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Toward a Systematic Nomenclature for (Neo)Lignanamides

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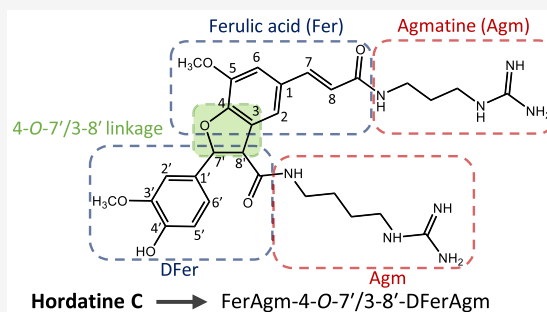


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ABSTRACT: Phenylalkenoic acid amides, often referred to as phenol amides or hydroxycinnamic acid amides, are bioactive phytochemicals, whose bioactivity can be enhanced by coupling to form dimers or oligomers. Phenylalkenoic acid amides consist of a (hydroxy)cinnamic acid derivative (i.e., the phenylalkenoic acid subunit) linked to an amine-containing compound (i.e., the amine subunit) via an amide bond. The phenylalkenoic acid moiety can undergo oxidative coupling, either catalyzed by oxidative enzymes or due to autoxidation, which leads to the formation of (neo)lignanamides. Dimers described in the literature are often named after the species in which the compound was first discovered; however, the naming of these compounds lacks a systematic approach. We propose a new nomenclature, inspired by the existing system used for hydroxycinnamic acid dimers and lignin. In the proposed systematic nomenclature for (neo)lignanamides, compound names will be composed of three-letter codes and prefixes denoting the subunits, and numbers that indicate the carbon atoms involved in the linkage between the monomeric precursors. The proposed nomenclature is consistent, future-proof, and systematic.



Phenylalkenoic acid amides, often referred to as phenol amides or hydroxycinnamic acid amides, are present in a wide variety of plants and are predominantly found in plant reproductive organs and seeds. Phenylalkenoic acid amides consist of a phenylalkenoic acid subunit (i.e., a cinnamic acid derivative), linked to an amine subunit (Figure 1).^{1,2} Phenylalkenoic acid amides are reported to be bioactive compounds that possess, among others, antiviral, antimicrobial, and insecticidal activities.^{1,2} Upon wounding or microbial stress, plants produce dimeric products of phenylalkenoic acid amides. These compounds, called lignanamides or neo-lignanamides, are phenylalkenoic acid amides linked to another phenylalkenoic acid amide or a phenylalkenoic acid derivative (e.g., a monolignol).³ (Neo)Lignanamides usually possess an even higher biological activity than their monomeric precursors.^{3–8} Examples of increased bioactivity upon oxidative coupling include phenylalkenoic acid–tyramine dimers with higher hepatoprotective and antihyperlipidaemic activity than their monomeric precursor.^{8,9} Furthermore, (neo)lignanamides have been reported to possess antifungal, anti-inflammatory, antineurodegenerative, antioxidant, cytotoxic, and antitumor activities,⁵ which has piqued scientific interest in these compounds.

A wide variety of phenylalkenoic acid amides exist due to the diversity in monomeric units that can be combined. *p*-Coumaric acid, caffeic acid, ferulic acid, and sinapic acid are the most common phenylalkenoic acid subunits; however, other phenylalkenoic acid subunits can be incorporated as

well.¹ An even larger number of different amine subunits can be incorporated, of which tyramine is the most reported amine subunit.^{1,10} From the combination of at least 14 different phenyl subunits and 19 amine subunits, at least 247 different phenylalkenoic acid amides can be formed. Oxidative coupling of these compounds results in further diversification, as different linkage types can be formed and different precursors can be combined. Reported coupling products are either homodimers or heterodimers, consisting of a phenylalkenoic acid amide linked to a different phenylalkenoic acid amide or a phenylalkenoic acid derivative.³ Heterodimers with different amine subunits or with different phenyl subunits have both been reported.^{4,8} At least 14 linkage types have been reported and, when only considering the precursors and the linkage types, at least 902 538 (247 monomers × (247 + 14 monolignols) × 14 linkage types) dimers can theoretically be formed, excluding stereoisomers. Dimers are the most common coupling products; however larger oligomers can also be formed.¹¹

