QP

Organizacion CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

DVN
NOV

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 07-90851

54. **TÍTULO** UREAS Y AMIDAS AROMATICAS Y SUS USOS COMO DEGUSTACIONES, MODIFICADORES DEL SABOR DULCE Y/O UMANI Y MEJORADORES DEL GUSTO

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** SENOMIX INDORPORATED

DOMICILIO SAN DIEGO, CALIFORNIA, ESTADOS UNIDOS DE AMERICA

74. **APODERADO** EMILIO FERRERO

C.C. 438.019 de Usaquén

22. **BOGOTÁ, D. C.,**

5/10/25

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-090851- -00000-0000
Fecha: 2007-09-04 16:48:47 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 714

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

4/SEPT/2007

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)

Nombre: **SENOMIX INCORPORATED** sociedad constituida y existente bajo las leyes del Estado de Delaware, Estados Unidos de América.

Dirección: 4767 Nexus Center Drive,
San Diego,
California 92121,
Estados Unidos de América.

Domicilio: San Diego
California 92121,
Estados Unidos de América

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número _____

3 REPRESENTANTE O APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número 438.019 T.P 31.929

4 INVENTOR (ES) (72)

1. **Catherine TACHDJIAN**
3905 Caminito Terviso,
San Diego,
California 92122,
Estados Unidos de América

2. **Andrew P. PATRON**
1707 Tara Way,
San Marcos,
California 92078,
Estados Unidos de América

3. **Ming QI**
Cain Lun Lu,
720 Nong Building 2,
#401 Pudong Zhangjiang Hitech Park,
Sangai 201203,
China

4. **Sara ADAMINSKI-WERNER**
1349 Gregoty Street,
San Diego,
California 92102,
Estados Unidos de América

5. **Xiao-Qing TANG**
Ramsdell Court,
San Diego,
California,
92131
Estados Unidos de América

6. **Chen QING**
5536 Porter Crrek Road,
San Diego,
California 92130,
Estados Unidos de América

7. **Vincent DARMOHUSODO**
4178 Decoro Street #44,
San Diego,
California 92122,
Estados Unidos de América

8. **Marketa LEBL-RINNOVA**
4620 Alabama Street,
San Diego,
California 92116,
Estados Unidos de América

9. **Chad PRIEST**
824 Devonshire Drive,
Encinitas,
California 92024,
Estados Unidos de América

5 **PCT (86)**
Solicitud Internacional No. PCT/US2006/004132 Fecha: 06 de febrero de 2006
Publicación Internacional No. WO 2006/084246 A3 Fecha: 10 de agosto de 2006

6 **Título (54)**
UREAS Y AMIDAS AROMATICAS Y SUS USOS COMO DEGUSTANTES, MODIFICADORES DEL SABOR DULCE Y/O UMAMI Y MEJORADORES DEL GUSTO

7 **Clasificación Internacional (51)** A23L 001/226

8 **Prioridad** SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	04 de febrero de 2005	11/051,567

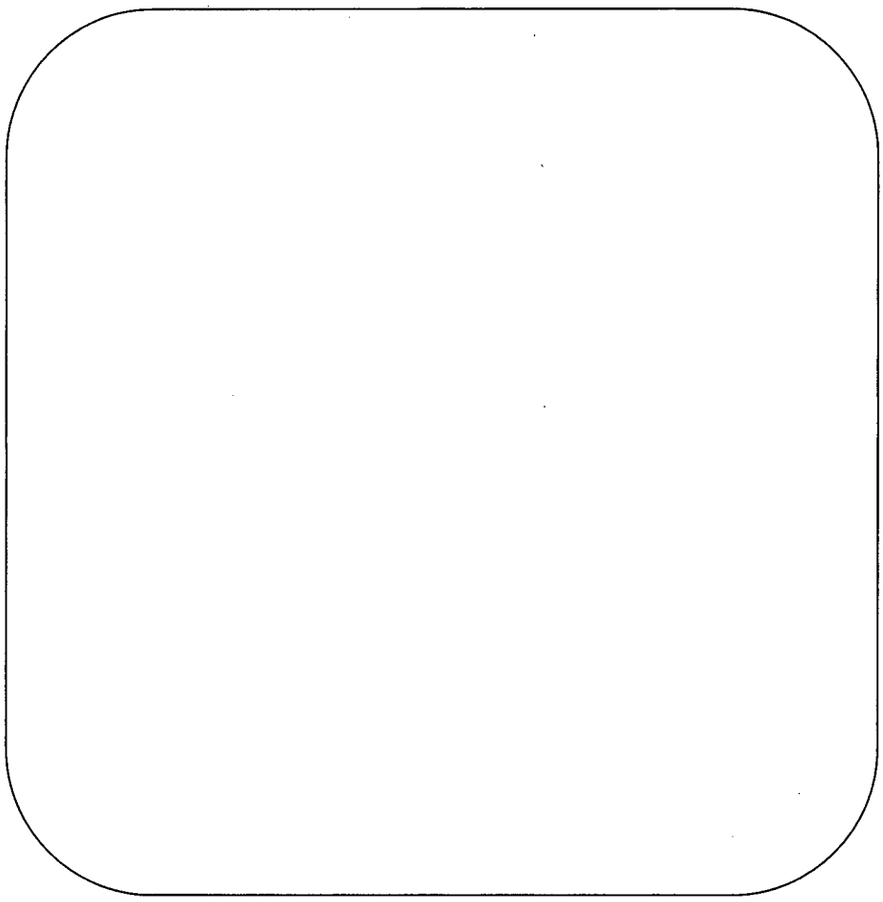
9 **Comprobante de pago No.:** 07,64,952 **Fecha:** 13 de agosto de 2007

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 482.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

SCT/MVN

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2006/084246 A3

   Descripción:

   Páginas 274 en el idioma original

   Páginas 394 en español

   Reivindicaciones: Número (s) 76

   Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 August 2006 (10.08.2006)

PCT

(10) International Publication Number
WO 2006/084246 A3

(51) International Patent Classification:
A23L 1/226 (2006.01) *A23L 1/231* (2006.01)

(21) International Application Number:
PCT/US2006/004132

(22) International Filing Date: 6 February 2006 (06.02.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11/051,567 4 February 2005 (04.02.2005) US

(71) Applicant *(for all designated States except US)*: **SENOMYX, INC.** [US/US]; 4767 Nexus Center Drive, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TACHDJIAN, Catherine** [US/US]; 3905 Caminito Terviso, San Diego, California 92122 (US). **PATRON, Andrew, P.** [US/US]; 1701 Tara Way, San Marcos, California 92078 (US). **QI, Ming** [CN/US]; Cai Lun Lu, 720 Nong Building 2, #401, Pudong Zhangjiang HiTech Park, Shanghai 201203 (CN). **ADAMINSKI-WERNER, Sara** [US/US]; 1349 Gregory Street, San Diego, California 92102 (US). **TANG, Xiao-Qing** [CN/US]; 11861 Ramsdell Court, San Diego, California 92131 (US). **QING, Chen** [CN/US]; 5536 Porter Creek Road, San Diego, California 92130 (US). **DARMOHUSODO, Vincent** [US/US]; 4178 Decoro Street, #44, San Diego, California 92122 (US). **LEBL-RINNOVA, Marketa** [CZ/US]; 4620 Alabama Street, San Diego, California 92116 (US). **PRIEST, Chad** [US/US]; 824 Devonshire Drive, Encinitas, California 92024 (US).

(74) Agents: **MURPHY, Mark** et al.; NEEDLE & ROSENBERG, P.C., Suite 1000, 999 Peachtree Street, Atlanta, Georgia 30309-3915 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
25 January 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AROMATIC AMIDES AND UREAS AND THEIR USES AS SWEET AND/OR UMAMI FLAVOR MODIFIERS, TASTANTS AND TASTE ENHANCERS

(57) Abstract: The inventions disclosed herein relate to non-naturally occurring amide compounds that are capable, when contacted with comestible food or drinks or pharmaceutical compositions at concentrations preferably on the order of about 100 ppm or lower, of serving as savory ("umami") or sweet taste modifiers, savory or sweet flavoring agents and savory or sweet flavor enhancers, for use in foods, beverages, and other comestible or orally administered medicinal products or compositions, optionally in the presence of or in mixtures with conventional flavoring agents such as monosodium glutamate or known natural and artificial sweeteners.

WO 2006/084246 A3

AROMATIC AMIDES AND UREAS AND THEIR USES AS SWEET AND/OR UMAMI FLAVOR MODIFIERS, TASTANTS AND TASTE ENHANCERS

This application claims the priority of U.S. utility patent application serial number 11/051,567, filed February 04, 2005, the entire disclosure of which is hereby incorporated herein by this reference for all purposes.

FIELD OF THE INVENTION

The present invention relates to the discovery of flavor or taste modifiers, such as a flavoring or flavoring agents and flavor or taste enhancers, more particularly, savory ("umami") or sweet taste modifiers, savory or sweet flavoring agents and savory or sweet flavor enhancers, for foods, beverages, and other comestible or orally administered medicinal products or compositions.

BACKGROUND OF THE INVENTION

For centuries, various natural and unnatural compositions and/or compounds have been added to comestible (edible) foods, beverages, and/or orally administered medicinal compositions to improve their taste. Although it has long been known that there are only a few basic types of "tastes," the biological and biochemical basis of taste perception was poorly understood, and most taste improving or taste modifying agents have been discovered largely by simple trial and error processes.

There has been significant recent progress in identifying useful natural flavoring agents, such as for example sweeteners such as sucrose, fructose, glucose, erythritol, isomalt, lactitol, mannitol, sorbitol, xylitol, certain known natural terpenoids, flavonoids, or protein sweeteners. *See for example* a recent article entitled "Noncariogenic Intense Natural Sweeteners" by Kinghorn, *et al.* (Med Res Rev 18 (5) 347-360, 1998), which discussed recently discovered natural materials that are much more intensely sweet than common natural sweeteners such as sucrose, fructose, and the like. Similarly, there has been recent progress in identifying and commercializing new artificial sweeteners, such as aspartame, saccharin, acesulfame-K, cyclamate, sucralose, and alitame, *etc.*, *see* a recent article by Ager, *et al.*(Angew Chem Int. Ed. 1998, 37, 1802-1817). The entire disclosure of the two references identified above are hereby incorporated herein by reference, for the purpose of describing at least in part the knowledge of those of ordinary skill in the art regarding known sweetening agents.

However, there remains in the art a need for new and improved flavoring agents. For example, one of the five known basic tastes is the "savory" or "umami" flavor of

monosodium glutamate ("MSG"). MSG is known to produce adverse reactions in some people, but very little progress has been made in identifying artificial substitutes for MSG. It is known that a few naturally occurring materials can increase or enhance the effectiveness of MSG as a savory flavoring agent, so that less MSG would be needed for a given flavoring application. For example the naturally occurring nucleotide compounds inosine monophosphate (IMP) or guanosine monophosphate (GMP) are known to have a multiplier effect on the savory taste of MSG, but IMP and GMP are very difficult and expensive to isolate and purify from natural sources, or synthesize, and hence have only limited practical application to most commercial needs in food or medicinal compositions. New tastant compounds that would provide the savory flavor of MSG itself, so as to substitute for MSG as a savory tastant, or new compounds that enhance the effectiveness of MSG so as to substitute for IMP or GMP as MSG enhancers, could be of very high value.

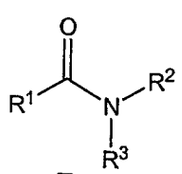
Similarly, discovery of compounds that are either new "High Intensity" sweeteners (*i.e.* they are many times sweeter than sucrose) would be of value, or any compounds that significantly increase the sweetness of known natural or artificial sweeteners, so that less of those caloric or non-caloric sweeteners would be required, could be of very high utility and value.

In recent years substantial progress has been made in biotechnology in general, and in better understanding the underlying biological and biochemical phenomena of taste perception. For example, taste receptor proteins have been recently identified in mammals which are involved in taste perception. Particularly, two different families of G protein coupled receptors believed to be involved in taste perception, T2Rs and T1Rs, have been identified. (*See, e.g.*, Nelson, *et al.*, *Cell* (2001) 106(3):381-390; Adler, *et al.*, *Cell* (2000) 100(6):693-702; Chandrashekar, *et al.*, *Cell* (2000) 100:703-711; Matsunami, *et al.*, *Number* (2000) 404:601-604; Li, *et. al.*, *Proc. Natl. Acad. Sci. USA* (2002) 99:4962-4966; Montmayeur, *et al.*, *Nature Neuroscience* (2001) 4(S):492-498; U.S. Patent 6,462,148; and PCT publications WO 02/06254, WO 00/63166 art, WO 02/064631, and WO 03/001876, and U.S. patent publication US 2003-0232407 A1). The entire disclosures of the articles, patent applications, and issued patents cited immediately above are hereby incorporated herein by reference, for all purposes, including their disclosures of the identities and structures of T2Rs and T1Rs mammalian taste receptor proteins and methods for artificially expressing those receptors in cell lines and using the resulting cell lines for screening compounds as potential "savory" or "sweet" flavoring agents.

Whereas the T2R family includes a family of over 25 genes that are involved in bitter taste perception, the T1Rs only includes three members, T1R1, T1R2 and T1R3. (*see* Li, *et al., Proc. Natl. Acad. Sci. USA* (2002) 99:4962-4966.) Recently it was disclosed in WO 02/064631 and/or WO 03/001876 that certain T1R members, when co-expressed in suitable mammalian cell lines, assemble to form functional taste receptors. Particularly it was found that co-expression of T1R1 and T1R3 in a suitable host cell results in a functional T1R1/T1R3 savory ("umami") taste receptor that responds to savory taste stimuli, including monosodium glutamate. Similarly, it was found that co-expression of T1R2 and T1R3 in a suitable host cell results in a functional T1R2/T1R3 "sweet" taste receptor that responds to different taste stimuli including naturally occurring and artificial sweeteners. (*See* Li, *et al.* (*Id.*). The references cited above also disclosed assays and/or high throughput screens that measure T1R1/T1R3 or T1R2/T1R3 receptor activity by fluorometric imaging in the presence of the target compounds. We employed the above-described assays and/or high throughput screening methods to identify initial "lead" compounds that modulate the activity of T1R1/T1R3 "savory" taste receptors, or T1R2/T1R3 "sweet" taste receptors, then embarked on a long, complex and iterative process of investigation, evaluation, and optimization, so as to arrive at the various inventions described below.

SUMMARY OF THE INVENTION

The invention has many aspects, all of which relate to methods of using or compositions containing certain non-naturally occurring amide compounds and/or amide derivative compounds having the generic structure shown below in Formula (I):



(I)

wherein R^1, R^2 and R^3 can be and are independently further defined in various ways, as is further detailed below. In all the embodiments of the amide compounds of Formula (I) the R^1 group is an organic residue comprising at least three carbon atoms, with a variety of alternative limits on the size and/or chemical characteristics of the R^1 group, as will be further described below. In many but not all embodiments, the amide compounds of Formula (I) are "primary" amides, *i.e.* one of R^2 and R^3 is an organic group comprising at least three carbon atoms, while the other of R^2 and R^3 is hydrogen.

The amide compounds of Formula (I) also comprise certain sub-classes of amide derivatives or classes of derivatives related to amides, such as for example ureas, urethanes, oxalamides, acrylamides, and the like, as will be further described below.

Some of the amide compounds of Formula (I) have been previously synthesized by methods known in the prior art for various purposes. Nevertheless, many of the amide compounds of Formula (I) disclosed herein are novel compounds that have not been previously synthesized at all. Nevertheless, to the knowledge of the inventors it has not been previously recognized that such amides can be utilized at very low concentrations in comestible compositions as savory or sweet flavoring agents, or savory or sweet taste enhancers.

Unexpectedly, we show below that many of the subgenuses and species of the "amide" compounds of Formula (I) are shown below to bind to and/or activate one or both of the T1R1/T1R3 "savory" ("umami") or T1R2/T1R3 sweet receptors *in-vitro*, at relatively low concentrations on the order of micromolar or lower concentrations. The amide compounds are also believed to similarly interact with savory or sweet flavor receptors of animals or humans *in vivo*, as has been confirmed by actual human taste tests of some of compounds of Formula (I).

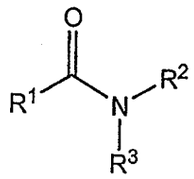
Accordingly, most or all of the subgenuses and species of the "amide" compounds of Formula (I) further described hereinbelow can, at useful and surprisingly low concentrations, be used in comestible compositions as savory or sweet flavoring agents, or savory or sweet agent enhancers. Accordingly, in some embodiments, the invention relates to methods for modulating the savory or sweet taste of a comestible or medicinal product comprising:

a) providing at least one comestible or medicinal product, or one or more precursors thereof, and

b) combining the comestible or medicinal product or one or more precursors thereof with at least a savory flavor modulating amount, or a sweet flavor modulating amount, of at least one non-naturally occurring amide compound, or a comestibly acceptable salt thereof, so as to form a modified comestible or medicinal product;

wherein the amide compound is within the scope of any of the compounds of Formula (I) as shown below, or any of its various subgenuses of compounds or species compounds as are further described below:

10



(I)

wherein R^1 comprises an organic or hydrocarbon residue having at least three carbon atoms and optionally one or more heteroatoms independently selected from oxygen, nitrogen, sulfur, halogens, or phosphorus; and

wherein optionally one of R^2 and R^3 is H, and wherein at least one of the other of R^2 and R^3 comprises an organic or hydrocarbon residue having at least three carbon atoms and optionally one or more heteroatoms independently selected from oxygen, nitrogen, sulfur, halogens, or phosphorus.

Additional optional limitations on the chemical and physical characteristics of the R^1, R^2, and R^3 groups will be described below.

The invention also relates to the comestible or medicinal products produced by the methods and/or processes mentioned above, and to comestible or medicinal products or compositions, or their precursors that contain the amide compounds of Formula (I), which include but are not necessarily limited to food, drink, medicinal products and compositions intended for oral administration, and the precursors thereof.

In many embodiments, one or more of the amide compounds of Formula (I) further identified, described, and/or claimed herein, or a comestibly acceptable salt thereof, can be used in mixtures or in combination with other known savory or sweet compounds, or used as flavor enhancers in comestible food, beverage and medicinal compositions, for human or animal consumption.

In some embodiments, the amide compounds of Formula (I), while having little or perhaps even no sweet or savory flavor when tasted in isolation, can be employed at very low concentrations in order to very significantly enhance the effectiveness of other savory or sweet flavor agents in a comestible or medicinal composition, or a precursor thereof. The inventions described herein also relate to the flavor-modified comestible or medicinal products that contain flavor modulating amounts of one or more of the amide compounds disclosed herein.

Many of the amide compounds of Formula (I) and/or its various subgenuses of amide compounds, when used together with MSG or alone, increase or modulate a response *in vitro,* and savory taste perception in humans at surprisingly low concentrations. Many of

the amide compounds of the invention are T1R1/T1R3 receptor agonists and accordingly can, at surprisingly low concentrations on the order of micromolar concentrations or less, induce savory taste perception in humans on their own, independently of the presence or absence of MSG in a comestible composition. Moreover, many of the amide compounds Formula (I) can enhance, potentiate, modulate or induce other natural and synthetic savory flavoring agents, such as MSG, for example.

In related embodiments of the compounds of Formula (I) and their uses, some of the amide compounds of Formula (I) are potent T1R2/T1R3 receptor agonists at concentrations of micromolar or less, but in many cases do not independently induce sweet taste perception in humans independently of the presence of other sweeteners. In other words, some of the amide compounds of Formula (I) are not perceived by human beings as being sweet tastants in isolation from other sweeteners. Nevertheless, many of these same amide compounds of Formula (I) can strongly enhance, potentiate, modulate or induce the perception in humans of the sweet taste of other natural, semi-synthetic, or synthetic sweet flavoring agents, such as for example sucrose, fructose, glucose, erythritol, isomalt, lactitol, mannitol, sorbitol, xylitol, certain known natural terpenoids, flavonoids, or protein sweeteners, aspartame, saccharin, acesulfame-K, cyclamate, sucralose, and alitame, and the like, or a mixture thereof.

Unexpectedly, it has also been discovered that in many embodiments of the compounds of Formula (I) there are significant structural similarities and/or overlaps between the amide compounds that can produce or enhance both the sweet and savory tastes of comestible or medicinal compositions, even though it is believed that the relevant biological taste receptor proteins are significantly different. Even more unexpectedly, it has been discovered that at least some of the amide compounds of Formula (I) disclosed herein can induce or enhance both the sweet and savory tastes of the comestible or medicinal products. Therefore in some aspects the invention is related to compounds of Formula (I) or its various subgenuses and species compounds that modulate (*e.g.*, induce, enhance or potentiate) the flavor of known natural or synthetic sweetener agents.

In some embodiments, the invention relates to novel compounds, flavoring agents, flavor enhancers, flavor modifying compounds, and/or compositions containing the compounds of Formula (I), and its various subgenuses and species compounds.

In other embodiments, the invention is directed to compounds of Formula (I) or its various subgenuses and species compounds that modulate (*e.g.*, induce, enhance or

potentiate) the flavor of monosodium glutamate (MSG), or synthetic savory flavoring agents.

In some embodiments, the invention relates to comestible or medicinal compositions suitable for human or animal consumption, or precursors thereof, containing at least one compound of Formula (I), or a comestibly or pharmaceutically acceptable salt thereof. These compositions will preferably include comestible products such as foods or beverages, medicinal products or compositions intended for oral administration, and oral hygiene products, and additives which when added to these products modulate the flavor or taste thereof, particularly by enhancing (increasing) the savory and/or sweet taste thereof.

The present invention also relates to novel genuses and species of amide compounds within the scope of the compounds of Formula (I), and derivatives, flavoring agents, comestible or medicinal products or compositions, including savory or sweet flavoring agents and flavor enhancers containing the same.

The foregoing discussion merely summarizes certain aspects of the inventions and is not intended, nor should it be construed, as limiting the invention in any way.

DETAILED DESCRIPTION OF THE INVENTION

The present invention can be understood more readily by reference to the following detailed description of various embodiments of the invention and the Examples included therein and to the chemical drawings and Tables and their previous and following description. Before the present compounds, compositions, and/or methods are disclosed and described, it is to be understood that unless otherwise specifically indicated by the claims, the invention is not limited to specific foods or food preparation methods, specific comestibles or pharmaceutical carriers or formulations, or to particular modes of formulating the compounds of the invention into comestible or medicinal products or compositions intended for oral administration, because as one of ordinary skill in relevant arts is well aware, such things can of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

DEFINITIONS

As used herein, the term "medicinal product" includes both solids and liquid compositions which are ingestible non-toxic materials which have medicinal value or comprise medicinally active agents such as cough syrups, cough drops, aspirin and chewable medicinal tablets.

An oral hygiene product includes solids and liquids such as toothpaste or mouthwash.

A "comestibly, biologically or medicinally acceptable carrier or excipient" is a solid or liquid medium and/or composition that is used to prepare a desired dosage form of the inventive compound, in order to administer the inventive compound in a dispersed/diluted form, so that the biological effectiveness of the inventive compound is maximized. A comestibly, biologically or medicinally acceptable carrier includes many common food ingredients, such as water at neutral, acidic, or basic pH, fruit or vegetable juices, vinegar, marinades, beer, wine, natural water/fat emulsions such as milk or condensed milk, edible oils and shortenings, fatty acids, low molecular weight oligomers of propylene glycol, glyceryl esters of fatty acids, and dispersions or emulsions of such hydrophobic substances in aqueous media, salts such as sodium chloride, wheat flours, solvents such as ethanol, solid edible diluents such as vegetable powders or flours, or other liquid vehicles; dispersion or suspension aids; surface active agents; isotonic agents; thickening or emulsifying agents, preservatives; solid binders; lubricants and the like.

A "flavor" herein refers to the perception of taste and/or smell in a subject, which include sweet, sour, salty, bitter, umami, and others. The subject may be a human or an animal.

A "flavoring agent" herein refers to a compound or a biologically acceptable salt thereof that induces a flavor or taste in an animal or a human.

A "flavor modifier" herein refers to a compound or biologically acceptable salt thereof that modulates, including enhancing or potentiating, and inducing, the tastes and/or smell of a natural or synthetic flavoring agent in an animal or a human.

A "flavor enhancer" herein refers to a compound or biologically acceptable salt thereof that enhances the tastes or smell of a natural or synthetic flavoring agent.

"Savory flavor" herein refers to the savory "umami" taste typically induced by MSG (mono sodium glutamate) in an animal or a human.

"Savory flavoring agent," "savory compound" or "savory receptor activating compound" herein refers to a compound or biologically acceptable salt thereof that elicits a detectable savory flavor in a subject, *e.g.*, MSG (mono sodium glutamate) or a compound that activates a T1R1/T1R3 receptor *in vitro*. The subject may be a human or an animal.

"Sweet flavoring agent," "sweet compound" or "sweet receptor activating compound" herein refers to a compound or biologically acceptable salt thereof that elicits a

detectable sweet flavor in a subject, *e.g.* sucrose, fructose, glucose, and other known natural saccharide-based sweeteners, or known artificial sweeteners such as saccharine, cyclamate, aspartame, and the like as is further discussed herein, or a compound that activates a T1R2/T1R3 receptor *in vitro*. The subject may be a human or an animal.

A "savory flavor modifier" herein refers to a compound or biologically acceptable salt thereof that modulates, including enhancing or potentiating, inducing, and blocking, the savory taste of a natural or synthetic savory flavoring agents, *e.g.*, monosodium glutamate (MSG) in an animal or a human.

A "sweet flavor modifier" herein refers to a compound or biologically acceptable salt thereof that modulates, including enhancing or potentiating, inducing, and blocking, the sweet taste of a natural or synthetic sweet flavoring agents, *e.g.*, sucrose, fructose, glucose, and other known natural saccharide-based sweeteners, or known artificial sweeteners such as saccharine, cyclamate, aspartame, and the like, in a animal or a human.

A "savory flavor enhancer" herein refers to a compound or biologically acceptable salt thereof that enhances or potentiates the savory taste of a natural or synthetic savory flavoring agents, *e.g.*, monosodium glutamate (MSG) in an animal or a human.

A "sweet flavor enhancer" herein refers to a compound or biologically acceptable salt thereof that enhances or potentiates the sweet taste of a natural or synthetic sweet flavoring agents, *e.g.*, sucrose, fructose, glucose, and other known natural saccharide-based sweeteners, or known artificial sweeteners such as saccharine, cyclamate, aspartame, and the like as is further discussed herein in an animal or a human.

An "umami receptor activating compound" herein refers to a compound that activates an umami receptor, such as a T1R1/T1R3 receptor.

A "sweet receptor activating compound" herein refers to a compound that activates a sweet receptor, such as a T1R2/T1R3 receptor.

An "umami receptor modulating compound" herein refers to a compound that modulates (activates, enhances or blocks) an umami receptor.

A "sweet receptor modulating compound" herein refers to a compound that modulates (activates, enhances or blocks) a sweet receptor.

An "umami receptor enhancing compound" herein refers to a compound that enhances or potentiates the effect of a natural or synthetic umami receptor activating compound, *e.g.*, monosodium glutamate (MSG).

A "sweet receptor enhancing compound" herein refers to a compound that enhances or potentiates the effect of a natural or synthetic sweet receptor activating compound, *e.g.*, sucrose, fructose, glucose, and other known natural saccharide-based sweeteners, or known artificial sweeteners such as saccharine, cyclamate, aspartame, and the like as is further discussed herein.

A "savory flavoring agent amount" herein refers to an amount of a compound (including the compounds of Formula (I), as well as known savory flavoring agents such as MSG) that is sufficient to induce savory taste in a comestible or medicinal product or composition, or a precursor thereof. A fairly broad range of a savory flavoring agent amount for the compounds of Formula (I) can be from about 0.001 ppm to 100 ppm, or a narrow range from about 0.1 ppm to about 10 ppm. Alternative ranges of savory flavoring agent amounts can be from about 0.01 ppm to about 30 ppm, from about 0.05 ppm to about 15 ppm, from about 0.1 ppm to about 5 ppm, or from about 0.1 ppm to about 3 ppm.

A "sweet flavoring agent amount" herein refers to an amount of a compound (including the compounds of Formula (I), as well as known sweeteners) that is sufficient to induce sweet taste in a comestible or medicinal product or composition, or a precursor thereof. A fairly broad range of a sweet flavoring agent amount for the compounds of Formula (I) can be from about 0.001 ppm to 100 ppm, or a narrow range from about 0.1 ppm to about 10 ppm. Alternative ranges of sweet flavoring agent amounts can be from about 0.01 ppm to about 30 ppm, from about 0.05 ppm to about 15 ppm, from about 0.1 ppm to about 5 ppm, or from about 0.1 ppm to about 3 ppm.

A "savory flavor modulating amount" herein refers to an amount of a compound of Formula (I) that is sufficient to alter (either increase or decrease) savory taste in a comestible or medicinal product or composition, or a precursor thereof, sufficiently to be perceived by a human subject. A fairly broad range of a savory flavor modulating amount can be from about 0.001 ppm to 100 ppm, or a narrow range from about 0.1 ppm to about 10 ppm. Alternative ranges of savory flavor modulating amounts can be from about 0.01 ppm to about 30 ppm, from about 0.05 ppm to about 15 ppm, from about 0.1 ppm to about 5 ppm, or from about 0.1 ppm to about 3 ppm.

A "sweet flavor modulating amount" herein refers to an amount of a compound of Formula (I) that is sufficient to alter (either increase or decrease) sweet taste in a comestible or medicinal product or composition, or a precursor thereof, sufficiently to be perceived by a human subject. A fairly broad range of a sweet flavor modulating amount can be from

16

about 0.001 ppm to 100 ppm, or a narrow range from about 0.1 ppm to about 10 ppm. Alternative ranges of sweet flavor modulating amounts can be from about 0.01 ppm to about 30 ppm, from about 0.05 ppm to about 15 ppm, from about 0.1 ppm to about 5 ppm, or from about 0.1 ppm to about 3 ppm.

A "savory flavor enhancing amount" herein refers to an amount of a compound for Formula (I) that is sufficient to enhance the taste of a natural or synthetic flavoring agents, *e.g.*, monosodium glutamate (MSG) when they are both present in a comestible or medicinal product or composition. A fairly broad range of a savory flavor enhancing amount can be from about 0.001 ppm to 100 ppm , or a narrow range from about 0.1 ppm to about 10 ppm. Alternative ranges of savory flavor enhancing amounts can be from about 0.01 ppm to about 30 ppm, from about 0.05 ppm to about 15 ppm, from about 0.1 ppm to about 5 ppm, or from about 0.1 ppm to about 3 ppm.

A "sweet flavor enhancing amount" herein refers to an amount of a compound of Formula (I) that is sufficient to enhance the taste of a natural or synthetic flavoring agents, *e.g.*, sucrose, fructose, glucose, and other known natural saccharide-based sweeteners, or known artificial sweeteners such as saccharine, cyclamate, aspertame, and the like as is further discussed herein) in a comestible or medicinal product or composition. A fairly broad range of a sweet flavor enhancing amount can be from about 0.001 ppm to 100 ppm, or a narrow range from about 0.1 ppm to about 10 ppm. Alternative ranges of sweet flavor enhancing amounts can be from about 0.01 ppm to about 30 ppm, from about 0.05 ppm to about 15 ppm, from about 0.1 ppm to about 5 ppm, or from about 0.1 ppm to about 3 ppm.

An "umami receptor modulating amount" herein refers to an amount of a compound that is sufficient to modulate (activate, enhance or block) an umami receptor. A preferable range of an umami receptor modulating amount is 1 pM to 100 mM and most preferably 1 nM to 100 μM and most preferably 1nM to 30 μM. A fairly broad range of a umami flavor enhancing amount can be from about 0.001 ppm to 100 ppm , or a narrow range from about 0.1 ppm to about 10 ppm. Alternative ranges of umami flavor enhancing amounts can be from about 0.01 ppm to about 30 ppm, from about 0.05 ppm to about 15 ppm, from about 0.1 ppm to about 5 ppm, or from about 0.1 ppm to about 3 ppm.

A "T1R1/T1R3 receptor modulating or activating amount" is an amount of compound that is sufficient to modulate or activate a T1R1/T1R3 receptor. These amounts are preferably the same as the umami receptor modulating amounts.

An "umami receptor" is a taste receptor that can be modulated by a savory compound. Preferably an umami receptor is a G protein coupled receptor, and more preferably the umami receptor is a T1R1/T1R3 receptor.

Compounds of the invention modulate an umami receptor and preferably are agonists of the T1R1/T1R3 receptor. An agonist of this receptor has the effect of activating the G protein signaling cascade. In many cases, this agonist effect of the compound on the receptor also produces a perceived savory flavor in a taste test. It is desirable, therefore, that such inventive compounds serve as a replacement for MSG, which is not tolerated by some in, for example, comestible products.

In addition, this agonist effect also is responsible for the synergistic savory taste effect, which occurs when a compound of the invention is combined with another savory flavoring agent such as MSG. The nucleotides, IMP or GMP, are conventionally added to MSG, to intensify the savory flavor of MSG, so that relatively less MSG is needed to provide the same savory flavor in comparison to MSG alone. Therefore, it is desirable that combining compounds of the invention with another savory flavoring agent such as MSG advantageously eliminates the need to add expensive nucleotides, such as IMP, as a flavor enhancer, while concomitantly reducing or eliminating the amount of a savory compound such as MSG needed to provide the same savory flavor in comparison to the savory compound or MSG alone.

A "sweet receptor modulating amount" herein refers to an amount of a compound that is sufficient to modulate (activate, enhance or block) a sweet receptor. A preferable range of a sweet receptor modulating amount is 1 pM to 100 mM and most preferably 1 nM to 100 μM and most preferably 1nM to 30 μM.

A "T1R2/T1R3 receptor modulating or activating amount" is an amount of compound that is sufficient to modulate or activate a T1R2/T1R3 receptor. These amounts are preferably the same as the sweet receptor modulating amounts.

A "sweet receptor" is a taste receptor that can be modulated by a sweet compound. Preferably a sweet receptor is a G protein coupled receptor, and more preferably the sweet receptor is a T1R2/T1R3 receptor.

Many compounds of Formula (I) can modulate a sweet receptor and preferably are agonists of the T1R2/T1R3 receptor. An agonist of this receptor has the effect of activating the G protein signaling cascade. In many cases, this agonist effect of the compound on the receptor also produces a perceived sweet flavor in a taste test. It is desirable, therefore, that

18

such inventive compounds serve as a replacement for sucrose, fructose, glucose, and other known natural saccharide-based sweeteners, or known artificial sweeteners such as saccharine, cyclamate, aspartame, and the like, or mixtures thereof as is further discussed herein.

A "synergistic effect" relates to the enhanced savory and/or sweet flavor of a combination of savory and/or or sweet compounds or receptor activating compounds, in comparison to the sum of the taste effects or flavor associated effects associated with each individual compound. In the case of savory enhancer compounds, a synergistic effect on the effectiveness of MSG may be indicated for a compound of Formula (I) having an EC50 ratio (defined hereinbelow) of 2.0 or more, or preferably 5.0 or more, or 10.0 or more, or 15.0 or more. An EC50 assay for sweet enhancement has not yet been developed, but in the case of both savory and sweet enhancer compounds, a synergistic effect can be confirmed by human taste tests, as described elsewhere herein.

When the compounds described here include one or more chiral centers, the stereochemistry of such chiral centers can independently be in the R or S configuration, or a mixture of the two. The chiral centers can be further designated as R or S or R,S or d,D, l,L or d,l, D,L. Correspondingly, the amide compounds of the invention, if they can be present in optically active form, can actually be present in the form of a racemic mixture of enantiomers, or in the form of either of the separate enantiomers in substantially isolated and purified form, or as a mixture comprising any relative proportions of the enantiomers.

Regarding the compounds described herein, the suffix "ene" added to any of the described terms means that the substituent is connected to two other parts in the compound. For example, "alkylene " is $(CH_2)_n$, "alkenylene" is such a moiety that contains a double bond and "alkynylene" is such a moiety that contains a triple bond.

As used herein, "hydrocarbon residue" refers to a chemical sub-group or radical within a larger chemical compound which contains only carbon and hydrogen atoms. The hydrocarbon residue may be aliphatic or aromatic, straight-chain, cyclic, branched, saturated or unsaturated. In many embodiments the hydrocarbon residues are of limited dimensional size and molecular weight, and may comprise 1 to 18 carbon atoms, 1 to 16 carbon atoms, 1 to 12 carbon atoms, 1 to 10 carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms.

The hydrocarbon residue, when described as "substituted" , contains or is substituted with one or more independently selected heteroatoms such as O, S, N, P, or the

halogens (fluorine, chlorine, bromine, and iodine), or one or more substituent groups containing heteroatoms (OH, NH_2, NO_2, SO_3H, and the like) over and above the carbon and hydrogen atoms of the substituent residue. Substituted hydrocarbon residues may also contain carbonyl groups, amino groups, hydroxyl groups and the like, or contain heteroatoms inserted into the "backbone" of the hydrocarbon residue.

As used herein, "inorganic" group or residue refers to a neutral, cationic, or anionic radical substituents on the organic molecules disclosed or claimed herein that have from one to 16 atoms that do not include carbon, but do contain other heteroatoms from the periodic table that preferably include one or more atoms independently selected from the group consisting of H, O, N, S, one or more halogens, or alkali metal or alkaline earth metal ions. Examples of inorganic radicals include, but are not limited to H, Na+, Ca++ and K+, halogens which include fluorine, chlorine, bromine, and iodine, OH, SH, SO_3H, SO_3^-, PO_3H, PO_3^-, NO, NO_2 or NH_2, and the like.

As used herein, the term "alkyl," "alkenyl" and "alkynyl" include straight- and branched-chain and cyclic monovalent substituents that respectively are saturated, unsaturated with at least one double bond, and unsaturated with at least one triple bond.

"Alkyl" refers to a hydrocarbon group that can be conceptually formed from an alkane by removing hydrogen from the structure of a non-cyclic hydrocarbon compound having straight or branched carbon chains, and replacing the hydrogen atom with another atom or organic or inorganic substitutent group. In some embodiments of the invention, the alkyl groups are "C1 to C6 alkyl" such as methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, amyl, tert-amyl, hexyl and the like. Many embodiments of the invention comprise "C1 to C4 alkyl" groups (alternatively termed "lower alkyl" groups) that include methyl, ethyl, propyl, iso-propyl n-butyl, iso-butyl, sec-butyl, and t-butyl groups. Some of the preferred alkyl groups of the invention have three or more carbon atoms preferably 3 to 16 carbon atoms, 4 to 14 carbon atoms, or 6 to 12 carbon atoms.

The term"alkenyl"denotes a hydrocarbon group or residue that comprises at least one carbon-carbon double bond. In some embodiments, alkenyl groups are "C_2 to C_7 alkenyls" which are exemplified by vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, as well as dienes and trienes of straight and branched chains. In other embodiments, alkenyls are limited to two to four carbon atoms.

The term "alkynyl" denotes a hydrocarbon residue that comprises at least one carbon-carbon triple bond. Preferred alkynyl groups are "C2 to C7 alkynyl" such as ethynyl, propynyl, 2-butynyl, 2-pentynyl, 3-pentynyl, 2- hexynyl, 3-hexynyl, 4-hexynyl, 2-heptynyl, 3-heptynyl, 4- heptynyl, 5-heptynyl as well as di- and tri-ynes of straight and branched chains including ene-ynes.

The terms "substituted alkyl," "substituted alkenyl," "substituted alkynyl," and "substituted alkylene" denote that the alkyl, alkenyl, alkynyl and alkylene groups or radicals as described above have had one or more hydrogen atoms substituted by one or more, and preferably one or two organic or inorganic substituent groups or radicals, that can include halogen, hydroxy, C_1 to C_7 alkoxy, alkoxy-alkyl, oxo, C_3 to C_7 cycloalkyl, naphthyl, amino, (monosubstituted)amino, (disubstituted)amino, guanidino, heterocycle, substituted heterocycle, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_7 acyl, C_1 to C_7 acyloxy, nitro, carboxy, carbamoyl, carboxamide, N-(C_1 to C_6 alkyl)carboxamide, N,N-di(C_1 to C_6 alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C_1 to C_4 alkylthio or C_1 to C_4 alkylsulfonyl groups. The substituted alkyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents. In many embodiments of the invention, a preferred group of substituent groups include hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups. In many embodiments of the invention that comprise the above lists of substituent groups, an even more preferred group of substituent groups include hydroxy, SEt, SCH_3, methyl, ethyl, isopropyl, trifluromethyl, methoxy, ethoxy, and trifluoromethoxy groups.

Examples of the above substituted alkyl groups include the 2-oxo-prop-1-yl, 3-oxo-but-1-yl, cyanomethyl, nitromethyl, chloromethyl, trifluoromethyl, hydroxymethyl, tetrahydropyranyloxymethyl, trityloxymethyl, propionyloxymethyl, aminomethyl, carboxymethyl, allyloxycarbonylmethyl, allyloxycarbonylaminomethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, trifluoromethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-aminopropyl, 1-chloroethyl, 2-chloroethyl, 1-bromoethyl, 2-chloroethyl, 1-fluoroethyl, 2-fluoroethyl, 1- iodoethyl, 2-iodoethyl, 1-chloropropyl, 2-chloropropyl, 3- chloropropyl, 1-bromopropyl, 2-bromopropyl, 3-bromopropyl, 1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 2-aminoethyl, 1-aminoethyl, N-benzoyl-2-aminoethyl, N-acetyl-2-aminoethyl, N-benzoyl-1-aminoethyl, N-acetyl-1-aminoethyl and the like.

Examples of substituted alkenyl groups include styrenyl, 3-chloro-propen-1-yl, 3-chloro-buten-1-yl, 3-methoxy-propen-2-yl, 3-phenyl-buten-2-yl, 1-cyano-buten-3-yl and the like. The geometrical isomerism is not critical, and all geometrical isomers for a given substituted double bond can be included.

Examples of substituted alkynyl groups include phenylacetylen-1-yl, 1-phenyl-2-propyn-1-yl and the like.

Haloalkyls are substituted alkyl groups or residues wherein one or more hydrogens of the corresponding alkyl group have been replaced with a halogen atom (fluorine, chlorine, bromine, and iodine). Preferred haloalkyls can have one to four carbon atoms. Examples of preferred haloalkyl groups include trifluoromethyl and pentafluoroethyl groups.

Haloalkoxy groups alkoxy groups or residues wherein one or more hydrogens from the R group of the alkoxy group are a halogen atom (fluorine, chlorine, bromine, and iodine). Preferred haloalkoxy groups s can have one to four carbon atoms. Examples of preferred haloalkoxy groups include trifluoromethyoxy and pentafluoroethoxy groups.

The term "oxo" denotes a carbon atom bonded to two additional carbon atoms substituted with an oxygen atom doubly bonded to the carbon atom, thereby forming a ketone radical or residue.

"Alkoxy" or "alkoxyl" refers to an -OR radical or group, wherein R is an alkyl radical. In some embodiments the alkoxy groups can be C_1 to C_8, and in other embodiments can be C_1 to C_4 alkoxy groups wherein R is a lower alkyl, such as a methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and like alkoxy groups. The term "substituted alkoxy" means that the R group is a substituted alkyl group or residue. Examples of substituted alkoxy groups include trifluoromethoxy, hydroxymethyl, hydroxyethyl, hydroxypropyl, and alkoxyalkyl groups such as methoxymethyl, methoxyethyl, polyoxoethylene, polyoxopropylene, and similar groups.

"Alkoxyalkyl" refers to an –R-O-R' group or radical, wherein R and R' are alkyl groups. In some embodiments the alkoxyalkyl groups can be C_1 to C_8, and in other embodiments can be C_1 to C_4. In many embodiments, both R and R' are a lower alkyl, such as a methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and like alkoxy groups. Examples of alkoxyalkyl groups include, methoxymethyl, ethoxyethyl, methoxypropyl, and methoxybutyl and similar groups.

"Hydroxyalkyl" refers to an –R-OH group or radical, wherein R is an alkyl group. In some embodiments the hydoxyalkyl groups can be C_1 to C_8, and in other embodiments can be C_1 to C_4. In many embodiments, R is a lower alkyl. Examples of alkoxyalkyl groups include, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl 3-hydroxypropyl, and similar groups.

"Acyloxy" refers to an RCO_2- ester group where R is an alkyl, cycloalkyl, aryl, heteroaryl, substituted alkyl, substituted cycloalkyl, substituted aryl, or substituted heteraryl group or radical wherein the R radical comprises one to seven or one to four carbon atoms. In many embodiments, R is an alkyl radical, and such acyloxy radicals are exemplified by formyloxy, acetoxy, propionyloxy, butyryloxy, pivaloyloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy and the like. In other embodiments the R groups are C_1-C_4 alkyls.

As used herein, "acyl" encompasses the definitions of alkyl, alkenyl, alkynyl and the related hetero-forms which are coupled to an additional organic residue through a carbonyl group to form a ketone radical or group. Preferred acyl groups are "C_1 to C_7 acyl" such as formyl, acetyl, propionyl, butyryl, pentanoyl, pivaloyl, hexanoyl, heptanoyl, benzoyl and the like. More preferred acyl groups are acetyl and benzoyl.

The term "substituted acyl" denotes an acyl group wherein the R group substituted by one or more, and preferably one or two, halogen, hydroxy, oxo, alkyl, cycloalkyl, naphthyl, amino, (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_7 alkoxy, alkoxy-alkyl, C_1 to C_7 acyl, C1 to C7 acyloxy, nitro, C_1 to C_6 alkyl ester, carboxy, alkoxycarbonyl, carbamoyl, carboxamide, N-(C_1 to C_6 alkyl)carboxamide, N,N-di(C_1 to C_6 alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C_1 to C_4 alkylthio or C_1 to C_4 alkylsulfonyl groups. The substituted acyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

Examples of C_1 to C_7 substituted acyl groups include 4-phenylbutyroyl, 3-phenylbutyroyl, 3 phenylpropanoyl, 2- cyclohexanylacetyl, cyclohexanecarbonyl, 2-furanoyl and 3 dimethylaminobenzoyl.

Cycloalkyl residues or groups are structurally related to cyclic monocylic or bicyclic hydrocarbon compounds wherein one or more hydrogen atoms have been replaced with an organic or inorganic substituent group. The cycloalkyls of the current inventions comprise at least 3 up to 12, or more preferably 3 to 8 ring carbon atoms, or more preferably 4 to 6 ring carbon atoms. Examples of such cyclalkyl residues include cyclopropyl, cyclobutyl,

cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl rings, and saturated bicyclic or fused polycyclic cycloalkanes such as decalin groups, polycyclic norbornyl or adamantly groups, and the like.

Preferred cycloalkyl groups include "C3 to C7 cycloalkyl" such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl rings. Similarly, the term "C5 to C7 cycloalkyl" includes cyclopentyl, cyclohexyl or cycloheptyl rings.

"Substituted cycloalkyl" denote a cycloalkyl rings as defined above, substituted by 1 to four, or preferably one or two substituents independently selected from a halogen, hydroxy, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfoxide, C_1 to C_4 alkylsulfonyl, C_1 to C_4 substituted alkylthio, C_1 to C_4 substituted alkylsulfoxide, C_1 to C_4 substituted alkylsulfonyl, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, C_1 to C_6 substituted alkyl, C_1 to C_4 alkoxy-alkyl, oxo (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, phenyl, substituted phenyl, phenylthio, phenylsulfoxide, phenylsulfonyl, amino. In many embodiments of substituted cycloalkyl groups, the substituted cycloalkyl group will have 1, 2, 3, or 4 substituent groups independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

The term "cycloalkylene" means a cycloalkyl, as defined above, where the cycloalkyl radical is bonded at two positions connecting together two separate additional groups. Similarly, the term "substituted cycloalkylene" means a cycloalkylene where the cycloalkyl radical is bonded at two positions connecting together two separate additional groups and further bearing at least one additional substituent.

The term "cycloalkenyl" indicates preferably a 1,2, or 3-cyclopentenyl ring, a 1,2,3 or 4-cyclohexenyl ring or a 1,2,3,4 or 5-cycloheptenyl ring, while the term "substituted cycloalkenyl" denotes the above cycloalkenyl rings substituted with a substituent, preferably by a C_1 to C_6 alkyl, halogen, hydroxy, C_1 to C_7 alkoxy, alkoxy-alkyl, trifluoromethyl, carboxy, alkoxycarbonyl oxo, (monosubstituted)amino, (disubstituted)amino, phenyl, substituted phenyl, amino, or protected amino.

The term "cycloalkenylene" is a cycloalkenyl ring, as defined above, where the cycloalkenyl radical is bonded at two positions connecting together two separate additional groups. Similarly, the term "substituted cycloalkenylene" means a cycloalkenylene further substituted preferably by halogen, hydroxy, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfoxide, C_1 to C_4 alkylsulfonyl, C_1 to C_4 substituted alkylthio, C_1 to C_4 substituted alkylsulfoxide, C_1 to

C_4 substituted alkylsulfonyl, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy-alkyl, oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, alkoxycarbonyl, phenyl, substituted phenyl, phenylthio, phenylsulfoxide, phenylsulfonyl, amino, or substituted amino group.

The term "heterocycle" or "heterocyclic ring" denotes optionally substituted 3 to 8-membered rings having one or more carbon atoms connected in a ring that also comprise 1 to 5 ring heteroatoms, such as oxygen, sulfur and/or nitrogen inserted into the ring. These heterocyclic rings can be saturated, unsaturated or partially unsaturated, but are preferably saturated. An "amino-substituted heterocyclic ring" means any one of the above-described heterocyclic rings is substituted with at least one amino group. Preferred unsaturated heterocyclic rings include furanyl, thiofuranyl, pyrrolyl, pyridyl, pyrimidyl, pyrazinyl, benzoxazole, benzthiazole,quinolinlyl, and like heteroaromatic rings. Preferred saturated heterocyclic rings include piperidyl, aziridinyl, piperidinyl, piperazinyl, tetrahydrofurano, pyrrolyl, and tetrahydrothiophen-yl. rings.

The term "substituted heterocycle" or "substituted heterocyclic ring" means the above-described heterocyclic ring is substituted with, for example, one or more, and preferably one or two, substituents which are the same or different which substituents preferably can be halogen, hydroxy, thio, alkylthio, cyano, nitro, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, C_1 to C_4 substituted alkoxy, alkoxy-alkyl, C_1 to C_4 acyl, C_1 to C_4 acyloxy, carboxy, alkoxycarbonyl, carboxymethyl, hydroxymethyl, alkoxy-alkyl amino, monosubstituted)amino, (disubstituted)amino carboxamide, N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino groups, or substituted with a fused ring, such as benzo-ring. In many embodiments of substituted heterocyclic groups, the substituted cycloalkyl group will have 1, 2, 3, or 4 substituent groups independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

An "aryl" groups refers to a monocyclic, linked bicyclic or fused bicyclic radical or group comprising at least one six membered aromatic "benzene" ring. Aryl groups preferably comprise between 6 and 12 ring carbon atoms, and are exemplified by phenyl, biphenyl, naphthyl indanyl, and tetrahydronapthyl groups. Aryl groups can be optionally substituted with various organic and/or inorganic substitutent groups, wherein the

substituted aryl group in combination with all its substituents comprise between 6 and 18, or preferably 6 and 16 total carbon atoms. Preferred optional substituent groups include 1, 2, 3, or 4 substituent groups independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

The term "heteroaryl" means a heterocyclic aryl derivative which preferably contains a five-membered or six-membered conjugated and aromatic ring system having from 1 to 4 heteroatoms independently selected from oxygen, sulfur and/or nitrogen, inserted into the unsaturated and conjugated heterocyclic ring. Heteroaryl groups include monocyclic heteroaromatic, linked bicyclic heteroaromatic or fused bicyclic heteroaromatic moieties. Examples of heteroaryls include pyridinyl, pyrimidinyl, and pyrazinyl, pyridazinyl, pyrrolyl, furanyl, thiofuranyl, oxazoloyl, isoxazolyl, phthalimido, thiazolyl, quinolinyl, isoquinolinyl, indolyl, or a furan or thiofuran directly bonded to a phenyl, pyridyl, or pyrrolyl ring and like unsaturated and conjugated heteroaromatic rings. Any monocyclic, linked bicyclic, or fused bicyclic heteroaryl ring system which has the characteristics of aromaticity in terms of electron distribution throughout the ring system is included in this definition. Typically, the heteroaromatic ring systems contain 3-12 ring carbon atoms and 1 to 5 ring heteroatoms independently selected from oxygen, nitrogen, and sulfur atoms.

The term "substituted heteroaryl" means the above-described heteroaryl is substituted with, for example, one or more, and preferably one or two, substituents which are the same or different which substituents preferably can be halogen, hydroxy, protected hydroxy, thio, alkylthio, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, alkoxy-alkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, alkoxycarbonyl, carboxymethyl, hydroxymethyl, amino, (monosubstituted)amino, (disubstituted)amino, carboxamide, N-(C1 to C6 alkyl)carboxamide, N, N-di(C1 to C6 alkyl)carboxamide, trifluoromethyl, N-((C1 to C6 alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino groups. In many embodiments of substituted heteroaryl groups, the substituted cycloalkyl group will have 1, 2, 3, or 4 substituent groups independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

Similarly, "arylalkyl" and "heteroarylalkyl" refer to aromatic and heteroaromatic systems which are coupled to another residue through a carbon chain, including substituted or unsubstituted, saturated or unsaturated, carbon chains, typically of 1-6C. These carbon chains may also include a carbonyl group, thus making them able to provide substituents as an acyl moiety. Preferably, arylalkyl or heteroarylalkyl is an alkyl group substituted at any position by an aryl group, substituted aryl, heteroaryl or substituted heteroaryl. Preferred groups also include benzyl, 2-phenylethyl, 3-phenyl-propyl, 4-phenyl-n-butyl, 3-phenyl-n-amyl, 3-phenyl-2-butyl, 2-pyridinylmethyl, 2-(2-pyridinyl)ethyl, and the like.

The term "substituted arylalkyl" denotes an arylalkyl group substituted on the alkyl portion with one or more, and preferably one or two, groups preferably chosen from halogen, hydroxy, oxo, amino, (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, alkoxy-alkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, nitro, carboxy, alkoxycarbonyl, carbamoyl, carboxamide, N-(C_1 to C_6 alkyl)carboxamide, N, N-(C_1 to C_6 dialkyl)carboxamide, cyano, N-(C_1 to C_6 alkylsulfonyl)amino, thiol, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfonyl groups; and/or the phenyl group may be substituted with one or more, and preferably one or two, substituents preferably chosen from halogen, hydroxy, protected hydroxy, thio, alkylthio, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, alkoxy-alkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, alkoxycarbonyl, carboxymethyl, hydroxymethyl, amino, (monosubstituted)amino, (disubstituted)amino, carboxamide, N-(C_1 to C_6 alkyl) carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C1 to C6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino, cyclic C_2 to C_7 alkylene or a phenyl group, substituted or unsubstituted, for a resulting biphenyl group. The substituted alkyl or phenyl groups may be substituted with one or more, and preferably one or two, substituents which can be the same or different.

Examples of the term "substituted arylalkyl" include groups such as 2-phenyl-1-chloroethyl, 2-(4-methoxyphenyl)ethyl, 4-(2,6-dihydroxy phenyl)-n-hexyl, 2-(5-cyano-3-methoxyphenyl)-n-pentyl, 3-(2,6-dimethylphenyl)propyl, 4-chloro-3-aminobenzyl, 6-(4-methoxyphenyl)-3-carboxy-n-hexyl, 5-(4-aminomethylphenyl)- 3-(aminomethyl)-n-pentyl, 5-phenyl-3-oxo-n-pent-1-yl and the like.

The term "arylalkylene" specifies an arylalkyl, as defined above, where the arylalkyl radical is bonded at two positions connecting together two separate additional groups. The definition includes groups of the formula: -phenyl-alkyl- and alkyl-phenyl-alkyl-. Substitutions on the phenyl ring can be 1,2, 1,3 or 1,4. The term "substituted arylalkylene" is an arylalkylene as defined above that is further substituted preferably by halogen, hydroxy, protected hydroxy, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfoxide, C_1 to C_4 alkylsulfonyl, C_1 to C_4 substituted alkylthio, C_1 to C_4 substituted alkylsulfoxide, C_1 to C_4 substituted alkylsulfonyl, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy-alkyl, oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, alkoxycarbonyl, phenyl, substituted phenyl, phenylthio, phenylsulfoxide, phenylsulfonyl, amino, or protected amino group on the phenyl ring or on the alkyl group.

The term "substituted phenyl" specifies a phenyl group substituted with one or more, and preferably one or two, moieties preferably chosen from the groups consisting of halogen, hydroxy, protected hydroxy, thio, alkylthio, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, alkoxy-alkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, alkoxycarbonyl, carboxymethyl, hydroxymethyl, amino, (monosubstituted)amino, (disubstituted)amino, carboxamide, N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or phenyl, wherein the phenyl is substituted or unsubstituted, such that, for example, a biphenyl results. In many embodiments of substituted phenyl groups, the substituted cycloalkyl group will have 1, 2, 3, or 4 substituent groups independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

The term "phenoxy" denotes a phenyl bonded to an oxygen atom. The term "substituted phenoxy" specifies a phenoxy group substituted with one or more, and preferably one or two, moieties preferably chosen from the groups consisting of halogen, hydroxy, protected hydroxy, thio, alkylthio, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, alkoxy-alkyl, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, alkoxycarbonyl, carboxymethyl, hydroxymethyl, amino, (monosubstituted)amino, (disubstituted)amino, carboxamide, N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C1 to C6 alkyl)carboxamide, trifluoromethyl, N-((C1 to C6 alkyl)sulfonyl)amino and N-phenylsulfonyl)amino.

The term "substituted phenylalkoxy" denotes a phenylalkoxy group wherein the alkyl portion is substituted with one or more, and preferably one or two, groups preferably selected from halogen, hydroxy, protected hydroxy, oxo, amino, (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, C_1 to C_7 alkoxy, alkoxy-alkyl, C_1 to C_7 acyl, C_1 to C_7 acyloxy, nitro, carboxy, alkoxycarbonyl, carbamoyl, carboxamide, N-(C_1 to C_6 alkyl)carboxamide, N, N-(C_1 to C_6 dialkyl)carboxamide, cyano, N-(C_1 to C_6 alkylsulfonyl)amino, thiol, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfonyl groups; and/or the phenyl group can be substituted with one or more, and preferably one or two, substituents preferably chosen from halogen, hydroxy, protected hydroxy, thio, alkylthio, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, alkoxy-alkyl, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, alkoxycarbonyl carboxymethyl, hydroxymethyl, amino, (monosubstituted)amino, (disubstituted)amino, carboxamide, N-(C_1 to C_6 alkyl) carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N ((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or a phenyl group, substituted or unsubstituted, for a resulting biphenyl group. The substituted alkyl or phenyl groups may be substituted with one or more, and preferably one or two, substituents which can be the same or different.

The term "substituted naphthyl" specifies a naphthyl group substituted with one or more, and preferably one or two, moieties either on the same ring or on different rings chosen from the groups consisting of halogen, hydroxy, protected hydroxy, thio, alkylthio, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, alkoxy-alkyl, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, alkoxycarbonyl, carboxymethyl, hydroxymethyl, amino, (monosubstituted)amino, (disubstituted)amino, carboxamide, N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino or N (phenylsulfonyl)amino.

The terms "halo" and "halogen" refer to the fluoro, chloro, bromo or iodo atoms. There can be one or more halogen, which are the same or different. Preferred halogens are chloro and fluoro. Although many of the compounds of the invention having halogen atoms as substituents are highlky effective in binding to the relevant taste receptors, such halogenated organic compounds can in some cases have undesirable toxicological properties when administered to an animal in vivo. Therefore, in many embodiments of the compounds of Formula (I), if a halogen atom (including a fluoro or chloro atom) is listed as

29

a possible substitutent, an alternative and preferred group of substitutents expressly contemplated hereby would NOT include the halogen groups.

The term "(monosubstituted)amino" refers to an amino (NHR) group wherein the R group is chosen from the group consisting of phenyl, C_6-C_{10} substituted phenyl, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_2 to C_7 alkenyl, C_2 to C_7 substituted alkenyl, C_2 to C_7 alkynyl, C_2 to C_7 substituted alkynyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl and heterocyclic ring. The (monosubstituted)amino can additionally have an amino-protecting group as encompassed by the term "protected (monosubstituted)amino."

The term "(disubstituted)amino" refers to an amino group (NR2) with two substituents independently chosen from the group consisting of phenyl, C_6-C_{10} substituted phenyl, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 acyl, C_2 to C_7 alkenyl, C_2 to C_7 alkynyl, C_7 to C_{12} phenylalkyl, and C_7 to C_{12} substituted phenylalkyl. The two substituents can be the same or different.

The term "amino-protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups of the molecule. The term "protected (monosubstituted)amino" means there is an amino-protecting group on the monosubstituted amino nitrogen atom. In addition, the term "protected carboxamide" means there is an amino-protecting group on the carboxamide nitrogen. Similarly, the term "protected N-(C_1 to C_6 alkyl)carboxamide" means there is an amino-protecting group on the carboxamide nitrogen.

The term "alkylthio" refers to -SR groups wherein R is an optionally substituted C_1-C_7 or C_1-C_4organic group, preferably an alkyl, cycloalkyl, aryl, or heterocyclic group, such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, t-butylthio and like groups.

The term "alkylsulfoxide" indicates $-SO_2R$ groups wherein R is an optionally substituted C_1-C_7 or C_1-C_4organic group, preferably an alkyl, cycloalkyl, aryl, or heterocyclic group, such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, t-butylthio and like groups ,such as methylsulfoxide, ethylsulfoxide, n-propylsulfoxide, isopropylsulfoxide, n-butylsulfoxide, sec-butylsulfoxide and the like.

The term "alkylsulfonyl" indicates –S(O)R groups wherein R is an optionally substituted C_1-C_7 or C_1-C_4 organic group, which include for example groups such as

methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, t-butylsulfonyl and the like.

The terms "phenylthio," "phenylsulfoxide," and "phenylsulfonyl" specify a sulfoxide (–S(O)-R) , or sulfone (-SO_2R)wherein the R group is a phenyl group. The terms "substituted phenylthio," "substituted phenylsulfoxide," and "substituted phenylsulfonyl" means that the phenyl of these groups can be substituted as described above in relation to "substituted phenyl."

The term "alkoxycarbonyl" means an "alkoxy" group attached to a carobonyl group, (-C(O)-OR, wherein R is an alkyl group, preferably a C_1-C_4 alkyl group. The term "substituted alkoxycarbonyl" denotes a substituted alkoxy bonded to the carbonyl group, which alkoxy may be substituted as described above in relation to substituted alkyl.

The term "phenylene" means a phenyl group where the phenyl radical is bonded at two positions connecting together two separate additional groups. Examples of "phenylene" include 1,2-phenylene, 1,3-phenylene, and 1,4-phenylene.

The term "substituted alkylene" means an alkyl group where the alkyl radical is bonded at two positions connecting together two separate additional groups and further bearing an additional substituent. Examples of "substituted alkylene" includes aminomethylene, 1-(amino)-1,2-ethyl, 2-(amino)-1,2-ethyl, 1-(acetamido)-1,2-ethyl, 2-(acetamido)-1,2-ethyl, 2-hydroxy-1,1-ethyl, 1-(amino)-1,3-propyl.

The term "substituted phenylene" means a phenyl group where the phenyl radical is bonded at two positions connecting together two separate additional groups, wherein the phenyl is substituted as described above in relation to "substituted phenyl."

The terms "cyclic alkylene," "substituted cyclic alkylene," "cyclic heteroalkylene," and "substituted cyclic heteroalkylene," defines such a cyclic group or radical pbonded ("fused") to a phenyl radical, resulting in a fused bicyclic ring group or radical. The non-fused members of the cyclic alkylene or heteralkylene ring may contain one or two double bonds, or often are saturated. Furthermore, the non-fused members of the cyclic alkylene or heteralkylene ring, can have one or two methylene or methine groups replaced by one or two oxygen, nitrogen or sulfur atoms, or NH, NR, S(O) or SO2 groups, where R is a lower alkyl group.

The cyclic alkylene or heteroalkylene group may be substituted once or twice by the same or different substituents preferably selected from the group consisting of the following moieties: hydroxy, protected hydroxy, carboxy, protected carboxy, oxo, protected oxo, C_1 to

C_4 acyloxy, formyl, C_1 to C_7 acyl, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfoxide, C_1 to C_4 alkylsulfonyl, halo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, hydroxymethyl or a protected hydroxymethyl. The cyclic alkylene or heteroalkylene group fused onto the benzene radical can contain two to ten ring members, but it preferably contains three to six members. Examples of saturated cyclic alkylene groups are 2,3-dihydro-indanyl and a tetralin ring systems. When the cyclic groups are unsaturated, examples include a naphthyl ring or indolyl group or radical. Examples of fused cyclic groups which each contain one nitrogen atom and one or more double bond, preferably one or two double bonds, are when the benzene radical is fused to a pyridyl, pyranyl, pyrrolyl, pyridinyl, dihydropyrolyl, or dihydropyridinyl groups or radicals. Examples of fused cyclic groups which each contain one oxygen atom and one or two double bonds are illustrated by a benzene radical ring fused to a furnanyl, pyranyl, dihydrofuranyl, or dihydropyranyl ring. Examples of fused cyclic groups which each have one sulfur atom and contain one or two double bonds are when the benzene radical is fused to a thienyl, thiopyranyl, dihydrothienyl or dihydrothiopyranyl ring. Examples of cyclic groups which contain two heteroatoms selected from sulfur and nitrogen and one or two double bonds are when the benzene radical ring is fused to a thiazolyl, isothiazolyl, dihydrothiazolyl or dihydroisothiazolyl ring. Examples of cyclic groups which contain two heteroatoms selected from oxygen and nitrogen and one or two double bonds are when the benzene ring is fused to an oxazolyl, isoxazolyl, dihydrooxazolyl or dihydroisoxazolyl ring. Examples of cyclic groups which contain two nitrogen heteroatoms and one or two double bonds occur when the benzene ring is fused to a pyrazolyl, imidazolyl, dihydropyrazolyl or dihydroimidazolyl ring or pyrazinyl.

The term "carbamoyl" refers to a carbamate group or radical, which often derived from the reaction of an organic isocyanate compound R_1-NCO with an alcohol R_2-OH, to yield a carbamate compound having the structure R_1-NH-C(O)-OR_2 wherein the nature of the R_1 and R_2 radicals are further defined by the circumstances.

One or more of the compounds of the invention, may be present as a salt. The term "salt" encompasses those salts that form with the carboxylate anions and amine nitrogens and include salts formed with the organic and inorganic anions and cations discussed below. Furthermore, the term includes salts that form by standard acid-base reactions with basic groups (such as nitrogen containing heterocycles or amino groups) and organic or inorganic acids. Such acids include hydrochloric, hydrofluoric, trifluoroacetic, sulfuric, phosphoric,

acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, D-camphoric, glutaric, phthalic, tartaric, lauric, stearic, salicyclic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and like acids.

The term "organic or inorganic cation" refers to positively charged counter-ions for the carboxylate anion of a carboxylate salt. Inorganic positively charged counter-ions include but are not limited to the alkali and alkaline earth metals, (such as lithium, sodium, potassium, calcium, magnesium, *etc.*) and other divalent and trivalent metallic cations such as barium, aluminum and the like, and ammonium $(NH_4)^+$ cations. Organic cations include ammonium cations derived from acid treatment or alkylation of primary-, secondary, or tertiary amines such as trimethylamine, cyclohexylamine; and the organic cations, such as dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzylammonium, dibenzylethylenediammonium, and like cations. *See*, for example, "Pharmaceutical Salts," Berge, *et al., J. Pharm. Sci.* (1977) 66:1-19, which is incorporated herein by reference. Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, and the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine and arginine. Furthermore, any zwitterionic form of the instant compounds formed by a carboxylic acid and an amino group is referred to by this term. For example, a cation for a carboxylate anion will exist when R^2 or R^3 is substituted with a (quaternary ammonium)methyl group. A preferred cation for the carboxylate anion is the sodium cation.

The compounds of the invention can also exist as solvates and hydrates. Thus, these compounds may crystallize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of the mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

The term "amino acid" includes any one of the twenty naturally-occurring amino acids or the D-form of any one of the naturally-occurring amino acids. In addition, the term "amino acid" also includes other non-naturally occurring amino acids besides the D-amino acids, which are functional equivalents of the naturally-occurring amino acids. Such non-naturally-occurring amino acids include, for example, norleucine ("Nle"), norvaline ("Nva"), L- or D- naphthalanine, ornithine ("Orn"), homoarginine (homoArg) and others well known in the peptide art, such as those described in M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised ed., Springer-Verlag, New York, NY, 1984 and

1993, and Stewart and Young, "Solid Phase Peptide Synthesis," 2nd ed., Pierce Chemical Co., Rockford, IL, 1984, both of which are incorporated herein by reference. Amino acids and amino acid analogs can be purchased commercially (Sigma Chemical Co.; Advanced Chemtech) or synthesized using methods known in the art.

"Amino acid side chain" refers to any side chain from the above-described "amino acids."

"Substituted" herein refers to a substituted moiety, such as a hydrocarbon, *e.g.*, substituted alkyl or benzyl wherein at least one element or radical, *e.g.*, hydrogen, is replaced by another, *e.g.*, a hydrogen is replaced by a halogen as in chlorobenzyl.

A residue of a chemical species, as used in the specification and concluding claims, refers to a structural fragment, or a moiety that is the resulting product of the chemical species in a particular reaction scheme or subsequent formulation or chemical product, regardless of whether the structural fragment or moiety is actually obtained from the chemical species. Thus, an ethylene glycol residue in a polyester refers to one or more –OCH_2CH_2O- repeat units in the polyester, regardless of whether ethylene glycol is used to prepare the polyester.

The term "organic residue" or "organic group" defines a carbon containing residue or group, *i.e.* a residue comprising at least one carbon atom. Organic residues can contain various heteroatoms, or be bonded to another molecule through a heteroatom, including oxygen, nitrogen, sulfur, phosphorus, or the like. Examples of organic residues include but are not limited to alkyl or substituted alkyls, alkoxy or substituted alkoxy, hydroxyalkyls and alkoxyalkyls, mono or di-substituted amino, amide groups, CN, CO_2H, CHO, COR^6, CO_2R^6, SR^6, $S(O)R^6$, $S(O)_2R^6$, alkenyl, cycloalkyl, cycloalkenyl, aryl, and heteroaryl: wherein R^6 is an alkyl. More specific examples of species of organic groups or residues include but are not limited to $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$,methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, CH_2OCH_3, CH_2OH, CH_2NH_2, CH_2NHCH_3, or $CH_2N(CH_3)_2$ groups or residues. Organic resides can comprise 1 to 18 carbon atoms, 1 to 15, carbon atoms, 1 to 12 carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms.

By the term "effective amount" of a compound as provided herein is meant a sufficient amount of one or more compounds in a composition that is sufficient to provide the desired regulation of a desired biological function, such as gene expression, protein function, or more particularly the induction of either of Umami or sweet taste perception in

an animal or a human. As will be pointed out below, the exact amount required will vary from subject to subject, depending on the species, age, general condition of the subject, specific identity and formulation of the comestible composition, *etc.* Thus, it is not possible to specify an exact "effective amount." However, an appropriate effective amount can be determined by one of ordinary skill in the art using only routine experimentation.

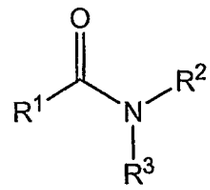
It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an aromatic compound" includes mixtures of aromatic compounds.

Often, ranges are expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not. For example, the phrase "optionally substituted lower alkyl" means that the lower alkyl group may or may not be substituted and that the description includes both unsubstituted lower alkyl and lower alkyls where there is substitution.

The Amide Compounds Of The Invention

The compounds of the invention are all organic (carbon containing) compounds that all have at least one "amide" group therein, have the following general structure, which will be hereinafter referred to as the amide compounds having Formula (I) shown below:



(I)

The amide compounds of Formula (I) do not include amide compounds that are known to naturally occur in biological systems or foods, such as peptides, proteins, nucleic acids, certain amino sugars and/or amino polysaccharides, glycopeptides or glycoproteins, or the like. The amide compounds of Formula (I) of the invention are man-made and artificial synthetic amide compounds, although the Applicants do not exclude the possibility that compounds of Formula (I) could conceivably be purposely prepared, either in their specified form or in the form of a peptide or protein-modified "prodrug" form by human beings utilizing one or more of the methods of modern biotechnology.

For the various embodiments of the compounds of Formula (I), the R^1, R^2 and R^3 groups can be and are independently further defined and/or limited in various ways, as will now be further detailed, so as to form and/or include a substantial number of subgenuses and/or species of compounds of Formula (I). It is hereby specifically contemplated that any of the subgenuses and/or species of compounds of Formula (I) described herein can, either in their specified form or as a comestibly acceptable salt, be combined in an effective amount with a comestible or medicinal product or precursor thereof by the processes and/or methods described elsewhere herein, or by any such other processes as would be apparent to those of ordinary skill in preparing comestible or medicinal products or precursor thereof, to form a savory and/or sweet flavor modified comestible or medicinal product, or a precursor thereof.

In some embodiments of the compounds of Formula (I), R^1 is a hydrocarbon residue that may contain one or more heteroatoms or an inorganic residue, and R^2 and R^3 are each independently H or a hydrocarbon residue that may contain one or more heteroatoms; more preferably, R^1, R^2 and R^3 are independently selected from the group consisting of arylalkenyl, heteroarylalkenyl, arylalkyl, heteroarylalkyl, alkyl, alkoxy-alkyl, alkenyl,

cycloalkyl, cycloalkenyl, aryl, heteroaryl, $-R^4OH$, $-R^4CN$, $-R^4CO_2H$, $-R^4CO_2R^5$, $-R^4COR^5$, $-R^4CONR^5R^6$, $-R^4NR^5R^6$, $-R^4N(R^5)COR^6$, $-R^4SR^5$, $-R^4SOR^5$, $-R^4SO_2R^5$, $-R^4SO_2NR^5R^6$ and $-R^4N(R^5)SO_2R^6$, or optionally substituted groups thereof and preferably one of R^2 or R^3 is H; wherein each R^4 is independently a hydrocarbon residue that may contain one or more heteroatoms, preferably independently selected from small (C_1-C_6) alkylene or (C_1-C_6) alkoxyalkylene; and wherein each R^5 and R^6 are independently H or a hydrocarbon residue that may contain one or more heteroatoms, preferably independently selected from small (C_1-C_6) alkyl or (C_1-C_6) alkoxyalkyl.

In many embodiments of the compounds of Formula (I), R^1 comprises an organic or hydrocarbon-based residue having at least three carbon atoms and optionally one to 20, 15, 10, 8, 7, 6, or 5 heteroatoms independently selected from oxygen, nitrogen, sulfur, halogens, or phosphorus.

In many embodiments of the compounds of Formula (I), one of R^2 and R^3 is optionally H, and one or both of R^2 and R^3 comprises an organic or hydrocarbon-based residue having at least three carbon atoms and optionally one to ten heteroatoms independently selected from oxygen, nitrogen, sulfur, halogens, or phosphorus.

The compounds of Formula (I) are relatively "small molecules" as compared to many biological molecules, and can often have a variety of limitations on their overall absolute physical size, molecular weight, and physical characteristics, so that they can be at least somewhat soluble in aqueous media, and are of appropriate size to effectively bind to the relevant heterodimeric T1R1/T1R3 or T1R2/T1R3 taste receptors, which share a common T1R3 protein subunit.

While not wishing to be bound by any theory, it is believed that MSG binds to the T1R1 subunit of T1R1/T1R3 "savory" taste receptors, and several known sweeteners bind to the T1R2 subunit of T1R2/T1R3 sweet receptors. Accordingly, our unexpected and surprising discovery that the amide compounds of Formula (I) can share many overlapping physical and chemical features, and can sometimes bind to either one or both of the savory and sweet receptors, is perhaps in retrospect reasonable and/or rational from a chemical/ biochemical/ biological point of view.

As an example of the overlapping physical and chemical properties and/or physical/chemical limitations on the savory and/or sweet amides of Formula (I), in most embodiments of the compounds of Formula (I), the molecular weight of the compounds of Formula (I) should be less than about 800 grams per mole, or in further related

embodiments less than or equal to about 700 grams per mole, 600 grams per mole, 500 grams per mole, 450 grams per mole, 400 grams per mole, 350 grams per mole, or 300 grams per mole.

Similarly, the compounds of Formula (I) can have preferred ranges of molecular weight, such as for example from about 175 to about 500 grams per mole, from about 200 to about 450 grams per mole, from about 225 to about 400 grams per mole, from about 250 to about 350 grams per mole.

In a related series of embodiments, R^1 has between 3 and 16 carbon atoms or 4 and 14 carbon atoms or 5 and 12 carbon atoms, and 0, 1, 2, 3, 4, or 5 heteroatoms selected from oxygen, nitrogen, sulfur, fluorine, or chlorine, and/or at least one of R^2 or R^3 has been 3 and 16 carbon atoms and 0, 1, 2, 3, 4, or 5 heteroatoms independently selected from oxygen, nitrogen, sulfur, fluorine, or chlorine; or preferably at least one of R^2 or R^3 has between 4 and 14 carbon atoms and 0, 1, 2, 3, 4, or 5 heteroatoms independently selected from oxygen, nitrogen, sulfur, fluorine; or even more preferably, at least one of R^2 or R^3 has between 5 and 12 carbon atoms and 0, 1, 2, or 3 heteroatoms independently selected from oxygen, nitrogen, and sulfur.

In addition to the above described general physical and chemical characteristics and/or limitations, which can be shared by the various subgenuses of the sweet and savory compounds of Formula (I), the compounds of Formula (I) can also share more specifically definable chemical structural features or chemical groups or residues, as is further described below.

For example, in some embodiments, R^1, R^2, and R^3 can be independently selected from the group consisting of an arylalkenyl, heteroarylalkenyl, arylalkyl, heteroarylalkyl, alkyl, alkoxy-alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, $-R^4OH$, $-R^4OR^5$, $-R^4CN$, $-R^4CO_2H$, $-R^4CO_2R^5$, $-R^4COR^5$, $-R^4SR^5$, and $-R^4SO_2R^5$, and optionally substituted derivative thereof comprising 1, 2, 3, or 4 carbonyl, amino groups, hydroxyl, or halogen groups, and wherein R^4 and R^5 are C_1-C_6 hydrocarbon residues.

In further related embodiments of the amide compounds of Formula (I), R^1, R^2 and R^3 can be independently selected from the group consisting of an arylalkenyl, heteroarylalkenyl, arylalkyl, heteroarylalkyl, alkyl, alkoxy-alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, aryl and heteroaryl groups, and optionally substituted derivatives thereof comprising 1, 2, 3 or 4 carbonyl, amino groups, hydroxyl, or chlorine, or fluorine groups. In both of the embodiments just mentioned, an alternative and preferred set of

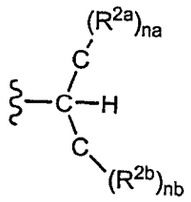
38

optional substituent groups would be substituents independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy substituent groups.

The R^2 and/or R^3 Groups

In many embodiments of the compounds of Formula (I), one of R^2 and R^3 is hydrogen and the other R^2 or R^3 group is an organic residue or group. Therefore it should be understood that a statement hereinbelow that "at least one of R^2 and R^3 ...." contemplates as one embodiment that one or R^2 and R^3 is hydrogen and the other of R^2 and R^3 has the structure subsequently described, and as another embodiment that both of R^2 and R^3 have the described structure.

In many embodiments, at least one of R^2 and R^3 is a branched or cyclic organic residue having a carbon atom directly bonded to both (a) the amide nitrogen atom and (b) two additional carbon atoms from other organic residues, which are branched or cyclic organic residues comprising additional hydrogen atoms and up to 10 optional additional carbon atoms, and optionally from zero to five heteroatoms independently selected from oxygen, nitrogen, sulfur, fluorine, and chlorine. Such branched R^2 and R^3 groups include organic radicals having the formula:

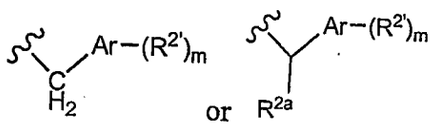


wherein na and nb are independently selected from 1, 2, and 3, and each R^{2a} or R^{2b} substituent residue is independently selected from hydrogen, a halogen, a hydroxy, or a carbon-containing residue optionally having from zero to five heteroatoms independently selected from oxygen, nitrogen, sulfur, and a halogen. In some such embodiments, the R^{2a} or R^{2b} are independent substituent groups, but in other embodiments one or more of the R^{2a} or R^{2b} radicals can be bonded together to form ring structures.

In some such embodiments of the compounds of Formula (I), at least one of the R^2 and R^3 is a branched alkyl radical having 5 to 12 carbon atoms, or at least one of R^2 and R^3 is a cycloalkyl or cycloalkenyl ring comprising 5 to 12 ring carbon atoms. In such embodiments of R^2 and R^3 the branched alkyl radical or the cycloalkyl or cycloalkenyl ring

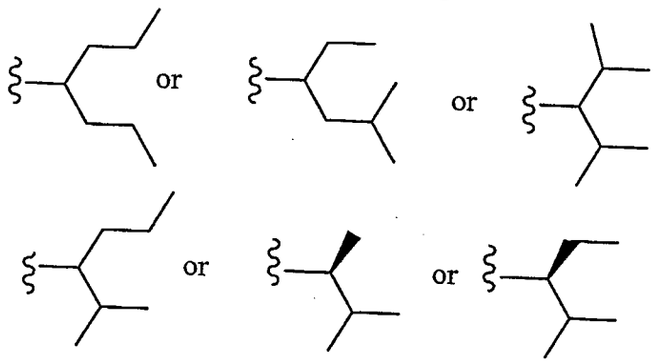
can be optionally substituted with 1, 2, 3, or 4 substituent groups independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy.

In other embodiments of the amide compounds of Formula (I), at least one of the R^2 and R^3 is a "benzylic" radical having the structure



wherein Ar is an aromatic or heteraromatic ring such as phenyl, pyridyl, furanyl, thiofuranyl, pyrrolyl, or similar aromatic ring systems, m is 0,1, 2, or 3, and each $R^{2'}$ is independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, and each R^{2a} substituent group can be independently selected from the group consisting of an alkyl, alkoxy-alkyl, alkenyl, cycloalkenyl, cycloalkyl, $-R^4OH$, $-R^4O\,R^5$, $-R^4CN$, $-R^4CO_2H$, $-R^4CO_2R^5$, $-R^4COR^5$, $-R^4SR^5$, and $-R^4SO_2R^5$ group.

In many embodiments of the compounds of Formula (I), at least one of R^2 or R^3 is a C_3-C_{10} branched alkyl. In many such embodiments, the other of R^2 or R^3 is hydrogen. These C_3-C_{10} branched alkyls have been found to be highly effective R^2 groups for both savory and sweet amide compounds. In some embodiments, R^3 is a C_4-C_8 branched alkyl. Examples of such branched alkyls include the following structures.



In further embodiments the branched alkyls may optionally contain, inserted into what would have been an alkyl chain, one or two heteroatoms such as nitrogen, oxygen, or sulfur atoms to form amines, ethers, and/or thioethers, sulfoxides, or sulfones respectively, or one or two heteroatomic substituents bonded to the alkyl chains independently selected

from a hydroxy, fluoro, chloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

In further embodiments of the compounds of Formula (I), at least one of R^2 or R^3 is an α-substituted carboxylic acid or α-substituted carboxylic acid lower alkyl ester. Preferably, at least one of R^2 or R^3 is an α-substituted carboxylic acid lower alkyl (especially methyl) ester. In some such preferred embodiments, the α-substituted carboxylic acid or α-substituted carboxylic acid ester residue corresponds to that of a naturally occurring and optically active α-amino acid or an ester thereof, or its opposite enantiomer.

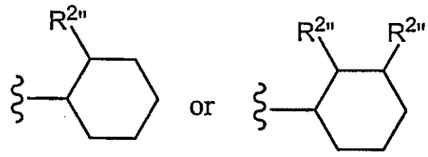
In many embodiments of the compounds of Formula (I), at least one of R^2 or R^3 is a 5 or 6 membered aryl or heteroaryl ring, optionally substituted with 1, 2, 3 or 4 substituent groups selected from the group consisting of hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical. In related embodiments, the subtitutents for the aryl or heteroaryl ring are selected from alkyl, alkoxyl, alkoxy-alkyl, OH, CN, CO_2H, CHO, COR^6, CO_2R^6, SR^6, halogen, alkenyl, cycloalkyl, cycloalkenyl, aryl, and heteroaryl: and R^6 is C_1-C_6 alkyl. Preferably the aryl or heteroaryl ring is substituted with 1, 2, 3 or 4 substituent groups selected from the group consisting of hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

In some embodiments of the compounds of Formula (I), at least one of R^2 or R^3 is a phenyl, pyridyl, furanyl, thiofuranyl, or pyrrolyl ring optionally substituted with one or two substituents independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy.

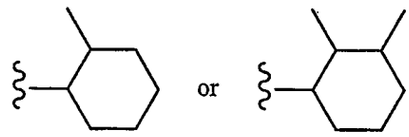
In many embodiments of the compounds of Formula (I), at least one of R^2 or R^3 is a cycloalkyl, cycloalkenyl, or saturated heterocyclic ring having 3 to 10 ring carbon atoms, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, hydroxy, and halogen. In some further embodiments, at least one of R^2 or R^3 is a cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl ring, or piperidyl ring optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy.

41

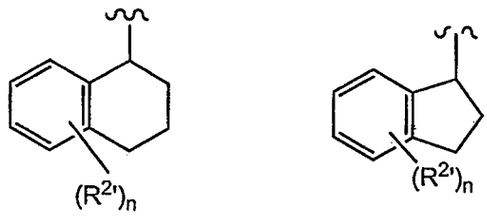
In some preferred embodiments, at least one of R^2 or R^3 is a cyclohexyl ring, optionally substituted with 1, 2, or 3 substitutent groups selected from NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, hydroxy, and halogen groups, and the other of R^2 or R^3 is hydrogen. For example, in some such embodiments, R^3 is hydrogen and R^2 can have one of the following structures:



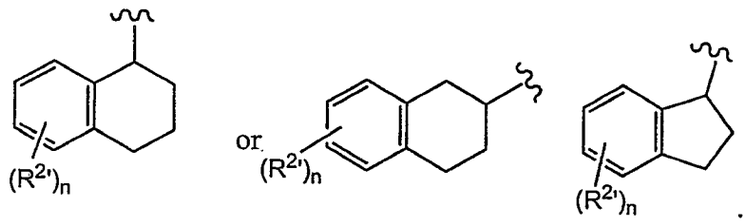
wherein $R^{2'}$ and $R^{2''}$ are independently selected from hydroxy, fluoro, chloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups, or preferably methyl groups. Examples of such methyl substituted cyclohexyl rings have the formula



In many embodiments of the compounds of Formula (I), especially compounds having enhancer activity for other sweeteners, or enhancer activity for savory compounds such as MSG, R^3 is hydrogen and R^2 is a cyclopentyl or cyclohexyl ring having a phenyl ring fused thereto, *i.e.* a 1-(1,2,3,4) tetrahydronapthalene ring radical or an 2,3-dihydro-1H-indene ring radical having the structures:



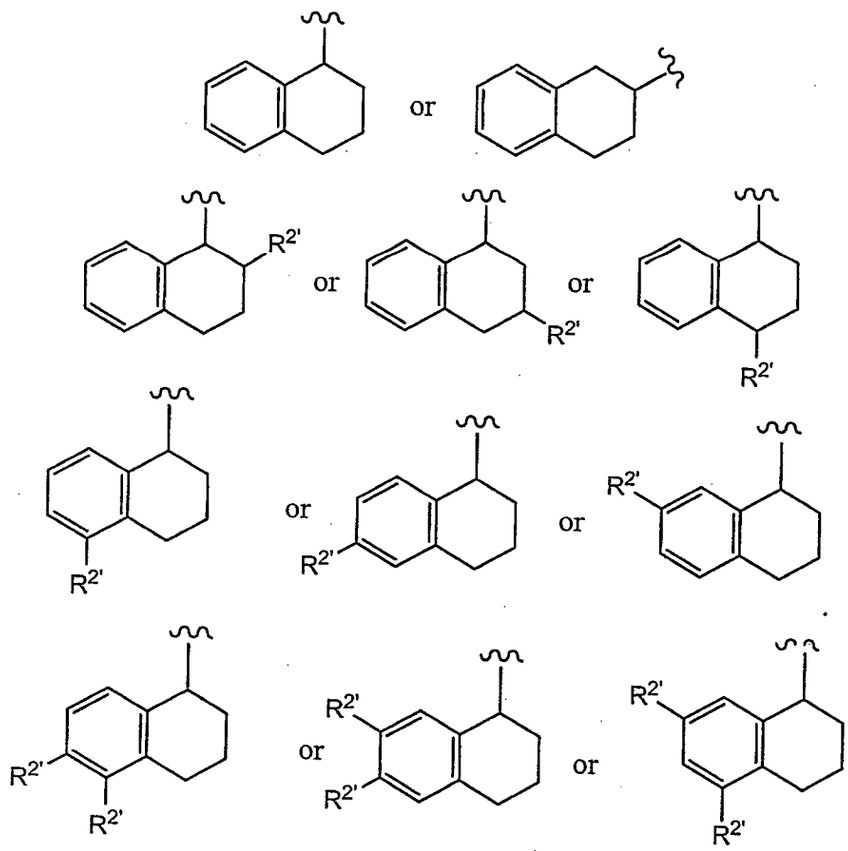
wherein n is 0,1, 2, or 3, and each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring. In other embodiments, each $R^{2'}$ is bonded to the aromatic ring as is shown below:



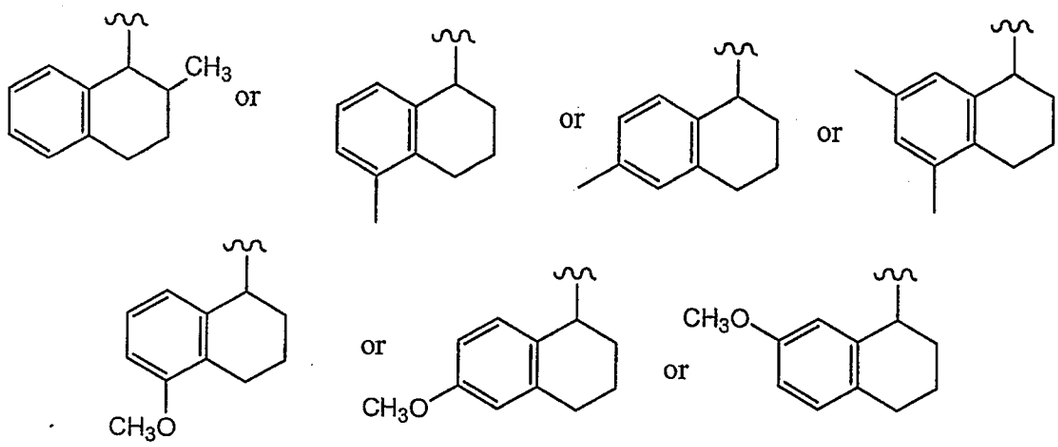
42

In the tetrahydronapthalenyl and indanyl embodiments shown above, each $R^{2'}$ can be independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical. In alternative but related embodiments, each $R^{2'}$ can be independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxyl, C_1-C_4 alkoxy-alkyl, C_1-C_4 hydroxy-alkyl, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, and halogen, wherein R^6 is C_1-C_4 alkyl. In some preferred embodiments, each $R^{2'}$ can be independently selected from the group consisting of hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3 , SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy.

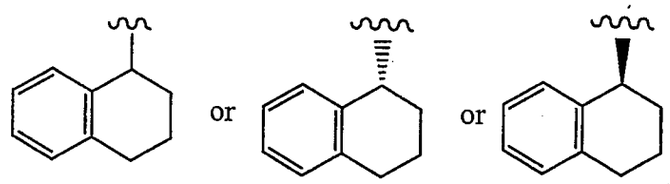
In some embodiments at least one of R^2 or R^3 is a 1-(1,2,3,4) tetrahydronapthalene ring with certain preferred substitution patterns. In particular, in some embodiments of the compounds of formula (I)at least one of R^2 or R^3 is a cyclohexyl ring having one of the formulas:



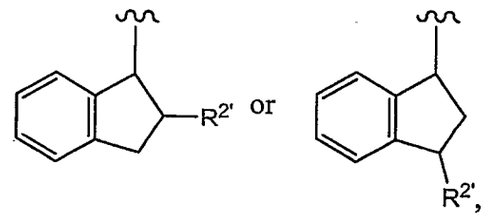
wherein each $R^{2'}$ can be independently selected from the groups described above. Similarly, in some preferred embodiments, at least one of R^2 or R^3 may include one of the structures:



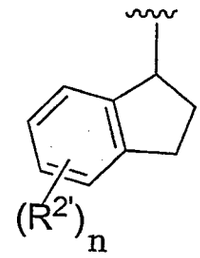
In some embodiments at least one of R^2 or R^3 is an unsubstituted 1-(1,2,3,4) tetrahydronapthalene ring in racemic or optically active form, as shown below:



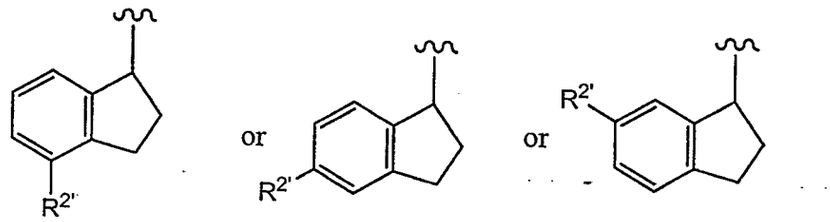
Similarly in the indanyl series R^2 can have the structures

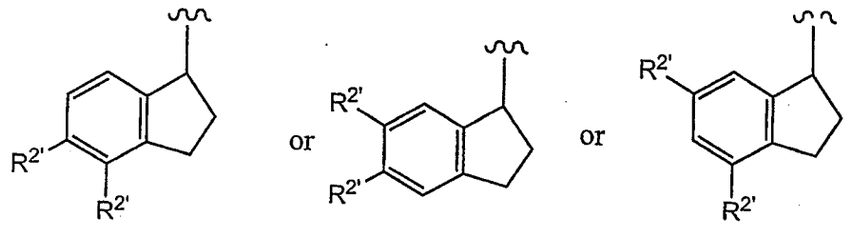


or the $R^{2'}$ substituents can bound to the aromatic ring as show below,

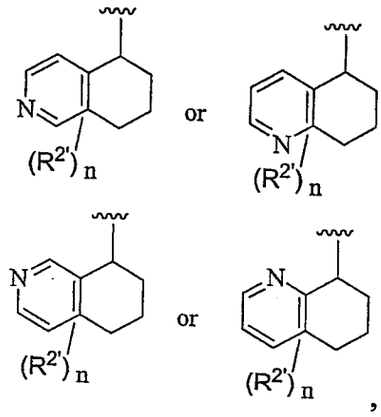


or in more specific embodiments, R2 can have one of the exemplary structures show below;

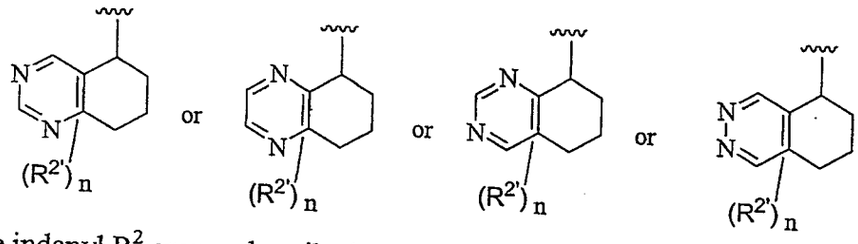




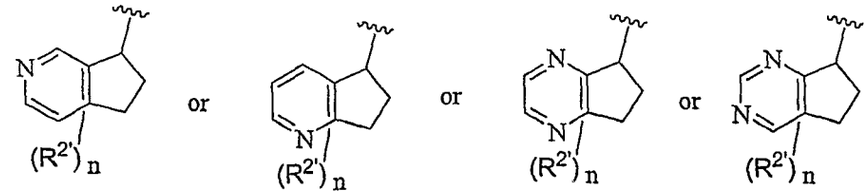
In some embodiments of the amide compounds of the invention, the tetrahydronapthalene and indane ring systems of the R^2 groups described above can be modified to comprise one or more heteroatoms or heteroatomic groups into the bicyclic ring systems, to form new heterocyclic and bicyclic analogs of the tetrahydronapthalene and indane ring systems, so as to form new R^2 groups. For example, it is possible to substitute a nitrogen atom for one of the aromatic rings of a tetrahydronapthalenyl group to form new tetrahydroquinolinyl or tetrahydroisoquinolinyl radicals having the structures shown below:



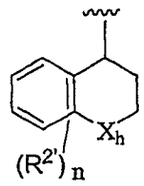
wherein the $R^{2'}$ groups can be bonded to either the aromatic or non-aromatic rings, and can be defined in any of the ways described above in connection with the tetrahydronapthalenyl groups. It will be apparent to those of ordinary skill in the art that at least one additional nitrogen atom could be similarly inserted to form additional and isomeric heteroaryl groups, such as the following exemplary R^2 groups:



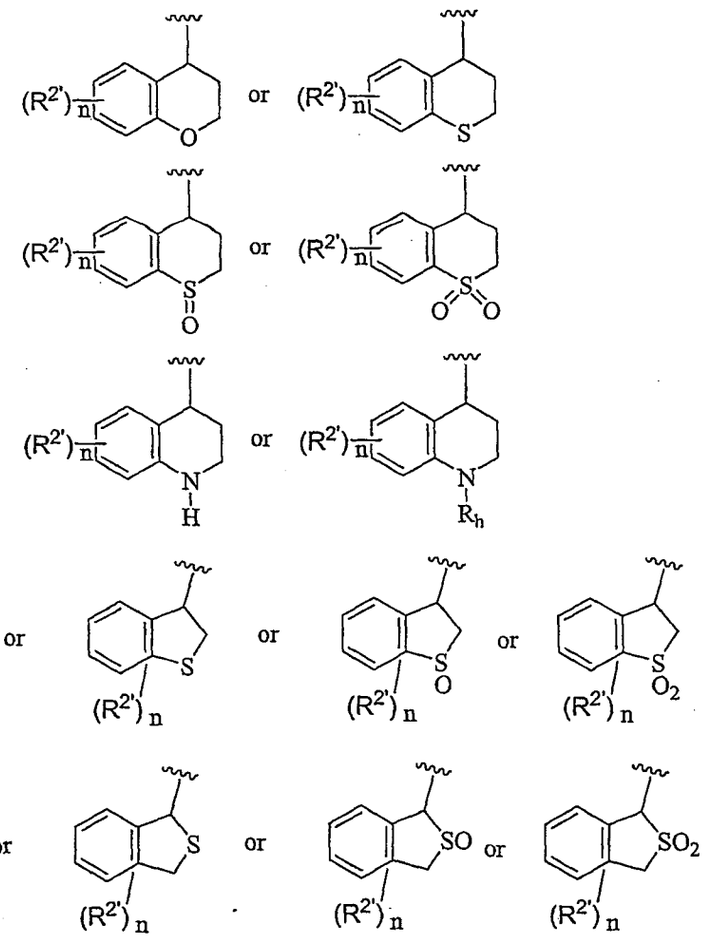
The indanyl R^2 groups described above can be similarly modified with one or more nitrogen atoms to form additional bicyclic heteroaryl R^2groups, such as for example the following structures:



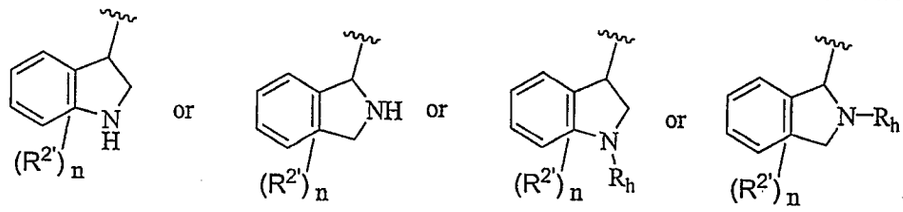
Additionally, one or more heteroatoms or heteratomic groups can be inserted into the cyclopentyl or cyclohexyl groups of the tetrahydronapthalenyl or indanyl groups described above to form additional fused bicyclic heteroaryls, which include but are not limited to the exemplary structures listed below:



wherein n is 0, 1, 2, or 3, each $R^{2'}$ can be defined in any of the ways described above, and X_h is O, S, SO, SO_2, NH, or NR_h, wherein R_h is a C_1-C_4 organic radical. Examples of such R^2 groups are listed below:

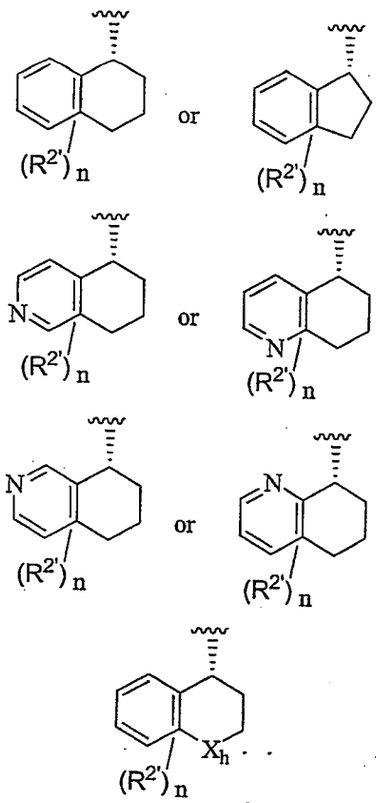


46



It will also be understood by those of ordinary skill in the art that optical and/or diastereomeric isomerism can occur on the unsaturated five and six membered rings of the R^2 groups described above, and in many other of the R^1, R^2, and R^3 groups disclosed herein, and that the differing optical isomers (enantiomers) and/or diastereomers can have differing biological activities with respect to the relevant sweet and savory taste receptors. Prediction of which diasteromer or enantiomer of a particular R^2 group is most likely to be biologically effective can be difficult, and the finding that one particular isomer is more effective for one ring system may not necessarily mean that an analogous isomer of a differently substituted group will be similarly effective.

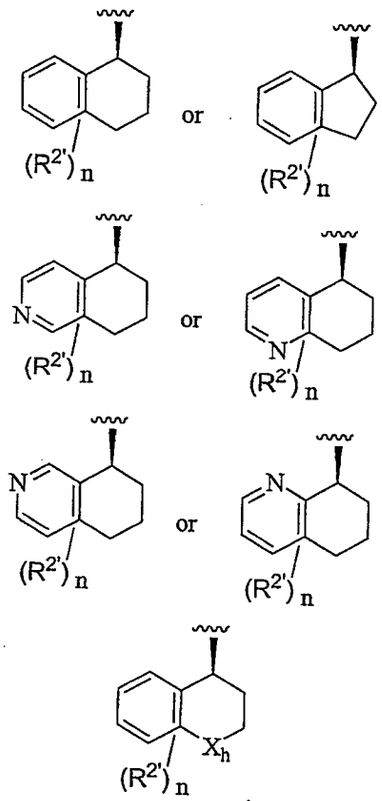
Applicants have nevertheless found that in many embodiments, the compounds of Formula (I) are particularly effective as sweet enhancers when R^2 comprises a substituted or unsubstituted tetrahydronapthalenyl, indanyl, tetrahydroquinolinyl, tetrahydronapthalenyl, or the related heterocyclic analogs disclosed above when they comprise an enantiomeric excess of the absolute optical configurations illustrated in the drawings below:



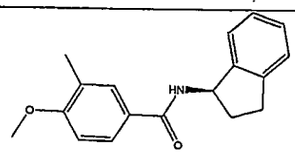
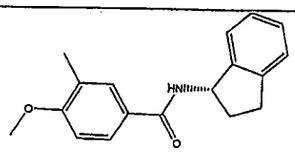
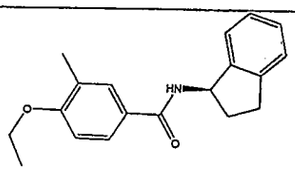
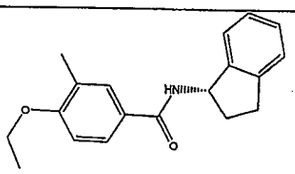
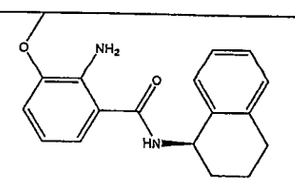
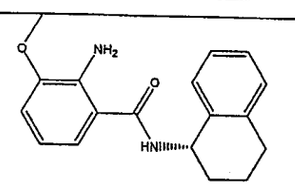
47

One of ordinary skill is aware that the designation of a particular compound as either "R" or "S" under the Cahn-Ingold-Prelog system of nomenclature for optically active compounds can depend upon the exact nature and number of the substituent groups, but the compounds of Formula (I) having the bicyclic R^2 ligands and the absolute optical configurations shown in the drawings immediately above are typically "R" at the optically active carbon shown above, and those compounds usually give superior binding to T1R2/T1R3 sweet receptors. It should be noted however that the opposite "S" isomers do typically have some, although typically lower, activity for binding T1R2/T1R3 sweet receptors and/or as sweet enhancer compounds.

Applicants have also found that the T1R1/T1R3 savory receptors often show a notable tendency to more strongly bind compounds of Formula (I) that have the R^2 groups shown above the opposite "S" configurations, namely:



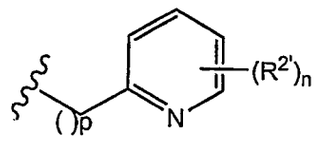
Again, though the T1R1/T1R3 savory receptors often show a significant preference for the "S" isomers of compounds comprising the R^2 groups shown above, the "R" isomers can retain significant although diminished biological activity as savory tastants or savory enhancer compounds for MSG. The data table below provides relevant examples of data on the binding of opposite enantiomers to the T1R1/T1R3 savory receptors, to illustrate this point.

COMPOUND	COMPOUND NAME AND OPTICAL CONFIGURATION	AFFINITY FOR T1R1/T1R3 SAVORY RECEPTOR EC_{50} UM
	(R)-N-(2,3-dihydro-1H-inden-1-yl)-4-methoxy-3-methylbenzamide	2.13
	(S)-N-(2,3-dihydro-1H-inden-1-yl)-4-methoxy-3-methylbenzamide	0.08
	(R)-N-(2,3-dihydro-1H-inden-1-yl)-4-ethoxy-3-methylbenzamide	4.53
	(S)-N-(2,3-dihydro-1H-inden-1-yl)-4-ethoxy-3-methylbenzamide	0.85
	(R)-2-amino-3-methoxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	0.09
	(S)-2-amino-3-methoxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	0.01

When the specification, claims, and/or drawings of this document indicate that a compound is present in optically active form, as is implied by the discussion and drawings immediately above, it is to be understood that the indicated compounds of Formula (I) are present in at least a small enantiomeric excess (*i.e.* more than about 50% of the molecules have the indicated optical configuration). Further embodiments preferably comprise an enantiomeric excess of the indicated isomer of at least 75%, or 90%, or 95%, or 98%, or 99%, or 99.5%. Depending on the difference in the biological activities, the cost of

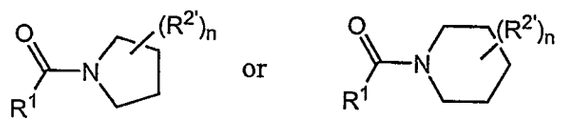
production, and/or any differences in toxicity between the two enantiomers, for a given compound it may be advantageous to produce and sell for human consumption a racemic mixture of the enantiomers, or a small or large enantiomeric excess one of the enantiomers of a given compound.

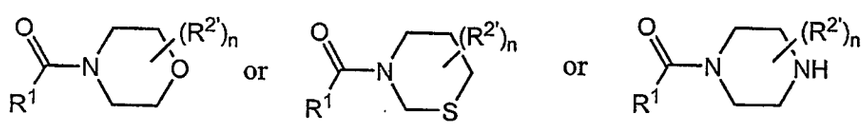
In other embodiments of the amide compounds of Formula (I), including the savory oxalamide compounds of Formula (V) as disclosed below, one of R^2 and R^3 is hydrogen, and the other of R^2 and R^3 is an alkylene substituted pyridinyl radical having the structure:

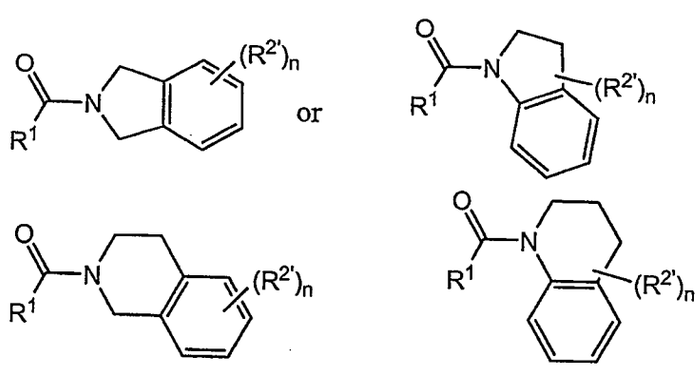


wherein p is, 1 or 2; and n is 0, 1, or 2, and $R^{2'}$ can be any of the substitutent groups defined above.

In other embodiments of the amide compounds of Formula (I), in some embodiments of the compounds of Formula (I), the R^2 and R^3 groups are not hydrogen and are joined together to make an optionally substituted heterocyclic amine ring, examples of which are shown below:







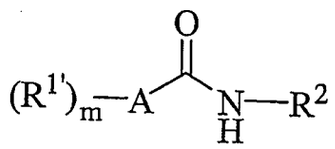
and n is 0, 1, or 2, and $R^{2'}$ can be any of the substitutent groups defined above. As will be further described below, ureas are a subgenus of the amide compounds of Formula (I) that can preferably have such cyclic embodiments of the R^2 / R^3 groups,

50

and such compounds are particularly useful as sweet enhancer compounds and/or tastants.

Amide Compounds Comprising Aryl or Heteroaryl R^1 Groups

In many preferred subgenuses of the amide compounds of Formula (I) having one or both of savory and sweet receptor agonist activity, in a preferred subgenus of the amide compounds R^1 is an optionally substituted aryl or heteroaryl group. More specifically, there are many subgenuses of the amide compounds of Formula (I) that have the following formula (II):



(II)

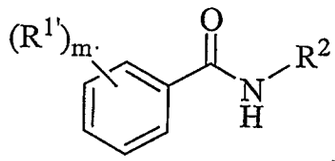
wherein A comprises a 5 or 6 membered aryl or heteroaryl ring, and m is 0, 1, 2, 3 or 4.

In such compounds of Formulas (I) and/or (II), each $R^{1'}$ can be independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, and a C_1-C_4 organic radical. In related embodiments, each $R^{1'}$ is independently selected from the group consisting of alkyl, alkoxy, alkoxy-alkyl, hydroxyalkyl, OH, CN, CO_2H, CO_2R^6,CHO, COR^6, SR^6, halogen, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, aryl, and heteroaryl; and R^6 is C_1-C_6 alkyl. In some related but alternative embodiments of the compounds of Formulas (I) and/or (II), each $R^{1'}$ and/or each $R^{2'}$ can be independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxyl, C_1-C_4 alkoxy-alkyl, C_1-C_4 hydroxy-alkyl, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, and halogen, wherein R^6 is C_1-C_4 alkyl. In many preferred embodiments of the compounds of Formulas (I) and/or (II), each $R^{1'}$ is independently selected from the group consisting of hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, n-propyl, n-butyl, 1-methyl-propyl, isobutyl, t-butyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups. In such compounds of Formula (II), R^2 can be any of the structures contemplated above, or the like.

In some embodiments, the A group of Formula (II) comprises an aryl ring, *i.e.* it contains somewhere within it's structure at least one six-membered aromatic phenyl ring. The aryls include at least benzene and napthalene rings, which may not, but in many

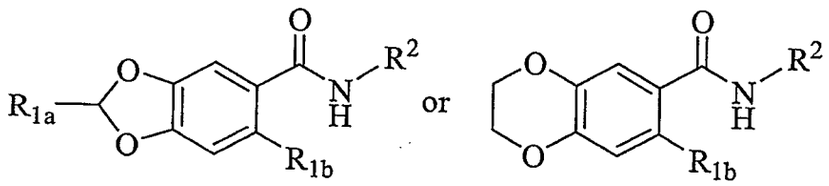
embodiments are, further sustituted with at least 1, 2, or 3 $R^{1'}$ subtituent groups, which can be defined by any of the alternatives recited above. In such embodiments the benzenyl and napthalenyl ring can, but need not necessarily be bonded directly to the carbonyl carbon atom of the amide compound.

In many embodiments of the compounds of Formula (II), the A group is a phenyl ring that is directly bonded to the carbonyl carbon atom of the amide group, and R^3 is H, so as to form a benzamide compound having the formula shown below:



In such compounds of Formula (II), R^2 can be any of the structures contemplated above, or the like. Such compounds having branched alkyl R^2 groups are preferred savory tastants and/or savory enhancers. Such compounds having any of the optionally substituted tetrahydronapthalene, indanyl, or structually related hetercyclic R2 disclosed above are highly effective sweet enhancer compounds.

In some preferred embodiments of the compounds wherein A is a benzenyl ring, one or two of the $R^{1'}$ substituent groups can be bonded together to form a saturated alkylenedioxy ring on an phenyl ring, as exemplified by the following preferred subgenuses (II a) and (IIb):

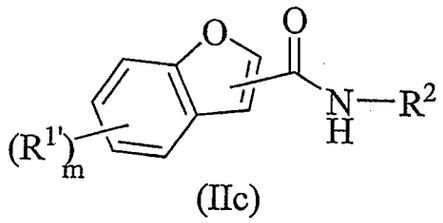


(IIa) (IIb)

wherein R_{1a} and R_{1b} are independently hydrogen or a lower alkyl, or alternatively R_{1a} and R_{1b} are independently hydrogen or methyl, or alternatively both R_{1a} and R_{1b} are hydrogen.

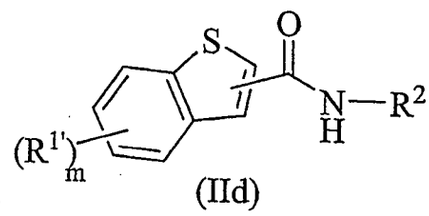
In many embodiments of the amide compounds of Formula (II), A is heteroaryl ring, and typically a monocyclic or fused bicyclic heteroaryl ring. The fused bicyclic heteraryls are typified by the following benzofurans (Formula IIc) and benzothiofurans (Formula (IId):

52



(IIc)

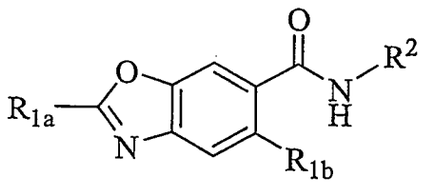
or



(IId)

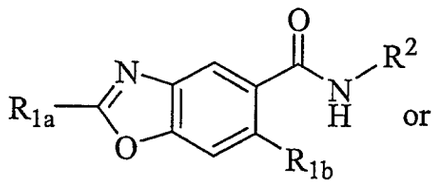
wherein m is 0, 1, 2, or 3 and each $R^{1'}$ can be bonded to either the phenyl or heteroaryl rings and each $R^{1'}$ is independently selected from, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy.

Additional examples of fused bicyclic heteroaryls as A groups are typified by the following benzoxazole compounds (Formula IIe) and (Formula (IIf):



(IIe)

or

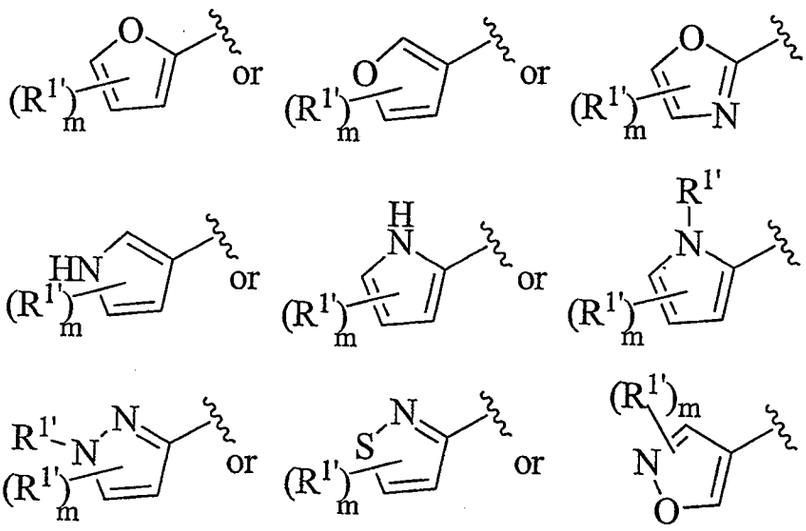


(IIf)

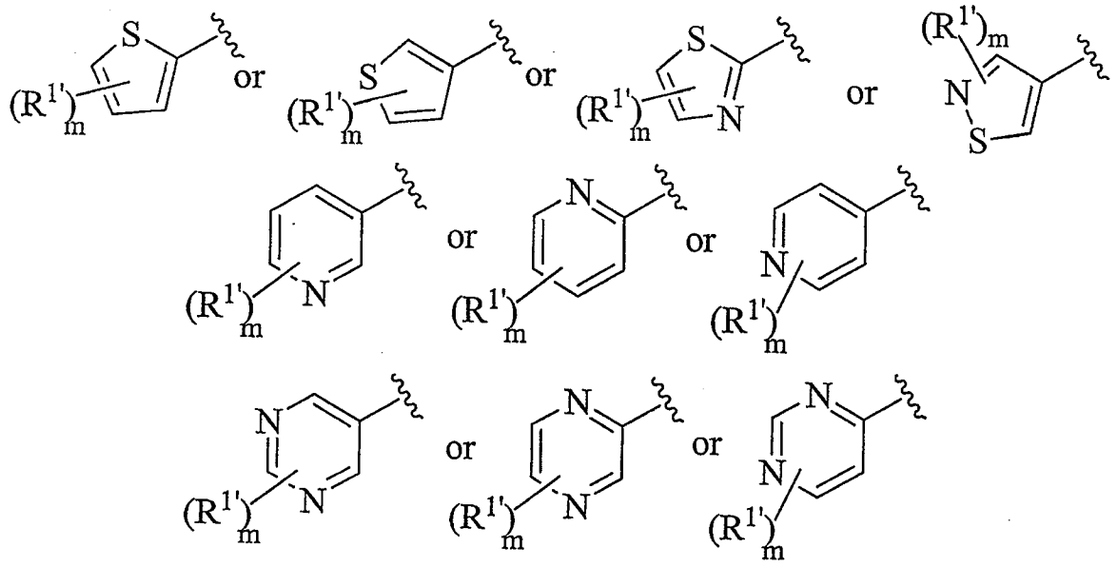
or

wherein R_{1a} or R_{1b} is independently hydrogen or a lower alkyl.

In many embodiments of the amide compounds of Formula (II), A is a monocyclic heteroaryl ring. The monocyclic heteroaryl amide compounds that can be used as an A group in Formula (II) are typified by the following structures:

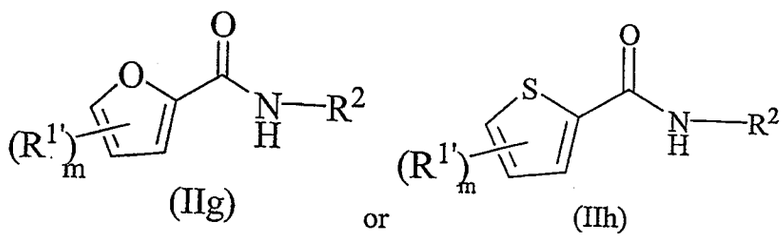


S3

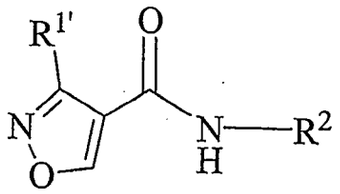


wherein m is 0, 1, 2, or 3. In such compounds of Formula (II), each $R^{1'}$ can be independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, and a C_1-C_4 organic radical. In some related but alternative embodiments of the compounds of Formula (II), each $R^{1'}$ can be independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxyl, C_1-C_4 alkoxy-alkyl, C_1-C_4 hydroxy-alkyl, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, and halogen, wherein R^6 is C_1-C_4 alkyl. In many preferred embodiments each $R^{1'}$ is independently selected from the group consisting of hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, n-propyl, n-butyl, 1-methyl-propyl, isobutyl, t-butyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups. In such compounds of Formula (II), R^2 can be any of the structures contemplated above, or the like.

