-C	4,15,20,25 (CO, 10)	*th/t/th*	$C_{35}H_{62}O_8$	610	*A. muricata* [44]

**th: threo; er: erythro; t: trans.*

†U: Uvaria; A: Annona; G: Goniothalamus; X: Xylopia.

Another non-adjacent bis-THF acetogenin has been also named squamostatin-B [92] (indicated here by us as squamostatin-B 'bis'), but in our opinion is similar to almunequin or squamostatin-A (see Table 7). So far, all non-adjacent bis-THF show five different relative stereochemical relationships across the bis-THF skeleton, *trans/threo-erythro/trans/threo*, *trans/threo-threo/trans/threo*, *trans/threo-threo/trans/erythro*, *cis/threo-threo/trans/threo* and *cis/threo-threo/trans/erythro*.

Table 4. Mono-THF α-monohydroxylated γ-lactone acetogenins

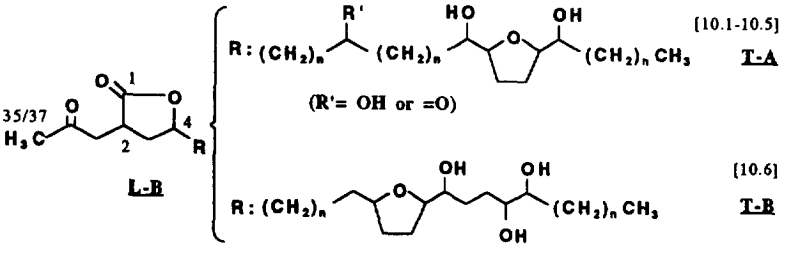
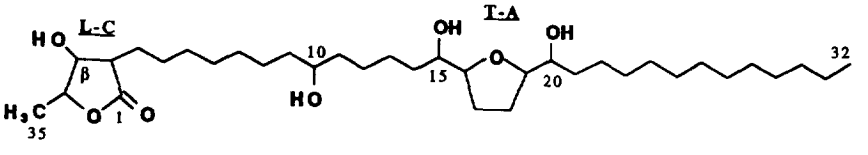
	Hydroxyl positions	THF and diols relat. config.*	Molecular formula	M^+	Annonaceae species† [reference]
		IV—*Mono-THF α-monohydroxylated acetogenins*			
					
9—THF α-Monohydroxylated, 'gigantetrocin-A type':					
9.1 Gigantetrocin-A =densicomacin-2	4,14,17,18	*t/th-th*	$C_{35}H_{64}O_7$	596	*G. giganteus* [45] *A. densicoma* [42]
9.2 Gigantriocin	14,17,18	*t/th-th*	$C_{35}H_{64}O_6$	580	*G. giganteus* [45]
9.3 Densicomacin-1	4,14,17,18	*t/er-th*	$C_{35}H_{64}O_7$	596	*A. densicoma* [42]
9.4 Gigantetronenin (C_{21}=C_{22})	4,14,17,18	*t/th-th*	$C_{37}H_{66}O_7$	622	*G. giganteus* [46]
9.5 Gigantrionenin (C_{21}=C_{22})	14,17,18	*t/th-th*	$C_{37}H_{66}O_6$	606	*G. giganteus* [46]
9.6 Gigantetrocin-B	4,14,17,18	*t/th-th*‡	$C_{35}H_{64}O_7$	596	*A. muricata* [47]
9.7 Muricatetrocin-A/B	4,16,19,20	*er* or *th-th*	$C_{35}H_{64}O_7$	596	*A. muricata* [47]
9.8 Senegalene (C_{29}=C_{30})	4,12,13,21	*th-t/th*	$C_{37}H_{66}O_7$	622	*A. senegalensis* [48]
9.9 Muricatin-A	4,14,17,18,23	*t/th-th*	$C_{35}H_{64}O_8$	612	*A. muricata* [44]
9.10 Muricatin-B	4,14,17,18,19	*t/th-th/er*	$C_{35}H_{64}O_8$	612	*A. muricata* [44]

**th: threo; er: erythro; t: trans.*

†*G: Goniothalamus; A: Annona.*

‡Gigantetrocin-B (**9.6**): 17,18-diepimer from gigantetrocin-A (**9.1**).

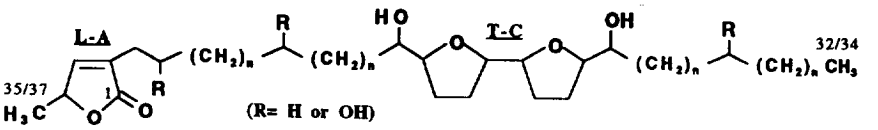
Table 5. Saturated lactone mono-THF acetogenins

	Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species† [reference]
		V—*Iso-acetogenins, mono-THF*			
					
