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Natural Alkamides: Pharmacology, Chemistry and Distribution

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1. Introduction

Alkamides are a broad and expanding group of bioactive natural compounds found in at least 33 plant families. Despite the relatively simple molecular architecture of alkamides (fig. 1), these natural products show broad structural variability and an important range of biological activities, such as immunomodulatory, antimicrobial, antiviral, larvicidal, insecticidal, diuretic, pungent, analgesic, cannabimimetic and antioxidant activities. Additionally, alkamides are involved in the potentiation of antibiotics and the inhibition of prostaglandin biosynthesis, RNA synthesis and the arachidonic acid metabolism, among others.

Many plant species containing alkamides have been used in traditional medicine by different civilizations around the world. Many of the plants containing these natural products have been used in the treatment of toothaches and sore throats (Rios-Chavez et al., 2003). These compounds are present in different organs of the plant, such as roots (*Heliopsis longipes*, *Echinaceae purpurea*, *Achillea wilhelmsii*, A*cmella oppositifolia*, *Asiasarum heterotropoide, Cissampelos glaberrima*, etc.), leaves and stems (*Aristolochia gehrtii*, *Phyllanthus fraternus*, *Amaranthus hypochondriacus*, *Achyranthes ferruginea*, etc.), the pericarpium (*Zanthoxylum piperitum* and *Piper spp*.), the placenta of *Capsicum spp*., the fruits of *Piper longum*, the flowers of *Spilanthes acmella*, the seeds of the *Piper* species and tubers of *Lepidium meyenii*. It is believed that alkamides act as plant growth regulators, promoting or inhibiting the growth and formation of roots in a dose-dependent manner and showing a positive effect in plant biomass production (Campos-Cuevas, et al., 2008).

Structurally, natural alkamides commonly have an aliphatic, cyclic or aromatic amine residue, and a C8 to C18 saturated or unsaturated chain (including double or triple bonds, or both) acid, which can also be aromatic. The nature of the acid (carbon chain lengths, unsaturation level, stereochemistry, etc.) and the amine residues are characteristic of each family and genus of plants such that these characteristics serve as chemotaxonomic criteria (fig. 1). Because the nitrogen atom of alkamides is not part of a heterocyclic ring, these compounds are classified as protoalkaloids or pseudoalkaloids.

Alkamides represent a class of lipidic compounds structurally related to animal endocannabinoids. Notably, based on the structural similarity of these compounds to

anandamide (*N*-arachidonoylethanolamine), an endogenous cannabinoid cerebral neurotransmitter, alkamides are highly active in the central nervous system (CNS, fig. 2).

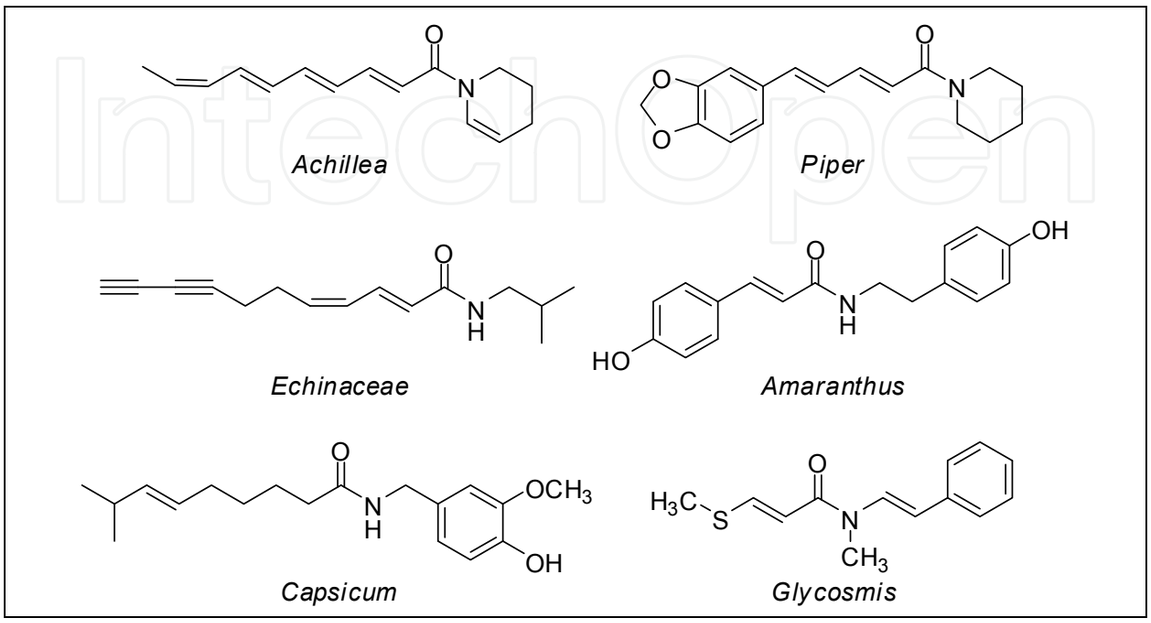


Fig. 1. Characteristic alkamides from different plant genera.

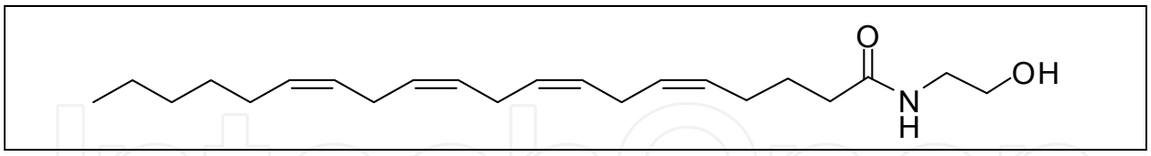


Fig. 2. Anandamide (*N*-arachidonoylethanolamine) structure.

In general, when alkamide-producing plants are chewed, a pungent taste is released causing itching and salivation. Chloroform is the best solvent for the extraction of alkamides, though both methanol and ethanol have also been used. Pure alkamides are sensitive to oxidation and polymerization of double and triple bonds occur during the drying, handling and storage of these compounds. Notably, alkamides are promising chemical and pharmacological entities that are useful therapeutics for the treatment of several important illnesses. This chapter describes the distribution of alkamides, the chemical aspects used to distinguish these important natural products and the pharmacological properties of the plants from which these compounds are isolated.

2. Aliphatic alkamides

Plants belonging to the Asteraceae, Convolvulaceae, Euphorbiaceae, Menispermaceae and Rutaceae families specialize in the biosynthesis of alkamides with both amine and acid aliphatic residues. Chemical analysis of these species revealed that aliphatic alkamides are the major and most characteristic components of several Asteraceae plants based on the number of isolated compounds from each plant and the yield obtained for each alkamide. In contrast, Convolvulaceae, Euphorbiaceae, Menispermaceae and Rutaceae families produce alkamides along with other types of natural products, resulting in alkamides being the minor components.

2.1 Alkamides from the Asteraceae family

The Asteraceae family is characterized by the accumulation of aliphatic alkamides. *Aaronsohnia*, *Achilea*, *Acmella*, *Anacyclus*, *Artemisia*, *Echinaceae*, *Heliopsis*, *Spilanthes*, *Salmea*, *Sanvitalia* and *Wedelia* are genera that belong to this alkamide-producing family. These genera share the biogenetic capacity to combine C8 to C18 (with exception of C17) olefinic and acetylenic acid residues with the more widespread *N*-isobutyl, *N*-2-methylbutyl, *N*-phenethyl and cyclic amines [piperidinyl (piperidide), 2,3-dehydro-piperidinyl (piperideide), pyrrolidinyl and pyrrolidyl]. However, other minor amides including *N*-4-methylbutyl, *N*-tyramidyl and *O*-methyl-tyramidyl residues have also been found (fig. 3).

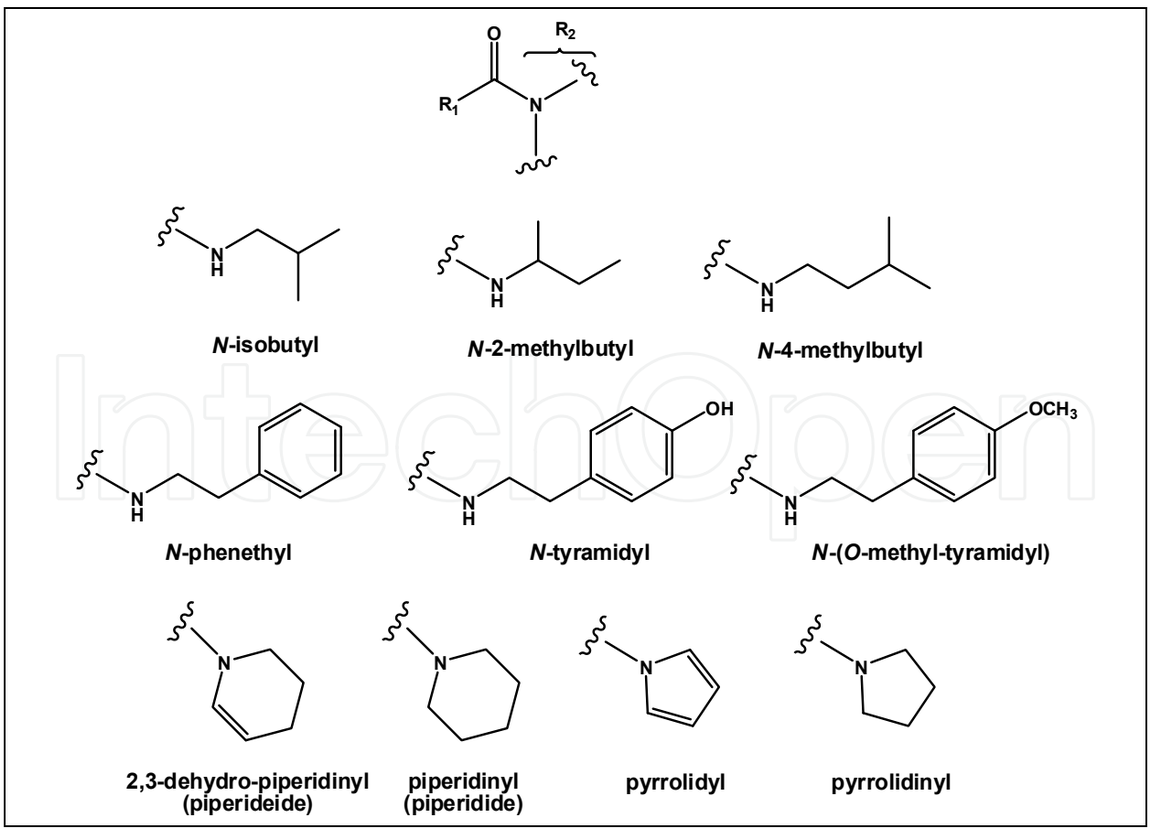


Fig. 3. Amine residues (R_2) of aliphatic alkamides from the Asteraceae family.

Currently, the most commonly found alkamides in the Asteraceae family include a C10, C11 and C12 long chain residue acids, which represent approximately 72% of aliphatic alkamides isolated from this family. The second most important group of these natural products includes C14 and C18 long chain residue acids, constituting approximately 13% of Asteraceae alkamides. Most phytochemical and pharmacological studies have been conducted with *Achillea*, *Acmella*, *Sphilantes*, *Echinaceae* and *Heliopsis* genera, which will be discussed in subsequent sections.

2.1.1 *Achillea* genus

The occurrence of alkamides with cyclic amide moieties is confined to the Anthemideae tribe, being *Achillea* species especially rich in both pyrrolidides and piperidides and their corresponding dehydroderivatives. Apart from the more widespread isobutylamides, this genus is characterized by the frequent occurrence of saturated and unsaturated 5- and 6-ring amides (Greger et al., 1987a, 1987b). The accumulation of amides with characteristic olefinic and acetylenic patterns is characteristic of this genus. These amides are mainly accumulated in the subterranean parts of these plants (table 1).

