# *Invited Review*

## Annonaceous Acetogenins: Recent Progress

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The Annonaceous acetogenins are promising new antitumor and pesticidal agents that are found only in the plant family Annonaceae. Chemically, they are derivatives of long-chain fatty acids. Biologically, they exhibit their potent bioactivities through depletion of ATP levels via inhibiting complex I of mitochondria and inhibiting the NADH oxidase of plasma membranes of tumor cells. Thus, they thwart ATP-driven resistance mechanisms. This review presents the progress made in the chemistry, biology, and development of these compounds since December 1995.

The Annonaceae (custard-apple family), considering its large size (130 genera and 2300 species), is chemically one of the least known of the tropical plant families.[1] Phytochemical studies and, to a lesser extent, pharmacological studies on Annonaceous species have intensified in the last 15 years; this is largely due to the discovery of the Annonaceous acetogenins, a class of natural compounds with a wide variety of biological activities.[2−6] Before 1982, most investigations centered upon the many isoquinoline alkaloids in this family. About 320 secondary natural products from 150 species belonging to 41 genera were summarized from 288 publications in 1982 by the group of Professor André Cavé in France.[1] The discovery of uvaricin in 1982,[7] the first of the Annonaceous acetogenins, as an in vivo active antileukemic (P-388) agent, invigorated wide interest in this family. The Annonaceous acetogenins are now one of the most rapidly growing classes of new natural products and offer exciting anthelminitic, in vivo and cytotoxic antitumor, antimalarial, antimicrobial, antiprotozoal, and pesticidal activities and special promise of becoming new chemotypes for antitumor and pesticidal agents.

Structurally, the Annonaceous acetogenins are a series of C-35/C-37 natural products derived from C-32/C-34 fatty acids that are combined with a 2-propanol unit. They are usually characterized by a long aliphatic chain bearing a terminal methyl-substituted $\alpha,\beta$-unsaturated $\gamma$-lactone ring (sometimes rearranged to a ketolactone), with one, two, or three tetrahydrofuran (THF) rings located along the hydrocarbon chain and a number of oxygenated moieties (hydroxyls, acetoxyls, ketones, epoxides) and/or double bonds being present. To a lesser extent, tetrahydropyran (THP) ring compounds and acyclic compounds are also found.[8−12] The Annonaceous acetogenins are the most powerful of the known inhibitors of complex I (NADH: ubiquinone oxidoreductase) in mammalian and insect mitochondrial electron transport systems;[13−16] in addition, they are potent inhibitors of NADH oxidase of the plasma membranes of cancer cells;[17] these actions decrease oxidative, as well as, cytosolic ATP production. The consequence of such ATP deprivation is apoptosis (programmed cell death).[18] Recently, we have shown that the acetogenins also inhibit cancer cells that are multidrug resistant (MDR),[19−21] and in addition, they combat pesticide-resistant German cockroaches effectively.[22] Thus, they thwart biological resistance.

Since publishing our last four reviews,[3−6] which summarized research on the Annonaceous acetogenins through December 1995, 10 new species of Annonaceae have been reported to contain acetogenins; they are *Annona glabra*,[23−26] *A. jahnii*,[12] *A. spinescens*,[27,28] *A. nutans*,[29] *A. crassiflora*,[30] *Goniothalamus donnaiensis*,[31−34] *G. gardneri*, [35] *Uvaria microcarpa*,[36] *U. pauci-ovulata*,[37] and *Disepalum anomalum*.[38] In our last review, we reported the isolation of mucocin,[8] the first acetogenin containing a tetrahyropyran (THP) ring nonadjacent to a THF ring. The isolations of four more THP-bearing acetogenins have now been reported; these are muconin,[9] which contains a nonhydroxylated THP ring adjacent to another THF ring, pyranicin and pyragonicin,[10] the first mono-THP ring acetogenins with no THF rings at all, and jimenezin,[11] containing a hydroxylated THP ring adjacent to a THF ring. Also newly discovered are the first hydroxylated-THF ring compounds mucoxin,[9] goniotriocin,[39] and donnaienin.[33]

Coriaheptocins A and B, the first heptahydroxylated acetogenins, were isolated from the roots of *Annona coriacea* by the group of Cavé;[40] we have found a nonring octahydroxylated acetogenin (unpublished), as confirmed by $^{13}$C NMR, CIMS, and acetylation, but we have had difficulty in locating the positions of these hydroxyls along the aliphatic chains. Recently, Cavé's group has also found several important biogenetic precursors containing two to three double bonds each separated by two carbon units.[29] This evidence strongly suggests that the acetogenins are actually lacceroic (C-32) and ghedoic acid (C-34) derivatives.[29]

A new compound, spinencin,[27] is the first bis-adjacent THF acetogenin to have the relative stereochemistry (going from lower to higher numbered positions across the rings) of threo-trans-threo-cis-erythro. Jiang et al. have isolated several C-34 epimeric pairs of acetogenins from *Goniothalamus donnainesis*, adding a new subtype to the $\gamma$-lac-

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tone ring configuration.[31,23] The method of countercurrent chromatography is now being used to separate known and new acetogenins.[41,42]

The emergence of the Annonaceous acetogenins as potential agents to thwart biological resistance was first manifested in the work of Oberlies et al.[19−21] in tumor cells and in the work of Alali et al.[22] in insects; it was found that the acetogenins could effectively combat multidrug resistant cancer cells and pesticide-resistant cockroaches, respectively. The work of Shimada et al.[43,44] on the placement of acetogenins, representing several structural classes, within liposomal membranes, now provides a new hypothesis as to how these compounds interact with lipid bilayers to exert their activity on membrane-bound enzymes. Additionally, in cooperation with a group in Japan, our recent work on the structure−activity relationships (SAR) in the isolated submitochondrial particles and work with computer models drastically challenge our understanding of the relevance of the relative stereochemistry across the THF rings.[45]

In our first review in 1990, 28 Annonaceous acetogenins isolated from 11 species were described; in our second review in 1993, 61 acetogenins isolated from 16 species were summarized; in our third review in 1995, another 80 acetogenins from 20 species of Annonaceous acetogenins were reported; and in our fourth review in 1996, 76 new acetogenins from 26 species were tabulated.[3−6] In this review, which covers scientific progress made in the biology, chemistry, and development of Annonaceous acetogenins from December 1995 to July 1998, data have been compiled on 137 new acetogenins from 24 species (Appendix 1). At the time of preparation (August 1998) of this current review, over 350 Annonaceous acetogenins have been isolated from 37 species. Our preliminary efforts show that about 50%, of over 80 Annonaceous species screened, are significantly bioactive and are worthy of fractionation; thus, this class of compounds can be expected to continue to grow, at an exponential rate in the future, provided that financial support for such research efforts can be found. With the demise of the world's tropical rain forests, such work is compelling before the great chemical diversity, contained within these endangered species, is lost.

## Classification

In our last review,[3] the Annonaceous acetogenins were classified according to their relative stereostructures across the THF rings; while that classification is more informative than any other method, it leads to a plethora of subclasses, and we will use herein our earlier system of classification with some additions and modifications. The Annonaceous acetogenins seem to be best classified into mono-THF, adjacent bis-THF, nonadjacent bis-THF, non-THF ring, tri-THF, and nonclassical acetogenins (THP and ring-hydroxylated THF compounds), followed by subclassification of the $\gamma$-lactone, substituted $\gamma$-lactone, or ketolactone variations (Figure 1).

The names, classfications, chemical and biological data, and references to the new compounds, reported December 1995−July 1998, are tabulated in Appendix 1.

## Biogenesis

Biogenetically, the Annonaceous acetogenins seem to be derived from the polyketide pathway. The THF, THP, and epoxide rings are suggested to arise from isolated double bonds through epoxidation and cyclization.[3,4] The discovery of earlier precursors (nonring compounds, epoxides, ketones, diols, and double bonds), the location of double bonds

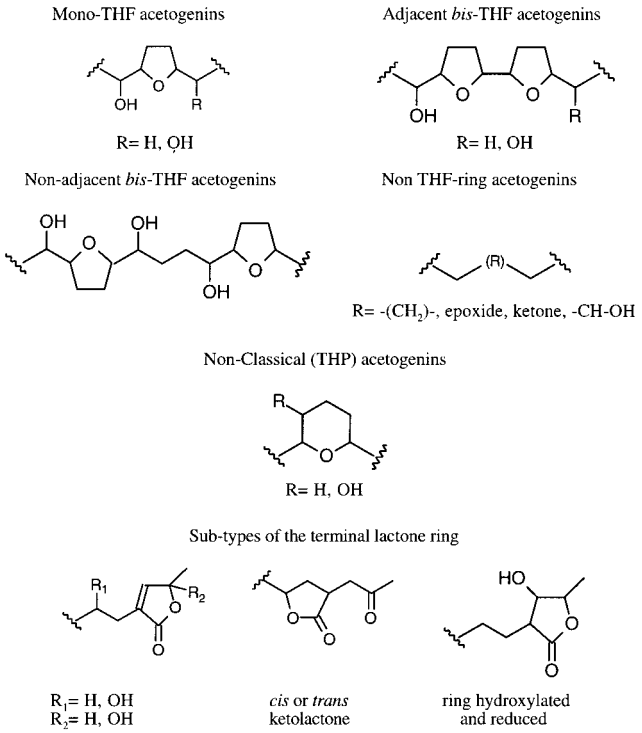



**Figure 1.** Core units for classification of Annonaceous acetogenins.

in the appropriate positions, and the semisynthesis of additional THF rings from double bond-containing acetogenins strongly support this hypothesis. The discoveries of muridienins, proposed precursors of the mono-THF acetogenins, and chatenaytrienins, proposed precursors of the bis-THF acetogenins, add new evidence that acetogenins are more likely to be derived from lacceroic (C-32) and ghedoic (C-34) fatty acids after enzymatic combination with a three-carbon unit.[29] We could not find these free acids or their esterified products in the oily extracts of the paw paw, *Asimina triloba*; this might suggest that these free acids actually serve as short-lived intermediates in the biosynthetic process and are shuffled along complex enzyme subunits rather than being released as end products that can later be metabolized by $\gamma$-lactone formation, dehydrogenation, epoxidation, and cyclization. The sequence of these events is still unknown. The time is at hand to conduct feeding experiments with isotopically labeled precursors to verify the biogenetic pathways and the sequence of events leading to these compounds. Plant tissue culture methods have not yet produced sufficient cell growth to permit such studies.

One wonders why the plants in this family choose to biosynthesize more than 350 different acetogenins, with all of them being either C-32 or C-34 fatty acid derivatives, and not produce C-36 or C-38 or even C-30 or C-28 compounds. The dimensions of cell and mitochondrial membranes[43] (the sites of the target enzymes) may dictate this; this particular chain length has likely evolved because it provides the optimum activity and protection of the plant against herbivores and pests. Shorter acetogenins lose activity, and it may be logical to assume that longer ones will also be less active.

The biogenetic story of goniocin is particularly interesting. This tri-THF ring acetogenin was first isolated in our laboratory by Gu et al. in 1994 from *Goniothalamus giganteus*.[46] All previously isolated acetogenins from this plant, representing over 30 different compounds,[47] had an *R* configuration at C-10 including cyclogoniodenin T,[48] a semisynthetic tri-THF enantiomer of goniocin; however,

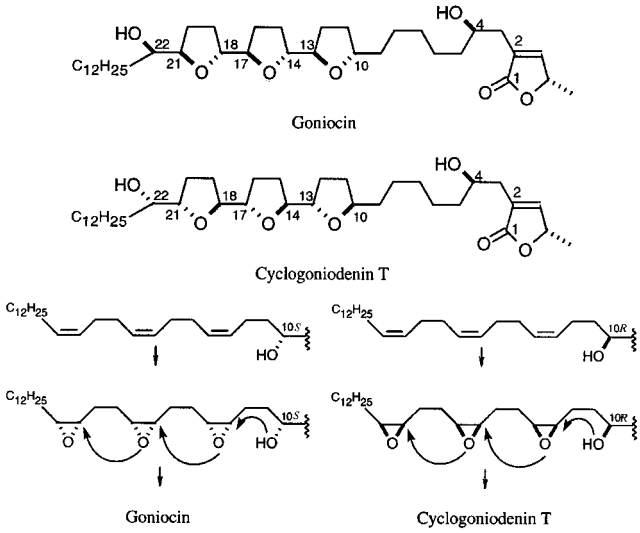



**Figure 2.** Biogenetic schemes for goniocin and cyclogoniodenin T.

using NMR-derived information, goniocin was assigned an *S* absolute stereocenter at C-10. This means that goniocin and cyclogoniodenin T have to be epimeric at each of the seven chiral centers across the tri-THF ring system. The absolute stereochemistries of all of these compounds had been determined using Mosher ester methodology.[49] To help verify this remarkable coexistence of these naturally multicentered enantiomers, Sinha et al. at Scripps[50,51] totally synthesized both compounds and confirmed that their absolute configurations were, indeed, correct as proposed. They relied upon the subtle differences of the chemical shifts of the methoxy group of the Mosher ester derivatives of both compounds and comparison with the original spectra of goniocin.[46,50,51] They interpreted this unique coexistence to be a result of two alternative modes of tandem ring-closure routes, both starting with epimeric 10-hydroxy intermediates (Figure 2).[51]

## Extraction, Isolation, and Purification

The Annonaceous acetogenins are readily soluble in most organic solvents. Ethanol extraction of the dried plant material followed by solvent partitions, to concentrate the compounds, is still the method of choice in our laboratory.[4] Two methods are in use to monitor the fractionation, which is mainly achieved by open column chromatography; these are bioactivity-guided fractionation using the brine shrimp lethality test (BST)[52,53] and/or TLC spot visualization using Kedde's reagent.[4] Kedde's reagent is not specific for the acetogenins; it detects the unsaturated conjugated lactones and does not detect the translactonized ketolactones; thus, the BST is superior in guiding fractionation and quickly leads to the most bioactive compounds. After open column chromatography, HPLC is then the most efficient method to purify individual compounds from the complex mixtures of the closely related acetogenins. Reversed-phase $C_{18}$ HPLC is superior to silica gel normal-phase HPLC in achieving separation of single-positional epimeric pairs, diastereomeric acetogenins, and/or closely related isomers.

Countercurrent chromatography (CCC) has now been used for the first time in isolating Annonaceous acetogenins; this was demonstrated by the independent work of Duret et al.[41] and Hopp et al.[42] While Duret et al. were the first to use the technique, Hopp et al. were the first to isolate new compounds using CCC. Duret et al. have used a biphasic mixture of heptane/ethyl acetate/methanol/water to isolate four pairs of acetogenins, which were then purified with HPLC. Hopp et al. developed a biphasic system, hexane/dichloromethane and methanol/water (10:5:7:3), because it yielded nearly identical bioactivity in the two phases. Using the BST, after a sample of the bioactive fraction F005 had been partitioned between the two phases, Hopp et al. were able to isolate quickly four known and three new acetogenins; the last purification step was achieved by HPLC. CCC could be utilized to provide adequate amounts for further testing the major compounds from the crude extracts, in relatively short time.

By far, the major contribution to the detection, isolation, characterization, and dereplication of Annonaceous acetogenins in the last two years has come through the application of liquid chromatography−electrospray ionization mass spectrometry (LC/EIMS) techniques.[54,55] Using the positive-ion mode and under conditions of atmospheric pressure in-source collision-induced dissociation (APICID), the acetogenins have provided reproducibly characteristic ion patterns and fragment ions.[54] Analyzing the selected ion chromatograms (SIC), the presence of these acetogenins and other derivatives in crude plant extracts and chromatographic fractions can be readily detected. Utilizing the LC/(+)ESI-APCID-MS technique, acetogenins produce characteristic ion patterns consisting of $[M + Na]^+$ and $[M + H]^+$ molecular ions, as well as ions showing the consecutive losses of $H_2O$ from the $[M + H]^+$ ion. LC/MS screening of a 2 $\mu$g aliquot of a bioactive crude methanol-soluble fraction of *Rollinia mucosa* detected the presence of some 40 known acetogenins in this plant species, in addition to four new acetogenins of diverse structure.[54] As an example of the utility of this method, Gu et al. then applied the LC/(+)-ESI-MS method to direct the isolation of two of the new compounds.[55]

In another study which evaluated the monthly variations of acetogenin content in crude $CH_2Cl_2$ extracts of twigs collected from a single paw paw (*A. triloba*) tree, Gu et al. used the LC/MS/MS technique to quantify the contents of the three most biologically potent acetogenins.[56] The quantified contents of these acetogenins showed good correlation with potencies as observed in the BST and demonstrated the highest activities in extracts from the May and June samples. These results clearly demonstrated seasonal variations in acetogenin content and suggest that May and June are the best time to collect paw paw twigs for maximizing bioactivities. Most recently, these methods have confirmed that the BST-active extracts of the zebra swallowtail (*Eurytides marcellus*) butterflies and larvae, which are obligate parasites on the paw paw leaves, contain the potent acetogenins bullatacin, bullatalicin, trilobacin, and/or asimicin.[57] This well-defined LC/MS/MS method will undoubtedly be widely applied in the quantitative analysis of other desirable natural components in crude extracts in the future.

## Structural Elucidation

Synthetic models of known stereochemistry are used routinely to predict the relative stereochemistry of both the THF and the $\gamma$-lactone ring systems bearing the nearby 4-hydroxyl of the acetogenins.[58−62] The locations of the THF ring and/or the free hydroxyls continue to be determined by careful analysis of mass spectral fragments.[2−4] No significant changes have been introduced in the methods for structural elucidation of Annonaceous acetogenins in the last two years. Nevertheless, the following three contributions merit discussion.

Duret et al. have noticed that the non-4-hydroxylated $\gamma$-lactone moiety of the Annonaceous acetogenins may be

epimerized upon treatment with weak base.[63] The two resulting C-36/C-34 epimers have identical MS, $^1$H and $^{13}$C NMR, IR, and UV spectra. However, determination of the specific rotation of the mixtures and enzymatic oxidation after chemical degradation, have allowed characterization of these epimers. To determine the absolute stereochemistry at the C-36 or C-34 centers of such Annonaceous acetogenins, comparison by circular dichroism is used;[3,4] thus, basic conditions must be avoided in extraction, fractionation, and isolation to preserve the natural integrity of the $\gamma$-lactone. HPLC detection of NADH released from the enzymatic oxidation of L- or D-lactic acid, obtained by the cleavage of the terminal $\alpha,\beta$-unsaturated $\gamma$-methyl-$\gamma$-lactone, to pyruvic acid by lactate dehydrogenase was used to quantify the epimerization chemically.[64] To date, with more than 350 acetogenins isolated, all of the natural Annonaceous acetogenins, except when so epimerized, possess the *S* absolute configuration at their C-36 or C-34 positions.

Shi et al. have successfully applied the Mosher ester method to determine the absolute stereochemistry at 1,2-vicinal diols.[65] This method uses only small amounts of material that are sufficient to achieve the per-Mosher esters. They observed that the cancellation/enforcement effect of overlapping MPTA planes could still be analyzed and utilized to predict the absolute stereochemistry of the 1,2-vicinal diol compounds, assuming that MPTA groups could still freely rotate, in the long aliphatic chain, and preserve their ideal conformations.

Alali et al. have tabulated interesting observations on the chemical shift differences of 1,3-diols.[10] A pseudothreo or -erythro spatial relationship can be easily deduced by analyzing the $^1$H and $^{13}$C NMR chemical shift differences of the carbinol centers in comparison with an isolated hydroxyl group at a carbinol center in a long chain. In comparison with an isolated hydroxyl oxymethine along a hydrocarbon chain, hydroxyl oxymethines of 1,3-pseudothreo diols usually experience downfield shifts ca. +0.32 ppm in the $^1$H NMR spectrum and an upfield chemical shift of ca. −2.8 ppm in the $^{13}$C NMR spectrum. On the other hand, 1,3-pseudoerythro diols usually experience a downfield chemical shift of ca. +0.32 ppm and ca. +0.50 ppm in both the $^1$H and $^{13}$C NMR spectra, respectively. Accordingly, it can be predicted that tonkinin A, tonkinin B, tonkinesin A, and tonkinesin B all have a pseudothreo relationship between their carbinol centers at C-15 and C-17.[10,66]

## Synthesis

Due to the waxy nature of the Annonaceous acetogenins, X-ray crystallography is difficult, and definite stereochemical assignments are not easily made. Since the discovery of the first acetogenin, uvaricin, in 1982, which was published without any stereochemical assignments of its seven stereocenters, it was obvious that synthetic models were urgently needed to aid the complete structural elucidations of these multi-stereocentered compounds.[7] Several synthetic models, especially those that do not require derivatization, have been proven to be very helpful in predicting the relative stereochemistry of the THF ring systems, with their flanking hydroxyls, and of the 4-hydroxylated $\gamma$-lactone.[58−60,62] Additional synthetic models are still needed to predict the relative stereochemistry of several of the expanding new types of acetogenins, e.g., the hydroxylated-THP compounds, tri-THF compounds, and the bis-THF compounds with one flanking hydroxyl, and these models could be logical targets for further syntheses.

The potent and diverse bioactivities of Annonaceous acetogenins have recently caught the eye of many groups of synthetic chemists.[2−4,67−69] Convergent strategies are usually chosen to synthesize these compounds. These are based on the coupling of a THF ring core and a terminal $\gamma$-lactone synthon. To achieve the specific stereochemistry, either chiral starting materials ($\alpha$-amino acids, sugars) or some asymmetric reactions using chiral catalysts (Sharpless epoxidation, Sharpless dihydroxylation) are employed.

Kienan et al. successfully synthesized goniocin[46] and cyclogoniodenin T[48] and its unique tri-THF stereoisomer, 17,18-bis-*epi*-goniocin, using tandem cyclization with rhenium oxide.[50,51] Inspired by Hoye's work, Kienan et al. also synthesized mucocin, the first THP-bearing acetogenin, using *all-trans*-1,5,9-cyclododecatriene, and they completed the synthesis in 20 steps.[70] This work confirmed our proposed relative as well as absolute stereochemistry of mucocin and, also, added credibility both to Born's rule,[59] in being able to predict the relative stereochemistry of the hydroxyl-flanked THP ring as well as the hydroxyl-flanked THF ring, and to the intramolecular formaldehyde closure reaction,[71] in facilitating the absolute stereochemical assignments of closely located carbinol centers. As demonstrated by their total synthesis of trilobacin, Kienan et al. designed an efficient convergent synthetic strategy that provided a useful entry to a 32-membered chemical library of stereoisomeric bis-THF acetogenins.[72] Thus, combinatorial chemistry has been applied in this field.

A noteworthy strategy is the efficient bidirectional synthetic approach to the C-2 symmetric stereoisomers of 2,2′-bis-THF acetogenins as reported by Marshall et al. in the last two years.[73] Utilizing $\gamma,\gamma'$-dioxygenated dialdehyde and a nonracemic $\alpha$- or $\gamma$-oxygenated allylic stannane, they were able to synthesize (+)-asimicin, asiminocin, and asiminecin.[74,75] While it is not as efficient, they have now modified this method and extended it to the synthesis of the bis-THF acetogenins with asymmetrical cores.[76]

Several elegant attempts have been directed toward the synthesis of core synthons that could be utilized to produce biologically active natural and nonnatural analogues of the acetogenins. This can be seen in the work of Sasaki et al.,[77] Towne and McDonald,[78] Figadère et al.,[79] Ruan et al.,[80] Li et al.,[81] Gesson et al.,[82] Koret et al.,[83] Seepersaud et al.,[84] Zhang et al.,[85] and Zanardi et al.[86] The semisynthetic work of Ye et al.[87] has shown that certain chlorinated derivatives of the natural acetogenins lose activity; this suggests that the C-4 hydroxyl and the THF flanking hydroxyls may be involved in some electron-donating hydrogen-bonding interactions at the target site or in the membranes. We anticipate that nitrogen or sulfur derivatives might enhance or modify the activity, selectivity, and/or the potency of acetogenins. Sasaki et al. have synthesized several bullatacin analogues in order to test their metal-binding ability.[88] The implications of their work will be discussed in the following section dealing with mechanism of action.

The following compounds have also been recently synthesized: longifolicin,[89] 15-*epi*-annonin I,[90] 4-deoxygigantecin (the first bis nonadjacent THF acetogenin to be synthesized),[91] (+)-squamocin K, (+)-5*S*-hydroxyparviflorin, and (+)-parviflorin,[92] (+)-squamostanal-A,[93] and (8′*R*)- and (8′*S*)-corossoline.[94] The methods employed are diverse, and the reader is encouraged to consult the original papers.

## Mechanism of Action

The acetogenins are known to be very potent cytotoxic compounds. Demonstrated targets were previously discussed as the reduced nicotinamide adenine dinucleotide

(NADH): ubiquinone oxidoreductase in complex I, which is a membrane-bound protein of the mitochondrial electron transport system[13−15] and the ubiquinone-linked NADH oxidase in the plasma membranes of cancerous cells.[17] Annonaceous acetogenins are now considered as the most potent, effective in nanomolar concentrations, among the diverse inhibitors of mitochondrial complex I.[16,122,138] While no work has been conducted on the molecular inhibitory mechanisms of these compounds, the work of Shimada et al.[43,44] and Miyoshi et al.[45] using liposomal membranes and the submitochondrial vesicle particles, respectively, may, on one hand, explain and verify our structure−activity relationship profiles and, on the other hand, drastically challenge our understanding of the significance of the relative and absolute stereochemistries of the THF or THP ring systems. Studying the conformations of the Annonaceous acetogenins within liposomes made of dimyristoylphosphatidylcholine (DMPC) and on the basis of $^1$H NMR intermolecular nuclear Overhauser effects (NOEs), differential calormetric scanning data, and DMPC−$Mn^{2+}$ peak-broadening studies, Shimada et al. found that the Annonaceous acetogenins, containing either mono-, adjacent bis-, or nonadjacent bis-THF ring moieties, have their THF ring moieties residing at the interfacial regions of the lipid membranes.[43,44] It was concluded that the THF group(s) serve as a hydrophilic anchor in the lipid membranes. It was also found that the position of the THF ring anchor along the acetogenin chain determines the depths of penetration of the lactone functional group within the lipid bilayer. Thus, the lactone ring, tethered to spacer moieties of different lengths, penetrates the lipid membrane to different depths, acts directly with the protein receptor site(s), and adapts to the geometry of specific cell types. This would seem to explain cell type selectivities as seen with several of these compounds.[3,4]

In a study to determine the essential structural factors, Miyoshi et al. used 22 representative acetogenin compounds to conduct a mechanistic and structural activity study against submitochondrial particles.[45] They also studied the three-dimensional structure of the bis-THF ring moieties of the different possible stereoisomers optimized by quantum chemical calculations (MNDO-AM1). Implementation of COMPASS (COMmon geometrical Pattern Search System) and molecular field fitting for all combinations of the stable conformations of each molecule, in this work led to several important conclusions. First, the inhibition mechanism of Annonaceous acetogenins was found to be noncompetitive against exogenous ubiquinones; this conclusion is not in agreement with the results of Friedrich et al.[95] and Delgi Espositi et al.[96] where Annonaceous acetogenins were concluded to bind competitively with respect to the ubiquinone at complex I. Second, while both rotenone and the Annonaceous acetogenins do bind noncompetitively against exogenous ubiquinone at complex I, they have different binding sites; however, most Annonaceous acetogenins (except rolliniastatin-2 and cherimolin-1) and rotenone were found to be mutually exclusive inhibitors.[96,136] Third, stereochemistry surrounding the THF rings, surprisingly, seems to be much less important for activity at the enzyme level than in previous bioassays; this was corroborated by an exhaustive conformational space search analysis that indicated that the model compounds, with different stereochemical arrangements around the THF moieties, were in fairly good superimposition. Fourth, like the findings of González et al.[122,137] and Gallardo et al.,[138] proper length and flexibility of the alkyl spacer moiety, which links the THF and the α,β-unsaturated γ-lactone ring moieties, were essential for potent activity.[45] Indeed, as Miyoshi et al. stated, if the THF rings serve as an anchor at the interface of the membrane, the stereochemical differences within the THF rings of the acetogenins should not make much difference in their bioactivity profiles. This work is in good agreement with the earlier results obtained by Shimada et al.[43,44] and with several of our earlier SAR studies in isolated mitochondrial whole cells, and insects.[21,22,71,97−99]

While the acetogenins are not ionophoric in living cells,[100] several investigators have studied the ion complexation ability of the Annonaceous acetogenins.[2,88,101] There is no evidence that $Ca^{2+}$ or $Mg^{2+}$ complexation contribute to the potent cytotoxic or pesticidal activities of these compounds. Some researchers have proposed, with little justification, that complexation with the Fe−S cluster, in the proven protein target, may contribute to their activity; yet, the same resarchers studied $Ca^{2+}$ and $Mg^{2+}$ complexation of acetogenins in organic solvents. Investigations of $Fe^{2+}$− and FeS−acetogenin complexation in aqueous media are suggested.