10—'Iso' mono-THF, 'isoannonacin type':					
10.1 Isoannonacin	10,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. densicoma* [30]
10.2 Isoannonacinone	15,20 (CO, 10)	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. densicoma* [30]
10.3 Squamone	15,20 (CO, 9)	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. squamosa* [49]
10.4 Isoannoreticuin	9,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. reticulata* [33]
10.5 Annonacinone-A	10,15,20	*th/t/er*	$C_{35}H_{64}O_7$	596	*As. triloba* [50]
10.6 Gigantetrocinone	14,17,18	*t/th-th*	$C_{35}H_{64}O_7$	596	*As. triloba* [50]
		VI—*β-Hydroxy-acetogenins, mono-THF*			
11—β-Hydroxymethyl γ-lactones, 'jetein type':					
11.1 Jetein	10,15,20,33	*th/t/er*	$C_{35}H_{66}O_7$	598	*A. cherimolia* [51]
					

**th: threo; er: erythro; t: trans.*

†*A: Annona; As: Asimina.*

Table 6. Adjacent bis-THF γ-lactone acetogenins

		Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species† [reference]
VII—*Adjacent bis-THF acetogenins*						
						
12—Dihydroxylated, 'uvaricin type':						
12.1	Uvaricin	15 (OAc-24)	*th/t/th/t/er*	$C_{39}H_{68}O_7$	648	*U. acuminata* [1]
12.2	Desacetyluvaricin =squamocin-L	15,24	*th/t/th/t/er*	$C_{37}H_{66}O_6$	606	*U. acuminata* [53] *A. squamosa* [54]
12.3	Neoannonin =squamocin-J	13,22	*th/t/th/t/er*	$C_{35}H_{62}O_6$	578	*A. squamosa* [55] *A. squamosa* [54]
12.4	Isodesacetyluvaricin =4-deoxy-asimicin =squamocin-M	15,24	*th/t/th/t/th*	$C_{37}H_{66}O_6$	606	*U. narum* [56] *A. bullata* [24] *A. squamosa* [54]
12.5	Membranacin	15,24	*th/c/th/c/er*	$C_{37}H_{66}O_6$	606	*R. membranacea* [57]
12.6	Squamocin-I	13,22	*er/t/th/t/th*	$C_{35}H_{62}O_6$	578	*A. squamosa* [54]
12.7	Squamocin-K =atemoyin	13,22	*th/t/th/t/th*	$C_{35}H_{62}O_6$	578	*A. squamosa* [54] *A. atemoya* [58]
12.8	Squamocin-N	15,24	*th/c/th/c/th*	$C_{37}H_{66}O_6$	606	*A. squamosa* [54]
13—Trihydroxylated and tetrahydroxylated (with OH in 4), 'asimicin type':						
13.1	Asimicin =annonastatin =squamocin-H	4,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [59] *A. squamosa* [31] *A. squamosa* [54]
13.2	Rolliniastatin-1 =4-hydroxy-25-desoxyneorollinicin	4,15,24	*th/c/th/c/er*	$C_{37}H_{66}O_7$	622	*R. mucosa* [60] *R. papilionella* [61]
13.3	Rolliniastatin-2 or bullatacin =14-hydroxy-25-desoxyrollinicin =annonin-VI =squamocin-G	4,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*R. mucosa* [62] *A. bullata* [63] *A. reticulata* [64] *A. squamosa* [65] *A. squamosa* [54]
13.4	Molvizarin	4,13,22	*th/t/th/t/er*	$C_{35}H_{62}O_7$	594	*A. cherimolia* [66]
13.5	Trilobacin	4,15,24	*th/t/er/t/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [67]
13.6	Rioclarin	4,15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*R. membranacea* [57]
13.7	Purpureacin-2	4,12,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. purpurea* [68]
13.8	Parviflorin or squamocin-E	4,13,22	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*As. parviflora* [69] *A. squamosa* [54]
13.9	Annoglaucin	4,10,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. glauca* [70]
13.10	Glaucanisin	4,13,22	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*A. glauca* [71]
14—Trihydroxylated and dihydroxylated ketonic (without OH in 4), 'squamocin type':						
14.1	Squamocin =rollinicin	15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*A. squamosa* [72] *R. papilionella* [73]
14.2	Isorollinicin‡	15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*R. papilionella* [73]
14.3	Squamocinone	15,24 (CO, 28)	*th/t/th/t/er*	$C_{37}H_{64}O_7$	620	*U. narum* [74]
14.4	Motrilin or annonin-III =squamocin-C	15,24,29	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*A. cherimolia* [66] *A. squamosa* [7] *A. squamosa* [54]
14.5	Squamocin-B	13,22,26	*th/t/th/t/er*	$C_{35}H_{62}O_7$	594	*A. squamosa* [54]
14.6	Squamocin-D or asiminacin	15,24,28	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*A. squamosa* [54] *As. triloba* [75]
14.7	Squamocin-F	12,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*A. squamosa* [54]
14.8	Asimin	10,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [75]
14.9	Asiminecin	15,24,29	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [75]
14.10	Bullatin	10,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*As. triloba* [76]
14.11	Bullanin	15,24,30	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*As. triloba* [76]
14.12	Bullacin	6,13,22	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*A. bullata* [77]

