

Amide Magic: A walk through taste and sensation from a molecular viewpoint

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Ingredient Challenges

Needs to consider and address:

- Regulatory - FEMA GRAS, Natural, N.I., Artificial, Flavor ingredient or food additive?
- Labeling - Natural flavor preparation, process flavor, smoke, extract etc.
- Food Industry - Consumer / marketing pressure
- Application – Specific or general
- Cost – As consumed, need to consider use level in target application(s)
- Performance – Unique? Stability, Solubility

Ultimate success is a combination / compromise of all these factors

Ingredient Categorization

Flavor ingredient

- Traditional

Top note volatile, non-volatiles, citrus oils, natural extracts.....

- Non-traditional

Flavor enhancer (IMP, NHDC), Coolers, Retronasal effects, warming agents, other flavor ingredient Lo-Han Quo etc

Non-flavor ingredient

Artificial Sweetner (Sucralose, Ace-K), Carrier, surfactant, polymer etc.

Physiological Target Classification -

Chemosensory receptors

OR's, G_{olf}

TRPM8 – Cooling

TRPA1 Or TRPV1 – Warming, Salt?

Multimodal nociceptors - Tingle

T1R's – Sweet, Umami

T2R's – Bitter

ENaC - Salt

MGluR4 – Umami?

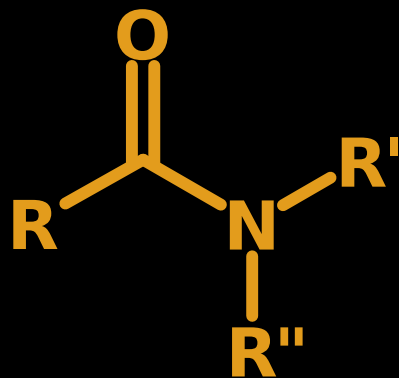
TRPM5 – Taste?

Fat? CD36, DRK's

Amide Magic?

The extraordinary characteristics of Amide moiety were previously presented to the society by Dr. Mark Erman of Millenium Specialty Chemicals

'Cooling Compounds' presentation to the Society of Flavor Chemists (December 2003)

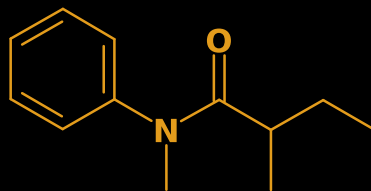


In this industry, outside the field of olfaction, amides are the most interesting class of compounds for basic research endeavor.

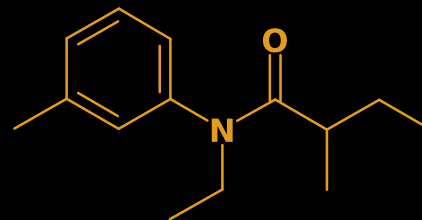
Amide Magic?

Amides usually possess process one or more of the following the following properties

- 1 Taste
- 2 Sensation
- 3 No perceived effect at flavor concentrations
4. Occasionally olfaction



Gardamide



Quest

Patent Application WO 2003000648 A1

Ingredient Inspiration – Where from?

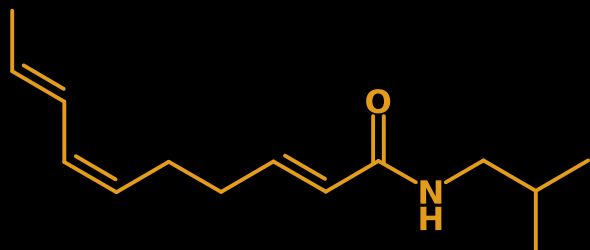
Traditional flavor ingredient ‘inspirations’*

- Analysis of food or natural product
- SAR
- Competitor Analysis / Scientist knowledge / Gap analysis
- Experience of platform in category
- Educated guesswork

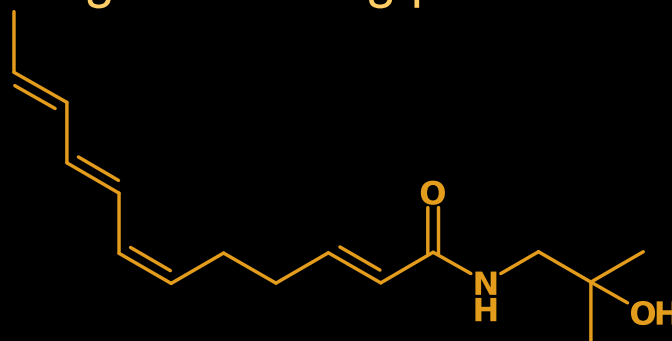
*Excludes ingredients from natural synthesis, natural product isolation and genomic based ingredient discovery

Ingredient Inspiration – Where from?

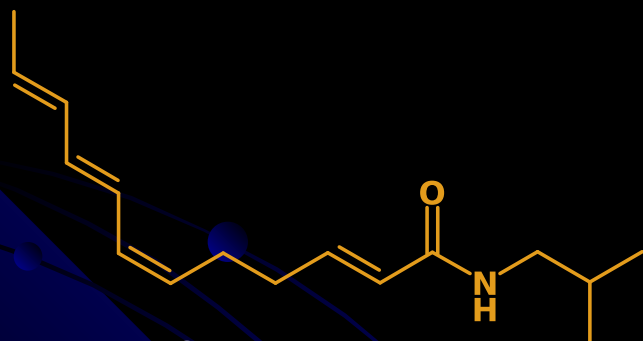
Analysis of food or natural product – Tingle ‘Numbing paresthesia’