In some preferred embodiments of the monocyclic heteroaryl amide compounds, A is a substituted furan, thiofuran, or oxazole ring, so as to form compounds having Formulas (IIg), (IIh) and (IIi):



(IIg) or (IIh)



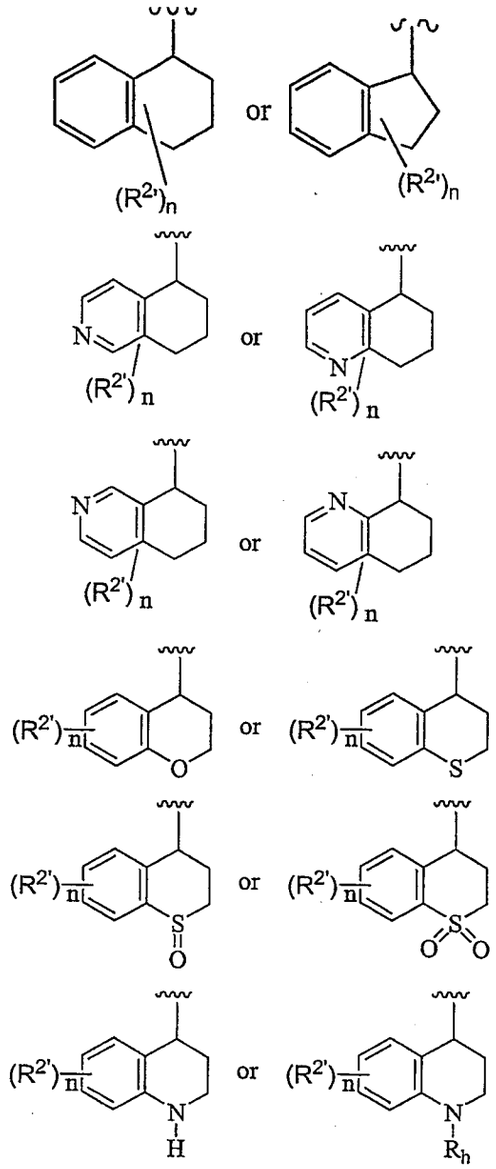
(IIi)

wherein m is 0, 1, 2, or 3. In some such embodiments, m is 1 or 2 and each $R^{1'}$ can be independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, n-propyl, n-butyl, 1-methyl-propyl, isobutyl, t-butyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

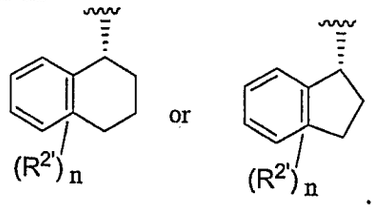
In many embodiments of the compounds of the various subgenuses of Formula (II) described immediately above, at least one of R^2 or R^3 can be a C_3-C_{10} branched alkyl; an α-substituted carboxylic acid or an α-substituted carboxylic acid lower alkyl ester; a 5 or 6 membered aryl or heteroaryl ring, optionally substituted with 1, 2, 3 or 4 substituent groups selected from the group consisting of hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups; a cyclohexyl, optionally substituted with 1, 2, or 3 methyl groups.

The isoxazole compounds of Formula (IIi) can be unexpectedly superior as sweet enhancer compounds when $R^{1'}$ is a C_1-C_8 organic radical, such as for example C_1- C_8 alkyl (normal or branched), C_1- C_8 alkoxyl, C_1- C_8 alkoxy-alkyl, C_1- C_8 hydroxy-alkyl, C_1- C_8 amino-alkyl, or a C_1- C_8 optionally substituted aryl or heteroaryl having a five or six membered aromatic ring, In yet additional embodiments, the $R^{1'}$ group of the isoxazole ring is hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, n-propyl, n-butyl, 1-methyl-propyl, isobutyl, t-butyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, CH_2OCH_3, CH_2OH, CH_2NH_2, CH_2NHCH_3, or $CH_2N(CH_3)_2$ group.

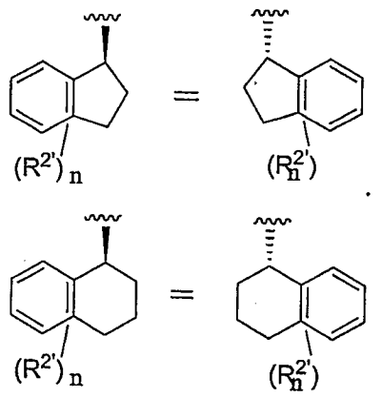
In some embodiments, the isoxazole compounds of Formula (IIi) comprise an R^2 group which is a 1-(1,2,3,4) tetrahydronapthalene ring, an 2,3-dihydro-1H-indene ring or one of their heterocyclic analog compounds having one of the formulas shown below:



wherein n is 0, 1, 2, or 3, preferably 1 or 2, and each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring and is independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy; as were described hereinabove with respect to the general amide compounds of Formula (I). In their applications as sweet enhancers, it is typically preferable that compounds of Formula (IIa-i) that comprise the bicyclic R^2 groups illustrated above comprise at least an enantiomeric excess of the "R" optical configuration as is illustrated below



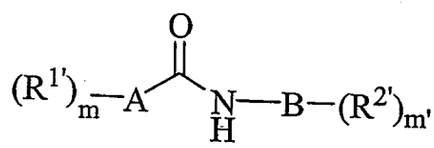
In contrast, when compounds having Formulas (IIa-i) with bicyclic R^2 groups such as those above are employed as "Umami" tastants or as agents for enhancing Umami flavor of MSG, it has been found that the use of bicyclic indanyl or tetrahydronapthyl R^2 groups comprising the opposite "S" configuration, as exemplified below, can be advantageous:



The subgenuses of aromatic or heteroaromatic amide compounds of Formula(II) described immediately above contain many excellent agonists of T1R1/T1R3 savory ("umami") taste receptors, and/or T1R2/T1R3 sweet taste receptors, at very low concentrations of the amide compound on the order of micromolar concentrations or less, and can induce a noticeable sensation of a savory umami flavor in humans, and/or can serve as enhancers of the savory umami flavor of MSG, or significantly enhance the effectiveness of a variety of known sweeteners, especially saccharide based sweeteners.

Accordingly, many of the aromatic or heteroaromatic amide compounds of Formula (II) can be utilized as savory or sweet flavoring agents or savory or sweet flavor enhancers when contacted with a wide variety of comestible products and/or compositions, or their precursors, to produce taste modified comestible or medicinal compositions, as is described elsewhere herein.

In another subgenus of the compounds of Formula (I), the amide compound has Formula (III):

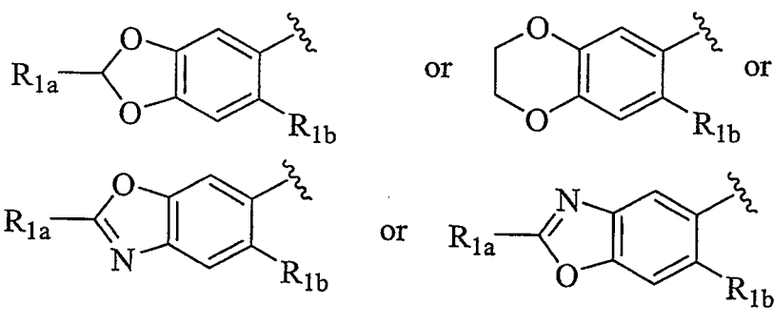


(III)

wherein A comprises a 5 or 6 membered aryl or heteroaryl ring; m is 0, 1, 2, 3 or 4; each $R^{1'}$ is independently selected from alkyl, alkoxyl, alkoxy-alkyl, hydroxyalkyl, OH, CN, CO_2H, CHO, COR^6, CO_2R^6 , SH, SR^6, halogen, alkenyl, cycloalkyl, cycloalkenyl, aryl, and heteroaryl and R^6 is C_1-C_6 alkyl; B is a 5 or 6 membered aryl or heteroaryl ring; m' is 0, 1, 2, 3 or 4; $R^{2'}$ is selected from the group consisting of alkyl, alkoxyl, alkoxy-alkyl, OH, CN, CO_2H, CHO, COR^6, CO_2R^6, SR^6, halogen, alkenyl, cycloalkyl, cycloalkenyl, aryl, and heteroaryl: and R^6 is C_1-C_6 alkyl.

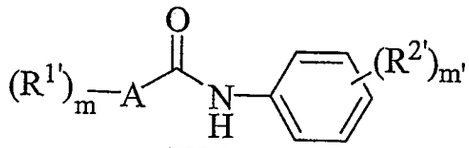
In the compounds of Formula (III), the optional $R^{1'}$ and $R^{2'}$ substituent groups can also be independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3,SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

In the compounds of Formula (III), both the A and B rings comprise a five or six membered aryl or heteroaryl ring. For the A ring, any of the various embodiments of the A rings recited above for the compounds of Formula (II), including phenyl and the monocyclic and bicyclic heteroaryls can be suitable. In some bicyclic embodiments, the A ring of the compounds of Formula (III) have the following structures:



wherein R_{1a} and R_{1b} are independently hydrogen or a lower alkyl.

In the compounds of Formula (III), the B rings are typically an optionally substituted monocyclic five or six membered aryl or heteroaryl ring, such as a phenyl, pyridyl, furanyl, thiofuranyl, pyrrolyl, and like monocycles. In some embodiments compounds of Formula (III) wherein B is phenyl, *i.e.* wherein the amide compound is readily derived from an substituted aniline precursor, as is shown below for compound subgenus (IIIa):



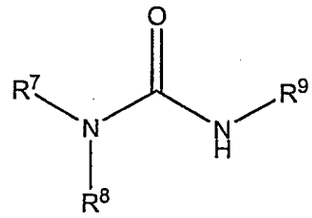
(IIIa)

58

A number of aniline derivative compounds of Formula (IIIa) appear to have been previously synthesized, but it is believed to be previously unknown in the art that such compounds can be used as very effective umami and/or sweet flavorant compounds, at concentrations on the order of millimolar or less, or on the order of micromolar concentrations, *see* for example compound A1 in Table 1 below.

Urea Compounds

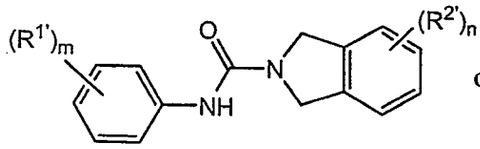
In another subgenus of the amide compounds of Formula (I), the amide compound are the urea compounds having the Formula (IV):



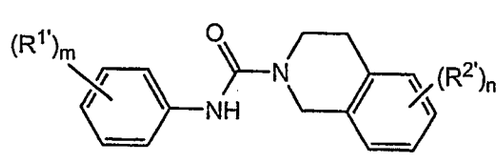
(IV)

wherein R^7, R^8 and R^9 are each a hydrocarbon residue that may contain one or more heteroatoms or an inorganic residue, and preferably is independently selected from arylalkenyl, heteroarylalkenyl, arylalkyl, heteroarylalkyl, alkyl, alkoxy-alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl and heteroaryl groups, each of which may be optionally substituted, or one of R^7 or R^8 can be and often is H. As one of ordinary skill in the art will appreciate, these urea compounds are a subgenus of the amide compounds of Formula (I) wherein R^7 and R^8 and the nitrogen atom bound thereto are equivalent to the R^1 groups of Formula (I) that are organic residues, and R^9 is the equivalent of the R^2 and/or R^3 radicals of Formulas (I) and/or (II).

In some embodiments of the urea compounds of Formula (IV), R^7 and R^8 together form a heterocyclic or heteroaryl ring having 5, 6, or 7 ring atoms that may be optionally substituted with 1, 2, or 3 substituents independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups. Examples of such urea compound can have the Formulas (IVa) and (IVb):



or

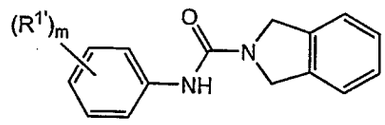


(IVa) (IVb)

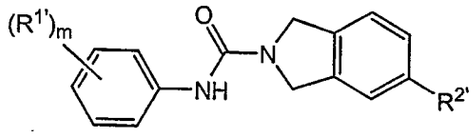
89

wherein m and n are independently 0, 1, 2, or 3, and each $R^{1'}$ and $R^{2'}$ can be defined in any of the ways described hereinabove for the compounds of Formula (I). In many embodiments, $R^{1'}$ and $R^{2'}$ can be independently selected from fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy. In some embodiments, n is 0.

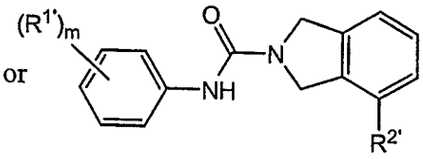
It has however been unexpectedly discovered that certain embodiments of the urea compounds of Formula (IVa) shown above (which comprise dihydroindole rings) are particularly effective as enhancers of the sweet taste of known sweeteners if m is 1, 2, or 3, and one or two small $R^{2'}$ substituents for the dihydroindole ring are arrayed in certain favored geometries. Accordingly, in some preferred embodiments, the urea compounds of Formula (IVa) have the structures shown below:



or

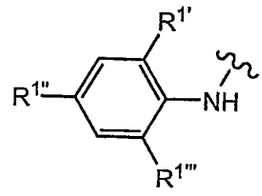


or



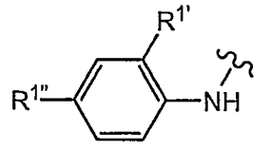
wherein m is 1, 2, or 3, and each $R^{1'}$ and $R^{2'}$ can be independently selected from fluoro, chloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, SEt, SCH_3, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, or two $R^{1'}$ groups together form a methylenedioxy ring. In preferred embodiments of these compounds, $R^{2'}$ is methyl or methoxy.

In some embodiments, the aniline radical of the dihydroindole urea compound has the structure:

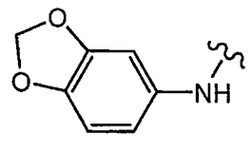


wherein $R^{1'}$, $R^{1''}$ and $R^{1'''}$ are independently selected from hydrogen, fluoro, chloro, bromo, methyl, and methoxy (provided that at least one of $R^{1'}$, $R^{1''}$ and $R^{1'''}$ is not hydrogen. Preferably, the aniline radical has the formula:

60



wherein $R^{1'}$ and $R^{1''}$ are independently selected from fluoro, chloro, bromo, methyl, and methoxy. In certain other preferred embodiments, the aniline radical has the formula:

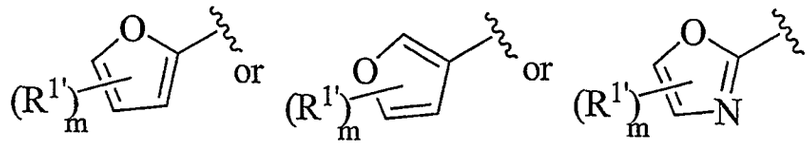


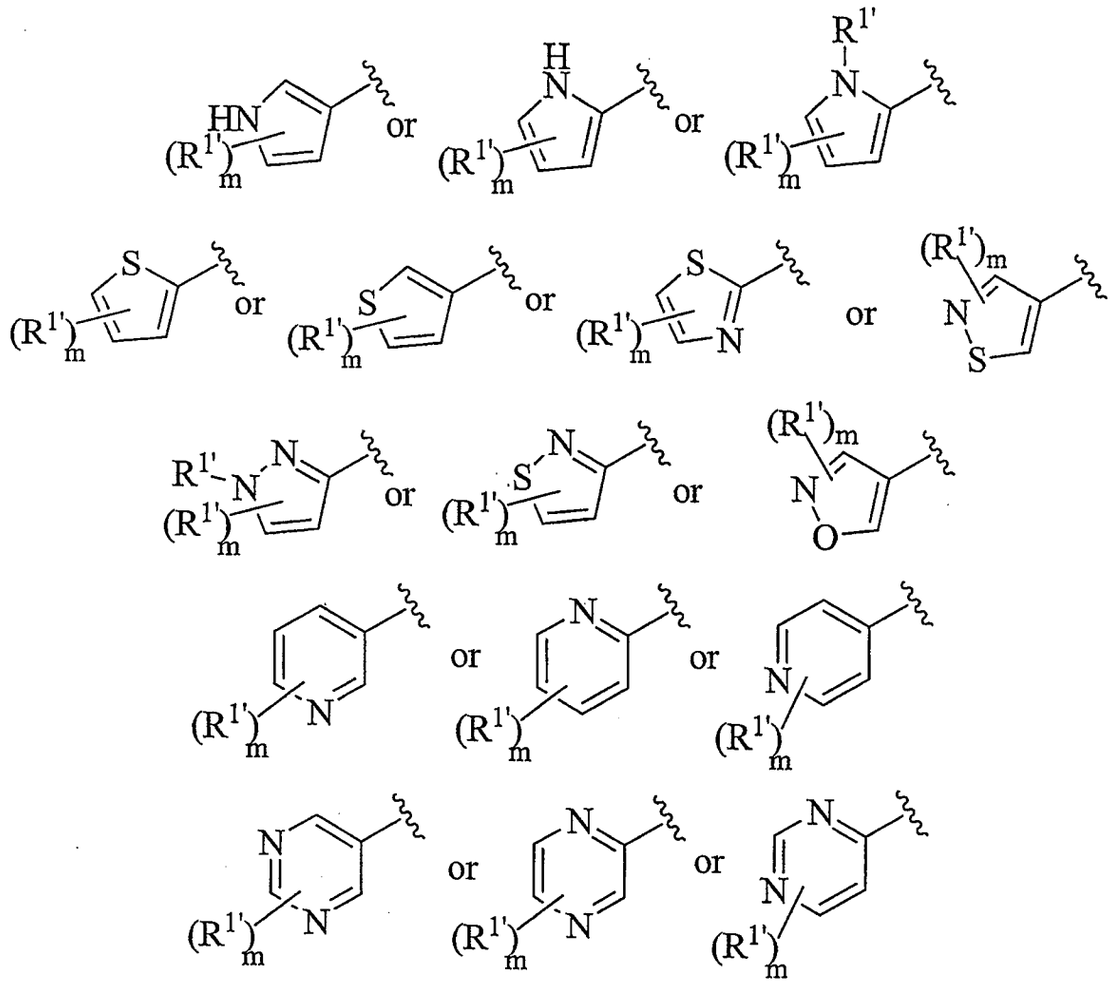
In additional embodiments of the urea compounds of Formula (IV), R^9 and one of R^7 and R^8 are independently selected from arylalkenyls, heteroarylalkenyls, arylalkyls, heteroarylalkyls, alkyls, alkoxy-alkyls, alkenyls, cycloalkyls, cycloalkenyls, aryls and heteroaryls, each of which carbon containing groups may be optionally substituted with 1, 2, or 3 substituents independently selected from hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

In additional embodiments of the urea compounds of Formula (IV), R^9 and one of R^7 and R^8 are independently selected from arylalkyl, heteroarylalkyl, alkyl, cycloalkyl, aryl, heterocycle, and heteroaryl, each of which may optionally comprise one to five heteroatoms independently selected from oxygen, nitrogen, sulfur, chlorine, and fluorine.

In additional embodiments of the urea compounds of Formula (IV), R^9 and one of R^7 and R^8 are independently selected from alkyl, phenyl, cyclohexyl, or pyridyl, each of which may optionally comprise one to four substituents independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy.

In additional embodiments of the urea compounds of Formula (IV), at least one of R^7 and R^8 has one of the heteroaromatic formulas:





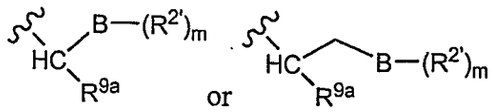
wherein m is 0,1, 2, or 3, and each $R^{1'}$ independently selected from hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups. In such embodiments, R^9 is preferably a C_3-C_{10} branched alkyl, arylalkyl, or a cycloalkyl that can be optionally substituted with 1, 2, or 3 substituents independently selected from hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups. Amide compounds of Formula (II) can be readily synthesized from well known and/or readily commercially available aryl or heteroaryl carboxylic acid precursors.

In additional embodiments of the urea compounds of Formula (IV), at least one of R^7 and R^8 is a phenyl ring optionally substituted with 1, 2, or 3 substituents independently selected from hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and

62

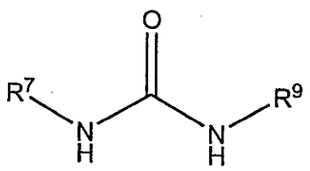
trifluoromethoxy groups. In such embodiments, R^9 is preferably a C_3-C_{10} branched alkyl, arylalkyl, or a cycloalkyl that can be optionally substituted with 1, 2, or 3 substituents independently selected from hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

In additional embodiments of the urea compounds of Formula (IV), R^9 is a C_3-C_{10} branched alkyl. In additional embodiments of the urea compounds of Formula (IV), R^9 has the structure:



wherein B is a phenyl, pyridyl, furanyl, thiofuranyl, pyrrole, cyclopentyl,cyclohexyl, or piperidyl ring, m is 0,1, 2, or 3, and each $R^{2'}$ is independently selected from hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups, and R^{9a} is a selected from the group consisting of an alkyl, alkoxy-alkyl, alkenyl, cycloalkenyl,cycloalkyl, $-R^4OH$, $-R^4O\,R^5$ $-R^4CN$, $-R^4CO_2H$, $-R^4CO_2R^5$, $-R^4COR^5$, $-R^4SR^5$, and $-R^4SO_2R^5$ comprising 1 to 12 carbon atoms.

It has also been discovered that certain subgenuses of the urea compounds of Formula (IV) are unexpectedly effective Umami tastants and/or enhancers of MSG. The relevant urea compound have Formula (Ivc) shown below:



(IVc)

wherein

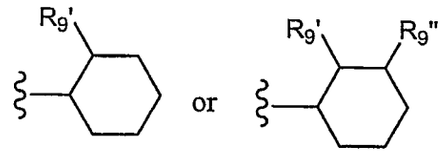
i) R^7 is a phenyl ring optionally substituted with 1, 2, or 3 substituents independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups, or where two of the substituents form a methylenedioxy ring, and

ii) R^9 is a C_3-C_{10} radical selected from a branched alkyl, arylalkyl, or cycloalkyl, wherein the C_3-C_{10} radical optionally comprises 1, 2, or 3

63

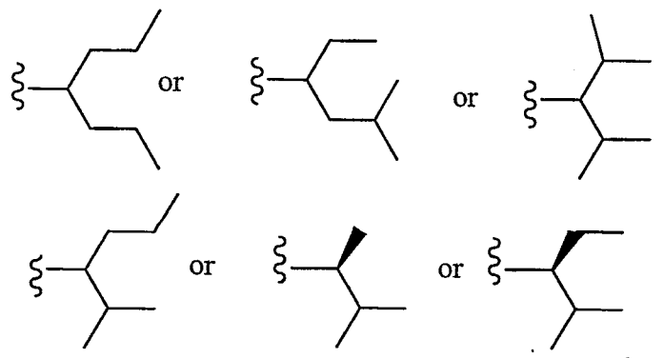
substituents independently selected from hydroxy, fluoro, chloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

In some embodiments of the compounds of Formula (IVc) R^9 has one of the following structures:

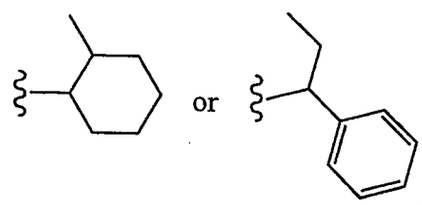


wherein $R_{9'}$ and $R_{9''}$ are independently selected from hydroxy, fluoro, chloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups, and preferably $R_{9'}$ and $R_{9''}$ are methyl.

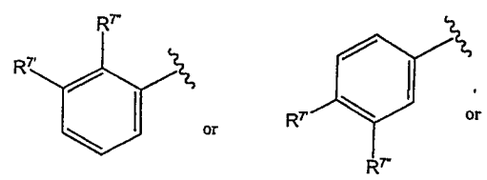
In other embodiments of the Umami ureas of Formula (IVc), R^9 is a C_4-C_8 branched alkyl, which can include for example the following structures:

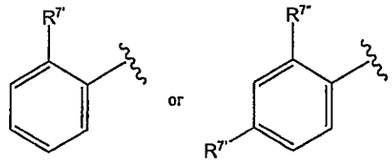


In additional embodiments of the Umami ureas of Formula (IVc), R^9 has one of the following structures:

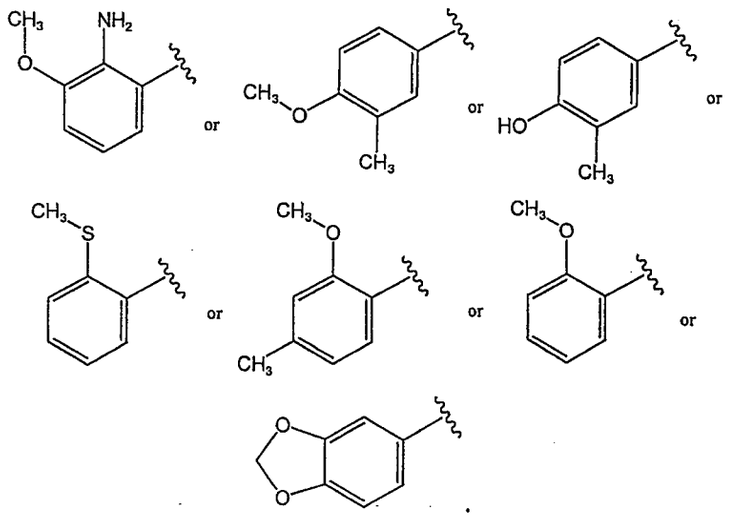


In some embodiments of the Umami ureas of Formula (IVc), R^7 has the structure:



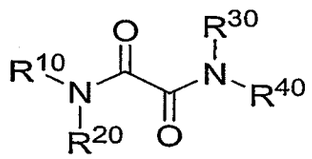


wherein $R_{7'}$ and $R_{7''}$ are independently selected from hydroxy, fluoro, chloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups, and in preferred embodiments, R^7 has one of the structures:



Oxalamide Compounds

In another subgenus of the amide compounds of Formula (I), the amide compound is an oxalamide compound having Formula (V):



(V)

wherein $R^{10}$and R^{30} are each independently selected a hydrocarbon residue that may contain one or more heteroatoms, or preferably, R^{10} and R^{30} are independently selected from the group consisting of arylalkyl, heteroarylalkyl, heterocycle-alkyl, or optionally substituted groups thereof, and

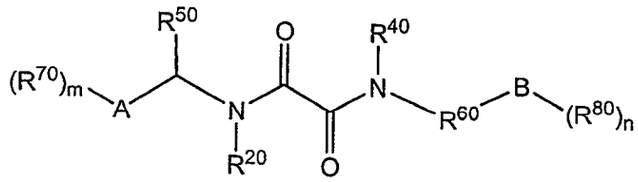
R^{20} and R^{40} are each independently H or a hydrocarbon residue that may contain one or more heteroatoms; preferably R^{20}, and R^{40} are H or C_1-C_3 alkyl, or optionally substituted groups thereof. More preferably R^{20} and R^{40} are H. Moreover, there can be 0, 1, 2, 3, or 4 optional substituent groups for R^{10} and R^{30} independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3,SCH_3, SEt, methyl,

ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

In preferred embodiment of the oxalamide compounds of Formula (V), $R^{10}$and R^{30} are independently selected hydrocarbon residues having at least three carbon atoms and optionally one to ten heteroatoms independently selected from oxygen, nitrogen, sulfur, halogens, or phosphorus, and wherein $R^{20}$and R^{40} are independently selected from hydrogen and a hydrocarbon residue having at least three carbon atoms and optionally one to ten heteroatoms independently selected from oxygen, nitrogen, sulfur, halogens, or phosphorus.

In many preferred embodiment of the oxalamide compounds of Formula (V), $R^{20}$and R^{40} are hydrogen. In such embodiments, R^{10} and R^{30} can be independently selected from the group consisting of arylalkyls, heteroarylalkyls, cycloalkyl-alkyls, and heterocycle-alkyls comprising five to 15 carbon atoms, wherein each of R^{10} and R^{30} can optionally comprise one to one to four substituents independently selected from hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

In many embodiments of the oxalamide compounds of Formula (V), the oxalamide compound has the Formula (Va):



(Va)

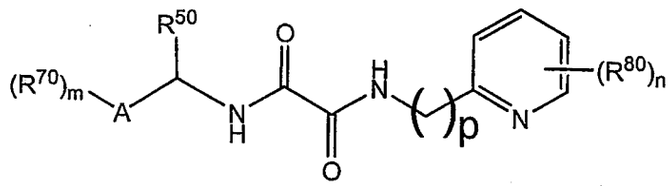
wherein A and B are independently an aryl, heteroaryl, cycloalkyl, or a heterocycle comprising 5 to 12 ring atoms; m and n are independently 0, 1, 2, 3 or 4-8; $R^{20}$and R^{40} are hydrogen, R^{50} is hydrogen or an alkyl or substituted alkyl residue comprising one to four carbon atoms; R^{60} is absent or a C_1-C_5 alkylene or a C_1-C_5 substituted alkylene; R^{70} and R^{80} are independently selected from the group consisting of hydrogen, alkyl, alkoxyl, alkoxy-alkyl, OH, SR^9, halogen, CN, NO_2, CO_2R^9, COR^9, $CONR^9R^{10}$, NR^9R^{10}, NR^9COR^{10}, SOR^9, SO_2R^9, $SO_2NR^9R^{10}$, $NR^9SO_2R^{10}$, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocycle; R^9 and R^{10} are independently selected from H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkenyl.

In preferred embodiments of the oxalamide compounds of Formula (Va), R^{60} is a -CH_2CH_2- group, A and B are independently selected from phenyl, pyridyl, furanyl,

thiofuranyl and pyrrolyl rings and R^{70} and R^{80} are independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

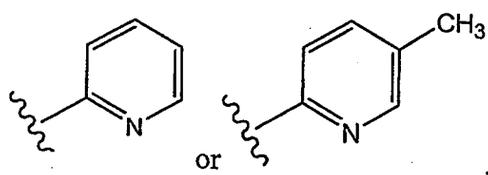
In some embodiments of the oxalamide compounds of Formula (Va), A and B are independently a phenyl, pyridyl, furanyl, benzofuranyl, pyrrole, benzothiophene, piperidyl, cyclopentyl, cyclohexyl, or cycloheptyl ring; m and n are independently 0, 1, 2, or 3; $R^{20}$and R^{40} are hydrogen; R^{50} is hydrogen or methyl; R^{60} is a C_1-C_5 or preferably C_2 alkylene; R^{70} and R^{80} are independently selected from hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

In many embodiments of the oxalamide compounds of Formula (V), the oxalamide compound has the Formula (Vb):



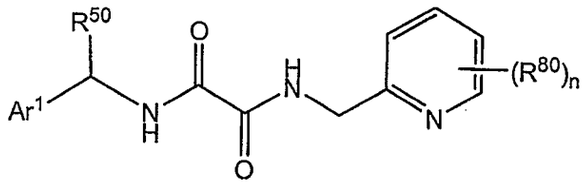
(Vb)

wherein A is a phenyl, pyridyl, furanyl, pyrrole, piperidyl, cyclopentyl, cyclohexyl, or cycloheptyl ring; m and n are independently 0, 1, 2, or 3; R^{50} is hydrogen or methyl; P is 1 or 2; and R^{70} and R^{80} are independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy , or two of R^{70} together form a methylenedioxy ring. In some embodiments of the oxalamide compounds of Formula (Vb), the pyridyl-R^{80} radical has the structure:



or

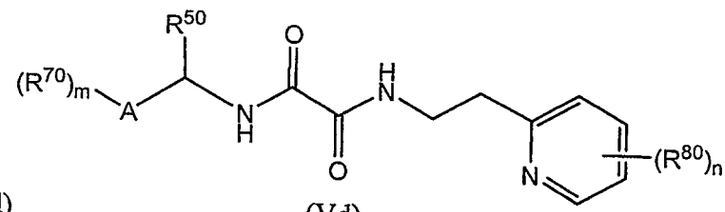
In certain preferred embodiments of the amide compounds of Formula (V), the oxalamide compound has the Formula (Vc):



(Vc)

wherein Ar^1 is a substituted aryl or heteroaryl ring comprising five to 12 carbon atoms; R^{50} is hydrogen or methyl; n is 0, 1, 2, or 3; each R^{80} is independently selected from the group consisting of hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups. In some embodiments of the oxalamide compounds of Formula (Vc), Ar^1 is a 2-, 3-, or 4-mono-substituted phenyl, 2,4-, 2,3-, 2,5, 2,6, 3,5-, or 3,6-disubstituted phenyl, 3-alkyl-4-substituted phenyl, a tri-substituted phenyl wherein the substituent groups are independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, or two adjacent substituents together form a methylenedioxy ring on the phenyl ring. In some embodiments of the oxalamide compounds of Formula (Vc), Ar^1 is a substituted heteroaryl ring comprising 5 to 12 carbon atoms and wherein the substituent groups are independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy.

In certain preferred embodiments of the amide compounds of Formula (V), the oxalamide compound has the Formula (Vd):



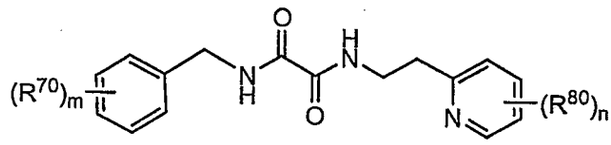
(Vd) (Vd)

wherein A is a substituted aryl or heteroaryl ring comprising five to 12 carbon atoms; R^{50} is hydrogen or methyl; n is 0, 1, 2, or 3; each R^{80} is independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl,

68

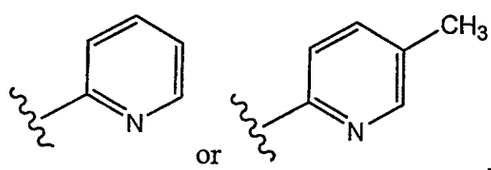
trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy. Preferably, A is a phenyl, pyridyl, furanyl, pyrrole, piperidyl, cyclopentyl, cyclohexyl, or cycloheptyl ring optionally substituted with 1, 3, or 3 substituent groups independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

In certain preferred embodiments of the amide compounds of Formula (V), the oxalamide compound has the Formula (Ve):



(Ve)

wherein m and n are independently 0, 1, 2, or 3; R^{70} and R^{80} are independently selected from the group consisting of hydrogen, alkyl, alkoxyl, alkoxy-alkyl, OH, SR^9, halogen, CN, NO_2, CO_2R^9, COR^9, $CONR^9R^{10}$, NR^9R^{10}, NR^9COR^{10}, SOR^9, SO_2R^9, $SO_2NR^9R^{10}$, $NR^9SO_2R^{10}$, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocycle; and R^9 and R^{10} are independendently selected from H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkenyl groups. Preferably, R^{70} and R^{80} are independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups. Preferably, the pyridyl-R^{80} radical of the oxalamide compound of Formula (Ve) has the structure:

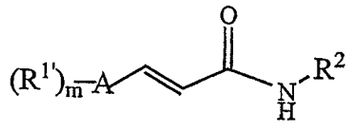


As can be noted by inspection of the Examples attached hereinbelow, oxalamide compounds of Formulas (Va)-(Ve) are excellent agonists of T1R1/T1R3 savory ("umami") taste receptors at very low concentrations on the order of micromolar concentrations or less, induce a noticeable sensation of a savory umami flavor in humans, and/or can serve as enhancers of the savory umami flavor of MSG. Accordingly, oxalamide compounds of Formulas (Vc), (Vd) and (Ve) can be utilized as savory flavoring agents or savory flavor

enhancers when contacted with a wide variety of comestible products and/or compositions, or their precursors, as is described elsewhere herein.

Acrylamide Compounds

In another subgenus of the amide compounds of Formula (I), the amide compound is an acrylamide compound having Formula (VI):



(VI)

wherein A is a 5 or 6 membered aryl or heteroaryl ring; m is 0, 1, 2, 3 or 4; each $R^{1'}$ is independently selected from alkyl, alkoxyl, alkoxy-alkyl, OH, CN, CO_2H, CO_2R^6, CHO, COR^6, SR^6, halogen, alkenyl, cycloalkyl, cycloalkenyl, aryl, and heteroaryl, and R^2 can be any of the various embodiments of R^2 described hereinabove with respect to the amides of Formula (I).

In some of the acrylamide compounds of Formula (VI), A is a phenyl ring and m is 1, 2, 3 or 4, or preferably m is 1 or 2, and $R^{1'}$ can be independently selected from hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups. In some of the acrylamide compounds of Formula (VI), R^2 is a C_3-C_{10} alkyl, or an α-substituted carboxylic acid lower alkyl ester.

Comestibly or Pharmaceutically Acceptable Compounds

Many of the amide compounds of Formula (I) or its various enumerated subgenuses comprise acidic or basic groups, so that depending on the acidic or basic character ("pH") of the comestible or medicinal compositions in which they are formulated, they may be present as salts, which are preferably comestibly acceptable (*i.e.* designated as generally recognized as safe, or GRAS) or pharmaceutically acceptable salts (many of which have been recognized by the Federal Food and Drug Administration).

The amide compounds of Formula (I) having acidic groups, such as carboxylic acids, will tend (at near neutral physiological pH) to be present in solution in the form of anionic carboxylates, and therefore will in preferred embodiments have an associate comestibly and/or pharmaceutically acceptable cation, many of which are known to those of ordinary skill in the art. Such comestibly and/or pharmaceutically acceptable cations include alkali metal cations (lithium, sodium, and potassium cations), alkaline earth metal

cations (magnesium, calcium, and the like), or ammonium $(NH_4)^+$ or organically substituted ammonium cations such as $(R\text{-}NH_3)^+$ cations.

The amide compounds of Formula (I) having basic substituent groups, such as amino or nitrogen containing heterocyclic groups, will tend (at near neutral physiological pH, or at the acidic pH common in many foods) to be present in solution in the form of cationic ammonium groups, and therefore will in preferred embodiments have an associate comestibly and/or pharmaceutically acceptable anion, many of which are known to those of ordinary skill in the art. Such comestibly and/or pharmaceutically acceptable anionic groups include the anionic form of a variety of carboxylic acids (acetates, citrates, tartrates, anionic salts of fatty acids, *etc.*), halides (especially fluorides or chlorides), nitrates, and the like.

The amide compounds of Formula (I) and its various subgenuses should preferably be comestibly acceptable, *i.e.* deemed suitable for consumption in food or drink, and should also be pharmaceutically acceptable. The typical method of demonstrating that a flavorant compound is comestibly acceptable is to have the compound tested and/or evaluated by an Expert Panel of the Flavor and Extract Manufacturers Association and declared as to be "Generally Recognized As Safe" ("GRAS"). The FEMA/GRAS evaluation process for flavorant compounds is complex but well known to those of ordinary skill in the food product preparation arts, as is discussed by Smith *et al.* in an article entitled "GRAS Flavoring Substances 21," Food Technology, 57(5), pgs. 46-59, May 2003, the entire contents of which are hereby incorporated herein by reference.

When being evaluated in the FEMA/GRAS process, a new flavorant compound is typically tested for any adverse toxic effects on laboratory rats when fed to such rats for at least about 90 days at a concentration 100-fold, or 1000-fold, or even higher concentrations than the proposed maximum allowable concentration of the compound in a particular category of food products being considered for approval. For example, such testing of the amide compounds of the invention might involve combining the amide compound with rat chow and feeding it to laboratory rats such as Crl:CD(SD)IGS BR rats, at a concentration of about 100 milligrams/Kilogram body weight/day for 90 days, and then sacrificing and evaluating the rats by various medical testing procedures to show that the amide compound of Formula (I) causes no adverse toxic effects on the rats.

The Compounds of the Invention as Savory or Sweet Taste Enhancers

The amide compounds of Formula (I) and its various compound sub-genuses and species, as described above are intended to be savory or sweet taste flavorant compounds or flavor modifiers for comestible or medicinal products. As is apparent from the teachings and Examples herein, many compounds of Formula (I) are agonists of an hT1R1/hT1R3 "savory" receptor, or an hT1R2/hT1R3 sweet receptor, at least at relatively high amide compound concentrations, and accordingly many of the amide compounds of Formula (I) can have utility as savory or sweet flavorants or flavor enhancers, in their own right, at least at relatively high concentrations.

Nevertheless, it is preferable to use as little of such artificial flavorants as possible, so as to minimize both cost and any undesirable health side effects of administration of the compounds of Formula (I) at high concentration levels. Accordingly, it is desirable to test the compounds of Formula (I) for their effectiveness as taste receptor agonists at lower concentration levels, so as to identify the best and most effective amide compounds within the compounds of Formula (I). As was disclosed in WO 03/001876, and U.S. Patent publication US 2003-0232407 A1, and as described hereinbelow, laboratory procedures now exist for measuring the agonist activities of compounds for an hT1R1/hT1R3 "savory" and hT1R2/hT1R3 sweet receptors. Such measurement methods typically measure an "EC_{50}", *i.e.* the concentration at which the compound causes 50% activation of the relevant receptor.

Preferably, the amide compounds of Formula (I) that are savory flavor modifiers have an EC_{50} for the hT1R1/hT1R3 receptor of less than about 10 μM. More preferably, such amide compounds have an EC_{50} for the hT1R1/hT1R3 receptor of less than about 5 μM, 3 μM, 2 μM, 1 μM, or 0.5 μM.

Preferably, the amide compounds of Formula (I) that are sweet flavor modifiers or sweet flavor enhancers have an EC_{50} for the hT1R2/hT1R3 receptor of less than about 10 μM. More preferably, such amide compounds have an EC_{50} for the hT1R2/hT1R3 receptor of less than about 5 μM, 3 μM, 2 μM, 1 μM, or 0.5 μM.

In some embodiments, the amide compounds of Formula (I) are savory flavor modulators or enhancers of the agonist activity of monosodium glutamate for an hT1R1/hT1R3 receptor. Hereinbelow is described an assay procedure for so-called EC_{50} ratios, *i.e.* for dissolving a compound of Formula (I) in water containing MSG, and measuring the degree to which the amide compound lowers the amount of MSG required to activate 50% of the available hT1R1/hT1R3 receptors. Preferably, the amide compounds of

Formula (I), when dissolved in a water solution comprising about *1* μM of the amide compound will decrease the observed EC_{50} of monosodium glutamate for an hT1R1/hT1R3 receptor expressed in an HEK293-G□15 cell line by at least 50%, *i.e.* the amide compound will have an EC50 ratio of at least 2.0, or preferably 3.0, 5.0, or 7.0.

Although no specific EC_{50} ratio assays for sweet enhancers have yet been developed, it is believed the amide compounds of Formula (I), and more specifically many of the amides of Formula (II) can modulate the binding of a known sweetener such as for example sucrose, fructose, glucose, erythritol, isomalt, lactitol, mannitol, sorbitol, xylitol, a known natural terpenoid, flavonoid, or protein sweetener, aspartame, saccharin, acesulfame-K, a cyclamate, sucralose, alitame or erythritol to an hT1R2/hT1R3 receptor. Appropriate assays for such sweet enhancement properties can be readily developed by one of ordinary skill in the arts by using appropriate cell lines expressing hT1R2/hT1R3 receptors.

The above identified assays are useful in identifying the most potent of the amide compounds of Formula (I) for savory and/or sweet taste modifier or enhancer properties, and the results of such assays are believed to correlate well with actual savory or sweet taste perception in animals and humans, but ultimately the results of the assays can be confirmed, at least for the most potent of the compounds of Formula (I), by human taste testing. Such human taste testing experiments can be well quantified and controlled by tasting the candidate compounds in aqueous solutions, as compared to control aqueous solution, or alternatively by tasting the amides of the inventions in actual food compositions.

Accordingly, in order to identify the more potent of the savory taste modifiers or agents, or enhancers of the Umami flavor of MSG in a comestible or medicinal composition, a water solution comprising a savory flavor modifying amount of the amide compound should have a savory taste as judged by the majority of a panel of at least eight human taste testers.

Correspondingly, in order to identify the more potent of the savory taste enhancers of Formula (I), a water solution comprising a savory flavor modifying amount of an amide compound of Formula (I) and 12 mM monosodium glutamate, would have an increased savory taste as compared to a control water solution comprising 12 mM monosodium glutamate, as determined by the majority of a panel of at least eight human taste testers. Preferably, in order to identify the more potent of the savory taste enhancers, a water solution comprising a savory flavor modifying amount (preferably about 30, 10, 5, or 2 ppm) of the amide compound of Formula (I) and 12 mM monosodium glutamate will have

an increased savory taste as compared to a control water solution comprising 12 mM monosodium glutamate and 100 μM inosine monophosphate, as determined by the majority of a panel of at least eight human taste testers.

Similar human taste testing procedures can be used to identify which of the compounds of Formula (I) are the more effective sweet taste agents or sweet taste enhancing agents. Preferred sweet taste modifiers of Formula (I) can be identified when a modified comestible or medicinal product has a sweeter taste than a control comestible or medicinal product that does not comprise the amide compound, as judged by the majority of a panel of at least eight human taste testers.

Preferred sweet taste enhancers of Formula (I) can be identified when a water solution comprising a sweet tasting amount of a known sweetener selected from the group consisting of sucrose, fructose, glucose, erythritol, isomalt, lactitol, mannitol, sorbitol, xylitol, a known natural terpenoid, flavonoid, or protein sweetener, aspartame, saccharin, acesulfame-K, cyclamate, sucralose, and alitame, and a sweet flavor modifying amount of the amide compound (preferably about 30, 10, 5, or 2 ppm) has a sweeter taste than a control water solution comprising the sweet tasting amount of the known sweetener, as judged by the majority of a panel of at least eight human taste testers. In such taste test experiments, sucrose would preferably be present at a concentration of about 6 grams/100 milliliters, a 50:50 mixture of glucose and fructose would preferably be present at a concentration of about 6 grams/100 milliliters, aspartame would preferably be present at a concentration of about 1.6 mM, acesulfame-K would preferably be present at a concentration of about 1.5 mM, cyclamate would preferably be present at a concentration of about 10 mM, sucralose would preferably be present at a concentration of about 0.4 mM, or alitame would preferably be present at a concentration of about 0.2 mM.

Using the Compounds of Formula (I) to Prepare Comestible Compositions

Flavors, flavor modifiers, flavoring agents, flavor enhancers, savory ("umami") flavoring agents and/or flavor enhancers, the compounds of Formula (I) and its various subgenuses and species of compounds have application in foods, beverages and medicinal compositions wherein savory or sweet compounds are conventionally utilized. These compositions include compositions for human and animal consumption. This includes foods for consumption by agricultural animals, pets and zoo animals.

Those of ordinary skill in the art of preparing and selling comestible compositions (*i.e.* edible foods or beverages, or precursors or flavor modifiers thereof) are well aware of a

74

large variety of classes, subclasses and species of the comestible compositions, and utilize well-known and recognized terms of art to refer to those comestible compositions while endeavoring to prepare and sell various of those compositions. Such a list of terms of art is enumerated below, and it is specifically contemplated hereby that the various subgenuses and species of the compounds of Formula (I) could be used to modify or enhance the savory and/or sweet flavors of the following list comestible compositions, either singly or in all reasonable combinations or mixtures thereof:

One or more confectioneries, chocolate confectionery, tablets, countlines, bagged selflines/softlines, boxed assortments, standard boxed assortments, twist wrapped miniatures, seasonal chocolate, chocolate with toys, alfajores, other chocolate confectionery, mints, standard mints, power mints, boiled sweets, pastilles, gums, jellies and chews, toffees, caramels and nougat, medicated confectionery, lollipops, liquorice, other sugar confectionery, gum, chewing gum, sugarized gum, sugar-free gum, functional gum, bubble gum, bread, packaged/industrial bread, unpackaged/artisanal bread, pastries, cakes, packaged/industrial cakes, unpackaged/artisanal cakes, cookies, chocolate coated biscuits, sandwich biscuits, filled biscuits, savory biscuits and crackers, bread substitutes, breakfast cereals, rte cereals, family breakfast cereals, flakes, muesli, other rte cereals, children's breakfast cereals, hot cereals, ice cream, impulse ice cream, single portion dairy ice cream, single portion water ice cream, multi-pack dairy ice cream, multi-pack water ice cream, take-home ice cream, take-home dairy ice cream, ice cream desserts, bulk ice cream, take-home water ice cream, frozen yoghurt, artisanal ice cream, dairy products, milk, fresh/pasteurized milk, full fat fresh/pasteurized milk, semi skimmed fresh/pasteurized milk, long-life/uht milk, full fat long life/uht milk, semi skimmed long life/uht milk, fat-free long life/uht milk, goat milk, condensed/evaporated milk, plain condensed/evaporated milk, flavored, functional and other condensed milk, flavored milk drinks, dairy only flavored milk drinks, flavored milk drinks with fruit juice, soy milk, sour milk drinks, fermented dairy drinks, coffee whiteners, powder milk, flavored powder milk drinks, cream, cheese, processed cheese, spreadable processed cheese, unspreadable processed cheese, unprocessed cheese,

spreadable unprocessed cheese, hard cheese, packaged hard cheese, unpackaged hard cheese, yoghurt, plain/natural yoghurt, flavored yoghurt, fruited yoghurt, probiotic yoghurt, drinking yoghurt, regular drinking yoghurt, probiotic drinking yoghurt, chilled and shelf-stable desserts, dairy-based desserts, soy-based desserts, chilled snacks, fromage frais and quark, plain fromage frais and quark, flavored fromage frais and quark, savory fromage frais and quark, sweet and savory snacks, fruit snacks, chips/crisps, extruded snacks, tortilla/corn chips, popcorn, pretzels, nuts, other sweet and savory snacks, snack bars, granola bars, breakfast bars, energy bars, fruit bars, other snack bars, meal replacement products, slimming products, convalescence drinks, ready meals, canned ready meals, frozen ready meals, dried ready meals, chilled ready meals, dinner mixes, frozen pizza, chilled pizza, soup, canned soup, dehydrated soup, instant soup, chilled soup, uht soup, frozen soup, pasta, canned pasta, dried pasta, chilled/fresh pasta, noodles, plain noodles, instant noodles, cups/bowl instant noodles, pouch instant noodles, chilled noodles, snack noodles, canned food, canned meat and meat products, canned fish/seafood, canned vegetables, canned tomatoes, canned beans, canned fruit, canned ready meals, canned soup, canned pasta, other canned foods, frozen food, frozen processed red meat, frozen processed poultry, frozen processed fish/seafood, frozen processed vegetables, frozen meat substitutes, frozen potatoes, oven baked potato chips, other oven baked potato products, non-oven frozen potatoes, frozen bakery products, frozen desserts, frozen ready meals, frozen pizza, frozen soup, frozen noodles, other frozen food, dried food, dessert mixes, dried ready meals, dehydrated soup, instant soup, dried pasta, plain noodles, instant noodles, cups/bowl instant noodles, pouch instant noodles, chilled food, chilled processed meats, chilled fish/seafood products, chilled processed fish, chilled coated fish, chilled smoked fish, chilled lunch kit, chilled ready meals, chilled pizza, chilled soup, chilled/fresh pasta, chilled noodles, oils and fats, olive oil, vegetable and seed oil, cooking fats, butter, margarine, spreadable oils and fats, functional spreadable oils and fats, sauces, dressings and condiments, tomato pastes and purées, bouillon/stock cubes,

stock cubes, gravy granules, liquid stocks and fonds, herbs and spices, fermented sauces, soy based sauces, pasta sauces, wet sauces, dry sauces/powder mixes, ketchup, mayonnaise, regular mayonnaise, mustard, salad dressings, regular salad dressings, low fat salad dressings, vinaigrettes, dips, pickled products, other sauces, dressings and condiments, baby food, milk formula, standard milk formula, follow-on milk formula, toddler milk formula, hypoallergenic milk formula, prepared baby food, dried baby food, other baby food, spreads, jams and preserves, honey, chocolate spreads, nut-based spreads, and yeast-based spreads.

Preferably, the compounds of Formula (I) can be used to modify or enhance the savory or sweet flavor of one or more of the following sub-genuses of comestible compositions: confectioneries, bakery products, ice creams, dairy products, sweet and savory snacks, snack bars, meal replacement products, ready meals, soups, pastas, noodles, canned foods, frozen foods, dried foods, chilled foods, oils and fats, baby foods, or spreads, or a mixture thereof.

In general an ingestible composition will be produced that contains a sufficient amount of at least one compound within the scope of Formula (I) or its various subgenuses described hereinabove to produce a composition having the desired flavor or taste characteristics such as "savory" or "sweet" taste characteristics.

Typically at least a savory flavor modulating amount, a sweet flavor modulating amount, a savory flavoring agent amount, a sweet flavoring agent amount, a savory flavor enhancing amount, a sweet flavor enhancing amount of one or more of the compounds of Formula (I) will be added to the comestible or medicinal product, optionally in the presence of known savory flavor agents such as MSG, or known sweeteners, so that the savory or sweet flavor modified comestible or medicinal product has an increased savory and/or sweet taste as compared to the comestible or medicinal product prepared without the amide compound, as judged by human beings or animals in general, or in the case of formulations testing, as judged by a majority of a panel of at least eight human taste testers, via procedures described elsewhere herein.

The concentration of savory or sweet flavoring agent needed to modulate or improve the flavor of the comestible or medicinal product or composition will of course vary dependent on many variables, including the specific type of ingestible composition, what

77

known savory or sweet flavoring agents are also present and the concentrations thereof, and the effect of the particular compound on such savory compounds. As noted, a significant application of the compounds of Formula (I) is for modulating (inducing, enhancing or inhibiting) the savory taste or other taste properties of other natural or synthetic savory tastants, such as MSG. A broad but also low range of concentrations of the amide compounds of Formula (I) would typically be required, *i.e.* from about 0.001 ppm to 100 ppm , or narrower alternative ranges from about 0.1 ppm to about 10 ppm, from about 0.01 ppm to about 30 ppm, from about 0.05 ppm to about 15 ppm, from about 0.1 ppm to about 5 ppm, or from about 0.1 ppm to about 3 ppm. In many embodiments, MSG would also be present at a concentration of at least about 10 ppm, or preferably 100 or 1000 ppm.

Examples of foods and beverages wherein compounds according to the invention may be incorporated included by way of example the Wet Soup Category, the Dehydrated and Culinary Food Category, the Beverage Category, the Frozen Food Category, the Snack Food Category, and seasonings or seasoning blends.

"Wet Soup Category" means wet/liquid soups regardless of concentration or container, including frozen Soups. For the purpose of this definition soup(s) means a food prepared from meat, poultry, fish, vegetables, grains, fruit and other ingredients, cooked in a liquid which may include visible pieces of some or all of these ingredients. It may be clear (as a broth) or thick (as a chowder), smooth, pureed or chunky, ready-to-serve, semi-condensed or condensed and may be served hot or cold, as a first course or as the main course of a meal or as a between meal snack (sipped like a beverage). Soup may be used as an ingredient for preparing other meal components and may range from broths (consommé) to sauces (cream or cheese-based soups).

"Dehydrated and Culinary Food Category" means: (i) Cooking aid products such as: powders, granules, pastes, concentrated liquid products, including concentrated bouillon, bouillon and bouillon like products in pressed cubes, tablets or powder or granulated form, which are sold separately as a finished product or as an ingredient within a product, sauces and recipe mixes (regardless of technology); (ii) Meal solutions products such as: dehydrated and freeze dried soups, including dehydrated soup mixes, dehydrated instant soups, dehydrated ready-to-cook soups, dehydrated or ambient preparations of ready-made dishes, meals and single serve entrées including pasta, potato and rice dishes; and (iii) Meal embellishment products such as: condiments, marinades, salad dressings, salad toppings, dips, breading, batter mixes, shelf stable spreads, barbecue sauces, liquid recipe mixes,

concentrates, sauces or sauce mixes, including recipe mixes for salad, sold as a finished product or as an ingredient within a product, whether dehydrated, liquid or frozen.

"Beverage Category" means beverages, beverage mixes and concentrates, including but not limited to, alcoholic and non-alcoholic ready to drink and dry powdered beverages.

Other examples of foods and beverages wherein compounds according to the invention may be incorporated included by way of example carbonated and non-carbonated beverages, *e.g.*, sodas, fruit or vegetable juices, alcoholic and non-alcoholic beverages, confectionary products, *e.g.*, cakes, cookies, pies, candies, chewing gums, gelatins, ice creams, sorbets, puddings, jams, jellies, salad dressings, and other condiments, cereal, and other breakfast foods, canned fruits and fruit sauces and the like.

Additionally, the subject compounds can be used in flavor preparations to be added to foods and beverages. In preferred instances the composition will comprise another flavor or taste modifier such as a savory tastant.

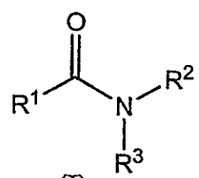
Methods for Modifying the Taste of Comestible or Medicinal Compositions

In many embodiments, the inventions relate to methods for modulating the savory or sweet taste of a comestible or medicinal product comprising:

a) providing at least one comestible or medicinal product, or one or more precursors thereof, and

b) combining the comestible or medicinal product or one or more precursors thereof with at least a savory flavor modulating amount or a sweet flavor modulating amount of at least one non-naturally occurring amide compound, or a comestibly acceptable salt thereof, so as to form a modified comestible or medicinal product;

wherein the amide compound has the formula:



(I)

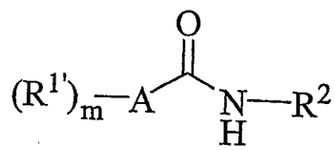
herein the amide compound is an amide of Formula (I), or any of its various subgenuses or species compounds described herein, wherein R^1, R^2, and R^3 can be defined in the many ways also described hereinabove. Examples of such methods include but are not limited to the methods embodied below.

In some exemplary embodiments, the invention relates to a method for enhancing the sweet taste of a comestible or medicinal product comprising:

a) providing at least one comestible or medicinal product, or one or more precursors thereof, and

b) combining the comestible or medicinal product or one or more precursors thereof with at least a sweet flavor modulating amount of at least one non-naturally occurring amide compound, or a comestibly acceptable salt thereof, so as to form a modified comestible or medicinal product;

wherein the amide compound has the structure

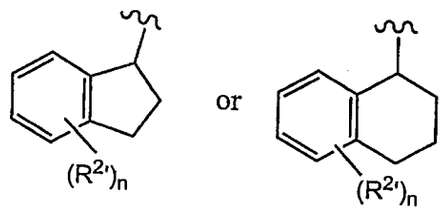


wherein A is an aryl or heteroaryl ring having from 3 to 12 ring atoms;

m is 0, 1, 2, 3 or 4;

each $R^{1'}$ is independently selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkoxyl, C_1-C_4 alkoxy-alkyl, C_1-C_4 hydroxy-alkyl, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, and halogen, wherein R^6 is C_1-C_4 alkyl;

R^2 has the formula



wherein n is 0,1, 2, or 3, and each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring and is independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy.

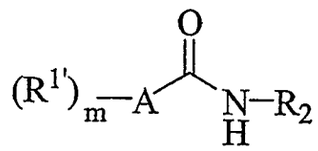
In related but novel embodiments, the invention relates to methods for enhancing the sweet taste of a comestible or medicinal product comprising:

a) providing at least one comestible or medicinal product, or one or more precursors thereof, and

b) combining the comestible or medicinal product or one or more precursors thereof with at least one aromatic or heteroaromatic amide compound, or a

comestibly acceptable salt thereof, so as to form a modified comestible or medicinal product comprising at least about 0.001 ppm of the amide compound;

wherein the amide compound has the structure:

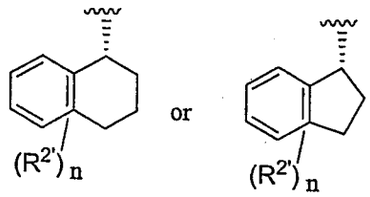


wherein A is a five or six membered aryl or heteroaryl ring;

m is 1, 2, or 3;

each $R^{1'}$ is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, a C_1-C_8 organic radical;

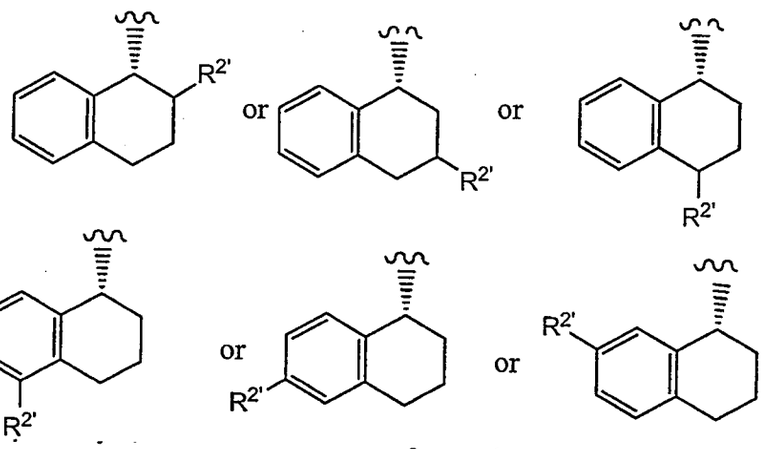
R^2 is a radical having the structure

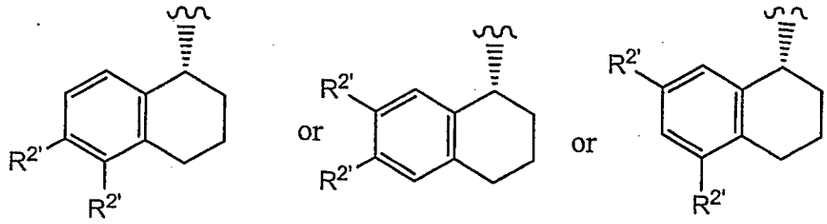


wherein R^2 comprises the indicated optical configuration in enantiomeric excess, n is 1, 2, or 3, each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring of R^2 and each $R^{2'}$ is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical, and

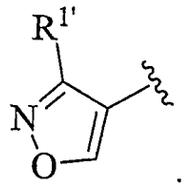
wherein the modified comestible or medicinal product further comprises at least a sweet flavoring agent amount of one or more natural, semi-synthetic, or synthetic sweet flavoring agents, or a mixture thereof.

2. In such methods, R^2 preferably has one of the structures:





wherein each $R^{2'}$ is independently selected from the group consisting of hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy. Additionally, in such methods, the A group is preferably a phenyl group, or has the formula:



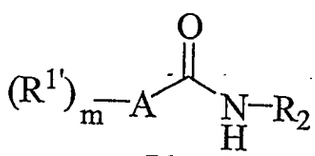
wherein $R^{1'}$ is hydrogen, hydroxyl, NH_2, SH, halogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 haloalkoxy, C_1-C_8 alkoxyl, C_1-C_8 alkoxy-alkyl, C_1-C_8 hydroxy-alkyl, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, and halogen, wherein R^6 is C_1-C_4 alkyl. In further embodiments, $R^{1'}$ is a C_1-C_8 alkyl. In yet additional embodiments, the $R^{1'}$ of the isoxazole ring is hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, n-propyl, n-butyl, 1-methyl-propyl, isobutyl, t-butyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy , CH_2OCH_3, CH_2OH, CH_2NH_2, CH_2NHCH_3, or $CH_2N(CH_3)_2$.

In further embodiments, the invention relates to methods for increasing the sweet taste of a comestible or medicinal product comprising:

a) providing at least one comestible, or one or more precursors thereof, and

b) combining the comestible or medicinal product or one or more precursors thereof with at least one heteroaromatic amide compound, or a comestibly acceptable salt thereof, so as to form a modified comestible or medicinal product comprising at least about 0.001 ppm of the amide compound;

wherein the amide compound has the structure:

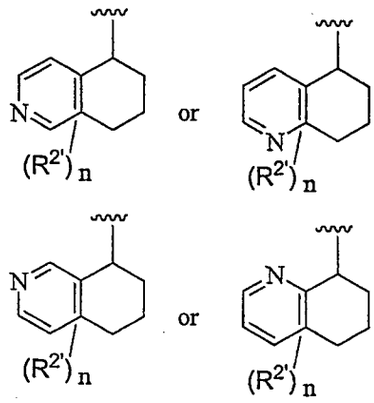


wherein A is a five or six membered aryl or heteroaryl ring;

m is 0, 1, 2, 3 or 4;

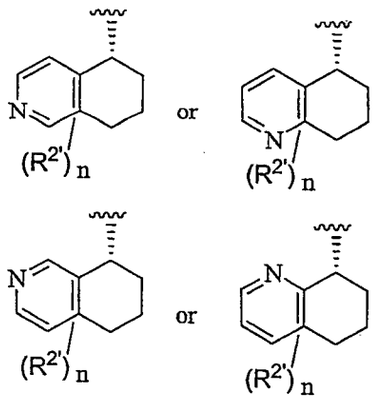
each $R^{1'}$ is independently selected from the group consisting of hydrogen, hydroxyl, NH_2, SH, halogen, or a C_1-C_8 organic radical,

R^2 is a tetrahydroquinolinyl or tetrahydroisoquinolinyl radical having the structure



wherein n is 0, 1, 2, or 3, each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring of R^2 and each $R^{2'}$ is independently selected from the group consisting of hydrogen, hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical.

In such methods, wherein R^2 can preferably be an radical having the structure:



wherein the R^2 radical is present in the indicated optical configuration in enantiomeric excess.

In yet additional embodiments, the invention relates to methods for increasing the sweet taste of a comestible or medicinal product comprising:

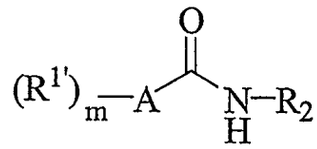
a) providing at least one comestible, or one or more precursors thereof, and

b) combining the comestible or medicinal product or one or more precursors thereof with at least one aromatic or heteroaromatic amide compound, or a comestibly acceptable salt thereof, so as to form a modified comestible or

83

medicinal product comprising at least about 0.001 ppm of the amide compound;

wherein the amide compound has the structure

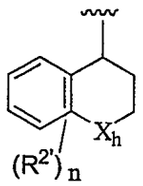


wherein A is a five or six membered aryl or heteroaryl ring;

m is 0, 1, 2, 3 or 4;

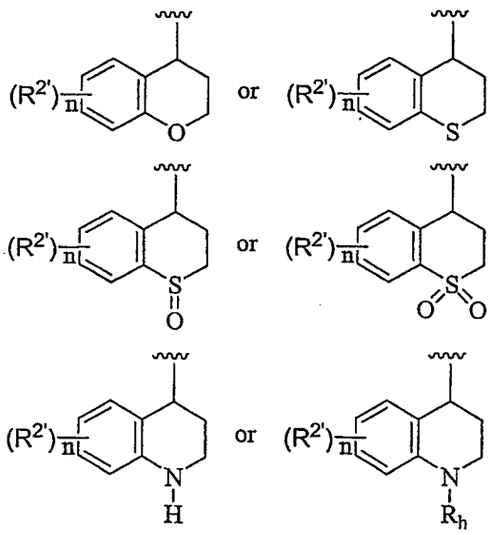
each $R^{1'}$ is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical,

R^2 is a bicyclic heterocyclic radical having the structure



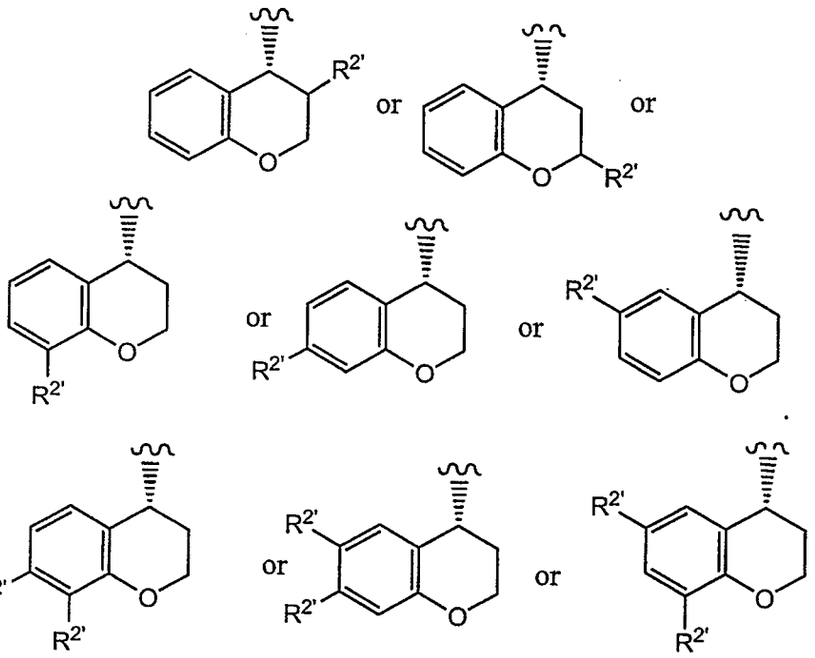
wherein n is 0, 1, 2, or 3, each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring of R^2 and each $R^{2'}$ is independently selected from the group consisting of hydrogen, hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical, and X_h is O, S, SO, SO_2, NH, or NR_h, wherein R_h is a C_1-C_4 organic radical.

In such embodiments, R^2 can preferably have the formula:

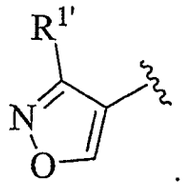


wherein each $R^{2'}$ is bonded to the phenyl ring of the R^2 radical, n is 0, 1, or 2, and each $R^{2'}$ is independently selected from the group consisting of, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl,

vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, and the R^2 ligand can preferably be present in an enantiomeric excess of the "R" configuration, as exemplified by the following specifically enumerated R^2 radicals:



Again, in such embodiments, the A group is preferably a phenyl group, or has the formula:



wherein $R^{1'}$ is hydrogen, hydroxyl, NH_2, SH, halogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 haloalkoxy, C_1-C_8 alkoxyl, C_1-C_8 alkoxy-alkyl, C_1-C_8 hydroxy-alkyl, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, and halogen, wherein R^6 is C_1-C_4 alkyl. In further embodiments, $R^{1'}$ is a C_1-C_8 alkyl. In yet additional embodiments, the $R^{1'}$ of the isoxazole ring is hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, n-propyl, n-butyl, 1-methyl-propyl, isobutyl, t-butyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy , CH_2OCH_3, CH_2OH, CH_2NH_2, CH_2NHCH_3, or $CH_2N(CH_3)_2$.

In additional embodiments, the invention provides methods for enhancing the sweet taste of a comestible or medicinal product comprising:

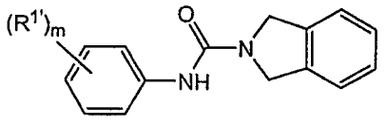
85

a) providing at least one comestible or medicinal product, or one or more precursors thereof, and

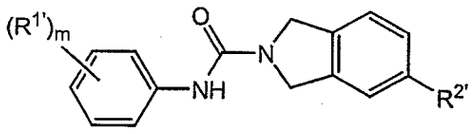
b) combining the comestible or medicinal product or one or more precursors thereof with at least one urea compound, or a comestibly acceptable salt thereof, so as to form a modified comestible or medicinal product comprising at least about 0.001 ppm of the urea compound;

c) wherein the modified comestible or medicinal product further comprises a known natural or artificial sweetener,

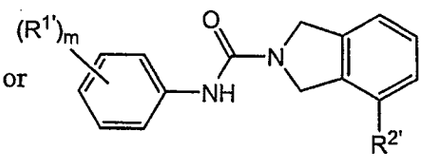
wherein the urea compound has the formula:



or



or



wherein m is 1, 2, or 3, and each $R^{1'}$ and $R^{2'}$ is independently selected from fluoro, chloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, SEt, SCH_3, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, or two $R^{1'}$ groups together form a methylenedioxy ring.

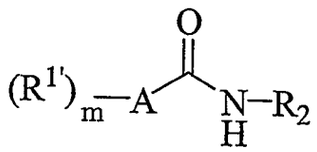
In additional embodiments, the invention relates to methods for enhancing the savory taste of a comestible or medicinal product comprising:

a) providing at least one comestible, or one or more precursors thereof, and

b) combining the comestible or medicinal product or one or more precursors thereof with at least about 0.001 ppm of at least one aromatic or heteroaromatic amide compound, or a comestibly acceptable salt thereof, so as to form a modified comestible or medicinal product, and

c) wherein the modified comestible or medicinal product optionally comprises artificially added monosodium glutamate;

wherein the aromatic or heteroaromatic amide compound has the structure

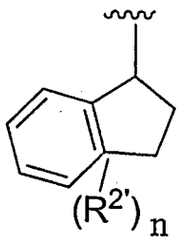


wherein A is a five or six membered aryl or heteroaryl ring;

m is 1, 2, 3 or 4;

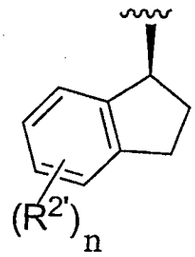
each $R^{1'}$ is independently selected from the group consisting of hydrogen, hydroxyl, NH_2, SH, halogen, or a C_1-C_8 organic radical, or a monocyclic aryl or heteroaryl group,

R^2 is a 1-indanyl radical having the structure:



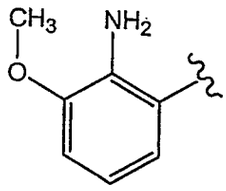
wherein n is 1 or 2, and each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring of R^2 and each $R^{2'}$ is independently selected from the group consisting of hydrogen, hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical.

In such embodiments, R^2 is an optically active 1-indanyl radical having the structure

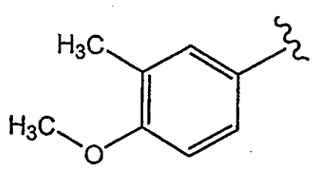


wherein R^2 comprises the indicated optical configuration in enantiomeric excess, and each $R^{2'}$ is bonded to the aromatic ring of R^2.

In such embodiments, n is preferably 1, and/or $R^{2'}$ is preferably selected from group consisting of hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups. In such embodiments, the A group is preferably phenyl, as exemplified by the following specific structures:



or



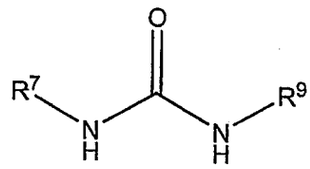
In yet additional embodiments, the invention relates to method for enhancing the savory taste of a comestible or medicinal product comprising:

a) providing at least one comestible, or one or more precursors thereof; and

b) combining the comestible or medicinal product or one or more precursors thereof with at least one urea compound, or a comestibly acceptable salt thereof, so as to form a modified comestible or medicinal product comprising at least about 0.001 ppm of the urea compound, and

c) wherein the modified comestible or medicinal product optionally comprises artificially added monosodium glutamate;

wherein the urea compound has the structure:



(IVc)

and wherein

i) R^7 is a phenyl ring optionally substituted with 1, 2, or 3 substituents independently selected from hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups, or where two of the substituents form a methylenedioxy ring, and

ii) R^9 is a C_3-C_{10} radical selected from a branched alkyl, arylalkyl, or cycloalkyl, wherein the C_3-C_{10} radical optionally comprises 1, 2, or 3 substituents independently selected from hydroxy, fluoro, chloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

The invention also relates to the modified comestible or medicinal products produced by the processes disclosed above.

The invention also relates to similar processes for producing comestible or medicinal products well known to those of ordinary skill in the art. The amide compounds of Formula (I) and its various subgenuses can be combined with or applied to the comestible or medicinal products or precursor thereof in any of innumerable ways known to cooks, food preparers the world over, or producers of comestible or medicinal products. For example, the amide compounds of Formula (I) could be dissolved in or dispersed in or one of many comestibly acceptable liquids, solids, or other carriers, such as water at neutral, acidic, or

basic pH, fruit or vegetable juices, vinegar, marinades, beer, wine, natural water/fat emulsions such as milk or condensed milk, edible oils and shortenings, fatty acids, certain low molecular weight oligomers of propylene glycol, glyceryl esters of fatty acids, and dispersions or emulsions of such hydrophobic substances in aqueous media, salts such as sodium chloride, vegetable flours, solvents such as ethanol, solid edible diluents such as vegetable powders or flours, and the like, and then combined with precursors of the comestible or medicinal products, or applied directly to the comestible or medicinal products.

Making The Amide Compounds of Formula (I)

The starting materials used in preparing the compounds of the invention, *i.e.* the various structural subclasses and species of the amide compounds of Formula (I) and their synthetic precursors, especially the organic carboxylic acids and benzoic acids, isocyanates, and the various amines, anilines, amino acids, etc, were often known compounds, or made by known methods of the literature, or are commercially available from various sources well known to those of ordinary skill in the art, such as for example, Sigma-Aldrich Corporation of St. Louis Missouri USA and their subsidiaries Fluka and Riedel-de Haën, at their various other worldwide offices, and other well know suppliers such as Fisher Scientific, TCI America of Philadelphia PA, ChemDiv of San Diego CA, Chembridge of San Diego CA, Asinex of Moscow Russia, SPECS/BIOSPECS of the Netherlands, Maybridge of Cornwall England, Acros, TimTec of Russia, Comgenex of South San Francisco CA and ASDI Biosciences of Newark Delaware.

It will be apparent to the skilled artisan that methods for preparing precursors and functionality related to the compounds claimed herein are generally described in the literature. The skilled artisan given the literature and this disclosure is well equipped to prepare any of the necessary starting materials and/or claimed compounds. In some of the Examples cited below, starting materials were not readily available, and therefore were synthesized, and the synthesis of the starting materials is therefore exemplified.

It is recognized that the skilled artisan in the art of organic chemistry can readily carry out manipulations without further direction, that is, it is well within the scope and practice of the skilled artisan to carry out these manipulations. These include reduction of carbonyl compounds to their corresponding alcohols, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic, etherifications, esterification, saponification, nitrations, hydrogenations, reductive amination and the like. These

89

manipulations are discussed in standard texts such as March's *Advanced Organic Chemistry* (3d Edition, 1985, Wiley-Interscience, New York), Feiser and Feiser's *Reagents for Organic Synthesis*, Carey and Sundberg, *Advanced Organic Chemistry* and the like, the entire disclosures of which are hereby incorporated by reference in their entirety for their teachings regarding methods for synthesizing organic compounds.

The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus avoiding any undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many of these manipulations can be found for example in T. Greene and P. Wuts, *Protecting Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons (1999).

The following abbreviations have the indicated meanings:

CH_3CN = Acetonitrile

$CHCl_3$ = Chloroform

DIC = N,N'-Diisopropylcarbodiimide

DIPEA = Diisopropylethylamine

DMAP = 4-(dimethylamino)-pyridine

DMF= N,N-dimethylformamide

EDCI = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochoride

DCM = Dichloromethane

ESIMS = electron spray mass spectrometry

Et_3N = triethylamine

EtOAc = ethyl acetate

EtOH = Ethyl Alcohol

Fmoc = N-(9-fluorenylmethoxycarbonyl-

HCl = Hydrochloric acid

H_2SO_4 = Sulfuric acid

HOBt = 1-Hydroxybenzotriazole

MeOH = Methyl Alcohol

$MgSO_4$ = magnesium sulfate

$NaHCO_3$ = sodium bicarbonate

NaOH = Sodium Hydroxide

Na_2SO_4 = Sodium Sulfate

Ph = phenyl

r.t.= room temperature

SPOS = solid phase organic synthesis

THF = tetrahydrofuran

TLC = thin layer chromatography

Alkyl group abbreviations

Me = methyl

Et = ethyl

n-Pr = normal propyl

i-Pr = isopropyl

n-Bu = normal butyl

i-Bu = isobutyl

t-Bu = tertiary butyl

s-Bu = secondary butyl

n-Pen = normal pentyl

i-Pen = isopentyl

n-Hex = normal hexyl

i-Hex = isohexyl

Polymer supported reagent abbreviations

PS-Trisamine = Tris-(2-aminoethyl)amine polystyrene

PS-NCO = methylisocyanate polystyrene

$PS\text{-}TsNHNH_2$ = toluensulfonylhydrazone polystyrene

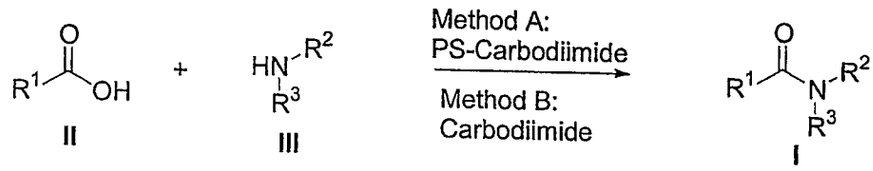
Synthetic Methods

The following Schemes and Examples are provided for the guidance of the reader, and represent a variety of methods for making the amide compounds disclosed herein. The disclosed methods are exemplary only, not limiting, and it will be apparent to one or ordinary skill in the art that other methods, many of which are known in the art, may be employed to prepare the amide compounds of the various embodiments of the invention. Such methods specifically include solid phase based chemistries, including combinatorial chemistry.

91

Amides are often prepared by the condensation of carboxylic acids and/or their derivatives (such as esters, acid halides etc) with primary or secondary amines, often in the presence of dehydrating agents, coupling agents, and/or appropriate catalysts. Large numbers of suitable starting materials, such as primary and secondary amines, and carboxylic acids and their derivatives, can be readily synthesized by methods known in the literature or are readily available commercially. In some cases, methods for synthesis of certain amine or carboxylic acid starting materials are given below.

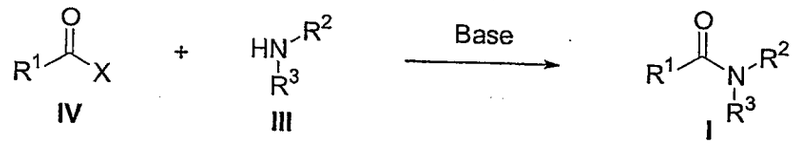
Scheme 1a



II III I

As shown in Scheme 1a, amide derivatives (I) can be prepared from the coupling of acid derivatives (II) with amines (III), for example in the presence of a coupling reagent such as 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride and a base. In Method A, a polymer supported (PS) carbodiimide is used. Method B uses a non-polymer supported carbodiimide.

Scheme 1b – Alternative Method for Preparing Amides



IV III I

X = halide

As shown in Scheme 1b, amide derivatives (I) are alternatively prepared from the coupling of acid halides, esters, or anhydrides (IV) with amines (III) in the presence of a base.

Scheme 1c – Synthesis of Amides Via Combinatorial Arrays

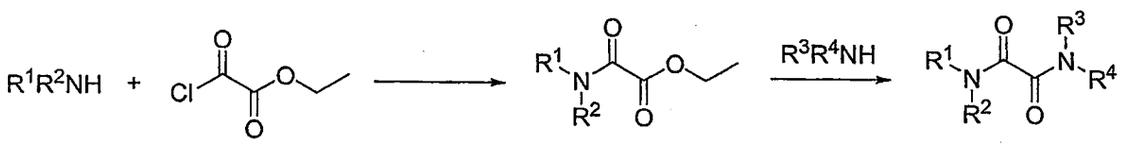
The following procedure was used and can be used to synthesize amides in combinatorial array.

- Use acetonitrile as system solvent.
- Weigh amines into 8 mL vials.
- Using Tecan, dissolve amines to 100 mM in DCM/CH_3CN (1:2, from trough).
- Weigh acid into 8 mL vials.

92

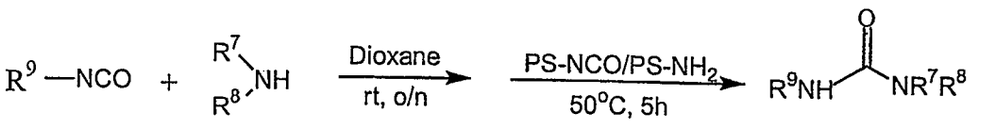
- Using Tecan, dissolve acids to 110 mM in DCM/CH_3CN (1:2, from trough).
- Preload 1.2 mL Greiner plate with 30 mg PS-carbodiimide resin using Peli 1400 Case Titer plate II. Use acetonitrile as the system solvent for synthesis.
- Add 200 mL (20 mmol, 1 equiv.) of amine to each well of the synthesis plates.
- Add 200 mL (22 mmol, 1.1 equiv.) of acid to each well of the synthesis plates.
- Add 110 mL (22 mmol, 1.1 equiv.) of HOBt (0.20 M in DMF) to each well of the synthesis plates by 8-channel pipette.
- Seal plates with cap mat and shake (normal speed) at room temperature overnight.
- Load 20 mg/well PS-Trisamine resin into the synthesis plates using Titer plate loader thin-I. *Adjust resin amount based on its loading.*
- Add 200 mL of DCM/CH_3CN to plate.
- Foil seal plates and shake (fast speed) at room temperature overnight.
- Use methanol as system solvent for transfer to storage plate.
- Transfer 150 mL to the storage plate then wash 2 times with 150 mL of methanol (shake slowly for 5 min.). Perform transfers from Top in each well. (Needle height –2).
- Dry plates in Genevac.
- Make up analytical plates (2.5 mM theoretical) and submit for analysis.
- Dilution plates made up based on analytical results.

Scheme 1c. Preparation of Oxalamides

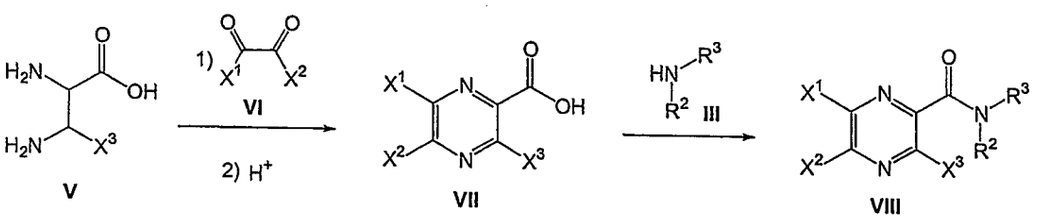


As a general procedure, one amine is allowed to react with ethyl oxalyl chloride in the presence of tertiary amine in organic solvent, such as dioxane, acetonitrile, tetrahydrofuran, tetrahydropyran, and dimethylformamide, at room temperature for 0.5 – 2 hours. Then the second amine is added and the suspension is heated at 80 °C using oil bath overnight or at 160 °C in a microwave reactor for 5 minutes. The reaction mixture can be subject to preparative HPLC, or an aqueous work-up and the crude product can typically be readily purified by recrystalization, flash column chromatography, or other methods well known to those of ordinary skill in the art to afford the pure oxalamide. Yields reported below were not optimized.

Scheme 1d. Preparation of Ureas



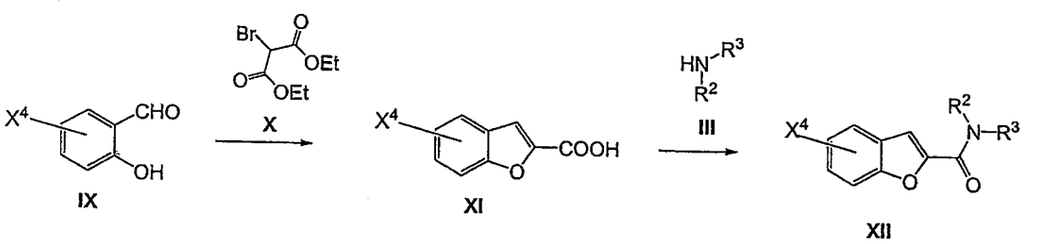
Scheme 2



X^1, X^2 and X^3 are each independently alkyl or alkoxy

Scheme 2 describes a method for preparation of pyrazines derivatives (VIII). For instance, reaction of substituted or unsubstituted 2,3-diaminopropionic acids (V) with 2,3-diones (VI) under heating conditions in the presence of base yields, after acidification, the substituted pyrazine-2-carboxylic acid (VII). The acid is condensed with various amines (III) to produce the desired amide (XIII) using the conditions shown in Scheme 1a.

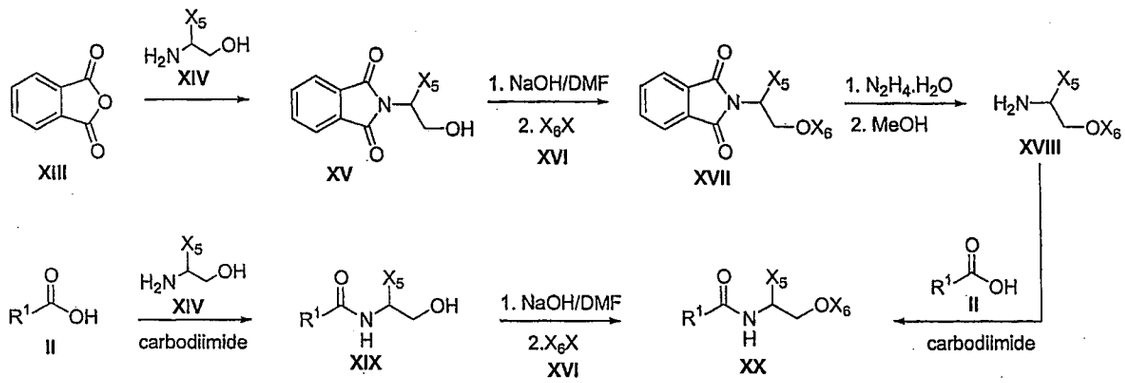
Scheme 3



X^4 is alkyl, halide, alkoxy or thioalkyl.

Scheme 3 describes a method for preparation of benzofuran derivatives (XII). For instance, reaction of 2-hydroxybenzaldehydes (IX) with 2-bromo-malonic acid diethyl ester (X) under heating conditions in the presence of base yields substituted benzofuran-2-carboxylic acid (XI). The acid is condensed with various amines (III) to produce the desired amide (XII) using the conditions shown in Scheme 1a.

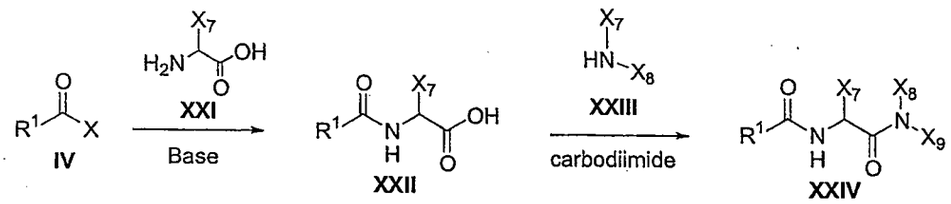
Scheme 4



X_5 is H, alkyl, aryl, aryl-alkyl, heteroaryl-alkyl
X_6 is alkyl, alkoxyalkyl, arylalkyl, heteroarylalkyl
X is halide.

Scheme 4 describes methods of preparation of an alkoxyalkyl amide (XX). In one method phthalic anhydride (XIII) is heated with amino alcohol (XIV) to give the alcohol (XV) which is then reacted with alkyl halide (XVI) in presence of a base to produce the alkoxy (XVII). Treatment of the phtalimide (XVII) with hydrazine produce the desired amine (XVIII) that is further condensed with the acid (II) as described in scheme 1a to provide the alkoxyalkylamide (XX). Alternatively acid (II) is condensed with the amino alcohol (XIV) using the method describe in scheme 1a to provide the alcohol (XIX) that is further alkylated to give (XX).

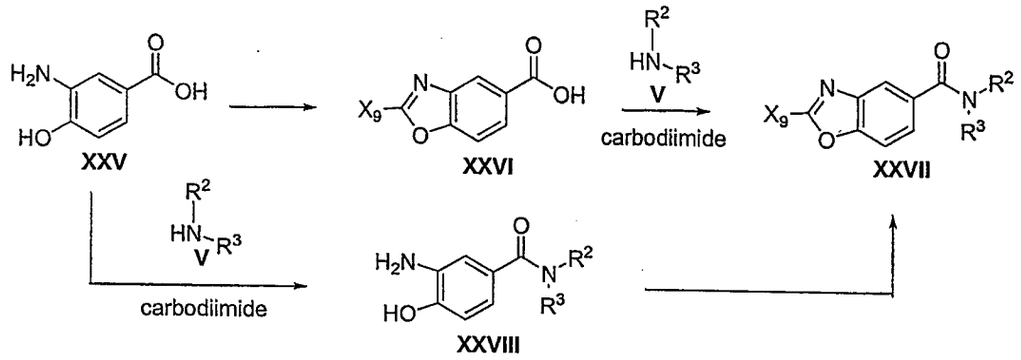
Scheme 5



X is halide
X_7 is H, alkyl, alkoxyalkyl, aryl, aryl-alkyl, heteroaryl-alkyl
X_8 and X_9 are each independently H, alkyl, alkoxyalkyl, arylalkyl and heteroarylalkyl.

Scheme 5 describes a methods for the preparation of amido-amide (XXIV). Alkyl halide (IV) is treated with amino acid (XXI) as described in scheme 1b to give the corresponding acid (XXII) that is further condensed with amine (XXIII) as described in scheme 1a to provide the amido amide derivative (XXIV).

Scheme 6

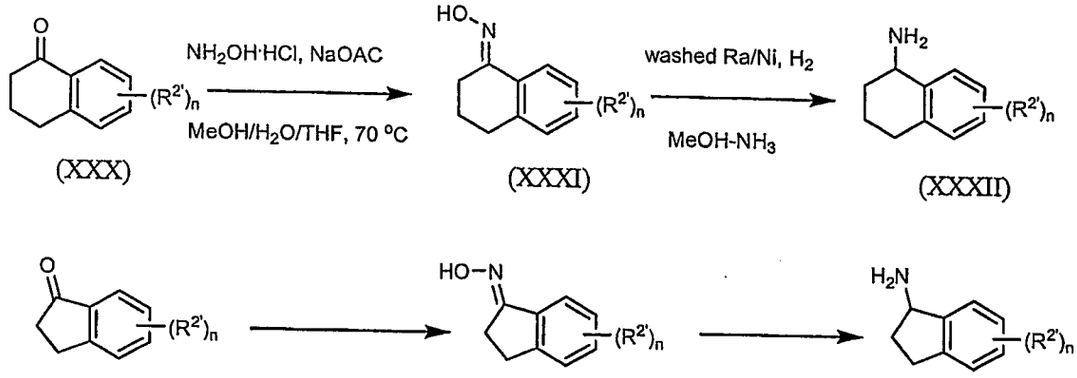


Scheme 6 describes methods for the preparation of benzooxazole (XXVIII). Amino phenol (XXV) can be condensed with a variety of reagents to form the benzoxazole (XXVI) having a wide variety of substituent X_9 using a method described in the literature (*see e.g., J. Med. Chem.* 28 (1985) 1255) and/or by the method cited in Examples 39 to 47. The benzooxazole intermediate (XXVI) is then condensed with amine (V) using the method described in scheme 1a to give the amide (XXVII). Alternatively the amide (XXVII) is prepared by first condensing the amino phenol (XXV) with the amine (V) to give the aminophenol intermediate (XXVIII) that is further converted to the benzoxazole (XXVII) using the various method described above.

A very wide variety of carboxylic acid derivatives that are suitable precursors of the R1 groups of the amides of Formulas (I), and various subgenuses of the compounds of Formula (I) are readily available by methods or ready adaptation of methods known in the prior art, or are available commercially. In particular, the substituted aryl or heteroaryl carboxylic acid compounds that are precursors of the compounds of Formula (II) are often readily available commercially, or through use of very well known synthetic methodologies. Similarly, many amine compounds that are suitable precursors of the amide compounds of Formula (I) are readily available commercially or through known methods of synthesis. Nevertheless, disclosed in the Schemes and/or Examples below are methods for synthesizing certain starting building block precursors of the R^1 and R^2 groups.

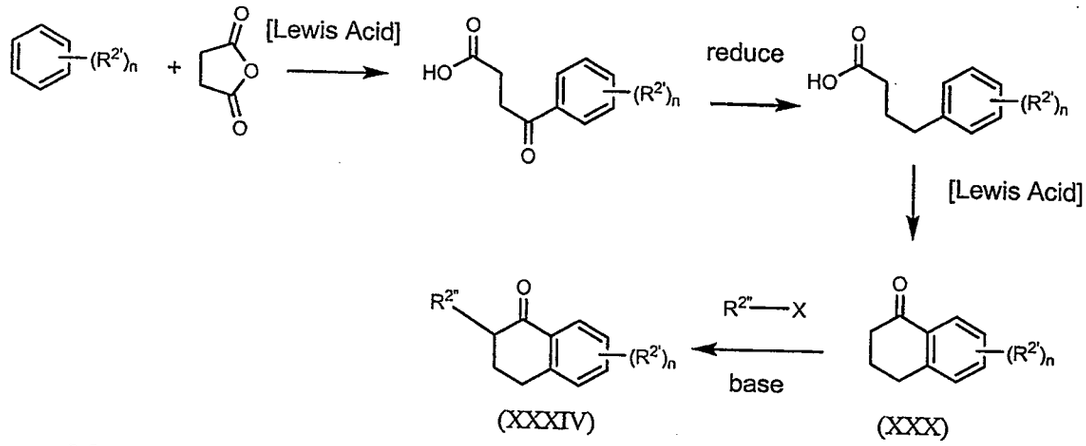
96

Scheme 7: Preparation of Racemic Substituted 1,2,3,4-tetrahydronaphthalen-1-amines



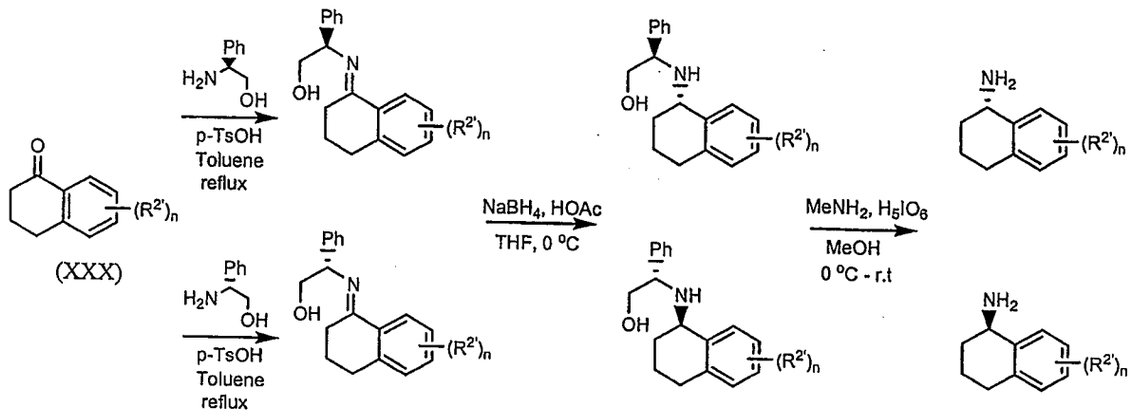
As shown in Scheme 7, racemic 1,2,3,4-tetrahydronaphthalen-1-amines (XXXII) can be readily prepared by converting substituted 3,4-dihydronaphthalen-1(2*H*)-ones (wherein independently selected R substituents can be present on either ring) to the oxime (XXXII) by treatment with hydroxylamine. Hydrogenation of the oximes in presence of Ra/Ni in MeOH-NH_3, or reduction with various known reducing agents, readily provide the racemic substituted 1,2,3,4-tetrahydronaphthalen-1-amine derivatives (XXXII). Racemic substituted indanones are readily produced by an analogous reaction sequence, as shown above.

Scheme 8: Preparation of substituted 3,4-dihydronaphthalen-1(2H)-one



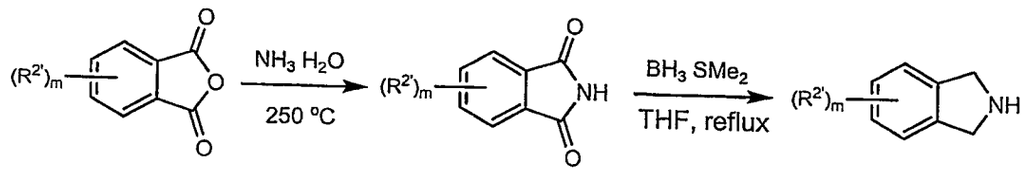
Many substituted dihydronapthaleneones of are readily commercially available or can be prepared using many conventional methods, such as those as illustrated above.

Scheme 9: Enantioselective Preparation of Substituted 1,2,3,4-tetrahydronaphthalen-1-amines



As described in Scheme 9, chiral substituted 1,2,3,4-tetrahydronaphthalen-1-amines derivatives (*S* enantiomers, or *R* enantiomer) can be prepared from dihydronapthalenyl ketones such as (XXX) using an asymmetric synthesis (*see* Stalker, R. A. *et al.*, *Tetrahedron* **2002**, *58*, 4837-4849). Ketone (XXX) is converted to the chiral imine (Va or Vb) by condensation with *S*- or *R*-phenylglycinol respectively. The imine is then enantioselectively reduced to the amine with sodium borohydride, followed by oxidative cleavage of the chiral auxiliary, to provides the amine of the illustrated optical configurations with enantiomeric excesses greater than 99%.

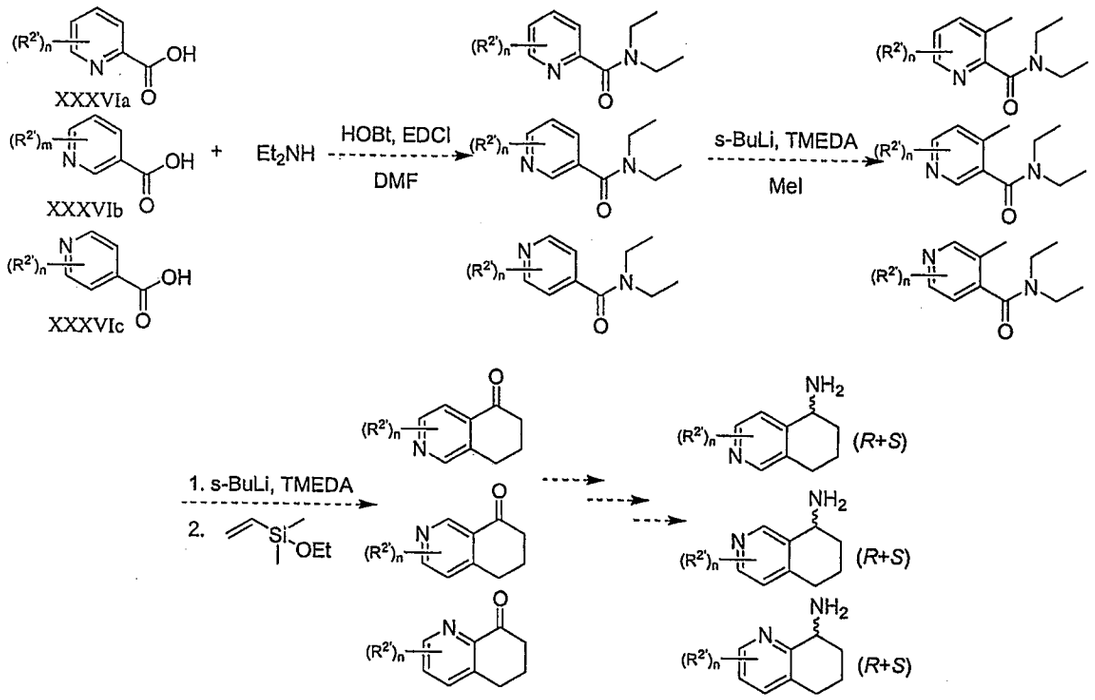
Scheme 10: Preparation of Substituted Isoindolines:



(XXXV)

Scheme 10 describes a method to prepare substituted isoindolines (XXXV) from substituted phthalic anhydrides by treatment of the phthalic anhydrides with a concentrated ammonia solution to give the substituted phthalimide (*see* Noyes, W. A., Porter, P. K. *Org. Syn., Coll. Vol. 1*, 457), followed by reduction of the phthalimide with borane methyl sulfide complex (*see* Gawley, R. E., Chemburkar, S. R., Smith, A. L., Anklekar, T. V. *J. Org. Chem.* 1988, *53*, 5381).

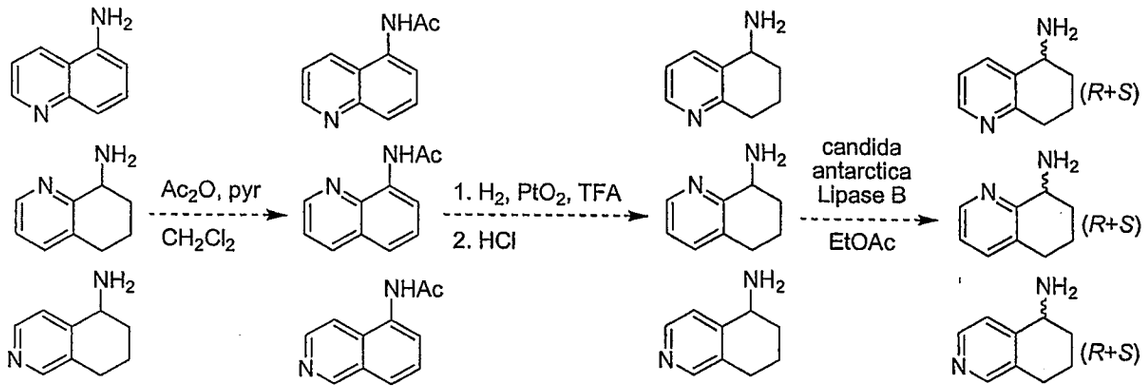
Scheme 11: Preparation of Substituted Quinoline and Isoquinolines



A variety of substituted heteroaromatic tetralins can be synthesized from pyridine carboxylic acids (XXXVa-c). Reaction of the carboxylic acid with diethylamine in the presence of HOBt and EDCI provides an activated aromatic amide, which allows for methylation *ortho* to the amide when treated with *s*-BuLi, TMEDA and MeI (*see* Date, M.; Watanabe, M.; Furukawa, S. *Chem. Pharm. Bull.* 1990, *38*, 902-906). The methylated diethylamides can then be cyclized to the desired dihydroquinolin-8(5H)-one or dihydroisoquinolin-5(6H)-one by treatment with *s*-BuLi, TMEDA and ethoxydimethylvinyl silane. Conversion of the ketone to the desired racemic or enantiomerically pure quinoline-8-amines or isoquinoline-5- amines (XVa-c) can be achieved as described in Schemes 6 or 9.

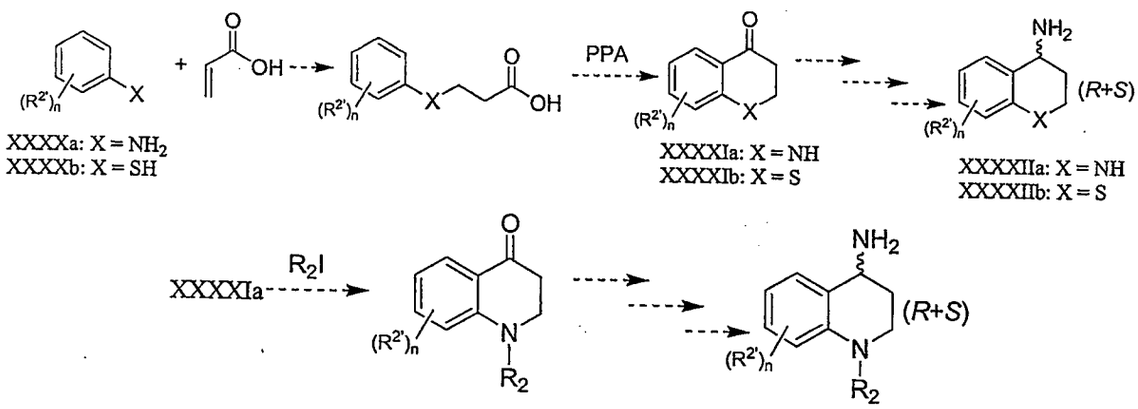
99

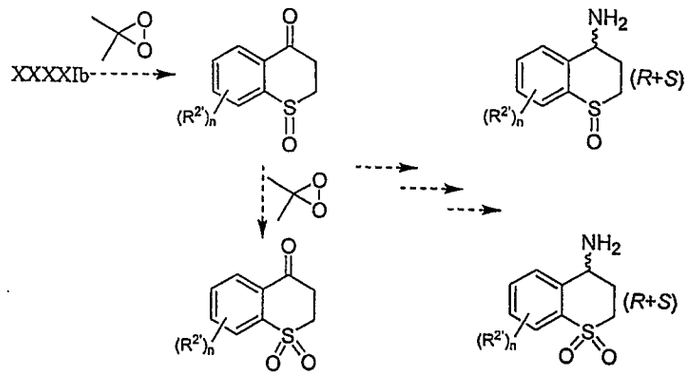
Scheme 12: Synthesis of Unsubstituted Tetrahydroquinolines and Tetrahydroisoquinolines.



Unsubstituted tetrahydroquinolines and tetrahydroisoquinolines can be synthesized as described by McEachern and coworkers (*see* Skupinska, K. A.; McEachern, E. J.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* 2002, *67*, 7890-7893) starting from amino substituted quinoline or isoquinoline precursors. Acetylation of the amino quinoline or isoquinoline, followed by hydrogenation of the cyclohexyl ring in the presence of Adam's catalyst, followed by deacetylation provide the racemic amino-cyclohexanes which can be resolved with candida antartica lipase (CALB) in presence of EtOAc *via* enantioselective acetylation of only the R isomer. Separation of the R-acetamide from the S-amine then deacetylation provides the desired enantiomerically pure S-amines, and the R-amines can be obtained by hydrolysis of the R-acetamides. (*See* Skupinska, K. A.; McEachern, E. J.; Baird, I. R.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* 2003, *68*, 3546-3551).

Scheme 13: Syntheses of Substituted 1,2,3,4-tetrahydroquinolin-4-amine and 3,4-dihydro-2*H*-thiochromen-4-amine Precursors of R^2.





The syntheses of 1,2,3,4-tetrahydroquinolin-4-amine and 3,4-dihydro-2*H*-thiochromen-4-amine precursors of R^2, can be achieved via a Michael addition of aniline (XXXXa)or thiophenol (XXXXb) to acrylic acid (*see* Ahn, Y.; Cohen, T. *J. Org. Chem.* 1994, *59*, 3142-3150), followed by cyclization with polyphosphoric acid (PPA) to provide the cyclized heterocyclic ketones (XXXXIa and XXXXIb) (*see* Higuchi, R. I.; Edwards, J. P.; Caferro, T. R.; Ringgenberg, J. D.; Kong, J. W.; Hamann, L. G.; Arienti, K. L.; Marschke, K. B.; Davis, R. L.; Farmer, L. J.; Jones, T. K. *Bioorg. Med. Chem. Lett.* 1999, *9*, 1335-1340 and Kinoshita, H.; Kinoshita, S.; Munechika, Y.; Iwamura, T.; Watanabe, Sh.-I.; Kataoka, T. *Eur. J. Org. Chem.* 2003, 4852-4861). Alkylation of the nitrogen amino ketone (XXXXIa) provides an *N*-alkylated ketone (XXV), and the desired amines (XXIVa, XXIVb and XXVI) can be obtained in racemic mixtures by the method of Scheme 7 ir enantioselectively using the method described in Scheme 9. Oxidation of the 2,3-dihydrothiochromen-4-one (XXXXIb) to the sulfoxide can be achieved by treatment with limited quantities of dimethyldioxirane, while treatment with an excess of the oxidizing agent results in formation of the sulfone (*see* Patonay, T.; Adam, W.; Lévai, A.; Kövér, P.; Németh, M.; P, E.-M.; Peters, K. *J. Org. Chem.* 2001, *66*, 2275-2280). The desired enantiomerically pure amines (XXIX and XXX) can be synthesized as outlined in Scheme 9.

In view of the disclosures, teachings, treatises, and references cited above, all of which are hereby incorporated herein by reference, one of ordinary skill in the art of synthetic organic chemistry is thoroughly equipped to prepare the necessary and/or claimed compounds by those methods given the literature and this disclosure.

Measuring the Biological Activity of the Compounds of The Invention

Cell based technologies and assays, such as those disclosed in WO 02/064631, andWO 03/001876, and U.S. Patent Publication US 2003-0232407 A1 were used both to initially screen a wide variety of classes of compounds for agonist or antagonist activity for

T1R1/T1R3 "savory" taste receptors, or T1R2/T1R3 "sweet" taste receptors that had been expressed in appropriate cell lines. Once initial "hits" were obtained for amide compounds in such cell lines, the same assays and also certain cell and/or receptor-based assays were used as analytical tools to measure the ability of the compounds of Formula (I) to enhance the savory taste of MSG or the sweet taste of known sweeteners such as sucrose, fructose, and were used to provide empirical data to guide an interative process of synthesizing and testing structural variants of the amide compounds, in combination with occasional human taste testing of high interest compounds, so as to design, test, and identify species and genuses of compounds with increased and optimized levels of desirable biological activities.

Many embodiments of the inventions relate to the identification of specific compounds and classes of the amide compounds of Formula (I) that modulate (increase or decrease) the activity of the T1R1/T1R3 (preferably hT1R1/hT1R3) savory taste receptor (umami receptor), alone or in combination with another compound that activates hT1R1/hT1R3, *e.g.*, MSG. Particularly, in many embodiments the invention relate to the amides of Formula (I) that modulate the activity of hT1R1/hT1R3 (human umami receptor) *in vitro* and/or *in vivo*. In another aspect, the invention relates to compounds that modulate the human perception of savory (umami) taste, alone or in combination with another compound or flavorant, when added to a comestible or medicinal product or composition.

Many embodiments of the inventions relate to the identification of classes and/or species of the amide compounds of Formula (I) that modulate (increase or decrease) the activity of the T1R2/T1R3 (preferably hT1R2/hT1R3) sweet taste receptor (alone or in combination with another compound that activates hT1R2/hT1R3, or otherwise induces a sweet taste, *e.g.*, sucrose, glucose, fructose, and the like. Particularly, the invention relates to the amides of Formula (I) that modulate the activity of hT1R2/hT1R3 (human sweet receptor) *in vitro* and/or *in vivo*. In another aspect, the invention relates to compounds that modulate the human perception of sweet taste, alone or in combination with another compound or flavorant composition, when added to a comestible or medicinal product or composition.

In some embodiments of the invention, it has been very unexpectedly discovered that at least some of the amide compounds of Formula (I) can modulate the human perception of both umami and sweet taste, alone or in combination with another compound or flavorant composition, when added to a comestible or medicinal product or composition.

102

***In Vitro* hT1R1/hT1R3 Umami Taste Receptor Activation Assay**

In order to identify new savory flavoring agents and enhancers, including compounds with savory agonist and enhancer activities (dual activity), the compounds of Formula (I) were screened in primary assays and secondary assays including compound dose response and enhancement assay. In a primary assay for potential ability to modulate umami taste, amide compounds of Formula (I) that can be either savory flavoring agents in their own right or flavor enhancers of MSG are identified and scores of their activities are given as percentage of the maximum MSG intensity (%). In compound dose response, an EC_{50} is calculated to reflect the potency of the compound as a savory agonist or enhancer.

An HEK293 cell line derivative (*See e.g.,* Chandrashekar, *et al.,* Cell (2000) 100: 703-711) which stably expresses Gα15 and hT1R1/hT1R3 under an inducible promoter (*see* WO 03/001876 A2) was used to identify compounds with savory tasting properties.

Compounds covered in this document were initially selected based on their activity on the hT1R1/hT1R3-HEK293-Gα15 cell line. Activity was determined using an automated fluorometric imaging assay on a FLIPR instrument (Fluorometric Intensity Plate Reader, Molecular Devices, Sunnyvale, CA) (designated FLIPR assay). Cells from one clone (designated clone I-17) were seeded into 384-well plates (at approximately 48,000 cells per well) in a medium containing Dulbecco's modified Eagle's medium (DMEM) supplemented with GlutaMAX (Invitrogen, Carlsbad, CA), 10% dialyzed fetal bovine serum (Invitrogen, Carlsbad, CA), 100 Units/ml Penicillin G, 100 μg/ml Streptomycin (Invitrogen, Carlsbad, CA) and 60 pM mifepristone (to induce expression of hT1R1/hT1R3, (*see* WO 03/001876 A2). I-17 cells were grown for 48 hours at 37°C. I-17 cells were then loaded with the calcium dye Fluo-3AM (Molecular Probes, Eugene, OR), 4 μM in a phosphate buffered saline (D-PBS) (Invitrogen, Carlsbad, CA), for 1.5 hours at room temperature. After replacement with 25 μl D-PBS, stimulation was performed in the FLIPR instrument and at room temperature by the addition of 25 μl D-PBS supplemented with different stimuli at concentrations corresponding to twice the desired final level. Receptor activity was quantified by determining the maximal fluorescence increases (using a 480 nm excitation and 535 nm emission) after normalization to basal fluorescence intensity measured before stimulation.

For dose-responses analysis, stimuli were presented in duplicates at 10 different concentrations ranging from 1.5 nM to 30 μM. Activities were normalized to the response obtained with 60 mM monosodium glutamate, a concentration that elicits maximum

receptor response. EC_{50}s (concentration of compound that causes 50% activation of receptor) were determined using a non-linear regression algorithm, where the Hill slope, bottom asymptotes and top asymptotes were allow to vary. Identical results were obtained when analyzing the dose-response data using commercially available software for non-linear regression analysis such as GraphPad PRISM (San Diego, California).

In order to determine the dependency of hT1R1/hT1R3 for the cell response to different stimuli, selected compounds were subjected to a similar analysis on I-17 cells that had not been induced for receptor expression with mifepristone (designated as un-induced I-17 cells). The un-induced I-17 cells do not show any functional response in the FLIPR assay to monosodium glutamate or other savory-tasting substances. Compounds were presented to un-induced umami cells at 10 μM–or three times the maximum stimulation used in the dose-response analysis. Compounds covered in this document do not show any functional response when using un-induced umami cells in the FLIPR assay.

In some aspects of the present invention, an EC_{50} of lower than about 10 mM is indicative of compounds that induce T1R1/T1R3 activity and is considered a savory agonist. Preferably a savory agonist will have EC_{50} values of less than about 1 mM; and more preferably will have EC_{50} values of less than about 20 μM, 15 μM, 10 μM, 5μM, 3 μM, 2 μM, 1 μM, 0.8 μM or 0.5 μM.

In umami taste enhancement activity assay experiments, which produce an "EC_{50} ratio" measurement of how effectively the amide compounds of the invention enhance the savory flavorant (typically MSG) already in a test solution. A series of measurements of the dose response is run in solutions comprising MSG alone, then a second dose response is run with MSG in combination with predetermined amounts of a candidate compound of Formula (I) at the same time.

In this assay, increasing concentrations of monosodium glutamate (ranging from 12 μM to 81 mM) were presented, in duplicates, in the presence or absence of a fixed concentration of the test compound. Typical compound concentrations tested were 30 μM, 10 μM, 3 μM, 1 μM, 0.3 μM, 0.1 μM and 0.03 μM. The relative efficacy of compounds of Formula (I) at enhancing the receptor was determined by calculating the magnitude of a shift in the EC_{50} for monosodium glutamate. Enhancement was defined as a ratio ($EC_{50}R$) corresponding to the EC_{50} of monosodium glutamate, determined in the absence of the test compound, divided by the EC_{50} of monosodium glutamate, determined in the presence of the test compound. Compounds exhibiting $EC_{50}R > 2.0$ were considered enhancers.

Stated alternatively, "EC_{50} ratio" as compared to MSG is calculated based on the following definitions:

EC_{50} Ratio *vs.* MSG = EC_{50} (MSG)/EC_{50} (MSG + [Compound])

wherein "[compound]" refers to the concentration of the compound of Formula (I) used to elicit (or enhance or potentiate) the MSG dose response.

It should be noted that the EC_{50} ratio measured can depend somewhat on the concentration of the compound itself. Preferred savory enhancers would have a high EC_{50} Ratio *vs.* MSG at a low concentration of the compound used. Preferably the EC_{50} ratio experiments to measure umami enhancement are run at a concentration of a compound of Formula (I) between about 10 μM to about 0.1 μM, or preferably at 1.0 μM or 3.0 μM.

An EC_{50} ratio of greater than 1 is indicative of a compound that modulates (potentiates) hT1R1/hT1R3 activity and is a savory enhancer. More preferably, the savory taste enhancer compounds of Formula (I) will have EC_{50} ratio values of at least 1.2, 1.5, 2.0, 3.0, 4.0, 5.0, 8.0, or 10.0, or even higher.

In one aspect, the extent of savory modulation of a particular compound is assessed based on its effect on MSG activation of T1R1/T1R3 *in vitro*. It is anticipated that similar assays can be designed using other compounds known to activate the T1R1/T1R3 receptor.

Specific compounds and generic classes of compounds that been shown to modulate hT1R1/hT1R3 based on their EC_{50} ratios evaluated according to the above formula are identified in the detailed description of the invention, the examples, and the claims.

The procedures used for human taste testing of the umami/savory compounds of Formula (I) are reported hereinbelow. Comparable EC_{50} assays for activity of the compounds of Formula (I) for sweet receptor agonism and/or sweet taste perception in humans are also reported hereinbelow.