The door is now open for further studies of the molecular inhibitory mechanism of Annonaceous acetogenins against their protein targets, i.e., mitochondrial NADH ubiquinone oxidoreductase and plasma membrane NADH oxidase. Regardless of their future utility as chemotherapeutic, pesticidal, antimicrobial, etc. agents, they should become, at the least, useful tools, in the future, to probe the biochemistry of these active sities.

## Structural−Activity Relationships

On the basis of the recent work of Miyoshi et al.,[45] Oberlies et al.,[21] He et al.,[97] Alali et al.,[22] Landolt et al.,[98] Gu et al.,[71] Alfonso et al.,[99] and Delgi Esposti et al.,[96] the following generalizations can be stated concerning the SARs of the Annonaceous acetogenins: (1) The bis-adjacent-THF acetogenins are the most potent among this family; the nonadjacent bis-THF compounds are, in general but not always, superior to the mono-THF compounds, which, in turn, are more potent than the nonring THF acetogenins. (2) The α,β-unsaturated γ-lactone at the end of the chain is crucial for activity. (3) If all other structural features are identical, the shorter C-35 acetogenins are more potent than the C-37 compounds. (4) The spacer, i.e., the distance between the OH-flanked THF and the γ-lactone, is critical to the potency and selectivity of the acetogenins; e.g., a 13-carbon space in the OH-flanked mono- and bis-THF compounds is optimum for activity. (5) Neither the 4-OH group nor the 10-OH group is essential for activity. (6) Three hydroxyl groups, two flanking the THF ring(s) and another somewhere in the long hydrocarbon chain, provide both the optimal position and polarity needed for the most potent activity, and beyond the tetra-hydroxylated acetogenins the activity drops drastically. (7) A ketone instead of a hydroxyl functional group decreases the activity. (8) Ketolactone acetogenins are still active but usually less active and more selective than their parent compounds; they may have different space group distances for optimal activity than their parent compounds, but this point needs further study. (9) The THP ring compounds are as active as the THF compounds and have the same mechanisms of action.

In their recent SAR study of Annonaceous acetogenins in purified rat liver mitochondria,[99] Alfonso et al. noted that the activity of the nonadjacent bis-THF ring acetogenins depends on the distance between the two THF rings; i.e., the activity decreases to that of a mono-THF ring aceto-

genin if the distance is too long. It was also observed that when one THF ring is replaced with a tetrahydropyran ring (THP) the activity remains comparable. Stereochemical differences did not show any significant differences in potency.

## Biological Activity

As previously noted, this class of diverse, but still closely related, compounds, has several interesting and potent biological activities, including antibacterial, antimalarial, in vivo antitumor, parasiticidal, and pesticidal effects.[2−6] Potentially of greatest importance, in the last two years the Annonaceous acetogenins have emerged as promising new leads to thwart resistance in multidrug resistant (MDR) tumors and in pesticide-resistant insects.[19−22]

**In vitro and in vivo Cytotoxicity Results.** Some Annonaceous acetogenins may be among the most potent cytotoxic agents ever known; e.g., trilobacin[102] and asiminocin[103] have shown $ED_{50}$ values of $<10^{-12}$ $\mu$g/mL in several human tumor cell lines. Yet, cytotoxic selectivities, among various cell lines, have been observed concurrently, e.g., squamotacin with an $ED_{50}$ value of $10^{-8}$ $\mu$g/mL against the human prostate cell line (PC-3),[104] mosin C with an $ED_{50}$ of $10^{-4}$ $\mu$g/mL against pancreatic carcinoma cells (PACA-2),[105] and pyranicin with an $ED_{50}$ of $10^{-2}$ $\mu$g/mL also against PACA-2.[10] A series of acetogenins all show greater cytotoxic effects to cancerous vs noncancerous cells.[19] Thus, these agents are not "general cytotoxins" as some authorities continue to profess. It is not yet clear how the acetogenins can inhibit the growth of 50% of in vitro grown cancerous cells at concentrations of $<10^{-12}$ $\mu$g/mL. Several factors, such as intracellular transportion, metabolism, and inactivation and receptor geometry may all contribute to this phenomenon of selectivity, and it is even possible that hydrogen peroxide, induced by apoptosis and resulting radical oxygen formation, diffuses into neighboring cells where it is lethal.

While extensive and comprehensive in vivo testing has yet to be conducted, the Annonaceous acetogenins have, indeed, already shown promising in vivo results. Uvaricin originally showed in vivo activity against 3PS (murine lymphocytic leukemia) (157% T/C at 1.4 mg/kg),[7] and the rollinones (147% T/C at 1.4 mg/kg) and asimicin (124% T/C at 25 $\mu$g/kg) were active in the same assay.[6] It must be remembered that the murine leukemias are used as indicators of in vivo antitumor activity, in general, and are not just predictors for antileukemic agents. At the Upjohn Co., bullatacin and (2,4-*cis* and *trans*)-bullatacinones were tested against L1210 (murine leukemia) in normal mice and in tumor xenografts of A2780 (human ovarian carcinoma) in athymic mice.[15] Bullatacin, effective at only 50 $\mu$g/kg, was over 300 times more potent than paclitaxel against L1210, and bullatacin, at 50 $\mu$g/kg, and bullatalicin, at 1 mg/kg, were almost equivalent to *cis*-platinum; in addition, the acetogenins caused much less weight loss than the standards.[4] Previously unpublished results, obtained by the late G. Grindey at the Eli Lilly Co., showed similar effectiveness of bullatacin (67% tumor inhibition at 50 $\mu$g/kg) against X-5563 plasma cell myeloma grafts in normal mice. With water-soluble derivatives in hand and with better understanding of their SAR, development of the optimum compounds into clinically useful antitumor agents should be a top priority.

**Annonaceous Acetogenins vs Multidrug Resistant Cells.** MDR tumors, whether intrinsic or acquired, continue to limit the life span of cancer patients in remission. MDR tumors are usually associated with an increased

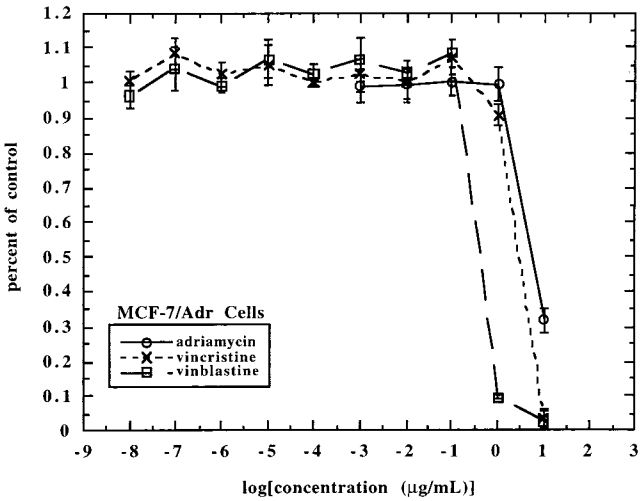



**Figure 3.** Effect of exposure for 6 days to the standard antineoplastic drugs, adriamycin, vincristine, and vinblastine, against MCF-7/Adr cells. Values are expressed as percentages of the vehicle-treated controls with each point representing the normalized average of four values and the error bars representing the standard deviation about each average. The concentration values are log dose units in $\mu$g/mL.

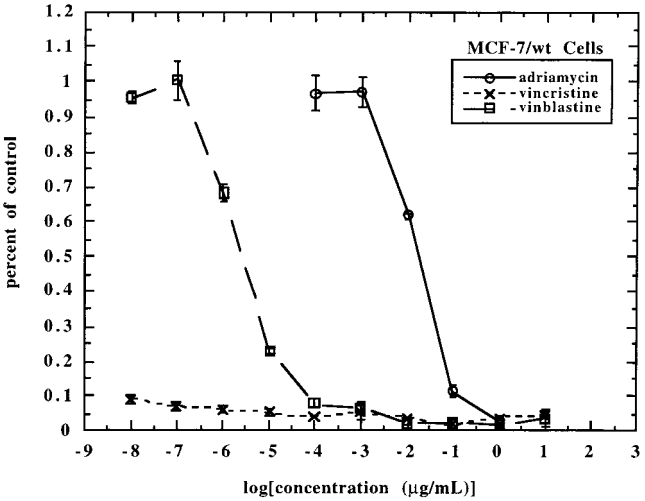



**Figure 4.** Effect of exposure for 6 days to the standard antineoplastic drugs, adriamycin, vincristine, and vinblastine against MCF-7/wt cells. Values are expressed as percentages of the vehicle-treated controls with each point representing the normalized average of four values and the error bars representing the standard deviation about that average. The concentration values are log dose units in $\mu$g/mL.

expression of P-glycoprotein, a 170 kDa transmembrane energy-dependent drug efflux pump. In our recent work,[20,21] we showed that acetogenins, because of their potent ability to block ATP production, can selectively inhibit the growth of MDR tumors cells in vitro. A thorough examination of the acetogenins against in vivo models of multidrug resistance is now suggested. Using both wild-type and adriamycin-resistant human mammary adenocarcinoma cells in vitro (MCF-7/wt and MCF-7/Adr, respectively), Oberlies et al. observed that the MCF-7/Adr cells were more susceptible to acetogenin treatment and elicited a linear dose response curve. Alternatively, against the MCF-7/wt cells, a plateau near the $IC_{50}$ value was observed (this is commonly seen with acetogenins). This observation led to the hypothesis that the acetogenins were cytotoxic to the MCF-7/Adr cells but more cytostatic to the MCF-7/wt cells. For example, in contrast to adriamycin, vincristine, and vinblastine (Figures 3 and 4), bullatacin was effective at inhibiting the growth of the MDR MCF-7/Adr cells and exhibited a linear dose−response curve over a concentra-

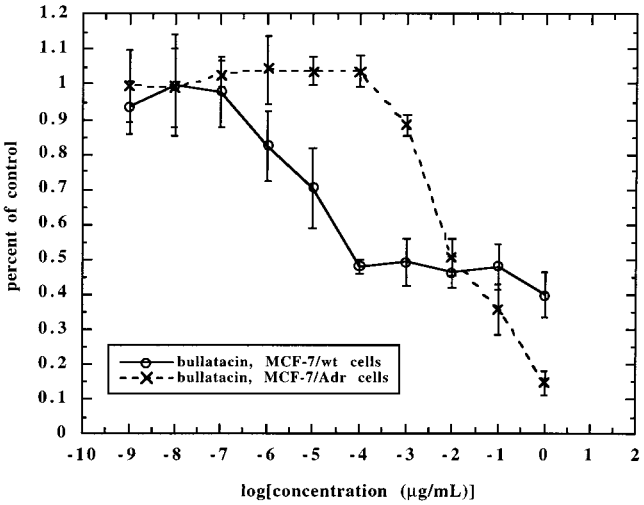



**Figure 5.** Comparison of the effects of exposure for 6 days to bullatacin against MCF-7/wt vs MCF-7/Adr cells. Values are expressed as percentages of the vehicle-treated controls with each point representing the normalized average of four values and the error bars representing the standard deviation about each average. The concentration values are log dose units in $\mu$g/mL.

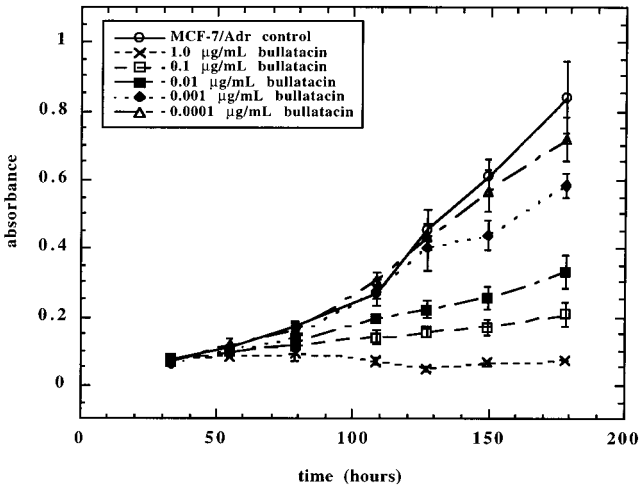



**Figure 6.** Periodic analysis (every 24 h) of the effects of serial dilution of bullatacin against MCF-7/Adr cells. Values are expressed as average absorbances ($n$ = 6 for the vehicle treated control, $n$ = 4 for the bullatacin treated wells), and the error bars represent the standard deviation about each average. The concentration values are log dose units in $\mu$g/mL.

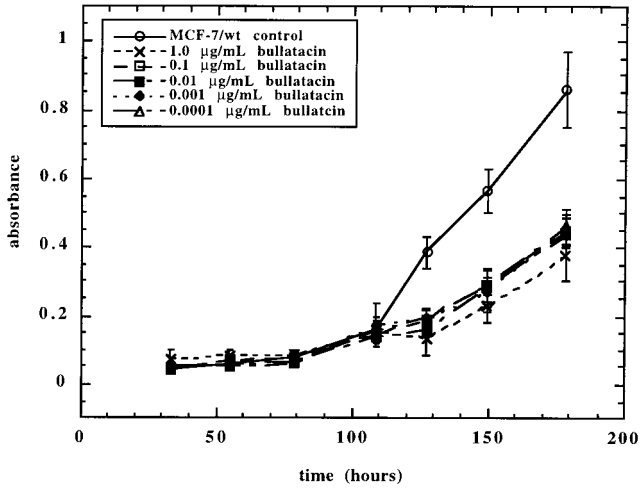



**Figure 7.** Periodic analysis (every 24 h) of the effects of serial dilution of bullatacin against MCF-7/wt cells. Values are expressed as average absorbances ($n$ = 6 for the vehicle treated control, $n$ = 4 for the bullatacin treated wells), and the error bars represent the standard deviation about each average. The concentration values are log dose units in $\mu$g/mL.

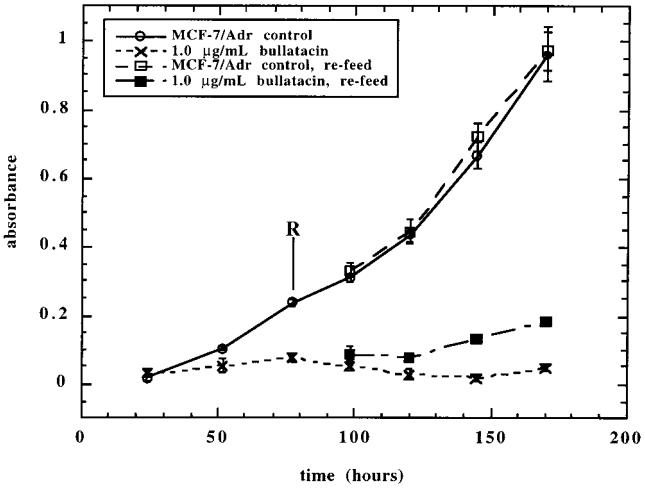



**Figure 8.** Periodic analysis (every 24 h) of the effects of 1.0 $\mu$g/mL of bullatacin against MCF-7/Adr cells with refeeding of fresh media in half of the plates. Values are expressed as average absorbances ($n$ = 6 for both control and drug treated wells), and the error bars represent the standard deviation about each average. The "R" indicates when refeeding was initiated.

tion range of 1.0 $\mu$g/mL to 1.0 $\times$ $10^{-4}$ $\mu$g/mL (Figure 5). However, using the same doses, there was the usual plateau near the $IC_{50}$ value against the parental MCF-7/wt cells. At the most concentrated dose of 1.0 $\mu$g/mL, bullatacin inhibited nearly all of the growth of the MDR MCF-7/Adr cells but only 50% of the growth of the MCF-7/wt cells (Figure 5). This observation was examined further by analyzing the growth of both cell lines periodically over the 7 days of the assay (Figures 6 and 7). In the MDR MCF-7/Adr cells, bullatacin inhibited cell growth by varying amounts in a dose-dependent fashion, i.e., nearly zero cell growth at the most concentrated dose of 1.0 $\mu$g/mL vs nearly 100% cell growth at the least concentrated dose of 1.0 $\times$ $10^{-4}$ $\mu$g/mL (Figure 6). Alternatively, the cell growth of the parental MCF-7/wt cells was only inhibited by 50%, relative to the growth of the vehicle treated controls, regardless of the dose of bullatacin (Figure 7). A linear dose–response curve in the MCF-7/Adr cells after a 6-day treatment (Figure 5) reflects dose dependent cell growth when analyzed on a daily basis (Figures 4, 6, and 7). Likewise, dose independent cell growth was confirmed in the MCF-7/wt cells both at the end of 6 days of bullatacin exposure (Figure 5) as well as over the 7 days of the assay (Figure 7).[20]

Both cell lines were then analyzed to determine if they were still viable after bullatacin treatment (Figures 8 and 9). A 48-h exposure to bullatacin (1.0 $\mu$g/mL) was cytotoxic to the MDR MCF-7/Adr cells since these cells would not regrow after being fed with fresh media (Figure 8). However, the MCF-7/wt cells were able to grow to a level near that of the vehicle-treated control upon being fed fresh media; thus, bullatacin was more cytostatic than cytotoxic to these wild-type cells (Figure 9). A similar refeeding experiment, using 1.0 $\mu$g/mL of adriamycin, showed the opposite results; the MCF-7/Adr cells were completely unaffected by the antineoplastic agent, whereas the MCF-7/wt cells were no longer viable after adriamycin treatment.[20]

To understand better the cytotoxicity against MDR MCF-7/Adr cells and to suggest the structures optimum for future synthetic and biological evaluation, a SAR study was

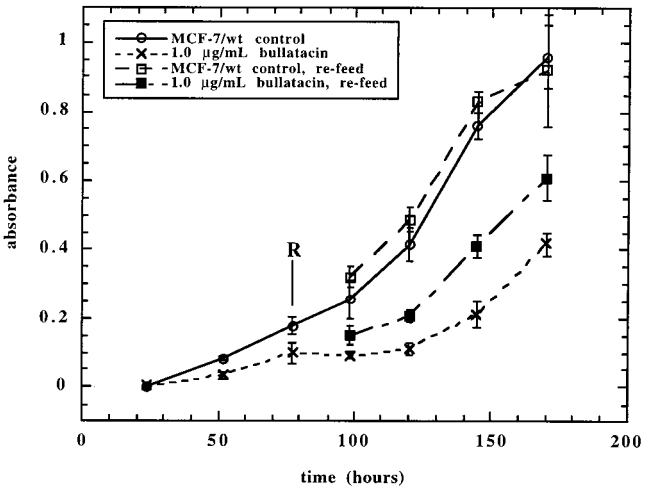



**Figure 9.** Periodic analysis (every 24 h) of the effects of 1.0 $\mu$g/mL of bullatacin against MCF-7/wt cells with refeeding of fresh media in half of the plates. Values are expressed as average absorbances ($n = 6$ for both control and drug treated wells), and the error bars represent the standard deviation about each average. The "R" indicates when refeeding was initiated.

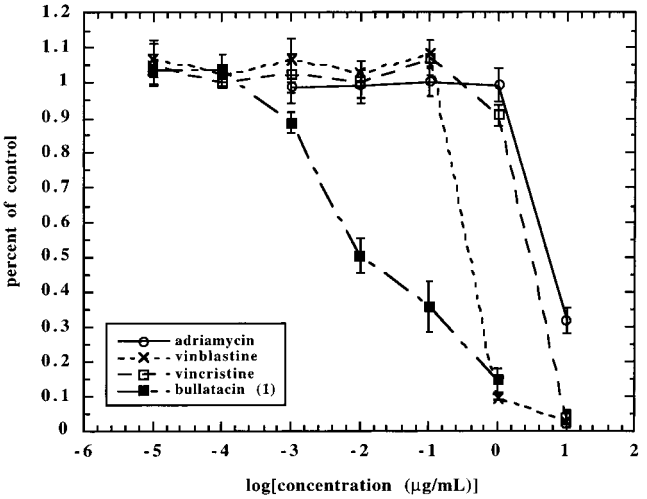



**Figure 10.** Comparison of the cell growth inhibition potential of bullatacin vs the standard antineoplastic compounds adriamycin, vinblastine, and vincristine against multidrug-resistant MCF-7/Adr cells. Values are expressed as percentages of the vehicle-treated controls with each point representing the normalized average of four values and the error bars representing the standard deviation about each average. The concentration values are log dose units in $\mu$g/mL.

conducted with 14 structurally diverse acetogenins (seven bis-adjacent, two bis-nonadjacent, and five mono-THF ring compounds).[21] All compounds were tested with adriamycin, vincristine, and vinblastine, as standard chemotherapeutic agents (Figure 10). Thirteen of the 14 acetogenins were generally more potent than all three of the standard drugs. Bullatacin is 258 times more cytotoxic against MCF-7/Adr than adriamycin. Acetogenins with the stereochemistry threo-trans-threo-trans-erythro (from C-15 to C-24) were the most potent among the bis-adjacent acetogenins.[21] The most potent compound, gigantetrocin A (a mono-THF ring acetogenin), was two times as potent as bullatacin.[21] The optimal length of the alkyl chain between the THF ring and the $\gamma$-lactone was 15 carbons as recently corroborated by Miyoshi et al.[45] with the purified mitochondrial enzyme. Shortening the length of the alkyl chain decreased the potency significantly in this particular cell line. While Oberlies et al.[21] have observed slight differences in potency between stereoisomeric acetogenins, all previous studies, based on cellfree systems, i.e., electron-transport inhibition in rat liver mitochondrial suspensions[98,99] and with the purified enzyme,[45] did not. As previously mentioned, this might be attributed to such factors such as, but not restricted to, membrane transport, intracellular transport, or metabolic inactivation in the whole cell assay systems, which are better mimics of in vivo effects.

Adriamycin has been reported to us to accumulate in bullatacin-treated MDR tumor cells, but we have not evaluated the original data (personal communication).[106] Concurrent therapy of acetogenins with the traditional antitumor agents would, thus, potentially extend patient survival times, and in addition, those patients who have already developed MDR would be expected to benefit substantially by acetogenin treatment.

**Annonaceous Acetogenins vs Resistant and Susceptible Insects and Pests.** Six compounds, representing the mono-THF (gigantetrocin A, annomontacin), adjacent bis-THF (asimicin, parviflorin), and nonadjacent bis-THF (sylvaticin, bullatalicin) classes of Annonaceous acetogenins, were compared with technical grades of synthetic amidinohydrazone (hydramethylnon), carbamate (propoxur, bendiocarb), organophosphate (chlorpyrifos), and pyrethroid (cypermethrin) insecticides to determine their dietary toxicities to insecticide-resistant and insecticide-susceptible strains of the German cockroach, *Blattella germanica*.[22] As a widespread urban insect, cockroaches are controlled primarily by the use of conventional synthetic insecticides that provide a relatively rapid and efficient means of reducing cockroach populations.[22] Most of these insecticides interfere with the proper functioning of the cockroach nervous system or other physiological processes after entering the body following direct contact, exposure to vapor, or ingestion. Repeated applications of these insecticides have resulted in the development of resistance to the chlorinated hydrocarbon, organophosphate, carbamate, and pyrethroid classes of synthetic insecticides. The development of novel insecticide classes with new biochemical mechanisms as targets is needed to help to overcome this resistance problem.

Acetogenins have been frequently described in the literature as being toxic to mosquito larvae, European corn borers, spider mites, melon aphids, Mexican bean beetles, bean leaf beetles, striped cucumber beetles, blowfly larvae, Colorado potato beetles, and free-living nematodes.[15,97,107] The acetogenins typically occur as complex mixtures of over 40 different compounds within the plant extract; thus, application as mixtures in crude extracts has been suggested.[107]

On the basis of our preliminary testing (topical bioassays), acetogenins are more toxic by ingestion than by contact to cockroaches.[22] Thus, tests were conducted at 1000 ppm of all test compounds in the diet (bait). Differential susceptibility occurred among *B. germanica* nymphs of both strains to this variety of the acetogenins and to the five conventional synthetic insecticides. The speed of killing values ($LT_{50}$) against insecticide-susceptible (Jwax) and insecticide-resistant (Muncie), second and fifth instars, permitted ranking of all 11 compounds. The adjacent bis-THF acetogenins showed the highest potency among the three acetogenin classes (Tables 1 and 2). The acetogenins caused high percentages of mortality and delays in development of the fifth instars of both strains (Figure 11). In the Jwax-susceptible German cockroach strain, nymphal development was mainly affected by gigantetrocin A and annomontacin, whereas in Muncie, a resistant German cockroach strain, nymphal development was mainly affected by gigantetrocin A and bullatalicin.

**Table 1.** $LT_{50}$ Values[a] for German Cockroach Second Instars

| compound type | active ingredient | Jwax (susceptible strain) | Muncie (resistant strain) |
|---|---|---|---|
| natural | parviflorin | 1.0 | 0.8 |
| | asimicin | 2.1 | 1.9 |
| | sylvaticin | 2.1 | 3.6 |
| | bullatalicin | 7.2 | 6.3 |
| | annomontacin | 4.1 | 2.4 |
| | gigantetrocin A | 4.8 | 10.6 |
| synthetic | cypermethrin | 0.2 | 0.5 |
| | chlorpyrifos | 0.7 | 2.6 |
| | hydramethylnon | 6.0 | 5.8 |
| | propoxur | 47.9 | 181.1 |
| | bendiocarb | 50.8 | 128.1 |

[a] Number of days before death of 50% of the population following exposure to toxic baits at a dose of 1000 ppm.

**Table 2.** $LT_{50}$ Values[a] for German Cockroach Fifth Instars

| compound type | active ingredient | Jwax (susceptible strains) | Muncie (resistant strain) |
|---|---|---|---|
| natural | parviflorin | 0.8 | 1.2 |
| | asimicin | 2.3 | 3.8 |
| | sylvaticin | 2.1 | 8.2 |
| | bullatalicin | 5.8 | 10.3 |
| | annomontacin | 24.7 | 3.8 |
| | gigantetrocin A | 20.4 | 17.8 |
| synthetic | cypermethrin | *b* | 0.2 |
| | chlorpyrifos | 0.5 | 4.2 |
| | hydramethylnon | 10.4 | 6.1 |
| | propoxur | 20.4 | 34.1 |
| | bendiocarb | 43.8 | 39.3 |

[a] Number of days before death of 50% of the population following exposure to toxic baits at a dose of 1000 ppm. [b] There was a single response value to cypermethrin; no lethal time estimate was made.

Most of the acetogenins tested performed better than the conventional insecticides against both stages of both strains (Tables 1 and 2). No growth-regulation effects were caused by any of the compounds tested. Low resistance ratios (RRs) were obtained for most compounds (except chlorpyrifos) (Table 3). Low resistance ratio values for second instars ranged from 0.9 to 2.2 with the natural acetogenins and from 1.0 to 3.8 with the synthetic compounds; the fifth instars ranged from 0.2 to 3.9 with the natural acetogenins and from 0.6 to 8.0 with the synthetic compounds (Table 3). Hydromethylnon, an electron-transport complex III inhibitor, not surprisingly, showed the lowest RR among the synthetic pesticides.[22] The high mortality observed with the low resistance ratios, shown in this study,[22] suggested an excellent potential for the use of Annonaceous acetogenins in baits against cockroaches, and it is predictable that such pesticide-resistance also includes ATP-dependent factors.

These compounds are proven to induce emesis in pigs; this is a definite safety factor should someone ingest excessive amounts of these materials either intentionally or unintentionally; indeed, a fluidextract of paw paw seeds was once sold as an emetic by the Eli Lilly Co. (Asta Laboratories, unpublished data).[107] The methanolic-soluble fraction, F005, of paw paw bark, gave negative results in the Ames mutagenicity test (Sitek Research Laboratories, unpublished results); nine out of 10 tests were negative on the histidine mutants of *Salmonella typhimurium*, and one slight positive (2.5% above control) occurred after enzyme activation of the extract. Further research is now needed to develop more refined treatment strategies for the inclusion of effective baited formulations, containing mixtures of acetogenins obtained from plant extracts, into integrated pest management programs to control resistant *B. germanica*.

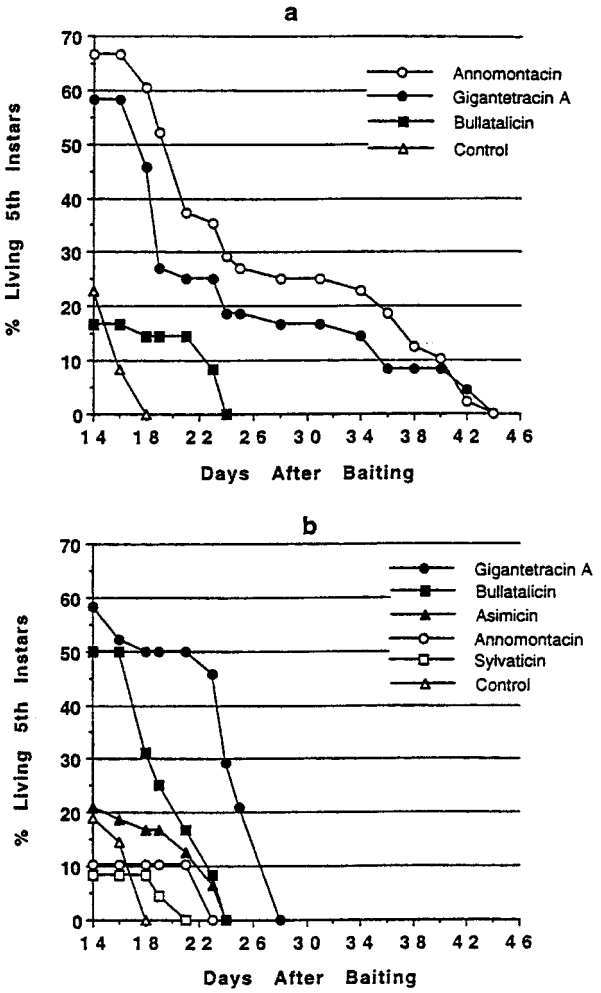



**Figure 11.** Effects of Annonaceous acetogenins (1000 ppm in bait) on development of fifth instars of (a) the Jwax and (b) Muncie strains of *Blattella germanica*.

