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thematic review

Thematic Review Series: Sphingolipids

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

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Abstract "Sphingosin" was first described by J. L. W. Thudichum in 1884 and structurally characterized as 2*S*,3*R*,4*E*-2-aminooctadec-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 backbones 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.**

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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 (2*S*,3*R*,4*E*)-2-aminooctadec-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 dihydrosphingosine **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-

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Abbreviations: SPT, serine palmitoyltransferase.

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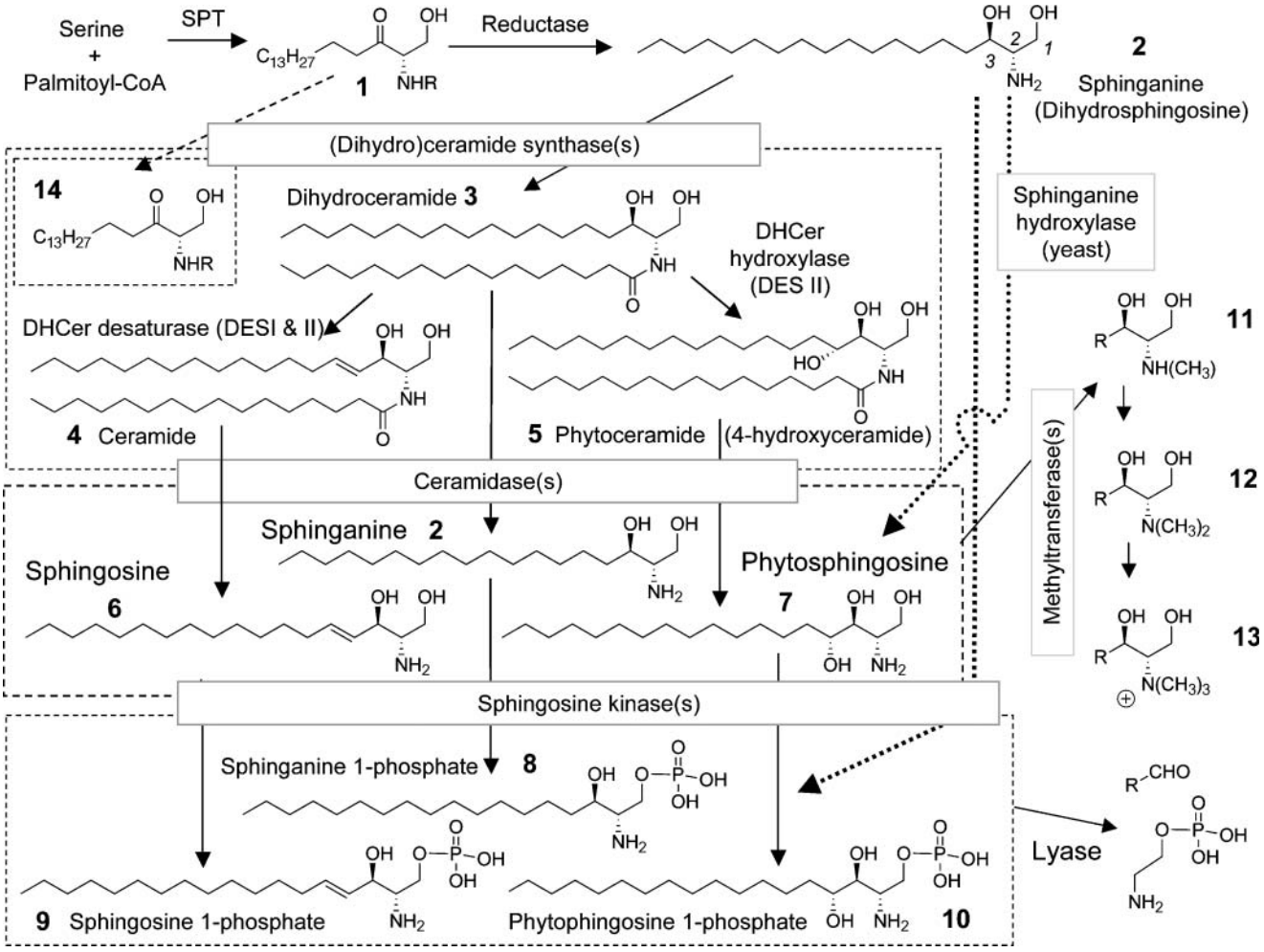


Fig. 1. Biosynthesis and turnover of the three major categories of sphingoid bases in mammalian cells. DHR, dihydroceramide; SPT, serine palmitoyltransferase.

ered 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' [(2*S*,3*R*)-2-aminooctadecane-1,3-diol]...[and]... 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** (2*S*,3*S*,4*R*-2-aminooctadecane-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 (4*E*)-sphing-4-enine and (4*E*)-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-