2.1.2 *Acmella* genus

A name frequently used in folk medicine for species containing alkamides is "the tooth herb". These plants exhibit analgesic properties and are frequently used as odontologic agents. For example, *Acmella decumbens* roots have a pungent taste and when chewed a numbing sensation is felt on the tongue. *Acmella radicans* is another species also used for the treatment of toothache (Rios-Chavez et al., 2003).

Alkamides from the *Acmella* genus consist of an *N*-isobutyl, *N*-2-methylbutyl or *N*-phenethyl amine and C8 to C12 acid residues. Of the seven *Acmella* species that have been chemically analyzed, four species have been observed to produce affinin (spilanthol, *N*-isobutyl-2*E*,6*Z*,8*E*-decatrienamide, **70**), an alkamide with established analgesic properties (Rios et al., 2007). Several affinin analogues are present in extracts from these *Acmella* species (see table 1), which probably contribute to the analgesic sensation induced by these plants.

2.1.3 *Spilanthes* genus

For years *Spilanthes acmella* has been used as traditional folk medicine to treat toothaches, stammering, and stomatitis. Previous studies have demonstrated the diuretic, antibacterial, and anti-inflammatory activities of *Spilanthes acmella*. Spilanthol (**70**), the main alkamide isolated from this plant, exhibits antiseptic activity. Additionally, spilanthol (**70**) is involved in immune stimulation and the attenuation of the inflammatory responses in murine RAW 264.7 macrophages (Wu et al., 2008).

2.1.4 *Echinaceae* genus

Echinacea is a native herb from North America and Europe that is used as an immunostimulant. Extracts from the *Echinacea* species are widely used due to the strong belief that the components of the extract stimulate the immune system and help to prevent infections, colds, respiratory infections and influenza. However, the clinical efficacy of this

Tribe	Genus	Species	Alka-mide	R_1 (including C=O)		R_2	Reference
				Chain	Double and triple bonds		
Anthe-mideae	*Aaronsohnia*	*pubescens*	**1**	C10	2*E*,4*E*-dies-6-(thien-2-yl)	*N*-isobutyl	(Muller-Jakic et al., 1994)
	Achillea	*ageratifolia*	**2**	C12	2,6-epoxy	pyrrolidyl	(Muller-Jakic et al., 1994) (Greger et al., 1987b)
			3	C16	2*E*,7*Z*-dienyl	pyrrolidyl	
			4	C16	7*Z*-en-9-yne	pyrrolidyl	
			5	C16	2*E*,7*Z*-dien-10-yne	pyrrolidyl	
			6	C16	2*E*,6*E*,8*E*-trien-10-yne	pyrrolidyl	
			7	C14	2*E*,4*E*-dien-8-yne	pyrrolidinyl	
			8	C14	2*E*,4*E*,7*Z*,10*Z*-tetraenyl	pyrrolidinyl	
			9	C16	6*E*,8*E*-dien-10-yne	pyrrolidinyl	
			10	C16	4*E*,7*Z*-dien-10-yne	pyrrolidinyl	
			11	C16	2*E*,6*E*,8*E*-trien-10-yne	pyrrolidinyl	
		beibersteinii	**12**	C14	2*E*,4*E*,12*E*-trien-8,10-diyne	piperidinyl	(Muller-Jakic et al., 1994)
		chamaeme-lifolia	**13**	C18	12-oxo	piperidinyl	(Greger et al., 1987a)
			14	C18	12-oxo	pyrrolidyl	
			15	C18	2*E*-en-12-oxo	piperidinyl	
			16	C18	2*E*-en-12-oxo	pyrrolidyl	
			17	C18	2*E*,4*E*,9*Z*-trien-12-yne	*N*-isobutyl	
			18	C18	2*E*,8*E*,10*E*-trien-12-yne	piperidinyl	
			19	C18	2*E*,4*E*,8*E*,10*E*-tetraen-12-yne	*N*-isobutyl	
			20	C18	2*E*,4*E*,8*E*,10*Z*- tetraen-12-yne	*N*-isobutyl	
		crithmifolia	**21**	C11	2*E*,4*E*-dien-8,10-diyne	*N*-isobutyl	(Muller-Jakic et al., 1994)
		distans subsp. *distans*	**22**	C10	2*E*,4*E*-dienyl	*N*-isobutyl	(Lazarevic et al., 2010)
			23	C10	2*E*,4*E*-dienyl	piperidinyl	
			24	C10	2*E*,4*E*-dienyl	2,3-dehydro-piperidinyl	
			25	C10	2*E*,4*E*,6*Z*-trienyl	2,3-dehydro-piperidinyl	
		lycaonica	**26**	C15	2*E*,4*E*-dien-12-oxo	*N*-isobutyl	(Greger et al., 1987a)
			27	C18	2*E*-enyl	piperidinyl	

Tribe	Genus	Species	Alka-mide	R_1 (including C=O)		R_2	Reference
				Chain	Double and triple bonds		
			28	C18	2*E*,9*Z*-dienyl	piperidinyl	
			29	C18	9*Z*-en-12-yne	piperidinyl	
			30	C18	2*E*,9*Z*-dien-12-yne	piperidinyl	
			31	C18	9*Z*,14*Z*-dien-12-yne	piperidinyl	
			32	C18	2*E*,9*Z*-dien-12,14-diyne	piperidinyl	
		millefolium	**22**	C10	2*E*,4*E*-dienyl	*N*-isobutyl	(Muller-Jakic et al., 1994) (Greger & Hofer, 1989) (Greger & Hofer, 1990) (Greger, H. & Werner, 1990)
			33	C10	2*E*,4*E*-dien-8,10-diyne	*N*-isobutyl	
			34	C10	2*E*,4*E*,8*Z*-trienyl	*N*-isobutyl	
			35	C14	2*E*,4*E*-dien-8,10-diyne	*N*-isobutyl	
			36	C14	2*E*,4*E*,12*E*-trien-8,10-diyne	*N*-isobutyl	
			37	C14	2*E*,4*E*,12*Z*-trien-8,10-diyne	*N*-isobutyl	
			38	C15	2*E*,9*Z*-dien-12,14-diyne	*N*-isobutyl	
			39	C10	2*E*,4*E*-dien-8,10-diyne	*N*-isobutyl	
			40	C10	2*E*,4*E*-dienyl	*N*-tyramidyl	
			41	C10	2*E*,4*E*-dienyl	*N*-(*O*-methyl-tyramidyl)	
			23	C10	2*E*,4*E*-dienyl	piperidinyl	
			42	C10	2*E*,4*E*,8*Z*-trienyl	piperidinyl	
			24	C10	2*E*,4*E*-dienyl	2,3-dehydro-piperidinyl	
			25	C10	2*E*,4*E*,6*Z*-trienyl	2,3-dehydro-piperidinyl	
			43	C10	2*E*,4*E*-dien-8,10-diyne	2,3-dehydro-piperidinyl	
			44	C10	2*E*,4*E*,8*Z*-trienyl	2,3-dehydro-piperidinyl	
			45	C10	2*E*,4*E*,6*E*-trienyl	2,3-dehydro-piperidinyl	
			46	C10	2*E*,4*E*,6*Z*,8*Z*-tetraenyl	2,3-dehydro-piperidinyl	
			47	C10	2*E*,4*E*,6*E*,8*Z*-tetraenyl	2,3-dehydro-piperidinyl	
			48	C11	2*E*,4*E*,6*E*,8*E*-tetraenyl	2,3-dehydro-piperidinyl	
			49	C11	2*E*,4*E*-dien-8,10-diyne	piperidinyl	
			50	C11	2*E*,4*E*-dien-8,10-diyne	2,3-dehydro-piperidinyl	
		nana	**51**	C14	2*E*,4*E*,10*Z*-trien-8-yne	pyrrolidinyl	(Muller-Jakic et al., 1994)
		spinulifolia	**52**	C13	2*E*,4*E*-trien-8,10,12-triyne	piperidinyl	(Muller-Jakic et al., 1994)

Tribe	Genus	Species	Alka-mide	R_1 (including C=O)		R_2	Reference
				Chain	Double and triple bonds		
		ptarmica	**22**	C10	2*E*,4*E*-dienyl	*N*-isobutyl	(Lazarevic et al., 2010)
			53	C10	2*E*-en-4-yne	*N*-isobutyl	
		wilhelmsii	**54**	C10	2*E*,8*Z*-dien-4,6-diyne	*N*-isobutyl	(Muller-Jakic et al., 1994) Greger, 1987c]
			55	C10	2*E*,4*E*-dienyl	*N*-(3-methylbutyl)	
			56	C10	2*E*,8*Z*-dien-4,6-diyne	*N*-(3-methylbutyl)	
			57	C10	2*E*-en-4,6,8-triyne	*N*-(3-methylbutyl)	
			58	C10	2*E*,4*E*-dienyl	*N*-phenethyl	
			59	C10	2*Z*,8*E*-dien-4,6-diyne	*N*-phenethyl	
			60	C10	2*E*-en-4,6,8-triyne	*N*-phenethyl	
			61	C14	2*E*,4*E*,6*Z*,12*Z*-tetraen-8,10-diyne	*N*-isobutyl	
			62	C14	2*E*,4*E*,6*E*,12*Z*-tetraen-8,10-diyne	*N*-isobutyl	
			63	C14	2*E*,4*E*-dien-8,10-diyne	*N*-(3-methylbutyl)	
			64	C14	2*E*,4*E*,12*Z*-trien-8,10-diyne	*N*-(3-methylbutyl)	
			65	C14	2*E*,4*E*,6*Z*,12*Z*-tetraen-8,10-diyne	*N*-(3-methylbutyl)	
			66	C14	2*E*,4*E*,6*E*,12*Z*-tetraen-8,10-diyne	*N*-(3-methylbutyl)	
	Anacyclus	*pyrethrum*	**40**	C10	2*E*,4*E*-dienyl	*N*-tyramidyl	(Muller-Jakic et al., 1994)
	Artemisia	*dracunculus*	**22**	C10	2*E*,4*E*-dienyl	*N*-isobutyl	(Saadali et al., 2001)
			67	C11	2*E*,4*E*-dien-7,9-diyne	*N*-isobutyl	
			23	C10	2*E*,4*E*-dienyl	piperidinyl	
Berbe-sininae	*Salmea*	*scandens*	**68**	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	(Herz & Kulanthaivel, 1985) (Bohlmann et al., 1985)
			69	C12	2*E*,4*E*,8*Z*,10*Z*-tetraenyl	*N*-isobutyl	
Ecliptinae Less.	*Wedelia*	*parviceps*	**70**	C10	2*E*,6*Z*,8*E*-trienyl	*N*-isobutyl	(Johns et al., 1982)
Galin-soginae B. and H	*Acmella*	*alba*	**68**	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	(Bohlmann et al., 1980)
		ciliata	**71**	C8	2*E*,4*Z*-dienyl	*N*-isobutyl	(Martin & Becker,