***In Vitro* hT1R2/hT1R3 Sweet Taste Receptor Activation Assay:**

An HEK293 cell line derivative (Chandrashekar, J., Mueller, K.L., Hoon, M.A., Adler, E., Feng, L., Guo, W., Zuker, C.S., Ryba, N.J.,. *Cell,*2000, *100*, 703-711.) that stably expresses G□15 and hT1R2/hT1R3 (Li, X., Staszewski, L., Xu, H., Durick, K., Zoller, M., Adler, E. *Proc Natl Acad Sci U S A* 2002, *99*, 4692-4696.), *see also* World Patent No. WO 03/001876 A2) was used to identify compounds with sweet taste enhancing properties.

Compounds covered in this document were initially selected based on their activity on the hT1R2/hT1R3-HEK293-G□15 cell line (Li, *et al. vide supra*). Activity was determined using an automated fluorometric imaging assay on a FLIPR instrument

(Fluorometric Intensity Plate Reader, Molecular Devices, Sunnyvale, CA) (designated FLIPR assay). Cells from one clone (designated S-9 cells) were seeded into 384-well plates (at approximately 50,000 cells per well) in a medium containing DMEM Low Glucose (Invitrogen, Carlsbad, CA), 10% dialyzed fetal bovine serum (Invitrogen, Carlsbad, CA), 100 Units/ml Penicillin G, and 100 □g/ml Streptomycin (Invitrogen, Carlsbad, CA) (Li, *et al. vide supra*) *see also* World Patent No. WO 03/001876 A2). S-9 cells were grown for 24 hours at 37 °C. S-9 cells were then loaded with the calcium dye Fluo-3AM (Molecular Probes, Eugene, OR), 4 □M in a phosphate buffered saline (D-PBS) (Invitrogen, Carlsbad, CA), for 1 hour at room temperature. After replacement with 25 □l D-PBS, stimulation was performed in the FLIPR instrument and at room temperature by the addition of 25 □l D-PBS supplemented with different stimuli at concentrations corresponding to twice the desired final level. Receptor activity was quantified by determining the maximal fluorescence increases (using a 480 nm excitation and 535 nm emission) after normalization to basal fluorescence intensity measured before stimulation.

For dose-responses analysis, stimuli were presented in duplicates at 10 different concentrations ranging from 60 nM to 30 □M. Activities were normalized to the response obtained with 400 mM D-fructose, a concentration that elicits maximum receptor response. EC50s were determined using a non-linear regression algorithm (using a Senomyx, Inc. software), where the Hill slope, bottom asymptotes and top asymptotes were allow to vary. Identical results were obtained when analyzing the dose-response data using commercially available software for non-linear regression analysis such as GraphPad PRISM (San Diego, CA).

In order to determine the dependency of hT1R2/hT1R3 for the cell response to different stimuli, selected compounds were subjected to a similar analysis on HEK293-G□15 cells (not expressing the human sweet receptor). The HEK293-G□15 cells do not show any functional response in the FLIPR assay to D-Fructose or any other known sweeteners. Similarly, compounds covered in this document do not induce any functional response when using HEK293-G□15 cells in the FLIPR assay.

EXAMPLES

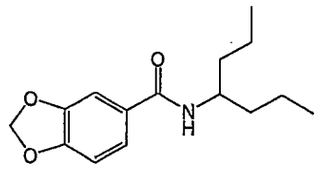
The following examples are given to illustrate a variety of exemplary embodiments of the invention and are not intended to be limiting in any manner.

For the purpose of this document, the compounds individually disclosed in the following Examples 1-174 and corresponding Tables A-E can be referred in shorthand by

the number of the example. For example, as shown immediately bellow, Example 1 discloses a synthesis of a particular compound (N-(heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide), and the results of experimental assays of its biological effectiveness, which compound is and can be referred to herein in shorthand form as Compound 1. Similarly, the first compound illustrated in Table A can be referred to elsewhere herein as Compound A1.

Example 1

N-(heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide

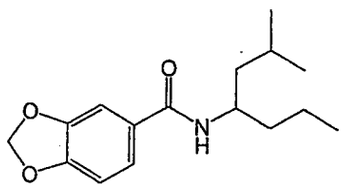


To a solution of heptan-4-amine (8.06 mL, 54 mmol) in triethylamine (15.3 mL, 108 mmol) and dichloromethane (135 mL), was added, dropwise at 0°C, a solution of benzo[1,3]dioxole-5-carbonyl chloride (10 g, 54 mmol) dissolved in dichloromethane (135 mL). The reaction mixture was stirred for 1 h. Solvent was removed under reduced pressure and the residue was dissolved in EtOAc. The organic layer was washed successively with 1 N aq. HCl, 1 N aq. NaOH, water, brine, dried ($MgSO_4$) and concentrated. The residue was recrystallized in EtOAc and Hexanes to afford 6.9 g of N-(heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide (48.3%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, 6H), 1.38 (m, 6H), 1.53 (m, 2H), 4.11 (m, 1H), 5.63 (m, 1H), 6.01 (s, 2H), 7.98 (d, 1H), 7.27 (s, d, 2H). MS(M+H, 264).

The compound had EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.2 μM, and when present at 0.03 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 6.92.

Example 2

N-(2-methylheptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide



Prepared in a similar manner to example 1 using benzo[d][1,3]dioxole-5-carbonyl chloride and 2-methylheptan-4-amine (example 2a). ^1H NMR (500 MHz, $CDCl_3$): δ 0.93 (m, 9H); 1.38 (m, 5H); 1.53 (m, 1H); 1.66 (m, 1H); 4.21 (m, 1H); 5.61 (d, 1H); 6.01 (s, 2H); 6.82 (d, 1H); 7.26 (m, 2H). MS (278, M+H).

107

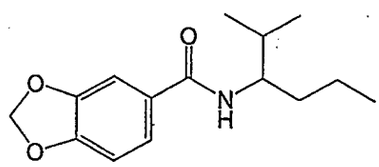
a. preparation of 2-methylheptan-4-amine:

To a solution of 2-methylheptan-4-one (4.24 g, 33.07 mmol), in methanol (60 mL), were added ammonium acetate (25.50 g, 330.71 mmol) and sodium cyanoborohydride (2.08 g, 33.07 mmol). The reaction mixture was stirred at room temperature for about 24 hours. The solvent was removed under reduced pressure and the residue was diluted with water and basified with 15 % NaOH aqueous and extracted with ether. The extract was washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated to give 3.3 g of 2-methylheptan-4-amine (77%). MS (M+H, 130).

The compound had EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.22 μM.

Example 3

N-(2-methylhexan-3-yl)benzo[d][1,3]dioxole-5-carboxamide



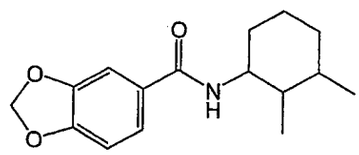
Prepared in a similar manner to example 1 using benzo[d][1,3]dioxole-5-carbonyl chloride and 2-methylhexan-3-amine (example 3a). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (m, 9H); 1.37 (m, 3H); 1.56 (m, 1H); 1.83 (m, 1H); 4.01 (m, 1H); 5.67 (d, 1H); 6.02 (s, 2H); 6.82 (d, 1H); 7.28 (m, 2H). MS (M+H, 264).

a. 2-methylhexan-3-amine was prepared using the same procedure described in example 2a starting from 2-methylhexan-3-one. Yield:40%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (d, 3H); 0.91 (m, 6H); 1.20-1.29 (m, 2H);1.38-1.47 (m, 2H); 1.47 (s, 2H); 1.58 (m, 1H); 2.51 (m, 1H). MS (M+H,116).

The compound had EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.61 μM.

Example 4

N-(2,3-dimethylcyclohexyl)benzo[d][1,3]dioxole-5-carboxamide



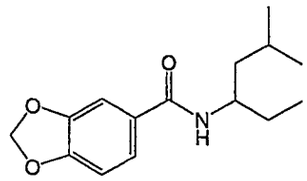
2,3-dimethylcyclohexanamine (20 μmol) and benzo[d][1,3]dioxole-5-carboxylic acid (1.1 eq) were each dissolved in acetonitrile/dichloromethane (200 μL, 2:1). PS-

Carbodiimide resin (2 eq) was loaded into a 1.2 mL 96 well Greiner plate, followed by the addition of amine and acid solutions. Hydroxybenzotriazole (1.1eq) was dissolved in DMF (100 mL) and was added into the reaction well. The reaction was shaken overnight at room temperature. Once the reaction was completed, PS-Trisamine resin (1.5 eq) was added into the reaction mixture and the solution was allowed to shake overnight at room temperature. Acetonitrile (200 mL) was added into the reaction well, and the top clear solution was transferred into a new plate. The solution was evaporated to give N-(2,3-dimethylcyclohexyl)benzo[d][1,3]dioxole-5-carboxamide. MS (M+H, 276.20).

The compound had EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.45 μM, and when present at 1 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 8.4.

Example 5

N-(5-methylhexan-3-yl)benzo[d][1,3]dioxole-5-carboxamide



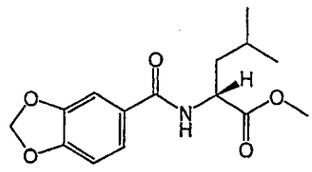
Prepared in a similar manner to example 1 using benzo[d][1,3]dioxole-5-carbonyl chloride and 5-methylhexan-3-amine (example 5a). Yield: 48 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (m, 9H); 1.37 (t, 3H); 1.45 (m, 1H); 1.64 (m, 2H); 4.13 (m, 1H); 5.61 (d, 1H); 6.01 (s, 2H); 6.82 (d, 1H); 7.27 (m, 2H). MS (M+H, 264).

a. 2-methylhexan-3-amine was prepared using the same procedure described in example 2a starting from 5-methylhexan-3-one. Yield:54%. MS (M+H,116).

The compound had EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.57 μM.

Example 6

(R)-methyl 2-(benzo[d][1,3]dioxole-6-carboxamido)-4-methylpentanoate



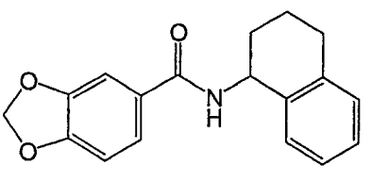
Prepared in a similar manner to example 1 using benzo[d][1,3]dioxole-5-carbonyl chloride and D-leucine methyl ester hydrochloride. Yield: 83 %. ^{1}H NMR (500 MHz,

$CDCl_3$): δ 0.98 (m, 6H); 1.63-1.67 (m, 1H); 1.71-1.76 (m, 2H); 3.76 (s, 3H);4.83 (m, 1H); 6.03 (s, 2H); 6.38 (d, 1H); 6.83 (d, 1H); 7.32 (s, 1H); 7.33 (d, 1H). MS (M+H, 294). m.p: 89-90 °C.

The compound had EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.34 μM, and when present at 0.1 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 4.9.

Example 7

N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzo[d][1,3]dioxole-5-carboxamide

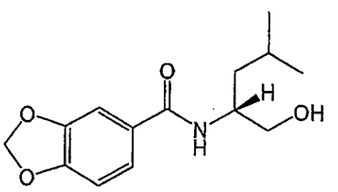


Prepared in a similar manner to example 4 using benzo[d][1,3]dioxole-5-carboxylic acid and 1,2,3,4-tetrahydronaphthalen-1-amine. MS (M+H, 296.6).

The compound had EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.71 μM, and when present at 0.3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 7.8.

Example 8

(R)-N-(1-hydroxy-4-methylpentan-2-yl)benzo[d][1,3]dioxole-5-carboxamide



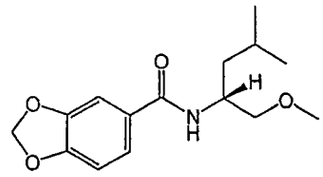
Prepared in a similar manner to example 4 using benzo[d][1,3]dioxole-5-carboxylic acid and (R)-aminoleucinol. MS (M+H, 266.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 9 μM, and when present at 3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 2.

Example 9

(R)-N-(1-methoxy-4-methylpentan-2-yl)benzo[d][1,3]dioxole-5- benzo[d][1,3]dioxole-5-carboxylic acid

(110)



Prepared in a similar manner to example 4 using (R)-1-methoxy-4-methyl and pentan-2-amine (example 9a). Yield: 55%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (m, 6H); 1.43 (m, 1H); 1.55 (m, 1H); 1.65 (m, 1H); 3.36 (s, 3H);3.46 (m, 2H); 4.33 (m, 1H); 6.01 (s, 2H); 6.13 (d, 1H); 6.82 (d, 1H); 7.28 (m, 2H). MS (M+H, 280).

a. (R)-1-methoxy-4-methylpentan-2-amine

To a solution of (R)-2-(1-methoxy-4-methylpentan-2-yl)isoindoline-1,3-dione (example 9b) (3.87 g, 14.84 mmol) in methanol (30 mL), was added hydrazine hydrate (0.866 ml, 17.81 mmol) and the reaction mixture was warmed up to 45 °C for about 3 hours. The mixture was acidified with 2N HCl and stirred at 45 °C for 30 min. The solution was cooled to room temperature, filtered and evaporated. The residue was taken up with 2N NaOH and extracted with ether, dried over MgSO4, filtered and evaporated to give 1.51 g of (R)-1-methoxy-4-methylpentan-2-amine. Yield 77 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (m, 6H); 1.17 (m, 2H); 1.58 (s, 2H); 1.71 (m, 1H); 3.02 (m, 1H); 3.10 (m, 1H); 3.32 (m, 1H); 3.35 (s, 3H).

b. (R)-2-(1-methoxy-4-methylpentan-2-yl)isoindoline-1,3-dione

(R)-2-(1-hydroxy-4-methylpentan-2-yl)isoindoline-1,3-dione (example 9c) (5.88 g, 23.87 mmol) was dissolved in dry THF (25 mL) and hexamethyl-phosphoramide (30 mL) and the solution cooled to 0 °C. Sodium hydride (60 % in mineral oil, 1.15 g, 28.65 mmol) was added and after 10 minutes iodomethane (7.43 ml, 119.35 mmol) was added dropwise and the solution was warmed up slowly to room temperature and stirred over night. The reaction mixture was poured into ice/water, extracted with EtOAC, washed with brine, dried over MgSO4, filtered and evaporated. The residue was purified on silica gel (20 % EtOAC in hexane) to give 3.92 g of (R)-2-(1-methoxy-4-methylpentan-2-yl)isoindoine-1,3-dione (63 %).

c. (R)-2-(1-hydroxy-4-methylpentan-2-yl)isoindoline-1,3-dione:

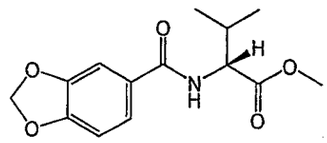
Phthalic anhydride (10.30 g, 69.55 mmol) and D-Leucinol (8.15 g, 69.55 mmol) were mixed in THF (100 mL), the reaction mixture was heated at 85 °C and refluxed for 18 hours. After cooling to room temperature, water was added and the solution was extracted with EtOAC, the extracts were washed with 1 N HCl, water, aq. $NaHCO_3$, water and brine,

dried over $MgSO_4$, filtered and evaporated to give 8.1 g of (R)-2-(1-hydroxy-4-methylpentan-2-yl)isoindoline-1,3-dione (47 %). ^1H NMR (500 MHz, $CDCl_3$): δ 0.94 (m, 6H); 1.54 (m, 2H); 1.99 (m, 1H); 3.86 (m, 1H); 4.04 (m, 1H); 4.47 (m, 1H); 7.72 (m, 2H); 7.83 (m, 2H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3.5 μM.

Example 10

(R)-methyl 2-(benzo[d][1,3]dioxole-6-carboxamido)-3-methylbutanoate

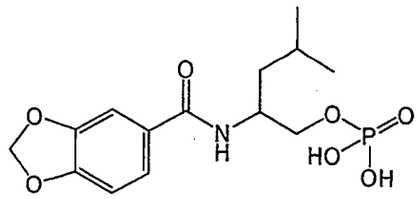


Prepared in a similar manner to example 4 using benzo[d][1,3]dioxole-5-carboxylic acid and (R)-methyl 2-amino-3-methylbutanoate.Yield: 50%. MS (M+H; 280.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.16 μM.

Example 11

2-(benzo[d][1,3]dioxole-6-carboxamido)-4-methylpentyl dihydrogen phosphate



N-(1-hydroxy-4-methylpentan-2-yl)benzo[d][1,3]dioxole-5-carboxamide (example 11a) (0.57 mmol, 151 mg) was dissolved in anhydrous acetonitrile (2 ml) and 1 ml of 0.45 M solution of tetrazole in acetonitrile was added under nitrogen and stirred for 5 min. Then 0.627 (1.1 eq, 207 μl) of dibenzyl diisopropyl phosphoroamidite was added drop wise under nitrogen. The mixture was stirred for 1h. The solvent was evaporated and a crude intermediate was dissolved in DCM and washed twice with 2% potassium carbonate and brine and dried with sodium sulphate. The material was dried down and oxidized with 5 ml of tert.butylhydroperoxide (4 M solution in nonane) for 30 min. The solvent was evaporated and the dibenzylester intermediate was purified (preparative TLC). The benzyl groups were hydrolyzed using trifluoroacetic acid (3 ml of a mixture of 95% TFA and 5% water, 1.5 h, rt). The final product was dried down providing 69 mg (35%) of pure material. ^1H NMR

112

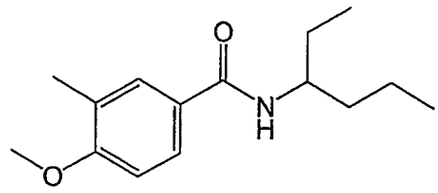
(500 MHz, $CDCl_3$): δ 0.88-0.90 (t, 6H), 1.23-1.27 (m, 2H), 1.36-1.37 (m, 1H), 1.53-1.62 (m, 2H), 3.93 (s, 1H), 3.98 (s, 1H), 4.32 (s, 1H), 5.90 (s, 2H), 6.66-6.67 (d, 1H), 6.98-6.99 (b, 2H), 7.14 (s, 2H); ^{31}P: δ 0.51(s). MS (M+H , 346.0).

a. N-(1-hydroxy-4-methylpentan-2-yl)benzo[d][1,3]dioxole-5-carboxamide was prepared in a similar manner to example 4 from piperonylic acid and 2-amino-4-methyl-pentan-1-ol.

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 10.9 μM.

Example 12

N-(hexan-3-yl)-4-methoxy-3-methylbenzamide

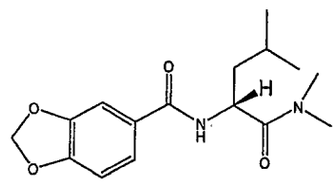


Prepared in a similar manner to example 4 using 4-methoxy-3-methylbenzoic acid and hexan-3-amine (example 28a). ^1H NMR (500 MHz, $CDCl_3$): δ 0.94 (m, 6H); 1.41 (m, 4H); 1.46 (m, 1H); 1.64 (m, 1H); 2.24 (s, 3H); 3.87(s, 3H); 4.08 (m, 1H); 5.69 (d, 1H); 6.83 (d, 1H); 7.54 (s, 1H); 7.62 (d, 1H). MS (M+H, 250).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.12 μM.

Example 13

(R)-N-(1-(dimethylamino)-4-methyl-1-oxopentan-2-yl) benzo [d] [1,3] dioxole-5-carboxamide



(R)-2-(benzo[d][1,3]dioxole-6-carboxamido)-4-methylpentanoic acid (example 13a) (52 mg, 0.19 mmol) in DMF (4 mL) and dimethyl amine (2M in Methanol, 36 μL, 2 eq) were condensed in presence of HOBt (26 mg, 1eq) and of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (44 mg,1.2 eq) at room temperature overnight. The reaction mixture was evaporated and the residue was dissolved in

ethylacetate and washed successively with saturated $NaHCO_3$ and water, dried over $MgSO_4$ filtered and evaporated to give 48.6 mg of the product (84%). The material was further purified using RPHPLC. ^1H NMR (500 MHz, $CDCl_3$): δ 0.93-0.94 (d, 3H), 1.03-1.05 (d, 3H), 1.48-1.52 (m, 1H), 1.59-1.63 (m,1H), 2.98 (s, 3H), 3.14 (s, 3H), 5.17-5.21 (m, 1H), 6.01 (s, 2H), 6.80-6.82 (d, 1H), 6.89-6.91(d, 1H), 7.29-3.30 (d,1H), 7.33-7.35 (dd, 1H). MS (M+H; 307.2).

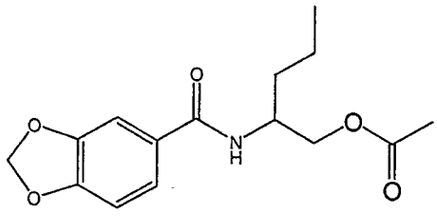
a. (R)-2-(benzo[d][1,3]dioxole-6-carboxamido)-4-methylpentanoic acid:

Prepared in a similar manner to example 1 using benzo[d][1,3]dioxole-5-carbonyl chloride and D-Leucine. Yield: 55%. MS (M+H, 280.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.06 μM.

Example 14

2-(benzo[d][1,3]dioxole-6-carboxamido)pentyl acetate



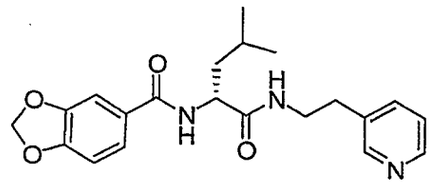
To a solution of N-(1-hydroxypentan-2-yl)benzo[d][1,3]dioxole-5-carboxamide (example 14a) (59.8mg, 0.238mmol) in dichloromethane (5 mL) was added triethylamine (166 mL, 1.19 mmol). Acetyl anhydride (112.5mL, 1.19mmol) was slowly added and the mixture was stirred under argon at ambient temperature overnight. The solution was washed successively with a saturated solution of sodium bicarbonate, water and brine. The organic layer was dried over anhydrous sodium sulfate. Filtration followed by solvent removal under reduced pressure afforded 50.8 mg of 2-(benzo[d][1,3]dioxole-6-carboxamido)pentyl acetate (73%). ^1H NMR($CDCl_3$): □0.95 (t, 3H, J = 7.2 Hz), 1.43(m, 2H), 1.57(m, 2H), 2.1 (s, 3H), 4.11(dd, 1H, J = 3.5 Hz, J = 11.5 Hz), 4.27(dd, 1H, J = 3.5 Hz, J = 11.4 Hz), 4.29 (m, 1H), 6.02 (s, 2H), 6.1 (m, 1H), 6.82 (d, 1H, J = 8.4 Hz), 7.27 (m, 2H). MS (M+H, 294).

a. N-(1-hydroxypentan-2-yl)benzo[d][1,3]dioxole-5-carboxamide was prepared in a similar manner to example 4 using benzo[d][1,3]dioxole-5-carboxylic acid and 2-aminopentan-1-ol. Yield: 76%. MS (M+H, 252).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 11.9 μM, and when present at 3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 4.1.

Example 15

(R)-N-(4-methyl-1-oxo-1-(2-(pyridin-3-yl)ethylamino)pentan-2-yl) benzo [d][1,3]dioxole-5-carboxamide

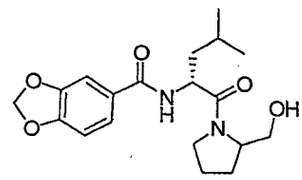


Prepared in a similar manner to example 13 using 2-(3-pyridyl)ethylamine and (R)-2-(benzo[d][1,3]dioxole-6-carboxamido)-4-methylpentanoic acid (example 13a). (MS M+ 384.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.7 μM.

Example 16

N-((R)-1-(2-(hydroxymethyl)pyrrolidin-1-yl)-4-methyl-1-oxopentan-2-yl)benzo[d][1,3]dioxole-5-carboxamide

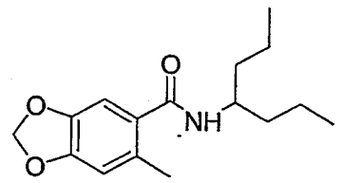


Prepared in a similar manner to example 13 using R/S propinol and (R)-2-(benzo[d][1,3]dioxole-6-carboxamido)-4-methylpentanoic acid (example 13a). (MS M+ 363.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3 μM.

Example 17

N-(heptan-4-yl)-6-methylbenzo[d][1,3]dioxole-5-carboxamide

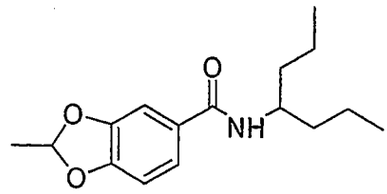


Prepared in a similar manner to example 4 using 6-methylbenzo[d][1,3]dioxole-5-carboxylic acid and heptan-4-amine. MS (M+H, 278.67).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.11 μM.

Example 18

N-(heptan-4-yl)-2-methylbenzo[d][1,3]dioxole-5-carboxamide



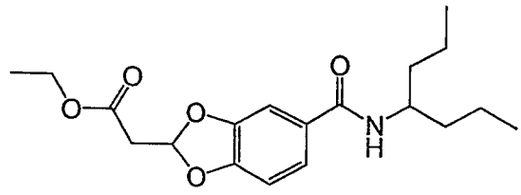
N-(heptan-4-yl)-3,4-dihydroxybenzamide (example 18a) (0.5 mmol) was dissolved in toluene (1.6 mL). P-Toluenesulfonic acid monohydrate (0.3eq) was added to the reaction, followed by addition of acetaldehyde (2eq). The reaction was performed using microwave (180C, 300W) and ran for 10 minutes. The solvent was evaporated. The residue was dissolved in methanol (1 ML) and purified by HPLC. Yield 20%, MS (M+H 278.10).

a. N-(heptan-4-yl)-3,4-dihydroxybenzamide was prepared in a similar manner to example 4 using 3,4-dihydroxybenzoic acid and heptan-4-amine. Yield: 25%. MS (M+H, 252.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.1 μM, and when present at 0.03 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 3.68.

Example 19

Ethyl 2-(5-(heptan-4-ylcarbamoyl)benzo[d][1,3]dioxol-2-yl)acetate



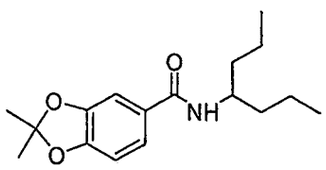
N-(heptan-4-yl)-3,4-dihydroxybenzamide (example 18a) (0.29 mmol, 75 mg) was dissolved in dry acetone with 6 eq excess (242 mg) of potassium carbonate then 1.2 eq excess (36 μl) of propynoic acid ethyl ester was added and a mixture was refluxed for 24 h. The solvent was evaporated and a solid was dissolved in dichloromethane and extracted

with 10% $NaHCO_3$ and water. The crude product was purified by chromatography on silica gel to give 72 mg of desired product (71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91-0.94 (t, 6H), 1.23-1.30 (m, 4H), 1.37-1.41 (4H), 2.97-2.98 (d, 2H), 3.70-3.74 (dd, 2H), 4.12-4.17 (m, 1H), 4.2-4.24 (m, 3H), 5.61-5.64 (d, 1H), 6.58-6.60 (t, 1H), 6.79-6.81 (d, 1H), 7.23 (s, 1H), 7.60-7.85 (b, 1H). MS (M+ H, 350.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 14 μM, and when present at 3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 2.5.

Example 20

N-(heptan-4-yl)-2,2-dimethylbenzo[d][1,3]dioxole-5-carboxamide



Prepared in a similar manner to example 4 using sodium 2,2-dimethylbenzo[d][1,3]dioxole-5-carboxylate and 4-heptylamine (example 20a). Yield 30%. ^{1}H NMR: 0.92 (t, 6H, J = 7.2 Hz), 1.42 (m, 6H), 1.53 (m, 2H), 1.68 (s, 6H), 4.12 (m, 1H), 5.61(d, 1H, J = 8.9 Hz), 6.72 (d, 1H, J= 8Hz), 7.16 (d, 1H, J = 1.5 Hz), 7.22 (dd, 1H, J = 1.5 Hz, J = 17 Hz). MS (M+H, 292).

a. Sodium 2,2-dimethylbenzo[d][1,3]dioxole-5-carboxylate and 4-heptylamine:

Ethyl 2,2-dimethylbenzo[d][1,3]dioxole-5-carboxylate (example 20b)(461mg, 2.08 mmol) was stirred in dioxane (16mL) and 1.0N aqueous NaOH (4.16 mL) for 20 hours at room temperature. The solvent was removed under reduced pressure to afford the desired product (449mg). (M-H, 193).

b. Ethyl 2,2-dimethylbenzo[d][1,3]dioxole-5-carboxylate:

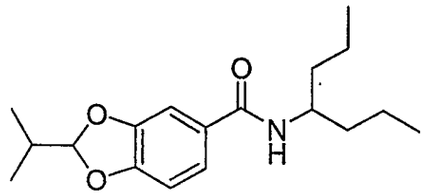
Ethyl 3,4-dihydroxybenzoate (910.9 mg, 5mmol) was combined with 2,2-dimethoxypropane (1.23 mL, 10 mmol) and a catalytic amount of p-toluene sulfonic acid in toluene. The mixture was heated to reflux using a Dean-Stark trap for 20 hours. After solvent removal under reduced pressure, the crude was dissolved in ethyl acetate and washed successively with a saturated aqueous solution of sodium bicarbonate, water, and brine. The organic layer was dried over anhydrous sodium sulfate. Purification by chromatography on silica gel using a gradient hexane:ethyl acetate, 90:10 to 75:25, afforded a white powder (539.1mg, 49%). ^{1}H NMR($CDCl_3$): 1.36 (t, 3H, J = 7.2Hz), 1.69 (s, 6H),

4.32 (q, 2H, J = 7.1 Hz, J = 14.2 Hz), 6.74 (d, 1H, d, J = 8.2Hz), 7.38 (d, 1h, J = 1.7 Hz), 7.61 (dd, 1H, J = 1.8 Hz, J = 8.3 Hz).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 2.7 μM.

Example 21

N-(heptan-4-yl)-2-isopropylbenzo[d][1,3]dioxole-5-carboxamide



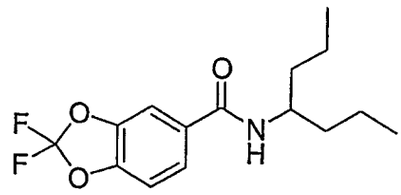
Prepared in a similar manner to example 4 using 2-isopropylbenzo[d][1,3]dioxole-5-carboxylic acid (example 21a) and 4-hepthylamine. Yield: 34%. ^{1}H NMR($CDCl_3$): □ 0.92 (t, 6H, J = 7.2Hz), 1.04 (d, 6H, J = 6.9 Hz), 1.40 (m, 6H), 1.43 (m, 2H), 2.15 (m, 1H), 4.11 (m, 1H), 5.62 (d, 1H, J = 8.9Hz), 5.96 (d, 1H, J = 4.4 Hz), 6.75 (d, 1H, J = 8.0 Hz), 7.19 (d, 1H, J = 1.8 Hz), 7.22 (d, 1H, J = 1.9 Hz), 7.23 (d, 1H, J = 1.6 Hz). MS (M+H, 291).

a. 2-isopropylbenzo[d][1,3]dioxole-5-carboxylic acid: 3,4-dihydrobenzoic acid (154.12 mg, 1mmol)and isobutyraldehyde (182 μL, 2 mmoles) were combined in toluene (3mL) and a catalytic amounts of p-toluene sulfonic acid was added. The mixture was subjected to the microwave for 10 minutes at 180 °C with a power set at 275. The solution was filtered and evaporated to afford 100mg of the desired product (48%). MS (M-H, 207).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 11.5 μM, and when present at 3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 2.2 .

Example 22

2,2-difluoro-N-(heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide

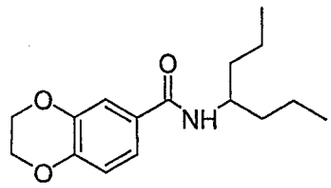


Prepared in a similar manner to example 4 using 2,2-difluorobenzo[d][1,3]dioxole-5-carboxylic acid and 4-hepthylamine. (M+H, 300.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.51 μM, and when present at 1 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 2.87.

Example 23

2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid (1-propyl-butyl)-amide

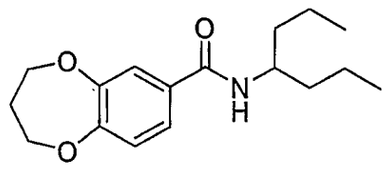


Prepared in a similar manner to example 4 using 2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid and heptan-4-amine. MS (M+H, 278.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.49 μM.

Example 24

N-(heptan-4-yl)-3,4-dihydro-2H-benzo[b][1,4]dioxepine-7-carboxamide

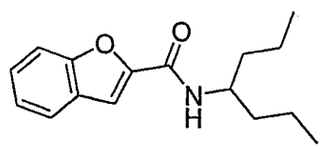


Prepared in a similar manner to example 4 using 2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid and heptan-4-amine. MS (M+H, 292.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 6.4 μM.

Example 25

benzofuran-2-carboxylic(1-propylbutyl)amide

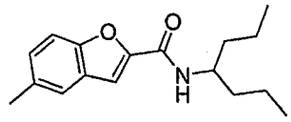


Prepared in a similar manner to example 1 using benzofuran-2-carbonyl chloride and heptan-4-amine. Yield: 73%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (t, 6H, J = 7.2 Hz), 1.41 (m, 8H), 3.01 (s, 3H), 4.18 (m, 1H), 6.29 (d, 1H, J = 9.94 Hz), 7.20 (d, 1H, J = 8.62 Hz), 7.37 (m, 2H), 7.44 (s, 1H). MS (M+H, 260)

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.88 μM, and when present at 0.3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 2.6.

Example 26

N-(heptan-4-yl)-5-methylbenzofuran-2-carboxamide



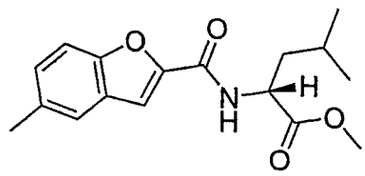
Prepared in a similar manner to example 4 using 5-methylbenzofuran-2-carboxylic acid (example 26a) and heptan-4-amine. Yield: 46%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, 6H, J = 7.2 Hz), 1.41 (m, 10H), 2.44 (s, 1H), 4.18 (m, 1H), 6.29 (d, 1H, J = 8.6 Hz), 7.21 (d, 1H, J = 8.4 Hz), 7.37(m, 2H), 7.44 (s, 1H). MS (M+H, 274).

a. 5-methylbenzofuran-2-carboxylic acid: 2-Hydroxy-5-methylbenzaldehyde (544.2 mg, 4 mmol) was combined with diethylbromomalonate (1 mL, 6 mmol) and potassium carbonate (1.1 g, 8 mmol) in methyl ethyl ketone (5 mL) and the mixture was heated to reflux overnight. The solvent was removed by rotary evaporation to afford a crude oil. The oil was then taken in a 10% solution of potassium hydroxide in ethanol (10 mL) and heated to reflux for 45 minutes. The solvent was removed under reduced pressure and the residue was then treated with a 2.0 N solution of H_2SO_4. The free acid was then extracted with copious amounts of ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. Ethyl acetate removal afforded 566mg of 5-Methyl-2-carboxybenzofuran (80%) as of a yellowish powder. ^{1}H NMR (500 MHz, CD_3OD): □2.44 (s, 3H), 7.30 (d, 1H, J = 8.7 Hz), 7.45 (d, 1H, J = 8.5 Hz), 7.51 (d, 2H, J = 7.5 Hz).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.94 μM.

Example 27

(R)-methyl 4-methyl-2-(5-methylbenzofuran-2-carboxamido)pentanoate



Prepared in a similar manner to example 4 using 5-methylbenzofuran-2-carboxylic acid (example 26a) and D-leucine methyl ester. ^{1}H NMR (500 MHz, $CDCl_3$): □0.98 (d, 3H,

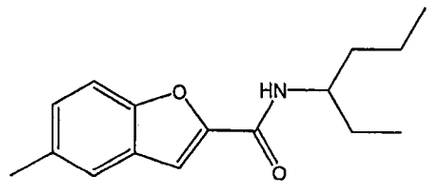
120

J = 6.26 Hz), 1.00 (d, 3H, J = 6.17 Hz), 1.56 (s, 3H), 1.76 (m, 3H), 2.48 (s, 3H), 3.78 (s, 3H), 4.86 (m, 1H), 6.95 (m, 1H), 7.23 (dd, 1H, J = 8.54 Hz, J = 1.55 Hz), 7.40 (m, 2H). 7.44 (dd, 1H, J = 1.72, J = 0.9 Hz). MS 304 (M+H, 304).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.11 μM.

Example 28

N-(hexan-3-yl)-5-methylbenzofuran-2-carboxamide



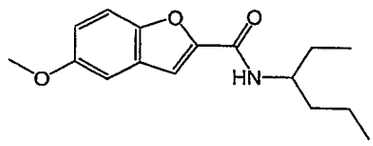
Prepared in a similar manner to example 4 using 5-methylbenzofuran-2-carboxylic (example 26a) and hexan-3-amine (example 28a) .Yield: 49%. ^{1}H NMR (500 MHz, $CDCl_3$): □0.94 (m, 6H), 1.40-1.68 (m, 6H), 2.36 (s, 3H), 4.07 (m, 1H), 5.74 (d, 1H, J = 8.97 Hz), 7.16 (d, 1H, J = 7.80 Hz), 7.31 (dd, 1H, J = 1.73 Hz, J = 1.73 Hz), 7.66 (d, 1H, J = 1.72 Hz). MS (M+H, 260).

a. Hexan-3-amine was prepared using the same procedure described in example 2a starting from hexan-3-one. Yield: 58 %. ^{1}H NMR (500 MHz, $CDCl_3$): □0.94 (m, 6H); 1.36-1.58 (m, 6H); 2.83 (m, 1H); 3.12 (s, 2H). MS: (102, M+H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.74 μM.

Example 29

N-(hexan-3-yl)-5-methoxybenzofuran-2-carboxamide



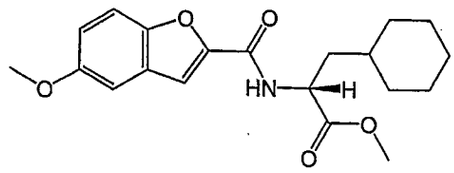
Prepared in a similar manner to example 4 using 5-methoxybenzofuran-2-carboxylic acid and hexan-3-amine (example 28a). Yield: 32%. ^{1}H NMR (500 MHz, $CDCl_3$): □ 0.96 (m, 6H); 1.40-1.67 (m, 6H); 3.85 (s, 3H); 4.09 (m, 1H); 6.28 (d, 1H); 7.01 (dd, 1H); 7.08 (d, 1H); 7.38 (m, 2H). MS (276, M+H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.4 μM.

121

Example 30

(R)-methyl 3-cyclohexyl-2-(5-methoxybenzofuran-2-carboxamido) propanoate

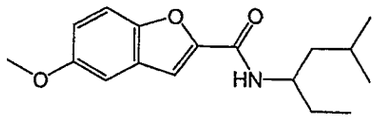


Prepared in a similar manner to example 4 using 5-methoxybenzofuran-2-carboxylic acid and (R)-methyl 2-amino-3-cyclohexylpropanoate. Yield: 45%. MS (M+H, 260.3).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.14 μM.

Example 31

5-methoxy-N-(5-methylhexan-3-yl)benzofuran-2-carboxamide

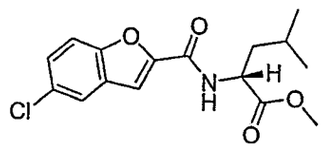


Prepared in a similar manner to example 4 using 5-methoxybenzofuran-2-carboxylic acid and 5-methylhexan-3-amine (example 5a). Yield: 67%. ^{1}H NMR (500 MHz, $CDCl_3$): □ 0.96 (m, 9H); 1.39-1.52 (m, 3H); 1.66 (m, 2H); 3.85 (s, 3H); 4.17 (m, 1H); 6.24 (d, 1H); 7.01 (dd, 1H); 7.08 (d, 1H); 7.38 (m, 2H). MS (290, M+H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.04 μM.

Example 32

Preparation of (R)-methyl 4-chloro-2-(5-methylbenzofuran-2-carboxamido)pentanoate



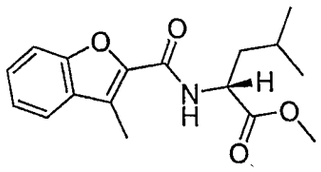
Prepared in a similar manner to example 4 using 5-chlorobenzofuran-2-carboxylic acid and D-leucine methyl ester. MS (M+H, 324).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.82 μM.

Example 33

(R)-methyl 4-methyl-2-(3-methylbenzofuran-2-carboxamido)pentanoate

122

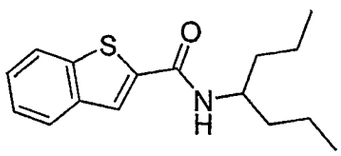


Prepared in a similar manner to example 4 using 3-methylbenzofuran-2-carboxylic acid and D-leucine methyl ester. MS (M+H, 304).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.18 μM.

Example 34

N-(heptan-4-yl)benzo[b]thiophene-2-carboxamide

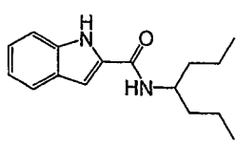


Prepared in a similar manner to example 4 using benzo[b]thiophene-2-carboxylic acid and 4-hepthylamine. MS (M+H, 276).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.21 μM.

Example 35

N-(heptan-4-yl)-1H-indole-2-carboxamide



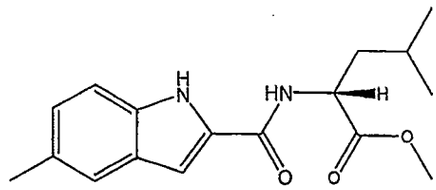
Prepared in a similar manner to example 4 using 1H-indole-2-carboxylic acid and 4-hepthylamine. MS (M+H, 259).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 6.8 μM.

Example 36

(R)-methyl 4-methyl-2-(5-methyl-1H-indole-2-carboxamido)pentanoate

123

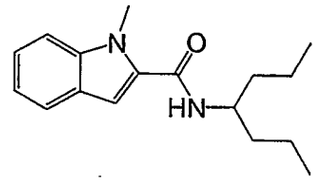


Prepared in a similar manner to example 4 using 5-Methyl-1H-indole-2-carboxylic acid and D-leucine methyl ester. Yield: 50%. ^{1}H NMR (500 MHz, $CDCl_3$): □0.98(d, 3H, J= 6.3Hz), 1.00(d, 3H, J = 6.1 Hz), 2.44 (s, 3H), 3.784(s, 3H), 4.87(m, 1H), 6.56 (d, 1H, J = 8.39 Hz), 6.85 (dd, 1H, J =1.94 Hz, J = 0.68 Hz), 7.12 (dd, 1H, J = 8.46 Hz, J = 1.55 Hz), 7.31(d, 1H, J = 8.45 Hz), 7.42 (s, 1H).. MS (MH+, 303).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 6.6 μM.

Example 37

N-(heptan-4-yl)-1-methyl-1H-indole-2-carboxamide

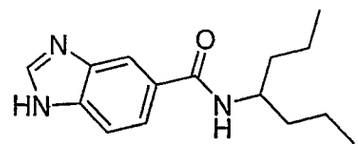


Prepared in a similar manner to example 4 using 1-methyl-1H-indole-2-carboxylic acid and 4-hepthylamine. Yield 45%. ^{1}H NMR (500 MHz, $CDCl_3$): □0.95 (t, 6H, J = 7.2 Hz), 1.46 (m, 4H), 1.57 (m, 4H), 4.05 (s, 3H), 4.15 (m, 1H), 5.85 (d, 1H), 6.80 (s, 1H), 7.14 (t, 1H, J = 7.4 Hz), 7.31 (t, 1H, J = 7.5 Hz), 7.38 (d, 1H, J = 8.4 Hz), 7.62 (d, 1H, J = 8 Hz). MS (M+H, 273).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.79 μM.

Example 38

N-(heptan-4-yl)-1H-benzo[d]imidazole-5-carboxamide



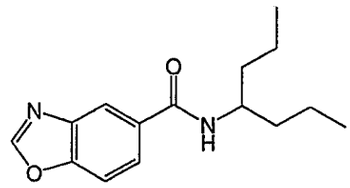
Prepared in a similar manner to example 4 using 1H-benzo[d]imidazole-5-carboxylic acid and 4-hepthylamine. Yield: 80%. ^{1}H NMR (500 MHz, $CDCl_3$): □0.94 (t,

6H, J = 7.2 Hz), 1.42 (m, 6H), 1.57 (m, 2H), 4.21 (m, 1H), 6.18 (m, 1H), 7.64 (m, 2H), 8.16 (m, 1H), 8.28 (s, 1H). MS (M+H, 260).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 18.6 μM.

Example 39

benzooxazole-5-carboxylic acid (1-propylbutyl)amide



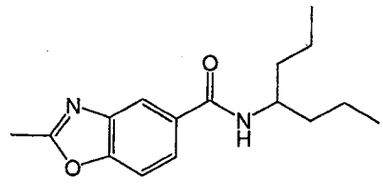
Prepared in a similar manner to example 4 using benzooxazol-5-carboxylic acid (Example 39a) and 4-heptylamine. ^{1}H NMR (500 MHz, $CDCl_3$): □ 8.16 (d, J = 5.4 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.64 (d, J = 8.6 Hz, 1H),5.82 (d, J = 8.6 Hz, 1H) 4.10-4.22 (m, 1H), 1.58-1.62 (m, 4H), 1.40-1.49 (m, 4H), 0.95 (t, J = 7.2 Hz, 6H); ESIMS: 261 (M^+H).

a. benzooxazol-5-carboxylic acid: A mixture of 3-amino-4-hydroxybenzoic acid (500 mg, 3.26 mmol) and trimethyl orthoformate (5 mL) was heated at 65°C for 2 h under argon. The reaction mixture was cooled to room temperature, filtered and washed with hexanes. The filtrate was concentrated in vacuo to afford the product as a white solid (78 mg, 15%): ^{1}H NMR (500 MHz, $CDCl_3$): □8.57 (d, J = 1.5 Hz, 1H), 8.20 (dd, J = 8.4, 1.8 Hz, 1H), 8.20 (s, 1H), 7.67 (d, J = 9.0 Hz, 1H). MS (M+H, 164).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.91 μM.

Example 40

2-Methyl-benzooxazole-5-carboxylic acid (1-propyl-butyl)-amide



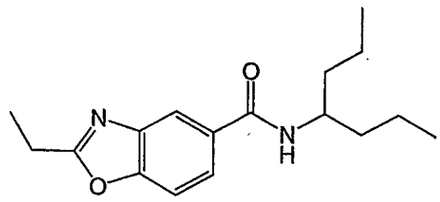
Prepared in a similar manner to example 4 starting from 2-methyl benzooxazol-5-carboxylic acid (example 40) and 4-heptylamine. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 1.6 Hz, 1H), 7.77 (d, J = 8.5, 1.6 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H),5.79 (d, J = 8.9 Hz, 1H for NH) 4.10-4.22 (m, 1H), 2.66 (s, 3H), 1.58-1.65 (m, 4H), 1.38-1.55 (m, 4H), 0.94 (t, J = 7.2 Hz, 6H); MS(APCI, M+1): 275.2.

a. 2-methyl benzooxazol-5-carboxylic acid: A mixture of 3-amino-4-hydroxybenzoic acid (1.5 g, 9.79 mmol) and trimethyl orthoacetate (15 mL, large excess) was heated at 65 °C for 5 hrs under argon. The reaction mixture was cooled to room temperature, filtered, washed with hexanes. The filtrate was concentrated in vacuo to afford the product as a yellow solid (1.4 g, 80%): ^{1}H NMR (500 MHz , CD_3OD) δ 8.26 (d, J= 1.7 Hz, 1H), 8.07 (dd, J= 8.5, 1.6 Hz, 1H), 7.67 (d, J= 8.2 Hz, 1H), 2.67 (s, 1H); MS(APCI, M+1): 178.10.

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.33 μM.

Example 41

2-Ethyl-benzooxazole-5-carboxylic acid (1-propyl-butyl)-amide



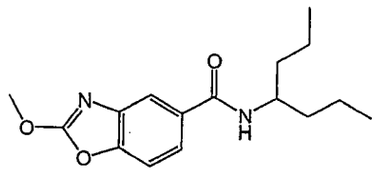
A mixture of 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide (example 41a) and trimethyl orthopropyrate was heated at 65 °C for 5 hr under N_2. The reaction mixture was cooled to room temperature and concentrated in vacuo. The resulting residue was purified on silica gel via Preparative-TLC (3% MeOH in CH_2Cl_2) to afford the product as a white solid (42 mg, 73%): mp 107-108 °C; MS(APCI, M+1): 289.10.

a. 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide was prepared in a similar manner to example 4 using 3-Amino-4-hydroxybenzoic acid and 4-heptylamine. Yield 57 %.^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (t, 6H); 1.26-1.51 (m, 8H); 4.09 (m, 1H); 6.74 (m, 1H); 7.05 (s, 1H); 7.43 (m, 2H); 7.77 (m, 2H).MS: (251, M+H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.68 μM.

Example 42

2-Methoxy-benzooxazole-5-carboxylic acid (1-propyl-butyl)-amide

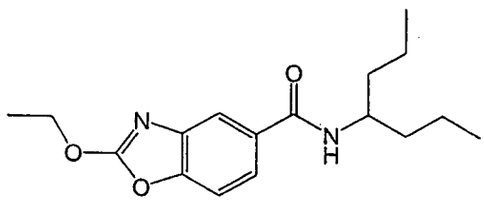


Prepared in a similar manner to example 41 using 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide (example 4aa) and tetramethylorthocarbonate. Yield: 60%. mp 137-138 °C; MS (M+H, 291.10).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.69 μM.

Example 43

2-Ethoxy-benzooxazole-5-carboxylic acid (1-propyl-butyl)-amide

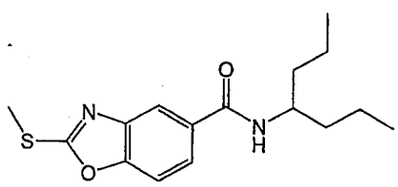


Prepared in a similar manner to example 41 using 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide (example 41a) and tetraethoxymethane: mp 128-129 °C; MS (M+H, 305.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 5 μM.

Example 44

N-(heptan-4-yl)-2-(methylthio)benzo[d]oxazole-5-carboxamide



To a solution of N-(Heptan-4-yl)-2-(mercapto)benzo[*d*]oxazole-5-carboxamide (example 44a) (50 mg, 0.17 mmol) in DMF (3 mL) at 0 °C was added K_2CO_3 (29 mg, 0.17 mmol) and MeI (29 mg, 0.20). The resulting reaction mixture was heated at 80 °C overnight. The solvent was removed under reduced pressure. The residue was diluted with dichloromethane and washed with water, dried (Na_2SO_4), filtered, concentrated in vacuo, purified via PTLC (15% EtOAc in hexanes) to afford the product as a white solid (50 mg, 96%): mp 113-114 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 1.8 Hz, 1H), 7.73 (dd, J = 8.5, 1.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 5.76 (d, J = 8.4 Hz, 1H), 4.15-4.25 (m, 1H),

127

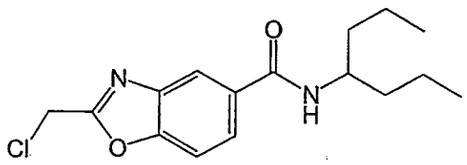
2.77 (s, 3H), 1.58-1.65 (m, 2H), 1.1.38-1.55 (m, 6H), 0.94 (t, J = 7.2 Hz, 6H); MS(APCI, M+): 307.2.

a. N-(Heptan-4-yl)-2-(mercapto)benzo[*d*]oxazole-5-carboxamide: To a solution 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide (example 41a) (250 mg, 1.0 mmol) in EtOH was added KSCSOEt (160 mg, 1.0 mmol). The resulting reaction mixture was heated at 80 °C overnight. The solvent was removed under reduced pressure. And the residue was taken up in water. The resulting mixture was acidified with HOAc to pH ~ 5 and then filtered. The residue was washed with water to afford the product as a white solid (160 mg, 55%). MS (M+H, 293.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3.1 μM.

Example 45

Chloromethyl benzooxazol-5-carboxylic acid (1-propyl-butyl)amide

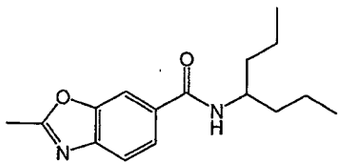


Prepared in a similar manner to example 41 using 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide (example 41a) and trimethyl chloro-orthoacetate. Yield: 65%. mp 108.5-109 °C. MS (M+H, 309.05).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.23 μM.

Example 46

2-Methyl-benzooxazole-6-carboxylic acid (1-propyl-butyl)-amide



Prepared in a similar manner to example 4 using 2-methyl benzooxazol-6-carboxylic acid (example 46a) and 4-heptylamine Yield 50%: ^{1}H NMR (500 MHz , CD_3OD) δ 8.19 (d, J = 1.4 Hz, 1H), 8.05 (dd, J = 8.3, 1.5 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 2.68 (s, 1H); MS (M+1, 178.10).

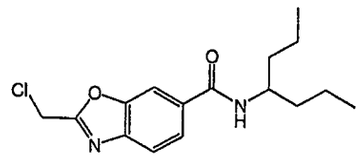
a. 2-methyl benzooxazol-6-carboxylic acid was prepared in a similar manner to example 40a from 4-amino-3-hydroxybenzoic acid (50%): ^{1}H NMR (500 MHz , CD_3OD) δ

8.19 (d, J = 1.4 Hz, 1H), 8.05 (dd, J = 8.3, 1.5 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 2.68 (s, 1H); MS (M+H, 178.10).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 2.1μM.

Example 47

2-Chloromethyl-benzooxazole-6-carboxylic acid (1-propyl-butyl)-amide



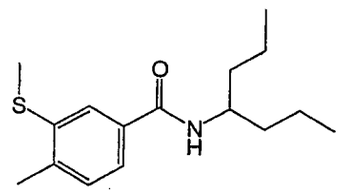
Prepared in a similar manner to example 41 using 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide (example 47a) and trimethyl chloro-orthoacetate. The product was obtained as a white solid (45 mg, 73%): mp 137.0-137.5 °C; MS (M+H, 309.05.

a. 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide was prepared in a similar manner to example 41a from 4-amino-3-hydroxybenzoic acid. Yield: 50%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, 6H); 1.41 (m, 6H); 1.54 (m, 2H); 4.13 (m, 1H); 5.81 (d, 1H); 6.63 (d, 1H), 6.95 (d, 1H); 7.82 (s, 1H). MS: (251, M+H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.45 μM.

Example 48

4-methyl-3-methylsulfanyl-N-(1-propylbutyl)benzamide



Preapared in a similar manner as example 4 using 4-methyl-3-(methylthio)benzoic acid (example 48a) and 4-heptylamine. Yield: 50%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (t, 6H, J = 7.2 Hz), 1.40-1.41 (m, 8H), 2.35 (s, 3H), 2.51 (s, 1H), 4.15 (m, 1H), 5.75 (d, 1H, J = 8.5 Hz), 7.15 (d, 1H, J = 7.8 Hz), 7.31 (d, 1H, J = 7.8 Hz), 7.65 (d, 1H, J = 1.5 Hz). MS (M+H, 280).

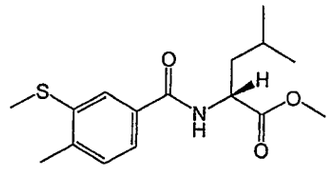
a. 4-methyl-3-(methylthio)benzoic acid: 3-Amino-4-methylbenzoic acid was suspended in ice-water (55 mL), and concentrated HCl (8.56 mL) was slowly added. An aqueous solution of sodium nitrite (2.4 g in 5.5 mL) was added to the suspension over a period of 15 minutes and the mixture was stirred for another 15 minutes. Then, an aqueous

solution of sodium acetate (9.31 g in 18 mL) was added dropwise. The reaction was allowed to proceed for 45 min. A heavy orange precipitate was obtained. The precipitate was filtered off and washed with small portions of ice-cold water. The solid was combined with a solution of potassium xanthogenate (11.93 g) and potassium carbonate (8.22 g) in 250 mL of water. The reaction vessel was placed in a preheated oil bath at 70°C and the mixture was stirred for 25 minutes. The reddish solution was taken out of the bath and stirred for 15 minutes or until the temperature reached 30°C. Sodium hydroxide (0.782 g) was added and stirred to dissolution. Dimethylsulfate (5.70 mL) was added. The mixture was stirred for 1 hour at room temperature then briefly refluxed. Solvent removal under reduced pressure yielded an orange solid. The solid was treated with a 2.0 N solution of H_2SO_4 and extracted with EtOAc. The extracts were washed with water then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a reddish crude solid. The solid was adsorbed on silica gel and purified by column chromatography (gradient 5 to 50% ethyl acetate in hexane) to give 4-methyl-3-(methylthio)benzoic acid as a pale yellow powder (2 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.54 (s, 3H), 7.24 (d, 1H, J = 7.8 Hz), 7.79 (d, 1H, J = 7.8 Hz), 7.86 (d, 1H, J = 1.5 Hz).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.21 μM.

Example 49

(R)-methyl 4-methyl-2-(4-methyl-3-(methylthio)benzamido)pentanoate



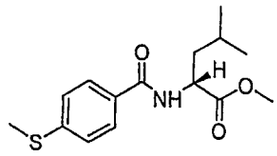
Prepared in a similar manner to example 4 using 3-methyl-4-(methylthio)benzoic acid (example 48a) and D Leucine methyl ester. Yield: 45%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (d, 3H, J= 6.36Hz), 0.99 (d, 3H, J = 6.1 Hz), 1.64-1.77 (m, 2H), 2.36 (s, 3H), 2.51(s, 3H), 3.77 (s, 3H), 4.85(m, 1H), 6.50 (d, 1H, J = 8.10 Hz), 7.18 (d, 1H, J =7.83 Hz), 7.38 (dd, 1H, J = 7.77 Hz, J = 1.78Hz), 7.65 (d, 1H, J = 1.65 Hz). MS (M+H, 310).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.1 μM.

Example 50

(R)-methyl 4-methyl-2-(4-(methylthio)benzamido)pentanoate

130

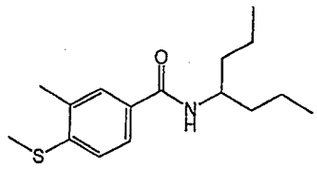


Prepared in a similar manner to example 4 using 4-(methylthio)benzoic acid and D Leucine methyl ester. MS (M+H, 296).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.16 μM.

Example 51

N-(heptan-4-yl)-3-methyl-4-(methylthio)benzamide



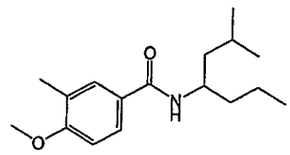
Prepared in a similar manner to example 4 using 3-methyl-4-(methylthio)benzoic acid (example 51a) and 4-hepthylamine. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (t, 6H); 1.37-1.46 (m, 6H); 1.54-1.56 (m, 2H); 2.35 (s, 3H); 2.49 (s, 3H); 4.17 (m, 1H); 5.73 (d, 1H); 7.14 (d, 1H); 7.52 (s, 1H);7.58 (d, 1H). MS (280, M+H) m.p: 129-131 °C.

a. 3-methyl-4-(methylthio)benzoic acid was prepared using the same procedure described in example 48a starting from 3-Amino-4-methylbenzoic acid. Yield 30 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H); 2.53 (s, 3H); 7.17 (d, 1H); 7.85 (s, 1H); 7.93 (d, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.12 μM.

Example 52

4-methoxy-3-methyl-N-(2-methylheptan-4-yl)benzamide



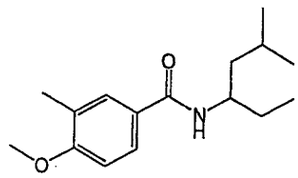
Prepared in a similar manner as described in example 4 using 4-methoxy-3-methylbenzoic acid and 2-methyl-4-heptanamine (example 2a). Yield: 45%.^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (m, 9H); 1.39 (m, 5H); 1.53 (m, 1H); 1.67 (m, 1H); 2.24 (s, 3H); 3.86

(s, 3H); 4.23 (m, 1H); 5.64 (d, 1H); 6.82 (d, 1H); 7.54 (s, 1H); 7.61 (d, 1H). MS (278, M+H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.1 μM.

Example 53

4-methoxy-3-methyl-N-(5-methylhexan-3-yl)benzamide

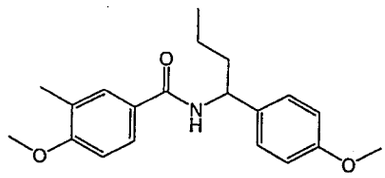


Prepared in a similar manner to example 4 using 4-methoxy-3-methylbenzoic acid and 5-methylhexan-3-amine (example 5a). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (m, 9H); 1.38 (m, 2H); 1.47 (m, 1H); 1.65 (m, 2H); 2.24 (s, 3H); 3.86 (s, 3H); 4.16 (m, 1H); 5.65 (d, 1H); 6.83 (d, 1H); 7.54 (s, 1H); 7.61 (d, 1H). MS (264, M+H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.09 μM.

Example 54

4-methoxy-N-(1-(4-methoxyphenyl)butyl)-3-methylbenzamide



Prepared in a similar manner to example 4 using 3-methyl-4-methoxy-benzoic acid and 1-(4-methoxyphenyl)butan-1-amine (example 54a).Yield 52%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, 3H); 1.31-1.41 (m, 2H); 1.82-1.92 (m, 2H); 2.22 (s, 3H); 3.79 (s, 3H);3.86 (s, 3H); 5.11 (m, 1H); 6.14 (d, 1H); 6.81 (d, 1H); 6.88 (d, 2H). 7.28 (d, 2H); 7.53 (s, 1H); 7.61 (d, 1H). MS (328, M+H).

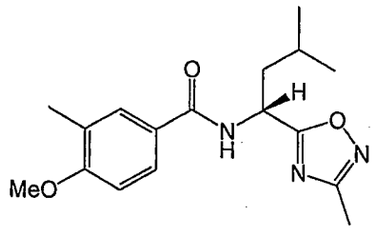
a. 1-(4-methoxyphenyl)butan-1-amine was prepared as described in example 2a from 1-(4-methoxyphenyl)butan-1-one. Yield 90%. MS (M+H, 180).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3.14 μM.

132

Example 55

(R)-4-methoxy-3-methyl-N-(3-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)butyl)benzamide



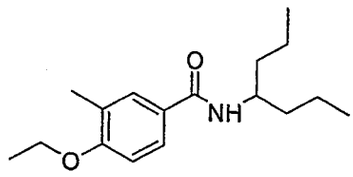
Prepared in a similar manner to example 4 using 4-methoxy-3-methylbenzoic acid and 3-methyl-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-butylamine (Example 55a). MS (M+H, 318).

a. (R)-3-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)butan-1-amine: Boc-D-Leu-OH (0.23 g, 1 mmol) was treated with N-hydroxyacetamidine (74 mg, 1 eq) and DIC (155 µL, 1 eq) in dioxane (2 mL) at room temperature overnight. Another portion of DIC (1 equiv) was added and the reaction mixture was heated at 110°C for 4 hours. After removal of the solvent, the residue was treated with 50% TFA/DCM (2 mL) for 1 h and then the solvent was evaporated. The crude mixture was purified by preparative HPLC (C-18 column, MeOH-H_2O mobile phase and formic acid as modifier) to give 75 mg of the amine (45% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (d, 3H), 0.99 (d, 3H), 1.70-1.78 (m, 1H), 1.92-1.98 (m, 2H), 2.39 (s, 3H), 3.50 (b, 2H, NH_2), 4.65 (t, 1H). MS (M+H, 170).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 5.4 µM.

Example 56

4-ethoxy-N-(heptan-4-yl)-3-methylbenzamide



Prepared in a similar manner as example 4 using 4-ethoxy-3-methyl benzoic acid (example 56a) and 4-heptylamine. Yield: 75%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (t, 6H); 1.37-1.45 (m, 6H); 1.53-1.59 (m, 2H); 2.24 (s, 3H); 4.07 (q, 2H); 4.15 (m, 1H); 5.67 (d, 1H); 6.80 (d, 1H); 7.54 (s, 1H); 7.58 (d, 1H). MS (278, M+H).

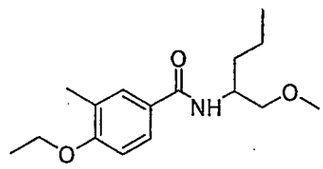
a. 4-ethoxy-3-methyl benzoic acid: 4-hydroxy-3-methyl benzoic acid (10 g) was dissolved in DMF (400 mL) followed by the addition of sodium carbonate (3eq). Ethyl

iodide (3eq) was dissolved in DMF (50 mL) was added dropwise to the reaction mixture and the solution was stirred overnight. After the reaction was completed, the solvent was evaporated. The residue was dissolved in ethyl acetate and washed with water. The organic layer was isolated and evaporated. The residue was dissolved in 200mL methanol/water (3:1). Lithium hydroxide (3eq) was added and allowed to stir overnight. Upon the completion of hydrolysis, the solvent was removed and the product was crystallized using ethyl acetate/hexane mixture to give 8.2 g of 4-ethoxy-3-methyl benzoic acid. Yield: 70%, MS (M-H, 179.20).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.17 μM.

Example 57

4-ethoxy-N-(1-methoxypentan-2-yl)-3-methylbenzamide



Prepared in a similar manner as example 4 using 4-ethoxy-3-methyl benzoic acid (example 56a) and 1-methoxypentan-2-amine (example 57a). Yield: 33%. MS (M+H, 280.1).

a. 1-methoxypentan-2-amine was prepared in a similar manner to example 9a from 2-(1-methoxypentan-2-yl)isoindoline-1,3-dione (example 57b). Yield 67%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, 3H); 1.24 -1.45 (m, 4H); 1.52 (s, 2H); 2.94 (m, 1H); 3.12 (t, 1H); 3.33 (m, 1H); 3.35 (s, 3H).

b. 2-(1-methoxypentan-2-yl)isoindoline-1,3-dione was prepared in a similar manner to example 9b from 2-(1-hydroxypentan-2-yl)isoindoline-1,3-dione (example 57c). Yield: 82%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, 3H); 1.32 (m, 2H); 1.64 (m, 1H); 2.03 (m, 1H); 3.31 (s, 3H); 3.54 (m, 1H); 3.98 (t, 1H); 4.50 (m, 1H); 7.70 (m, 2H); 7.82 (m, 2H).

c. 2-(1-hydroxypentan-2-yl)isoindoline-1,3-dione was prepared in a similar manner to example 9c using isobenzofuran-1,3-dione and 2-aminopentan-1-ol. Yield 62%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, 3H); 1.33 (m, 2H); 1.76 (m, 1H); 1.95 (m, 1H); 3.88 (m, 1H); 4.06 (m, 1H); 4.39 (m, 1H); 7.72 (m, 2H); 7.83 (m, 2H).

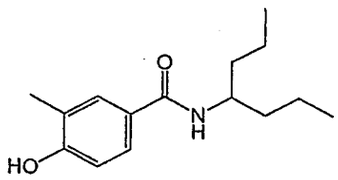
The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor

expressed in an HEK293 cell line of 0.69 μM.

134

Example 58

4-hydroxy-3-methyl-N-(1-propyl-butyl)-benzamide

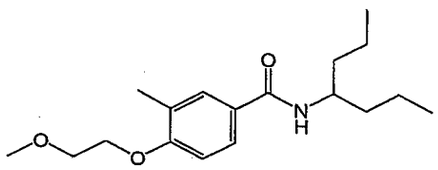


Prepared in a similar manner as described in example 4 using 4-hydroxy-3-methyl benzoic acid and 4-heptylamine. MS (M+H, 250.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.92 μM.

Example 59

N-(heptan-4-yl)-4-(2-methoxyethoxy)-3-methylbenzamide

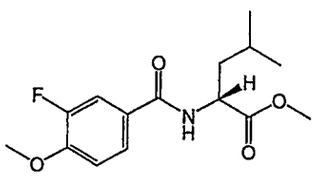


Potassium hydroxide (4 mmol) was dissolved in ethanol (5 mL) and heated at 80°C. 4-hydroxy-3-methyl-N-(1-propyl-butyl)-benzamide (example 58) (1mmol) was added into the solution followed by chloroethanol (3 mmol). The reaction was stirred overnight at 80°C. The reaction mixture was concentrated down and dissolved in 5% citric acid. he mixture was stirred for 1 hour. The aqueous mixture was extracted three times with ethyl acetate. The combined ethyl acetate was washed with water and dried down over sodium sulfate. The organic layer was concentrated down and purified by HPLC to yield 39% of N-(heptan-4-yl)-4-(2-methoxyethoxy)-3-methylbenzamide. MS (M+H, 308.25).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.21 μM.

Example 60

(R)-methyl 2-(3-fluoro-4-methoxybenzamido)-4-methylpentanoate

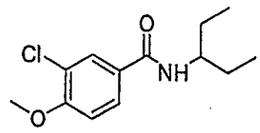


Prepared in a similar manner to example 4 using 3-fluoro-4-methoxybenzoic acid and D-leucine methyl ester. MS (M+H, 298).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.3 μM.

Example 61

3-chloro-4-methoxy-N-(pentan-3-yl)benzamide

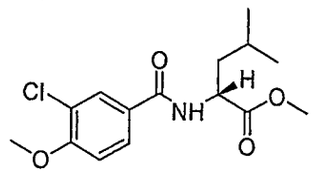


Prepared in a similar manner to example 4 using 3-pentylamine and 3-chloro-4-methoxy benzoic acid. Yield 40%. MS (M+H, 256.20).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.56 μM, and when present at 0.3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 6.28.

Example 62

(R)-methyl 2-(3-chloro-4-methoxybenzamido)-4-methylpentanoate

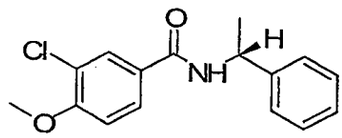


Prepared in a similar manner to example 4 using 3-chloro-4-methoxy benzoic acid and D-leucine methyl ester hydrochloride. MS (M+H, 314.10).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.08 μM, and when present at 0.01 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 13.18.

Example 63

(R)-3-chloro-4-methoxy-N-(1-phenylethyl)benzamide



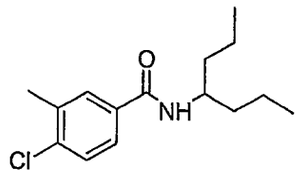
Prepare in a similar manner to example 4 using (R)-1-phenylethanamine and 3-chloro-4-methoxy benzoic acid. MS (M+H, 290.0).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 2.5 μM, and when present at 0.3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 2.7 .

136

Example 64

4-Chloro-3-methyl-N-(1-propyl-butyl)-benzamide

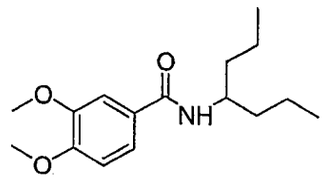


Prepared in a similar manner to example 4 using 4-chloro-3-methyl benzoic acid and heptan-4-amine. MS (M+H, 268).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.8 μM.

Example 65

3,4-Dimethoxy-N-(1-propyl-butyl)-benzamide

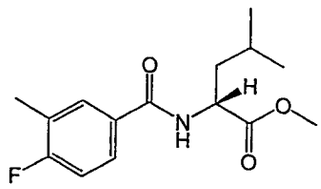


Prepared in a similar manner to example 4 using 3,4dimethoxy benzoic acid and heptan-4-amine. MS (M+H, 279.37).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.36 μM.

Example 66

(R)-methyl 2-(4-fluoro-3-methylbenzamido)-4-methylpentanoate

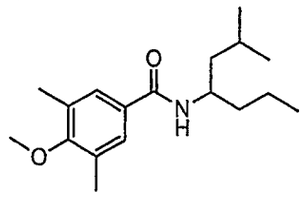


Prepared in a similar manner to example 4 using 4-fluoro-3-methylbenzoic acid and D-leucine methyl ester. MS (M+H, 282).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.32 μM.

Example 67

4-methoxy-3,5-dimethyl-N-(2-methylheptan-4-yl)benzamide

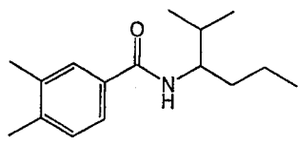


Prepared in a similar manner to example 4 using 4-methoxy-3,5-dimethylbenzoic acid and 2-methylheptan-4-amine (example 2a). MS (M+H, 292.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.85 μM.

Example 68

3,4-dimethyl-N-(2-methylhexan-3-yl)benzamide

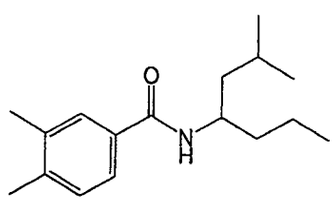


Prepared in a similar manner to example 4 using 3,4-dimethylbenzoic acid and hexan-3-amine (example 3a). ^1H NMR (500 MHz, $CDCl_3$): δ 0.94 (m, 9H); 1.39 (m, 3H); 1.56 (m, 1H); 1.84 (m, 1H); 2.30 (s, 3H); 2.31 (s, 3H); 4.04 (m, 1H); 5.76 (d, 1H); 7.18 (d, 1H); 7.46 (d, 1H); 7.55 (s, 1H); MS (248, M+H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.11 μM.

Example 69

3,4-dimethyl-N-(2-methylheptan-4-yl)benzamide

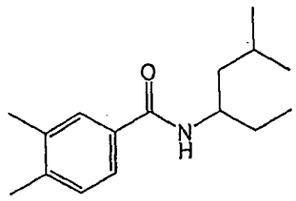


Prepared in a similar manner to example 4 using 3,4-dimethylbenzoic acid and 2-methylheptan-4-amine (example 2a). ^1H NMR (500 MHz, $CDCl_3$): δ 0.94 (m, 9H); 1.40 (m, 5H); 1.53 (m, 1H); 1.68 (m, 1H); 2.29 (s, 3H); 2.30 (s, 3H); 4.24 (m, 1H); 5.69 (d, 1H); 7.17 (d, 1H); 7.46 (d, 1H); 7.54 (s, 1H). MS (262, M+H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.13 μM.

Example 70

3,4-dimethyl-N-(5-methylhexan-3-yl)benzamide

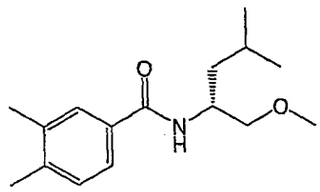


Prepared in a similar manner to example 4 using 3,4-dimethylbenzoic acid and 5-methylhexan-3-amine (example 5a). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (m, 9H); 1.38 (m, 2H); 1.46 (m, 1H); 1.65 (m, 2H); 2.29 (s, 3H); 2.30 (s, 3H); 4.18 (m, 1H); 5.70 (d, 1H); 7.17 (d, 1H); 7.46 (d, 1H); 7.55 (s, 1H). MS (248, M+H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.17 μM.

Example 71

(R)-N-(1-methoxy-4-methylpentan-2-yl)-3,4-dimethylbenzamide



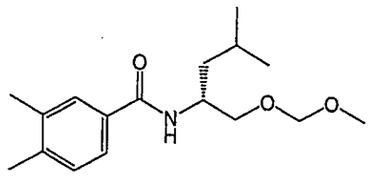
To a solution of (R)-N-(1-hydroxy-4-methylpentan-2-yl)-3,4-dimethylbenzamide (1.59 g, 6.39 mmol) (example 71a) in dry DMF (20 mL) was added powdered NaOH (281 mg, 7 mmol) an the solution was stirred at 0°C for 2 hrs. Iodomethane (1 eq, 6.39 mmol) was added in DMF (10 ml) drop-wise over period of 1 hr. The temperature was kept at 0°C and the mixture was stirred for 1 hr. The reaction was quenched by adding 300 ml of water. The aqueous layer was extracted with dichloromethane, dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on silica-gel (toluene-ethyl acetate; 5-20% gradient) to give 1.23 g (R)-N-(1-methoxy-4-methylpentan-2-yl)-3,4-dimethylbenzamide (73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94-0.97 (t, 6H), 1.41-1.47 (M, 1H), 1.54-1.60 (m, 1H), 1.64-1.68 (m, 1H), 2.29 (d, 6H), 3.36 (s, 3H), 3.45-3.50 (m, 2H), 4.34-4.39 (m, 1H), 6.23-6.25 (d, 1H), 7.16-7.17 (d, 1H), 7.47-7.49 (dd, 1H), 7.56 (s, 1H). MS (M+H, 264.3).

a. (R)-N-(1-hydroxy-4-methylpentan-2-yl)-3,4-dimethylbenzamide was prepared in a similar manner as described in example 4 using 3,4-dimethylbenzoic acid and with (R)-aminoleucinol . Yield: 75%. MS (M+H, 250.3).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.2 μM.

Example 72

(R)-N-(1-(methoxymethoxy)-4-methylpentan-2-yl)-3,4-dimethylbenzamide

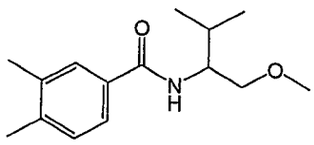


To a solution of (R)-N-(1-hydroxy-4-methylpentan-2-yl)-3,4-dimethylbenzamide (Example 71a) (0.24 mmol) dissolved in dry DMF (2mL) was added at 0°C powdered NaOH (0.36 mmol, 14.5 mg, 1.5 eq) and the mixture was stirred for 1 hr at 0°C. Then chloro-methoxy-methane (19.3μl, 1 eq) was added and the reaction stirred at 0°C for 1 hour. The reaction was quenched with water (30 mL) and the mixture was extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and evaporated. The crude product was purified by preparative TLC (20% ethyl acetate/hexanes) to give 37.7 mg of (R)-N-(1-(methoxymethoxy)-4-methylpentan-2-yl)-3,4-dimethylbenzamide (53%). ^1H NMR (500 MHz, $CDCl_3$): δ 0.98-1.00 (t, 6H), 1.49-1.53 (m, 1H), 1.58-1.64 (m, 1H), 1.69-1.73 (m, 2H), 2.32-2.33 (d, 6H), 3.38-3.39 (t, 3H), 3.64-3.72 (ddd, 2H), 4.41-4.44 (m, 1H), 4.65-4.69 (dd, 2H), 6.37-6.39 (d, 1H), 7.19-7.21 (d, 1H), 7.50-7.52 (dd, 1H), 7.60 (sb, 1H). MS (M+H , 294.3).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.06 μM.

Example 73

N-(1-Methoxymethyl-2-methyl-propyl)-3,4-dimethyl-benzamide



Prepared in a similar manner to example 71 using N-(1-hydroxy-3-methylbutan-2-yl)-3,4-dimethylbenzamide (example 73a) and methyl iodide. Yield 87%. ^1H NMR (500 MHz, $CDCl_3$): δ 0.97-1.00 (dt, 6H), 1.96-2.00 (m, 1H), 2.29 (s, 3H), 2.30 (s, 3H), 3.35 (s, 3H), 3.42-3.45 (dd, 1H), 3.60-3.62 (dd,1H), 4.01-4.05 (m, 1H), 6.31-6.33 (d, 1H), 7.16-7.18 (d, 1H), 7.48-7.50 (dd, 1H), 7.56-7.57 (d, 1H). MS (M+H, 250).

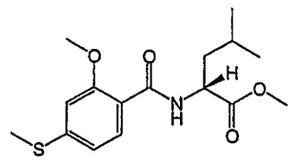
140

a. N-(1-hydroxy-3-methylbutan-2-yl)-3,4-dimethylbenzamide was prepared in a similar manner to example 71a using 3,4-dimethoxybenzoic acid and 2-amino-3-methylbutan-1-ol. Yield 75%. MS (M+H, 236.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.87 μM.

Example 74

(R)-methyl 2-(2-methoxy-4-(methylthio)benzamido)-4-methylpentanoate

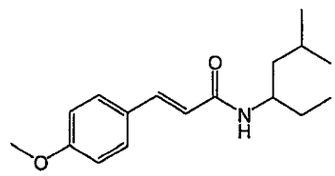


Prepared in a similar manner to example 4 using 2-methoxy-4-(methylthio)benzoic acid and D-leucine methyl ester. MS (M+H, 326).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 15.8 μM.

Example 75

N-(2-methylheptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide

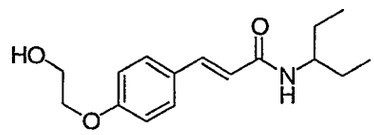


Prepared in a similar manner to example 4 using 3-(4-Methoxy-phenyl)-acrylic acid and 5-methylhexan-3-amine (example 5a). Yield: 59%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (m, 9H); 1.33 (t, 2H); 1.43 (m, 1H); 1.58-1.67 (m, 2H); 3.83 (s, 3H); 4.11 (m, 1H); 5.19 (d, 1H); 6.25 (d, 1H); 6.88 (d, 2H);7.44 (d, 2H); 7.58 (d, 1H). MS (276, M+H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.24 μM.

Example 76

N-(1-Ethyl-propyl)-3-[4-(2-hydroxy-ethoxy)-phenyl]-acrylamide



N-(1-Ethyl-propyl)-3-(4-hydroxy-phenyl)-acrylamide (example 76a) (0.44 mmol, 103 mg) was dissolved in absolute ethanol with KOH (0.7 mmol, 37 mg). The mixture was

(41)

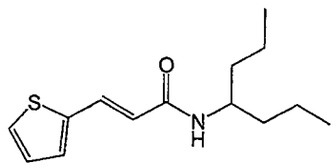
stirred at 80°C for 1 hr. Then 2-chloro-ethanol (1.76 mmol, 118 μL) was added dropwise and the mixture was refluxed overnight. Following evaporation the crude product was dissolved in dichloromethane and washed with water and 5% citric acid. The organic phase was evaporated and the residue was purified by chromatography on silica gel to give 73 mg of desired product (60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92-0.95 (t, 6H), 1.25 (s, 1H),1.40-1.46 (m, 2H), 1.59-1.64 (m, 2H), 3.93-3.94 (m, 1H), 3.95-3.98 (m, 2H), 4.09-4.11 (m, 2H), 5.28-5.30 (d, 1H), 6.26-6.29 (d, 1H), 6.88-6.90 (d, 2H), 7.43-7.45 (d, 2H), 7.56-7.59 (d, 1H). MS (M+H, 278.1).

a. N-(1-Ethyl-propyl)-3-(4-hydroxy-phenyl)-acrylamide was prepared in a similar manner as described in example 4 from 4-hydroxy-cinnamic acid and 3-pentylamine. MS (M+H, 234.10).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 5.8 μM.

Example 77

(E)-N-(heptan-4-yl)-3-(thiophen-2-yl)acrylamide

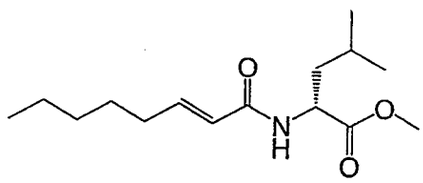


Prepared in a similar manner as described in example 4 from (E)-3-(thiophen-2-yl)acrylic acid and 4-hepthylamine. MS (M+H, 252).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.44 μM.

Example 78

(R,E)-methyl 4-methyl-2-oct-2-enamidopentanoate



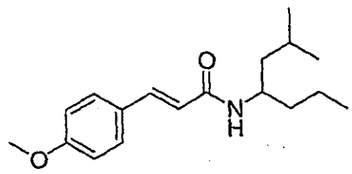
Prepared in a similar manner as described in example 4 from (E)-oct-2-enoic acid and D-leucine methyl ester. MS (M+H, 270).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.92 μM.

142

Example 79

3-(4-Methoxy-phenyl)-N-(3-methyl-1-propyl-butyl)-acrylamide

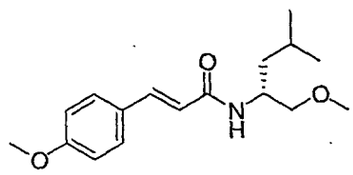


Prepared in a similar manner to example 4 using 3-(4-methoxy-phenyl)-acrylic acid and 3-methyl-1-propyl-butylamine (example 2a). Yield: 65%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90-0.95 (m, 9H), 1.30-1.39 (m, 5H), 1.49-1.50 (m, 1H), 1.64-1.67 (m, 1H), 3.82 (s, 3H), 4.17-4.18 (m, 1H), 5.18-5.20 (d, 1H), 6.22-6.26 (d, 1H), 6.86-6.89 (d, 2H), 7.42-7.45 (d, 2H), 7.56-7.59 (d, 1H). MS (M+H, 290.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.84 μM.

Example 80

N-(1-Methoxymethyl-3-methyl-butyl)-3-(4-methoxy-phenyl)-acrylamide

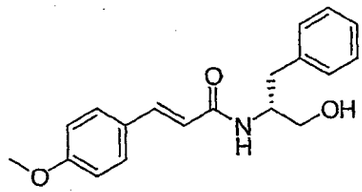


Prepared in a similar manner as described in example 71 from 3-(4-methoxy-phenyl)-acrylic acid and D-leucinol. Yield: 41%. ^{1}H NMR (500 MHz, $CDCl_3$): δ0.93-0.96 (t, 6H), 1.38-1.42 (m, 1H), 1.48-1.54 (m, 1H), 1.63-1.66 (m, 1H), 3.36 (s, 3H), 3.41-3.46 (m, 2H), 3.82-3.83 (s, 3H), 4.29-4.31 (m, 1H), 5.69-5.71 (d, 1H), 6.24-6.27 (d, 1H), 6.87-6.89 (d, 2H), 7.43 (s, 1H), 7.44 (s, 1H), 7.56-7.59 (d, 1H). MS (M+H, 292.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.90 μM.

Example 81

N-(1-Benzyl-2-hydroxy-ethyl)-3-(4-methoxy-phenyl)-acrylamide



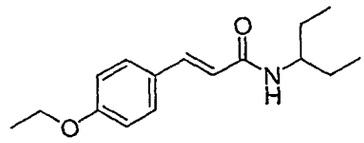
Prepared in a similar manner as described in example 4 from 3-(4-methoxy-phenyl)-acrylic acid and D-phenylalaninol. MS (M+H, 312.3).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor

expressed in an HEK293 cell line of 1.1 μM.

Example 82

3-(4-Ethoxy-phenyl)-N-(1-ethyl-propyl)-acrylamide

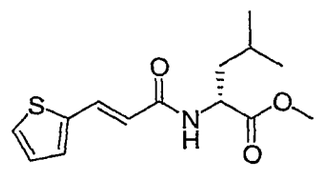


Prepared in a similar manner to example 4 using 3-(4-ethoxy-phenyl)-acrylic acid and 3-pentylamine.MS (M+H, 262.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.35 μM.

Example 83

4-Methyl-2-(3-t hiophen-2-yl-acryloylamino)-pentanoic acid methyl ester

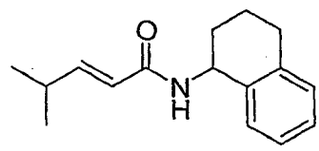


Prepared in a similar manner as described in example 4 from 3-thiophen-2-yl-acrylic acid and D-leucine methyl ester. MS (M+H, 282.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.59 μM.

Example 84

4-Methyl-pent-2-enoic acid (1,2,3,4-tetrahydro-naphthalen-1-yl)-amide

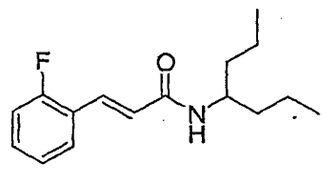


Prepared in a similar manner as described in example 4 from 4-methyl-pent-2-enoic acid and 1,2,3,4-tetrahydro-naphthalen-1-ylamine. MS (M+H, 244.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.5 μM.

Example 85

3-(2-Fluoro-phenyl)-N-(1-propyl-butyl)-acrylamide



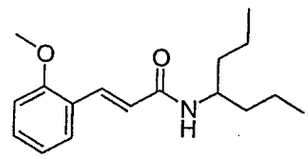
144

Prepared in a similar manner as described in example 4 from 3-(2-fluoro-phenyl)-acrylic acid and 4-heptylamine. MS (M+H, 264.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.16 μM.

Example 86

3-(2-Methoxy-phenyl)-N-(1-propyl-butyl)-acrylamide

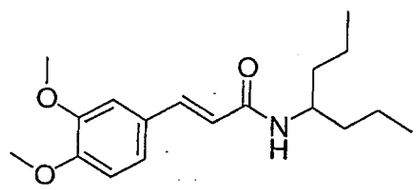


Prepared in a similar manner as described in example 4 from 3-(2-methoxy-phenyl)-acrylic acid and 4-heptylamine. MS (M+H, 276.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.90 μM.

Example 87

3-(3,4-Dimethoxy-phenyl)-N-(1-propyl-butyl)-acrylamide

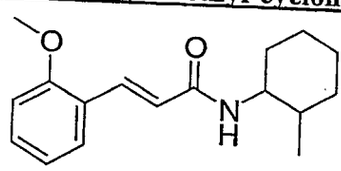


Prepared in a similar manner as described in example 4 from 3-(3,4-dimethoxy-phenyl)-acrylic acid and 4-heptylamine. MS (M+H, 306.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.97 μM, and when present at 0.3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 2.4.

Example 89

3-(2-Methoxy-phenyl)-N-(2-methyl-cyclohexyl)-acrylamide



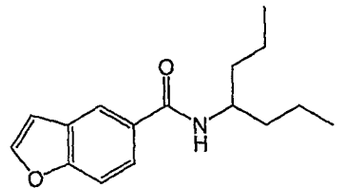
Prepared in a similar manner as described in example 4 from 3-(2-methoxy-phenyl)-acrylic acid and 2-methyl-cyclohexylamine. MS (M+H, 274.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3.4 μM.

145

Example 90

N-(heptan-4-yl)benzofuran-5-carboxamide

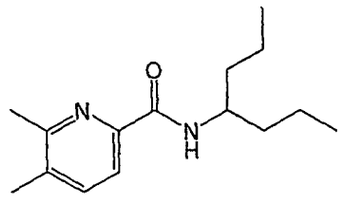


Prepared in a similar manner to example 4 using benzofuran-5-carboxylic acid and heptan-4-amine. Yield 41%. MS (M+H, 260.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.19 μM.

Example 91

N-(heptan-4-yl)-5,6-dimethylpicolinamide



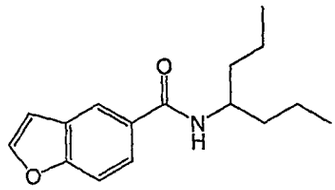
Prepared in a similar manner to example 4 using 5,6-Dimethylpicolinic acid (Example 91a) and 4-heptylamine. Yield: 49%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91-0.94 (t, 6H), 1.38-1.48 (m, 4H), 1.49-1.61 (m, 4H), 2.32 (s, 3H), 2.52 (s, 3H), 4.11-4.13 (m, 1H), 7.52-7.53 (d,1H), 7.93-7.94 (d, 1H). MS (M+H, 249.1).

a. 5,6-Dimethylpicolinic acid: 5,6-dimethylpicolinonitrile (example 91b) was refluxed in concentrated HCl (15 mL) overnight. The solvent was evaporated and the solid residue was co-evaporated several times with EtOH. Drying provided 453 mg of 5,6-Dimethylpicolinic acid (80%) as a white solid. MS (M+H, 152.1).

b. 5,6-dimethylpicolinonitrile: 2,3-lutidine (13.25 mmol) was refluxed overnight with 18 ml of glacial AcOH and 6 ml of hydrogen peroxide. The solvent was evaporated and the residue was co-evaporated two times with water, basified with Na_2CO_3 and extracted with chloroform. The organic layer was dried over Na_2SO_4 and evaporated to give 1.45 g of a crystalline product. The product (615 mg, 5 mmol) was reacted with trimethylsilane carbonitrile (5.5 mmol) in dichloromethane (10 mL) at room temperature for 5 min followed by addition of dimethylcarbamoyl chloride (5 mmol) and the solution was stirred at room temperature for 3 days. The reaction mixture was treated with 10% potassium carbonate (10 mL), the organic layer was separated and the aqueous layer was

Example 90

N-(heptan-4-yl)benzofuran-5-carboxamide

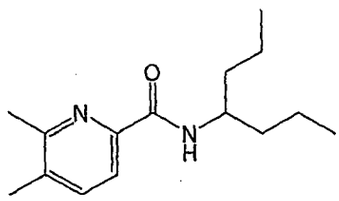


Prepared in a similar manner to example 4 using benzofuran-5-carboxylic acid and heptan-4-amine. Yield 41%. MS (M+H, 260.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.19 μM.

Example 91

N-(heptan-4-yl)-5,6-dimethylpicolinamide



Prepared in a similar manner to example 4 using 5,6-Dimethylpicolinic acid (Example 91a) and 4-heptylamine. Yield: 49%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91-0.94 (t, 6H), 1.38-1.48 (m, 4H), 1.49-1.61 (m, 4H), 2.32 (s, 3H), 2.52 (s, 3H), 4.11-4.13 (m, 1H), 7.52-7.53 (d,1H), 7.93-7.94 (d, 1H). MS (M+H, 249.1).

a. 5,6-Dimethylpicolinic acid: 5,6-dimethylpicolinonitrile (example 91b) was refluxed in concentrated HCl (15 mL) overnight. The solvent was evaporated and the solid residue was co-evaporated several times with EtOH. Drying provided 453 mg of 5,6-Dimethylpicolinic acid (80%) as a white solid. MS (M+H, 152.1).

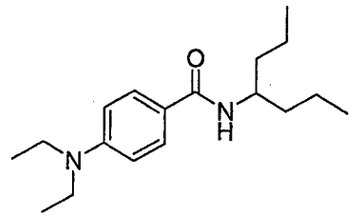
b. 5,6-dimethylpicolinonitrile: 2,3-lutidine (13.25 mmol) was refluxed overnight with 18 ml of glacial AcOH and 6 ml of hydrogen peroxide. The solvent was evaporated and the residue was co-evaporated two times with water, basified with Na_2CO_3 and extracted with chloroform. The organic layer was dried over Na_2SO_4 and evaporated to give 1.45 g of a crystalline product. The product (615 mg, 5 mmol) was reacted with trimethylsilane carbonitrile (5.5 mmol) in dichloromethane (10 mL) at room temperature for 5 min followed by addition of dimethylcarbamoyl chloride (5 mmol) and the solution was stirred at room temperature for 3 days. The reaction mixture was treated with 10% potassium carbonate (10 mL), the organic layer was separated and the aqueous layer was

extracted 2 times with dichloromethane. The organic phase was dried over Na_2SO_4 and evaporated to give 495 mg of 5,6-dimethylpicolinonitrile (75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.53 (s, 3H), 7.43-7.45 (d, 1H), 7.51-7.52 (d, 1H); ^{13}C: δ 19.71, 22.80, 117.87, 126.36, 130.60, 136.58, 137.66, 159.84). MS (M+H, 133.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 2.8 μM.

Example 92

4-(diethylamino)-N-(heptan-4-yl)benzamide

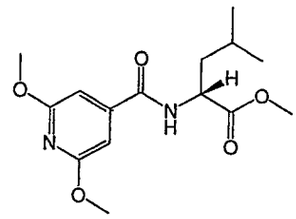


Prepared in a similar manner to example 4 using 4-diethylamino benzoic acid and 4-heptylamine. (31% %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92(t, 6H, J = 7.17 Hz), 1.18 (t, 6H, J = 7.04 Hz), 1.41(m, 4H), 1.55(m, 4H), 3.39 (m, 4H), 4.15 (m, 1H), 5.62 (m, 1H), 6.64 (d, 2H, J = 10.26Hz), 7.64 (d, 2H, J = 10.26 Hz). MS (M+H, 291).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 7.6 μM.

Example 93

(R)-methyl 2-(2,6-dimethoxyisonicotinamido)-4-methylpentanoate

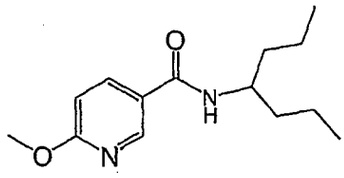


Prepared in a similar manner to example 4 using 2,6-Dimethoxy-isonicotinic acid and D-leucine methyl ester. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (d, 3H, J=7.27 Hz), 0.93 (d, 3H, J = 7.26 Hz), 1.41-1.58 (m, 8H), 3.95 (s, 3H), 4.08 (s, 3H), 4.15 (m, 1H), 6.43 (d, 1H, J = 8.32 Hz), 7.47 (m, broad, 1H), 8.41 (d, 1H, J = 8.34 Hz). MS (M+H; 311).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.91 μM.

Example 94

N-(heptan-4-yl)-6-methoxynicotinamide



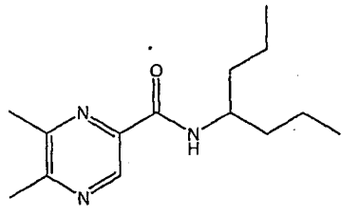
Prepared in a similar manner to example 4 using sodium 6-methoxynicotinate (example 94a) and 4-hepthylamine. Yield: 44%. MS (M+H, 251).

a. methyl 6-methoxynicotinate (2.097g, 12.56mmol) was dissolved in dioxane (30mL). An aqueous solution of NaOH (1.0N, 25mL) was added to the solution and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure to provide 2.2 g of sodium 6-methoxynicotinate.

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 2.66 μM.

Example 95

5,6-dimethylpyrazine-2-carboxylic acid (1-propylbutyl)amide



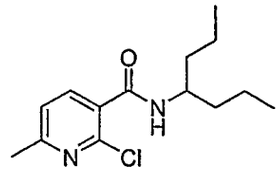
Prepared in a similar manner to example 4 using 5,6-dimethyl-pyrazine-2-carboxylic acid (example 95a) and 4-heptylamine. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91-0.94 (t, 6H), 1.35-1.42 (m, 4H), 1.48-1.51 (m, 2H), 1.55-1.60 (m, 2H), 2.57-2.60 (d, 6H), 4.13-4.16 (m, 1H), 7.52-7.53 (d, 1H), 9.09 (s, 1H); MS (M+H, 250).

a. 5,6-dimethyl-pyrazine-2-carboxylic acid: To a solution of 2,3-diaminopropionic acid (1.0 g, 9.6 mmol) in methanol (20 mL) was added butane-2,3-dione (728 μL; 11.5 mmol) and NaOH (1.4 g; 56.6 mmol). The mixture was refluxed for 2 h and then cooled to room temperature while air was bubbled through for 1 hour. The white precipitate was filtered and the gelatinous product was concentrated under vacuum. The crude product was taken up in dichloromethane, washed with 10% citric acid, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give 5,6-dimethyl-pyrazine-2-carboxylic acid as a volatile solid. The compound was used as is in the next step.

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.01 μM.

Example 96

2-chloro-N-(heptan-4-yl)-6-methylnicotinamide

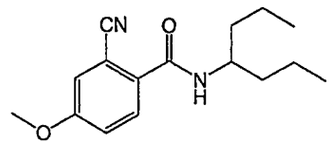


Prepared in a similar manner to example 4 using 2-chloro-6-methylnicotinic acid and 4-Heptylamine. MS (M+H, 269).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3.9 μM.

Example 97

2-cyano-N-(heptan-4-yl)-4-methoxybenzamide

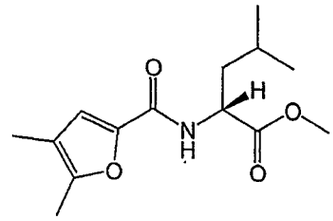


Prepared in a similar manner to example 4 using 2-cyano-4-methoxybenzoic acidand 4-Heptylamine. Yield: 73%. ^{1}H NMR (CD_3OD): □0.94 (t, 6H, J = 7.3 Hz), 1.38 (m, 4H), 1.53 (m, 4H), 4.02 (s, 3H),4.12 (m, 1H), 7.27 (d, 1H, J = 9.40 Hz), 8.11 (d, 2H, J = 2.21 Hz). MS (M+H, 275).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.39 μM, and when present at 1 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 4.52.

Example 98

(R)-methyl 2-(2,3-dimethylfuran-5-carboxamido)-4-methylpentanoate

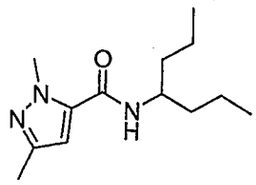


Prepared in a similar manner to example 4 using 4,5-dimethyl-furan-2-carboxylic acid and D-leucine methyl ester. Yield: 27 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, 6H), 1.66 (m, 3H), 1.96 (s, 3H), 2.26 (s, 3H), 3.75 (s, 3H), 4.78 (m, 1H), 6.51 (d, 1H), 6.89 (s, 1H). MS (M+H, 268).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.59 μM.

Example 99

N-(heptan-4-yl)-1,3-dimethyl-1H-pyrazole-5-carboxamide

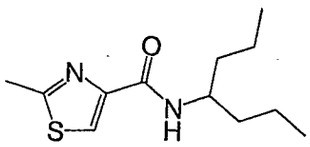


Prepared in a similar manner to example 4 using 1,3-dimethyl-1H-pyrazole-5-carboxylic acid and 4-heptylamine. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (t, 6H, J = 7.2 Hz), 1.41 (m, 4H), 1.50 (m, 4H), 2.27 (s, 3H), 3.77 (s, 3H), 4.09 (m, 1H), 6.49 (d, 1H), 6.53 (s, 1H). MS (M+H, 238).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 7.8 μM.

Example 100

N-(heptan-4-yl)-2-methylthiazole-4-carboxamide

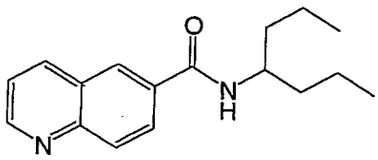


Prepared in a similar manner to example 4 using 1,3-dimethyl-1H-pyrazole-5-carboxylic acid and 4-heptylamine. MS (M+H, 241).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 7.2 μM.

Example 101

N-(heptan-4-yl)quinoline-6-carboxamide

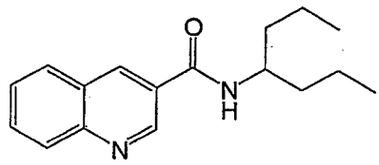


Prepared in a similar manner to example 4 using quinoline-6-carboxylic acid and 4-hepthylamine. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.2 Hz, 6H), 1.42-1.58 (m, 6H), 1.62-1.70 (m, 2H), 4.18-4.20 (m, 1H), 5.95 (d, J = 9.0 Hz, 1H), 7.49 (br s, 1H), 8.04 (dd, J = 8.5, 1.5 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 8.27 (d, J = 8.2 Hz, 1H), 8.30 (s, 1H), 8.99 (br s, 1H); MS (M+H, 271.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3.2 μM.

Example 102

N-(heptan-4-yl)quinoline-3-carboxamide

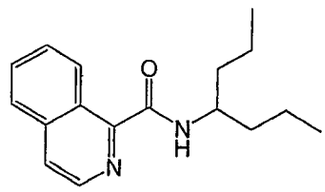


Prepared in a similar manner to example 4 using quinoline-3-carboxylic acid and hepthylamine: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 6H), 1.40-1.58 (m, 6H), 1.60-1.67 (m, 2H), 4.20-4.30 (m, 1H), 6.01 (d, J = 8.8 Hz, 1H), 7.61 (t, J = 7.5, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 8.57 (d, J = 1.2 Hz, 1H), 9.26 (br s, 1H); MS (M+H, 271.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 15.8 μM.

Example 103

N-(heptan-4-yl)isoquinoline-1-carboxamide

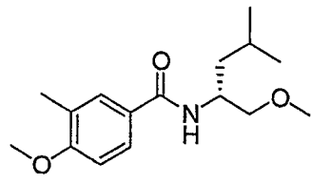


Prepared in a similar manner to example 4 using isoquinoline-1-carboxylic acid and heptamine: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, J = 7.05 Hz, 6H), 1.42-1.56 (m, 6H), 1.58-1.66 (m, 2H), 4.20-4.32 (m, 1H), 5.83 (d, J = 9.1 Hz, 1H), 7.36 (d, J = 4.2, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.88 (d, J = 4.9, 1H); MS(APCI, M+): 271.2.

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 14.2 μM.

Example 104

4-Methoxy-N-(1-methoxymethyl-3-methyl-butyl)-3-methyl-benzamide

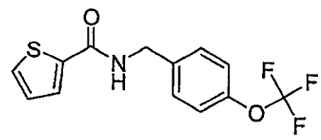


Prepared in a similar manner as described in example 71 from 4-methoxy-3-methyl-benzoic acid and D-leucinol. Yield: 86%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94—0.97 (t, 6H), 1.42-1.47 (m, 1H), 1.54-1.60 (m, 1H), 1.64-1.68 (m, 2H), 2.24 (s, 3H), 3.37 (s, 3H), 3.46-3.48 (m, 2H), 3.87 (s, 3H), 4.35-4.38 (m, 1H), 6.14-6.16 (d, 1H), 6.82-6.84 (d, 1H), 7.56 (d, 1H), 7.61-7.63 (dd, 1H). MS (M+H, 280.3).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.24 μM.

Example 105

N-(4-(trifluoromethoxy)benzyl)thiophene-2-carboxamide

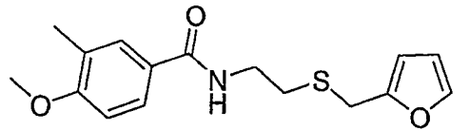


Prepared in a similar manner as described in example 4 from thiophene-2-carboxylic acid and (4-(trifluoromethoxy)phenyl)methanamine. MS (M+H, 303).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 2.4 μM.

Example 106

N-(2-(furan-2-ylmethylthio)ethyl)-4-methoxy-3-methylbenzamide

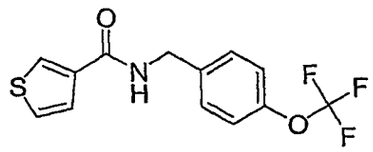


Prepared in a similar manner as described in example 4 from 4-methoxy-3-methylbenzoic acid and 2-(furan-2-ylmethylthio)ethanamine. Yield 58%. ^{1}H NMR (500 MHz, $CDCl_3$) 2.23 (s, 3H), 2.76 (t, 2H, J = 6.37 Hz), 3.59 (q, 2H, J = 12.2 Hz), 3.76 (s, 2H), 3.86 (s, 3H), 6.22 (dd, 1H, J = 3.49 Hz, J = 2.67 Hz), 6.30 (dd, 1H, J = 3.04 Hz, J = 1.78 Hz), 6.46 (m, 1H, broad), 6.83 (d, 1H, J = 8.51 Hz), 7.34(dd, 1H, J = 1.97 Hz, J = 1 Hz), 7.56 (d, 1H, J = 1.72 Hz), 7.61(dd, 1H, J = 8.53 Hz, J = 2.25 Hz). MS (M+H, 306).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 5.6 μM.

Example 107

Thiophene-3-carboxylic acid 4-trifluoromethoxy-benzylamide

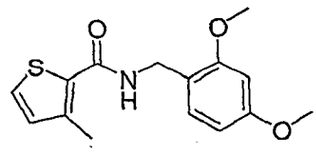


Prepared in a similar manner to example 4 using thiophene-3-carboxylic acid and 4-trifluoromethoxy-benzylamine. MS (M+H, 302.0).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 2.2 μM, and when present at 3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 8.5.

Example 108

3-Methyl-thiophene-2-carboxylic acid 2,4-dimethoxy-benzylamide

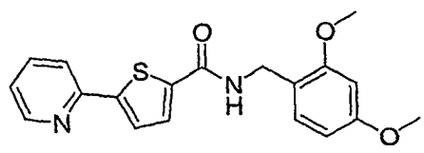


Prepared in a similar manner to example 4 using 3-methyl-thiophene-2-carboxylic acid and 2,4-dimethoxy-benzylamine. MS (M+H, 292.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 5.6 μM, and when present at 3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 5.8.

Example 109

5-Pyridin-2-yl-thiophene-2-carboxylic acid 2,4-dimethoxy-benzylamide

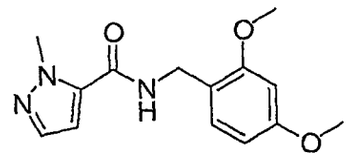


Prepared in a similar manner to example 4 using 5-pyridin-2-yl-thiophene-2-carboxylic acid and 2,4-dimethoxy-benzylamine. MS (M+H, 355.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 2.86 μM, and when present at 3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 8.

Example 110

2-Methyl-2H-pyrazole-3-carboxylic acid 2,4-dimethoxy-benzylamide

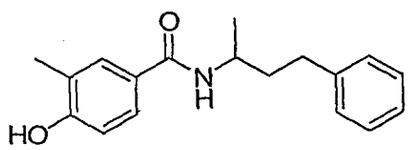


Prepared in a similar manner to example 4 using 2-methyl-2H-pyrazole-3-carboxylic acidand 2,4-dimethoxy-benzylamine. MS (M+H, 276.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 6 μM, and when present at 3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 7.9.

Example 111

4-Hydroxy-3-methyl-N-(1-methyl-3-phenyl-propyl)-benzamide

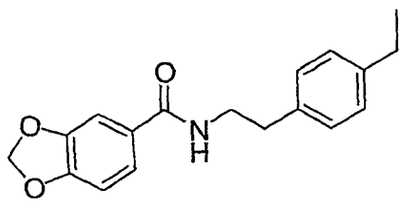


Prepared in a similar manner to example 4 using 4-hydroxy-3-methyl-benzoic acid and 1-methyl-3-phenyl-propylamine. MS (M+H, 284.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 2.7 μM, and when present at 0.3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 7.

Example 112

Benzo[1,3]dioxole-5-carboxylic acid [2-(4-ethyl-phenyl)-ethyl]-amide

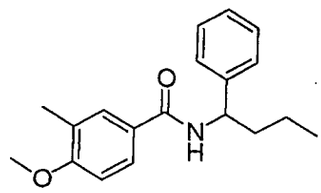


Prepared in a similar manner to example 4 using benzo[1,3]dioxole-5-carboxylic acid and 2-(4-ethyl-phenyl)-ethylamine. MS (M+H, 298.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3.86 μM.

Example 113

4-Methoxy-3-methyl-N-(1-phenyl-butyl)-benzamide

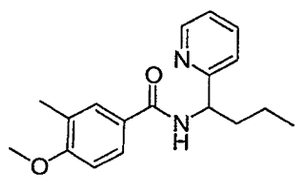


Prepared in a similar manner to example 4 using 4-methoxy-3-methyl-benzoic acid and 1-phenyl-butylamine. MS (M+H, 298.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 2.5 μM.

Example 114

4-Methoxy-3-methyl-N-(1-pyridin-2-yl-butyl)-benzamide

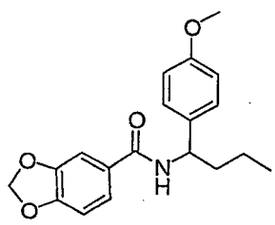


Prepared in a similar manner to example 4 using 4-methoxy-3-methyl-benzoic acid and 1-pyridin-2-yl-butylamine. ^1H NMR (500 MHz, $CDCl_3$): δ 0.91-0.92 (t, 3H), 1.25-1.3 (m, 2H, 1.85-1.9 (m, 2H), 3.86 (s, 3H), 5.25-5.3 (m, 1H), 6.80-6.82 (d, 1H), 7.2-7.3 (m, 2H), 7.42-7.44 (d, 1H), 7.6-7.7 (m, 3H), 8.6 (d, 1H). MS (M+H, 299.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.54 μM.

Example 115

Benzo[1,3]dioxole-5-carboxylic acid [1-(4-methoxy-phenyl)-butyl]-amide

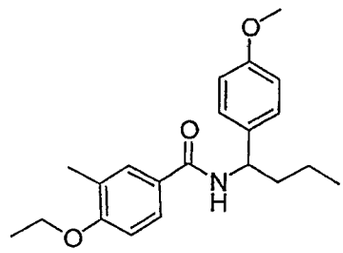


Prepared in a similar manner to example 4 using benzo[1,3]dioxole-5-carboxylic acid and 1-(4-methoxy-phenyl)-butylamine ^1H NMR (500 MHz, $CDCl_3$): δ 0.93-0.95 (t, 3H), 1.30-1.39 (m, 2H), 1.80-1.90 (m, 2H), 3.79 (s, 3H), 5.08-5.09 (dd, 1H), 6.00 (s, 2H), 6.10-6.12 (d, 1H), 6.79-6.80 (d, 1H), 6.87(s, 1H), 6,88 (s, 1H), 7.25-7.28 (m, 4H). MS (M+H, 328.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 4.12 μM.

Example 116

4-Ethoxy-N-[1-(4-methoxy-phenyl)-butyl]-3-methyl-benzamide

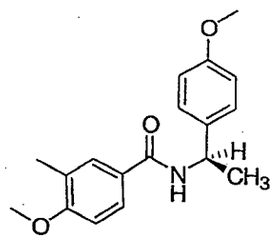


Prepared in a similar manner to example 4 using 4-ethoxy-3-methyl-benzoic acid and 1-(4-methoxy-phenyl)-butylamine. ^1H NMR (500 MHz, $CDCl_3$): δ 0.93-0.96 (t, 3H), 1.31-1.41 (m, 2H), 1.41-1.45 (t, 3H), 1.82-1.92 (m, 2H), 2.28 (s, 3H), 3.79 (s, 3H), 4.04-4.08 (q, 2H), 5.10-5.12 (d, 1H), 6.12-6.14 (d, 1H), 6.78-6.80 (d, 1H), 6.87 (s, 1H), 6.88 (s, 1H), 7.26-7.29 (m, 2H), 7.52-7.53 (d, 1H), 7.57-7.59 (d, 1H). MS (M+H, 342.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3.9 μM.

Example 117

4-Methoxy-N-[1-(R)-(4-methoxy-phenyl)-ethyl]-3-methyl-benzamide

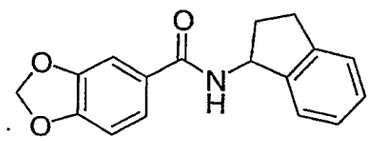


Prepared in a similar manner to example 4 using 4-methoxy-3-methyl-benzoic acid and 1-(R)-(4-methoxy-phenyl)-ethylamine. MS (M+H, 300.1).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 2.8 μM.

Example 118

Benzo[1,3]dioxole-5-carboxylic acid indan-1-ylamide

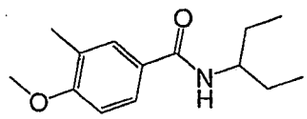


Prepared in a similar manner to example 4 using benzo[1,3]dioxole-5-carboxylic acid and indan-1-ylamine. MS (M+H, 282.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.2 μM, and when present at 0.3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 5.33.

Example 119

4-methoxy-3-methyl-N-(pentan-3-yl)benzamide

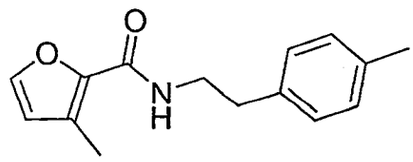


Prepared in a similar manner as described in example 4 from 4-methoxy-3-methylbenzoic acid and pentan-3-amine. MS (M+H, 236)

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.4 μM.

Example 120

3-methyl-N-(p-tolylethyl)furan-2-carboxamide

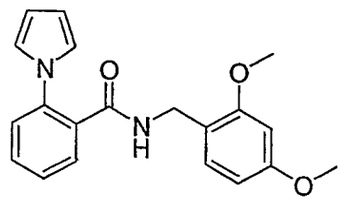


Prepared in a similar manner as described in example 4 from 3-methylfuran-2-carboxylic acid and 2-p-tolylethanamine. MS (M+H, 244).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 6 μM, and when present at 1 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 3.3.

Example 121

N-(2,4-dimethoxybenzyl)-2-(1H-pyrrol-1-yl)benzamide

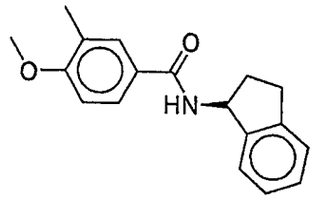


Prepared in a similar manner to example 4 using 1-(2-(1H-pyrrol-1-yl)phenyl)ethanone and 2,4-dimethoxy-benzylamine. MS (M+H, 337.2).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.66 μM, and when present at 1 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 11.

Example 121-1

(S)-N-(2,3-Dihydro-1H-inden-1-yl)-4-methoxy-3-methylbenzamide

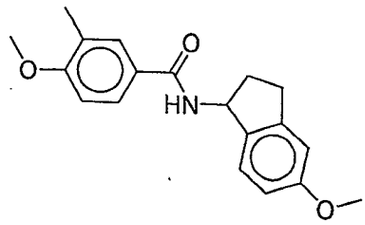


Prepared in a similar manner to example 4 using 4-methoxy-3-methylbenzoic acid and (S)-2,3-dihydro-1H-inden-1-amine. Yield 63%. ^{1}H NMR (500 MHz, *d*MSO): δ 1.94-1.99 (m, 1H), 2.17 (s, 3H), 2.41-2.46 (m, 1H), 2.82-2.87 (m, 1H), 2.96-3.01 (m, 1H), 3.83 (s, 3H), 5.53-5.57 (dd, 1H), 6.98-6.99 (d, 1H), 7.16-7.23 (m, 3H), 7.26-7.27 (m,1H), 7.75-7.80 (m, 2H), 8.54-8.55 (d, 1H). MS (M+H, 282).

The compound had EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.08 μM.

Example 121-2

(R/S)-4-Methoxy-N-(5-methoxy-2,3-dihydro-1H-inden-1-yl)-3-methylbenzamide



Prepared in a similar manner to example 4 using 4-methoxy-3-methylbenzoic acid and 5-methoxy-2,3-dihydro-1H-inden-1-amine (Example 121-2a)(47%). MS (M+H, 312).

The compound had EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.08 μM.

Example 121-2a: 5-methoxy-2,3-dihydro-1H-inden-1-amine

5-Methoxy-2,3-dihydroinden-1-one (1g, 6.17mmol) was added to a solution of hydroxylamine HCl (730mg, 10.5mmol) in 10ml of water. The mixture was brought up to 70°C and a solution of sodium acetate (1.4g, 16.7mmol) in 7mL of H_2O, 14ml of MeOH, 3ml of THF was added. After stirring for 1.5 h at 70°C, 10ml of H_2O was added to produce a precipitate and the suspension was allowed to stir for 2 h. The precipitate was collected by filtration to give 5-methoxy-2,3-dihydroinden-1-one oxime almost quantitatively and was used in the next step without further purification. The oxime (0.5g, 2.82mmol) was dissolved in MeOH and a catalytic amount of Raney nickel and 25mL of ammonia solution in MeOH (7N) was added. The reaction was stirred at r.t.overnight under H_2. The slurry was

filtered over celite and concentrated *in vacuo*, diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude title amine (yield, 45%). The crude amine was used without further purification.

Additional "amide" compounds that were synthesized and experimentally tested and found to have a relatively high level of effectiveness as an activator of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line. The results of that testing are shown below in Table A.