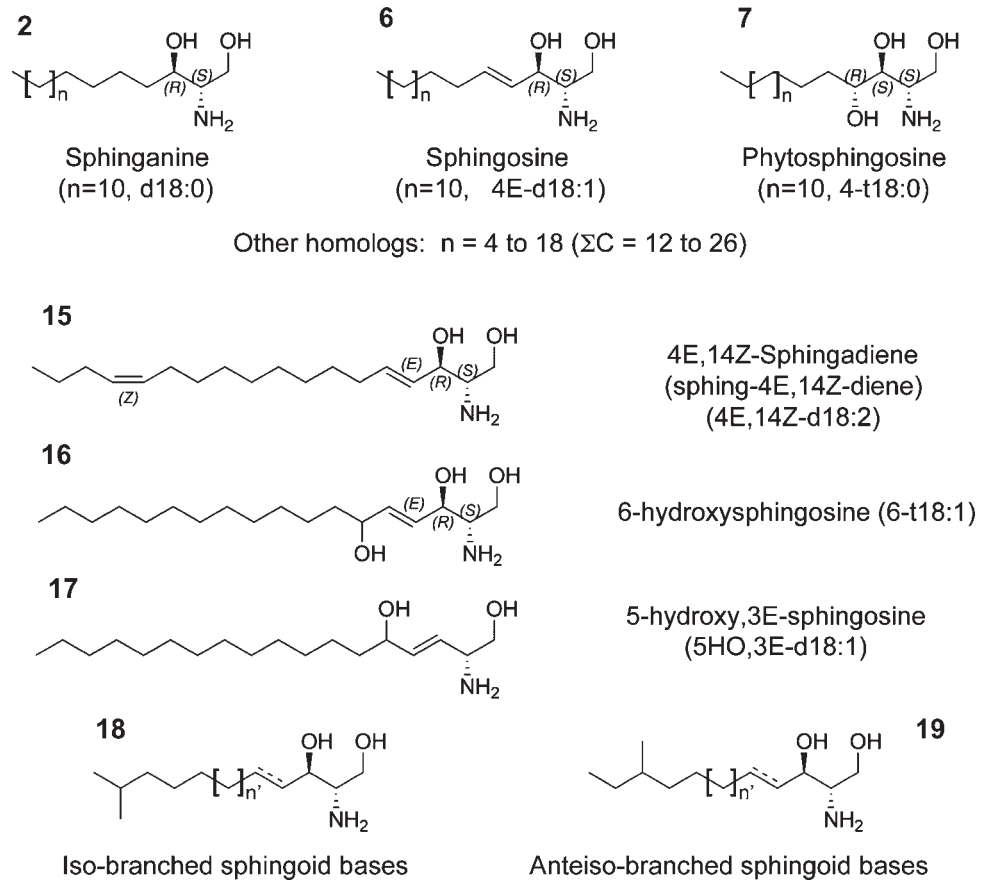


Fig. 2. Sphingoid bases of mammalian tissues.

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 4*E*-d18:1 (and sometimes d18:1$^{\Delta 4t}$), 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 eisosasphingosine (2*S*,3*R*,4*E*-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 4*E*,14*Z*-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,3*E*-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 5*R* and 5*S* 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 harderian 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).

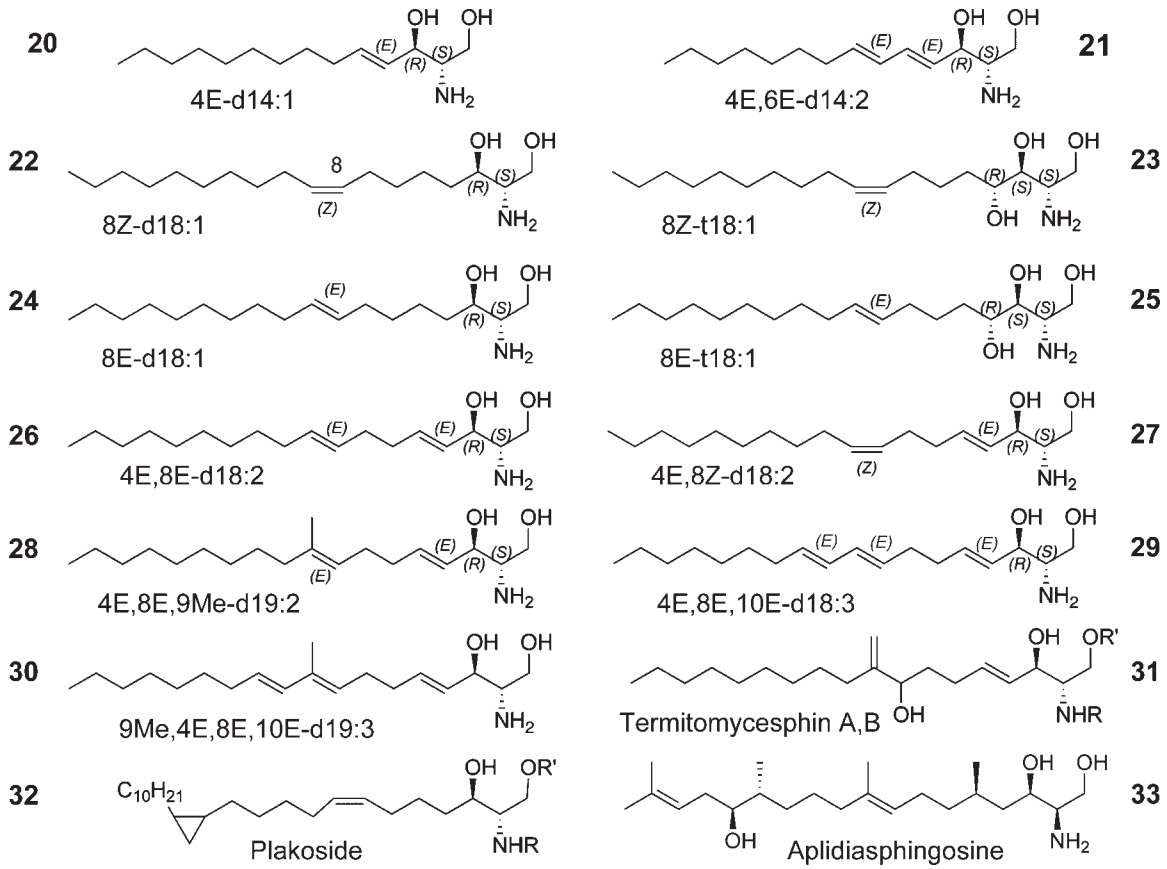


Fig. 3. Sphingoid bases found in diverse organisms other than mammals.