Tribe	Genus	Species	Alka-mide	R_1 (including C=O)		R_2	Reference
				Chain	Double and triple bonds		
			72	C10	6*Z*,8*E*-dienyl	*N*-isobutyl	1984)
			70	C10	2*E*,6*Z*,8*E*-trienyl	*N*-isobutyl	(Martin & Becker,
			68	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	1985)
			73	C12	2*E*,4*Z*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	
			74	C8	2*Z*,4*E*-dienyl	*N*-2-methylbutyl	
			75	C10	2*E*,6*Z*,8*E*-trienyl	*N*-2-methylbutyl	
			76	C10	3*E*,6*Z*,8*E*-trienyl	*N*-phenethyl	
			77	C10	2*E*,6*Z*,8*E*-trienyl	*N*-phenethyl	
			78	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-phenethyl	
		decumbens	**79**	C9	2*Z*-en-6,8-diyne	*N*-phenethyl	(Casado et al.,
			80	C10	2*E*,4*E*-dien-9-yne	*N*-phenethyl	2009)
			81	C11	4*E*,6*E*-en-10-yne	*N*-isobutyl	
		mauritiana	**82**	C12	2*E*,4*E*,8*E*,10*Z*-tetraenyl	*N*-isobutyl	(Casado et al., 2009)
		oloracea	**70**	C10	2*E*,6*Z*,8*E*-trienyl	*N*-isobutyl	(Greger et al.,
			75	C10	2*E*,6*Z*,8*E*-trienyl	*N*-2-methylbutyl	1985)
		oppositifolia	**70**	C10	2*E*,6*Z*,8*E*-trienyl	*N*-isobutyl	(Calle et al., 1988)
			75	C10	2*E*,6*Z*,8*E*-trienyl	*N*-2-methylbutyl	(Molina et al.,
			68	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	1996)
		radicans	**83**	C8	2*E*-enyl	*N*-isobutyl	(Rios-Chavez et al., 2003)
			84	C8	2*E*,4*Z*-dienyl	*N*-isobutyl	
			70	C10	2*E*,6*Z*,8*E*-trienyl	*N*-isobutyl	
			68	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	
			21	C11	2*E*,4*E*-dien-8,10-diyne	*N*-isobutyl	
			75	C10	2*E*,6*Z*,8*E*-trienyl	*N*-2-methylbutyl	
			85	C12	2*E*,4*Z*,8*E*,10*E*-tetraenyl	*N*-2-methylbutyl	
			86	C8	2*E*,4*Z*-dienyl	*N*-phenethyl	
			87	C8	2*Z*,4*E*-dienyl	*N*-phenethyl	
			77	C10	2*E*,6*Z*,8*E*-trienyl	*N*-phenethyl	
			88	C9	2*E*-en-6,8-diyne	*N*-phenethyl	

Tribe	Genus	Species	Alka-mide	R_1 (including C=O)		R_2	Reference
				Chain	Double and triple bonds		
			89	C9	*cis*-2,3-epoxy-6,8-diyne	*N*-phenethyl	
			90	3-phe-C3	3-phenyl- 2-propenyl	*N*-phenethyl	
	Spilanthes	*acmella*	**91**	C9	2*E*-en-6,8-diyne	*N*-isobutyl	(Pandey et al., 2011) (Boonen et al., 2010) (Ramsewak et al., 1999)
			70	C10	2,6,8-trienyl	*N*-isobutyl	
			92	C10	2*E*,7*Z*-dienyl	*N*-isobutyl	
			70	C10	2*E*,6*Z*,8*E*-trienyl	*N*-isobutyl	
			93	C10	2,4,6,8-tetraenyl	*N*-isobutyl	
			94	C12	2*E*,7*Z*,9*E*-trienyl	*N*-isobutyl	
			69	C12	2*E*,4*E*,8*Z*,10*Z*-tetraenyl	*N*-isobutyl	
			95	C11	*2E*-en-8,10-diyne	*N*-isobutyl	
			96	C11	*2E*,6*Z*-dien-8,10-diyne	*N*-isobutyl	
			97	C11	2*E*,7*Z*,9*E*-trienyl	*N*-isobutyl	
			98	C13	2*E,*7*Z*-dien-10,12-diyne	*N*-isobutyl	
			99	C13	7*Z*-en-10,12-diyne	*N*-isobutyl	
			75	C10	2*E*,6*Z*,8*E*-trienyl	*N*-2-methylbutyl	
			100	C11	2*E*-en-8,10-diyne	*N*-2-methylbutyl	
			101	C11	2*E*,4*Z*-dien-8,10-diyne	*N*-2-methylbutyl	
			89	C9	2-epoxy-6,8-diyne	*N*-phenethyl	
		ocymifolia	**102**	C9	cinnamamidyl	N-2-phenylethyl	(Ramsewak et al., 1999)
Heli-anthinae	*Echinaceae*	*angustifolia*	**95**	C11	2*E*-en-8,10-diyne	*N*-isobutyl	(Bauer et al., 1989) (Bauer & Reminger, 1989) (Woelkar et al., 2005) (Muller-Jakic et al., 1994) (Schulthess et al., 1990) (Chen et al., 2005)
			103	C11	2*Z*-en-8,10-diyne	*N*-isobutyl	
			104	C11	2*E*,4*Z*-dien-8,10-diyne	*N*-isobutyl	
			105	C11	2*Z*,4*E*-dien-8,10-diyne	*N*-isobutyl	
			106	C12	2*E*,4*E*-dienyl	*N*-isobutyl	
			107	C12	2*E*,4*E*,8*Z*-trienyl	*N*-isobutyl	
			68	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	
			69	C12	2*E*,4*E*,8*Z*,10*Z*-tetraenyl	*N*-isobutyl	
			108	C12	2*E*-en-8,10-diyne	*N*-isobutyl	
			109	C12	2*E*,4*Z*-dien-8,10-diyne	*N*-isobutyl	
			110	C12	2*E*,4*Z,*10*Z*-trien-8-yne	*N*-isobutyl	

Tribe	Genus	Species	Alka-mide	R_1 (including C=O)		R_2	Reference
				Chain	Double and triple bonds		
			111	C12	2*Z*,4*E*,10*Z*-trien-8-yne	*N*-isobutyl	
			112	C14	2*E*-en-10,12-diyne	*N*-isobutyl	
			38	C15	2*E*,9*Z*-dien-12,14-diyne	*N*-isobutyl	
			113	C16	2*E*,9*Z*-dien-12,14-diyne	*N*-isobutyl	
			114	C11	2*Z*-en-8,10-diyne	*N*-2-methylbutyl	
			115	C12	2*E*-en-8,10-diyne	*N*-2-methylbutyl	
			116	C12	2*E*,4*Z*-dien-8,10-diyne	*N*-2-methylbutyl	
		angustifolia var. *strigosa*	**95**	C11	2*E*-en-8,10-diyne	*N*-isobutyl	(Senchina et al., 2006)
			103	C11	2*Z*-en-8,10-diyne	*N*-isobutyl	
			105	C11	2*Z*,4*E*-dien-8,10-diyne	*N*-isobutyl	
			106	C12	2*E*,4*E*-dienyl	*N*-isobutyl	
			107	C12	2*E*,4*E*,8*Z*-trienyl	*N*-isobutyl	
			68	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	
			69	C12	2*E*,4*E*,8*Z*,10*Z*-tetraenyl	*N*-isobutyl	
			108	C12	2*E*-en-8,10-diyne	*N*-isobutyl	
			117	C12	2*E*,4*E*,10*E*-trien-8-yne	*N*-isobutyl	
			118	C12	2*E*,4*Z*-dien-8,10-diyne	*N*-isobutyl	
			101	C11	2*E*,4*Z*-dien-8,10-diyne	*N*-2-methylbutyl	
		pallida	**104**	C11	2*E*,4*Z*-dien-8,10-diyne	*N*-isobutyl	(Bauer & Reminger, 1989) (Senchina et al., 2006) (Schulthess et al., 1990) (Chen et al., 2005)
			105	C11	2*Z*,4*E*-dien-8,10-diyne	*N*- isobutyl	
			106	C12	2*E*,4*E*-dienyl	*N*-isobutyl	
			107	C12	2*E*,4*E*,8*Z*-trienyl	*N*-isobutyl	
			68	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	
			69	C12	2*E*,4*E*,8*Z*,10*Z*-tetraenyl	*N*-isobutyl	
			118	C12	2*E*,4*Z*-dien-8,10-diyne	*N*-isobutyl	
			119	C12	2*Z*,4*E*-dien-8,10-diyne	*N*-isobutyl	
		pallida var. *pallida*	**38**	C15	2*E*,9*Z*-dien-12,14-diyne	*N*-isobutyl	(Binns et al, 2002)
		pallida var. *angustifolia*	**95**	C11	2*E*-en-8,10-diyne	*N*-isobutyl	(Binns et al, 2002)
			103	C11	2*Z*-en-8,10-diyne	*N*-isobutyl	
			68	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	

Tribe	Genus	Species	Alka-mide	R_1 (including C=O)		R_2	Reference
				Chain	Double and triple bonds		
			69	C12	2*E*,4*E*,8*Z*,10*Z*-tetraenyl	*N*-isobutyl	
			38	C15	2*E*,9*Z*-dien-12,14-diyne	*N*-isobutyl	
		pallida var. *tennesseensis*	**95**	C11	2*E*-en-8,10-diyne	*N*-isobutyl	[(Binns et al, 2002)
			103	C11	2*Z*-en-8,10-diyne	*N*-isobutyl	
			38	C15	2*E*,9*Z*-dien-12,14-diyne	*N*-isobutyl	
		pallida var. *sanguinea*	**95**	C11	2*E*-en-8,10-diyne	*N*-isobutyl	(Binns et al, 2002)
			103	C12	2*Z*-en-8,10-diyne	*N*-isobutyl	
			38	C15	2*E*,9*Z*-dien-12,14-diyne	*N*-isobutyl	
		purpurea	**95**	C11	2*E*-en-8,10-diyne	*N*-isobutyl	(Bauer & Reminger, 1989) (Senchina et al., 2006) (Schulthess et al., 1990) (Chen et al., 2005) (Cech et al., 2006) (Binns et al., 2002) (Perry et al., 1997)
			103	C11	2*Z*-en-8,10-diyne	*N*-isobutyl	
			104	C11	2*E*,4*Z*-dien-8,10-diyne	*N*-isobutyl	
			105	C11	2*Z*,4*E*-dien-8,10-diyne	*N*-isobutyl	
			106	C12	2*E*,4*E*-dienyl	*N*-isobutyl	
			107	C12	2*E*,4*E*,8*Z*-trienyl	*N*-isobutyl	
			68	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	
			69	C12	2*E*,4*E*,8*Z*,10*Z*-tetraenyl	*N*-isobutyl	
			108	C12	2*E*-en-8,10-diyne	*N*-isobutyl	
			117	C12	2*E*,4*E*,10*E*-trien-8-yne	*N*-isobutyl	
			118	C12	2*E*,4*Z*-dien-8,10-diyne	*N*-isobutyl	
			119	C12	2*Z*,4*E*-dien-8,10-diyne	*N*-isobutyl	
			120	C12	2*E*,4*Z*,10*E*-trien-8-yne	*N*-isobutyl	
			98	C13	2*E*,7*Z*-dien-10,12-diyne	*N*-isobutyl	
			38	C15	2*E*,9*Z*-dien-12,14-diyne	*N*-isobutyl	
			121	C16	2*E*,9*Z*-12*Z*,14*E*-tetraenenyl	*N*-isobutyl	
			101	C11	2*E*,4*Z*-dien-8,10-diyne	*N*-2-methylbutyl	
			122	C12	2*E*,4E-dien-8,10-diyne	*N*-2-methylbutyl	
			116	C12	2*E*,4*Z*-dien-8,10-diyne	*N*-2-methylbutyl	
		sanguinea	**95**	C11	2*E*-en-8,10-diyne	*N*-isobutyl	(Senchina et al., 2006)
			103	C11	2*Z*-en-8,10-diyne	*N*-isobutyl	
			104	C11	2*E*,4*Z*-dien-8,10-diyne	*N*-isobutyl	
			105	C11	2*Z*,4*E*-dien-8,10-diyne	*N*-isobutyl	