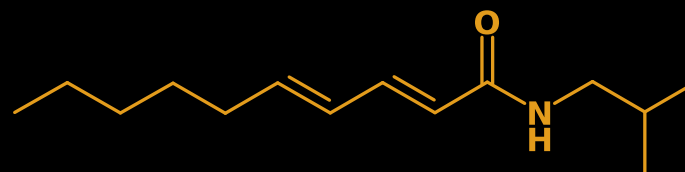
Spilanthol



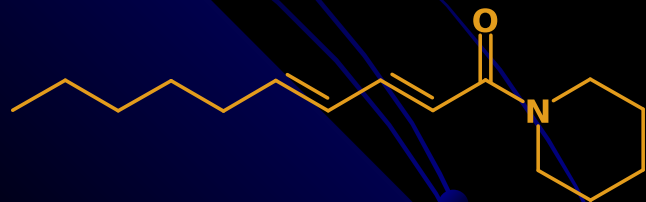
Hydroxy sanshool



Sanshool



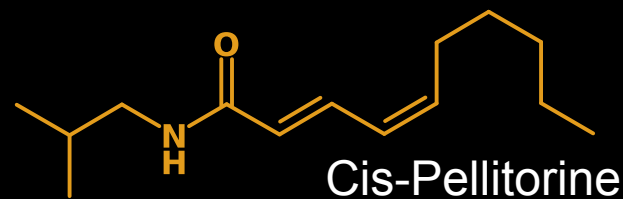
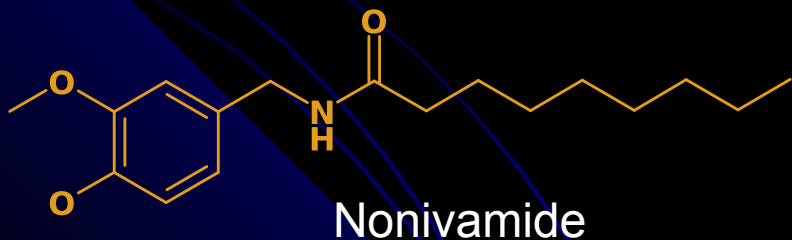
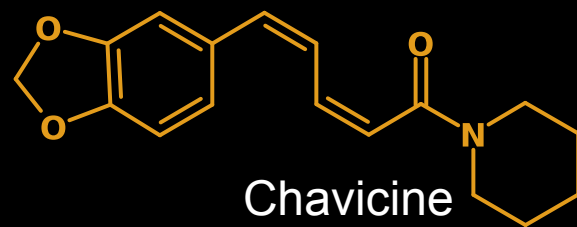
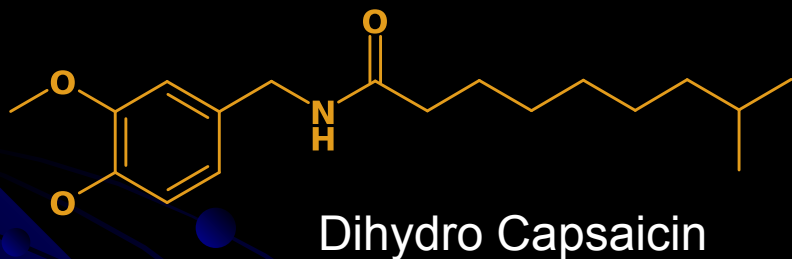
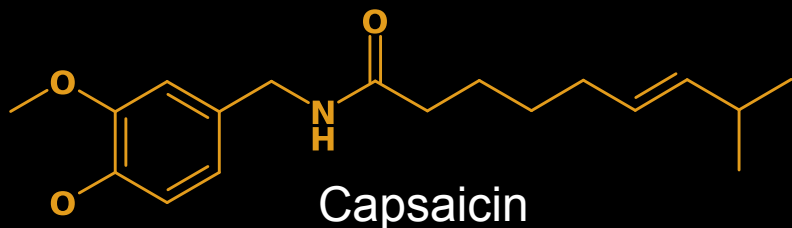
Pellitorine



IFF Patent Applications
US 2005075368 A1
WO 2004043906 A2

Ingredient Inspiration – Where from?

Analysis of food or natural product – Warming (TRPV1, TRPA1)

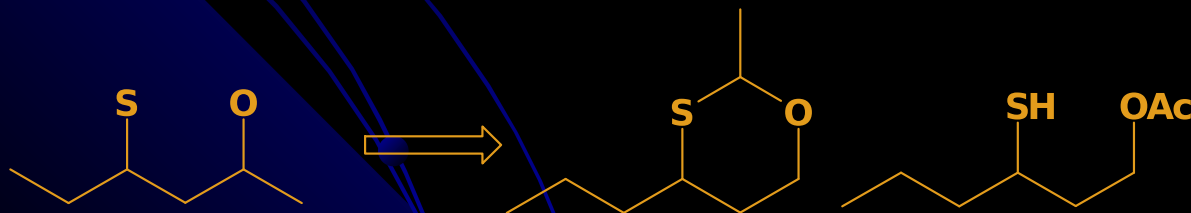
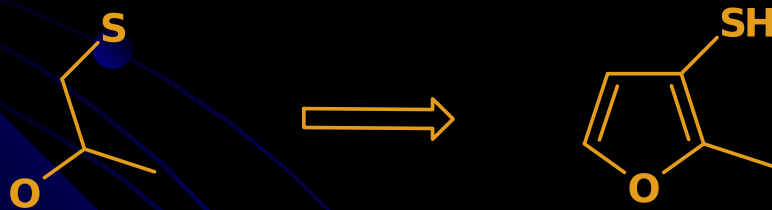
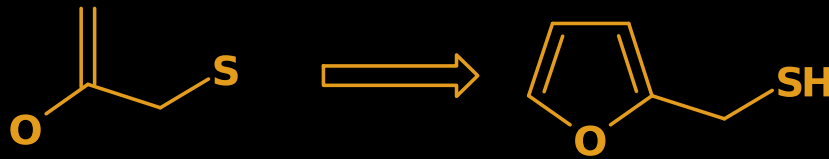


Symrise Patent Application
WO 2004000787 A2

Ingredient Inspiration – Where from?