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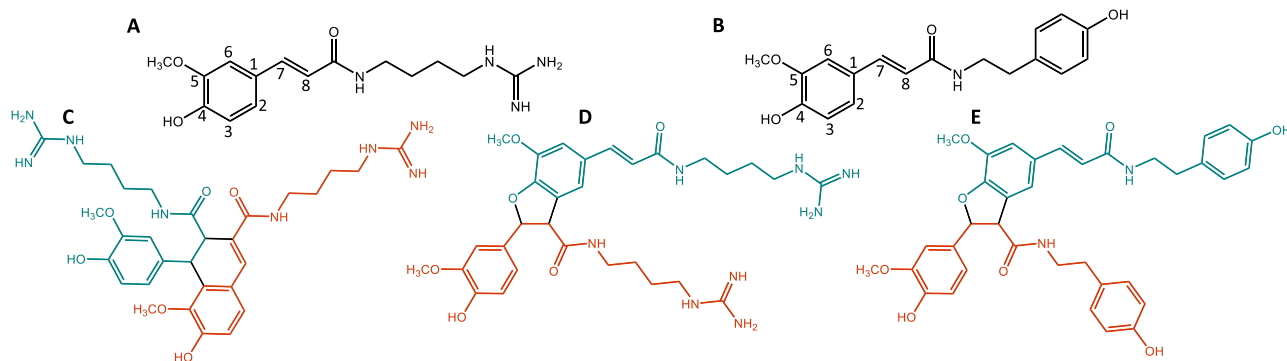


Figure 1. Two examples of phenylalkenoic acid amides, feruloylglutamine (A) and feruloyltyramine (B), and three dimers: two homodimers of feruloylglutamine (C and D) and a homodimer of feruloyltyramine (E). The trivial names currently used for the dimers shown are murinamide A (structure 54 in Figure S1), hordatine C (33), and grossamide A (26).

Currently, each new (neo)lignanamide is given a trivial name, often derived from the name of the plant in which the compound was first identified, e.g., hordatines from *Hordeum* and cannabisins from *Cannabis*.

To indicate different dimers from the same plant species, capital letters are included as part of the compound name. These capital letters, used in alphabetical order, only indicate the order in which compounds were discovered. The capital letters do not indicate specific linkage types or precursors. Thus, there is no system in place for the naming of these compounds. With the growing number of reported dimers, and because the same dimers are found in multiple plant species,¹² a more systematic nomenclature is needed.

Dimers of the same precursor have completely different names, as is illustrated for feruloyltyramine, for which dimers named lyciumamide K, grossamide A (Figure 1), cannabisins D–G and O, hyoscyamide, corydalisin C, and an unnamed dimer have been reported.^{6,7,11–16} The lack of information embedded in these names is exemplified clearly by cannabisin G and hyoscyamide, which are the *cis*- and *trans*-isomers of the same compound.^{14,17} The main difference between all of the reported feruloyltyramine dimers is the type of linkage between the monomers. The linkage type between the monomers is not indicated, and dimers with a similar linkage type may have completely different names. Lignan-amides are formed by lignan-like linkage types, in which both β -carbon atoms are involved. The smaller group of neolignan-amides are formed by neolignan-like linkage types, in which at least one non- β -carbon is involved.³ Murinamide A (Figure 1), lyciumamide I, lyciumamide J, cannabisins B–D, flavifloramide A, and flavifloramide B all possess the same linkage type; however, this is not reflected in their names.^{5,8,15,18}

The nomenclature used for phenylalkenoic acid amide dimers present in oat is a bit more systematic. For these dimers of avenanthramides (i.e., phenolic anthranilic acid amides), which are called bisavenanthramides and are produced in oat leaves as a mixture of isomers,¹⁹ the precursor is indicated in the name by using a capital letter and the linkage type is indicated using a number.²⁰ However, this nomenclature cannot accommodate heterodimers. In addition, the use of arbitrary numbers and letters forces the reader to search for the corresponding structures. Therefore, a systematic nomenclature based on the chemical structure of the precursors and linkage types would provide significant advantages over the current approach.

One of the enzymes responsible for the oxidative coupling of phenylalkenoic acids, leading to the formation of (neo)-lignan-amides, is peroxidase. Generally, the peroxidase reaction is not selective to the position or stereochemistry of the generated linkage. An *in vitro* reaction of avenanthramide B with peroxidase resulted in the generation of a mixture of at least five isomers of bisavenanthramides with different linkage types.²⁰ The only isomers with regio- and stereoselective linkages are occasionally isolated from a species, as exemplified by the hordatines in barley (*Hordeum vulgare*)⁴ and murinamides in *Hordeum murinum*.⁵ In this context, a nomenclature that can specify the linkages between monomers would be helpful for understanding the regio- and stereoselective biosynthetic reactions.

Thus, a consistent, systematic, and future-proof nomenclature for (neo)lignan-amides is proposed. Norlignan-amides, coupling products of phenylalkenoic acid amides of which at least one carbon atom is removed upon coupling, will not be incorporated in the proposed nomenclature.²¹ The nomenclature should be applicable for dimers and larger oligomers formed from any phenylalkenoic acid amide and monolignol precursors, to make it a suitable system for existing and to-be-discovered coupling products. The name of each coupling product should indicate the precursors and the linkage type, including relative (*cis* and *trans*) and absolute (*R* and *S*) configuration, to allow for the name to be readily translated to their chemical structure.