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*-dimethyl-sphingosine 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 4*E*-d14:1 (**20** in Fig. 3) and the conjugated diene 4*E*,6*E*-d14:2 **21** found in *Drosophila* (54). Nematodes have both iso-branched (4*E*,15-methyl-d17:1) and anteiso-branched (4*E*,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, 4*E*-d18:1), with only a single 4*E* double bond. Plant 4,8-dienes sometimes have branching methyl groups (or hydroxyls at other positions) (62); however, branched sphingoid bases such as 4*E*,8*E*,9-methyl-d19:2 (**28** in Fig. 3) and 4*E*,8*Z*,9-methyl-d19:2 (data not shown) are considered to be more typical of fungal sphingolipids (63, 64), including human pathogens such as *Cryptococcus neoformans* (64, 65). It 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 albuminosus* (67). Other interesting examples will be elaborated upon in discussion of **Table 1** and **Figs. 4 and 5**.

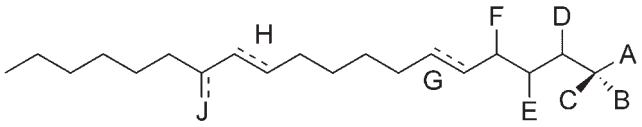
Sphingoid bases with three double bonds, such as (4*E*, 8*E*,10*E*)-2-amino-4,8,10-octadecatriene-1,3-diol (4*E*,8*E*,10*E*-d18:3; **29** in Fig. 3), are found in the spermatozoa of the starfish, *Asterias amurensis* (68), and the branched version, 2-amino-9-methyl-4,8,10-octadecatriene-1,3-diol (**30** 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 antitumorial 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 *Sphingomonaspaucimobilis* 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,

TABLE 1. Sphingoid base-like inhibitors of serine palmitoyltransferase



Compound Name	J	H	G	F	E	D	C	B	A	Ref.
Myriocin (**36** in Fig. 4)	O		=	H	OH (*S*)	OH (*S*)	COOH	NH_2	CH_2OH	(76, 84–86)
Sphingofungin A	OH		=	OH (*S*)	OH (*R*)	OH (*R*)	COOH	$NHCNHNH_2$	H	(76, 86, 91)
Sphingofungin B	OH		=	OH (*S*)	OH (*R*)	OH (*R*)	COOH	NH_2	H	(76, 86, 91)
Sphingofungin C	OH		=	*O*-Acetyl (*S*)	OH (*R*)	OH (*R*)	COOH	NH_2	H	(76, 86, 91)
Sphingofungin D	OH		=	OH (*S*)	OH (*R*)	OH (*R*)	COOH	HN-Acetyl	H	(76, 86, 91)
Sphingofungin E	O		=	OH (*S*)	OH (*R*)	OH (*R*)	NH_2	COOH	CH_2OH	(76, 86, 91)
Sphingofungin F	O		=	OH (*S*)	OH (*R*)	OH (*R*)	COOH	NH_2	CH_3	(76, 86, 91)
Sulfamisterin (**37** in Fig. 4)	O			H	H	OSO_3Na (*R*)	COOH	NH_2	CH_2OH	(89)
Mycestericin A	O	=		H	OH (*R*)	OH (*S*)	COOH	NH_2	CH_2OH	(85)
Mycestericin B	OH			H	OH (*R*)	OH	COOH	NH_2	CH_2OH	(85)
Mycestericin C	O			H	OH (*S*)	OH (*S*)	H	H	H	(85)
Mycestericin D	O		=	H	H	OH (*S*)	NH_2	COOH	CH_2OH	(85)
Mycestericin E						OH (*R*)				
Mycestericin F	O		=	H	H	OH (*S*)	NH_2	COOH	CH_2OH	(85)
Mycestericin G						OH (*R*)				
Malonofungin	O			*O*-Ac (*S*)	OH (*R*)	OH (*R*)	NH_2	COOH	COOH	(93)
Fumifungin	OH			OH	O-Ac	OH	NH_2, COOH, and H (stereochemistry not specified)			(94)

