Thematic Review Series: Sphingolipids

Biodiversity of sphingoid bases ("sphingosines") and related amino alcohols

Sarah T. Pruett, Anatoliy Bushnev, Kerri Hagedorn, Madhura Adiga, Christopher A. Haynes, M. Cameron Sullards, Dennis C. Liotta, and Alfred H. Merrill, Jr.

Department of Chemistry, Emory University, Atlanta, GA 30322; and Schools of Biology, Chemistry, and Biochemistry and the Parker H. Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, GA 30332-0230

Abstract  “Sphingosin” was first described by J. L. W. Thudichum in 1884 and structurally characterized as 2S,3R,4E-2-aminoocatdec-4-ene-1,3-diol in 1947 by Herb Carter, who also proposed the designation of “lipides derived from sphingosine as sphingolipides.” This category of amino alcohols is now known to encompass hundreds of compounds that are referred to as sphingoid bases and sphingoid base-like compounds, which vary in chain length, number, position, and stereochemistry of double bonds, hydroxyl groups, and other functionalities. Some have especially intriguing features, such as the tail-to-tail combination of two sphingoid bases in the α,ω-sphingoids produced by sponges. Most of these compounds participate in cell structure and regulation, and some (such as the fumonisins) disrupt normal sphingolipid metabolism and cause plant and animal disease. Many of the naturally occurring and synthetic sphingoid bases are cytotoxic for cancer cells and pathogenic microorganisms or have other potentially useful bioactivities; hence, they offer promise as pharmaceutical leads. This thematic review gives an overview of the biodiversity of the backbone of sphingolipids and the broader field of naturally occurring and synthetic sphingoid base-like compounds.—Pruett, S. T., A. Bushnev, K. Hagedorn, M. Adiga, C. A. Haynes, M. C. Sullards, D. C. Liotta, and A. H. Merrill, Jr. Biodiversity of sphingoid bases (“sphingosines”) and related amino alcohols. J. Lipid Res. 2008. 49: 1621–1639.

Supplementary key words sphinganine • phytosphingosine • fumonisin • myriocin • long-chain base • anti-tumor • anti-fungal

Sphingolipids are composed of a structurally related family of backbones termed sphingoid bases, which are sometimes referred to as “long-chain bases” or “sphingosines” after the original designation of the first isolated compound from brain as “sphingosin” by J. L. W. Thudichum in 1884 (1). Today, the term “sphingosine” is usually reserved for (2S,3R,4E)-2-aminoocatdec-4-ene-1,3-diol (compound 6 in Fig. 1), which has important biological functions in cell signaling per se (2, 3) as well as after derivatization to the 1-phosphate (compound 9 in Fig. 1) (2, 4, 5), N-acylated metabolites (ceramides; compound 4 in Fig. 1) (2, 6, 7), and more complex phosphosphingolipids and glycosphingolipids with head groups attached to the hydroxyl on carbon 1. The structural diversity of the latter compounds is widely appreciated, with hundreds of head group variants for mammals alone, as was reviewed recently (8, 9) and addressed at a number of "omics" web sites, such as SphinGOMAP (www.sphingomap.org), the Japanese Lipid Bank (http://www.lipidbank.jp) and Glycoforum (http://www.glycoforum.gr.jp/), the Lipid Maps Consortium (www.lipidmaps.org), the Consortium for Functional Glycomics (http://www.functionalglycomics.org/fg/), and the Complex Carbohydrate Research Center at the University of Georgia (http://www.ccrc.uga.edu/~moremen/glycomics/).

Somewhat less well appreciated is that sphingoid bases also display considerable structural diversity, as was elegantly reviewed by K. A. Karlsson almost 40 years ago (10, 11). In remembrance of Herbert E. Carter, who first elucidated the structure of sphingosine (6) and dihydro-sphingosine (2) (12) and “proposed to designate those lipides derived from sphingosine as sphingolipides” (13), this thematic review summarizes and updates points made previously regarding the structural diversity of sphingoid bases (10, 11) and expands the topic to include sphingoid bases and sphingoid base-like compounds that have been discov-

Abbreviations: SPT, serine palmitoyltransferase.

1 Present address of S. T. Pruett: Yerkes National Primate Research Center, Emory University, Atlanta, GA 30329.

2 To whom correspondence should be addressed.
e-mail: al.merrill@biology.gatech.edu
ried in intervening years. In addition to being fascinating for their biodiversity, some of these naturally occurring compounds (and synthetic analogs) are promising drug leads, while others cause disease, as exemplified by the fumonisins (14).

DIVERSITY IN THE SPHINGOID BASE BACKBONES OF SPHINGOLIPIDS

Within a few decades after the structure for sphingosine 6 had been determined (12) and sensitive methods for the analysis of sphingoid bases devised (15), there was evidence for >60 structural variations (10, 11). The 1997 International Union of Pure and Applied Chemists-International Union of Biochemists Joint Commission on Biochemical Nomenclature (16) proposed that “Sphingoids are long-chain aliphatic amino alcohols...represented by the compound originally called ‘dihydrosphingosine’ [(2S,3R)-2-amino-octadecane-1,3-diol]....imply a chain length of 18 carbon atoms.” Dihydrosphingosine (compound 2 in Fig. 1; also called “sphinganine”) is one of the major sphingoid bases found in many organisms as well as an early intermediate in the de novo biosynthesis of sphingosine via desaturation of dihydroceramides (3) to produce ceramides (4) (17) and for the formation of “phytosphingosine” 7 (2S,3S,4R-2-amino-octadecane-1,3,4-triol) and what is colloquially referred to as “phytoceramide” (compound 5 in Fig. 1) via hydroxylation of sphinganine (18) or dihydroceramide (17). The alternative names (4E)-sphing-4-enine and (4E)-sphingenine are sometimes used to designate the specific location of the double bond of sphingosine.

The International Union of Pure and Applied Chemists-International Union of Biochemists Joint Commission (16) and others (19) have recommended naming chain length homologs by the root chemical name of the parent hydrocarbon (e.g., a 20 carbon sphinganine is called an icosasphinganine and one with 14 carbon atoms is called tetradecasphinganine), and the position and stereochemistry of substituents such as double bonds (with E/Z preferred over trans/cis), hydroxyl groups, methyl groups, etc., should be stated explicitly, if known. Examples of such compounds are shown in Figs. 2 and 3. A useful shorthand nomenclature is to give the number of hydroxyl groups (“d” for the two (di)-hydroxyls of sphingosine and sphinganine and “t” (tri-) for the additional hydroxyl in 4-Fig. 1.

Biosynthesis and turnover of the three major categories of sphingoid bases in mammalian cells. DHR, dihydroceramide; SPT, serine palmitoyltransferase.
hydroxysphinganine] followed by the number of carbon atoms in the backbone and the number of double bonds, with the location and configuration given as a prefix or suffix. Therefore, sphingosine is designated 4E-d18:1 (and sometimes d18:13^H), dihydrosphingosine is designated d18:0, and phytosphingosine (4-hydroxysphinganine) is designated t18:0.

**Mammalian sphingoid bases**

The predominance of 18 carbon sphingoid bases (d18:0, d18:1, and t18:0) in most mammalian sphingolipids is consistent with the preference of mammalian serine palmitoyltransferase (SPT) for saturated fatty acyl-CoAs with 16 ± 1 carbon atoms, combined with the abundance of palmitoyl-CoA (20, 21); nonetheless, small amounts of sphingoid bases with other chain lengths of 12 to 26 carbons have been reported (22, 23). The most common chain length variant is eisosaphingosine (2S,3R,4E-d20:1), which has been found in substantial amounts in gangliosides from brain (24) and human stomach and intestinal mucosa (25) and in sphingomyelin from rats bearing Morris hepatoma 7777 (26). Sphingoid bases with 16 carbon atoms are found in substantial proportions in bovine sphingolipids (e.g., 25–30% in milk sphingomyelin), which also have small amounts of other even and odd carbon chain length homologs (27, 28). Milk gangliosides appear to contain the unusual sphingoid bases 3-ethoxy-d15:0, 3-ethoxy-d17:0, and 9-methyl-3-ethoxy-d15:0 (29). Sphingomyelin and cerebrosides in black epidermis from the Antarctic minke whale also have a high proportion (~25%) of 16 carbon sphingoid bases (30).

Variation in the number and position of double bonds and hydroxyl groups also occurs. Plasma, brain, and human aorta contain a 4E,14Z-diene 15 (31, 32), and 6-hydroxysphingosine 16 is present in skin sphingolipids (23, 33, 34). An unusual sphingosine with the double bond between carbons 3 and 4 (5-hydroxy,3E-sphingosine; compound 17 in Fig. 3) has been found in acid-hydrolyzed brain extracts (35). While it is possible that 17 is a by-product of the acid hydrolysis (36, 37) (as will be discussed below for Fig. 8), it is nonetheless interesting that the N-octanoyl derivatives of both the 5R and 5S stereoisomers of 17 have been reported to be more potent than ceramide in inhibition of the proliferation of a human breast cancer cell line (MCF-7 cells) (38). This is surprising because the 4,5-trans-(E) double bond is usually necessary for ceramide signaling (39).

Sphingoid bases with branched side chains (such as the iso-18 and anteiso-19 configurations shown in Fig. 2) have been reported in sphingolipids from bovine milk and kidney (40), atherosclerotic human aorta (32), and pig hardarian gland (41, 42) (which is not present in all mammals, including humans). Branched-chain sphingoid bases might become associated with mammalian tissues by microorganisms that are part of normal or pathogenic microflora, as illustrated by an iso-d15:0 sphingoid base that is found in *Porphyromonas gingivalis* from diseased dental tissues (43).

![Fig. 2. Sphingoid bases of mammalian tissues.](image-url)
Interestingly, it appears that the poor absorption of “non-mammalian” sphingoid bases, such as the plant 4,8-diene, is due to the efflux of these compounds via P-glycoprotein in the apical membranes of enterocytes (44, 45), which raises the possibility that if this system is not working properly, there might be uptake of such compounds into mammalian tissues.