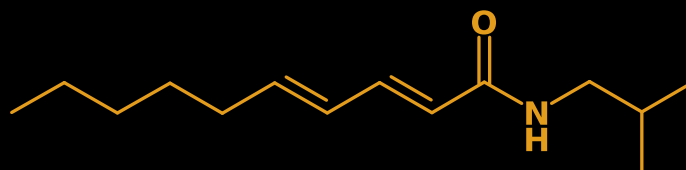
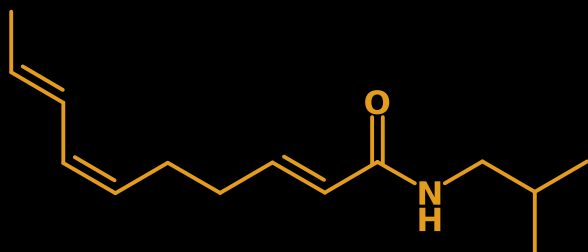
Structure Activity Relationship - Traditional

Traditional example – high impact sulfur chemicals with the S-O ‘odorophore’

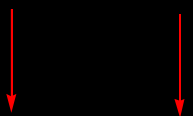


Ingredient Inspiration – Where from?

Structure Activity Relationship – Tingle (Trigeminal receptors)



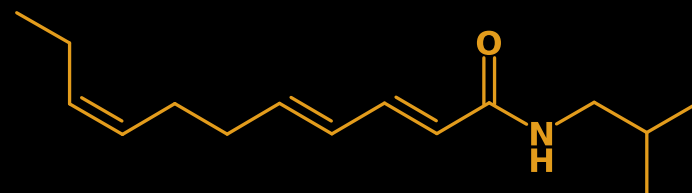
Z-double bond or E/Z-double bond



Additional double bond

C_nH_{2n}
Spacer

Amide linkage with conjugate double bond



IFF Patent Application
US 7098350

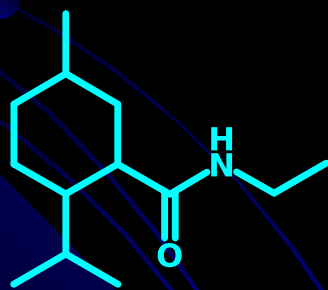
Givaudan Patent Application
WO 2004011415 A1

Ingredient Inspiration – Where from?

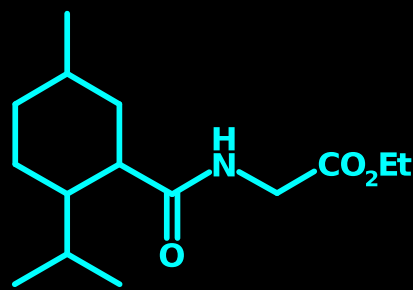
Structure Activity Relationship – Cooling (TRPM8)

- Cooling compounds are generally believed to require:
- A hydrogen bonding group
- A compact hydrocarbon skeleton
- Correct hydrophilic/hydrophobic balance
- Molecular weight between 150 and 350.

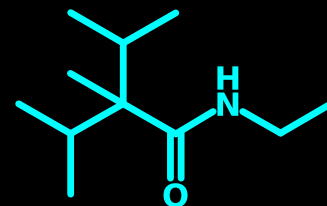
Watson, H.R.; Hems, R.; Roswell, D.G. and Spring, D.J., New Compounds with the Menthol Cooling Effect; J. Soc. Cosmet. Chem. 1978, 29, 185-200



WS 3



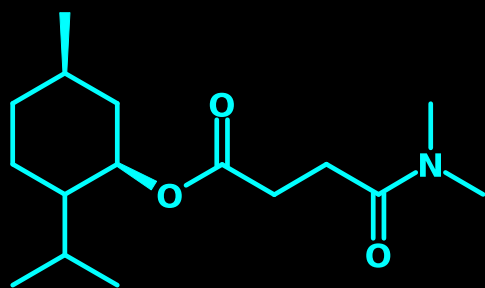
WS 5



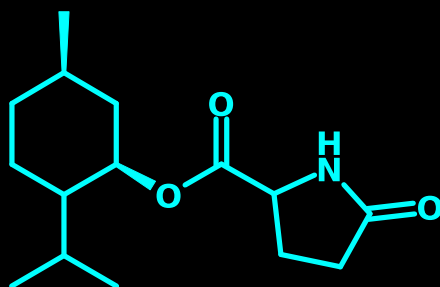
WS 23

Ingredient Inspiration – Where from?

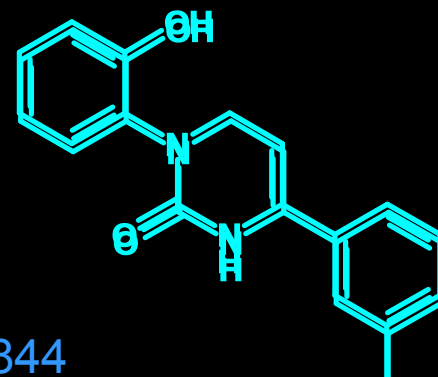
Competitor Analysis / Scientist knowledge / Gap analysis - Cooling