Tribe	Genus	Species	Alka-mide	R_1 (including C=O)		R_2	Reference
				Chain	Double and triple bonds		
Zinniinae B. and H.	*Heliopsis*	*tennesseensis*	**106**	C12	2*E*,4*E*-dienyl	*N*-isobutyl	
			107	C12	2*E*,4*E*,8*Z*-trienyl	*N*-isobutyl	
			68	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	
			69	C12	2*E*,4*E*,8*Z*,10*Z*-tetraenyl	*N*-isobutyl	
			108	C12	2*E*-en-8,10-diyne	*N*-isobutyl	
			118	C12	2*E*,4*Z*-dien-8,10-diyne	*N*-isobutyl	
			101	C11	2*E*,4*Z*-dien-8,10-diyne	*N*-2-methylbutyl	
			116	C12	2*E*,4*Z*-dien-8,10-diyne	*N*-2-methylbutyl	
		simulata	**95**	C11	2*E*-en-8,10-diyne	*N*-isobutyl	(Bauer & Foster, 1991)
			103	C11	2*Z*-en-8,10-diyne	*N*-isobutyl	
			68	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	
			69	C12	2*E*,4*E*,8*Z*,10*Z*-tetraenyl	*N*-isobutyl	
			98	C13	2*E*,7*Z*-dien-10,12-diyne	*N*-isobutyl	
		tennesseensis	**95**	C11	2*E*-en-8,10-diyne	*N*-isobutyl	(Senchina et al., 2006) (Bauer et al, 1990)
			103	C11	2*Z*-en-8,10-diyne	*N*-isobutyl	
			106	C12	2*E*,4*E*-dienyl	*N*-isobutyl	
			68	C12	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	
			9	C12	2*E*,4*E*,8*Z*,10*Z*-tetraenyl	*N*-isobutyl	
			108	C12	2*E*-en-8,10-diyne	*N*-isobutyl	
			114	C11	2*Z*-en-8,10-diyne	*N*-2-methylbutyl	
			115	C12	2*E*-en-8,10-diyne	*N*-2-methylbutyl	
		longipes	**70**	C10	2*E*,6*Z*,8*E*-trienyl	*N*-isobutyl	(Rios et al., 2007) (Molina et al., 1996) (Rios et al., 2011)
			123	C10	2*E*-enyl	*N*-isobutyl	
			124	C10	2*E*,6*Z*-dienyl	*N*-isobutyl	
			125	C10	2*E*,6*Z*-dien-*syn*-8,9-dihydroxyl	*N*-isobutyl	
			126	C10	2*E*,7*E*-dien-*syn*-6,9-dihydroxyl	*N*-isobutyl	
			127	C11	3*Z*-en-8,10-diyne	*N*-isobutyl	
			95	C11	2*E*-en-8,10-diyne	*N*-isobutyl	
			104	C11	2*E*,4*Z*-dien-8,10-diyne	*N*-isobutyl	
	Sanvitalia	*ocymoides*	**128**	C14	2*E*,4*E*,8*Z*,10*E*-tetraenyl	*N*-isobutyl	(Dominguez et al., 1987)
			129	C14	2*E*,4*E*,8*Z*-trienyl	*N*-isobutyl	

Table 1. Alkamides from the Asteraceae family.

agent has not been proven. *E. angustifolia*, *E. pallida* and *E. purpurea* are three species of *Echinacea* that are used in commercial preparations with reported alkamide profiles. These species contain complex mixtures of alkamides that are good chemotaxonomic characters (table 1). The major alkamides in *E. purpurea* roots are the C12-2,4-diene and C12-2,4-diene-diyne type, while the C11 diene-diynes were highest in vegetative stems (Binns et al., 2002). *E. angustifolia* roots are characterized by the presence of di-, tri- and tetraenes in coexistence with mono- and diynes, all of them with variable insaturation degree at the C2, C4, C9 or C10 position. In *E. pallida*, the major compounds are polienes (also di-, tri- and tetraenes) and diynes (C2 or C2 and C4 unsaturated)

Lipophilic alkamides from *Echinacea* show immunostimulatory activity and have been used for the treatment of cold, flu, respiratory infections and inflammations, making a considerable contribution to the activities attributed to *Echinaceae* plants (Bauer, 1989a, 1989b, 1990, 1991). Studies on the mechanisms of action of the immunomodulatory activity of *Echinacea* have indicated that alkylamides can act as cannabinomimetics. Endogenous ligands for cannabinoid receptors such as anandamide (fig. 2), an animal alkamide that shares structural similarity with the *Echinacea* alkylamides, can bind to CB2 cannabinoid receptors (LaLone et al., 2010). The cannabinoid receptors CB1 and CB2 have been implicated in the modulation of the CNS and the inflammatory response. CB1 receptors are present in neurons from the central and peripheral nervous system and are concentrated in the brain. CB2 receptors are mainly present in immune cells, such as macrophages.

2.1.5 *Heliopsis* genus

Heliopsis longipes is a Mexican plant that was broadly used by the Náhuatl civilization as flavoring in food preparation. The stems of this climber are used in traditional medicine as a condiment, buccal anesthetic, analgesic in pain toothache, antiparasitic, anti-inflammatory and antiulcerative agent and to prepare homemade insecticides that, similar to pyrethrins, are toxic and exhibit paralyzing effects. Chewing of a little piece of the *Heliopsis longipes* stem results in intense salivation and a local analgesic effect (Molina et al., 1996). An ethanolic extract of this plant exhibited antinociceptive effects on acute thermal and chemical inflammation induced nociception in mice with a mechanism partly linked to the lipoxygenase and/or cyclooxygenase systems (Cariño-Cortés et al., 2010). This extract exhibited synergistic interactions with diclofenac in the Hargreaves model of thermal hyperalgesia (Acosta-Madrid et al., 2009). Various unsaturated aliphatic alkamides have also been identified and characterized from the roots of this plant (table 1), such as affinin (**70**), its most abundant and bioactive alkamide. The analgesic activity of affinin was determined by measuring the release of GABA in mice brain slices (Rios et al., 2007). Furthermore, dose-dependent antinociceptive effects have been observed to be a result of the activation of opiodergic, serotoninergic and GABAergic systems (Déciga-Campos et al., 2010).

2.2 Aliphatic alkamides from other plant families

Convolvulaceae, Euphorbiaceae, Menispermaceae and Rutaceae are other plant families that produce aliphatic alkamides. *N*-isobutyl, 2'-hydroxy-*N*-isobutyl, NH_2 and pyrrolidinyl amine residues have been identified in the structures of alkamides isolated from these plants (table 2).

Species	Alka-mide	Name	R_1		R_2	Reference
			Chain (including C=O)	saturation, unsaturation		
Ipomoea quinquefolia (Convolvulaceae)	**130**	Alkaloid MQ-A_1	C15	$C_{14}H_{29}$ branched	pyrrolidinyl	(Tofern et al., 1999)
	131	Alkaloid MQ-A_2	C16	$C_{15}H_{31}$ branched	pyrrolidinyl	
	132	Alkaloid MQ-B_2	C16	$C_{15}H_{31}$ linear	pyrrolidinyl	
	133	Alkaloid MQ-A_3	C17	$C_{16}H_{33}$ branched	pyrrolidinyl	
	134	Alkaloid MQ-A_4	C18	$C_{17}H_{35}$ branched	pyrrolidinyl	
	135	Alkaloid MQ-B_4	C18	$C_{17}H_{35}$ linear	pyrrolidinyl	
	136	Alkaloid MQ-A_5	C19	$C_{18}H_{37}$ branched	pyrrolidinyl	
Merremia aquatica (Convolvulaceae)	**132**	Alkaloid MQ-B_2	C16	$C_{15}H_{31}$ linear	pyrrolidinyl	
	133	Alkaloid MQ-A_3	C17	$C_{16}H_{33}$ branched	pyrrolidinyl	
	136	Alkaloid MQ-A_5	C19	$C_{18}H_{37}$ branched	pyrrolidinyl	
Phyllanthus fraternus subsp. *togoensis* (Euphorbiaceae)	**137**	*E,E*-2,4-octadienamide	C8	2*E*,4*E*-diene	NH_2	(Sittie et al., 1998) (Sailaja & Setty, 2006)
	138	*E,Z*-2,4-decadienamide	C10	2*E*,4*Z*-diene	NH_2	
Cissampelos glaberrimma (Menispermaceae)	**139**	octa-2*E*,4*E*-dienoic acid isobutylamide	C8	2*E*,4*E*-diene	*N*-isobutyl	(Rosario et al., 1996)
	140	deca-2*E*,4*E*-dienoic acid isobutylamide	C10	2*E*,4*E*-diene	*N*-isobutyl	
	141	decden-2-oic acid isobutylamide	C10	2*E*-ene	*N*-isobutyl	
	142	decanoic acid isobutylamide	C10	---	*N*-isobutyl	

Species	Alka-mide	Name	R_1		R_2	Reference
			Chain (inclu-ding C=O)	saturation, unsaturation		
Zanthoxylum integrifoliolum (Rutaceae)	**143**	lanyuamide I	C14	2*E*,4*E*,12-oxo	*N*-isobutyl	(Chen et al., 1999)
	144	lanyuamide II	C14	2*E*,4*E*,8*Z*-12-oxo	*N*-isobutyl	
	145	lanyuamide III	C14	2*E*,4*E*,8*Z*-11*E*-tetraene	*N*-isobutyl	
	146	tetrahydrobungeanool	C14	2*E*,4*E*-diene	2'-hidroxy-*N*-isobutyl	
	147	γ-sanshool	C14	2*E*,4*E*,8*Z*-10*E*,12*E*-pentaene	*N*-isobutyl	
	148	hydroxy-γ-sanshool	C14	2*E*,4*E*,8*Z*-10*E*,12*E*-pentaene	2'-hidroxy-*N*-isobutyl	
	140	(2*E*,4*E*,8*Z*,11*E*)-2'-hydroxy-*N*-isobutyl-tetradecatetraenamide	C14	2*E*,4*E*,8*Z*-11*E*-tetraene	2'-hidroxy-*N*-isobutyl	
	150	(2*E*,4*E*,8*Z*,11*Z*)-2'-hydroxy-*N*-isobutyl-tetradecatetraenamide	C14	2*E*,4*E*,8*Z*-11*Z*-tetraene	2'-hidroxy-*N*-isobutyl	
	151	hazaleamide	C14	2*E*,4*E*,8*Z*-11*Z*-tetraene	*N*-isobutyl	

Table 2. Aliphatic alkamides from Convolvulaceae, Euphorbiaceae, Menispermaceae and Rutaceae plant families.

2.2.1 Convolvulaceae alkamides

Convolvulaceae alkamides are also known as alkaloids MQ. These alkamides are characterized by linear or branched saturated acid residues. All Convolvulaceae alkamides have a pyrrolidinyl residue as the amine group and have been isolated from the *Ipomoea* and *Merremia* genera (compounds **130-136**).

2.2.2 Euphorbiaceae alkamides

Phyllanthus fraternus is used by traditional healers and tribes in the northern region of India as a folklore remedy for the treatment of malaria and various liver diseases. An aqueous extract of this plant exhibited antioxidant activity, preventing the oxidation of proteins and lipids. Additionally, aqueous extracts of *Phyllanthus fraternus* protect against allyl alcohol-induced oxidative stress in liver mitochondria (Sailaja & Setty, 2006). Two aliphatic alkamides C_4 isomers , *E*,*E*-2,4-octadienamide (**137**) and *E*,*Z*-2,4-decadienamide (**138**), have been isolated from this plant. Both isomers lack an alkyl residue at the amine group, which is typically joined to an acid residue (Sittie et al., 1998). Instead, these compounds possess an α,β,γ,δ-unsaturated conjugated amide, a feature believed to enhance antiplasmodial activity. Notably, *in vitro* assays of these two isomers demonstrated that these compounds possess moderate antiplasmodial activity.