**Table 3.** Resistance Ratios for Annonaceous Acetogenins and Conventional Synthetic Toxicant Baits for Second and Fifth Instars of *Blattella Germanica*

| compound type | active ingredient[a] | second instar RR[a] (95% CL) | fifth instar RR[a] (95% CL) |
|---|---|---|---|
| natural | parviflorin | 0.9 (0.6−1.4)* | 1.5 (1.0−2.2)* |
| | asimicin | 0.9 (0.8−1.1)* | 1.6 (1.3−2.1 |
| | sylvaticin | 1.7 (1.3−2.1) | 3.9 (1.1−14.0) |
| | bullatalicin | 0.9 (0.8−1.0)* | 1.8 (1.4−2.3) |
| | annomontacin | 0.6 (0.5−0.7) | 0.2 (0.1−0.2) |
| | gigantetrocin A | 2.2 (1.9−2.6) | 0.9 (0.7−1.1)* |
| synthetic | cypermethrin | 2.0 (0.4−10.0)* | |
| | chlorpyrifos | 3.8 (2.5−5.8) | 8.0 (4.1−15.4) |
| | hydramethylnon | 1.0 (0.5−2.1)* | 0.6 (0.2−2.3)* |
| | propoxur | 3.8 (1.9−7.5) | 1.7 (−) |
| | bendiocarb | 2.5 (1.6−4.1) | 0.9 (0.1−9.9)* |

[a] Resistance ratios (95% confidence limits, CL) at $LT_{50}$ value estimates. There was a single response value for cypermethrin against fifth instars of the Jwax strain; no lethal time was estimated, and the RR was not calculated. In some instances, the use of a large *t* value caused nonrealistic confidence limits (CL) to be calculated. Whenever the 95% CL of a ratio includes 1 (values with an asterisk), no significant differences exist between the probit levels of mortalities being compared.

The activities of 44 Annonaceous acetogenins were evaluated in the yellow fever mosquito larva microtiter

plate (YFM) assay.[97] The results clearly demonstated that most acetogenins have potent pesticidal properties. The SAR observed indicated that the compounds bearing adjacent bis-THF rings with three hydroxyls groups are the most potent. Bullatacin and trilobin gave the best activities against YFM with $LC_{50}$ values of 0.1 and 0.67 mg/L or ppm (parts per million), respectively. Compounds showing $LC_{50}$ values below 1.0 ppm in this assay are usually considered significant as new lead candidates for pesticidal development.

## Conclusions

The biological properties of the Annonaceous acetogenins continue to attract the attentions of biochemists, biologists, botanists, chemists, entomologists, pharmacognosists, and phytochemists. Recent investigations indicate that the cytotoxic effects of Annonaceous acetogenins can thwart classical MDR in the adriamycin-resistant human mammary adenocarcinoma (MCF-7/Adr) cell model. Thorough in vivo studies are now needed to support the results proposed from the above-mentioned in vitro work. The pesticidal properties of the Annonaceous acetogenins make them well-suited for the control of insect pests including cockroaches in an urban setting. A concentration of only 1000 ppm in a dietary formulation produced high mortality and was associated with delays in nymphal development of second and fifth instars of both susceptible and resistant German cockroaches. Further research is now necessary to develop refined pesticidal strategies for the inclusion of such highly effective and environmentally friendly formulations to control pests. To meet the demands of further in vitro and in vivo pharmacological evaluation, we especially encourage the synthesis of those selectively cytotoxic acetogenins that are rare in nature, e.g., squamotacin, which is specific for prostate tumor cells; synthetic targets can also include a wide diversity of analogues based on the SAR generalizations, as determined using the natural compounds, as mentioned above. The high potency, selectivity, wide chemical and biological diversity, and effectiveness of these compounds against resistance could well make them become the next class of useful natural antitumor and pesticidal agents.

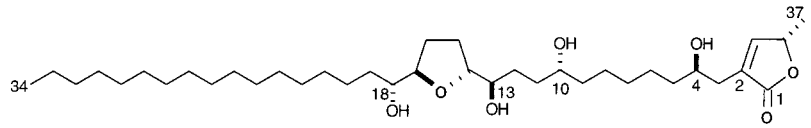
**Acknowledgment.** The studies described in this review carried out at Purdue University were supported, in part, by R01 Grant No. CA 30909 from the National Cancer Institute, National Institutes of Health. F.Q.A acknowledges generous financial support from Mrs. Marilyn Cochran of San Angelo, TX, and X.-X.L. acknowledges fellowship support from the Purdue Research Foundation.

## Appendix 1

**Table 4.** Annonaceous Acetogenins Reported between June 1995 and August 1998 (* Indicates Relative Stereochemistry)

Mono-THF Acetogenins

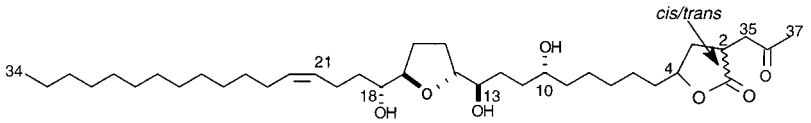
**1. goniotetracin**[39] ($C_{37}H_{68}O_7$, MW 624)




| Position | 4 | 10 | 13 | 14 | 17 | 18 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.83 m | 3.64 m | 3.45 m | 3.82 m | 3.82 m | 3.41 m |
| **$^{13}$C** (δ) | 69.9 | 71.6 | 74.0 | 82.6 | 82.7 | 74.3 |

White amorphous powder. $[\alpha]_D$: +16.1° (*c* 0.056, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 208 (log $\epsilon$ 3.52). IR ($\nu_{max}$, film, $cm^{-1}$): 3418, 2919, 2850, 2359, 1732, 1468, 1319, 1206. MS: EIMS *m/z* 351, 333, 325, 307, 281, 263, 255, 241, 223, 205, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $2.0 \times 10^{-1}$, A-549 $ED_{50}$ $3.9 \times 10^{-1}$, MCF-7 $ED_{50}$ 1.7, HT-29 $ED_{50}$ 1.5, A-498 $ED_{50}$ 1.5, PC-3 $ED_{50}$ $2.1 \times 10^{-1}$, PACA-2 $ED_{50}$ $2.6 \times 10^{-2}$. Source: *Goniothalamus giganteus*, stem bark.

**gonioneninone** (reported as a cis and trans mixture)[108] ($C_{37}H_{66}O_7$, MW 622)




**2. (2,4-*cis*)-gonioneninone**

| Position | 10 | 13 | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.63 m | 3.45 m | 3.83 m | 3.83 m | 3.43 m | 5.34 ddd | 5.40 ddd |
| **$^{13}$C** (δ) | 71.5 | 74.3 | 82.6 | 82.6 | 73.5 | 128.9 | 130.8 |

**3. (2,4-*trans*)-gonioneninone**

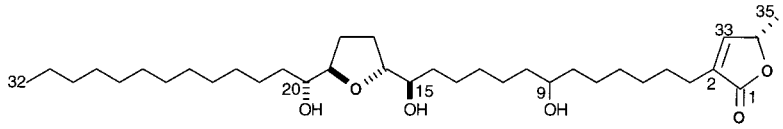
| Position | 10 | 13 | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.63 m | 3.45 m | 3.83 m | 3.83 m | 3.43 m | 5.34 ddd | 5.40 ddd |
| **$^{13}$C** (δ) | 71.5 | 74.3 | 82.6 | 82.6 | 73.5 | 128.9 | 130.8 |

White amorphous powder. $[\alpha]_D$: +16.0° (*c* 0.05, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3415, 2922, 2851, 1766, 1717, 1466. MS: EIMS *m/z* 351, 333, 323, 281, 263, 253, 235, 241, 223, 205, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50} < 3.0 \times 10^{-1}$, A-549 $ED_{50}$ 1.8, MCF-7 $ED_{50}$ 3.7, HT-29 $ED_{50}$ 2.9, A-498 $ED_{50}$ 2.2, PC-3 $ED_{50}$ 1.5, PACA-2 $ED_{50}$ $4.5 \times 10^{-2}$. Source: *Goniothalamus giganteus*, stem bark.

**Table 4. (Continued)**

Mono-THF Acetogenins (Continued)

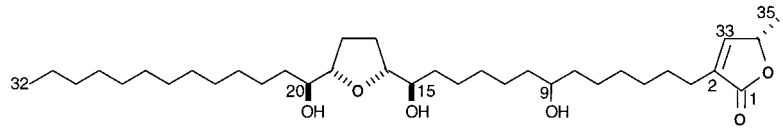
**4. 4-deoxyannoreticuin***[109] ($C_{35}H_{64}O_6$, MW 580)



| Position | 9 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.58 m | 3.41 m | 3.80 m | 3.80 m | 3. 41m |
| **$^{13}$C** (δ) | 71.90 | 74.08 | 82.53 | 82.64 | 74.06 |

White amorphous powder. $[\alpha]_D$: +6.8° (*c* 0.015, $CH_2Cl_2$). UV ($\lambda_{max}$, MeOH, nm): 218 (log $\epsilon$ 3.61). IR ($\nu_{max}$, film, $cm^{-1}$): 3423, 2926, 2854, 1755. MS: EIMS *m/z* 345, 311, 293, 275, 211, 193. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities ($\mu$g/mL): BST $LC_{50}$ 8.9, A-549 $ED_{50}$ 3.9, MCF-7 $ED_{50}$ 2.2, HT-29 $ED_{50}$ 1.7, A-498 $ED_{50}$ 2.2, PC-3 $ED_{50}$ 2.7, PACA-2 $ED_{50}$ 2.9. Source: *Annona squamosa,* stem bark.

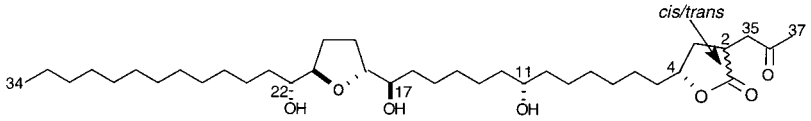
**5. *cis*-4-deoxyannoreticuin***[109] ($C_{35}H_{64}O_6$, MW 580)



| Position | 9 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.59 m | 3.42 m | 3.82 m | 3.82 m | 3.42 m |
| **$^{13}$C** (δ) | 71.86 | 74.37 | 82.67 | 82.67 | 74.37 |

White amorphous powder. $[\alpha]_D$: +6.8° (*c* 0.015, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 218 (log $\epsilon$ 3.61). IR ($\nu_{max}$, film, $cm^{-1}$): 3423, 1916, 2854, 1755. MS: EIMS *m/z* 345, 311, 293, 275, 211, 193. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities ($\mu$g/mL): BST $LC_{50}$ 6.8, A-549 $ED_{50}$ 2.0, MCF-7 $ED_{50}$ 1.7, HT-29 $ED_{50}$ 1.4, A-498 $ED_{50}$ 1.8, PC-3 $ED_{50}$ 2.1, PACA-2 $ED_{50}$ 1.1. Source: *Annona squamosa,* stem bark.

**squamoxinone**[109] (reported as a cis and trans mixture) ($C_{37}H_{68}O_7$, MW 624)



**6. (2,4-*cis*)-squamoxinone**

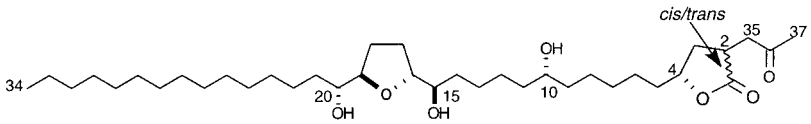
| Position | 11 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3. 59 m | 3.41 m | 3.80 m | 3.80 m | 3.41 m |
| **$^{13}$C** (δ) | 71.86 | 74.02 | 82.63 | 82.58 | 73.97 |

**7. (2,4-*trans*)-squamoxinone**

| Position | 11 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3. 59 m | 3.41 m | 3.80 m | 3.80 m | 3.41 m |
| **$^{13}$C** (δ) | 71.86 | 74.02 | 82.63 | 82.58 | 73.97 |

White amorphous powder. $[\alpha]_D$: +13.3° (*c* 0.023, $CH_2Cl_2$). UV ($\lambda_{max}$, MeOH, nm): 203 (log $\epsilon$ 3.20). IR ($\nu_{max}$, film, $cm^{-1}$): 3445, 2919, 2850, 1755. MS: EIMS *m/z* 407, 389, 371, 337, 319, 255. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities ($\mu$g/mL): BST $LC_{50}$ 2.7, A-549 $ED_{50}$ 1.9, MCF-7 $ED_{50}$ 1.7, HT-29 $ED_{50}$ 1.4, A-498 $ED_{50}$ 1.5, PC-3 $ED_{50}$ 2.2, PACA-2 $ED_{50}$ $4.5 \times 10^{-3}$. Source: *Annona squamosa,* stem bark.

**xylomaticinone**[39] (reported as a cis and trans mixture) ($C_{37}H_{69}O_7$, MW 624)



**8. (2,4-*cis*)-xylomaticinone**

| Position | 10 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.59 m | 3.41 m | 3.80 m | 3.80 m | 3.41 m |
| **$^{13}$C** (δ) | 71.7 | 73.97 | 82.60 | 82.66 | 74.04 |

**9. (2,4-*trans*)-xylomaticinone**

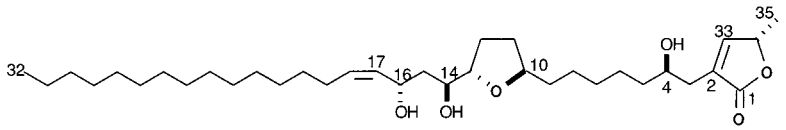
| Position | 10 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.59 m | 3.41 m | 3.80 m | 3.80 m | 3.41 m |
| **$^{13}$C** (δ) | 71.7 | 73.97 | 82.60 | 82.66 | 74.04 |

White wax. $[\alpha]_D$: +26.2° (*c* 0.08, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3454, 2916, 2848, 1756, 1716, 1470, 1070. MS: EIMS *m/z* 379, 361, 343, 309, 297, 291, 279, 273, 241, 227, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities ($\mu$g/mL): BST $LC_{50}$ $0.4 \times 10^{-1}$, A-549 $ED_{50}$ $1.4 \times 10^{-2}$, MCF-7 $ED_{50}$ $7.6 \times 10^{-4}$, HT-29 $ED_{50}$ $7.4 \times 10^{-4}$, A-498 $ED_{50}$ $1.2 \times 10^{-1}$, PC-3 $ED_{50}$ $5.7 \times 10^{-2}$, PACA-2 $ED_{50}$ $7.4 \times 10^{-2}$. Source: *Annona squamosa,* stem bark.

**Table 4. (Continued)**

Mono-THF Acetogenins (Continued)

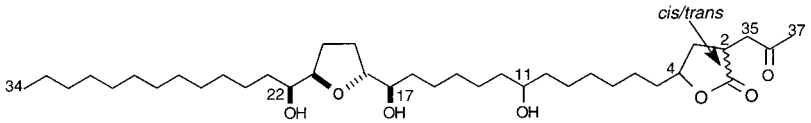
**10. goniotrionin**[10] ($C_{35}H_{62}O_6$, MW 578)



| Position | 10 | 13 | 14 | 16 | 17 | 18 |
|---|---|---|---|---|---|---|
| $^1$H (δ) | 3.89 m | 3.85 m | 3.73 dt | 4.78 dt | 5.48 m | 5.44 m |
| $^{13}$C (δ) | 79.3 | 81.8 | 71.5 | 65.0 | 131.6 | 132.2 |

Whitish wax. UV ($\lambda_{max}$, MeOH, nm): 218 (log $\epsilon$ 3.46). IR ($\nu_{max}$, film, cm$^{-1}$): 3368, 2916, 2849, 1740, 1721, 1467, 1328, 1086, 1058, 841. MS: EIMS *m/z* 297, 281, 263, 253, 245, 239, 221, 203. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities ($\mu$g/mL): A-549 $ED_{50}$ 7.7 × $10^{-3}$, MCF-7 $ED_{50}$ 5.3 × $10^{-6}$, HT-29 $ED_{50}$ 3.4 × $10^{-1}$, A-498 $ED_{50}$ 2.0 × $10^{-3}$, PC-3 $ED_{50}$ 3.6 × $10^{-1}$, PACA-2 $ED_{50}$ 5.4 × $10^{-3}$. Source: *Goniothalamus giganteus*, stem bark.

**squamoxine B***[42] (reported as a cis and trans mixture) ($C_{37}H_{68}O_7$, MW 630)



**11. (2,4-*cis*)-squamoxine B**

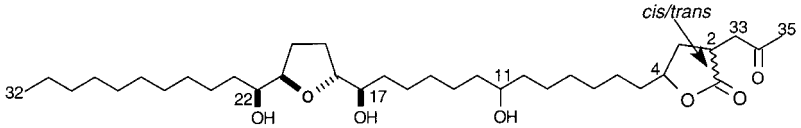
| Position | 11 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| $^1$H (δ) | 3.58 m | 3.39 m | 3.82 m | 3.87 m | 3.82 m |
| $^{13}$C (δ) | 71.84 | 74.28 | 83.18 | 82.14 | 71.52 |

**12. (2,4-*trans*)-squamoxine B**

| Position | 11 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| $^1$H (δ) | 3.58 m | 3.39 m | 3.82 m | 3.87 m | 3.82 m |
| $^{13}$C (δ) | 71.84 | 74.28 | 83.18 | 82.14 | 71.52 |

White amorphous powder. $[\alpha]_D$: +23.6° (*c* 0.20, $CH_2Cl_2$). UV ($\lambda_{max}$, MeOH, nm): 203 (log $\epsilon$ 2.85). IR ($\nu_{max}$, film, cm$^{-1}$): 3444, 2916, 1770, 1715, 1470. MS: EIMS *m/z* 425, 389, 337, 319, 301, 255. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities ($\mu$g/mL): BST $LC_{50}$ 4.6 × $10^{-2}$, A-549 $ED_{50}$ 3.8 × $10^{-3}$, MCF-7 $ED_{50}$ 1.4 × $10^{-3}$, HT-29 $ED_{50}$ 2.7 × $10^{-3}$, A-498 $ED_{50}$ 4.0 × $10^{-3}$, PC-3 $ED_{50}$ 5.0 × $10^{-2}$, PACA-2 $ED_{50}$ 8.3 × $10^{-4}$. Source: *Annona squamosa*, stem bark.

**squamoxinone C***[42] (reported as a cis and trans mixture) ($C_{35}H_{64}O_7$, MW 624)



**13. (2,4-*cis*)-squamoxinone C**

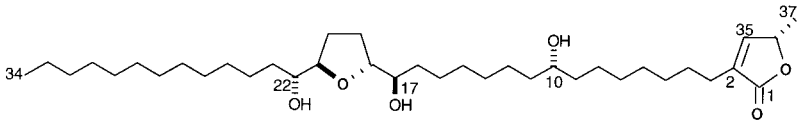
| Position | 11 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| $^1$H (δ) | 3.58 m | 3.39 m | 3.82 m | 3.87 m | 3.82 m |
| $^{13}$C (δ) | 71.84 | 74.28 | 83.18 | 82.14 | 71.52 |

**14. (2,4-*trans*)-squamoxinone C**

| Position | 11 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| $^1$H (δ) | 3.58 m | 3.39 m | 3.82 m | 3.87 m | 3.82 m |
| $^{13}$C (δ) | 71.84 | 74.28 | 83.18 | 82.14 | 71.52 |

White wax. $[\alpha]_D$: −13.3° (*c* 0.023, $CH_2Cl_2$). UV ($\lambda_{max}$, MeOH, nm): 207 (log $\epsilon$ 3.35). IR ($\nu_{max}$, film, cm$^{-1}$): 3390, 2921, 2851, 1770, 1705, 1470. MS: EIMS *m/z* 389, 337, 319, 301, 255. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities ($\mu$g/mL): BST $LC_{50}$ 9.7 × $10^{-2}$, A-549 $ED_{50}$ 2.1 × $10^{-1}$, MCF-7 $ED_{50}$ 1.1 × $10^{-3}$, HT-29 $ED_{50}$ 3.5 × $10^{-1}$, A-498 $ED_{50}$ 6.7 × $10^{-3}$, PC-3 $ED_{50}$ 2.24, PACA-2 $ED_{50}$ 9.5 × $10^{-3}$. Source: *Annona squamosa*, stem bark.

**15. 4-deoxyannomontacin**[47] ($C_{37}H_{68}O_6$, MW 608)



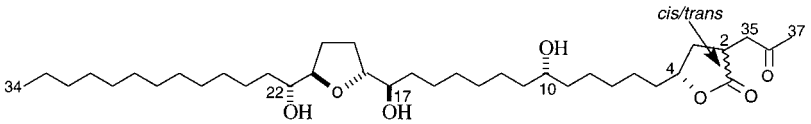
| Position | 10 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| $^1$H (δ) | 3.58 m | 3.40 q | 3.80 q | 3.80 q | 3.40 q |
| $^{13}$C (δ) | 71.88 | 74.01 | 82.66 | 82.61 | 74.01 |

White wax. $[\alpha]_D$: +10.9° (*c* 0.060, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 228 (log $\epsilon$ 2.86). IR ($\nu_{max}$, film, cm$^{-1}$): 3443, 2921, 2850, 2360, 1742, 1455, 1374, 1318, 1191, 1068, 1028. MS: EIMS *m/z* 413, 395, 377, 359, 391, 373, 339, 321, 303, 269, 251, 225. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR), TMS (EIMS), peracetate ($^1$H NMR). Biological activities ($\mu$g/mL): BST $LC_{50}$ 1.3 × $10^{-1}$, A-549 $ED_{50}$ 6.5 × $10^{-7}$, MCF-7 $ED_{50}$ 5.8 × $10^{-7}$, HT-29 $ED_{50}$ 1.4 × $10^{-1}$, A-498 $ED_{50}$ 1.5 × $10^{-1}$, PC-3 $ED_{50}$ 1.7 × $10^{-1}$, PACA-2 $ED_{50}$ 1.0 × $10^{-5}$. Source: *Goniothalamus giganteus*, stem bark.

**Table 4. (Continued)**

Mono-THF Acetogenins (Continued)

**annomontacinone**[47] (reported as a cis and trans mixture) ($C_{37}H_{68}O_7$, MW 624)




**16. (2,4-*cis*)-annomontacinone**

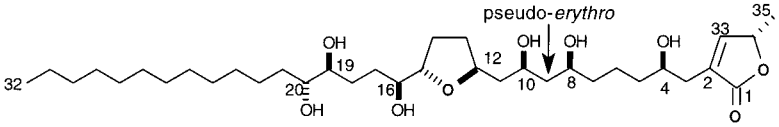
| Position | 10 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.58 m | 3.40 q | 3.80 q | 3.80 q | 3.40 q |
| **$^{13}$C** (δ) | 71.86 | 74.00 | 82.64 | 82.57 | 74.06 |

**17. (2,4-*trans*)-annomontacinone**

| Position | 10 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.58 m | 3.40 q | 3.80 q | 3.80 q | 3.40 q |
| **$^{13}$C** (δ) | 71.86 | 74.00 | 82.64 | 82.57 | 74.06 |

Whitish wax. $[\alpha]_D$: +13.6° (*c* 0.022, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3433, 2920, 2850, 1754, 1717, 1550, 1460, 1182, 1075, 727. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), per-MTPA esters ($^1$H NMR), formal acetal ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ $3.1 \times 10^{-1}$, A-549 $ED_{50}$ 2.6, MCF-7 $ED_{50}$ 3.2, HT-29 $ED_{50}$ $2.6 \times 10^{-1}$, A-498 $ED_{50}$ 1.4, PC-3 $ED_{50}$ 1.0, PACA-2 $ED_{50}$ $6.8 \times 10^{-1}$. Source: *Goniothalamus giganteus*, stem bark.

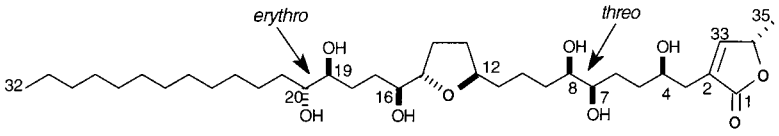
**18. muricoreacin***[110] ($C_{35}H_{64}O_9$, MW 628)




| Position | 8 | 10 | 12 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.86 m | 4.06 m | 4.15 m | 3.90 m | 3.49 m | 3.59 m | 3.59 m |
| **$^{13}$C** (δ) | 71.6 | 72.2 | 79.1 | 82.3 | 73.8 | 74.8 | 74.6 |

White solid. $[\alpha]_D$: +1.6° (*c* 0.06, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 220 (log ε 3.65). IR ($\nu_{max}$, film, $cm^{-1}$): 3347, 2916, 2849, 1743, 1470. MS: EIMS *m/z* 429, 411, 393, 375, 357, 341, 339, 323, 305, 287, 269, 257, 251, 239, 221, 213, 203, 199, 195, 181, 177, 141, 123. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Biological activities (μg/mL): BST $LC_{50}$ 19, A-549 $ED_{50}$ $2.3 \times 10^{-1}$, MCF-7 $ED_{50}$ 1.3, HT-29 $ED_{50}$ $5.7 \times 10^{-1}$, A-498 $ED_{50}$ $7.1 \times 10^{-1}$, PC-3 $ED_{50}$ $2.5 \times 10^{-2}$, PACA-2 $ED_{50}$ 2.3. Source: *Annona muricata*, leaves.

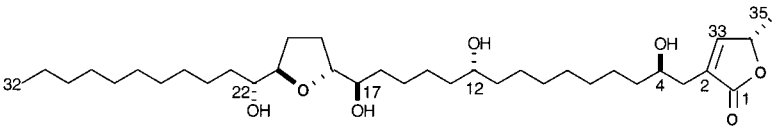
**19. murihexocin***[110] ($C_{37}H_{68}O_7$, MW 628)




| Position | 7 | 8 | 12 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.43 m | 3.43 m | 3.94 m | 3.86 m | 3.47 m | 3.60 m | 3.60 m |
| **$^{13}$C** (δ) | 73.9 | 74.0 | 79.3 | 81.7 | 74.0 | 74.5 | 74.5 |

White solid. $[\alpha]_D$: +37.5° (*c* 0.04, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 220 (log ε 3.69). IR ($\nu_{max}$, film, $cm^{-1}$): 3367, 2915, 2849, 1743, 1474. MS: EIMS *m/z* 429, 411, 393, 375, 357, 341, 339, 323, 305, 299, 287, 281, 269, 263, 251, 245, 211, 199, 193, 181, 163, 141, 123. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Biological activities (μg/mL): BST $LC_{50}$ 10, A-549 $ED_{50}$ 1.1, MCF-7 $ED_{50}$ 3.8, HT-29 $ED_{50}$ 1.3, A-498 $ED_{50}$ 2.5, PC-3 $ED_{50}$ $8.6 \times 10^{-1}$, PACA-2 $ED_{50}$ $4.9 \times 10^{-1}$. Source: *Annona muricata*, leaves.

**20. glacin A**[25] ($C_{35}H_{64}O_7$, MW 596)



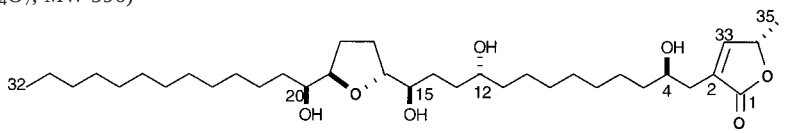

| Position | 12 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.60 m | 3.41 m | 3.80 m | 3.80 m | 3.41 m |
| **$^{13}$C** (δ) | 71.82 | 74.07 | 82.65 | 82.59 | 73.98 |

Whitish waxy solid. $[\alpha]_D$: +6.0° ($CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 218 (log ε 3.83). IR ($\nu_{max}$, film, $cm^{-1}$): 3461, 2919, 2851, 1734, 1717, 1464, 1318, 1203, 1075. MS: EIMS *m/z* 425, 407, 355, 337, 319, 301, 269, 251, 241, 233, 223, 171, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities μg/mL): BST $LC_{50}$ $1.1 \times 10^{-1}$, A-549 $ED_{50}$ 1.5, MCF-7 $ED_{50}$ $4.4 \times 10^{-3}$, HT-29 $ED_{50}$ 2.3, A-498 $ED_{50}$ 1.3, PC-3 $ED_{50}$ $9.8 \times 10^{-3}$, PACA-2 $ED_{50}$ $8.6 \times 10^{-3}$. Source: *Annona glabra*, leaves.

