Neotame
Neotame is an artificial, high potency sweetener with the official name (3S)-3-(3,3-Dimethylbutylamino)-4-[[((2S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino]-4-oxobutanoic acid and as such a derivate of aspartame. Its sweetness averages 7,000-13,000-times the sweetness of saccharose and 60-times the sweetness of aspartame. The sweetness itself is long-lasting and intensifies the taste of fruits, mint and chocolate. In the European Union Neotame is licensed as food additive E 961 since January 2010, in Australia as early as 2001.

Synthesis
Neotame gets synthesized from aspartame and 3,3-dimethylbutanal in ethanol. The reaction performs under high hydrogen-pressure with palladium on carbon as a catalyst. For purification, the catalyst gets filtrated. Whilst the solvent ethanol gets distilled off, the volume of the reaction solution is kept constant by adding water. When cooling down, Neotame precipitates as white sediment, which will be centrifuged and washed by water. Ultimately, the product gets dried in vacuum. The purity will be above 97%.

Gustatory cognition of sweetness
The AH-B-X-Theory, also called ‘sweetness triangle’ assumes that three moieties, AH, B and X need to interact with the taste buds. Thereby the moieties need to have the following properties.
AH: Electronegative heteroatom with at least one hydrogen bond (alcohol, amine)
B: Atom with relatively acid Hydrogen (carboxylic acid, alcohol)
X: Nonpolar moiety (alkyl-/ benzylremain)
This three moieties need to have a certain intramolecular assembly, namely that of a L-shaped one. If they can’t assemble this way, there won’t be a sweet taste recognized by the taste proteins. Therefore not all stereoisomers taste sweet, because not all of them fulfill the layout demands given by the protein.

Neotame, a sweetener; Project DaMocles, 2014
E. Westphal, T. Wissel, M. Wolf, O. Yampolskyy, L. Zhao
**Effect on the metabolism**
At nearly 80% of the incorporated Neotame the ester-moiety gets hydrolyzed to the according carboxylic acid and methyl alcohol. Furthermore, the carboxylic acid of the hydrolysis gets decomposed to phenylalanine, L-aspartic acid and 3,3-dimethylbutanol. The phenylalanine is the most critical hydrolysis product, since there is a disease called Phenylketonuria that prevents the metabolization of phenylalanine.

After 72h, approximately 98% of the incorporated Neotame are already set apart. Neither Neotame nor his metabolic products could be proven as repro-, terato- or genotoxic in a long-term study on rats, mice, rabbits and humans.

The Cesare Maltoni Cancer Research Center, however, attributes the metabolites of aspartame and thus the one of Neotam, (for instance a compound made of, among others, formaldehyde formed of methanol) in a study from 2010 on male rats and mice, carcinogene properties. Also observed was the decreased food intake of the laboratory animals, which ultimately lead to a loss of bodyweight. Nevertheless Neotame is classified as harmless.

The maximum on a human tested dose of 15 mg/kg is uncritical. The ADI-value is set on 2 mg/kg bodyweight/day.

**Use in industry**
Neotame is mainly used to sweet soft drinks, ice cream, glazes and bubble gum. Thereby an amount of 8-17 mg/kg for soft drinks, 15-35 mg/kg for ice cream/ glazes and about 250 mg/kg for bubble gum is used. Since Neotame already melts at 80-83°C and decomposes soon after that point, it can’t be used for purposes like baking.
Aspartame and its derivatives

<table>
<thead>
<tr>
<th>Aspartame</th>
<th>Alitame</th>
<th>Neotam</th>
<th>Superaspartame</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Aspartame" /></td>
<td><img src="image2.png" alt="Alitame" /></td>
<td><img src="image3.png" alt="Neotam" /></td>
<td><img src="image4.png" alt="Superaspartame" /></td>
</tr>
<tr>
<td>N-(L-α-Aspartyl)-L-phenylalanine, 1-methyl ester</td>
<td>(3S)-3-amino-4-[(1R)-1-methyl-2-oxo-2-[(2,2,4,4-tetramethyl-3-thietanyl)amino][ethyl]amino]-4-oxobutanoic acid</td>
<td>(3S)-3-(3,3-Dimethylbutylamino)-4-[[2S]-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino]-4-oxobutanoic acid</td>
<td>(p-Cyanophenyl-)carbamoyl-L-aspartyl-L-phenylalanine ester</td>
</tr>
</tbody>
</table>

Relative sweetness compared to saccharose

| 200-fold | 2,000-3,000-fold | 7,000-13,000-fold | 14,000-fold |

If the oxygen in the urea-unit in Superaspartame is being swapped with sulfur, one creates a sweetener with the sweetness 50,000-folds the sweetness of saccharose, the Thiosuperastpartame.

Sources

- Sucrose, Sucralyse and Fructose: Correlations between hydrophobicity potential profiles and AH-B-X assignments, Friedel W. Lichtenthaler & Stefan Immel, Institut für Organische Chemie, Technische Hochschule Darmstadt, 1993
- Aspartame Administered in Feed, Beginning Prenatally Through Life Span, Induces Cancers of the Liver and Lung in Male Swiss Mice, M. Sofritti, F. Delpoggi, M. Manservigi, E. Tibaldi, M. Lauriola, L. Falcioni and L. Bua, American Journal of Industrial Medicine, 2010
- http://www.suessstoff-verband.de/suessstoffe/neotam/ (As of 07.05.2014)