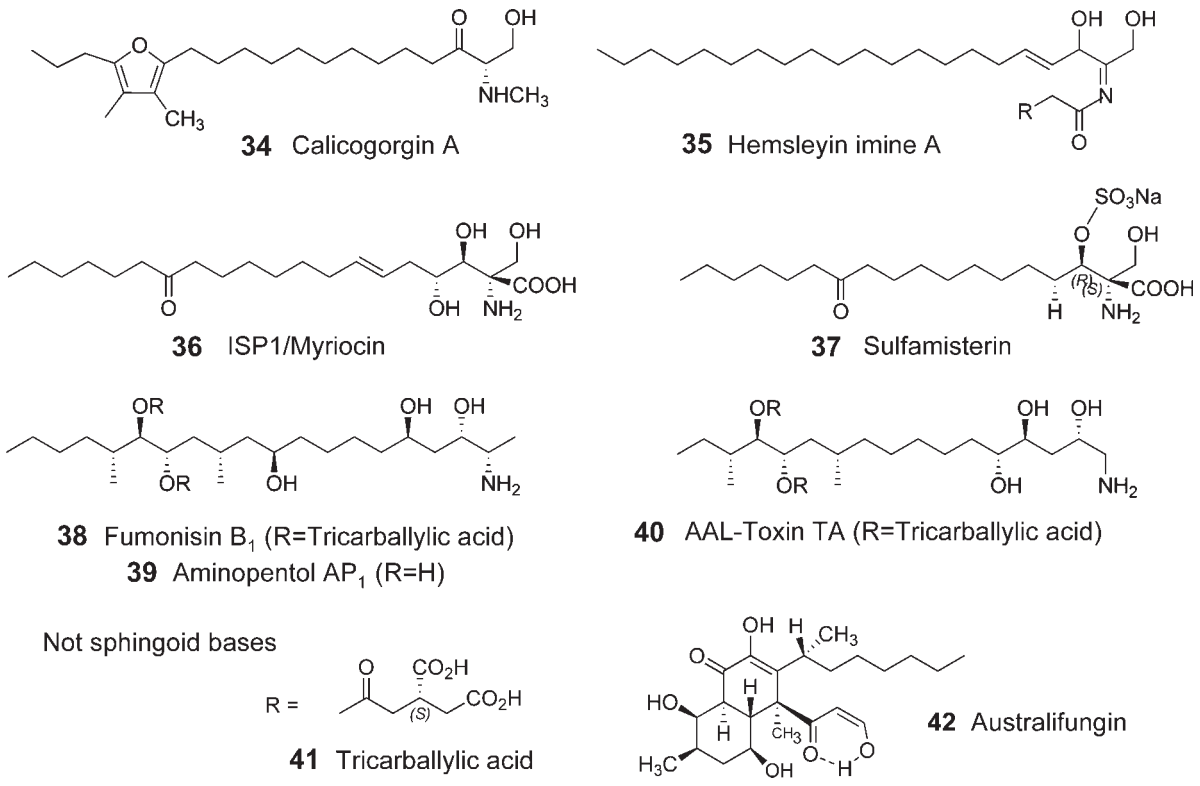


Fig. 4. Sphingoid base-like compounds that mimic metabolites and/or inhibit early steps of sphingolipid metabolism. In the category "not sphingoid bases" are tricarballylic acid, which is the "R" group found on fumonisins and AAL toxins, and australifungin, which is shown as an example of a ceramide synthase inhibitor that is not a sphingoid base-like compound.

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 SPHINGOLIPID 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 sinclairii*) (76, 84, 86), myriocin (isolated from *Myrioccocum albomyces*) (87), and thermozycidin (from *Mycelia sterilia*) (88); sulfamisterin from *Pycnidiella* 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 mycestericins (from *Mycelia sterilia*) (85), malonofungin (from *Phaeramularia fusimaculans*) (93), and fumifungin 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 lipoxamycin (96) and viridiofungins (97).

ISP-1/myriocin **36** has been studied most extensively because it is highly potent, with an IC_{50} in the nanomolar range (84), and commercially available. Spectroscopic studies suggest that ISP-1/myriocin inhibits activity by forming an external aldimine 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 sulfomisterin (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 cytotoxic ceramide in response to a wide variety of stresses (98), suppresses virus infectivity (99, 100), alters brain amines (101), and suppresses athero-