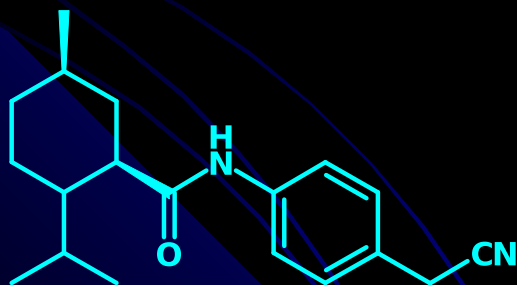
IFF Patent US 6884906



Quest Patent US 6451844



Unilever Patent
US 7045624



Givaudan Patent Application
WO 2005049553 A1



Hasegawa Patent Application
JP 2004059474

Roles of the Human Taste System



Nutrient Detection

Carbohydrates: sweet

Minerals: salty

Protein: amino acid or *umami*



Toxin Avoidance

Alkaloids

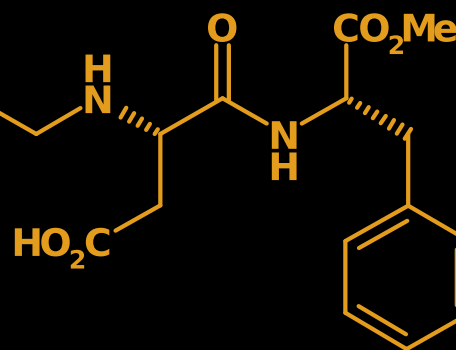
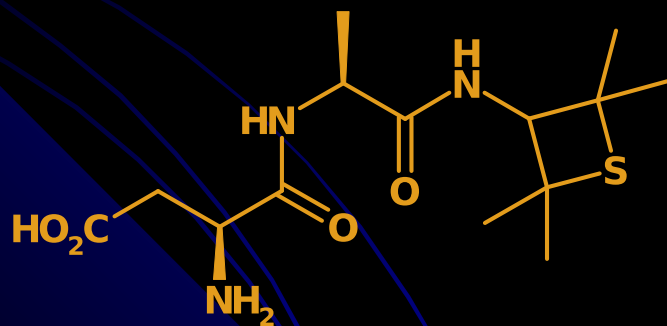
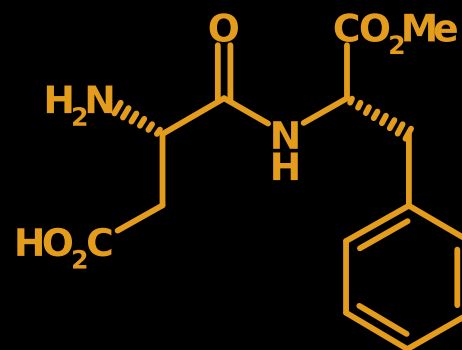
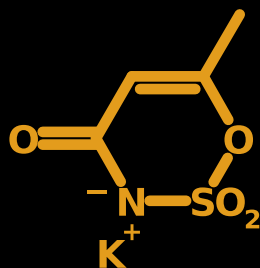
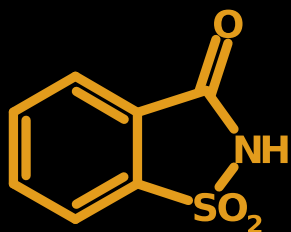
Toxins

*Pharmaceuticals

} bitter

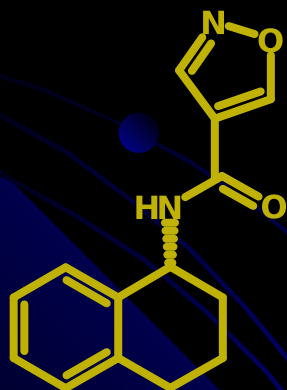
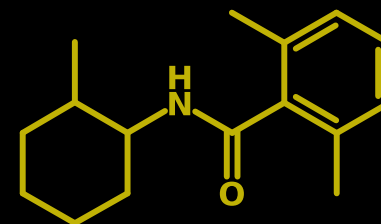
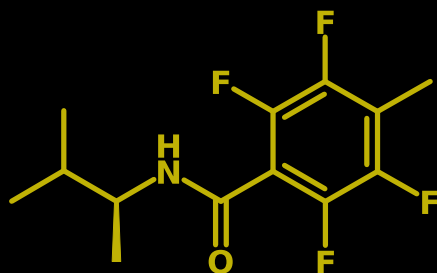
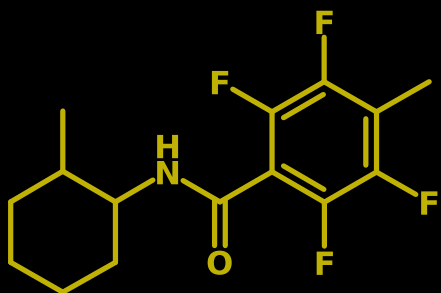
Ingredient Inspiration – Where from?

Competitor Analysis Flavorist knowledge / Gap analysis - Sweet taste



Experience of platform in category or educated guesswork?

Search for new sweet tasting molecules

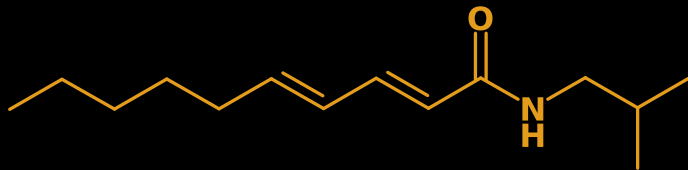


Senomyx Patent Application WO 2005041684 A2

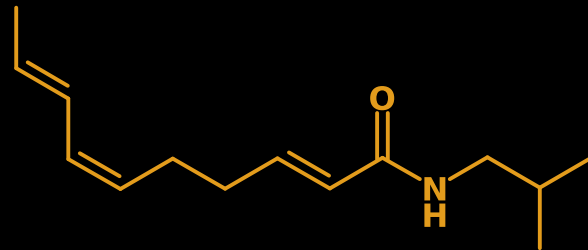
Experience of platform in category

Search for new umami taste molecules – Part 1, the serendipitous discovery

Natural 'leads'