Table A - Umami Amides

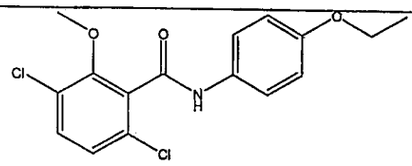
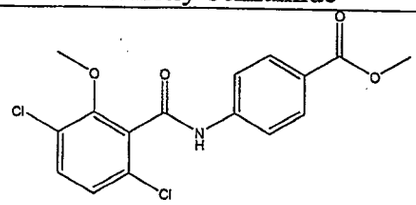
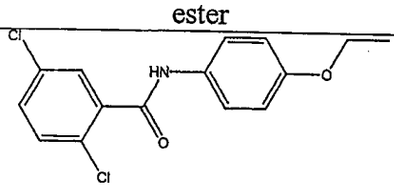
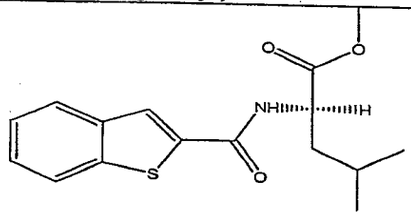
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A1	 3,6-Dichloro-N-(4-ethoxy-phenyl)-2-methoxy-benzamide	0.22	2.74	1
A2	 4-(3,6-Dichloro-2-methoxy-benzoylamino)-benzoic acid methyl ester	0.93	6.98	0.01
A3	 2,5-dichloro-N-(4-ethoxyphenyl)benzamide	1.08	6.14	0.03
A4	 2-[(Benzo[b]thiophene-2-carbonyl)-amino]-4-methyl-pentanoic acid methyl ester	0.4		

Table A - Umami Amides

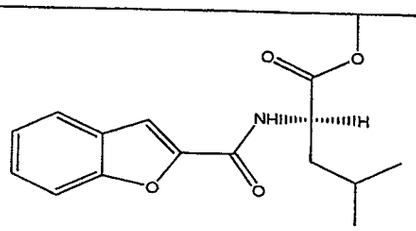
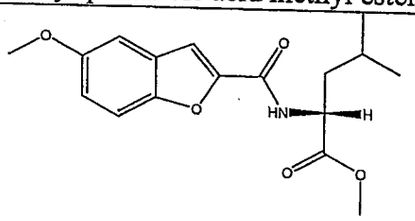
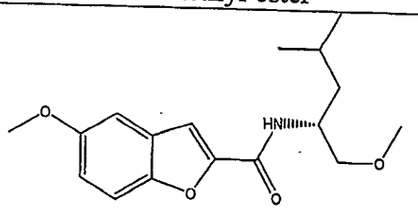
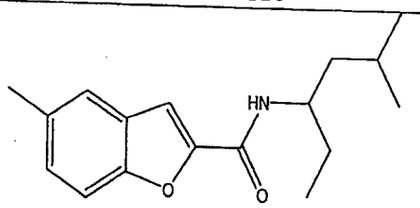
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A5	 2-[(Benzofuran-2-carbonyl)-amino]-4-methyl-pentanoic acid methyl ester	0.31		
A6	 2-[(5-Methoxy-benzofuran-2-carbonyl)-amino]-4-methyl-pentanoic acid methyl ester	0.32	2.86	1
A7	 (R)-5-methoxy-N-(1-methoxy-4-methylpentan-2-yl)benzofuran-2-carboxamide	0.46		
A8	 5-methyl-N-(5-methylhexan-3-yl) benzofuran-2-carboxamide	0.5		

Table A - Umami Amides

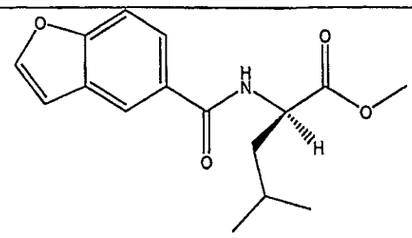
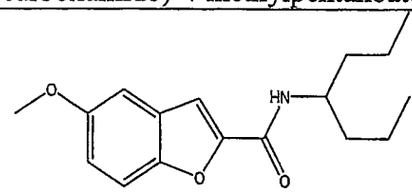
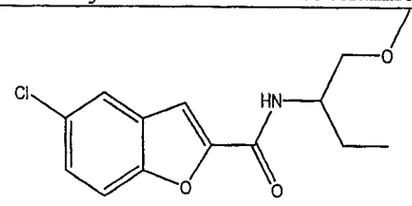
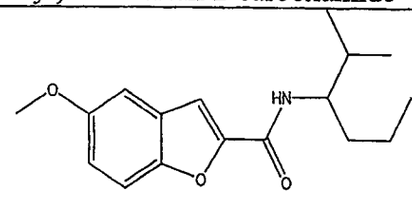
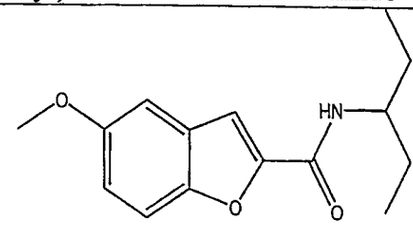
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A9	 2-[(Benzofuran-5-carbonyl)-amino]-4-methyl-pentanoic acid methyl ester(R)-methyl 2-(benzofuran-5-carboxamido)-4-methylpentanoate	0.71		
A10	 N-(heptan-4-yl)-5-methoxybenzofuran-2-carboxamide	0.91	4.51	1
A11	 5-chloro-N-(1-methoxybutan-2-yl)benzofuran-2-carboxamide	1.05	6.5	0.3
A12	 5-methoxy-N-(2-methylhexan-3-yl)benzofuran-2-carboxamide	1.13		
A13	 5-methoxy-N-(pentan-3-yl)benzofuran-2-carboxamide	1.14	4.46	1

Table A - Umami Amides

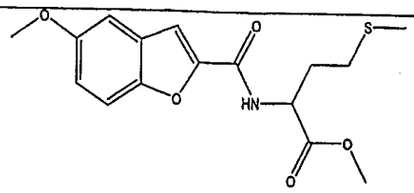
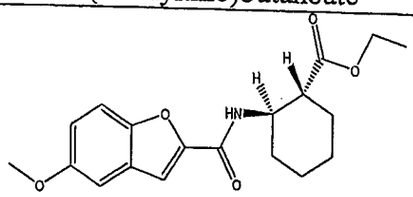
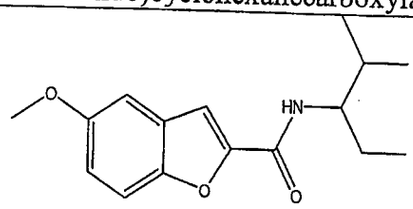
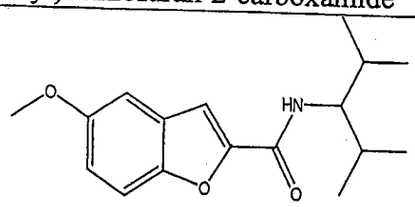
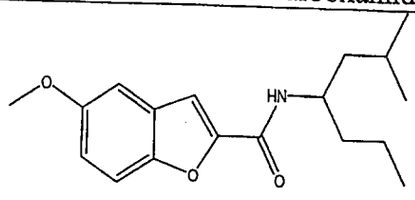
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A14	 2-[(5-Methoxy-benzofuran-2-carbonyl)-amino]-4-methylsulfanyl-butyric acid methyl ester methyl 2-(5-methoxybenzofuran-2-carboxamido)-4-(methylthio)butanoate	1.14		
A15	 (1R,2R)-ethyl 2-(5-methoxybenzofuran-2-carboxamido)cyclohexanecarboxylate	1.14		
A16	 5-methoxy-N-(2-methylpentan-3-yl)benzofuran-2-carboxamide	1.18		
A17	 N-(2,4-dimethylpentan-3-yl)-5-methoxybenzofuran-2-carboxamide	1.2		
A18	 5-methoxy-N-(2-methylheptan-4-yl)benzofuran-2-carboxamide	1.27		

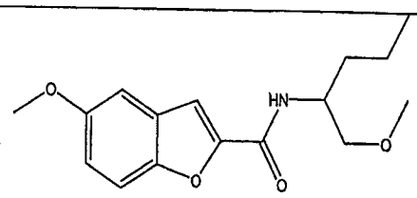
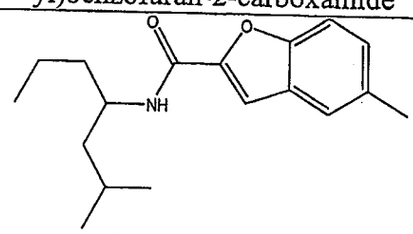
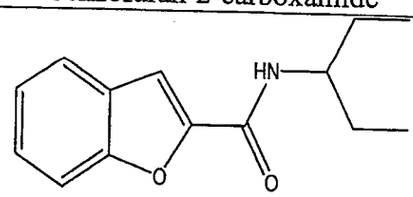
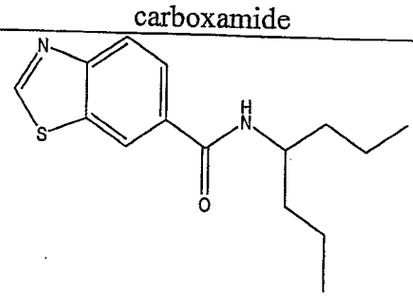
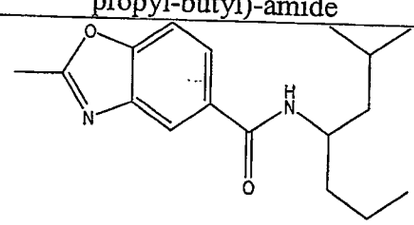
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A19	 5-methoxy-N-(1-methoxypentan-2-yl)benzofuran-2-carboxamide	1.3		
A20	 5-methyl-N-(2-methylheptan-4-yl) benzofuran-2-carboxamide	1.32		
A21	 N-(pentan-3-yl)benzofuran-2-carboxamide	1.52	3.74	1
A22	 Benzothiazole-6-carboxylic acid (1-propyl-butyl)-amide	1.58		
A23	 2-methyl-N-(2-methylheptan-4-yl)benzo[d]oxazole-5-carboxamide	0.38		

Table A - Umami Amides

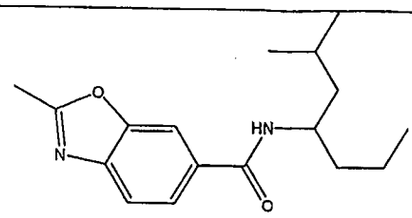
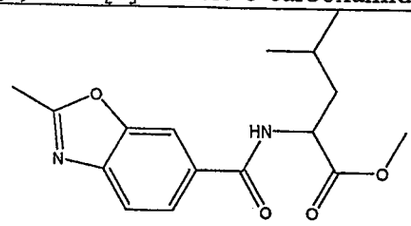
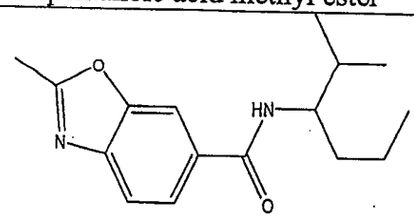
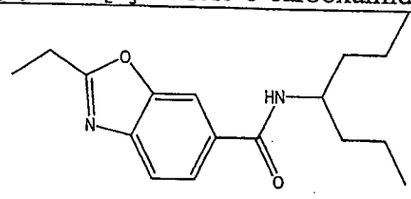
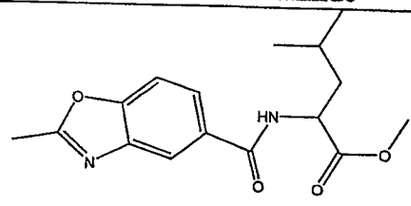
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A24	 2-methyl-N-(2-methylheptan-4-yl)benzo[d]oxazole-6-carboxamide	1.12		
A25	 (R)-4-Methyl-2-[(2-methyl-benzooxazole-6-carbonyl)-amino]-pentanoic acid methyl ester	1.48		
A26	 2-methyl-N-(2-methylhexan-3-yl)benzo[d]oxazole-6-carboxamide	1.6		
A27	 2-ethyl-N-(heptan-4-yl)benzo[d] oxazole-6-carboxamide	1.61		
A28	 (R)- 4-Methyl-2-[(2-methyl-benzooxazole-5-carbonyl)-amino]-pentanoic acid methyl ester	1.69		

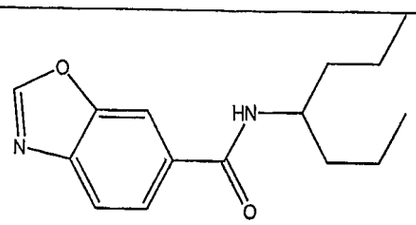
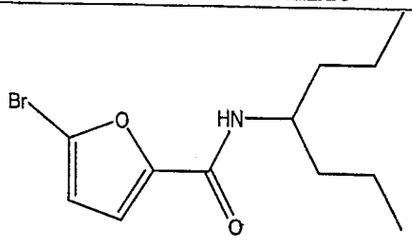
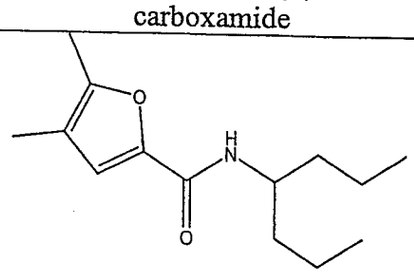
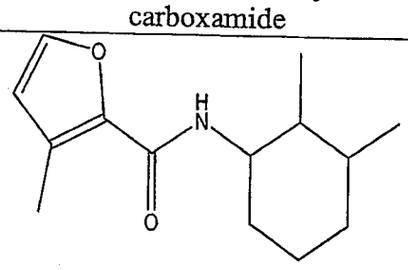
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A29	 N-(heptan-4-yl)benzo[d] oxazole-6-carboxamide	1.91		
A30	 5-bromo-N-(heptan-4-yl)furan-2-carboxamide	0.49	12.6	1
A31	 N-(heptan-4-yl)-4,5-dimethylfuran-2-carboxamide	0.62	10.04	1
A32	 N-(2,3-dimethylcyclohexyl)-3-methylfuran-2-carboxamide	1.15		

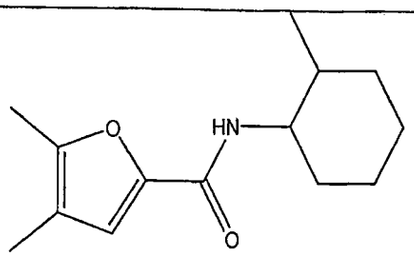
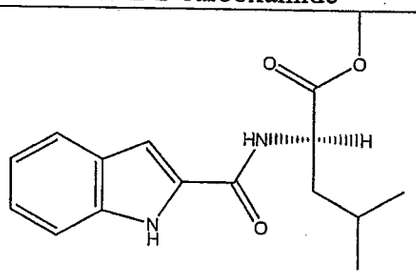
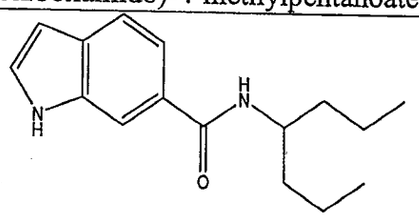
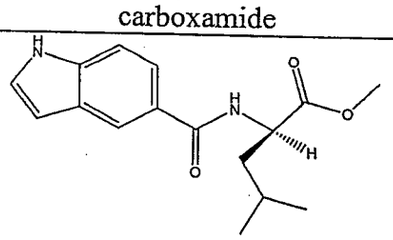
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A33	 4,5-dimethyl-N-(2-methylcyclohexyl) furan-2-carboxamide	1.33		
A34	 (R)-methyl 2-(1H-indole-2-carboxamido)-4-methylpentanoate	0.53		
A35	 N-(heptan-4-yl)-1H-indole-6-carboxamide	0.82	8.81	1
A36	 (R)-methyl 2-(1H-indole-5-carboxamido)-4-methylpentanoate	1.01		

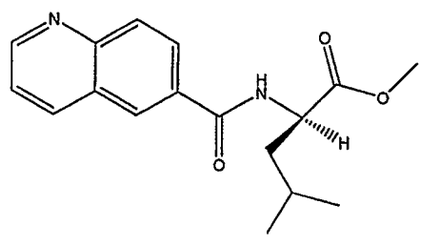
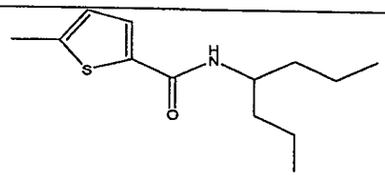
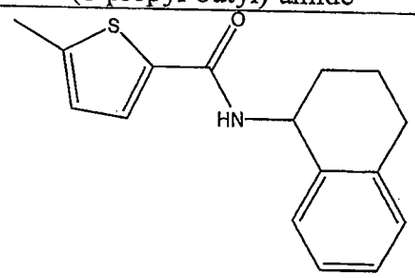
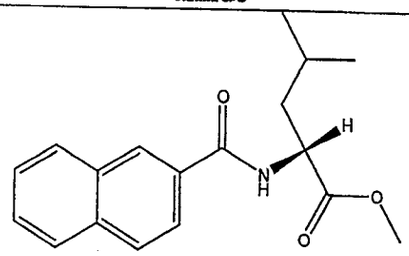
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A37	 (R)-methyl 4-methyl-2-(quinoline-6-carboxamido)pentanoate	1.5		
A38	 5-Methyl-thiophene-2-carboxylic acid (1-propyl-butyl)-amide	1.22	6.54	1
A39	 5-Methyl-thiophene-2-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-1-yl)-amide	1.31	2.3	1
A40	 (R)-methyl 2-(2-naphthamido)-4-methylpentanoate	0.37		

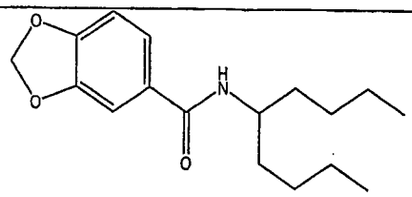
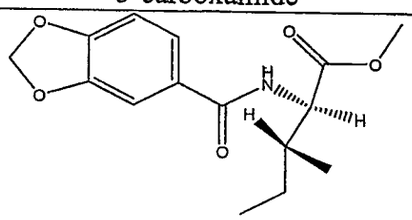
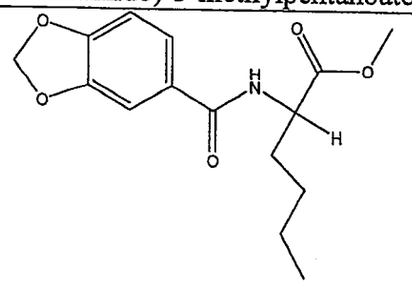
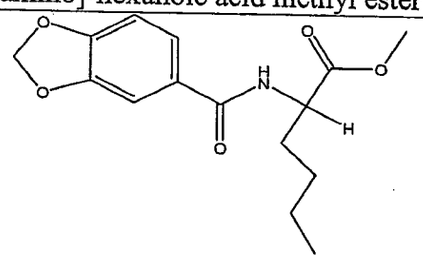
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A41	 N-(nonan-5-yl)benzo[d][1,3]dioxole-5-carboxamide	0.7	2.14	3
A42	 (2R,3R)-methyl 2-(benzo[d][1,3]dioxole-5-carboxamido)-3-methylpentanoate	0.35		
A43	 2-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-hexanoic acid methyl ester	0.49		
A44	 (R)-2-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-hexanoic acid methyl ester	0.61		

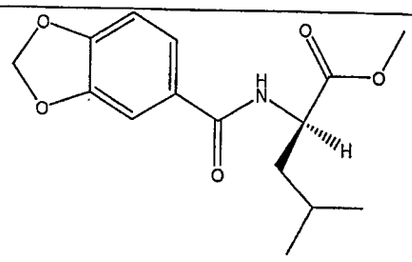
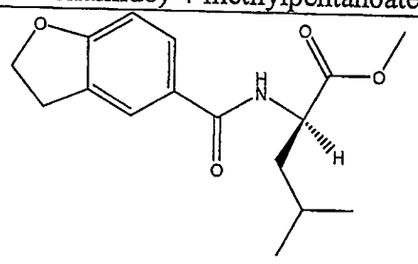
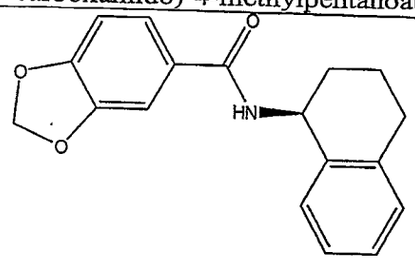
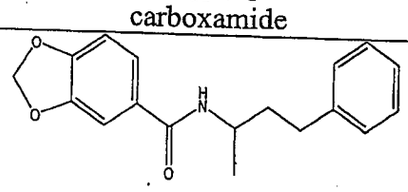
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A45	 (R)-ethyl 2-(benzo[d][1,3]dioxole-5-carboxamido)-4-methylpentanoate	0.88		
A46	 (R)-methyl 2-(2,3-dihydrobenzofuran-5-carboxamido)-4-methylpentanoate	1.32		
A47	 (S)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzo[d][1,3]dioxole-5-carboxamide	1.33	6.42	0.1
A48	 N-(4-phenylbutan-2-yl)benzo[d][1,3]dioxole-5-carboxamide	1.51	9.27	1

Table A - Umami Amides

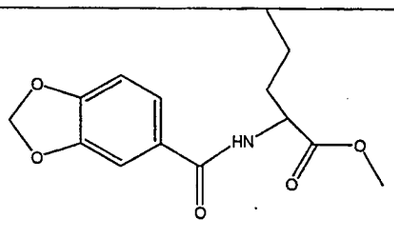
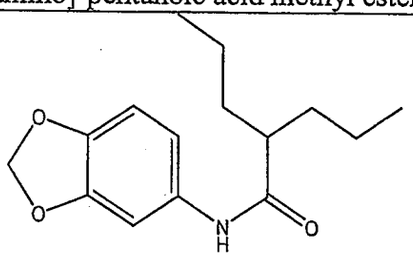
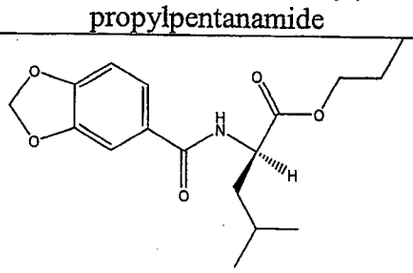
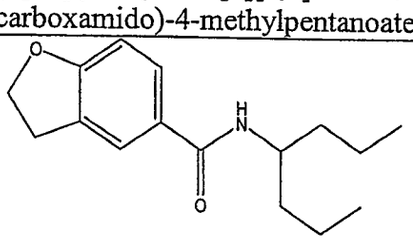
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A49	 2-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-pentanoic acid methyl ester	1.54	9.53	1
A50	 N-(benzo[d][1,3]dioxol-5-yl)-2-propylpentanamide	1.57		
A51	 (R)-propyl 2-(benzo[d][1,3]dioxole-5-carboxamido)-4-methylpentanoate	1.58		
A52	 N-(heptan-4-yl)-2,3-dihydrobenzofuran-5-carboxamide	1.65		

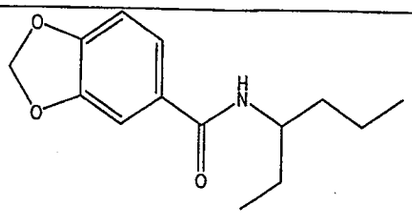
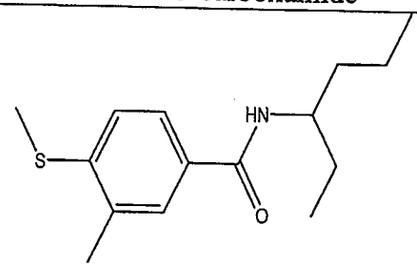
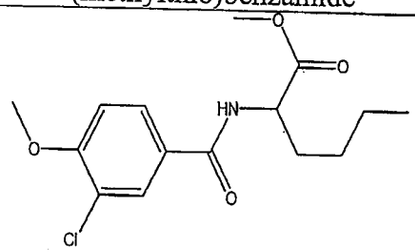
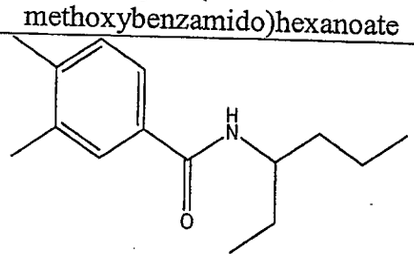
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A53	 N-(hexan-3-yl)benzo[d][1,3] dioxole-5-carboxamide	1.83		
A54	 N-(hexan-3-yl)-3-methyl-4-(methylthio)benzamide	0.12		
A55	 methyl 2-(3-chloro-4-methoxybenzamido)hexanoate	0.12		
A56	 N-(hexan-3-yl)-3,4-imethylbenzamide	0.14		

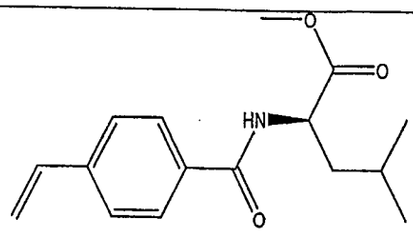
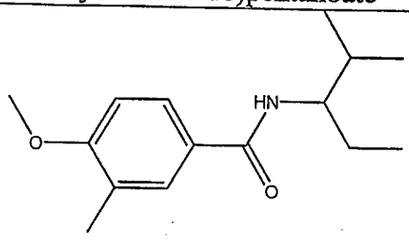
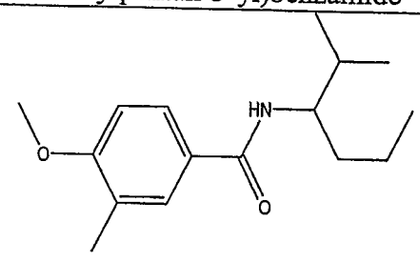
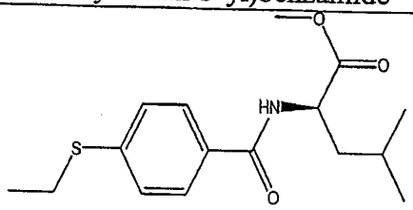
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A57	 (R)-methyl 4-methyl-2-(4-vinylbenzamido)pentanoate	0.18		
A58	 4-methoxy-3-methyl-N-(2-methylpentan-3-yl)benzamide	0.2		
A59	 4-methoxy-3-methyl-N-(2-methylhexan-3-yl)benzamide	0.2		
A60	 (R)-methyl 2-(4-(ethylthio)benzamido)-4-methylpentanoate	0.2		

Table A - Umami Amides

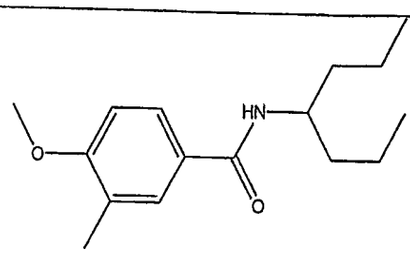
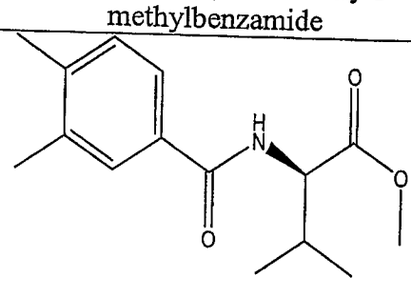
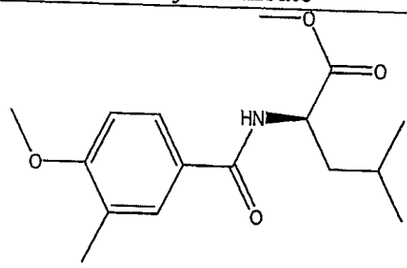
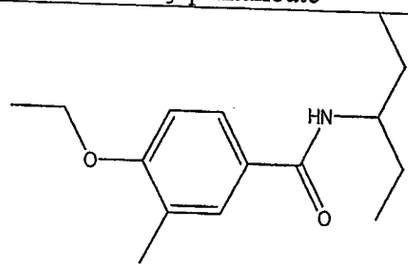
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A61	 N-(heptan-4-yl)-4-methoxy-3-methylbenzamide	0.22		
A62	 (R)-methyl 2-(3,4-dimethylbenzamido)-3-methylbutanoate	0.25		
A63	 (R)-methyl 2-(4-methoxy-3-methylbenzamido)-4-methylpentanoate	0.25		
A64	 4-ethoxy-3-methyl-N-(pentan-3-yl)benzamide	0.26		

Table A - Umami Amides

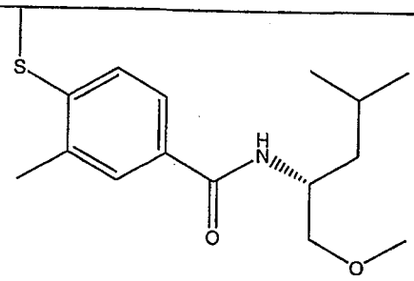
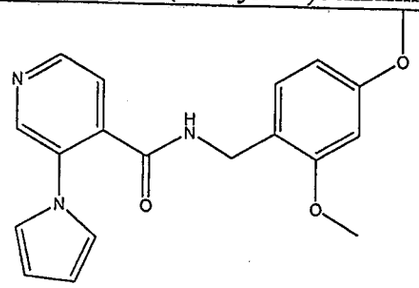
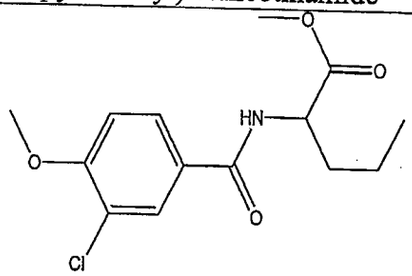
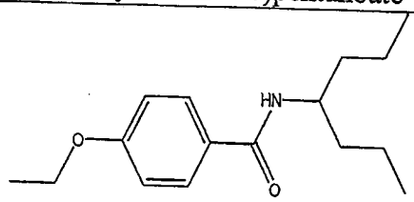
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A65	 (R)-N-(1-methoxy-4-methylpentan-2-yl)-3-methyl-4-(methylthio)benzamide	0.29		
A66	 N-(2,4-dimethoxybenzyl)-3-(1H-pyrrol-1-yl)isonicotinamide	0.29		
A67	 methyl 2-(3-chloro-4-methoxybenzamido)pentanoate	0.29	10.75	1
A68	 4-ethoxy-N-(heptan-4-yl)benzamide	0.32	2.62	0.3

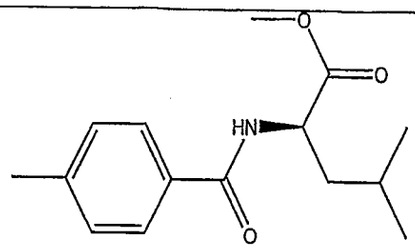
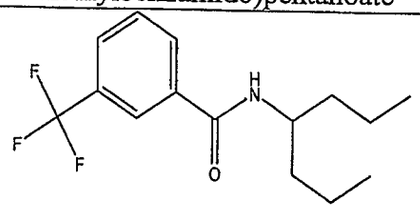
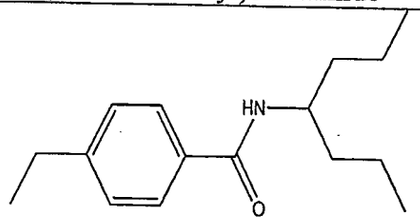
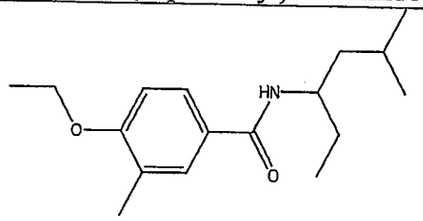
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A69	 (R)-methyl 4-methyl-2-(4-methylbenzamido)pentanoate	0.32		
A70	 N-(heptan-4-yl)-3-(trifluoromethyl)benzamide	0.33		
A71	 4-ethyl-N-(heptan-4-yl)benzamide	0.34		
A72	 4-ethoxy-3-methyl-N-(5-methylhexan-3-yl)benzamide	0.34		

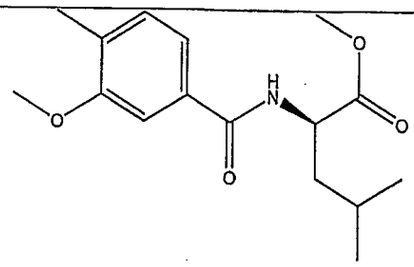
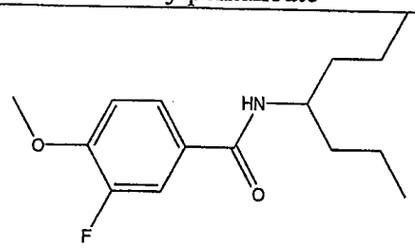
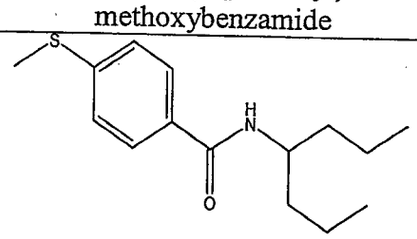
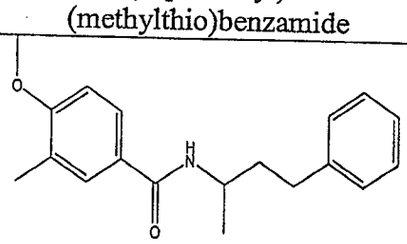
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A73	 (R)-methyl 2-(3-methoxy-4-methylbenzamido)-4-methylpentanoate	0.34		
A74	 3-fluoro-N-(heptan-4-yl)-4-methoxybenzamide	0.35	4.98	0.3
A75	 N-(heptan-4-yl)-4-(methylthio)benzamide	0.39		
A76	 4-methoxy-3-methyl-N-(4-phenylbutan-2-yl)benzamide	0.4		

Table A - Umami Amides

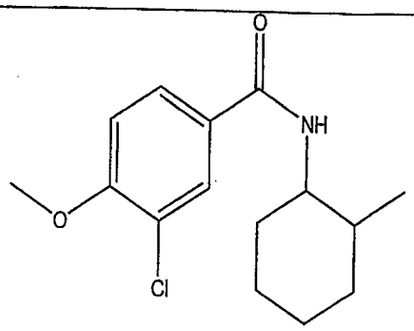
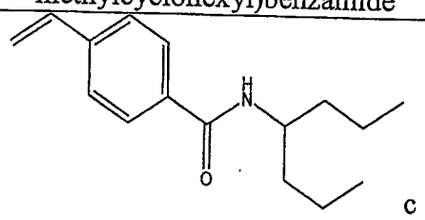
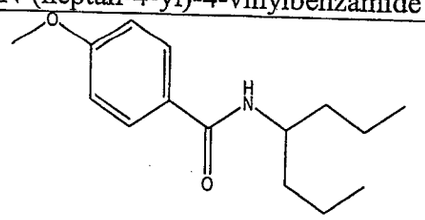
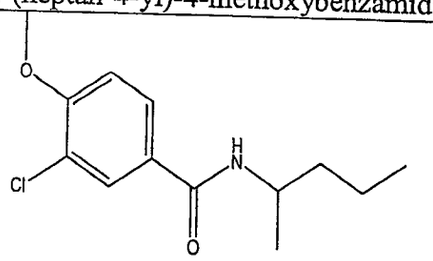
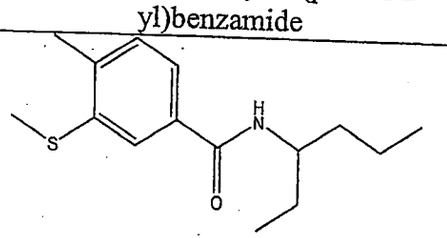
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A77	 3-chloro-4-methoxy-N-(2-methylcyclohexyl)benzamide	0.44		
A78	 N-(heptan-4-yl)-4-vinylbenzamide	0.46	10.22	0.3
A79	 N-(heptan-4-yl)-4-methoxybenzamide	0.46		
A80	 3-chloro-4-methoxy-N-(pentan-2-yl)benzamide	0.47	5.12	0.1
A81	 N-(hexan-3-yl)-4-methyl-3-(methylthio)benzamide	0.5		

Table A - Umami Amides

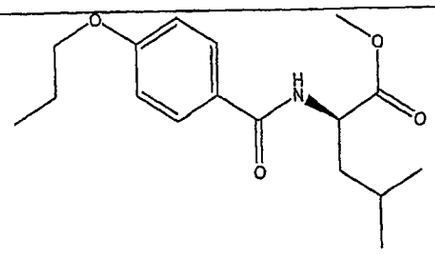
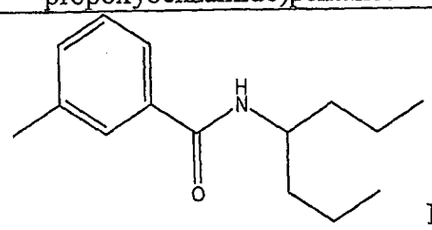
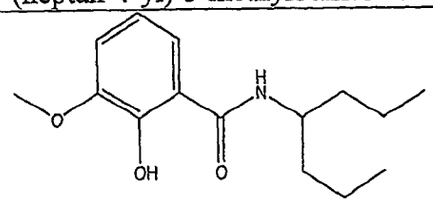
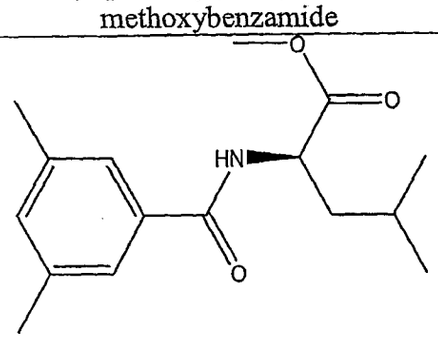
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A82	 (R)-methyl 4-methyl-2-(4-propoxybenzamido)pentanoate	0.51		
A83	 N-(heptan-4-yl)-3-methylbenzamide	0.52		
A84	 N-(heptan-4-yl)-2-hydroxy-3-methoxybenzamide	0.53		
A85	 (R)-methyl 2-(3,5-dimethylbenzamido)-4-methylpentanoate	0.53		

Table A - Umami Amides

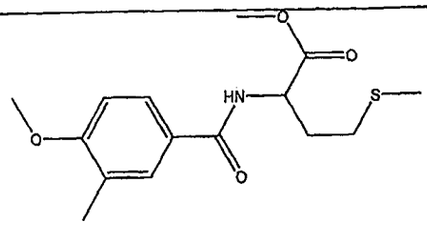
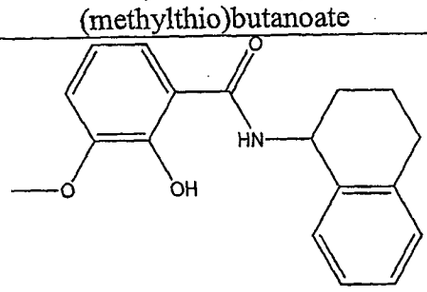
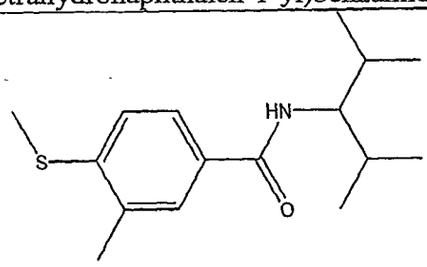
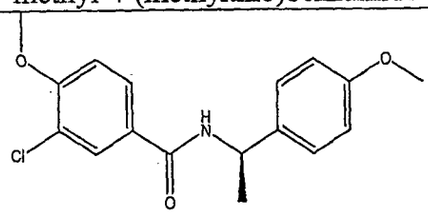
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A86	 methyl 2-(4-methoxy-3-methylbenzamido)-4-(methylthio)butanoate	0.53		
A87	 2-hydroxy-3-methoxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	0.54	3.8	1
A88	 N-(2,4-dimethylpentan-3-yl)-3-methyl-4-(methylthio)benzamide	0.55		
A89	 (R)-3-chloro-4-methoxy-N-(1-(4-methoxyphenyl)ethyl)benzamide	0.6	2.85	1

Table A - Umami Amides

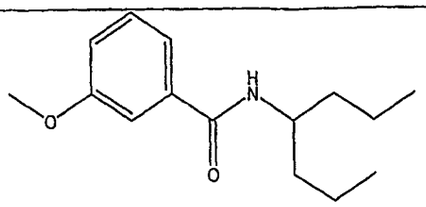
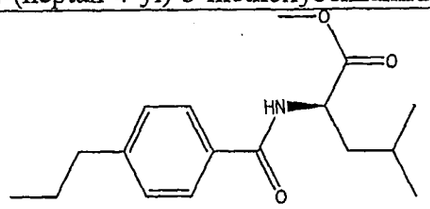
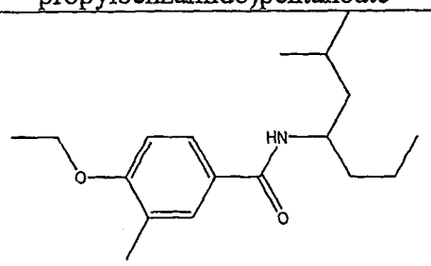
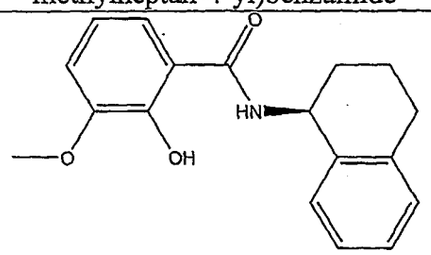
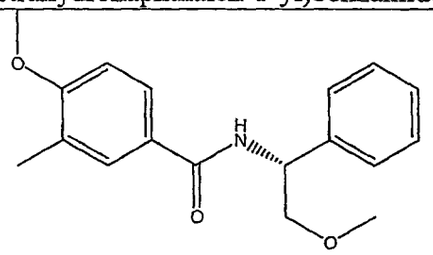
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A90	 N-(heptan-4-yl)-3-methoxybenzamide	0.61		
A91	 (R)-methyl 4-methyl-2-(4-propylbenzamido)pentanoate	0.62		
A92	 4-ethoxy-3-methyl-N-(2-methylheptan-4-yl)benzamide	0.65		
A93	 (S)-2-hydroxy-3-methoxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	0.7	5.7	1
A94	 (R)-4-methoxy-N-(2-methoxy-1-phenylethyl)-3-methylbenzamide	0.72		

Table A - Umami Amides

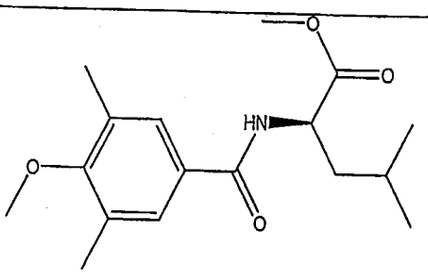
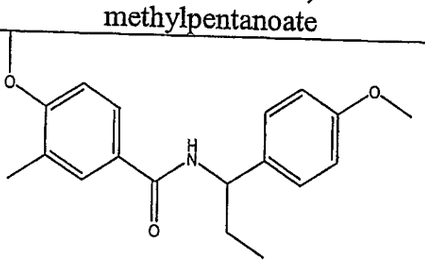
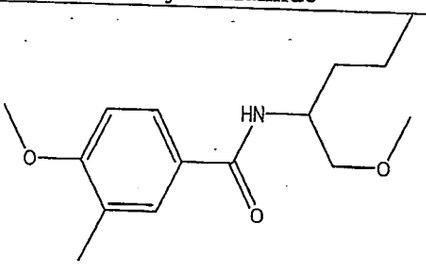
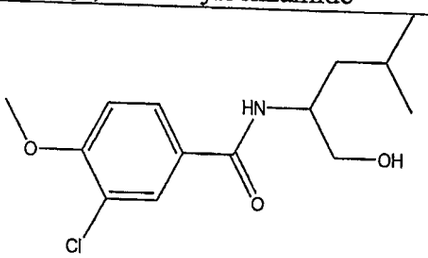
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A95	 (R)-methyl 2-(4-methoxy-3,5-dimethylbenzamido)-4-methylpentanoate	0.74		
A96	 4-methoxy-N-(1-(4-methoxyphenyl)propyl)-3-methylbenzamide	0.76		
A97	 4-methoxy-N-(1-methoxypentan-2-yl)-3-methylbenzamide	0.85		
A98	 3-chloro-N-(1-hydroxy-4-methylpentan-2-yl)-4-methoxybenzamide	0.88		

Table A - Umami Amides

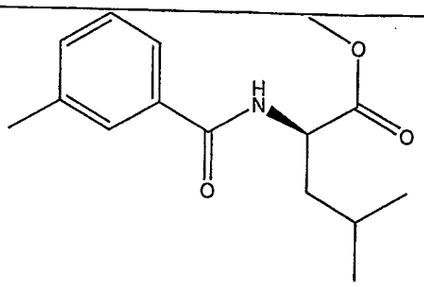
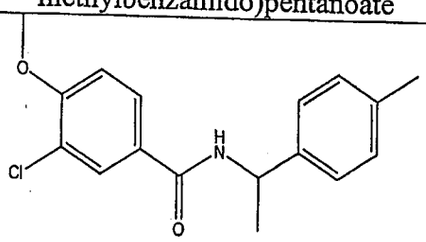
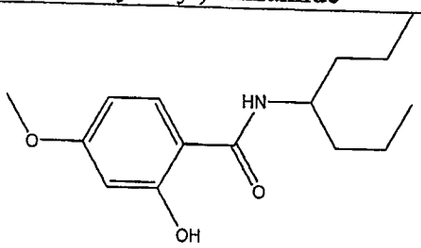
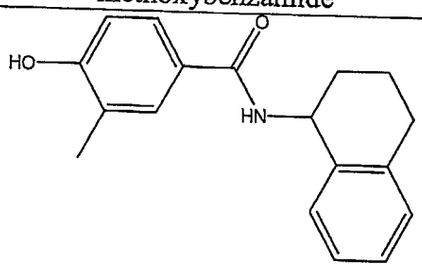
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A99	 (R)-methyl 4-methyl-2-(3-methylbenzamido)pentanoate	0.89		
A100	 3-chloro-4-methoxy-N-(1-p-tolylethyl)benzamide	1.1		
A101	 N-(heptan-4-yl)-2-hydroxy-4-methoxybenzamide	1.16	7.62	1
A102	 4-hydroxy-3-methyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	1.32	9.49	1

Table A - Umami Amides

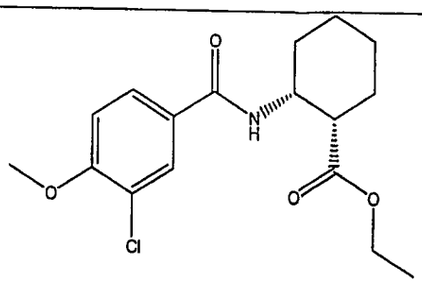
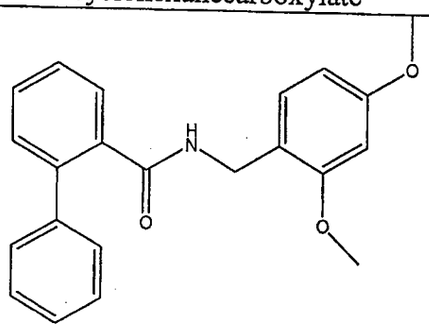
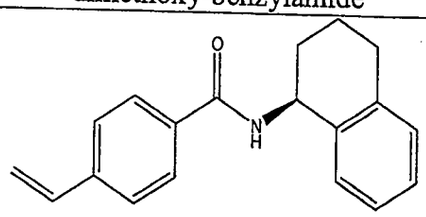
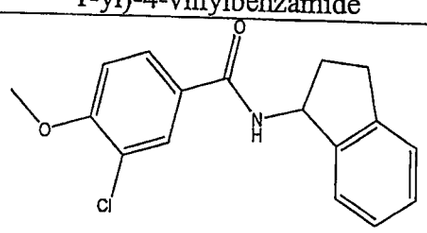
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A103	 (1S,2R)-ethyl 2-(3-chloro-4-methoxybenzamido) cyclohexanecarboxylate	1.36		
A104	 Biphenyl-2-carboxylic acid 2,4-dimethoxy-benzylamide	1.37		
A105	 (S)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-4-vinylbenzamide	1.38	2.79	1
A106	 3-chloro-N-(2,3-dihydro-1H-inden-1-yl)-4-methoxybenzamide	1.39	4.01	0.3

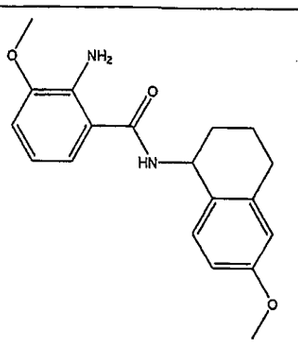
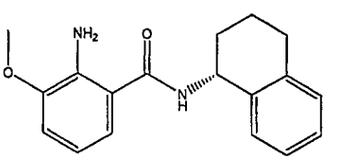
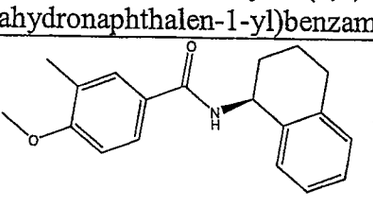
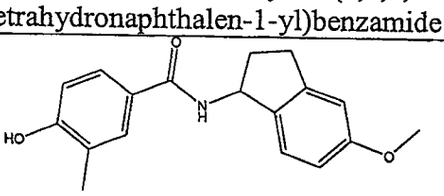
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A107	 2-amino-3-methoxy-N-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	0.07		
A108	 (R)-2-amino-3-methoxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	0.09		
A109	 (S)-4-methoxy-3-methyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	0.08		
A110	 4-hydroxy-N-(5-methoxy-2,3-dihydro-1H-inden-1-yl)-3-methylbenzamide	0.3		

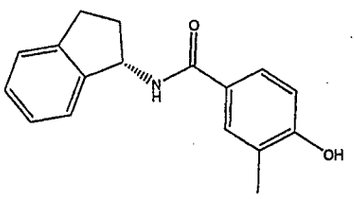
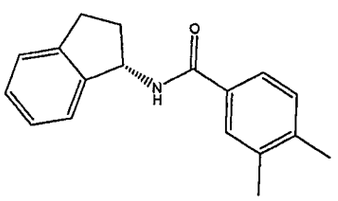
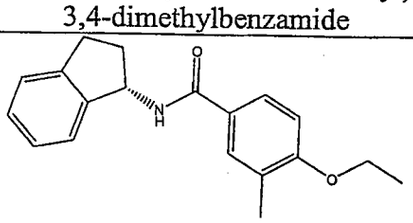
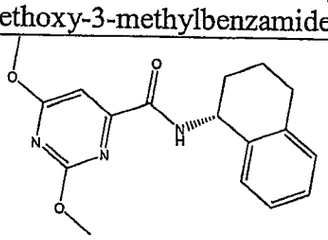
Table A - Umami Amides				
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A111	 (S)-N-(2,3-dihydro-1H-inden-1-yl)-4-hydroxy-3-methylbenzamide	0.66		
A112	 (S)-N-(2,3-dihydro-1H-inden-1-yl)-3,4-dimethylbenzamide	0.79		
A113	 (S)-N-(2,3-dihydro-1H-inden-1-yl)-4-ethoxy-3-methylbenzamide	0.85		
A114	 (R)-2,6-dimethoxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidine-4-carboxamide	2.35		

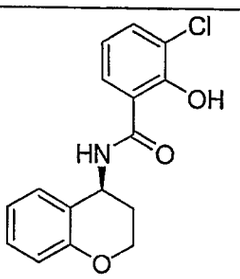
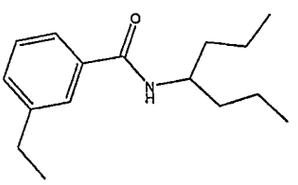
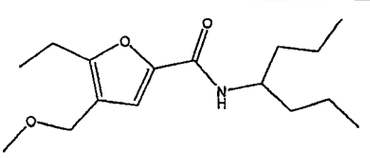
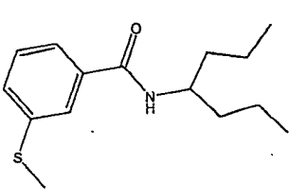
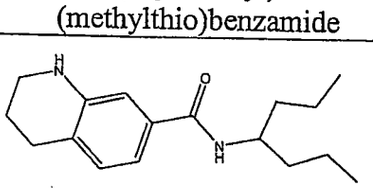
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A115	 (s)-3-chloro-N-(chroman-4-yl)-2-hydroxybenzamide	5.0		
A116	 3-ethyl-N-(heptan-4-yl)benzamide	0.01		
A117	 5-ethyl-N-(heptan-4-yl)-4-(methoxymethyl)furan-2-carboxamide	0.03		
A118	 N-(heptan-4-yl)-3-(methylthio)benzamide	0.03		
A119	 N-(heptan-4-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide	0.05		

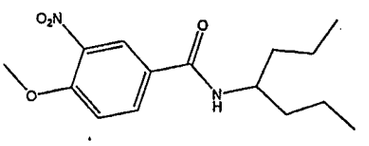
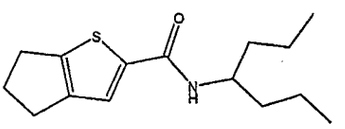
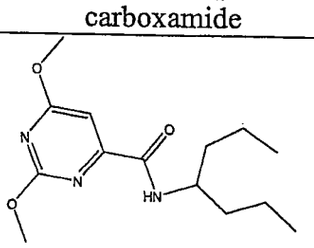
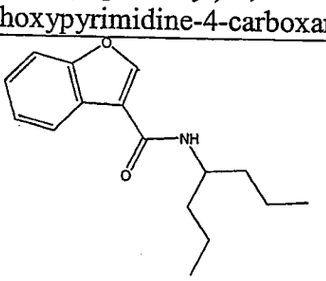
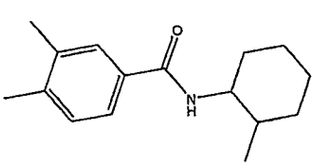
Table A - Umami Amides				
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A120	 N-(heptan-4-yl)-4-methoxy-3-nitrobenzamide	0.08		
A121	 N-(heptan-4-yl)-5,6-dihydro-4H-cyclopenta[b]thiophene-2-carboxamide	0.15		
A122	 N-(heptan-4-yl)-2,6-dimethoxypyrimidine-4-carboxamide	0.22		
A123	 N-(heptan-4-yl)benzofuran-3-carboxamide	0.51		
A124	 3,4-dimethyl-N-(2-methylcyclohexyl)benzamide	0.01		

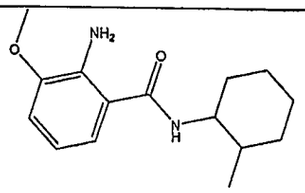
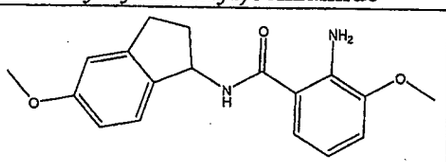
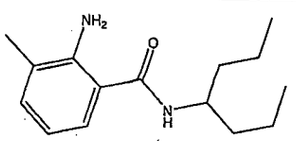
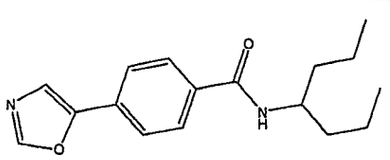
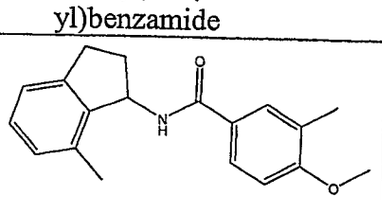
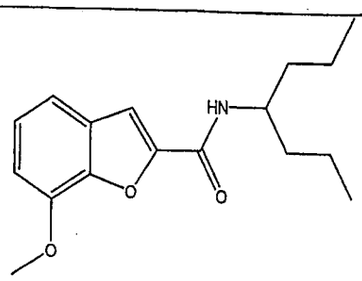
Table A - Umami Amides				
Compound No.	**Compound**	**Umami EC_{50} (μM)**	**Ec_{50} ratio (vs. MSG)**	**@(μM)**
A125	 2-amino-3-methoxy-N-(2-methylcyclohexyl)benzamide	0.02		
A126	 2-amino-3-methoxy-N-(5-methoxy-2,3-dihydro-1H-inden-1-yl)benzamide	0.04		
A127	 2-amino-N-(heptan-4-yl)-3-methylbenzamide	0.14		
A128	 N-(heptan-4-yl)-4-(oxazol-5-yl)benzamide	0.4		
A129	 4-methoxy-3-methyl-N-(7-methyl-2,3-dihydro-1H-inden-1-yl)benzamide	1.03		

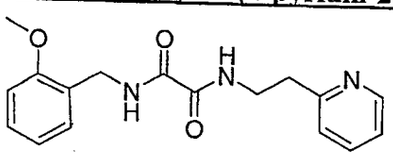
Table A - Umami Amides				
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@(μM)
A130	 N-(heptan-4-yl)-7-methoxybenzofuran-2-carboxamide	0.16		

Numerous amide compounds of Formula (I) that fall within the subgenus of "oxalamide " compounds described elsewhere herein were also synthesized and experimentally tested for effectiveness as activator of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line

Example 122

General procedure A for the preparation of an oxalamide

Synthesis of N-(2-Methoxy-benzyl)-N'-(2-pyridin-2-yl-ethyl)-oxalamide

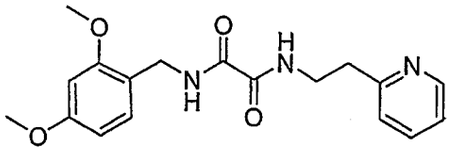


2-Methoxybenzyl amine (5 mmol) was mixed with triethylamine (2 equiv.) in anhydrous Dioxane. Ethyl oxalyl chloride (1 equiv.) was added and the mixture was shaken at room temperature for 0.5-2 hours. Then 2-(2-pyridinyl)ethyl amine (1 equiv.) was added and the suspension was heated at 80 °C overnight. The solution was concentrated and the residue was dissolved in ethyl acetate and washed with water. The organic layer was dried by sodium sulfate and solvent was evaporated to give the crude product, which was purified by flash column chromatography to afford the title compound: yield 70%, m.p. 118-119 °C; m/e = 314 [M+1]; 1H NMR ($CDCl_3$): □ 3.02 (t, 2H), 3.76 (dt, 2H), 3.86 (s, 3H), 4.47 (d, 2H), 6.80-6.90 (m, 2H), 7.14-7.18 (m, 2H), 7.20-7.30 (m, 2H), 7.55-7.62 (m, 1H), 7.75-7.83 (m, 1H), 8.05-8.12 (m, 1H), 8.55-8.63 (m, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.34 μM, and when present at 0.3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 18.85.

Example 123

N-(2,4-Dimethoxy-benzyl)-N'-(2-pyridin-2-yl-ethyl)-oxalamide

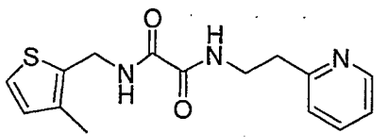


Prepared in a similar manner to example 122 using 2,4-dimethoxybenzyl amine, ethyl oxalyl chloride and 2-(2-pyridinyl)ethyl amine. Yield 72%, m.p. 123-124 °C; m/e = 344 [M+1]; ^{1}H NMR ($CDCl_3$): δ 3.02 (t, 2H); 3.73 (dd, 2H); 3.78 (s, 3H); 3.82 (s, 3H); 4.38 (d, 2H) 6.40 (dd, 1H); 6.44 (d, 1H); 7.14 (m, 3H); 7.59 (m, 1H); 7.82 (t, 1H); 8.11 (t, 1H); 8.56 (d, 1H); ^{13}C NMR: δ 36.9, 38.9, 39.4, 55.6, 55.6, 98.8, 104.1, 117.8, 121.9, 123.5, 130.7, 136.8, 149.6, 158.8, 158.8, 159.6, 160.1, 161.0.

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.09 μM, and when present at 0.3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 6.51.

Example 124

N-(3-Methyl-thiophen-2-ylmethyl)-N'-(2-pyridin-2-yl-ethyl)-oxalamide

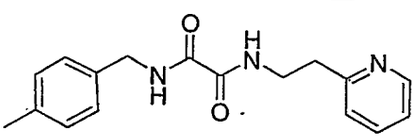


Prepared in a similar manner to example 122 using (3-methyl-thiophen-2-yl)-methylamine, ethyl oxalyl chloride and 2-(2-pyridinyl)ethyl amine. Yield 40%; m.p. 122-124 °C; m/e = 304 [M+1]; ^{1}H NMR (*DMSO-d_6*): δ 2.19 (s, 3H), 2.92-2.95 (t, 2H), 3.48-3.52 (dd, 2H), 4.37-4.38 (d, 2H), 6.79-6.80 (d, 1H), 7.20-7.27 (m, 3H), 7.67-7.71 (dt, 1H), 8.48-8.49 (d, 1H), 8.87-8.89 (t, 1H), 9.25-9.28 (t, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.37 μM.

Example 125

General Procedure B for the Synthesis of an Oxalamide N-(4-methyl-benzyl)-N'-(2-pyridin-2-yl-ethyl)-oxalamide

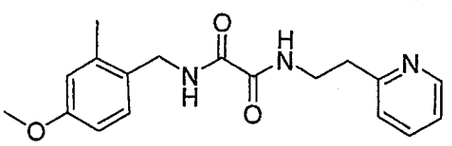


4-Methylbenzyl amine (1 mmol) was allowed to react with ethyl oxalyl chloride (1 equiv.) in the presence of triethyl amine (2 equiv.) in acetonitrile at room temperature for 0.5 – 1 hour. Then 2-(2-pyridinyl)ethyl amine (1 equiv.) was added and the suspension was heated at 160 °C in a microwave reactor for 5 minutes. The reaction mixture was subject to preparative HPLC to give the pure title oxalamide: yield 60%; m.p. 152-154 °C; m/e = 298 [M+1]; ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H), 3.10 (t, 2H), 3.75 (dt, 2H), 4.43 (d, 2H), 7.10-7015 (m, 4H), 7.18-7.22 (m, 2H), 7.65-7.73 (m, 2H), 8.12 (b, 1H), 8.60 (d, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.41 μM.

Example 126

N-(2-Methyl-4-methoxybenzyl)-N'-(2-pyridin-2-yl-ethyl)-oxalamide

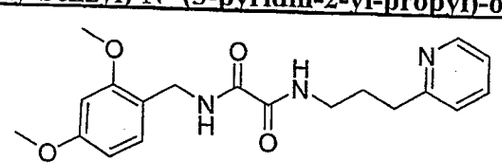


Prepared in a similar manner to example 122 using 2-methyl-4-methoxybenzyl amine, ethyl oxalyl chloride and 2-(2-pyridinyl)ethyl amine. Yield 51%; m.p. 133-134 °C; m/e = 328 [M+1]; ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H); 3.04 (t, 2H); 3.74-3.77 (m, 2H); 3.78 (s, 3H); 4.40 (d, 2H); 6.69-6.73 (m, 2H); 7.13-7.18 (m, 3H); 7.51 (t, 1H); 7.60-7.63 (m, 1H); 8.17 (t, 1H); 8.58 (d, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.11 μM.

Example 127

N-(2,4-Dimethoxy-benzyl)-N'-(3-pyridin-2-yl-propyl)-oxalamide

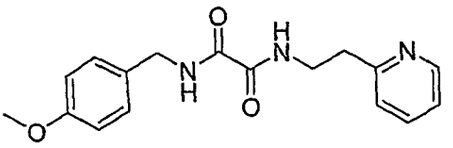


Prepared in a similar manner to example 125 using 2,4-dimethoxybenzyl amine, ethyl oxalyl chloride and 3-(2-pyridinyl)propyl amine. Yield 60%; m/e = 358 [M+1]; ^{1}H NMR ($CDCl_3$): δ 1.99-2.04 (m, 2H); 2.84 (t, 2H); 3.36 (dd, 2H); 3.79 (s, 3H); 3.82 (s, 3H) 4.60 (d, 2H); 6.41-6.45 (m, 2H); 7.10-7.17 (m, 3H); 7.57-7.60 (m, 1H); 7.81 (t, 1H); 7.89 (t, 1H); 8.54 (d, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.84 μM.

Example 128

N-(4-Methoxybenzyl)-N'-(2-pyridin-2-yl-ethyl)-oxalamide

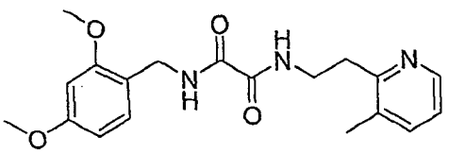


Prepared in a similar manner to example 125 using 4-methoxybenzyl amine, ethyl oxalyl chloride and 2-(2-pyridinyl)ethyl amine. Yield 50%; m.p. 156-158 °C; ^{1}H NMR: 3.05 (t, 3H), 3.72-3.77 (m, 2H), 3.79 (s, 3H), 4.40 (d, 2H), 6.86 (d, 2H), 7.16-7.22 (m, 4H), 7.65-7.69 (m, 3H), 8.15 (b, 1H), 8.62 (d, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.75 μM.

Example 129

N-(2,4-Dimethoxybenzyl)-N'-(2-(3-methylpyridin-2-yl)ethyl)oxalamide



Prepared in a similar manner to example 125 using 2,4-dimethoxybenzyl amine, ethyl oxalyl chloride and 2-(3-methylpyridin-2-yl)ethyl amine (example 129a). Yield 10%; m/e = 358 [M+1]; ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H), 3.01 (t, 2H), 3.75-3.82 (m, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 4.39 (d, 2H), 6.41 (dd, 1H), 6.44 (d, 1H), 7.10 (t, 1H), 7.15 (d, 1H), 7.45 (d, 1H), 7.81 (bs, 1H), 8.28 (bs, 1H), 8.40 (d, 1H).

a. 2-(3-Methylpyridin-2-yl)ethyl amine: To a solution of 2-(3-methylpyridine-2-yl)acetonitrile (example 129b) (95 mg, 0.72 mmol) in THF (0.5 mL) was added 1 M BH_3·THF (2.2 mL, 2.2 mmol) dropwise at room temperature. The resulting mixture was heated in a microwave reactor at 130 °C for 7 min. Then, 6 N aqueous HCl (1 mL) was added dropwise at room temperature. The resulting mixture was heated in a microwave reactor at 120 °C for 4 min. The reaction mixture was washed with Et_2O (3x3 mL), then cooled to 0 °C and 10 N aqueous NaOH (0.8 mL) was added. The aqueous solution was saturated with K_2CO_3. The product was extracted with $CHCl_3$ (6x5 mL). The organic

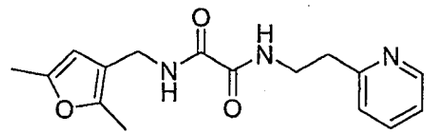
extracts were dried (1:1 K_2CO_3/Na_2SO_4), filtered, concentrated in vacuo to afford an oil (85 mg, 86%), which was used directly in Example 8. m/e = 137 [M+1].

b. 2-(3-Methylpyridine-2-yl)acetonitrile: To a solution of n-BuLi (2.5 N in hexanes, 7.92 mL, 19.8 mmol) at -78 °C under N_2 was added dry THF (75 mL), followed immediately by a solution of dry MeCN (1.15 mL, 21.78 mmol) in anhydrous THF (30 mL) over a 5-min period. The resulting reaction mixture was stirred continuously at -78 °C for 1 h. Then 2-bromo-3-methylpyridine (516 mg, 3 mmol) was added. The resulting reaction mixture was stirred at -78 °C for 1 h, then warmed to room temperature, and quenched with water. The organic solvent was evaporated in vacuo, dissolved in CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), concentrated, purified via column chromatography (20% EtOAc in hexanes) to afford the product quantitatively: m/e = 133 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.64 μM.

Example 130

N-(2,5-Dimethyl-furan-3-ylmethyl)-N'-(2-pyridin-2-yl-ethyl)-oxalamide

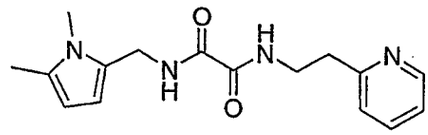


Prepared in a similar manner to example 122 using 2,5-dimethyl-furan-3-ylmethylamine, ethyl oxalyl chloride and 2-(2-pyridinyl)ethyl amine. Yield 51%; m.p. 112-115 °C; m/e = 302 [M+1]; ^{1}H NMR (*DMSO-d_6*): δ 2.14 (s, 3H), 2.18 (s, 3H), 2.91-2.94 (t, 2H), 3.47-3.51 (dd, 2H), 3.98-3.99 (d, 2H), 5.89 (s, 1H), 7.20-7.25 (m, 2H), 7.68-7.71 (dt, 1H), 8,48-8.49 (d, 1H), 8.81-8.84 (t, 1H), 8.97-9.00 (t, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.01 μM.

Example 131

N-(1,5-Dimethyl-1H-pyrrol-2-ylmethyl)-N'-(2-pyridin-2-yl-ethyl)-oxalamide



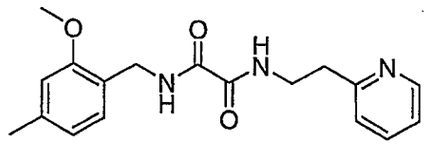
Prepared in a similar manner to example 122 using 1,5-dimethyl-1H-pyrrol-2-ylmethyl amine, ethyl oxalyl chloride and 2-(2-pyridinyl)ethyl amine. Yield 25%; m.p. 147-

149 °C; m/e = 301 [M+1]; ^{1}H NMR (*DMSO-d_6*): δ 2.11 (s, 3H), 2.92-2.95 (t, 2H), 3.38 (s, 3H), 3.48-3.52 (q, 2H), 4.24-4.25 (d, 2H), 5.64-5.65 (d, 1H), 5.79-5.65 (d, 1H), 7.20-7.25 (m, 2H), 7.68-7.71 (dt, 1H), 8.48-8.49 (d, 1H), 8.82-8.86 (m, 2H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 2.3 μM.

Example 132

N-(2-methoxy-4-methylbenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide



Prepared in a similar manner to example 125 using (2-methoxy-4-methylphenyl)methanamine (example 132a), ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine, yield 20%. m.p: 128-131 °C; m/e = 328 [M+1]; ^{1}H NMR($CDCl_3$): 2.33 (s, 3H); 3.02 (t, 2H); 3.73 (m, 2H); 3.84 (s, 3H); 4.42(d, 2H); 6.70 (m, 2H); 7.14 (m, 3H); 7.60 (m, 1H); 7.86 (s, 1H); 8.09 (s, 1H); 8.56 (d, 1H).

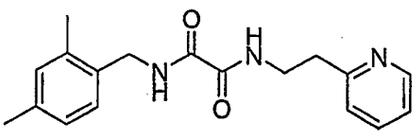
a. (2-methoxy-4-methylphenyl)methanamine: To a solution of 2-methoxy-4-methylbenzamide (example 132b) (200 mg, 1.21 mmol) in THF (0.5 mL) was added 1 M BH_3•THF (2.4 ml, 2.42 mmol) slowly at room temperature. The resulting mixture was heated in a microwave reactor at 130 °C for 7 min. Then 6 N aqueous HCl (1 mL) was added dropwise at room temperature. The resulting mixture was heated in a microwave reactor at 120 °C for 4 min. The reaction mixture was washed with Et_2O (3x3 mL), then cooled to 0 °C and 10 N aqueous NaOH (0.8 mL) was added. The aqueous solution was saturated with K_2CO_3. The product was extracted with $CHCl_3$ (6x5 mL). The organic extracts were dried (1:1 K_2CO_3/Na_2SO_4), filtered, concentrated in vacuo to afford 180 mg of (2-methoxy-4- methylphenyl)methanamine which was used directly in Example 11.

b. 2-methoxy-4-methylbenzamide: 2-methoxy-4-methylbenzoic acid (500 mg, 3.01 mmol) was mixed with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (577 mg, 3.01 mmol) and 1-hydroxybenzotriazole (407 mg, 3.01 mmol) in 25 ml of dichloromethane at r.t. and stirred for 5 min. 2M ammonia solution in methanol (4.5 ml, 9.03 mmol) was added, the reaction mixture was stirred at r.t. for about 5 hr. then it was diluted with dichloromethane, washed with 1N HCl, sat. $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and evaporated to give 440 mg of 2-methoxy-4-methylbenzamide, yield 88%.

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.04 uM.

Example 133

N-(2,4-dimethylbenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide



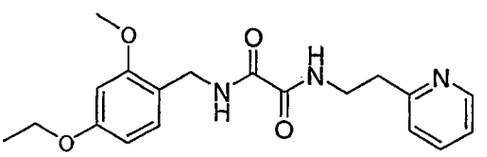
Prepared in a similar manner to example 125 using (2,4-dimethylphenyl)methanamine (example 133a), ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine, yield 60%; m.p. 148-149 °C; m/e= 312 [M+1]; ^{1}H NMR ($CDCl_3$): 2.28 (s, 3H); 2.30 (s, 3H); 3.05 (t, 2H); 3.76 (dd, 2H); 4.43 (d, 2H); 6.99 (m, 2H); 7.11 (d, 1H); 7.17 (m, 2H); 7.54 (s, 1H); 7.62 (m, 1H); 8.17 (s, 1H); 8.58 (d, 1H).

a. (2,4-Dimethylphenyl)methanamine: Lithium aluminum hydride 1M solution in THF (15.2 ml, 15.2 mmol) was placed in a pre-dried flask under argon at 0 °C; a solution of 2,4-dimethylbenzonitrile (1.0 g, 7.6 mmol) in 15 ml of anhydrous ether was added drop wisely. After the addition, the reaction mixture was warmed up slowly to r.t. and stirred for 3 hr. then it was cooled to 0 °C, anhydrous sodium sulfate was added, and 1ml of water was added drop wisely. The mixture was diluted with ethyl acetate, the insoluble matter was filtered out, the filtrate was washed with water and brine, dried over $MgSO_4$, filtered and evaporated to give 1.03 g of pure (2,4-dimethylphenyl)methanamine in quantitative yield without purification.

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.07 μM.

Example 134

N-(4-ethoxy-2-methoxybenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide



Prepared in a similar manner to example 125 using (4-ethoxy-2-methoxyphenyl)methanamine (example 134a), ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine; yield 10%; m.p. 117-118 °C; m/e = 358 [M+1]; ^{1}H NMR ($CDCl_3$): 1.40 (t, 3H); 3.03 (t, 2H); 3.74 (dd, 2H); 3.82 (s, 3H); 4.01 (dd, 2H); 4.39 (d, 2H); 6.39 (d, 1H); 6.44 (s, 1H); 7.15 (m, 3H), 7.61 (m, 1H); 7.81 (s, 1H); 8.10 (s, 1H); 8.56 (d, 1H).

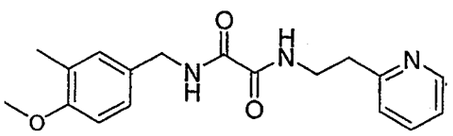
a. (4-ethoxy-2-methoxyphenyl)methanamine: To a solution of 4-ethoxy-2-methoxybenzaldehyde (example 134b) (880 mg, 4.88 mmol) in 50 ml of anhydrous methanol, were added ammonium acetate (7.5 g, 97.60 mmol) and sodium cyanoborohydride (613 mg, 9.76 mmol). The reaction mixture was stirred at r.t. for about 4 hr. then it was concentrated on a rotary evaporator, the residue was diluted with water and basified with 15 % aqueous NaOH, extracted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered and the solvent was evaporated, the residue was column chromatographed on silica gel (DCM/MeOH 9:1) to afford 150 mg of product; yield 17 % (The method was not optimized).

b. 4-Ethoxy-2-methoxybenzaldehyde: To a solution of 4-hydroxy-2-methoxybenzaldehyde (1.0 g, 6.57 mmol) in 10 ml of acetone, was added potassium carbonate (0.91 g, 6.57 mmol) and iodoethane (1.6 ml, 19.71 mmol), the reaction mixture was stirred at r.t. over night. Acetone was removed on a rotary evaporator; the residue was diluted with water and ethyl acetate; extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered and evaporated to give crude product, which was column chromatographed on silica gel (ethyl acetate/hexane = 1:4) to give 943 mg of product; yield 80%.

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.1 μM.

Example 135

N-(4-Methoxy-3-methylbenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide



Prepared in a similar manner to example 125 using (4-methoxy-3-methylphenyl)-methanamine (example 135a), ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine, yield 12%; m.p. 145-147 °C; m/e= 328 [M+1]; ^1H NMR ($CDCl_3$): 2.19 (s, 3H); 3.04 (t, 2H); 3.76 (dd, 2H); 3.81 (s, 3H); 4.37 (d, 2H); 6.76 (d, 1H); 7.06 (m, 2H); 7.16 (m, 2H); 7.61 (m, 1H); 7.66 (s, 1H); 8.18 (s, 1H); 8.58 (d, 1H).

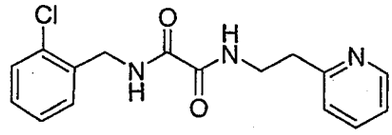
a. 4-Methoxy-3-methylphenyl)methanamine: Prepared in a similar manner to example 134a using 4-methoxy-3-methylbenzaldehyde, ammonium acetate, and sodium cyanoborohydride in MeOH; yield 22% (110 mg).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor

expressed in an HEK293 cell line of 1.04 μM.

Example 136

N-(2-chlorobenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide:

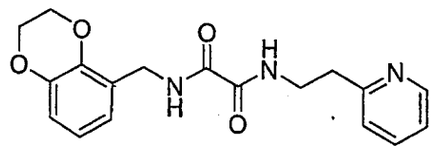


Prepared in a similar manner to example 125 using (2-chlorophenyl)methanamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine; yield 45%; *m/e* = 318 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.01 μM.

Example 137

N-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)-N'-(2-(pyridin-2-yl)ethyl) oxalamide

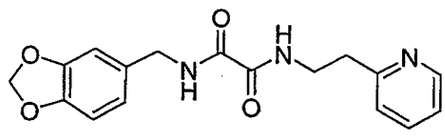


Prepared in a similar manner to example 122 using (2,3-dihydrobenzo[b][1,4] dioxin-5-yl)methanamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine; yield 50%; *m/e* = 342 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.3 μM.

Example 138

N-(benzo[d][1,3]dioxol-5-ylmethyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

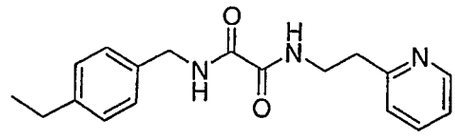


Prepared in a similar manner to example 125 using benzo[d][1,3]dioxol-5-ylmethanamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine; yield 35%; *m/e* = 328 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.5 μM.

Example 139

N-(4-Ethylbenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

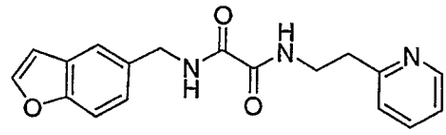


Prepared in a similar manner to example 125 using 4-ethylbenzylamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine; yield 38%; *m/e* = 312 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.79 μM.

Example 140

N-(Benzofuran-5-ylmethyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

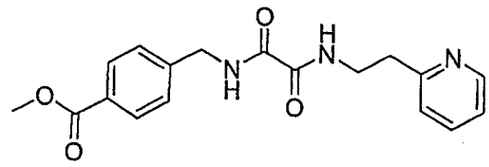


Prepared in a similar manner to example 125 using benzofuran-5-ylmethylamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine; yield 64%; *m/e* = 324 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.78 μM.

Example 141

N-((4-Methoxycarbonylphenyl)methyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

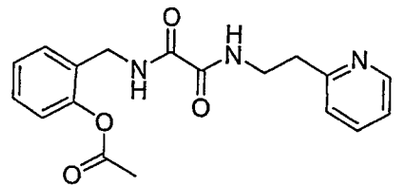


Prepared in a similar manner to example 122 using 4-methoxycarbonylphenyl methylamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine; yield 52%; *m/e* = 342 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3.63 μM.

Example 142

N-((2-Carbamoylphenyl)methyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide



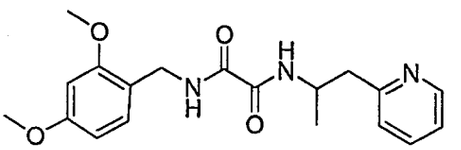
Prepared in a similar manner to example 122 using 2-carbamoylphenyl

methylamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine; yield 48%; *m/e* = 342 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 8.5 μM.

Example 143

N-(2,4-Dimethoxybenzyl)-N'-(1-(pyridin-2-yl)propan-2-yl)oxalamide



Prepared in a similar manner to example 125 using 2,4-dimethoxybenzylamine, ethyl oxalyl chloride, and 1-(pyridin-2-yl)propan-2-yl amine (example 143a); yield 34%; *m/e* = 357 [M+1].

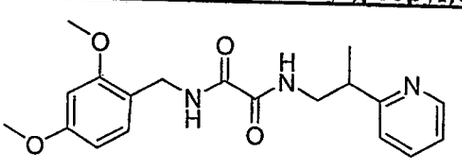
a. 1-(Pyridin-2-yl)propan-2-yl amine: Prepared in a similar manner to example 129a using 2-(pyridine-2-yl)propanenitrile (example 143b); crude product was used directly in example 143; yield 53%; *m/e* = 137 [M+1].

b. 2-(pyridine-2-yl)propanenitrile: 5 mmol of 2-(pyridine-2-yl)acetonitrile was dissolved in 8 ml anhydrous THF and placed in an ice bath. Potassium t-butoxide (1 equiv) was added and reaction was stirred for 30 minutes. Methyl iodide (1 equiv) was dissolved in 5 mL anhydrous THF and added slowly over 30 minutes. Reaction was stirred overnight at room temperature. Solvent was evaporated and crude mixture was dissolved in ethyl acetate and washed with water. Ethyl acetate layer was evaporated and product was purified by preparative TLC (30% Ethyl acetate/Hexane); yield 71%; *m/e* = 133 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.4 μM.

Example 144

N-(2,4-Dimethoxybenzyl)-N'-(2-(pyridin-2-yl)propyl)oxalamide



Prepared in a similar manner to example 125 using 2,4-dimethoxybenzylamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)propylamine (example 144a); yield 35%; *m/e* = 357 [M+1].

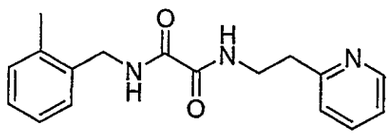
a. 2-(pyridin-2-yl)propylamine: 10 mmol of 2-methylpyridine was dissolved in

anhydrous THF and kept under inert condition at 0 °C. Butyl lithium (1.2 equiv) was added dropwise and stirred for additional 15 minutes at 0 °C while letting temperature to go back to room temperature. After stirring at room temperature for 1 hour, the reaction mixture was cooled again to 0 °C and acetonitrile (2 equiv) was added dropwise. Reaction was stirred overnight at room temperature. After cooling the reaction to 0 °C, 30 mL of methanol was added into the reaction mixture. Sodium borohydride (3 equiv) was added in portion slowly at 0 °C. Reaction was stirred for another hour letting temperature to rise to room temperature. The reaction mixture was diluted with water and extracted exhaustively with ethyl acetate. The combined extracts were washed with water, brine and dried down over sodium sulfate. Solution was concentrated down and dissolved in ether. Product was extracted with 3 N aqueous HCl, and the acidic extract was washed with ether and made basic with NaOH. Product was extracted exhaustively with ether. The combined ether extracts was washed with water and dried down over sodium sulfate. Solvent was evaporated down to yield sufficiently pure product; yield 47%; *m/e* = 137 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.07 μM.

Example 145

N-(2-Methoxybenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

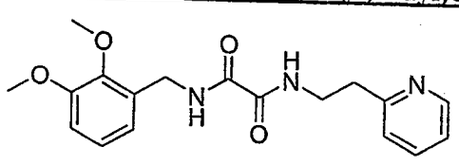


Prepared in a similar manner to example 125 using 2-methylbenzylamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethylamine; *m/e* = 298 [M+1]; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.11 (t, 2H), 3.78 (dt, 2H), 4.46 (d, 2H), 7.15-7.26 (m, 6H), 7.50-7.55 (m, 1H), 7.62-7.67 (m, 1H), 8.12-8.15 (m, 1H), 8.60 (d, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.59 μM.

Example 146

N-(2,3-Dimethoxybenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide



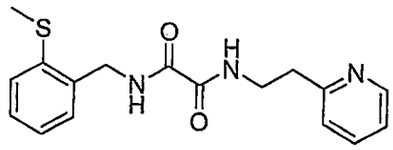
Prepared in a similar manner to example 125 using 2,3-dimethoxybenzylamine,

ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethylamine; *m/e* = 343 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.69 μM.

Example 147

N-(2-(Methylthio)benzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

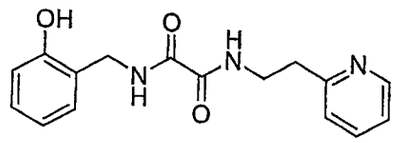


Prepared in a similar manner to example 125 using 2-methylthiobenzylamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethylamine; *m/e* = 330 [M+1]; ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 3.08 (t, 2H), 3.77 (dt, 2H), 4.55 (d, 2H), 7.11-7.14 (m, 1H), 7.15-7.20 (m, 2H), 7.22-7.27 (m, 3H), 7.62 (t, 1H), 7.78-7.83 (m, 1H), 8.08-8.11 (m, 1H), 8.56 (d, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.96 μM.

Example 148

N-(2-Hydroxybenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

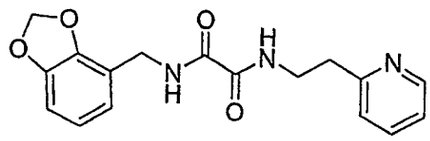


Prepared in a similar manner to example 125 using 2-hydroxybenzylamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethylamine; *m/e* = 300 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3.11 μM.

Example 149

N-(Benzo[d][1,3]dioxol-4-ylmethyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide



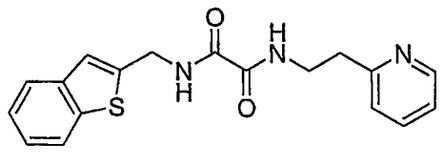
Prepared in a similar manner to example 125 using benzo[d][1,3]dioxol-4-ylmethyl amine (example 149a), ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethyl amine; yield 12%; *m/e* = 328 [M+1]; ^{1}H NMR ($CDCl_3$): δ 3.12 (m, 2H), 3.77-3.80 (m, 2H), 4.46-4.47 (d, 2H), 5.98 (s, 2H), 6.74-6.79 (m, 3H), 7.24 (m, 1H), 7.7-7.8 (m, 3H), 8.10-8.15 (m, 1H), 8.58-8.59 (m, 1H).

a. Benzo[d][1,3]dioxol-4-ylmethyl amine: Prepared in a similar manner to example 134a from benzo[d][1,3]dioxole-4-carbaldehyde and ammonium acetate. The crude material contained app. 20 % of the product (*m/e* = 152.2 [M+1]) and was used directly in example 149.

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.17 μM.

Example 150

N-(Benzo[b]thiophen-2-ylmethyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

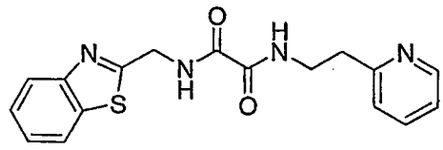


Prepared in a similar manner to example 125 using benzo[b]thiophen-2-ylmethanamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethyl amine; yield 32%; *m/e* = 240 [M+1]; ^{1}H NMR (DMSO-d_6): δ 2.92-2.95 (t, 2H), 3.48-3.53 (m, 2H), 4.55-4.56 (d, 2H), 7.20-7.25 (m, 2H), 7.38-7.41 (m, 2H), 7.50 (s, 1H), 7.66-7.70 (m, 1H), 7.95-7.99 (m, 2H), 8.47-8.49 (d, 1H), 8.88-8.90 (t, 1H), 9.29-9.31 (t, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.74 μM.

Example 151

N-(Benzo[d]thiazol-2-ylmethyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

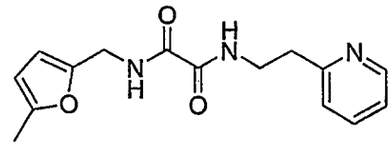


Prepared in a similar manner to example 125 using benzo[d]thiazol-2-ylmethanamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethyl amine; yield 33%; *m/e* = 341 [M+1]; ^{1}H NMR (DMSO-d_6): δ 2.95-2.98 (t, 2H), 3.52-3.57 (m, 2H), 4.72-4.73 (d, 2H), 7.22-7.24 (m, 1H), 7.25-7.27 (d, 1H), 7.40-7.44 (t, 1H), 7.48-7.51 (t, 1H), 7.69-7.72 (dt, 1H), 7.95-7.96 (d, 1H), 8.05-8.07 (d, 1H), 8.49-8.50 (d, 1H), 8.96-8.98 (t, 1H), 9.67-9.70 (t, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 4.4 μM.

Example 152

N-((5-Methylfuran-2-yl)methyl)-N2-(2-(pyridin-2-yl)ethyl)oxalamide

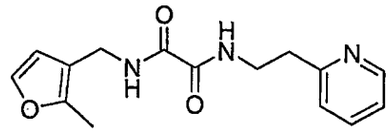


Prepared in a similar manner to example 125 using (5-methylfuran-2-yl)methanamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethyl amine; yield 38%; *m/e* = 288 [M+1]; ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H), 2.92-2.95 (t, 2H), 3.48-3.52 (m, 2H), 4.23-4.24 (d, 2H),5.96-5.97 (d, 1H), 6.06-6.07 (d, 1H), 7.20-7.25 (m, 2H), 7.68-7.71 (t, 1H), 8.48-8.49 (d, 1H), 8.85-8.87 (t, 1H), 9.04-9.07 (t, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 4.9 μM.

Example 153

N-((2-Methylfuran-3-yl)methyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide



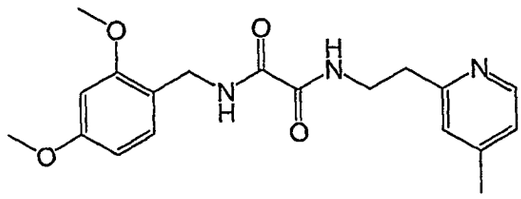
Prepared in a similar manner to example 125 using (2-methylfuran-3-yl)methanamine (example 153a), ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethyl amine; yield 50%; *m/e* = 288 [M+1]; ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H), 2.91-2.94 (t, 2H), 3.48-3.52 (q, 2H), 4.05-4.06 (d, 2H), 6.30-6.31 (d, 1H), 7.20-7.25 (m, 2H), 7.38-7.39 (d, 1H), 7.67-7.71 (dt, 1H), 8.48-8.49 (d, 1H), 8.83-8.86 (t, 1H), 9.04-9.07 (t, 1H).

a. (2-Methylfuran-3-yl)methanamine: A solution of 10 mmol (1.256 ml) of methyl 2-methylfuran-3-carboxylate and 38.9 mmol (2.1 g) of NaOMe in 20 ml of formamide was stirred at 100 °C for 30 min. The reaction mixture was poured into ice-water (20 ml) and extracted with ethyl acetate (3x). The extract was dried over MgSO4 and concentrated to give 1.05 g (83%) of 2-methylfuran-3-carboxamide as oil (*m/e* = 126.2 [M+1]). The amide was dissolved in dry THF (10 ml) and drop-wise added to 15 ml of 1M $LiAlH_4$ with 15 ml THF at 0 °C under argon. Then the mixture was stirred for 5 hrs at 60 °C. Following cooling, 50% aqueous THF (30 ml) was added to the mixture at 5-10 °C. The resulting precipitate was removed by filtration and the filtered solution was dried and concentrated to give an oily product (0.93 g, 84%).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.82 μM.

Example 154

N-(2,4-Dimethoxybenzyl)-N'-(2-(4-methylpyridin-2-yl)ethyl)oxalamide



Prepared in a similar manner to Example 122 using 2,4-dimethoxybenzylamine, ethyl oxalyl chloride, and 2-(4-methylpyridin-2-yl)ethyl amine (example 154a); yield 11%; *m/e* = 358 [M+1]; m.p. 144-145 °C; ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 2.97 (t, 2H), 3.71 (q, 2H), 3.79 (s, 3H), 3.83 (s, 3H), 4.39 (d, 2H), 6.40 (dd, 1H), 6.44 (d, 1H), 6.97 (s, 1H), 6.98 (d, 1H), 7.15 (d, 1H), 7.81 (br s, 1H), 8.08 (br s, 1H), 8.41 (d, 1H).

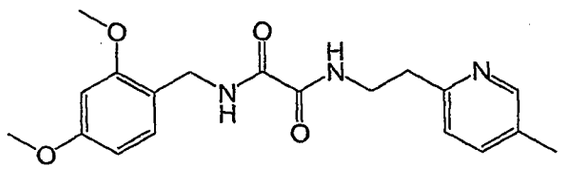
a. 2-(4-Methylpyridin-2-yl)ethyl amine: Prepared in a similar manner to example 129 using 2-(4-methylpyridin-2-yl)acetonitrile (example 154b); yield 83%; *m/e* = 137 [M+1].

b. 2-(4-Methylpyridin-2-yl)acetonitrile: Prepared in a similar manner to example 129b using 2-bromo-4-methylpyridine, acetonitrile and n-BuLi; yield 88%; *m/e* = 133 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1.64 μM

Example 155

N-(2,4-Dimethoxybenzyl)-N'-(2-(5-methylpyridin-2-yl)ethyl)oxalamide



Prepared in a similar manner to Example 122 using 2,4-dimethoxybenzylamine, ethyl oxalyl chloride, and 2-(5-methylpyridin-2-yl)ethyl amine (example 155a); yield 9%; *m/e* = 358 [M+1]; m.p. 124-125 °C; ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H), 2.97 (t, 2H), 3.70 (q, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 4.38 (d, 2H), 6.40 (dd, 1H), 6.44 (d, 1H), 7.03 (d, 1H), 7.14 (d, 1H), 7.40 (dd, 1H), 7.81 (br s, 1H), 8.08 (br s, 1H), 8.38 (d, 1H).

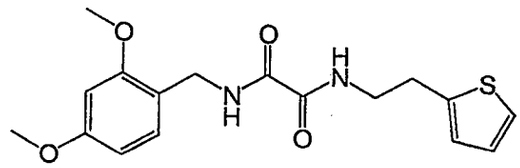
a. 2-(5-Methylpyridin-2-yl)ethyl amine: Prepared in a similar manner to 129a using 2-(5-methylpyridin-2-yl)acetonitrile (155b); yield 40%; *m/e* = 137 [M+1].

b. 2-(5-Methylpyridin-2-yl)acetonitrile: Prepared in a similar manner to 129b using 2-bromo-5-methylpyridine, acetonitrile and n-BuLi; yield 68%; *m/e* = 133 [M+1].

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.07 μM.

Example 156

N-(2,4-Dimethoxybenzyl)-N'-(2-(thiophen-2-yl)ethyl)oxalamide

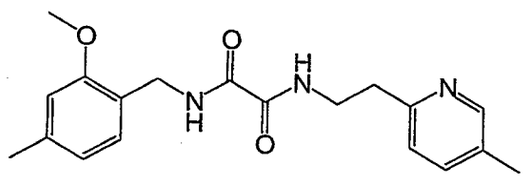


Prepared in a similar manner to Example 122 using 2,4-dimethoxybenzylamine, ethyl oxalyl chloride and 2-(thiophen-2-yl)ethyl amine; yield 72%; *m/e* = 349 [M+1]; m.p. 146-147 °C; ^{1}H NMR ($CDCl_3$): δ 3.06 (t, 2H), 3.58 (q, 2H), 3.80 (s, 3H), 3.83 (s, 3H), 4.40 (d, 2H), 6.41 (dd, 1H), 6.45 (d, 1H), 6.84 (dd, 1H), 6.93 (dd, 1H), 7.15 (d, 1H), 7.16 (d, 1H), 7.61 (br s, 1H), 7.81 (br s, 1H).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 4.87 μM.

Example 157

N^1-(2-methoxy-4-methylbenzyl)-N^2-(2-(5-methylpyridin-2-yl)ethyl)oxalamide



^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.29 (3H, s); 2.33 (3H, s); 2.97 (2H, t, J = 6.5 Hz); 3.71 (2H, q, J = 6.5 Hz); 3.83 (3H, s); 4.40 (2H, d, J = 6.2 Hz); 6.68 (1H, s); 6.69 (1H, d, J = 7.7 Hz); 7.02 (1H, d, J = 7.9 Hz); 7.09 (1H, d, J = 7.5 Hz); 7.40 (1H, dd, J_1 = 1.8 Hz, J_2 = 7.8 Hz); 7.85 (1H, br t); 8.06 (1H, br t); 8.38 (1H, s, J = 7.5 Hz).

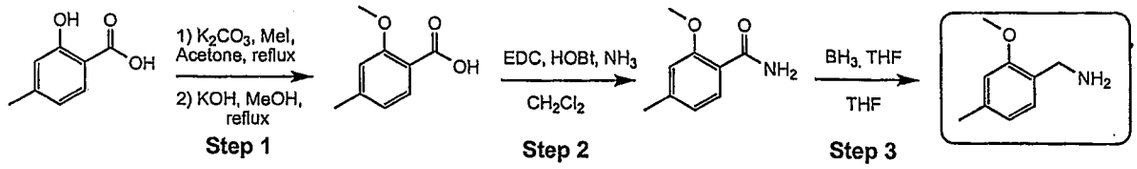
13C NMR ($CDCl_3$, 500 MHz): 18.3, 21.8, 36.5, 39.1, 39.6, 55.5, 111.5, 121.3, 122.3, 123.0, 129.9, 131.3, 137.4, 139.6, 150.0, 155.7, 157.7, 159.7, 160.1.

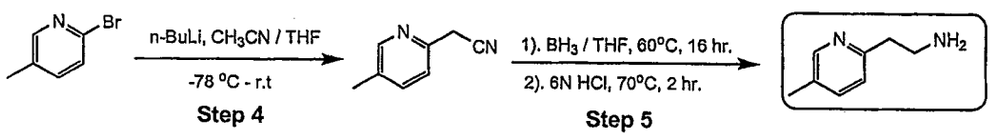
Elemental Analysis: Calculated for $C_{18}H_{21}N_3O_3.1/4\ H_2O$: C, 65.97; H, 6.85; N, 12.15. Found: C, 66.10; H, 7.34; N, 12.17. **MS** (342, M+1). White powder, melting point = 133.5-134 °C

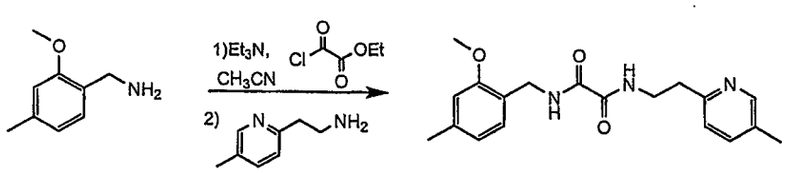
The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.03 μM.

The compound was synthesized via the reaction sequence illustrated in the diagram

below, and the details of each of the six synthetic steps are subsequently provided below.







Step 1: To a solution of 2-hydroxy-4-methylbenzoic acid (25g, 0.164 mol) in acetone (350 mL) was added K_2CO_3 (68 g, 0.492 mmol) followed by MeI (41 mL, 0.656 mmol) and the reaction mixture heated at reflux for 48 hrs. After cooling to r.t. the reaction mixture was filtered and the filtrate was evaporated to give the crude methyl 2-methoxy-4-methylbenzoate. KOH (11.3 g, 1.2 eq) was dissolved in MeOH (300 mL) and the crude ester was added to the mixture and the solution heated at reflux 48hrs. After cooling the reaction mixture was acidified with aq. HCl (1N) and extracted with ethyl acteate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was triturated with Ethyl acetate/Hexane to give 20 g of 2-methoxy-4-methylbenzoic acid as a cream white solid (85% yield)

Step 2: To a mixture of 2-methoxy-4-methylbenzoic acid (20 g , 120.4 mmol), EDC (23.1 g, 120.4 mmol) and HOBt (16.3 g, 120.4 mmol) in dichloromethane (1 L) was added NH_3 (7N in MeOH, 52 mL, 3 eq) dropwise. The reaction mixture was stirred at room temperature overnight then washed successively with HCl (1N), saturated aq.$NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and evaporated. The residue was recrystallized from ethyl acetate/ hexane to give 16.5 gr of 2-methoxy-4-methylbenzamide (83% yield).

Step 3: To a solution of 2-methoxy-4-methylbenzamide (14.55 g , 88.08 mmol) in dry THF (50 mL) was added dropwise Borane-tetrahydrofuran complex (1.0 M in THF, 220 mL, 2.5 eq) at 0 °C under N_2 atmosphere. The reaction mixture was then heated to 60 °C overnight. The reaction was cooled to room temperature, aq.HCl (6 N, 37 mL) was added

carefully and the reaction mixture was then heated at 70 °C for 2 hrs. After cooling, water was added and the resulting solution was washed with ether. The aqueous layer was basified with aq. NaOH (10 N) at 0 °C and saturated with K_2CO_3 then extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to give 8.5 g of (2-methoxy-4-methylphenyl)methanamine. (64% yield)

Step 4: To a solution of anhydrous acetonitrile (10.1 mL, 191.83 mmol, 3.3 eq) in dry THF (500 mL) was added dropwise n-BuLi (2.5 M in Hexane, 69.8 mL, 174.39 mmol, 3 eq) at -78 °C under N_2 atmosphere. The resulting white suspension was stirred at -78 °C for 1 hr, and then a solution of 2-bromo-5-methylpyridine (10.0 g, 58.13 mmol, 1eq) in dry THF (30 mL) was added. The reaction mixture was kept at -78 °C for 1 hr then warmed up slowly to r.t and stirred for another 1 hr. Ice/water was added and the layer was separated. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and evaporated to give 18 g of crude 2-(5-methylpyridin-2-yl)acetonitrile. Since the product is very volatile, it was not dried under high vacuum and still contains some solvent.

Step 5: To a solution of 18 g of crude 2-(5-methylpyridin-2-yl)acetonitrile in dry THF (100 mL) was added dropwise Borane-tetrahydrofuran complex (1.0 M in THF, 232 mL, 232.5 mmol, 4 eq) at 0 °C under N_2 atmosphere. The reaction mixture was then heated to 60 °C overnight. The reaction was cooled to room temperature, aq.HCl (6 N, 40 mL) was added carefully and the reaction mixture was then heated at 70 °C for 2 hrs. After cooling, water was added and the resulting solution was washed with ether. The aqueous layer was basified with aq. NaOH (10 N) at 0 °C and saturated with K_2CO_3 then extracted with ether (5 x 100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to give 7.6 g of crude 2-(5-methylpyridin-2-yl)ethanamine. (96% crude yield)

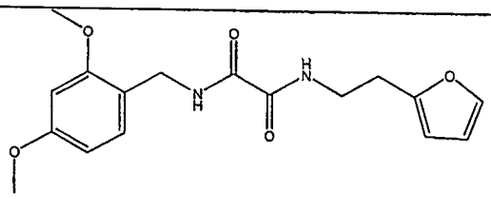
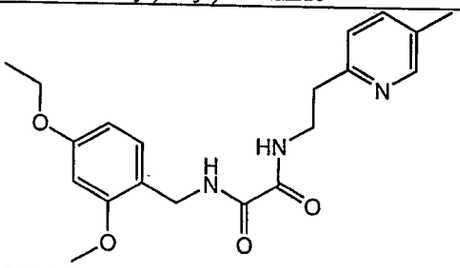
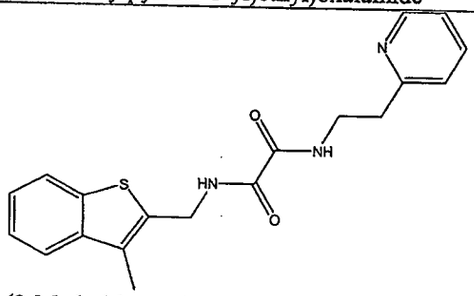
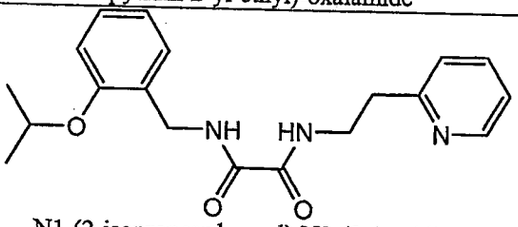
When evaporating the ether, the water bath temperature was kept at 25°C since the boiling point of the amine is probably around 100 °C

Step 6: A mixture of 2g of (2-methoxy-4-methylphenyl)methanamine (from step 3) and Et_3N (3.7 mL, 2eq) in dry CH_3CN (45 mL) was cooled to 0 °C under N_2 atmosphere and ethyl 2-chloro-2-oxoacetate (1.47 mL, 1 eq) was added dropwise. After the addition was complete, the reaction mixture was stirred at room temperature for 4 hours and 2-(5-methylpyridin-2-yl)ethanamine (2.52 g, 1.4 eq, from step 5) was added. The reaction was heated at reflux for 24 hours. After cooling the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate and washed successively with water and brine, dried over $MgSO_4$, filtered and evaporated. The residue was chromatographed on

silica gel (eluent: 25-35% acetone in hexane) and recrystallized from ethyl acetate /hexane and ethanol/water to give 650 mg of N^1-(2-methoxy-4-methylbenzyl)-N^2-(2-(5-methylpyridin-2-yl)ethyl)oxalamide (15%).

Additional "oxalamide" compounds were synthesized and experimentally tested and found to have a relatively high level of effectiveness as an activator of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line. The results of that testing are shown below in Table B.

Table B - Umami Oxalamides

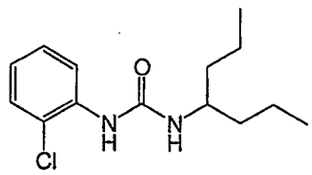
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)
B1	 N1-(2,4-dimethoxybenzyl)-N2-(2-(furan-2-yl)ethyl)oxalamide	0.18	
B2	 N1-(4-ethoxy-2-methoxybenzyl)-N2-(2-(5-methylpyridin-2-yl)ethyl)oxalamide	0.19	
B3	 N-(3-Methyl-benzo[b]thiophen-2-ylmethyl)-N'-(2-pyridin-2-yl-ethyl)-oxalamide	0.81	
B4	 N1-(2-isopropoxybenzyl)-N2-(2-(pyridin-2-yl)ethyl)oxalamide	1.22	

Numerous amide compounds of Formula (I) that fall within the subgenus of "urea"

compounds described elsewhere herein as Formula (IV) were also synthesized and experimentally tested for effectiveness as activator of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line.

Example 158

1-(4-chlorophenyl)-3-(heptan-4-yl)urea

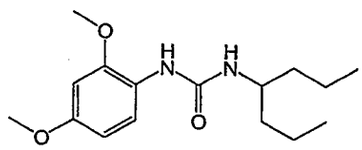


To a solution of heptan-4-amine (0.18 mL, 1 mmol) in CH_2Cl_2 (5 mL) was added 1-chloro-2-isocyanatobenzene (0.12 mL, 1 mmol) at room temperature. The reaction mixture was stirred for 2 h. A white solid was precipitated out. The reaction mixture was filtered. The solid was washed with CH_2Cl_2 to afford 1-(4-chlorophenyl)-3-(heptan-4-yl)urea (180 mg, 67%) as a white solid. mp: 135-136 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (t, 6H), 1.45 (m, 6H), 1.53 (m, 2H), 3.80 (br s, 1H), 4.33 (d, 1H), 6.00 (s, 1H), 6.95 (td, 1H), 7.23 (dt, 1H), 7.33 (dd, 1H), 8.13 (dd, 1H). MS(M+H, 269).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.37 μM, and when present at 1 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 4.95.

Example 159

1-(2,4-dimethoxyphenyl)-3-(heptan-4-yl)urea

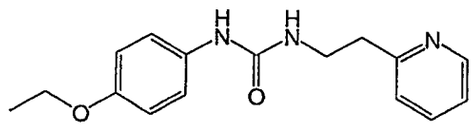


Prepared in a similar manner to example 158 using heptan-4-amine and 1-isocyanato-2,4-dimethoxybenzene. Yield: 88%. mp: 172-173 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (t, 6H), 1.45 (m, 8H), 3.82 (s, 3H), 3.83 (m, 1H), 3.84 (s, 1H), 4.32 (br s, 1H), 6.34 (br s, 1H), 6.49 (d, 1H), 6.50 (s, 1H), 7.71 (d, 1H). MS (M+H, 295).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.98 μM, and when present at 0.3 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 7.61.

Example 160

1-(4-ethoxyphenyl)-3-(2-(pyridine-2-yl)ethyl)urea

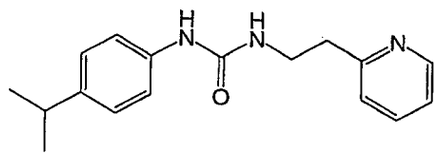


Prepared in a similar manner to example 158 using 2-(pyridine-2-yl)ethanamine and 1-ethoxy-4-isocyanatobenzene. Yield: 95%. mp: 163-164 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (t, 3H), 3.03 (t, 2H), 3.68 (t, 2H), 4.03 (q, 2H), 5.69 (br s, 1H), 6.45 (br s, 1H), 6.84 (m, 2H), 7.14 (m, 3H), 7.20 (d, 1H), 7.64 (dt, 1H), 8.43 (dd, 1H). MS (M+H,286).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 4.1 μM, and when present at 1 μM enhanced the effectiveness of monosodium glutamate with an EC_{50} ratio of 4.2.

Example 161

1-(4-isopropylphenyl)-3-(2-(pyridine-2-yl)ethyl)urea



Prepared in a similar manner to example 158 using 2-(pyridine-2-yl)ethanamine and 1-isocyanato-4-isopropylbenzene. Purified via column chromatography (1% MeOH in CH_2Cl_2 to 3% MeOH in CH_2Cl_2) to afford 1-(4-isopropylphenyl)-3-(2-(pyridine-2-yl)ethyl)urea (130 mg, 50%) as a white solid. mp: 72-73 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (d, 6H), 2.89 (m, 1H), 3.06 (t, 2H), 3.70 (t, 2H), 5.80 (br s, 1H), 6.55 (br s, 1H), 7.19 (m, 5H), 7.24 (d, 1H), 7.68 (dt, 1H), 8.46 (d, 1H). MS (M+H, 284).

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0.98 μM.

Additional "urea" compounds were synthesized and experimentally tested and found to have a relatively high level of effectiveness as an activator of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line. The results of that testing are shown below in Table C.

Table C - Umami Ureas

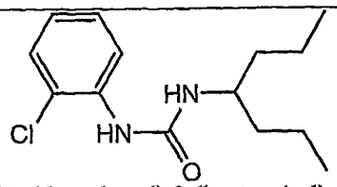
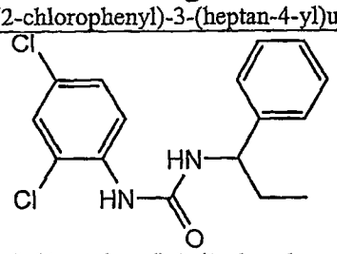
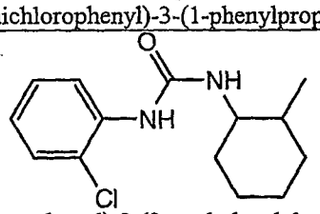
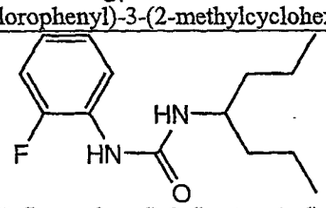
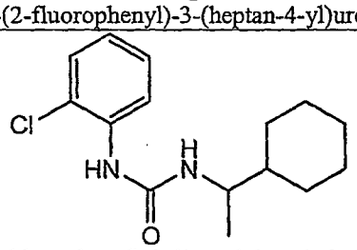
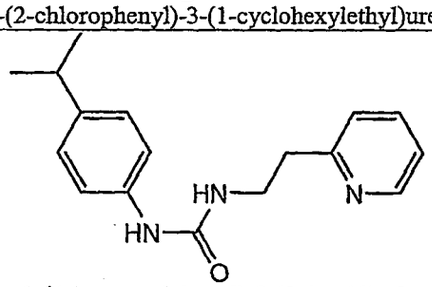
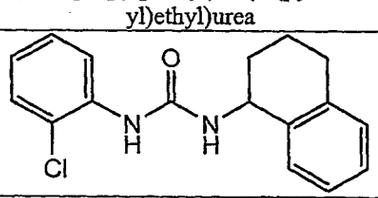
Compound No.	IUPAC Name	Umami EC_{50} µM	Ec50 ratio (vs. MSG)	Con. (µM)
C1	 1-(2-chlorophenyl)-3-(heptan-4-yl)urea	0.37	4.95	1
C2	 1-(2,4-dichlorophenyl)-3-(1-phenylpropyl)urea	0.49	4.52	1
C3	 1-(2-chlorophenyl)-3-(2-methylcyclohexyl)urea	0.52	3.24	3
C4	 1-(2-fluorophenyl)-3-(heptan-4-yl)urea	0.79	12.15	3
C5	 1-(2-chlorophenyl)-3-(1-cyclohexylethyl)urea	0.84	9.08	1
C6	 1-(4-isopropylphenyl)-3-(2-(pyridin-2-yl)ethyl)urea	0.98		
C7		0.99	3.68	1

Table C - Umami Ureas

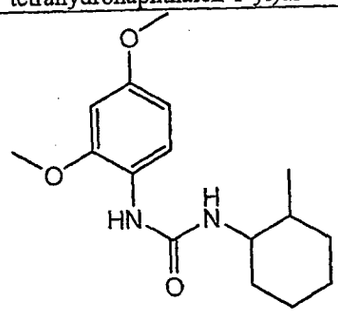
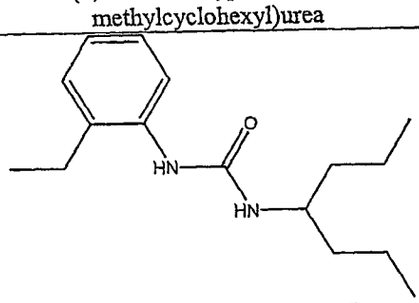
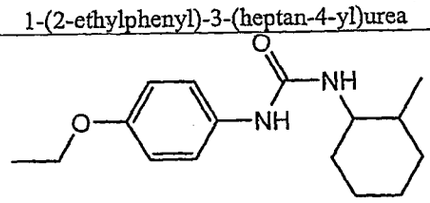
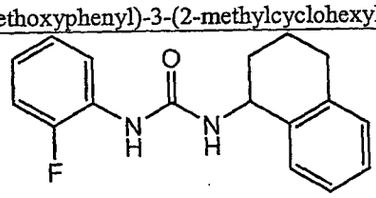
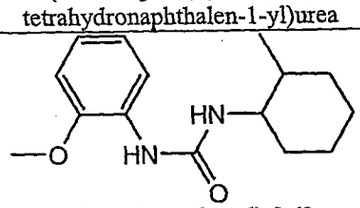
Compound No.	IUPAC Name	Umami EC_{50} μM	Ec50 ratio (vs. MSG)	Con. (μM)
	1-(2-chlorophenyl)-3-(1,2,3,4-tetrahydronaphthalen-1-yl)urea			
C8	 1-(2,4-dimethoxyphenyl)-3-(2-methylcyclohexyl)urea	1.41	2.62	0.3
C9	 1-(2-ethylphenyl)-3-(heptan-4-yl)urea	1.42		
C10	 1-(4-ethoxyphenyl)-3-(2-methylcyclohexyl)urea	1.51	2.1	0.3
C11	 1-(2-fluorophenyl)-3-(1,2,3,4-tetrahydronaphthalen-1-yl)urea	1.65	4.49	1
C12	 1-(2-methoxyphenyl)-3-(2-methylcyclohexyl)urea	1.67		

Table C - Umami Ureas

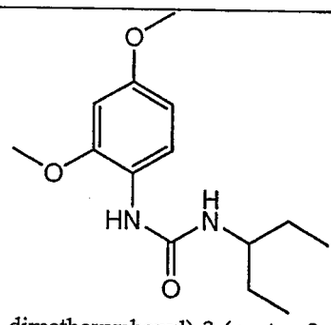
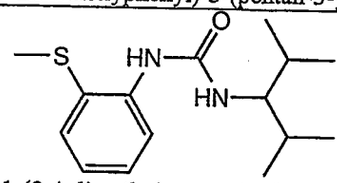
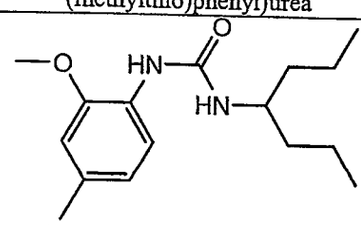
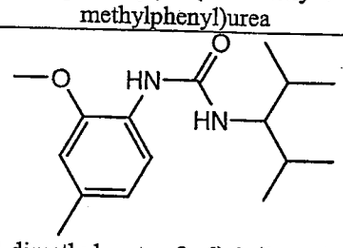
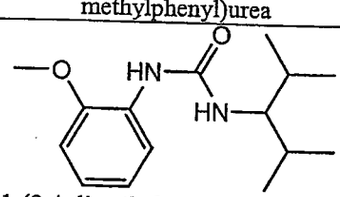
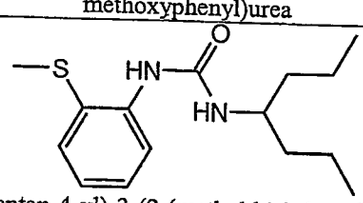
Compound No.	IUPAC Name	Umami EC_{50} μM	Ec50 ratio (vs. MSG)	Con. (μM)
C13	 1-(2,4-dimethoxyphenyl)-3-(pentan-3-yl)urea	1.72	11.87	1
C14	 1-(2,4-dimethylpentan-3-yl)-3-(2-(methylthio)phenyl)urea	0.14		
C15	 1-(heptan-4-yl)-3-(2-methoxy-4-methylphenyl)urea	0.16		
C16	 1-(2,4-dimethylpentan-3-yl)-3-(2-methoxy-4-methylphenyl)urea	0.21		
C17	 1-(2,4-dimethylpentan-3-yl)-3-(2-methoxyphenyl)urea	0.24		
C18	 1-(heptan-4-yl)-3-(2-(methylthio)phenyl)urea	0.26		

Table C - Umami Ureas

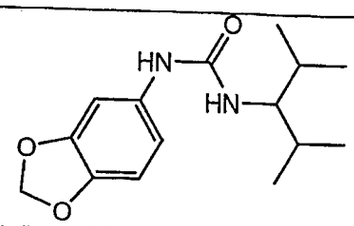
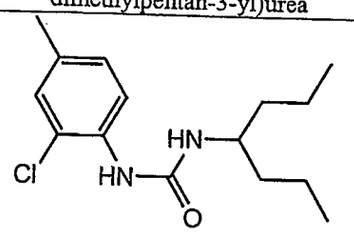
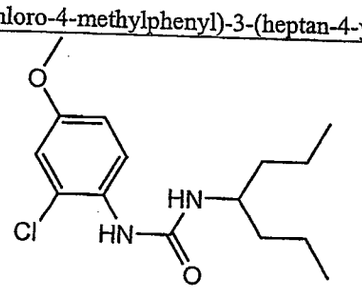
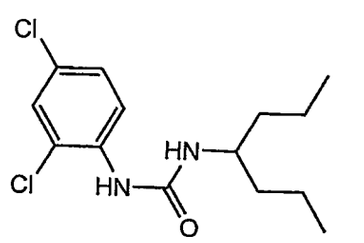
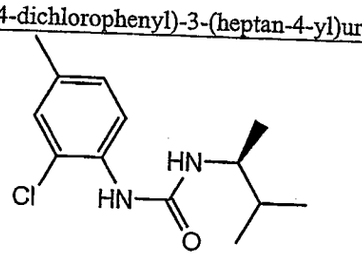
Compound No.	IUPAC Name	Umami EC_{50} μM	Ec50 ratio (vs. MSG)	Con. (μM)
C19	 1-(benzo[d][1,3]dioxol-5-yl)-3-(2,4-dimethylpentan-3-yl)urea	0.32		
C20	 1-(2-chloro-4-methylphenyl)-3-(heptan-4-yl)urea	0.09		
C21	 1-(2-chloro-4-methoxyphenyl)-3-(heptan-4-yl)urea	0.11		
C22	 1-(2,4-dichlorophenyl)-3-(heptan-4-yl)urea	0.18		
C23	 (S)-1-(2-chloro-4-methylphenyl)-3-(3-methylbutan-2-yl)urea	0.38		

Table C - Umami Ureas

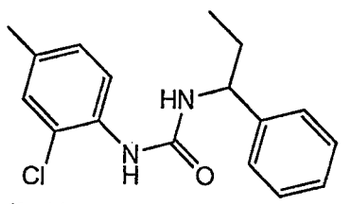
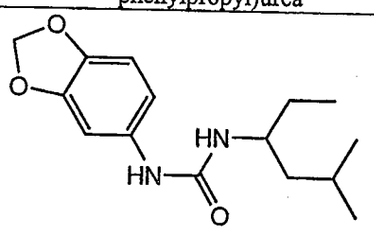
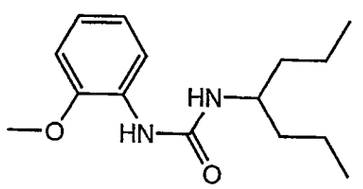
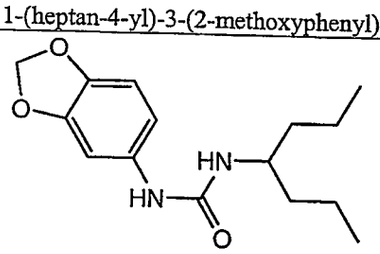
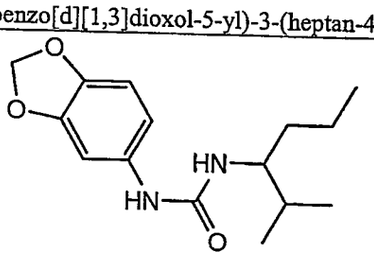
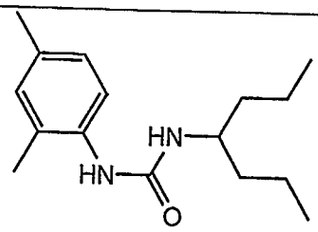
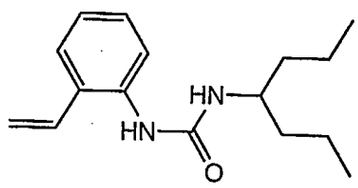
Compound No.	IUPAC Name	Umami EC_{50} μM	Ec50 ratio (vs. MSG)	Con. (μM)
C24	 1-(2-chloro-4-methylphenyl)-3-(1-phenylpropyl)urea	0.48		
C25	 1-(benzo[d][1,3]dioxol-5-yl)-3-(5-methylhexan-3-yl)urea	0.48		
C26	 1-(heptan-4-yl)-3-(2-methoxyphenyl)urea	0.49		
C27	 1-(benzo[d][1,3]dioxol-5-yl)-3-(heptan-4-yl)urea	0.54		
C28	 1-(benzo[d][1,3]dioxol-5-yl)-3-(2-methylhexan-3-yl)urea	0.57		

Table C - Umami Ureas

Compound No.	IUPAC Name	Umami EC_{50} μM	Ec50 ratio (vs. MSG)	Con. (μM)
C29	 1-(2,4-dimethylphenyl)-3-(heptan-4-yl)urea	0.79		
C30	 1-(heptan-4-yl)-3-(2-vinylphenyl)urea	0.79		

Numerous amide compounds of Formula (I) that fall within the subgenus of "acrylamide" compounds described elsewhere herein were also synthesized and experimentally tested for effectiveness as activator of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line. The results of that testing are shown below in Table D.