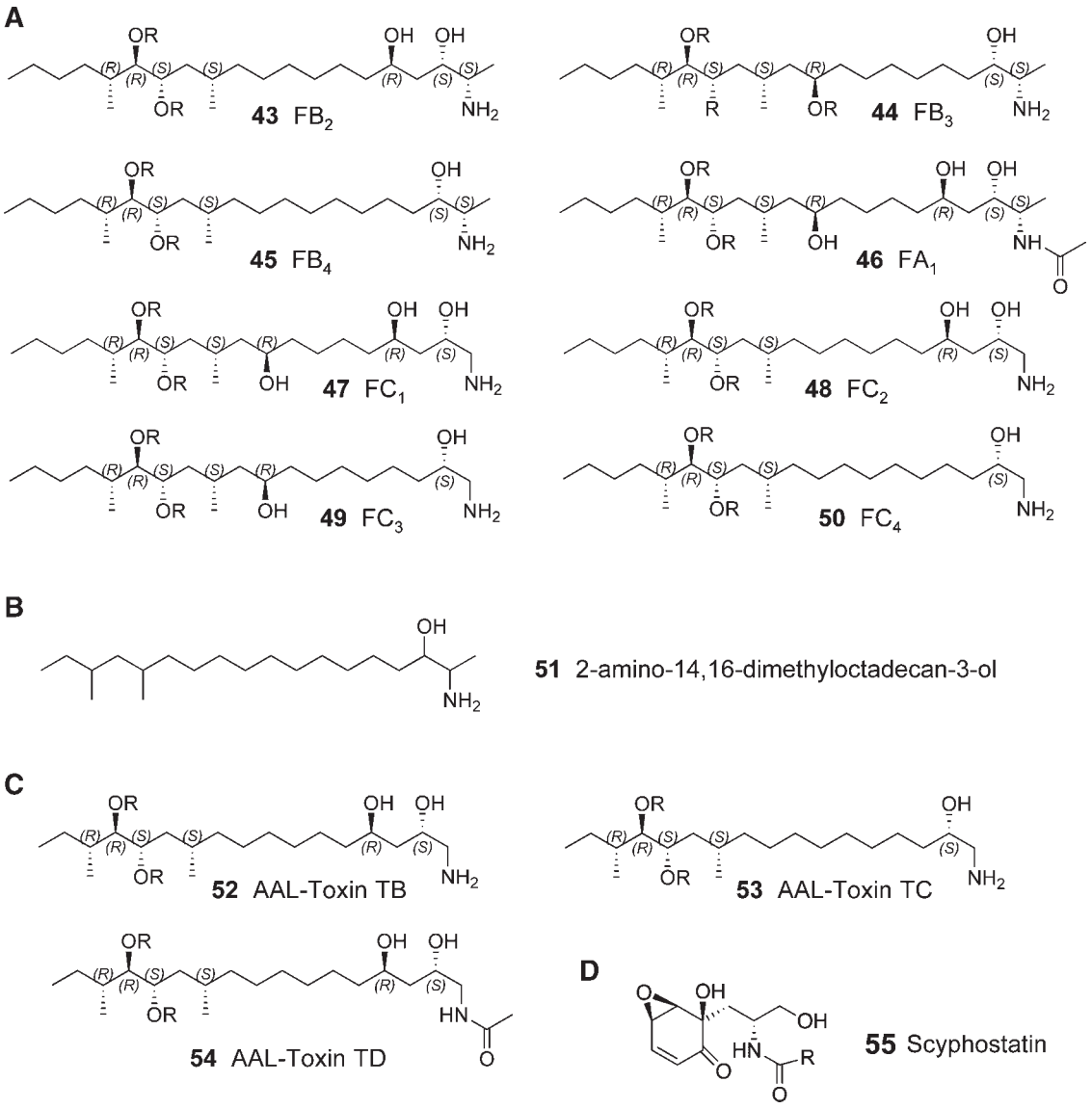


Fig. 5. Structures of the major members of the fumonisin (A) and AAL toxin (C) families. Also shown are a compound with a fumonisin-like backbone but without side chain hydroxyls (B) and the sphingomyelinase inhibitor scyphostatin (D).

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 B_1 **38** in Fig. 4 and additional family members **43–50** in Fig. 5), which are mycotoxins produced by *Fusarium verticolloides*. 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 AP_1 **39** from FB_1 **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-

fective at detoxifying contaminated maize by washing away of the fumonisins rather than just the removal of the tricarballylic 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 leukoencephalomalacia in South Africa in 1970; observation that this fungus was also prevalent in moldy corn consumed by people in high-incidence areas of esophageal cancer in the Transkei region of South Africa; demonstration 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 elucidation of the fumonisins; and demonstration that purified fumonisins cause these symptoms.

Soon after the structure of fumonisin B_1 was elucidated (118), the similarity to sphinganine led to the discovery of its inhibition of ceramide synthase (14). This was significant 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 contrast 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 surprising that fumonisins have a wide range of pathologic effects, since inhibition of ceramide synthase (Fig. 1) causes not only the depletion of ceramides and complex sphingolipids but also the buildup of highly bioactive compounds (sphinganine, sphinganine 1-phosphate, *N*-acetyl-sphinganine, 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 carcinogenicity 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 currently 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 disease 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 fumonisins (**47–50**) and the AAL toxins (**40** and **52–54**) lack the 1-hydroxymethyl group, and the A series fumonisin (represented by FA_1 **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 cytotoxic for the rat hepatoma cell line H4IIE-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-deoxysphinganines (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/ceramide) analog toxins (129, 130). This categorization has been employed to compare not only the structure and function of these compounds but also their biosynthesis (131), because sphingoid base analogs minus the 1-hydroxyl (compounds **38**, **39**, **43–45**, and **51**) versus the 1-hydroxymethyl (compounds **40**, **47–50**, and **52–54**) groups are biosynthesized 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 sphingolipid metabolism have been found (132), such as rustmicin, which inhibits inositol phosphoceramide synthase (133); however, with the exception of scyphostatin (compound **55** in Fig. 5), a neutral sphingomyelinase inhibitor from *Trichopeziza 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 identical to sphinganine but lacking the 1-hydroxyl. This compound (spisulosine **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 molecular 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 inactivation 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). Spisulosine 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 atypical 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 acylated by ceramide synthase (114); hence, it is possible that 1-deoxyceramides may play a role in the biological effects.