2.2.3 Menispermaceae alkamides

The roots of some species of the *Cissampelos* genus exhibit significant activity against mechanical, chemical and arthritic pain, increasing the pain threshold and dictating the medicinal value of the plants of this genus. For example, *C. glaberrimma* is a plant whose bioactivity is a reflection of its alkamide content (alkamides **139-142**, Rosario et al., 1996).

2.2.4 Rutaceae alkamides

The fruits of *Zanthoxylum integrifoliolum* possess a pungent taste. Chemical analysis enabled the isolation and identification of nine isobutylamides (**143-151**). These amides have a 2*E*,4*E*-dienamide moiety, including an oxo, diene, tetraene or pentaene acidic fragment (table 2). However, no activity has been reported for these molecules.

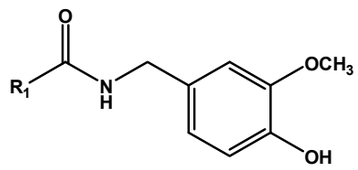
Amides have also been isolated from the *Glycosmis* genus (Rutaceae); however, those isolated from this genus are sulfur-containing amides, a rare group of secondary metabolites that have an aromatic amine residue. *Glycosmis* alkamides will be discussed in section 3.3 (*vide infra*).

3. Aromatic alkamides

Alkamides isolated from Solanaceae, Piperaceae, Brassicaceae and Rutaceae plant families either have one aromatic ring at the amine residue, at the acid residue or both. Capsaicinoids, amides from *Lepidium meyenii*, and sulfur derivatives from the *Glycosmis* genus are alkamides with one aromatic ring at the amine residue. Piperine and its analogs are amides with one aromatic residue at the acid fragment. Alkamides that have an aromatic ring at the amine and acid residues are distributed among a large group of plants.

3.1 The alkamides from Solanaceae family: Capsaicinoids

Capsicum (also known as "chile" or "chilli") are species used as vegetables, condiments, and for an important number of medicinal preparations. The fruits of *Capsicum* have been utilized in food preparation, for medicinal applications to tone body muscles after workouts, hot infusions for toothache and muscle pain and aerosols such as *Capsicum* extracts that are used as personal protection. This species are the source of highly pungent capsacinoids that induce a hot or burning sensation. Capsaicinoids are the major chemical constituents from the following five domesticated species of *Capsicum* (peppers) genus: *C. annuum* L., *C. baccatum* L., *C. chinense* Jacq., *C. frutescens* L. and *C. pubescens*. All of these species have *N*-vanillylamides (all contain a 4-hydroxy-3-methoxybenzyl amine group) of C8 to C18 fatty acids (table 3).



Alka-mide	Name	R_1		Reference
		long chain (including C=O)	Chain	
152	caprylic acid vanillylamide	C8	linear	(Kozukue et al., 2005) (Kobata et al., 2010)
153	nonivamide	C9	linear	
154	nordihydrocapsaicin	C9	7-CH_3	
155	norcapsaicin	C9	5*E*; 7-CH_3	
156	decylic acid vanillylamide	C10	linear	
157	dihydrocapsaicin	C10	8-CH_3	
158	capsaicin	C10	6*E*; 8-CH_3	
159	homocapsaicin-I	C11	6*E*; 9-CH_3	
160	homocapsaicin-II	C11	6*E*; 8-CH_3	
161	homodihydrocapsaicin-I	C11	9-CH_3	
162	homodihydrocapsaicin-II	C11	8-CH_3	
163	*N*-vanillyl-hexadecanamide (palvanil)	C16	linear	
164	*N*-vanillyl-octadecanamide (stevanil)	C18	linear	
165	*N*-vanillyl-9*E*-octadecenamide (olvanil)	C18	9*E*	
166	*N*-vanillyl-9*E*,12*E*-octadecadienamide (livanil)	C18	9*E*,12*E*	

Table 3. Capsaicinoids from *Capsicum annuum.*

Some capsaicinoids exhibit strong pungent sensory properties when consumed as part of the diet. Additionally, capsaicinoids possess a variety of biological properties that may affect human health (Kozuke et al., 2010), such as antiviral, antibacterial, antifungal, insecticidal, antioxidative, anti-inflammatory and anticancer activities. Furthermore, capsaicinoids influence neuronal structures that contain substances that are associated with pain transmission and neurogenic inflammation. As a result, these compounds are used as topical analgesics for treating pain. The aforementioned properties are the basis for the use of capsaicinoids to prevent or reduce chronic and age-related pain (Kozuke et al., 2005). Capsaicin (**158**) and dihydrocapsaicin (**157**) are notable among natural capsaicinoids because they constitute approximately 90% of the total capsaicinoids in many varieties of peppers. The burning sensation caused by capsaicin is induced by the direct activation of a nonselective cation channel-transient receptor potential, vanilloid 1 (TRPV1), located at the end of sensory nerves. Several physiological activities caused by capsaicin are related to the activation of the TRPV1 receptor. Meghvansi and coworkers have written a review of capsaicinoids in which their ethnopharmacological applications are discussed (Meghvansi et al., 2010). Long acyl chain capsaicinoids exhibiting similar activities to capsaicin, such as anti-inflammatory, antinociceptive and enhanced adrenaline secretion, have been recently reported. The advantages of these compounds are the lack of irritancy or pungency due to the lower accessibility of TRPV1 in the tongue due to higher lipophilicity compared to capsaicin (Kobata et al., 2010).

3.2 The alkamides from *Lepidium meyenii* (Brassicaceae)

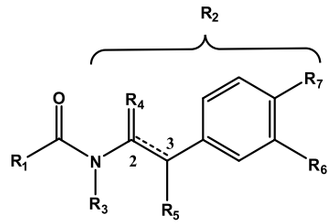
The roots from of *L. meyenii* are used to enhance fertility and sexual behavior in men and women. Additionally, *L. meyenii* roots serve as a traditional remedy for menopausal symptoms, the regulation of hormone secretion, immunostimulation, memory improvement, as an antidepressant or anticancer agent, and to prevent anemia. Phytochemical analysis of the roots of this plant led to the identification of *m*-methoxybenzyl and *N*-benzyl amine residues and macamides, linear C16, C18 or C24 alkamides with one or two double bonds and possible oxidation of C_5, C_9 or C_{13} (table 4).

3.3 The alkamides from *Glycosmis* (Rutaceae)

Sulfur-containing amides (phenethyl/styrylamine-derived amides) form a rare group of secondary metabolites in the Rutaceae family. These amides are only present in the leaves of plants that belong to the *Glycosmis* genus. Sulfur-containing amides represent a typical chemical profile of this genus. The acid moieties of these alkamides are probably derived from cysteine, which can be oxidized to sulfones and sulfoxides or shortened by β-oxidation (as in ritigalin). With the exception of simple methylamides, the amine residues are characterized by the presence of phenethyl or styryl groups (derived from phenylalanine) that can be linked to different prenyloxy (dambullins) or geranyloxy groups in *para* position (gerambullins). More recently, a group of similar (methylsulfonyl)propenoic acid amides has been detected in which dopamine is linked to various oxidized geranyl chains (sakerines). Some of these alkamides exhibit pronounced antifungal and/or insecticidal activity (Greger & Zechner, 1996) (table 5).

Alkamide	Name	R_1		R_2	Reference
		long chain (including C=O)	chain		
167	*N*-(*m*-methoxybenzyl)hexadecanamide	C16	$C_{15}H_{31}$	*m*-methoxybenzyl	(Zhao et al., 2005) (Muhammad et al, 2002)
168	*N*-benzylhexadecanamide	C16	$C_{15}H_{31}$	*N*-benzyl	
169	*N*-benzyl-9-oxo-12*Z*-octadecenamide	C18	9-oxo-12*Z*	*N*-benzyl	
170	*N*-benzyl-9-oxo-12*Z*,15*Z*-octadecadienamide	C18	9-oxo-12*Z*,15*Z*	*N*-benzyl	
171	*N*-benzyl-13-oxooctadeca-9*E*,11*E*-dienamide	C18	13-oxo-9*E*,11*E*	*N*-benzyl	
172	*N*-benzyl-5-oxo-6*E*,8*E*-octadecadienamide	C18	5-oxo-6*E*,8*E*	*N*-benzyl	
173	*N*-benzyl-15*Z*-tetracosenamide	C24	15*Z*	*N*-benzyl	

Table 4. Alkamides from *Lepidium meyenii*.



Species	Alk	Name	R_1	R_2	
G. angustifolia	**174**	penamide A	*E*-CH_3-S-CH=CH-	R_3=CH_3; R_4=O; R_5=R_6=R_7=H	(Greger et al., 1994)
	175	penamide B	*Z*-CH_3-S-CH=CH-	R_3=CH_3; R_4=O; R_5=R_6=R_7=H	
	176	dambullin	*E*-CH_3-SO_2-CH=CH-	R_3=H; R_4=H,H; R_5=R_6=H; R_7=*O*-isopentenyl	
	177	methyldambullin	*E*-CH_3-SO_2-CH=CH-	R_3=CH_3; R_4=H,H; R_5=R_6=H; R_7=*O*-isopentenyl	
	178	gerambullin	*E*-CH_3-SO_2-CH=CH-	R_3=H; R_4=H,H; R_5=R_6=H; R_7=*O*-geranyl	
	179	methylgerambullin	*E*-CH_3-SO_2-CH=CH-	R_3=CH_3; R_4=H,H; R_5=R_6=H; R_7=*O*-geranyl	
	180	gerambulindiol	*E*-CH_3-SO_2-CH=CH-	R_3=R_5=R_6=H; R_4=H,H; R_7=*O*-6,7-dihydroxy-geranyl	
	181	methylgerambullone	*E*-CH_3-SO_2-CH=CH-	R_3=CH_3; R_4=H,H; R_5=R_6=H; R_7=*O*-5-oxo-geranyl	
	182	methylisogerambullone	*E*-CH_3-SO_2-CH=CH-	R_3=CH_3; R_4=H,H; R_5=R_6=H; R_7=*O*-5-oxo-isogeranyl	
G. chlorosperma	**183**	penangin	*E*-CH_3-S-CH=CH-	-NH(CH_3)	(Greger et al., 1993a)
	184	isopenangin	*Z*-CH_3-S-CH=CH-	-NH(CH_3)	
	185	sinharine	CH_3-S-CH_2-CH_2-	2,3-*trans*; R_3=H; R_4=R_5=R_6=R_7=H	
	186	methylsinharine	CH_3-S-CH_2-CH_2-	2,3-*trans*; R_3=CH_3; R_4=R_5=R_6=R_7=H	
	187	gerambullol	*E*-CH_3-SO_2-CH=CH-	R_3=R_5=R_6=H; R_4=H,H; R_7=*O*-8-hydroxygeranyl	
	188	β-hydroxy-gerambullin	*E*-CH_3-SO_2-CH=CH-	R_3=R_6=H; R_4=H,H; R_5=OH; R_7=*O*-geranyl	
	189	β-hydroxy-gerambullol	*E*-CH_3-SO_2-CH=CH-	R_3=R_6=H; R_4=H,H; R_5=OH; R_7=8-hydroxy-*O*-geranyl	
	190	β-hydroxy-gerambullal	*E*-CH_3-SO_2-CH=CH-	R_3=R_6=H; R_4=H,H; R_5=OH, R_7=*O*-geran-8-al	
	191	sakerinol A	*E*-CH_3-SO_2-CH=CH-	R_3=R_5=H; R_4=H,H; R_6=OH, R_7=8-hydroxy-*O*-geranyl	
	192	*O*-methyl-sakerinol A	*E*-CH_3-SO_2-CH=CH-	R_3=R_5=H; R_4=H,H; R_6=OCH_3, R_7=8-hydroxy-*O*-geranyl	
			176		
	193	sakambullin	*E*-CH_3-SO_2-CH=CH-	R_3=R_5=H; R_4=H,H; R_6=OH; R_7=*O*-isopentenyl	
	194	*O*-methyl-sakambullin	*E*-CH_3-SO_2-CH=CH-	R_3=R_5=H; R_4=H,H; R_6=OCH_3; R_7=*O*-isopentenyl	
	195	sakerol	*E*-CH_3-SO_2-CH=CH-	R_3=H; R_4=H,H; R_5=R_6=H; R_7=5-hydroxy-*O*-isopentenyl	