Small amounts of N- and O-methyl-sphingoid bases are sometimes found in mammalian sphingolipids and are thought mostly to be artifacts of the extraction and handling (36, 37) (as will be discussed below); however, a sphingosine N-methyltransferase activity has been found in mouse brain (46), and recent studies of mice treated with safingol, the L-threo stereoisomer of sphinganine, have found that it undergoes significant N-methylation (N-methyl, N,N-dimethyl, and N,N,N-trimethyl; compounds 11–13 in Fig. 1) and that under these conditions, there is also methylation of endogenous sphingosine and sphinganine (47), which suggests that the methyltransferases are inducible. The endogenous formation of N,N-dimethylsphingosine is interesting because this compound inhibits protein kinase C (48) and sphingosine kinase (49) as well as affects multiple cellular processes (50) and potently induces apoptosis in cancer cell lines (51).

**Sphingoid bases of sphingolipids from other species**

Fungi, plants, insects, and aquatic organisms extend the structural and compositional variation even further, as illustrated in Fig. 3. Insects have primarily 14 and 16 carbon sphingoid bases (52, 53) such as 4E-d14:1 (20 in Fig. 3) and the conjugated diene 4E,6E-d14:2 21 found in Droso-

ophila (54). Nematodes have both iso-branched (4E,15-
methyl-d17:1) and anteiso-branched (4E,14-methyl-d17:1) sphingoid bases (compare 18 and 19 in Fig. 3) (55, 56) in several categories of novel glycosphingolipids, including phosphocholine-containing glycosphingolipids that have been found in the parasitic nematodes Onchocerca volvulus (57) and Ascaris suum (58), with the latter also containing sulfatides (which is not common in invertebrates) (58). A 15-carbon atom (unbranched) phytosphingosine (in amide linkage with a 21:0 iso-branched α-hydroxy fatty acid) has been found in urine of the female hairy crab, Erimacrus isenbeckii, and serves as a sex pheromone to elicit precopulatory behavior in males (59).

Recent studies of a group of viruses (Coccolithovirus) that infect the marine calcifying microalga Emiliania huxleyi have revealed that the viral genome contains a cluster of putative sphingolipid biosynthetic genes, including a SPT (Fig. 1) that utilizes myristoyl-CoA when expressed in yeast (60). This might cause an infected host to produce a 16 carbon chain length sphingoid base, which is interesting because at least one virus (picornavirus) has a capsid protein with a hydrophobic pocket that has been suggested to bind sphingosine (61).

Other types of structural variation include the location of the double bond(s), as shown for compounds 22 and 24.
in Fig. 3, where the double bond is at the 8,9 position versus 4,5 for sphingosine 6. Double bonds are also seen in the phytosphingosine-type compounds 23 and 25 that are common backbones of plants (62), which also have 4,8-dienes (25–27), but interestingly, very little of the prevalent species of mammals (sphingosine, 4E,18:1) with only a single 4E double bond. Plant 4,8-dienes sometimes have branching methyl groups (or hydroxyls at other positions) (62); however, branched sphingoid bases such as 4E,8E,9-methyl-d19:2 (28 in Fig. 3) and 4E,8Z9-methyl-d19:2 (data not shown) are considered to be more typical of fungal sphingolipids (63, 64), including human pathogens such as Cryptococcus neoformans (63, 64), which appears that fungi produce different types of backbones for incorporation into different categories of more complex sphingolipids, based on studies of the mycelial forms of Histoplasma capsulatum, which found compound 28 in glucosylceramides but phytosphingosine 7 as the major backbone of the glycosylinositol phosphorylceramides (66). Fungi are sources for a wide variety of unique sphingoid bases, such as the compounds named termitomycesphins (31 in Fig. 3) from the Chinese mushroom Termitomyces albominosus (67). Other interesting examples will be elaborated upon in discussion of Table 1 and Figs. 4 and 5.

Sphingoid bases with three double bonds, such as (4E, 8E,10E)-2-amino-4,8,10-octadecatriene-1,3-diol (4E,8E,10E-d18:3; 29 in Fig. 3), are found in the spermatozoa of the starfish, Asterias amurensis (68), and the branched version, 2-amino-9-methyl-4,8,10-octadecatriene-1,3-diol (30 in Fig. 3), has been identified in squid nerve sphingomyelin (69). Sponges are another source of sphingoid bases with interesting features, such as the cyclopropane ring in the alkyl side chain of plakosides (32 in Fig. 3), a family of immunosuppressive prenylated galactosphingolipids produced by Plakortis simplex (70). Sphingoid bases with a terpenoid alkyl chain, the aplidiasphingosines (compound 33 in Fig. 4; 1,2-amino-5,9,13,17-tetramethyl-8,16-octadecadiene-1,3,14-triol), have been isolated from the marine tunicate Aplidium species (71, 72) and noted to have antimicrobial and antitumoral activity (71, 73).

Many of the species in the genus Sphingomonas, which are Gram-positive bacteria with glycosphingolipids instead of lipopolysaccharide in the outer membrane, have sphingoid bases with a cyclopropane ring, such as the 13,14-cyclopropane-eicosasphinganine produced by Sphingomonas adhaesiva (74). Because the SPT of Sphingomonas paucimobilis is a cytoplasmic homodimer instead of the membrane-bound heterodimer found in most other organisms, it has been possible to elucidate the crystal structure of the holo form of S. paucimobilis SPT at 1.3 A resolution (75) and to conduct in-depth spectroscopic studies of the catalytic mechanism of this pyridoxal 5'-phosphate-dependent enzyme (76) and comparative studies of the three novel SPT genes from Sphingobacterium multivorum, Sphingobacterium spiritivorum, and Bdellovibrio stolpii (77).

3-Keto sphingoid bases

The first product of de novo sphingoid base biosynthesis, 3-ketosphinganine (1 in Fig. 1), is often not detected in organisms and tissues, because under most circumstances it is rapidly reduced to sphinganine (78); nonetheless, rat liver mitochondria have been reported to contain N-acylated and O-glycosylated derivatives of 3-keto bases (79), and 3-ketodihydroceramide (compound 14 in Fig. 1) has been detected in cells when SPT activity is very high (2); therefore, it appears that when this keto intermediate is not reduced rapidly enough, it is acylated by the next enzyme of the pathway. This might have biological consequences,

| Compound Name | J | H | G | F | E | D | C | B | A | Ref. |
|---------------|---|---|---|---|---|---|---|---|---|-----|
| Myriocin (36 in Fig. 4) | O | = | H | OH (S) | OH (S) | COOH | NH₂ | CH₃OH | (76, 84–86) |
| Sphingofungin A | OH | = | OH (S) | OH (R) | OH (R) | COOH | NH₂ | NHCNH₂H₂ | (76, 86, 91) |
| Sphingofungin B | OH | = | OH (S) | OH (R) | OH (R) | COOH | NH₂ | H | (76, 86, 91) |
| Sphingofungin C | OH | = | OAcetyl (S) | OH (R) | OH (R) | COOH | NH₂ | H | (76, 86, 91) |
| Sphingofungin D | OH | = | OH (S) | OH (R) | OH (R) | NH₂ | COOH | CH₃OH | (76, 86, 91) |
| Sphingofungin E | OH | = | OH (S) | OH (R) | OH (R) | COOH | NH₂ | CH₃ | (76, 86, 91) |
| Sphingofungin F | OH | = | OH (S) | OH (R) | OH (R) | COOH | NH₂ | CH₃ | (76, 86, 91) |
| Sulfamisterin (37 in Fig. 4) | O | H | H | OH (R) | OH (R) | COOH | NH₂ | CH₃OH | (89) |
| Mycestericin A | O | = | H | OH (R) | OH (S) | COOH | NH₂ | CH₃OH | (85) |
| Mycestericin B | OH | = | H | OH (R) | OH (S) | H | H | H | (85) |
| Mycestericin C | O | = | H | OH (S) | OH (S) | NH₂ | COOH | CH₃OH | (85) |
| Mycestericin D | OH | = | H | OH (R) | OH (S) | NH₂ | COOH | CH₃OH | (85) |
| Mycestericin E | OH | = | OH (S) | OH (R) | OH (R) | NH₂ | COOH | CH₃OH | (85) |
| Mycestericin F | O | = | H | H | OH (S) | NH₂ | COOH | CH₃OH | (85) |
| Mycestericin G | OH | = | OH (R) | OH (S) | OH (R) | NH₂ | COOH | CH₃OH | (85) |
| Malonofungin | O | OAc (S) | OH (R) | OH (R) | COOH | NH₂ | COOH | COOH | (93) |
| Fumitubifungin | OH | OH | OAc | OH | NH₂, COOH, and H (stereochemistry not specified) | (94) |
because short-chain 3-ketoceramides have been found to be strong inducers of apoptosis in human leukemia HL-60 cells (80). A family of 3-keto sphingoid base-like compounds, the calicogorgins (34 in Fig. 4), have been found in marine invertebrates and are repellent and lethal against the snail Drupella fragum (81, 82). Another type of oxidized backbone, an imine, is found in hemsleyin imine A (2-octadecanoylimino-heneicosan-1,3-diol; compound 35), which was isolated (83) from the rhizomes of Hemsleya macrocarpa var. clavata, a perennial plant found in northwestern China that is used as folk medicine for the treatment of bronchitis, bacillary dysentery, and tuberculosis.