**Table 4. (Continued)**

Mono-THF Acetogenins (Continued)

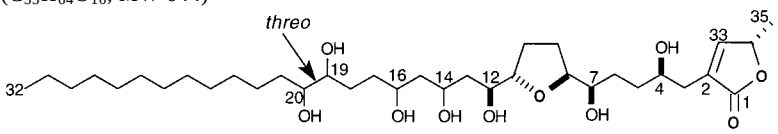
**21. glabracin B**[25] ($C_{35}H_{64}O_7$, MW 596)



| Position | 12 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.63 m | 3.44 m | 3.80 m | 3.80 m | 3.80 m |
| **$^{13}$C** (δ) | 71.66 | 74.57 | 83.06 | 82.19 | 71.56 |

Whitish waxy solid. $[\alpha]_D$: +4.8° ($CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 221 (log $\epsilon$ 3.65). IR ($\nu_{max}$, film, $cm^{-1}$): 3423, 2921, 2850, 1736, 1543, 1452, 1318, 1275, 1120, 1066. MS: EIMS *m/z* 397, 379, 343, 327, 309, 291, 273, 269, 251, 233, 199, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $2.7 \times 10^{-1}$, A-549 $ED_{50}$ 1.3, MCF-7 $ED_{50}$ $5.2 \times 10^{-2}$, HT-29 $ED_{50}$ $8.7 \times 10^{-2}$, A-498 $ED_{50}$ 2.6, PC-3 $ED_{50}$ $5.6 \times 10^{-2}$, PACA-2 $ED_{50}$ $1.5 \times 10^{-2}$. Source: *Annona glabra*, leaves.

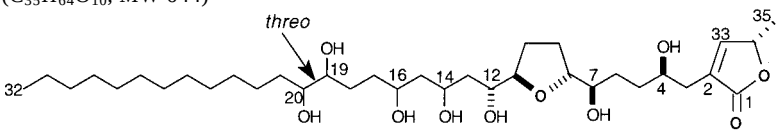
**22. coriaheptocin A***[40] ($C_{35}H_{64}O_{10}$, MW 644)



| Position | 7 | 8 | 11 | 12 | 14 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.74 m | 3.90 m | 3.88 m | 3.45 m | 3.86 m | 3.87 m | 3.75 m | 3.80 m |
| **$^{13}$C** (δ) | 71.0 | 82.2 | 83.0 | 74.0 | 68.0 | 67.7 | 71.6 | 71.0 |

White waxy solid. $[\alpha]_D$: +19° (*c* 1.08, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 208.8 (log $\epsilon$ 4.6). NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), acetonide ($^1$H NMR). Source: *Annona coriacea*, roots.

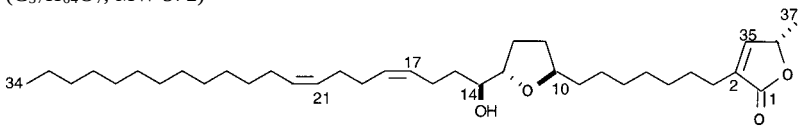
**23. coriaheptocin B***[40] ($C_{35}H_{64}O_{10}$, MW 644)



| Position | 7 | 8 | 11 | 12 | 14 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.45 m | 3.78 m | 3.81 m | 3.40 m | 3.90 m | 3.90 m | 3.74 m | 3.79 m |
| **$^{13}$C** (δ) | 74.3 | 82.9 | 82.5 | 74.3 | 67.8 | 67.4 | 71.3 | 70.9 |

White waxy solid. $[\alpha]_D$: +25° (*c* 1.00, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 207.2 (log $\epsilon$ 4.0). NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), acetonide ($^1$H NMR). Source: *Annona coriacea*, roots.

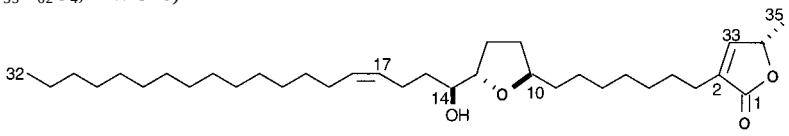
**24. coriacyclodienin**[111] ($C_{37}H_{64}O_7$, MW 572)



| Position | 10 | 13 | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.86 m | 3.78 td | 3.38 m | 5.40 m | 5.40 m | 5.40 m | 5.40 m |
| **$^{13}$C** (δ) | 79.2 | 81.8 | 73.5 | 130.4 | 129.5 | 129.8 | 129.0 |

White oil. $[\alpha]_D$: +8.0° (*c* 1.2, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 208 (log $\epsilon$ 3.87). IR ($\nu_{max}$, film, $cm^{-1}$): 3522, 2929, 2856, 1762, 1076. MS: EIMS *m/z* 363, 295, 277, 265, 247, 223. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Source: *Annona coriacea*, roots.

**25. coriacycloenin**[111] ($C_{35}H_{62}O_4$, MW 546)



| Position | 10 | 13 | 14 | 17 | 18 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.87 m | 3.78 td | 3.38 m | 5.35 m | 5.38 m |
| **$^{13}$C** (δ) | 79.2 | 81.8 | 73.6 | 130.6 | 129.0 |

White waxy solid. $[\alpha]_D$: +6.0° (*c* 0.5, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 207 (log $\epsilon$ 3.40). IR ($\nu_{max}$, film, $cm^{-1}$): 3488, 2929, 2856, 1761, 1465, 1075. MS: EIMS *m/z* 295, 277, 265, 247, 223. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Source: *Annona coriacea*, roots.

**gardnerinin**[35] (reported as a pair of epimers) ($C_{35}H_{64}O_9$, MW 628)

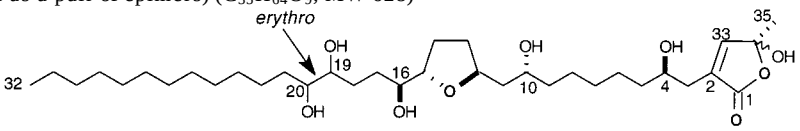


**Table 4. (Continued)**

Mono-THF Acetogenins (Continued)

**26. gardnerinin**

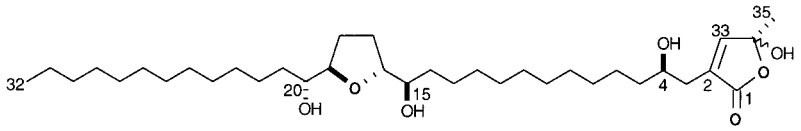
| Position | 10 | 12 | 15 | 16 | 19 | 20 | 34 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.81 m | 4.00 m | 3.86 m | 3.42 m | 3.58 m | 3.64 m | --- |
| **$^{13}$C** (δ) | 71.70 | 77.95 | 82.51 | 73.53 | 74.34 | 74.43 | 105.09 |

**27. 34-*epi*-gardnerinin**

| Position | 10 | 12 | 15 | 16 | 19 | 20 | 34 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.81 m | 4.0 m | 3.86 m | 3.42 m | 3.58 m | 3.64 m | --- |
| **$^{13}$C** (δ) | 71.70 | 77.95 | 82.51 | 73.53 | 74.34 | 74.43 | 105.58 |

White waxy solid. Mp: 78−80 °C. $[\alpha]_D$: +14.0° (*c* 0.07, $CH_3OH$). IR ($\nu_{max}$, film, $cm^{-1}$): 3386, 2922, 2852, 1749, 1466, 1072, 928. MS: EIMS *m/z* 413, 395, 377, 483, 465, 447, 329, 311, 293, 269, 251, 229, 211. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: phenylhydrazone ($^1$H NMR), per-MTPA esters ($^1$H NMR), acetonide ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): KB $IC_{50}$ >10, HCT-8 $IC_{50}$ 6.6, Bel 7402 $IC_{50}$ >10. Source: *Goniothalamus gardneri*, roots.

**donnaienin A**[32] (reported as a pair of epimers) ($C_{35}H_{64}O_7$, MW 596)




**28. donnaienin A**

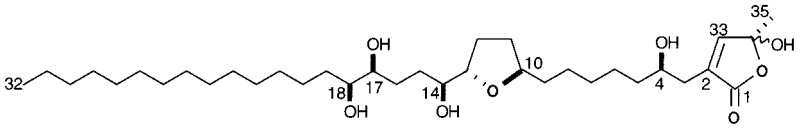
| Position | 15 | 16 | 19 | 20 | 34 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.41 m | 3.77 m | 3. 77 m | 3.41 m | --- |
| **$^{13}$C** (δ) | 74.4 | 82.6 | 82.6 | 74.3 | 104.9 |

**29. 34-*epi*-donnaienin A**

| Position | 15 | 16 | 19 | 20 | 34 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.41 m | 3.77 m | 3. 77 m | 3.41 m | --- |
| **$^{13}$C** (δ) | 74.4 | 82.6 | 82.6 | 74.3 | 105.2 |

White amorphous powder. Mp: 96−98 °C. $[\alpha]_D$: −7.6° (*c* 0.07, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 205 (ε 6831). IR ($\nu_{max}$, film, $cm^{-1}$): 3390, 2920, 2850, 1762, 1467. MS: EIMS *m/z* 597, 579, 561, 543, 525, 379, 361, 343, 309, 291. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: phenylhydrozone ($^1$H NMR), per-MTPA esters ($^1$H NMR), acetonide ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): KB $IC_{50}$ <1, HCT-8 $IC_{50}$ <10. Source: *Goniothalamus donnaiensis*, roots.

**donnaienin B**[32] (reported as an epimeric pair) ($C_{35}H_{64}O_8$, MW 612)




**30. donnaienin B**

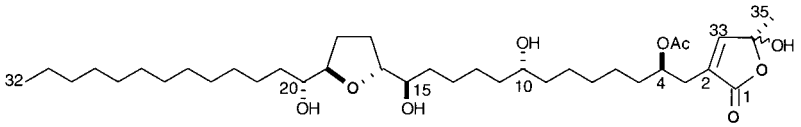
| Position | 10 | 13 | 14 | 17 | 18 | 34 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.91 m | 3.80 m | 3.41 m | 3.41 m | 3.41 m | --- |
| **$^{13}$C** (δ) | 79.6 | 82.0 | 74.7 | 74.3 | 74.2 | 105.0 |

**31. 34-*epi*-donnaienin B**

| Position | 10 | 13 | 14 | 17 | 18 | 34 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.91 m | 3.80 m | 3.41 m | 3.41 m | 3.41 m | --- |
| **$^{13}$C** (δ) | 79.4 | 82.0 | 74.7 | 74.3 | 74.2 | 105.2 |

White amorphous powder. Mp: 70−72 °C. $[\alpha]_D$: −19.0° (*c* 0.09, MeOH). UV ($\lambda_{max}$, MeOH, nm): 208 (ε 6815). IR ($\nu_{max}$, film, $cm^{-1}$): 3395, 2923, 2852, 1752, 1465. MS: EIMS *m/z* 367, 349, 331, 313, 297, 279, 261. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: phenylhydrazone ($^1$H NMR), per-MTPA esters ($^1$H NMR), acetonide ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): KB $IC_{50}$ 10. Source: *Goniothalamus donnaiensis*, roots.

**donnaienin C**[34] (reported as an epimeric pair) ($C_{37}H_{66}O_9$, MW 654)




**32. donnaienin C**

| Position | 4 | 10 | 15 | 16 | 19 | 20 | 34 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 5.04 m | 3.61 m | 3.42 m | 3.80 m | 3.80 m | 3.42 m | --- |
| **$^{13}$C** (δ) | 72.3 | 71.6 | 74.2 | 82.6 | 82.6 | 74.1 | 104.7 |

**Table 4. (Continued)**

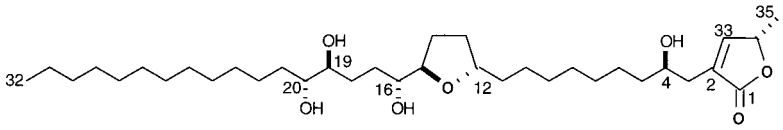
Mono-THF Acetogenins (Continued)

**33. 34-*epi*-donnaienin C**

| Position | 4 | 10 | 15 | 16 | 19 | 20 | 34 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 5.04 m | 3.61 m | 3.42 m | 3.80 m | 3.80 m | 3.42 m | --- |
| **$^{13}$C** (δ) | 72.2 | 71.5 | 74.1 | 82.5 | 82.5 | 74.0 | 104.7 |

White amorphous powder. Mp: 92−94 °C. $[\alpha]_D$: +17.4° (*c* 0.08, MeOH). IR ($\nu_{max}$, film, cm$^{-1}$): 3402, 2920, 2850, 1736. MS: EIMS *m/z* 455, 437, 419, 401, 385, 367, 349, 331, 299, 281, 269, 251, 199. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: phenylhydrazone ($^1$H NMR), per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): KB $IC_{50}$ >10, HCT-8 $IC_{50}$ >10, Bel $IC_{50}$ 7.1. Source: *Goniothalamus donnaiensis*, roots.

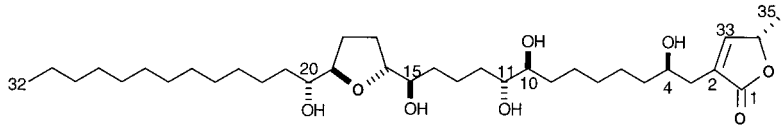
**34. glaucafilin**[112] ($C_{35}H_{65}O_7$, MW 596)




| Position | 12 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.89 m | 3.82 m | 3.45 m | 3.60 m | 3.60 m |
| **$^{13}$C** (δ) | 79.3 | 81.7 | 74.3 | 74.4 | 74.7 |

Solid. $[\alpha]_D$: +30° (*c* 0.2, $CHCl_3$). UV ($\lambda_{max}$, EtOH, nm): 209 (log ε 3.9). IR ($\nu_{max}$, film, cm$^{-1}$): 3367, 2920, 2851, 1743, 1439, 1376, 1061, 1032, 952, 756. MS: EIMS *m/z* 379, 361, 343, 309, 291, 286, 269, 251. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Annona glauca*, seeds.

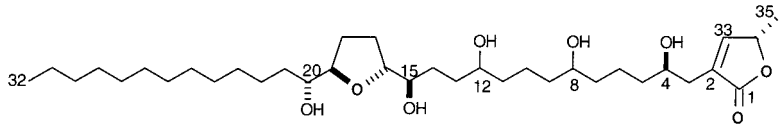
**35. annomuricin E***[113] ($C_{35}H_{64}O_8$, MW 612)




| Position | 10 | 11 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.60 m | 3.60 m | 3.45 m | 3.79 m | 3.79 m | 3.43 m |
| **$^{13}$C** (δ) | 74.2 | 74.3 | 74.5 | 82.8 | 82.6 | 73.9 |

White solid. $[\alpha]_D$: +12.5° (*c* 0.04, MeOH). UV ($\lambda_{max}$, MeOH, nm): 218 (log ε 3.76). IR ($\nu_{max}$, film, cm$^{-1}$): 3381, 2920, 2851, 1744, 1466. MS: EIMS *m/z* 377, 359, 353, 341, 335, 325, 317, 307, 289, 271, 269, 253, 251, 241, 223, 205, 199, 141, 123. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: acetonide ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ 18.4, A-549 $ED_{50}$ 1.1 × 10$^{-1}$, MCF-7 $ED_{50}$ 1.5 × 10$^{-1}$, HT-29 $ED_{50}$ 6.7 × 10$^{-1}$, A-498 $ED_{50}$ 1.4, PC-3 $ED_{50}$ 1.5 × 10$^{-1}$, PACA-2 $ED_{50}$ 2.4 × 10$^{-1}$. Source: *Annona muricata*, leaves.

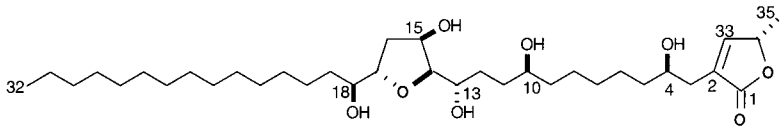
**36. muricapentocin***[113] ($C_{35}H_{64}O_8$, MW 612)




| Position | 8 | 12 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.61 m | 3.66 m | 3.45 m | 3.79 m | 3.79 m | 3.40 m |
| **$^{13}$C** (δ) | 71.3 | 71.3 | 74.3 | 82.8 | 82.3 | 74.2 |

White solid. $[\alpha]_D$: +8.0° (*c* 0.05, MeOH). UV ($\lambda_{max}$, MeOH, nm): 220 (log ε 3.54). IR ($\nu_{max}$, film, cm$^{-1}$): 3398, 2920, 2851, 1743, 1458. MS: EIMS *m/z* 377, 359, 343, 341, 325, 307, 289, 271, 269, 231, 213, 199, 195, 177, 141, 123. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: acetonide ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ 1.8, A-549 $ED_{50}$ 1.9 × 10$^{-1}$, MCF-7 $ED_{50}$ 1.9, HT-29 $ED_{50}$ 7.1 × 10$^{-2}$, A-498 $ED_{50}$ 1.7, PC-3 $ED_{50}$ 4.5 × 10$^{-1}$, PACA-2 $ED_{50}$ 5.0 × 10$^{-2}$. Source: *Annona muricata*, leaves.

**37. donnaienin**[33] ($C_{35}H_{64}O_8$, MW 612)



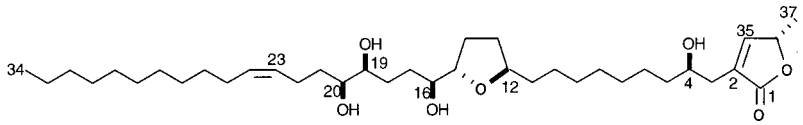

| Position | 10 | 13 | 14 | 15 | 17 | 18 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.70 m | 3.62 m | 3.75 m | 4.38 m | 4.14 m | 3.47 m |
| **$^{13}$C** (δ) | 72.0 | 71.5 | 89.0 | 73.6 | 81.2 | 73.8 |

White amorphous powder. Mp: 90−92 °C. $[\alpha]_D$: +0° (*c* 0.25, MeOH). IR ($\nu_{max}$, film, cm$^{-1}$): 3429, 2920, 2850, 1746, 1469. MS: EIMS *m/z* 385, 367, 349, 331, 313, 299, 281, 263, 245, 241, 227, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), formal acetal ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): KB $IC_{50}$ >10, HCT-8 $IC_{50}$ >10, Bel $IC_{50}$ 6.7. Source: *Goniothalamus donnaiensis*, roots.

**Table 4. (Continued)**

Mono-THF Acetogenins (Continued)

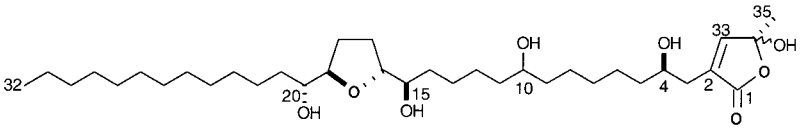
**38. glabranin**[23] ($C_{37}H_{66}O_7$, MW 622)



| Position | 12 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.82 | 3.82 | 3.40 | 3.40 | 3.40 | 5.35 | 5.38 |
| **$^{13}$C** (δ) | 79.31 | 81.72 | 74.42 | 74.23 | 74.59 | 128.60 | 130.18 |

Amorphous powder. MS: EIMS *m/z* 493, 475, 379, 361, 309, 295, 293, 291, 269, 267, 251, 249, 225. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (100 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR). Source: *Annona glabra*, seeds.

**goniodonin**[31] (reported as an epimeric pair) ($C_{35}H_{64}O_8$, MW 612)



**39. goniodonin**

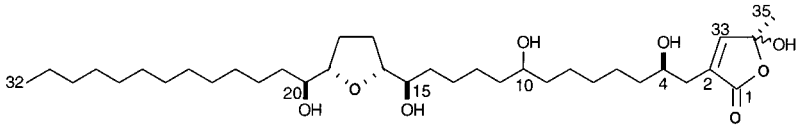
| Position | 10 | 15 | 16 | 19 | 20 | 34 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.63 m | 3.41 m | 3.78 m | 3.78 m | 3.41 m | --- |
| **$^{13}$C** (δ) | 71.5 | 74.4 | 82.5 | 82.7 | 74.3 | 105.0 |

**40. 34-*epi*-goniodonin**

| Position | 10 | 15 | 16 | 19 | 20 | 34 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.63 m | 3.41 m | 3.78 m | 3.78 m | 3.41 m | --- |
| **$^{13}$C** (δ) | 71.5 | 74.4 | 82.5 | 82.7 | 74.3 | 105.3 |

White amorphous powder. Mp: 78−80 °C. $[\alpha]_D$: +3.4° (*c* 0.17, MeOH). IR ($\nu_{max}$, film, $cm^{-1}$): 3514, 2921, 2852, 1734, 1467. MS: EIMS *m/z* 595, 577, 559, 541, 523, 413, 395, 377, 359, 341, 343, 325, 307, 289,271, 257, 239, 221, 157, 139, 121. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: phenylhydrazone ($^1$H NMR), per-MTPA esters ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): HCT-8 $IC_{50}$ <10. Source: *Goniothalamus donnaiensis*, roots.

***cis*-goniodonin**[31] (reported as an epimeric pair) ($C_{35}H_{64}O_8$, MW 612)



**41. *cis*-goniodonin**

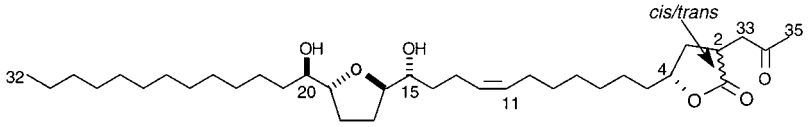
| Position | 10 | 15 | 16 | 19 | 20 | 34 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.63 m | 3.41 m | 3.78 m | 3.78 m | 3.41 m | --- |
| **$^{13}$C** (δ) | 71.4 | 74.5 | 82.6 | 82.6 | 74.2 | 105.0 |

**42. 34-*epi*-*cis*-goniodonin**

| Position | 10 | 15 | 16 | 19 | 20 | 34 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.63 m | 3.41 m | 3.78 m | 3.78 m | 3.41 m | --- |
| **$^{13}$C** (δ) | 71.4 | 74.5 | 82.6 | 82.6 | 74.2 | 105.3 |

White amorphous powder. Mp: 80−82 °C. $[\alpha]_D$: +3.8° (*c* 0.10, MeOH). IR ($\nu_{max}$, film, $cm^{-1}$): 3413, 2920, 2851, 1735, 1465. MS: EIMS *m/z* 595, 577, 559, 541, 523, 413, 395, 377, 359, 341, 343, 325, 307, 289, 271, 257, 239, 221, 157, 139, 121. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: phenylhydrazone ($^1$H NMR), per-MTPA esters ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): HCT-8 $IC_{50}$ <10. Source: *Goniothalamus donnaiensis*, roots.

**isomurisolenin**[114] (reported as cis and trans mixture) ($C_{35}H_{62}O_6$, MW 578)



**43. (2,4-*cis*)-isomurisolenin**

| Position | 11 | 12 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 5.36 | 5.38 | 3.40 m | 3.80 m | 3.80 m | 3.40 m |
| **$^{13}$C** (δ) | 130.7 | 128.9 | 74.0 | 82.6 | 82.5 | 74.0 |

**44. (2,4-*trans*)-isomurisolenin**

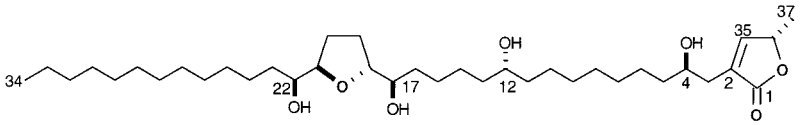
| Position | 11 | 12 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 5.36 | 5.38 | 3.40 m | 3.80 m | 3.80 m | 3.40 m |
| **$^{13}$C** (δ) | 130.7 | 128.9 | 74.0 | 82.6 | 82.5 | 74.0 |

White waxy solid. $[\alpha]_D$: +32.9° (*c* 0.31, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3500, 2910, 2860, 1760, 1710, 1460, 1250, 1050, 800. MS: EIMS *m/z* 391, 379, 373, 361, 291, 265, 211, 141. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (100 MHz, $CDCl_3$). Biological activities (μg/mL): Hep. 2, 2, 15 $ED_{50}$ $1.4 \times 10^{-1}$, Hep G2 $ED_{50}$ $4.7 \times 10^{-2}$, KB $ED_{50}$ 1, CCM2 $ED_{50}$ $8.5 \times 10^{-2}$. Source: *Annona reticulata*, seeds.

**Table 4. (Continued)**

Mono-THF Acetogenins (Continued)

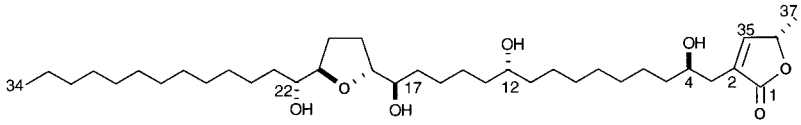
**45. annoglacin A**[26] ($C_{37}H_{69}O_7$, MW 624)



| Position | 12 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.60 m | 3.40 m | 3.80 m | 3.80 m | 3.80 m |
| **$^{13}$C** (δ) | 71.84 | 74.28 | 83.18 | 82.15 | 71.54 |

White waxy solid. $[\alpha]_D$: +15.0° ($CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 219 (log $\epsilon$ 3.62). IR ($\nu_{max}$, film, $cm^{-1}$): 3413, 2920, 2850, 2280, 1742, 1657, 1630, 1551, 1528, 1467, 1321, 1075, 850, 791. MS: EIMS *m/z* 425, 407, 355, 337, 319, 301, 269, 251, 233, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $4.9 \times 10^{-1}$, A-549 $ED_{50}$ $5.3 \times 10^{-3}$, MCF-7 $ED_{50}$ $9.6 \times 10^{-4}$, HT-29 $ED_{50}$ $5.3 \times 10^{-3}$, A-498 $ED_{50}$ $9.0 \times 10^{-1}$, PC-3 $ED_{50}$ $2.0 \times 10^{-3}$, PACA-2 $ED_{50}$ $5.1 \times 10^{-7}$. Source: *Annona glabra*, leaves.

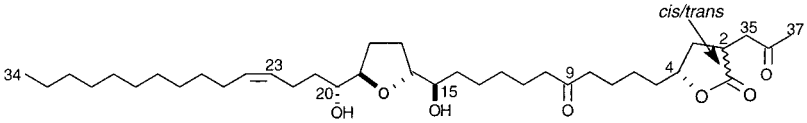
**46. annoglacin B**[26] ($C_{37}H_{69}O_7$, MW 624)



| Position | 12 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.60 m | 3.41 m | 3.80 m | 3.80 m | 3.41 m |
| **$^{13}$C** (δ) | 71.83 | 74.00 | 82.57 | 82.64 | 74.08 |

White waxy solid. $[\alpha]_D$: +15.7° ($CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 218 (log $\epsilon$ 3.48). IR ($\nu_{max}$, film, $cm^{-1}$): 3453, 2920, 2851, 1735, 1548, 1530, 1512, 1462, 1409, 1318, 1275, 1106, 1075, 1022, 965, 855, 673. MS: EIMS *m/z* 425, 407, 355, 337, 319, 301, 269, 251, 233, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $1.7 \times 10^{-1}$, A-549 $ED_{50}$ $2.8 \times 10^{-3}$, MCF-7 $ED_{50}$ $6.2 \times 10^{-4}$, HT-29 $ED_{50}$ $5.3 \times 10^{-3}$, A-498 $ED_{50}$ $4.0 \times 10^{-1}$, PC-3 $ED_{50}$ $8.4 \times 10^{-4}$, PACA-2 $ED_{50}$ $1.2 \times 10^{-6}$. Source: *Annona glabra*, leaves.

**mosinone**[105] (reported as a cis and trans mixture) ($C_{37}H_{64}O_7$, MW 620)



**47. (2,4-*cis*)-mosinone**

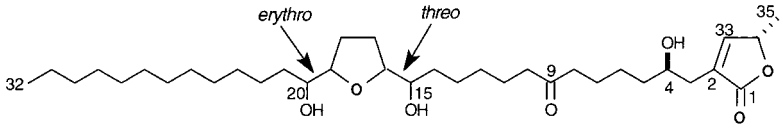
| Position | 9 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | --- | 3.40 m | 3.80 m | 3.80 m | 3.41 m | 5.36 m | 5.39 m |
| **$^{13}$C** (δ) | 210.80 | 73.49 | 82.63 | 82.63 | 73.91 | 128.92 | 130.78 |

**48. (2,4-*trans*)-mosinone**

| Position | 9 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | --- | 3.40 m | 3.80 m | 3.80 m | 3.41 m | 5.36 m | 5.39 m |
| **$^{13}$C** (δ) | 210.80 | 73.49 | 82.63 | 82.63 | 73.91 | 128.92 | 130.78 |

White waxy solid. $[\alpha]_D$: +4.8° (*c* 0.016, $CH_2Cl_2$). UV ($\lambda_{max}$, MeOH, nm): 202 (log $\epsilon$ 2.96). MS: EIMS *m/z* 395, 377, 359, 325, 307, 289, 225, 207. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $4.4 \times 10^{-1}$, A-549 $ED_{50}$ >1, MCF-7 $ED_{50}$ >1, HT-29 $ED_{50}$ >1, A-498 $ED_{50}$ >1, PC-3 $ED_{50}$ $3.2 \times 10^{-2}$, PACA-2 $ED_{50}$ $2.2 \times 10^{-1}$. Source: *Annona squamosa*, stem bark.