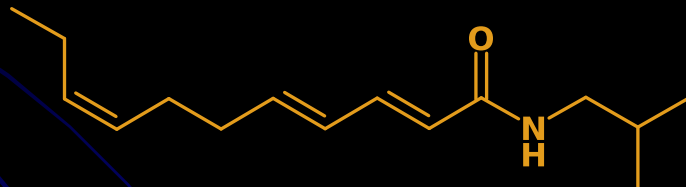


Strongly tingle 6, pungent at high concentrations



Very strong tingle with brine aftertaste

Best found



IFF

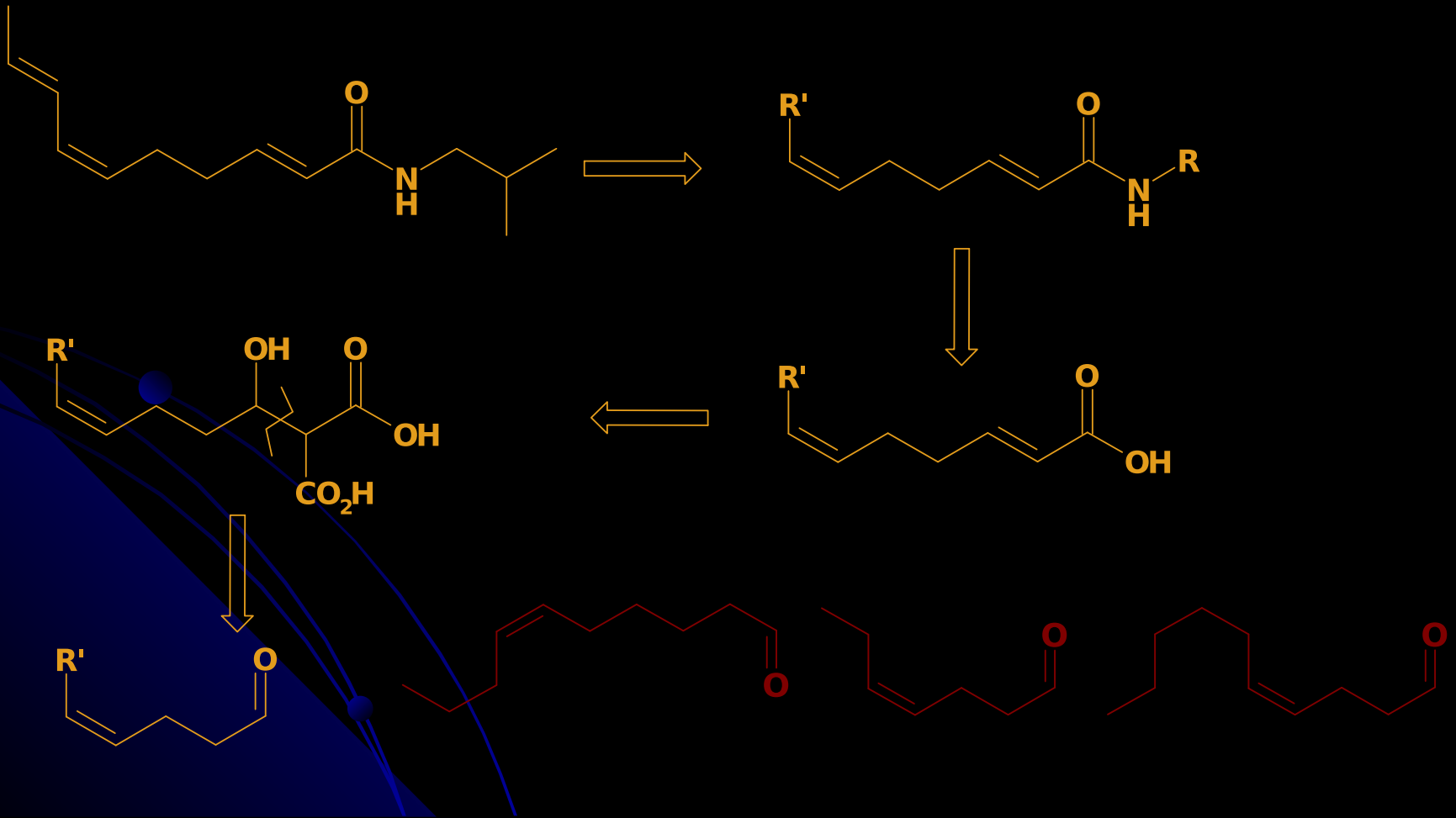
Patent US 7098350

Givaudan Patent Application WO 2004011415

Experience of platform in category

Search for new umami taste molecules – Part 1, the serendipitous discovery

Approach to 'new tingle molecules'



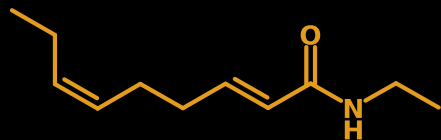
Experience of platform in category

Search for new umami taste molecules – Part 1, the serendipitous discovery

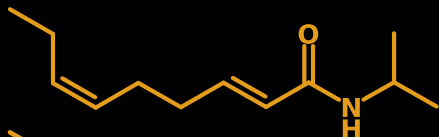
'Interesting findings'