(*Continued*)

Table 6. *Continued*

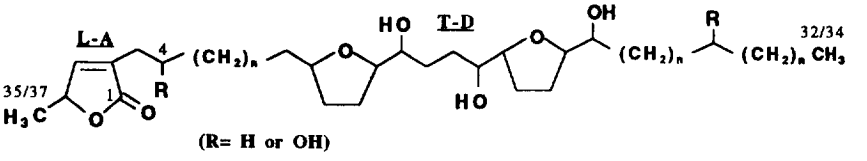
	Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species† [reference]
15—Trihydroxylated and tetrahydroxylated (with OH in 5), 'panalicin type':					
15.1 Panalicin	5,15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*U. narum* [74]
15.2 Narumicin-I	5,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*U. narum* [56]
15.3 Narumicin-II	5,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*U. narum* [56]

**th: threo; er: erythro; t: trans; c: cis.*

†*U: Uvaria; A: Annona; R: Rollinia; As: Asimina.*

‡Isorollinicin (**14.2**): epimer from squamocin (**14.1**).

Table 7. Non-adjacent bis-tetrahydrofuran γ-lactone acetogenins

	Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species† [reference]
VIII—*Non-Adjacent bis-THF acetogenins*					
 (R= H or OH)					
16—*Nonadjacent bis-THF (with OH in 4), 'sylvaticin type'*:					
16.1 *Sylvaticin* =uleicin-C	4,16,19,24	*t/th-er/t/th*	$C_{37}H_{66}O_8$	638	*R. sylvatica* [78] *R. ulei* [79]
16.2 Gigantecin	4,14,17,22	*t/th-th/t/th*	$C_{37}H_{66}O_8$	638	*G. giganteus* [80, 81]
16.3 Cherimolin-1 or bullatalicin =annonin-VIII =squamostatin-B	4,16,19,24	*t/th-th/t/er*	$C_{37}H_{66}O_8$	638	*A. cherimolia* [82, 83] *A. bullata* [84, 85] *A. squamosa* [86] *A. squamosa* [87]
16.4 Cherimolin-2 or bullatanocin =annonin-IV =purpureacin-1 =squamostatin-C =crassiflorin	4,16,19,24	*t/th-th/t/th*	$C_{37}H_{66}O_8$	638	*A. cherimolia* [83] *A. bullata* [85] *A. squamosa* [86] *A. purpurea* [68] *A. squamosa* [88] *A. crassiflora* [89]
16.5 Parvifloracin	4,14,17,22	*t/th-th/t/th*	$C_{35}H_{62}O_8$	610	*As. parviflora* [69]
16.6 12,15-*cis*-Bullatalicin	4,16,19,24	*c/th-th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [90]
16.7 12,15-*cis*-Bullatanocin	4,16,19,24	*c/th-th/t/th*	$C_{37}H_{66}O_8$	638	*A. bullata* [90]
17—Nonadjacent bis-THF (without OH in 4), 'squamostatin-A or almuniquin type':					
17.1 Squamostatin-A or almunequin =annonin-XVI =squamostatin-B 'bis'	16,19,24,28	*t/th-th/t/er*	$C_{37}H_{66}O_8$	638	*A. squamosa* [91,87] *A. cherimolia* [83] *A. squamosa* [86] *A. squamosa* [92]
17.2 4-Deoxygigantecin	14,17,22	*t/th-th/t/th*	$C_{37}H_{66}O_7$	622	*G. giganteus* [27]
17.3 Squamostatin-D	16,19,24	*t/th-th/t/er*	$C_{37}H_{66}O_7$	622	*A. squamosa* [88]
17.4 Squamostatin-E	16,19,24	*t/th-th/t/th*	$C_{37}H_{66}O_7$	622	*A. squamosa* [87]

**th: threo; er: erythro; t: trans; c: cis.*

†*R: Rollinia; G: Goniothalamus; A: Annona; As: Asimina.*

TRI-THF ACETOGENINS

In 1994, the isolation from *G. giganteus* bark of the only tri-THF acetogenin known was reported; this has a *trans/threo/trans/threo/trans/threo* relative configuration [101] (Table 9).