SPHINGOID BASES AND SPHINGOID BASE-LIKE COMPOUNDS THAT DISRUPT SPHINGOLID METABOLISM

SPT inhibitors

Several categories of fungi produce SPT inhibitors that are sphingoid base-like compounds, as summarized in Table 1 and illustrated for a few examples in Fig. 4: compound 36 in Fig. 4, which has been named ISP-1 (from Isaria inaequalis) (76, 84, 86), myriocin (isolated from Myriococcus alboniger) (87), and thermozycidin (from Mycelia sterilia) (88); sulfamisterin from Pycnidia species (37 in Fig. 4) (89); a sulfated, 18 carbon myriocin-like analog (minus the 4-hydroxyl group); sphingofungins produced by Aspergillus and Paecilomyces (76, 86, 90–92) and other compounds with similar structural features (Table 1), the mycostericins (from Mycelia sterilia) (85), malonofungin (from Phaeomucor ramosus) (93), and fumitremorgin from Aspergillus fumigatus (94). Some of these have not only been found to be potent inhibitors of SPT but also to have immunosuppressive activity, although inhibition of this enzyme is not obligatory for immunosuppression by some of the compounds in this structural series (95), because a more specific immunosuppressive agent (FTY720) has been found that is not an SPT inhibitor. Many also have antifungal activity, as do other categories of SPT inhibitors that are not sphingoid base analogs, such as lipoxamycins (96) and viridiofungins (97).

ISP-1/myriocin 36 has been studied most extensively because it is highly potent, with an IC₅₀ in the nanomolar range (84), and commercially available. Spectroscopic studies suggest that ISP-1/myriocin inhibits activity by forming an external aldime with pyridoxal 5′-phosphate in the active site of SPT, as does the substrate serine (76). Indeed, all of the SPT inhibitors share this resemblance to serine (Table 1). It is noteworthy that the sulfate group of sulfamisterin (37) only reduces the potency of sulfamisterin by ∼10-fold versus ISP-1/myriocin when assayed in a cell-free system, which implies that this enzyme can accommodate both the extra size and charge at this position (89).

There is growing interest in the pharmaceutical potential of SPT inhibition because ISP-1/myriocin interferes with the production of cytocidal ceramide in response to a wide variety of stresses (98), suppresses virus infectivity (99, 100), alters brain amines (101), and suppresses athero-
sclerotic lesions (102–104). It has been noted that the Isaria (= Cordyceps) group of fungi also includes Cordyceps sinensis Sacc., which has been used in Chinese traditional medicine as a drug (Chinese name, dong chong xia cao) for eternal youth (85, 105).

Ceramide synthase inhibitors

Fungi produce diverse sphingoid base-like compounds (typified by compounds 38–40 in Fig. 4) and nonsphingoid base-like compounds (compound 42 in Fig. 4) that inhibit ceramide synthases, the enzymes that are responsible for the acylation of sphingoid bases (106, 107) (Fig. 1). The first to be discovered (14) were the fumonisins (represented by fumonisin B1 38 in Fig. 4 and additional family members 43–50 in Fig. 5), which are mycotoxins produced by Fusarium verticilloides. This fungus commonly infests maize and causes diseases of plants (108) and animals (including humans) (109, 110) that consume these compounds as food contaminants (111). The traditional method of preparation of corn (maize) for tortillas involves treating the maize with lime (nixtamalization) followed by extensive washing, which removes a substantial portion of the fumonisins and hydrolyzes the tricarballylic acid side chains (compound 41 in Fig. 4) that are ester linked to side chain hydroxyls (as "R" on compound 38 and 43–50). The compounds that are produced are usually referred to as “aminopentols” numbered according to the parent fumonisin (such as AP1 39 from FB1 38 in Fig. 4) (112, 113). Removal of the tricarballylic acid(s) diminishes the potency of the inhibition of ceramide synthase (which has been suggested to be due to the interaction of the polyanionic side chains with the binding site for the fatty acyl-CoA cosubstrate) (109) but also converts the compound into a ceramide synthase substrate that is acylated to produce cytotoxic N-acylaminopentols (114–116); therefore, it appears that nixtamalization will be most ef-

---

Fig. 5. Structures of the major members of the fumonisin (A) and AAL toxin (C) families. Also shown are a compound with a fumonisin-like backbone but without side chain hydroxyls (B) and the sphingomyelinase inhibitor scyphostatin (D).
fective at detoxifying contaminated maize by washing away of the fumonisins rather than just the removal of the tri-
carballylic side chains.

The discovery of the fumonisins in South Africa in 1988
is a classic story of scientific sleuthing by W. S. A. Marasas
(117) and coworkers, beginning with the isolation of
F. verticillioides (originally named F. moniliforme) from
moldy corn implicated in a field outbreak of equine leuko-
encephalomalacia in South Africa in 1970; observation that
this fungus was also prevalent in moldy corn con-
sumed by people in high-incidence areas of esophageal
cancer in the Transkei region of South Africa; demon-
stration that feeding culture material from F. verticillioides
strain MRC 826 to horses recapitulated the equine disease
and also caused porcine pulmonary edema syndrome in
pigs and liver cancer in rats; isolation and structural elu-
cidation of the fumonisins; and demonstration that puri-
fied fumonisins cause these symptoms.

Soon after the structure of fumonisin B1 was elucidated
(118), the similarity to sphinganine led to the discovery
of its inhibition of ceramide synthase (14). This was signifi-

cant not only because it provided a specific target for this
mycotoxin but also because it was the first case in which a
defect in sphingolipid biosynthesis causes disease, in con-
trast to the many diseases that were then known to be
caused by genetic defects in sphingolipid turnover (e.g.,
Niemann-Pick, Gaucher’s disease, etc.) (119). It is not sur-
prising that fumonisins have a wide range of pathologic ef-
fects, since inhibition of ceramide synthase (Fig. 1) causes
not only the depletion of ceramides and complex sphingo-
lipids but also the buildup of highly bioactive compounds
(sphinganine, sphinganine 1-phosphate, N-acetyl-sphinga-
nine, and other sphingoid bases depending on the time
of treatment and dosage) (109, 110). Fumonisin also
causes a “mystery” compound to appear (120), which was
recently found to be 1-deoxy-sphinganine (N. C. Zitomer,
personal communication). In addition to the tissue damage
(e.g., equine leukoencephalomalacia, porcine pulmonary
edema, hepatotoxicity, and renal toxicity) and carcinogenic-
ity generally associated with fumonisin consumption (117),
one might suspect that changes in so many bioactive species
could adversely affect health in more ways than are cur-
rently appreciated, and recent laboratory (121–124) and
epidemiologic (125) studies have implicated fumonisins in
birth defects.

Figure 5 shows the types of structural variants found in
fumonisins and a related family of mycotoxins, the AAL toxins (represented by AAL toxin TA 40 in Fig. 4),
which are produced by Alternaria alternata and cause dis-
ease in plants (108, 126, 127). All are sphingoid base-like
amino alcohols, but the B series fumonisins (38, 39, and
43–45) are 1-deoxy-sphingoid bases, the C series fumoni-
sins (47–50) and the AAL toxins (40 and 52–54) lack the
1-hydroxymethyl group, and the A series fumonisins (repre-
sented by FA, 46) and AAL-toxin TD (54) are N-acetylated.

Another metabolite, 2-amino-14,16-dimethyloctadecan-3-ol
(compound 51 in Fig. 5), has been isolated from a strain of
Fusarium avenaceum cultured on rice and found to be cyto-
toxic for the rat hepatoma cell line H4IE-W and a porcine
epithelial kidney cell line at micromolar concentrations
(128). This compound is more “sphinganine-like” because
it does not have the side chain hydroxyls; therefore, it
should undergo substantial acylation like other 1-deoxy-
sphinganines (114). The authors comment that F. avenaceum
has the potential to produce the metabolite under field
conditions that might occur in northern Europe (128),
meaning in regions that have heretofore been found to
have little fumonisin contamination because F. verticillioides
requires a warmer climate.

The broad category of toxins that mimic sphingolipids
has been referred to as sphinganine (or sphingosine/ser-
amide) analog toxins (129, 130). This categorization has
been employed to compare not only the structure and func-
tion of these compounds but also their biosynthesis (131),
because sphingoid base analogs minus the 1-hydroxyl (com-
ounds 38, 39, 43–45, and 51) versus the 1-hydroxymethyl
(compounds 40, 47–50, and 52–54) groups are biosynthe-
sized from alanine versus glycine, respectively, instead of
serine, which is the source of the 1-hydroxyl and 2-amino
groups of sphingoid bases (Fig. 1).

Other steps of sphingolipid metabolism

Naturally occurring inhibitors of other steps of sphingo-
lipid metabolism have been found (132), such as rustemicin,
which inhibits inositol phosphoceramide synthase (133);
however, with the exception of scyphostatin (compound
55 in Fig. 5), a neutral sphingomyelinase inhibitor from
Trichopeza mollissima (134), most do not fit in the category
of sphingoid bases or sphingoid base-like compounds.

“Simpler” 1-deoxy-sphingoid bases

In addition to the relatively complex 1-deoxy-sphingoid
bases discussed above, plants and marine organisms have a
wide variety of simpler compounds, even a species that is
equivalently to sphinganine but lacking the 1-hydroxyl. This
compound (spilusolins 56 in Fig. 6) has been isolated from
the clam Spisula polynyma (Stimpson’s surf clam or
Atlantic surf clam; syn. Mactromeris polynyma) (135). It is
also referred to as “ES-285” (the “285” refers to its molecu-
lar weight) as an investigational marine anticancer drug
(136) because it inhibits the proliferation of numerous
cancer cell lines. The mechanisms for its effects are not
known, but it disrupts actin stress fibers through the inac-
tivation of Rho (135) and has been suggested to induce
cell death in the prostate cancer cell lines PC-3 and LNCaP
via stimulation of the de novo synthesis of ceramide and
protein kinase Cζ activation (137). Spilusolins has also
been found to activate caspase 3 and 12 and to modify the
phosphorylation of p53, but it did not affect JNK, Erks,
or Akt; therefore, it has been suggested to trigger an atyp-
cal cell death program compared with other sphingosine-
dependent apoptosis pathways (138).