**49. mosin B***[105] ($C_{35}H_{62}O_7$, MW 594)



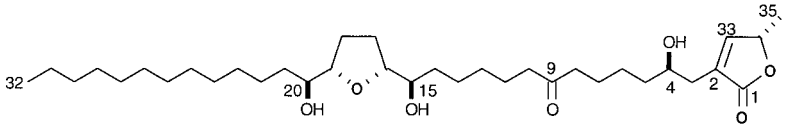
| Position | 9 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | --- | 3.38 m | 3.81 m | 3.82 m | 3.87 m |
| **$^{13}$C** (δ) | 211.38 | 74.21 | 83.18 | 82.14 | 71.51 |

White waxy solid. $[\alpha]_D$: +11.5° (*c* 0.005, $CH_2Cl_2$). UV ($\lambda_{max}$, MeOH, nm): 222 (log $\epsilon$ 3.57). MS: EIMS *m/z* 325, 307, 289, 225, 207. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $2.9 \times 10^{-1}$, A-549 $ED_{50}$ $9.4 \times 10^{-1}$, MCF-7 $ED_{50}$ >1, HT-29 $ED_{50}$ >1, A-498 $ED_{50}$ $>1 \times 10^{-1}$, PC-3 $ED_{50}$ >1, PACA-2 $ED_{50}$ $1.2 \times 10^{-4}$. Source: *Annona squamosa*, stem bark.

**Table 4. (Continued)**

Mono-THF Acetogenins (Continued)

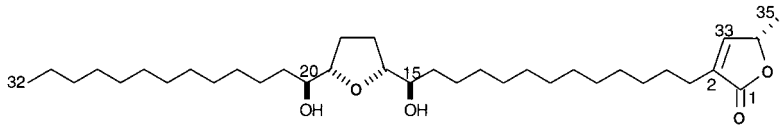
**50. mosin C**[105] ($C_{35}H_{62}O_7$, MW 594)



| Position | 9 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | --- | 3.42 m | 3.81 m | 3.81 m | 3.42 m |
| **$^{13}$C** (δ) | 211.50 | 74.38 | 82.66 | 82.66 | 74.28 |

White waxy solid. $[\alpha]_D$: −2.7° (*c* 0.007, $CH_2Cl_2$). UV ($\lambda_{max}$, MeOH, nm): 216 (log $\epsilon$ 3.56). MS: EIMS *m/z* 325, 307, 289, 225, 207. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities ($\mu$g/mL): BST $LC_{50}$ $1.5 \times 10^{-1}$, A-549 $ED_{50}$ $6.0 \times 10^{-1}$, MCF-7 $ED_{50}$ >1, HT-29 $ED_{50}$ >1, A-498 $ED_{50}$ >1, PC-3 $ED_{50}$ >1, PACA-2 $ED_{50}$ $1.2 \times 10^{-4}$. Source: *Annona squamosa*, bark stem.

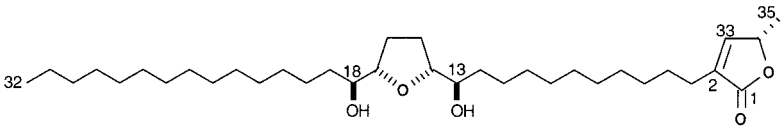
**51. *cis*-solamin***[115] ($C_{35}H_{65}O_5$, MW 564)



| Position | 15 | 16 | 19 | 20 |
|---|---|---|---|---|
| **$^1$H** (δ) | 3.41 m | 3.81 m | 3.81 m | 3.41 m |
| **$^{13}$C** (δ) | 74.3 | 82.8 | 82.8 | 74.3 |

White powder. Mp: 63−66 °C. $[\alpha]_D$: +22° (*c* 0.55, MeOH). UV ($\lambda_{max}$, MeOH, nm): 217.2 (log $\epsilon$ 3.61). IR ($\nu_{max}$, film, $cm^{-1}$): 3420, 2916, 2840, 1759, 1471, 1321, 1114, 1080, 1033, 962, 845, 751, 717. MS: EIMS *m/z* 347, 295, 251, 199, 111, 97. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Annona muricata*, roots.

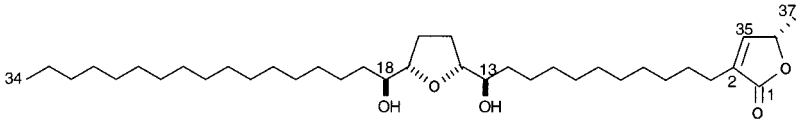
**52. *cis*-panatellin***[115] ($C_{35}H_{65}O_5$, MW 564)



| Position | 13 | 14 | 17 | 18 |
|---|---|---|---|---|
| **$^1$H** (δ) | 3.41 m | 3.81 m | 3.81 m | 3.41 m |
| **$^{13}$C** (δ) | 74.3 | 82.7 | 82.7 | 74.3 |

White powder. Mp: 62−64 °C. $[\alpha]_D$: +20° (*c* 0.60, MeOH). UV ($\lambda_{max}$, MeOH, nm): 219.6 (log $\epsilon$ 3.65). IR ($\nu_{max}$, film, $cm^{-1}$): 3420, 2917, 2841, 1760, 1471, 1324, 1120, 1078, 1033, 963, 753. MS: EIMS *m/z* 319, 297, 279, 267, 249, 227, 111, 97. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Annona muricata*, roots.

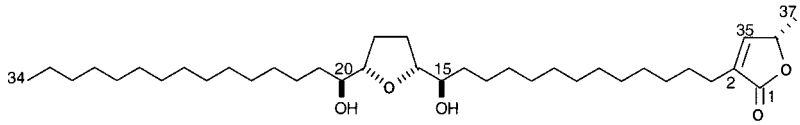
**53. *cis*-uvarimicin IV***[115] ($C_{37}H_{69}O_5$, MW 592)



| Position | 13 | 14 | 17 | 18 |
|---|---|---|---|---|
| **$^1$H** (δ) | 3.41 m | 3.82 m | 3.82 m | 3.41 m |
| **$^{13}$C** (δ) | 74.3 | 82.7 | 82.7 | 74.3 |

White powder. Mp: 60−62 °C. $[\alpha]_D$: +20° (*c* 0.15, MeOH). UV ($\lambda_{max}$, MeOH, nm): 221.3 (log $\epsilon$ 3.58). IR ($\nu_{max}$, film, $cm^{-1}$): 3422, 2916, 2839, 1762, 1473, 1325, 1124, 1077, 1034, 965, 748. MS: EIMS (*m/z*) 337, 325, 319, 267, 255, 249, 111, 97. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Annona muricata*, roots.

**54. *cis*-uvarimicin I***[115] ($C_{37}H_{69}O_5$, MW 592)



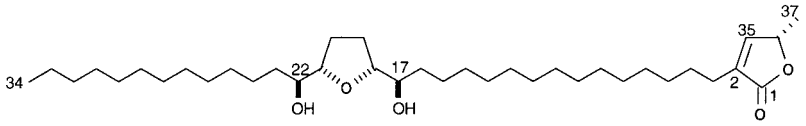
| Position | 15 | 16 | 19 | 20 |
|---|---|---|---|---|
| **$^1$H** (δ) | 3.41 m | 3.81 m | 3.81 m | 3.41 m |
| **$^{13}$C** (δ) | 74.3 | 82.7 | 82.7 | 74.3 |

White powder. Mp: 60−62 °C. $[\alpha]_D$: +18° (*c* 0.40, MeOH). UV ($\lambda_{max}$, MeOH, nm): 220.8 (log $\epsilon$ 3.63). IR ($\nu_{max}$, film, $cm^{-1}$): 3423, 2916, 2840, 1760, 1474, 1325, 1120, 1073, 1032, 968, 742, 717. MS: EIMS *m/z* 347, 297, 295, 227, 111, 97. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Annona muricata*, roots.

**Table 4. (Continued)**

Mono-THF Acetogenins (Continued)

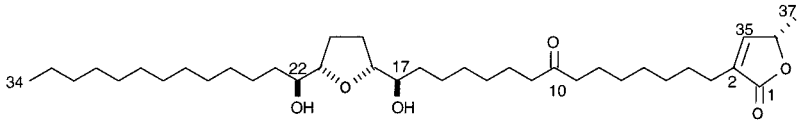
**55. *cis*-reticulatacin***[115] ($C_{37}H_{69}O_5$, MW 592)



| Position | 17 | 18 | 21 | 22 |
|---|---|---|---|---|
| $^1$**H** (δ) | 3.41 m | 3.81 m | 3.81 m | 3.41 m |
| $^{13}$**C** (δ) | 74.3 | 82.7 | 82.7 | 74.3 |

White powder. Mp: 60−62 °C. $[\alpha]_D$: +1° (*c* 0.40, MeOH). UV ($\lambda_{max}$, MeOH, nm): 220.8 (log $\epsilon$ =3.63). IR ($\nu_{max}$, film, cm$^{-1}$): 3423, 2916, 2840, 1760, 1474, 1325, 1120, 1073, 1032, 968, 742, 717. MS: EIMS *m/z* 393, 323, 269, 199, 111, 97. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Annona muricata*, roots.

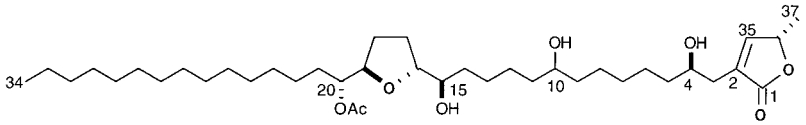
**56. *cis*-reticulatacin-10-one***[115] ($C_{37}H_{67}O_6$, MW 606)



| Position | 10 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| $^1$**H** (δ) | --- | 3.41 m | 3.81 m | 3.81 m | 3.41 m |
| $^{13}$**C** (δ) | 211.4 | 74.3 | 82.7 | 82.7 | 74.3 |

White powder. Mp: 62−64 °C. $[\alpha]_D$: +23° (*c* 0.18, MeOH). UV ($\lambda_{max}$, MeOH, nm): 219.6 (log $\epsilon$ 3.59). IR ($\nu_{max}$, film, cm$^{-1}$): 3416, 2911, 2839, 1753, 1700, 1464, 1410, 1373, 1068, 1032, 958, 915. MS: EIMS *m/z* 407, 389, 371, 337, 319, 291, 251, 223, 199, 195, 181, 111, 97. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Annona muricata*, roots.

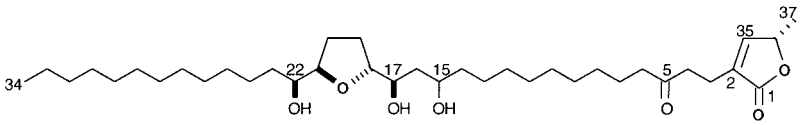
**57. dispalin**[38] ($C_{39}H_{71}O_8$, MW 666)



| Position | 10 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.40 m | 3.40 m | 3.82 m | 3.82 m | 5.09 m |
| $^{13}$**C** (δ) | 71.6 | 74.1 | 82.2 | 83.0 | 78.0 |

Waxy solid. $[\alpha]_D$: +19.6° (*c* 1.0, $CHCl_3$). MS: EIMS (TMS) *m/z* 685, 613, 543, 509, 453, 419, 363, 339, 295, 279, 269, 209, 205, 213, 197, 123. NMR: $^1$H NMR (270 MHz, $CDCl_3$), $^{13}$C NMR (54 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), TMS (EIMS). Source: *Disepalum anomalum*, stem bark.

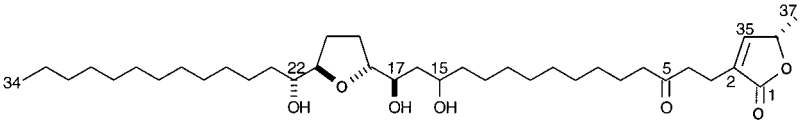
**58. tonkinin A***[66] ($C_{37}H_{66}O_7$, MW 622)



| Position | 5 | 15 | 16 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | --- | 3.80 m | 1.54 m | 3.73 m | 3.89 m | 3.89 m | 3.89 m |
| $^{13}$**C** (δ) | 209.45 | 68.62 | 37.58 | 71.53 | 83.12 | 82.28 | 71.83 |

Crystal. Mp: 98−100 °C. $[\alpha]_D$: +20.09° (*c* 0.112, $CHCl_3$). IR ($\nu_{max}$, film, cm$^{-1}$): 3357, 2919, 2849, 1751, 1714, 1070. MS: EIMS *m/z* 569, 405, 387, 353, 335, 309, 291, 199, 181, 153. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), TMS (EIMS). Biological activities ($\mu$g/mL): HCT-8 $IC_{50}$ $5.9 \times 10^{-1}$, HL-60 $IC_{50}$ $1.6 \times 10^{-2}$, KB $IC_{50}$ >10, A2780 $IC_{50}$ >10. Source: *Uvaria tonkinensis*, roots.

**59. tonkinin B***[66] ($C_{37}H_{66}O_7$, MW 622)



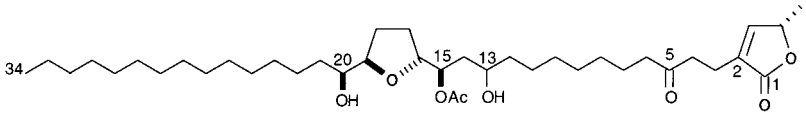
| Position | 5 | 15 | 16 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | --- | 3.81 m | 1.60 m | 3.76 m | 3.88 m | 3.88 m | 3.41 m |
| $^{13}$**C** (δ) | 209.44 | 68.46 | 37.56 | 71.49 | 82.80 | 82.47 | 71.44 |

Waxy solid. Mp: 95−96 °C. $[\alpha]_D$: +28.20° (*c* 0.098, $CHCl_3$). IR ($\nu_{max}$, film, cm$^{-1}$): 3410, 2920, 2849, 1738, 1711, 1068, 1029. MS: EIMS *m/z* 423, 405, 387, 353, 335, 309, 291, 269, 181, 168, 153. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), TMS (EIMS). Biological activities ($\mu$g/mL): HCT-8 $IC_{50}$ 2.4, HL-60 $IC_{50}$ $6.0 \times 10^{-2}$, KB $IC_{50}$ >10, A2780 $IC_{50}$ >10. Source: *Uvaria tonkinensis*, roots.

**Table 4. (Continued)**

Mono-THF Acetogenins (Continued)

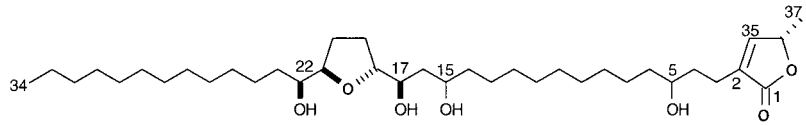
**60. tonkinin C***[66] ($C_{39}H_{68}O_8$, MW 664)



| Position | 5 | 13 | 14 | 15 | 19 | 20 |
|---|---|---|---|---|---|---|
| $^1$**H** (δ) | --- | 3.36 m | 1.53 m | 5.08 m | 3.84 m | 3.84 m |
| $^{13}$**C** (δ) | 209.40 | 70.37 | 38.58 | 71.54 | 82.47 | 71.44 |

Amorphous powder. Mp: 40−42 °C. $[\alpha]_D$: +10.8° (*c* 0.119, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3430, 2919, 2850, 1759, 1723, 1468, 1377, 1255, 1077, 1030. MS: EIMS *m/z* 586, 568, 479, 465, 461, 447, 405, 395, 387, 351, 335, 269, 181, 168, 153. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), per-MTPA esters ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): HCT-8 $IC_{50}$ 8.6 × $10^{-1}$, HL-60 $IC_{50}$ 4.2 × $10^{-4}$, KB $IC_{50}$ >10, A2780 $IC_{50}$ >10. Source: *Uvaria tonkinensis*, roots.

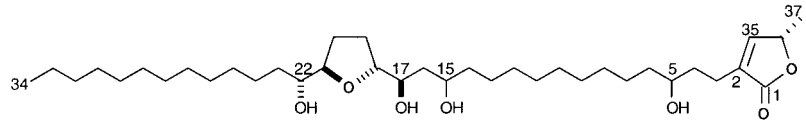
**61. tonkinesin A***[66] ($C_{37}H_{68}O_7$, MW 624)



| Position | 5 | 15 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.60 m | 3.80 m | 3.73 m | 3.90 m | 3.90 m | 3.90 m |
| $^{13}$**C** (δ) | 70.83 | 68.78 | 71.89 | 83.07 | 82.28 | 71.67 |

Powder. Mp: 97−99 °C. $[\alpha]_D$: +26.92° (*c* 0.026, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3379, 2918, 2850, 1741. MS: EIMS *m/z* 407, 389, 355, 337, 311, 293, 269, 155. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: TMS (EIMS). Source: *Uvaria tonkinesis*, roots.

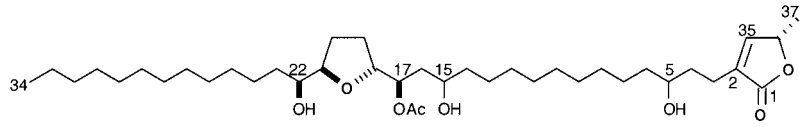
**62. tonkinesin B***[66] ($C_{37}H_{68}O_7$, MW 624)



| Position | 5 | 15 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.81 m | 3.81 m | 3.75 m | 3.88 m | 3.88 m | 3.41 m |
| $^{13}$**C** (δ) | 70.86 | 68.61 | 71.56 | 82.75 | 82.61 | 74.10 |

Powder. Mp: 80−81 °C. $[\alpha]_D$: +24.5° (*c* 0.049, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3433, 2920, 2850, 1747, 1082. MS: EIMS *m/z* 625, 607, 589, 571, 553, 425, 407, 389, 371, 355, 337, 319, 311, 293, 269,155. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: TMS (EIMS). Source: *Uvaria tonkinesis*, roots.

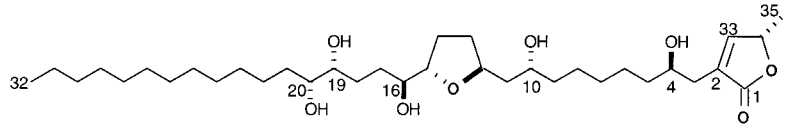
**63. tonkinesin C***[66] ($C_{39}H_{70}O_8$, MW 666)



| Position | 5 | 15 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.55 m | 3.36 m | 5.06 m | 3.84 m | 3.84 m | 3.84 m |
| $^{13}$**C** (δ) | 70.73 | 70.39 | 71.35 | 82.79 | 82.66 | 71.54 |

Oil. $[\alpha]_D$: +25.2° (*c* 0.651, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3465, 2923, 2852, 1737, 1245. MS: EIMS *m/z* 467, 407, 389, 371, 337, 319, 311, 301, 293, 155. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: TMS (EIMS). Source: *Uvaria tonkinesis*, roots.

**64. annopentocin A**[116] ($C_{35}H_{64}O_8$, MW 612)



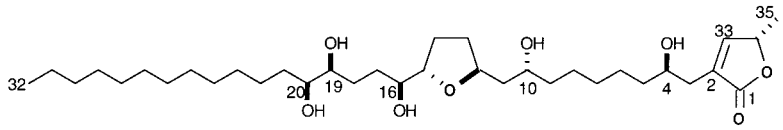
| Position | 10 | 12 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.80 m | 4.18 m | 3.91 m | 3.45 m | 3.42 m | 3.42 m |
| $^{13}$**C** (δ) | 71.6 | 80.0 | 82.4 | 73.9 | 74.3 | 74.5 |

White amorphous powder. $[\alpha]_D$: +12° (*c* 14, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 215 (ε 9600). IR ($\nu_{max}$, film, $cm^{-1}$): 3395, 2930, 2855, 1745, 1470. MS: EIMS (TMS)*m/z* 701, 611, 521, 503, 469, 431, 413, 385, 379, 341, 323, 295, 289, 271, 213, 181. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: acetonide ($^1$H NMR), per-MTPA esters ($^1$H NMR), peracetate ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ 8.9, A-549 $ED_{50}$ 1.7 × $10^{-1}$, MCF-7 $ED_{50}$ 1.8 × $10^1$, HT-29 $ED_{50}$ 1.6, A-498 $ED_{50}$ 6.1 × $10^{-1}$, PC-3 $ED_{50}$ 1.1, PACA-2 $ED_{50}$ 3.6 × $10^{-2}$. Source: *Annona muricata*, leaves.

**Table 4. (Continued)**

Mono-THF Acetogenins (Continued)

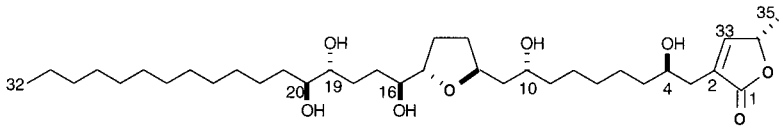
**65. annopentocin B**[116] ($C_{35}H_{64}O_8$, MW 612)




| Position | 10 | 12 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.80 m | 4.18 m | 3.90 m | 3.47 m | 3.41 m | 3.41 m |
| **$^{13}$C** (δ) | 71.6 | 80.0 | 82.4 | 73.9 | 74.3 | 74.6 |

White oil. $[\alpha]_D$: +15° (*c* 10, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 214 ($\epsilon$ 9800). IR ($\nu_{max}$, film, $cm^{-1}$): 3400, 2935, 2845, 1749, 1465. MS: EIMS (TMS)*m/z* 701, 611, 521, 503, 469, 431, 413, 385, 379, 341, 323, 295, 289, 271, 213, 181. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: acetonide ($^1$H NMR), per-MTPA esters ($^1$H NMR), peracetate ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ 1.1 × $10^1$, A-549 $ED_{50}$ 2.7 × $10^{-2}$, MCF-7 $ED_{50}$ 3.6, HT-29 $ED_{50}$ 1.6, A-498 $ED_{50}$ 3.8 × $10^{-1}$, PC-3 $ED_{50}$ 2.1 × $10^{-1}$, PACA-2 $ED_{50}$ 1.6 × $10^{-1}$. Source: *Annona muricata*, leaves.

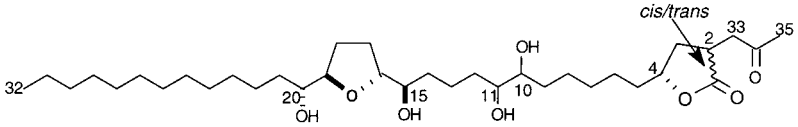
**66. annopentocin C**[116] ($C_{35}H_{64}O_8$, MW 612)




| Position | 10 | 12 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.80 m | 4.18 m | 3.92m | 3.48 m | 3.58 m | 3.62 m |
| **$^{13}$C** (δ) | 71.7 | 80.0 | 82.4 | 73.8 | 74.6 | 74.8 |

White oil. $[\alpha]_D$: +9° (*c* 11, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 214 ($\epsilon$ 9750). IR ($\nu_{max}$, film, $cm^{-1}$): 3410, 2930, 2835, 1741, 1455. MS: EIMS (TMS)*m/z* 701, 611, 521, 503, 469, 431, 413, 385, 379, 341, 323, 295, 289, 271, 213, 181. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: acetonide ($^1$H NMR), per-MTPA esters ($^1$H NMR), peracetate ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ 1.4 × $10^1$, A-549 $ED_{50}$ 2.1 × $10^{-2}$, MCF-7 $ED_{50}$ 3.0 × $10^{-1}$, HT-29 $ED_{50}$ 1.2, A-498 $ED_{50}$ 2.6 × $10^{-1}$, PC-3 $ED_{50}$ 2.3 × $10^{-1}$, PACA-2 $ED_{50}$ 4.3 × $10^{-1}$. Source: *Annona muricata*, leaves.

**annomuricin-D-one**[116] (reported as a cis and trans mixture) ($C_{35}H_{64}O_8$, MW 612)




**67. (2,4-*cis*)-annomuricin-D-one**

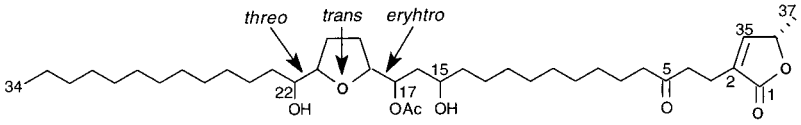
| Position | 10 | 11 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.45 m | 3.45 m | 3.41 m | 3.80 m | 3.80 m | 3.41 m |
| **$^{13}$C** (δ) | 73.9 | 74.3 | 74.4 | 82.25 | 82.7 | 74.5 |

**68. (2,4-*trans*)-annomuricin-D-one**

| Position | 10 | 11 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.45 m | 3.45 m | 3.41 m | 3.80 m | 3.80 m | 3.41 m |
| **$^{13}$C** (δ) | 73.9 | 74.3 | 74.4 | 82.5 | 82.7 | 74.5 |

White powder. $[\alpha]_D$: +15° (*c* 10, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 205 ($\epsilon$ 7750). IR ($\nu_{max}$, film, $cm^{-1}$): 3425, 2925, 2835, 1765, 1715, 1455, 1367. MS: EIMS (TMS) *m/z* 629,587, 559, 539,497, 469, 449, 407, 379, 359, 341, 317, 313, 289, 271, 251, 223, 181. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR), formal acetal ($^1$H NMR), TMS (EIMS). Biological activities: BST $LC_{50}$ 4.8, A-549 $ED_{50}$ <$10^{-2}$, MCF-7 $ED_{50}$ 6.1 × $10^{-1}$, HT-29 $ED_{50}$ <$10^{-2}$, A-498 $ED_{50}$ 1.2 × $10^{-1}$, PC-3 $ED_{50}$ 1.3, PACA-2 $ED_{50}$ <$10^{-2}$. Source: *Annona muricata*, leaves.

**69. uvaribonone***[134] ($C_{39}H_{68}O_8$ MW 664)



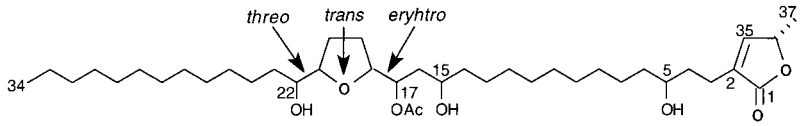

| Position | 5 | 15 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | - | 3.42 m | 5.10 m | 3.83 m | 3.83 m | 3.39 m |
| **$^{13}$C** (δ) | 209.3 | 70.1 | 71.7 | 82.8 | 82.9 | 74.1 |

Waxy solid. Mp: 42−44 °C. $[\alpha]_D$: +15° (*c* 0.06, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3470, 2925, 2825, 1755, 1740, 1720, 1661. MS: EIMS (TMS)*m/z* 604, 586, 568, 465, 405, 395, 387, 335, 317, 309, 291, 269, 251, 199, 181, 153, 125. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: TMS (EIMS). Source: *Uvaria boniana*, bark.

**Table 4. (Continued)**

Mono-THF Acetogenins (Continued)

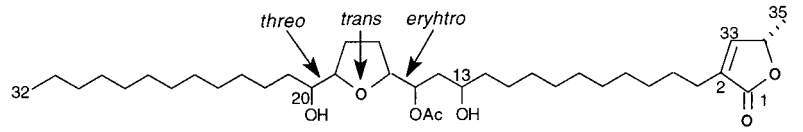
**70. uvaribonin***[134] ($C_{39}H_{70}O_8$ MW 666)




| Position | 5 | 15 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.58 m | 3.40 m | 5.10 m | 3.82 m | 3.82 m | 3.40 m |
| **$^{13}$C** (δ) | 70.8 | 70.1 | 71.7 | 82.2 | 82.9 | 74.1 |

Waxy solid. Mp: 50−52 °C. $[\alpha]_D$: +13° (*c* 0.06, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3450, 2935, 2862, 1755, 1742, 1725. MS: EIMS (TMS) *m/z* 588, 570, 552, 467, 407, 397, 389, 371, 337, 319, 311, 301, 293, 269, 251, 199, 181, 155, 137, 111, 109, 97. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: TMS (EIMS). Source: *Uvaria boniana*, bark.