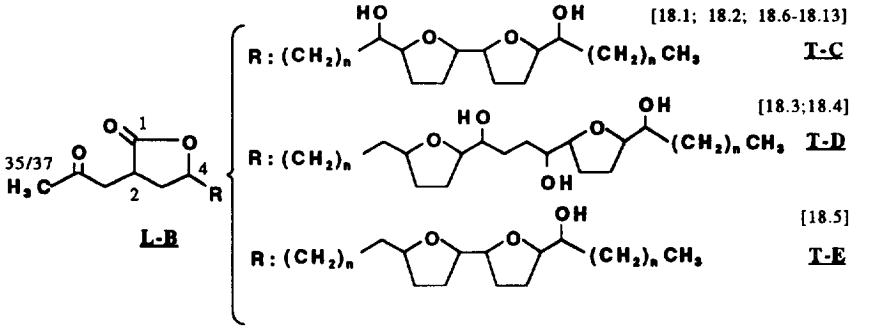
BIOLOGICAL ACTIVITY OF ANNONACEOUS ACETOGENINS

It is well known that the Annonaceous acetogenins show potent biological activity as insecticides, acaricides, fungicides, antiparasitics and also as antitumour

Table 8. Saturated lactone bis-THF acetogenins

		Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species† [reference]

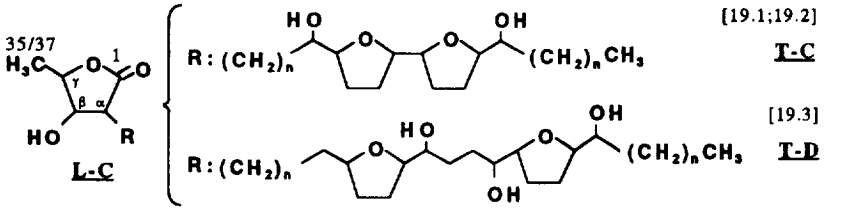
IX—*Iso-acetogenins, bis-THF*



18—'*Iso*' *bis-THF*, '*bullatacinone type*':

18.1	*Bullatacinone*	15,24	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*A. bullata* [63, 5]
18.2	Rollinone	15,24	*th/c/th/c/er*	$C_{37}H_{66}O_7$	622	*R. papilionella* [93, 94]
18.3	Bullatalicinone or isocherimolin-1	16,19,24	*th-th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [95, 85] *A. cherimolia* [96]
18.4	Bullatanocinone	16,19,24	*th-th/t/th*	$C_{37}H_{66}O_8$	638	*A. bullata* [85]
18.5	Bulladecinone	20,23,24	*t/th/t/th-er*	$C_{37}H_{66}O_8$	638	*A. bullata* [97]
18.6	32-OH-bullatacinone	15,24,32	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [98]
18.7	31-OH-bullatacinone	15,24,31	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [98]
18.8	30-OH-bullatacinone	15,24,30	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [98]
18.9	Isomolvizarin-1	13,22	*th/t/th/t/er*	$C_{35}H_{62}O_7$	594	*A. cherimolia* [96]
18.10	Isomolvizarin-2	13,22	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*A. cherimolia* [96]
18.11	10-OH-bullatacinone	10,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [99]
18.12	12-OH-bullatacinone	12,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [99]
18.13	29-OH-bullatacinone	15,24,29	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [99]

X—*β-Hydroxy-acetogenins, bis-THF*



19—β-Hydroxymethyl γ-lactones, '*laherradurin type*':

19.1	Laherradurin	15,24,35	*th/t/th/t/er*	$C_{37}H_{68}O_7$	624	*A. cherimolia* [100, 83]
19.2	Itrabin	13,22,33	*th/t/th/t/er*	$C_{35}H_{64}O_7$	596	*A. cherimolia* [51]
19.3	Otivarin	16,19,24,35	*t/th-th/t/er*	$C_{37}H_{68}O_8$	640	*A. cherimolia* [82, 83]

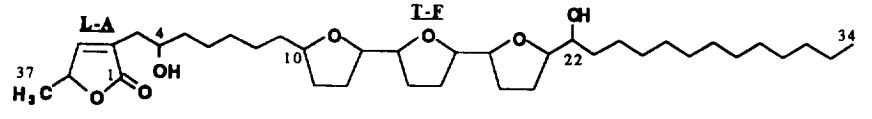
**th: threo; er: erythro; t: trans; c: cis.*

†*A: Annona; R: Rollinia.*

Table 9. Tri-tetrahydrofuran γ-lactone acetogenin

		Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species† [reference]

XI—*Tri-THF acetogenin*



20—Tri-THF acetogenin, '*goniocin type*':

20.1	Goniocin	4,22	*t/th/t/th/t/th*	$C_{37}H_{64}O_7$	620	*G. giganteus* [101]

**th: threo; t: trans.*

‡*G: Goniothalamus.*

agents [2–6]. Recent biochemical work has reported that the mode of action of the acetogenins targets on the mitochondrial NADH:ubiquinone oxidoreductase, also known as the respiratory complex I of mitochondria. The ability of the bioactive Annonaceous acetogenins to inhibit mitochondrial respiration at site I was first noted by Londershausen *et al.* [7] and confirmed by several authors [102, 103]. Extensive studies on the mechanism by which the Annonaceous acetogenins inhibit the complex I are currently in progress [8].