Table D - Umami Acrylamides

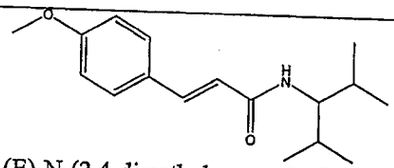
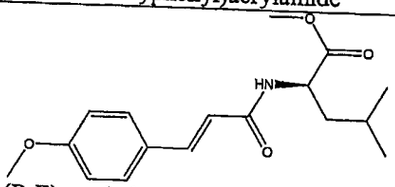
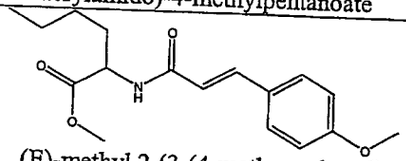
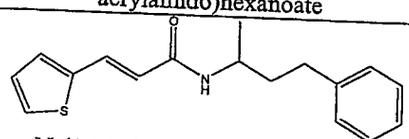
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@ (μM)
D1	 (E)-N-(2,4-dimethylpentan-3-yl)-3-(4-methoxyphenyl)acrylamide	0.29	3.46	1
D2	 (R,E)-methyl 2-(3-(4-methoxyphenyl) acrylamido)-4-methylpentanoate	0.32		
D3	 (E)-methyl 2-(3-(4-methoxyphenyl) acrylamido)hexanoate	0.63		
D4	 N-(1-Methyl-3-phenyl-propyl)-3-	0.69	9.73	1

Table D - Umami Acrylamides

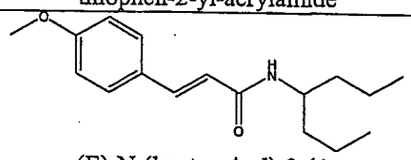
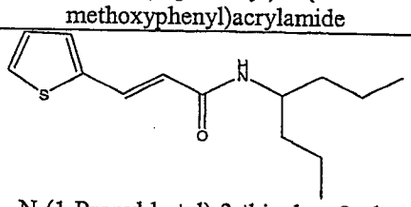
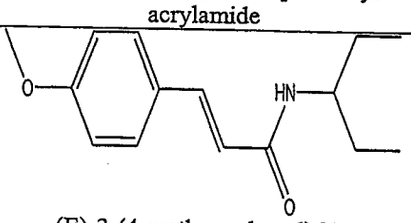
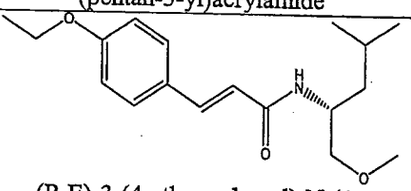
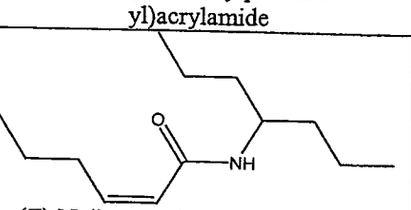
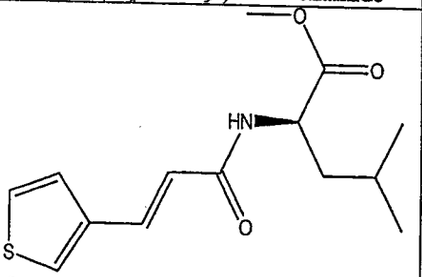
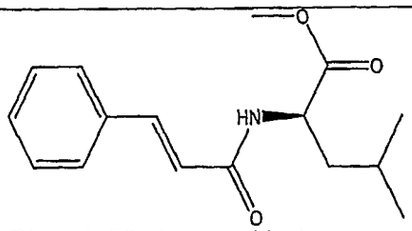
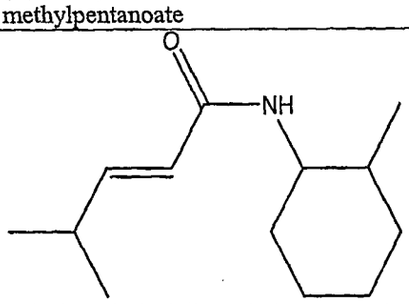
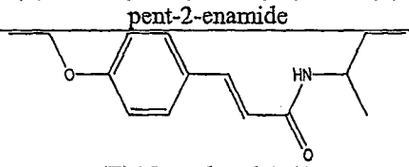
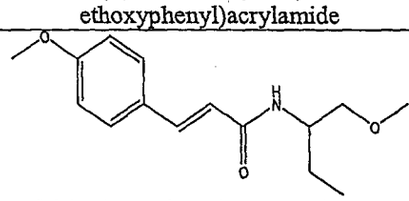
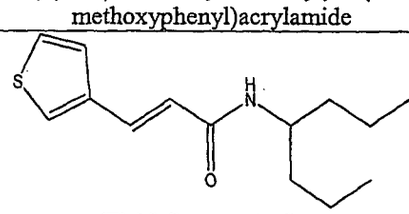
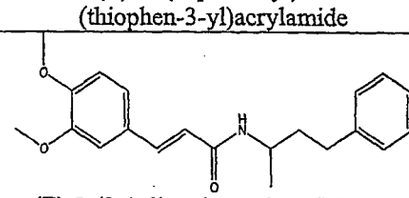
Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@ (μM)
	thiophen-2-yl-acrylamide			
D5	 (E)-N-(heptan-4-yl)-3-(4-methoxyphenyl)acrylamide	0.72	3.48	0.3
D6	 N-(1-Propyl-butyl)-3-thiophen-2-yl-acrylamide	0.75	6.3	1
D7	 (E)-3-(4-methoxyphenyl)-N-(pentan-3-yl)acrylamide	0.82	9.62	1
D8	 (R,E)-3-(4-ethoxyphenyl)-N-(1-methoxy-4-methylpentan-2-yl)acrylamide	0.94		
D9	 (Z)-N-(heptan-4-yl)hex-2-enamide	0.98		
D10	 (R,E)-methyl 4-methyl-2-(3-(thiophen-3-yl)acrylamido)pentanoate	1.09		

Table D - Umami Acrylamides

Compound No.	Compound	Umami EC_{50} (μM)	Ec_{50} ratio (vs. MSG)	@ (μM)
D11	 (R)-methyl 2-cinnamamido-4-methylpentanoate	1.17		
D12	 (E)-4-methyl-N-(2-methylcyclohexyl) pent-2-enamide	1.28		
D13	 (E)-N-sec-butyl-3-(4-ethoxyphenyl)acrylamide	1.31	2.7	0.3
D14	 (E)-N-(1-methoxybutan-2-yl)-3-(4-methoxyphenyl)acrylamide	1.43	8.48	1
D15	 (E)-N-(heptan-4-yl)-3-(thiophen-3-yl)acrylamide	1.54	2.22	0.3
D16	 (E)-3-(3,4-dimethoxyphenyl)-N-(4-phenylbutan-2-yl)acrylamide	1.56	3.13	1

Umami/Savory Flavor Experiments Using Human Panelists:

General Panelist Selection: Basic screening of sensory taste testers: Potential

panelists were tested for their abilities to rank and rate intensities of solutions representing the five basic tastes. Panelists ranked and rated intensity of five different concentrations of each of the five following compounds: sucrose (sweet), sodium chloride (salty), citric acid (sour), caffeine (bitter), and monosodium glutamate (savory). In order to be selected for participation in testing, panelists needed to correctly rank and rate samples for intensity, with a reasonable number of errors.

Preliminary Taste Tests: The panelists selected in the above procedure were deemed qualified for performing Preliminary Taste Testing procedures. The preliminary taste tests are used to evaluate new compounds for intensity of basic tastes and off-tastes. A small group of panelists (n=5) taste approximately 5 concentrations of the compound (range typically between 1-100 μM, in half-log cycles, *e.g.*, 1, 3, 10, 30, and 100 μM) in water and in a solution of 12 mM MSG to evaluate enhancement. Panelists rate the five basic tastes (sweet, salty, sour, bitter, and savory) as well as off-tastes (such as chemical, metallic, sulfur) on a labeled magnitude scale. Samples are served in 10 mL portions at room temperature. The purpose of the test is to determine the highest concentration at which there is no objectionable off-taste, and determine if obvious savory taste or enhancement of savory taste exists at any of the concentrations tested.

If the compound is effective and does not have objectionable off-tastes, it is tested with a trained (expert panel) in a larger study.

Trained Panelist Selection: A trained expert panel was used to further evaluate compounds that had been tested with the preliminary taste test.

Panelists for the trained panel were selected from the larger group of qualifying taste panelists. Panelists were further trained on savory taste by ranking and rating experiments using MSG and IMP combinations. Panelists completed a series of ranking, rating, and difference from reference tests with savory solutions. In ranking and rating experiments, panelists evaluated easy MSG concentrations (0, 6, 18, 36 mM) and more difficult MSG concentrations (3, 6, 12, 18 mM MSG) in water.

Compound testing with Trained Panel: Compounds tested by the trained panel were evaluated in difference from reference experiments. Panelists were given a reference sample (12 mM MSG + 100 μM IMP) and asked to rate samples on a scale of –5 to +5 in terms of difference in savory taste from the reference (score: –5 = much less savory taste than the reference; 0 = same savory taste as the reference; +5 = much more savory taste than the reference). Test samples were solutions with varying amounts of MSG, IMP, and the

compound. Typically, each session compares the reference sample to numerous test samples. Tests typically included various samples with varying concentrations of MSG and IMP, as well as one blind sample of the reference itself, to evaluate panel accuracy. Results of the taste tests are describe in table 3 and shows that compounds of the invention have been found to provide savory taste or enhancement of the savory taste at 3 μM + MSG when compared to 100 μM IMP + MSG. Compounds were tested against the reference in samples with and without 12 mM MSG. All samples were presented in 10 ml volumes at room temperature. Two sessions were completed for each compound tested to evaluate panel reproducibility.

Taste Test in Product Prototype: could be done similarly as described above.

Table 3. Savory Taste Test Results

Compound No.	Chemical Name	Taste Data
Example 1	N-(heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide	12 mM MSG + 3 μM cpd as strong as 12mM MSG + 100 μM IMP
Example 6	(R)-methyl 2-(benzo[d][1,3] dioxole-6-carboxamido)-4-methylpentanoate	12 mM MSG + 10 μM cpd as strong as 12mM MSG + 100 μM IMP
Example 71	(R)-N-(1-methoxy-4-methylpentan-2-yl)-3,4-dimethylbenzamide	12 mM MSG + 3 μM cpd as strong as 12mM MSG + 100 μM IMP
Example 98	(R)-methyl-2-(2,3-dimethylfuran-5-carboxamido)-4-methylpentanoate	12 mM MSG + 10 μM cpd as strong as 12mM MSG + 100 μM IMP
Example 104	4-Methoxy-N-(1-methoxymethyl-3-methyl-butyl)-3-methyl-benzamide	12 mM MSG + 3 μM cpd as strong as 12mM MSG + 100 μM IMP
Example 123	N-(2,4-Dimethoxy-benzyl)-N'-(2-pyridin-2-yl-ethyl)-oxalamide	12 mM MSG + 1 μM cpd as strong as 12mM MSG + 100 μM IMP 1 μM cpd as strong as 12mM MSG
Example 132	N-(2methoxy-4-methylbenzyl)-N'-(2(5-methylpyridin-2-yl)ethyl)oxalamide	12 mM MSG + 1 μM cpd as strong as 12mM MSG + 100 μM IMP 1 μM cpd as strong as 12mM MSG
Example 157	N^1-(2-methoxy-4-methylbenzyl)-N^2-(2-(5-methylpyridin-2-yl)ethyl)oxalamide	12 mM MSG + 0.3 μM cpd as strong as 12mM MSG + 100 μM IMP 0.3 μM cpd as strong as 12mM MSG

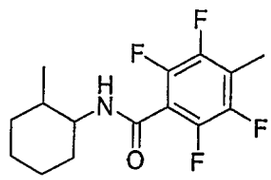
Compound No.	Chemical Name	Taste Data
Example 121-1	(S)-N-(2,3-Dihydro-1H-inden-1-yl)-4-methoxy-3-methylbenzamide	12 mM MSG + 1 μM cpd as strong as 12mM MSG + 100 μM IMP 1 μM cpd as strong as 12mM MSG

Sweet Amide Examples

Numerous amide compounds of Formula (I) were synthesized and experimentally tested for effectiveness as activator of a hT1R2/hT1R3 "sweet" receptor expressed in an HEK293 cell line. Examples of the synthesis and biological effectiveness testing in terms of Sweet EC_{50} measurements for such sweet compounds are listed below. Moreover, many of the "sweet" amides of Formula (I) were also screened for activity in the umami EC_{50} and EC_{50} ratio assays, and as illustrated below, some of the amide compounds of Formula (I) have significant activity and potential to simultaneously serve as savory and sweet taste enhancers for use in comestible and medicinal products and compositions.

Example 162

2,3,5,6-tetrafluoro-4-methyl-N-(2-methylcyclohexyl)benzamide

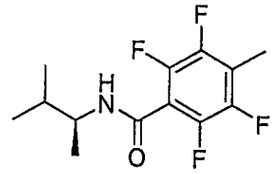


2,3,5,6 –tetrafluoro-*p*-toluic acid (4.00 g, 19.22 mmol), HOBt (5.19 g, 38.44 mmol) and EDCI (4.42 g 23.06 mmol) were mixed in 200 ml of anhydrous DCM and 30 ml of anhydrous DMF. The mixture was cooled to 0°C and allowed to stir under Ar for 15 minutes. To the mixture was added 2-methylcyclohexanamine (3.05 mL, 23.06 mmol) and the reaction mixture was allowed to slowly warm to ambient temperature and stirred overnight. The reaction mixture was diluted with DCM , washed with 1N HCl, water, aqueous $NaHCO_3$, water and brine, drying over $MgSO_4$, filtration and removal of solvent *in vacuo,* afforded the crude product as a pale yellow solid Recrystallization ($EtOH/H_2O$) and drying *in vacuo* gave 5.23 g of the title compound as a white solid (mixture of 2 diasteromers, 90%). ^1H NMR ($CDCl_3$) δ 0.95, 1.01 (d, J= 7.0, 6,6 Hz, 3H) 1.1-2.1 (m, 9H), 2.29 (m, 3H), 3.70, 4.29 (m, 1H), 5.65, 5.92 (m, 1H). MS (304.1, M+H). m. p. 202-204 °C.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.39 μM.

Example 163

(S)-2,3,5,6-tetrafluoro-4-methyl-N-(3-methylbutan-2-yl)benzamide

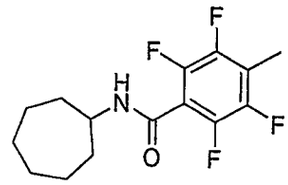


Prepared in a similar manner to Example 162 using (S)-3-methylbutan-2-amine and 2,3,5,6 –tetrafluoro-*p*-toluic acid (93%). ^{1}H NMR ($CDCl_3$) δ 0.98 (d, J= 6.9 Hz, 6H) 1.18 (d, J= 6.8 Hz, 3H), 2.29 (m, 3H), 4.09 (m, 1H), 5.72 (bs, 1H).MS (304.1, M+H) m. p. 146-147 °C.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.6 μM.

Example 164

N-cycloheptyl-2,3,5,6-tetrafluoro-4-methylbenzamide

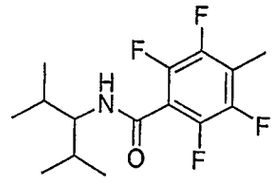


Prepared in a similar manner to Example 162 using cycloheptylamine and 2,3,5,6 – tetrafluoro-*p*-toluic acid (94%). ^{1}H NMR ($CDCl_3$) δ 1.53 (m, 6H), 1.57 (m, 4H), 2.03 (m, 2H) 2.28 (m, 3H), 4.17 (m, 1H), 5.85 (bs, 1H).MS (304.1, M+H) m. p. 164-165 °C.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 1.85 μM.

Example 165

N-(2,4-dimethylpentan-3-yl)-2,3,5,6-tetrafluoro-4-methylbenzamide

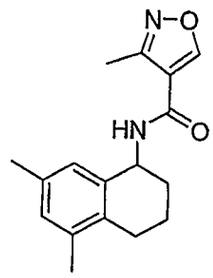


Prepared in a similar manner to Example 162 using 2,4-dimethylpentan-3-amine and 2,3,5,6 –tetrafluoro-*p*-toluic acid (90%). ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.7 Hz, 6H), 1.00 (d, J = 6.8 Hz, 6H), 1.85 (m, 2H), 2.29 (m, 3H), 3.82 (m, 1H), 5.52 (bd, 1H).MS (306.1, M+H) m. p. 184-187 °C.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.81μM.

Example 166

***N*-(5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylisoxazole-4-carboxamide**



To a solution of 3-methylisoxazole-4-carboxylic acid (83 mg, 0.0.67 mmol), HOBt (100 mg, 0.74 mmol) and EDCI·HCl (142 mg, 0.74 mmol) in DMF (4 mL), was added 5,7-dimethyl-1,2,3,4-tetrahydronaphthyl-1-amine (example 166a) (130 mg, 0.74 mmol). The reaction mixture was stirred for 24h at rt, at which time the solvent was removed under reduced pressure and the residue was purified by flash-column chromatography (10:1 Hex:EtOAc) to afford 134 mg of *N*-(5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylisoxazole-4-carboxamide (70 %) as a white foamy solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.74 (m, 2H), 1.86 (m, 2H), 2.16 (s, 3H), 2.19 (s, 3H), 2.43 (s, 3H), 2.55 (m, 2H), 5.10 (m, 1H), 6.86 (s, 1H), 6.89 (s, 1H), 8.60 (d, 1H, J = 8.40 Hz), 9.27 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.6, 19.1, 19.6, 20.6, 25.8, 29.4, 46.9, 115.4, 126.4, 129.1, 132.6, 134.1, 135.8, 136.6, 158.5, 159.6, 159.9. MS(M+H, 285). Mp 57-58 °C.

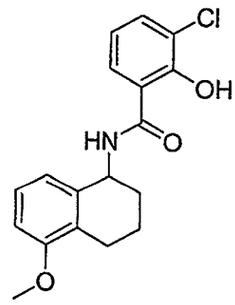
a. 5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-amine: A catalytic amount of Raney nickel (slurry in water) was washed with dry MeOH under argon in a round bottom flask. To a solution of the washed Raney Ni in methanolic ammonia (25 mL, 7N), was added 5,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one oxime (example 166b) (420 mg, 2.22 mmol), and the mixture was stirred under a balloon of H_2 for 20 hr. Upon completion, the reaction was filtered through celite, the filtrate was concentrated *in vacuo*, diluted with EtOAC, washed with water and brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford 360 mg of 5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-amine (93 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.66-1.83 (m, 4H), 1.96 (m, 2H), 2.19 (s, 3H), 2.28 (s, 3H), 2.55 (m, 1H), 2.66 (m, 1H), 3.97 (m, 1H), 6.88 (s, 1H), 7.09 (s, 1H).

b. Preparation of 5,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one oxime: To a mixture of 5,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one (2.0 g, 11.48 mmol) and hydroxylamine hydrochloride (1.6 g, 19.73 mmol) in 10 ml of water at 70 °C, were added MeOH (14 mL), THF (3 mL) and a solution of sodium acetate (2.53 g, 30.83 mmol, in 7 mL of H_2O). Stirring was continued for 85 min at 70 °C, at which time a precipitate was formed and 10 ml of water were added. The resulting mixture was stirred at room temperature for 2 hr. Upon completion, the product was collected by filtration to afford 2.12 g of 5,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one oxime (98 %). MS (M+H, 190).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.76 μM.

Example 167

3-chloro-2-hydroxy-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl) benzamide



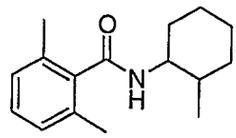
Prepared in similar manner to Example 166using 5-methoxy-1,2,3,4-tetrahydronaphthalen-1-amine (Example 167a). Yield 40 %. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.73 (m, 1H), 1.83 (m, 1H), 1.96 (m, 2H), 2.61 (m, 2H), 3.78 (s, 3H), 5.27 (m, 1H), 6.78 (d, 1H, J = 7.82 Hz), 6.86 (m, 2H), 7.14 (t, 1H, J = 7.98 Hz), 7.60 (dd, 1H, J = 7.88, 1.30 Hz), 7.94 (dd, 1H, J = 8.03, 1.39 Hz), 9.30 (d, 1H, J = 8.06 Hz), 13.80 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 19.5, 22.7, 28.9, 47.4, 55.3, 108.6, 115.8, 118.7, 119.8, 121.1, 125.9, 126.2, 126.4, 133.8, 137.3, 156.7, 156.8, 168.7. MS(M+H, 332). Mp 175-176 °C.

a. 5-methoxy-1,2,3,4-tetrahydronaphthalen-1-amine: Prepared in a similar manner to example 166a using 5-methoxy-3,4-dihydronaphthalen-1(2H)-one. Yield 94 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.63-1.79 (m, 4H), 1.94 (m, 2H), 2.60 (m, 1H), 2.71 (m, 1H), 3.82 (s, 3H), 3.97 (m, 1H), 6.71 (d, 1H), 7.02 (d, 1H), 7.17 (t, 1H).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.21 μM.

Example 168

2,6-dimethyl-N-(2-methylcyclohexyl)benzamide

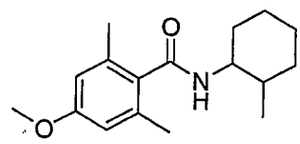


Prepared in a similar manner to Example 162 using 2,6-dimethylbenzoic acid and 2-methylcyclohexylamine.Yield: 59%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88-0.94 (3H, dd), 1.14-1.89 (9H, m), 2.21-2.22 (6H, d), 3.39-3,45 (1H, m), 7.02-7.03 (2H,d), 7.12-7.15 (1H, t), 8.11-8.13 (1H, d). MS(M+H, 246.2).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 1.88 μM.

Example 169

4-methoxy-2,6-dimethyl-N-(2-methylcyclohexyl)benzamide



Prepared in a similar manner to Example 166 using 4-methoxy-2,6-dimethylbenzoic acid (example 169a) and 2-methylcyclohexylamine. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86-0.92 (3H, dd), 1.00-1.85 (m, 9H), 2.18-2.19 (6H, d), 3.33-3.45 (1H, m), 3.71-3.72 (3H, d), 6.59 (2H, s), 7.98-8.05 (1H, m). MS (276.2, M+H).

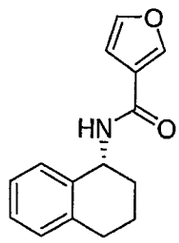
a. 4-methoxy-2,6-dimethylbenzoic acid: 2-Bromo-5-methoxy-1,3-dimethylbenzene (example 169b) (3.38 g , 15.79 mmol) was without further purification dissolved in 100 ml of dry THF. The mixture was cooled to -78°C and under argon n-butyllithium (1.6 M solution in hexanes, 9.9 ml, 15,8 mmol) was added drop wise over 15 min and the mixture was stirred for 15 more min at -78°C. Than small pieces of dry ice were added and the mixture was stirred 20 min at -78°C. Then the cooling was removed and the mixture was stirred as long as evolution of carbon dioxide continued. Then the mixture was poured over ice (100 ml) and acidified using 6N HCl. The organic layer was separated and water phase was extracted with EtOAc. Organic extracts were combined, washed with brine, water, dried over $MgSO_4$ and concentrated under vacuum. The product 4-methoxy-2,6-dimethylbenzoic acid was obtained as a white solid (2.7 g, 95%). (M+H, 181).

b. 2-Bromo-5-methoxy-1,3-dimethylbenzene : 20 mmol of 1-methoxy-3,5-dimethylbenzene (2.82 ml) was dissolved in 100 ml of dry acetonitrile followed by 22 mmol (3.56 g) of N-bromosuccinimide. The mixture was stirred at room temperature overnight. Then the solvent vas evaporated under reduced pressure and a solid was filtered off and washed with hexanes providing 2-bromo-5-methoxy-1,3-dimethylbenzene (3.9 g, 92%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.41 (6H, s), 3.78 (3H, s), 6.67 (2H, s).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 2.1 μM.

Example 170

(R)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)furan-3-carboxamide

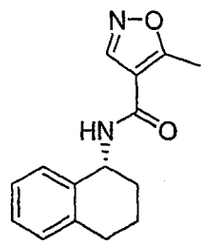


To a solution of furan-3-carboxylic acid (100 mg, 0.68 mmol), HOBt (240 mg, 1.78 mmol) and EDCI·HCl (196 mg, 1.03 mmol) in CH_2Cl_2 (8 mL) and DMF (1.5 mL) at 0 °C, was added (*R*)-1,2,3,4-tetrahydronaphthalen-1-amine (160 μL, 1.06 mmol). The reaction was stirred at rt for 24h, after which CH_2Cl_2 was added. The resulting solution was washed with saturated $NaHCO_3$, H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Recrystallization from EtOH/H_2O afforded (*R*)-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-2,5-dihydrofuran-3-carboxamide. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.89 (m, 3H), 2.12 (m, 1H), 2.84 (m, 2H), 5.35 (m, 1H), 5.96 (br d, 1H, J = 7.75 Hz), 6.59 (dd, 1H, J = 1.90, 0.86 Hz), 7.13 (m, 1H), 7.19 (m, 2H), 7.32 (m, 1H), 7.43 (t, 1H, J = 1.73 Hz), 7.93 (m, 1H). MS(M+H, 242).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 6.6 μM.

Example 171

(*R*)-5-methyl-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide

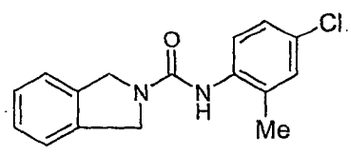


Prepared in a similar manner to Example 170 using 5-methylisoxazole-4-carboxylic acid. Purified by preparative TLC (5:1 Hex:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.80 (m, 3H), 2.12 (m, 1H), 2.74 (s, 3H), 2.85 (m, 2H), 5.35 (m, 1H), 5.89 (br d, 1H, J = 7.75 Hz), 7.10 (m, 1H), 7.18 (m, 2H), 7.32 (m, 1H), 8.26 (s, 1H). MS(M+H, 257).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 8.1 μM.

Example 172

N-(4-chloro-2-methylphenyl)isoindoline-2-carboxamide

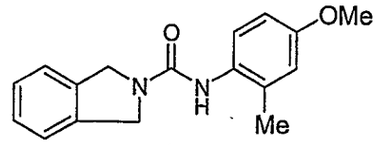


To a solution of isoindoline (238 mg, 2.0 mmol) in dry 1,4-dioxane (10 mL) was added 4-chloro-2-methylphenyl isocyanate (335 mg, 2.0 mmol) under argon at room temperature. The reaction mixture was then stirred at RT overnight. The solvent was evaporated under reduced pressure, and the residue was purified by recrystallization from ethanol to give the title compound (540 mg, 94 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.24 (s, 2H), 4.76 (s, 4H), 7.20 (dd, J = 2.5, 8.5 Hz, 1H), 7.27 (d, J = 2.5 Hz, 1H), 7.30-7.32 (m, 2H), 7.34-7.37 (m, 2H), 7.42 (d, J = 8.5 Hz, 1H), 7.84 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 17.7, 51.9, 122.8, 125.6, 126.8, 127.3, 128.1, 129.5, 134.7, 136.8, 154.2; MS(MH^+, 287); EA calc'd for $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.27; N, 9.77; Found C, 66.82; H, 5.41; N, 9.92.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.89 μM.

Example 173

N-(4-methoxy-2-methylphenyl)isoindoline-2-carboxamide

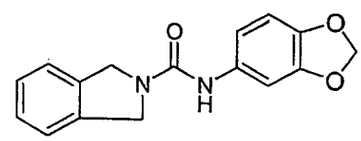


To a solution of isoindoline (576 mg, 4.0 mmol) in dry 1,4-dioxane (20 mL) was added 4-methoxy-2-methylphenyl isocyanate (815 mg, 5.0 mmol) under argon at room temperature. The reaction mixture was then stirred at RT overnight. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (EtOAc/hexanes: 1:1) to give the title compound (1.18 g, 84 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.19 (s, 3H), 3.72 (s, 3H), 4.73 (s, 4H), 6.72 (dd, J = 2.5 Hz, 8.5 Hz, 1H), 6.78 (d, J = 2.5 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.30-7.32 (m, 2H), 7.34-7.36 (m, 2H), 7.74 (s, 1H), ^{13}C NMR (DMSO-d_6): δ 18.2, 51.9, 55.1, 110.9, 115.1, 122.8, 127.2, 127.8, 130.6, 135.1, 137.0, 154.9, 156.5; MS(MH^+, 283); EA calc'd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92; Found C, 72.16; H, 6.82; N, 9.98.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 4.5 μM.

Example 174

N-(3,4-methylenedioxyphenyl)isoindoline-2-carboxamide

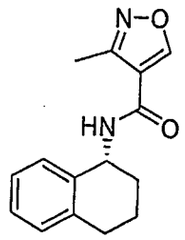


To a solution of 3,4-(methylenedioxy)aniline (150 mg, 1.09 mmol) in dry DCM (4 mL) was added dropwise phenyl chloroformate (0.138 ml, 1.09 mmol) and triethylamine (0.153 ml, 1.09 mmol). After the reaction mixture was stirred at r.t for 8 hr., isoindoline (0.123 ml, 1.09 mmol) and triethylamine (0.153 ml, 1.09 mmo) were added, and the reaction mixture was stirred overnight. The solvent was then removed under reduced pressure, and the residue was purified by chromatographed on silica gel (EtOAC/Hexane: 1:3) to give the title compound (185 mg, 60%) as a white solid: m.p:165-166 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 4.82 (s, 4H); 5.93 (s, 2H); 6.20 (s, 1H); 6.73 (s, 2H); 7.17 (s, 1H); 7.30 (m, 4H). MS (MH^+, 283).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 1.05 μM.

Example 175

3-Methyl-isoxazole-4-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-1-yl)-amide

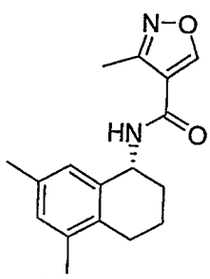


To a solution of 3-Methyl-isoxazole-4-carboxylic acid (0.52 g, 4.06 mmol) in DCM (15 mL) and DMF (2 mL), was added HOBt (1.1 g, 8.14 mmol) and EDCI (0.896 g 4.67 mmol). The clear yellow solution was cooled to 0 C and allowed to stir under Ar for 15 minutes. To the solution was added (R)-1-Amino-1,2,3,4-tetrahydronaphthalene (0.73 mL, 5.04 mmoland the reaction mixture was allowed to slowly warm to ambient temperature and was stirred for overnight. Dilution with DCM (50 mL) was followed by aqueous extraction ($NaHCO_3$ water, brine (50 mL), drying over $MgSO_4$, filtration and removal of solvent *in vacuo*. Silica gel chromatography (0 – 25% Hexane:EtOAc) afforded the title compound (650 mg; 62.5 %) as a sticky solid. ^1H NMR ($CDCl_3$) δ 1.88 (m, 3H), 2.12 (m, 1H), 2.51 (s, 3H), 2.81 (m, 2H), 5.32 (m, 1H), 5.99 (bd, 1H), 7.13 (m, 1H), 7.20 (m, 2H) 7.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.22, 20.15, 29.41, 30.35, 47.93, 116.73, 126.72, 127.88, 128.88, 129.65, 136.25, 138.00, 158.45, 160.28. ESIMS: 257 (M^+H) EA calc'd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93; found C, 70.61; H, 6.11; N, 11.09.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 5.8μM.

Example 176

(*R*)-*N*-(5,7-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylisoxazole-4-carboxamide



To a solution of 3-methylisoxazole-4-carboxylic acid (41.7 mg, 0.339 mmol) in 3 mL DMF were added EDCI·HCl (71 mg, 0.373 mmol) and HOBt (50 mg, 0.373 mmol). The mixture was stirred at rt for 20 min, at which time (*R*)-5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-amine (example a) (65 mg, 0.37 mmol) was added. The reaction mixture was stirred at rt overnight, diluted with EtOAc, washed successively with 1 N HCl, H_2O, sat'd $NaHCO_3$, H_2O and brine. The resulting solution was dried over $MgSO_4$, filtered, concentrated *in vacuo* and flash-column chromatographed (15-20 % EtOAc in hexane) to yield (*R*)-*N*-(5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylisoxazole-4-carboxamide (55 mg, 57 % from (*S*)-2-((*R*)-5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ylamino)-2-phenylethanol (example b). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.74 (m, 2H), 1.86 (m, 2H), 2.16 (s, 3H), 2.19 (s, 3H), 2.43 (s, 3H), 2.55 (m, 2H), 5.10 (m, 1H), 6.86 (s, 1H), 6.89 (s, 1H), 8.60 (d, 1H, J = 8.40 Hz), 9.27 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.6, 19.1, 19.6, 20.6, 25.8, 29.4, 46.9, 115.4, 126.4, 129.1, 132.6, 134.1, 135.8, 136.6, 158.5, 159.6, 159.9. MS(M+H, 285). Mp = 124-125 ^{0}C.

a. Preparation of (*R*)-5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-amine: To a solution of (*S*)-2-((*R*)-5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ylamino)-2-phenylethanol (example b) (100 mg, 0.339 mmol) in 2.5 mL of MeOH at rt were added methylamine (1.4 mL, 2 M solution in MeOH) and periodic acid (200 mg, 0.880 mmol, in 2 mL H_2O). The reaction mixture was stirred at rt for 4 h, at which time it was extracted with ether. To the combined ether extracts was added 2 mL of 2N HCl, and the biphasic mixture was stirred for 30 min, concentrated in vacuo, and the remaining aqueous phase was washed with ether, basified with 6 N NaOH solution at 0 ^{0}C, extracted with ether, dried over K_2CO_3, filtered and concentrated *in vacuo* to yield 65 mg of crude (*R*)-5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-amine, carried onto the next step without further purification.

b. Preparation of (*S*)-2-((*R*)-5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ylamino)-2-phenylethanol: To a solution of (*S*)-2-(5,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-ylideneamino)-2-phenylethanol (example c) (908 mg, 3.10 mmol) dissolved in 15 mL anhydrous THF was added glacial acetic acid. The mixture was cooled to 0 °C, at which time $NaBH_4$ was slowly added. The reaction was stirred under Ar at 0 °C for 2h, at which time 15 mL CH_2Cl_2 were added followed by 10 mL sat'd $NaHCO_3$. The organic layer was separated and washed successively with sat'd $NaHCO_3$ (4 x 20 mL) and brine (1x). The solution was dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash-column chromatography (4:1 Hex:EtOAc) to yield (*S*)-2-((*R*)-5,7-dimethyl-1,2,3,4-

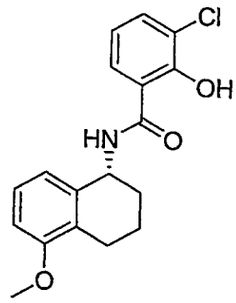
tetrahydronaphthalen-1-ylamino)-2-phenylethanol as a white waxy solid (30 % from tetralone). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (m, 1H), 1.55 (m, 2H), 1.90 (m, 1H), 2.11 (s, 3H), 2.22 (s, 3H), 2.35 (ddd, 1H, J = 17.32, 10.84, 6.47 Hz), 2.57 (m, 1H), 3.25 (ddd, 1H, J = 10.63, 8.90, 6.01 Hz), 3.41 (dt, 1H, J = 10.70, 4.65 Hz), 3.50 (bs, 1H), 3.86 (dd, 1H; J = 8.70, 4.23 Hz), 4.93 (t, 1H, J = 5.44 Hz), 6.82 (s, 1H), 6.85 (s, 1H), 7.24 (td, 1H, J = 7.22, 1.22 Hz), 7.34 (t, 2H, J = 7.42 Hz), 7.42 (dd, 2H, J = 7.08, 1.28 Hz). MS(M+H, 296).

c. Preparation of (*S*)-2-(5,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-ylideneamino)-2-phenylethanol: To a 50 mL round-bottom flask equipped with a Dean-Stark trap and reflux condenser were added 5,7-dimethyl tetralone (540 mg, 3.10 mmol), (*S*)-phenylglycinol (468 mg, 3.40 mmol), toluenesulfonic acid monohydrate (30 mg, 0.16 mmol) and xylenes (30 mL). The reaction was refluxed for 8h, cooled to rt, diluted with toluene and washed successively with sat'd $NaHCO_3$ (1x), H_2O (5x) and brine (1x). The resulting solution was dried over $MgSO_4$, filtered, concentrated *in vacuo* and carried onto the next step without further purification.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.52 μM.

Example 177

(*R*)-3-Chloro-2-hydroxy-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl) benzamide

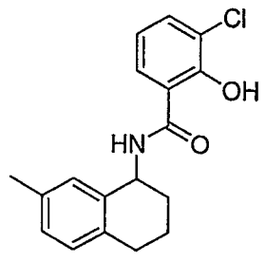


Prepared in a similar manner to Example 176 starting from 5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one. The amide coupling was performed using 3-chlorosalicylic acid. Yield 27 % overall. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.73 (m, 1H), 1.83 (m, 1H), 1.96 (m, 2H), 2.61 (m, 2H), 3.78 (s, 3H), 5.27 (m, 1H), 6.78 (d, 1H, J = 7.82 Hz), 6.86 (m, 2H), 7.14 (t, 1H, J = 7.98 Hz), 7.60 (dd, 1H, J = 7.88, 1.30 Hz), 7.94 (dd, 1H, J = 8.03, 1.39 Hz), 9.30 (d, 1H, J = 8.06 Hz), 13.80 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 19.5, 22.7, 28.9, 47.4, 55.3, 108.6, 115.8, 118.7, 119.8, 121.1, 125.9, 126.2, 126.4, 133.8, 137.3, 156.7, 156.8, 168.7. MS(M+H, 332). Mp 175-176 °C.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.18 μM.

Example 178

3-Chloro-2-hydroxy-*N*-(7-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide



To a solution of 3-chlorosalicylic acid (33 mg, 0.19 mmol), HOBt (28 mg, 0.21 mmol) and EDCI·HCl (40 mg, 0.21 mmol) dissolved in 1 mL DMF was added a solution of 7-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (example a) (33 mg, 0.20 mmol) in 1 mL DMF. The resulting mixture was stirred at rt for 24 h, at which time it was concentrated *in vacuo* and purified by preparative LCMS to yield 3-chloro-2-hydroxy-*N*-(7-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.74 (m, 1H), 1.82 (m, 1H), 1.97 (m, 2H), 2.21 (s, 3H), 2.73 (m, 2H), 5.26 (m, 1H), 6.89 (m, 1H), 6.98 (s, 1H), 7.02 (t, 2H, J = 8.32 Hz), 7.60 (m, 1H), 7.95 (m, 1H), 9.32 (m, 1H), 13.83 (s, 1H). MS(M+H, 316).

a. Preparation of 7-methyl-1, 2,3,4-tetrahydronaphthalen-1-amine: A catalytic amount of Raney nickel (slurry in water) was washed with dry MeOH under argon in a round bottom flask. To a solution of the washed Raney Ni in methanolic ammonia (15 mL, 7N), was added 7-methyl-3,4-dihydronaphthalen-1(2*H*)-one oxime (example b) (218 mg, 1.24 mmol), and the mixture was stirred under a balloon of H_2 for 20 h. Upon completion, the reaction was filtered through celite, the filtrate was concentrated *in vacuo*, diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford 7-methyl-1,2,3,4-tetrahydronaphthalen-1-amine as a brown syrup, carried onto next step without further purification. MS(M+H, 161).

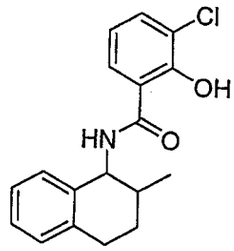
b. To a solution of 7-methyl-3,4-dihydronaphthalen-1(2*H*)-one (200 mg, 1.24 mmol) and hydroxylamine hydrochloride (148 mg, 2.12 mmol) in 1.08 mL H_2O, 1.52 mL MeOH and 320 μL THF, was added a solution of sodium acetate (274 mg, 3.34 mmol) dissolved in 760 μL H_2O. The mixture was stirred at 70 ^{0}C for 2 h, cooled to rt and diluted with 2 mL of H_2O. The resulting mixture was stirred for 96 h, the water was pipetted away

from the resulting syrup and the residual H_2O was azeotroped with toluene to yield a brown syrup, carried onto the next step without further purification.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 1.48 μM.

Example 179

3-Chloro-2-hydroxy-*N*-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide

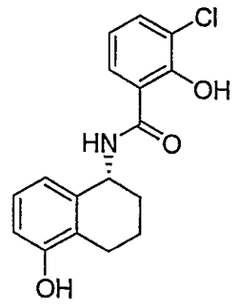


Prepared in a similar manner to Example 178 starting from 2-methyl-3,4-dihydronaphthalen-1(2*H*)-one to yield two mixtures of isomeric products (170 mg, 49 %). MS(M+H, 316). Mp of mixture 161-162 °C. Product A: ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.00 (d, 3H, J = 6.80 Hz), 1.64 (qd, 1H, J = 11.47, 5.90 Hz), 2.09 (m, 1H), 5.39 (dd, 1H, J = 9.08, 4.77 Hz), 6.89 (t, 1H, J = 7.94 Hz), 7.17 (m, 4H), 7.59 (dd, 1H, J = 7.88, 1.38 Hz), 8.00 (dd, 1H, J = 8.17, 1.42 Hz), 8.96 (d, 1H, J = 9.07 Hz), 13.70 (s, 1H).). ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.0, 25.5, 28.4, 32.6, 39.0, 49.9, 115.9, 118.6, 121.1, 125.9, 126.5, 127.2, 128.8, 129.5, 133.8, 133.9, 136.3, 137.0, 156.6, 168.8. Product B: ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.00 (d, 3H, J = 6.80 Hz), 1.64 (qd, 1H, J = 11.47, 5.90 Hz), 2.09 (m, 1H), 5.39 (dd, 1H, J = 9.08, 4.77 Hz), 6.89 (t, 1H, J = 7.94 Hz), 7.17 (m, 4H), 7.59 (dd, 1H, J = 7.88, 1.38 Hz), 8.00 (dd, 1H, J = 8.17, 1.42 Hz), 8.96 (d, 1H, J = 8.92 Hz), 13.85 (s, 1H).). ^{13}C NMR (125 MHz, DMSO-d_6): δ 19.0, 28.4, 29.7, 34.4, 54.2, 115.7, 118.8, 121.2, 125.9, 126.0, 126.7, 127.2, 128.6, 133.9, 136.6, 137.0, 156.9, 169.6.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.38 μM.

Example 180

3-Chloro-2-hydroxy-*N*-(5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide

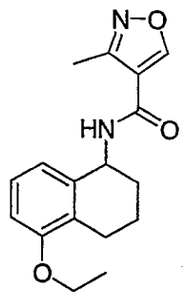


Prepared in a similar manner to Example 178 starting from 5-hydroxy-3,4-dihydronaphthalen-1(2H)-one, and the pure enantiomer was isolated using chiral HPLC purification. MS(M+H, 318). Mp 148-151 °C.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 1.17 μM.

Example 181

3-Chloro-*N*-(5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-2-hydroxybenzamide



Prepared in a similar manner to Example 178 starting from 5-ethoxy-3,4-dihydronaphthalen-1(2*H*)-one (example a). The amide coupling was performed using 3-methylisoxazole-4-carboxylic acid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.33 (t, 3H, J = 6.98 Hz), 1.73 (m, 2H), 1.89 (m, 2H), 2.42 (s, 3H), 2.60 (m, 2H), 4.01 (m, 2H), 5.12 (m, 1H), 6.81 (t, 2H, J = 8.65 Hz), 7.11 (t, 1H, J = 7.94 Hz), 8.62 (d, 1H, J = 8.51 Hz), 9.26 (s, 1H). MS(M+H, 301).

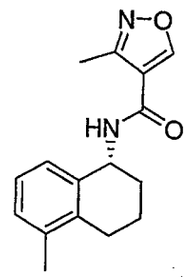
a. Preparation of 5-ethoxy-3,4-dihydronaphthalen-1(2*H*)-one: To a solution of 5-hydroxy-3,4-dihydronaphthalen-1(2*H*)-one (600 mg, 3.70 mmol) and K_2CO_3 (2.56 g, 18.5 mmol) in 18 mL DMF, was added ethyl iodide (1.48 mL, 18.5 mmol). The reaction was heated to 180 ^{0}C for 20 min in a microwave reactor. Upon completion, the reaction was diluted with EtOAc, washed with 1N HCl (2x), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting red crystals were purified by flash-column

chromatography (2:1 Hex:EtOAc) to obtain 5-ethoxy-3,4-dihydronaphthalen-1(2*H*)-one as a light yellow solid (490 mg, 70 %). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.36 (t, 3H, J = 6.95 Hz), 2.01 (quint, 2H, J = 6.48 Hz), 2.54 (m, 2H), 2.81 (t, 2H, J = 6.12 Hz), 4.07 (q, 2H, J = 7.00 Hz), 7.19 (dd, 1H, J = 8.02, 0.80 Hz), 7.28 (t, 1H, J = 8.02 Hz), 7.46 (dd, 1H, J = 7.72, 0.96 Hz).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 4.5 μM.

Example 182

(*R*)-3-Methyl-*N*-(5-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide

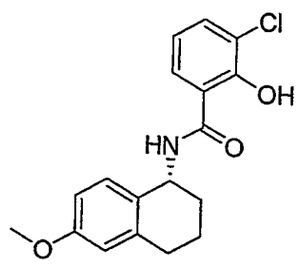


Prepared in a similar manner to Exampl 178 starting from 5-methyl-3,4-dihydronaphthalen-1(2*H*)-one[1]. The amide coupling was performed using 3-methylisoxazole-4-carboxylic acid. The pure enantiomer was isolated using chiral HPLC purification. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.75 (m, 2H), 1.91 (m, 2H), 2.19 (s, 3H), 2.42 (s, 3H), 2.61 (m, 2H), 5.13 (m, 1H), 7.06 (m, 3H), 8.62 (d, 1H, J = 8.51 Hz), 9.25 (s, 1H). MS(M+H, 271).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 2.80μM.

Example 183

(*R*)-3-Chloro-2-hydroxy-*N*-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide



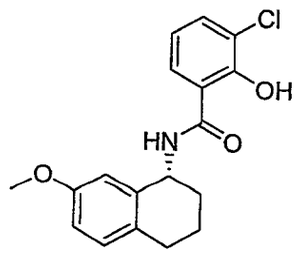
[1] Zhang, X.; De Los Angeles, J. E.; He, M.-Y.; Dalton, J. T.; Shams, G.; Lei, L.; Patil, P. N.; Feller, D. R.; Miller, D. D.; Hsu, F.-L. *J. Med. Chem.* 1997, *40*, 3014-3024.

Prepared in a similar manner to Example 178 starting from 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one. The pure enantiomer was isolated using chiral HPLC purification. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.74 (m, 1H), 1.83 (m, 1H), 1.97 (m, 2H), 2.77 (m, 2H), 3.72 (s, 3H), 5.23 (m, 1H), 6.70 (d, 1H, J = 2.60 Hz), 6.74 (dd, 1H, J = 8.60, 2.78 Hz), 6.87 (t, 1H, J = 8.03 Hz), 7.08 (d, 1H, J = 8.52 Hz), 7.60 (dd, 1H, J = 7.88, 1.38 Hz), 7.94 (dd, 1H, J = 8.13, 1.43 Hz), 9.25 (d, 1H, J = 8.34 Hz), 13.83 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.1, 29.1, 29.6, 46.9, 55.0, 112.5, 113.1, 115.8, 118.6, 121.1, 126.2, 128.4, 129.2, 133.8, 138.7, 156.8, 158.2, 168.7. MS(M+H, 332). Mp 111-113 ^{0}C.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.85μM.

Example 184

(*R*)-3-Chloro-2-hydroxy-*N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide

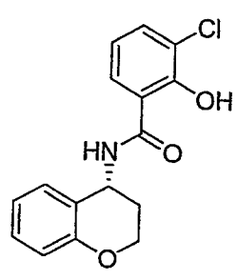


Prepared in a similar manner to Example 178 starting from 7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one. The pure enantiomer was isolated using chiral HPLC purification. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.74 (m, 1H), 1.82 (m, 1H), 1.97 (m, 2H), 2.71 (m, 2H), 3.66 (s, 3H), 5.24 (m, 1H), 6.70 (d, 1H, J = 2.69 Hz), 6.79 (dd, 1H, J = 8.44, 2.78 Hz), 6.87 (t, 1H, J = 7.96 Hz), 7.06 (d, 1H, J = 8.46 Hz), 7.60 (dd, 1H, J = 7.88, 1.28 Hz), 7.95 (dd, 1H, J = 8.01, 2.60 Hz), 9.33 (m, 1H), 13.75 (s, 1H). MS(M+H, 332).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.26μM.

Example 185

(*R*)-3-Chloro-*N*-(3,4-dihydro-2*H*-chromen-4-yl)-2-hydroxybenzamide

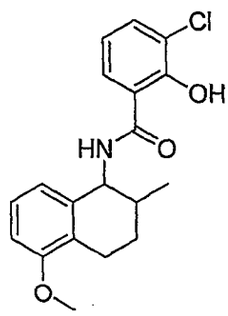


Prepared in a similar manner to Example 178 starting from 2,3-dihydrochromen-4-one. The pure enantiomer was isolated using chiral HPLC purification. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.12 (m, 2H), 4.27 (m, 2H), 5.33 (m, 1H), 6.81 (d, 1H, J = 8.27 Hz), 6.89 (td, 2H, J = 7.49, 0.72 Hz), 7.17 (d, 2H, J = 7.40 Hz), 7.60 (d, 1H, J = 7.32 Hz), 7.93 (d, 1H, J = 8.03 Hz), 9.40 (br. s, 1H), 13.65 (s, 1H). MS(M+H, 304).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 1.03μM.

Example 186

3-Chloro-2-hydroxy-*N*-(5-methoxy-2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide



Prepared in a similar manner to Example 178 starting from 5-methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (example a) to provide a mixture of two sets of enantiomers. Enantiomeric pair A: ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.92 (d, 3H, J = 6.78 Hz), 1.67 (m, 1H), 1.76 (m, 1H), 2.02 (m, 2H), 2.80 (m, 1H), 3.79 (s, 3H), 5.34 (m, 1H), 6.79 (d, 1H, J = 7.69), 6.84 (d, 1H, J = 7.82 Hz), 7.13 (t, 1H, J = 7.90 Hz), 7.56 (m, 1H), 7.93 (m, 1H), 8.90 (br. s, 1H). MS(M+H, 346). Enantiomeric pair B: ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.99 (d, 3H, J = 6.47 Hz), 1.55 (m, 1H), 1.67 (m, 1H), 1.76 (m, 1H), 2.02 (m, 2H), 2.80 (m, 1H), 3.78 (s, 3H), 4.92 (m, 1H), 6.72 (d, 1H, J = 7.85 Hz), 6.84 (m, 1H), 7.13 (m, 1H), 7.56 (m, 1H), 7.93 (m, 1H), 9.25 (br. s, 1H). MS(M+H, 346).

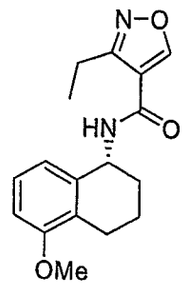
a. Preparation of 5-methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one: To a solution of LDA (2.85 mL, 2.0 M solution in heptane/THF/ethylbenzene) in 2 mL THF at –78 ^{0}C was added a solution of 5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (1.00 g, 5.70 mmol) in 2 mL THF. The mixture was stirred at -78 ^{0}C for 20 min, at which time MeI was added dropwise. The reaction was warmed to rt over 17 h and quenched with sat'd NH_4Cl. The suspension was extracted with Et_2O, dried over $MgSO_4$, filtered, concentrated *in vacuo* and flash-column chromatographed (9:1 Hex:EtOAc) to yield 5-methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one as a clear oil (374 mg, 35 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ

1.24 (d, 3H, J = 6.72 Hz), 1.83 (m, 1H), 2.20 (dq, 1H, J = 13.32, 4.50 Hz), 2.58 (m, 1H), 2.74 (ddd, 1H, J = 16.66, 11.35, 4.92 Hz), 3.08 (dt, 1H, J = 17.80, 4.32 Hz), 3.86 (s, 3H), 7.00 (dd, 1H, J = 7.90, 0.70 Hz), 7.26 (t, 1H, J = 7.82 Hz), 7.64 (dd, 1H, J = 7.86, 0.72 Hz).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.50μM.

Example 187

(*R*)-3-Ethyl-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide



To a solution of 3-ethylisoxazole-4-carboxylic acid (example a) (30 mg, 0.21 mmol), HOBt (41 mg, 0.30 mmol) and EDCI·HCl (58 mg, 0.30 mmol) dissolved in 2 mL DMF, was added (*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-amine (example c) (53 mg, 0.30 mmol). The reaction was stirred at rt for 24 h, at which time it was concentrated *in vacuo* and purified by preparative TLC (10:1 Hex:EtOAc) to provide (*R*)-3-Ethyl-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 1.30 (t, 3H, J = 7.20 Hz), 1.84 (m, 2H), 1.97 (m, 2H), 2.68 (m, 2H), 2.96 (q, 2H, J = 7.60 Hz), 3.81 (s, 3H), 5.21 (m, 1H), 6.80 (d, 1H, J = 7.60 Hz), 6.85 (d, 1H, J = 7.60 Hz), 7.14 (d, 1H, J = 8.00 Hz), 8.98 (s, 1H). MS(M+H, 301).

a. Preparation of 3-ethylisoxazole-4-carboxylic acid: To a solution of ethyl 3-ethylisoxazole-4-carboxylate (example b) (422 mg, 2.49 mmol) in 2 mL of 1:1 EtOH:H_2O, was added NaOH (110 mg, 2.74 mmol). The reaction was stirred at rt for 24 h, at which time it was neutralized with 1N HCl, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a white solid carried onto next step without further purification.

b. Preparation of ethyl 3-ethylisoxazole-4-carboxylate: To a solution was prepared by the method of McMurry, J. E.; *Org. Syn. Coll.* Vol. 6, 781, of ethyl 3-(pyrrolidin-1-yl)acrylate (2.0 g, 11.8 mmol), Et_3N (4.7 mL) and nitropropane (1.38 mL, 15.4 mmol) in 12 mL $CHCl_3$ at 0 ^{0}C, was added a solution of $POCl_3$ (1.21 mL, 13.00 mmol) in 2.5 mL $CHCl_3$ via addition funnel over 3 h. Upon complete addition of $POCl_3$ mixture,

the reaction was warmed to rt, stirred for 20 h and quenched with H_2O. The organic layer was separated and washed successively with 1N HCl, 5 % NaOH and brine. The resulting solution was dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash-column chromatography (4:1 Hex:EtOAc) to yield ethyl 3-ethylisoxazole-4-carboxylate as a white solid (1.43 g, 72 %). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.21 (t, 3H, J = 7.62 Hz), 1.28 (t, 3H, J = 7.30 Hz), 2.85 (q, 2H, J = 7.47 Hz), 4.26 (q, 2H, J = 6.98 Hz), 9.51 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 11.9, 14.0, 18.5, 60.5, 79.1, 160.8, 162.7, 164.7, 164.8.

c. Preparation of (*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-amine: To a solution of (*S*)-2-((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylamino)-2-phenylethanol (example d) (3.22 g, 10.83 mmol) in 70 mL of MeOH at 0 ^{0}C were added methylamine (7.5 mL, 40 % solution in H_2O) and periodic acid (6.4 g, 28.15 mmol, in 50 mL H_2O). The reaction mixture was stirred at rt for 4 h, at which time it was extracted with ether. To the combined ether extracts was added 30 mL of 2N HCl, and the biphasic mixture was stirred for 30 min, concentrated *in vacuo*, and the remaining aqueous phase was washed with ether, basified with 6 N NaOH solution at 0 ^{0}C, extracted with ether, dried over K_2CO_3, filtered and concentrated *in vacuo* to yield 1.72 g of crude (*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-amine (90 %), carried onto the next step without further purification.

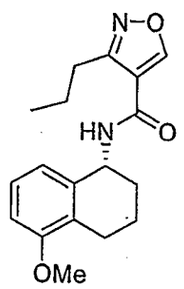
d. Preparation of (*S*)-2-((*R*)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylamino)-2-phenylethanol: To a solution of $NaBH_4$ (781 mg, 20.63 mmol), dissolved in 40 mL anhydrous THF under Ar at 0 ^{0}C, was added glacial acetic acid (3.48 mL, 60.10 mmol) dropwise. The mixture was stirred at 0 ^{0}C for 15 min or until the gas evolution was complete. A solution of (*S*)-2-(5-methoxy-3,4-dihydronaphthalen-1(2*H*)-ylideneamino)-2-phenylethanol (example e) (5.3 g, 17.94 mmol) dissolved in 25 mL anhydrous THF was added to the $NaBH(OAc)_3$ mixture, and the reaction was stirred for 3 h at 0 ^{0}C. Upon completion, the reaction was quenched by addition of sat'd K2CO3, diluted with EtOAc, and the organic layer was dried over MgSO4, filtered, concentrated in vacuo and purified by flash-column chromatography (15-25 % EtOAc in Hex) to yield (*S*)-2-((*R*)-5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ylamino)-2-phenylethanol as a white waxy solid (3.22 g, 60 % from tetralone). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.70 (m, 3H), 1.84 (m, 1H), 2.51 (m, 1H), 2.74 (m, 1H), 3.50 (dd, 1H, J = 10.73, 7.95 Hz), 3.71 (dd, 1H, J = 10.76, 4.67 Hz), 3.77 (m, 1H), 3.81 (s, 3H), 3.99 (dd, 1H, J = 7.95, 4.60 Hz), 6.72 (d, 1H, J = 7.98 Hz), 6.96 (d, 1H, J = 7.70 Hz), 7.15 (t, 1H, J = 7.90 Hz), 7.29 (m, 1H), 7.36 (m, 4H). MS(M+H, 298).

e. Preparation of (*S*)-2-(5-methoxy-3,4-dihydronaphthalen-1(2*H*)-ylideneamino)-2-phenylethanol: To a 50 mL round-bottom flask equipped with a Dean-Stark trap and reflux condenser were added 5-methoxy tetralone (3.7 g, 21.0 mmol), (*S*)-phenylglycinol (3.17 g, 23.1 mmol), toluenesulfonic acid monohydrate (200 mg, 1.05 mmol) and xylenes (40 mL). The reaction was refluxed overnight, cooled to rt, diluted with toluene and washed successively with sat'd $NaHCO_3$ (1x), H_2O (5x) and brine (1x). The resulting solution was dried over $MgSO_4$, filtered, concentrated *in vacuo* and carried onto the next step without further purification.

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.40 μM.

Example 188

(*R*)-3-Propyl-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide

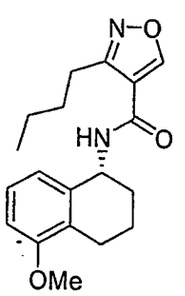


Prepared in a similar manner to Example 187 using 3-propylisoxazole-4-carboxylic acid. ^{1}H NMR (400 MHz, CD_3OD): δ 1.01 (t, 3H, *J* = 7.60 Hz), 1.74 (sext, 2H, *J* = 8.00 Hz), 1.83 (m, 2H), 1.96 (m, 2H), 2.67 (m, 2H), 2.90 (t, 2H, *J* = 7.20 Hz), 3.80 (s, 3H), 5.20 (m, 1H), 6.80 (d, 1H, *J* = 7.60 Hz), 6.85 (d, 1H, *J* = 7.60 Hz), 7.14 (d, 1H, *J* = 8.00 Hz), 8.98 (s, 1H). MS(M+H, 315).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.24 μM.

Example 189

(*R*)-3-Butyl-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide

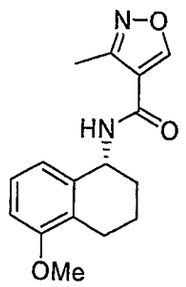


Prepared in a similar manner to Example 187 using 3-butylisoxazole-4-carboxylic acid. ^{1}H NMR (400 MHz, CD_3OD): δ 0.96 (t, 3H, J = 7.20 Hz), 1.40 (sext, 2H, J = 6.80 Hz), 1.69 (quint, 2H, J = 7.60 Hz), 1.84 (m, 2H), 1.97 (m, 2H), 2.67 (m, 2H), 2.92 (t, 2H, J = 7.20 Hz), 3.80 (s, 3H), 5.20 (m, 1H), 6.80 (d, 1H, J = 7.60 Hz), 6.85 (d, 1H, J = 7.60 Hz), 7.14 (d, 1H, J = 8.00 Hz), 8.98 (s, 1H). MS(M+H, 329).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.36 μM.

Example 190

(*R*)-3-methyl-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide

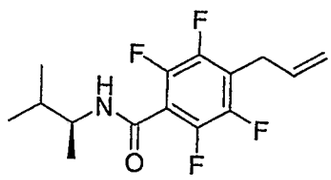


Prepared in a similar manner to Example 187 using 3-methylisoxazole-4-carboxylic acid. ^{1}H NMR (400 MHz, CD_3OD): δ 1.84 (m, 3H), 1.97 (m, 3H), 2.48 (s, 3H), 3.80 (s, 3H), 5.21 (m, 1H), 6.80 (d, 1H, J = 7.60 Hz), 6.85 (d, 1H, J = 7.60 Hz), 7.14 (d, 1H, J = 8.00 Hz), 8.98 (s, 1H). MS(M+H, 287).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.95 μM.

Example 191

(S)-4-allyl-2,3,5,6-tetrafluoro-N-(3-methylbutan-2-yl)benzamide



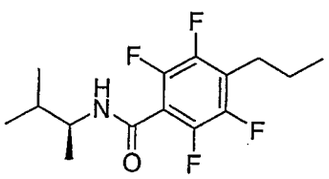
In a Smith process vial was added 2,3,5,6 -tetrafluoro-4-allylbenzoic acid (238 mg, 1.02 mmol), HOBt (260 mg, 2.13 mmol), EDCI (225 mg 1.18 mmol), triethylamine (0.160 mL, 1.15 mmol), ACN (2.5 mL) and DMF (0.5 mL). To the solution was added (S)-3-methylbutan-2-amine (163.3 uL, 1.24 mmol) and the solution was sealed and transferred to

the microwave. After heating in the microwave (150 °C, 5 min fixed hold time), the reaction mixture was diluted with DCM, washed with 1N HCl, water, aqueous $NaHCO_3$, water and brine, dried over MgSO4, filtered and solvent was removed in vacuo, to give the crude product as a pale yellow solid. Recrystallization from EtOH/H_2O gave the title compound as white needles (105 mg, 34%). ^{1}H NMR (DMSO-d6) δ 0.88 (d, J = 6.8 Hz, 6H) 1.07 (d, J = 6.8 Hz, 3H), 1.70 (m, 1H), 3.50 (d, J = 6 Hz, 2H), 3.83 (m, 1H), 5.02 (d, J = 17 Hz, 1H), 5.10 (dd, J = 1.3, 10.1 Hz, 1H), 5.94 (m, 1H), 8.64 (d, J = 8.6 Hz, 1H). MS (304.1, M + H).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.14 μM.

Example 192

(S)- 2,3,5,6-tetrafluoro-N-(3-methylbutan-2-yl)-4-propylbenzamide

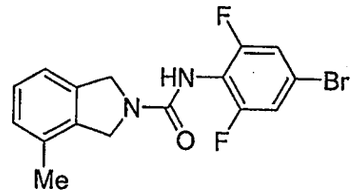


In a Smith process vial was added (S)-4-allyl-2,3,5,6-tetrafluoro-N-(3-methylbutan-2-yl)benzamide (see Example 191) (80.3 mg, 0.26 mmol), ammonium formate (86 mg, 5 eq), Pd/C (10%, 9.2 mg) and EtOH (2.5 mL). The solution was sealed and transferred to the microwave. After heating in the microwave (140° C, 6 min fixed hold time), the reaction mixture was diluted with acetonitrile (2 mL), filtered through Celite, and volatile solvents were removed in vacuo, to give the crude product as a pale yellow solid (93 mg). Recrystallization from EtOH/water gave the title compound as white whispery crystals (45 mg, 56%). 1H NMR (DMSO-d6) δ 0.88 (s, 9H), 0.90 (m, 9H), 1.05 (d, J = 6.8 Hz, 3 H), 1.60 (m, 2 H), 1.70 (m, 1H), 2.71 (t, J = 7. 5 Hz, 2H), 3.80 (m, 1H), 8.64 (d, J= 8.8 Hz, 1H). MS (306.3, M+H).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.14 μM.

Example 193

N-(4-bromo-2,6-difluorophenyl)-4-methylisoindoline-2-carboxamide



Prepared in a similar manner to Example 172 using 2,6-difluoro-4-bromophenyl isocyanate and 4-methylisoindoline (**Example 193a**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.25 (s, 3H), 4.65 (s, 2H), 4.71 (s, 2H), 7.10 (d, J = 7.4 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.52 (d, J = 7.1 Hz, 2H), 8.29 (s, 1H). MS (MH^+, 369, 367).

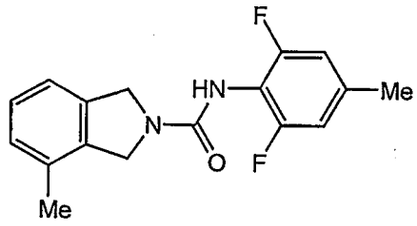
The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.02 μM.

Example 193a: 4-Methylisoindoline: A solution of 3-methylphthalimide (1.61 g, 10.0 mmol; **Example 193b**) and borane methyl sulfide complex (2.0 M solution in THF, 20 mL, 40.0 mmol) in dry THF (20 mL) was refluxed under argon for 48 h. After it was cooled down to 0 °C, the reaction mixture was carefully quenched with MeOH (10 mL), and then with 3 N HCl (10 mL). The solution was then refluxed for another 2 h, and cooled down to 0 °C again with an ice bath, and neutralized with 3 N NaOH. The mixture was extracted with Et_2O (3X), and the combined organic layers were washed with brine, dried over solid NaOH. Evaporation of the solvent gave the crude 4-methylisoindoline as brown oil which was used directly in the urea synthesis without further purification. MS (MH^+, 134).

Example 193b: 3-Methylphthalimide: A stirred powder of 3-methylphthalic anhydride (3.24 g, 20.0 mmol) was treated with concentrated ammonia solution (~ 28 %, 10 mL). The solution was gradually heated to 250 °C until the mixture was in a state of quiet fusion. It required about one hour before all the water had gone and about another one hour before the temperature of the reaction mixture reached 250 °C and the mixture was a homogeneous melt. The hot reaction mixture was cooled down and solidified to give 3-methylphthalimide as an off-white solid which was practically pure without further treatment. The analytical sample was purified by sublimation to give 3-methylphthalimide as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.59 (s, 3H), 7.59 (d, J = 7.4 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.67 (t, J = 7.4 Hz, 1H), 10.35 (b, 1H). MS (MH^+, 162).

Example 194

N-(2,6-difluoro-4-methylphenyl)-4-methylisoindoline-2-carboxamide

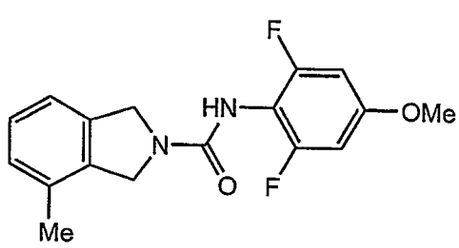


Methylmagnesium chloride (3.0 M in THF, 0.1 mL, 0.3 mmol) was added slowly to anhydrous $ZnCl_2$ (68 mg, 0.3 mmol) in dry THF (1 mL) under argon. The resulted white slurry was stirred at 50 °C for 3 h. In a separate flask a solution of N-(4-bromo-2,6-difluorophenyl)-4-methylisoindoline-2-carboxamide (example 192) (37 mg, 0.1 mmol) in dry THF (2 mL) was sequentially treated with $PdCl_2$(dppf) (8 mg, 0.01 mmol) and CuI (9 mg, 0.05 mmol) under argon. The alkyl zinc slurry that had been stirring at 50 °C for 3 h was added slowly to the above solution. The reaction mixture was then stirred at 65 °C overnight. After it was cooled down to room temperature, the reaction solution was quenched with aqueous NH_4Cl solution, and extracted with methylene chloride (2X). The combined organic layers were washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography on silica (EtOAc/Hexane: 2:8) to give the title compound (24 mg, 79 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 2.30 (s, 3H), 4.66 (s, 2H), 4.70 (s, 2H), 6.95 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 7.4 Hz, 1H), 7.13 (d, J = 7.4 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 8.09 (s, 1H). MS (MH^+, 303).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of .060 μM.

Example 195

N-(2,6-difluoro-4-methoxyphenyl)-4-methylisoindoline-2-carboxamide



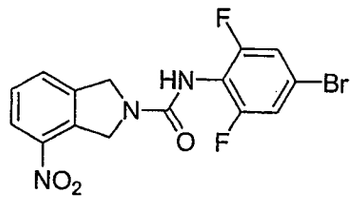
A solution of N-(4-bromo-2,6-difluorophenyl)-4-methylisoindoline-2-carboxamide (example 192) (22 mg, 0.06 mmol) in dry DMF (2 mL) was sequentially treated with CuBr

(6 mg, 0.04 mmol) and MeONa (25 % solution in MeOH, 5.0 equiv.) under argon. The reaction mixture was then stirred at 110 °C for 1 h under argon. After it was cooled down to room temperature, the reaction mixture was neutralized with 1 N HCl, and extracted with EtOAc (2X). The combined organic layers were washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography on silica eluting first with 20 % EtOAc in hexane to give the title compound (7 mg, 37 %) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 3.76 (s, 3H), 4.65 (s, 2H), 4.70 (s, 2H), 6.76 (d, J = 9.4 Hz, 2H), 7.08 (d, J = 7.4 Hz, 1H), 7.13 (d, J = 7.4 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.98 (s, 1H). MS (MH^+, 319).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of .067 μM.

Example 196

N-(4-Bromo-2,6-difluorophenyl)-4-nitroisoindoline-2-carboxamide



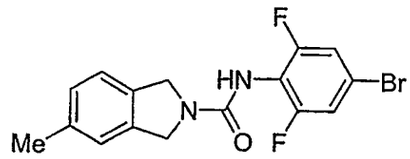
Prepared in a similar manner to Example 172 using 2,6-difluoro-4-bromophenyl isocyanate and 4-nitroisoindoline (**Example 196a**). MS (MH^+, 398, 400).

Example 196a: 4-Nitroisoindoline: A solution of 3-nitrophthalimide (1.95 g, 10.0 mmol) and borane methyl sulfide complex (2.0 M solution in THF, 20 mL, 20.0 mmol) in dry THF (20 mL) was refluxed under argon for 48 h. After it was cooled down to 0 °C, the reaction mixture was carefully quenched with MeOH (10 mL), and then with 3 N HCl (10 mL). The solution was then refluxed for another 3 h, and cooled down to 0 °C again with an ice bath, and neutralized with concentrated ammonia solution. The mixture was extracted with Et_2O (3X), and the combined organic layers were washed with brine, dried over solid Na_2SO_4. Evaporation of the solvent gave the crude 4-nitroisoindoline as brown oil which was used directly in the urea synthesis without further treatment. MS (MH^+, 165).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 1.07 μM.

Example 197

N-(4-Bromo-2,6-difluorophenyl)-5-methylisoindoline-2-carboxamide



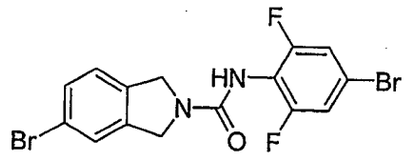
Prepared in a similar manner to Example 172 using 2,6-difluoro-4-bromophenyl isocyanate and 5-methylisoindoline (**Example 197a**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.32 (s, 3H), 4.69 (b, 4H), 7.12 (d, J = 7.8 Hz, 1H), 7.16 (s, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.1 Hz, 2H), 8.25 (s, 1H). MS (MH^+, 369, 367).

Example 197a: 5-Methylisoindoline: A solution of 4-methylphthalimide (1.61 g, 10.0 mmol) and borane methyl sulfide complex (2.0 M solution in THF, 15 mL, 30.0 mmol) in dry THF (10 mL) was refluxed under argon for 3 days. After it was cooled down to 0 °C, the reaction mixture was carefully quenched with MeOH (5 mL), and then with 3 N HCl (10 mL). The solution was then refluxed for another 2 h, and cooled down to 0 °C again with an ice bath, and finally neutralized with 3 N NaOH. The reaction mixture was extracted with Et_2O (3X), and the combined organic layers were washed with brine, dried over solid NaOH. Evaporation of the solvent under vacuum gave the crude 5-methylisoindoline as brown oil which was used directly in the urea synthesis without further purification. MS (MH^+, 134).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.52 μM.

Example 198

5-Bromo-N-(4-bromo-2,6-difluorophenyl)isoindoline-2-carboxamide



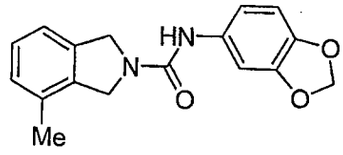
Prepared in a similar manner to Example 172 using 2,6-difluoro-4-bromophenyl isocyanate and 5-bromoisoindoline (**Example 198a**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.69 (bs, 2H), 4.73 (bs, 2H), 7.33 (d, J = 8.2 Hz, 1H), 7.50 (dd, J = 8.2 Hz, 1.7 Hz, 1H), 7.52 (d, J = 7.2 Hz, 2H), 7.59 (s, 1H), 8.31 (s, 1H). MS (MH^+, 433, 431, 435).

Example 198a: 5-Bromoisoindoline: Prepared in a similar manner to Example 192a using 4-bromophthalimide. MS (MH^+, 198, 200).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.42 μM.

Example 199

N-(3,4-(methylenedioxy)phenyl)-4-methylisoindoline-2-carboxamide

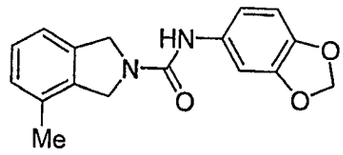


Prepared in a similar manner to Example 172 using 3,4-(methylenedioxy)phenyl isocyanate and 4-methylisoindoline (example 197a). ^{1}H NMR (500 MHz, DMSO-d_6): δ

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.42 μM.

Example 199

N-(3,4-(methylenedioxy)phenyl)-4-methylisoindoline-2-carboxamide



Prepared in a similar manner to Example 172 using 3,4-(methylenedioxy)phenyl isocyanate and 4-methylisoindoline (example 197a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.26 (s, 3H), 4.68 (s, 2H), 4.73 (s, 2H), 5.95 (s, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 7.09-7.22 (m, 3H), 7.25 (d, J = 2.1 Hz, 1H), 8.25 (s, 1H). MS (MH^+, 297).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.95 μM.

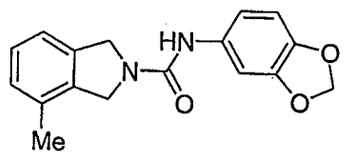
Example 200

(R)-N-(3,3-dimethylbutan-2-yl)-2,6-dimethyl-4-(methylthio)benzamide

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.42 μM.

Example 199

N-(3,4-(methylenedioxy)phenyl)-4-methylisoindoline-2-carboxamide

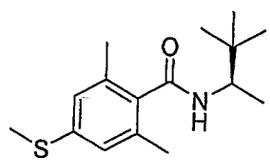


Prepared in a similar manner to Example 172 using 3,4-(methylenedioxy)phenyl isocyanate and 4-methylisoindoline (example 197a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.26 (s, 3H), 4.68 (s, 2H), 4.73 (s, 2H), 5.95 (s, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 7.09-7.22 (m, 3H), 7.25 (d, J = 2.1 Hz, 1H), 8.25 (s, 1H). MS (MH^+, 297).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.95 μM.

Example 200

(R)-N-(3,3-dimethylbutan-2-yl)-2,6-dimethyl-4-(methylthio)benzamide



Prepared in a similar manner to example 13 using (R)-3,3-dimethylbutan-2-amine and 2,6-dimethyl-4-(methylthio)benzoic acid (example 200a). Yield 23%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (s, 9H), 1.03-1.05 (s, 3H), 2.19 (s, 6H), 2.45 (s, 3H), 3.87-3.90 (m, 1H), 6.93 (s, 1H), 7.99-8.00 (d, 1H). MS (M+H, 280).

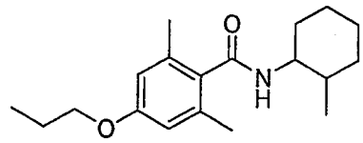
Example 200a: 2,6-dimethyl-4-(methylthio)benzoic acid: 3,5-Dimethylthioanisole (6.6 mmol) in 100 ml of dry acetonitrile was mixed with N-bromosuccinimide (6.6 mmol) and stirred overnight at r.t. The solvent was removed on vacuum and the solid residuum was treated with hexanes. A solid was filtered off, washed with hexanes and hexane fractions were combined and concentrated under reduced pressure providing yellow oil (99%). The crude bromide was dried on vacuum and then diluted with 75 ml of dry THF. The solution was cooled to -78°C under argon and 2.5 M solution of n-BuLi in hexanes (6.7 mmol) was added drop wise over period of 30 min. Then the mixture was stirred for additional 30 min and small pieces of dry ice were immersed in to the solution. After 30 min the cooling bath was removed and the mixture was left to warm to r.t. and stirred for

2 h. The mixture was poured over 100 ml of crushed ice and acidified using 6N HCl to pH 1. Organic phase was separated and water phase was extracted with ethylacetate. Organic extracts were combined and washed with brine and water, dried over $MgSO_4$ and concentrated in vacuum, providing a white solid (98%). ^{1}H NMR (500 MHz, *d*MSO): δ 2.23 (s, 6H), 2.46 (s, 3H), 6.96 (s, 2H), 13.0 (bs, 1H).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 1.02 μM.

Example 201

2,6-dimethyl-N-(2-methylcyclohexyl)-4-propoxybenzamide



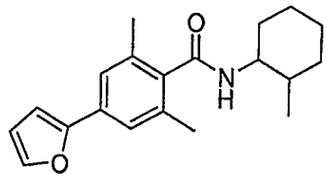
4-Hydroxy-2,6-dimethyl-N-(2-methylcyclohexyl)benzamide (example 201a) (0.38 mmol) was dissolved in 2 ml of a solution of absolute EtOH and 50 mg of KOH. The mixture was stirred at 80°C for 1 h and then propyl iodide (1.5 mmol) was added to the hot mixture drop wise. The mixture was stirred at 80°C overnight. The solvent was evaporated and the material was purified on silica gel. Yield 57%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91-0.97 (m, 6H), 1.03-1.04 (m, 1H), 1.14-1.18 (m, 2H), 1.24-1.26 (m, 1H), 1.35-1.36 (m, 1H), 1.55-1.6 (m, 1H), 1.67-1.73 (m, 4H), 1.84-1.86 (m, 1H), 2.18 (s, 6H), 3.32 (s, 3H), 3.36-3.42 (m, 1H), 3.88-3.90 (t, 2H), 6.58 (s, 2H), 7.98-8.00 (d, 1H). MS (M+H, 304).

Example 201a: 4-hydroxy-2,6-dimethyl-N-(2-methylcyclohexyl)benzamide: 4-Methoxy-2,6-dimethyl-N-(2-methylcyclohexyl)benzamide (example 69) (3 mmol) was dissolved in 30 ml of dry DCM and cooled to -78°C under argon. 1M solution of BBr_3 in DCM (3.3 mmol) was added drop wise and the cooling bath was removed. The mixture was stirred at r.t. for 34 h and then concentrated on vacuum. The residuum was dissolved in ethylacetate and washed with sat. $NaHCO_3$, water and brine. Organic phase was dried over $MgSO_4$ and concentrated on vacuum providing the product as a white foam (95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90-0.91 (s, 3H), 1.03-1.05 (s, 3H), 1.00-1.03 (m, 1H), 1.13-1.17 (m, 2H), 1.25-1.27 (m, 1H), 1.35-1.37 (m, 1H), 1.60-1.62 (d, 1H), 1.62-1.72 (m, 2H), 1.83-1.85 (m, 1H), 2.13 (s, 6H), 3.36-3.42 (m, 1H), 6.40 (s, 2H), 7.93-7.95 (d, 2H). MS (M+H, 262).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 0.69 μM.

Example 202

4-(furan-2-yl)-2,6-dimethyl-N-(2-methylcyclohexyl)benzamide



3,5-dimethyl-4-(2-methylcyclohexylcarbamoyl)phenyl trifluoromethanesulfonate (example 202a) (0.25 mmol) was dissolved in 10 ml of toluene, 2 ml of EtOH and 1.5 ml of water. Furan-2-ylboronic acid (0.25 mmol) and K_2CO_3 (0.5 mmol) was added and the mixture was degassed using an argon stream (20 min). Then a catalyst, $Pd(PPh_3)_4$ was added and the mixture was refluxed overnight at 80°C. The solvents were evaporated and the residuum was dissolved in ethylacetate and washed with water. Organic extracts were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The crude material was purified on preparative TLC plate providing the product as a white solid (40%). ^1H NMR (500 MHz, $CDCl_3$): δ 1.04-1.06 (s, 3H), 1.13-1.80 (m, 8H), 2.15-2.23 (m, 1H), 2.36 (s, 6H), 3.70-3.73 (m, 1H), 5.43-5.45 (d, 1H), 6.46-6.47 (m, 1H), 6.62-6.63 (d, 1H), 7.32 (s, 2H), 7.45-7.46 (d, 1H). MS (M+H, 312).

Example 202a: 3,5-dimethyl-4-(2-methylcyclohexylcarbamoyl)phenyl trifluoromethanesulfonate: To a solution of 4-Hydroxy-2,6-dimethyl-N-(2-methylcyclohexyl)benzamide (example 200a) (7.65 mmol) in DCM (50 ml) was added pyridine (9.18 mmol). The solution was cooled to 0°C and triflic anhydride (9.18 mmol) was added drop wise. Then the reaction mixture was warmed up slowly to r.t. and stirred overnight. The mixture was diluted with DCM, washed with 1N aq. HCl, sat. $NaHCO_3$, brine and organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure providing the product as a white solid (20%).

The compound had an EC_{50} for activation of a hT1R2/hT1R3 sweet receptor expressed in an HEK293 cell line of 1.02 μM.

Numerous amide compounds of Formula (I) were also synthesized and experimentally tested for effectiveness as activator of a hT1R2/hT1R3 "sweet" receptor expressed in an HEK293 cell line.

The results of that testing are shown below in Table E.

Table E - Sweet EnhancerAmides

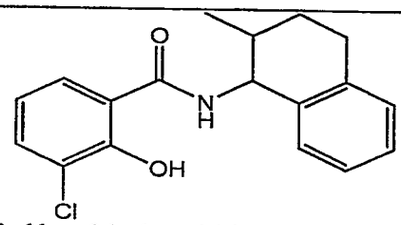
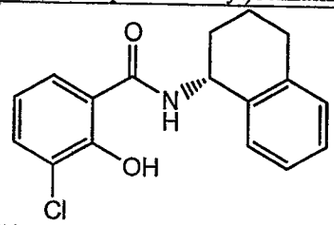
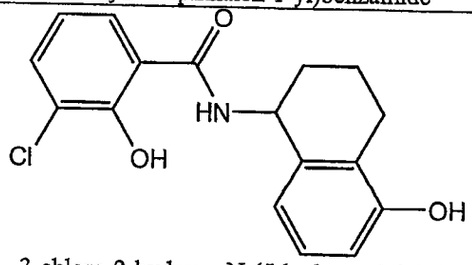
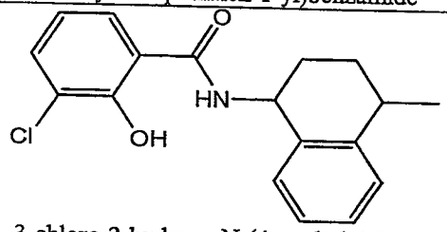
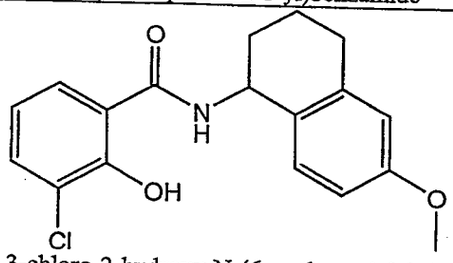
Compound No.	Compound	Sweet EC_{50} μM	Umami EC_{50} μM	Umami EC_{50} ratio
E1	 3-chloro-2-hydroxy-N-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	0.19		
E2	 (R)-3-chloro-2-hydroxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	0.65		
E3	 3-chloro-2-hydroxy-N-(5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	1.03		
E4	 3-chloro-2-hydroxy-N-(4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	1.61		
E5	 3-chloro-2-hydroxy-N-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	1.61		

Table E - Sweet Enhancer Amides

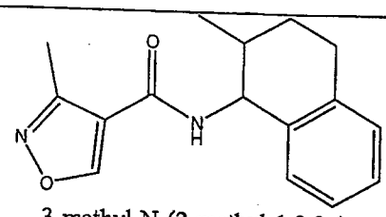
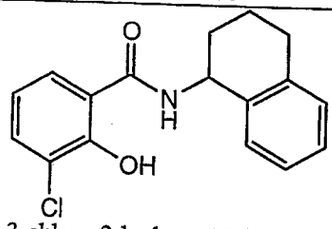
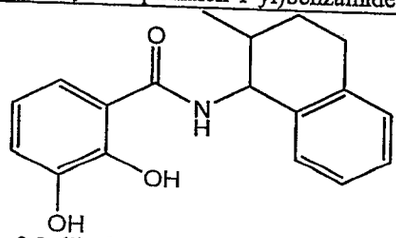
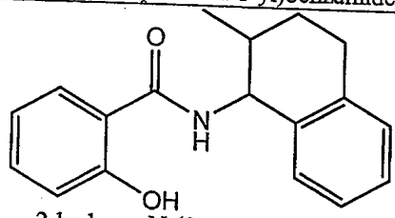
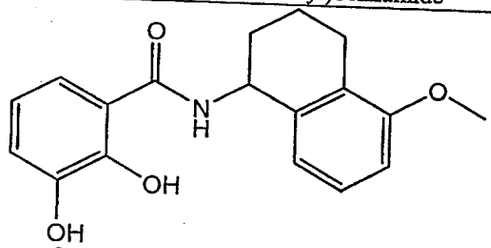
Compound No.	Compound	Sweet EC_{50} μM	Umami EC_{50} μM	Umami EC_{50} ratio
E6	 3-methyl-N-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide	1.48		
E7	 3-chloro-2-hydroxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	1.81		4.04
E8	 2,3-dihydroxy-N-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	1.98		
E9	 2-hydroxy-N-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	2.36		
E10	 2,3-dihydroxy-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	2.44		

Table E - Sweet EnhancerAmides

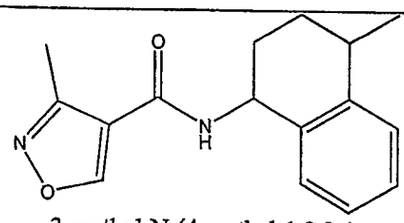
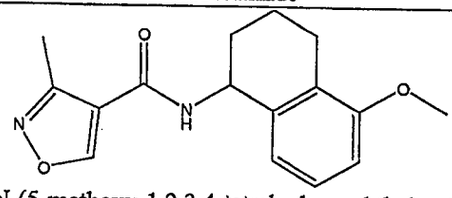
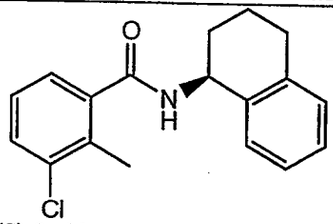
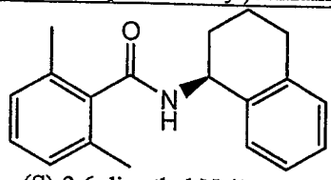
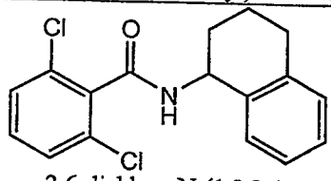
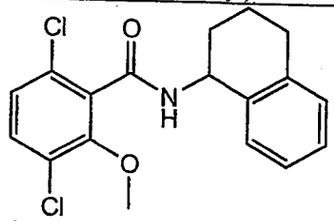
Compound No.	Compound	Sweet EC_{50} µM	Umami EC_{50} µM	Umami EC_{50} ratio
E11	 3-methyl-N-(4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide	2.46		
E12	 N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylisoxazole-4-carboxamide	2.85		
E13	 (S)-3-chloro-2-methyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	2.91		
E14	 (S)-2,6-dimethyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	2.91		
E15	 2,6-dichloro-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	3.02		
E16	 3,6-dichloro-2-methoxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	3.04		

Table E - Sweet EnhancerAmides

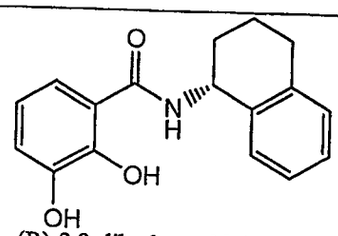
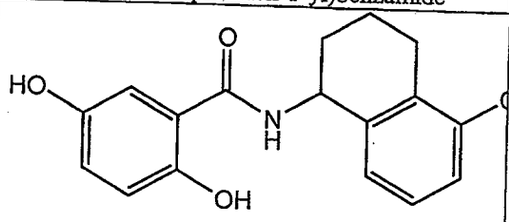
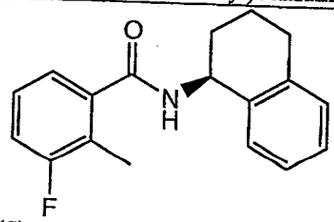
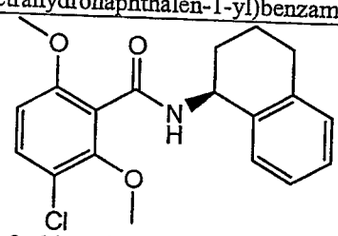
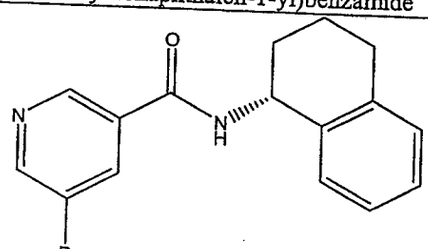
Compound No.	Compound	Sweet EC_{50} μM	Umami EC_{50} μM	Umami EC_{50} ratio
E17	 (R)-2,3-dihydroxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	3.13		
E18	 2,5-dihydroxy-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	3.38		
E19	 (S)-3-fluoro-2-methyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	3.57		
E20	 (S)-3-chloro-2,6-dimethoxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	4.13		
E21	 (R)-5-bromo-N-(1,2,3,4-tetrahydronaphthalen-1-yl)nicotinamide	4.19		

Table E - Sweet EnhancerAmides

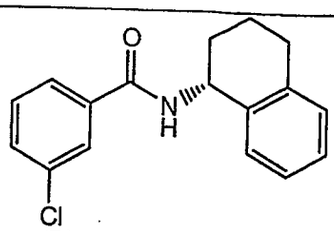
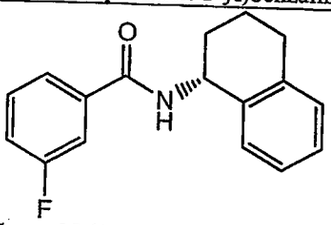
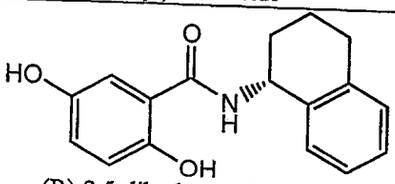
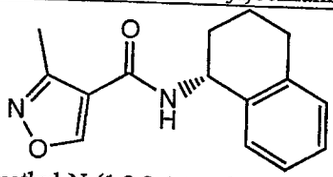
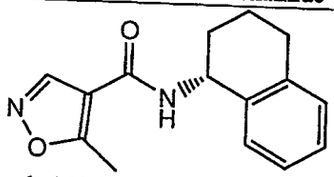
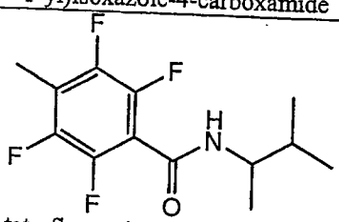
Compound No.	Compound	Sweet EC_{50} µM	Umami EC_{50} µM	Umami EC_{50} ratio
E22	 (R)-3-chloro-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	4.52		
E23	 (R)-3-fluoro-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	4.86		
E24	 (R)-2,5-dihydroxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	6.04		
E25	 (R)-3-methyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide	7.79		
E26	 (R)-5-methyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide	8.09		
E27	 2,3,5,6-tetrafluoro-4-methyl-N-(3-methylbutan-2-yl)benzamide	0.14		

Table E - Sweet EnhancerAmides

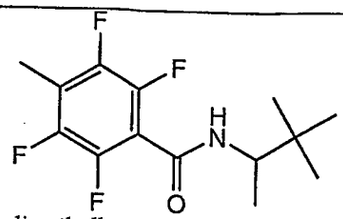
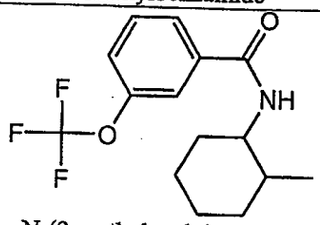
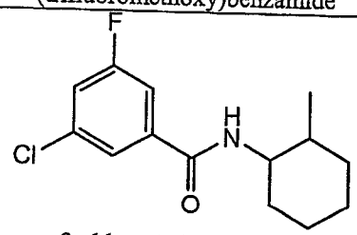
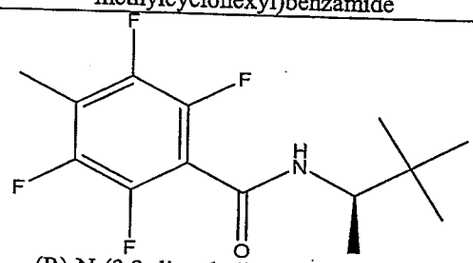
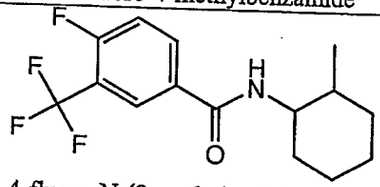
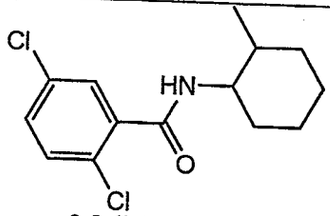
Compound No.	Compound	Sweet EC_{50} µM	Umami EC_{50} µM	Umami EC_{50} ratio
E28	 N-(3,3-dimethylbutan-2-yl)-2,3,5,6-tetrafluoro-4-methylbenzamide	0.21		
E29	 N-(2-methylcyclohexyl)-3-(trifluoromethoxy)benzamide	0.42		
E30	 3-chloro-5-fluoro-N-(2-methylcyclohexyl)benzamide	0.45		
E31	 (R)-N-(3,3-dimethylbutan-2-yl)-2,3,5,6-tetrafluoro-4-methylbenzamide	0.49		
E32	 4-fluoro-N-(2-methylcyclohexyl)-3-(trifluoromethyl)benzamide	0.51		
E33	 2,5-dichloro-N-(2-methylcyclohexyl)benzamide	0.63		

Table E - Sweet EnhancerAmides

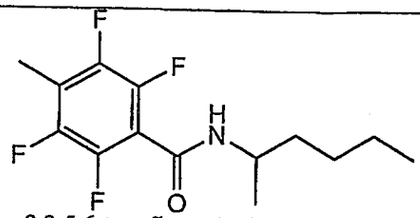
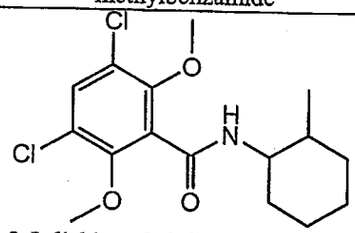
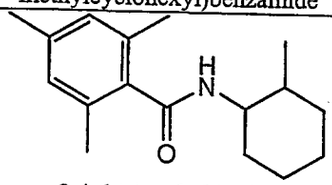
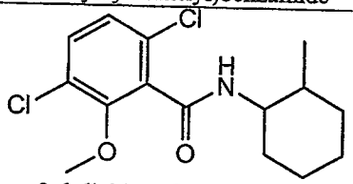
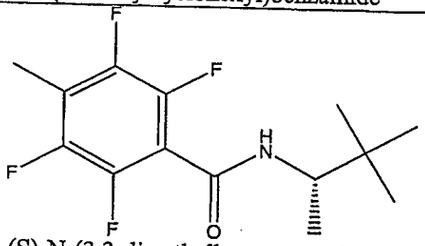
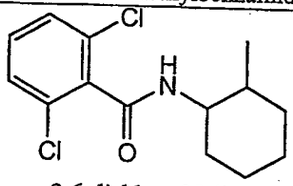
Compound No.	Compound	Sweet EC_{50} µM	Umami EC_{50} µM	Umami EC_{50} ratio
E34	 2,3,5,6-tetrafluoro-N-(hexan-2-yl)-4-methylbenzamide	0.71		
E35	 3,5-dichloro-2,6-dimethoxy-N-(2-methylcyclohexyl)benzamide	0.71		
E36	 2,4,6-trimethyl-N-(2-methylcyclohexyl)benzamide	0.72		
E37	 3,6-dichloro-2-methoxy-N-(2-methylcyclohexyl)benzamide	0.77		
E38	 (S)-N-(3,3-dimethylbutan-2-yl)-2,3,5,6-tetrafluoro-4-methylbenzamide	0.9		
E39	 2,6-dichloro-N-(2-methylcyclohexyl)benzamide	0.91		

Table E - Sweet EnhancerAmides

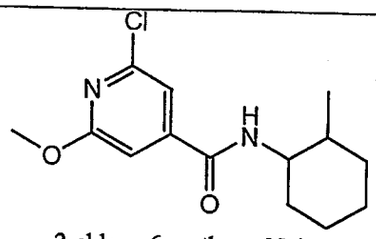
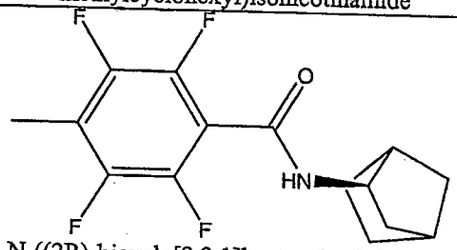
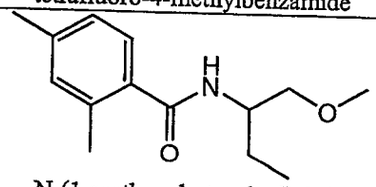
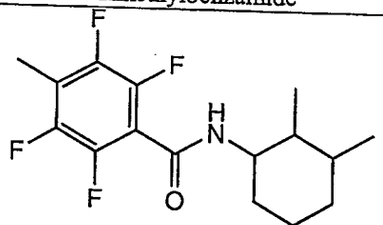
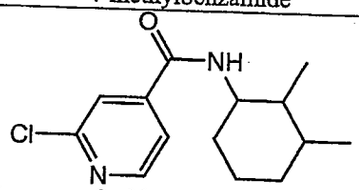
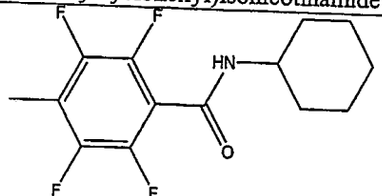
Compound No.	Compound	Sweet EC_{50} µM	Umami EC_{50} µM	Umami EC_{50} ratio
E40	 2-chloro-6-methoxy-N-(2-methylcyclohexyl)isonicotinamide	0.95		9.77
E41	 N-((2R)-bicyclo[2.2.1]heptan-2-yl)-2,3,5,6-tetrafluoro-4-methylbenzamide	1.02		
E42	 N-(1-methoxybutan-2-yl)-2,4-dimethylbenzamide	1.06		
E43	 N-(2,3-dimethylcyclohexyl)-2,3,5,6-tetrafluoro-4-methylbenzamide	1.08		
E44	 2-chloro-N-(2,3-dimethylcyclohexyl)isonicotinamide	1.08		
E45	 N-cyclohexyl-2,3,5,6-tetrafluoro-4-methylbenzamide	1.13		

Table E - Sweet Enhancer Amides

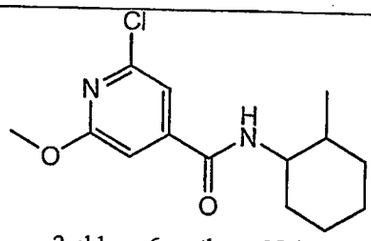
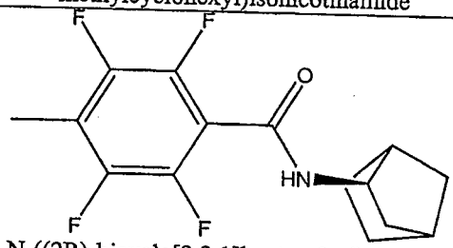
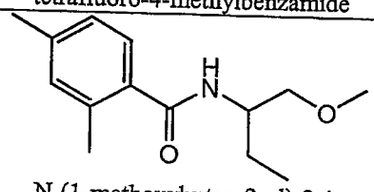
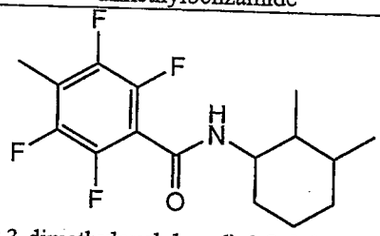
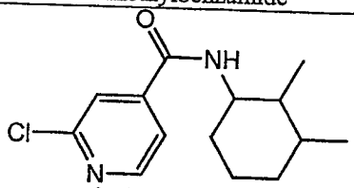
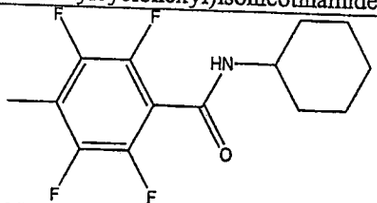
Compound No.	Compound	Sweet EC_{50} μM	Umami EC_{50} μM	Umami EC_{50} ratio
E40	 2-chloro-6-methoxy-N-(2-methylcyclohexyl)isonicotinamide	0.95		9.77
E41	 N-((2R)-bicyclo[2.2.1]heptan-2-yl)-2,3,5,6-tetrafluoro-4-methylbenzamide	1.02		
E42	 N-(1-methoxybutan-2-yl)-2,4-dimethylbenzamide	1.06		
E43	 N-(2,3-dimethylcyclohexyl)-2,3,5,6-tetrafluoro-4-methylbenzamide	1.08		
E44	 2-chloro-N-(2,3-dimethylcyclohexyl)isonicotinamide	1.08		
E45	 N-cyclohexyl-2,3,5,6-tetrafluoro-4-methylbenzamide	1.13		

Table E - Sweet EnhancerAmides

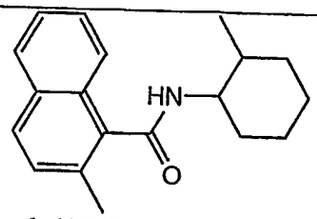
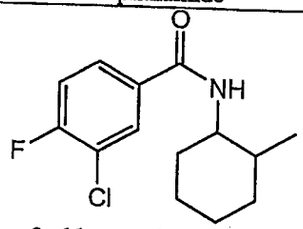
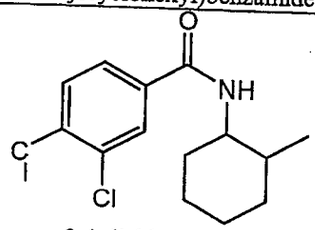
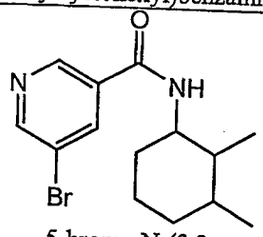
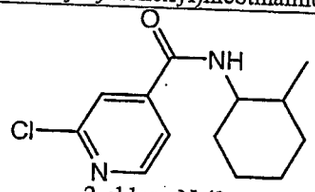
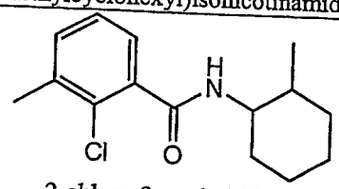
Compound No.	Compound	Sweet EC_{50} µM	Umami EC_{50} µM	Umami EC_{50} ratio
E52	 2-methyl-N-(2-methylcyclohexyl)-1-naphthamide	1.52		
E53	 3-chloro-4-fluoro-N-(2-methylcyclohexyl)benzamide	1.7		
E54	 3,4-dichloro-N-(2-methylcyclohexyl)benzamide	1.83		10.66
E55	 5-bromo-N-(2,3-dimethylcyclohexyl)nicotinamide	1.89		
E56	 2-chloro-N-(2-methylcyclohexyl)isonicotinamide	1.92		2.08
E57	 2-chloro-3-methyl-N-(2-methylcyclohexyl)benzamide	1.95		

Table E - Sweet EnhancerAmides

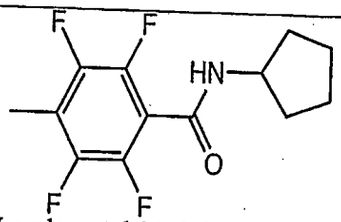
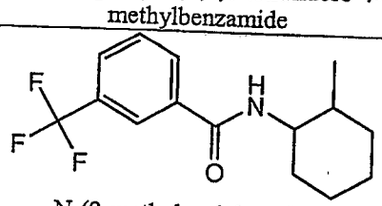
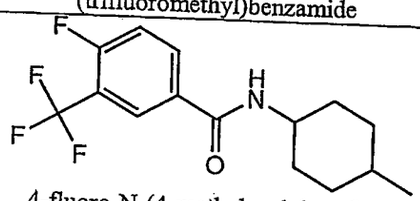
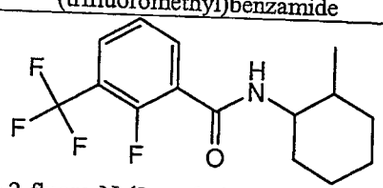
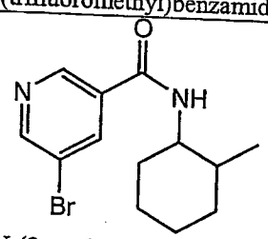
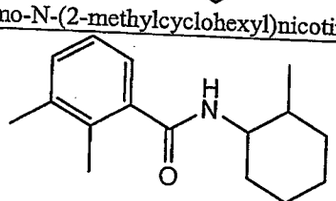
Compound No.	Compound	Sweet EC_{50} μM	Umami EC_{50} μM	Umami EC_{50} ratio
E58	 N-cyclopentyl-2,3,5,6-tetrafluoro-4-methylbenzamide	2.23		
E59	 N-(2-methylcyclohexyl)-3-(trifluoromethyl)benzamide	2.34		2.07
E60	 4-fluoro-N-(4-methylcyclohexyl)-3-(trifluoromethyl)benzamide	2.37		
E61	 2-fluoro-N-(2-methylcyclohexyl)-3-(trifluoromethyl)benzamide	2.4		
E62	 5-bromo-N-(2-methylcyclohexyl)nicotinamide	2.42		
E63	 2,3-dimethyl-N-(2-methylcyclohexyl)benzamide	2.6		

Table E - Sweet EnhancerAmides

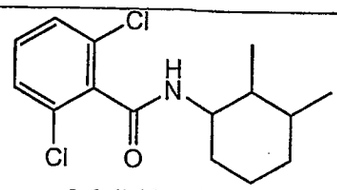
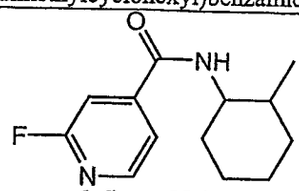
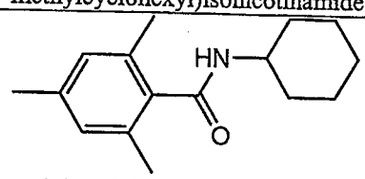
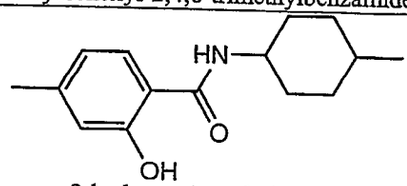
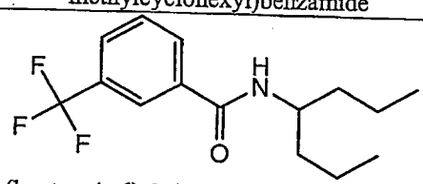
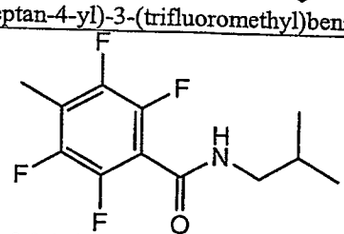
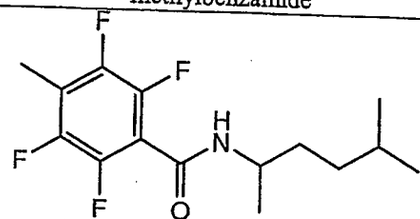
Compound No.	Compound	Sweet EC_{50} µM	Umami EC_{50} µM	Umami EC_{50} ratio
E64	 2,6-dichloro-N-(2,3-dimethylcyclohexyl)benzamide	2.77		
E65	 2-fluoro-N-(2-methylcyclohexyl)isonicotinamide	2.83		
E66	 N-cyclohexyl-2,4,6-trimethylbenzamide	2.86		
E67	 2-hydroxy-4-methyl-N-(4-methylcyclohexyl)benzamide	2.98		
E68	 N-(heptan-4-yl)-3-(trifluoromethyl)benzamide	3.03	0.33	
E69	 2,3,5,6-tetrafluoro-N-isobutyl-4-methylbenzamide	3.19		
E70	 2,3,5,6-tetrafluoro-4-methyl-N-(5-methylhexan-2-yl)benzamide	3.2		

Table E - Sweet EnhancerAmides

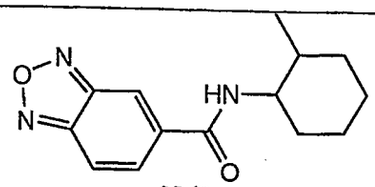
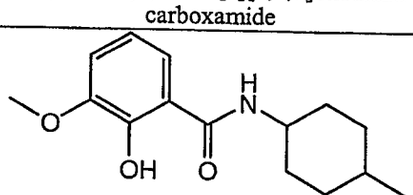
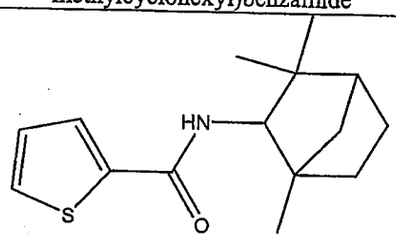
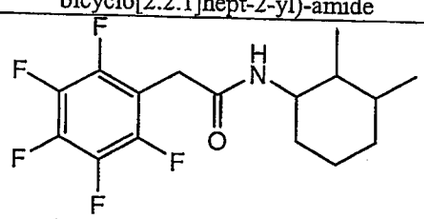
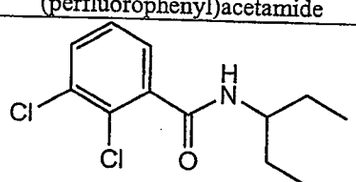
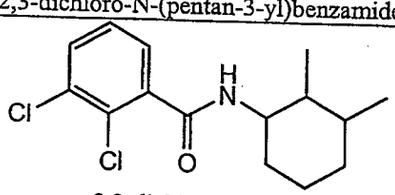
Compound No.	Compound	Sweet EC_{50} µM	Umami EC_{50} µM	Umami EC_{50} ratio
E71	 N-(2-methylcyclohexyl)benzo[c][1,2,5]oxadiazole-5-carboxamide	3.33		
E72	 2-hydroxy-3-methoxy-N-(4-methylcyclohexyl)benzamide	3.35		
E73	 Thiophene-2-carboxylic acid (1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide	3.36		
E74	 N-(2,3-dimethylcyclohexyl)-2-(perfluorophenyl)acetamide	3.62		
E75	 2,3-dichloro-N-(pentan-3-yl)benzamide	3.78		
E76	 2,3-dichloro-N-(2,3-dimethylcyclohexyl)benzamide	3.99		

Table E - Sweet EnhancerAmides

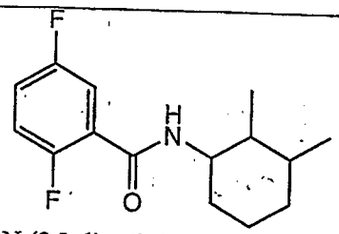
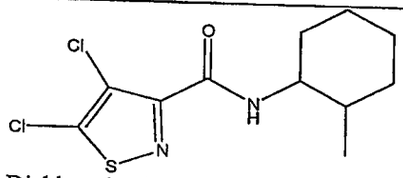
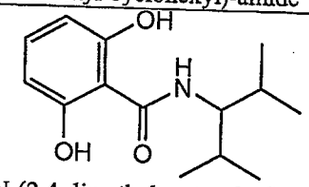
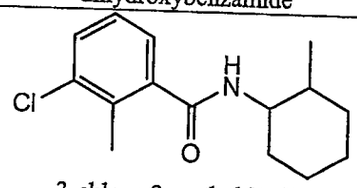
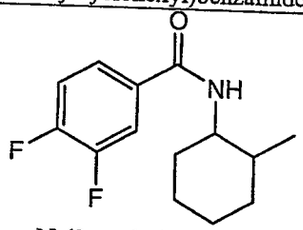
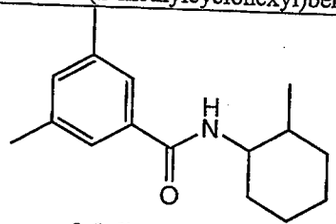
Compound No.	Compound	Sweet EC_{50} μM	Umami EC_{50} μM	Umami EC_{50} ratio
E77	 N-(2,3-dimethylcyclohexyl)-2,5-difluorobenzamide	4.11		
E78	 4,5-Dichloro-isothiazole-3-carboxylic acid (2-methyl-cyclohexyl)-amide	4.24	8.51	
E79	 N-(2,4-dimethylpentan-3-yl)-2,6-dihydroxybenzamide	4.28		
E80	 3-chloro-2-methyl-N-(2-methylcyclohexyl)benzamide	4.29		
E81	 3,4-difluoro-N-(2-methylcyclohexyl)benzamide	4.37		6.98
E82	 3,5-dimethyl-N-(2-methylcyclohexyl)benzamide	4.48		

Table E - Sweet Enhancer Amides

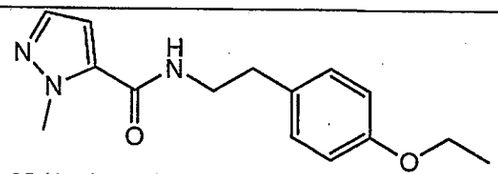
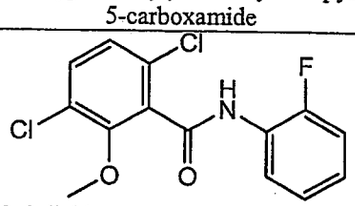
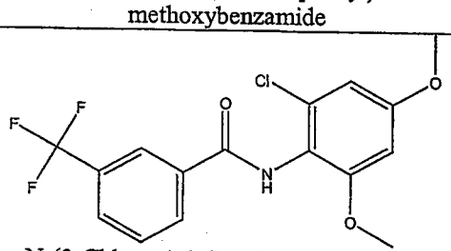
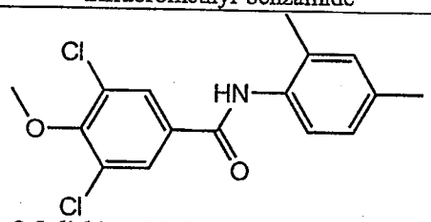
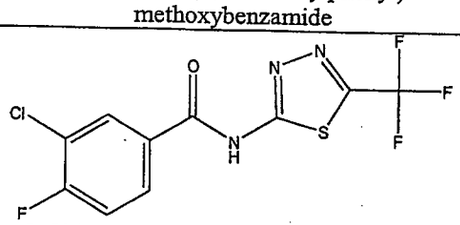
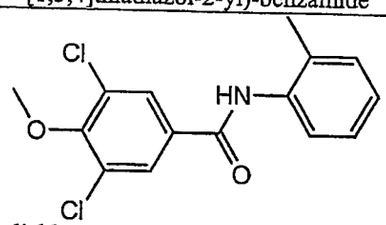
Compound No.	Compound	Sweet EC_{50} μM	Umami EC_{50} μM	Umami EC_{50} ratio
E83	 N-(4-ethoxyphenethyl)-1-methyl-1H-pyrazole-5-carboxamide	4.68		
E84	 3,6-dichloro-N-(2-fluorophenyl)-2-methoxybenzamide	0.83		16.51
E85	 N-(2-Chloro-4,6-dimethoxy-phenyl)-3-trifluoromethyl-benzamide	1.42		
E86	 3,5-dichloro-N-(2,4-dimethylphenyl)-4-methoxybenzamide	1.48		
E87	 3-Chloro-4-fluoro-N-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-benzamide	1.55		
E88	 3,5-dichloro-4-methoxy-N-o-tolylbenzamide	1.84		

Table E - Sweet EnhancerAmides

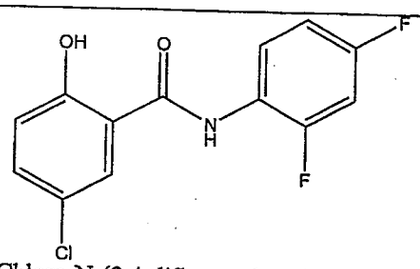
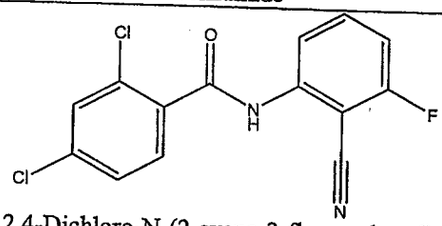
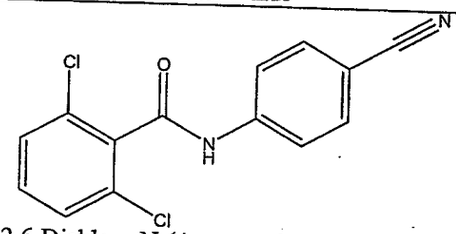
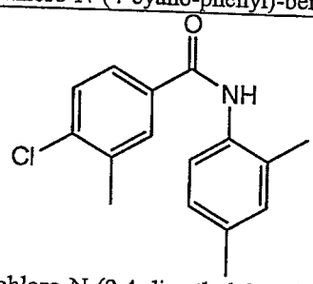
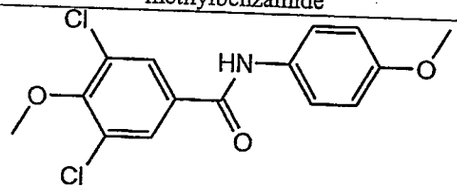
Compound No.	Compound	Sweet EC_{50} µM	Umami EC_{50} µM	Umami EC_{50} ratio
E89	 5-Chloro-N-(2,4-difluoro-phenyl)-2-hydroxy-benzamide	2.56		
E90	 2,4-Dichloro-N-(2-cyano-3-fluoro-phenyl)-benzamide	2.71		
E91	 2,6-Dichloro-N-(4-cyano-phenyl)-benzamide	2.74		
E92	 4-chloro-N-(2,4-dimethylphenyl)-3-methylbenzamide	2.74		
E93	 3,5-dichloro-4-methoxy-N-(4-methoxyphenyl)benzamide	3.24		

Table E - Sweet EnhancerAmides

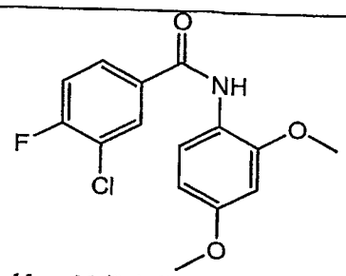
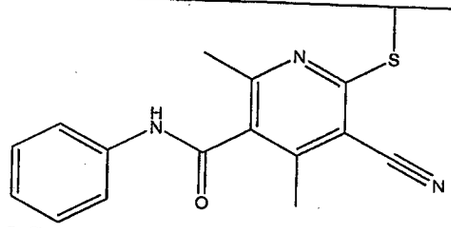
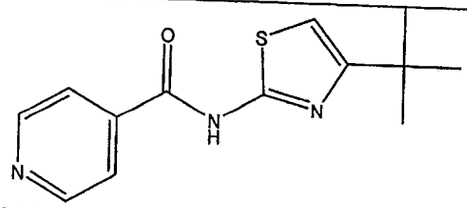
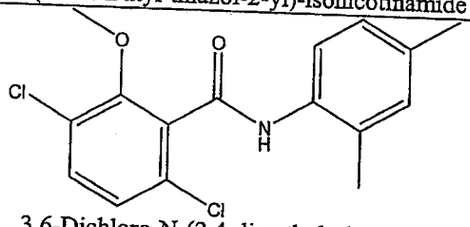
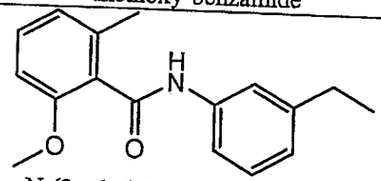
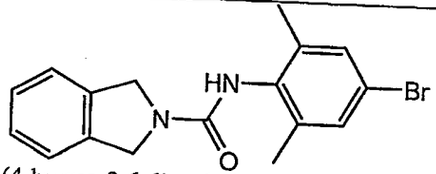
Compound No.	Compound	Sweet EC_{50} µM	Umami EC_{50} µM	Umami EC_{50} ratio
E94	 3-chloro-N-(2,4-dimethoxyphenyl)-4-fluorobenzamide	3.56		
E95	 5-Cyano-2,4-dimethyl-6-methylsulfanyl-N-phenyl-nicotinamide	3.58		
E96	 N-(4-tert-Butyl-thiazol-2-yl)-isonicotinamide	3.73		
E97	 3,6-Dichloro-N-(2,4-dimethyl-phenyl)-2-methoxy-benzamide	4.25		
E98	 N-(3-ethylphenyl)-2-methoxy-6-methylbenzamide	4.63		
E99	 N-(4-bromo-2,6-dimethylphenyl)isoindoline-2-carboxamide	0.93		

Table E - Sweet EnhancerAmides

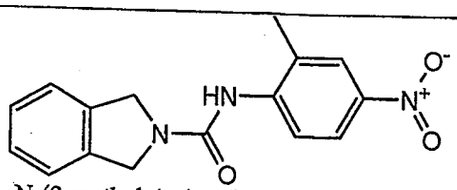
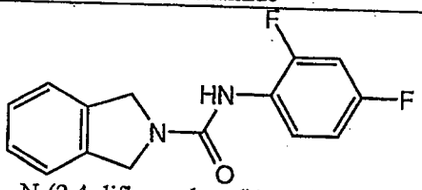
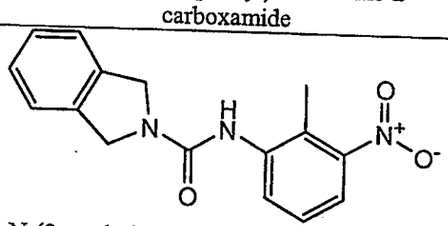
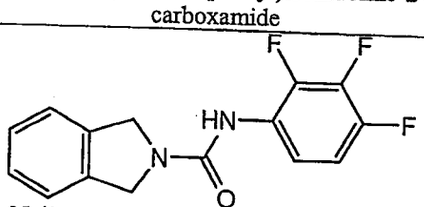
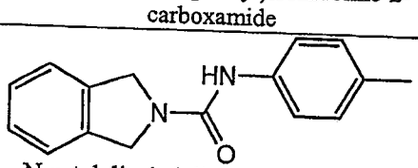
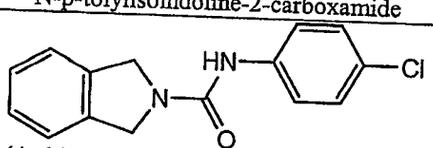
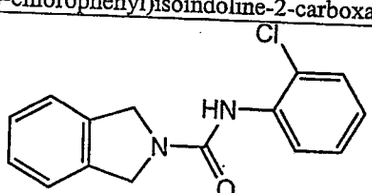
Compound No.	Compound	Sweet EC_{50} μM	Umami EC_{50} μM	Umami EC_{50} ratio
E100	 N-(2-methyl-4-nitrophenyl)isoindoline-2-carboxamide	1.3		
E101	 N-(2,4-difluorophenyl)isoindoline-2-carboxamide	1.37		
E102	 N-(2-methyl-3-nitrophenyl)isoindoline-2-carboxamide	2.01		
E103	 N-(2,3,4-trifluorophenyl)isoindoline-2-carboxamide	2.58		
E104	 N-p-tolylisoindoline-2-carboxamide	3.05		
E105	 N-(4-chlorophenyl)isoindoline-2-carboxamide	3.4		
E106	 N-(2-chlorophenyl)isoindoline-2-carboxamide	3.85		

Table E - Sweet EnhancerAmides

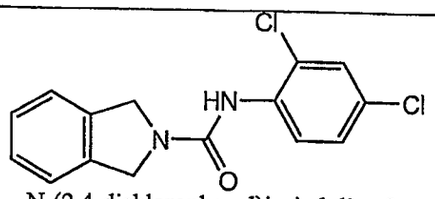
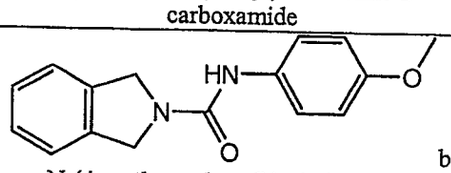
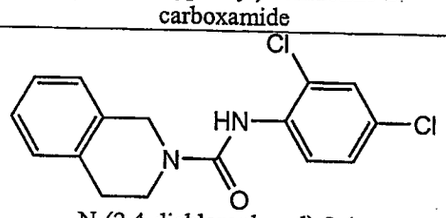
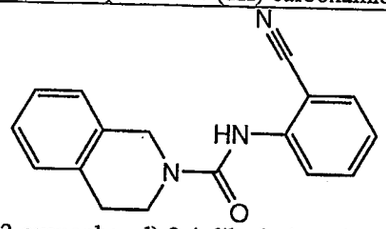
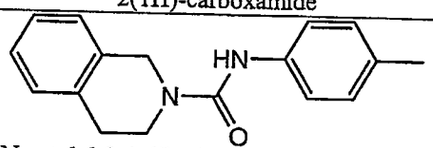
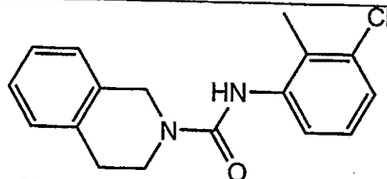
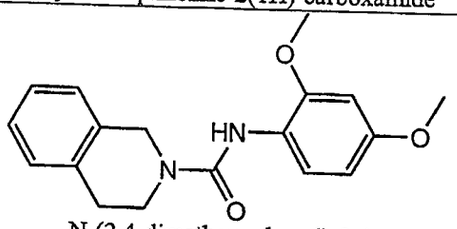
Compound No.	Compound	Sweet EC_{50} μM	Umami EC_{50} μM	Umami EC_{50} ratio
E107	 N-(2,4-dichlorophenyl)isoindoline-2-carboxamide	4.15		
E108	 N-(4-methoxyphenyl)isoindoline-2-carboxamide	4.99		
E109	 N-(2,4-dichlorophenyl)-3,4-dihydroisoquinoline-2(1H)-carboxamide	2.34		
E110	 N-(2-cyanophenyl)-3,4-dihydroisoquinoline-2(1H)-carboxamide	2.5		
E111	 N-p-tolyl-3,4-dihydroisoquinoline-2(1H)-carboxamide	4.27		
E112	 N-(3-chloro-2-methylphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxamide	4.33		
E113	 N-(2,4-dimethoxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxamide	4.44		

Table E - Sweet EnhancerAmides

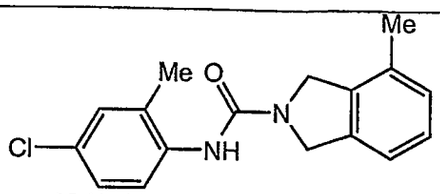
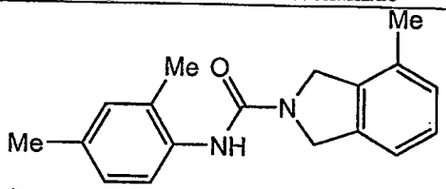
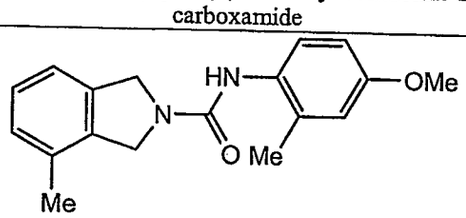
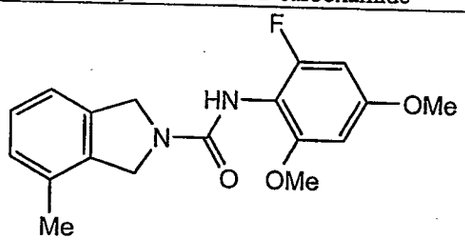
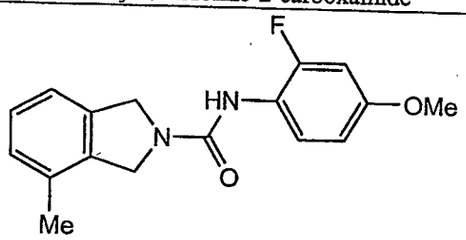
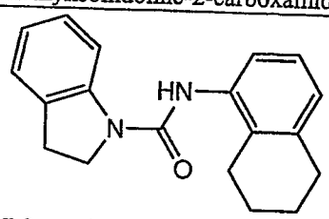
Compound No.	Compound	Sweet EC_{50} μM	Umami EC_{50} μM	Umami EC_{50} ratio
E114	 N-(4-chloro-2-methylphenyl)-4-methylisoindoline-2-carboxamide	0.19		
E115	 N-(2,4-dimethylphenyl)-4-methylisoindoline-2-carboxamide	0.25		
E116	 N-(4-methoxy-2-methylphenyl)-4-methylisoindoline-2-carboxamide	0.71		
E117	 N-(2-fluoro-4,6-dimethoxyphenyl)-4-methylisoindoline-2-carboxamide	0.09		
E118	 N-(2-fluoro-4-methoxyphenyl)-4-methylisoindoline-2-carboxamide	0.1		
E119	 N-(5,6,7,8-tetrahydronaphthalen-1-yl)indoline-1-carboxamide	1.06		

Table E - Sweet EnhancerAmides

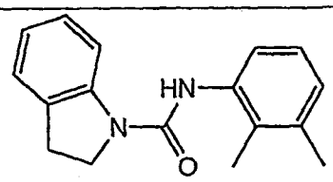
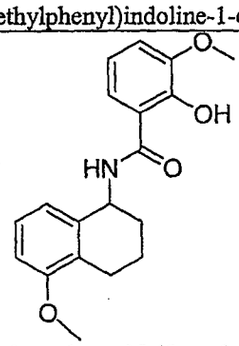
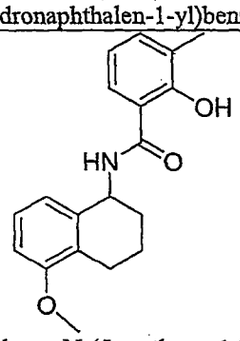
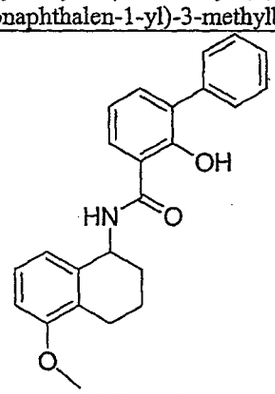
Compound No.	Compound	Sweet EC_{50} μM	Umami EC_{50} μM	Umami EC_{50} ratio
E120	 N-(2,3-dimethylphenyl)indoline-1-carboxamide	2.38		
E121	 2-hydroxy-3-methoxy-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	1.61		
E122	 2-hydroxy-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylbenzamide	1.95		
E123	 2-hydroxy-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-phenylbenzamide	2.56		

Table E - Sweet EnhancerAmides

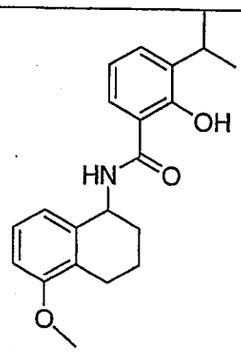
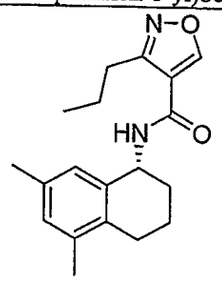
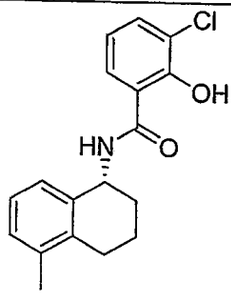
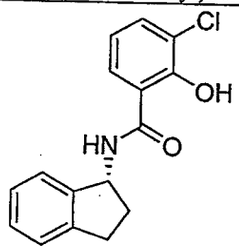
Compound No.	Compound	Sweet EC_{50} μM	Umami EC_{50} μM	Umami EC_{50} ratio
E124	 (2-hydroxy-3-isopropyl-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	2.64		
E125	 (R)-N-(5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-propylisoxazole-4-carboxamide	0.62		
E126	 (R)-3-chloro-2-hydroxy-N-(5-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide	0.89		
E127	 (R)-3-chloro-N-(2,3-dihydro-1H-inden-1-yl)-2-hydroxybenzamide	0.95		2.81 (10 M cpd)

Table E - Sweet EnhancerAmides

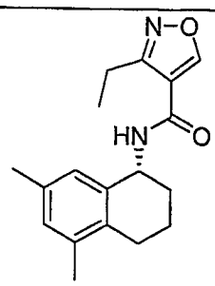
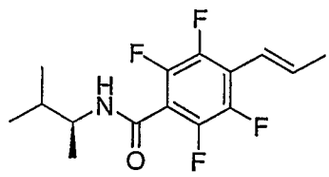
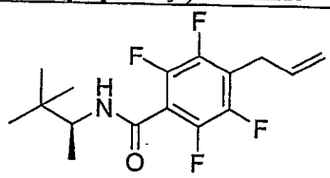
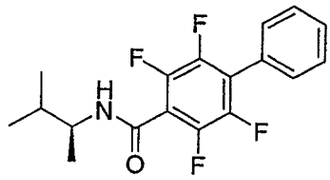
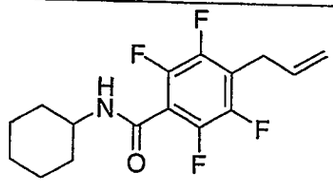
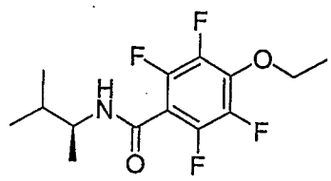
Compound No.	Compound	Sweet EC_{50} µM	Umami EC_{50} µM	Umami EC_{50} ratio
E128	 (R)-N-(5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-ethylisoxazole-4-carboxamide	1.24		
E129	 (S,E)-2,3,5,6-tetrafluoro-N-(3-methylbutan-2-yl)-4-(prop-1-enyl)benzamide	0.41		
E130	 (S)-4-allyl-N-(3,3-dimethylbutan-2-yl)-2,3,5,6-tetrafluorobenzamide	0.43		
E131	 (S)-2,3,5,6-tetrafluoro-N-(3-methylbutan-2-yl)-4-phenyl benzamide	0.44		
E132	 4-allyl-N-cyclohexyl-2,3,5,6-tetrafluorobenzamide	0.55		

Table E - Sweet EnhancerAmides

Compound No.	Compound	Sweet EC_{50} µM	Umami EC_{50} µM	Umami EC_{50} ratio
E133	 (S)-4-ethoxy-2,3,5,6-tetrafluoro-N-(3-methylbutan-2-yl)benzamide	0.6		

Sweet Flavor and Sweet Flavor Enhancement Measurement Using Human Panelists

Purpose: To investigate the intensity of various tastes and off-tastes of an experimental compound. To determine the maximum concentration of the experimental compound that does not elicit an undesirable characteristic or off-taste.