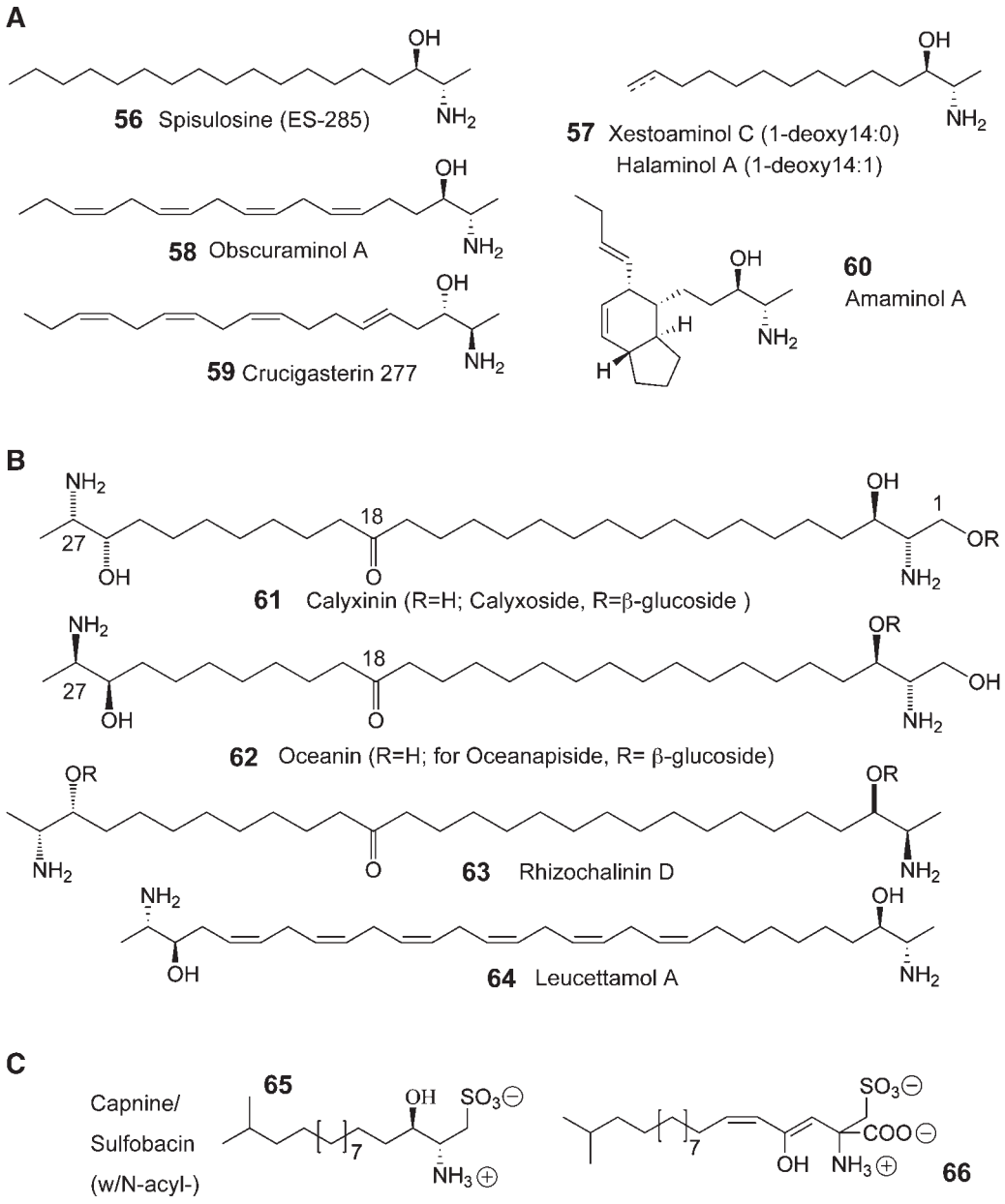


Fig. 6. Novel sphingoid base-like compounds. A: 1-Deoxy compounds. B: α,ω-Bifunctional sphingoid bases. C: Sphingoid base-like compounds with sulfonic acid.

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 2*R*,3*S* rather than 2*S*,3*R* 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-SPHINGOIDS: "TWO-HEADED" 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 "α,ω-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-β-glucoside named calyxoside from sponges of the genus *Calyx* in the family *Oceanapiidae*, resembles sphinganine (numbering from position 1) on one end and a 1-deoxy-sphinganine at the other end (with the opposite, *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 *Oceanapia phillipensis* (146–148). While oceanin is very similar to calyxinin with the same stereochemistry as a sphingoid base for carbons 2 and 3 (*S,R-erythro*) as well as a *threo* stereochemistry on the ω-amino alcohol, the latter is opposite for these compounds (i.e., oceanin is 26*R*,27*R* versus 26*S*,27*S* for calyxinin). They differ also in the position of *O*-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/-conjugate amidase, a mycobacterial detoxification enzyme, 50- to 100-fold more potently than the aglycone (149). In contrast, the carbohydrate has little, and perhaps a slightly negative, effect on the antifungal activity of oceanapiside versus oceanin against *Candida glabrata*, with minimum inhibitory concentrations of 10 and 3 μg/ml, respectively (144).

Two other α,ω-sphingoid base-like compounds are shown in Fig. 6: rhizochalin D (63), from *Rhizochalina incrustata*, which is a 1-deoxy-sphingoid base (both amino alcohols with *threo* stereochemistry) on both ends and glycosylated at carbon 3 (142, 144, 148); and leucettamol A (64), which has both 1-deoxy amino alcohols with *erythro* stereochemistry and polyunsaturation in the alkyl chain. This compound represents a large family of polyunsaturated "leucettamols" found in *Leucetta* species, which differ in the numbers and locations of double bonds in the alkyl chain (142, 150, 151). Another compound not shown, BRS1, is a 30 carbon bis-amino,bis-hydroxy polyunsaturated lipid from an Australian calcareous sponge (*Calcarea*) (152). Each of these has been found to have some form of biological activity, such as antibacterial activity against *Staphylococcus aureus* and cytotoxicity for Ehrlich carcinoma cells for rhizochalin (153) and inhibition of phorbol ester binding to protein kinase C for BRS1 (which is a known feature of sphingosine) (152).

One can envision that the purpose of the two sphingoid base (-like) moieties is to allow these compounds to interact simultaneously 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, sulfobacins, and other 1-sulfonosphingoids

Gliding bacteria of the genus *Cytophaga* synthesize sulfonolipids that contain capnine (1-deoxy,15-methyl-hexadecasphinganine-1-sulfonic acid; compound **65** in Fig. 6) (154), which appears to be the same as the backbone for the sulfobacins that have been isolated from the culture broth of *Chryseobacterium* species (*Flavobacterium* species) *NR 2993* and for which the stereochemistry has been assigned (2*R*,3*R*) (155). Studies of capnine biosynthesis (156, 157) using isotopically labeled precursors have suggested that the biosynthesis of capnine occurs by the condensation of 13-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 *Cytophaga johnsonae* was able to incorporate sulfur from sulfate into cysteate and sulfonolipid, which further indicates that cysteine per se is not an obligatory intermediate of capnine biosynthesis (158). Sulfobacins A and B (which vary in the *N*-acyl fatty acid) have been found to be von Willebrand factor receptor antagonists (159). Another sulfonolipid (compound **66** in Fig. 6) that has features similar to the SPT inhibitors (particularly sulfamisterin **37**) has been found in the halophilic bacterium *Salinibacter ruber* (160).

Heteroyclic 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 4E-(*R*)-dysidazirine **67** (161) and (*S*)-antazirine **68** (162), which were isolated from the marine sponge *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).

Penaresidin A and B (**69** in Fig. 7) (163–165) and penazetidine A **70** (166) are azetidines produced by *Penares* sponges. Penaresidins have been reported to activate AT-Pases (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 penaresidin B with a simple alkyl chain have been found to be considerably (i.e., up to 10-fold, or an IC_{50} of ~1 μM) more cytotoxic against lung (A549) and colon (HT29) cancer cell lines and showed antibacterial activity against Gram-positive bacteria (*Bacillus subtilis*, *Micrococcus luteus*, and *Staphylococcus aureus*) and, in one case, against Gram-negative *Escherichia coli* (165).