In other studies, 1-deoxy-sphingoid bases have been shown
to be more cytotoxic than sphingosine against HT29 cells
(139). This category of compound is also known to be ac-
ylated by ceramide synthase (114); hence, it is possible that
1-deoxyceramides may play a role in the biological effects.
Other spisulosine-related compounds include the shorter chain length xestoaminols (represented by xestoaminol C, 1-deoxy14:0, from Xestospongia species and halaminol A, 1-deoxy14:1, from Haliclona n. species; 57 in Fig. 6) (140), and the polyunsaturated obscuraminols (represented by obscuraminol A 58 in Fig. 6) from Pseudodistoma obscurum (141). The obscuraminols were isolated from a chloroform extract of this sponge that was cytotoxic for mouse lymphoma P-388, human lung carcinoma A-549, and human colon carcinoma HT-29 tumor cell lines, but the isolated compounds were only mildly cytotoxic. Crucigasterins (represented by crucigasterin 277; 59 in Fig. 6), from Pseudodistoma crucigaster (142), are similar to these compounds but have 2R,3S rather than 2S,3R stereochemistry (135, 137, 141). Crucigasterins show antimicrobial activity against Bacillus subtilis and are cytotoxic against mouse lymphocytic leukemia L1210 cells (142).

There are also 1-deoxy-sphingoid base-like compounds with five and six member rings as part of the side chain (amaminol A, isolated from tunicates of family Polyclinidae; compound 60 in Fig. 6) (143). This type of compound might be formed by cyclization of a polyene such as 58 or 59.

α,ω-SPHINGOID BASE-LIKE COMPOUNDS

A fascinating series of compounds, which have been referred to as “α,ω-bifunctionalized amino alcohols” (144),
so we have called them \textit{\textalpha;\textomega;} sphingoid base-like compounds, resemble “two-headed” sphingoid bases (i.e., two sphingoid bases connected tail to tail; compounds 61–64 in Fig. 6). Calyxinin 61, the aglycone of a sphingoid base 1-B-glucoside named calyxoside from sponges of the genus \textit{Calyx} in the family \textit{Oceanapidae}, resembles sphinganine (numbering from position 1) on one end and a 1-deoxy-sphinganine at the other end (with the opposite, \textit{threo}, stereochemistry) (145). It has been proposed that calyxoside is probably not formed from the union of the tails of two identical smaller lipids because the ketone is not at the expected position (unless the ketone is created later) (144, 145).

Oceanin (62 in Fig. 6) is the aglycone of oceanapiside from \textit{Oceanapia philippensis} (146–148). While oceanin is very similar to calyxinin with the same stereochemistry as a sphingoid base for carbons 2 and 3 (\textit{S,erythro}) as well as a \textit{threo} stereochemistry on the \textomega; amino alcohol, the latter is opposite for these compounds (i.e., oceanin is 26\textit{R,27R} versus 26\textit{S,27S} for calyxinin). They differ also in the position of \textomega;glucosylation for oceanapiside (the hydroxyl at carbon 3) and calyxoside (carbon 1) and were once thought to have the ketone in different positions (11 vs. 18); however, this has been revised and the structures shown in Fig. 6 reflect the most recent report (148). The carbohydrate plays a major role in some of the biological activities of oceanapiside, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit mycothiol-/S/-conjuga te amidase, a mycobacterial activities of \textit{Oceanapiaide}, which has been reported to inhibit they are unstable in the liver. In contrast, the carbohydrate has little, and perhaps a slightly negative, effect on the antifungal activity with two binding sites on a single target or perhaps to interact with more than one target to effect their biological response (144). This might include interaction with two binding sites on a dimeric enzyme of sphingolipid metabolism (or signaling) or perhaps the active sites of two enzymes in close proximity in a multienzyme complex. It is also possible that the length of these compounds enables them to span a membrane bilayer for structural or signaling purposes.

**Capnines, sulfofabcins, and other 1-sulfonosphingoids**

Gliding bacteria of the genus \textit{Cytophaga} synthesize sulfofabcins that contain capnine (1-deoxy,15-methyl-hexadecaphosphagine-1-sulfonic acid; compound 65 in Fig. 6) (154), which appears to be the same as the backbone for the sulfofabcins that have been isolated from the culture broth of \textit{Chryseobacterium} species (\textit{Flavobacterium} species) NR 2993 and for which the stereochemistry has been assigned (2\textit{R,3\textit{R}}) (155). Studies of capnine biosynthesis (156, 157) using isotopically labeled precursors have suggested that the biosynthesis of capnine occurs by the condensation of 15-methylmyristoyl-CoA with cysteic acid in a reaction analogous to the condensation of palmitoyl-CoA with serine for the biosynthesis of sphingolipids. A cysteine auxotroph of \textit{Cytophaga johnsonae} was able to incorporate sulfur from sulfate into cysteate and sulfofabcin, which further indicates that cysteine per se is not an obligatory intermediate of capnine biosynthesis (158).

**Heterocyclic sphingoid base-like compounds**

There are a large number of sphingoid base-like compounds in which the amino group is part of a heterocyclic ring, as illustrated in Fig. 7. The simplest heterocycle is the aziridine (azacyclopropene) ring found in 4\textit{E}(\textit{R})-dysidazirine 67 (161) and (\textit{S})-antazirine 68 (162), which were isolated from the marine sponge \textit{Dysidea fragilis} (Dysideidae). These do not formally qualify as sphingoid bases because they are not amino alcohols; however, it is easy to envision how the aziridine ring might be formed via a 2-amino,3-keto intermediate similar to that formed in de novo sphingolipid biosynthesis (e.g., compound 1 in Fig. 1).

Penaseridin A and B (69 in Fig. 7) (163–165) and penazetidine A 70 (166) are azetidines produced by \textit{Penares} sponges. Penaseridins have been reported to activate ATPases (164), and penazetidine A is an inhibitor of protein kinase C (166, 167). Both have shown cytotoxicity against a variety of cell types, and analogs of penaseridin B with a simple alkyl chain have been found to be considerably (i.e., up to 10-fold, or an IC\textsubscript{50} of \textsim;1 \textmu M) more cytotoxic against lung (A549) and colon (HT29) cancer cell lines and showed antibacterial activity against Gram-positive bacteria (\textit{Bacillus subtilis}, \textit{Micrococcus luteus}, and \textit{Staphylococcus aureus}) and, in one case, against Gram-negative \textit{Escherichia coli} (165).

Pramanicin (compound 71 in Fig. 7) (168) is an interesting sphingoid base-like pyrrole biosynthesized from ser-
ine by *Stagonospora* species ATCC 74235 that, in addition to having a highly polar, five-member heterocyclic head group, has an aliphatic side chain with both a vinyl ketone and an epoxide. This compound is active against a number of fungi, including *Cryptococcus neoformans*. Pramanicin has also been found to disturb the vasorelaxation of dog carotid artery by selectively acting on the endothelial cells, causing relaxation through the endothelium-dependent nitric oxide pathway to activate endothelial nitric oxide synthase (169), and the epoxide is required for the optimal effects (170). It also activates caspases and induces apoptosis in Jurkat leukemia cells (171).

There are a very large number of six-member ring heterocyclic compounds that appear to be derived from sphingoid bases (e.g., compounds 72–76 in Fig. 7). While these might not be as readily recognizable as sphingoid bases, disconnection of the heterocyclic ring (as displayed in the brackets beside compound 72 in Fig. 7) reveals an acyclic species that is essentially a sphingoid base. Prosopinine 72 and its isomer prosophylline (data not shown), which have been isolated from the spiny shrub *Prosopis*, are antibacterial and anesthetic (172, 173). Micropine 73 (from *Micropus phillippenis*) has a side chain with three conjugated double bonds and has shown antimicrobial activity against several bacteria, including *Pseudomonas auriginosa* and *S. aureus* (172).

Prosafrinine (compound 74 in Fig. 7), which has been isolated from *Prospis africana* leaves (174), represents a cyclized 1-deoxy-sphingoid base (by the same retrosynthetic logic shown in the brackets beside 72). A wide variety of diastereomers and chain length variants of prosafrinine have been found in *Cassia spectabilis* (175, 176) and *Cassia leptomphylla* (175, 177–179). Azimine (compound 75 in Fig. 7) and carpaine (data not shown) are complex cyclic dimers produced by the plant *Azima tetracantha* (180, 181).

The pseudodistomins (represented by 76 in Fig. 7) are diamine analogs that have been isolated from the sponges *Pseudodistoma kanoko* and *Pseudodistoma amegalarva*, and subspecies in this family differ in the stereochemistry of the amino alcohol and the alkyl chains (147, 150, 182). Some have been found to be cytotoxic against murine lymphoma L1210 cells (151), which might make them interesting antitumor candidates (183), but others cause DNA damage in cell culture (184).

There are also heterocyclic sphingoid base-like compounds that have more than one ring, such as the lepadins (represented by leparin D 77 in Fig. 7) and clavopictines (represented by 78) from *Prostheceraeus villatus*, *Clavelina lepadiformis*, and *Aplidium tabascum* and pictamine (data not shown) from *Clavelina picta* (174, 185–188). It has been noted that pictamine and the lepadins can also be envisioned to contain an acetylcholine mimetic in their backbone, and this might account for their biological activity blocking nicotinic acetylcholine receptors (174, 185, 186, 188). Oceanalin A (compound 79 in Fig. 7) is an α,ω-bifunctionalized sphingoid base-tetrahydroisoquinoline.
from the sponge *Oceanapia* species that in its glycoside form (R = galactose) has in vitro antifungal activity against *C. glabrata* and has been suggested to block sphingolipid biosynthesis by inhibiting ceramide synthase (189).