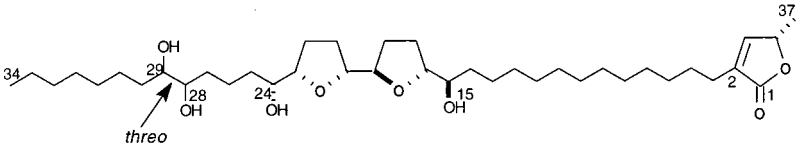
**71. uvaribonianin***[134] ($C_{37}H_{66}O_8$ MW 644)




| Position | 13 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.41 m | 5.10 m | 3.82 m | 3.82 m | 3.40 m |
| **$^{13}$C** (δ) | 70.1 | 71.7 | 82.8 | 82.9 | 74.1 |

Waxy solid. $[\alpha]_D$: +13° (*c* 0.06, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3480, 2928, 2830, 1755. MS: EIMS (TMS) *m/z* 562, 544, 526, 423, 363, 353, 345, 293, 275, 269, 267, 251, 249, 199, 181, 111, 97. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: TMS (EIMS). Source: *Uvaria boniana*, bark.

**72. uvarigin**[135] ($C_{37}H_{68}O_6$ MW 608)

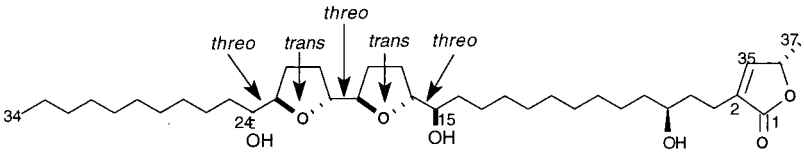



| Position | 15 | 16 | 19 | 20 | 23 | 24 | 28 | 29 |
|---|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.36 m | 3.84 m | 3.84 m | 3.84 m | 3.91 m | 3.82 m | 3.36 m | 3.36m |
| **$^{13}$C** (δ) | 73.9 | 83.3 | 82.5 | 82.0 | 82.6 | 71.4 | 74.0 | 74.3 |

Crystal. Mp: 85−86 °C. $[\alpha]_D$: +30.5° (*c* 0.02, MeOH). IR ($\nu_{max}$, film, $cm^{-1}$): 3445, 2915, 2850, 1745, 1630, 1460, 1065. MS: EIMS (TMS) *m/z* 554, 409, 391, 373, 355, 343, 339, 321, 295, 269, 251, 111, 83. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: TMS (EIMS). Source: *Uvaria grandiflora*, roots.

Adjacent Bis-THF Acetogenins

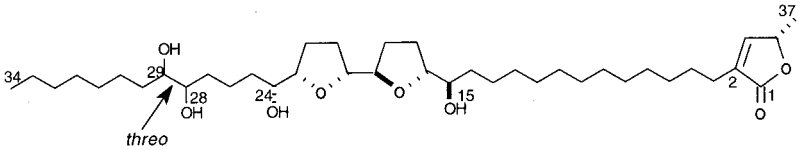
**73. uvarigrandin A**[135] ($C_{37}H_{66}O_7$ MW 622)




| Position | 5 | 15 | 16 | 23 | 24 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.58 | 3.39 | 3.83 | 3.83 | 3.39 |
| **$^{13}$C** (δ) | 70.8 | 74.0 | 83.1 | 83.1 | 74.0 |

Waxy solid. Mp: 30−33 °C. $[\alpha]_D$: +28.5° (*c* 0.11, MeOH). IR ($\nu_{max}$, film, $cm^{-1}$): 3450, 2930, 1760, 1660, 1470, 1325, 1070. MS: EIMS (TMS) *m/z* 554, 409, 391, 373, 355, 343, 339, 321, 295, 269, 251, 111, 83. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: TMS (EIMS). Source: *Uvaria grandiflora*, roots.

**74. spinencin**[27] ($C_{37}H_{66}O_8$, MW 638)



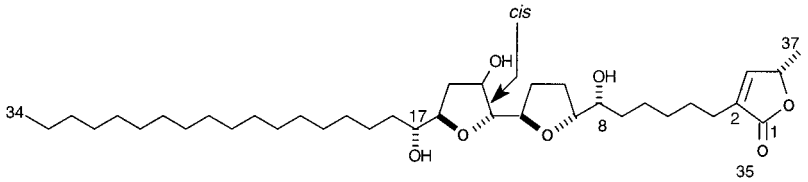

| Position | 15 | 16 | 19 | 20 | 23 | 24 | 28 | 29 |
|---|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.36 m | 3.84 m | 3.84 m | 3.84 m | 3.91 m | 3.82 m | 3.36 m | 3.36m |
| **$^{13}$C** (δ) | 73.9 | 83.3 | 82.5 | 82.0 | 82.6 | 71.4 | 74.0 | 74.3 |

Transparent oil. $[\alpha]_D$: +24° (*c* 0.1, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 204.6 (log $\epsilon$ 3.86). IR ($\nu_{max}$, film, $cm^{-1}$): 3785, 3677, 2995, 2860, 1751. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), acetonide ($^1$H NMR). Source: *Annona spinescens*, seeds.

**Table 4. (Continued)**

Adjacent Bis-THF Acetogenins (Continued)

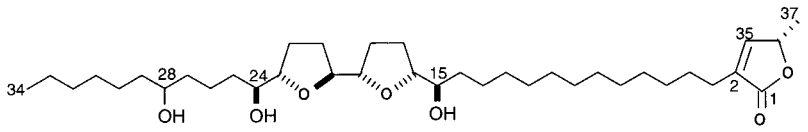
**75. mucoxin***[9] ($C_{37}H_{67}O_7$, MW 622)




| Position | 8 | 9 | 12 | 13 | 14 | 16 | 17 |
|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.42 m | 3.95 m | 4.31 m | 3.71 m | 4.32 m | 4.04 m | 3.53 m |
| $^{13}$**C** (δ) | 73.6 | 83.4 | 78.9 | 83.5 | 72.8 | 79.9 | 73.7 |

Colorless oil. MS: EIMS *m/z* 337, 319, 269, 267, 251, 249, 197. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): A-549 $ED_{50}$ $3.6 \times 10^{-2}$, MCF-7 $ED_{50}$ $3.7 \times 10^{-3}$, HT-29 $ED_{50}$ $6.1 \times 10^{-1}$, A-498 $ED_{50}$ $8.4 \times 10^{-1}$, PC-3 $ED_{50}$ $3.1 \times 10^{-1}$, PACA-2 $ED_{50}$ $3.3 \times 10^{-1}$. Source: *Rollinia mucosa*, leaves.

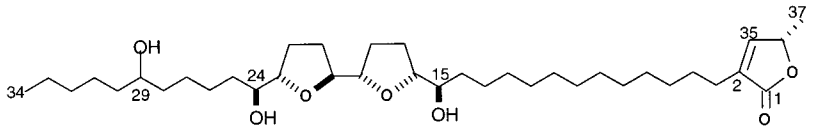
**76. carolin A***[28] ($C_{37}H_{66}O_7$, MW 622)




| Position | 15 | 16 | 19 | 20 | 23 | 24 | 28 |
|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.39 m | 3.87 m | 3.87 m | 3.87 m | 3.93 m | 3.78 m | 3.56 m |
| $^{13}$**C** (δ) | 73.9 | 83.0 | 82.6 | 82.4 | 81.9 | 71.6 | 71.3 |

Transparent oil. $[\alpha]_D$: +22° (*c* 1, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 208 (log ε 4.6). IR ($\nu_{max}$, film, $cm^{-1}$): 3675, 3474, 1749, 1652, 1458. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: per-acetate ($^1$H NMR), formal acetal ($^1$H NMR). Biological activities (μg/mL): KB $ED_{50}$ $1 \times 10^{-7}$, VERO KB $ED_{50}$ $2 \times 10^{-3}$. Source: *Annona spinescens*, seeds.

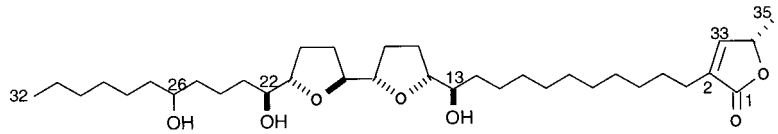
**77. carolin B***[28] ($C_{37}H_{66}O_7$, MW 622)




| Position | 15 | 16 | 19 | 20 | 23 | 24 | 29 |
|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.35 m | 3.89 m | 3.89 m | 3.89 m | 3.90 m | 3.78 m | 3.55 m |
| $^{13}$**C** (δ) | 73.9 | 83.0 | 82.6 | 82.4 | 81.9 | 71.5 | 71.3 |

Transparent oil. $[\alpha]_D$: +5° (*c* 0.5, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 208 (log ε 3.6). IR ($\nu_{max}$, film, $cm^{-1}$): 3677. 3575, 1753, 1619. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR). Biological activities (μg/mL): KB $ED_{50}$ $5 \times 10^{-6}$, VERO $ED_{50}$ $3.7 \times 10^{-3}$. Source: *Annona spinescens*, seeds.

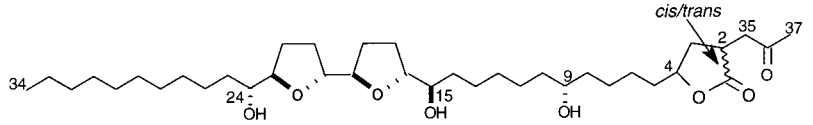
**78. carolin C***[28] ($C_{35}H_{62}O_7$, MW 594)




| Position | 13 | 14 | 17 | 18 | 21 | 22 | 26 |
|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.43 m | 3.85 m | 3.90 m | 3.90 m | 3.91 m | 3.79 m | 3.61 m |
| $^{13}$**C** (δ) | 73.9 | 83.2 | 82.6 | 82.0 | 82.7 | 71.2 | 71.5 |

Transparent oil. $[\alpha]_D$: +8° (*c* 0.5, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 205 (log ε 4.0). IR ($\nu_{max}$, film, $cm^{-1}$): 3657, 2479, 1751, 1625. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR). Biological activities (μg/mL): KB $ED_{50}$ $2 \times 10^{-4}$, VERO $ED_{50}$ $5 \times 10^{-2}$. Source: *Annona spinescens*, seeds.

**9-hydroxyasimicinone**[42] (reported as a cis and trans mixture) ($C_{37}H_{66}O_8$, MW 638)




**79. (2,4-*cis*)-9-hydroxyasimicinone**

| Position | 9 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.58 m | 3.39 m | 3.85 m | 3.85 m | 3.85 m | 3.85 m | 3.39 m |
| $^{13}$**C** (δ) | 71.64 | 74.05 | 83.06 | 81.79 | 81.76 | 83.16 | 73.96 |

**Table 4. (Continued)**

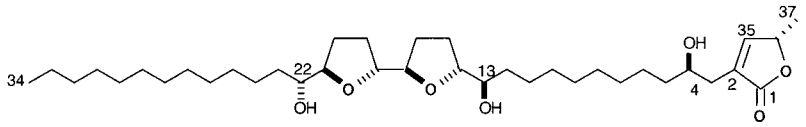
Adjacent Bis-THF Acetogenins (Continued)

**80. (2,4-*trans*)-9-hydroxyasimicinone**

| Position | 9 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.58 m | 3.39 m | 3.85 m | 3.85 m | 3.85 m | 3.85 m | 3.39 m |
| **$^{13}$C** (δ) | 71.64 | 74.05 | 83.06 | 81.79 | 81.76 | 83.16 | 73.96 |

White wax. $[\alpha]_D$: +19.3° (*c* 0.26, $CH_2Cl_2$). UV ($\lambda_{max}$, MeOH, nm): 203 (log $\epsilon$ 2.98). IR ($\nu_{max}$, film, $cm^{-1}$): 3460, 2930, 1769, 1714, 1463. MS: EIMS *m/z* 227, 209, 309, 291, 273, 379, 361. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $3.5 \times 10^{-1}$, A-549 $ED_{50}$ $7.7 \times 10^{-2}$, MCF-7 $ED_{50}$ $1.2 \times 10^{-3}$, HT-29 $ED_{50}$ 1.4, A-498 $ED_{50}$ $3.6 \times 10^{-2}$, PC-3 $ED_{50}$ $1.6 \times 10^{-1}$, PACA-2 $ED_{50}$ $1.7 \times 10^{-4}$. Source: *Annona squamosa*, stem bark.

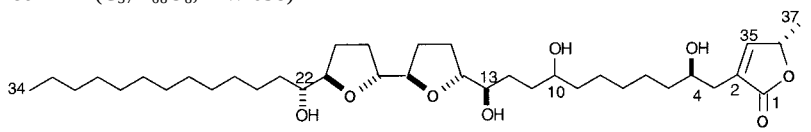
**81. glaucanetin***[117] ($C_{37}H_{66}O_7$, MW 622)



| Position | 13 | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.39 m | 3.85 m | 3.85 m | 3.85 m | 3.85 m | 3.39 m |
| **$^{13}$C** (δ) | 74.07 | 83.15 | 81.74 | 81.74 | 83.15 | 74.07 |

Solid. $[\alpha]_D$: +15° (*c* 0.20, MeOH). UV ($\lambda_{max}$, MeOH, nm): 209 (log $\epsilon$ 3.94). IR ($\nu_{max}$, film, $cm^{-1}$): 3349, 2930, 2857, 1745, 1652, 1515, 1464, 1320, 1204, 1069. MS: EIMS *m/z* 387, 335, 321, 317, 283, 269, 265, 247, 171, 141, 97. NMR: $^1$H NMR (200 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), TMS (EIMS). Source: *Annona glauca*, seeds.

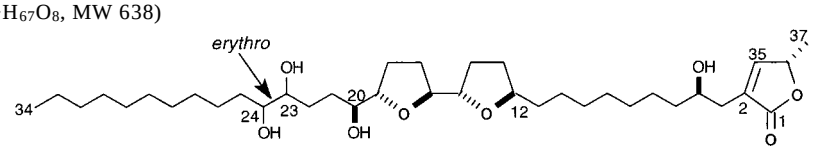
**82. 10-hydroxyglaucanetin***[117] ($C_{37}H_{68}O_8$, MW 638)



| Position | 10 | 13 | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.60 m | 3.39 m | 3.85 m | 3.85 m | 3.85 m | 3.85 m | 3.39 m |
| **$^{13}$C** (δ) | 71.55 | 74.04 | 82.82 | 81.71 | 81.83 | 83.19 | 74.04 |

Solid. $[\alpha]_D$: +17° (*c* 0.23, MeOH). UV ($\lambda_{max}$, MeOH, nm): 210 (log $\epsilon$ 4.00). IR ($\nu_{max}$, film, $cm^{-1}$): 3423, 2933, 2859, 1754, 1458, 1320, 1066. MS: EIMS *m/z* 421, 403, 385, 351, 339, 333, 321, 317, 281, 269, 263, 251, 245, 241, 205, 199, 181, 141, 97. NMR: $^1$H NMR (200 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), TMS (EIMS). Source: *Annona glauca*, seeds.

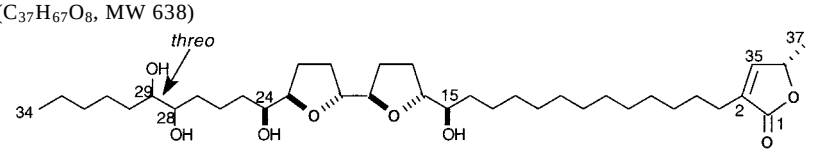
**83. bulladecin***[118] ($C_{37}H_{67}O_8$, MW 638)



| Position | 12 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.93 m | 3.87 m | 3.87 m | 3.87 m | 3.47 m | 3.60 m | 3.60 m |
| **$^{13}$C** (δ) | 79.9 | 81.2 | 82.1 | 82.7 | 74.2 | 74.5 | 74.7 |

White solid. $[\alpha]_D$: +11° (*c* 0.20, MeOH). UV ($\lambda_{max}$, MeOH, nm): 214 (log $\epsilon$ 4.85). MS: EIMS *m/z* 449, 431, 413, 379, 361, 291, 141, 123, 97. NMR: $^1$H NMR (200 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: per-acetate ($^1$H NMR), acetonide ($^1$H NMR). Source: *Annona atemoya*, seeds.

**84. atemotetrolin***[118] ($C_{37}H_{67}O_8$, MW 638)



| Position | 15 | 16 | 19 | 20 | 23 | 24 | 28 | 29 |
|---|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.40 m | 3.82 m | 3.92 m | 3.92 m | 3.92 m | 3.87 m | 3.40 m | 3.40 m |
| **$^{13}$C** (δ) | 74.2 | 83.2 | 82.6 | 82.1 | 82.8 | 71.4 | 74.2 | 74.2 |

Transparent oil. $[\alpha]_D$: +23° (*c* 0.20, MeOH). UV ($\lambda_{max}$, MeOH, nm): 219 (log $\epsilon$ 3.54). IR ($\nu_{max}$, film, $cm^{-1}$): 3447, 2927, 2851, 1756. MS: EIMS *m/z* 567, 533, 519, 501, 495, 483, 465, 435, 417, 399, 365, 347, 255, 237, 185, 167, 149, 101. NMR: $^1$H NMR (200 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), acetonide ($^1$H NMR). Source: *Annona atemoya*, seeds.

**trilobacinone**[119] (reported as a cis and trans mixture) ($C_{37}H_{66}O_7$, MW 622)

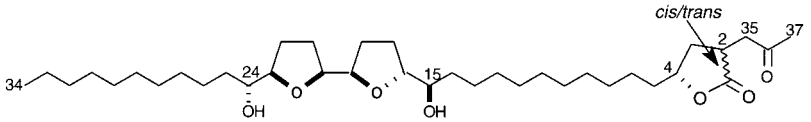


**Table 4. (Continued)**

Adjacent Bis-THF Acetogenins (Continued)

**85. (2,4-*cis*)-trilobacinone**

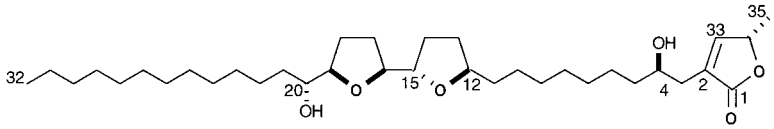
| Position | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.37 ddd | 3.83 m | 3.97 ddd | 4.04 ddd | 3.83 m | 3.39 ddd |
| $^{13}$**C** (δ) | 74.5 | 83.2 | 81.7 | 80.8 | 82.6 | 74.0 |

**86. (2,4-*trans*)-trilobacinone**

| Position | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.37 ddd | 3.83 m | 3.97 ddd | 4.04 ddd | 3.83 m | 3.39 ddd |
| $^{13}$**C** (δ) | 74.5 | 83.2 | 81.7 | 80.8 | 82.6 | 73.8 |

White wax. $[\alpha]_D$: +17.3° (*c* 0.22, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3354, 2923, 2845, 1742, 1722, 1591, 1456, 1403, 1361, 1170, 1121, 1116, 1079. MS: EIMS (TMS) *m/z* 523, 453, 433, 383,363, 313, 293, 243, 223. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ $2.0 \times 10^{-2}$, A-549 $ED_{50}$ $4.6 \times 10^{-4}$, MCF-7 $ED_{50}$ $1.3 \times 10^{-8}$, HT-29 $ED_{50}$ 1.6, A-498 $ED_{50}$ $4.9 \times 10^{-1}$, PC-3 $ED_{50}$ 2.8, PACA-2 $ED_{50}$ $6.9 \times 10^{-2}$. Source: *Asimina triloba*, stem bark.

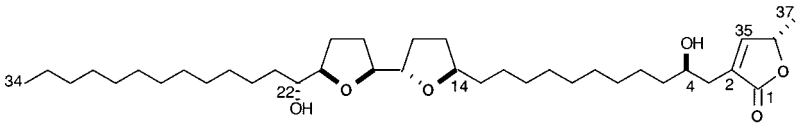
**87. rollidecin C**[55] ($C_{35}H_{62}O_6$, MW 578)




| Position | 12 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.92 m | 3.92 m | 3.92 m | 3.92 m | 3.36 m |
| $^{13}$**C** (δ) | 80.1 | 80.7 | 81.5 | 82.5 | 74.7 |

White waxy solid. Mp: 42−43 °C. UV ($\lambda_{max}$, MeOH, nm): 222 (log ε 3.50). IR ($\nu_{max}$, film, $cm^{-1}$): 3345, 2936, 2859, 1741, 1674, 1071. MS: EIMS *m/z* 409, 379, 309, 291, 141, 123. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Biological activities (μg/mL): A-549 $ED_{50}$ 1.3, MCF-7 $ED_{50}$ 1.1, HT-29 $ED_{50}$ $6.3 \times 10^{-2}$, A-498 $ED_{50}$ 1.4, PC-3 $ED_{50}$ $2.9 \times 10^{-1}$, PACA-2 $ED_{50}$ $1.1 \times 10^{-1}$. Source: *Rollinia mucosa*, leaves.

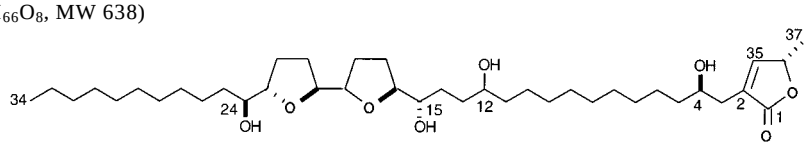
**88. rollidecin D**[55] ($C_{37}H_{66}O_6$, MW 606)




| Position | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.92 m | 3.92 m | 3.92 m | 3.92 m | 3.36 m |
| $^{13}$**C** (δ) | 80.2 | 80.7 | 81.6 | 82.6 | 74.8 |

White waxy solid. Mp: 41−42 °C. UV ($\lambda_{max}$, MeOH, nm): 222 (log ε 3.50). IR ($\nu_{max}$, film, $cm^{-1}$): 3345, 2936, 2859, 1741, 1674, 1071. MS: EIMS *m/z* 437, 407, 337, 319, 141, 123. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Biological activities (μg/mL): A-549 $ED_{50}$ 5.9, MCF-7 $ED_{50}$ 5.0, HT-29 $ED_{50}$ 5.4, A-498 $ED_{50}$ 4.0, PC-3 $ED_{50}$ 1.9, PACA-2 $ED_{50}$ 1.0. Source: *Rollinia mucosa*, leaves.

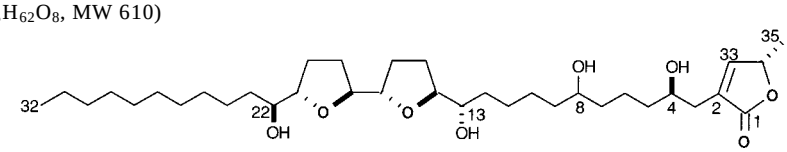
**89. articulin**[30] ($C_{37}H_{66}O_8$, MW 638)




| Position | 12 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.59 m | 3.39 m | 3.84 m | 3.84 m | 3.84 m | 3.84 m | 3.39 m |
| $^{13}$**C** (δ) | 71.67 | 74.04 | 83.17 | 81.74 | 81.85 | 82.84 | 74.15 |

Solid. $[\alpha]_D$: +9.6° (*c* 0.27, MeOH). IR ($\nu_{max}$, film, $cm^{-1}$): 3450, 2920, 2840, 1750, 1600, 1450, 1300, 1060, 1020, 920. MS: EIMS *m/z* 467, 449, 397, 379, 369, 309, 269, 241, 171, 141. NMR: $^1$H NMR (200 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): A-549 $ED_{50}$ $6 \times 10^{-3}$, MCF-7 $ED_{50}$ $4 \times 10^{-3}$, HT-29 $ED_{50}$ $6 \times 10^{-1}$, RPMI-7951 $ED_{50}$ $10^{-3}$, U-251 $ED_{50}$ $10^{-2}$. Source: *Annona crassiflora*, seeds.

**90. annonisin**[120] ($C_{35}H_{62}O_8$, MW 610)



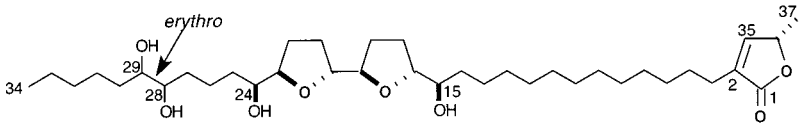

| Position | 8 | 13 | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.59 m | 3.38 m | 3.83 m | 3.83 m | 3.83 m | 3.83 m | 3.38 m |
| $^{13}$**C** (δ) | 71.4 | 74.1 | 83.2 | 81.8 | 81.8 | 83.2 | 74.1 |

White solid. $[\alpha]_D$: +30° (*c* 0.20, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 209 (log ε 3.90). IR ($\nu_{max}$, film, $cm^{-1}$): 3432, 2923, 2850, 1748, 1436, 1372, 1068, 1032, 957, 753. MS: CIMS (methane) *m/z* 611, 593, 575, 557, 539, 521, 463, 439, 421, 403, 385, 369, 351, 333, 315, 311, 293, 281, 263, 245, 241, 223, 195, 171, 141, 123, 111. EIMS *m/z* 403, 385, 369, 333, 293, 281, 263, 241, 223, 141, 97. NMR: $^1$H NMR (200 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), TMS (EIMS). Source: *Annona atemoya*, seeds.

**Table 4. (Continued)**

Adjacent Bis-THF Acetogenins (Continued)

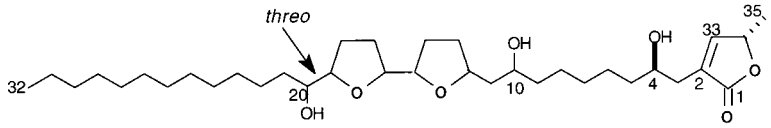
**91. rollitacin**[121] ($C_{37}H_{68}O_8$, MW 638)




| Position | 15 | 16 | 19 | 20 | 23 | 24 | 28 | 29 |
|---|---|---|---|---|---|---|---|---|
| $^1$H (δ) | 3.40 m | 3.86 m | 3.86 m | 3.93 m | 3.93 m | 3.86 m | 3.60 m | 3.60 m |
| $^{13}$C (δ) | 74.2 | 83.4 | 82.9 | 82.6 | 82.2 | 71.5 | 74.6 | 74.7 |

White waxy solid. $[\alpha]_D$: +15.7° (*c* 0.62, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 222 (log $\epsilon$ 3.54). IR ($\nu_{max}$, film, $cm^{-1}$): 3348, 2924, 1743, 1668, 1071. MS: EIMS (TMS) *m/z* 753, 663, 507, 489, 399, 367, 329, 173. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: formal acetal ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ $4.3 \times 10^{-1}$, A-549 $ED_{50}$ 1.6, MCF-7 $ED_{50}$ $2.5 \times 10^{-4}$, HT-29 $ED_{50}$ $4.6 \times 10^{-3}$, A-498 $ED_{50}$ 1.5, PC-3 $ED_{50}$ 1.1, PACA-2 $ED_{50}$ 3.0. Source: *Rollinia mucosa*, leaves.

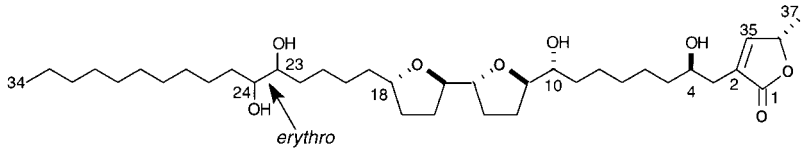
**92. rollinacin**[121] ($C_{35}H_{62}O_7$, MW 594)




| Position | **10** | **12** | **15** | **16** | **19** | **20** |
|---|---|---|---|---|---|---|
| $^1$H (δ) | 3.82 m | 4.22 m | 3.97 m | 3.92 m | 3.83 m | 3.38 m |
| $^{13}$C (δ) | 71.7 | 80.5 | 80.9 | 81.0 | 82.8 | 74.4 |

Oil. UV ($\lambda_{max}$, MeOH, nm): 222 (log $\epsilon$ 3.52). IR ($\nu_{max}$, film, $cm^{-1}$): 3446, 2938. 1731, 1670, 1079. MS: EIMS *m/z* 395, 377, 365, 325, 307, 289, 269, 241, 223, 205, 199, 181, 141, 123. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: formal acetal ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ 3.5, A-549 $ED_{50}$ $4.6 \times 10^{-2}$, MCF-7 $ED_{50}$ $1.6 \times 10^{-1}$, HT-29 $ED_{50}$ 2.1, A-498 $ED_{50}$ 1.6, PC-3 $ED_{50}$ 2.5, PACA-2 $ED_{50}$ 2.0. Source: *Rollinia mucosa*, leaves.