NADH:ubiquinone oxidoreductase is the largest and most complicated of the protein complexes in the inner mitochondrial membrane. Complex I transfers electrons from NADH to ubiquinone and links this process with translocation of protons across the inner membrane to generate an electrochemical gradient that drives ATP synthesis. Complex I has recently assumed new significance from several directions. Clinical interest has been generated by the implications of complex I deficiencies in a number of congenital or acquired diseases. The diseases predominantly affect organs with highest demand for ATP, such as brain and muscle, and include mitochondrial encephalomyopathies, stroke-like episodes, idiopathic Parkinson's disease, Huntington's disease and others [104, 105]. Further knowledge of these diseases and of their better medical treatment require a deeper understanding of the genetics, of the structure and of the function of this enzyme. Inhibitors of the mammalian complex I are extremely useful tools for the elucidation of structural and mechanistic aspects of the enzyme. Different types of inhibitors are needed to dissect functionally the pathways of electron and proton transport in the complex I and to understand better its functional mechanism [106, 107]. Another interesting aspect is the attention that complex I has also focused as a possible target for a new generation of antitumour drugs. The high ATP demand of tumour cells could explain the sensitivity of cultured carcinoma cell-lines to inhibitors of complex I.

On the other hand, evidence that several new acaricides and insecticides inhibit complex I as their primary biochemical lesion has focused renewed attention on the respiratory complex as a target with a potential for the discovery of novel pesticides. Rotenone, a natural insecticide of *Derris elliptica*, and piericidin-A, an antibiotic from *Streptoverticillium mobaraense*, are two natural products considered as classical inhibitors of complex I. As biochemical tools, their worth has been inestimable in an attempt to characterize the electron transport mechanism of mitochondrial complex I. However, as insecticides, the records of both compounds have been somewhat disappointing, with rapid environmental breakdown and adverse toxicology both being factors which have limited their potential as commercial insecticides [108]. The design of agrochemicals targeted to mitochondrial complex I could exploit the natural variation in the complex I structure for achieving selectivity and low toxicity towards plants and mammals. Fenazaquin (Magister®) is a good example. This new complex I inhibitor has been recently developed by the Dow Elanco Company and commercialized with success as an acaricide [109]. The use in agriculture of compounds targeted against components of the mitochondrial electron transport chain might also have consequences for bacterial activity in the soil. In fact, complex I inhibitors probably block the growth of denitrifying bacteria, which also possess complex I. This could be of interest as it would retard the loss of nitrate fertilizer from soils [110].

In our recent work [8] we have studied the inhibitory action of a series of Annonaceous acetogenins on the complex I of inverted submitochondrial particles from beef heart, which is the best preparation to study the native properties of the enzyme, and using undecylbenzoquinone or decylbenzoquinone as substrates, the externally added coenzyme Q analogues that provide accurate measurement of complex I activity [8, 111]. We have shown that the adjacent bis-THF acetogenin rolliniastatin-1 (**13.2**, Table 6) is the most potent inhibitor of mammalian complex I. It is closely followed in potency by its stereoisomer rolliniastatin-2 (**13.3**, Table 6) and by squamocin (**14.1**, Table 6), being both more potent than piericidin-A (previously considered the most potent complex I inhibitor known). Moreover, all the Annonaceous acetogenins tested were about one order of magnitude more potent than rotenone. Qualitatively, the Annonaceous acetogenins could be divided into three groups: (i) those that act like piericidin-A (i.e. **13.1** rolliniastatin-1 and **13.4** molvizarin, Table 6); (ii) those that act like rotenone (i.e. **19.3** otivarin and **14.1** squamocin, Tables 6 and 8); and (iii) those that act in a way that is mutually exclusive to piericidin-A, but not exclusive to rotenone (i.e. **13.3** rolliniastatin-2, Table 6).

The most recent data from our laboratory show that the nonadjacent bis-THF acetogenins (i.e. **16.3** cherimolin-1, **17.1** almunequin and **19.3** otivarin, Tables 7 and 8) act in a biphasic way when decylubiquinone is used as reaction substrate. However, when NADH oxidase activity is assayed, in which the electron acceptor in the complex I is the endogenous coenzyme Q, these acetogenins reduce the activity at quasi-proportional concentration dependence. The mono-THF acetogenin annonacin (**7.1**, Table 3) acts in a way that practically overlaps that of rotenone. Moreover, the IC_{50} of all acetogenins tested is about one-half on the NADH oxidase activity as that on the NADH: decylubiquinone reductase activity. Further extensive structure–activity investigations are needed to understand the quantitative and qualitative differences in the action of Annonaceous acetogenins on complex I function. Studies in this direction are under way and will exploit the natural Annonaceous acetogenins and their chemical derivatives to characterize the functional groups involved and the simplest structure able to inhibit complex I.