We propose a new nomenclature based on the system used for similar linkage types present in dimers of hydroxycinnamic acids (Figure 2) and in the lignin polymer. In these systems the carbon atoms in the phenyl ring are numbered 1 to 6, and numbering continues with the carbon atoms in the alkenic

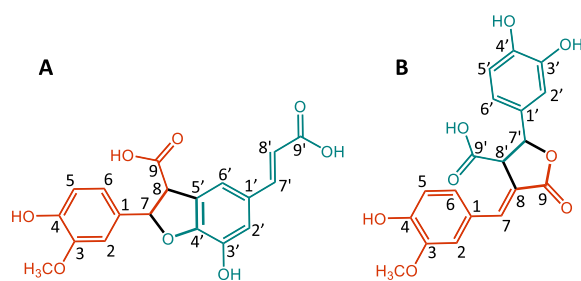


Figure 2. Examples of the numbering used for hydroxycinnamic acid dimers: ferulic acid and caffeic acid connected by 7–O–4' and 8–5' (A) and by 9–O–7' and 8–8' (B) linkages.²³

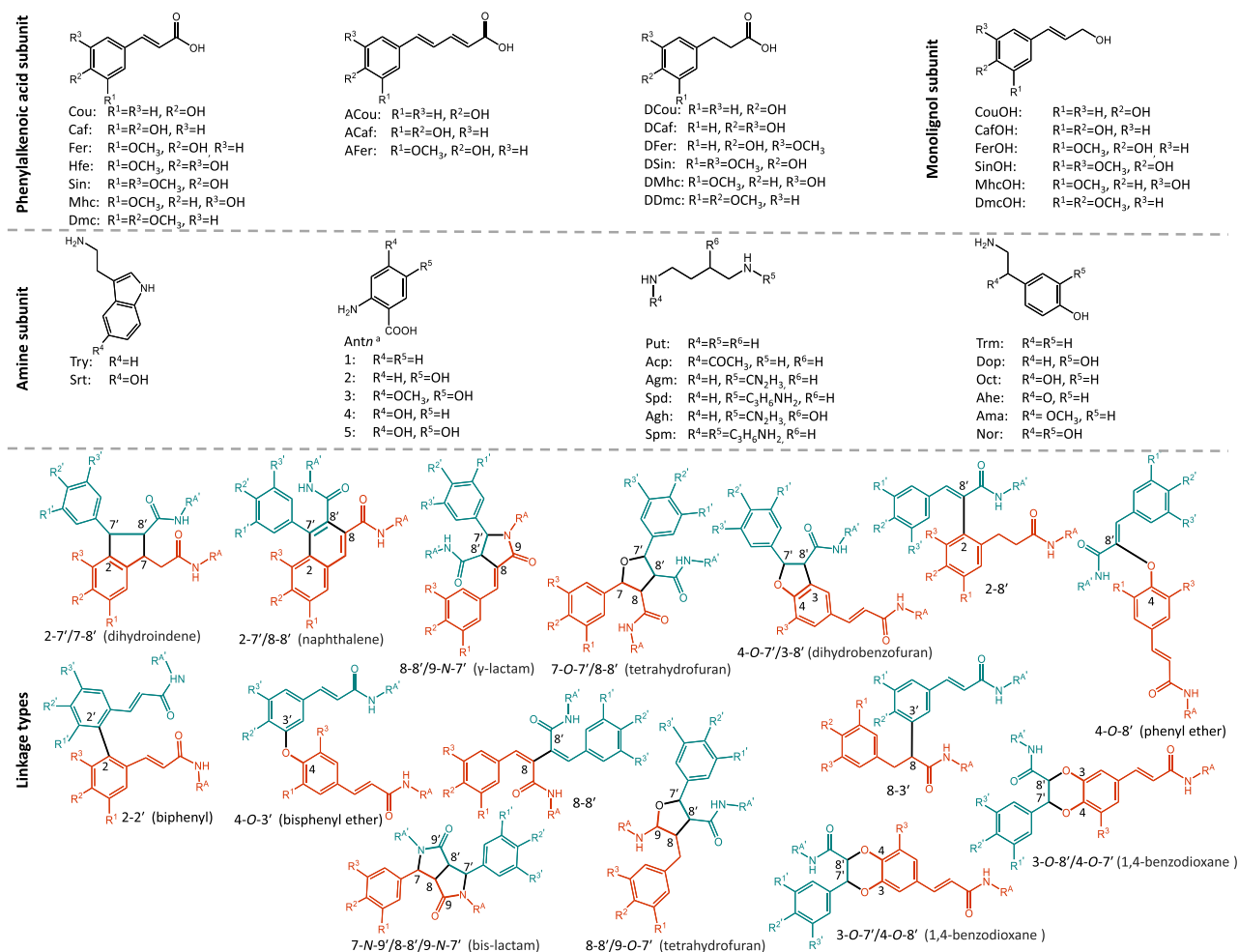


Figure 3. Overview of the different phenylalkenoic acid subunits and amine subunits reported in phenylalkenoic acid amides, the monolignols present in (neo)lignanamide, and the different linkage types occurring in (neo)lignanamide. The R^1 and R^2 groups might differ from the $R^{1'}$ and $R^{2'}$ groups depending on the precursors of the dimer. R^A indicates the remaining part of the amine group. For anthranilic acids (Ant) the “n” behind Ant will be replaced by the number of the corresponding anthranilic acid. Structural elements of the different linkage types are given between brackets.

