Alitame

1 Nonproprietary Names

None adopted.

2 Synonyms

L-Aspartyl-D-alanine-*N*-(2,2,4,4-tetramethylthietan-3-yl)amide; 3-(L-aspartyl-D-alaninamido)-2,2,4,4-tetramethylthietane.

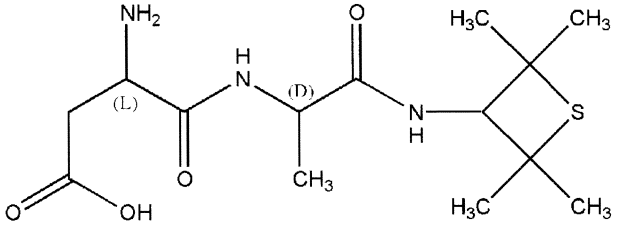
3 Chemical Name and CAS Registry Number

L-α-Aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide anhydrous [80863-62-3]
L-α-Aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate [99016-42-9]

4 Empirical Formula / Molecular Weight

Empirical Formula	Molecular Weight
$C_{14}H_{25}N_3O_4S$	331.44 (for anhydrous)
$C_{14}H_{25}N_3O_4S \cdot 2\frac{1}{2}H_2O$	376.5 (for hydrate)

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Alitame is an intense sweetening agent developed in the early 1980s and is approximately 2000 times sweeter than sucrose. It has an insignificant energy contribution of 6 kJ (1.4 kcal) per gram of alitame.

Alitame is currently primarily used in the food and confectionery industries at concentrations in the range 20–200 ppm.

8 Description

Alitame is a white nonhygroscopic crystalline powder; odorless or having a slight characteristic odor.

9 Pharmacopeial Specifications

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10 Typical Properties

Acidity/alkalinity: pH = 5–6 (5% w/v aqueous solution)
Isoelectric point: pH 5.6
Melting point: 136–147°C
Solubility: *see* Table I.

Table I: Solubility of alitame.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	1 in 5000 at 25°C
Ethanol	1 in 1.6 at 25°C
n-Heptane	Practically insoluble
Methanol	1 in 2.4 at 25°C
Propylene glycol	1 in 1.9 at 25°C
Water	1 in 8.3 at 5°C
	1 in 7.6 at 25°C
	1 in 3.3 at 40°C
	1 in 2.0 at 50°C

Specific rotation $[\alpha]_D^{25}$: +40° to +50° (1% w/v aqueous solution)

11 Stability and Storage Conditions

Alitame is stable in dry, room temperature conditions but undergoes degradation at elevated temperatures or when in solution at low pH. Alitame can degrade in a one-stage process to aspartic acid and alanine amide (under harsh conditions) or in a slow two-stage process by first degrading to its β-aspartic isomer and then to aspartic acid and alanine amide. At pH 5–8, alitame solutions at 23°C have a half-life of approximately 4 years. At pH 2 and 23°C the half-life is 1 year.

Alitame should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Alitame may be incompatible with oxidizing and reducing substances or strong acids and bases.

13 Method of Manufacture

Alitame may be synthesized by a number of routes.[1,2] For example, 3-(D-alaninamido)-2,2,4,4-tetramethylthietane is dissolved in water and L-aspartic acid *N*-thiocarboxyanhydride is then added in portions with vigorous stirring, maintaining the pH of 8.5–9.5. The pH is then adjusted to 5.5 and *p*-toluenesulfonic acid monohydrate is added over a period of one hour. The precipitated crystalline *p*-toluenesulfonate salt is collected by filtration. To obtain alitame from its salt, a mixture of Amberlite LA-1 (liquid anion exchange resin), dichloromethane, deionized water, and the salt is stirred for one hour, resulting in two clear layers. The aqueous layer is treated with carbon, clarified by filtration, and cooled to crystallize alitame.

Alternatively, tetramethylthietane amine is condensed with an *N*-protected form of D-alanine to give alanyl amide. This is then coupled to a protected analogue of L-aspartic acid to give a crude form of alitame. The crude product is then purified.

14 Safety

Alitame is a relatively new intense sweetening agent used primarily in foods and confectionary. It is generally regarded as a relatively nontoxic and nonirritant material.

Chronic animal studies in mice, rats, and dogs carried out for a minimum of 18 months at concentrations >100 mg/kg per day exhibited no toxic or carcinogenic effects. In people, no evidence of untoward effects were observed following ingestion of 15 mg/kg per day for two weeks.

Following oral administration 7–22% of alitame is unabsorbed and excreted in the feces. The remaining amount is hydrolyzed to aspartic acid and alanine amide. The aspartic acid is metabolized normally and the alanine amide excreted in the urine as a sulfoxide isomer, as the sulfone, or conjugated with glucuronic acid.

The WHO has set an acceptable daily intake of alitame at up to 0.1 mg/kg body-weight.[3]

LD_{50} (mouse, oral): >5 g/kg
LD_{50} (rabbit, skin): >2 g/kg
LD_{50} (rat, oral): >5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Alitame should be stored in tightly closed containers, and protected from exposure to direct sunlight and higher than normal room temperatures.

16 Regulatory Status

Alitame is approved for use in food applications in a number of countries worldwide including Australia, Chile, China, Mexico, and New Zealand.

17 Related Substances

Acesulfame potassium; aspartame; saccharin; saccharin sodium; sodium cyclamate.

18 Comments

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19 Specific References

1 Sklavounos C. Process for preparation, isolation and purification of dipeptide sweeteners. United States Patent No. 4,375,430; 1 Mar, 1983.
2 Brennan TM, Hendrick ME. Branched amides of L-aspartyl-D-amino acid dipeptides. United States Patent No. 4,411,925; 25 Oct, 1983.
3 FAO/WHO. Evaluation of certain food additives and contaminants. Forty-sixth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1997; No. 868.

20 General References

Anonymous. Use of nutritive and nonnutritive sweeteners—position of ADA. *J Am Diet Assoc* 1998; 98: 580–587.
Hendrick ME. Alitame. In: Nabors L, Gelardi R, eds. *Alternative Sweeteners*. New York: Marcel Dekker, 1991: 29–38.
Hendrick ME, *et al.* In: Grenby TH, ed. *Advances in Sweeteners*. Glasgow: Blackie, 1996: 226–239.

21 Author

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22 Date of Revision

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