**COMPOUNDS PRODUCED FROM THE REACTION OF SPHINGOID BASES AND SPHINGOLIPIDS UNDER OTHER “PHYSIOLOGIC” CONDITIONS**

In addition to the naturally occurring and synthetic compounds described above, there are also numerous conditions that structurally modify sphingoid bases, beginning with the well-known metabolic pathways (acylation, phosphorylation, and head group addition) to which N-methylation was recently added (47) (Fig. 1). There are also “lyso” derivatives that are thought to be formed by first biosynthesizing a complex sphingolipid (i.e., with amide-linked fatty acid and head group, such as sphingomyelin) followed by removal of the fatty acid (examples being lysosphingomyelin = sphingosylphosphocholine, and psychosine, which is a monohexosylsphingosine such as galactosylsphingosine).

A very interesting category of highly reactive products, sphingoid base chloramines (represented by compound 80 in Fig. 8), are created upon the reaction of the free amine with hypochlorous acid and hypochlorite, which are produced in some biological systems by myeloperoxidase, a heme-containing enzyme that neutrophils use to kill bacteria (190). As shown in the reaction pathway diagram in Fig. 8A, the intermediate chloramine eliminates HCl and undergoes chain cleavage to produce 2-hexadecenal (the same catabolic product that is formed by sphingoid base turnover enzymatically; Fig. 1) and 1-cyanomethanophosphocholine (if the sphingoid base is sphingosylphosphocholine, as shown in this example) by the likely mechanism in Fig. 8. Fatty aldehydes are also highly reactive compounds and have been associated with the pathogenesis of Sjögren-Larsson syndrome, an inherited neurocutaneous disorder caused by mutations in the enzyme that catalyzes the oxidation of fatty aldehydes to fatty acids (191). Fatty aldehydes are also encountered as natural components of food (and food additives) (192) and as insect pheromones (193, 194).

The reactions shown in Fig. 8B have long been known [dating back to studies by Herb Carter (36)] to occur during acid hydrolysis of sphingolipids (37). In addition, acyl chain migration can occur in ceramides under acidic conditions, as shown in Fig. 8C (195). Because biochemistry often capitalizes on the intrinsic chemical reactivity of compounds, one can envision how these chemical interconversions might occur in a biological context.

![Fig. 8. Common chemical reactions that modify sphingoid bases. A: The formation and decomposition of sphingoid base chloramines due to myeloperoxidase generated reactive chlorination species. B, C: Reactions of sphingoid bases and ceramides under acidic conditions.](image)
Synthetic analogs based on sphingoid bases

Due to the numerous associations between sphingolipids and disease, sphingoid bases, sphingoid base-like compounds, and derivatives of such compounds offer promise as therapeutic agents (196, 197), especially as antibacterial (198), antifungal (199), and anticancer (196, 197, 200) drugs. In addition to mimicking endogenous sphingolipids to activate or inhibit cellular targets of pharmaceutical interest, analogs might also be useful as modulators of endogenous sphingolipid metabolism to achieve this goal (201).

Figure 9 summarizes some of the sphingoid bases and analogs that have been developed as potential pharmaceutical leads and/or as tools to study the functions of sphingolipids. Safingol (L-threo-sphinganine, 84) is currently being evaluated in phase I human clinical trials because it has modest host toxicity (202) and displayed antitumor activity in preclinical studies when used in combination with another agent, such as mitomycin C (203) or fenretinide (204, 205). Safingol is acylated by mammalian ceramide synthase(s) (114) and was recently found to undergo substantial N-methylation (to N-methyl, N,N-dimethyl, and N,N,N-trimethyl derivatives) (47), which is interesting because N,N-dimethylsphingosine is cytotoxic for many cancer cell lines (51, 206, 207) (and presumably, the same may be the case for N,N,N-trimethylsafingol, 85). The formation of N-methyl derivatives in vivo is also interesting because administration of N,N,N-trimethylsphingosine (86) intravenously at the onset of ischemia has been found to reduce myocardial infarct size and improvement in cardiac function (208).

Synthetic 1-deoxy-sphinganines have been developed as potentially useful alternatives to natural sphingoid bases because they cannot be phosphorylated and degraded via sphingosine 1-phosphate lyase (209). One category (which has been given the name “enigmols,” represented by compound 87 in Fig. 9) shifts the 1-hydroxyl to carbon 5 to maintain the relative hydrophilicity of the parent sphinganine and thereby facilitate cellular delivery (209). Depending on the stereochemistry, 1-deoxy-sphingoid bases are also less rapidly acylated to 1-deoxy-dihydroceramide analogs (114). It is possible that such analogs affect the same cellular target(s) as 1-deoxy-sphinganine (spisulosine, ES-285, compound 56).

Other unusual sphingoid bases have been tested as the backbones for ceramide analogs; for example, (2S,3R)-(4E,6E)-2-amino-octadecadiene-1,3-diol (88 in Fig. 9) coupled with an eight carbon chain length fatty acid has been found to be more cytotoxic than ceramide for MCF-7 cells, which the authors suggest may be due in part to its causing a prolonged elevation of intracellular ceramide (210). A cationic, water-soluble derivative of safingol (L-threo-C6-pyridinium-ceramide-bromide; 89 in Fig. 9) has also been shown to inhibit the growth of various human head and neck squamous cell carcinoma cell lines alone or in combination with gemcitabine (211). N-Oleoyl-serinol (90) has been uti-
lized to modulate the path of development of embryonic stem cells as well as to suppress the formation of stem cell–derived tumors (teratomas), which is regarded to be a significant obstacle to stem cell therapy (212).

One of the most studied sphingolipid metabolic pathways is the drug FTY720 (also referred to as “fingolimod”; compound 91 in Fig. 9), which was developed in the course of looking for a less toxic form of the SPT inhibitor ISP-1/myriocin (85, 101, 213). FTY720 does not inhibit this enzyme, but it is phosphorylated by sphingosine kinase to yield an agonist for sphingosine 1-phosphate receptors that also behaves as an antagonist by desensitizing the sphingosine 1-phosphate receptor, resulting in immunosuppression (214). Although FTY720’s mechanisms of action are not fully understood, it appears to reduce the number of circulating lymphocytes by inhibiting lymphocyte egress from peripheral lymph nodes, hence, tissue-damaging T-cells cannot recirculate and infiltrate sites of inflammation. FTY720 effectively prevents transplant rejection, is being evaluated in human clinical trials for safety and tolerability in renal transplantation, and has shown promising results in phase II trials for multiple sclerosis (95, 213).

Fenretinide (4-hydroxyphenylretinamide; compound 92) is another ceramide-like agonist that has low toxicity and promising efficacy in some human clinical trials (e.g., risk reduction of second breast cancer in premenopausal women) (215) but not others, such as for advanced renal carcinoma (216) or the prevention of tumor recurrence in patients with transitional cell carcinoma of the bladder (217). Its mechanism of action is thought to involve the induction of de novo sphingolipid biosynthesis (204) and was initially thought to induce tumor cell death via ceramide; however, it has been shown instead to elevate dihydroceramide and autophagic cell death (2).

PERSPECTIVES ON SPHINGOID BASE LIPIDOMICS

This review has given an overview of the amazing biodiversity of sphingoid bases and sphingoid base-like compounds. This complexity presents a large conceptual challenge (i.e., what are the biochemical functions of these biomolecules?) and an equally serious analytical challenge, since one will ultimately need to identify which of these are present in a given biological system, then quantify all of the pertinent subspecies.

In principle, sphingoid bases are relatively easy to analyze by liquid chromatography, electrospray tandem mass spectrometry in positive ion mode (218). However, when studying these compounds in a living organism, it is not sufficient to analyze only the sphingoid bases per se but also all of the potential downstream metabolites, which multiplies the complexity of the analysis. An excellent in-depth review of methods for the analysis of complex (glyco)sphingolipids has been published (63), and methods for more narrow subclasses, such as all of the backbone metabolites and immediate products (such as sphingomyelins, ceramide phosphates, glucosylceramides, etc.) are also available (63, 218, 219). Nonetheless, much more sophisticated technologies will be needed to analyze a sphingolipidome of this complexity.

“Sphingolipidomic” analysis is becoming increasingly vital for studies of cell signaling to know, for example, the relative amounts of proapoptotic versus antiapoptotic ceramide and sphingosine 1-phosphate (220). In addition, sphingolipids can serve as biomarkers for disease (221, 222) and even as a biological signature, as illustrated by a study of the physiological status and bacterial diversity of estuarine microbial mats (223), which used the presence of sphingoid bases (d18:0, d19:0, and d21:1) and hydroxy fatty acids to predict the presence of organisms in the Bacteroides genus, because they are known to have sphingolipids (224).

The biodiversity of the sphingoid bases and sphingoid base-like compounds will continue to amaze, challenge, and amuse scientists for many years to come, just as Thudichum, Carter, and other giants of the early days of sphingolipid research experienced as they gave birth to this field.