In conclusion, it is striking that Annonaceous acetogenins are such specific inhibitors of mitochondrial NADH:ubiquinone oxidoreductase. A broad spectrum of the potential of these compounds has been

Table 10. Species from the Annonaceae with new acetogenins

Species	Organ		Compounds	Reference
Annona atemoya (*A. cherimolia* × *A. squamosa*)	Seed	—	Atemoyin (= **12.7** squamocin-K)	58, 54
Annona bullata	Bark	**5.5**	Uvariamicin-IV	24
		5.6	Bullatencin	24
		13.3	Bullatacin (or rolliniastatin-2)	63, 62
		14.12	Bullacin	77
		16.3	Bullatalicin (or cherimolin-1)	85, 83
		16.4	Bullatanocin (or cherimolin-2)	85, 83
		16.6	12,15-*cis*-bullatalicin	90
		16.7	12,15-*cis*-bullatanocin	90
		18.1	Bullatacinone	63, 5
		18.3	Bullatalicinone (or isocherimolin-1)	95, 96
		18.4	Bullatanocinone	85
		18.5	Bulladecinone	97
		18.6	32-OH-bullatacinone	98
		18.7	31-OH-bullatacinone	98
		18.8	30-OH-bullatacinone	98
		18.11	10-OH-bullatacinone	99
		18.12	12-OH-bullatacinone	99
		18.13	29-OH-bullatacinone	99
Annona cherimolia	Seed	**11.1**	Jetein	51
		13.4	Molvizarin	66
		14.4	Motrilin (or annonin-III)	66, 7
		16.3	Cherimolin-1 (or bullatalicin)	83, 85
		16.4	Cherimolin-2 (or bullatanocin)	83, 85
		17.1	Almunequin (or squamostatin-A)	83, 91
		19.1	Laherradurin	100, 83
		19.2	Itrabin	51
		19.3	Otivarin	82, 83
	Root	**18.3**	Isocherimolin-1 (or bullatalicinone)	96, 95
		18.9	Isomolvizarin-1	96
		18.10	Isomolvizarin-2	96
Annona crassiflora	Seed	—	crassiflorin (= **16.4** cherimolin-2)	89, 83
Annona densicoma	Seed	**7.1**	Annonacin	28
		7.3	Annonacinone	30
	Bark	**8.3**	8-Hydroxyannonacin	42
		9.3	Densicomacin-1	42
		10.1	Isoannonacin	30
		10.2	Isoannonacinone	30
Annona glabra	Seed	—	Known acetogenins (**12.2**, **13.1** and **14.1**)	112
Annona glauca	Root	**13.9**	Annoglaucin	70
	Seed	**13.10**	Glaucanisin	71
Annona montana	Seed	**7.5**	Annomontacin	32
		8.1	Annomonicin	41
		8.2	Montanacin	41
	Fruit	**3.6**	Diepoxymontin	19
Annona muricata	Seed	**2.1**	Epomuricenin-A (or epoxymurin-A)	16, 15
		2.3	Epomuricenin-B	16
		3.1	Diepomuricanin-A	17
		3.2	Corepoxylone	13
		5.4	Solamin	4
		6.1	Murisolin	25
		6.2	Corossolin	26
		6.3	Corossolone	26
		9.6	Gigantetrocin-B	47
		9.7	Muricatetrocin-A/B	47

(*Continued*)

Table 10. *Continued*

Species	Organ		Compounds	Reference
	Bark	**2.1**	Epoxymurin-A (or epomuricenin-A)	15, 16
		2.2	Epoxymurin-B	15
		8.6	Muricatin-C	44
		9.9	Muricatin-A	44
		9.10	Muricatin-B	44
	Leave	**8.4**	Annomuricin-A	43
		8.5	Annomuricin-B	43
Annona purpurea	Leave	**13.7**	Purpureacin-2	68
Annona reticulata	Bark	**5.2**	Reticulatacin (or uvariamicin-II)	23, 22
		7.11	Reticulacinone	36
	Leave	**7.6**	Annoreticuin	33
		7.7	Annoreticuinone	34
		10.4	Isoannoreticuin	33
	Seed	**1.3**	Reticulatamol	11
		1.4	Reticulatamone	12
		3.3	Dieporeticanin-1	18
		3.4	Dieporeticanin-2	18
		3.5	Dieporeticenin	18
		5.7	Reticulatain-1	12
		5.8	Reticulatain-2	12
Annona senegalensis	Seed	**7.15**	Annogalene (or xylomatenin)	40, 39
		7.16	Annosenegalin	40
		9.8	Senegalene	48
Annona squamosa	Seed	**7.4**	Annonacin-A	31
		7.12	Squamosten-A	37
		12.3	Neoannonin	55
		12.6	Squamocin-I	54
		12.7	Squamocin-K	54
		12.8	Squamocin-N	54
		13.8	Squamocin-E (or parviflorin)	54, 69
		14.1	Squamocin	72
		14.4	Annonin-III (or motrilin)	7, 66
		14.5	Squamocin-B	54
		14.6	Squamocin-D (or asiminacin)	54, 75
		14.7	Squamocin-F	54
		17.1	Squamostatin-A (or almunequin)	91, 83
		17.3	Squamostatin-D	88
		17.4	Squamostatin-E	87
	Bark	**10.3**	Squamone	49
Asimina triloba	Root/seed	**13.1**	Asimicin	59
	Bark	**10.5**	Annonacinone-A	50
		10.6	Gigantetrocinone	50
		13.5	Trilobacin	67
		14.6	Asiminacin (or squamocin-D)	75, 54
		14.8	Asimin	75
		14.9	Asiminecin	75
		14.10	Bullatin	76
		14.11	Bullanin	76
Asimina parviflora	Stem	**13.8**	Parviflorin (or squamocin-E)	69, 54
		16.5	Parvifloracin	69
Goniothalamus giganteus	Bark	**1.1**	Giganin	9
		6.4	Giganenin	27
		7.2	Goniothalamicin	29
		7.13	Gonionenin	38
		9.1	Gigantetrocin-A	45