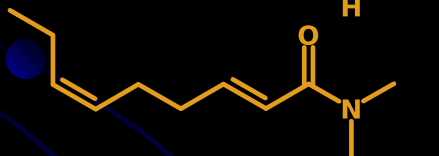
Umami 7, burn 3, tingle and salt



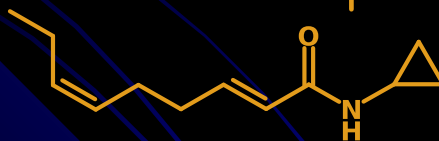
Umami 7, slight tingle



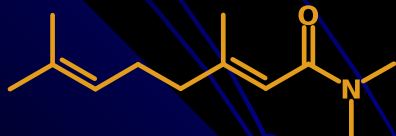
Umami 6, salt 1



Umami 7, tingle 1, salt 2



Umami 7, salt 3



Umami 4, tingle 2, salt 2

Published in IFF US Patent applications 20040202760 and 20040202619

Experience of platform in category

Search for new umami taste molecules – Part 1, the serendipitous discovery

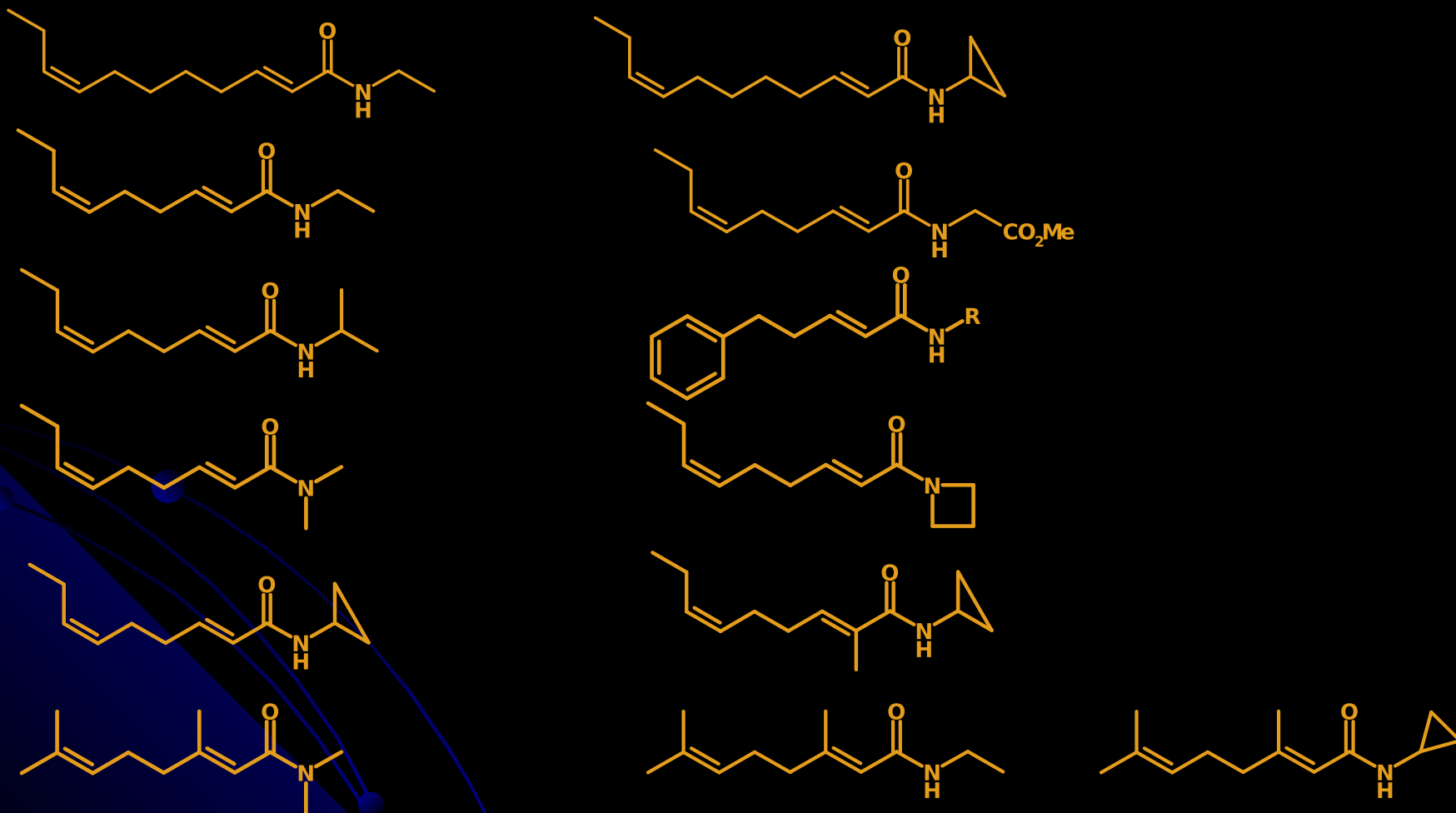
‘Summary of initial assumptions’

For umami from a small molecule appear to need:

- Molecular weight 180 – 220
- Small amine
- Large acid
- Unsaturation at C2-C3 and later in the chain
- Limited branching
- Primary amine > Secondary
- Cyclopropyl might be important?

Experience of platform in category

'However there were some findings in need of rationalization'

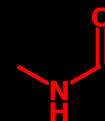
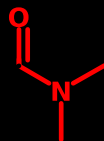
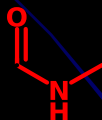


Educated Guesswork

Search for new umami taste molecules – Part 2, Focused discovery

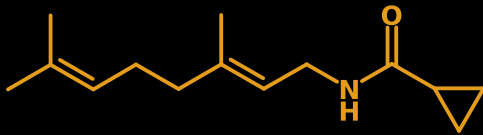
Based on initial assumptions and findings:

- Swap acid and amine chain lengths
- Expand Molecular weight $160 > 300$
- Large amine
- Small acid
- Retain Unsaturation at C2-C3 in amine moiety
- Retain limited branching but include rings
- Retain Primary amine $>$ Secondary but explore the latter
- Investigate if cyclopropyl really is important?

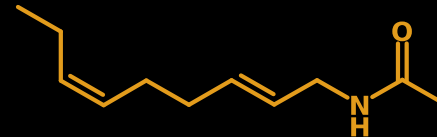


Educated Guesswork?