REFERENCES

1. Thudichum, J. L. W. 1884. A Treatise on the Chemical Constitution of Brain. Bailliere, Tindall, and Cox, London.
2. Zheng, W., J. Kollmeyer, H. Symolon, A. Momin, E. Munter, E. Wang, S. Kelly, J. C. Allegood, Y. Liu, Q. Peng, et al. 2006. Ceramides and other bioactive sphingolipid backbones in health and disease: lipidomic analysis, metabolism and roles in membrane structure, dynamics, signaling and autophagy. Biochem. Biophys. Acta. 1758:1864–1884.
3. Dickson, R. C. 2008. Thematic review series: sphingolipids. New insights into sphingolipid metabolism and function in budding yeast. J. Lipid Res. 49:909–921.
4. Spiegel, S., and S. Milstien. 2003. Sphingosine-1-phosphate: an enigmatic signalling lipid. Nat. Rev. Mol. Cell Biol. 4:397–407.
5. Alvarez, S. E., S. Milstien, and S. Spiegel. 2007. Autocrine and paracrine roles of sphingosine-1-phosphate. Trends Endocrinol. Metab. 18:300–307.
6. Hannun, Y. A., and L. M. Obeid. 2002. The ceramide-centric universe of lipid-mediated cell regulation: stress encounters of the lipid kind. J. Biol. Chem. 277:25847–25850.
7. Kitatani, K., J. Idkowiak-Baldys, and Y. A. Hannun. 2008. The sphingolipid salvage pathway in ceramide metabolism and signaling. Cell. Signal. 20:1010–1018.
8. Merrill, A. H., Jr., M. D. Wang, M. Park, and M. C. Sullards. 2007. Ceramides and other bioactive sphingolipid backbones in health and disease: lipidomic analysis, metabolism and roles in membrane structure, dynamics, signaling and autophagy. Biochem. Biophys. Acta. 1758:1864–1884.
9. Yu, R. K., M. Yamagisawa, and T. Ariga. 2008. Glycosphingolipid structures. In Comprehensive Glycobiology. J. P. Kamerling, editor. Elsevier, Oxford, UK. in press.
10. Karlsson, K. A. 1970. On the chemistry and occurrence of sphingolipid long-chain bases. Chem. Phys. Lipids. 5:6–43.
11. Karlsson, K. A. 1970. Sphingolipid long chain bases. Lipids. 5:878–891.
12. Carter, H. E., F. J. Glick, W. P. Norris, and G. E. Phillips. 1947. Biochemistry of the sphingolipids. III. Structure of sphingosine. J. Biol. Chem. 170:285–294.
13. Carter, H. E., W. J. Haines, W. E. Ledyard, and W. P. Norris. 1947. Biochemistry of the sphingolipides. I. Preparation of sphingolipides from beef brain and spinal cord. J. Biol. Chem. 169:77–82.
14. Wang, E., W. P. Norred, C. W. Bacon, R. T. Riley, and A. H. Merril, Jr. 1991. Inhibition of sphingolipid biosynthesis by fumonisin. Implications for diseases associated with Fusarium moniliforme. J. Biol. Chem. 266:14486–14490.
15. Sweeley, C. C., and E. A. Moscatelli. 1959. Qualitative microanalysis and estimation of sphingolipid bases. J. Lipid Res. 1:40–47.
16. Chester, M. A. 1998. IUPAC-IUB Joint Commission on Biochem-
Omae, F., M. Miyazaki, A. Enomoto, M. Suzuki, Y. Suzuki, and A. Suzuki. 2004. DES2 protein is responsible for phytoceramide bio-
synthesis in the mouse small intestine. Biochem. J. 379: 687–695.

Fahy, E., S. Subramanian, H. A. Brown, C. K. Glass, A. H. Merrill, Jr., R. C. Murphy, C. R. Raetz, D. W. Russell, Y. Seyama, W. Shaw, et al. 2005. A comprehensive classification system for lipids. J. Lipid Res. 46: 839–861.

Merrill, A. H., Jr., and R. D. Williams. 1984. Utilization of different fatty acyl-CoA thioesters by serine palmitoyltransferase from rat brain. J. Lipid Res. 25: 185–188.

Haynes, C. A., J. C. Allegood, K. Sims, E. W. Wang, M. C. Sullards, and A. H. Merrill, Jr. 2008. Quantitation of fatty acyl-coenzyme A fatty acyl-CoA thioesters by serine palmitoyltransferase from rat liver. J. Lipid Res. 49: 1113–1125.

Farwanah, H., B. Pierstorff, C. E. Schmelzer, K. Raith, R. H. Neubert, T. Koter, and K. Sandhoff. 2007. Separation and mass spectrometric characterization of covalently bound skin ceramides using LC/APCI-MS and NanoESI-MS/MS. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 852: 562–570.

Stewart, M. E., and D. T. Downing. 1999. A new 6-hydroxy-4-
sphingenines: ceramides with an unusual sphingoid backbone. J. Org. Chem. 68: 355–359.

Bielawska, A. H. M. Crane, D. Liotta, L. M. Obeid, and Y. A. Hamann. 1993. Selectivity of ceramide-mediated biology. Lack of activity of ceramides from zwitterionic glycosphingolipids of adult Caenorhabditis elegans. Eur. J. Biochem. 219: 107–112.

Morrison, W. R. 1973. Long-chain bases and growth inhibitory activity of chiral 5-hydroxy-2-N-acyl-(3E)-
sphingenines: ceramides with an unusual sphingoid backbone. J. Org. Chem. 68: 355–359.

Chun, J. H. S. Byun, G. Arthur, and R. Bittman. 2003. Synthesis and growth inhibitory activity of chiral 5-hydroxy-2-N-acyl-(3E)-
sphingenines: ceramides with an unusual sphingoid backbone. J. Org. Chem. 68: 355–359.

Kadowaki, H., E. G. Bremer, J. E. Evans, F. B. Jungalwala, and R. H. McCluer. 1983. Acetonitrile-hydrochloric acid hydrolysis of gan-
tivines of sphingosine. Isolation and characterization of diacetate de-

Carter, H. E., O. Nalbandov, and P. A. Tavormina. 1951. Biochem.

Kisic, A., M. Tsuda, R. J. Kulmacz, W. K. Wilson, and G. J. Schroepfer, Jr. 1995. Sphingolipid bases: a revision of the O-methyl deriva-
tives of sphingosine. Isolation and characterization of diacetate de-

Martin, M. J., S. Martin-Sosa, and P. Hueso. 2001. Bovine milk gangliosides: changes in ceramide moieties with stage of lactation. Lipids 36: 291–298.

Yonoki, K., H. Ishikawa, Y. Fukui, and M. Ohnishi. 2008. Chemical properties of epidermal lipids, especially sphingolipids, of the Ant-

Renkonen, O., and E. L. Hirvisalo. 1969. Structure of plasma sphingomyelins. J. Chromatogr. A. 114E: 164–185.

Keranen, A. 1976. Fatty acids and long-chain bases of gangliosides of human gastrointestinal mucosa. Chem. Phys. Lipids. 17: 14–21.

Merrill, A. H., Jr., E. Wang, and P. W. Wertz. 1986. Differences in the long chain (sphingoid) base composition of sphingomyelins from rats bearing Morris hepatoma 7777. Lipids. 21: 529–530.

Byrdwell, W. C., and R. H. Perry. 2007. Liquid chromatography with dual parallel mass spectrometry and 39P nuclear magnetic resonance spectroscopy for analysis of sphingomyelin and dihydroxyphosphogly-

Karanos, T., M. Kinosita, M. Ohnishi, J. Nagata, and M. Saito. 2003. Digestion of maize sphingolipids in rats and uptake of sphin-
gadienine by Caco-2 cells. J. Nutr. 133: 2777–2782.

Sugawara, T., Y. Takata, and A. H. Merrill, Jr. 1995. Sphingolipid bases: a revisitation of the O-methyl deriva-
tives of sphingosine. Isolation and characterization of diacetate de-

Takacs. 2000. Human sphingosine kinase: molecular cloning, func-
tional characterization and tissue distribution. Gene. 251: 19–26.

Kim, H. L., and D. S. In. 2008. N,N-Dimethyl-D-erythro-sphingosine increases intracellular Ca2+ concentration via Na+-Ca2+ exchanger in HCT116 human colon cancer cells. Arch. Pharm. Res. 31: 54–59.

Sweeney, E. A., C. Sakakura, T. Shiraehama, A. Masamune, H. Ohta, S. Hakomori, and Y. Igarashi. 1996. Sphingosine and its methylated derivative N,N-dimethylsphingosine (DMS) induce apoptosis in a subpopulation of human cancer cell lines. Int. J. Cancer. 66: 358–366.

Wiegandt, H. 1992. Insect glycolipids. Biochem. Biophys. Acta. 1123: 117–126.

Fzyst, H., D. R. Herr, G. L. Harris, and J. D. Saba. 2004. Character-
ization of free endogenous C14 and C16 sphingoid bases from Drosophila melanogaster. J. Lipid Res. 45: 54–62.

Fzyst, H., X. Zhang, D. R. Herr, H. S. Byun, R. Bittman, V. H. Phan, G. L. Harris, and J. D. Saba. 2008. Identification and characterization by electrospray mass spectrometry of endogenous Drosophila sphingadienes. J. Lipid Res. 49: 597–606.

Gerdt, S., R. D. Dennis, G. Borgonie, R. Schnabel, and R. Geyer. 1999. Isolation, characterization and immunolocalization of phos-
phorylcholine-substituted glycolipids in developmental stages of Caenorhabditis elegans. Eur. J. Biochem. 266: 952–963.

Chitwood, D. J., W. R. Lusby, M. J. Thompson, J. P. Kochansky, and O. W. Howarth. 1995. The glycosylceramides of the nematode Caenorhabditis elegans contain an unusual, branched-chain sphin-
goid base. Lipids. 30: 567–573.

Wuhrer, M., S. Rickhoff, R. D. Dennis, G. Lochnit, P. T. Sobolay, S. Baumreicher, and R. Geyer. 2000. Phosphocholine-containing, zwiterionic glycosphingolipids of adult Onchocerca volvulus as highly conserved antigenic structures of parasitic nematodes. Biochem. J. 348: 417–423.

Lochnit, G., S. Nispel, R. D. Dennis, and R. Geyer. 1998. Structural analysis and immunohistochemical localization of two acidic glyco-
sphingolipids from the porcine, parasitic nematode, Ascaris suum. Glycobiology. 8: 801–899.

Asai, N., N. Fusetani, and S. Matsunaga. 2001. Sex pheromones of the hair crab Erimacrus isenbeckii. II. Synthesis of ceramides. J. Nat. Prod. 64: 1210–1215.

Fzyst, H., D. R. Herr, G. L. Harris, and J. D. Saba. 2004. Charac-
sphingolipids from the porcine, parasitic nematode, Ascaris suum.

Kadowaki, H., E. G. Bremer, J. E. Evans, F. B. Jungalwala, and R. H. McCluer. 1983. Acetoni-trile-hydrochloric acid hydrolysis of gan-
tivines for high performance liquid chromatographic analysis of their long chain bases. J. Lipid Res. 24: 1389–1397.