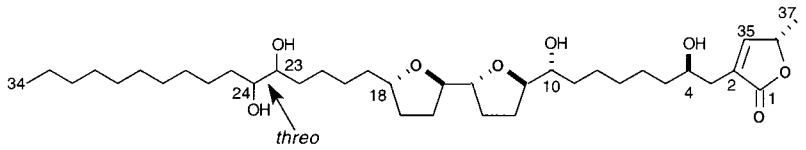
**93. glabracin A**[24] ($C_{37}H_{68}O_7$, MW 638)




| Position | 10 | 11 | 14 | 15 | 18 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| $^1$H (δ) | 3.42 m | 3.80 m | 3.80 m | 3.80 m | 3.80 m | 3.61 m | 3.61 m |
| $^{13}$C (δ) | 74.13 | 82.65 | 82.07 | 82.30 | 79.89 | 74.48 | 74.71 |

White wax solid. $[\alpha]_D$: −11.6° (*c* 0.013, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 220 (log $\epsilon$ 3.89). IR ($\nu_{max}$, film, $cm^{-1}$): 3330, 2919, 2850, 1747, 1717, 1469, 1320, 1203, 1064, 956, 758. MS: EIMS *m/z* 467, 449, 431, 413, 397, 379, 361, 327, 311, 309, 293, 291, 275, 241, 223, 205, 171, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $1.3 \times 10^{-1}$, A-549 $ED_{50}$ $2.8 \times 10^{-6}$, MCF-7 $ED_{50}$ $4.2 \times 10^{-6}$, HT-29 $ED_{50}$ $5.7 \times 10^{-6}$, A-498 $ED_{50}$ 1.0, PC-3 $ED_{50}$ 1.1, PACA-2 $ED_{50}$ 1.8. Source: *Annona glabra*, leaves.

**94. glabracin B**[24] ($C_{37}H_{68}O_7$, MW 638)



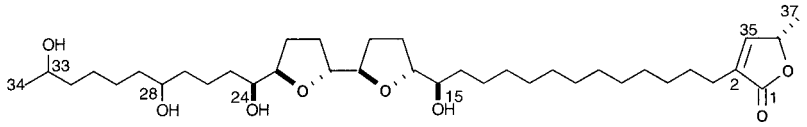

| Position | 10 | 11 | 14 | 15 | 18 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| $^1$H (δ) | 3.42 m | 3.80 m | 3.80 m | 3.80 m | 3.80 m | 3.43 m | 3.43 m |
| $^{13}$C (δ) | 74.18 | 82.78 | 82.60 | 81.80 | 79.31 | 74.05 | 74.35 |

White waxy solid. $[\alpha]_D$: +16.9° (*c* 0.05, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 223 (log $\epsilon$ 3.58). IR ($\nu_{max}$, film, $cm^{-1}$): 3382, 2926, 2854, 1748, 1540, 1456, 1318, 1270, 1199, 1072. MS: EIMS *m/z* 467, 449, 431, 413, 397, 379, 361, 327, 311, 309, 293, 291, 275, 241, 223, 205, 171, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $3.1 \times 10^{-1}$, A-549 $ED_{50}$ $1.6 \times 10^{-1}$, MCF-7 $ED_{50}$ $1.8 \times 10^{-3}$, HT-29 $ED_{50}$ $1.9 \times 10^{-2}$, A-498 $ED_{50}$ 1.4, PC-3 $ED_{50}$ 1.2, PACA-2 $ED_{50}$ $2.8 \times 10^{-1}$. Source: *Annona glabra*, leaves.

**Table 4. (Continued)**

Adjacent Bis-THF Acetogenins (Continued)

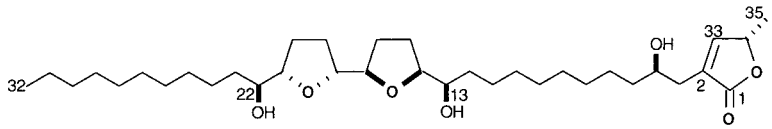
**95. microcarpacin**[36] ($C_{37}H_{66}O_8$, MW 638)



| Position | 15 | 24 | 28 | 33 | 34 |
|---|---|---|---|---|---|
| $^1$H (δ) | 3.40 m | 3.85 m | 3.61 m | 3.83 m | 1.18 d |
| $^{13}$C (δ) | 74.20 | 71.54 | 71.54 | 67.92 | 22.02 |

White waxy solid. Mp: 63−65 °C. $[\alpha]_D$: +12.4° (*c* 0.23, MeOH). UV ($\lambda_{max}$, MeOH, nm): 218 (log $\epsilon$ 4.07). IR ($\nu_{max}$, film, cm$^{-1}$): 3383, 2922, 1749, 1652, 1467, 1375, 1324, 1203, 1118, 1075, 949, 916, 871, 722. MS: EIMS *m/z* 537, 519, 509, 501, 491, 483, 473, 465, 447, 435, 429, 417, 399,343, 325, 307, 295, 289, 277, 265, 203, 185, 173, 167, 155, 149, 137, 111, 101, 83. NMR: $^1$H NMR (600 MHz, $CDCl_3$), $^{13}$C NMR (150 MHz, $CDCl_3$). Source: *Uvaria microcarpa*, seeds.

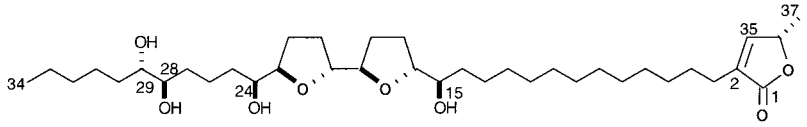
**96. rollimembrin**[122] ($C_{35}H_{62}O_7$, MW 594)



| Position | 13 | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|
| $^1$H (δ) | 3.81 m | 3.81 m | 3.85 m | 3.85 m | 3.90 m | 3.40 m |
| $^{13}$C (δ) | 73.97 | 83.02 | 81.11 | 80.99 | 83.02 | 71.87 |

White amorphous solid. $[\alpha]_D$: +17.5° (*c* 0.4, MeOH). UV ($\lambda_{max}$, MeOH, nm): 210 (log $\epsilon$ 3.95). IR ($\nu_{max}$, film, cm$^{-1}$): 3430, 2924, 2849, 1750, 1647, 1462, 1316, 1200, 1070. MS: EIMS *m/z* 483, 465, 423, 353, 335, 317, 311, 293, 283, 265, 247, 241, 223, 153, 141, 123, 111. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (100 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities: NADH oxidase $IC_{50}$ 0.33 nM. Source: *Rollinia membranacea*, seeds.

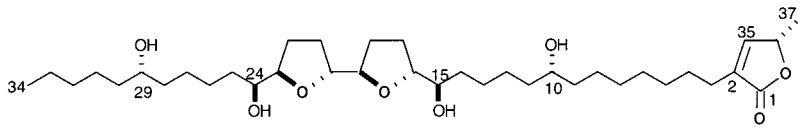
**97. purpurediolin**[123] ($C_{37}H_{66}O_8$, MW 638)



| Position | 15 | 16 | 23 | 24 | 28 | 29 |
|---|---|---|---|---|---|---|
| $^1$H (δ) | 3.40 m | 3.83 m | 3.93 m | 3.86 m | 3.59 m | 3.59 m |
| $^{13}$C (δ) | 74.1 | 83.3 | 82.9 | 71.6 | 74.6 | 74.7 |

White wax. Mp: 35−39 °C. $[\alpha]_D$: +20° (*c* 1.3, MeOH). UV ($\lambda_{max}$, MeOH, nm): 207 (log $\epsilon$ 3.89). IR ($\nu_{max}$, film, cm$^{-1}$): 3650, 3023, 2928, 1751, 1641, 1423, 1215, 1028, 930. MS: EIMS (TMS) *m/z* 753, 663, 573, 507, 489, 483, 437, 417, 399, 367, 347, 309, 173, 111, 83, 73. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: acetonide ($^1$H NMR), per-MTPA esters ($^1$H NMR), TMS (EIMS). Biological activities ($\mu$g/mL): BST $LC_{50}$ 7.0 × 10$^{-2}$, A-549 $ED_{50}$ 4.4 × 10$^{-1}$, MCF-7 $ED_{50}$ 9.2 × 10$^{-1}$, HT-29 $ED_{50}$ < 10$^{-7}$, A-498 $ED_{50}$ 1.4, PC-3 $ED_{50}$ 3.5 × 10$^{-1}$, PACA-2 $ED_{50}$ 1.4. Source: *Annona purpurea*, seeds.

**98. purpurenin**[123] ($C_{37}H_{66}O_8$, MW 638)



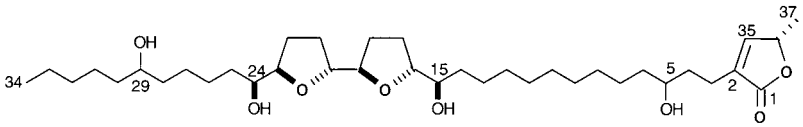
| Position | 10 | 15 | 16 | 23 | 24 | 29 |
|---|---|---|---|---|---|---|
| $^1$H (δ) | 3.58 m | 3.40 m | 3.83 m | 3.93 m | 3.85 m | 3.58 m |
| $^{13}$C (δ) | 71.8 | 74.0 | 83.2 | 82.8 | 71.5 | 71.8 |

Pale yellow wax. Mp: 36−38 °C. $[\alpha]_D$: +27° (*c* 1.0, MeOH). UV ($\lambda_{max}$, MeOH, nm): 208 (log $\epsilon$ =4.09). IR ($\nu_{max}$, film, cm$^{-1}$): 3100−3700, 3021, 2940, 2859, 1751, 1642, 1428, 1215, 1074, 927. MS: EIMS (TMS) *m/z* 765, 731, 675, 641, 595, 585, 551, 505, 495, 455, 461, 415, 365, 331, 297, 275, 241, 173, 151, 111, 107, 83, 73. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), per-MTPA esters ($^1$H NMR), formal acetal ($^1$H NMR), TMS (EIMS). Biological activities ($\mu$g/mL): BST $LC_{50}$ 2.9 × 10$^{-2}$, A-549 $ED_{50}$ 1.3, MCF-7 $ED_{50}$ 1.7, HT-29 $ED_{50}$ 3.2 × 10$^{-1}$, A-498 $ED_{50}$ 1.3, PC-3 $ED_{50}$ 1.1, PACA-2 $ED_{50}$ 2.0. Source: *Annona purpurea*, seeds.

**Table 4. (Continued)**

Adjacent Bis-THF Acetogenins (Continued)

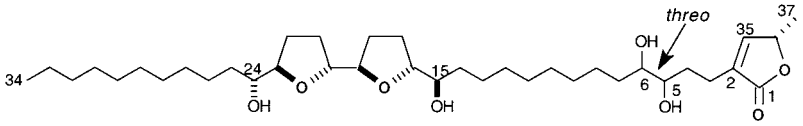
**99. espelicin***[37] ($C_{37}H_{66}O_8$, MW 638)



| Position | 5 | 15 | 16 | 19 | 20 | 23 | 24 | 29 |
|---|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.59 m | 3.39 m | 3.83 m | 3.83 m | 3.83 m | 3.83 m | 3.87 m | 3.59 m |
| $^{13}$**C** (δ) | 70.8 | 74.0 | 83.2 | 82.5 | 82.2 | 82.8 | 71.3 | 71.8 |

White waxy solid. MS: FABMS *m/z* 645, 627, 519, 489, 487, 457, 415, 387, 363, 345, 333, 317, 291, 221, 161, 160, 154, 137, 136, 121. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Uvaria pauci-ovulata*, stem bark.

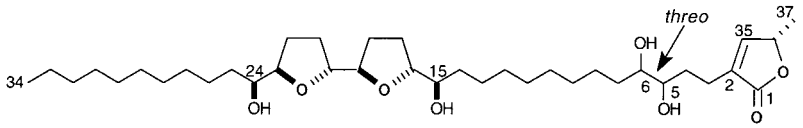
**100. uvariasolin I***[37] ($C_{37}H_{66}O_8$, MW 638)



| Position | **5** | **6** | **15** | **16** | **19** | **20** | **23** | **24** |
|---|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.38 m | 3.38 m | 3.38 m | 3.82 m | 3.82 m | 3.82 m | 3.82 m | 3.38 m |
| $^{13}$**C** (δ) | 74.4 | 73.2 | 74.0 | 83.2 | 81.8 | 81.8 | 83.2 | 74.0 |

White waxy solid. MS: FABMS *m/z* 519, 489, 473, 459, 431, 403, 361, 333, 317, 275, 247, 205. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Uvaria pauci-ovulata*, stem bark.

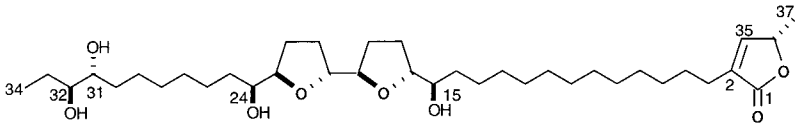
**101. uvariasolin II***[37] ($C_{37}H_{66}O_8$, MW 638)



| Position | **5** | **6** | **15** | **16** | **19** | **20** | **23** | **24** |
|---|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.40 m | 3.40 m | 3.40 m | 3.85 m | 3.85 m | 3.85 m | 3.85 m | 3.85 m |
| $^{13}$**C** (δ) | 74.4 | 73.2 | 74.0 | 83.2 | 82.5 | 82.3 | 82.8 | 71.3 |

White waxy solid. MS: FABMS *m/z* 519, 489, 473, 459, 431, 403, 361, 333, 317, 275, 247, 205. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Uvaria pauci-ovulata*, stem bark.

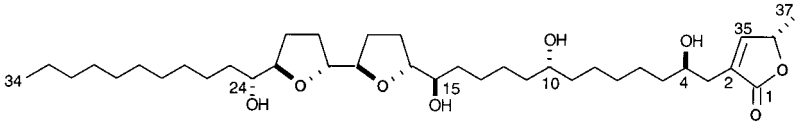
**102. bullatetrocin**[124] ($C_{37}H_{66}O_8$, MW 638)



| Position | **15** | **16** | **19** | **20** | **23** | **24** | **31** | **32** |
|---|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.40 m | 3.85 m | 3.85 m | 3.93 m | 3.93 m | 3.86 m | 3.65 m | 3.65 m |
| $^{13}$**C** (δ) | 74.2 | 83.3 | 82.5 | 82.2 | 82.8 | 71.5 | 71.5 | 71.6 |

Colorless wax. $[\alpha]_D$: +16.3° (*c* 0.27, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3350, 2923, 2846, 1742, 1594, 1455, 1359, 1125, 1103. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), per-MTPA esters ($^1$H NMR), acetonide ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ $3.1 \times 10^{-1}$, A-549 $ED_{50}$ $3.5 \times 10^{-1}$, MCF-7 $ED_{50}$ $5.0 \times 10^{-1}$, HT-29 $ED_{50}$ $3.3 \times 10^{-1}$, A-498 $ED_{50}$ >1, PC-3 $ED_{50}$ >1, PACA-2 $ED_{50}$ >1. Source: *Asimina triloba*, stem bark.

**103. 10-hydroxyasimicin**[124] ($C_{37}H_{66}O_8$, MW 638)



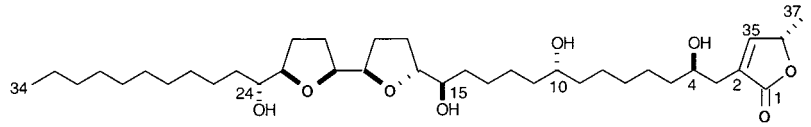
| Position | 10 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.60 m | 3.39 m | 3.86 m | 3.86 m | 3.86 m | 3.86 m | 3.39 m |
| $^{13}$**C** (δ) | 71.7 | 74.1 | 83.1 | 81.8 | 81.8 | 83.2 | 74.0 |

Colorless wax. $[\alpha]_D$: +17.3° (*c* 0.22, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3376, 2922, 2856, 1740, 1600, 1467, 1318, 1116, 1074. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), per-MTPA esters ($^1$H NMR), acetonide ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ $4.3 \times 10^{-1}$, A-549 $ED_{50}$ $6.7 \times 10^{-1}$, MCF-7 $ED_{50}$ $3.3 \times 10^{-1}$, HT-29 $ED_{50}$ $7.6 \times 10^{-1}$, A-498 $ED_{50}$ >1, PC-3 $ED_{50}$ $5.3 \times 10^{-1}$, PACA-2 $ED_{50}$ >1. Source: *Asimina triloba*, stem bark.

**Table 4. (Continued)**

Adjacent Bis-THF Acetogenins (Continued)

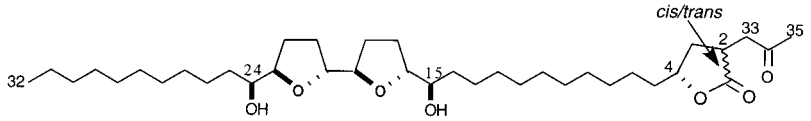
**104. 10-hydroxytrilobacin**[124] ($C_{37}H_{66}O_8$, MW 638)



| Position | 10 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.59 m | 3.39 m | 3.83 m | 3.97 m | 4.05 m | 3.83 m | 3.39 m |
| **$^{13}$C** (δ) | 71.8 | 74.5 | 83.2 | 81.6 | 80.9 | 82.6 | 73.9 |

Colorless oil. $[\alpha]_D$: +8.3° (*c* 0.36, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3365, 2928, 2856, 1752, 1590, 1456, 1420, 1120, 1036. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), per-MTPA esters ($^1$H NMR), acetonide ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ $2.6 \times 10^{-1}$, A-549 $ED_{50}$ $1.0 \times 10^{-8}$, MCF-7 $ED_{50}$ $1.9 \times 10^{-8}$, HT-29 $ED_{50}$ 1.4, A-498 $ED_{50}$ $1.0 \times 10^{-2}$, PC-3 $ED_{50}$ $3.8 \times 10^{-1}$, PACA-2 $ED_{50}$ $2.0 \times 10^{-1}$. Source: *Asimina triloba*, stem bark.

**squamolinone**[125] (reported as a cis and trans mixture) ($C_{35}H_{62}O_7$, MW 594)



**105. (2,4-*cis*)-squamolinone**

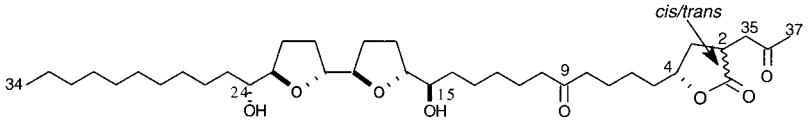
| Position | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.40 m | 3.86 m | 3.93 m | 3.86 m | 3.93 m | 3.86 m |
| **$^{13}$C** (δ) | 74.09 | 83.18 | 82.39 | 82.18 | 82.83 | 71.56 |

**106. (2,4-*trans*)-squamolinone**

| Position | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.40 m | 3.86 m | 3.93 m | 3.86 m | 3.93 m | 3.86 m |
| **$^{13}$C** (δ) | 74.09 | 83.18 | 82.39 | 82.18 | 82.83 | 71.56 |

White amorphous powder. $[\alpha]_D$: +21.4° (*c* 0.073, $CH_2Cl_2$). UV ($\lambda_{max}$, MeOH, nm): 203 (log ε 2.85). IR ($\nu_{max}$, film, $cm^{-1}$): 3426, 2920, 2850, 1767. MS: EIMS *m/z* 363, 345, 311, 283. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $7.4 \times 10^{-2}$, A-549 $ED_{50}$ 1.9, MCF-7 $ED_{50}$ 1.8, HT-29 $ED_{50}$ 1.7, A-498 $ED_{50}$ 1.8, PC-3 $ED_{50}$ 2.6, PACA-2 $ED_{50}$ 1.1. Source: *Annona squamosa*, stem bark.

**9-oxoasimicinone**[125] (reported as a cis and trans mixture) ($C_{37}H_{64}O_8$, MW 636)



**107. (2,4-*cis*)-9-oxoasimicinone**

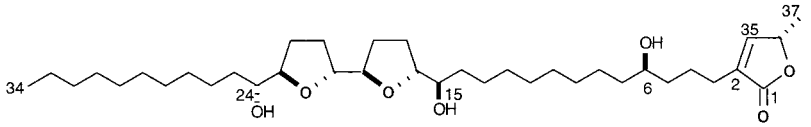
| Position | 9 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | - | 3.39 m | 3.83 m | 3.86 m | 3.86 m | 3.83 m | 3.39 m |
| **$^{13}$C** (δ) | 211.05 | 74.05 | 83.11 | 81.80 | 81.77 | 83.16 | 73.93 |

**108. (2,4-*trans*)-9-oxoasimicinone**

| Position | 9 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | | 3.39 m | 3.83 m | 3.86 m | 3.86 m | 3.83 m | 3.39 m |
| **$^{13}$C** (δ) | 211.02 | 74.05 | 83.11 | 81.80 | 81.77 | 83.16 | 73.93 |

White amorphous powder. $[\alpha]_D$: +19.7° (*c* 0.10, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 203 (log ε 3.55). IR ($\nu_{max}$, film, $cm^{-1}$): 3390, 2921, 2851, 1770, 1705. MS: EIMS *m/z* 377, 359, 341, 325, 307, 289, 225, 207. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $6.7 \times 10^{-1}$, A-549 $ED_{50}$ $5.7 \times 10^{-3}$, MCF-7 $ED_{50}$ $2.6 \times 10^{-1}$, HT-29 $ED_{50}$ $4.0 \times 10^{-3}$, A-498 $ED_{50}$ $4.6 \times 10^{-1}$, PC-3 $ED_{50}$ 1.1, PACA-2 $ED_{50}$ 1.2. Source: *Annona squamosa*, stem bark.

**109. bullacin**[125] ($C_{37}H_{66}O_7$, MW 622)



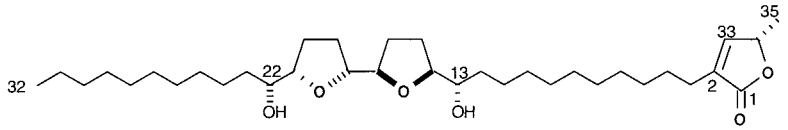
| Position | 6 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.62 m | 3.39 m | 3.84 m | 3.88 m | 3.88 m | 3.84 m | 3.39 m |
| **$^{13}$C** (δ) | 71.37 | 73.80 | 82.86 | 81.65 | 81.65 | 82.86 | 73.80 |

White amorphous powder. $[\alpha]_D$: +43.8° (*c* 0.03, $CH_2Cl_2$). UV ($\lambda_{max}$, MeOH, nm): 211 (log ε 3.79). IR ($\nu_{max}$, film, $cm^{-1}$): 3418, 2925, 2853, 1756. MS: EIMS *m/z* 433, 415, 397, 363, 345, 327, 311, 293, 275, 169, 151. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), per-MTPA esters ($^1$H NMR), formal acetal ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ $1.9 \times 10^{-2}$, A-549 $ED_{50}$ $9.0 \times 10^{-7}$, MCF-7 $ED_{50}$ $2.5 \times 10^{-7}$, HT-29 $ED_{50}$ $4.5 \times 10^{-3}$, A-498 $ED_{50}$ >1, PC-3 $ED_{50}$ >1, PACA-2 $ED_{50}$ $4.1 \times 10^{-1}$. Source: *Annona squamosa*, stem bark.

**Table 4. (Continued)**

Adjacent Bis-THF Acetogenins (Continued)

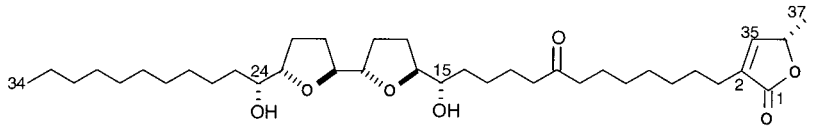
**110. membrarollin**[137] ($C_{35}H_{62}O_6$ MW 578)



| Position | 13 | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.40 dt | 3.81 m | 3.87 m | 3.87 m | 3.90 m | 3.85 m |
| $^{13}$**C** (δ) | 74.00 | 83.02 | 81.10 | 80.99 | 83.02 | 71.91 |

White wax. $[\alpha]_D$: +10° (*c* 0.8, MeOH). UV ($\lambda_{max}$, MeOH, nm): 210 (log $\epsilon$ 3.95). IR ($\nu_{max}$, film, cm$^{-1}$): 3370, 2940, 2880, 1750, 1456, 1380, 1039. MS: EIMS *m/z* 578, 560, 542, 436, 407, 390, 337, 319, 311, 267, 241, 223, 171, 153, 111, 97. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (100 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR), *p*-bromophenylurethane ($^1$H NMR). Biological activities: NADH oxidase $IC_{50}$ 0.3 nM. Source: *Rollinia membranacea*, seeds.

**111. guanaconne**[138] ($C_{37}H_{64}O_7$ MW 620)

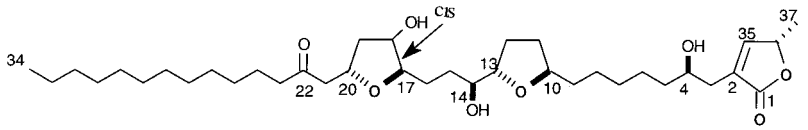


| Position | 10 | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | - | 3.39 m | 3.78 m | 3.92 m | 3.78 m | 3.78 m | 3.84 m |
| $^{13}$**C** (δ) | 211.46 | 73.86 | 83.23 | 82.50 | 82.25 | 82.79 | 71.19 |

Colorless wax. $[\alpha]_D$: +22° (*c* 1, EtOH). UV ($\lambda_{max}$, MeOH, nm): 208 (log $\epsilon$ 3.83). IR ($\nu_{max}$, film, cm$^{-1}$): 3416, 2922, 1751, 1647, 1548, 1066. MS: EIMS *m/z* 449, 379, 361, 311, 309, 293, 291, 241, 223, 195. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (100 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities: NADH oxidase $IC_{50}$ 1.5 nM. Source: *Annona spraguei*, seeds.

Nonadjacent Bis-THF Acetogenins

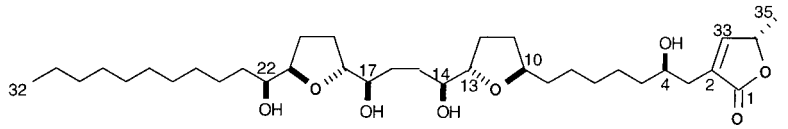
**112. goniotriocin***[39] ($C_{37}H_{65}O_8$, MW 636)



| Position | 10 | 13 | 14 | 17 | 20 | 22 |
|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.88 m | 3.75 q | 3.41 dt | 3.80 dt | 4.62 ddd | --- |
| $^{13}$**C** (δ) | 79.3 | 81.9 | 74.7 | 82.7 | 73.4 | 209.6 |

White wax. $[\alpha]_D$: +10.0° (*c* 0.03, $CHCl_3$). IR ($\nu_{max}$, film, cm$^{-1}$): 3378, 2925, 2853, 1750, 1718, 1458, 1066. MS: CIMS (isobutane) *m/z* 637, 619, 601, 583. EIMS *m/z* 425, 407, 389, 381, 371,363, 345, 339, 337, 321, 281, 263, 245, 197, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities ($\mu$g/mL): BST $LC_{50}$ 2.7, A-549 $ED_{50}$ $3.3 \times 10^{-2}$, MCF-7 $ED_{50}$ $3.3 \times 10^{-5}$, HT-29 $ED_{50}$ $1.2 \times 10^{-3}$, A-498 $ED_{50}$ 1.1, PC-3 $ED_{50}$ $2.6 \times 10^{-1}$, PACA-2 $ED_{50}$ 1.4. Source: *Goniothalamus giganteus*, stem bark.

**113. trilobalicin***[119] ($C_{35}H_{62}O_8$, MW 610)



| Position | 10 | 13 | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|---|
| $^1$**H** (δ) | 3.87 m | 3.80 m | 3.41 m | 3.41 m | 3.86 m | 3.87 m | 3.80 m |
| $^{13}$**C** (δ) | 79.3 | 82.0 | 74.4 | 74.6 | 83.3 | 82.2 | 71.6 |

White wax. $[\alpha]_D$: +13.6° (*c* 0.125, $CHCl_3$). IR ($\nu_{max}$, film, cm$^{-1}$): 3333, 2919, 2866, 1738, 1594, 1456, 1398, 1116. MS: EIMS *m/z* 585, 545, 495, 455, 405, 365, 353, 313, 275, 263, 223, 213. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR), TMS (EIMS). Biological activities ($\mu$g/mL): BST $LC_{50}$ 5.8, A-549 $ED_{50}$ $5.8 \times 10^{-8}$, MCF-7 $ED_{50}$ $1.6 \times 10^{-7}$, HT-29 $ED_{50}$ 2.3, A-498 $ED_{50}$ $6.0 \times 10^{-3}$, PC-3 $ED_{50}$ $9.8 \times 10^{-1}$, PACA-2 $ED_{50}$ $2.8 \times 10^{-1}$. Source: *Asimina triloba*, stem bark.