(*Continued*)

Table 10. *Continued*

Species	Organ		Compounds	Reference
		9.2	Gigantriocin	45
		9.4	Gigantetronenin	46
		9.5	Gigantrionenin	46
		16.2	Gigantecin	80, 81
		17.2	4-Deoxygigantecin	27
		20.1	Goniocin	101
Rollinia membranacea	Seed	**3.7**	Diepomuricanin-B	20
		3.8	Diepoxyrollin	20
		4.1	Tripoxyrollin	14
		12.5	Membranacin	57
		13.6	Rioclarin	57
Rollinia mucosa	Seed	**13.2**	Rolliniastatin-1	60
		13.3	Rolliniastatin-2 (or bullatacin)	62, 63
Rollinia papilionella	Root	**14.2**	Isorollinicin	73
		18.2	Rollinone	93, 94
Rollinia sylvatica	Fruit	**16.1**	Sylvaticin	78
Rollinia ulei	Leave	—	Epoxyrollin-A (= **3.3** dieporeticanin-1)	21, 18
		—	Uleicin-C (= **16.1** sylvaticin)	79, 78
Uvaria acuminata	Root	**12.1**	Uvaricin	1
		12.2	Desacetyluvaricin	53
Uvaria narum	Root	**5.1**	Uvariamicin-I	22
		5.2	Uvariamicin-II (or reticulatacin)	22, 23
		5.3	Uvariamicin-III	22
		12.4	Isodesacetyluvaricin	56
		14.3	Squamocinone	74
		15.1	Panalicin	74
		15.2	Narumicin-I	56
		15.3	Narumicin-II	56
Xylopia aromatica	Bark	**1.2**	Venezenin	10
		7.8	Xylopianin	35
		7.9	Xylopiacin	35
		7.10	Xylomaticin	35
		7.14	Xylopien	39
		7.15	Xylomatenin (or annogalene)	39, 40

Table 11. Names of acetogenins from Annonaceae cited in this review (alphabetical order)

	Acetogenin	Reference
17.1	Almunequin (or squamostatin-A)	83, 91
7.15	Annogalene (or xylomatenin)	40, 39
13.9	Annoglaucin	70
8.1	Annomonicin	41
7.5	Annomontacin	32
8.4	Annomuricin-A	43
8.5	Annomuricin-B	43
7.1	Annonacin	28
7.4	Annonacin-A	31
7.3	Annonacinone	30
10.5	Annonacinone-A	50
13.1	Annonastatin	31
14.4	Annonin-III (or motrilin)	7, 66
16.4	Annonin-IV	86
13.3	Annonin-VI	65
16.3	Annonin-VIII	86
17.1	Annonin-XVI	86
7.6	Annoreticuin	33

(*Continued*)

Table 11. *Continued*

	Acetogenin	Reference
7.7	Annoreticuinone	34
7.16	Annosenegalin	40
13.1	Asimicin	59
14.8	Asimin	75
14.6	Asiminacin (or squamocin-D)	75, 54
14.9	Asiminecin	75
12.7	Atemoyin	58
14.12	Bullacin	77
18.5	Bulladecinone	97
14.11	Bullanin	76
13.3	Bullatacin (or rolliniastatin-2)	63, 62
18.1	Bullatacinone	63, 5
16.3	Bullatalicin (or cherimolin-1)	85, 83
16.6	12,15-*cis*-Bullatalicin	90
18.3	Bullatalicinone (or isocherimolin-1)	95, 96
16.4	Bullatanocin (or cherimolin-2)	85, 83
16.7	12,15-*cis*-Bullatanocin	90
18.4	Bullatanocinone	85
5.6	Bullatencin	24
14.10	Bullatin	76
16.3	Cherimolin-1 (or bullatalicin)	83, 85
16.4	Cherimolin-2 (or bullatanocin)	83, 85
3.2	Corepoxylone	13
6.2	Corossolin	26
6.3	Corossolone	26
16.4	Crassiflorin	89
9.3	Densicomacin-1	42
9.1	Densicomacin-2	42
12.4	4-Deoxyasimicin	24
17.2	4-Deoxygigantecin	27
12.2	Desacetyluvaricin	53
3.1	Diepomuricanin-A	17
3.7	Diepomuricanin-B	20
3.3	Dieporeticanin-1	18
3.4	Dieporeticanin-2	18
3.5	Dieporeticenin	18
3.6	Diepoxymontin	19
3.8	Diepoxyrollin	20
2.1	Epomuricenin-A (or epoxymurin-A)	16, 15
2.3	Epomuricenin-B	16
2.1	Epoxymurin-A (or epomuricenin-A)	15, 16
2.2	Epoxymurin-B	15
3.3	Epoxyrollin-A	21
3.1	Epoxyrollin-B	21
6.4	Giganenin	27
1.1	Giganin	9
16.2	Gigantecin	80, 81
9.1	Gigantetrocin-A	45
9.6	Gigantetrocin-B	47
10.6	Gigantetrocinone	50
9.4	Gigantetronenin	46
9.2	Gigantriocin	45
9.5	Gigantrionenin	46
13.10	Glaucanisin	71
20.1	Goniocin	101
7.13	Gonionenin	38
7.2	Goniothalamicin	29
8.3	8-Hydroxyannonacin	42
18.11	10-Hydroxy-bullatacinone	99
18.12	12-Hydroxy-bullatacinone	99
18.13	29-Hydroxy-bullatacinone	99