acid moiety attached to the ring; that is, the carbon closest to the phenyl ring is 7 followed by 8, etc. (Figure 2).²² By numbering both precursors and indicating the carbon atoms of one of the precursors with a prime, the carbon atoms involved in the dimerization can be readily and systematically indicated.^{23,24} By indicating the carbon atoms involved, the structure of the coupling product can be described. If either an oxygen or a nitrogen atom is involved in the linkage, the precursor that donates the oxygen or nitrogen atom is indicated without a prime. Figure 3 shows the different phenyl and amine subunits that have been reported as subunits of phenylalkenoic acid amides, monolignols, and all known linkage types for (neo)lignanamide. The abbreviations used in Figure 3 are explained in Table 1.

Some literature abbreviations commonly used for the amine subunits present in phenylalkenoic acid amides overlap with abbreviations used for amino acids (Ser and Tyr). These amino acid three-letter codes have been firmly established in a wide variety of scientific fields, and conjugation of phenylalkenoic acids with amino acids has been reported.²⁵ Therefore, to avoid any confusion, new abbreviations are introduced for serotonin (Srt) and tyramine (Trm).

Some of the phenyl and amine group abbreviations contain an extra character. The five types of anthranilic acid groups are numbered one to five in the literature;²⁶ therefore this numbering will also be used within the proposed nomenclature. The abbreviation for anthranilic acid is Antⁿ, where the “n” behind “Ant” is replaced by a number to indicate which of the five anthranilic acids is incorporated. Two extra letters are used for the phenyl groups: the prefix “A” represents avenalamic acids containing an extra $CH=CH$ group in the side chain of the phenyl group and “D” represents the hydrogenation of the C–C double bond in the side chain of dihydrophenylalkenoic acids. Upon (neo)lignanamide formation, often the double bond present in the phenylalkenoic acid is saturated, which should also be indicated by using the prefix “D”.

(Neo)Lignanamide can also consist of a phenylalkenoic acid amide linked to a monolignol unit. This group can be named using the same nomenclature; however it should be indicated clearly whether a phenylalkenoic acid amide or a monolignol moiety is incorporated. Monolignols (i.e., cinnamyl alcohols) are indicated by adding “OH” to the abbreviation used for the corresponding phenylalkenoic acid, e.g., “Cou” for *p*-coumaric acid and “CouOH” for *p*-coumarol

Table 1. Abbreviations Used for the Phenylalkenoic Acid Subunits, Amine Subunits, and Monolignols^{1–3,9,10,33,34}

abbreviation	full name
Phenylalkenoic acid subunits	
Cou	<i>p</i> -coumaric acid
Caf	caffeic acid
Fer	ferulic acid
Hfe	5-hydroxyferulic acid
Sin	sinapic acid
Mhc	3-methoxy-5-hydroxycinnamic acid
Dmc	3,4-dimethoxycinnamic acid
ACou ^a	avenalumatic acid
ACaf	5-hydroxyavenalumatic acid
AFer	5-methoxyavenalumatic acid
DCou ^b	dihydro- <i>p</i> -coumaric acid
DCaf	dihydrocaffeic acid
DFer	dihydroferulic acid
DSin	dihydrosinapic acid
Amine subunits	
Try	tryptamine
Srt	serotonin
Antr ^c	anthranilic acid
Put	putrescine
Acp	acetylputrescine
Agm	agmatine
Spd	spermidine
Agh	hydroxyagmatine
Spm	spermine
Trm	tyramine
Dop	dopamine
Oct	octopamine
Ahe	2-amino-1-(4-hydroxyphenyl)ethanone
Ama	α -(aminomethyl)-4-methoxybenzyl alcohol
Nor	noradrenaline
Monolignols	
CouOH ^d	<i>p</i> -coumaryl alcohol
CafOH	caffeyl alcohol
FerOH	coniferyl alcohol
SinOH	sinapyl alcohol
MhcOH	3-methoxy-5-hydroxycinnamyl alcohol
DmcOH	3,4-dimethoxycinnamic acid

^aA represents an extra CH=CH group in the alkenoic acid chain. ^bD represents hydrogenation of the C–C double bond in the alkenoic acid chain. ^cThe “n” behind “Ant” represents one of the five types of anthranilates (see Figure 3). ^dThe “OH” indicated in the abbreviation does not indicate hydroxylation of a phenylalkenoic acid but rather the presence of a hydroxy group instead of a carboxylic group.

alcohol.³ Lignanamide have been reported where the hydroxy of the monolignol is acetylated, resulting in the formation of an acetoxy group.²⁷ In this case the “OH” will be replaced with “OAc”, resulting in, for example, “CouOAc”.