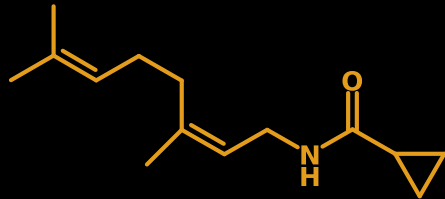
Search for new umami taste molecules – Part 2, Focused discovery



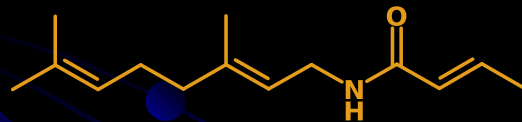
Umami 9



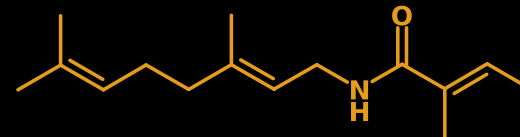
Umami 7



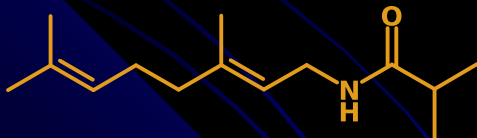
Umami 7, IMP like



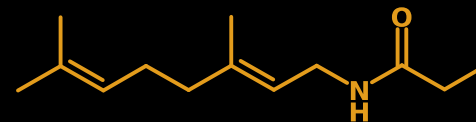
Umami 7



Umami 6



Umami 5
Tingle 2



Umami 7

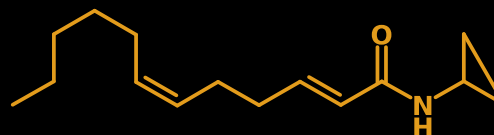
Why Educated Guesswork?

Over 100 molecules synthesized with very similar structures

Next best candidates from either molecular set:



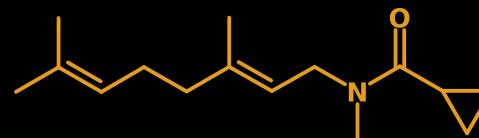
Umami 5
Salt 3
Burn 2



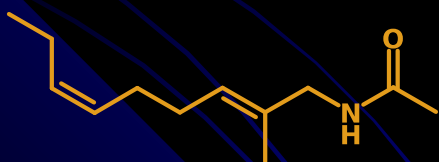
Umami 3
Warming 5



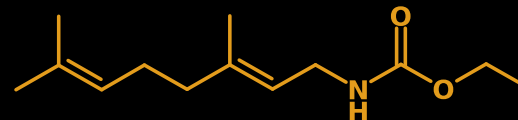
Umami 3



Umami 2



Umami 4



Umami 4

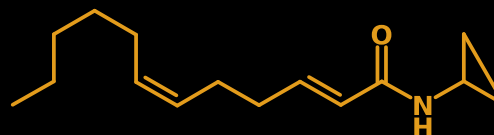
Why Educated Guesswork?

Receptor interplay. Also seem to be hitting TRPV1, T1R2 / T1R3, Trigeminal receptors and Salt VR1?

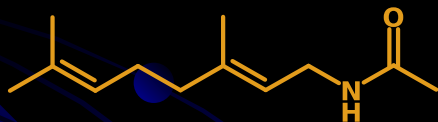
Next best candidates from either molecular set were also non-specific, or not Umami



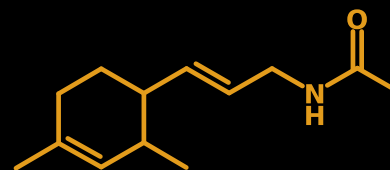
Umami 5
Salt 3
Burn 2



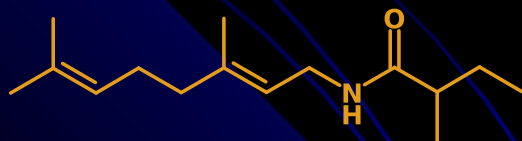
Umami 3
Warming 5



Umami 2
Tingle 2
Burn 8

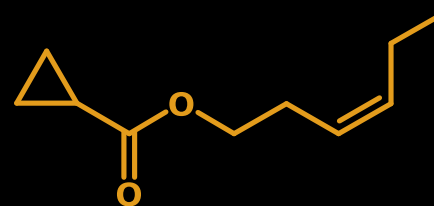
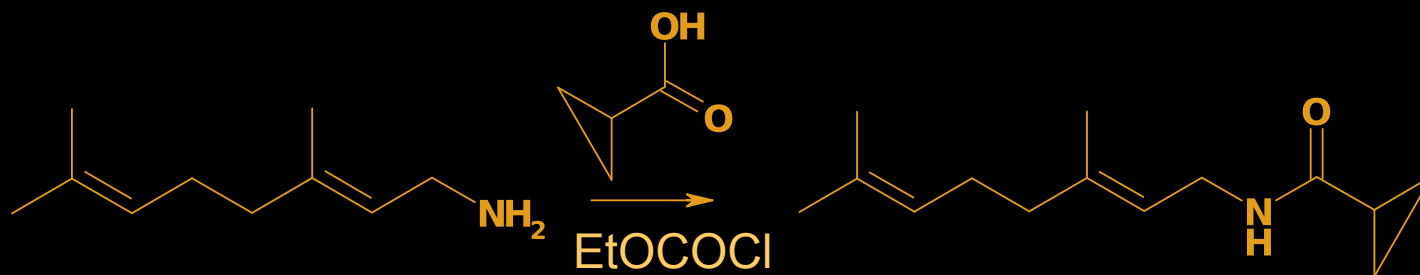