Overview: Various concentrations of the experimental compound (normally aqueous solutions containing 1, 3, 10, and 30uM concentrations of the experimental compound; and optionally 50uM and/or 100uM concentrations) are individually tasted by trained human subjects and rated for intensity of several taste attributes. The experimental compound may also be tasted when dissolved in a "key tastant" solution.

Procedure: An appropriate quantity of the experimental compound is dissolved in water typically also containing 0.1% ethanol, which is utilized to aid initial dispersion of the compound in the aqueous stock solution. When appropriate, the experimental compound may also be dissolved in aqueous solutions of a "key tastant" (for example, 4% sucrose, 6% sucrose, 6% fructose/glucose, or 7% fructose/glucose, at pH 7.1 or 2.8).

Five human Subjects are used for preliminary taste tests. The Subjects have a demonstrated ability to taste the desired taste attributes, and are trained to use a Labeled Magnitude Scale (LMS) from 0 (Barely Detectible Sweetness) to 100 (Strongest Imaginable Sweetness). Subjects refrain from eating or drinking (except water) for at least 1 hour prior to the test. Subjects eat a cracker and rinse with water four times to clean the mouth before taste tests.

The aqueous solutions are dispensed in 10 ml volumes into 1 oz. sample cups and served to the Subjects at room temperature. Samples of the experimental compound dissolved in an appropriate key tastant (e.g., 4% sucrose, 6% fructose, or 6% fructose/glucose, typically at pH 7.1) at various concentrations of the experimental compound may also be served to the Subjects. Subjects also receive a reference sample of

the key tastant (*e.g.*, sucrose, fructose, or fructose/glucose, typically at pH 7.1) at different concentrations for comparison.

Subjects taste the solutions, starting with the lowest concentration, and rate intensity of the following attributes on the Labeled Magnitude Scale (LMS) for sweetness, saltiness, sourness, bitterness, savory (umami), and other (off-taste). Subjects rinse three times with water between tastings. If a particular concentration elicits an undesirable characteristic or off-taste, subsequent tastings of higher concentrations are eliminated. After a break, Subjects taste a solution of the key tastant (e.g., 4% sucrose, 6% fructose, or 6% fructose/glucose, typically at pH 7.1) without the experimental compound. Then solutions of the key tastant plus experimental compound are tasted in increasing order of concentration. The key tastant solution can be retasted for comparison with key tastant + experimental compound solutions if necessary. Discussion among panelists is permitted.

The maximum concentration of an experimental compound that does not elicit an objectionable characteristic or off-taste is the highest concentration that a particular compound will be tested at in subsequent sensory experiments. To confirm preliminary test results, the test may be repeated with another small group of panelists.

The preliminary profiling test is always the first test performed on a new experimental compound. Depending on the results of the preliminary profiling test, additional more quantitative tests may be performed to further characterize the experimental compound.

"Difference from Reference" Human Taste Test Procedures

Purpose: To determine how the intensity of a test sample of an experimental compound differs from that of a reference sample in terms of sweetness. This type of study requires a larger panel (typically 15-20 Subjects) in order to obtain statistically significant data.

Overview: A group of 10 or more panelists taste pairs of solutions where one sample is the "Reference" (which typically does not include an experimental compound and is an approved substance or Generally Recognized As Safe (GRAS) substance, *i.e.*, a sweetener) and one sample is the "Test" (which may or may not include an experimental compound). Subjects rate the difference in intensity of the test sample compared to the reference sample for the key attribute on a scale of –5 (much less sweet than the reference) to +5 (much more sweet than the reference). A score of 0 indicates the test sample is equally as sweet as the reference.

Procedure:

Ten or more Subjects are used for the "Difference from Reference" tests. Subjects have been previously familiarized with the key attribute taste and are trained to use the -5 to +5 scale. Subjects refrain from eating or drinking (except water) for at least 1 hour prior to the test. Subjects eat a cracker and rinse with water four times to clean the mouth.

Test solutions can include the experimental compound in water, the experimental compound plus a key tastant (*e.g.*, 4% sucrose, 6% sucrose, 6% fructose, 6% fructose/glucose, or 7% fructose/glucose, at pH 7.1 or 2.8), and a range of key tastant only solutions as references.

Samples of the key tastant without the experimental compound are used to determine if the panel is rating accurately; *i.e.*, the reference is tested against itself (blind) to determine how accurate the panel is rating on a given test day. The solutions are dispensed in 10 ml volumes into 1 oz. sample cups and served to the Subjects at room temperature.

Subjects first taste the reference sample then immediately taste the test sample and rate the difference in intensity of the key attribute on the Difference from Reference scale (-5 to +5). All samples are expectorated. Subjects may retaste the samples but can only use the volume of sample given. Subjects must rinse at least twice with water between pairs of samples. Eating a cracker between sample pairs may be required depending on the samples tasted.

The scores for each test are averaged across Subjects and standard error is calculated. Panel accuracy can be determined using the score from the blind reference test. ANOVA and multiple comparison tests (such as Tukey's Honestly Significant Difference test) can be used to determine differences among pairs, provided the reference sample is the same among all tests. If the identical test pair is tested in another session, a Student's t-test (paired, two-tailed; alpha = 0.05) can be used to determine if there is any difference in the ratings between sessions.

A number of different reference sweeteners have been utilized for the measurement of sweet taste enhancement. For example, for testing (R)-3-methyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide, a reference sample consisting of 4% sucrose was used, which has a greater than the threshold level sweetness (i.e., 2% sucrose), and a sweetness in the region of sweet taste perception where human subjects are most sensitive to small changes in sweet taste perception. For the testing of 2,3,5,6-tetrafluoro-4-methyl-N-(2-methylcyclohexyl)benzamide, a-50:50 mix of fructose:glucose was used to

better model high fructose corn syrup solutions commonly utilized in the beverage industry. A 6% fructose/glucose mixture was demonstrated to be approximately equal in sweet taste perception as 6% sucrose, which is within the range where panelists are sensitive to small changes in sweet taste perception. After initial studies in 6% fructose/glucose at pH 7.1, studies shift to evaluating the performance of the compound in a product prototype more similar to a cola beverage, *i.e.* higher concentrations of sweetener and lower pH.

The results of some human taste tests of the sweet amide compounds of the invention in aqueous compositions intended to model the composition of a carbonated beverage are shown below in Table F

Table F. Sweet Taste Test Results

Compound No.	Contents of Solution	pH	Perceived Equivalent Sweet Solution
175	50 μM Compound 175 + 4% sucrose	*	6% sucrose
171	30 μM Compound 171 + 6% fructose/glucose	*	Greater than 6% but less than 8% fructose/glucose
170	30 μM Compound 170 + 6% fructose/glucose	pH 7.1	Greater than 6% but less than 8% fructose/glucose
162	10 μM Compound 162 + 6% fructose/glucose	pH 7.1	Greater than or equal to 8% fructose/glucose
162	10 μM Compound 162 + 7% fructose/glucose	pH 2.8	Greater than or equal to 9% fructose/glucose
168	30 μM Compound 168 + 6% fructose/glucose	pH 7.1	Equal to 8% fructose/glucose
163	10 μM Compound 163 + 6% fructose/glucose	pH 7.1	Greater than 6% but less than 8% fructose/glucose
191	5 μM Compound 191 + 6% fructose/glucose	pH 7.1	Greater than 6% but less than 8% fructose/glucose
192	3 μM Compound 192 + 6% fructose/glucose	pH 7.1	Greater than 6% but less than 8% fructose/glucose
176	10 μM Compound 176 + 7% fructose/glucose	pH 2.8	Equal to 10.5% fructose/glucose
176	10 μM Compound 176 + 7% fructose/glucose	pH 7.1	Equal to 10% fructose/glucose
177	3 μM Compound 177 + 6% fructose/glucose	pH 7.1	Equal to 10% fructose/glucose

*The pH of these aqueous solutions was not measured or controlled.

Example 203

Soup Preparation Using an Ethanol Stock Solution

A compound of the invention is diluted using 200 proof ethanol to 1000x the desired concentration in soup. The compound can be sonicated and heated (if stable) to ensure

complete solubility in ethanol. The soup from bouillon base is made by adding 6 g of vegetable bouillon base in 500 mL of hot water in a glass or stoneware bowl. The water is heated to 80°C. The concentration of MSG in the dissolved bouillon is 2.2 g/L and there is no IMP added. After the bouillon base is dissolved, the ethanol stock solution is added to the soup base. For 500 mL of soup, 0.5 mL of the 1000x ethanol stock is added for a final ethanol concentration of 0.1 %. If the ethanol interferes with the taste of the soup, a higher concentration of ethanol stock solution can be prepared provided the compound is soluble.

Example 204

Chip Preparation

A salt mixture of a compound of the invention is made by mixing with salt such that a 1.4% of the salt mixture added w/w to chips would result in the desired concentration of the compound. For 1 ppm final of the compound on chips, 7 mg of the compound is mixed with 10 g of salt. The compound is ground using a mortar and pestle with the salt and the compound and salt are mixed well. The chips are broken into uniform small pieces by using a blender. For each 98.6 g of chips, 1.4 g of the salt mixture is weighed out. The chip pieces are first heated in a microwave for 50 seconds or until warm. The pieces are spread out on a large piece of aluminum foil. The salt mixture is spread evenly over the chips. The chips are then placed in a plastic bag making sure that all the salt is place in the bag as well. The salt mixture and chips are then shaken to ensure that the salt is spread evenly over the chips.

Example 205

Cookie Preparation

A compound of the invention is diluted using 200 proof ethanol to 1000x the desired concentration in the final product. The compound can be sonicated and heated (if stable) to ensure complete solubility in ethanol. The solution containing the compound of the invention is then mixed with other liquid ingredients (i.e., water, liquid egg, and flavorings) until well blended. The mixture is blended with a dry emulsifier such as lecithin and further blended with shortening. The shortening is blended with dry components (i.e., flour, sugar, salt, cocoa) which have been well mixed. Dough is portioned out onto a baking sheet, and baked at desired temperature until done.

Example 206

Juice Preparation

A compound of the invention is diluted using 200 proof ethanol to 1000x the desired concentration in juice. The compound is further blended with the alcohol component of natural and/or artificial flavors to make a "key". The flavor key is blended with a portion of juice concentrate to assure homogeneity. The remainder of the juice concentrate is diluted with water and mixed. Sweeteners, such as HFCS (High Fructose Corn Syrup), aspartame, or sucralose, are mixed in and blended. The flavor/compound portion is added as a final step, and blended.

Example 207

Spicy Tomato Juice or Bloody Mary Mix

A compound of the invention is added as a dry ingredient to a spice blend, which may optionally include monosodium glutamate, and blended thoroughly. Spice blend is dispersed into a portion of tomato paste, blended, and that blended paste is further blended into the remaining paste. The paste is then diluted with water to make spicy tomato juice or Bloody Mary mix, which may optionally be processed at high temperature for a short time.

Example 208

Human Taste Tests of Low Sodium Tomato Juice

Human taste tests were conducted in order to evaluate the ability of the compounds of the invention to enhance the savory flavor of low sodium tomato juice (which naturally comprises some monosodium glutamate).

Sample Preparation Procedure

The final tomato juice samples for taste testing were prepared so as to comprise 90% (by volume) pre-made low sodium tomato juice stock (pH 4.2, 80~100mg Na / 8oz, 16mM of naturally occurring MSG), 5% (by volume) of stock solutions formulated to produce selected final levels of sodium of final juice, and 5% (by volume) of a stock solution of the compound of the invention. Selected oxalamide compounds of the invention were dissolved in LSB (low sodium phosphate buffer), to provide a stock solution at 20 times the desired final concentration in the final tomato juice. The desired final sodium concentration of the final tomato juice was most experiments 73.6 mM (400 mg sodium in 8 oz. of juice), therefore a stock solution of NaCl was made at 1.48 M NaCl. The pH for the stock solutions was adjusted to 4.2 using a 1 M citric acid solution, and the stock solutions were sonicated to ensure the additive compounds were completely dissolved. To produce a 1,000

mL final sample of tomato juice sample for taste testing, 50 mL of the test compound stock solution, and 50 mL of the sodium chloride were added to 900 mL of the pre-made low sodium tomato juice stock.

Human Taste Tests

Sixteen human subjects were used in the taste testing. The subjects refrained from eating or drinking (except water) for at least 1 hour prior to the test. Subjects ate a cracker and rinsed with water to cleanse the mouth before the start of the test. 15mL samples were served in 2oz. sample cups at room temperature. Panelists rinsed with water between samples, and were encouraged to eat a cracker to remove all tastes before moving to the next sample. Samples were presented in randomized counterbalanced order within each tasting session (with different blinding codes). The panelists were asked to evaluate umaminess (savory level) make comments on the samples on an unstructured line scale (scoring 0-10), in duplicate sessions. There were 5 minutes breaks between tasting sessions, and a total of 4 sessions over a 2 day period. The samples tasted are given below

Samples Tasted
400mg Na / 8 oz tomato juice
400mg Na + 3uM Compound 123 / 8 oz tomato juice
400mg Na + 3uM Compound 157 / 8 oz tomato juice

Scores were averaged across panelists and sessions, and evaluated using a 2-way ANOVA (factors: panelists and samples) and Duncan's multiple comparison test (alpha = 0.05) to determine significant differences in intensity ratings. Results are summarized below.

Table G. Tomato Juice Taste Test Results

Compound	Chemical Name	Taste Data
123	N1-(2,4-dimethoxybenzyl) N2-(2-(pyridin-2-yl)ethyl) oxalamide	3 μM cpd enhanced the savory taste of 16 mM glutamate (naturally existing) in low sodium tomato juice by 1.4 to 1.5-fold
157	N1-(2-methoxy-4-methylbenzyl)-N2-(2-(5-methylpyridin-2-yl)ethyl) oxalamide	3 μM cpd enhanced the savory taste of 16 mM glutamate (naturally existing) in low sodium tomato juice by 1.8 to 1.9-fold

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is

intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

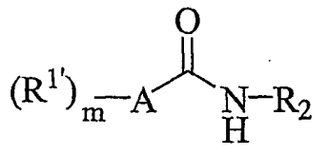
WE CLAIM:

1. A method for increasing the sweet taste of a comestible or medicinal product comprising:

   a) providing at least one comestible or medicinal product, or one or more precursors thereof, and

   b) combining the comestible or medicinal product or one or more precursors thereof with at least one aromatic or heteroaromatic amide compound, or a comestibly acceptable salt thereof, so as to form a modified comestible or medicinal product comprising at least about 0.001 ppm of the amide compound;

   wherein the amide compound has the structure:

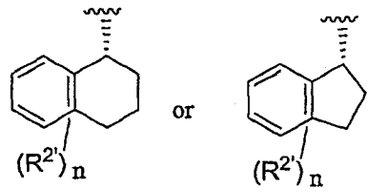


   wherein A is a five or six membered aryl or heteroaryl ring;

   m is 1, 2, or 3;

   each $R^{1'}$ is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, a C_1-C_8 organic radical;

   R^2 is a radical having the structure:



   wherein R^2 comprises the indicated optical configuration in enantiomeric excess, n is 1, 2, or 3, each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring of R^2, and each $R^{2'}$ is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical, and

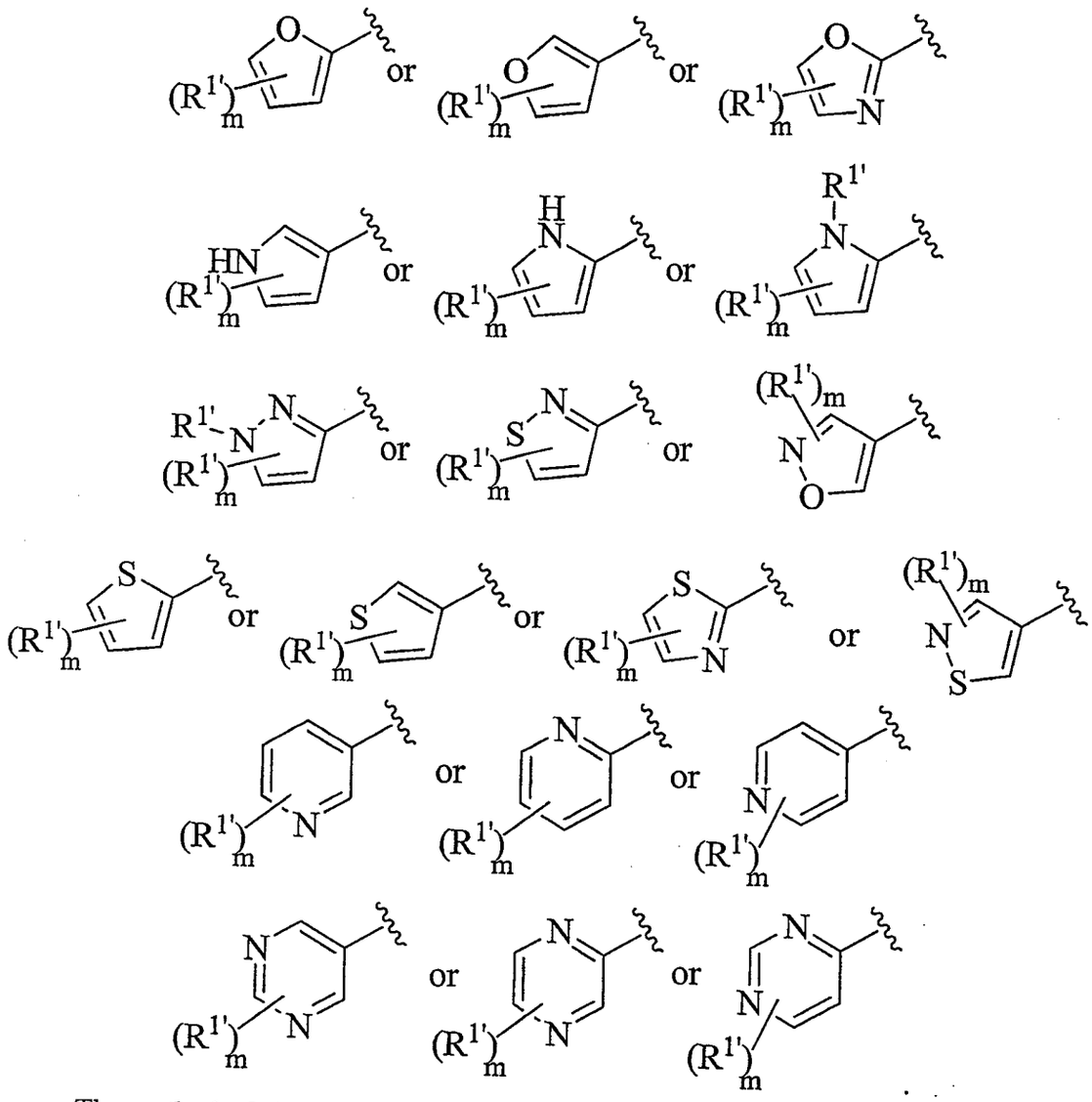
   wherein the modified comestible or medicinal product further comprises at least a sweet flavoring agent amount of one or more natural, semi-synthetic, or synthetic sweet flavoring agents, or a mixture thereof.

2. The method of claim 1 wherein the R_2 radical has the indicated optical configuration in at least 90% enantiomeric excess.

3. The method of claim 1 wherein each $R^{1'}$ and each $R^{2'}$ is independently selected from the group consisting of hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, SEt, methyl, ethyl, isopropyl, n-propyl, n-butyl, 1-methyl-propyl, isobutyl, t-butyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

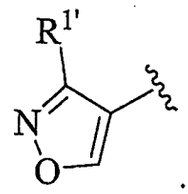
4. The method of claim 1 wherein A is a phenyl ring.

5. The method of claim 1 wherein the A radical has one of the following formulas:



6. The method of claim 5 wherein m is 1 or 2, and each $R^{1'}$ is independently selected from hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, SEt, methyl, ethyl, isopropyl, n-propyl, n-butyl, 1-methyl-propyl, isobutyl, t-butyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups.

7. The method of claim 1 wherein the A radical has the structure:



wherein $R^{1'}$ is hydrogen, hydroxyl, NH_2, SH, halogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 haloalkoxy, C_1-C_8 alkoxyl, C_1-C_8 alkoxy-alkyl, C_1-C_8 hydroxy-alkyl, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, $S(O)R^6$, $S(O)_2R^6$, and halogen, wherein R^6 is C_1-C_4 alkyl.

8. The method of claim 7 wherein $R^{1'}$ is a C_1-C_8 alkyl.

9. The method of claim 7 wherein $R^{1'}$ is hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, SEt, methyl, ethyl, isopropyl, n-propyl, n-butyl, 1-methyl-propyl, isobutyl, t-butyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy , CH_2OCH_3, CH_2OH, CH_2NH_2, CH_2NHCH_3, or $CH_2N(CH_3)_2$ group.

10. The method of claim 1 wherein the amide compound has one of the following formulas:

(R)-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-propylisoxazole-4-carboxamide;

(R)-3-butyl-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide;

(R)-3-ethyl-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide;

(R)-N-(5,7-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylisoxazole-4-carboxamide;

(R)-3-Chloro-2-hydroxy-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl) benzamide; or

(R)-3-Chloro-2-hydroxy-*N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide.

11. The method of any one of claims 1-10 wherein the natural, semi-synthetic, or synthetic sweet flavoring agents are selected from the group consisting of sucrose, fructose, glucose, erythritol, isomalt, lactitol, mannitol, sorbitol, xylitol, aspartame, saccharin, acesulfame-K, cyclamate, sucralose, and alitame, or a mixture thereof.

12. The method of any one of claims 1-10 wherein the modified comestible or medicinal product modified comestible or medicinal product has a sweeter taste than a control comestible or medicinal product that does not comprise the amide compound, as judged by the majority of a panel of at least eight human taste testers.

13. The method of any one of claims 1-10 wherein the modified comestible or medicinal product is selected from the group consisting of confectioneries, bakery products, ice creams, dairy products, sweet and savory snacks, snack bars, meal replacement products, ready meals, soups, pastas, noodles, canned foods, frozen foods, dried foods, chilled foods, oils and fats, baby foods, and spreads.

14. The method of any one of claims 1-10 wherein the modified comestible or medicinal product comprises one or more meats, poultry, fish, vegetables, grains, or fruits.

15. The method of any one of claims 1-10 wherein the modified comestible or medicinal product is a frozen food, an uncooked food, or a fully or partially cooked food.

16. The method of any one of claims 1-10 wherein the modified comestible or medicinal product is a soup, a dehydrated or concentrated soup, or a dry soup.

17. The method of any one of claims 1-10 wherein the modified comestible or medicinal product is a snack food.

18. The method of any one of claims 1-10 wherein the modified comestible or medicinal product is a cooking aid product, a meal solution product, a meal enhancement product, a seasoning, or a seasoning blend.

19. The method of any one of claims 1-10 wherein the modified comestible or medicinal product is a cake, cookie, pie, candy, chewing gum, gelatin, ice cream, sorbet, pudding, jam, jelly, salad dressing, condiment, cereal, canned fruit, or fruit sauce.

20. The method of any one of claims 1-10 wherein the modified comestible or medicinal product is a beverage, a beverage mix, or a beverage concentrate.

21. The method of any one of claims 1-10 wherein the modified comestible or medicinal product is a soda, or juice.

22. The method of any one of claims 1-10 wherein the modified comestible or medicinal product is an alcoholic beverage.

23. The method of any one of claims 1-10 wherein the modified comestible or medicinal product is an oral hygiene product.

24. The method of any one of claims 1-10 wherein the amide compound is present in the modified comestible or medicinal product in a concentration from about 0.01 ppm to about 30 ppm.

25. The method of any one of claims 1-10 wherein the modified comestible or medicinal product has a sweeter taste than a control comestible or medicinal product that does not comprise the compound, as judged by the majority of a panel of at least eight human taste testers.

26. The method of any one of claims 1-10 wherein the amide compound has an EC_{50} for binding an hT1R2/hT1R3 receptor expressed in an HEK293-Gα15 cell line of less than about 2 μM.

27. A comestible or medicinal product produced by the process of any one of claims 1-26.

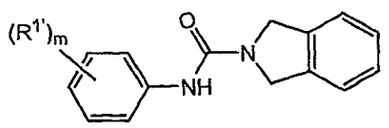
28. A method for enhancing the sweet taste of a comestible or medicinal product comprising:

a) providing at least one comestible or medicinal product, or one or more precursors thereof, and

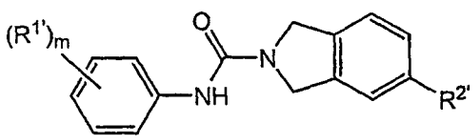
b) combining the comestible or medicinal product or one or more precursors thereof with at least one urea compound, or a comestibly acceptable salt thereof, so as to form a modified comestible or medicinal product comprising at least about 0.001 ppm of the urea compound;

c) wherein the modified comestible or medicinal product further comprises a known natural or artificial sweetener,

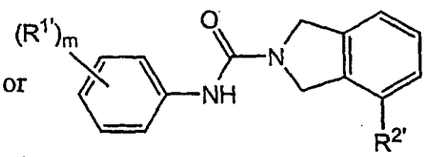
wherein the urea compound has the formula:



or

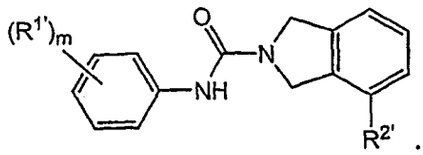


or



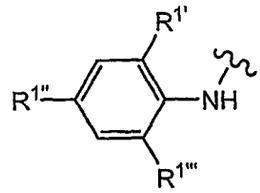
wherein m is 1, 2, or 3, and each $R^{1'}$ and $R^{2'}$ is independently selected from fluoro, chloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, SEt, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, or two $R^{1'}$ groups together form a methylenedioxy ring.

29. The method of claim 28 wherein the urea compound has the formula:



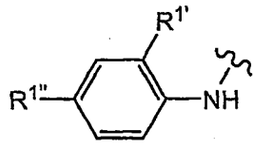
30. The method of claim 29 wherein $R^{2'}$ is methyl or methoxy.

31. The method of claim 28 wherein the aniline radical has the formula:



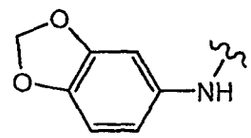
wherein $R^{1'}$, $R^{1''}$ and $R^{1'''}$ are independently selected from hydrogen, fluoro, chloro, bromo, methyl, and methoxy.

32. The method of claim 28 wherein the aniline radical has the formula:



wherein $R^{1'}$ and $R^{1''}$ are independently selected from fluoro, chloro, bromo, methyl, and methoxy.

33. The method of claim 28 wherein the $R^{1'}$ groups together form a methylenedioxy ring radical having the formula:



34. The method of claim 28 wherein the urea compound comprises from about 0.1 ppm to about 100 ppm of the modified comestible or medicinal product, and wherein the modified comestible or medicinal product has a sweeter taste than a control comestible or medicinal product that does not comprise the urea compound, as judged by the majority of a panel of at least eight human taste testers.

35. The method of any one of claims 28-34 wherein the natural, semi-synthetic, or synthetic sweet flavoring agents are selected from the group consisting of sucrose, fructose, glucose, erythritol, isomalt, lactitol, mannitol, sorbitol, xylitol, aspartame, saccharin, acesulfame-K, cyclamate, sucralose, and alitame, or a mixture thereof.

36. The method of any one of claims 28-34 wherein the modified comestible or medicinal product modified comestible or medicinal product has a sweeter taste than

a control comestible or medicinal product that does not comprise the amide compound, as judged by the majority of a panel of at least eight human taste testers.

37. The method of any one of claims 28-34 wherein the modified comestible or medicinal product is selected from the group consisting of confectioneries, bakery products, ice creams, dairy products, sweet and savory snacks, snack bars, meal replacement products, ready meals, soups, pastas, noodles, canned foods, frozen foods, dried foods, chilled foods, oils and fats, baby foods, and spreads.

38. The method of any one of claims 28-34 wherein the modified comestible or medicinal product comprises one or more meats, poultry, fish, vegetables, grains, or fruits.

39. The method of any one of claims 28-34 wherein the modified comestible or medicinal product is a frozen food, an uncooked food, or a fully or partially cooked food.

40. The method of any one of claims 28-34 wherein the modified comestible or medicinal product is a soup, a dehydrated or concentrated soup, or a dry soup.

41. The method of any one of claims 28-34 wherein the modified comestible or medicinal product is a snack food.

42. The method of any one of claims 28-34 wherein the modified comestible or medicinal product is a cooking aid product, a meal solution product, a meal enhancement product, a seasoning, or a seasoning blend.

43. The method of any one of claims 28-34 wherein the modified comestible or medicinal product is a cake, cookie, pie, candy, chewing gum, gelatin, ice cream, sorbet, pudding, jam, jelly, salad dressing, condiment, cereal, canned fruit, or fruit sauce.

44. The method of any one of claims 28-34 wherein the modified comestible or medicinal product is a beverage, a beverage mix, or a beverage concentrate.

45. The method of any one of claims 28-34 wherein the modified comestible or medicinal product is a soda, or juice.

46. The method of any one of claims 28-34 wherein the modified comestible or medicinal product is an alcoholic beverage.

47. The method of any one of claims 28-34 wherein the modified comestible or medicinal product is an oral hygiene product.

48. A comestible or medicinal product produced by the process of any one of claims 28-47.

49. A comestible composition comprising greater than about 0.001 ppm of one or more of the compounds:

3-ethyl-N-(heptan-4-yl)benzamide;

5-ethyl-N-(heptan-4-yl)-4-(methoxymethyl)furan-2-carboxamide;

3,4-dimethyl-N-(2-methylcyclohexyl)benzamide;

2-amino-3-methoxy-N-(2-methylcyclohexyl)benzamide;

N-(heptan-4-yl)-3-(methylthio)benzamide; or

N-(heptan-4-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide;

or a comestibly acceptable salt thereof, or a mixture thereof.

50. A comestible composition comprising greater than about 0.001 ppm of one or more of the compounds:

(S)-N-(2,3-Dihydro-1H-inden-1-yl)-4-methoxy-3-methylbenzamide;

4-Methoxy-N-(5-methoxy-2,3-dihydro-1H-inden-1-yl)-3-methylbenzamide;

(S)-4-Methoxy-N-(5-methoxy-2,3-dihydro-1H-inden-1-yl)-3-methylbenzamide;

2-Amino-3-methoxy-N-(5-methoxy-2,3-dihydro-1H-inden-1-yl)benzamide

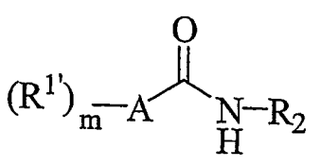
2-amino-3-methoxy-N-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide;

(S)-2-amino-3-methoxy-N-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide;

(S)-2-amino-3-methoxy-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide;

or a comestibly acceptable salt thereof, or a mixture thereof.

51. A comestible or medicinal composition comprising a comestible or medicinal product or one or more precursors thereof, and at least about 0.0001 ppm of an amide compound having the structure:

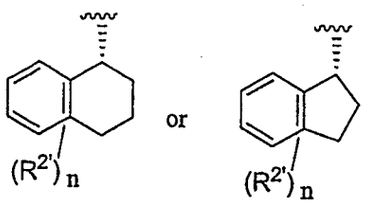


wherein A is a five or six membered aryl or heteroaryl ring;

m is 1, 2, or 3;

each $R^{1'}$ is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, a C_1-C_8 organic radical;

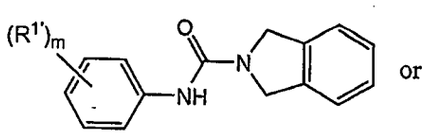
R^2 is a radical having the structure:

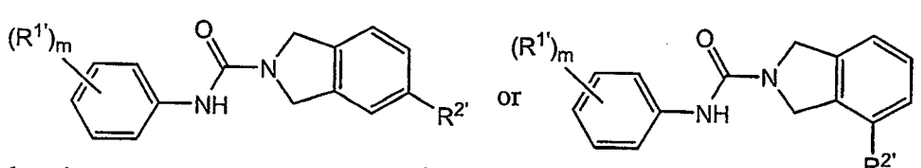


wherein R^2 comprises the indicated optical configuration in enantiomeric excess, n is 1, 2, or 3, each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring of R^2, and each $R^{2'}$ is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical; and or a comestibly acceptable salt thereof;

wherein the modified comestible or medicinal product further comprises at least a sweet flavoring agent amount of one or more natural, semi-synthetic, or synthetic sweet flavoring agents, or a mixture thereof.

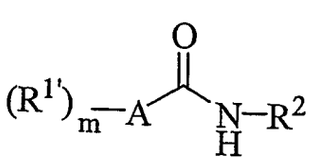
52. A modified comestible or medicinal product comprising at least one comestible or medicinal product, or one or more precursors thereof, and at least about 0.001 ppm of at least one urea compound having the formula:





wherein m is 1, 2, or 3, and each $R^{1'}$ and $R^{2'}$ is independently selected from fluoro, chloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, SEt, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, or two $R^{1'}$ groups together form a methylenedioxy ring: or a comestibly acceptable salt thereof.

53. A modified comestible or medicinal product comprising at least one comestible or medicinal product, or one or more precursors thereof, and at least about 0.001 ppm of at least one compound having the structure:



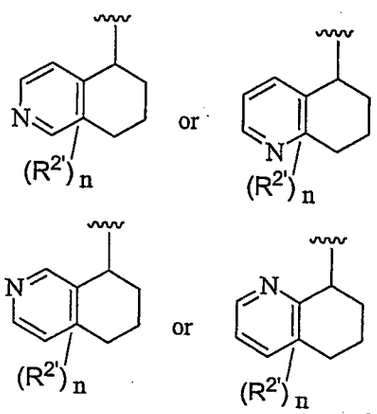
wherein A is a five or six membered aryl or heteroaryl ring;

m is 0, 1, 2, 3, or 4;

each $R^{1'}$ is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, a C_1-C_8 organic radical;

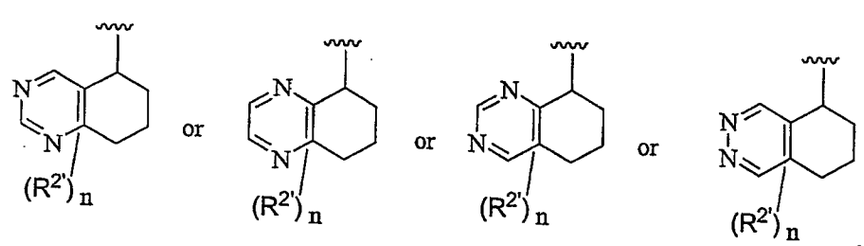
R^2 comprises a tetrahydronapthalene or indane ring modified to comprise one or more heteroatoms or heteroatomic groups independently selected from oxygen, nitrogen, or sulfur.

54. The modified comestible or medicinal product of claim 53, wherein R^2 has the structure:



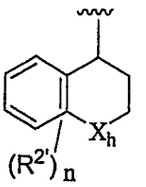
wherein n is 1, 2, or 3, each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring of R^2, and each $R^{2'}$ is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical.

55. The modified comestible or medicinal product of claim 53, wherein R^2 has one of the structures:



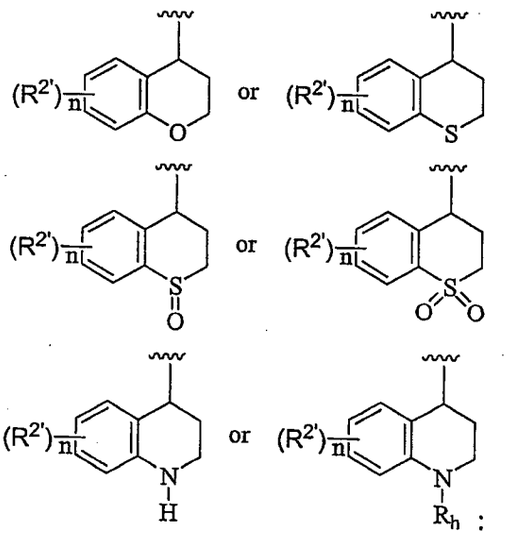
wherein n is 1, 2, or 3, each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring of R^2, and each $R^{2'}$ is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical.

56. The modified comestible or medicinal product of claim 53, wherein R^2 has the structure



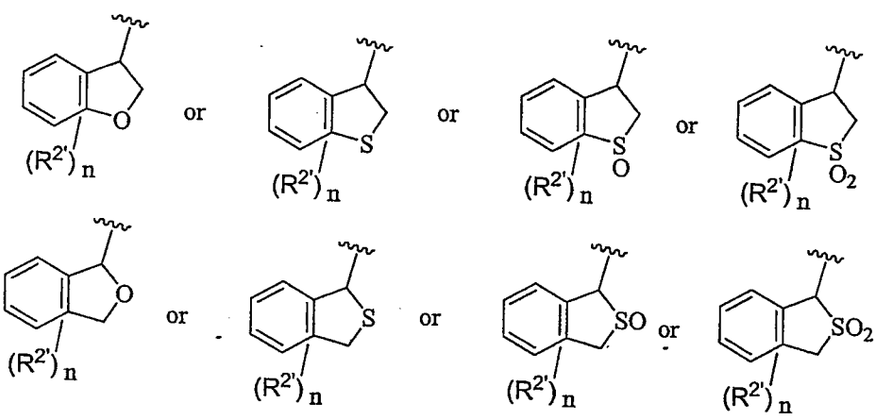
wherein n is 0, 1, 2, or 3; X_h is O, S, SO, SO_2, NH, or NR_h, wherein R_h is a C_1-C_4 organic radical; each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring of R^2;and each $R^{2'}$is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical.

57. The modified comestible or medicinal product of claim 53, wherein R^2 has the structure:



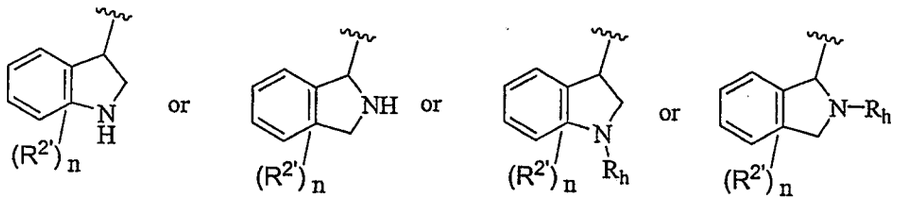
wherein n is 0, 1, 2, or 3; wherein R_h is a C_1-C_4 organic radical; and each $R^{2'}$is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical

58. The modified comestible or medicinal product of claim 53, wherein R^2 has the structure:



wherein n is 1, 2, or 3, each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring of R^2, and each $R^{2'}$ is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical.

59. The modified comestible or medicinal product of claim 53, wherein R^2 has the structure:



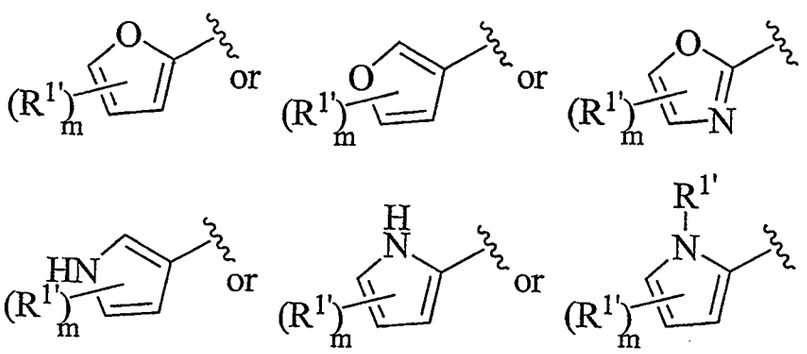
wherein n is 1, 2, or 3, each $R^{2'}$ can be bonded to either the aromatic or non-aromatic ring of R^2, and each $R^{2'}$ is independently selected from the group consisting of hydroxyl, NH_2, SH, halogen, or a C_1-C_4 organic radical.

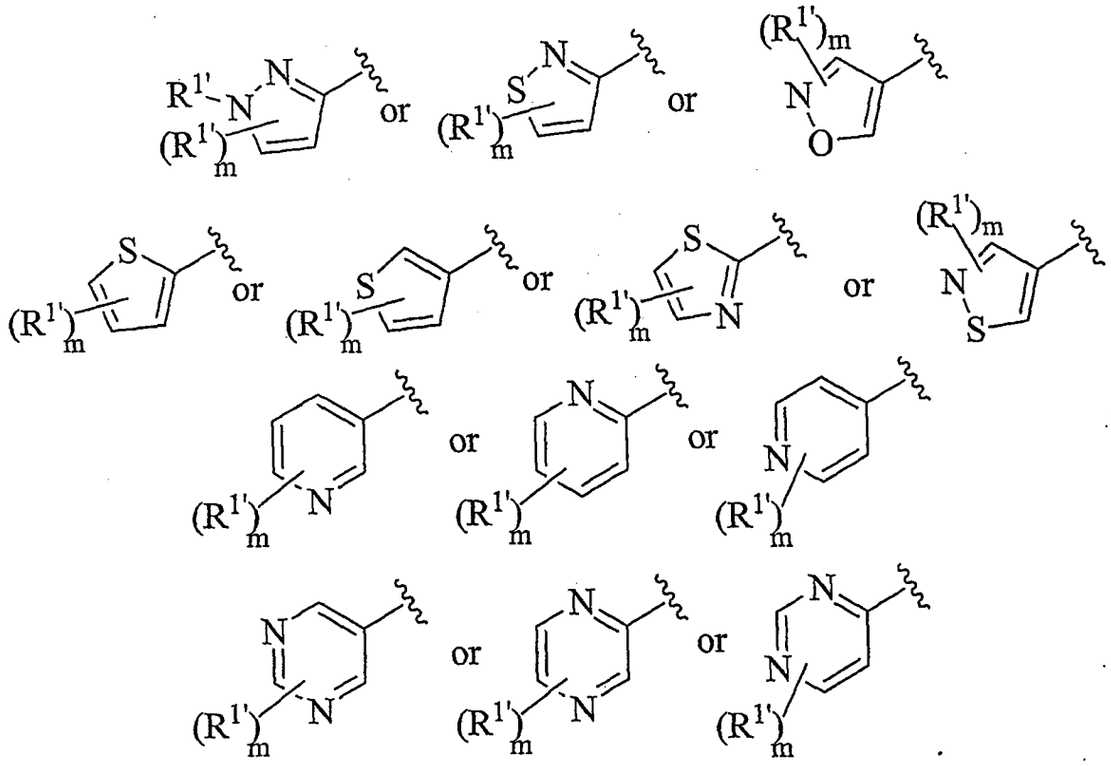
60. The modified comestible or medicinal product of each of claims 54-59 wherein the C_1-C_4 organic radical is independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy.

61. The modified comestible or medicinal product of any one of claims 53-60 wherein A is a phenyl ring.

62. The modified comestible or medicinal product of claim 53 wherein the C_1-C_8 organic radical is independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy.

63. The modified comestible or medicinal product of any one of claims 53-60 wherein the A radical has one of the following formulas:





64. The modified comestible or medicinal product of claim 63 wherein the C_1-C_8 organic radical is independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy.

65. The modified comestible or medicinal product of any one of claims 53-64 wherein the modified comestible or medicinal product further comprises at least a sweet flavoring agent amount of one or more natural, semi-synthetic, or synthetic sweet flavoring agents, or a mixture thereof.

66. The modified comestible or medicinal product of any one of claims 53-64 wherein the natural, semi-synthetic, or synthetic sweet flavoring agents comprise sucrose, fructose, glucose, erythritol, isomalt, lactitol, mannitol, sorbitol, xylitol, aspartame, saccharin, acesulfame-K, cyclamate, sucralose, and alitame, or a mixture thereof.

67. The modified comestible or medicinal product of any one of claims 53-64 wherein the modified comestible or medicinal product comprises one or more meats, poultry, fish, vegetables, grains, or fruits.

68. The modified comestible or medicinal product of any one of claims 53-64 wherein the modified comestible or medicinal product is a frozen food, an uncooked food, or a fully or partially cooked food.

69. The modified comestible or medicinal product of any one of claims 53-64 wherein the modified comestible or medicinal product is a soup, a dehydrated or concentrated soup, or a dry soup.

70. The modified comestible or medicinal product of any one of claims 53-64 wherein the modified comestible or medicinal product is a snack food.

71. The modified comestible or medicinal product of any one of claims 53-64 wherein the modified comestible or medicinal product is a cooking aid product, a meal solution product, a meal enhancement product, a seasoning, or a seasoning blend.

72. The modified comestible or medicinal product of any one of claims 53-64 wherein the modified comestible or medicinal product is a cake, cookie, pie, candy, chewing gum, gelatin, ice cream, sorbet, pudding, jam, jelly, salad dressing, condiment, cereal, canned fruit, or fruit sauce.

73. The modified comestible or medicinal product of any any one of claims 53-64 wherein the modified comestible or medicinal product is a beverage, a beverage mix, or a beverage concentrate.

74. The modified comestible or medicinal product of any one of claims 53-64 wherein the modified comestible or medicinal product is a soda, or juice.

75. The modified comestible or medicinal product any one of claims 53-64 wherein the modified comestible or medicinal product is an alcoholic beverage.

76. The modified comestible or medicinal product of any one of claims 53-64 wherein the modified comestible or medicinal product is an oral hygiene product.

295

COLO 15159-841-003-4

UREAS Y AMIDAS AROMÁTICAS Y SUS USOS COMO DEGUSTANTES, MODIFICADORES DEL SABOR DULCE Y/O UMAMI Y MEJORADORES DEL GUSTO

Esta solicitud reivindica la prioridad de la solicitud de patente de utilidad estadounidense número de serie 11/051,567, presentada en Febrero 04, 2005, la descripción completa se incorpora aquí como referencia para todos los propósitos.

CAMPO DE LA INVENCIÓN

La presente invención se relaciona con el descubrimiento de modificadores de gusto o sabor, tal como un saborizante o agentes saborizantes y mejoradores de gusto o sabor, más particularmente, modificadores de sabor dulce o salado o picante ("umami"), agentes saborizantes de dulce o salado o picante y mejoradores de sabor de dulce o salado o picante, para comidas, bebidas y otros productos o composiciones comestibles o medicinales administrados oralmente.

ANTECEDENTES DE LA INVENCIÓN

Por centurias, varias composiciones naturales y no naturales y/o compuestos se han agregado a alimentos comestibles (sabrosos), bebidas, y/o composiciones medicinales administradas oralmente para mejorar su gusto. Aunque se ha sabido hace mucho tiempo que hay solo unos pocos tipos básicos de "gustos", las bases biológicas y bioquímicas de percepción del gusto están mal entendidas, y la mayoría de la mejora del sabor o de los agentes de modificación del gusto ha sido descubierta en gran parte por procesos simples de ensayo y error. Esto ha sido un progreso significativo en la identificación de agentes

296

saborizantes naturales útiles, tales como por ejemplo endulzantes tales como sacarosa, fructosa, glucosa, eritritol, isomaltosa, lactitol, manitol, sorbitol, xilitol, ciertos terpenoides naturales conocidos, flavonoidos, o endulzantes de proteína. *Ver por ejemplo* un artículo reciente titulado "Noncariogenic Intense Natural Sweeteners" por Kinghorn, *et al.* (Med Res Rev 18 (5) 347-360, 1998), el cual habla de materiales naturales descubiertos recientemente que son más intensamente dulces que los endulzantes naturales comunes tales como sacarosa, fructosa, y similares. De forma similar, ha habido progresos recientes en la identificación y comercialización de endulzantes artificiales nuevos, tales como aspartamo, sacarina, acesulfamo-K, ciclamato, sucralosa, y alitamo, etc., ver un artículo reciente por Ager, *et al.* (Angew Chem Int. Ed. 1998, 37, 1802-1817). La descripción completa de las dos referencias identificadas anteriormente se incorporan aquí como referencia, con el propósito de describir al menos en parte el conocimiento de aquellos medianamente versados en la técnica con respecto a los agentes endulzantes conocidos.

Sin embargo, subsiste una necesidad en la técnica de agentes saborizantes mejorados y nuevos. Por ejemplo, uno de los cinco gustos básicos conocidos de los sabores son "salado o picante" o "umami" de glutamato monosódico ("MSG"). Se conoce que el MSM produce reacciones adversas en algunas personas, pero muy poco progreso ha sido hecho en la identificación de sustitutos artificiales para MSG. Se conoce que unos pocos materiales de ocurrencia natural pueden incrementar o mejorar la eficacia del MSG como un agente saborizante salado o picante, de modo que menos MSG sería necesario para una aplicación saborizante dada. Por ejemplo se conocen los compuestos de nucleótido de ocurrencia natural monofosfato de inosina (IMP) o monofosfato de guanosina (GMP) por tener efecto multiplicador en el sabor salado o picante de MSG, pero el

IMP y GMP son muy difíciles y costosos de aislar y purificar de fuentes naturales, o sintetizar, y por lo tanto solo hay aplicación práctica limitada para más necesidades comerciales en alimentos o composiciones medicinales. Serían de muy alto valor nuevos compuestos degustantes que suministrarían el sabor salado o picante de MSG en si mismo, para sustituir MSG como un sabor salado o picante, o nuevos compuestos que mejoren la eficacia de MSG para sustituir IMP o GMP como mejoradores MSG,.

De forma similar, sería de valor el descubrimiento de compuestos que son nuevos endulzantes de "Alta Intensidad" (es decir ellos son mucho más dulces que la sacarosa), o cualesquiera compuestos que incrementen significativamente el dulce de endulzantes artificiales o naturales conocidos, de modo que menos de aquellos endulzantes calóricos o no calóricos serían requeridos, podrían ser de valor y utilidad muy alta.

En años recientes se han hecho progresos sustanciales, en biotecnología y en mejor entendimiento de los fenómenos biológicos y bioquímicos subyacentes de percepción del gusto. Por ejemplo, recientemente han sido identificadas proteínas receptoras del gusto en mamíferos las cuales están involucradas en la percepción de gusto. Particularmente, se cree que están involucradas dos familias diferentes de receptores acoplados a proteína G en la percepción de gusto, han sido identificadas T2Rs y T1Rs,. (Ver, por ejemplo, Nelson, *et al, Cell* (2001) 106(3):381-390; Adler, *et al, Cell* (2000) 100(6):693-702; Chandrashekar, *et al, Cell* (2000) 100:703-711; Matsunami, *et al, Number* (2000) 404:601-604; *Li, et. al, Proc. Natl. Acad. Sci. USA* (2002) 99:4962-4966; Montmayeur, *et al, Nature Neuroscience* (2001) 4(S):492-498; Patente Estadounidense 6,462,148; y las publicaciones PCT WO 02/06254, técnica WO 00/63166, WO 02/064631, y WO

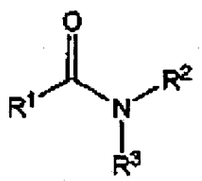
03/001876, y publicación de patente Estadounidense US 2003-0232407 A1). Las descripciones completas de los artículos, solicitudes de patente y patentes publicadas citadas inmediatamente antes se incorporan aquí como referencia, para todos los propósitos, que incluyen la descripción de las identidades y estructuras de proteínas receptoras del gusto de mamíferos T2Rs y T1Rs y métodos para expresión artificial de aquellos receptores en líneas de células y la utilización de líneas de células resultantes para exhibición de compuestos como agentes saborizantes de "dulce" o "salado o picante" potenciales.

Mientras que la familia T2R incluye una familia de más 25 genes que se involucran en la percepción de gusto amargo, el T1Rs solo incluye tres miembros, T1R1, T1R2 y T1R3. (ver Li, *et al, Proc. Natl. Acad. Sci USA* (2002) 99:4962-4966.) Recientemente se ha descrito en la WO 02/064631 y/o WO 03/001876 que ciertos miembros de T1R, cuando se co-expresan en líneas celulares de mamíferos adecuadas, se reúnen para formar receptores del sabor funcionales. Se encuentra particularmente que la co-expresión de T1R1 y T1R3 en una célula huésped adecuada resulta en un receptor de sabor salado o picante ("umami") T1R1/T1R3 funcional que responde a estímulos de sabor salado o picante, incluyendo glutamato monosódico. De forma similar, se encuentra que la co-expresión de T1R2 y T1R3 en una célula huésped adecuada resulta en un receptor de gusto "dulce" T1R2/T1R3 funcional que responde a diferentes estímulos del gusto que incluye endulzantes artificiales y de ocurrencia natural. (Ver Li, *et al.* (Id.). las referencias citadas anteriormente también describen ensayos y/o exhiben alto rendimiento que mide la actividad del receptor T1R1/T1R3 o T1R2/T1R3 mediante la formación de imagen fluorométrica en la presencia de los compuestos objetivo. Nosotros empleamos los ensayos y/o métodos de exhibición de alto rendimiento descritos anteriormente para identificar

compuestos (carga) iniciales que modulan la actividad de los receptores del sabor de "salado o picante" T1R1/T1R3, o los receptores del sabor de "dulce" T1R2/T1R3, cuando se embarcan en un largo, complejo e iterativo proceso de investigación, evaluación, y optimización, para llegar a las varias invenciones descritas adelante.

RESUMEN DE LA INVENCIÓN

La invención tiene muchos aspectos, todos los cuales se relacionan con métodos de utilización o composiciones que contienen ciertos compuestos de amida de ocurrencia no natural y/o compuestos derivados de amida que tienen la estructura genérica que se muestra adelante en la Fórmula (I):



(I)

en donde R^1, R^2 y R^3 pueden ser y se definen adicional e independientemente de varias formas, como se detalla adicionalmente adelante. En todas las modalidades de los compuestos de amida de Fórmula (I) el grupo R^1 es un residuo orgánico que comprende al menos tres átomos de carbono, con una variedad de límites alternativos en las características químicas y/o de tamaño del grupo R^1, como se describirá adicionalmente adelante. En muchas pero no en todas las modalidades, los compuestos de amida de Fórmula (I) son amidas "primarias", *es decir* uno de R^2 y R^3 es un grupo orgánico que comprende al menos tres átomos de carbono, mientras que el otro de R^2 y R^3 es hidrógeno.

Los compuestos de amida de Fórmula (I) también comprenden ciertas subclases de derivados de amida o clases de derivados relacionados con amidas, tal como por ejemplo ureas, uretanos, oxalamidas, acrilamidas, y similares, como se describirá adicionalmente adelante.

Algunos de los compuestos de amida de Fórmula (I) se han sintetizado previamente por métodos conocidos en la técnica anterior para varios propósitos. No obstante, muchos de los compuestos de amida de Fórmula (I) descritos aquí son compuestos novedosos que no han sido sintetizados previamente del todo. No obstante, en el conocimiento de los inventores no se ha reconocido previamente que tales amidas se puedan utilizar en concentraciones muy bajas en composiciones comestibles como agentes saborizantes dulces o salados o picantes, o mejoradores del sabor dulce o salado o picante.

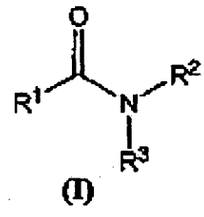
Inesperadamente, mostramos adelante que muchos de los subgéneros y especies de los compuestos "amida" de Fórmula (I) se muestran adelante por unir a y/o activar uno o ambos de los receptores del sabor dulce T1R2/T1R3 o "salado o picante" ("umami") T1R1/T1R3 *in-vitro*, en concentraciones relativamente bajas en el orden de concentraciones bajas o micromolares. Se cree también que los compuestos de amida en forma similar interactúan con receptores del sabor dulce o salado o picante de animales o humanos *in vivo*, como se ha confirmado mediante ensayos actuales del gusto humano de algunos de los compuestos de Fórmula (I).

De acuerdo con esto, la mayoría o todos los subgéneros o especies de los compuestos "amida" de Fórmula (I) descritos adicionalmente aquí adelante pueden, en concentraciones sorprendentemente bajas y útiles ser utilizados en

composiciones comestibles como agentes saborizantes dulces o salados o picantes, o agentes mejoradores del sabor dulce o salado o picante. De acuerdo con esto, en algunas modalidades, la invención se relaciona con métodos para modular el sabor dulce o salado o picante de un producto comestible o medicinal que comprende:

a) suministrar al menos un producto comestible o medicinal, o uno o más precursores de estos, y

b) combinar el producto comestible o medicinal o uno o más precursores de estos con al menos una cantidad que modula el sabor salado o picante, o una cantidad que modula el sabor dulce, de al menos un compuesto amida de ocurrencia no natural, o una sal comestiblemente aceptable de este, para formar un producto comestible o medicinal modificado; en donde el compuesto amida está dentro del alcance de cualquiera de los compuestos de Fórmula (I) como se muestra adelante, o cualquiera de los varios subgéneros de compuestos o especies de compuestos como se describen adicionalmente adelante:



(I)

en donde R^1 comprende un residuo de hidrocarburo u orgánico que tiene al menos tres átomos de carbono y opcionalmente uno o más heteroátomos independientemente seleccionados de oxígeno, nitrógeno, azufre, halógenos, o fósforo; y

en donde opcionalmente uno de R^2 y R^3 es H, y en donde al menos uno del otro de R^2 y R^3 comprende un residuo de hidrocarburo u orgánico que tiene al menos tres átomos de carbono y opcionalmente uno o más heteroátomos independientemente seleccionados de oxígeno, nitrógeno, azufre, halógenos, o fósforo.

Limitaciones opcionales adicionales de las características físicas y químicas de los grupos R^1, R^2, y R^3 serán descritas adelante.

La invención también se relaciona con los productos comestibles o medicinales producidos por los métodos y/o procesos mencionados anteriormente, y con productos comestibles o medicinales o composiciones, o sus precursores que contienen los compuestos de amida de Fórmula (I), que incluyen pero no están necesariamente limitados a alimentos, bebidas, productos medicinales y composiciones previstas para administración oral, y los precursores de estas.

En muchas modalidades, uno o más de los compuestos de amida de Fórmula (I) que se identifican, describen y/o reivindican adicionalmente aquí, o una sal comestiblemente aceptable de estos, se pueden utilizar en mezclas o en combinación con otros compuestos de sabor dulce o salado o picante, o se utilizan como mejoradores del sabor en alimentos comestibles, bebidas y composiciones medicinales, para consumo humano o animal.

En algunas modalidades, los compuestos de amida de Fórmula (I), mientras que tienen poco o quizás ningún sabor salado o picante o dulce cuando se degustan en aislamiento, se pueden emplear en concentraciones muy bajas con el fin de mejorar muy significativamente la eficacia de otros agentes de sabor de

dulce o salado o picante en una composición medicinal o comestible, o un precursor de esta. Las invenciones descritas aquí también se relacionan con los productos medicinales o comestibles modificados en sabor que contienen cantidades que modulan el sabor de uno o más de los compuestos de amida descritos aquí.

Muchos de los compuestos de amida de Fórmula (I) y/o sus varios subgéneros de compuestos de amida, cuando se utilizan junto con MSG o solos, incrementan o modulan una respuesta *in vitro*, y percepción del sabor salado o picante en humanos en concentraciones sorprendentemente bajas. Muchos de los compuestos de amida de la invención son agonistas del receptor T1R1/T1R3 y de acuerdo con esto pueden, en concentraciones sorprendentemente bajas en el orden de concentraciones micromolares o menores, inducir percepción del sabor salado o picante en humanos, independientemente de la presencia o ausencia de MSG en una composición comestible. Más aún, muchos de los compuestos de amida de Fórmula (I) pueden mejorar, potenciar, modular o inducir otros agentes saborizantes salados o picantes sintéticos y naturales, tal como MSG, por ejemplo.

En modalidades relacionadas de los compuestos de Fórmula (I) y sus usos, algunos de los compuestos de amida de Fórmula (I) son agonistas del receptor T1R2/T1R3 potentes en concentraciones de micromolares o menores, pero en muchos casos no inducen independientemente la percepción del sabor dulce en humanos independientemente de la presencia de otros endulzantes. En otras palabras, algunos de los compuestos de amida de Fórmula (I) no son percibidos por los seres humanos por ser degustantes dulces en aislamiento de otros endulzantes. No obstante, muchos de estos mismos compuestos de amida de Fórmula (I) pueden mejorar, potenciar, modular o inducir fuertemente la

percepción en humanos del sabor dulce de otros agentes saborizantes de dulce sintéticos, semisintéticos o naturales, tal como por ejemplo sacarosa, fructosa, glucosa, eritritol, isomaltosa, lactitol, manitol, sorbitol, xilitol, ciertos terpenoides naturales conocidos, flavonoides, o endulzantes de proteína, aspartamo, sacarina, acesulfamo-K, ciclamato, sucralosa, y alitamo, y similares, o una mezcla de estos.

Inesperadamente, también se ha descubierto que en muchas modalidades de los compuestos de Fórmula (I) hay similitudes estructurales significativas y/o superposiciones entre los compuestos de amida que pueden producir o mejorar los sabores dulces o salados o picantes de comestibles o composiciones medicinales, aunque se cree que las proteínas biológicas importantes receptoras del gusto son significativamente diferentes. Aún más inesperadamente, se ha descubierto que al menos algunos de los compuestos de amida de Fórmula (I) descritos aquí pueden inducir o mejorar los sabores dulces o salados o picantes de los productos comestibles o medicinales. Por lo tanto en algunos aspectos la invención se relaciona con compuestos de la Fórmula (I) o sus varios subgéneros y especies de compuestos que modulan (por ejemplo, inducen, mejoran o potencian) el sabor de agentes endulzantes sintéticos o naturales conocidos. En algunas modalidades, la invención se relaciona con compuestos novedosos, agentes saborizantes, mejoradores de sabor, compuestos que modifican el sabor, y/o composiciones que contienen los compuestos de Fórmula (I), y sus varios subgéneros y especies de compuestos.

En otras modalidades, la invención se dirige a los compuestos de Fórmula (I) o sus varios subgéneros y especies de compuestos que modulan (por ejemplo, inducen, mejoran o potencian) el sabor de glutamato monosódico (MSG), o agentes saborizantes salados o picantes sintéticos.

En algunas modalidades, la invención se relaciona con composiciones comestibles o medicinales adecuadas para consumo humano o animal, o precursores de estas, que contienen al menos un compuesto de la Fórmula (I), o una sal comestible o farmacéuticamente aceptable de este.

Estas composiciones incluyen preferiblemente productos comestibles tales como alimentos o bebidas, productos medicinales o composiciones previstas para administración oral, y productos de higiene oral, y aditivos que cuando se agregan a estos productos modulan el sabor o gusto de estos, particularmente por mejorar (incremento) el sabor dulce y/o salado o picante de estos.

La presente invención también se relaciona con géneros y especies novedosas de los compuestos de amida que caen dentro del alcance de los compuestos de Fórmula (I), y derivados, agentes saborizantes, productos comestibles o medicinales o composiciones, que incluyen agentes saborizantes dulces o salados o picantes y mejoradores de sabor que contienen los mismos.

La siguiente discusión solamente resume ciertos aspectos de las invenciones y no se deben entender, ni interpretar, como limitantes de la invención en ninguna forma.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presenten invención se puede entender más fácilmente con referencia a la siguiente descripción detallada de las varias modalidades de la invención y los Ejemplos incluidos allí y a las estructuras químicas y Tablas y su descripción

previa y posterior. Se describen antes los presentes compuestos, composiciones, y/o métodos y, se debe entender que a menos que se indique de otra forma específicamente por las reivindicaciones, la invención no se limita a alimentos específicos, o a métodos de preparación de alimentos, formulaciones o portadores farmacéuticos o comestibles específicos, o para modos particulares de formulación de los compuestos de la invención en productos comestibles o medicinales o composiciones previstas para administración oral, ya que una persona medianamente versada en la técnica será consciente, que tales enseñanzas por supuesto, pueden variar. Se debe entender también que la terminología utilizada aquí es sólo para el propósito de describir las modalidades particulares y no se debe entender como limitante.

DEFINICIONES

Como se utiliza aquí, el término "producto medicinal" incluye composiciones sólidas y líquidas que son materiales no tóxicos ingeribles que tienen valor medicinal o comprenden agentes activos medicinales tales como jarabes para la tos, gotas para la tos, aspirina y comprimidos medicinales masticables.

Un producto de higiene oral incluye sólidos y líquidos tales como pasta dentífrica o enjuague oral.

Un "excipiente o portador comestible, biológica o medicinalmente aceptable" es un medio sólido o líquido y/o composición que se utiliza para preparar una forma de dosificación deseada del compuesto de la invención, con el fin de administrar el compuesto de la invención en una forma diluida/dispersa, para que se maximice la eficacia biológica del compuesto de la invención. Un portador

comestible, biológica o medicinalmente aceptable incluye muchos ingredientes de alimento comunes, tales como agua a pH neutro, acídico o básico, jugos de frutas o vegetales, vinagre, escabechados, cerveza, vino, emulsiones de agua/grasa tales como leche o leche condensada, aceites comestibles y mantecas, ácidos grasos, oligómeros de bajo peso molecular de propilenglicol, ésteres de glicerilo de ácidos grasos, y dispersiones o emulsiones de tales sustancias hidrófobas en medio acuoso, sales tales como cloruro de sodio, harinas de trigo, disolventes tales como etanol, diluyentes comestibles sólidos tales como polvos o harinas vegetales, u otros vehículos líquidos; auxiliares de suspensión o dispersión; agentes tensoactivos; agentes isotónicos; agentes de espesamiento o emulsificantes, preservativos; ligadores sólidos; lubricantes y similares.

Un "sabor" aquí se refiere a la percepción del gusto y/o olfato en un sujeto, que incluye dulce, agrio, salado, amargo, umami, y otros. El sujeto puede ser un humano o un animal.

Un "agente saborizante" aquí se refiere a un compuesto o una sal aceptable biológicamente de este que induce un sabor o gusto en un animal o humano.

Un "modificador de sabor" aquí se refiere a un compuesto o sal aceptable biológicamente de este que modula, incluyendo mejoramiento o potenciación, y que induce, el gusto y/o olor de un agente saborizante natural o sintético en un animal o humano.

Un "mejorador de sabor" aquí se refiere a un compuesto o sal aceptable biológicamente de este que mejora los gustos u olores de un agente saborizante natural o sintético.

"Sabor salado o picante" aquí se refiere al sabor "umami" salado o picante típicamente inducido por MSG (glutamato monosódico) en un animal o humano.

"Agente saborizante salado o picante," " compuesto salado o picante" o "compuesto que activa el receptor del sabor salado o picante" aquí se refiere a un compuesto o sal aceptable biológicamente de este que elicita un sabor salado o picante detectable en un sujeto, por ejemplo, MSG (glutamato monosódico) o un compuesto que activa un receptor T1R1/T1R3 *in vitro*. El sujeto puede ser un humano o un animal.

"Agente saborizante dulce," "compuesto dulce" o "compuesto que activa el receptor dulce" aquí se refiere a un compuesto o sal aceptable biológicamente de este que elicita un sabor dulce detectable en un sujeto, por ejemplo, sacarosa, fructosa, glucosa, y otros endulzantes basados en sacáridos conocidos, o endulzantes artificiales conocidos tales como sacarinas, ciclamato, aspartamo, y similares como se discute adicionalmente aquí, o un compuesto que activa un receptor T1R2/T1R3 *in vitro*. El sujeto puede ser un humano o un animal.

Un "modificador de sabor salado o picante" aquí se refiere a un compuesto o sal aceptable biológicamente de este que modula, incluyendo mejoramiento o potenciación, que induce, y que bloquea, el sabor salado o picante de agentes saborizantes salados o picantes sintéticos o naturales, por ejemplo, glutamato monosódico (MSG) en un animal o humano.

Un "modificador de sabor dulce" se refiere a un compuesto o sal aceptable biológicamente de este que modula, incluyendo mejoramiento o potenciación,

309

induce, y bloquea, el sabor dulce de agentes saborizantes dulces naturales o sintéticos, por ejemplo, sacarosa, fructosa, glucosa, y otros endulzantes basados en sacáridos conocidos, o endulzantes artificiales conocidos tales como sacarinas, ciclamato, aspartamo, y similares, en un animal o un humano.

Un "mejorador de sabor salado o picante" aquí se refiere a un compuesto o sal aceptable biológicamente de este que mejora o potencia el sabor salado o picante de agentes saborizantes salados o picantes sintéticos o naturales, por ejemplo, glutamato monosódico (MSG) en un animal o humano.

A "mejorador de sabor dulce" aquí se refiere a un compuesto o sal aceptable biológicamente de este que mejora o potencia el sabor dulce de agentes saborizantes dulces naturales o sintéticos, por ejemplo, sacarosa, fructosa, glucosa, y otros endulzantes basados en sacáridos conocidos, o endulzantes artificiales conocidos tales como sacarinas, ciclamato, aspartamo, y similares como se discute adicionalmente aquí en un animal o humano.

Un "compuesto que activa el receptor umami" aquí se refiere a un compuesto que activa un receptor umami, tal como un receptor T1R1/T1R3.

Un "compuesto que activa el receptor dulce" aquí se refiere a un compuesto que activa un receptor dulce, tal como un receptor T1R2/T1R3.

Un "compuesto que modula el receptor umami" aquí se refiere a un compuesto que modula (activa, mejora o bloquea) un receptor umami.

Un "compuesto que modula el receptor dulce" aquí se refiere a un compuesto que modula (activa, mejora o bloquea) un receptor dulce.

Un "compuesto que mejora el receptor umami" aquí se refiere a un compuesto que mejora o potencia el efecto de un compuesto que activa el receptor umami natural o sintético, por ejemplo, glutamato monosódico (MSG).

Un "compuesto que mejora el receptor dulce" aquí se refiere a un compuesto que mejora o potencia el efecto de compuesto que activa el receptor dulce natural o sintético, por ejemplo, sacarosa, fructosa, glucosa, y otros endulzantes basados en sacáridos conocidos, o endulzantes artificiales conocidos tales como sacarinas, ciclamato, aspartamo, y similares como se discute adicionalmente aquí.

Una "cantidad de agente saborizante salado o picante" aquí se refiere a una cantidad de un compuesto (que incluye los compuestos de Fórmula (I), así como también agentes saborizantes salados o picantes conocidos tales como MSG) que es suficiente para inducir el sabor salado o picante en un producto o composición comestible o medicinal, o un precursor de esta. Un rango bastante amplio de una cantidad de agente saborizante salado o picante para los compuestos de Fórmula (I) puede ser de aproximadamente 0.001 ppm a 100 ppm, o un rango estrecho de aproximadamente 0.1 ppm a aproximadamente 10 ppm. Rangos alternativos de cantidad de agente saborizante salado o picantes pueden ser de aproximadamente 0.01 ppm a aproximadamente 30 ppm, de aproximadamente 0.05 ppm a aproximadamente 15 ppm, de aproximadamente 0.1 ppm a aproximadamente 5 ppm, o de aproximadamente 0.1 ppm a aproximadamente 3 ppm.

Una "cantidad de agente saborizante dulce" aquí se refiere a una cantidad de un compuesto (que incluye los compuestos de Fórmula (I), así como también endulzantes conocidos) que es suficiente para inducir sabor dulce en un producto o composición comestible o medicinal, o un precursor de esta. Un rango bastante amplio de una cantidad de agente saborizante dulce para los compuestos de Fórmula (I) puede ser de aproximadamente 0.001 ppm a 100 ppm, o un rango estrecho de aproximadamente 0.1 ppm a aproximadamente 10 ppm. Rangos alternativos de cantidad de agente saborizante dulces pueden ser de aproximadamente 0.01 ppm a aproximadamente 30 ppm, de aproximadamente 0.05 ppm a aproximadamente 15 ppm, de aproximadamente 0.1 ppm a aproximadamente 5 ppm, o de aproximadamente 0.1 ppm a aproximadamente 3 ppm.

Una "cantidad que modula el sabor salado o picante" aquí se refiere a una cantidad de un compuesto de Fórmula (I) que es suficiente para alterar (incrementar o disminuir) sabor salado o picante en un producto o composición comestible o medicinal, o un precursor de esta, que es suficiente para ser percibido por un sujeto humano. Un rango bastante amplio de una cantidad que modula el sabor salado o picante puede ser de aproximadamente 0.001 ppm a 100 ppm, o un rango estrecho de aproximadamente 0.1 ppm a aproximadamente 10 ppm. Rangos alternativos de cantidades que modulan el sabor salado o picante pueden ser de aproximadamente 0.01 ppm a aproximadamente 30 ppm, de aproximadamente 0.05 ppm a aproximadamente 15 ppm, de aproximadamente 0.1 ppm a aproximadamente 5 ppm, o de aproximadamente 0.1 ppm a aproximadamente 3 ppm.

Una "cantidad que modula el sabor dulce" aquí se refiere a una cantidad de un compuesto de Fórmula (I) que es suficiente para alterar (incrementar o disminuir) el sabot dulce en un producto o composición comestible o medicinal, o un precursor de esta, que es suficiente para ser percibido por un sujeto humano. Un rango bastante amplio de una cantidad que modula sabor dulce puede ser de aproximadamente 0.001 ppm a 100 ppm, o un rango estrecho de aproximadamente 0.1 ppm a aproximadamente 10 ppm. Rangos alternativos de cantidades que modulan el sabor dulce pueden ser de aproximadamente 0.01 ppm a aproximadamente 30 ppm, de aproximadamente 0.05 ppm a aproximadamente 15 ppm, de aproximadamente 0.1 ppm a aproximadamente 5 ppm, o de aproximadamente 0.1 ppm a aproximadamente 3 ppm.

Un "una cantidad que mejora el sabor salado o picante" aquí se refiere a una cantidad de un compuesto de Fórmula (I) que es suficiente para mejorar el gusto de agentes saborizantes naturales o sintéticos, por ejemplo, glutamato monosódico (MSG) cuando ellos están presentes en un producto o composición comestible o medicinal. Un rango bastante amplio de una cantidad que mejora el sabor salado o picante puede ser de aproximadamente 0.001 ppm a 100 ppm, o un rango estrecho de aproximadamente 0.1 ppm a aproximadamente 10 ppm. Rangos alternativos de una cantidad que mejora el sabor salado o picantes pueden ser de aproximadamente 0.01 ppm a aproximadamente 30 ppm, de aproximadamente 0.05 ppm a aproximadamente 15 ppm, de aproximadamente 0.1 ppm a aproximadamente 5 ppm, o de aproximadamente 0.1 ppm a aproximadamente 3 ppm.

Una "cantidad que mejora el sabor dulce" aquí se refiere a una cantidad de un compuesto de Fórmula (I) que es suficiente para mejorar el gusto de agentes

saborizantes naturales o sintéticos, por ejemplo, sacarosa, fructosa, glucosa, y otros endulzantes basados en sacáridos conocidos, o endulzantes artificiales conocidos tales como sacarinas, ciclamato, aspartamo, y similares (como se discute adicionalmente aquí) en un producto o composición comestible o medicinal. Un rango bastante amplio de una cantidad que mejora el sabor dulce puede ser de aproximadamente 0.001 ppm a 100 ppm, o un rango estrecho de aproximadamente 0.1 ppm a aproximadamente 10 ppm. Rangos alternativos de cantidad que mejora el sabor dulces pueden ser de aproximadamente 0.01 ppm a aproximadamente 30 ppm, de aproximadamente 0.05 ppm a aproximadamente 15 ppm, de aproximadamente 0.1 ppm a aproximadamente 5 ppm, o de aproximadamente 0.1 ppm a aproximadamente 3 ppm.

Una "cantidad que modula el receptor umami" se refiere aquí a una cantidad de un compuesto que es suficiente para modular (activar, mejorar o bloquear) un receptor umami. Un rango preferible de una cantidad que modula el receptor umami es 1 pM a 100 mM y más preferiblemente 1 nM a 100 µM y más preferiblemente 1 nM a30 µM. Un rango bastante amplio de una cantidad que mejora el sabor umami puede ser de aproximadamente 0.001 ppm a 100 ppm, o un rango estrecho de aproximadamente 0.1 ppm a aproximadamente 10 ppm. Rangos alternativos de cantidades que mejoran el sabor umami pueden ser de aproximadamente 0.01 ppm a aproximadamente 30 ppm, de aproximadamente 0.05 ppm a aproximadamente 15 ppm, de aproximadamente 0.1 ppm a aproximadamente 5 ppm, o de aproximadamente 0.1 ppm a aproximadamente 3 ppm.

Una "cantidad que activa o modula el receptor T1R1/T1R3" es una cantidad de compuesto que es suficiente para modular o activar un receptor T1R1/T1R3.

Estas cantidades son preferiblemente las mismas como las cantidades que modulan el receptor umami.

Un "receptor umami" es un receptor del gusto que se puede modular por un compuesto salado o picante. Preferiblemente un receptor umami es un receptor acoplado a la proteína G, y más preferiblemente el receptor umami es un receptor T1R1/T1R3.

Los compuestos de la invención modulan un receptor umami y preferiblemente son agonistas del receptor T1R1/T1R3. Un agonista de este receptor tiene el efecto de activar la cascada de señalización de proteína G. En muchos casos, este efecto agonista del compuesto en el receptor también produce un sabor salado o picante percibido en un prueba de sabor. Es deseable, por lo tanto, que tales compuestos inventivos sirven como un reemplazo para MSG, que no es tolerado por algunos en, por ejemplo, productos comestibles.

Adicionalmente, este efecto agonista también es responsable del efecto sinergístico del sabor salado o picante, que ocurre cuando un compuesto de la invención se combina con otro agente saborizante salado o picante tal como MSG. Los nucleótidos, IMP o GMP, se agregan convencionalmente a MSG, para intensificar el sabor salado o picante de MSG, de modo que relativamente menos de MSG se necesita para suministrar el mismo sabor salado o picante en comparación con solo MSG. Por lo tanto, es deseable que los compuestos combinados de la invención con otro agente saborizante salado o picante tal como MSG ventajosamente elimina la necesidad de agregar nucleótidos costosos, tales como IMP, como un mejorador de sabor, mientras que reducen concomitantemente o eliminan la cantidad de un compuesto salado o picante tal

como MSG necesaria para suministrar el mismo sabor salado o picante en comparación al compuesto salado o picante o MSG solo.

Una "cantidad que modula el receptor dulce" aquí se refiere a una cantidad de un compuesto que es suficiente para modular (activar, mejorar o bloquear) un receptor dulce. Un rango preferible de una cantidad que modula el receptor dulce es 1 pM a 100 mM y más preferiblemente 1 nM a 100 µM y más preferiblemente 1 nM a 30 µM.

Una "cantidad que activa o modula el receptor T1R2/T1R3" es una cantidad de compuesto que es suficiente para modular o activar un receptor T1R2/T1R3. Estas cantidades son preferiblemente las mismas cantidades que modulan el receptor dulce.

Un "receptor de dulce" es un receptor del gusto que se puede modular por un compuesto dulce. Preferiblemente un receptor dulce es un receptor acoplado a la proteína G, y más preferiblemente el receptor dulce es un receptor T1R2/T1R3.

Muchos compuestos de Fórmula (I) pueden modular un receptor dulce y preferiblemente son agonistas del receptor T1R2/T1R3. Un agonista de este receptor tiene el efecto de activar la cascada de señalización de proteína G. En muchos casos, este efecto agonista del compuesto en el receptor también produce un sabor dulce percibido en una prueba de sabor. Es deseable, por lo tanto, que tales compuestos de la invención sirvan como un reemplazo para sacarosa, fructosa, glucosa, y otros endulzantes basados en sacáridos conocidos, o endulzantes artificiales conocidos tales como sacarinas, ciclamato, aspartamo, y similares, o mezclas de estos como se discute adicionalmente aquí.

Un "efecto sinergístico" se relaciona con el sabor de dulce y/o salado o picante de una combinación de compuestos que activan el receptor o compuestos dulces y/o salados o picantes, en comparación con la suma de los efectos del gusto o efectos asociados con sabor asociados con cada compuesto individual. En el caso de compuestos mejoradores de sabor salado o picante, un efecto sinergístico en la eficacia de MSG se puede indicar por un compuesto de Fórmula (I) que tiene una proporción EC50 (definida aquí adelante) de 2.0 o más, o preferiblemente 5.0 o más, o 10.0 o más, o 15.0 o más. Un ensayo EC50 para mejorar el sabor no todavía no ha sido desarrollado, pero en el caso de los compuestos mejoradores del sabor dulce y salado o picante, un efecto sinergístico se pueden confirmar por ensayos de gusto humano, como se describe en otra parte aquí.

Cuando los compuestos descritos aquí incluyen uno o más centros quirales, la estereoquímica de tales centros quirales puede independiente estar en la configuración R o S, o una mezcla de las dos. Los centros quirales puede ser designados adicionalmente como R o S o R,S o d,D, l,L o d,l, D,L. Correspondientemente, los compuestos de amida de la invención, si ellos pueden estar presentes en forma activa, pueden actualmente estar presentes en la forma de una mezcla racémica de enantiómeros, o en la forma de cualquiera de los enantiómeros separados en forma purificada y sustancialmente aislada, o como una mezcla que comprende cualesquiera proporciones relativas de los enantiómeros.

En relación con los compuestos descritos aquí, el sufijo "en" agregado a Cualquiera de los términos descritos significa que el sustituyente se conecta en

dos otras partes en el compuesto. Por ejemplo, "alquileno" es $(CH_2)_n$, "alquenileno" es tal una porción que contiene un enlace doble y "alquinileno" es tal una porción que contiene un triple enlace.

Como se utiliza aquí, "residuo de hidrocarburo" se refiere a un subgrupo químico o radical dentro de un compuesto químico grande que contiene solo átomos de carbono e hidrógeno. El residuo de hidrocarburo puede ser alifático o aromático, de cadena recta, cíclica, ramificada, saturado o insaturado. En muchas modalidades los residuos de hidrocarburo son de tamaño dimensional y peso molecular limitado, y pueden comprender de 1 a 18 átomos de carbono, 1 a 16 átomos de carbono, 1 a 12 átomos de carbono, 1 a 10 átomos de carbono, 1 a 8 átomos de carbono, 1 a 6 átomos de carbono, o 1 a 4 átomos de carbono.

El residuo de hidrocarburo, cuando se describe como "sustituido", contiene o se sustituye con uno o más heteroátomos independientemente seleccionados tales como O, S, N, P, o los halógenos (flúor, cloro, bromo, y yodo), o uno o más grupos sustituyentes que contienen heteroátomos (OH, NH_2, NO_2, SO_3H, y similares) sobre y sobre los átomos de carbono e hidrógeno del residuo sustituyente. Los residuos de hidrocarburo sustituidos pueden también contener grupos carbonilo, grupos amino, grup os hidroxilo y similares, o contiene heteroátomos insertados dentro de la "estructura" del residuo de hidrocarburo.

Como se utiliza aquí, grupo o residuo "inorgánico" se refiere a sustituyentes radicales aniónicos, catiónicos o neutros en las moléculas orgánicas descritos o reivindicados aquí que tienen de uno a 16 átomos que no incluyen carbono, pero contienen otros heteroátomos de la tabla periódica que preferiblemente que incluyen uno o más átomos independientemente seleccionados del grupo que

consiste de H, O, N, S, uno o más halógenos, o iones de metal álcali, o de metales alcalinotérreos. Ejemplos de radicales inorgánicos incluyen, pero no se limitan a H, Na+, Ca_1 y K+, halógenos que incluye flúor, cloro, bromo, y yodo, OH, SH, SO_3H, $SO_3^{"}$, PO_3H, $PO_3^{"}$, NO, NO_2 o NH_2, y similares.

Como se utiliza aquí, el término "alquilo," "alquenilo" y "alquinilo" incluye sustituyentes monovalentes de cadena recta y ramificada y cíclicos que respectivamente son saturados e insaturados con al menos un enlace doble, e insaturado con al menos un enlace triple.

"Alquilo" se refiere a un grupo hidrocarburo que se puede formar conceptualmente a partir de un alcano al remover hidrógeno de la estructura de un compuesto de hidrocarburo no cíclico que tiene cadenas de carbono rectas o ramificadas, y que reemplazan el átomo de hidrógeno con otro átomo o grupo sustituyente orgánico e inorgánico. En algunas modalidades de la invención, los grupos alquilo son "alquilo C1 a C6" tal como metilo, etilo, propilo, isopropilo, n-butilo, iso-butilo, sec-butilo, terc-butilo, amilo, terc-amilo, hexilo y similares. Muchas de las modalidades de la invención comprenden grupos "alquilo C1 a C4" (alternativamente llamados grupos "alquilo inferiores") que incluyen grupos metilo, etilo, propilo, iso-propilo n-butilo, iso-butilo, sec-butilo, y t-butilo. Alguno de los grupos alquilo preferidos de la invención tienen tres o más átomos de carbono preferiblemente 3 a 16 átomos de carbono, 4 a 14 átomos de carbono, o 6 a 12 átomos de carbono.

El término "alquenilo" denota un residuo o grupo hidrocarburo que comprende al menos un enlace doble carbono-carbono. En algunas modalidades, los grupos alquenilo son "alquenilos C_2 a C_7" que se ejemplifican por vinilo, alilo, 2-

butenilo, 3-butenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 2-hexenilo, 3-hexenilo, 4-hexenilo, 5-hexenilo, 2-heptenilo, 3-heptenilo, 4-heptenilo, 5-heptenilo, 6-heptenilo, así como también dienos y trienos de cadenas rectas o ramificadas. En otras modalidades, alquenilos se limitan de dos a Cuatro átomos de carbono.

El término "alquinilo" denota un residuo de hidrocarburo que comprende al menos un enlace triple carbono-carbono. Los grupos alquinilo preferidos son alquinilo C2 a C7" tal como etinilo, propinilo, 2-butinilo, 2-pentinilo, 3-pentinilo, 2-hexinilo, 3-hexinilo, 4-hexinilo, 2-heptinilo, 3-heptinilo, 4-heptinilo, 5-heptinilo así como también di- y tri-enos de cadenas rectas o ramificadas que incluyen ene-inos.

Los términos "alquilo sustituido," "alquenilo sustituido," "alquinilo sustituido," y "alquileno sustituido" denotan que los grupos o radicales alquilo, alquenilo, alquinilo y alquileno como se describió anteriormente han tenido uno o más átomos de hidrógeno sustituidos por uno o más, y preferiblemente uno o dos grupos o radiclaes sustituyentes orgánicos o inorgánicos, que pueden incluir halógeno, hidroxi, grupos alcoxi C_1 a C_7, alcoxi-alquilo, oxo, cicloalquilo C_3 a C_7, naftilo, amino, (monosustituido)amino, (disustituido)amino, guanidino, heterociclo, heterociclo sustituido, imidazolilo, indolilo, pirrolidinilo, acilo C_1 a C_7, aciloxi C_1 a C_7, nitro, carboxi, carbamoilo, carboxamida, N-(alquilo C_1 a C_6)carboxamida, N,N-di(alquilo C_1 a C_6)carboxamida, ciano, metilsulfonilamino, tiol, alquiltio C_1 a C_4 o alquilosulfonilo C_1 a C_4. Los grupos alquilo sustituidos se pueden sustituir una vez o más, y preferiblemente una vez o dos veces, con los mismos o diferentes sustituyentes. En muchas modalidades de la invención, un grupo preferido de los grupos sustituyentes incluye hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, grupos metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi,

isopropoxi, y trifluorometoxi. En muchas modalidades de la invención que comprende la lista anterior de grupos sustituyentes, un grupo aún más preferido de los grupos sustituyentes incluyen hidroxi, SEt, SCH_3, grupos metilo, etilo, isopropilo, triflurometilo, metoxi, etoxi, y trifluorometoxi.

Ejemplos de los anteriores grupos alquilo sustituidos incluyen el 2-oxo-prop-1-ilo, 3-oxo-but-1-ilo, cianometilo, nitrometilo, clorometilo, trifluorometilo, hidroximatilo, tetrahidropiraniloximatilo, tritiloximatilo, propioniloximatilo, aminometilo, carboximatilo, aliloxicarbonilmetilo, aliloxicarbonilaminometilo, metoximatilo, etoximatilo, t-butoximatilo, acetoximatilo, clorometilo, trifluorometilo, 6-hidroxihexilo, 2,4-dicloro(n-butil), 2-aminopropilo, 1-cloroetilo, 2-cloroetilo, 1-bromoetilo, 2-cloroetilo, 1-fluoroetilo, 2-fluoroetilo, 1-yodoetilo, 2-yodoetilo, 1-cloropropilo, 2-cloropropilo, 3- cloropropilo, 1-bromopropilo, 2-bromopropilo, 3-bromopropilo, 1-fluofopropilo, 2-fluoropropilo, 3-fluoropropilo, 2-aminoetilo, 1-aminoetilo, N-benzoil-2-aminoetilo, N-acetil-2-aminoetilo, N-benzoil-1-aminoetilo, N-acetil-1-aminoetilo y similares.

Ejemplos de grupos alquenilo sustituidos incluyen estirenilo, 3-cloro-propen-1-ilo, 3-cloro-buten-1-ilo, 3-metoxi-propen-2-ilo, 3-fenil-buten-2-ilo, 1-ciano-buten-3-ilo y similares. El isomerismo geométrico no es crítico y se pueden incluir todos los isómeros geométricos para un enlace doble sustituido dado.

Ejemplos de grupos alquinilo sustituidos incluyen fenilacetilen-1-ilo, 1-fenil-2-propin-1-ilo y similares.

Los haloalquilos son grupos o residuos alquilo sustituidos en donde uno o más hidrógenos del correspondiente grupo alquilo ha sido reemplazado con un

átomo de halógeno (flúor, cloro, bromo, y yodo). Los haloalquilos preferidos pueden tener uno a Cuatro átomos de carbono. Ejemplos de grupos haloalquilo preferidos incluyen grupos trifluorometilo y pentafluoroetilo.

Los residuos o grupos alcoxi o grupos haloalcoxi en donde uno o más hidrógenos del grupo R del grupo alcoxi son un átomo de halógeno (flúor, cloro, bromo, y yodo). Los grupos haloalcoxi preferidos s pueden tener de uno a Cuatro átomos de carbono. Ejemplos de grupos haloalcoxi preferidos incluyen grupos trifluorometioxi y pentafluoroetoxi.

El término "oxo" den ota un átomo de carbono unido a dos átomos de carbono adicionales sustituidos con un átomo de oxígeno unido doblemente al átomo de carbono, con lo cual se forma un residuo o radical cetona.

"Alcoxi" o "alcoxilo" se refiere a un grupo o radical -OR, en donde R es un radical alquilo. En algunas modalidades los grupos alcoxi pueden ser C_1 a C_8, y en otras modalidades los grupos alcoxi pueden ser C_1 a C_4 en donde R es un alquilo inferior, tal como a metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi, t-butoxi y grupos alcoxi. El término "alcoxi sustituido" significa que el grupo R es un residuo o grupo alquilo sustituido. Ejemplos de grupos alcoxi sustituidos incluyen trifluorometoxi, hidroximatilo, hidroxietilo, hidroxipropilo, y grupos alcoxialquilo tales como metoximatilo, metoxietilo, polioxoetileno, polioxopropileno, y grupos similares.

"Alcoxialquilo" se refiere a un radical o grupo -R-O-R', en donde R y R' son grupos alquilo. En algunas modalidades los grupos alcoxialquilo pueden ser C_1 a C_8, y en otras modalidades pueden ser C_1 a C_4. En muchas modalidades, ambos R y R' son un alquilo inferior, tal como un grupo metoxi, etoxi, n-propoxi,

isopropoxi, n-butoxi, t-butoxi y grupos alcoxi similares. Ejemplos de grupos alcoxialquilo incluyen, metoximatilo, etoxietilo, metoxipropilo, y metoxibutilo y grupos similares.

"Hidroxialquilo" se refiere a un radical o grupo -R-OH, en donde R es un grupo alquilo. En algunas modalidades los grupos hidroxialquilo pueden ser C_1 a C_8, y en otras modalidades pueden ser C_1 a C_4. En muchas modalidades, R es un alquilo inferior. Ejemplos de grupos alcoxialquilo incluyen, hidroximatilo, 1-hidroxietilo, 2-hidroxietilo 3-hidroxipropilo, y grupos similares.

"Aciloxi" se refiere a un grupo éster-RCO_2 en donde R es un radical o grupo alquilo, cicloalquilo, arilo, heteroarilo, alquilo sustituido, cicloalquilo sustituido, arilo sustituido, o heterarilo sustituido en donde el radical R comprende uno a siete o uno a cuatro átomos de carbono. En muchas modalidades, R es un radical alquilo, y tales radicales aciloxi se ejemplifican por formiloxi, acetoxi, propioniloxi, butiriloxi, pivaloiloxi, pentanoiloxi, hexanoiloxi, heptanoiloxi y similares. En otras modalidades los grupos R son alquilos C_1-C_4.

Como se utiliza aquí, "acilo" abarca las definiciones de alquilo, alquenilo, alquinilo y las hetero-formas relacionados que se acoplan con un residuo orgánico adicional a través de un grupo carbonilo para formar un grupo o radical cetona. Los grupos acilo preferidos son "acilo C_1 a C_7" tal como formilo, acetilo, propionilo, butirilo, pentanoilo, pivaloilo, hexanoilo, heptanoilo, benzoilo y similares. Los grupos acilo más preferidos son acetilo y benzoilo.

El término "sustituido acilo" denota un grupo acilo en donde el grupo R sustituido por uno o más, y preferiblemente uno o dos, grupos halógeno, hidroxi,

oxo, alquilo, cicloalquilo, naftilo, amino, (monosustituido)amino, (disustituido)amino, guanidino, anillo heterocíclico, anillo heterocíclico sustituido, imidazolilo, indolilo, pirrolidinilo, alcoxi C_1 a C_7, alcoxi-alquilo, acilo C_1 a C_7, aciloxi C_1 a C_7, nitro, éster de alquilo C_1 a C_6, carboxi, alcoxicarbonilo, carbamoilo, carboxamida, N-(alquilo C_1 a C_6)carboxamida, N,N-di(alquilo C_1 a C_6)carboxamida, ciano, metilsulfonilamino, tiol, alquiltio C_1 a C_4 o alquilosulfonilo C_1 a C_4. Los grupos acilo sustituidos se pueden sustituir una vez o más, y preferiblemente una vez o dos veces, con los mismos o diferentes sustituyentes.

Ejemplos de grupos acilo C_1 a C_7 sustituidos incluyen 4-fenilbutiroilo, 3-fenilbutiroilo, 3 fenilpropanoilo, 2- ciclohexanilacetilo, ciclohexanocarbonilo, 2-furanoilo y 3 dimetilaminobenzoilo.

Los grupos o residuos cicloalquilo se relacionan estructuralmente con compuestos de hidrocarburos cíclicos monocíclicos o bicíclicos en donde uno o más átomos de hidrógeno han sido reemplazados con un grupo sustituyente orgánico o inorgánico. Los cicloalquilos de las invenciones actuales que comprenden al menos 3 hasta 12, o más preferiblemente 3 a 8 átomos de carbono en el anillo, o más preferiblemente 4 a 6 átomos de carbono en el anillo. Ejemplos de tales residuos cicloalquilo incluyen anillos ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, y cicloalcanos saturados bicíclicos o fusionados policíclicos tales como grupos decalin, norbornilo policíclico o grupos adamantil, y similares.

Los grupos cicloalquilo preferidos incluyen “cicloalquilo C3 a C7” tal como anillos ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo o cicloheptilo. De forma

similar, el término "cicloalquilo C5 a C7" incluye anillos ciclopentilo, ciclohexilo o cicloheptilo.

"Cicloalquilo sustituido" denotan anillos cicloalquilos como se definió anteriormente, sustituidos por 1 a cuatro, o preferiblemente uno o dos sustituyentes independientemente seleccionados de un halógeno, hidroxi, alquiltio C_1 a C_4, alquilosulfóxido C_1 a C_4, alquilosulfonilo C_1 a C_4, alquiltio sustituido C_1 a C_4, alquilosulfóxido sustituido C_1 a C_4, alquilosulfonilo sustituido C_1 a C_4, alquilo C_1 a C_4, alcoxi C_1 a C_4, alquilo C_1 a C_6 sustituido, alcoxi-alquilo C_1 a C_4, oxo (monosustituido)amino, (disustituido)amino, trifluorometilo, carboxi, fenilo, fenilo sustituido, feniltio, fenilsulfóxido, fenilsulfonilo, amino. En muchas modalidades de grupos cicloalquilo sustituidos, tendrá 1, 2, 3, o 4 grupos sustituyentes independientemente seleccionados de grupos hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

El término "cicloalquileno" significa un cicloalquilo, como se definió anteriormente, en donde el radical cicloalquilo está unido a dos posiciones conectadas junto con dos grupos adicionales separados. De forma similar, el término "cicloalquileno sustituido" significa un cicloalquileno en donde el radical cicloalquilo está unido a dos posiciones conectadas junto con dos grupos adicionales separados y adicionalmente soporta al menos un sustituyente adicional.

El término "cicloalquenilo" indica preferiblemente un anillo 1,2, o 3-ciclopentenilo, un anillo 1,2,3 o 4-ciclohexenilo o un anillo 1,2,3,4 o 5-cicloheptenilo, mientras que el término "cicloalquenilo sustituido" denota los anillos

cicloalquenilo anteriores sustituidos con un sustituyente, preferiblemente pir un alquilo C_1 a C_6, halógeno, hidroxi, alcoxi C_1 a C_7, alcoxi-alquilo, trifluorometilo, carboxi, alcoxicarbonilo oxo, (monosustituido)amino, (disustituido)amino, fenilo, fenilo sustituido, amino, o amino protegido.

El término "cicloalquenileno" es un anillo cicloalquenilo, como se definió anteriormente, en donde el radical cicloalquenilo está unido en dos posiciones conectadas junto con dos grupos adicionales separados. De forma similar, el término "cicloalquenileno sustituido" significa un cicloalquenileno adicionalmente sustituido preferiblemente por un grupo halógeno, hidroxi, alquiltio C_1 a C_4, alquilosulfóxido C_1 a C_4, alquilos ulfonilo C_1 a C_4, alquiltio sustituido C_1 a C_4, alquilosulfóxido sustituido C_1 a C_4, alquilosulfonilo C_1 a C_4 sustituido, alquilo C_1 a C_6, alcoxi C_1 a C_7, alquilo C_1 a C_6 sustituido, alcoxi-alquilo C_1 a C_7, oxo, (monosustituido)amino, (disustituido)amino, trifluorometilo, carboxi, alcoxicarbonilo, fenilo, fenilo sustituido, feniltio, fenilsulfóxido, fenilsulfonilo, amino, o amino sustituido.

El término "heterociclo" o "anillo heterocíclico" denota opcionalmente anillos de 3 a 8-miembros sustituidos que tienen uno o más átomos de carbono conectados en un anillo que también comprende anillo de 1 a 5 heteroátomos, tal como oxígeno, azufre y/o nitrógeno insertados dentro del anillo. Estos anillos heterocíclicos pueden ser saturados, insaturados o parcialmente insaturados, pero preferiblemente son saturados. Un "anillo heterocíclico amino-sustituido" significa cualquiera de uno de los anillos heterocíclicos anteriormente descritos que se sustituye con al menos un grupo amino. Anillos heterocíclicos insaturados preferidos incluyen furanilo, tiofuranilo, pirrolilo, piridilo, pirimidilo, pirazinilo, benzoxazol, benztiazol, quinolinlilo, y anillos heteroaromáticos similares. Anillos

heterocíclicos saturados preferidos incluyen anillos piperidilo, aziridinilo, piperidinilo, piperazinilo, tetrahidrofurano, pirrolilo, y tetrahidrotiofen-ilo.

El término "heterociclo sustituido" o "anillo heterocíclico sustituido" significa que el anillo heterocíclico anteriormente descrito se sustituye con, por ejemplo, uno o más, y preferiblemente uno o dos, sustituyentes que son los mismos o diferentes cuyos sustituyentes preferiblemente pueden ser grupos halógeno, hidroxi, tio, alquiltio, ciano, nitro, alquilo C_1 a C_4, alcoxi C_1 a C_4, alcoxi C_1 a C_4 sustituido, alcoxi-alquilo, acilo C_1 a C_4, aciloxi C_1 a C_4, carboxi, alcoxicarbonilo, carboximatilo, hidroximatilo, alcoxi-alquilo amino, monosustituido)amino, (disustituido)amino carboxamida, N-(alquilo C_1 a C_6)carboxamida, N,N-di(alquilo C_1 a C_6)carboxamida, trifluorometilo, N-((alquilo C_1 a C_6)sulfonil)amino, N-(fenilsulfonil) amino, o sustituido con un anillo fusionado, tal como anillo benzo. En muchas modalidades de grupos heterocíclicos sustituidos, el grupo cicloalquilo sustituido tendrá 1, 2, 3, o 4 grupos sustituyentes independientemente seleccionados de grupos hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

Un grupo "arilo" se refiere a un grupo o radical monocíclico, bicíclico ligado o bicíclico fusionado que comprende al menos un anillo "benceno" aromático de seis miembros. Los grupos arilo preferiblemente comprenden entre 6 y 12 átomos de carbono en el anillo, y se ejemplifican por grupos fenilo, bifenilo, naftilo indanilo, y tetrahidronaptilo. Los grupos arilo se pueden sustituir opcionalmente con varios grupos sustituyentes orgánicos y/o inorgánicos, en donde el grupo arilo sustituido en combinación con todos sus sustituyentes comprenden entre 6 y 18, o preferiblemente 6 y 16 átomos de carbono totales. Los grupos sustituyentes

opcionales preferidos incluyen 1, 2, 3, o 4 grupos sustituyentes independientemente seleccionados de grupos hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

El término "heteroarilo" significa un derivado de arilo heterocíclico que preferiblemente contiene un sistema de anillo aromático y conjugado de cinco miembros o seis miembros que tiene de 1 a 4 heteroátomos independientemente seleccionados de oxígeno, azufre y/o nitrógeno, insertados dentro del anillo heterocíclico conjugado e insaturado. Los grupos heteroarilo incluyen porciones heteroaromáticas monocíclicas, heteroaromáticas bicíclicas ligadas o heteroaromáticas bicíclicas fusionadas. Ejemplos de heteroarilos incluyen piridinilo, pirimidinilo, y pirazinilo, piridazinilo, pirrolilo, furanilo, tiofuranilo, oxazoloilo, isoxazolilo, ftalimido, tiazolilo, quinolinilo, isoquinolinilo, indolilo, o un furano o tiofurano unido directamente a un anillo a fenilo, piridilo, o pirrolilo y anillos heteroaromáticos conjugados e insaturados similares. Cualquier sistema de anillo heteroarilo monocíclico, bicíclico ligado, o bicíclico fusionado que tiene las características de aromaticidad en términos de distribución de electrón a través del sistema de anillo se incluye en esta definición. Típicamente, los sistemas de anillos heteroaromáticos contienen 3-12 átomos de carbono en el anillo y anillo de 1 a 5 heteroátomos independientemente seleccionados de átomos de oxígeno, nitrógeno, y azufre.

El término "heteroarilo sustituido" significa que el heteroarilo anteriormente descrito se sustituye con, por ejemplo, uno o más, y preferiblemente uno o dos, sustituyentes que son los mismos o diferentes cuyos sustituyentes preferiblemente pueden ser grupos halógeno, hidroxi, hidroxi protegido, tio, alquiltio, ciano, nitro,

alquilo C_1 a C_6, alquilo C_1 a C_7 sustituido, alcoxi C_1 a C_7, alcoxi sustituido C_1 a C_7, alcoxi-alquilo, acilo C_1 a C_7, acilo C_1 a C_7 sustituido, aciloxi C_1 a C_7, carboxi, alcoxicarbonilo, carboximatilo, hidroximatilo, amino, (monosustituido)amino, (disustituido)amino, carboxamida, N-(alquilo C1 a C6)carboxamida, N,N-di(alquilo C1 a C6)carboxamida, trifluorometilo, N-((alquilo C_1 a C_6)sulfonil)amino o N-(fenilsulfonil)amino. En muchas modalidades de los grupos heteroarilo sustituidos, el grupo cicloalquilo sustituido tendrá 1, 2, 3, o 4 grupos sustituyentes independientemente seleccionados de grupos hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

De forma similar, "arilalquilo" y "heteroarilalquilo" se refieren a sistemas aromáticos y heteroaromáticos que se acoplan con otro residuo a través de una cadena de carbono, que incluye cadenas de carbono sustituidas o no sustituidas, saturadas o insaturadas, típicamente de 1 a 6 C. Estas cadenas de carbono pueden también incluir un grupo carbonilo, así para hacerlas más capaces de suministrar sustituyentes como una porción acilo. Preferiblemente, arilalquilo o heteroarilalquilo es un grupo alquilo sustituido en cualquier posición por un grupo arilo, arilo sustituido, heteroarilo o heteroarilo sustituido. Grupos preferidos también incluyen bencilo, 2-feniletilo, 3-fenil-propilo, 4-fenil-n-butilo, 3-fenil-n-amilo, 3-fenil-2-butilo, 2-piridinilmetilo, 2-(2-piridinil)etilo, y similares.