Using Figure 3 and Table 1 the name of different phenylalkenoic acid amide dimers can be composed. For example, in the proposed system bisavenanthramide B1 (1) would be called DFerAnt2-7-*N*-9'/8-8'/9-*N*-7'-DFerAnt2 (Figure 4). The first carbon atom denoted in the linkage (i.e., C-7) originates from the precursor first mentioned in the name.

Our new systematic nomenclature is not restricted to dimers and can also be applied to trimers and larger oligomers, as is demonstrated for cannabisin O (17): FerTrm-4-*O*-8'-FerTrm-4'-*O*-7''/3'-8''-DFerTrm (Figure 4). At least 80 (neo)-

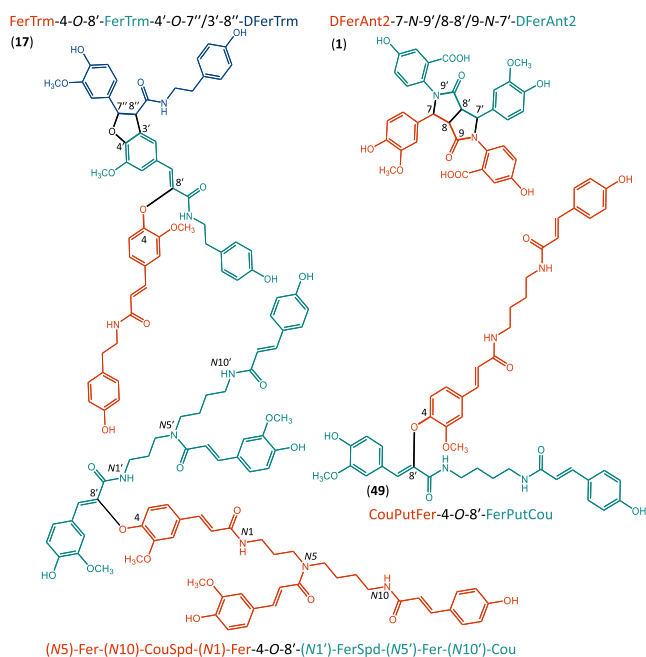


Figure 4. Structural formulas of FerTrm-4-*O*-8'-FerTrm-4'-*O*-7''/3'-8''-DFerTrm (compound 17, see Table 2 and Figure S1), DFerAnt2-7-*N*-9'/8-8'/9-*N*-7'-DFerAnt2 (compound 1), CouPutFer-4-*O*-8'-FerPutCou (compound 49), and (N5)-Fer-(N10)-CouSpd-(N1)-Fer-4-*O*-8'-(N1')-FerSpd-(N5')-Fer-(N10')-Cou.

lignanamide have been reported. Table 2 provides a comprehensive overview of all reported (neo)lignanamide with their old (trivial) names and new systematic names, and in Figure S1 all of the corresponding (neo)lignanamide structures are shown.

Besides the linkage types shown in Figure 3, several structural variations have been incorporated in the proposed systematic nomenclature. First, simultaneous to dimerization the C-7 can be hydroxylated, which is indicated by adding (7_{OH}) to the compound name, as is shown for (7_{OH})-DFerAnt2-8-8'/9-*N*-7'-DFerAnt2.²⁸ C-7 can also be substituted with an ethoxy group, which is indicated in a similar way by adding (7_{OEt}).^{29,30} Second, some amine subunits (e.g., putrescine) can be linked to multiple phenyl subunits. Coupling products of such structures will be indicated as illustrated by CouPutFer-4-*O*-8'-FerPutCou, in which the phenylalkenoic acid subunits (i.e., Fer) involved in the linkage are mentioned before and after mentioning the linkage type (Figure 4).³¹ Polyamines containing spermine or spermidine can be linked to three or even four phenylalkenoic acid moieties. As these amines are not symmetrical, the nitrogen atom to which the phenylalkenoic acid moiety is linked has to be indicated, similarly to how this is currently done for monomers of these compounds.³² An example of a spermidine substituted with three phenylalkenoic acids could be (N1,N5)-Fer-(N10)-CouSpd, a dimer of which, (N5)-Fer-(N10)-CouSpd-(N1)-Fer-4-*O*-8'-(N1')-FerSpd-(N5')-Fer-(N10')-Cou, is shown in Figure 4.