Carter, H. E., O. Nalbandov, and P. A. Tavormina. 1951. Biochem-
istry of the sphingolipides. VI. The O-methyl ethers of sphingosine. J. Biol. Chem. 192: 197–207.

Kisic, A., M. Tsuda, R. J. Kulmacz, W. K. Wilson, and G. J. Schroepfer, Jr. 1995. Sphingolipid bases: a revision of the O-methyl deriva-
tives of sphingosine. Isolation and characterization of diacetate de-

Chun, J., H. S. Byun, G. Arthur, and R. Bittman. 2003. Synthesis and growth inhibitory activity of chiral 5-hydroxy-2-N-acyl(3E)-
tabolism and atherosclerosis in apoE-deficient mice. J. Biol. Chem. 280: 10284–10289.

104. Garros, E. N., W. S. Kim, C. M. Quinn, W. Jessup, K. A. Rye, and B. Garner. 2008. Myotoxic slow the progression of established atherosclerosis lesions in apolipoprotein E gene knockout mice. J. Lipid Res. 49: 324–331.

105. Riley, R. T., and R. D. Plattner. 2000. Fermentation, partial purification, and use of serum palmitoyltransferases from Isaria (Coniothyrium) sinclairii. Methods Enzymol. 311: 348–361.

106. Pewzner-Jung, Y. S., Ben-Dor, and A. H. Futerman. 2006. When do Lasses (longevity assurance genes) become Cer7 (ceramide synthases)? Insights into the regulation of ceramide synthesis. J. Biol. Chem. 281: 25001–25005.

107. Lahiri, S., H. Lee, J. Mesicek, Z. Fuks, A. Haimovitz-Friedman, R. N. Kolesnick, and A. H. Futerman. 2007. Kinetic characterization of mammalian ceramide synthases: determination of K(m) values towards sphinganine. FEBS Lett. 581: 5290–5294.

108. Abbas, H. K., S. O. Duke, A. H. Merrill, Jr., E. Wang, and W. T. Shier. 1998. Phytochemistry of australifungin, AAL-toxins and fumonisin B1 to Lemma pausicostata. Phytochemistry. 47: 1509–1514.

109. Merrill, A. H., Jr., M. C. Sullards, E. Wang, K. A. Voss, and R. T. Riley. 2001. Sphingolipid metabolism: roles in signal transduction and disruption by fumonisins. Environ. Health Perspect. 109 (Suppl 2): 293–299.

110. Riley, R. T., E. Enongene, K. A. Voss, W. P. Norred, F. I. Meredith, R. P. Sharma, J. Spitsbergen, D. E. Williams, D. B. Carlson, and A. H. Merrill, Jr. 2001. Sphingolipid perturbations as mechanisms for fumonisin carcinogenesis. Environ. Health Perspect. 109 (Suppl 2): 308–310.

111. Trucksess, M. W., and P. M. Scott. 2008. Mycotoxins in botanicals and dried fruits: a review. Food Addit. Contam. 25: 181–192.

112. Murphy, P. A., S. Hendrich, E. C. Hopmans, C. C. Hauck, Z. Lu, G. Buseman, and G. Munkvold. 1996. Effect of processing on fumonisin content of corn. Adv. Exp. Mol. Biol. 392: 323–334.

113. Palencia, E., O. Torres, W. Hagler, F. I. Meredith, L. D. Williams, and R. T. Riley. 2003. Total fumonisins are reduced in tortillas using the traditional nixtamalization method of Mayan communities. J. Nutr. 133: 3200–3203.

114. Humpf, H. U., E. M. Schmelz, F. I. Meredith, H. Vesper, T. R. Vales, E. Wang, D. S. Menalldino, D. C. Liotta, and A. H. Merrill, Jr. 1998. Acylation of naturally occurring and synthetic 1-decysosphinganines by ceramide synthase. Formation of N-palmitoyl-aminopentos for produces a toxic metabolite of hydrolyzed fumonisin, API, and a new category of ceramide synthase inhibitor. J. Biol. Chem. 273: 19060–19064.

115. Seiterlein, M., H. U. Humpf, K. A. Voss, M. C. Sullards, J. C. Allegood, E. Wang, and A. H. Merrill, Jr. 2007. Hydrolyzed fumonisins HBFI and FB2 are acylated in vitro and in vivo by ceramide synthase to form cytotoxic N-acetylmetabolites. Mol. Nutr. Food Res. 51: 1120–1130.

116. Abou-Karam, M., H. K. Abbas, and W. T. Shier. 2004. N-Fatty acyla tion of hydrolyzed fumonisin B1, but not of intact fumonisin B1, strongly enhances in vitro mammalian toxicity. J. Toxol. Toxicol. Toxin Rev. 23: 123–151.

117. Marasas, W. F., E. V. Losos, and J. Hille. 1998. Sphingolipid perturbations as mechanisms for fumonisin carcinogenesis. A. H. Merrill. J. Biol. Chem. 273: 19060–19064.

118. Marasas, W. F., E. V. Losos, and J. Hille. 1998. Sphingolipid perturbations as mechanisms for fumonisin carcinogenesis. J. Biol. Chem. 267: 19060–19064.

119. Seiterlein, M., H. U. Humpf, K. A. Voss, M. C. Sullards, J. C. Allegood, E. Wang, and A. H. Merrill, Jr. 2007. Hydrolyzed fumonisins HBFI and FB2 are acylated in vitro and in vivo by ceramide synthase to form cytotoxic N-acetylmetabolites. Mol. Nutr. Food Res. 51: 1120–1130.

117. Marasas, W. F., E. V. Losos, and J. Hille. 1998. Sphingolipid perturbations as mechanisms for fumonisin carcinogenesis. J. Biol. Chem. 273: 19060–19064.

118. Marasas, W. F., E. V. Losos, and J. Hille. 1998. Sphingolipid perturbations as mechanisms for fumonisin carcinogenesis. J. Biol. Chem. 267: 19060–19064.

119. Seiterlein, M., H. U. Humpf, K. A. Voss, M. C. Sullards, J. C. Allegood, E. Wang, and A. H. Merrill, Jr. 2007. Hydrolyzed fumonisins HBFI and FB2 are acylated in vitro and in vivo by ceramide synthase to form cytotoxic N-acetylmetabolites. Mol. Nutr. Food Res. 51: 1120–1130.

120. Abou-Karam, M., H. K. Abbas, and W. T. Shier. 2004. N-Fatty acyla tion of hydrolyzed fumonisin B1, but not of intact fumonisin B1, strongly enhances in vitro mammalian toxicity. J. Toxol. Toxicol. Toxin Rev. 23: 123–151.

121. Marasas, W. F., E. V. Losos, and J. Hille. 1998. Sphingolipid perturbations as mechanisms for fumonisin carcinogenesis. J. Biol. Chem. 273: 19060–19064.

122. Marasas, W. F., E. V. Losos, and J. Hille. 1998. Sphingolipid perturbations as mechanisms for fumonisin carcinogenesis. J. Biol. Chem. 267: 19060–19064.

123. Seiterlein, M., H. U. Humpf, K. A. Voss, M. C. Sullards, J. C. Allegood, E. Wang, and A. H. Merrill, Jr. 2007. Hydrolyzed fumonisins HBFI and FB2 are acylated in vitro and in vivo by ceramide synthase to form cytotoxic N-acetylmetabolites. Mol. Nutr. Food Res. 51: 1120–1130.

124. Abou-Karam, M., H. K. Abbas, and W. T. Shier. 2004. N-Fatty acyla tion of hydrolyzed fumonisin B1, but not of intact fumonisin B1, strongly enhances in vitro mammalian toxicity. J. Toxol. Toxicol. Toxin Rev. 23: 123–151.

125. Marasas, W. F., E. V. Losos, and J. Hille. 1998. Sphingolipid perturbations as mechanisms for fumonisin carcinogenesis. J. Biol. Chem. 273: 19060–19064.

126. Seiterlein, M., H. U. Humpf, K. A. Voss, M. C. Sullards, J. C. Allegood, E. Wang, and A. H. Merrill, Jr. 2007. Hydrolyzed fumonisins HBFI and FB2 are acylated in vitro and in vivo by ceramide synthase to form cytotoxic N-acetylmetabolites. Mol. Nutr. Food Res. 51: 1120–1130.

127. Marasas, W. F., E. V. Losos, and J. Hille. 1998. Sphingolipid perturbations as mechanisms for fumonisin carcinogenesis. J. Biol. Chem. 273: 19060–19064.
synergism within long-chain α,ω-bis-αminooalcohols. Bioorg. Med. Chem. Lett. 12: 2159–2162.

145. Zhou, B.-N., M. P. Mattern, R. K. Johnson, and D. G. I. Kingston. 2001. Structure and stereochemistry of a novel biactive sphingo-
dial from Cytophaga johnsonae. Tetrahedron. 57: 9549–9554.

146. Nicholas, G. M., T. W. Hong, T. F. Molinski, M. L. Lerch, M. T. Cancilla, and C. B. Lebrilla. 1999. Oceanapain, an antifungal bis-alpha,omega-αminoo alcohol glycoside from the marine sponge Oceanapia philippinensis. J. Nat. Prod. 62: 1678–1681.

147. Nicholas, G. M., and T. F. Molinski. 2000. Enantiomeric differentiation of the dimeric sphingolipid oceanapain from the marine sponge Oceanapia philippinensis. Determination of remote stereochemistry. J. Am. Chem. Soc. 122: 4011–4019.

148. Makarieva, T. N., P. S. Dmitrenok, A. M. Zenkarenko, V. A. Denisenko, A. G. Gazi, R. L. C. Skepper, T. F. Molinski, and V. A. Stonik. 2007. Rhizochalasin C and D from the sponge Rhizochalasina incrustata. A rare threo-sphingolipid and a facile method for determination of the carbohydrate position in alpha,omega-bifunctionalized ketal-
sphingolipids. J. Nat. Prod. 70: 1991–1998.