El término "arilalquilo sustituido" denota un grupo arilalquilo sustituido en la porción alquilo con uno o más, y preferiblemente uno o dos, grupos preferiblemente escogidos de grupos halógeno, hidroxi, oxo, amino, (monosustituido)amino, (disustituido)amino, guanidino, anillo heterocíclico, anillo heterocíclico sustituido, alquilo C_1 a C_6, alquilo C_1 a C_6 sustituido, alcoxi C_1 a C_7,

alcoxi C_1 a C_7 sustituido, alcoxi-alquilo, acilo C_1 a C_7, acilo C_1 a C_7 sustituido, aciloxi C_1 a C_7, nitro, carboxi, alcoxicarbonilo, carbamoilo, carboxamida, N-(alquilo C_1 a C_6)carboxamida, N,N-(dialquilo C_1 a C_6)carboxamida, ciano, N-(alquilosulfonil C_1 a C_6)amino, tiol, alquiltio C_1 a C_4, alquilosulfonilo C_1 a C_4; y/o el grupo fenilo se puede sustituir con uno o más, y preferiblemente uno o dos, sustituyentes preferiblemente escogidos de halógeno, hidroxi, hidroxi protegido, tio, alquiltio, ciano, nitro, alquilo C_1 a C_6, alquilo C_1 a C_6 sustituido, alcoxi C_1 a C_7, alcoxi C_1 a C_7 sustituido, alcoxi-alquilo, acilo C_1 a C_7, acilo C_1 a C_7 sustituido, aciloxi C_1 a C_7, carboxi, alcoxicarbonilo, carboximatilo, hidroximatilo, amino, (monosustituido)amino, (disustituido)amino, carboxamida, N-(alquilo C_1 a C_6) carboxamida, N,N-di(alquilo C_1 a C_6)carboxamida, trifluorometilo, N-((alquilo C_1 a C_6)sulfonil)amino, N-(fenilsulfonil)amino, alquileno C_2 a C_7 cíclico o un grupo fenilo, sustituido o no sustituido, para un grupo bifenilo resultante. Los grupos alquilo o fenilo sustituidos se pueden sustituir con uno o más, y preferiblemente uno o dos, sustituyentes que pueden ser los mismos o diferentes.

Ejemplos del término "arilalquilo sustituido" incluyen grupos tales como 2-fenil-1-cloroetilo, 2-(4-metoxifenil)etilo, 4-(2,6-dihidroxi fenil)-n-hexilo, 2-(5-ciano-3-metoxifenil)-n-pentilo, 3-(2,6-dimetilfenil)propilo, 4-cloro-3-aminobencilo, 6-(4-metoxifenil)-3-carboxi-n-hexilo, 5-(4-aminometilfenil)- 3-(aminometil)-n-pentilo, 5-fenil-3-oxo-n-pent-1-ilo y similares.

El término "arilalquileno" especifica un arilalquilo, como se definió anteriormente, en donde el radical arilalquilo está unido en dos posiciones conectadas con dos grupos adicionales separados. La definición incluye grupos de la fórmula: -fenil-alquil- y alquil-fenil-alquil-. Las sustituciones en el anillo fenilo pueden ser 1,2, 1,3 o 1,4. El término "arilalquileno sustituido" es un arilalquileno

como se definió anteriormente que se sustituye preferiblemente por un grupo halógeno, hidroxi, hidroxi protegido, alquiltio C_1 a C_4, alquilosulfóxido C_1 a C_4, alquilosulfonilo C_1 a C_4, alquiltio sustituido C_1 a C_4, alquilosulfóxido sustituido C_1 a C_4, alquilosulfonilo sustituido C_1 a C_4, alquilo C_1 a C_6, alcoxi C_1 a C_7, alquilo C_1 a C_6 sustituido, alcoxi-alquilo C_1 a C_7, oxo, (monosustituido)amino, (disustituido)amino, trifluorometilo, carboxi, alcoxicarbonilo, fenilo, fenilo sustituido, feniltio, fenilsulfóxido, fenilsulfonilo, amino, o amino protegido en el anillo fenilo o en el grupo alquilo.

El término "fenilo sustituido" especifica un grupo fenilo sustituido con uno o más, y preferiblemente uno o dos, porciones preferiblemente escogidas de los grupos que consisten de halógeno, hidroxi, hidroxi protegido, tio, alquiltio, ciano, nitro, alquilo C_1 a C_6, alquilo C_1 a C_6 sustituido, alcoxi C_1 a C_7, alcoxi C_1 a C_7 sustituido, alcoxi-alquilo, acilo C_1 a C_7, acilo C_1 a C_7 sustituido, aciloxi C_1 a C_7, carboxi, alcoxicarbonilo, carboximatilo, hidroximatilo, amino, (monosustituido)amino, (disustituido)amino, carboxamida, N-(alquilo C_1 a C_6)carboxamida, N,N-di(alquilo C_1 a C_6)carboxamida, trifluorometilo, N-((alquilo C_1 a C_6)sulfonil)amino, N-(fenilsulfonil)amino o fenilo, en donde el fenilo es sustituido o no sustituido, tales que, por ejemplo, resulta un bifenilo. En muchas modalidades de los grupos fenilo sustituidos, el grupo cicloalquilo sustituido tendrá 1, 2, 3, o 4 grupos sustituyentes independientemente seleccionados de grupos hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

El término "fenoxi" denota un fenilo unido a un átomo de oxígeno. El término "fenoxi sustituido" especifica un grupo fenoxi sustituido con uno o más, y preferiblemente uno o dos, porciones preferiblemente escogidas de los grupos que

consisten de halógeno, hidroxi, hidroxi protegido, tio, alquiltio, ciano, nitro, alquilo C_1 a C_6, alcoxi C_1 a C_7, alcoxi C_1 a C_7 sustituido, alcoxi-alquilo, acilo C_1 a C_7, aciloxi C_1 a C_7, carboxi, alcoxicarbonilo, carboximatilo, hidroximatilo, amino, (monosustituido)amino, (disustituido)amino, carboxamida, N-(alquilo C_1 a C_6)carboxamida, N,N-di(alquilo C1 a C6)carboxamida, trifluorometilo, N-((alquilo C_1 a C_6)sulfonil)amino y N-fenilsulfonil)amino.

El término "feniloalcoxi sustituido" denota un grupo fenilalcoxi en donde la porción alquilo se sustituye con uno o más, y preferiblemente uno o dos, grupos preferiblemente seleccionados de grupos halógeno, hidroxi, hidroxi protegido, oxo, amino, (monosustituido)amino, (disustituido)amino, guanidino, anillo heterocíclico, anillo heterocíclico sustituido, alcoxi C_1 a C_7, alcoxi-alquilo, acilo C_1 a C_7, aciloxi C_1 a C_7, nitro, carboxi, alcoxicarbonilo, carbamoilo, carboxamida, N-(alquilo C_1 a C_6)carboxamida, N,N-(dialquilo C_1 a C_6)carboxamida, ciano, N-(alquilosulfonil C1 a C6)amino, tiol, alquiltio C_1 a C_4, alquilosulfonilo C_1 a C_4; y/o el grupo fenilo se puede sustituir con uno o más, y preferiblemente uno o dos, sustituyentes preferiblemente escogidos de halógeno, hidroxi, hidroxi protegido, tio, alquiltio, ciano, nitro, alquilo C_1 a C_6, alcoxi C_1 a C_7, alcoxi-alquilo, acilo C_1 a C_7, aciloxi C_1 a C_7, carboxi, alcoxicarbonilo carboximatilo, hidroximatilo, amino, (monosustituido)amino, (disustituido)amino, carboxamida, N-(alquilo C_1 a C_6) carboxamida, N,N-di(alquilo C_1 a C_6)carboxamida, trifluorometilo, N ((alquilo C_1 a C_6)sulfonil) amino, N-(fenilsulfonil)amino o un grupo fenilo, sustituido o no sustituido, para un grupo bifenilo resultante. Los grupos alquilo o fenilo sustituidos se pueden sustituir con uno o más, y preferiblemente uno o dos, sustituyentes que pueden ser los mismos o diferentes.

El término "naftilo sustituido" especifica un grupo naftilo sustituido con uno o más, y preferiblemente uno o dos, porciones en el mismo anillo o en anillos diferentes escogidos de los grupos que consisten de halógeno, hidroxi, hidroxi protegido, tio, alquiltio, ciano, nitro, alquilo C_1 a C_6, alcoxi C_1 a C_7, alcoxi-alquilo, acilo C_1 a C_7, aciloxi C_1 a C_7, carboxi, alcoxicarbonilo, carboximatilo, hidroximatilo, amino, (monosustituido)amino, (disustituido)amino, carboxamida, N-(alquilo C_1 a C_6)carboxamida, N,N-di(alquilo C_1 a C_6)carboxamida, trifluorometilo, N-((alquilo C_1 to C_6)sulfonil)amino o N (fenilsulfonil)amino.

Los términos "halo" y "halógeno" se refieren a los átomos de flúor, cloro, bromo o yodo. Estos pueden tener uno o más halógeno, que son los mismos o diferentes. Los halógenos preferidos son cloro y flúor. Aunque muchos de los compuestos de la invención tienen átomos de halógenos como sustituyentes son altamente efectivos en unión con los importantes receptores del sabor, tales compuestos orgánicos halogenados pueden en algunos casos tener propiedades toxicológicas no deseadas cuando se administran a un animal *in vivo*. Por lo tanto, en muchas modalidades de los compuestos de Fórmula (I), si un átomo de halógeno (que incluye un átomo de flúor o cloro) se lista como un posible sustituyente, un grupo preferido y alternativo de sustituyentes expresamente contemplados aquí NO incluyen los grupos halógenos.

El término "(monosustituido)amino" se refiere a un grupo amino (NHR) en donde el grupo R se escoge del grupo que consiste de fenilo, fenilo C_6-C_{10} sustituido, alquilo C_1 a C_6, alquilo C_1 a C_6 sustituido, acilo C_1 a C_7, acilo C_1 a C_7 sustituido, alquenilo C_2 a C_7, alquenilo C_2 a C_7 sustituido, alquinilo C_2 a C_7, alquinilo C_2 a C_7 sustituido, fenilalquilo C_7 a C_{12}, fenilalquilo sustituido C_7 a C_{12} y anillo heterocíclico. El (monosustituido)amino puede adicionalmente tener un

grupo protector amino según se abarca por el término " (monosustituido)amino protegido."

El término "(disustituido)amino" se refiere a un grupo amino (NR2) con dos sustituyentes independientemente escogidos del grupo que consiste de fenilo, C_6-C_{10} fenilo sustituido, alquilo C_1 a C_6, alquilo C_1 a C_6 sustituido, acilo C_1 a C_7, alquenilo C_2 a C_7, alquinilo C_2 a C_7, fenilalquilo C_7 a C_{12}, y fenilalquilo C_7 a C_{12} sustituido. Los dos sustituyentes pueden ser los mismos o diferentes. El término "grupo protegido amino" como se utiliza aquí se refiere a sustituyentes del grupo amino comúnmente empleados para bloquear y proteger la funcionalidad amino mientras que se hacen reaccionar con otros grupos ficnionales de la molécula. El término "(monosustituido)amino protegido" significa que es un grupo protector amino en el átomo de nitrógeno amino sustituido. Adicionalmente, el término "carboxamida protegida" significa que es un grupo protector amino en el nitrógeno carboxamida. De forma similar, el término "N-(alquilo C_1 a C_6)carboxamida protegido" significa que es un grupo protector amino en el nitrógeno carboxamida.

El término "alquiltio" se refiere a grupos -SR en donde R es un grupo orgánico C_1-C_4 o C_1-C_7 opcionalmente sustituido, preferiblemente un grupo alquilo, cicloalquilo, arilo, o heterocíclico, tal como metiltio, etiltio, n-propiltio, isopropiltio, n-butiltio, t-butiltio y grupos similares.

El término "alquilosulfóxido" indica grupos -SO_2R en donde R es un grupo orgánico C_1-C_4 o C_1-C_7 opcionalmente sustituido, preferiblemente un grupo alquilo, cicloalquilo, arilo, o heterocíclico, tal como metiltio, etiltio, n-propiltio, isopropiltio, n-butiltio, t-butiltio y grupos similares, tal como metilsulfóxido, etilsulfóxido, n-propilsulfóxido, isopropilsulfóxido, n-butilsulfóxido, sec-butilsulfóxido y similares.

El término "alquilosulfonil" indica grupos -S(O)R en donde R es un grupo orgánico C_1-C_4 o C_1-C_7 opcionalmente sustituido, que incluye por ejemplo grupos tales como metilsulfonilo, etilsulfonilo, n-propilsulfonilo, isopropilsulfonilo, n-butilsulfonilo, t-butilsulfonilo y similares.

Los términos "feniltio," "fenilsulfóxido," y "fenilsulfonilo" especifican un sulfóxido (-S(O)-R), o sulfona (-SO_2R) en donde el grupo R es un grupo fenilo. Los términos "fenilotio sustituido," "fenilsulfóxido sustituido," y "fenilsulfonilo sustituido" significa que el fenilo de estos grupos se puede sustituir como se describió anteriormente en relación con el "fenilo sustituido."

El término "alcoxicarbonilo" significa un grupo "alcoxi" adherido a un grupo carbonilo, (-C(O)-OR, en donde R es un grupo alquilo, preferiblemente un grupo alquilo C_1-C_4. El término "alcoxicarbonilo sustituido" denota un alcoxi sustituido unido al grupo carbonilo, cuyo alcoxi se puede sustituir como se describió anteriormente en relación con el alquilo sustituido.

El término "fenileno" significa un grupo fenilo en donde el radical fenileno está unido en dos posiciones conectadas junto con dos grupos adicionales separados. Ejemplos de "fenileno" incluyen 1,2-fenileno, 1,3-fenileno, y 1,4-fenileno.

El término "alquileno sustituido" significa un grupo alquilo en donde el radical alquilo está unido a dos posiciones conectadas junto con dos grupos adicionales separados y adicionalmente soporta un sustituyente adicional. Ejemplos de "alquileno sustituido" incluyen aminometileno, 1-(amino)- 1,2-etilo, 2-

(amino)-1,2-etilo, 1-(acetamido)-1,2-etilo, 2-(acetamido)-1,2-etilo, 2-hidroxi- 1,1 - etilo, 1-(amino)-1,3-propilo.

El término "feniloeno sustituido" significa un grupo fenilo en donde el radical fenileno está unido en dos posiciones conectadas junto con dos grupos adicionales separados, en donde el fenilo se sustituye como se describió anteriormente en relación con el "fenilo sustituido."

Los términos "alquileno cíclico," "alquileno cíclico sustituido," "heteroalquileno cíclico," y "heteroalquileno cíclico sustituido," define tal un radical o grupo cíclico unido ("fusionado") a un radical fenilo, resultando en un radical o grupo de anillo bicíclico fusionado. Los miembros no fusionados del anillo heteroalquileno o alquileno cíclico pueden contener uno o dos enlaces dobles, o se saturan frecuentemente. Adicionalmente, los miembros no fusionados del anillo heteroalquileno o alquileno cíclico, pueden tener uno o dos grupos metileno o metina reemplazados por uno o dos átomos de oxígeno, nitrógeno o azufre, o grupos NH, NR, S(O) o SO2, en donde R es un grupo alquilo inferior.

El grupo heteroalquileno o alquileno cíclico se puede sustituir una vez o dos veces por los mismos o diferentes sustituyentes preferiblemente seleccionados del grupo que consiste de las siguientes porciones: hidroxi, hidroxi protegido, carboxi, carboxi protegido, oxo, oxo protegido, aciloxi C_1 a C_4, formilo, acilo C_1 a C_7, alquilo C_1 a C_6, alcoxi C_1 a C_7, alquiltio C_1 a C_4, alquilosulfóxido C_1 a C_4, alquilosulfonilo C_1 a C_4, halo, amino, amino protegido, (monosustituido)amino, (monosustituido)amino protegido, (disustituido)amino, hidroximatilo o un hidroximatilo protegido. El grupo heteroalquileno o alquileno cíclico que se fusiona en el radical benceno puede contener de dos a diez miembros por anillo, pero

preferiblemente contains tres a seis miembros. Ejemplos de grupos alquileno cíclicos saturados son 2,3-dihidro-indanilo y sistemas de anillo tetralina. Cuando los grupos cíclicos son insaturados, ejemplos incluyen un anillo naftilo o radical o grupo indolilo. Ejemplos de grupos cíclicos fusionados los cuales cada uno contienen un átomo de nitrógeno y uno o más enlaces dobles, preferiblemente uno o dos enlaces dobles, son cuando el radical benceno se fusiona con radicales o grupos piridilo, piranilo, pirrolilo, piridinilo, dihidropirolilo, o dihidropiridinilo. Ejemplos de grupos cíclicos fusionados de los cuales cada uno contiene un átomo de oxígeno y uno o dos enlaces dobles se ilustran por un anillo radical de benceno fusionado a un anillo furnanilo, piranilo, dihidrofuranilo, o dihidropiranilo. Ejemplos de grupos cíclicos fusionados los cuales cada uno tienen un átomo de azufre y contienen uno o dos enlaces dobles son cuando el radical de benceno se fusiona a un anillo tienilo, tiopiranilo, dihidrotienilo o dihidrotiopiranilo. Ejemplos de grupos cíclicos que contienen dos heteroátomos seleccionados de azufre y nitrógeno y uno o dos enlaces dobles son cuando el radical de benceno se fusiona a un anillo tiazolilo, isotiazolilo, dihidrotiazolilo o dihidroisotiazolilo. Ejemplos de grupos cíclicos que contienen dos heteroátomos seleccionados de oxígeno y nitrógeno y uno o dos enlaces dobles son cuando el anillo de benceno se fusiona a un anillo oxazolilo, isoxazolilo, dihidrooxazolilo o dihidroisoxazolilo. Ejemplos de grupos cíclicos que contienen dos heteroátomos de nitrógeno y uno o dos enlaces dobles ocurren cuando el anillo de benceno se fusiona a un anillo pirazolilo, imidazolilo, dihidropirazolilo o dihidroimidazolilo o pirazinilo.

El término "carbamoilo" se refiere a un grupo o radical carbamato, que a menudo se deriva de la reacción de un compuesto isocianato orgánico R_1-NCO con un alcohol R_2-OH, para producir un compuesto carbamato que tiene la

337

estructura R_1-NH-C(O)-OR_2 en donde los radicales de R_1 y R_2 naturales se definen adicionalmente por las circunstancias.

Uno o más de los compuestos de la invención, pueden estar presentes como una sal. El término "sal" abarca aquellas sales que se forman con los aniones carboxilato y nitrógenos de amina y que incluyen sales formadas con los aniones y cationes orgánicos e inorgánicos como se discute adelante. Adicionalmente, el término incluye sales que se forman mediante reacciones de ácido-base estándar con grupos básicos (tales como heterociclos o grupos amino que contienen nitrógeno) y ácidos irgánicos e inorgánicos. Tales ácidos incluyen clorhídrico, fluhídrico, trifluoroacético, sulfúrico, fosfórico, acético, succínico, cítrico, láctico, maleico, fumárico, palmítico, cólico, pamoico, múcico, D-glutámico, D-canfórico, glutárico, ftálico, tartárico, laúrico, esteárico, salicíclico, metanosulfónico, bencenosulfónico, sórbico, pícrico, benzoico, cinámico, y ácidos similares.

El término "catión orgánico o inorgánico" se refiere a un contraión cargado positivamente para el anión carboxilato de una sal de carboxilato. Un contraión inorgánico cargado positivamente incluye pero no se limitan a los metales alcalinos y alcalinotérreos, (tales como litio, sodio, potasio, calcio, magnesio, etc.) y otros cationes metálicos divalentes y trivalentes tales como bario, aluminio y similares, y cationes de amonio $(NH_4)^+$. Cationes orgánicos incluyen cationes de amonio derivados de tratamiento ácido o alquilación de aminas primarias-, secundarias, o terciarias tales como trimetilamina, ciclohexilamina; y los cationes orgánicos, tales como dibencilamonio, bencilamonio, 2-hidroxietilamonio, bis(2-hidroxietil)amonio, feniletilbencilamonio, dibenciletilenodiamonio, y cationes similares. *Ver*, por ejemplo, "Pharmaceutical Salts," Berge, *et al, J. Pharm. Sci.*

(1977) 66:1-19, que se incorpora aquí como referencia. Otros cationes abarcados por el término anterior incluyen la forma protonada de procaína, quinina y N-metilglucosamina, y las formas protonadas de aminoácidos básicos tales como glicina, ornitina, histidina, fenilglicina, lisina y arginina. Adicionalmente, cualquier forma zwiteriónica de los compuestos instantáneos formados por un ácido carboxílico y un grupo amino es referido por este término. Por ejemplo, un catión para un anión de carboxilato existirá cuando R^2 o R^3 se sustituya con un grupo (amonio cuaternario)metilo. Un catión preferido para el anión carboxilato es el catión sodio.

Los compuestos de la invención también pueden existir como solvatos e hidratos. Así, estos compuestos se pueden cristalizar con, por ejemplo, aguas de hidratación, o uno, un número de, o cualquier fracción de estos de moléculas del disolvente del licor madre. Los solvatos e hidratos de tales compuestos se incluyen dentro del alcance de esta invención.

El término "aminoácido" incluye cualquiera de uno de los veinte aminoácidos de ocurrencia natural o la forma D de cualquiera de uno de los aminoácidos de ocurrencia natural. Adicionalmente, el término "aminoácido" también incluye otros aminoácidos de ocurrencia no natural además de los D-aminoácidos, que son equivalentes funcionales de los aminoácidos de ocurrencia natural. Tales aminoácidos de ocurrencia no natural incluyen, por ejemplo, norleucina ("Nle"), norvalina ("Nva"), 1- o D-naftalanina, ornitina ("Orn"), homoarginina (homoArg) y otros bien conocidos en la técnica de péptidos, tales como aquellos descritos en M. Bodanzsky, "Principles of Peptide Síntesis," 1st y 2nd revised ed., Springer- Verlag, New York, NY, 1984 y 1993, y Stewart y Young, "Solid Phase Peptide Síntesis," 2nd ed., Pastelrce Chemical Co., Rockford, IL,

1984, los cuales se incorporan aquí como referencia. Los aminoácidos y análogos de aminoácido se pueden comprar comercialmente (Sigma Chemical Co.; Advanced Chemtech) o se sintetizan utilizando métodos conocidos en la técnica.

"Aminoácido de cadena lateral" se refiere a cualquier cadena lateral de los "aminoácidos." Anteriormente descritos.

"Sustituido" aquí se refiere a una porción sustituida, tal como un hidrocarburo, por ejemplo, alquilo sustituido o bencilo en donde al menos un elemento o radical, por ejemplo, hidrógeno, se reemplaza por otro, por ejemplo, un hidrógeno se reemplaza por un halógeno como en clorobencilo.

Un residuo de unas especies químicas, como se utiliza en la especificación y se concluye en las reivindicaciones, se refiere a un fragmento estructural o una porción que es el producto resultante de las especies químicas en un esquema de reacción particular o formulación posterior o producto químico, sin importar si el fragmento o porción estructural se obtienen actualmente de las especies químicas. Así un residuo de etilenglicol en un poliéster se refiere a uno o más unidades repetidas de $-OCH_2CH_2O-$ en el poliéster, sin importar si el etilenglicol se utiliza para preparar el poliéster.

El término "residuo orgánico" o "grupo orgánico define un grupo o residuo que contiene carbono, es decir un residuo que comprende al menos un átomo de carbono. Residuos orgánicos pueden contener varios heteroátomos, o estar unidos a otra molécula a través de un heteroátomo, que incluye oxígeno, nitrógeno, azufre, fósforo, o similares. Ejemplos de residuos orgánicos incluyen pero no se limitan a grupos alquilo o alquilo sustituidos, alcoxi o alcoxi sustituido,

hidroxialquilos y alcoxialquilos, mono o di-sustituido amino, amida, CN, CO_2H, CHO, COR^6, CO_2R^6, SR^6, $S(O)R^6$, $S(O)_2R^6$, alquenilo, cicloalquilo, cicloalquenilo, arilo, y heteroarilo: en donde R^6 es un alquilo. Ejemplos más específicos de especies de residuos o grupos orgánicos incluyen pero no se limitan a residuos o grupos $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$,metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, trifluorometoxi, CH_2OCH_3, CH_2OH, CH_2NH_2, CH_2NHCH_3, o $CH_2N(CH_3)_2$. Los residuos orgánicos pueden comprender de 1 a 18 átomos de carbono, 1 a 15, átomos de carbono, 1 a 12 átomos de carbono, 1 a 8 átomos de carbono, 1 a 6 átomos de carbono, o 1 a 4 átomos de carbono.

Por el término "cantidad efectiva" de un compuesto como se suministra aquí significa una cantidad suficiente de uno o más compuestos en una composición que es suficiente para suministrar la regulación deseada de una función biológica deseada, tal como expresión de gen, función de proteína, o más particularmente la inducción de la percepción de sabor dulce o umami en un animal o un humano. Como será indicado adelante, la cantidad exacta requerida variará de sujeto a sujeto, dependiendo de las especies, edad, condición general del sujeto, identidad específica y formulación de la composición comestible, etc. Así, no es posible especificar una "cantidad efectiva" exacta. Sin embargo, una cantidad efectiva apropiada se puede determinar por una persona medianamente versada en la técnica utilizando solo experimentación de rutina.

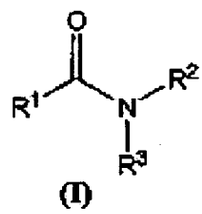
Se debe notar que, como se utiliza en la especificación y las reivindicaciones adjuntas, las formas singulares "un," "una" y "el" incluye referentes plurales a menos que el contexto claramente dicte otra cosa. Así, por ejemplo, la referencia a "un compuesto aromático" incluye mezclas de compuestos

aromáticos. A menudo, los rangos se expresan aquí como de "aproximadamente" un valor particular, y/o a "aproximadamente" otro valor particular. Cuando tal un rango se expresa, otra modalidad incluye un valor particular y/o el otro valor particular. De forma similar, cuando los valores se expresan como aproximaciones, mediante el uso del antecedente "aproximadamente," se entenderá que el valor particular forma otras modalidades. Se entenderá adicionalmente que el criterio de valoración de cada uno de los rangos es significante en relación al otro criterio de valoración, e independientemente del otro criterio de valoración.

"Opcional" u "opcionalmente" significa que el evento o circunstancia descrito posteriormente puede o no ocurrir, y que la descripción incluye casos en donde dicho evento o circunstancia ocurre y casos en donde no. Por ejemplo, la frase "alquilo inferior opcionalmente sustituido" significa que el grupo alquilo inferior puede o no puede ser sustituido y que la descripción incluye alquilo inferior y alquilos inferiores en donde exista sustitución.

Los Compuestos de Amida de la Invención

Los compuestos de la invención son todos los compuestos orgánicos (que contienen carbono) que tienen al menos un grupo "amida" en ellos, tienen la siguiente estructura general, la cual será referida más abajo como los compuestos de amida que tienen la fórmula (I) mostrada adelante:



(I)

342

Los compuestos de amida de Fórmula (I) no incluyen compuestos de amida que se conocen por ocurrir de forma natural en sistemas biológicos o alimentos, tal como péptidos, proteínas, ácidos nucleicos, ciertos azúcares amino y/o polisacáridos amino, glicopéptidos o glicoproteínas, o similares. Los compuestos de amida de Fórmula (I) de la invención son artificiales y compuestos de amida sintéticos artificiales, aunque los Solicitantes no excluyen la posibilidad de que los compuestos de la Fórmula (I) se podrían preparar de forma deliberadamente concebible, es su forma específica o en la forma de un péptido o forma de "prodroga" modificada por proteína por seres humanos que utilizan uno o más de los métodos de la biotecnología moderna.

Para las varias modalidades de los compuestos de Fórmula (I), los grupos R^1, R^2 y R^3 pueden ser y son independientemente definidos adicionalmente y/o limitados en varias formas, como ahora será detallado más a fondo, para formar y/o incluir un número sustancial de subgéneros y/o especies de compuestos de Fórmula (I). Es por este medio que se contempla específicamente que cualquiera de los subgéneros y/o especies de compuestos de Fórmula (I) descritos aquí, pueden en su forma específica o como una sal aceptable comestiblemente, ser combinados en una cantidad efectiva con un producto comestible o medicinal o precursor de estos por los procesos y/o métodos descritos en otra parte aquí, o por cualquiera de tales otros procesos como sería evidente para aquellos medianamente versados en la técnica en la preparación del productos comestibles o medicinales o precursores de estos, para formar a un producto comestible o medicinal con sabor un dulce y/o salado o picante modificado, o un precursor de este.

En algunas modalidades de los compuestos de Fórmula (I), R^1 es un residuo de hidrocarburo que puede contener uno o más heteroátomos o un residuo inorgánico, y R^2 y R^3 son cada uno independientemente H o un residuo de hidrocarburo que puede contener uno o más heteroátomos; más preferiblemente, R^1, R^2 y R^3 se seleccionan independientemente del grupo que consiste de arilalquenilo, heteroarilalquenilo, arilalquilo, heteroarilalquilo, alquilo, alcoxi-alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, $-R^4OH$, $-R^4CN$, $-R^4CO_2H$, $-R^4CO_2R^5$, $-R^4COR^5$, $-R^4CONR^5R^6$, $-R^4NR^5R^6$, $-R^4N(R^5)COR^6$, $-R^4SR^5$, $-R^4SOR^5$, $-R^4SO_2R^5$, $-R^4SO_2NR^5R^6$ y $-R^4N(R^5)SO_2R^6$, u opcionalmente grupos sustituidos de estos y preferiblemente uno de R^2 o R^3 es H; en donde cada R^4 es independientemente un residuo de hidrocarburo que puede contener uno o más heteroátomos, preferiblemente independientemente seleccionados de alquileno (C_1-C_6) o alcoxialquileno (C_1-C_6) pequeños; y en donde cada R^5 y R^6 son independientemente H o un residuo de hidrocarburo que puede contener uno o más heteroátomos, preferiblemente independientemente seleccionados de alquilo (C_1-C_6) o alcoxialquilo (C_1-C_6) pequeños.

En muchas modalidades de los compuestos de Fórmula (I), R^1 comprende un residuo orgánico o un residuo basado hidrocarburo que tiene al menos tres átomos de carbono y opcionalmente de uno a 20, 15, 10, 8, 7, 6, o 5 heteroátomos independientemente seleccionados de oxígeno, nitrógeno, azufre, halógenos, o fósforo.

En muchas modalidades de los compuestos de Fórmula (I), uno de R^2 y R^3eis opcionalmente H, y uno o ambos de R^2 y R^3 comprenden un residuo basado en hidrocarburo u orgánico que tiene al menos tres átomos de carbono y

opcionalmente de uno a diez heteroátomos independientemente seleccionados de oxígeno, nitrógeno, azufre, halógenos, o fósforo.

Los compuestos de Fórmula (I) son relativamente "moléculas pequeñas" según se compara con muchas moléculas biológicas, y pueden a menudo tener una variedad de limitaciones en su tamaño físico absoluto total, peso molecular, y características físicas, para que ellos puedan ser al menos algo solubles en medio acuoso, y son del tamaño apropiado para unirse efectivamente a los receptores del saborT1R1/T1R3 o T1R2/T1R3 heterodiméricos importantes, que comparten una subunidad de proteína T1R3 común.

Mientras que se no se desea estar unido por cualquier teoría, se cree que el MSG se une a la subunidad T1R1 de receptores del sabor "salado o picante" T1R1/T1R3, y varios endulzantes conocidos se unen a la subunidad T1R2 de receptores dulces T1R2/T1R3. De acuerdo con esto, nuestro inesperado y sorprendente descubrimiento de que los compuestos de amida de Fórmula (I) pueden compartir muchas características químicas y físicas de superposición, y pueden a veces unirse a uno o ambos de los receptores del sabor dulce y salado o picante, es quizás en retrospectiva razonable y/o racional desde un punto de vista químico/bioquímico/biológico.

Como un ejemplo de las propiedades químicas y físicas de superposición y/o limitaciones químicas/físicas en las amidas dulces y/o salado o picante de Fórmula (I), en más modalidades de los compuestos de Fórmula (I), el peso molecular de los compuestos de Fórmula (I) debería ser menor de aproximadamente 800 gramos por mol, o en modalidades adicionales menos de o igual a aproximadamente 700 gramos por mol, 600 gramos por mol, 500 gramos

por mol, 450 gramos por mol, 400 gramos por mol, 350 gramos por mol, o 300 gramos por mol.

De forma similar, los compuestos de Fórmula (I) pueden tener rangos preferidos de peso molecular, tal como por ejemplo de aproximadamente 175 a aproximadamente 500 gramos por mol, de aproximadamente 200 a aproximadamente 450 gramos por mol, de aproximadamente 225 a aproximadamente 400 gramos por mol, de aproximadamente 250 a aproximadamente 350 gramos por mol.

En unas series relacionadas de modalidades, R^1 tiene entre 3 y 16 átomos de carbono o 4 y 14 átomos de carbono o 5 y 12 átomos de carbono, y 0, 1, 2, 3, 4, o 5 heteroátomos seleccionados de oxígeno, nitrógeno, azufre, flúor, o cloro, y/o al menos uno de R^2 o R^3 tienen 3 y 16 átomos de carbono y 0, 1, 2, 3, 4, o 5 heteroátomos independientemente seleccionados de oxígeno, nitrógeno, azufre, flúor, o cloro; o preferiblemente al menos uno de R^2 o R^3 tiene entre 4 y 14 átomos de carbono y 0, 1, 2, 3, 4, o 5 heteroátomos independientemente seleccionados de oxígeno, nitrógeno, azufre, flúor; o aún más preferiblemente, al menos uno de R^2 o R^3 tiene entre 5 y 12 átomos de carbono y 0, 1, 2, o 3 heteroátomos independientemente seleccionados de oxígeno, nitrógeno, y azufre.

Adicionalmente a las características y/o limitaciones químicas y físicas generales descritas anteriormente, las cuales pueden ser compartidas por los varios subgéneros de los compuestos de sabor dulce y salado o picante de Fórmula (I), los compuestos de Fórmula (I) pueden también compartir más específicamente características estructurales químicas definidas o residuos o grupos químicos, como se describe adicionalmente adelante.

Por ejemplo, en algunas modalidades, R^1, R^2, y R^3 pueden ser independientemente seleccionados del grupo que consiste de un arilalquenilo, heteroarilalquenilo, arilalquilo, heteroarilalquilo, alquilo, alcoxi-alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, $-R^4OH$, $-R^4OR^5$,- R^4CN, $-R^4CO_2H$, $-R^4CO_2R^5$, $-R^4COR^5$, $-R^4SR^5$, y $-R^4SO_2R^5$, y derivados opcionalmente sustituidos de estos que comprenden 1, 2, 3, o 4 grupos carbonilo, amino, hidroxilo, o grupos halógeno, y en donde R^4 y R^5 son residuo de hidrocarburos C_1-C_6.

En modalidades relacionadas de los compuestos de amida de Fórmula (I), R^1, R^2 y R^3 pueden ser independientemente seleccionados del grupo que consiste de unos grupos arilalquenilo, heteroarilalquenilo, arilalquilo, heteroarilalquilo, alquilo, alcoxi-alquilo, alquenilo, cicloalquilo, cicloalquenilo, heterociclo, arilo y heteroarilo, y opcionalmente derivados sustituidos de estos que comprenden 1, 2, 3 o 4 grupos carbonilo, amino, hidroxilo, o grupos cloro, o flúor. En ambas de las modalidades recién mencionadas, un conjunto alternativo y preferido de grupos sustituyentes opcionales serían sustituyentes independientemente seleccionados de los grupos hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi sustituyentes.

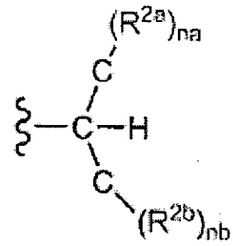
Los Grupos R^2 y/o R^3

En muchas modalidades de los compuestos de Fórmula (I), uno de R^2 y R^3 es hidrógeno y el otro grupo R^2 o R^3 es un residuo o grupo orgánico. Por lo tanto se debe entender que una declaración en adelante de que "al menos uno de R^2 y R^3...." se contempla como una modalidad de que uno o de R^2 y R^3 es hidrógeno y

347

el otro de R^2 y R^3 tiene la estructura posteriormente descrita, y como otra modalidad que ambos de R^2 y R^3 tienen la estructura descrita.

En muchas modalidades, al menos uno de R^2 y R^3 es un residuo orgánico ramificado o cíclico que tiene un átomo de carbono unido directamente a ambos (a) el átomos de nitrógeno amida y (b) dos átomos de carbono adicionales de otros residuo orgánicos, que son residuos orgánicos ramificados o cíclicos que comprenden átomos de hidrógeno adicionales y hasta 10 átomos de carbono opcionales adicionales, y opcionalmente de cero a cinco heteroátomos independientemente seleccionados de oxígeno, nitrógeno, azufre, flúor, y cloro. Tales grupos R^2 y R^3 incluyen radicales orgánicos que tienen la fórmula:

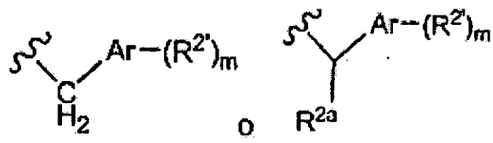


en donde na y nb se seleccionan independientemente de 1, 2, y 3, y cada residuo sustituyente R^{2a} o R^{2b} se selecciona independientemente de hidrógeno, un halógeno, un hidroxi, o un residuo que contiene carbono opcionalmente que tiene de cero a cinco heteroátomos independientemente seleccionados de oxígeno, nitrógeno, azufre, y a halógeno. En algunas de tales modalidades, los R^{2a} o R^{2b} son grupos independientemente sustituyentes, pero en otras modalidades uno o más de los radicales R^{2a} o R^{2b} pueden estar unidos juntos para formar estructuras de anillo.

348

En algunas de tales modalidades de los compuestos de Fórmula (I), al menos un de los R^2 y R^3 es un radical alquilo ramificado que tiene de 5 a 12 átomos de carbono, o al menos uno de R^2 y R^3 es un anillo cicloalquilo o ciloalquileno que comprende de 5 a 12 átomos de carbono en el anillo. En tales modalidades de R^2 y R^3 el radical alquilo ramificado o el anillo cicloalquilo o cicloalquenilo se pueden sustituir opcionalmente con 1, 2, 3, o 4 grupos sustituyentes independientemente seleccionados de hidroxi , fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

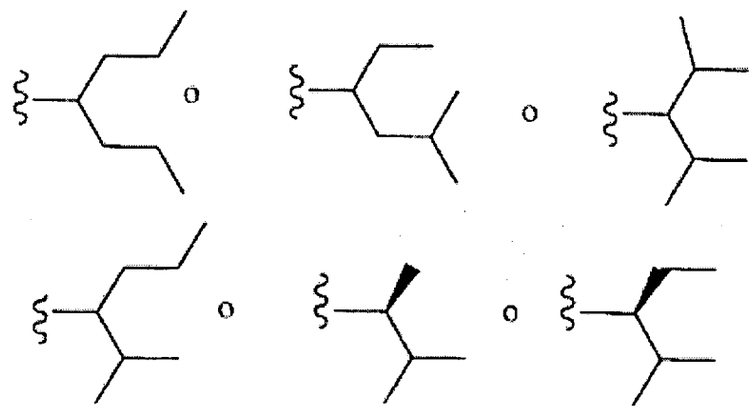
En otras modalidades de los compuestos de amida de Fórmula (I), al menos uno de los R^2 y R^3 es un radical "bencílico" que tiene la estructura



en donde Ar es un anillo aromático o heteroaromático tal como fenilo, piridilo, furanilo, tiofuranilo, pirrolilo, o sistemas de anillo aromático similares, m es 0, 1, 2, o 3, y cada $R^{2'}$ se selecciona independientemente de hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, y cada grupo sustituyente R^{2a} puede ser independientemente seleccionado del grupo que consiste de un grupo alquilo, alcoxi-alquilo, alquenilo, cicloalquenilo, cicloalquilo, -R^4OH, -R^4O R^5, -R^4CN, -R^4CO_2H, -$R^4CO_2R^5$, -R^4COR^5, -R^4SR^5, y -$R^4SO_2R^5$.

En muchas modalidades de los compuestos de Fórmula (I), al menos uno de R^2 o R^3 es un alquilo C_3-C_{10} ramificado. En muchas de tales modalidades, el

otro de R^2 o R^3 es hidrógeno. Aquellos alquilos C_3-C_{10} ramificados se ha encontrado que son grupos R^2 altamente efectivos para ambos compuestos de amida de sabor dulce y salado o picante. En algunas modalidades, R^3 es un alquilo C_4-C_8 ramificado. Ejemplos de tales alquilos ramificados incluyen las siguientes estructuras.



En modalidades adicionales los alquilos ramificados pueden opcionalmente contener, insertados en lo que había sido una cadena de alquilo, uno o dos heteroátomos tales como átomos de nitrógeno, oxígeno, o azufre para formar aminas, éteres, y/o tioéteres, sulfóxidos, o sulfonas respectivamente, o uno o dos sustituyentes heteroatómicos unidos a las cadenas alquilo independientemente seleccionados de grupos hidroxi, fluoro, cloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

En modalidades adicionales de los compuestos de Fórmula (I), al menos uno de R^2 o R^3 es un ácido carboxílico α-sustituido o éster de alquilo inferior de ácido carboxílico α-sustituido. Preferiblemente, al menos uno de R^2 o R^3 es un éster de alquilo inferior de ácido carboxílico α-sustituido (especialmente metilo). En algunas de tales modalidades preferidas, el ácido carboxílico α-sustituido o residuo de éster de ácido carboxílico α-sustituido corresponde a aquel de un α-aminoácido

350

activo ópticamente y de una ocurrencia natural o un éster de este, o su enantiómero opuesto.

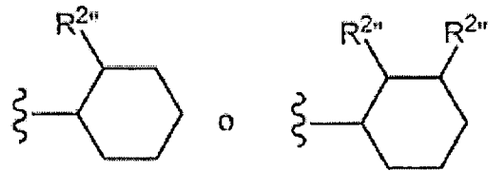
En muchas modalidades de los compuestos de Fórmula (I), al menos uno de R^2 o R^3 es un anillo arilo o heteroarilo de 5 o 6 miembros, opcionalmente sustituido con 1, 2, 3 o 4 grupos sustituyentes seleccionados del grupo que consiste de hidroxilo, NH_2, SH, halógeno, o un radical C_1-C_4 orgánico. En modalidades relacionadas, los sustituyentes para el anillo arilo o heteroarilo se seleccionan de alquilo, alcoxilo, alcoxi-alquilo, OH, CN, CO_2H, CHO, COR^6, CO_2R^6, SR^6, halógeno, alquenilo, cicloalquilo, cicloalquenilo, arilo, y heteroarilo: y R^6 es alquilo C_1-C_6. Preferiblemente el anillo arilo o heteroarilo se sustituye con 1, 2, 3 o 4 grupos sustituyentes seleccionados del grupo que consiste de hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, grupos metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

En algunas modalidades de los compuestos de Fórmula (I), al menos uno de R^2 o R^3 es un anillo fenilo, piridilo, furanilo, tiofuranilo, o pirrolilo opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados de hidroxi, flúor, cloro , NH_2, $NHCH_3$, N(CH3)2, CO_2CH_3, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

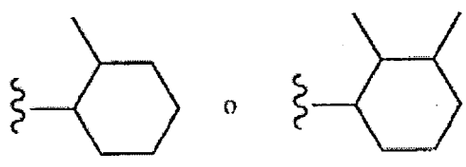
En muchas modalidades de los compuestos de Fórmula (I), al menos uno de R^2 o R^3 es un anillo cicloalquilo, cicloalquenilo, o anillo heterocíclico saturado que tiene de 3 a 10 átomos de carbono en el anillo, opcionalmente sustituidos con 1, 2, o 3 sustituyentes independientemente seleccionados del grupo que consiste de NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, alquilo C_1-C_4, haloalquilo C_1-C_4, alcoxi C_1-C_4, haloalcoxi C_1-C_4, hidroxi, y halógeno. En algunas modalidades

adiconales, al menos uno de R^2 o R^3 es un anillo ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, o anillo piperidilo opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados independientemente del grupo que consiste de hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

En algunas modalidades preferidas, al menos uno de R^2 o R^3 es un anillo ciclohexilo, opcionalmente sustituido con 1, 2, o 3 grupos sustituyentes seleccionados de grupos NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_{31} alquilo C_1-C_4, haloalquilo C_1-C_4, alcoxi C_1-C_4, haloalcoxi C_1-C_4, hidroxi, y halógeno, y el otro de R^2 o R^3 es hidrógeno. Por ejemplo, en algunas de tales modalidades, R^3 es hidrógeno y R^2 puede tener una de las siguientes estructuras:

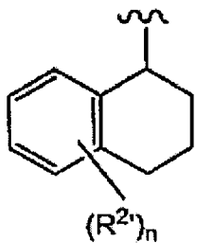


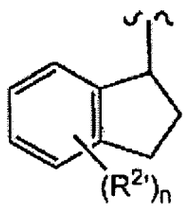
en donde $R^{2'}$ y $R^{2''}$ se seleccionan independientemente de grupos hidroxi, flúor, cloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, o preferiblemente grupos metilo. Ejemplos de tales anillos de ciclohexilo sustituidos con metilo tienen la fórmula



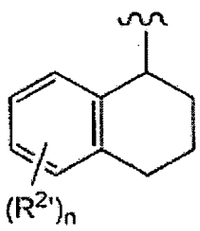
352

En muchas modalidades de los compuestos de Fórmula (I), especialmente los compuestos que tienen actividad mejoradora para otros endulzantes, o actividad mejoradora para compuestos salados o picantes tales como MSG, R^3 es hidrógeno y R^2 es un anillo ciclopentilo o ciclohexilo que tiene un anillo fenilo fusionado adicionalmente, *es decir* un radical anillo 1-(1,2,3,4) tetrahidronaftaleno o un radical anillo 2,3-dihidro-1H- indeno que tiene la estructuras:

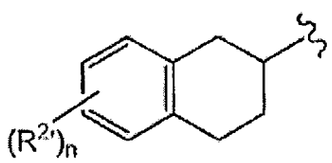


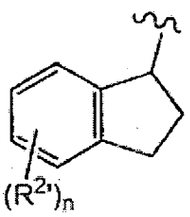


en donde n es 0,1, 2, o 3, y cada $R^{2'}$ puede estar unido al anillo aromático y no aromático . En otras modalidades, cada $R^{2'}$ está unido al anillo aromático como se muestra adelante:



o

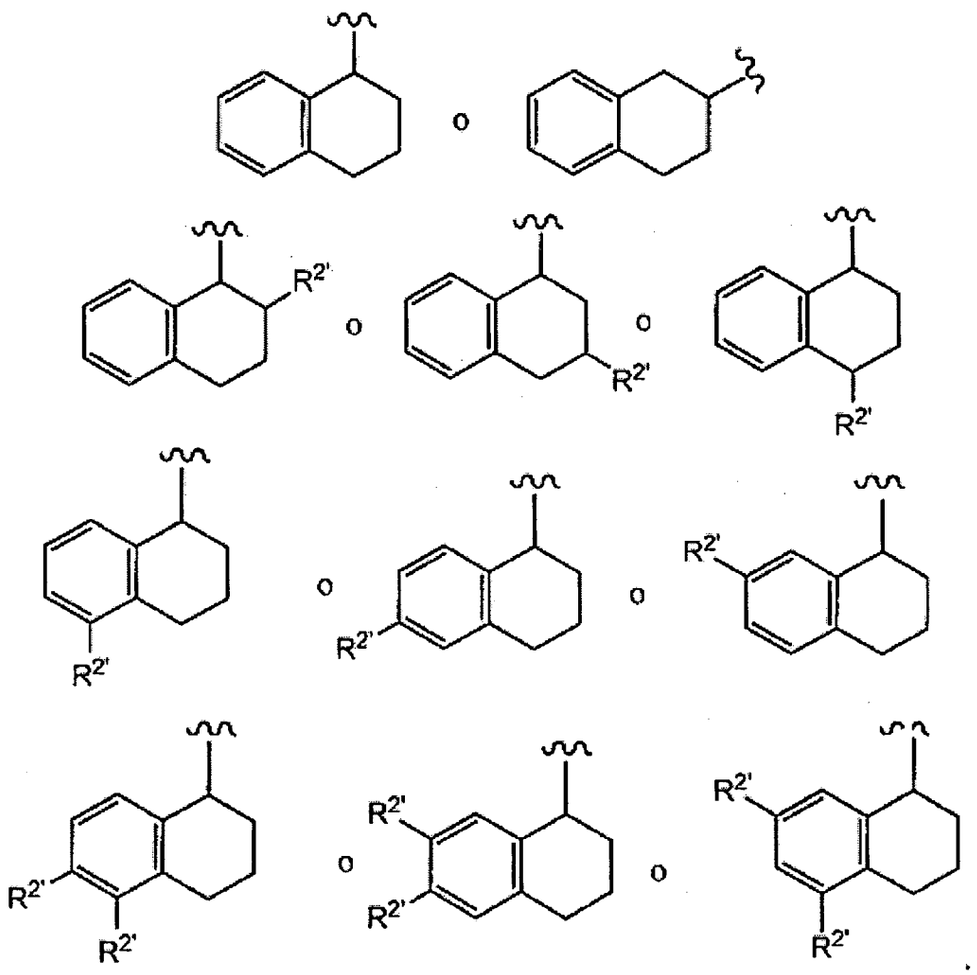




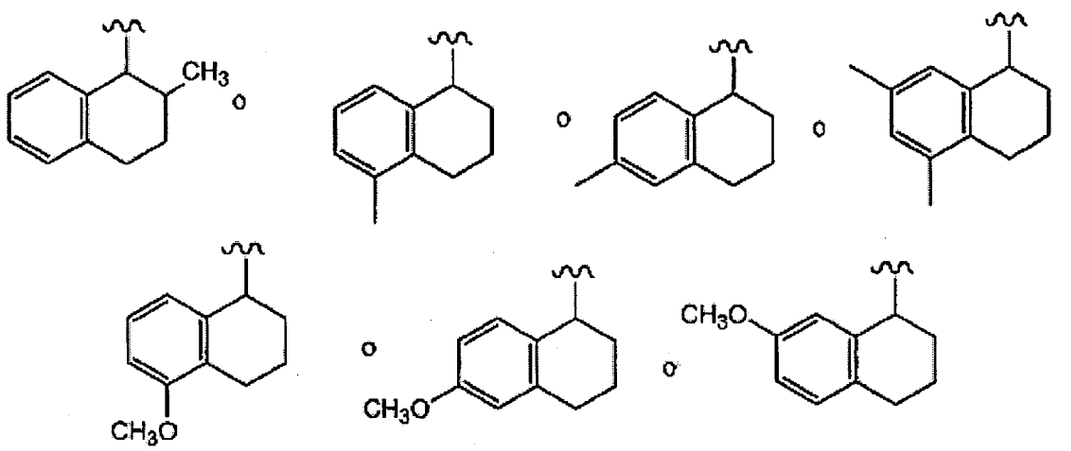
En las modalidades tetrahidronaftalenilo e indanilo mostradas anteriormente, cada $R^{2'}$ puede ser independientemente seleccionado del grupo que consiste de hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4. En modalidades alternativas pero relacionadas, cada $R^{2'}$ puede ser independientemente seleccionado del grupo que consiste de hidroxilo, NH_2, SH, halógeno, alquilo C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, alcoxilo C_1-C_4, alcoxi-

alquilo C_1-C_4, hidroxi-alquilo C_1-C_4, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, y halógeno, en donde R^6 es alquilo C_1-C_4. En algunas modalidades preferidas, cada R^2 pueden ser independientemente seleccionado del grupo que consiste de hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

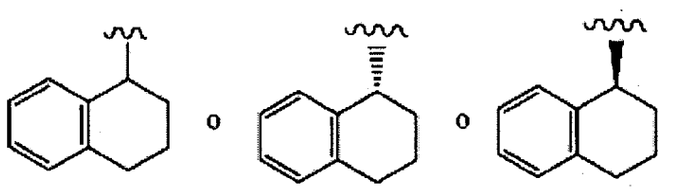
En algunas modalidades al menos uno de R^2 o R^3 es un anillo 1-(1,2,3,4) tetrahidronaftaleno con ciertos patrones de sustitución preferidos. En particular, en algunas modalidades de los compuestos de Fórmula (I) al menos uno de R^2 o R^3 es un anillo ciclohexilo que tiene una de las fórmulas:



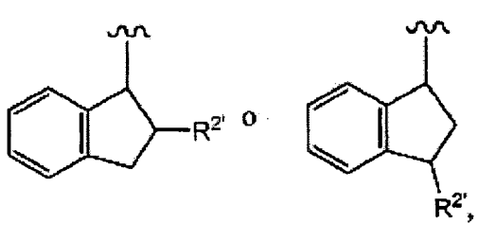
en donde cada $R^{2'}$ puede ser independientemente seleccionado de los grupos descritos anteriormente. De forma similar, en algunas modalidades preferidas, al menos uno de R^2 o R^3 puede incluir una de las estructuras:



En algunas modalidades al menos uno de R^2 o R^3 es un anillo 1-(1,2,3,4) tetrahidronaftaleno no sustituido en gorma ópticamente activa o racémica, como se muestra adelante:

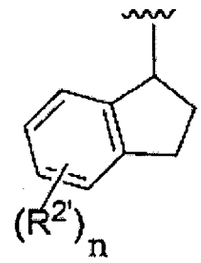


De forma similar en las series indanilo R^2 puede tener las estructuras

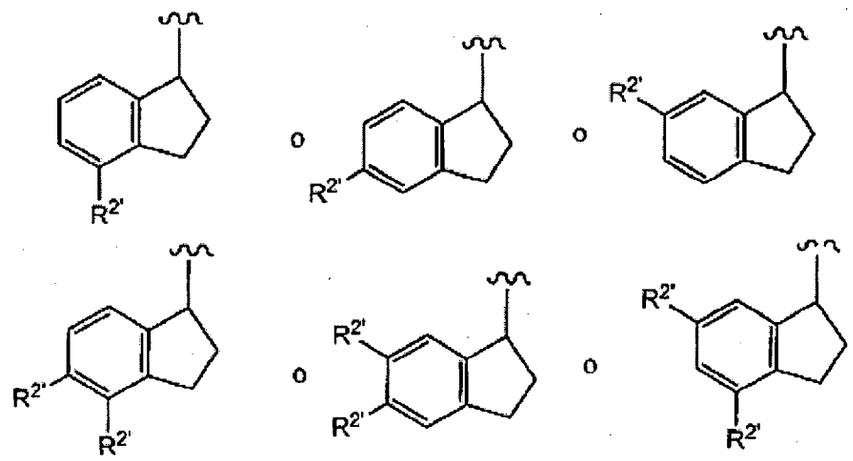


355

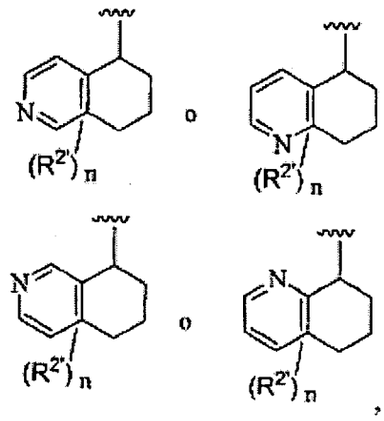
o los sustituyentes R^2 se pueden unir al anillo aromático como se muestra adelante,



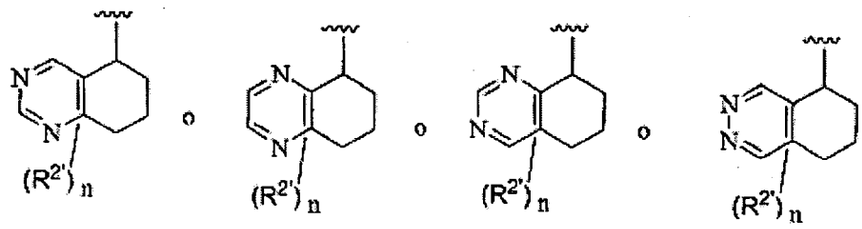
o en modalidades específicas, R2 puede tener una de las estructuras de ejemplo mostradas adelante;



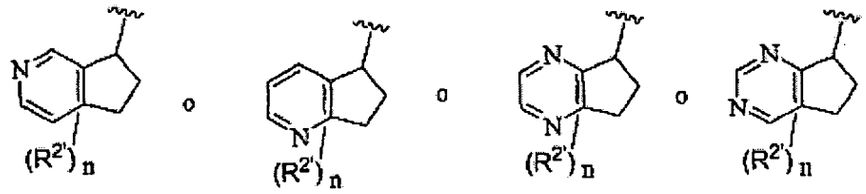
En algunas modalidades de los compuestos de amida de la invención, los sistemas de anillo indano y tetrahidronaftaleno de los grupos R^2 descritos anteriormente que comprenden uno o más heteroátomos o grupos heteroatómicos en los sistemas de anillos bicíclicos, para formar nuevos análogos bicíclicos y heterocíclicos de los sistemas de anillo indano y tetrahidronaftaleno, para formar nuevos grupos R^2. Por ejemplo, esto es posible al sustituir un átomo de nitrógeno para uno de los anillos aromáticos de un grupo tetrahidronaftalenilo para formar nuevos radicales tetrahidroquinolinilo o tetrahidroisoquinolinilo que tienen las estructuras mostrada adelante:



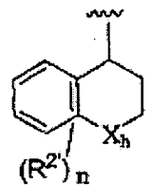
en donde los grupos $R^{2'}$ pueden estar unidos a los anillos aromáticos y no aromáticos, y se pueden definir en cualquiera de las formas descritas anteriormente en conexión con los grupos tetrahidronaftalenilo. Será evidente para aquellos medianamente versados en la técnica que al menos un átomo de nitrógeno adicional podría ser insertado de forma similar para formar grupos heteroarilo isoméricos y adicionales, tales como los siguientes grupos de ejemplo R^2:



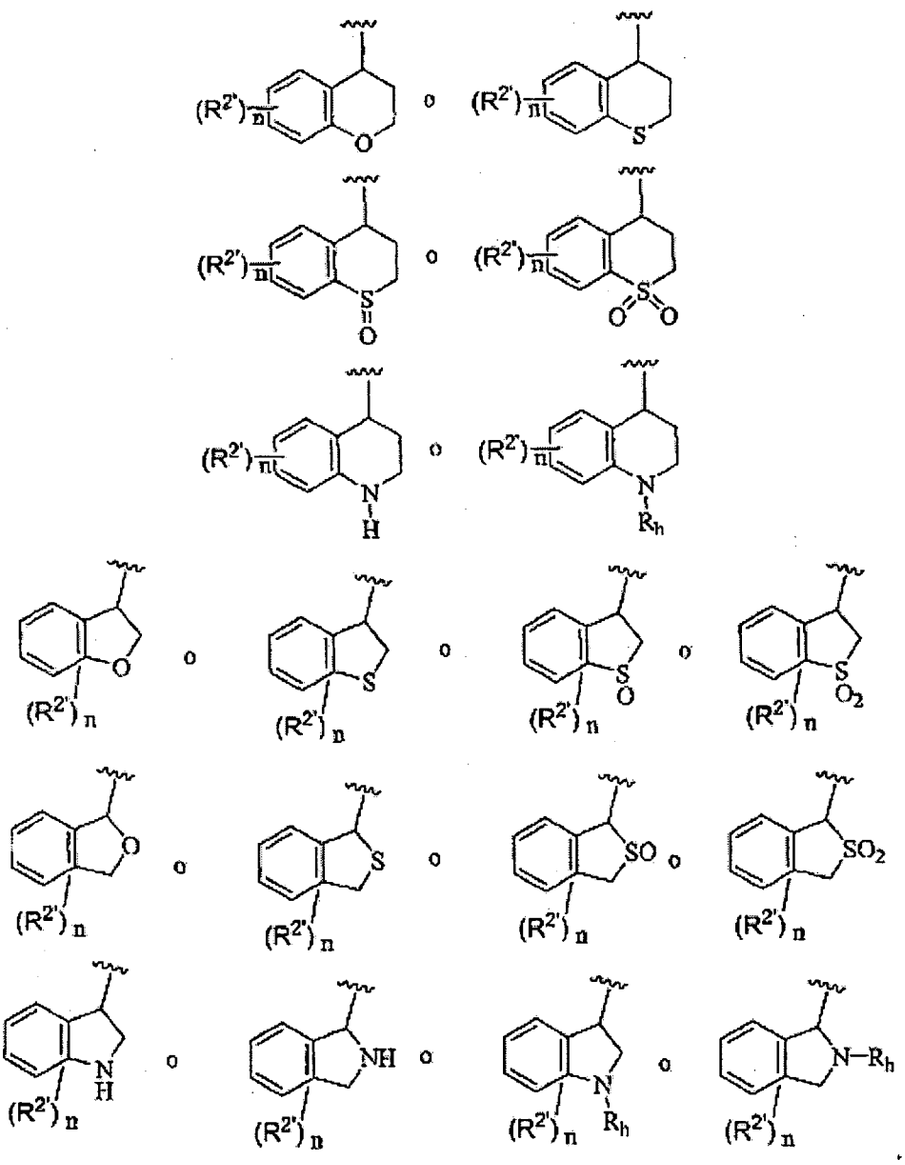
Los grupos indanilo R^2 descritos anteriormente pueden de forma similar ser modificados con uno o más átomos de nitrógeno para formar grupos R^2 heteroarilo bicíclicos adicionales, tales como por ejemplo las siguientes estructuras:



Adicionalmente, uno o más heteroátomos o grupos heteroatómicos se pueden insertar en los grupos ciclopentilo o ciclohexilo de los grupos tetrahidronaftalenilo o indanilo descritos anteriormente para formar heteroarilos bicíclicos fusionados adicionales, que incluyen pero no se limitan a las estructuras de ejemplo listadas adelante:



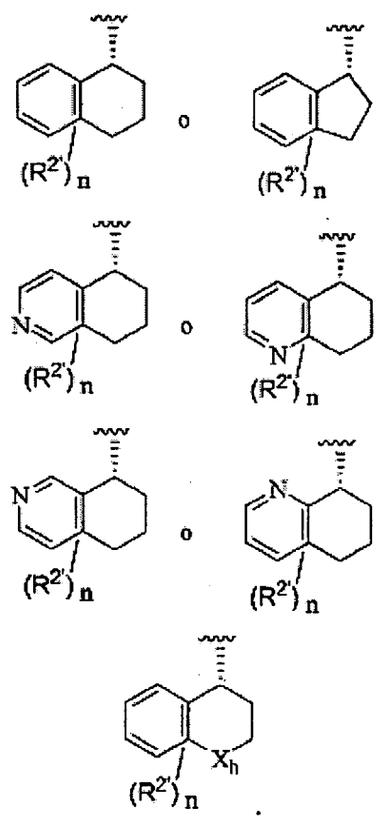
en donde n es 0, 1, 2, o 3, cada R^2 se puede definir en cualquiera de las formas descritas anteriormente, y X_h es O, S, SO, SO_2, NH, o NR_h, en donde R_h es un radical orgánico C_1-C_4. Ejemplos de tales grupos R^2 se listan adelante:



Será entendido también por aquellos medianamente versados en la técnica que el isomerismo óptico y/o diastereomérico puede ocurrir en los anillos de cinco o seis miembros insaturados de los grupos R^2 descritos anteriormente, y en muchos otros de los grupos R^1, R^2, y R^3 descritos aquí, y que los isómeros de diferenciación ópticos (enantiómeros) y/o diastereómeros pueden tener actividades biológicas diferentes con respecto a los receptores de sabor salado o picante y dulce importantes. Puede ser difícil la predicción de que el diastereómero o enantiómero de un grupo R^2 particular sea más probablemente biológicamente efectivo, y el hallazgo de un isómero particular es más efectivo para un sistema de

anillo que puede no necesariamente significar que un isómero análogo de un grupo sustituido diferentemente será similarmente efectivo.

Los solicitantes no obstante han encontrado que en muchas modalidades, los compuestos de Fórmula (I) son particularmente efectivos mejoradores de dulce cuando R^2 comprende un tetrahidronaftalenilo sustituido o no sustituido, indanilo, tetrahidroquinolinilo, tetrahidronaftalenilo, o los análogos heterocíclicos relacionados descritos anteriormente cuando ellos comprenden un exceso enantiomérico de las configuraciones ópticas absolutas ilustradas en las gráficas adelante:

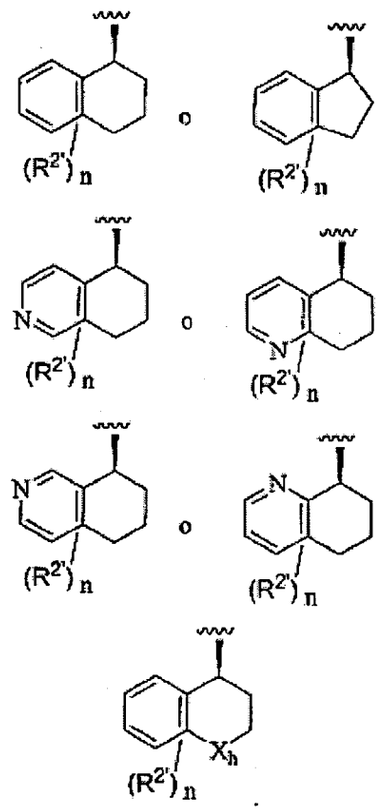


Una persona medianamente versada está enterada que la designación de un compuesto particular como cualquier "R" o "S" bajo el sistema de nomenclatura Cahn-Ingold-Prelog para compuestos activos ópticamente puede depender del

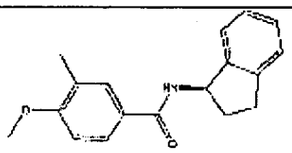
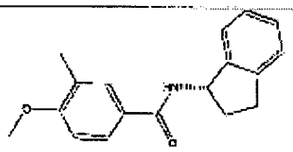
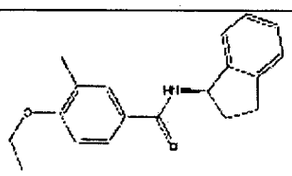
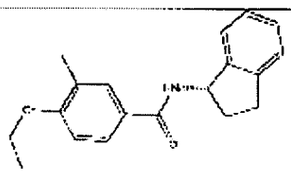
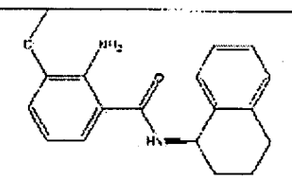
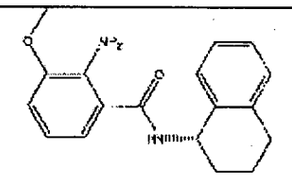
360

número exacto y de la naturaleza de los grupos de sustituyentes, pero los compuestos de Fórmula (I) que tiene los ligandos R^2 bicíclicos y las configuraciones ópticas absolutas mostradas en las gráficas inmediatamente anteriores son típicamente "R" en el carbono ópticamente activo mostrado anteriormente, y aquellos compuestos usualmente dan unión superior a receptores de dulce T1R2/T1R3. Se debe notar sin embargo que los isómeros "S" opuestos típicamente tie nen algunas, aunque típicamente in feriores, actividades para la unión de receptores de dulce T1R2/T1R3 y/o como compuestos mejoradores de sabor dulce.

Los Solicitantes también han encontrado que los receptores salado o picante T1R1/T1R3 a menudo muestran una notable tendencia a unir más fuertemente los compuestos de Fórmula (I) que tienen los grupos R^2 mostrados anteriormente lasa configuraciones "S" opuestas, a saber:



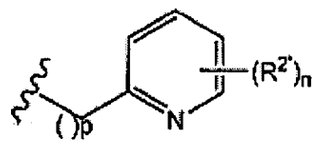
Otra vez, aunque los receptores salado o picante T1R1/T1R3 a menudo muestran una preferencia significativa para los isómeros "S" de los compuestos que comprenden de los grupos R^2 mostrados anteriormente, los isómeros "R" pueden retener actividad biológica significativa aunque disminuida como degustantes de sabor salado o picante o compuestos mejoradores salado o picante para MSG. La tabla mostrada adelante suministra ejemplos importantes de datos sobre la unión de enantiómeros opuestos a los receptores del sabor salado o picante T1R1/T1R3, para ilustrar este punto.

COMPUESTO	NOMBRE DEL COMPUESTO Y CONFIGURACIÓN ÓPTICA	AFINIDAD PARA RECEPTOR DE AJEDREA T1R1/T1R3 EC_{50} UM
	(R)-N-(2,3-dihidro-1H-inden-1-il)-4-metoxi-3-metilbenzamida	2.13
	(S)-N-(2,3-dihidro-1H-inden-1-il)-4-metoxi-3-metilbenzamida	0.08
	(R)-N-(2,3-dihidro-1H-inden-1-il)-4-etoxi-3-metilbenzamida	4.53
	(S)-N-(2,3-dihidro-1H-inden-1-il)-4-etoxi-3-metilbenzamida	0.85
	(R)-2-amino-3-metoxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	0.09
	(S)-2-amino-3-metoxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	0.01

Cuando la especificación, reivindicaciones, o gráficos de este documento indican que un compuesto está presente en una forma ópticamente activa, según se implica por la discusión y gráficas inmediatamente anteriores, se debe entender que los compuestos de Fórmula (I) indicados están presentes en al menos un pequeño exceso enantiomérico (es decir más de aproximadamente 50% de las moléculas que tienen la configuración óptica indicada). Modalidades adicionales preferiblemente comprenden un exceso enantiomérico del isómero indicado de al menos 75%, o 90%, o 95%, o 98%, o 99%, o 99.5%. Dependiendo de la diferencia

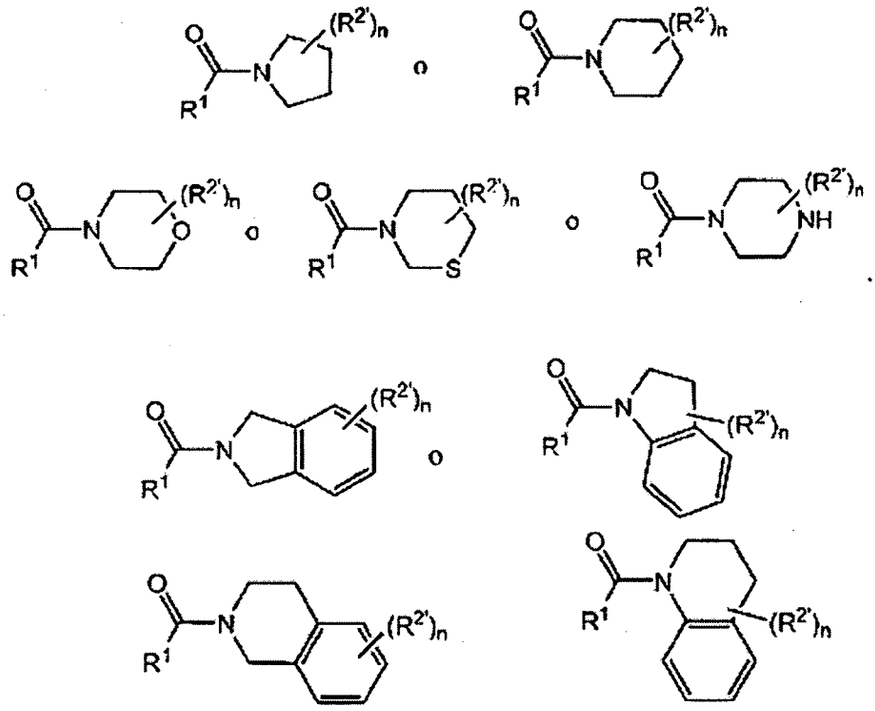
en las actividades biológicas el costo de producción y/o cualesquiera diferencias de toxicidad entre los dos enantiómeros, para un compuesto dado esto puede ser ventajoso para producir y vender para consumo humano una mezcla racémica de los enantiómeros o un exceso enantiomérico pequeño o grande de uno de los enantiómeros de un compuesto dado.

En otras modalidades de los compuestos de amida de Fórmula (I), incluyen los compuestos oxalamida salado o picante de Fórmula (V) como se describe adelante, uno de R^2 y R^3 es hidrógeno, y el otro de R^2 y R^3 es un radical piridinilo sustituido por alquileno que tiene la estructura:



en donde p es, 1 o 2; y n es 0, 1, o 2, y R^2 puede ser cualquiera de los grupos sustituyentes definidos anteriormente.

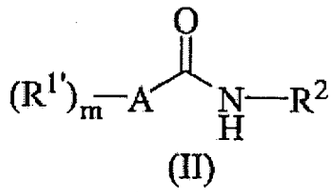
En otras modalidades de los compuestos de amida de Fórmula (I), en algunas modalidades de los compuestos de Fórmula (I), los grupos R^2 y R^3 no son hidrógeno y se unen para hacer un anillo amina heterocíclico opcionalmente sustituido, ejemplos de los cuales se muestran mostrada adelante:



y n es 0, 1, o 2, y R^2 puede ser cualquiera de los grupos sustituyentes definidos anteriormente. Como se describirá adicionalmente adelante, las ureas son un subgénero de los compuestos de amida de Fórmula (I) que pueden tenr preferiblemente tales modalidades cíclicas de los grupos R^2/R^3, y tales compuestos son particularmente útiles como compuestos mejoradores de dulce y/o degustantes.

Compuestos de Amida que Comprende de Grupos R^1 Arilo o Heteroarilo

En muchos subgéneros preferidos de los compuestos de amida de Fórmula (I) que tienen uno o ambos de la actividad agonista de los receptores del sabor dulce y salado o picante, en un subgénero preferido de los compuestos de amida R^1 es un grupo arilo o heteroarilo opcionalmente sustituido. Más específicamente, hay muchos subgéneros de los compuestos de amida de Fórmula (I) que tienen la siguiente Fórmula (II):



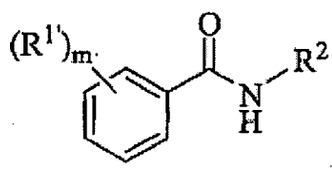
(II)

en donde A comprende un anillo heteroarilo de 5 o 6 miembros, y m es 0, 1, 2, 3 o 4.

en tales compuestos de las Fórmulas (I) y/o (II), cada $R^{1'}$ pu eden ser independientemente seleccionado del grupo que consiste de hidroxilo, NH_2, SH, halógeno, y un radical orgánico C_1-C_4. En modalidades relacionadas, cada $R^{1'}$ se selecciona independientemente del grupo que consiste de alquilo, alcoxi, alcoxi-alquilo, hidroxialquilo, OH, CN, CO_2H, CO_2R^6, CHO, COR^6, SR^6, halógeno, alquenilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, y heteroarilo; y R^6 es alquilo C_1-C_6. En algunas modalidades relacionadas pero alternativas de los compuestos de Fórmulas (I) y/o (II), cada $R^{1'}$ y/o cada $R^{2'}$ pueden ser independientemente seleccionados del grupo que consiste de hidroxilo, NH_2, SH, halógeno, alquilo C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, alcoxilo C_1-C_4, alcoxi-alquilo C_1-C_4, hidroxi-alquilo C_1-C_4, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, y halógeno, en donde R^6 es alquilo C_1-C_4. En muchas modalidades preferidas de los compuestos de Fórmulas (I) y/o (II), cada $R^{1'}$ se selecciona independientemente del grupo que consiste de grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, n-propilo, n-butilo, 1-metil- ropilo, isobutilo, t-butilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi. En tales compuestos de Fórmula (II), R^2 puede ser cualquiera de las estructuras contempladas anteriormente, o similares.

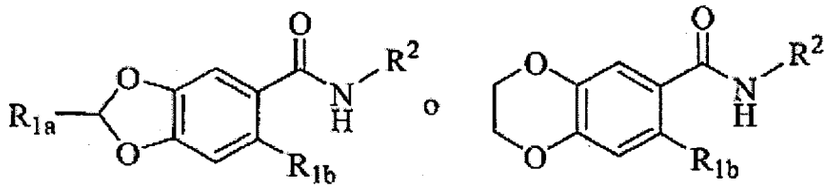
En algunas modalidades, el grupo A de Fórmula (II) comprende un anillo arilo, es decir contiene en algún lugar dentro de su estructura al menos un anillo fenilo aromático de seis miembros. Los arilos incluyen al menos anillos benceno y naftaleno, que no pueden, pero en muchas modalidades son sustituidos adicionalmente con al menos 1, 2, o 3 grupos sustituyentes $R^{1'}$, los cuales se pueden definir por cualquiera de las alternativas descritas anteriormente. En tales modalidades el anillo bencenilo y naftalenilo puede, pero no necesariamente estar directamente unido a el átomo de carbono carbonilo del compuesto amida.

En muchas modalidades de los compuestos de Fórmula (II), el grupo A es un anillo fenilo que está unido directamente al átomo de carbono carbonilo del grupo amida, y R^3 es H, para formar un compuesto benzamida que tiene la fórmula mostrada adelante:



En tales compuestos de Fórmula (II), R^2 puede ser cualquiera de las estructuras contempladas anteriormente, o similares. Tales compuestos que tienen grupos R^2 alquilo ramificados se prefieren como degustantes salado o picante y/o mejoradores salado o picante. Tales compuestos que tiene del tetrahidronaftaleno opcionalmente sustituido, indanilo, o heterorocíclico R2 relacionado estructuralmente descritos anteriormente son compuestos mejoradores de dulce altamente efectivos.

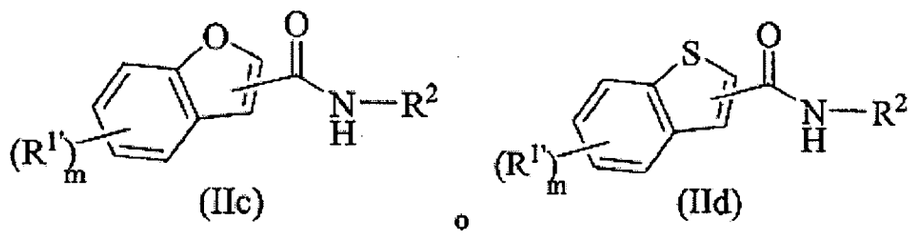
En algunas modalidades preferidas de los compuestos en donde A es un anillo bencenilo, uno o dos de los grupos $R^{1'}$ sustituyentes pueden estar unidos juntos para formar un anillo alquilenodioxi saturado en un anillo fenilo, como se ejemplifica por los siguientes subgéneros preferidos (IIa) y (IIb):



(IIa) o (IIb)

en donde R_{1a} y R_{1b} son independientemente hidrógeno o un alquilo inferior, o alternativamente R_{1a} y R_{1b} son independientemente hidrógeno o metilo, o alternativamente ambos R_{1a} y R_{1b} son hidrógeno.

En muchas modalidades de los compuestos de amida de Fórmula (II), A es anillo heteroarilo, y típicamente un anillo heteroarilo monocíclico o fusionado bicíclico. Los heteroarilos fusionados bicíclicos se representan por los siguientes benzofuranos (Fórmula IIc) y benzotiofuranos (Fórmula (IId):

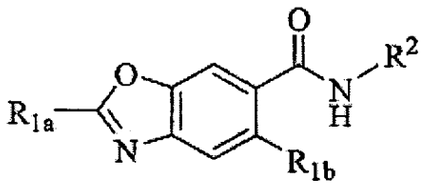


(IIc) o (IId)

en donde m es 0, 1, 2, o 3 y cada $R^{1'}$ pueden estar unido a los anillos fenilo o heteroarilo y cada $R^{1'}$ es independientemente seleccionado de, hidroxi, flúor,

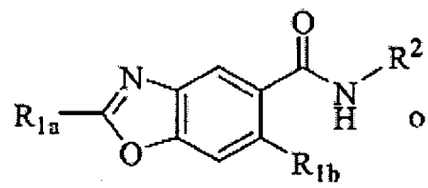
cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

Ejemplos adicionales de heteroarilos bicíclicos fusionados como grupos A se representan por los siguientes compuestos de benzoxazol (Fórmula IIe) y (Fórmula (IIf):



(IIe)

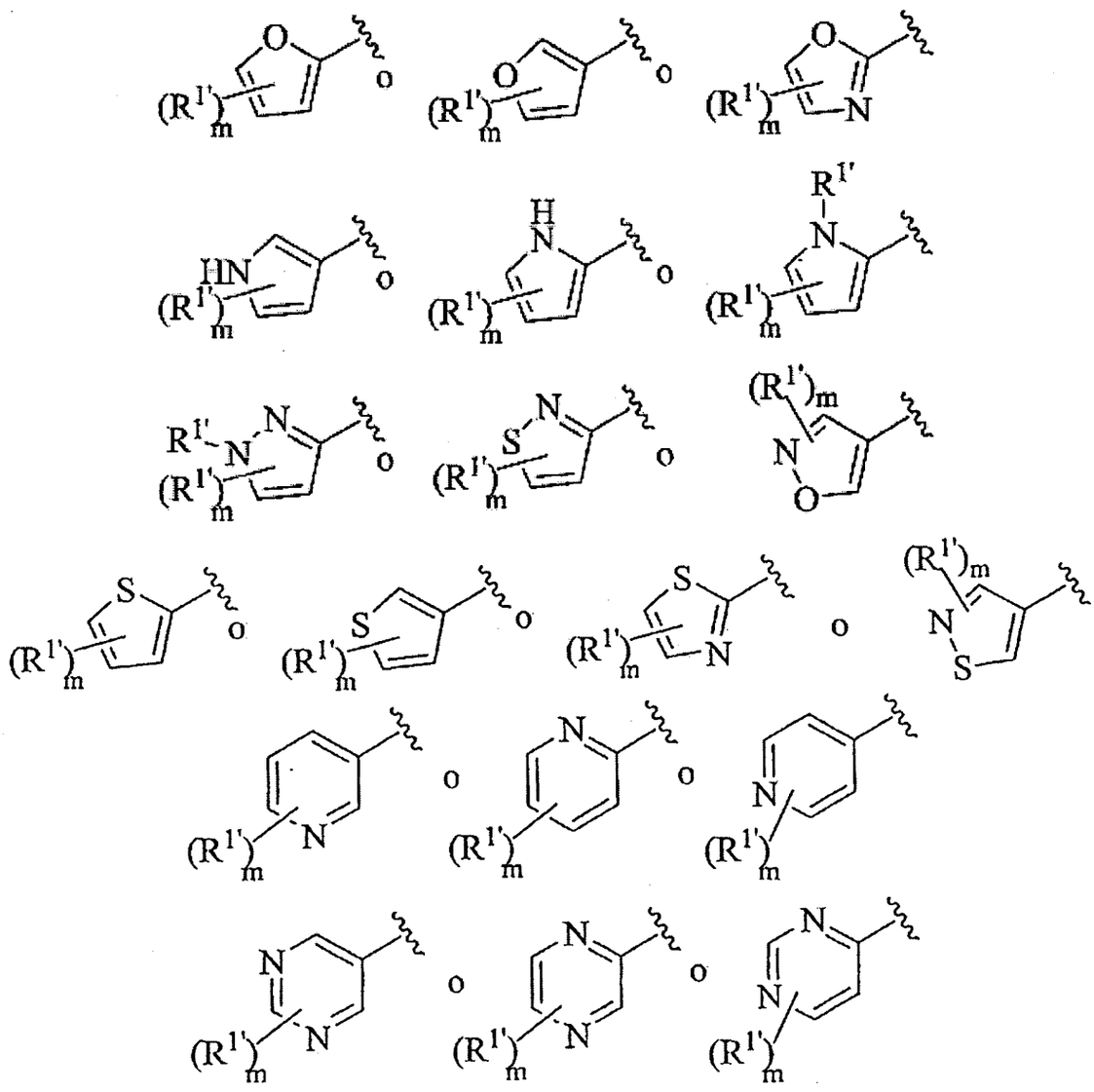
o



(IIf)

en donde R_{1a} o R_{1b} es independientemente hidrógeno o un alquilo inferior.

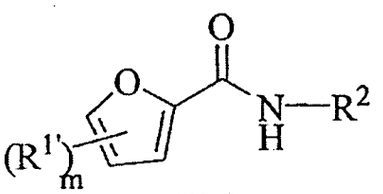
En muchas modalidades de los compuestos de amida de Fórmula (II), A es un anillo heteroarilo monocíclico. Los compuestos de amida heteroarilo monocíclicos que se pueden utilizar como un grupo A en la Fórmula (II) se representan por las siguientes estructuras:



en donde m es 0, 1, 2, o 3. En tales compuestos de Fórmula (II), cada $R^{1'}$ puede ser independientemente seleccionado del grupo que consiste de hidroxilo, NH_2, SH, halógeno, y un radical orgánico C_1-C_4. en algunas modalidades relacionadas pero alternativas de los compuestos de Fórmula (II), cada $R^{1'}$ puede ser independientemente seleccionado del grupo que consiste de hidroxilo, NH_2, SH, halógeno, alquilo C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, alcoxilo C_1-C_4, alcoxi-alquilo C_1-C_4, hidroxi-alquilo C_1-C_4, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, y halógeno, en donde R^6 es alquilo C_1-C_4. En muchas modalidades preferidas cada $R^{1'}$ se selecciona independientemente del grupo que consiste de grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$,

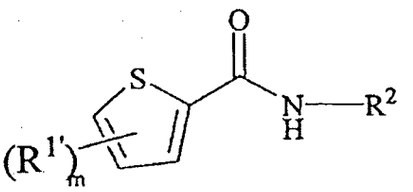
$COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, n-propilo, n-butilo, 1-metil-propilo, isobutilo, t-butilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi. En tales compuestos de Fórmula (II), R^2 puede ser cualquiera de las estructuras contempladas anteriormente, o similares.

En algunas modalidades preferidas de los compuestos de amida heteroarilo monocíclicos, A es un anillo furano sustituido, tiofurano, o oxazol, para formar compuestos que tienen las Fórmulas (IIg), (IIh) y (IIi):

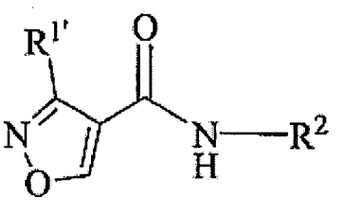


(IIg)

o



(IIh)



(IIi)

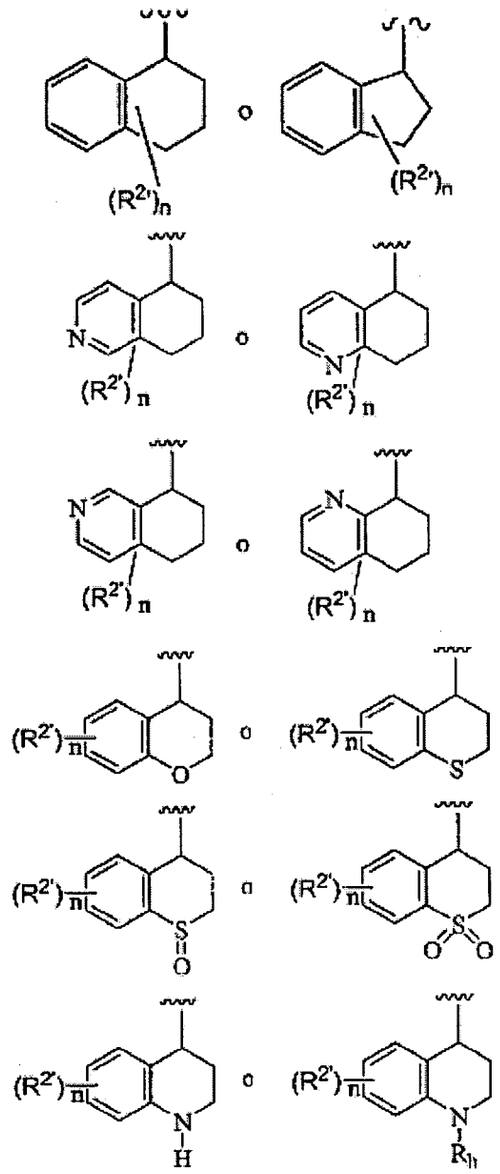
en donde m es 0, 1, 2, o 3. En algunas de tales modalidades, m es 1 o 2 y cada $R^{1'}$ puede ser independientemente seleccionado de grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, n-propilo, n-butilo, 1-metil-propilo, isobutilo, t-butilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

En muchas modalidades de los compuestos de los varios subgéneros de Fórmula (II) descritos inmediatamente antes, al menos uno de R^2 o R^3 puede ser un alquilo C_3-C_{10} ramificado; un ácido carboxilico α-sustituido o un éster de alquilo inferior de ácido carboxílico α-sustituido; un anillo arilo o heteroarilo de 5 o 6

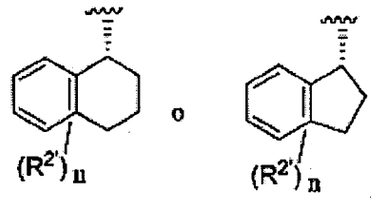
miembros, opcionalmente sustituido con 1, 2, 3 o 4 grupos sustituyentes seleccionados del grupo que consiste de grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi; un ciclohexilo, opcionalmente sustituido con 1, 2, o 3 grupos metilo.

Los compuestos isoxazol de Fórmula (IIi) pueden ser inesperadamente superiores como compuestos mejoradores de dulce cuando $R^{1'}$ es un radical orgánico C_1-C_8, tal como por ejemplo alquilo C_1-C_8 (normal o ramificado), alcoxilo C_1-C_8, alcoxi-alquilo C_1-C_8, hidroxi-alquilo C_1-C_8, amino-alquilo C_1-C_8, o un arilo C_1-C_8 opcionalmente sustituido o heteroarilo que tiene un anillo aromático de cinco o seis miembros, En todavía modalidades adicionales, el grupo $R^{1'}$ del anillo isoxasol es grupo hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, n-propilo, n-butilo, 1-metil-propilo, isobutilo, t-butilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, trifluorometoxi, CH_2OCH_3, CH_2OH, CH_2NH_2, CH_2NHCH_3, o $CH_2N(CH_3)_2$.

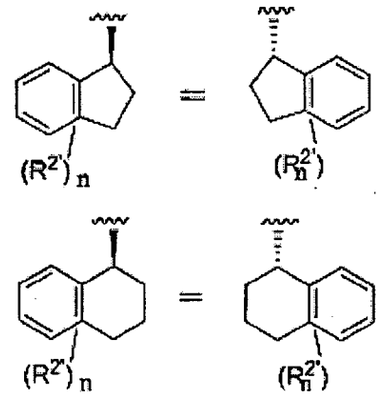
En algunas modalidades, los compuestos isoxazol de Fórmula (IIi) comprenden un grupo R^2 que es un anillo 1-(1,2,3,4) tetrahidronaftaleno, un anillo 2,3-dihidro-1H-indeno o uno de sus compuestos análogos heterocíclicos que tienen una de las fórmulas como se muestra adelante:



en donde n es 0, 1, 2, o 3, preferiblemente 1 o 2, y cada R^2 puede estar unido a el anillo aromático o no aromático y se selecciona independientemente de hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi; como se describió anteriormente aquí con respecto a los compuestos de amida de Fórmula general (I). En sus aplicaciones como mejoradores de dulce, típicamente se prefiere que los compuestos de Fórmula (IIa-i) que comprenden los grupos R^2 bicíclicos ilustrados anteriormente comprenden al menos un exceso enantiomérico de la configuración óptica "R" como se ilustra adelante



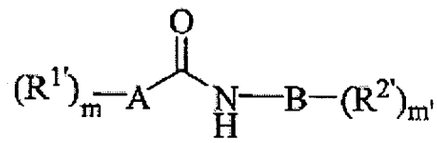
En contraste, cuando los compuestos que tienen Fórmulas (IIa-i) con grupos R^2 bicíclicos tales como aquellos descritos se emplean como degustantes "Umami" o como agentes para mejorar el sabor Umami de MSG, se ha encontrado que el uso de grupos R^2 indanilo o tetrahidronapthilo bicíclicos que comprenden la configuración "S" opuesta, como se ejemplifica adelante, puede ser ventajoso:



Los subgéneros de compuestos de amida aromáticos o heteroaromáticos de Formula(II) descritos inmediatamente antes contienen muchos agonistas excelentes de receptores del sabor ("umami") salado o picante T1R1/T1R3, y/o receptores del sabor dulce T1R2/T1R3, en concentraciones muy bajas del compuesto amida en el orden de concentraciones micromolares o menores, y pueden inducir una sensación apreciable de un sabor umami salado o picante en humanos, y/o pueden servir como mejoradores del sabor Umami del sabor salado o picante de MSG, o mejora significativamente la eficacia de una variedad de endulzantes conocidos, especialmente endulzantes basados en sacáridos.

De acuerdo con esto, muchos de los compuestos de amida aromáticos o heteroaromáticos de Fórmula (II) pueden ser utilizados como agentes saborizantes de dulce o salado o picante o mejoradores de sabor de dulce o salado o picante cuando se ponen en contacto con una amplia variedad del productos comestibles y/o composiciones, o sus precursores, para producir composiciones comestibles o medicinales de gusto modificado, como se describe en otra parte aquí.

En otros subgéneros de los compuestos de Fórmula (I), el compuesto amida tiene la Fórmula (III):



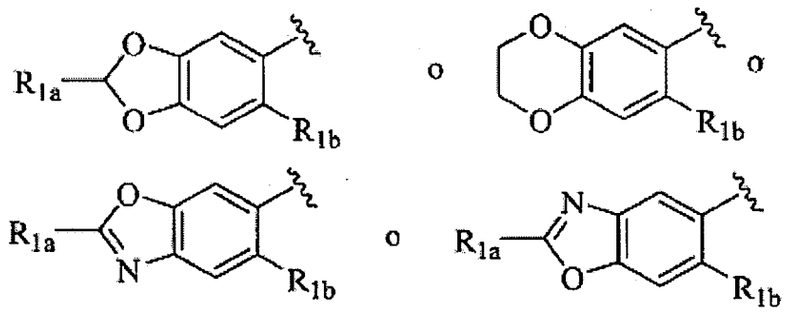
(III)

en donde A comprende un anillo heteroarilo de 5 o 6 miembros; m es 0, 1, 2, 3 o 4; cada $R^{1'}$ se selecciona independientemente de alquilo, alcoxilo, alcoxi-alquilo, hidroxialquilo, OH, CN, CO_2H, CHO, COR^6, CO_2R^6, SH, SR^6, halógeno, alquenilo, cicloalquilo, cicloalquenilo, arilo, y heteroarilo y R^6 es alquilo C_1-C_6; B es un anillo arilo o heteroarilo de 5 o 6 miembros; m' es 0, 1, 2, 3 o 4; $R^{2'}$ se selecciona del grupo que consiste de alquilo, alcoxilo, alcoxi-alquilo, OH, CN, CO_2H, CHO, COR^6, $CO_2R^{6'}$ SR^6, halógeno, alquenilo, cicloalquilo, cicloalquenilo, arilo, y heteroarilo: y R^6 es alquilo C_1-C_6.

En los compuestos de Fórmula (III), los grupos $R^{1'}$ y $R^{2'}$ sustituyentes opcionales pueden también ser independientemente seleccionados de grupos

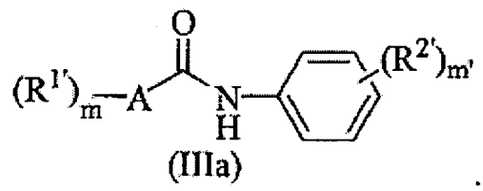
hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3,SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

En los compuestos de Fórmula (III), ambos anillos A y B comprenden un anillo arilo o heteroarilo de cinco o seis miembros. Para el anillo A, cualquiera de las varias modalidades de los anillos A mencionados anteriormente para los compuestos de Fórmula (II), que incluyen fenilo y los heteroarilos monocíclicos y bicíclicos pueden ser adecuados. En algunas modalidades bicíclicas, el anillo A de los compuestos de Fórmula (III) tiene las siguientes estructuras:



en donde R_{1a} y R_{1b} son independientemente hidrógeno o un alquilo inferior.

En los compuestos de Fórmula (III), los anillos B son típicamente un anillo arilo o heteroarilo de cinco o seis miembros monocíclico opcionalmente sustituido, tal como un fenilo, piridilo, furanoilo, tiofuranoilo, pirrolilo, y monociclos similares. En algunas modalidades los compuestos de Fórmula (III) en donde B es fenilo, es decir en donde el compuesto amida se deriva fácilmente de un precursor de anilina sustituido, como se muestra adelante para el subgénero de compuesto (IIIa):

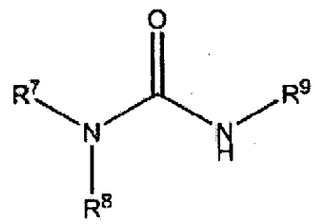


(IIIa)

Un número de compuestos derivados de anilina de Fórmula (IIIa) parecen haber sido sintetizados previamente, pero se cree que se desconozca previamente en la técnica que tales compuestos se pueden utilizar como compuestos saborizantes de sabor dulce y/o umami muy efectivos, en concentraciones en el orden de milimolares o menores, o en el orden de concentraciones micromolares, ver por ejemplo el compuesto A1 en la Tabla 1 adelante.

Compuestos de urea

En otros subgéneros de los compuestos de amida de Fórmula (I), el compuesto amida son los compuestos urea que tienen la Fórmula (IV):

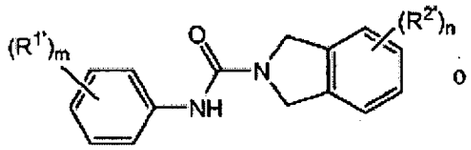


(IV)

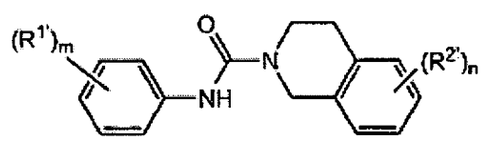
en donde R^7, R^8 y R^9 son cada uno un residuo de hidrocarburo que puede contener uno o más heteroátomos o un residuo inorgánico, y preferiblemente se selecciona independientemente de grupos arilalquenilo, heteroarilalquenilo, arilalquilo, heteroarilalquilo, alquilo, alcoxi-alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo y heteroarilo, cada uno de los cuales puede ser opcionalmente sustituido, o uno de R^7 o R^8 pueden ser y a menudo es H. Como apreciará una

persona medianamente versada en la técnica, aquellos compuestos de urea que son un subgénero de los compuestos de amida de Fórmula (I) en donde R^7 y R^8 y el átomo de nitrógeno unido a estos son equivalentes con los grupos R^1 de Fórmula (I) que son residuos orgánicos, y R^9 es el equivalente de los radicales R^2 y/o R^3 de Fórmulas (I) y/o (II).

En algunas modalidades de los compuestos de urea de Fórmula (IV), R^7 y R^8 juntos forman un anillo heterocíclico o heteroarilo que tiene 5, 6, o 7 átomos por anillo que pueden ser opcionalmente sustituidos con 1, 2, o 3 sustituyentes independientemente seleccionados de grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi. Ejemplos de tales compuestos de urea pueden tener las fórmulas (IVa) y (IVb):



(IVa)

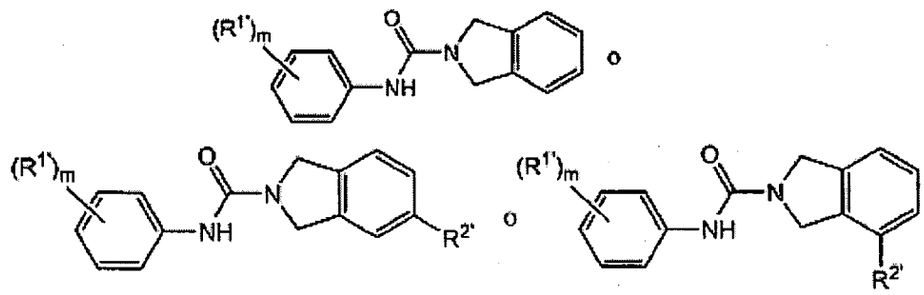


(IVb)

en donde m y n son independientemente 0, 1, 2, o 3, y cada R^1 y R^2 se puede definir por cualquiera de las formas anteriormente descritas para los compuestos de Fórmula (I). En muchas modalidades, R^1 y $R^{2'}$ pueden ser independientemente seleccionados de flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi. En algunas modalidades, n es 0.

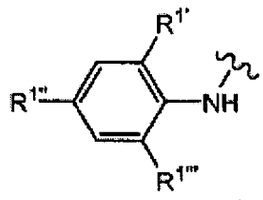
Sin embargo se ha descubierto inesperadamente que ciertas modalidades de los compuestos de urea de Fórmula (IVa) mostrados anteriormente (que

comprenden anillos dihidroindol) son particularmente efectivos como mejoradores del sabor dulce de endulzantes conocidos si m es 1, 2, o 3, y uno o dos sustituyentes $R^{2'}$ pequeños para el anillo dihidroindol se ponen en orden en ciertas geometrías favorecidas. De acuerdo con esto, en algunas modalidades preferidas, los compuestos de urea de Fórmula (IVa) tienen las estructuras mostradas adelante:

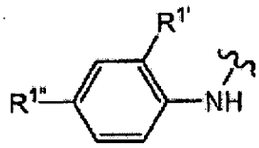


en donde m es 1, 2, o 3, y cada $R^{1'}$ y $R^{2'}$ pueden ser independientemente seleccionados de flúor, cloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, SEt, SCH_3, metilo, etilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, o dos grupos $R^{1'}$ juntos forman un anillo metilenodioxi. En modalidades preferidas de estos compuestos, R^2 es metilo o metoxi.

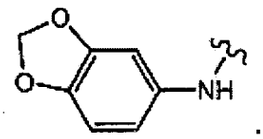
En algunas modalidades, el radical anilina de los compuestos de urea dihidroindil tiene la estructura:



en donde $R^{1'}$, $R^{1'''}$ y $R^{1''''}$ se seleccionan independientemente de hidrógeno, flúor, cloro, bromo, metilo, y metoxi (dado que al menos uno de $R^{1'}$, $R^{1'''}$ y $R^{1''''}$ no es hidrógeno. Preferiblemente, el radical anilina tiene la fórmula:



en donde $R^{1'}$ y $R^{1''}$ se seleccionan independientemente de flúor, cloro, bromo, metilo, y metoxi. En ciertas otras modalidades preferidas, el radical anilina tiene la fórmula:



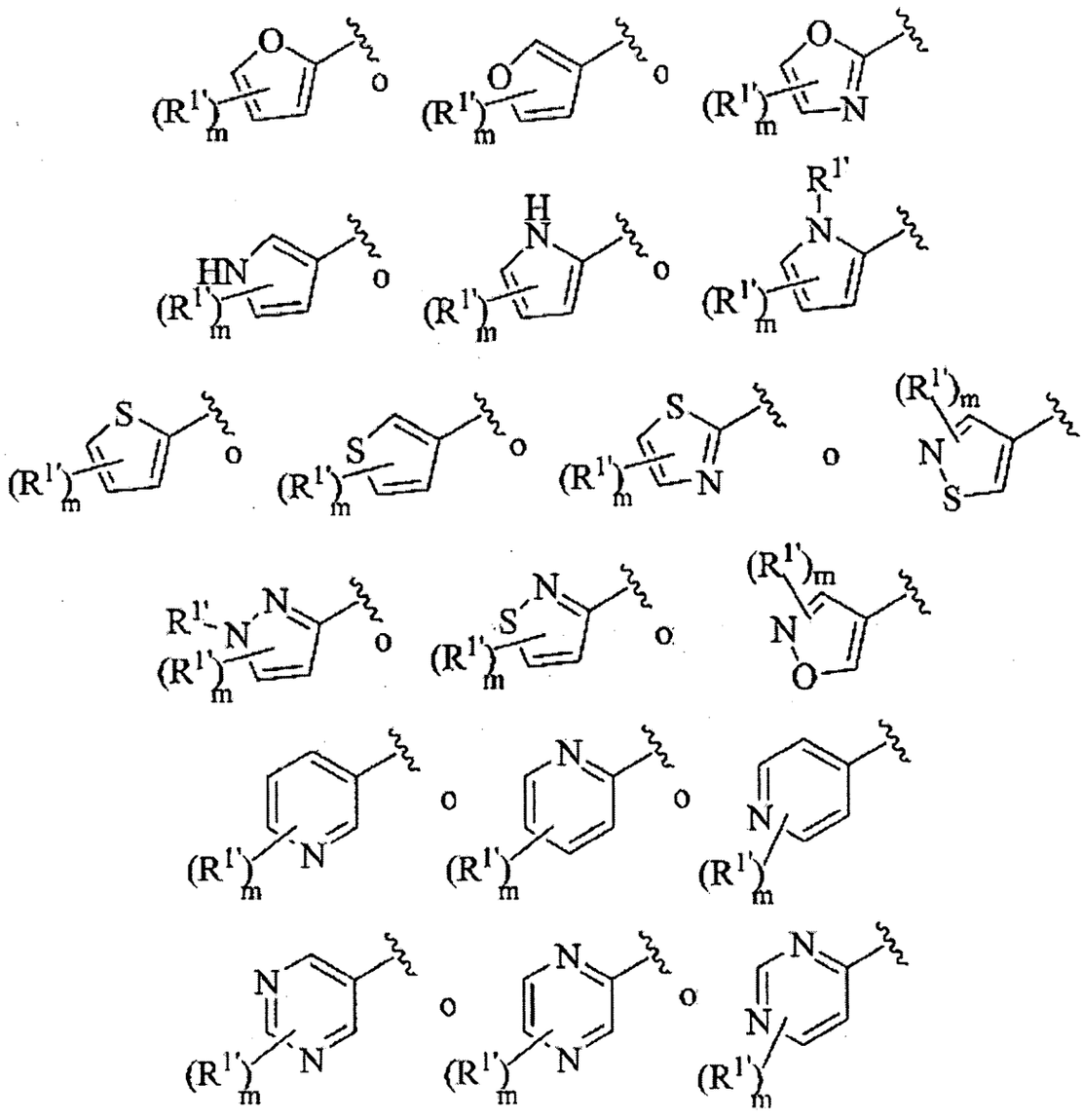
En modalidades adicionales de los compuestos de urea de Fórmula (IV), R^9 y uno de R^7 y R^8 se seleccionan independientemente de arilalquenilos, heteroarilalquenilos, arilalquilos, heteroarilalquilos, alquilos, alcoxi-alquilos, alquenilos, cicloalquilos, cicloalquenilos, arilos y heteroarilos, cada uno de los cuales contienen grupos carbono que pueden ser opcionalmente sustituidos con 1, 2, o 3 sustituyentes independientemente seleccionados de grupos hidrógeno, hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometlioxi.

En modalidades adicionales de los compuestos de urea de Fórmula (IV), R^9 y uno de R^7 y R^8 se seleccionan independientemente de arilalquilo, heteroarilalquilo, alquilo, cicloalquilo, arilo, heterociclo, y heteroarilo, cada uno de

los cuales puede opcionalmente comprender uno a cinco heteroátomos independientemente seleccionados de oxígeno, nitrógeno, azufre, cloro, y flúor.

En modalidades adicionales de los compuestos de urea de Fórmula (IV), R^9 y uno de R^7 y R^8 se seleccionan independientemente de alquilo, fenilo, ciclohexilo, o piridilo, cada uno de los cuales puede opcionalmente comprender uno a cuatro sustituyentes independientemente seleccionados de hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

En modalidades adicionales de los compuestos de urea de Fórmula (FV), al menos uno de R^7 y R^8 tienen una de las fórmulas heteroaromáticas:

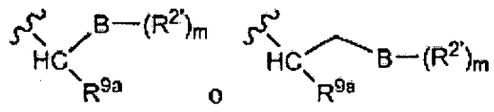


en donde m es 0,1, 2, o 3, y cada $R^{1'}$ independientemente se selecciona de hidrógeno, grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi. En tales modalidades, R^9 es preferiblemente un alquilo C_3-C_{10} ramificado, arilalquilo, o un cicloalquilo que se puede sustituir opcionalmente con 1, 2, o 3 sustituyentes independientemente seleccionados de hidrógeno, grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi. Los compuestos de amida de Fórmula (II) pueden ser fácilmente sintetizados a partir

de precursores de ácido carboxílico de arilo o heteroarilo bien conocidos y/o disponibles comercialmente.

En modalidades adicionales de los compuestos de urea de Fórmula (IV), al menos uno de R^7 y R^8 es un anillo fenilo opcionalmente sustituido con 1, 2, o 3 sustituyentes independientemente seleccionados de hidrógeno, grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometox. En tales modalidades, R^y es preferiblemente un alquilo C_3-C_{10} ramificado, arilalquilo, o un cicloalquilo que se puede sustituir opcionalmente con 1, 2, o 3 sustituyentes independientemente seleccionados de hidrógeno, grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

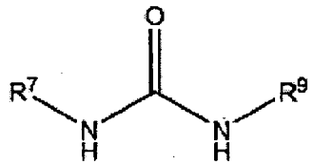
En modalidades adicionales de los compuestos de urea de Fórmula (IV), R^9 es un alquilo ramificado C_3-C_{10}. En modalidades adicionales de los compuestos de urea de Fórmula (IV), R^9 tiene la estructura:



en donde B es un anillo fenilo, piridilo, furanoilo, tiofuranoilo, pirrol, ciclopentilo, ciclohexilo, o piperidilo, m es 0, 1, 2, o 3, y cada $R^{2'}$ se selecciona independientemente de hidrógeno, grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, y R^{9a} es uno seleccionado del grupo que consiste de un alquilo, alcoxi-alquilo, alquenilo, cicloalquenilo, cicloalquilo, -

R^4OH, $-R^4O\ R^5$ $-R^4CN$, $-R^4CO_2H$, $-R^4CO_2R^5$, $-R^4COR^5$, $-R^4SR^5$, y $-R^4SO_2R^5$ que comprenden de 1 a 12 átomos de carbono.

Se ha descubierto también que ciertos subgéneros de los compuestos de urea de Fórmula (IV) son degustantes Umami efectivos inesperadamente y/o mejoradores de MSG. El compuesto de urea importante tiene la Fórmula (Ivc) mostrada adelante:



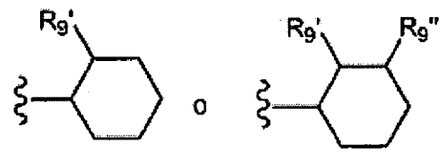
(IVc)

en donde

i) R^7 es un anillo fenilo opcionalmente sustituido con 1, 2, o 3 sustituyentes independientemente seleccionados de grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, o en donde dos de los sustituyentes forman un anillo metilenodioxi, y

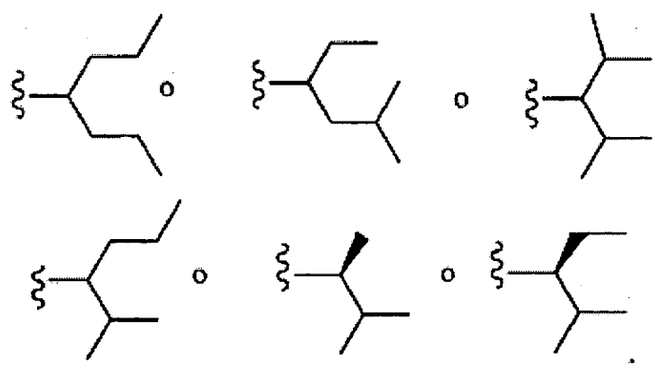
ii) R^9 es un radical C_3-C_{10} seleccionado de un ramificado alquilo, arilalquilo, o cicloalquilo, en donde el radical C_3-C_{10} opcionalmente comprende 1, 2, o 3 sustituyentes independientemente seleccionados de grupos hidroxi, flúor, cloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

En algunas modalidades de los compuestos de Fórmula (IVc) R^9 tiene una de las siguientes estructuras:

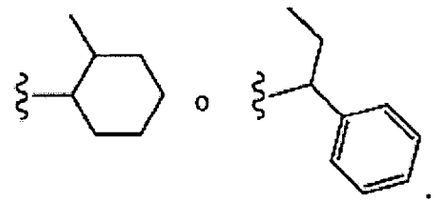


en donde $R_{9'}$ y $R_{9''}$ se seleccionan independientemente de grupos hidroxi, flúor, cloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, y preferiblemente $R_{9'}$ y $R_{9''}$ son metilo.

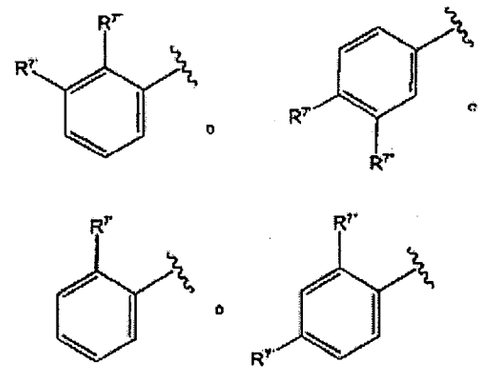
En otras modalidades de las ureas de Umami de Fórmula (IVc), R^9 es un alquilo C_4-C_8 ramificado, que puede incluir por ejemplo las siguientes estructuras:



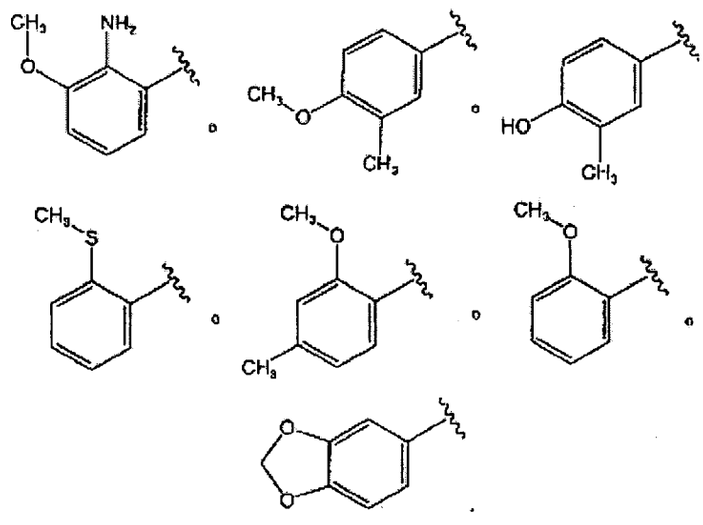
En modalidades adicionales de las ureas de Umami de Fórmula (IVc), R^9 tiene una de las siguientes estructuras:



En algunas modalidades de las ureas de Umami de Fórmula (IVc), R^7 tiene la estructura:

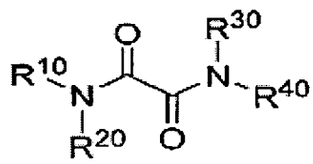


en donde $R_{7'}$ y $R_{7''}$ se seleccionan independientemente de grupos hidroxi, flúor, cloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, triftuorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, y en modalidades preferidas, R^7 tiene una de las estructuras:



Compuestos de oxalamida

En otros subgéneros de los compuestos de amida de Fórmula (I), el compuesto amida es un compuesto oxalamida que tiene la fórmula (V):



(V)

en donde R^{10} y R^{30} son cada uno independientemente seleccionados de un residuo de hidrocarburo que puede contener uno o más heteroátomos, o preferiblemente, R^{10} y R^{30} se seleccionan independientemente del grupo que consiste de arilalquilo, heteroarilalquilo, heterociclo-alquilo, o opcionalmente grupos sustituidos de estos, y

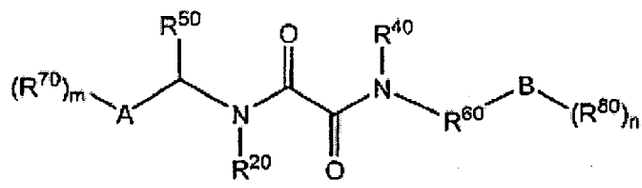
R^{20} y R^{40} son cada uno independientemente H o un residuo de hidrocarburo que puede contener uno o más heteroátomos; preferiblemente R^{20}, y R^{40} son H o alquilo C_1-C_3, u opcionalmente grupos sustituidos de estos. Más preferiblemente R^{20} y R^{40} son H. Más aún, puede haber 0, 1, 2, 3, o 4 grupos sustituyentes opcionales para R^{10} y R^{30} independientemente seleccionados de grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3,SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

En modalidad preferida de los compuestos de oxalamida de Fórmula (V), R^{10} y R^{30} son independientemente residuos de hidrocarburos seleccionados que tienen al menos tres átomos de carbono y opcionalmente de uno a diez

heteroátomos independientemente seleccionados de oxígeno, nitrógeno, azufre, halógenos, o fósforo, y en donde R^{20} y R^{40} se seleccionan independientemente de hidrógeno y un residuo de hidrocarburo que tiene al menos tres átomos de carbono y opcionalmente de uno a diez heteroátomos independientemente seleccionados de oxígeno, nitrógeno, azufre, halógenos, o fósforo.