Pramanicin (compound **71** in Fig. 7) (168) is an interesting sphingoid base-like pyrrole biosynthesized from ser-

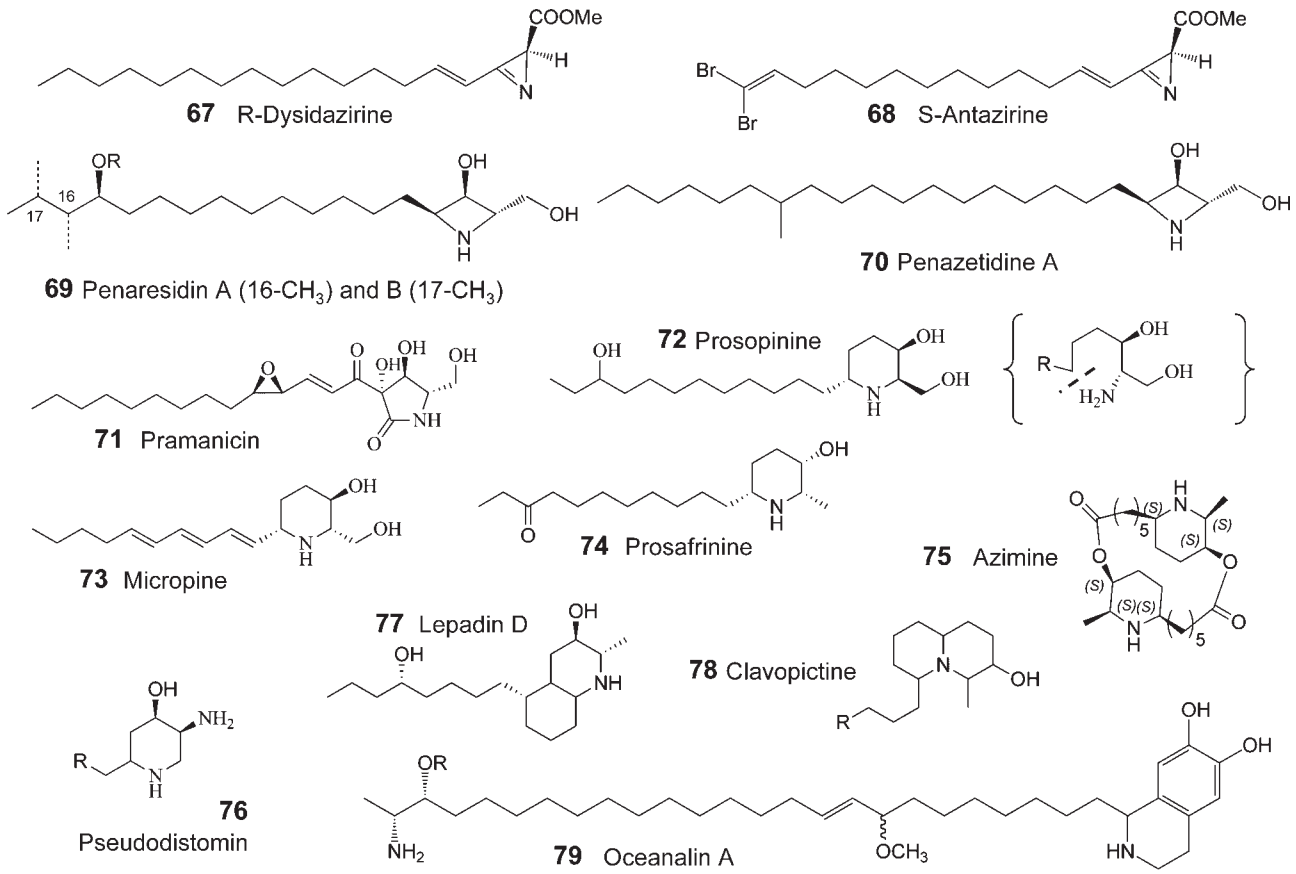


Fig. 7. Sphingoid base-like compounds with heterocyclic rings.

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 *Microcos phillippensis*) 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 *Prosopis 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 spectablis* (175, 176) and *Cassia leptophylla* (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 *Prosteceraeus 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 lysosphingomeylin = 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 sphingosylphosphorylcholine, 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.