149. Nicholas, G. M., L. L. Eckman, G. L. Newton, R. C. Fahey, S. Ray, and C. A. Bewley. 2003. Inhibition and kinetics of Mycobacterium tuberculosis and Mycobacterium smegmatis mycolic acid-SC conjugate ami-
dase by natural product inhibitors. Bioorg. Med. Chem. 11: 601–608.

150. Crews, P. D. P. Clark, and K. Tennyson. 2003. Variation in the alka-
loids among Indo-Pacific Leucetta sponges. J. Nat. Prod. 66: 177–182.

151. Kobayashi, J. I., K. Naitoh, Y. Doi, K. Deki, and M. Ishibashi. 1995. Pseudoundisin C, a new piperidine alkaloid with unusual abso-
lute configuration from the Okinawan tunicate Pseudoudistoma kawako. J. Org. Chem. 60: 9841–9845.

152. W. R. H., and D. W. J. de Vries. 1999. G. S. Jayatilake, B. J. Baker, and J. B. McClintock. 1997. Rhapsa-
153. Kamiyama, T., T. Umino, Y. Itezono, Y. Nakamura, T. Satoh, and K. Mori. 1996. Absolute stereochemistry of penaresidins A and B from the Okinawan marine sponge Dysidea fragilis. J. Org. Chem. 61: 873–875.

154. Brahmbhatt, V. V., F. F. Hsu, J. L. Kao, E. C. Frank, and D. A. Ford. 2004. Further bioactive and other piperidine alkaloids from the flowers and green fruits of Cassia leptophylla. Tetrahedron. 61: 5929–5945.

155. W. H. Y., N. Y. Touyou, T. Sasaki, H. Nemoto, J. A. Dani, and I. Kimura. 2005. Marine alkaloids (−)-pictamine and (−)-
156. Bolzani, V. D. S., A. A. L. Gunatilaka, and D. G. I. Kingston. 1996. Biactive and other piperidine alkaloids from Cassia leptophylla. J. Nat. Prod. 59: 1003–1010.

157. Ohshita, K., H. Ishiyama, Y. Takahashi, J. Ito, Y. Mikami, and J. Kobayashi. 2007. Synthesis of penaresidin derivatives and its bio-
logical activity. Bioorg. Med. Chem. 15: 4910–4916.

158. Tsuneki, H., Y. You, N. Touyou, T. Sasaki, H. Nemoto, J. A. Dani, and I. Kimura. 2005. Marine alkaloids (−)-pictamine and (−)-
159. B. V. F. F. Hsu, J. L. Kao, E. C. Frank, and D. A. Ford. 2004. New cis-decahydroquinoline alkaloids from the Australian ascidian Aplidium tabascum. J. Nat. Prod. 65: 454–457.

160. Foyer, A. J., A. D. Patil, L. Killmer, F. F. Hsu, J. L. Kao, and R. K. Johnson. 1997. New pseudoundisin A, a novel α,ω-bis-
161. T. M. Smalberger, and H. L. de Waal. 1967. Dimeric Bioactive and other piperidine alkaloids from Cassia leptophylla. J. Org. Chem. 33: 3006–3006.

162. Vogas, C., Jr., V. D. S. Bolzani, M. Furlan, E. J. Barreiro, M. C. M. Young, D. Tomazela, and M. N. Eberlin. 2004. Further bioactive piperidine alkaloids from the flowers and green fruits of Cassia leptophyllas. J. Nat. Prod. 67: 908–910.

163. Randl, S., and S. Blechert. 2004. Concise total synthesis of (−)-cassine. J. Nat. Prod. 67: 5934–5945.

164. Davis, C. A., R. A. Carril, and R. J. Quinlan. 2002. Lepadins F-H, new cis-decahydroquinoline alkaloids from the Australian ascidian Aplidium tabascum. J. Nat. Prod. 65: 454–457.

165. Foyer, A. J., A. D. Patil, L. Killmer, F. F. Hsu, J. L. Kao, and R. K. Johnson. 1997. New pseudoundisins, piperidine alkaloids from the ascidian Pseudoudistoma kawako. J. Org. Chem. 62: 450–453.

166. Steffan, B. 1991. Lepadin A, a decahydroquinoline alkaloid from the tunicate Clavelina ledelpiformis. Tetrahedron. 47: 8729–8732.

167. Toyouka, N. 2001. Synthesis and its application to the synthesis of biologically active natural products of new and versatile chiral building blocks. Yakugaku Zasshi. 121: 467–479.

168. Kong, F., and D. J. Faulkner. 1991. Pictamine, a quinolizidine alkaloid from the tunicate Clavelina picta. Tetrahedron Lett. 32: 3667–3668.

169. Brahmbhatt, V. V., F. F. Hsu, J. L. Kao, E. C. Frank, and D. A. Ford. 2004. New cis-decahydroquinoline alkaloids from the Australian ascidian Aplidium tabascum. J. Nat. Prod. 65: 454–457.
2007. Novel carbonyl and nitrile products from reactive chlorinat-
ing species attack of lyso sphingosylipid. *Chem. Phys. Lipids.* 145: 72–84.

191. Rizzo, W. B. 2007. Sjogren-Larsson syndrome: molecular genetics and biochemical pathogenesis of fatty aldehyde dehydrogenase deficiency. *Mol. Genet. Metab.* 90: 1–9.

192. Dannenberger, D., S. Lorenz, G. Nurnberg, N. Scollan, K. Ender, and K. Nurnberg. 2006. Analysis of fatty aldehyde composition, including 12-methyltridecanal, in plasmalogens from longissimus muscle of concentrate- and pasture-fed bulls. *J. Agric. Food Chem.* 54: 182–188.

193. Kalinova, B., M. Hoskovc, I. Liblikas, C. R. Unelius, and B. S. Hansson. 2001. Detection of sex pheromone components in *Manduca sexta* (L.). *Chem. Senses.* 26: 1175–1186.

194. Linn, C. E. Jr., M. J. Domingue, C. J. Musto, T. C. Baker, and W. L. Roelofs. 2007. Support for (Z)-11-hexadecanal as a pheromone antagonist in *Ostrinia nubilalis*; flight tunnel and single sensillum studies with a New York population. *J. Chem. Ecol.* 33: 909–921.

195. Van Overloop, H., G. Van der Hoeven, and P. P. Van Veldhoven. 2005. N-Acyl migration in ceramides. *J. Lipid Res.* 46: 812–816.

196. Shirahama, T., E. A. Sweeney, C. Sakakura, A. K. Singhal, K. Nishiyama, and T. Inoue. 1995. Selective apoptosis of pluripotent mouse and human stem cells by novel ceramide analogues prevents teratoma formation and enriches for neural precursors in ES cell-derived neural trans-

197. Zeidan, Y. H., and Y. A. Hannun. 2007. Translational aspects of sphingolipid metabolism. *Expert Opinion on Therapeutic Patents.* 16: 1129–1147.

198. Gundewar, S., and D. J. Lefer. 2008. Sphingolipid therapy in myo-

199. Thevissen, K., I. E. Francois, A. M. Aerts, and B. P. Cammue. 2005. Antagonist in *O. nubilalis* to MS therapeutic: S1P receptor modulator FTY720. *Prog. Drug Res.* 66: 361, 363–381.

200. Huwiler, A., and J. Pleischfiter. 2008. New players on the center stage: sphingosine 1-phosphate and its receptors as drug targets. *Biochem. Pharmacol.* 75: 1893–1900.

201. Veronesi, U., L. Mariani, A. Decensi, F. Formelli, T. Camerini, R. Miceli, M. G. Di Mauro, A. Costa, E. Marubini, M. B. Sporn, et al. 2006. Fifteen-year results of a randomized phase III trial of fenretinide to prevent second breast cancer. *Ann. Oncol.* 17: 1065–1071.

202. Vanhampayan, U., L. K. Heilbrun, R. E. Parchment, V. Jain, J. Zwiebel, R. R. Boinpally, P. LoRusso, and M. Hussain. 2005. Phase II trial of fenretinide in advanced renal carcinoma. *Invest. New Drugs.* 23: 179–185.

203. Sabichi, A. L., S. P. Lerner, E. N. Atkinson, H. B. Grossman, N. P. Caraway, C. P. Dinney, D. F. Penso, S. Matin, L. L. Pisters, et al. 2008. Phase III prevention trial of fenretinide in patients with resected non-muscle-invasive bladder cancer. *Clin. Cancer Res.* 14: 224–229.

204. Sulfrands, M. C., J. C. Allogood, S. Kelly, E. Wang, C. A. Haynes, H. Park, Y. Chen, and A. H. Merrill, Jr. 2007. Structure-specific, quantitative methods for analysis of sphingolipids by liquid chromatography-
tandem mass spectrometry; “inside-out” sphingolipidomics. *Methods Enzymol.* 432: 83–115.

205. Han, X., and R. W. Gross. 2003. Global analyses of cellular lip-

206. Shirahama, T., A. Sweeney, C. Sakakura, A. K. Singhal, K. Nishiyama, S. Akiyama, S. Hakomori, and Y. Igarashi. 1997. In vitro and in vivo induction of apoptosis by sphingosine and N,N-dimethylsphingosine treatment in lung cancer cells. *Exp. Mol. Med.* 29: 411–419.

207. Park, H. W., J. Y. Song, K. S. Kim, Y. Han, C. W. Kim, S. Y. Yi, and Y. S. Yun. 2004. Enhancement of radiosensitivity by combined ceramide and dimethylsphingosine treatment in lung cancer cells. *Exp. Mol. Med.* 36: 105–105.

208. Gündewar, S., and D. J. Lefer. 2008. Sphingolipid therapy in myo-

209. Menaldino, D. S., A. Bushney, A. Sun, D. C. Liotta, H. Symolon, K. Desai, D. L. Dileohay, Q. Peng, E. Wang, J. Allegood, et al. 2003. Sphingoid bases and de novo ceramide synthesis: enzymes in-

Sphingoid base biodiversity 1639