**gigantecinone**[126] (reported as a cis and trans mixture) ($C_{37}H_{66}O_8$, MW 638)

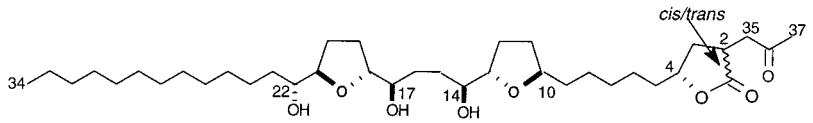


**Table 4. (Continued)**

Nonadjacent Bis-THF Acetogenins (Continued)

**114. (2,4-*cis*)-gigantecinone**

| Position | 10 | 13 | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|---|
| $^{1}$**H** (δ) | 3.88 m | 3.81 m | 3.42 m | 3.42 m | 3.81 m | 3.81 m | 3.42 m |
| $^{13}$**C** (δ) | 79.2 | 82.0 | 74.0 | 74.2 | 82.7 | 82.7 | 74.4 |

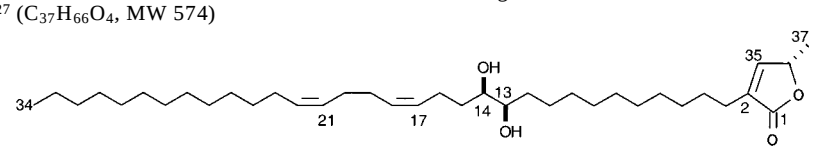
**115. (2,4-*trans*)-gigantecinone**

| Position | 10 | 13 | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|---|
| $^{1}$**H** (δ) | 3.88 m | 3.81 m | 3.42 m | 3.42 m | 3.81 m | 3.81 m | 3.42 m |
| $^{13}$**C** (δ) | 79.2 | 82.0 | 74.0 | 74.2 | 82.7 | 82.7 | 74.4 |

White wax. $[\alpha]_D$: +23.3° (*c* 0.15, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3507, 3389, 2908, 2837, 1749, 1708, 1461, 1190, 1167, 1049. MS: EIMS *m/z* 439, 421, 403, 369, 351, 339, 333, 321, 303, 281, 269, 263, 251, 199, 141. NMR: $^{1}$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^{1}$H NMR), per-MTPA esters ($^{1}$H NMR), formal acetal ($^{1}$H NMR). Biological activities (μg/mL): BST $LC_{50}$ 3.3, A-549 $ED_{50}$ $2.1 \times 10^{-1}$, MCF-7 $ED_{50}$ >1, HT-29 $ED_{50}$ >1, A-498 $ED_{50}$ $2.1 \times 10^{-1}$, PC-3 $ED_{50}$ $1.1 \times 10^{-3}$, PACA-2 $ED_{50}$ >1. Source: *Goniothalamus giganteus*, stem bark.

Non-THF or THP Acetogenins

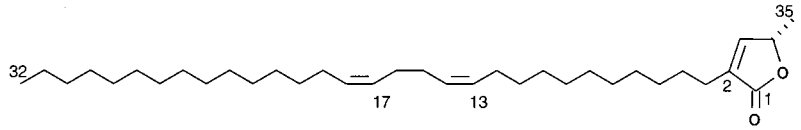
**116. montecristin**[127] ($C_{37}H_{66}O_4$, MW 574)




| Position | 13 | 14 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|
| $^{1}$**H** (δ) | 3.42 m | 3. 42m | 5.41 m | 5. 37 m | 5. 41 m | 5. 37 m |
| $^{13}$**C** (δ) | 73.93 | 74.35 | 128.78 | 130.43 | 129.20 | 130.04 |

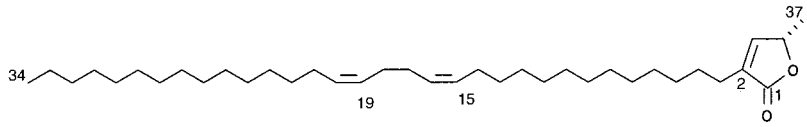
White wax. Mp: 62−65 °C. $[\alpha]_D$: +25° (*c* 0.1, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 211.7 (log ε 3.80). IR ($\nu_{max}$, film, $cm^{-1}$): 3300, 2900, 2840, 1740, 1650, 1120, 1080, 1030. NMR: $^{1}$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: acetonide ($^{1}$H NMR). Source: *Annona muricata*, roots.

**117. muridienin-1**[128] ($C_{35}H_{62}O_2$, MW 514)



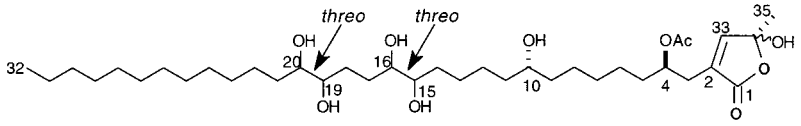

| Position | 13 | 14 | 17 | 18 |
|---|---|---|---|---|
| $^{1}$**H** (δ) | 5.38-5.41 m | 5.38-5.41 m | 5.38-5.41 m | 5.38-5.41 m |
| $^{13}$**C** (δ) | 128.96 | 130.20 | 129.44 | 130.20 |

**118. muridienin-2**[128] ($C_{37}H_{66}O_2$, MW 542)




| Position | 15 | 16 | 19 | 20 |
|---|---|---|---|---|
| $^{1}$**H** (δ) | 5.38-5.41 m | 5.38-5.41 m | 5.38-5.41 m | 5.38-5.41 m |
| $^{13}$**C** (δ) | 128.96 | 130.20 | 129.44 | 130.20 |

**donnaienin D**[34] (reported as an epimeric pair) ($C_{37}H_{66}O_9$, MW 672)




**119. donnaienin D**

| Position | 4 | 10 | 15 | 16 | 19 | 20 | 34 |
|---|---|---|---|---|---|---|---|
| $^{1}$**H** (δ) | 5.05 m | 3.62 m | 3.46 m | 3.46 m | 3.46 m | 3.46 m | --- |
| $^{13}$**C** (δ) | 71.3 | 69.4 | 73.7 | 73.6 | 73.2 | 73.1 | 104.8 |

**120. 34-*epi*-donnaienin D**

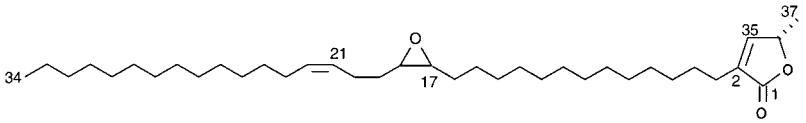
| Position | 4 | 10 | 15 | 16 | 19 | 20 | 34 |
|---|---|---|---|---|---|---|---|
| $^{1}$**H** (δ) | 5.05 m | 3.62 m | 3.46 m | 3.46 m | 3.46 m | 3.46 m | |
| $^{13}$**C** (δ) | 71.2 | 69.5 | 73.6 | 73.3 | 73.2 | 73.1 | 104.8 |

White amorphous powder. Mp: 78−81 °C. $[\alpha]_D$: +8.6° (*c* 0.21, MeOH). IR ($\nu_{max}$, film, $cm^{-1}$): 3360, 2918, 2849, 1751, 1468. MS: EIMS *m/z* 473, 413, 395, 377, 359, 341, 385, 367, 349, 325, 307,307, 289, 287, 269, 251, 199, 139, 121. NMR: $^{1}$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: phenylhydrazone ($^{1}$H NMR), per-MTPA esters ($^{1}$H NMR), acetonide ($^{1}$H NMR). Biological activities (μg/mL): KB $IC_{50}$ >10. HCT-8 $IC_{50}$ >10, Bel $IC_{50}$ >10. Source: *Goniothalamus donnaiensis*, roots.

**Table 4. (Continued)**

Non-THF or THP Acetogenins (Continued)

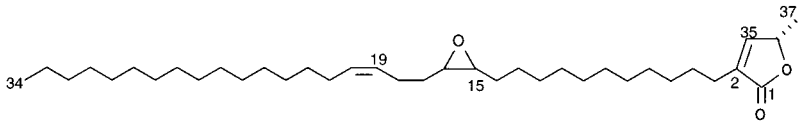
**121. epomusenin A**[129] ($C_{37}H_{67}O_4$, MW 558)



| Position | 17 | 18 | 21 | 22 |
|---|---|---|---|---|
| **$^1$H** (δ) | 2.93 m | 2.93 m | 5.38 m | 5.38 m |
| **$^{13}$C** (δ) | 56.78 | 56.78 | 128.44 | 131.17 |

Waxy solid. $[\alpha]_D$: +24° (*c* 0.5, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 210 (log $\epsilon$ 3.90). IR ($\nu_{max}$, film, $cm^{-1}$): 2910, 2860, 1760, 1460, 1310, 1190, 1090, 1020, 715. MS: EIMS *m/z* 539, 524, 468, 417, 403, 368, 351, 349, 323, 321, 279, 265, 237, 209, 167, 141, 112, 111, 97. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (100 MHz, $CDCl_3$). Source: *Rollina mucosa*, fruits.

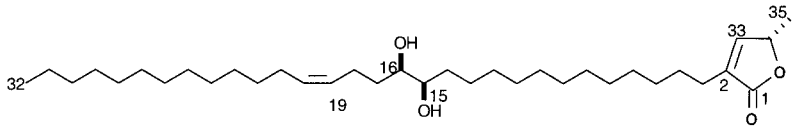
**122. epomusenin B**[129] ($C_{37}H_{67}O_4$, MW 558)



| Position | 15 | 16 | 19 | 20 |
|---|---|---|---|---|
| **$^1$H** (δ) | 2.93 m | 2.93 m | 5.38 m | 5.38 m |
| **$^{13}$C** (δ) | 56.78 | 56.78 | 128.44 | 131.17 |

Waxy solid. $[\alpha]_D$: +24° (*c* 0.5, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 210 (log $\epsilon$ 3.90). IR ($\nu_{max}$, film, $cm^{-1}$): 2910, 2860, 1760, 1460, 1310, 1190, 1090, 1020, 715. MS: EIMS *m/z* 539, 524, 468, 417, 368, 351, 349, 321, 295, 279, 265, 237, 209, 167, 141, 112, 111, 97. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (100 MHz, $CDCl_3$). Source: *Rollina mucosa*, fruits.

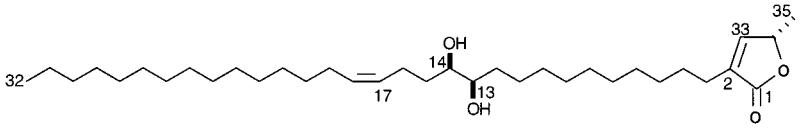
**123. cohibin A**[130] ($C_{35}H_{64}O_4$, MW 548)



| Position | 15 | 16 | 19 | 20 |
|---|---|---|---|---|
| **$^1$H** (δ) | 3.42 m | 3.42 m | 5.40 m | 5.38 m |
| **$^{13}$C** (δ) | 74.6 | 74.3 | 129.0 | 131.1 |

Powder. Mp: 60−62 °C. $[\alpha]_D$: +12° (*c* 0.1, MeOH). UV ($\lambda_{max}$, MeOH, nm): 212.2 (log $\epsilon$ 2.82). IR ($\nu_{max}$, film, $cm^{-1}$): 3300, 2900, 2840, 1740, 1650, 1470, 1120, 1080, 1030. MS: EIMS *m/z* 548, 295, 277, 267, 249, 111, 97. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: acetonide ($^1$H NMR). Source: *Annona muricata*, roots.

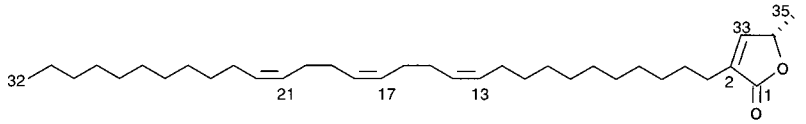
**124. cohibin B**[130] ($C_{35}H_{64}O_4$, MW 548)



| Position | 13 | 14 | 17 | 18 |
|---|---|---|---|---|
| **$^1$H** (δ) | 3.42 m | 3.42 m | 5.40 m | 5.38 m |
| **$^{13}$C** (δ) | 74.6 | 74.3 | 129.0 | 131.1 |

Powder. Mp: 60−62 °C. $[\alpha]_D$: +12° (*c* 0.1, MeOH). UV ($\lambda_{max}$, MeOH, nm): 212.2 (log $\epsilon$ 2.82). IR ($\nu_{max}$, film, $cm^{-1}$): 330, 2900, 2840, 1740, 1650, 1470, 1120, 1080, 1030. MS: EIMS *m/z* 548, 295, 249, 231, 111, 97. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Derivatives: acetonide ($^1$H NMR). Source: *Annona muricata*, roots.

**125. chatenaytrienin-1**[29] (reported as a mixture of chatenaytrienins 1 and 2) ($C_{35}H_{60}O_2$, MW 512)

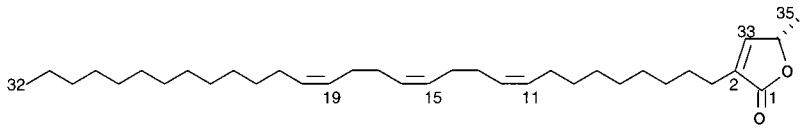


| Position | 13-14 | 17-18 | 21-22 |
|---|---|---|---|
| **$^1$H** (δ) | 5.36-5.41 | 5.36-5.41 | 5.36-5.41 |
| **$^{13}$C** (δ) | 129.1-130.4 | 129.1-130.4 | 129.1-130.4 |

**Table 4. (Continued)**

Non-THF or THP Acetogenins (Continued)

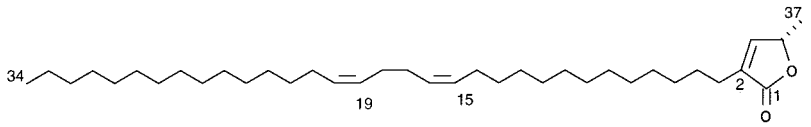
**126. chatenaytrienin-2**[29] (reported as a mixture of chatenaytrienins 1 and 2) ($C_{35}H_{60}O_2$, MW 512)




| Position | 11-12 | 15-16 | 19-20 |
|---|---|---|---|
| **$^1$H** (δ) | 5.36-5.41 | 5.36-5.41 | 5.36-5.41 |
| **$^{13}$C** (δ) | 129.1-130.4 | 129.1-130.4 | 129.1-130.4 |

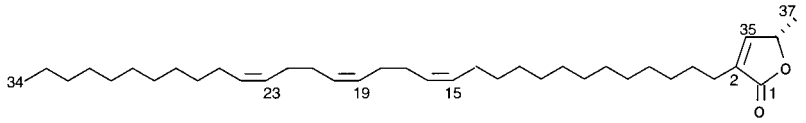
Oil. UV ($\lambda_{max}$, MeOH, nm): 214. MS: CIMS (isobutane) *m/z* 513. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Annona nutans*, roots.

**127. chatenaytrienin-3**[29] (reported as a mixture of chatenaytrienins 3 and 4) ($C_{37}H_{66}O_2$, MW 540)




| Position | 15 | 16 | 19 | 20 |
|---|---|---|---|---|
| **$^1$H** (δ) | 5.38-5.41 m | 5.38-5.41 m | 5.38-5.41 m | 5.38-5.41 m |
| **$^{13}$C** (δ) | 128.96 | 130.20 | 129.44 | 130.20 |

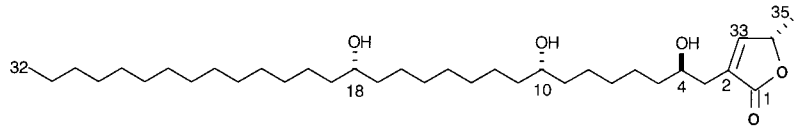
**128. chatenaytrienin-4**[29] (reported as a mixture of chatenaytrienins 3 and 4) ($C_{37}H_{66}O_2$, MW 540)




| Position | 13-14 | 17-18 | 21-22 |
|---|---|---|---|
| **$^1$H** (δ) | 5.36-5.41 | 5.36-5.41 | 5.36-5.41 |
| **$^{13}$C** (δ) | 129.1-130.4 | 129.1-130.4 | 129.1-130.4 |

Oil. $[\alpha]_D$: +25° (*c* 0.18, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 214. IR ($\nu_{max}$, film, $cm^{-1}$): 2929, 2857, 1761, 1657, 755. MS: CIMS *m/z* 541. NMR: $^1$H NMR (400 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Annona nutans*, roots.

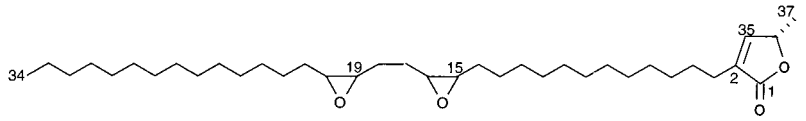
**129. longanin**[131] ($C_{35}H_{66}O_5$, MW 566)




| Position | 4 | 10 | 18 |
|---|---|---|---|
| **$^1$H** (δ) | 3.85 m | 3.61 m | 3.61 m |
| **$^{13}$C** (δ) | 69.9 | 71.7 | 71.8 |

Colorless wax. MS: EIMS (TMS) *m/z* 299, 295. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ $1.2 \times 10^1$, A-549 $ED_{50}$ $4.9 \times 10^{-2}$, MCF-7 $ED_{50}$ 3.4, HT-29 $ED_{50}$ $6.0 \times 10^{-1}$, A-498 $ED_{50}$ $3.9 \times 10^{-2}$, PC-3 $ED_{50}$ $4.0 \times 10^{-1}$, PACA-2 $ED_{50}$ $1.1 \times 10^{-2}$. Source: *Asimina longifolia*, leaves and twigs.

**130. diepoxyrollin**[132] ($C_{37}H_{66}O_4$, MW 574)



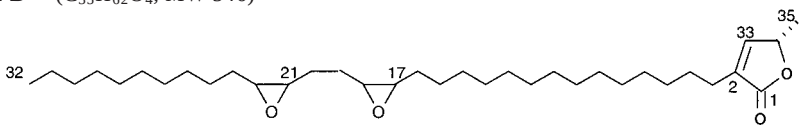

| Position | 15 | 16 | 19 | 20 |
|---|---|---|---|---|
| **$^1$H** (δ) | 2.94 | 2.94 | 2.94 | 2.94 |
| **$^{13}$C** (δ) | 57.28 | 57.28 | 56.38 | 56.38 |

White wax. $[\alpha]_D$: +11° (*c* 0.85, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm):208. IR ($\nu_{max}$, film, $cm^{-1}$): 2910, 2845, 1745. MS: EIMS *m/z* 295, 265, 251, 237, 223, 209, 195, 181, 167, 153, 139, 125, 111, 97. NMR: $^1$H NMR (200 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Rollinia membranacea*, seeds.

**Table 4. (Continued)**

Non-THF or THP Acetogenins (Continued)

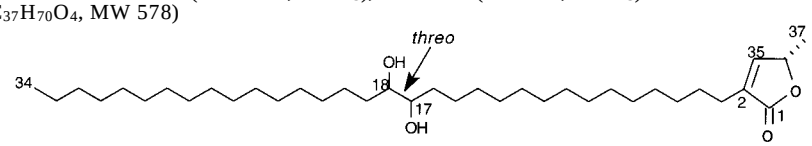
**131. diepomuricanin B**[132] ($C_{35}H_{62}O_4$, MW 546)



| Position | 17 | 18 | 21 | 22 |
|---|---|---|---|---|
| **$^1$H** (δ) | 2.94 | 2.94 | 2.94 | 2.94 |
| **$^{13}$C** (δ) | 57.28 | 57.28 | 56.38 | 56.38 |

White wax. $[\alpha]_D$: +10° (*c* 0.75, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 208. IR ($\nu_{max}$, film, $cm^{-1}$): 3400, 2910, 2845, 1745. MS: EIMS *m/z* 323, 293, 279, 97. NMR: $^1$H NMR (200 MHz, $CDCl_3$), $^{13}$C NMR (50 MHz, $CDCl_3$). Source: *Rollinia membranacea*, seeds.

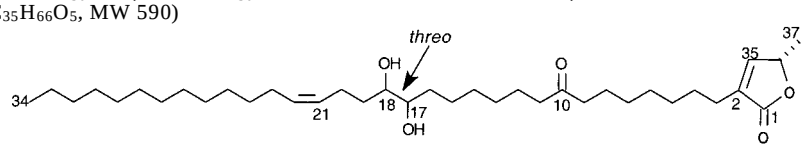
**132. tonkinelin**[133] ($C_{37}H_{70}O_4$, MW 578)



| Position | 17 | 18 |
|---|---|---|
| **$^1$H** (δ) | 3.42 m | 3.42 m |
| **$^{13}$C** (δ) | 74.53 | 74.53 |

White amorphous powder. Mp: 64−66 °C. $[\alpha]_D$: +14.5° (*c* 0.07, $CHCl_3$). IR ($\nu_{max}$, film, $cm^{-1}$): 3341, 2915, 2848, 1742, 1469. MS: EIMS *m/z* 579, 561, 543, 335, 323, 209, 195, 181, 167, 153, 139, 125, 111, 97. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: acetonide ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): HL-60 $IC_{50}$ 1.0, HCT-8 $IC_{50}$ 6.7, KB $IC_{50}$ >10, A2780 $IC_{50}$ >10. Source: *Uvaria tonkinesis*, root bark.

**133. annojahnin**[12] ($C_{35}H_{66}O_5$, MW 590)

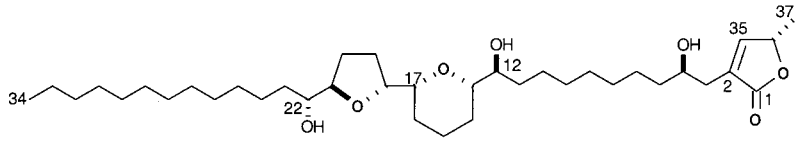


| Position | 10 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | --- | 3.41 m | 3.41 m | 5.38 ddd | 5.40 ddd |
| **$^{13}$C** (δ) | 211.6 | 74.3 | 74.1 | 128.8 | 131.0 |

Waxy solid. Mp: 70−72 °C. $[\alpha]_D$: +15.0° (*c* 0.008, MeOH). UV ($\lambda_{max}$, MeOH, nm): 220 (log ε 3.53). IR ($\nu_{max}$, film, $cm^{-1}$): 3360, 2918, 2897, 1737, 1703, 1648, 1467, 1282, 1199, 669. MS: EIMS *m/z* 367, 337, 319, 307, 283, 265, 253, 235, 223, 125, 97. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: acetonide ($^1$H NMR), per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $1.1 \times 10^1$, A-549 $ED_{50}$ 1.5, MCF-7 $ED_{50}$ 2.8, HT-29 $ED_{50}$ $5.9 \times 10^{-2}$, A-498 $ED_{50}$ 4.9, PC-3 $ED_{50}$ $1.6 \times 10^{-2}$, PACA-2 $ED_{50}$ $2.3 \times 10^{-2}$. Source: *Annona jahnii*, twigs.

Nonclassical Acetogenins

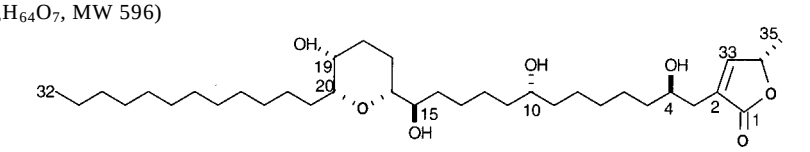
**134. muconin**[9] ($C_{37}H_{67}O_7$, MW 622)



| Position | 12 | 13 | 17 | 18 | 21 | 22 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.43 m | 3.16 m | 3.31 m | 3. 90 m | 3. 80 m | 3. 38 m |
| **$^{13}$C** (δ) | 74.2 | 80.9 | 80.0 | 81.2 | 82.8 | 74.1 |

White wax. MS: EIMS *m/z* 405, 387, 353, 335, 317, 269, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): A-549 $ED_{50}$ $4.5 \times 10^{-3}$, MCF-7 $ED_{50}$ $2.4 \times 10^{-4}$, HT-29 $ED_{50}$ $3.9 \times 10^{-1}$, A-498 $ED_{50}$ $1.8 \times 10^{-1}$, PC-3 $ED_{50}$ $5.8 \times 10^{-1}$, PACA-2 $ED_{50}$ $5.4 \times 10^{-4}$. Source: *Rollinia mucosa*, leaves.

**135. pyranicin**[10] ($C_{35}H_{64}O_7$, MW 596)



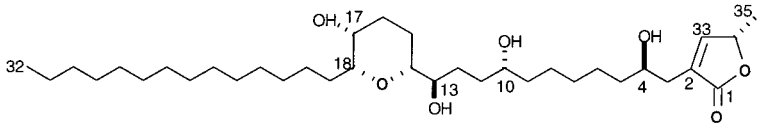
| Position | 10 | 15 | 16 | 19 | 20 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.60 m | 3.46 dt | 3.19 ddd | 3.61 m | 3.34 ddd |
| **$^{13}$C** (δ) | 71.7 | 73.9 | 81.1 | 66.1 | 80.0 |

White amorphous wax. $[\alpha]_D$: −9.7° (*c* 0.008, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 216 (log ε 3.32). IR ($\nu_{max}$, film, $cm^{-1}$): 3418, 2928, 2854, 1748, 1456, 1319, 1086. MS: EIMS *m/z* 426, 309, 291, 273, 269, 251, 241, 223, 205, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR). Biological activities (μg/mL): BST $LC_{50}$ $3 \times 10^{-1}$, A-549 $ED_{50}$ $2.8 \times 10^{-1}$, MCF-7 $ED_{50}$ $3.9 \times 10^{-1}$, HT-29 $ED_{50}$ 1.2, A-498 $ED_{50}$ $1.8 \times 10^{-1}$, PC-3 $ED_{50}$ $4.1 \times 10^{-1}$, PACA-2 $ED_{50}$ $1.3 \times 10^{-3}$. Source: *Goniothalamus giganteus*, stem bark.

**Table 4. (Continued)**

Nonclassical Acetogenins (Continued)

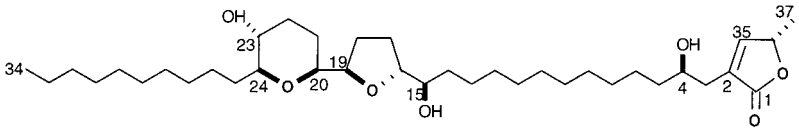
**136. pyragonicin**[10] ($C_{35}H_{64}O_7$, MW 596)



| Position | 10 | 13 | 14 | 17 | 18 |
|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.63 m | 3.50 dt | 3.24 ddd | 3.63 m | 3.36 ddd |
| **$^{13}$C** (δ) | 71.5 | 74.4 | 80.9 | 66.0 | 79.8 |

White amorphous wax. $[\alpha]_D$: −25.6° (*c* 0.008, $CHCl_3$). UV ($\lambda_{max}$, MeOH, nm): 215 (log ε 3.71). IR ($\nu_{max}$, film, $cm^{-1}$): 3479, 2920, 2851, 1748, 1456, 1318, 1084. MS: EIMS *m/z* 381, 297, 281, 279, 263, 245, 241, 223, 205, 141. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: peracetate ($^1$H NMR), per-MTPA esters ($^1$H NMR), formal acetal ($^1$H NMR), TMS (EIMS). Biological activities (μg/mL): BST $LC_{50}$ $9 \times 10^{-1}$, A-549 $ED_{50}$ 2, MCF-7 $ED_{50}$ 1.6, HT-29 $ED_{50}$ 2.8, A-498 $ED_{50}$ $1.3 \times 10^{-1}$, PC-3 $ED_{50}$ $1.2 \times 10^{-1}$, PACA-2 $ED_{50}$ $5.8 \times 10^{-2}$. Source: *Goniothalamus giganteus*, stem bark.

**137. jimenezin**[11] ($C_{37}H_{66}O_7$, MW 622)



| Position | 15 | 16 | 19 | 20 | 23 | 24 |
|---|---|---|---|---|---|---|
| **$^1$H** (δ) | 3.35 m | 3.90 m | 3.94 m | 3.24 ddd | 3.28 ddd | 3.00 ddd |
| **$^{13}$C** (δ) | 73.9 | 82.4 | 80.9 | 79.0 | 70.6 | 82.3 |

Yellow oil. $[\alpha]_D$: +8.3° (*c* 1.2, MeOH). UV ($\lambda_{max}$, MeOH, nm): 210.5 (log ε 3.97). IR ($\nu_{max}$, film, $cm^{-1}$): 3100−3650, 3023, 2928, 1750, 1641, 1423, 1215, 1028, 930. MS: EI-MS (TMS) *m/z* 525, 455, 453, 383, 313, 293, 223, 213, 123. NMR: $^1$H NMR (500 MHz, $CDCl_3$), $^{13}$C NMR (125 MHz, $CDCl_3$). Derivatives: per-MTPA esters ($^1$H NMR), TMS (EI-MS). Biological activities (μg/mL): BST $LC_{50}$ $5.7 \times 10^{-3}$, A-549 $ED_{50}$ $1.6 \times 10^{-2}$, MCF-7 $ED_{50}$ $>10^{-1}$, HT-29 $ED_{50}$ $4.3 \times 10^{-3}$, A-498 $ED_{50}$ $4.9 \times 10^{-2}$, PC-3 $ED_{50}$ $2.8 \times 10^{-4}$, PACA-2 $ED_{50}$ $1.7 \times 10^{-4}$. Source: *Rollinia mucosa*, seeds.

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