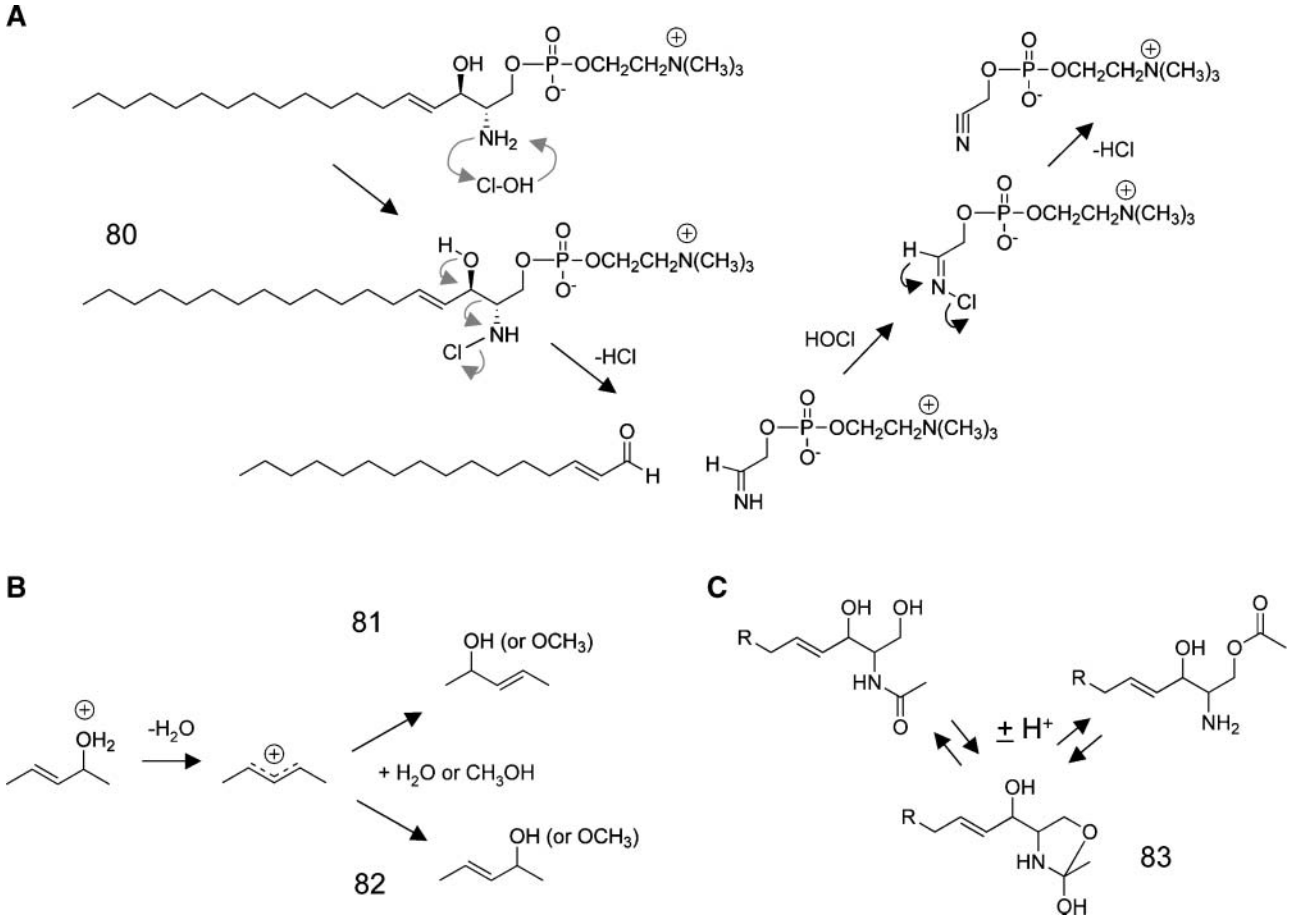


Fig. 8. Common chemical reactions that modify sphingoid bases. A: The formation and decomposition of sphingoid base chloramines due to myeloperoxidase generated reactive chlorination species. B, C: Reactions of sphingoid bases and ceramides under acidic conditions.

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*-dimethylsafingol, **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, (2*S*,3*R*)-(4*E*,6*E*)-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-

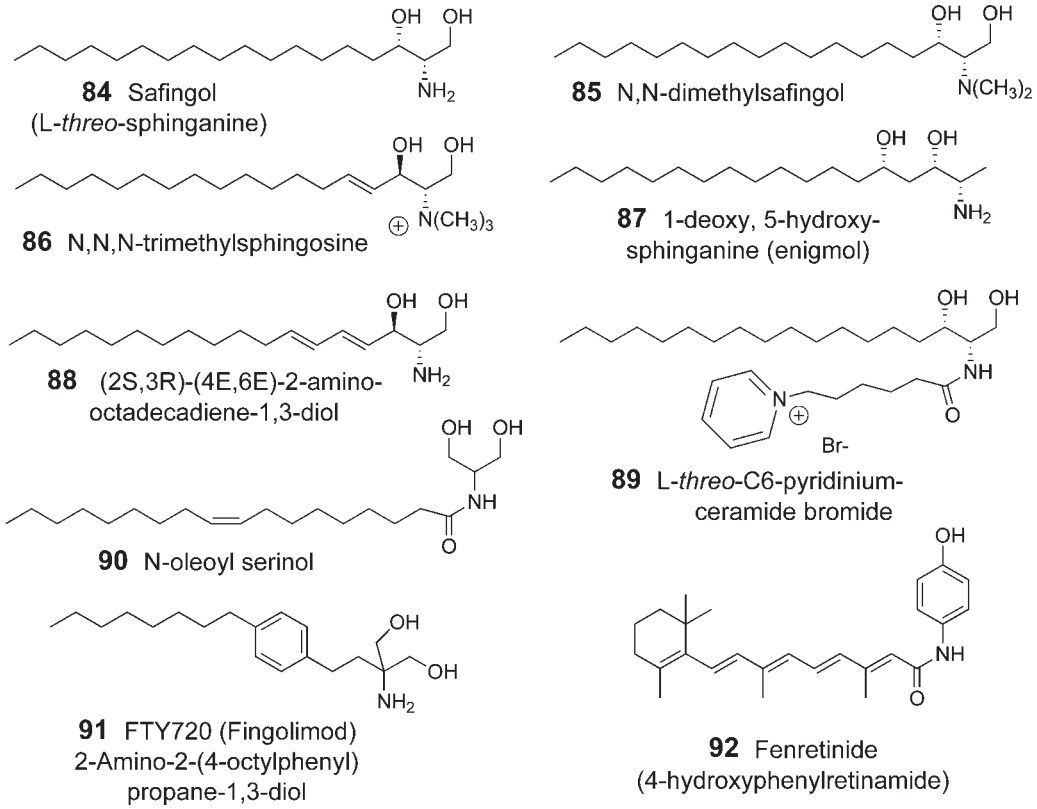


Fig. 9. Examples of compounds of interest as sphingoid base/ceramide analog pharmaceutical leads.

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 sphingoid base-like compounds 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 analog 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.

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