Third, the presence of stereogenic centers of which the configuration (*R* or *S*) is known can also be indicated in the systematic name. The configuration of stereogenic carbon atoms is mentioned together with the atom to which it refers; for example, if C-7' has an *S* configuration and the C-8' has an *R* configuration, this is indicated as (7'*S*,8'*R*), e.g.,

Table 2. Comprehensive Overview of the Former (Trivial or IUPAC) Names and Proposed Systematic Names of all Reported (Neo)Lignanamide Coupling Products^a

no.	proposed systematic name	former name	ref
1	DFerAnt2-7- <i>N</i> -9'/8-8'/9- <i>N</i> -7'-DFerAnt2	Bisavenanthramide B1	28
2	(7 _{OH})-DFerAnt2-8-8'/9- <i>N</i> -7'-DFerAnt2	Bisavenanthramide B3 ^b	20
3	(7 _{OH})-DFerAnt2-8-8'/9- <i>N</i> -7'-DFerAnt2	Bisavenanthramide B4 ^b	20
4	DFerAnt2-7- <i>O</i> -7'/8-8'-DFerAnt2	Bisavenanthramide B5	20
5	FerAnt2-8-8'/9- <i>N</i> -7'-DFerAnt2	Bisavenanthramide B6	20
6	CafTrm-2-7'/8-8'-CafTrm	Cannabisin A	35
7	CafTrm-2-7'/8-8'-DCafTrm	Cannabisin B	15
8	FerTrm-2-7'/8-8'-DCafTrm	Cannabisin C	15
9	FerTrm-2-7'/8-8'-DFerTrm	Cannabisin D	15
10	(7 _{OH})-DFerTrm-4- <i>O</i> -8'-FerTrm	Cannabisin E	14
11	FerTrm-4- <i>O</i> -8'-FerTrm	Cannabisin F ^d	14
12	(<i>E</i>)-FerTrm-8-8'-FerTrm	Cannabisin G ^e	14
13	CafTrm-8-8'-CafTrm	3,3'-Demethyl-cannabisin G	36
14	CafTrm-8-8'-FerTrm	3-Demethyl-cannabisin G	36
15	CafTrm-3- <i>O</i> -8'/4- <i>O</i> -7'-DCafTrm	Cannabisin M	11
16	CafTrm-3- <i>O</i> -8'/4- <i>O</i> -7'-DMhcTrm	Cannabisin N	11
17	FerTrm-4- <i>O</i> -8'-FerTrm-4'- <i>O</i> -7'/3'-8''-DFerTrm	Cannabisin O	11
18	CafTrm-3- <i>O</i> -7'/4- <i>O</i> -8'-DCafTrm	Cannabisin Q	37
19	FerTrm-4- <i>O</i> -8'-SinTrm	Corydalisin A	16
20	SinTrm-4- <i>O</i> -8'-SinTrm	Corydalisin B	16
21	SinTrm-2-7'/8-8'-DSinTrm	Corydalisin C	16
22	FerTrm-4- <i>O</i> -3'-FerTrm	<i>N</i> -feruloyl tyramine dimer	7
23	SinTrm-2-7'/8-8'-DFerTrm	Flavifloramide A	18
24	SinTrm-2-7'/8-8'-DSinTrm	Flavifloramide B	18
25	(7 _{OH})-DDmcTrm-2-7'/8-8'-DSinTrm	Foveolatamide	2
26	FerTrm-4- <i>O</i> -7'/3-8'-(7' <i>S</i> ,8' <i>R</i>)-DFerTrm	Grossamide A ^c	6, 12
27	CafTrm-4- <i>O</i> -7'/3-8'-DCafTrm	3,3'-Demethyl-grossamide A	36
28	DFerTrm-7- <i>N</i> -9'/8-8'/9- <i>N</i> -7'-DFerTrm	Heliotropamide	38
29	CafTrm-8-8'/9- <i>N</i> -7'-DCafTrm	3,3'-Demethyl-heliotropamide	11
30	(<i>Z</i>)-FerTrm-8-8'-FerTrm	Hyoscyamide ^e	17
31	CouAgm-4- <i>O</i> -7'/3-8'-DCouAgm	Hordatine A	4
32	FerAgm-4- <i>O</i> -7'/3-8'-DCouAgm	Hordatine B	4
33	FerAgm-4- <i>O</i> -7'/3-8'-DFerAgm	Hordatine C	30
34	(<i>E</i>)-DFerTrm-7- <i>O</i> -7'/8-8'-DFerOAc	Isojacpaniculine ^g	27
35	(<i>Z</i>)-DFerTrm-7- <i>O</i> -7'/8-8'-DFerOAc	Jacpaniculine ^g	27
36	FerTrm-8-8'/9- <i>N</i> -7'-DCafTrm	Limoniumin F	39
37	FerTrm-4- <i>O</i> -7'/3-8'-FerTrm	Limoniumin G	39
38	CafTrm-2-7'/8-8'-DFerTrm	Limoniumin H	39
39	SinAcp-2-7'/8-8'-DSinOH	Lycichinenamide	40
40	DCafTrm-3- <i>O</i> -8'/4- <i>O</i> -7'-DCafTrm	Lyciumamide D	8
41	DCafTrm-3- <i>O</i> -7'/4- <i>O</i> -8'-DCafTrm	Lyciumamide E	8
42	DCafTrm-2-2'-DCafTrm	Lyciumamide F	8
43	DCafTrm-2-8'-CafTrm	Lyciumamide G	8
44	SinTrm-2-7'/8-8'-DSinOH	Lyciumamide H	8
45	SinTrm-2-7'/8-8'-DSinAcp	Lyciumamide I	8
46	SinAcp-2-7'/8-8'-DSinTrm	Lyciumamide J	8
47	DFerTrm-7- <i>O</i> -7'/8-8'-DFerTrm	Lyciumamide K	13
48	DCafTrm-2-7'/7-8'-DCafTrm	Limoniastramide	41
49	CouPutFer-4- <i>O</i> -8'-FerPutCou	Mariamide A	31
50	SinTrm-2-7'/8-8'-DFerTrm	Melongenamide A	42
51	FerTrm-4- <i>O</i> -7'/3-8'-DFerOct	Melongenamide B	42
52	CouTrm-4- <i>O</i> -8'-CouTrm	Melongenamide C	42