G. citrifolia	**196**	glycothiomin A	*E*-CH_3-SO-CH=CH-	-NH(CH_3)	(Wu et al., 1995)
	197	glycothiomin B	*Z*-CH_3-SO-CH=CH-	-NH(CH_3)	
G. cyanocarpa	**198**	dehydronarinin A	CH_3-S-	2,3-*trans*; R_3=CH_3; R_4=R_5=R_6=R_7=H	(Greger & Zechner, 1996) (Greger & Hofer, 1993b)
	199	dehydronarinin B	CH_3-S-	2,3-*cis*; R_3=CH_3; R_4=R_5=R_6=R_7=H	
	200	thalebain B	isobutyl	2,3-*cis*; R_3=CH_3; R_4=R_5=R_6=R_7=H	
	201	methyllilukumbin A	*E*-CH_3-S-CH=CH-	2,3-*trans*; R_3=CH_3; R_4=R_5=R_6=R_7=H	
	202	dehydrothalebain A	isobut-2,3-enyl	2,3-*trans*; R_3=CH_3; R_4=R_5=R_6=R_7=H	
	203	dehydrothalebain B	isobut-2,3-enyl	2,3-*cis*; R_3=CH_3; R_4=R_5=R_6=R_7=H	
G. mauritiana	**204**	ritigalin	**183**, **184**, **185**, **198**, **199**, **200**, **201**, **202**, **203**	R_3=CH_3; R_4=O; R_5=R_6=R_7=H	
	205	niranin	CH_3-S-	R_3=CH_3; R_4=H,H; R_5=R_6=R_7=H	
	206	illukumbin A	CH_3-S-	2,3-*trans*; R_3=H; R_4=R_5=R_6=R_7=H	
	207	methyllilukumbin B	*Z*-CH_3-S-CH=CH-	2,3-*trans*; R_3=CH_3; R_4=R_5=R_6=R_7=H	
G. parviflora			*Z*-CH_3-S-CH=CH-	**204**	
G. pentaphylla			**183**, **184**, **185**, **201**, **207**		(Greger & Hofer, 1993b)

Table 5. Sulfur-containing alkamides from the *Glycosmis* species.

3.4 The Piperaceae family. Piperine and its analogs

Alkamides from the Piperaceae family are produced by plants that are classified as being in either the *Piper*, *Ottonia* or *Peperomia* genera. These alkamides are characterized by the presence of *N*-isobutyl, *N*-3-acetoxy-isobutyl, piperidinyl (piperidide), 5,6-dihydro-2(1*H*)pyridinone and pyrrolidinyl groups as amine residues, with *N*-isobutyl and piperidinyl being the most commonly found. The presence of carboxylic acid fragment is also characteristic of the alkamides isolated from plants that belong to the Piperaceae family. These fragments include the 3',4'-methylenedioxyphenyl as the most common terminal group. However, *p*-methoxyphenyl, 3',4',5'-trimethoxyphenyl and 4'-hydroxy-3'-methoxyphenyl groups can also be joined to a chain of 2, 4, 5, 6, 8, 9, 10, 11, 12 or 14 carbons, with one, two or three unsaturations at the even-numbered carbons (with the exception of C_{12}, fig. 4).

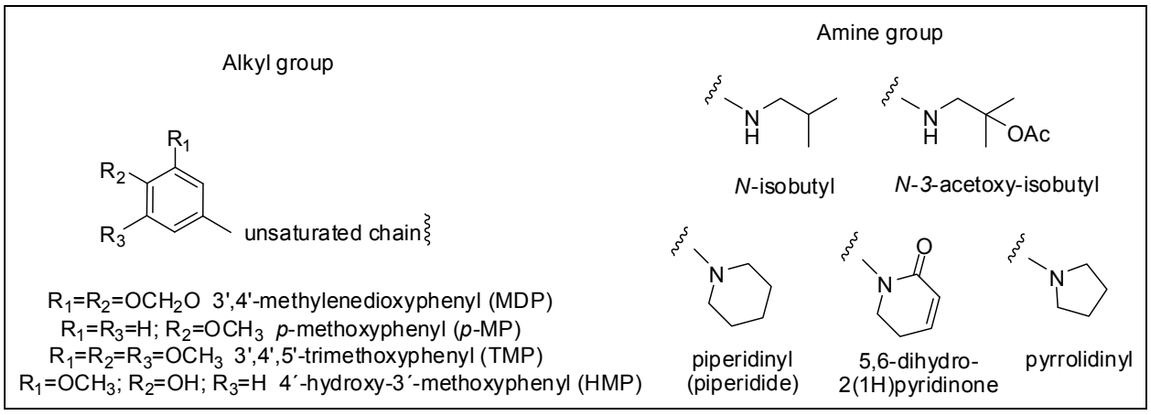


Fig. 4. The most common alkyl and amide residues of alkamides from the Piperaceae family.

Dimeric alkamides have been found in *P. chaba* and *P. nigrum*. *P. chaba* dimers are [4+2] adducts obtained from the combination of piperlonguminine and piperine [chabamide H (**208**) and I (**209**)], two molecules of pellitorine [chabamide J (**210**), and K (**211**)], two molecules of piperine [chabamide (**212**)], or two molecules of piperamine [chabamide F (**213**) and G (**214**)] (fig. 5). Notably, these dimeric alkamides exhibited potent cytotoxic activity against the COLO-205 cell line (Rao et al., 2011).

In contrast, *P. nigrum* dimers constituting [2+2] adducts are the combination of either two molecules of piperine [pipercyclobutanamide A (**215**) and nigramide R (**216**)] or from the piperine analogue piperrolein A [pipercyclobutanamide C (**217**)] (Rao et al, 2011; Subehan et al., 2006) (fig. 6).

The compounds produced by the Piperaceae family are pharmacologically very important, as several species of these plants are being used in folkloric medicine in different parts of the world. For example, the roots of plants from the *Ottonia* genus have a piquant taste and cause intense salivation when are in contact with the mouth. These roots exhibit local anesthetic and hallucinogenic effects and are used in the treatment of toothaches and sore throats. The toothache-relieving reputation of plants that belong to this genus led to the isolation of piperovatine (**222**), a buccal local anesthesic isobutyl amide isolated from *O.*

corcovadensis. Alkamides isolated from the *Ottonia* genus contain 1-oxo-5-(3',4'-methylenedioxyphenyl)-2*E*,4*E*-pentadien-1-yl and 1-oxo-6-(*p*-methoxyphenyl)-2*E*,4*E*-hexadien-1-yl residues as acidic fragments with *N*-isobutyl or *N*-3-acetoxy-isobutyl fragments as the amide residues (Antunes et al., 2001; Costa & Mors, 1981, table 6).

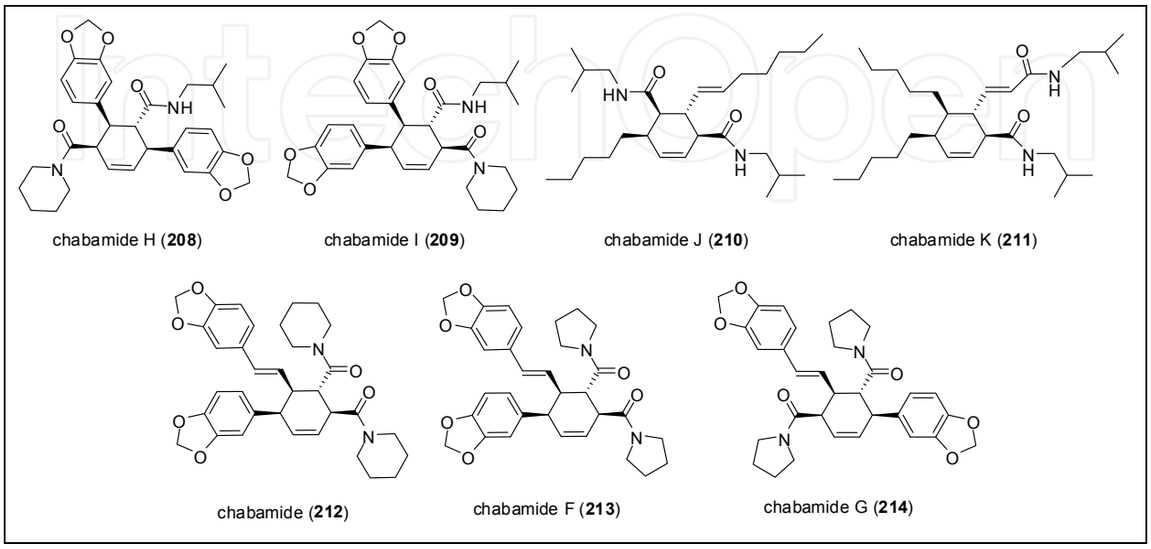


Fig. 5. Dimeric [4+2] alkamides from *Piper chaba.*

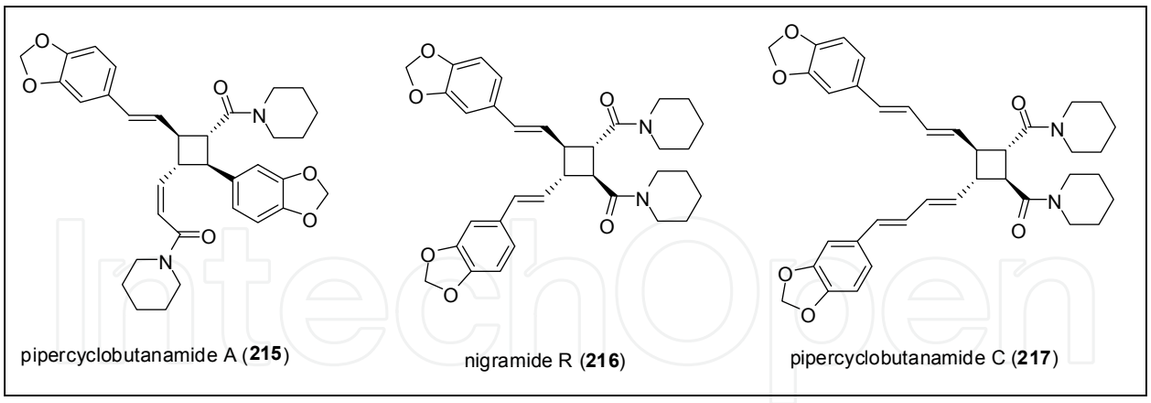


Fig. 6. Dimeric [2+2] alkamides from *Piper nigrum.*

The *Piper* species have been used in traditional medicine for thousands of years in China, India and Mexico, among other countries, for the treatment of several diseases and ailments. For example, *P. longum* is used for treatment of gonorrhea, menstrual and chronic intestinal pain, tuberculosis, sleeping problems, respiratory infections such as coughs, bronchitis and asthma, malarial fever, diarrhea, jaundice and arthritis. The beneficial effects of this species include analgesic and diuretic activities, relaxation of muscle tension, and the alleviation of anxiety.