Warming 7



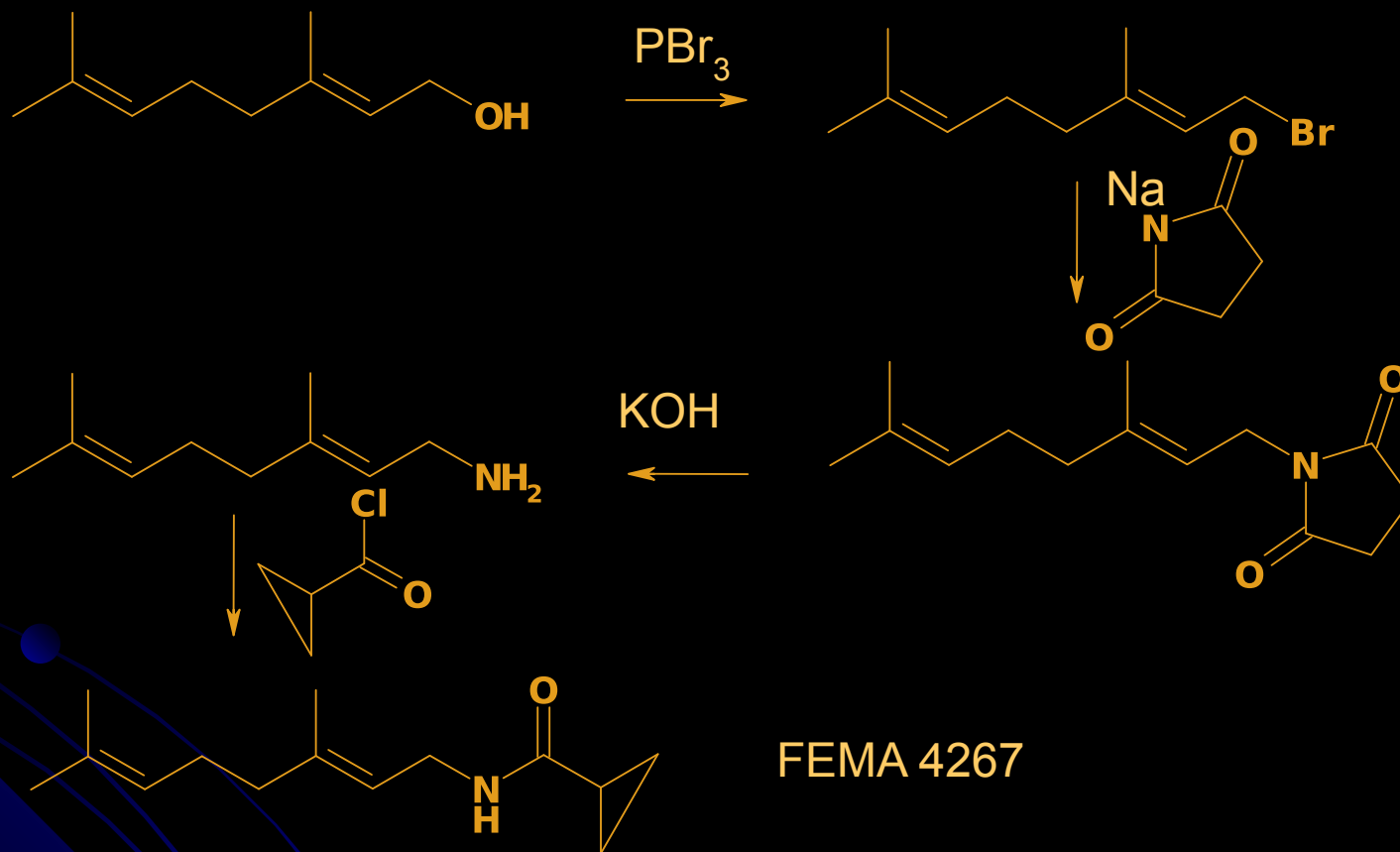
Sweet, comparable to NHDC

Preparation of umami compound



Montaverdi

Preparation of umami compound

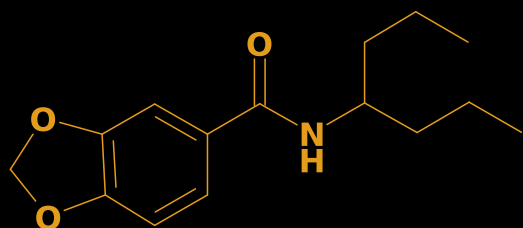


IFF Patent applications US 20060068071 A1 and US 20060057268 A1

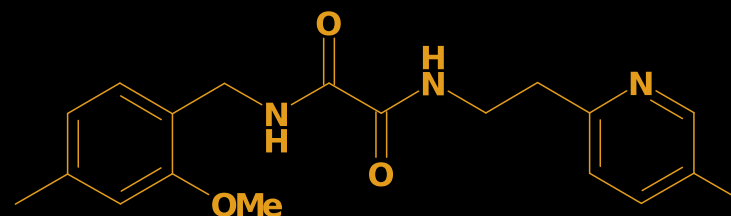
Competitive products - Benchmarking

Senomyx have patent pending Umami molecules

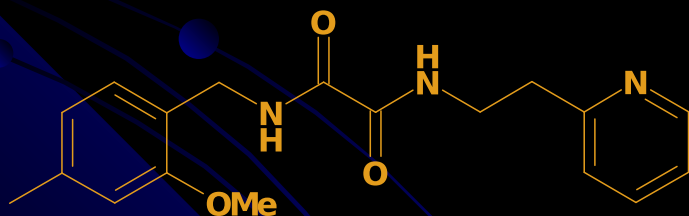
US 2006045953 A1, WO 2005041684 A2 and WO 2006084246



4232



4234



4231



4233

Summary

- Amides have diverse functionality in the field of sensates and basic taste.
- The combination size, log P, flexible chains, lipophilic and hydrophilic functionality allows these molecules to bind to receptor proteins
- Action can be specific single taste modality, or sensation e.g. Cooling) or multi faceted
- In general molecule are not high in flavor, but can modify flavor.
- Pharmacology works at ppm concentration (Cf. MSG)
- This class of compounds can be synthesized to hit specific targets, but SAR is highly limited.
- Potency can be found on at least the following receptors T1R's, T2R's, TRPM8, TRPV1, multimodal nociceptors

Research product for your tasting

Plain Potato Chips. Flavored with Natural and Artificial Taco Seasoning.

Free from added sources of Glutamate,

No added yeast of any kind

No added ribonucleotides

No added HVP

No added protein hydrolysates (Gluten, Casein, Whey etc)

No added tricks, Ammonium glutamate, succinic acid etc.

Simply a compounded flavor N&A.

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