Table 2. continued

no.	proposed systematic name	former name	ref
53	FerTrm-8'-O-4-FerTrm-2-7''/8-8''-(7''R,8''S)-DFerTrm	Melongenamide D ^f	42
54	FerOct-4-O-8'-FerOct	Melongenamide E	33
55	FerOct-4-O-8'-FerAma	Melongenamide F	33
56	FerAma-4-O-8'-FerOct	Melongenamide G	33
57	FerAgm-2-7'/8-8'-FerAgm	Murinamide A	5
58	FerAgm-8-8'/9-N-7'-DFerAgm	Murinamide B	5
59	FerTrm-4-O-7'/3-8'-DSinOAc	Tatarine E	43
60	FerTrm-4-O-7'/3-8'-DMhcTrm	Thoreliamide A	34
61	CafTrm-3-O-8'/4-O-7'-DSinOH	Thoreliamide B	34
62	FerTrm-8'-O-4-FerTrm-2-7''/8-8''-DFerTrm	Thoreliamide C ^f	34
63	FerTrm-4-O-7'/3-8'-(7'S,8'S)-DFerTrm	Tribulusamide A ^c	9
64	FerTrm-4-O-7'/3-8'-DFerAhe	Tribulusamide B	9
65	FerTrm-2-7'/8-8'-DFerTrm	Unnamed compound	44
66	DFerTrm-8-3'-FerTrm	Unnamed compound	44
67	SinTrm-2-7'/8-8'-DSinOH	(3S,4R)-6-hydroxy-4-(4-hydroxy-3,5-dimethoxyphenyl)-3-(hydroxymethyl)-N-(4-hydroxyphenethyl)-5,7-dimethoxy-3,4-dihydronaphthalene-2-carboxamide	45
68	CafTrm-3-O-8'/4-O-7'-DSinOH	(2S,3S,E)-3-[2,3-dihydro-2-(4-hydroxy-3,5-dimethoxyphenyl)-3-(hydroxymethyl)-1,4-benzodioxin-6-yl]-N-[2-(4-hydroxyphenethyl)ethyl]-2-propenamide	45
69	(E)-FerTrm-4-O-7'/3-8'-DMhcOH	(±)-(E)-3-(2-(3-hydroxy-5-methoxyphenyl)-3-(hydroxymethyl)-7-methoxy-2,3-dihydrobenzofuran-5-yl)-N-(4-hydroxyphenethyl)acrylamide ^h	29
70	(E)-FerTrm-4-O-7'/3-8'-DSinOH	(±)-(E)-3-(2-(4-hydroxy-3,5-dimethoxyphenyl)-3-(hydroxymethyl)-7-methoxy-2,3-dihydrobenzofuran-5-yl)-N-(4-hydroxyphenethyl)acrylamide ^t	29
71	(Z)-FerTrm-4-O-7'/3-8'-DMhcOH	(±)-(Z)-3-(2-(3-hydroxy-5-methoxyphenyl)-3-(hydroxymethyl)-7-methoxy-2,3-dihydrobenzofuran-5-yl)-N-(4-hydroxyphenethyl)acrylamide ^h	29
72	(Z)-FerTrm-4-O-7'/3-8'-DSinOH	(±)-(Z)-3-(2-(4-hydroxy-3,5-dimethoxyphenyl)-3-(hydroxymethyl)-7-methoxy-2,3-dihydrobenzofuran-5-yl)-N-(4-hydroxyphenethyl)acrylamide ^t	29
73	(7 _{OH})-DFerOH-8-8'/9-O-7'-DFerTrm	(±)-4-(ethoxy(4-hydroxy-3-methoxyphenyl)-methyl)-2-(4-hydroxy-3-methoxyphenyl)-N-(4-hydroxyphenethyl)tetrahydrofuran-3-carboxamide	29
74	FerTrm-4-O-8'-FerTrm	3-hydroxy-N-[2-(4-hydroxyphenyl)ethyl]-7-[4-(2-{N-[2-(4-hydroxyphenyl)ethyl]carbamoylethyl}-3-methoxyphenoxy)-4-methoxycinnamamide 4,8''-ether ^{ad}	46
75	(E)-CafTrm-3-O-8'/4-O-7'-DMhcTrm	(2,3-trans)-3-(3-hydroxy-5-methoxyphenyl)-N-(4-hydroxyphenethyl)-7-[(E)-3-[(4-hydroxyphenethyl)amino]-3-oxoprop-1-en-1-yl]-2,3-dihydrobenzo[b][1,4]dioxine-2-carboxamide	47
76	(Z)-CafTrm-3-O-8'/4-O-7'-DMhcTrm	(2,3-trans)-3-(3-hydroxy-5-methoxyphenyl)-N-(4-hydroxyphenethyl)-7-[(Z)-3-[(4-hydroxyphenethyl)amino]-3-oxoprop-1-en-1-yl]-2,3-dihydrobenzo[b][1,4]dioxine-2-carboxamide	47
77	SinTrm-2-8'-CafTrm	(E)-2-(4,5-dihydroxy-2-{3-[(4-hydroxyphenethyl)amino]-3-oxopropyl}phenyl)-3-(4-hydroxy-3,5-dimethoxyphenyl)-N-(4-hydroxyphenethyl)acrylamide	47
78	SinTrm-2-8'-CafAcp	(E)-2-(4,5-dihydroxy-2-{3-[(4-hydroxyphenethyl)amino]-3-oxopropyl}phenyl)-3-(4-hydroxy-3,5-dimethoxyphenyl)-N-(4-acetamidobutyl)acrylamide	47
79	FerTrm-2-8'-CafAcp	(E)-2-(4,5-dihydroxy-2-{3-[(4-hydroxyphenethyl)amino]-3-oxopropyl}phenyl)-3-(4-hydroxy-3-methoxyphenyl)-N-(4-acetamidobutyl)acrylamide	47
80	SinAcp-2-7'/8-8'-DFerTrm	(1,2-trans)-N-3-(4-acetamidobutyl)-1-(3,4-dihydroxyphenyl)-7-hydroxy-N-2-(4-hydroxyphenethyl)-6,8-dimethoxy-1,2-dihydronaphthalene-2,3-dicarboxamide	47