Species	Alk	Name	R_1	R_2	Reference
Ottonia corcovadensis	**218**	piperlonguminine	5-(MDP)-2*E*,4*E*-pentadienyl	*N*-isobutyl	(Costa & Mors, 1981).
	219	isopiperlonguminine	5-(MDP)-2*Z*,4*Z*-pentadienyl	*N*-isobutyl	
	220	corcovadine	5-(MDP)-2*E*,4*E*-pentadienyl	*N*-3-acetoxy-isobutyl	
	221	isocorcovadine	5-(MDP)-2*Z*,4*Z*-pentadienyl	*N*-3-acetoxy-isobutyl	
	222	piperovatine	6-(*p*-MP)-2*Z*,4*Z*-hexadienyl	*N*-isobutyl	
Ottonia propinqua	**223**	*N*-isobutyl-6-(*p*-methoxyphenyl)-2*E*,4*E*-hexadieneamide	6-(*p*-MP)-2*E*,4*E*-hexadienyl	*N*-isobutyl	(Antunes et al., 2001)
Piper chaba	**224**	pellitorine	2*E*,4*E*-decadienyl	*N*-isobutyl	(Patra & Ghosh, 1974) (Rao et al., 2011)
	218	piperlonguminine	5-(MDP)-2*E*,4*E*-pentadienyl	*N*-isobutyl	
	225	4,5-dihydropiperlonumine	5-(MDP)-2*E*-pentenyl	*N*-isobutyl	
	226	guineensine	13-(MDP)-2*E*,4*E*,14*E*-tridecatrienyl	*N*-isobutyl	
	227	brachystamide B	15-(MDP)-2*E*,4*E*,14*E*-pentadecatrienyl	*N*-isobutyl	
	228	sylvatine	5-(MDP)-2*E*,4*E*-pentadienyl	*N*-10-methyl-6*E*-undecenyl	
	229	trichostachine	5-(MDP)-2*E*,4*E*-pentadienyl	pyrrolidinyl	
	230	piperine	5-(MDP)-2*E*,4*E*-pentadienyl	5,6-dihydro-2(1H)pyridinone	
	231	piplartine	3-(TMP)-2*E*-propenyl	5,6-dihydro-2(1H)pyridinone	
Piper hispidum	**232**	(3*Z*,5*Z*)-*N*-isobutyl-8-(3',4'-methylenedioxy-phenyl)-heptadienamide	7-(MDP)-2*Z*,4*Z*-heptadienyl	*N*-isobutyl	(Navickiene et al., 2000)
	233	*N*-[3-(6'-methoxy-3',4'-methylenedioxyphenyl)-2*Z*-propenoyl]pyrrolidine	3-(MDP)-2*Z*-propenyl	pyrrolidinyl	
	234	piperamine	5-(MDP)-2*E*-pentenyl	pyrrolidinyl	
Piper longum	**235**	sarmentine	**224**, **228** 2*E*,4*E*-decadienyl	pyrrolidinyl	(Das et al., 1996)
	236	piperrolein B	9-(MDP)-8*E*-nonenyl	piperidinyl	(Lee et al., 2006)
	237	retrofractamide C	9-(MDP)-2*E*,8*E*-nonadienyl	*N*-isobutyl	
	238	pipernonaline	9-(MDP)-2*E*,8*E*-nonadienyl	piperidinyl	(H. Huang et al, 2010)
	239	(2*E*,4*Z*,8*E*)-*N*-[9-(3,4-methylenedioxyphenyl)-2,4,8-nonatrienoyl]piperidine	9-(MDP)-2*E*,4*Z*,8*E*-nonatrienyl	piperidinyl	(P.L. Huang et al., 2010)

Species	Alk	Name	R_1	R_2	Reference
	240	dehydropipernonaline	9-(MDP)-2*E*,4*E*,8*E*-nonatrienyl	piperidinyl	
	241	guineensine	13-(MDP)- 2*E*,4*E*,12*E*-tridecatrienyl	*N*-isobutyl	
	242	(+)-sesamine	11-(MDP)-2*E*,10*E*-undecadienyl	*N*-isobutyl	
	243	piperchabamide D	9-(MDP)-2*E*,8*E*-nonadienyl	piperidinyl	
Piper scatorum	**223**	*N*-isobutyl-6-(*p*-methoxyphenyl)-2*E*,4*E*-hexadieneamide	6-(*p*-MP)-2*E*,4*E*-hexadienyl	*N*-isobutyl	(Cotinguiba et al., 2009) (Navickiene et al., 2000)
			224, **228**		
Piper tuberculatum	**244**	(*Z*)-piplartine	3-(TMP)-2*Z*-propenyl	5,6-dihydro-2(1H)pyridinone	
	231	(*E*)-piplartine	3-(TMP)-2*E*-propenyl	5,6-dihydro-2(1H)pyridinone	
	245	8,9-dihydropiplartine	3-(TMPl)-propanyl	5,6-dihydro-2(1H)pyridinone	
	246	10,11-dihydropiperine	5-(MDP)-2*E*,4*E*-pentadienyl	piperidinyl	
	247	5,6-dihydropiperlongumininе	5-(MDP)-2*E*-pentenyl	*N*-isobutyl	
	248	fagaramide	3-(MDP)-2*E*-propenyl	*N*-isobutyl	
			224, **228**, **234**, **236**, **238**		
	249	2*E*-octadec-2-enoic acid piperidide	2*E*-octadecenyl	piperidinyl	(Subehan et al., 2006)
	250	*N*-cinnamoylpiperidine	2*E*-phenethenyl	piperidinyl	
	251	feruperine	5-(HMP)-2*E*,4*E*-pentadieyl		
	252	piperylin	5-(MDP)-2*E*,4*E*-pentadienyl	pyrrolidinyl	
	253	piperrolein A	7-(MDP)-6*E*-heptenyl	piperidinyl	
	254	piperamide-C7:1(6*E*)	7-(MDP)- 6*E*-heptenyl	pyrrolidinyl	
Piper nigrum	**255**	piperamide-A6:2 (2*E*,6*E*)	7-(MDP)-2*E*,6*E*-heptadienyl	piperidinyl	
	256	piperamide-C9:1(8*E*)	9-(MDP)-8*E*-nonenyl	pyrrolidinyl	
	257	retrofractamide C	9-(MDP)-2*E*,8*E*-nonadienyl	*N*-isobutyl	
	258	dehydropipernonaline	9-(MDP)-2*E*,4*Z*,8*E*-nonatrienyl	piperidinyl	
	250	piperamide-C9:3	9-(MDP)-2*E*,4*E*,8*E*-nonatrienyl	piperidinyl	
	260	(2*E*,4*E*,8*E*)pipercide	9-(MDP)-2*E*,4*E*,8*E*-nonatrienyl	pyrrolidinyl	
Peperomia duclouxii	**261**	pipercallosine	9-(MDP)-2*E*,4*E*-nonadienyl	*N*-isobutyl	(Li et al., 2007)
	262	pipercallosidine	7-(MDP)-2*E*-heptenyl	*N*-isobutyl	

Table 6. Alkamides from the Piperaceae family. MDP=3',4'-methylenedioxyphenyl; p-MP=*p*-methoxyphenyl; TMP= 3',4',5'-trimethoxyphenyl; HMP=4´-hydroxy-3´-methoxyphenyl.

In contrast, *P. hispidum* and *P. tuberculatum* exhibit antifungal activity and produce amides with the *cis* geometry in their side chains, a structural feature quite rare in nature (table 6, Navickiene et al., 2000).

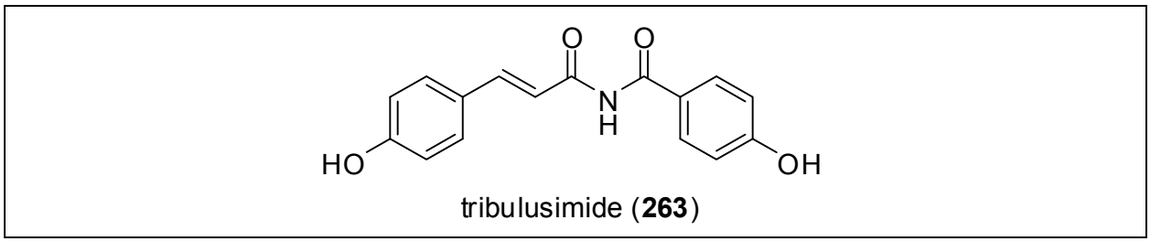
Pipernonaline (**238**) is an alkamide possessing mosquito larvicidal activity that has been isolated from *P. longum* (Huang et al., 2010), whereas some piperamides, such as (*Z*)-piplartine (**244**), (*E*)-piplartine (**231**), 8,9-dihydropiplartine (**245**) and pellitorine (**228**), isolated from P. *tuberculatum* seeds have been shown to inhibit the proliferation of *Trypanosoma cruzi* parasites. These alkamides are considered to be templates for the design of novel and potent hit compounds for the treatment of Chagas' disease (Cotinguiba et al., 2009).

Piperine (*E,E* isomer of 1-piperolypiperidine, **224**) is the major component in the fruits of several species of *Piper*, particularly *P. longum* and *P. nigrum*. This compound showed diverse biological activities such as antioxidant, anti-inflammatory, analgesic, antiplatelet aggregation, antihyperlipidemic, antihypertensive, cytoprotective, antitumor, antimicrobial, hepatoprotective and antidepressant activities. The structure of piperine resembles that of Capsaicin (158, table 3), the pungent component in the majority of the chilli peppers species. Similar to capsaicin, piperine also serves as a natural agonist of the vanilloid receptor (TRPV1 channel), which is involved in the neurotransmission of thermal and nociceptive stimuli.

Piplartine (5,6-dihydro-1-[(2*E*)-1-oxo3-(3′,4′,5′-trimethoxyphenyl)-2-propen-1-yl]-2(1*H*)-pyridinone, **244**, table 6) is another important alkamide isolated from the *Piper* species. This compound exhibits antifungal properties and has demonstrated antiplatelet aggregation, anxiolytic, antidepressant and antitumor activities in murine models. This naturally occurring alkamide is also a cytotoxic agent against cultured tumor cells, exhibiting promising anticancer properties. However, piplartine also shows mutagenic activity in yeast and cultured mammalian cells, inducing *in vitro* and *in vivo* chromosomal damage, potentially due to DNA breaks (Bezerra et al., 2009). The alkamides isolated from plants that belong to the Piper family are shown in table 6.

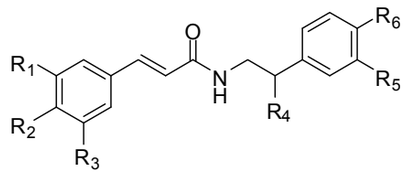
4. Other family plants - Alkamides with both fragments including aromatic residues

The cinnamoylbenzylamide tribulusimide (**263**, fig. 7) and several cinnamoylphenethylamides (table 7) and benzylphenethylamides (table 8) are the condensation products of cinnamic acid and benzylamine derivatives, cinnamic acid and phenethylamine and benzylic acid and phenethylamine, respectively. These alkamides have been isolated from a broad variety of plants that belong to at least 28 families. A selection of these alkamides are shown in table 9.



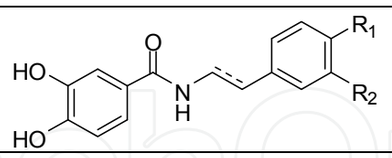
tribulusimide (**263**)

Fig. 7. Cinnamoylbenzylamide.