(*Continued*)

Table 11. *Continued*

	Acetogenin	Reference
18.8	30-Hydroxy-bullatacinone	98
18.7	31-Hydroxy-bullatacinone	98
18.6	32-Hydroxy-bullatacinone	98
13.2	4-Hydroxy-25-desoxyneorollinicin	61
13.3	14-Hydroxy-25-desoxyrollinicin	64
10.1	Isoannonacin	30
10.2	Isoannonacinone	30
10.4	Isoannoreticuin	33
18.3	Isocherimolin-1 (or bullatalicinone)	96, 95
12.4	Isodesacetyluvaricin	56
18.9	Isomolvizarin-1	96
18.10	Isomolvizarin-2	96
14.2	Isorollinicin	73
19.2	Itrabin	51
11.1	Jetein	51
19.1	Laherradurin	100, 83
12.5	Membranacin	57
13.4	Molvizarin	66
8.2	Montanacin	41
14.4	Motrilin (or annonin-III)	66, 7
9.7	Muricatetrocin-A/B	47
9.9	Muricatin-A	44
9.10	Muricatin-B	44
8.6	Muricatin-C	44
6.1	Murisolin	25
15.2	Narumicin-I	56
15.3	Narumicin-II	56
12.3	Neoannonin	55
19.3	Otivarin	82, 83
15.1	Panalaicin	74
16.5	Parvifloracin	69
13.8	Parviflorin (or squamocin-E)	69, 54
16.4	Purpureacin-1	68
13.7	Purpureacin-2	68
7.11	Reticulacinone	36
5.2	Reticulatacin (or uvariamicin-II)	23, 22
5.7	Reticulatain-1	12
5.8	Reticulatain-2	12
1.3	Reticulatamol	11
1.4	Reticulatamone	12
13.6	Rioclarin	57
13.2	Rolliniastatin-1	60
13.3	Rolliniastatin-2 (or bullatacin)	62, 63
14.1	Rollinicin	73
18.2	Rollinone	93, 94
9.8	Senegalene	48
5.4	Solamin	4
14.1	Squamocin	72
14.5	Squamocin-B	54
14.4	Squamocin-C	54
14.6	Squamocin-D (or asiminacin)	54, 75
13.8	Squamocin-E (or parviflorin)	54, 69
14.7	Squamocin-F	54
13.3	Squamocin-G	54
13.1	Squamocin-H	54
12.6	Squamocin-I	54
12.3	Squamocin-J	54
12.7	Squamocin-K	54
12.2	Squamocin-L	54
12.4	Squamocin-M	54
12.8	Squamocin-N	54

(Continued)

Table 11. *Continued*

	Acetogenin	Reference
14.3	Squamocinone	74
10.3	Squamone	49
17.1	Squamostatin-A (or almunequin)	91, 87, 83
16.3	Squamostatin-B	87
17.1	Squamostatin-B 'bis'	92
16.4	Squamostatin-C	88
17.3	Squamostatin-D	88
17.4	Squamostatin-E	87
7.12	Squamosten-A	37
16.1	Sylvaticin	78
4.1	Trieporeticanin	18
13.5	Trilobacin	67
4.1	Tripoxyrollin	14
16.1	Uleicin-C	79
5.1	Uvariamicin-I	22
5.2	Uvariamicin-II (or reticulatacin)	22, 23
5.3	Uvariamicin-III	22
5.5	Uvariamicin-IV	24
12.1	Uvaricin	1
1.2	Venezenin	10
7.15	Xylomatenin (or annogalene)	39, 40
7.10	Xylomaticin	35
7.9	Xylopiacin	35
7.8	Xylopianin	35
7.14	Xylopien	39

drawn here. Obviously, much work remains to be done to develop successful applications for the naturally occurring Annonaceous acetogenins (Tables 10 and 11) and their derivatives in the biochemical, medical, pharmaceutical and agrochemical fields.

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