^aAll the corresponding structures are shown in Figure S1. In other papers tribulusamide C, and the corresponding succinimide linkage, is reported to be a lignanone.^{3,48} However, as this compound is not a coupling product of at least one phenylalkenoic acid amide with a phenylalkenoic acid derivative or monolignol, it does not fit the definition of (neo)lignanamide.^{b,c,d e,f,g,h,i} Pairs of *cis*- and *trans*-isomers. For ^b and ^d these compounds are diastereomers, but their absolute configurations have not been reported. ^gThoreliamide C is reported to be a *trans* isomer of melongenamide D; however the relative configuration of the ring substituents has not been specified.

FerTrm-4-O-7'/3-8'-(7'S,8'R)-DFerTrm. However, it should be noted that dimers possessing a cyclic junction are mostly present as a racemate in nature; in the literature the *cis* or *trans* configuration of their constituents is often not specified. In cases where it is relevant to differentiate between the configuration of C=C bonds between isomers, the difference can be indicated using (*E*) and (*Z*), respectively, e.g., (*E*)-FerTrm-8-8'-FerTrm.

If, in the future, dimers are discovered that possess a phenyl subunit, an amine subunit, or linkage type that has not been covered in this paper, it can readily be integrated in the proposed nomenclature. For novel phenyl and amine subunits a new three-letter abbreviation should be introduced. Any new linkage types that may be discovered can be described by

indicating the connection of the involved carbon atoms and heteroatoms, as is the case for the other linkage types in the system. Substitution of the dimer can be indicated using a subscript following the number or the substituted carbon atom, in the same way as shown for C-7 hydroxylation (7_{OH}).

In conclusion, a systematic nomenclature, in which the precursors and linkages types are unambiguously indicated, is proposed for the growing group of (neo)lignanamide.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.jnatprod.0c00792>.

Figure S1: Overview of the structures of the compounds listed in Table 2 (PDF)

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Notes

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