Alkamide	Name	R_1	R_2	R_3	R_4	R_5	R_6
264	*p*-coumaroyltyramine	H	OH	H	H	H	OH
265	caffeoyltyramine	OH	OH	H	H	H	OH
266	feruloyltyramine	OCH_3	OH	H	H	H	OH
267	dihydro-feruloyltyramine	OCH_3	OH	H	H	H	OH
268	sinapoyltyramine	OCH_3	OH	OCH_3	H	H	OH
269	feruloylmethoxytyramine	OCH_3	OH	H	H	OCH_3	OH
270	terrestriamide	OCH_3	OH	H	=O	H	OH
271	feruloyldopamine	OCH_3	OH	H	H	OH	OH
272	coumaroyldopamine	H	OH	H	H	OH	OH
273	feruloyl-4-*O*-methyldopamine	OCH_3	OH	H	H	OH	OCH_3
274	feruloyl-3-*O*-methyldopamine	OCH_3	OH	H	H	OCH_3	OH
275	*p*-coumaroyl-3-*O*-methyldopamine	H	OH	H	H	OCH_3	OH
276	2-(4'-hydroxyphenyl) ethylcaffeic amide	OH	OH	H	H	H	OH
277	*N*-*cis*-feruloyloctopamine	OCH_3	OH	H	OH	H	OH
278	coumaroyloctopamine	H	OH	H	OH	H	OH
279	β-(*p*-hydroxy-phenylethyl) *p*-hydroxycinnamamide	H	OH	H	H	H	OH
280	3-methoxyaegeline	H	H	H	OH	OCH_3	OCH_3
281	3-methoxy-7-acetylaegeline	H	H	H	OAc	OCH_3	OCH_3
282	3-methoxy-7-cinnamoylaegeline	H	H	H	Ocinnamoyl	OCH_3	OCH_3

Table 7. Cinnamoylphenethylamides isolated from diverse plants.



Alk	Name	Δ	R_1	R_2
283	*N*-[2-(3,4-dihydroxyphenyl)ethyl]-3,4-dihydroxybenzamide	---	OH	OH
284	alatamide [*N*-(*E*)-(*p*-methoxystyryl)-benzamide]	2*E*	OCH_3	H
285	dihydroalatamide [*N*-benzoyltyramine methyl ether]	**---**	OCH_3	H

Table 8. Benzylphenethylamides isolated from diverse plants.

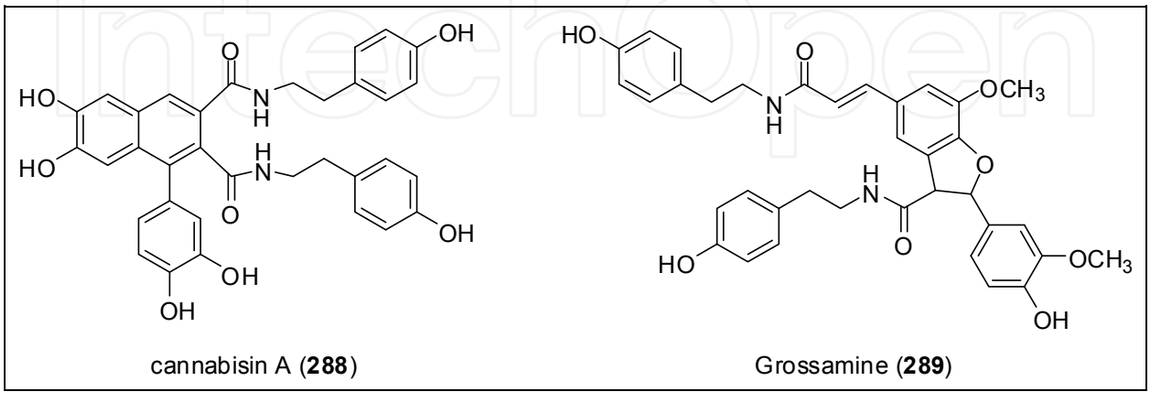
Despite the broad distribution of alkamides with both fragments, including aromatic residues among a wide variety of plant families, the presence of feruloyltyramine (**266**) is exceptionally important because it is a common compound found in the majority of alkamide-producing plants. The *Z*- and *E*-stereoisomers of feruloyltyramine have been isolated and are two of the most frequently characterized alkamides. The second most important alkamide is *p*-coumaroyltyramine (**264**), which is isolated also in both stereoisomeric forms, the *E*-stereoisomer being the most common (table 9).

Family	Species		Alkamide	Reference
Alliaceae	*Allium fistulosum*		**264**	(Nishioka et al., 1997)
Amaranthaceae	*Amaranthus*	*hypochondriacus*	**264, 265, 266, 268, 271, 273**	(Pedersen et al., 2010)
		mantegazzianus	**264, 265, 266, 268, 271, 273**	
	Achyranthes ferruginea		***trans*-273**	(Alam et al, 2003)
Anacardiaceae	*Mangifera indica*		**276**	(Ghosal & Chakrabarti, 1988)
Annonaceae	*Annona cherimola*		**264, *cis*-265, *cis*-266, 267, *cis*-269, *trans*-269**	(Chen et al., 1998)
Aristolochiaceae	*Aristolochia*	*gehrtii*	***cis*-264, *trans*-264, *cis*-266, *trans*-266, *cis*-275, *trans*-275**	(Navickiene & Lopes, 2001)
		gigantea	***trans*-264, *trans*-266, *cis*-275, 276, *cis*-277**	(Holzbach & Lopes, 2010)
Cannabidaceae	*Cannabis sativa*		**264, *trans*-265, *trans*-266**	(Sakakibara et al, 1991)
Chenopodiaceae	*Chenopodium album*		***trans*-273, *cis*-275**	(Horio et al., 1993)
Concolvulaceae	*Ipomoea aquatica*		***cis*-266, *trans*-266**	(Tseng et al., 1992)
Euphobiaceae	*Antidesma membranaceum*		***trans*-266, *cis*-277, *trans*-277**	(Buske et al., 1997)
Flacourtiaceae	*Casearia membranacea*		***cis*-266, *trans*-266**	(Chang et al., 2003)
Fumariaceae	*Dactylicapnos torulosa*		***trans*-266**	(Rucker et al., 1994)
Hernandiaceae	*Sparattanthelium tupiniquinorum*		***trans*-264, *trans*-266**	(Pereira et al., 2007)
Lauraceae	*Actinodaphne longifolia*		***trans*-266, *trans*-273**	(Tanaka et al., 1989)
Leguminosae	*Mucuna birdwoodiana*		***trans*-266**	(Goda et al., 1987)
Magnoliaceae	*Michelia alba*		***cis*-266, *trans*-266**	(Chen et al., 2008)
Malvaceae	*Hibiscus taiwanensis*		***cis*-266, *trans*-266**	(Wu et al., 2005)
Menispermaceae	*Sinomenium acutum*		**266**	(Otsuka et al., 1993)
Nyctagenaceae	*Mirabilis jalapa*		***trans*-273**	(Michalet et al., 2007)
Papaveraceae	*Hypecoum*	*imberbe*	***trans*-266**	(Hussain et al., 1982)
		parviflorum	***trans*-266**	
Piperaceae	*Peperomia duclouxii*		**268, *trans*-274, *trans*-271, 283**	(Li et al., 2007)
Plumbaginaceae	*Ceratostigma willmottianum*		***trans*-265, *trans*-266**	(Yue et al., 1997)
Polygonaceae	*Eskemukerjea megacarpum*		***trans*-266**	(Miyaichi et al., 2006)
Portulacaceae	*Portulaca oleracea*		***trans*-266**	(Mizutani et al., 1998)
Rutaceae	*Evodia belahe*		**279**	(Pedersen et al. , 2010)
	Pleiospermium alatum		**284, 285**	(Chatterjee et al., 1975)
	Zanthoxylum syncarpum		**280, 281, 282**	(Ross et al., 2005)
Solanaceae	*Solanum*	*khasianum*	***cis*-264, *trans*-264, *cis*-266, *trans*-266, *cis*-277, *trans*-277, *cis*-278, *trans*-278**	(Muhlenbeck et al., 1996)
		lycopersicum	**264, 266, 272, 273**	(Zacares et al., 2007)
		citrullifolium	***trans*-266**	(Turnock et al., 2001)
	Cestrum lanatum		***trans*-266**	
Zygophyllaceae	*Tribulus terrestris*		**24, *trans*-265, 271, 263**	(Lv et al., 2008)

Table 9. Distribution of alkamides including both acid and amide residues.

These alkamides have been associated with diverse biological activities, such as the potentiation of antibiotics, inhibition of prostaglandin biosynthesis, antioxidant activity and more. Furthermore, cinnamoylphenethylamines have been suggested to have an impact on human health if present in the diet (Pedersen et al., 2010).

Some dimeric alkamides have been isolated from *Cannabis sativa* (Cannabinaceae, Sakakibara et al., 1991) (fig. 8).



cannabisin A (**288**) Grossamine (**289**)

Fig. 8. Dimeric alkamides from *Cannabis sativa.*

5. Conclusion

Alkamides are natural products distributed among several medicinal plants that are a part of at least 33 families. These plants are used for a variety of medicinal purposes in many places throughout the world. Chemical and pharmacological research of these plants have established that alkamides contribute to the notable bioactivity of these plants. Asteraceae, Solanaceae, Rutaceae and Piperaceae are plant families that specialize in the biosynthesis of these natural products. Importantly, alkamides are chemical markers for plants in each family and genus.

Alkamides with both acid and amine aliphatic residues are characteristic compounds produced by the Asteraceae family, especially from the *Achillea*, *Acmella*, *Spilanthes*, *Echinaceae* and *Heliopsis* genera. Alkamides with one aromatic residue can be classified in the following two groups: (1) alkamides with an aromatic residue at the amine core and (2) alkamides with an aromatic residue at the acid. The first group has been isolated from the Solanaceae family, specifically from the *Capsicum* genus for which those alkamides are named "capsaicinoids". Other alkamides that belong to this group have been isolated from the *Lepidium* (Brassicaceae) and *Glycosmis* (Rutaceae) genera. *Glycosmis* alkamides are rare and have characteristic sulfur-containing structures. The second group corresponds to piperine and its analogs. These compounds are characteristic of the *Piper* genus (Piperaceae). Furthermore, the alkamides with both acid and amine aromatic residues are widely distributed among at least 28 plant families. Feruloyltyramine and *p*-coumaroyltyramine are the most commonly isolated alkamides that belong to this group of compounds.

Pure alkamides and plants that produce alkamides have a pungent and/or irritating taste as well as analgesic and anesthetic effects. Many alkamides are used to treat dental, muscular

and arthritic pain. Some alkamides are also consumed to enhance immune response and to relieve colds, respiratory infections and influenza. Anti-inflammatory activity is associated with all of these natural products. Despite the relatively simple structures of alkamides, these compounds have attracted several research groups to study their diversity, distribution and chemical and pharmacological behaviours. Additionally, alkamides have been observed to exhibit many other bioactivities, making these compounds a relatively new and promising family of natural products.

6. Acknowledgments

To CONACyT (Grant number 79584-Q). I am grateful to Enrique Salazar Leyva for technical assistance. I apologize to all colleagues whose studies were not cited due to space limitations.

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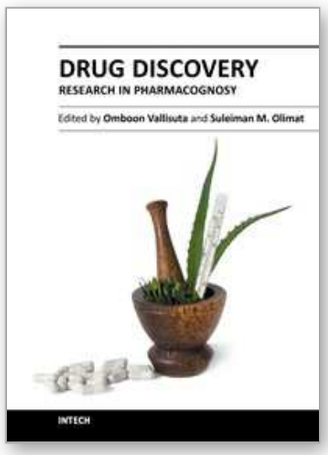

Drug Discovery Research in Pharmacognosy
Edited by Prof. Omboon Vallisuta

ISBN 978-953-51-0213-7
Hard cover, 244 pages
Publisher InTech
Published online 16, March, 2012
Published in print edition March, 2012

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