En muchas modalidades preferidas de los compuestos de oxalamida de Fórmula (V), R^{20} y R^{40} son hidrógeno. En tales modalidades, R^{10} y R^{30} pueden ser independientemente seleccionados del grupo que consiste de arilalquilos, heteroarilalquilos, cicloalquil-alquilos, y heterociclo-alquilos que comprende de cinco a 15 átomos de carbono, en donde cada uno de R^{10} y R^{30} pueden opcionalmente comprender uno a cuatro sustituyentes independientemente seleccionados de hidrógeno, grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

En muchas modalidades de los compuestos de oxalamida de Fórmula (V), el compuesto oxalamida tiene la Fórmula (Va):



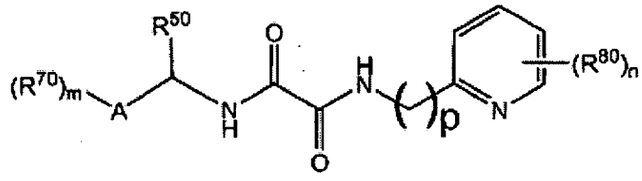
(Va)

en donde A y B son independientemente un arilo, heteroarilo, cicloalquilo, o un heterociclo que comprende de 5 a 12 átomos en el anillo; m y n son independientemente 0, 1, 2, 3 o 4-8; R^{20} y R^{40} son hidrógeno, R^{50} es hidrógeno o

un alquilo o residuo alquilo sustituido que comprende de uno a cuatro átomos de carbono; R^{60} está ausente o es un alquileno C_1-C_5 o a alquileno C_1-C_5 sustituido; R^{70} y R^{80} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo, alcoxilo, alcoxi-alquilo, OH, SR^9, halógeno, CN, NO_2, CO_2R^9, COR^9, $CONR^9R^{10}$, NR^9R^{10}, NR^9COR^{10}, SOR^9, SO_2R^9, $SO_2NR^9R^{10}$, $NR^9SO_2R^{10}$, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, y heterociclo; R^9 y R^{10} se seleccionan independientemente de H, alquilo C_1-C_6, cicloalquilo C_3-C_6, y alquenilo C_1-C_6. En modalidades preferidas de los compuestos de oxalamida de Fórmula (Va), R^{60} ies un grupo $-CH_2CH_2$, A y B se seleccionan independientemente de anillos fenilo, piridilo, furanoilo, tiofuranoilo y pirrolilo y R^{70} y R^{80} se seleccionan independientemente de grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

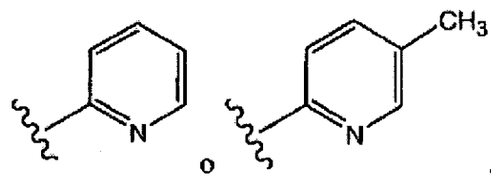
En algunas modalidades de los compuestos de oxalamida de Fórmula (Va), A y B son independientemente un anillo fenilo, piridilo, furanoilo, benzofuranoilo, pirrol, benzotiofeno, piperidilo, ciclopentilo, ciclohexilo, o cicloheptilo; m y n son independientemente 0, 1, 2, o 3; R^{20} y R^{40} son hidrógeno; R^{50} es hidrógeno o metilo; R^{60} es un alquileno C_2 o preferiblemente C_1-C_5; R^{70} y R^{80} se seleccionan independientemente de hidrógeno, grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

En muchas modalidades de los compuestos de oxalamida de Fórmula (V), el compuesto oxalamida tiene la Fórmula (Vb):

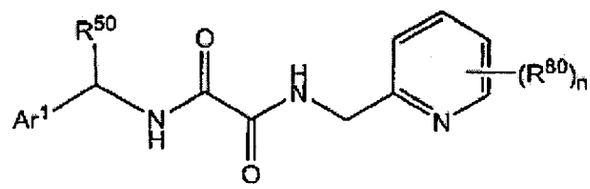


(Vb)

en donde A es un anillo fenilo, piridilo, furanoilo, pirrol, piperidilo, ciclopentilo, ciclohexilo, o cicloheptilo; m y n son independientemente 0, 1, 2, o 3; R^{50} es hidrógeno o metilo; p es 1 o 2; y R^{70} y R^{80} se seleccionan independientemente del grupo que consiste de hidrógeno, hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, o dos de R^{70} juntos forman un anillo metilenodioxi. En algunas modalidades de los compuestos de oxalamida de Fórmula (Vb), el radical piridil-R^{80} tiene la estructura:



En ciertas modalidades preferidas de los compuestos de amida de Fórmula (V), el compuesto oxalamida tiene la Fórmula (Vc):

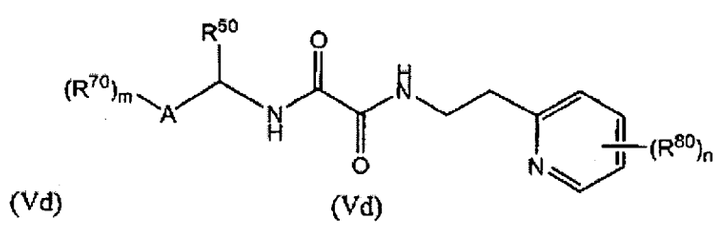


(Vc)

en donde Ar^1 es un anillo arilo sustituido o heteroarilo que comprende de cinco a 12 átomos de carbono; R^{50} es hidrógeno o metilo; n es 0, 1, 2, o 3; cada

R^{80} se selecciona independientemente del grupo que consiste de grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi. En algunas modalidades de los compuestos de oxalamida de Fórmula (Vc), Ar^1 es un 2-, 3-, o 4-mono-fenilo sustituido, 2,4-, 2,3-, 2,5, 2,6, 3,5-, o 3,6-difenilo sustituido, 3-alquil-4-fenilo sustituido, un tri-fenilo sustituido en donde los grupos sustituyentes se seleccionan independientemente del grupo que consiste de hidrógeno, hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CHs)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, o dos sustituyentes adyacentes juntos forman un anillo metilenodioxi en el anillo fenilo. En algunas modalidades de los compuestos de oxalamida de Fórmula (Vc), Ar^1 es un anillo heteroarilo sustituido que comprende de 5 a 12 átomos de carbono y en donde los grupos sustituyentes se seleccionan independientemente del grupo que consiste de hidrógeno, hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

En ciertas modalidades preferidas de los compuestos de amida de Fórmula (V), el compuesto oxalamida tiene la Fórmula (Vd):

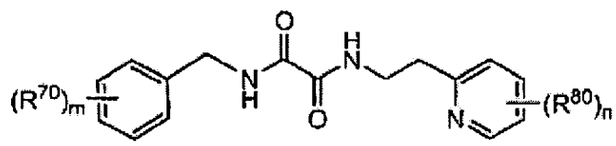


(Vd) (Vd)

en donde A es un anillo arilo sustituido o heteroarilo que comprende de cinco a 12 átomos de carbono; R^{50} es hidrógeno o metilo; n es 0, 1, 2, o 3; cada R^{80} se selecciona independientemente del grupo que consiste de hidrógeno,

hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi. Preferiblemente, A es un anillo fenilo, piridilo, furanoilo, pirrol, piperidilo, ciclopentilo, ciclohexilo, o cicloheptilo opcionalmente sustituido con 1, 3, o 3 grupos sustituyentes seleccionados independientemente del grupo que consiste de hidrógeno, grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

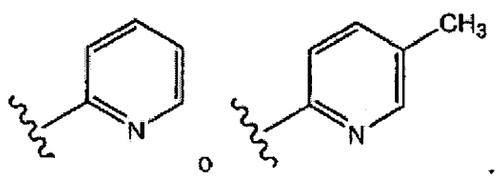
En ciertas modalidades preferidas de los compuestos de amida de Fórmula (V), el compuesto oxalamida tiene la Fórmula (Ve):



(Ve)

en donde m y n son independientemente 0, 1, 2, o 3; R^{70} y R^{80} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo, alcoxilo, alcoxi-alquilo, OH, SR^9, halógeno, CN, NO_2, CO_2R^9, COR^9, $CONR^9R^{10}$, NR^9R^{10}, NR^9COR^{10}, SOR^9, SO_2R^9, $SO_2NR^9R^{10}$, $NR^9SO_2R^{10}$, alquenilo, cicloalquilo, cicloalquenilo, arilo, heteroarilo, y heterociclo; y R^9 y R^{10} se seleccionan independientemente de H, grupos alquilo C_1-C_6, cicloalquilo C_3- C_6, y alquenilo C_1-C_6. Preferiblemente, R^{70} y R^{80} se seleccionan independientemente del grupo que consiste de hidrógeno, grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

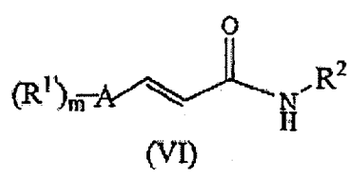
Preferiblemente, el radical piridil-R^{80} del compuesto de oxalamida de Fórmula (Ve) tiene la estructura:



Como se puede notar por la inspección de los Ejemplos adjuntos aquí adelante, compuestos de oxalamida de Fórmulas (Va)-(Ve) son excelentes agonistas de receptores del sabor ("umami") salado o picante T1R1/T1R3 en concentraciones muy bajas en el orden de concentraciones micromolares o menores, inducen una sensación apreciable de un sabor umami salado o picante en humanos, y/o pueden servir como mejoradores del sabor Umami del sabor salado o picante de MSG. De acuerdo con esto, compuestos de oxalamida de Fórmulas (Vc), (Vd) y (Ve) se pueden utilizar como agente saborizante salado o picante o sabor salado o picante mejoradores cuando entran en contacto con una amplia variedad de productos comestibles y/o composiciones, o sus precursores, como se describe aquí.

Compuestos Acrilamida

En otro subgénero de los compuestos amida de la fórmula (I), el compuesto amida es un compuestos acrilamida que tiene la fórmula (VI):



(VI)

En donde A es un anillo arilo o heteroarilo de 5 o 6 miembros; m es 0, 1, 2, 3 o 4; cada $R^{1'}$ se selecciona independientemente de alquilo, alcoxi, alcoxi-alquilo, OH, CN, CO_2H, CO_2R^6, CHO, COR^6, SR^6, halógeno, alquenilo, cicloalquilo, cicloalquenilo, arilo, y heteroarilo, y R^2 puede ser cualquiera de varias modalidades de R^2 descritas aquí anteriormente con respecto a las amidas de la fórmula (I).

En algunos de los compuestos acrilamida de la fórmula (VI), A es un anillo de fenilo y m es 1, 2, 3 o 4, o preferiblemente m es 1 o 2, y $R^{1'}$ se puede seleccionar independientemente de hidrógeno, hidroxi, fluor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y grupos trifluorometoxi. En algunos de los compuestos acrilamida de la fórmula (VI), R^2 es un alquilo C_3-C_{10}, o un éster de alquilo inferior de ácido carboxílico α-sustituido.

Compuestos Farmacéuticamente Aceptables o Comestibles

Muchos de los compuestos amida de la fórmula (I) o sus varios subgéneros enumerados comprenden grupos ácidos o básicos, de tal forma que dependiendo del carácter ácido o básico ("pH") de las composiciones comestibles o medicinales en el que ellos se formulan, pueden estar presentes como sales, que son preferiblemente comestiblemente aceptables (es decir diseñadas generalmente reconocidas como seguras, o GRAS) o sales farmacéuticamente aceptables (muchas de las cuales se han reconocido por la Administración Federal de Drogas y Alimentos).

Los compuestos amida de fórmula (I) que tienen grupos ácidos, tal como ácidos carboxílicos, tenderán (en un pH fisiológico cerca al neutro) a estar presentes en una solución en la forma de carboxilatos aniónicos, y por lo tanto tendrán en modalidades preferidas un catión comestiblemente asociado y/o farmacéuticamente aceptable, muchos de los cuales se conocen por aquellos expertos en la técnica. Tales cationes comestiblemente y/o farmacéuticamente aceptables incluyen cationes de metales álcali (cationes de litio, sodio y potasio), cationes de metales alcalinotérreos (magnesio, calcio, y similares), o cationes de amonio orgánicamente sustituidos tales como cationes $(R\text{-}NH_3)^+$.

Los compuestos amida de la fórmula (I) que tienen grupos de sustituyentes básicos, tal como amino o nitrógeno que contienen grupos heterocíclicos, tenderán (en un pH fisiológico cerca al neutro, o en un pH ácido común en muchos alimentos) a estar presentes en solución en la forma de grupos Catiónicos de amonio, y por lo tanto tendrán en modalidades preferidas una comestibilidad y/o anión farmacéuticamente aceptable, muchos de los cuales se conocen por aquellos expertos en la técnica. Tal comestibilidad y/o grupos aniónicos farmacéuticamente aceptables incluyen la forma aniónica de una variedad de ácidos carboxílicos (acetatos, citratos, tartratos, sales aniónicas de ácidos grasos, etc), haluros, (especialmente fluoruros o cloruros) nitratos, y similares.

Los compuestos amida de la fórmula (I) y sus varios subgéneros deben ser preferiblemente comestiblemente aceptables, es decir considerado adecuado para consumo en alimentos o bebidas, y también debe ser farmacéuticamente aceptable. El método típico `para demostrar que un compuesto saborizante es comestiblemente aceptable es tener el compuesto probado y/o evaluado por un Panel Experto de la Asociación de Fabricantes de Extractos y Sabores y declarado

como "Reconocido Generalmente como Seguro" ("GRAS"). El proceso de evaluación FEMA/GRAS para los compuesto saborizantes es complejo pero bien conocido por aquellos expertos en la técnica de preparación de productos alimenticios, como se discute por Smith et al. en un articulo titulado "Sustancias Saborizantes GRAS 21", Food Technology (57(5), pags 46-59, Mayo 2003, los contenidos completos de los cuales se icorporan aquí como referencia.

Cuando se evalúa en el proceso FEMA/GRAS un nuevo compuesto saborizante se ensaya típicamente para cualquier efecto toxico adverso en ratas de laboratorio cuando se alimentan tales ratas durante al menos aproximadamente 90 días en una concentración de 100 veces, o mil veces, o aun concentraciones mayores que la concentración máxima permisible propuesta del compuesto en una categoría particular de productos alimenticios que se consideran para aprobación. Por ejemplo, tales pruebas de los compuestos amida de la invención pueden involucrar combinar el compuesto amida con concentrado para rata y alimentar las ratas de laboratorio tal como ratas Crl: CD(SD)IGS BR, en una concentración de aproximadamente 100 miligramos/kilogramo de peso corporal/día durante 90 días, y luego sacrificar y evaluar las ratas mediante varios procedimientos de prueba medica para mostrar el compuesto amida de la fórmula (I) no origina efectos tóxicos adversos en las ratas.

Los Compuestos de la Invención como Mejoradores del sabor dulce o salado o picante

Los compuestos amida de fórmula (I) y sus varios compuestos subgéneros y especies, como se describió anteriormente están destinados a ser compuestos saborizantes del sabor dulce o salado o picante o modificadores de sabor para

productos medicinales comestibles. Como es evidente a partir de las enseñanzas y los ejemplos aquí, muchos compuestos de la fórmula (I) son agonistas de un receptor "salado o picante" hT1R1/hT1R3, o un receptor de dulce hT1R2/hT1R3, al menos en concentraciones de compuesto amida relativamente altas, y de acuerdo con esto muchos de los compuestos amida de la fórmula (I) pueden tener utilidad como saborizantes de dulce o salado o picante o mejoradores de sabor, en su propio derecho, al menos en relativamente altas concentraciones.

No obstante, es preferible utilizar un poco de tales saborizantes artificiales tanto como sea posible, para minimizar el costo y cualquier efecto colateral para la salud indeseable de la administración de compuestos de la fórmula (I) en niveles de alta concentración. De acuerdo con esto es deseable probar los compuestos de la fórmula (I) para su efectividad como agonista del receptor del sabor en niveles de concentración inferiores, para identificar los compuestos amida mejores y más efectivos dentro de los compuestos de la fórmula (I). Como se describe en la WO 03/001876, y la Publicación de Patente Estadounidense US 2003-0232407 A1, y como se describe aquí adelante, los procedimientos de laboratorio existen ahora para medir la actividad agonista de los compuestos para un receptor de dulce hT1R1/hT1R3 y "salado o picante" hT1R2/hT1R3. Tales métodos de medición miden típicamente un "EC_{50}", es decir, la concentración en el que el compuesto origina el 50% de activación del receptor importante.

Preferiblemente, los compuestos amida de la fórmula (I) que son modificadores del sabor salado o picante tienen un EC_{50} para el receptor hT1R1/hT1R3 menor de aproximadamente 10 μM. Más preferiblemente, tales compuestos amida tiene un EC_{50} para el receptor hT1R1/hT1R3 de menos de aproximadamente 5 μM, 3 μM, 2 μM, 1 μM, o 0.5 μM.

Preferiblemente, los compuestos de la fórmula (I) que son modificadores del sabor dulce o mejoradores del sabor dulce tienen un EC_{50} para el receptor hT1R2/hT1R3 de menos de aproximadamente 10 μM. Más preferiblemente, tales compuestos amida tienen un EC_{50} para el receptor hT1R2/hT1R3 de menos de aproximadamente 5 μM, 3 μM, 2 μM, 1 μM, o 0.5 μM.

En algunas modalidades, los compuestos amida de la fórmula (I) son mejoradores o moduladores del sabor salado o picante de la actividad agonista del glutamato monosódico para un receptor hT1R1/hT1R3. Aquí adelante se describe un procedimiento de ensayo para las llamadas proporciones EC_{50}, es decir, para disolver un compuesto de la fórmula (I) en agua que contiene MSG, y medir el grado al que el compuesto amida reduce la cantidad de MSG requerida para activar el 50% de los receptores hT1R1/hT1R3 disponibles. Preferiblemente, los compuestos amida de fórmula (I), cuando se disuelven en una solución de agua que comprende aproximadamente 1 μM del compuesto amida reducirán el EC_{50} observado de glutamato monosódico para un receptor hT1R1/hT1R3 expresado en una línea celular HEK293-GD□15 para al menos el 50%, es decir el compuesto amida tendrá una proporción EC_{50} de al menos 2.0, o preferiblemente 3.0, 5.0, o 7.0.

Aunque aún no se han desarrollado ensayos de proporción EC_{50} específicos para mejoradores de dulce, se cree que los compuestos amida de la fórmula (I), y más específicamente muchas de las amidas de la fórmula (II) pueden modular la unión de un endulzante conocido tal como por ejemplo sacarosa, fructosa, glucosa, eritritol, isomal, lactitol, manitol, sorbitol, silitol, un terpenoide natural conocido, falvonoide, o endulzante de proteína, aspartamo, sacarina,

acelsufame-K, un ciclamato, sucralosa, alitamo o eritritol a un receptor hT1R2/hT1R3. Ensayos apropiados para tales propiedades de mejora de dulce se pueden desarrollar fácilmente por un experto en la técnica al utilizar las líneas celulares apropiadas que expresan los receptores hT1R2/hT1R3.

Los ensayos identificados anteriormente son útiles en la identificación de los compuestos amidas más potentes de la fórmula (I) para propiedades mejoradotas o modificadoras del sabor dulce y/o salado o picante, y los resultados de tales ensayos se consideran que se correlacionan bien con la percepción del sabor dulce o salado o picante actual en animales y humanos, pero finalmente los resultados de los ensayos se pueden confirmar, al menos para el más potente de los compuestos de la fórmula (I), mediante prueba de gusto humano. Tales experimentos de pruebas de gusto humano se pueden cuantificar y controlar bien al probar los compuestos candidatos en soluciones acuosas, como se compara con soluciones acuosas de control o alternativamente al probar las amidas de la invención en composiciones alimenticias actuales.

De acuerdo con esto, con el fin de identificar los agentes o modificadores de sabor salado o picante, o mejoradores del sabor Umami de MSG en una composición medica o comestible, una solución de agua que comprende una cantidad modificadora del sabor salado o picante del compuesto amida tendrá un sabor salado o picante como se juzga por la mayoría de un panel de al menos ocho probadores humanos de sabor.

De forma correspondiente, con el fin de identificar los mejoradores de sabor salado o picante más potentes de la fórmula (I), una solución de agua que comprende una cantidad modificadora de sabor salado o picante de un compuesto

amida de la fórmula (I) y 12 mM de glutamato monosódico tendrán un sabor salado o picante incrementado según se compara con una solución de agua de control que comprende 12 mM de glutamato monosódico, como se determina por la mayoría de una panel de al menos ocho probadores humanos de sabor. Preferiblemente, con el fin de identificar los mejoradores de sabor salado o picante más potentes, una solución de agua que comprende un a cantidad modificadora de sabor salado o picante (preferiblemente aproximadamente 30, 10, 5, o 2 ppm) del compuesto amida de la fórmula (I) y 12 mM de glutamato monosódico tendrán un gusto de sabor incrementado según se compara con una solución de agua de control que comprende 12 mM de glutamato monosódico y 100 μM de monofosfato de inosina, como se determina por la mayoría de un panel de al menos de ocho probadores humanos de sabor.

Se pueden utilizar similares procedimientos para prueba humana de sabor para identificar cual de los compuestos de la fórmula (I) son los agentes de sabor dulce más efectivos o agentes mejoradores del sabor dulce. Modificadores del sabor dulce preferidos de la fórmula (I) se pueden identificar cuando un producto medicinal o comestible modificado tiene un gusto más dulce que un producto medicinal o comestible de control que no comprenden el compuesto amida, como se juzga por la mayoría de un panel de al menos ocho probadores de sabores humanos.

Mejoradores del sabor dulce preferidos de la fórmula (I) se pueden identificar cuando una solución de agua que comprende una cantidad de sabor dulce de un endulzante conocido seleccionado del grupo que consiste de sacarosa, fructosa, glucosa, eritritol, isomal, lactitol, manitol, sorbitol, xilitol, un terpenoide natural conocido, flavonoide, o proteína endulzante, aspartamo,

sacarina, acesulfame-K, ciclamato, sucralosa, y alitamo, y una cantidad modificadora del sabor dulce del compuesto amida (preferiblemente aproximadamente 30, 10, 5, o 2 ppm) tiene un gusto más dulce que una solución de agua de control que comprende la cantidad de sabor dulce del endulzante conocido, según se juzga por la mayoría de una panel de al menos ocho probadores de sabores humanos. En tales experimentos de prueba de gusto, la sacarosa estaría preferiblemente presente en una concentración de aproximadamente 6 gramos/100 mililitros, una mezcla 50:50 de glucosa y fructosa estarían preferiblemente en una concentración de aproximadamente 6 gramos/100 mililitros, el aspartamo estaría preferiblemente presente en una concentración de aproximadamente 1.6 mM, el acesulfame-K estaría preferiblemente presente en una concentración de aproximadamente 1.5 mM, el ciclamato estaría preferiblemente en una concentración de aproximadamente 10 mM, la sucralosa estaría preferiblemente presente en una concentración de aproximadamente 0.4 mM, o el alitame estaría preferiblemente presente en una concentración de aproximadamente 0.2 mM.

Utilización de los Compuestos de la Fórmula (I) para Preparar Composiciones Comestibles

Sabores, modificadores de sabor, agentes saborizantes, mejoradores de sabor, agentes saborizantes salados o picantes ("umami") y/o mejoradores de sabor, los compuestos de la fórmula (I) y sus varias subgéneros y especies de compuestos tienen aplicación en alimentos, bebidas y composiciones medicinales en donde los compuestos dulces o salados o picantes se utilizan convencionalmente. Estas composiciones incluyen composiciones para el

consumo animal y humano. Estos alimentos incluyen para consumo por animales de agricultura, mascotas y animales de zoológico.

Aquellos expertos en la técnica de preparación de composiciones comestibles (es decir bebidas o alimentos comestibles, o precursores o modificadores de sabor de estos) serán concientes de una gran variedad de clases, subclases y especies de composiciones comestibles, y utilizarán términos reconocidos y bien conocidos en la técnica para referirse a aquellas composiciones comestibles mientras se hace empeño en preparar y vender varias de aquellas composiciones. Tal una lista de términos de la técnica se enumeran adelante, y se contemplan específicamente aquí ya que los varios subgéneros y especies de los compuestos de la fórmula (I) se pueden utilizar para modificar o mejorar los sabores dulce y/o salado o picante de la siguiente lista de composiciones comestibles, ya sea singularmente o en todas las combinaciones razonables o mezclas de estos:

Uno o más confites, confites de chocolate, tabletas, "countlines", "selflines/softlines empaquetados", surtidos en cajas, surtidos en cajas estándar, miniaturas envueltas con torceduras, chocolates de estación, chocolate con juguetes, alfajores, otros confites de chocolate, mentas, mentas estándar, mentas energizantes, dulces cocidos, pastillas, jaleas y gomas masticables, caramelo masticable, caramelos y turrones, confites medicados, chupón, regaliz, otros confites de azúcar, goma, chicle, goma azucarada, goma sin azúcar, goma funcional, chicle bomba, pan, pan empacado/industrial, pan no empacado/artesanal, pasteles, tortas, tortas empacadas/industriales, tortas no empacadas/artesanales, galletas, galletas recubiertas de chocolate, sándwich de galleta, bizcocho relleno, bizcocho y galletas salado o picante, sustitutos del pan,

cereales para el desayuno, cereales rte, cereales para el desayuno de la familia, hojuelas, mezcla de cereales, otros cereales rte, cereales para el desayuno de los niños, cereales calientes, helado, porción única de helado de lácteos, porción única de helado de agua, helado de lácteos multipack, helado de agua multipack, helado para llevar, helado de lácteos para llevar, postres de helado, helado en bruto, helado de agua para llevar, yogurt congelado, helado artesanal, productos lácteos, leche, leche fresca/pasteurizada, leche entera fresca/pasteurizada, leche semi descremada fresca/pasteurizada, leche larga vida, leche larga vida de entera, leche semi descremada de larga vida, leche larga vida libre de grasa, leche de cabra, leche condensada/evaporada, leche condensada/evaporada natural, leche condensada funcional y otras saborizadas, bebidas lácteas saborizadas, solo bebidas lácteas saborizadas, bebidas lácteas saborizadas con jugos de fruta, leche de soya, bebidas de leche agria, bebidas lácteas fermentadas, blanqueadores del café, leche en polvo, bebidas de leche en polvo saborizadas, crema, queso, queso procesado, queso para untar procesado, que so procesado, queso no procesado, queso no procesado para untar, queso duro, queso duro empacado, queso duro desempacado, yogurt, yogurt natural/sencillo, yogurt saborizado, yogurt de fruta, yogurt probiótico, bebida de yogurt, bebida de yogurt regular, bebida de yogurt probiótica, postres firmes enfriados, postres a base de productos lácteos, postres a base de soya, pasabocas enfriados, queso y cuajada frescos, queso y cuajada finos frescos, queso y cuajada frescos saborizados, queso y cuajada frescos salados o picantes, pasabocas dulces y salados o picantes, pasabocas de fruta, trozos/crocante, pasabocas extruidos, pasteles de maíz/tortilla, palomitas de maíz, galleta tostada cubierta de sal, nueces, otros pasabocas dulces y salados o picantes, pasabocas en barra, granola en barra, barras para desayuno, barras energizantes, barra de frutas, otros pasabocas en barra, productos para el reemplazo de la comida, productos para adelgazar,

bebidas para convalecencia, comidas listas, comidas listas conservadas, comidas listas congeladas, comidas listas secas, comidas listas enfriadas, mezclas para la cena, pizza congelada, pizza enfriada, sopa, sopa conservada, sopa deshidratada, sopa instantánea, sopa enfriada, sopa uht, sopa congelada, pasta, pastas conservadas, pasta seca, pasta enfriada/seca, tallarines, tallarines planos, tallarines instantáneos, tallarines instantáneos en taza/tazón, bolsa de tallarines instantáneos, tallarines enfriados, bocado de tallarines, alimento conservado, carne y productos de carne conservados, pescado/mariscos conservados, vegetales conservados, tomates conservados, fríjol conservado, fruta conservada, comidas listas conservadas, sopa conservada, pasta conservada, otras alimentos conservados, alimento congelado, carne roja procesada congelada, pollo procesado congelado, pescado/mariscos procesados congelados, vegetales procesados congelados, sustitutos de la carne congelados, papa congelada, papas fritas cocidas al horno, otros productos de papa horneados, papas congeladas no horneadas, productos de panadería congelados, postres congelados, comidas listas congeladas, pizza congelada, sopa congelada, tallarines congelados, otros alimentos congelados, alimento seco, mezclas de postre, comidas listas secas, sopa deshidratada, sopa instantánea, pasta seca, tallarines planos, tallarines instantáneos, tallarines instantáneos en taza/tazón, bolsa de tallarines instantáneos, tallarines enfriados, carnes procesadas enfriadas, productos enfriados pescados/mariscos, pescados procesados enfriados, pescados recubiertos enfriados, pescados ahumados enfriados, kit de almuerzo enfriado, comidas listas enfriadas, pizza enfriada, sopa enfriada, pasta enfriada/fresca, tallarines enfriados, aceites y grasas, aceite de oliva, aceite de semillas y vegetales, grasas para cocinar, mantequilla, margarina, aceites y grasas para untar, aceites y grasa para untar funcionales, salsas, aliños y condimentos, pastas y puré de tomate, caldo/cubos comunes, cubos comunes, gránulos de

salsa de carne, pastas y provisiones líquidas, hierbas y especies, salsas fermentadas, salsas a base de soya, salsas de pastas, salsas húmedas, mezcla de polvos/salsas secas, salsa de tomate, mayonesa, mayonesa regular, mostaza, aliños, aliños regulares, aliños de bajo contenido graso, vinagretas, dips, productos encurtidos, otras salsas, aliños y condimentos, comida para bebe, fórmula de leche, fórmula de leche estándar, fórmula de leche en etapas, fórmula de leche de pequeñín, fórmula de leche hipoalergénica, comida para bebes preparada, comida para bebe seca, otra comida para bebe, producto para untar, mermeladas y preservantes, miel, chocolate para untar, productos para untar a base de nueces, y productos para untar a base de levadura.

Preferiblemente, los compuestos de la fórmula (I) se pueden utilizar para modificar o mejorar el sabor dulce o salado o picante de uno o más de los siguientes subgéneros de composiciones comestibles: confiterías, productos de panadería, helados, productos lácteos, bocados dulces y sabrosos, bocado en barra, productos de reemplazo de la comida, comidas listas, sopas, pastas, tallarines, alimentos conservados, alimentos congelados, alimentos secos, alimentos enfriados, grasas y aceites, comidas para bebe, o extensiones, o mezclas de estos.

En general una composición ingerible será producida por que contiene una cantidad suficiente de al menos un compuesto dentro del alcance de la fórmula (I) o sus varios subgéneros descritos aquí anteriormente para producir una composición que tiene las características de gusto o sabor deseadas tal como las características de gusto “dulce” o “salado o picante”.

Típicamente, al menos una cantidad moduladora del sabor salado o picante, una cantidad moduladora del sabor dulce, una cantidad de agente saborizante salado o picante, una cantidad de agente saborizante dulce, una cantidad mejoradora del sabor salado o picante, una cantidad mejoradora del sabor dulce de uno o más de los compuestos de la fórmula (I) se agregaran al producto medicinal o comestible, opcionalmente en la presencia de agentes de sabor salado o picante conocidos tal como MSG, o endulzantes conocidos, de tal forma que el producto medicinal o comestible modificado de sabor dulce o salado o picante tiene un sabor dulce y/o salado o picante incrementado comparado con el producto comestible medicinal preparados en el compuesto amida, como se juzga por los seres humanos o animales en general o en el caso de formulaciones de prueba juzgadas por la mayoría de una panel de al menos ocho probadores de sabores humanos, por vía de procedimientos como se describió aquí también.

La concentración de agente saborizante dulce o salado o picante necesario para modular o mejorar el sabor de la composición o producto medicinal o comestible variará por supuesto dependiendo de múltiples variables, que incluyen el tipo especifico de composición ingerible, lo que se conoce como agentes de sabor dulce o salado o picante también están presentes y las concentraciones de estos, y el efecto del compuesto particular de en tales compuestos salados o picantes. Como se anoto, una aplicación significativa de los compuestos de la fórmula (I) es para modular (inducir, mejorar o inhibir) el sabor salado o picante u otras propiedades de gusto de probadores del sabor salado o picante sintéticos o naturales, tal como MSG. Un amplio pero también bajo rango de concentraciones de los compuestos amida de la fórmula (I) se requerirán típicamente, es decir de aproximadamente 0.001 ppm a 100 ppm, o rangos alternativos más estrechos de aproximadamente 0.1 ppm a aproximadamente 10 ppm, de aproximadamente 0.01

ppm a aproximadamente 30 ppm, de aproximadamente 0.05 ppm a aproximadamente 15 ppm, de aproximadamente 0.1 ppm a aproximadamente 5 ppm, o de aproximadamente 0.1 ppm a aproximadamente 3 ppm. En muchas modalidades, el MSG también podría estar presente en una concentración de al menos aproximadamente 10 ppm, o preferiblemente 100 o 1000 ppm.

Ejemplos de alimentos y bebidas en donde los compuestos de acuerdo con la invención se pueden incorporar incluyen por vía de ejemplo la categoría de Sopa, la Categoría de Alimentos Culinarios y Deshidratados, la Categoría de Bebidas, la Categoría de Alimentos Congelados, la Categoría de Alimentos Pasabocas, y los sazonadores o mezclas de sazonadores.

La "Categoría de Sopa" significa sopas líquidas/húmedas con respecto a la concentración o contenedor que incluyen sopas congeladas. Para el propósito de esta definición sopa significa un alimento preparado a partir de carne, pollo, pescado, vegetales, granos, frutas y otros ingredientes cocinados en un líquido que puede incluir pasteles visibles de algunos o todos estos ingredientes. Puede ser claro (como un caldo) o espeso (como una sopa de pescado), suave, en puré o en trozos, lista para servir, semi condensada o condensada y puede ser servida caliente o fría, como un primer plato o como el plato principal de una comida como un pasabocas (como una bebida). La sopa se puede utilizar como un ingrediente para preparar otros componentes de la comida y puede variar de caldos (consomé) a salsas (cremas o sopas basadas en queso).

"Categoría Alimenticia Culinaria y Deshidratada" significa: (i) cocinar con la ayuda de productos tales como, polvos, gránulos, pastas, productos líquidos concentrados, que incluyen caldos concentrados, caldos y productos similares a

caldo en cubos comprimidos, tabletas o polvo o forma granulada, que se venden de forma separada como un producto terminado o como un ingrediente dentro de un producto, salsas y mezclas de recetas (independiente de tecnología); (ii) productos de soluciones de comida tales como: sopas secas congeladas y deshidratadas, que incluyen mezclas de sopas deshidratadas, sopas instantáneas deshidratadas, sopas listas para cocinar deshidratadas, preparaciones deshidratadas o ambientes de platos listos para uso, comidas y entradas únicas que incluyen pasta, papa y arroz; y (iii) productos de embellecimiento de comidas tales como: condimentos, adobos, aliños para ensaladas, trozos para ensaladas, dips, apanados, mezclas de pastas, pastas estables para parrillas, salsas para barbecue, mezclas de recetas líquidas, concentrados, salsas o mezclas de salsas, que incluyen mezclas de recetas para ensaladas, vendidas como un producto terminado o como un ingrediente dentro de un producto, sea deshidratado, líquido o congelado.

"Categorías de Bebidas" significa bebidas, concentrados y mezclas de bebidas, que incluyen pero no se limitan a, bebidas en polvo seco y listas para tomar alcohólicas y no alcohólicas.

Otros ejemplos de alimentos y bebidas en donde los compuestos de acuerdo con la invención se pueden incorporar incluyen por vía de ejemplo bebidas carbonatadas y no carbonatadas, por ejemplo, sodas, frutas o vegetales, bebidas alcohólicas y no alcohólicas, productos de confitería, por ejemplo, galletas, pasteles, dulces, gomas de mascar, gelatinas, helados, sorbetes, pudines, gelatinas, mermeladas, aliños para ensaladas, y otros condimentos, cereales, y otros alimentos para el desayuno, frutas enlatadas y salsas de frutas y similares.

Adicionalmente, los compuestos objetos se pueden utilizar en preparaciones saborizantes para ser agregadas a los alimentos y bebidas. En casos preferidos la composición comprenderá otro modificador del gusto o sabor tal como un sabor salado o picante.

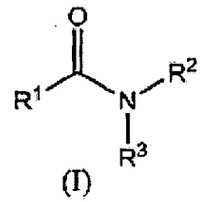
Métodos para Modificar el Sabor de Composiciones Medicinales o Comestibles

En muchas modalidades, las invenciones se relacionan con métodos para modular el sabor dulce o salado o picante de un producto medicinal o comestible que comprende:

a) suministrar al menos un producto medicinal o comestible, uno o más precursores de este, y

b) combinar el producto medicinal o comestible o uno o más precursores de este con al menos una cantidad de modulación de sabor salado o picante o una cantidad moduladora de sabor dulce de al menos un compuesto amida de ocurrencia no natural o una sal aceptable comestible de esta, para formar un producto medicinal o comestible modificado;

en donde el compuesto amida tiene la fórmula:



(I)

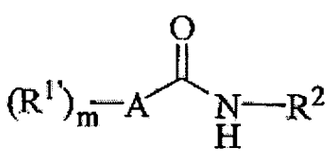
Aquí el compuesto amida es una amida de la fórmula (I), o cualquiera de sus varios subgéneros o especies de compuestos descritas aquí, en donde R^1, R^2, y R^3 se pueden definir de muchas formas también como se describió anteriormente. Ejemplos de tales métodos incluyen pero no se limitan a los métodos incorporados adelante.

En algunas modalidades de ejemplo, la invención se relaciona con un método para mejorar el sabor dulce de un producto comestible o medicinal que comprende:

a) suministrar al menos un producto comestible o medicinal, o uno o más precursores de estos, y

b) combinar el producto comestible o medicinal o uno o más precursores de estos con al menos una cantidad que modula el sabor dulce de al menos un compuesto de amida de ocurrencia no natural, o una sal comestiblemente aceptable de este, para formar un producto comestible o medicinal modificado;

en donde el compuesto amida tiene la estructura



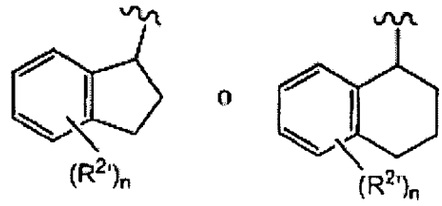
en donde A es un anillo arilo o heteroarilo que tiene de 3 a 12 átomos en el anillo;

m es o, 1, 2, 3 o 4;

410

cada $R^{1'}$ se selecciona independientemente del grupo que consiste de alquilo C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, alcoxilo C_1-C_4, alcoxi-alquilo C_1-C_4, hidroxi-alquilo C_1-C_4, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, y halógeno, en donde R^6 es alquilo C_1-C_4;

R^2 tiene la fórmula

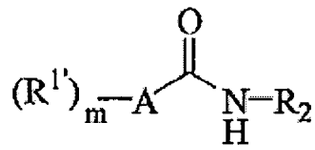


en donde n es 0, 1, 2, o 3, y cada $R^{2'}$ puede estar unido al anillo aromático y no aromático y se selecciona independientemente de hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi. En modalidades relacionadas pero novedosas, la invención se relaciona con métodos para mejorar el sabor dulce de un producto comestible o medicinal que comprende:

a) suministrar al menos un producto comestible o medicinal, o uno o más precursores de estos, y

b) combinar el producto comestible o medicinal o uno o más precursores de estos con al menos un compuesto amida aromático o heteroaromático, o una sal comestiblemente aceptable de este, para formar un producto comestible o medicinal modificado que comprende al menos aproximadamente 0.001 ppm del compuesto amida;

en donde el compuesto amida tiene la estructura:

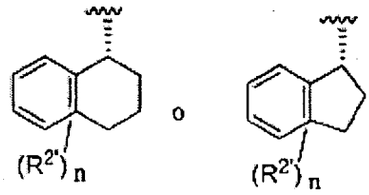


en donde A es un anillo arilo o heteroarilo de cinco o seis miembros;

m es 1, 2, o 3;

cada $R^{1'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, un radical orgánico C_1-C_8;

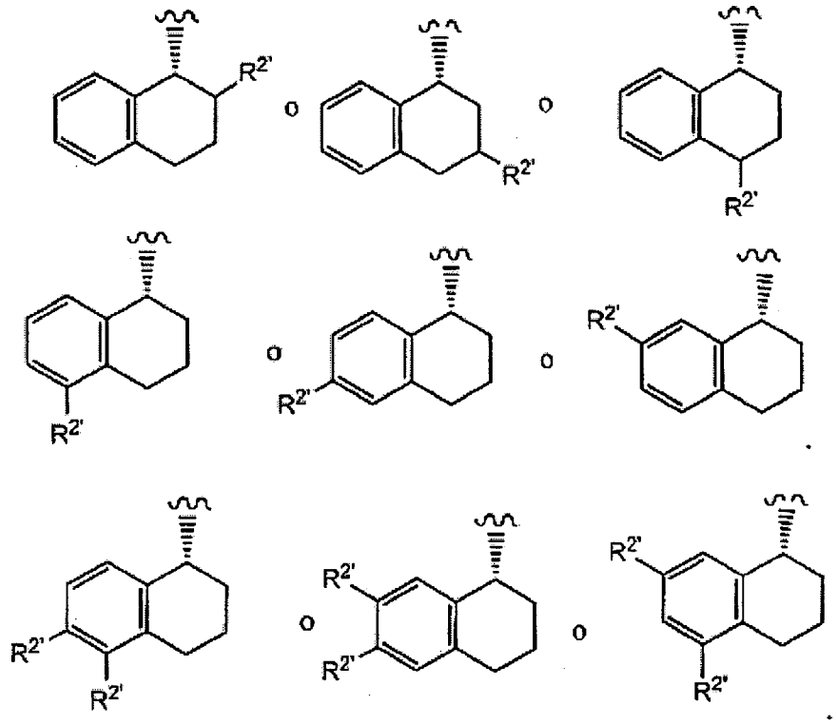
R^2 es un radical que tiene la estructura



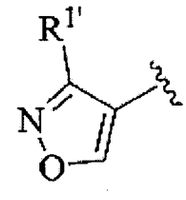
en donde R^2 comprende la configuración óptica indicada en exceso enantiomérico, n es 1, 2, o 3, cada $R^{2'}$ puede estar unido a el anillo aromático o no aromático de R^2 y cada $R^{2'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4, y

en donde el producto comestible o medicinal modificado comprende adicionalmente al menos una cantidad de agente saborizante dulce de uno o más agentes saborizantes dulces naturales, semi-sintéticos, o sintéticos, o una mezcla de estos.

En tales métodos, R^2 preferiblemente tiene una de las estructuras:



en donde cada $R^{2'}$ se selecciona independientemente del grupo que consiste de hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi. Adicionalmente, en tales métodos, el grupo A es preferiblemente un grupo fenilo, o tiene la fórmula:



en donde $R^{1'}$ es hidrógeno, hidroxilo, NH_2, SH, halógeno, alquilo C_1-C_8, haloalquilo C_1-C_8, haloalcoxi C_1-C_8, alcoxilo C_1-C_8, alcoxi-alquilo C_1-C_8, hidroxi-alquilo C_1-C_8, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, y halógeno, en donde R^6 es alquilo C_1-C_4. En modalidades adicionales, $R^{1'}$ es un alquilo C_1-C_8. En todavía modalidades adicionales, el $R^{1'}$ del anillo isoxasol es

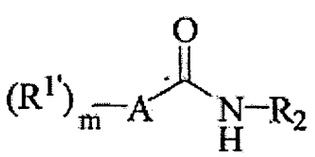
hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, n-propilo, n-butilo, 1-metil-propilo, isobutilo, t-butilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, trifluorometoxi, CH_2OCH_3, CH_2OH, CH_2NH_2, CH_2NHCH_3, o $CH_2N(CH_3)_2$.

En modalidades adicionales, la invención se relaciona con métodos para incrementar el sabor dulce de un producto comestible o medicinal que comprende:

a) suministrar al menos un comestible, o uno o más precursores de estos, y

b) combinar el producto comestible o medicinal o uno o más precursores de estos con al menos un compuesto amida heteroaromático, o una sal comestiblemente aceptable de este, para formar un producto comestible o medicinal modificado que comprende al menos aproximadamente 0.001 ppm del compuesto amida;

en donde el compuesto amida tiene la estructura:

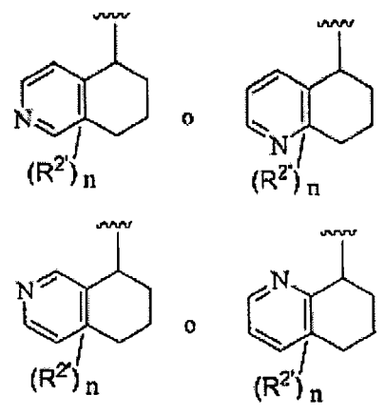


en donde A es un anillo arilo o heteroarilo de cinco o seis miembros;

m es 0, 1, 2, 3 o 4;

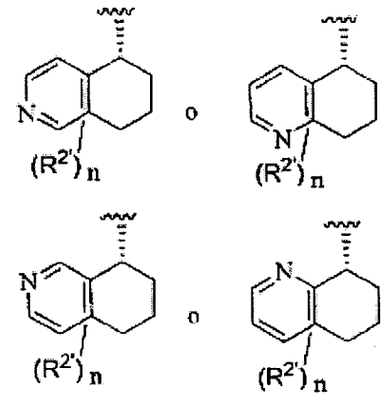
cada $R^{1'}$ se selecciona independientemente del grupo que consiste de hidrógeno, hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_8,

R^2 es un radical tetrahidroquinolinilo o tetrahidroisoquinolinilo que tiene la estructura



en donde n es 0, 1, 2, o 3, cada R^2 puede estar unido al anillo aromático y no aromático de R^2 y cada R^2 se selecciona independientemente del grupo que consiste de hidrógeno, hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4.

En tales métodos, en donde R^2 puede preferiblemente ser un radical que tiene la estructura:



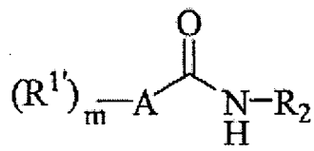
en donde el radical R^2 radical está presente en la configuración óptica indicada en exceso enantiomérico.

En todavía modalidades adicionales, la invención se relaciona con métodos para incrementar el sabor dulce de un producto comestible o medicinal que comprende

a) suministrar al menos un comestible, o uno o más precursores de estos, y

b) combinar el producto comestible o medicinal o uno o más precursores de estos con al menos un compuesto amida aromático o heteroaromático, o una sal comestiblemente aceptable de este, para formar un producto comestible o medicinal que comprende al menos aproximadamente 0.001 ppm del compuesto amida;

en donde el compuesto amida tiene la estructura

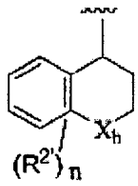


en donde A es un anillo arilo o heteroarilo de cinco o seis miembros;

m es 0, 1, 2, 3 o 4;

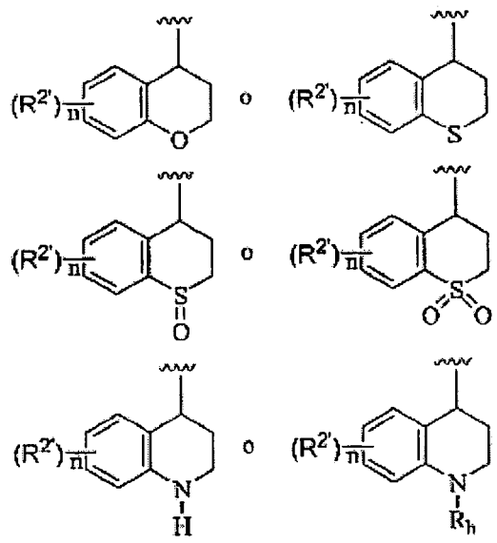
cada $R^{1'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4,

R^2 es un radical heterocíclico bicíclico que tiene la estructura

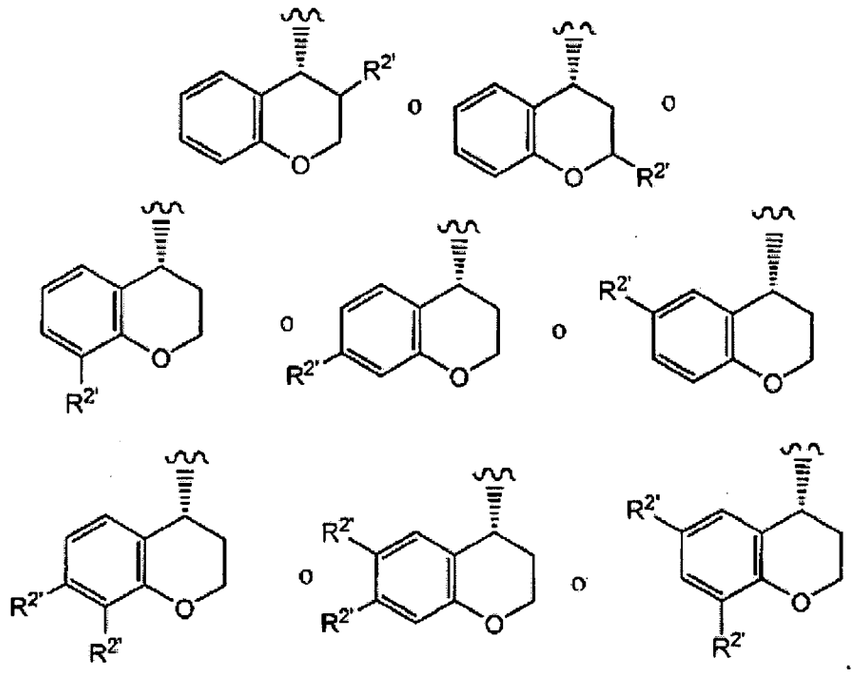


en donde n es 0, 1, 2, o 3, cada $R^{2'}$ puede estar unido al anillo aromático y no aromático de R^2 y cada R^2 se selecciona independientemente del grupo que consiste de hidrógeno, hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4, y X_h es O, S, SO, SO_2, NH, o NR_h, en donde R_h es un radical orgánico C_1-C_4.

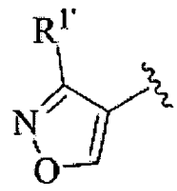
En tales modalidades, R^2 preferiblemente pueden tener la fórmula:



en donde cada $R^{2'}$ están unido a el anillo fenilo del radical R^2, n es 0, 1, o 2, y cada $R^{2'}$ se selecciona independientemente del grupo que consiste de, hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, y el ligando R^2 puede preferiblemente estar presente en un exceso enantiomérico de la configuración "R", como se ejemplifica por los siguientes radicales R^2 específicamente enumerados:



Otra vez, en tales modalidades, el grupo A es preferiblemente un grupo fenilo, o tiene la fórmula:



en donde $R^{1'}$ es hidrógeno, hidroxilo, NH_2, SH, halógeno, alquilo C_1-C_8, haloalquilo C_1-C_8, haloalcoxi C_1-C_8, alcoxilo C_1-C_8, alcoxi-alquilo C_1-C_8, hidroxi-alquilo C_1-C_8, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, y halógeno, en donde R^6 es alquilo C_1-C_4. En modalidades adicionales, $R^{1'}$ es un alquilo C_1-C_8. En todavía modalidades adicionales, el $R^{1'}$ del anillo isoxasol es hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, n-propilo, n-butilo, 1-metil-propilo, isobutilo, t-butilo, vinilo,

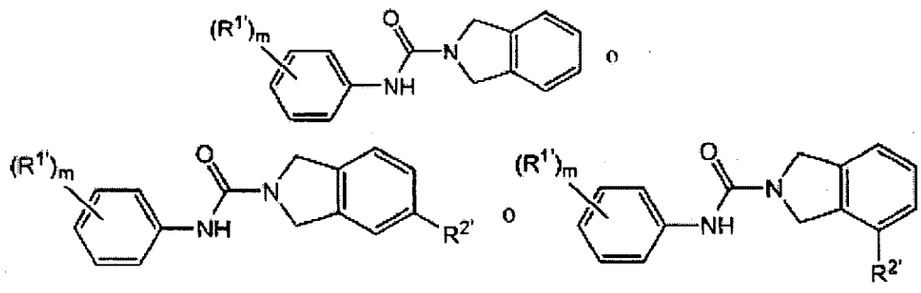
trifluorometilo, metoxi, etoxi, isopropoxi, trifluorometoxi, CH_2OCH_3, CH_2OH, CH_2NH_2, CH_2NHCH_3, o $CH_2N(CH_3)_2$.

En modalidades adicionales, la invención suministra métodos para mejorar el sabor dulce de un producto comestible o medicinal que comprende:

a) suministrar al menos un producto comestible o medicinal, o uno o más precursores de estos, y

b) combinar el producto comestible o medicinal o uno o más precursores de estos con al menos un compuesto de urea, o una sal comestiblemente aceptable de este, para formar un producto comestible o medicinal modificado que comprende al menos aproximadamente 0.001 ppm del compuesto de urea;

c) en donde el producto comestible o medicinal modificado comprende adicionalmente un endulzante artificial o natural conocido, en donde el compuesto de urea tiene la fórmula:



en donde m es 1, 2, o 3, y cada $R^{1'}$ y $R^{2'}$ se seleccionan independientemente de flúor, cloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, SEt, SCH_3,

metilo, etilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, o dos grupos R^1 juntos forman un anillo metilenodioxi.

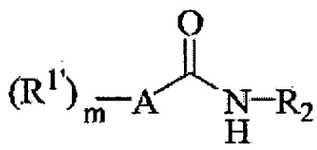
En modalidades adicionales, la invención se relaciona con métodos para mejorar el sabor salado o picante de un producto comestible o medicinal que comprende:

a) suministrar al menos un comestible, o uno o más precursores de estos, y

b) combinar el producto comestible o medicinal o uno o más precursores de estos con al menos aproximadamente 0.001 ppm de al menos un compuesto amida aromático o heteroaromático, o una sal comestiblemente aceptable de este, para formar un producto comestible o medicinal modificado, y

c) en donde el producto comestible o medicinal modificado opcionalmente comprende glutamato monosódico agregado artificialmente;

en donde el compuesto amida aromático o heteroaromático tiene la estructura

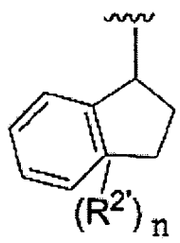


en donde A es un anillo arilo o heteroarilo de cinco o seis miembros;

m es 1, 2, 3 o 4;

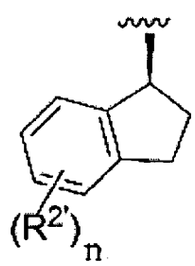
cada $R^{1'}$ se selecciona independientemente del grupo que consiste de hidrógeno, hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_8, o un grupo arilo o heteroarilo monocíclico,

R^2 es un radical 1-indanilo que tiene la estructura:



en donde n es 1 o 2, y cada R puede estar unido al anillo aromático y no aromático de R^2 y cada $R^{2'}$ se selecciona independientemente del grupo que consiste de hidrógeno, hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4.

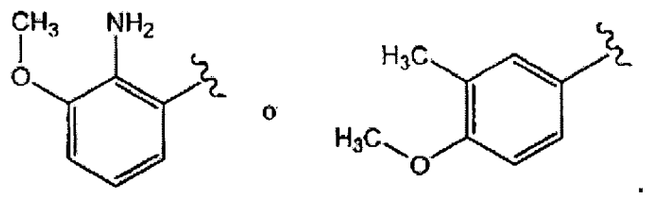
En tales modalidades, R^2 es un radical 1-indanilo ópticamente activo que tiene la estructura



en donde R^2 comprende la configuración óptica indicada en exceso enantiomérico, y cada $R^{2'}$ está unido al anillo aromático de R^2.

En tales modalidades, n es preferiblemente 1, y/o $R^{2'}$ se selecciona preferiblemente del grupo que consiste de hidrógeno, grupos hidroxi, flúor, cloro,

NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi. En tales modalidades, el grupo A es preferiblemente fenilo, como se ejemplifica por las siguientes estructuras específicas:

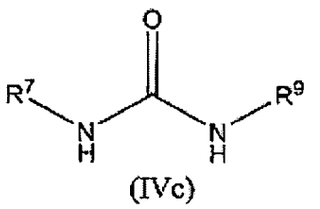


En todavía modalidades adicionales, la invención se relaciona con un método para mejorar el sabor salado o picante de un producto comestible o medicinal que comprende:

a) suministrar al menos un comestible, o uno o más precursores de estos; y

b) combinar el producto comestible o medicinal o uno o más precursores de estos con al menos un compuesto de urea, o una sal comestiblemente aceptable de este, para formar un producto comestible o medicinal modificado que comprende al menos aproximadamente 0.001 ppm del compuesto de urea, y

c) en donde el producto comestible o medicinal modificado opcionalmente comprende glutamato monosódico agregado artificialmente; en donde el compuesto de urea tiene la estructura:



(IVc)

y en donde

i) R^7 es un anillo fenilo opcionalmente sustituido con 1, 2, o 3 sustituyentes independientemente seleccionados de grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, o en donde dos de los sustituyentes forman un anillo metilenodioxi, y

ii) R^9 es un radical C_3-C_{10} seleccionado de un alquilo ramificado, arilalquilo, o cicloalquilo, en donde el radical C_3-C_{10} opcionalmente comprende 1, 2, o 3 sustituyentes independientemente seleccionados de grupos hidroxi, flúor, cloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

La invención también se relaciona con los productos comestibles o medicinales modificados producidos mediante el proceso descrito anteriormente.

La invención también se relaciona con procesos similares para la producción del productos comestibles o medicinales bien conocidos por aquellos medianamente expertos en la técnica. Los compuestos de amida de fórmula (I) y sus varios subgéneros se pueden combinar con o aplicar a los productos

comestibles o medicinales o los precursores de estos en cualquiera de innumérales vías conocidas para cocinar, alimentos preparados en todo el mundo, o productores de productos comestibles o medicinales. Por ejemplo, los compuestos de amida fórmula (I) se podrían disolver en o dispersar en , o uno de muchos líquidos, sólidos, u otros portadores comestiblemente aceptables, tales como agua a ph neutro, ácido o básico, jugos de frutas o vegetales , vinagres, marinadas, cerveza, vino ,agua natural/emulsiones de grasa tales como leche o leche condensada, aceites comestibles y mantequillas, ácidos grasos, ciertos oligómeros de bajo peso molecular o propilenglicol, ésteres de glicerilo o ácidos grasos, y dispersiones o emulsiones de tales sustancias hidrófobas en medio acuoso sales tales como cloruro de sodio, harinas vegetales, solventes tales como etanol, diluyentes comestibles sólidos como polvos vegetales o harinas, y similares, y luego se combina con precursores de los productos comestibles o medicinales, o se aplica directamente a los productos comestibles o medicinales.

Preparación de los Compuestos Amida de Fórmula (I)

Los materiales de partida utilizados para preparar los compuestos de la invención, *es decir*, las varios subclases estructurales y especies de los compuestos de amida de Fórmula (I) y sus propulsores sintéticos, especialmente los ácidos carboxílicos orgánicos y los ácidos benzoicos, isocianatos, y las varias aminas, anilinas, aminoácidos, etc, son compuestos a menudo conocidos, o se pueden hacer por métodos conocidos de la literatura, o están comercialmente disponibles de varias fuentes bien conocidas por aquellos expertos en la técnica, tal como por ejemplo, Sigma- Aldrich Corporation of St. Louis, Missouri USA y sus subsidiarias Fluka y Riedel-de Haen, y sus varias oficinas en el mundo, y otros asesores bien conocidos tales como Fisher Scientific, TCI America of Philadelphia,

PA, ChemDiv de San Diego, CA, Chembridge de San Diego, CA, Asinex de Moscow, Russia, SPECS/BIOSPECS de Holanda, Maybridge de Cornwall, Inglaterra, Acros, TimTec de Rusia, Comgenex del sur de San Francisco, CA, y ASDI Biosciences de Newark, Delaware.

Será evidenre para el experto en la técnica que los métodos de preparación de precursores y funcionalidad se relacionan con los compuestos reivindicados aquí que son generalmente descritos en la literatura. El experto en la técnica dada de la literatura y esta descripción está bien equipado para preparar cualquiera de los materiales de partida necesarios y/o compuestos reivindicados. En algunos de los ejemplos citados adelante, los materiales de partida no están fácilmente disponibles, y por lo tanto son sintetizados, y la síntesis de los materiales de partida es por lo tanto ejemplificada.

Se reconocerá que el experto en la técnica de química orgánica puede fácilmente llevar a cabo manipulaciones sin dirección adicional, esto está dentro del alcance y la práctica del experto en la técnica para llevar a cabo estas manipulaciones. Esto incluye la reducción de compuestos carbonilo a sus correspondientes alcoholes, oxidaciones, acilaciones, sustituciones aromáticas, tanto electrofílicas como nucleofílicas, eterificaciones esterificación, saponificación, nitraciones, hidrogenaciones, aminación reductiva y similares. Estas manipulaciones se discuten en textos estandares tales como March's *Advanced Organic Chemistry* (3d Edition, 1985, Wiley-Interscience, New York), Feiser and Feiser's *Reagents for Organic Synthesis*, y Carey y Sundberg, *Advanced Organic Chemistry* y similares, las descripciones completas se incorporan aquí como referencia en su totalidad para sus enseñanzas con relación a los métodos para sintetizar compuestos orgánicos.

El experto en la técnica también apreciara fácilmente que ciertas reacciones se llevaran mejor acabo cuando otra funcionalidad se enmascara o se protege de la molécula, evitando así cualquiera reacciones laterales indeseables y/o incrementando el rendimiento de la reacción. A menudo el experto en la técnica utiliza grupos protectores para lograr tales rendimientos incrementados o para evitar las reacciones indeseables. Estas reacciones se encuentran en la literatura y corresponden al alcance del experto. Ejemplos de muchas de esas manipulaciones que puedan encontrar por ejemplo T. Greene y P. Wuts, *Protecting Groups in Organic Synthesis*, 3[r] Ed., John Wiley & Sons (1999).

Las siguientes abreviaturas tienen los significados indicados:

CH_3CN = Acetonitrilo

$CHCl_3$ = Cloroformo

DIC = N,N'-Diisopropilcarbodiimida

DIPEA = Diisopropiletilamina

DMAP = 4-(dimetilamino)-piridina

DMF=N,N-dimetilformamida

EDCI = Clorhidrato de 1-(3-Dimetilaminopropil)-3-etilcarbodiimida

DCM = Diclorometano

ESIMS = espectrometría de masa de rociado de electrón

Et_3N = trietilamina

EtOAc = acetato de etilo

EtOH = Alcohol de etilo

Fmoc = N-(9-fluorenilmetoxicarbonil-

HCl = Ácido clorhídrico

H_2SO_4 = Ácido sulfúrico

HOBt = 1-Hidroxibenzotriazol

MeOH = Alcohol de metilo

$MgSO_4$ = sulfato de magnesio

$NaHCO_3$ = bicarbonato de sodio

NaOH = Hidróxido de sodio

Na_2SO_4 = Sulfato de sodio

Ph = fenilo

t.a.= temperatura ambiente

SPOS = síntesis orgánica de fase sólida

THF = tetrahidrofurano

TLC = cromatografía de capa fina

Abreviaturas de grupo alquilo

Me = metilo

Et = etilo

n-Pr = normal propilo

i-Pr = isopropilo

n-Bu = normal butilo

i-Bu = isobutilo

t-Bu = butilo terciario

s-Bu = butilo secundario

n-Pen = normal pentilo

i-Pen = isopentilo

n-Hex = normal hexilo

i-Hex = isohexilo

Abreviaturas de reactivos que soportan polímeros

PS-Trisamina = poliestireno de Tris-(2-aminoetil)amina

PS-NCO = poliestireno de metilisoccianato

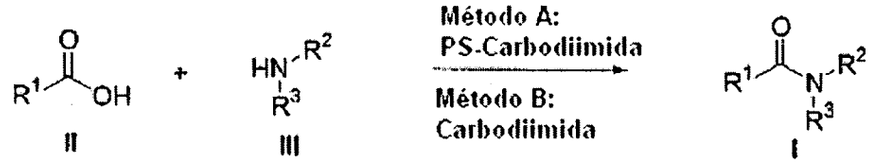
PS-TsNHNH$_2$ = poliestireno de toluensulfonilhidrazona

Métodos Sintéticos

Los siguientes Esquemas y Ejemplos se suministran para la guía del lector y representan una variedad de métodos para la elaboración de los compuestos de amida descritos aquí. Los métodos descritos son solo de ejemplo, no son limitantes, y serán evidentes para una persona medianamente versada en la técnica que otros métodos, muchos de los cuales son conocidos en la técnica, pueden ser empleados para preparar los compuestos de amida de las varias modalidades de la invención. Tales métodos Incluyen específicamente químicas basadas en fase sólida, que incluyen química combinatoria.

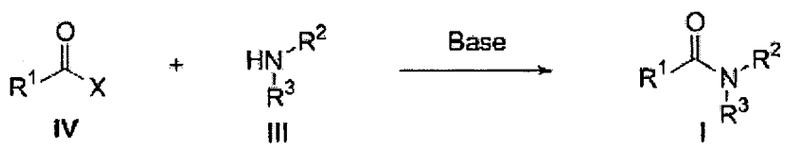
Las amidas a menudo se preparan por la condensación de ácidos carboxílicos y/o sus derivados (tal como ésteres, haluros de ácido etc) con aminas primarias y secundarias, a menudo en la presencia de agentes deshidratantes, agentes de acoplamiento, y/o catalizadores apropiados. Números grandes de materiales de partida adecuados, tales como aminas primarias y secundarias, y ácidos carboxílicos y sus derivados, se pueden sintetizar fácilmente por métodos conocidos en la literatura o son fácilmente disponibles comercialmente. En algunos casos, los métodos para síntesis de ciertos materiales de partida de amina o ácido carboxílico se dan adelante.

Esquema 1a



Como se muestra en el Esquema Ia, los derivados de amida (I) se pueden preparar a partir del acoplamiento de derivados de ácido (II) con aminas (III), por ejemplo en la presencia de un reactivo de acoplamiento tal como clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida y una base. En el Método A, se utiliza una carbodiimida que soporta polímero (PS). El Método B una carbodiimida que no soporta polímero.

Esquema 1b -Método Alternativo para Preparación de Amidas



X = haluro

Como se muestra en el Esquema Ib, los derivados de amida (I) se preparan alternativamente a partir del acoplamiento de haluros de ácido, ésteres, o anhídridos (IV) con aminas (III) en la presencia de una base.

Esquema Ic - Síntesis de Amidas por Vía de Series Combinatorias

Se utiliza el siguiente procedimiento y se pueden utilizar para sintetizar amidas en serie combinatoria.

• Usar acetonitrilo como sistema disolvente.

• Pesar aminas en frascos de 8 mL.

• Utilizar Tecan, disolver aminas a 100 mM en DCM/CH_3CN (1:2, de canal).

• Pesar ácido en frascos de 8 mL.

• Utilizar Tecan, disolver ácidos a 110 mM en DCM/CH_3CN (1:2, de canal).

• Precargar 1.2 mL de placa de Greinet con 30 mg de Resina PS-carbodiimida utilizar placas de nicrotítulo Peli 1400 Case II. Utilizar acetonitrilo como el disolvente para síntesis.

• Agregar 200 mL (20 mmol, 1 equiv.) de amina a cada pozo de las placas de síntesis.

• Agregar 200 mL (22 mmol, 1.1 equiv.) de acid a cada pozo de las placas de síntesis.

• Agregar 110 mL (22 mmol, 1.1 equiv.) de HOBt (0.20 M in DMF) a cada pozo de las placas de síntesis mediante pipeta de 8 canales.

• Sellar las placas con cap mat y agitar (velocidad normal) a temperatura ambiente durante la noche.

• Cargar 20 mg/pozo de resina PS-Trisamina en las placas de síntesis utilizar placas de microtítulo cargadas finas-I. Ajustar la cantidad de resina basada en su carga.

• Agregar 200 mL de DCMZCH_3CN a la placa.

• Envolver y sellar las placas y agitar (velocidad rápida) a temperatura ambiente durante la noche.

• Usar metanol como sistema disolvente para transferir la placa almacenada.

430

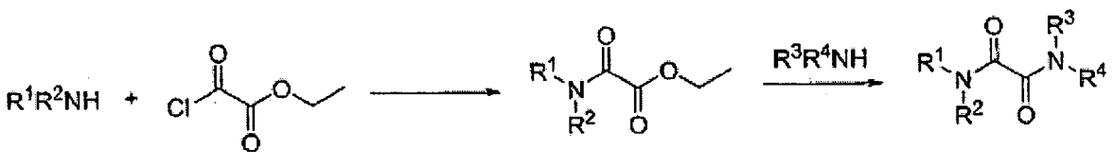
• Transferir 150 mL de la placa almacenada cuando se lava 2 veces con 150 mL de metanol (agitar lentamente durante 5 min.). realizar las transferencias de Top en cada pozo. (altura de la aguja -2).

• secar las placas en Genevac.

• Hacer placas analíticas (2.5 mM teóricas) y someter para el análisis.

• Hacer dilución de placas basados en resultados analíticos.

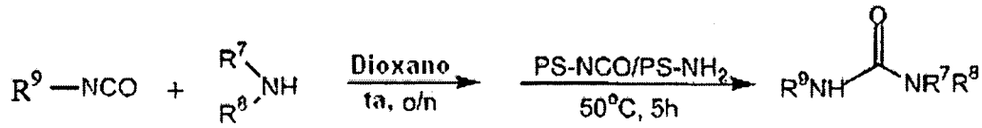
Esquema Ic. Preparación de Oxalamidas



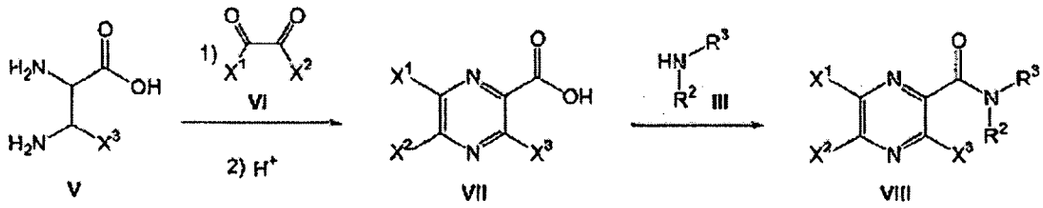
Como un procedimiento general, a una amina se le permite reaccionar con cloruro oxalilo de etilo en la presencia de amina terciaria en un disolvente orgánico, tal como dioxano, acetonitrilo, tetrahidrofurano, tetrahidropiran, y dimetilformamida, a temperatura ambiente durante 0.5 - 2 horas. Luego la segunda amina se agrega y la suspensión se calienta a 80° C utilizando un baño de aceite durante la noche o a 160° C en un reactor de microondas durante 5 minutos. La mezcla de reacción se puede someter a HPLC preparativo, o un trabajo acuoso y el producto crudo puede típicamente ser fácilmente purificado mediante recristalización, cromatografía de columna flash, u otros métodos bien conocidos por aquellos medianamente expertos en la técnica-para proporcionar la oxalamida pura. Los rendimientos reportados adelante no son óptimos.

431

Esquema Id. Preparación de Ureas



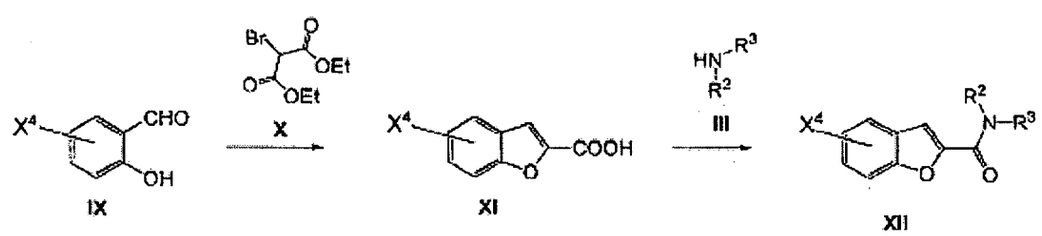
Esquema 2



X^1, X^2 y X^3 son cada uno independientemente alquilo o alcoxi

El Esquema 2 describe un método para la preparación de derivados de pirazinas (VIII). Por ejemplo, la reacción de ácidos 2,3-diaminopropionicos de sustituidos o no sustituidos (V) con 2,3-dionas (VI) bajo condiciones de calor en la presencia de un base produce, después de acidificación, el ácido pirazin-2-carboxílico sustituido (VII). El ácido se condensa con varias aminas (III) para producir la amida deseada (XIII) utilizando las condiciones mostradas en el Esquema Ia.

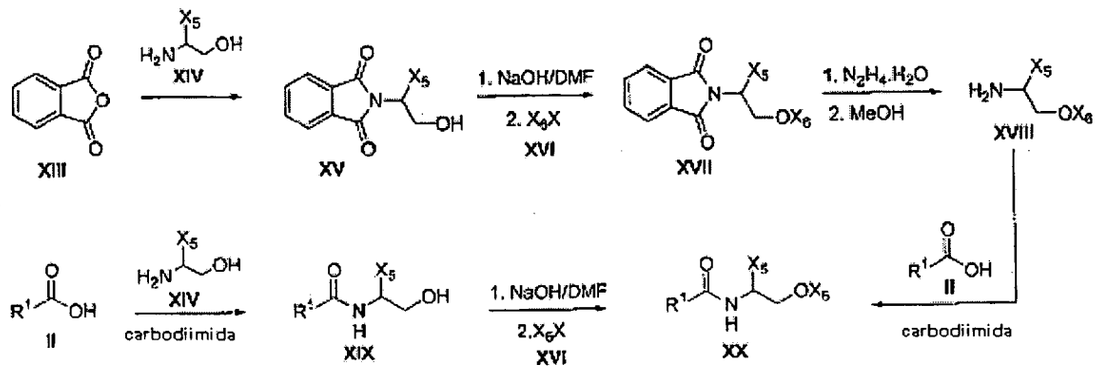
Esquema 3



X^4 es alquilo, haluro, alcoxi o tioalquilo.

El Esquema 3 describe un método para la preparación de derivados de benzofurano (XII). Por ejemplo, la reacción de 2-hidroxibenzaldehídos (IX) con éster de dietilo de ácido 2-bromo-malónico (X) bajo condiciones de calor en la presencia de base produce ácido benzofurano-2-carboxílico sustituido (XI). El ácido se condensa con varias aminas (III) para producir la amida deseada (XII) utilizando las condiciones mostradas en el Esquema Ia.

Esquema 4



X_5 es H, alquilo, arilo, aril-alquilo, heteroaril-alquilo

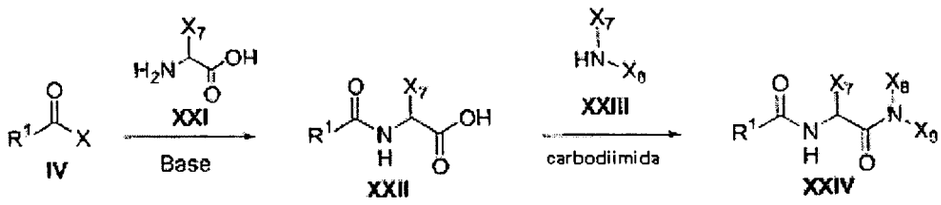
X_6 es alquilo, alcoxialquilo, arilalquilo, heteroarilalquilo

X es haluro

El Esquema 4 describe los métodos de preparación de una alcoxialquil amida (XX). En un método se calienta anhídrido ftálico (XIII) con amino alcohol (XIV) para dar el alcohol (XV) que luego se hacer reaccionar con haluro de alquilo (XVI)en la presencia de una base para producir el alcoxi (XVII). El tratamiento de ls phtalimida (XVII) con hidrazina produce la amina deseada (XVIII) que se condensa adicionalmente con el ácido (II) como se describen en el esquema Ia para suministrar la alcoxialquilamida (XX). Alternativamente el ácido (II) se

condensa con el amino alcohol (XIV) utilizando el método descrito en el esquema la para suministrar el alcohol (XIX) que se alquila adicionalmente para dar (XX).

Esquema 5



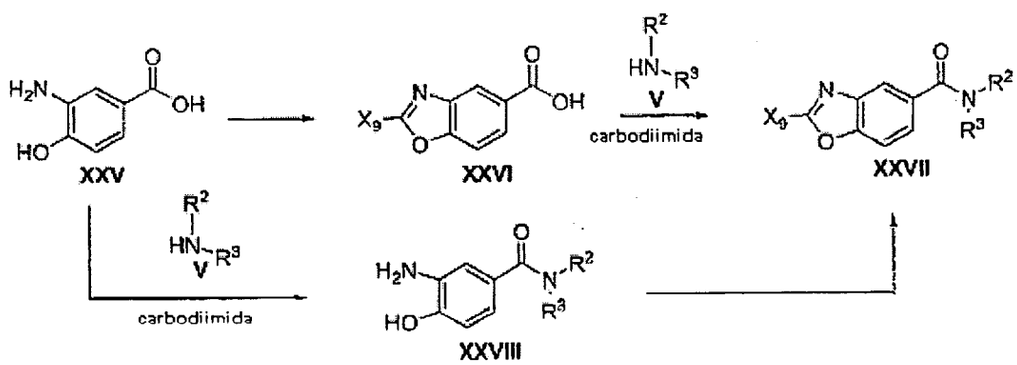
X es haluro

X_7 es H, alquilo, alcoxialquilo, arilo, aril-alquilo, heteroaril-alquilo

X_8 y X_9 son cada uno independientemente H, alquilo, alcoxialquilo, arilalquilo, y heteroarilalquilo

El Esquema 5 describe unos métodos para la preparación de amido-amida (XXIV). Haluro de alquilo (IV) se trata con aminoácido (XXI) como se describe en el esquema Ib para dar el ácido correspondiente (XXII) que se condensa adicionalmente con amina (XXIH) como se describe en el esquema Ia para suministrar el derivado amido amida (XXIV).

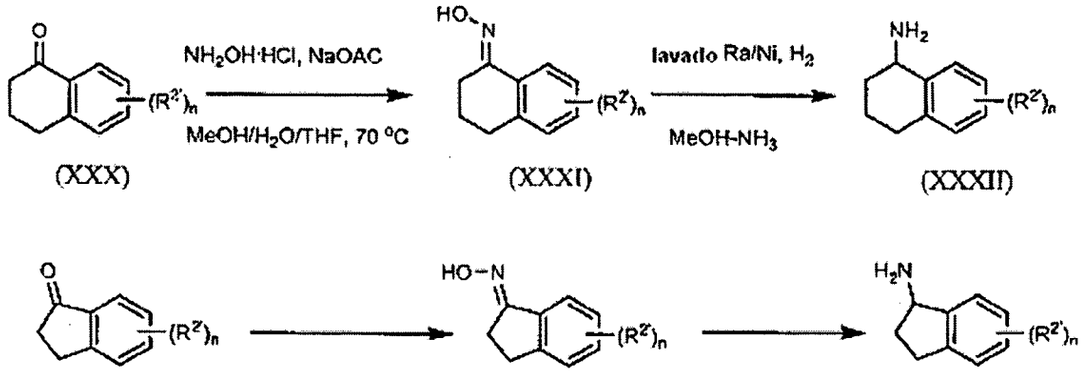
Esquema 6



El Esquema 6 describe métodos para la preparación de benzooxazol (XXVIII). El amino fenol (XXV) puede ser condensado con una variedad de reactivos para formar el benzoxazol (XXVI) que tiene una amplia variedad de sustituyentes X_9 utilizando un método descrito en la literatura (*ver por ejemplo, J. Med. Chem.* 28 (1985) 1255) y/o por el método citado en los Ejemplos 39 a 47. El intermediario benzoxazol (XXVI) luego se condensa con amina (V) utilizando el método descrito en el esquema la para dar la amida (XXVII). Alternativamente la amida (XXVII) se prepara al condensar primero el amino fenol (XXV) con la amina (V) para dar el intermediario aminofenol (XXVIII) que adicionalmente se convierte al benzoxazol (XXVII) utilizando los varios métodos descritos anteriormente.

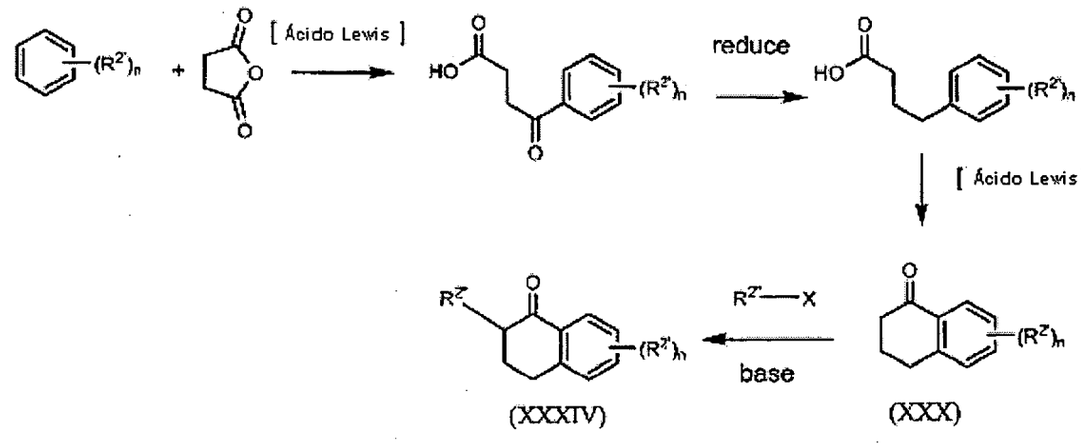
Una muy amplia variedad de derivados de ácido carboxílicos que son precursores adecuados de los grupos R1 de las amidas de Fórmulas (I), y varios subgéneros de los compuestos de Fórmula (I) son fácilmente disponibles por los métodos o de fácil adaptación por métodos conocidos en la técnica anterior, o están disponibles comercialmente. En particular, el arilo o heteroarilo sustituido de compuestos de ácido carboxílico que son precursores de los compuestos de Fórmula (II) son a menudo fácilmente disponibles comercialmente, o a través del uso de metodologías sintéticas bien conocidas en la técnica. De forma similar, muchos compuestos amina que son precursores adecuados de los compuestos de amida de Fórmula (I) son fácilmente disponibles comercialmente o a través de métodos de síntesis conocidos. No obstante, como se discute en los Esquemas y/o Ejemplos adelante dson métodos para sintetizar ciertos precursores de bloque de construcción de partida de los grupos R^1 y R^2.

Esquema 7: Preparación de 1,2,3,4-tetrahidronaftalen-1-aminas racémicas sustituidas



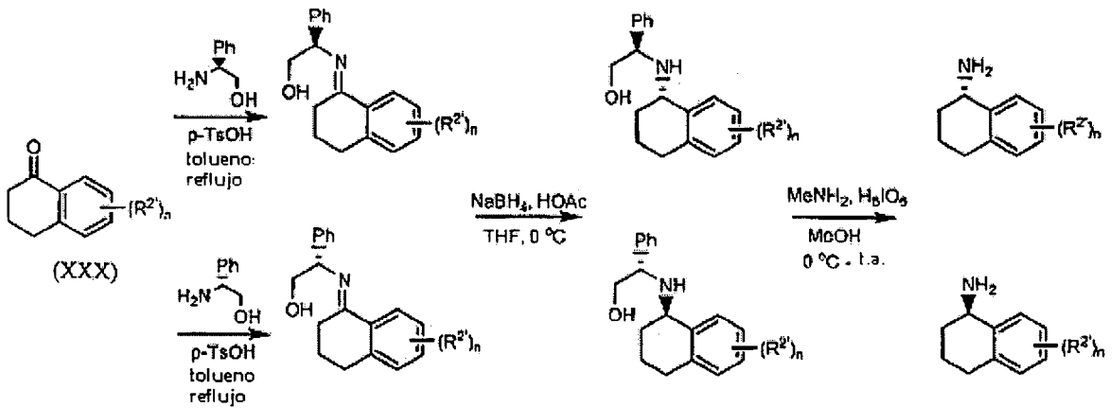
Como se muestra en el Esquema 7, 1,2,3, 4-tetrahidronaftalen-1-aminas racémicas (XXXII) se pueden preparar fácilmente al convertir 3,4-dihidronaftalen-1(2*H*)-onas sustituidas (en donde independientemente sustituyentes R seleccionados pueden estar presentes en el anillo) para la oxima (XXXII) por tratamiento con hidroxilamina. La Hidrogenación de las oximas en la presencia de Ra/Ni en MeOH-NH_3, o reducción con varios agentes reductores conocidos, fácilmente suministran los derivados de 1,2,3,4-tetrahidronaftalen-1-amina racémicos sustituidos (XXXII). Las indanonas racémicas sustituidas se producen fácilmente por una secuencia de reacción análoga, como se mostró anteriormente.

Esquema 8: Preparación de 3,4-dihidronaftalen-1(2H)-ona sustituida



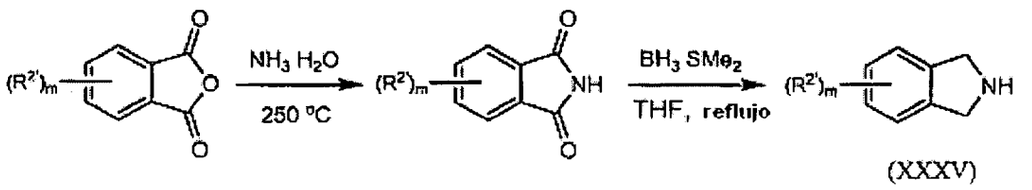
Muchas dihidronaftalenoonas sustituidas están fácil y comercialmente disponibles o se pueden preparar utilizando muchos métodos convencionales, tales como aquellos ilustrados anteriormente.

Esquema 9: Preparación Enantioselectiva de 1,2,3,4- tetrahidronaftalen-1-aminas sustituidas



Como se describe en el esquema 9, derivados de 1,2,3,4-tetrahidronaftalen-1-aminas quirales sustituidos (enantiómeros S, o enantiómero R) se pueden preparar de dihidronaftalenil cetonas tales como (XXX) utilizando una síntesis asimétrica (ver Stalker, R.A. *et al, Tetrahedron* **2002**, 58, 4837-4849). La cetona (XXX) se convierte a imina quiral (Va o Vb) por condensación con *S*- o *R*-fenilglicinol respectivamente. La imina luego se reduce enantioselectivamente a la amina con borohidruro de sodio, seguido por clivage oxidativo de los auxiliares quirales, para suministras la amina de las configuraciones ópticas ilustradas con exceso enantiomérico mayor de 99%.

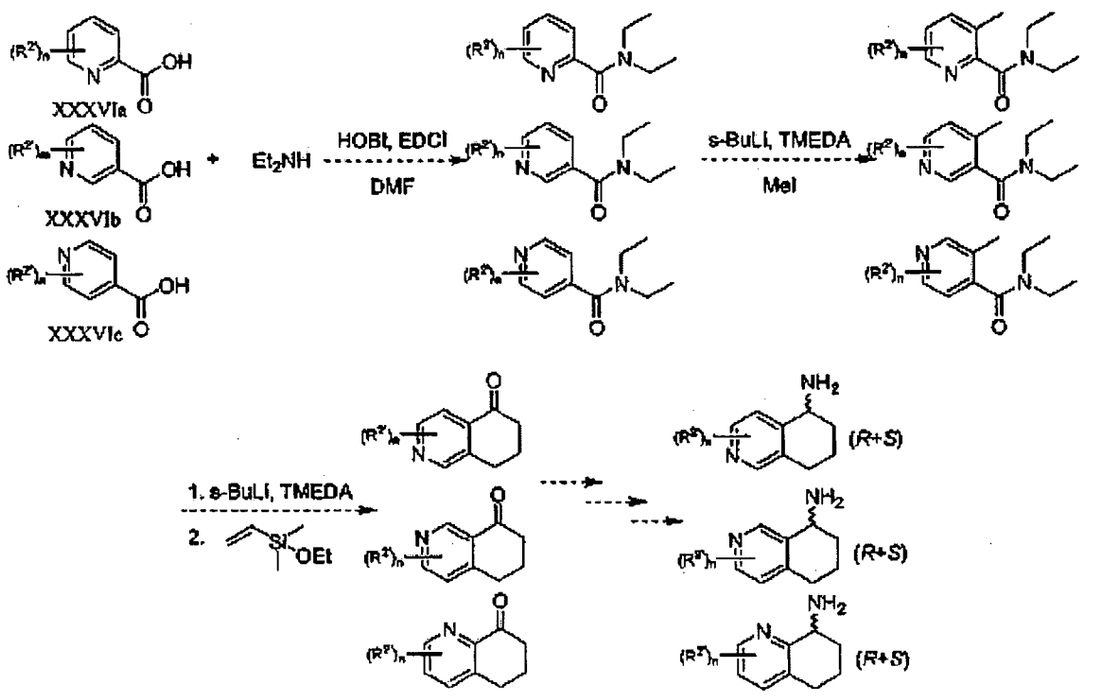
Esquema 10: Preparación de Isoindolinas Sustituidas:



(XXXV)

El Esquema 10 describe un método para preparar isoindolinas sustituidas (XXXV) de anhídridos ft álicos sustituidos por el tratamiento de los anhídridos ftálicos con una solución de amoniaco concentrada para dar la ftalimida sustituida (*ver* Noyes, W. A., Porter, P. K. *Org. Syn., Coll. Vol.* 1, 457), seguido por reducción de la ftalimida con complejo sulfuro de metil borano (*ver* Gawley, R. E., Chemburkar, S. R., Smith, A. L., Anklekar, T. V. *J. Org. Chem.* 1988, 53, 5381).

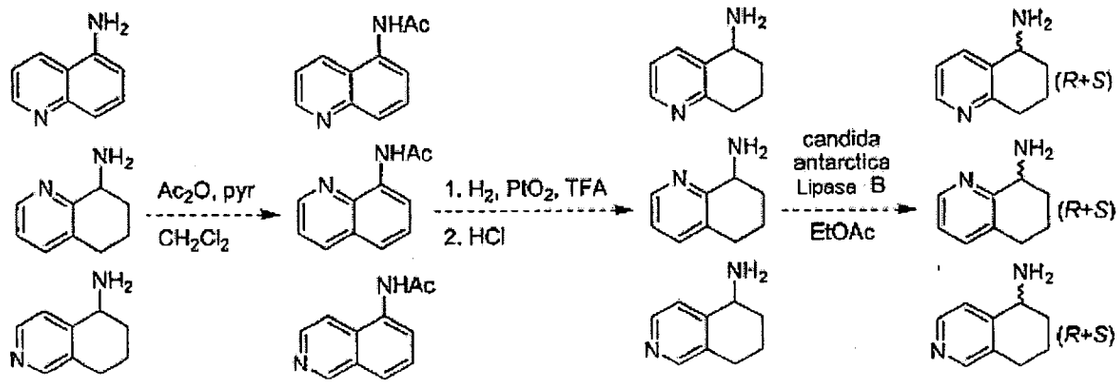
Esquema 11: Preparación de Quinolina e Isoquinolinas Sustituidas



Una variedad de tetralinas heteroaromáticas sustituidas se pueden sintetizar de piridina de ácidos carboxílicos (XXXVa-c). La reacción del ácido carboxílico con dietilamina en la presencia de HOBt y EDCI suministra una amida

aromática activa, que permite la metilación *orto* de la amida cuando se trata con 5-BuLi, TMEDA y MeI (*ver* Date, M.; Watanabe, M.; Furukawa, S. *Chem. Pharm. Bull.* 1990, 38, 902-906). Las dietilamidas metilatadas se pueden luego ciclicizar a la dihidroquinolin-8(5H)-ona deseada o dihidroisoquinolin-5(6H)-ona por el tratamiento con 5-BuLi, TMEDA y etoxidimetiliinil silano. La conversión de la cetona a la quinolin-8-aminas o isoquinolin-5- aminas (XVa-c) enantioméricamente puras, o racémicas deseadas se puede lograr como se describe en el Esquemas 6 o 9.

Esquema 12: Síntesis de Tetrahidroquinolinas y Tetrahidroisoquinolinas No Sustituidas.

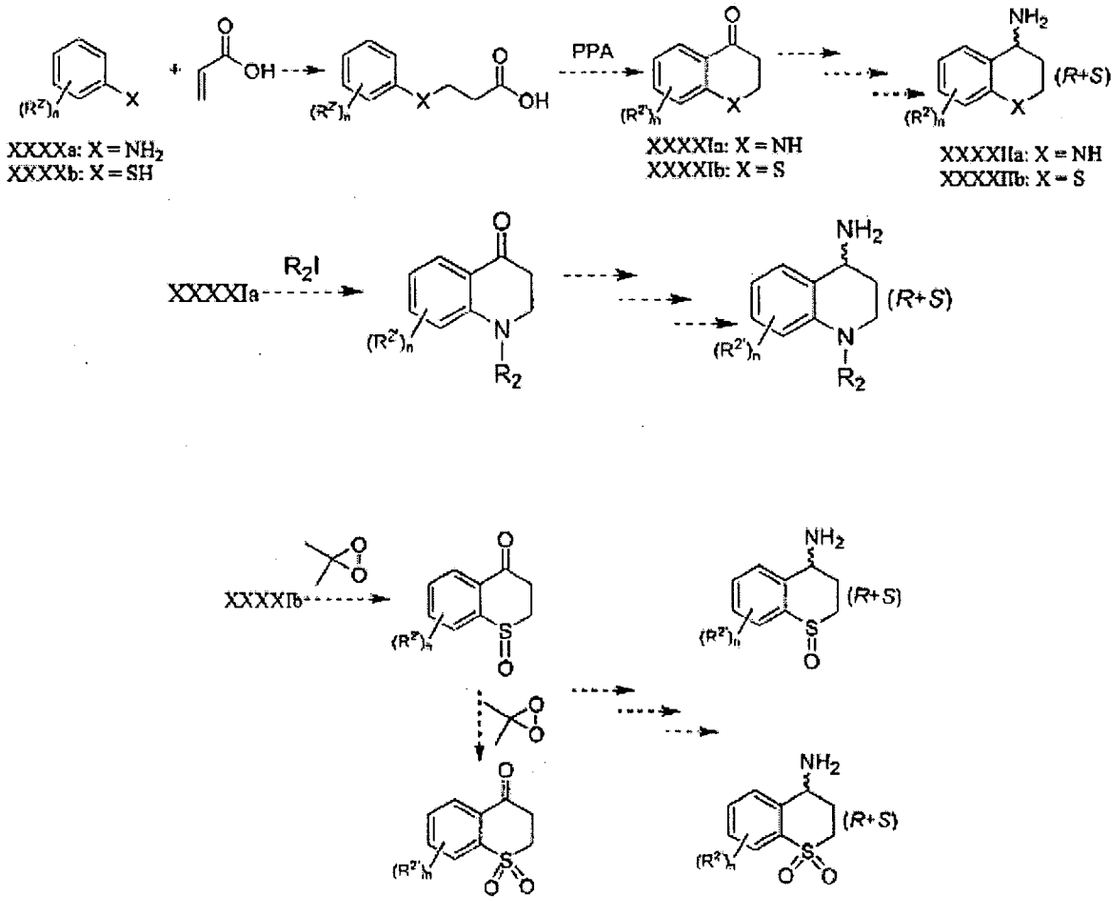


Tetrahidroquinolinas y tetrahidroisoquinolinas no sustituidas se pueden sintetizar como se describe por McEachern y colaboradores (ver Skupinska, K. A.; McEachern, E. J.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* 2002, 67, 7890-7893) partiendo de de los precursores de quinolina o isoquinolina amino sustituidas. La acetilación de las quinolina o isoquinolina amino sustituidas, seguido por la hidrogenación del anillo ciclohexilo en la presencia de catalizador Adam's, seguido por desacetilación que suministra los amino-ciclohexanos racémicos que se pueden resolver con Candida antartica lipass (CALB) en la presencia de EtOAc

439

por vía de acetillación enantioselectiva acetilation de solo el isómero R. la separación de la R-acetamida de la S-amina luego la desacetilación suministra las S-aminas, y las R-aminas enantioméricamente puras deseadas que se pueden obtener por hidrólisis de las R-acetamidas. (*Ver* Skupinska, K. A.; McEachern, E. J.; Baird, I. R.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* 2003, 68, 3546-3551).

Esquema 13: Síntesis de Precursores de R^2 de1,2,3,4-tetrahidroquinolin-4-amina sustituida y 3,4-dihidro-2*H*-tiocromen-4-amina



La síntesis de 1,2,3,4-tetrahidroquinolin-4-amina y 3,4-dihidro-2H-tiocromen-4-amina precursores de R^2, se pueden alcanzar por vía de una adición Michael de anilina (XXXXa)o tiofenol (XXXXb) para ácido acrílico (ver Aha, Y.; Cohen, T. J. Org. Chem. 1994, 59, 3142-3150), seguido por ciclización con ácido

polifosfórico (PPA) para suministrar las cetonas heterocíclicas ciclizadas (XXXXIa y XXXXIb) (ver Higuchi, R. I; Edwards, J. P.; Caferro, T. R.; Ringgenberg, J. D.; Kong, J. W.; Hamann, L. G.; Arienti, K. L.; Marschke, K. B.; Davis, R. L.; Farmer, L. J.; Jones, T. K. Bioorg. Med. Chem. Lett. 1999, 9, 1335-1340 and Kinoshita, H.; Kinoshita, S.; Munechika, Y.; Iwamura, T.; Watanabe, Sh.-L; Kataoka, T. Eur. J. Org. Chem. 2003, 4852-4861). La alquilación de la cetona amino nitrógeno (XXXXIa) suministra una cetona N-alquilatada (XXV), y las aminas deseadas (XXIVa, XXIVb y XXVI) se pueden obtener en mezclas racémicas mediante el método del esquema 7 ir enantioselectivamente utilizando el método descrito en el esquema 9. La oxidación del 2,3-dihidrotiocromen-4-ona (XXXXIb) con el sulfóxido se pueden alcanzar mediante tratamiento con cantidades limitadas de dimetil dioxidano, mientras que el tratamiento con un exceso de agente de oxidación resulta en la formación de la sulfona (ver Patonay, T.; Adam, W.; Lévai, A.; Kövér, P.; Németh, M.; P, E.-M.; Peters, K. J. Org. Chem. 2001, 66, 2275-2280). Las aminas enantioméricamente puras deseadas (XXIX y XXX) se pueden sintetizar como se destaca en el esquema 9.

En vista de la descripción, enseñanzas, tratados, y referencias citadas anteriormente, todas las cuales se incorporan aquí como referencia, un experto de la técnica de la química orgánica sintética esta equipado para preparar los compuestos necesarios y/o reivindicados por aquellos métodos dados en la literatura y en esta descripción.

Medición de la Actividad Biológica de los Compuestos de la Invención

Ensayos y tecnologías basados en células, tal como aquellos descritos en la WO 02/064631, y WO 03/001876, y la Publicación de Patente Estadounidense

441

US 2003-0232407 A1 se utilizan ambas para seleccionar inicialmente una amplia variedad de clases de compuestos para actividad agonista y antagonista paras los receptores de sabor "salado o picante" T1R1/T1R3, o receptores del sabor "dulce" T1R2/T1R3 que se han expresado en líneas celulares apropiadas. Una vez estos "hits" iniciales se obtienen para los compuestos amida en tales líneas celulares, los mismos ensayos y también ciertos ensayos basados en células y/o receptores se utilizan como herramientas analíticas para medir la capacidad e los compuestos de la fórmula (I) para mejorar el sabor salado o picante de MSG o el sabor dulce de endulzantes conocidos tales como sacarosa, fructosa, y se utilizan para suministrar datos empíricos para guiar un proceso del activo de síntesis y variantes estructurales de gusto de los compuestos amida, en combinación con pruebas de gusto humanas ocasionales de compuestos de alto interés, para diseñar, probar, e identificar especies y géneros de compuestos con niveles optimizados e incrementados de actividad biológica deseable.

Muchas modalidades de la invención se relacionan con la identificación de compuestos específicos y clases de compuestos amida de la fórmula (I) que modulan (incrementan o reducen) la actividad del receptor de sabor salado o picante (preferiblemente hT1R1/hT1R3) T1R1/T1R3 (receptor umami), solo o en combinación con otro compuesto que activa el hT1R1/hT1R3, por ejemplo, MSG. Particularmente, en muchas modalidades la invención se relaciona con amidas de la fórmula (I) que modula la actividad del hT1R1/hT1R3 (receptor umami humano) in vitro y/o in vivo. En otro aspecto, la invención se relaciona con compuestos que modulan la percepción humana del sabor salado o picante (umami), solo o en combinación con otro compuesto o saborizante, cuando se agrega a una composición o producto medicinal o comestible.

Muchas modalidades de las invención se relacionan con la identificación de clases y/o especies de los compuestos amida de la fórmula (I) que modulan (incrementan o reducen) la actividad del receptor de sabor dulce (preferiblemente hT1R2/hT1R3) T1R2/T1R3 (solo o en combinación con otro compuesto que activa el hT1R2/hT1R3, o induce de otra forma un sabor dulce (por ejemplo, sacarosa, glucosa, fructosa, y similares. Particularmente la invención se relaciona con las amidas de fórmula (I) que modulan la actividad del hT1R2/hT1R3 (receptor dulce humano) in vitro y/o in vivo. En otro aspecto, al invención se relaciona con compuestos que modulan la percepción humana del sabor dulce, solo o en combinación con otro compuesto o composición saborizante, cuando se agrega a una composición o producto medicinal o comestible.

En algunas modalidades de la invención, se ha descubierto muy inesperadamente que al menos algunos de los compuestos amida de la fórmula (I) pueden modular la percepción humana del sabor dulce o umami, solo o en combinación con otro compuesto o composición saborizante, cuando se agrega a una composición o producto medicinal o comestible.

Ensayo de Activación del Receptor del Gusto Umami hT1R1/hT1R3 in Vitro

Con el fin de identificar nuevos mejoradores y agentes saborizantes salados o picantes (actividad dual), compuestos de la fórmula (I) se seleccionan en ensayos primarios y secundarios que incluyen respuesta a la dosis del compuesto y ensayo de mejora. En un ensayo primario para la capacidad potencial para modular el gusto umami, los compuesto amida de la fórmula (I) que pueden ser agentes saborizantes salados o picantes por derecho propio o mejoradores de sabor de MSG se identifican y clasifican su actividad dada como un porcentaje de

intensidad máximo MSG (%). En la respuesta a la dosis del compuesto, se calcula un EC_{50} para reflejar la potencia del compuesto como un mejorador o agonista del sabor salado o picante.

Un derivado de línea celular HEK293 (ver por ejemplo, Chandrashekar, et al, Cell (2000) 100:703-711) que expresa establemente Gα15 y hT1R1/hT1R3 bajo un promotor inducible (ver WO 03/001876 A2) se utiliza para identificar compuestos con propiedades de uso de sabor dulce o salado.

Los compuestos cubiertos en este documento se seleccionan inicialmente con base en su actividad en la línea celular hT1R1/hT1R3-HEK293-Gα15. La actividad se determina utilizando un ensayo de formación de imagen fluorométrico automatizado en un instrumento FLIPR (Lector de Placa de Intensidad Fluorométrica, Molecular Devices, Sunnyvale, CA) (ensayo FLIPR diseñado). Las células de un clon (clon diseñado I-17) se cultivan en placas de 384 pozos (en aproximadamente 48,000 células por pozo) en un medio que contiene medio modificado Eagle de Dulbecco (DMEM) complementado con GlutaMAX (Invitrogen, Carlsbad, CA), 10% de suero bovino fetal dializado (Invitrogen, Carlsbad, CA), 100 unidades/ml de Penicilina G, 100 µg/ml estreptomicina (Invitrogen, Carlsbad, CA) y 60 pM de mifepristone (para inducir la expresión de hT1R1/hT1R3, (ver WO 03/001876 A2). Las células 1-17 se hacen crecer durante 48 horas a 37°C. Las células 1-17 se cargan con el tinte de calcio Fluo-3AM (Molecular Probes, Eugene, OR), 4 µM en salina amortiguada con fosfato (D-PBS) (Invitrogen, Carlsbad, CA), durante 1.5 horas a temperatura ambiente. Después de reemplazo con 25 µl de D-PBS, se desarrolla estimulación en el instrumento FLIPR y a temperatura ambiente mediante la adición de 25 µl de D-PBS complementado con estímulos diferentes en concentraciones que corresponden a

dos veces el nivel final deseado. La actividad del receptor se cuantifica al determinar el incremento de fluorescencia máximo (utilizando una excitación de 480 y una emisión de 535 nm) después de normalización a intensidad de fluorescencia medida antes de estimulación.

Para análisis de respuesta de dosis, se presentan estímulos en duplicados en 10 concentraciones diferentes que varían de 1.5 nM a 30 μM. Las actividades se normalizan a la respuesta obtenida con 60 mM de glutamato monosódico, una concentración que elicita la máxima respuesta de dosis. El. EC_{50} (concentración del compuesto que origina el 50% de activación del receptor) se determina usando un algoritmo de regresión no lineal, en donde la pendiente de Hill, la asíntota de fondo y la asíntota superior también nos permiten variar. Se obtienen resultados idénticos cuando se analizan los datos de respuestas de dosis utilizando software disponible comercialmente para análisis de regresión no lineal tal como GraphPad PRISM (San Diego, California).

Con el fin de determinar la dependencia del hT1R1/hT1R3 para la respuesta celular a diferentes estímulos, se someten los compuestos seleccionados a un análisis similar en las células 1-17 que no se han inducido para la expresión del receptor con mifepristona (designada como células 1-17 no inducida). Las células 1-17 no inducida no muestran ninguna respuesta funcional en el ensayo FLIPR para glutamato monosódico u otras sustancias de sabor salado o picante. Los compuestos se presentan para células umami no inducidas en 10 μM- o tres veces la estimulación máxima utilizada en el análisis de respuesta de dosis. Los compuestos cubiertos en este documento no muestran ninguna respuesta funcional cuando se utilizan las células umami no inducidas en el ensayo FLIPR.

En algunos aspectos de la presente invención, un EC_{50} de menos de aproximadamente 10 mM es indicador de compuesto que inducen actividad T1R1/T1R3 y se consideran un agonista del sabor salado o picante. Preferiblemente un agonista del sabor salado o picante tendrá valores EC_{50} menores de aproximadamente 1 mM; y más preferiblemente tendrán valores EC_{50} de menos de aproximadamente 20 µM, 15 µM, 10 µM, 5µM, 3 µM, 2 µM, 1 µM, 0.8 µM o 0.5 µM.

En experimentos de ensayo de actividad de mejoramiento de gusto umami, que producen una medición de "proporción EC_{50}" de cuan efectivamente los compuesto amida de la invención mejoran el sabor salado o picante (típicamente MSG) listos en una solución de ensayo. Una serie de mediciones de respuesta de dosis se ejecuta en soluciones que comprenden MSG solo, luego una segunda respuesta de dosis se ejecuta con MSG en combinación con cantidades predeterminadas de un compuesto candidato de la fórmula (I) al mismo tiempo. En este ensayo, incrementar las concentraciones de glutamato monosódico (que varían 12 µM a 81 mM) se presenta, en duplicados, en la presencia o ausencia de una concentración fija del compuesto de ensayo. Las concentraciones de compuesto típicas probadas son 30 µM, 10 µM, 3 µM, 1 µM, 0.3 µM, 0.1 µM y 0.03 µM. La eficacia relativa de los compuestos de fórmula (I) en el mejoramiento del receptor se determina al calcular la magnitud de un cambio en el EC_{50} para glutamato monosódico. La mejora se define como una proporción ($EC_{50}R$) que corresponde al EC_{50} de glutamato monosódico, determinado en la ausencia del compuesto de ensayo, dividido por el EC_{50} del glutamato monosódico, determinado en la presencia del compuesto de ensayo. Los compuestos que exhiben $EC_{50}R > 2.0$ se consideran mejoradores.

La "proporción EC_{50}" establecida alternativamente, según se compara con el MSG se calcula con base en las siguientes definiciones:

Proporción EC_{50} vs. MSG = EC_{50} (MSG)/EC_{50} (MSG + [compuesto]) en donde "[compuesto]" se refiere a la concentración del compuesto de fórmula (I) utilizada para elicitar (o mejorar en potenciar) la respuesta de dosis MSG.

Se debe notar que la proporción EC_{50} medida puede depender en algo en la concentración del compuesto en si mismo. Los mejoradores salado o picante preferidos tendrán una proporción EC_{50} alta vs. MSG en una concentración baja del compuesto utilizado. Preferiblemente los experimentos de proporción EC_{50} para medir la mejora umami se ejecutan en una concentración de un compuesto de fórmula (I) entre aproximadamente 10 µM a aproximadamente 0.1 µM, o preferiblemente en 1.0 µM o 3.0 µM.

Una proporción EC_{50} mayor de 1 es indicadora de un compuesto que modula (potencia) la actividad hT1R1/hT1R3 y es un mejorador salado o picante. Más preferiblemente, los compustos mejoradores de sabor salado o picante de la fórmula (I) tendrán valores de proporción EC_{50} de al menos 1.2, 1.5, 2.0, 3.0, 4.0, 5.0, 8.0, o 10.0, o aún mayores.

En un aspecto, el alcance de la modulación de sabor dulce o salado de un compuesto particular se evalúa con base en su efecto en la activación MSG de T1R1/T1R3 in vitro. Se anticipa que se pueden diseñar ensayos similares utilizando otros compuestos conocidos por activar el receptor T1R1/T1R3.

Clases genéricas y compuestos específicos de los compuestos que se han mostrado por modular el hT1R1/hT1R3 basado en sus proporciones EC_{50} evaluados de acuerdo con la anterior fórmula se identifican en al descripción detallada de la invención, los ejemplos, y las reivindicaciones.

Los procedimientos utilizados para probar el gusto humano de compuestos umami/sabor dulce o salado de la fórmula (I) se reportan aquí adelante. Ensayos EC_{50} comparables para la actividad de los compuestos de fórmula (I) para agonismo de receptor dulce y/o percepción del sabor dulce en humanos también se reporta aquí adelante.

Ensayo de Activación del Receptor del sabor dulce hT1R2/hT1R3 in Vitro:

Un derivado de la línea celular HEK293 (Chandrashekar, J., Mueller, K.L., Hoon, M.A., Adler, E., Feng, L., Guo, W., Zuker, C.S., Ryba, NJ., Cell, 2000, 100, 703-711.) que expresa establemente GD□15 y hT1R2/hT1R3 (Li, X., Staszewski, L., Xu, H., Durick, K., Zoller, M., Adler, E. Proc Natl Acad Sci USA 2002, 99, 4692-4696.), ver también Patente Mundial Número WO 03/001876 A2) se utiliza para identificar compuestos con propiedades mejoradoras del sabor dulce.

Los compuesto cubiertos en este documento se seleccionan inicialmente con base en su actividad en la línea celular hT1R2/hT1R3-HEK293-GD□15 (Li, et al. vide supra). La actividad se determina utilizando ensayo de formación de imágenes fluorométrico automatizado en un instrumento FLIPR (Lector de Palca de Intensidad Fluorométrica, Molecular Devices, Sunnyvale, CA) (designado ensayo FLIPR). Las células de un clon (células designadas S-9) se cultivan en placas de 384 pozos (en aproximadamente 50,000 células por pozo) en un medio

que contiene medio glucosa baja DMEM (Invitrogen, Carlsbad, CA), 10% de suero bovino fetal dializado (Invitrogen, Carlsbad, CA), 100 unidades/ml de Penicilina G, 100 □g/ml de estreptomicina (Invitrogen, Carlsbad, CA) ver también Patente Mundial No. WO 03/001876 A2). Se hacen crecer células S-9 durante 24 horas a 37°C. Las células S-9 se cargan luego con tinte de calcio Fluo-3AM (Molecular Probes, Eugene, OR), 4 □M en una salina amortiguada con fosfato (D-PBS) (Invitrogen, Carlsbad, CA), durante 1 hora a temperatura ambiente. Después del reemplazo con 25 □l de D-PBS, se desarrolla la estimulación en el instrumento FLIPR y a temperatura ambiente por la adición de 25 □l de D-PBS complementado con estímulos diferentes en concentraciones que corresponden a dos veces el nivel final deseado. La actividad del receptor se cuantifica al determinar los incrementos de fluorescencia máximos (utilizando una excitación de 480 nm y 535 nm de emisión) después de normalización para intensidad de fluorescencia basal medida antes de estimulación.

Para análisis de respuestas de dosis, se presentan estímulos en duplicados en 10 concentraciones diferentes que varían de 60 nM a 30 □M. Las actividades se normalizan a la respuesta obtenida con 400 mM de D-fructosa, una concentración que elicita máxima respuesta del receptor. El EC_{50} se determina utilizando un algoritmo de regresión no lineal (utilizando un software Senomyx, Inc.), en donde la pendiente Hill, la asíntota de fondo y la asíntota superior se les permite variar. Los resultados idénticos se obtienen cunado se analizan los datos de respuesta de dosis utilizando software comercialmente disponible para análisis de regresión no lineal tal como GraphPad PRISM (San Diego, CA).

Con el fin de determinar la dependencia de hT1R2/hT1R3 para la respuesta celular a diferentes estímulos los compuestos seleccionados se someten a un

análisis celular en las células HEK293-Gα15 (que no expresan el receptor dulce humano). Las células HEK293-Gα15 no muestran ninguna respuesta funcional en el ensayo FLIPR para D-Fructosa o cualquier otro endulzante conocido. De forma similar, los compuestos cubiertos en este documento no inducen ninguna respuesta funcional cuando se utilizan células HEK293-Gα15 en el ensayo FLIPR.

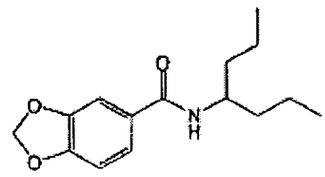
EJEMPLOS

Los siguientes ejemplos sedan para ilustrar una variedad de modalidades de ejemplo de la invención y no están destinadas a ser limitantes en ninguna forma.

Para los propósitos de este documento, los compuestos descritos individualmente en los siguientes ejemplos 1-174 y las Tablas correspondientes A-E se pueden referir en breve por el número ejemplo. Por ejemplo, como se muestra inmediatamente adelante, el Ejemplo 1 describe una síntesis de un compuesto particular (N-(heptan-4-il)benzo[d][1,3]dioxol-5-carboxamida), y los resultados de los ensayos experimentales de se eficacia biológica, cuyo compuesto es y se puede referir aquí en forma de taquigrafía como Compuesto 1. De forma similar, el primer compuesto ilustrado en la Tabla A se puede referir en otra parte como Compuesto A1.

Ejemplo 1

N-(heptan-4-il)benzo[d][1,3]dioxol-5-carboxamida

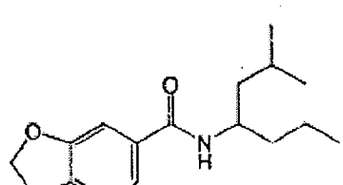


Se agrega a una solución de heptan-4-amina (8.06 mL, 54 mmol) en trietilamina (15.3 mL, 108 mmol) y diclorometano (135 mL), en forma de gota a 0° C, una solución de cloruro de benzo[1,3]dioxol-5-carbonilo (10 g, 54 mmol) disuelto en diclorometano (135 mL). La mezcla de reacción se agita durante 1 h. El disolvente se remueve bajo presión reducida y el residuo se disuelve en EtOAc. La capa orgánica se lava sucesivamente con HCl 1 N ac., NaOH 1 N ac., agua, solución salina, se seca ($MgSO_4$) y se concentra. El residuo se recristaliza en EtOAc y Hexanos para proporcionar 6.9 g de N-(heptan-4-il)benzo[d][1,3]dioxol-5-carboxamida (48.3%) como un sólido blanco. ^1H RMN (500 MHz, $CDCl_3$): δ 0.92 (t, 6H), 1.38 (m, 6H), 1.53 (m, 2H), 4.11 (m, 1H), 5.63 (m, 1H), 6.01 (s, 2H), 7.98 (d, 1H), 7.27 (s, d, 2H). MS(M+H, 264).

El compuesto tiene activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.2 μM, y cuando está presente en 0.03 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 6.92.

Ejemplo 2

N-(2-metilheptan-4-il)benzo[d][1,3]dioxol-5-carboxamida



Se prepara de una forma similar al ejemplo 1 utilizando cloruro de benzo[d][1,3]dioxol-5-carbonilo y 2-metilheptan-4-amina (ejemplo 2a). ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93 (m, 9H); 1.38 (m, 5H); 1.53 (m, 1H); 1.66 (m, 1H); 4.21 (m, 1H); 5.61 (d, 1H); 6.01 (s, 2H); 6.82 (d, 1H); 7.26 (m, 2H). MS (278, M+H).

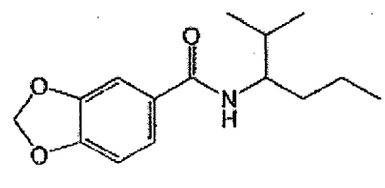
a. preparación de 2-metilheptan-4-amina:

A una solución de 2-metilheptan-4-ona (4.24 g, 33.07 mmol), en metanol (60 mL), se agregan acetato de amonio (25.50 g, 330.71 mmol) y cianoborohidruro de sodio (2.08 g, 33.07 mmol). La mezcla de reacción se agita a temperatura ambiente durante aproximadamente 24 horas. El disolvente se remueve bajo presión reducida y el residuo se diluye con agua y se basifica con 15 % de NaOH acuoso y se extrae con éter. El extracto se lava con solución salina, se seca sobre sulfato de magnesio anhidro, se filtra y se evapora para dar 3.3 g de 2-metilheptan-4-amina (77%). MS (M+H, 130).

El compuesto tiene activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.22 μM.

Ejemplo 3

N-(2-metilhexan-3-il)benzo[d][1,3]dioxol-5-carboxamida



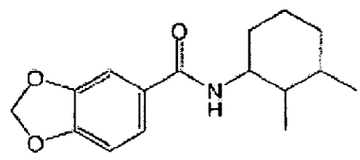
Se prepara de una forma similar al ejemplo 1 utilizando cloruro de benzo[d][1,3]dioxol-5-carbonilo y 2-metilhexan-3-amina (ejemplo 3a). ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93 (m, 9H); 1.37 (m, 3H); 1.56 (m, 1H); 1.83 (m, 1H); 4.01 (m, 1H); 5.67 (d, 1H); 6.02 (s, 2H); 6.82 (d, 1H); 7.28 (m, 2H). MS (M+H, 264).

a. 2-metilhexan-3-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 2a partiendo de 2-metilhexan-3-ona. Rendimiento: 40%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.86 (d, 3H); 0.91 (m, 6H); 1.20-1.29 (m, 2H);1.38-1.47 (m, 2H); 1.47 (s, 2H); 1.58 (m, 1H); 2.51 (m, 1H). MS (M+H,116).

El compuesto tiene activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.61 μM.

Ejemplo 4

N-(2,3-dimetilciclohexil)benzo[d][1,3]dioxol-S-carboxamida



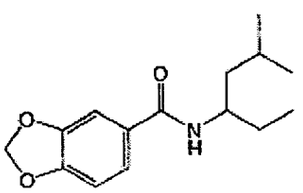
2,3-dimetilciclohexanamina (20 μmol) y ácido benzo[d][1,3]dioxol-5-carboxílico (1.1 eq) cada uno se disuelven en acetonitrilo/diclorometano (200 μL, 2:1). Resina dePS-carbodiimida (2 eq) se carga en una placa Greiner de 96 pozos de 1.2 mL, seguido por la adición de soluciones de amina y ácido. Hidroxibenzotriazol (1.1 eq) se disuelve en DMF (100 mL) y se agrega en el pozo de reacción. La reacción se agita durante la noche a temperatura ambiente. Una vez la reacción se completa, Se agrega resina PS-Trisamina (1.5 eq) en la mezcla

de reacción y a la solución se le permite agitar durante la noche a temperatura ambiente. Se agrega acetonitrilo (200 mL) en el pozo de reacción, y la solución clara superior se transfiere en una nueva placa. La solución se evapora para dar N-(2,3-dimetilciclohexil)benzo[d][1,3]dioxol-5-carboxamida. MS (M+H, 276.20).

El compuesto tiene activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.45 μM, y cuando está presente en 1 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 8.4.

Ejemplo 5

N-(5-metilhexan-3-il)benzo[d][1,3]dioxol-5-carboxamida



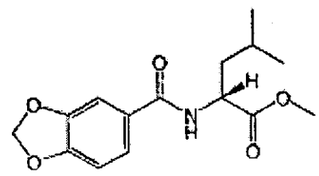
Se prepara de una forma similar al ejemplo 1 utilizando cloruro de benzo[d][1,3]dioxol-5-carbonilo y 5-metilhexan-3-amina (ejemplo 5a). Rendimiento: 48 %. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.94 (m, 9H); 1.37 (t, 3H); 1.45 (m, 1H); 1.64 (m, 2H); 4.13 (m, 1H); 5.61 (d, 1H); 6.01 (s, 2H); 6.82 (d, 1H); 7.27 (m, 2H). MS (M+H, 264).

a. 2-metilhexan-3 -amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 2a partiendo de 5-metilhexan-3-ona. Rendimiento: 54%. MS (M+H, 116).

El compuesto tiene activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.57 µM.

Ejemplo 6

(R)-metilo 2-(benzo[d][1,3]dioxol-6-carboxamido)-4-metilpentanoato

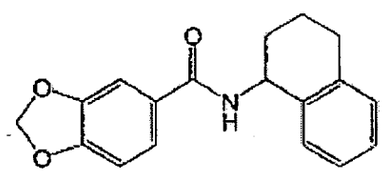


Se prepara de una forma similar al ejemplo 1 utilizando cloruro de benzo[d][1,3]dioxol-5-carbonilo y clorhidrato de éster de metilo D-leucina. Rendimiento: 83 %. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.98 (m, 6H); 1.63-1.67 (m, 1H); 1.71-1.76 (m, 2H); 3.76 (s, 3H);4.83 (m, 1H); 6.03 (s, 2H); 6.38 (d, 1H); 6.83 (d, 1H); 7.32 (s, 1H); 7.33 (d, 1H). MS (M+H, 294). p.f.: 89-90° C.

El compuesto tiene activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.34 µM, y cuando está presente en 0.1 µM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 4.9.

Ejemplo 7

N-(1,2,3,4-tetrahidronaftalen-1-il)benzo[d][1,3]dioxol-5-carboxamida

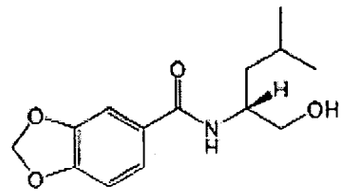


Se prepara de una forma similar al ejemplo 4 utilizando ácido benzo[d][1,3]dioxol-5-carboxílico y 1,2,3,4-tetrahidronaftalen-1-amina. MS (M+H, 296.6).

El compuesto tiene activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.71 μM, y cuando está presente en 0.3 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 7.8.

Ejemplo 8

(R)-N-(1-hidroxi-4-metilpentan-2-il)benzo[d][1,3]dioxol-5-carboxamida



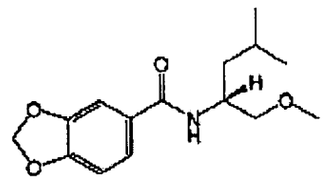
Se prepara de una forma similar al ejemplo 4 utilizando ácido benzo[d][1,3]dioxol-5-carboxílico y (R)-aminoleucinol. MS (M+H, 266.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 9 μM, y cuando está presente en 3 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 2.

Ejemplo 9

Acido (R)-N-(1-metoxi-4-metilpentan-2-il)benzo[d][1,3]dioxol-5-

benzo[d][1,3]dioxol-5-carboxílico



Se prepara de una forma similar al ejemplo 4 utilizando (R)-1-metoxi-4-metilo y pentan-2-amina (ejemplo 9a). Rendimiento: 55%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.95 (m, 6H); 1.43 (m, 1H); 1.55 (m, 1H); 1.65 (m, 1H); 3.36 (s, 3H);3.46 (m, 2H); 4.33 (m, 1H); 6.01 (s, 2H); 6.13 (d, 1H); 6.82 (d, 1H); 7.28 (m, 2H). MS (M+H, 280).

a. (R)-1-metoxi-4-metilpentan-2-amina

A una solución de (R)-2-(1-metoxi-4-metilpentan-2-il)isoindolin-1,3-diona (ejemplo 9b) (3.87 g, 14.84 mmol) en metanol (30 mL), se agrega hidrato de hidrazina (0.866 ml, 17.81 mmol) y la mezcla de reacción se calienta hasta 45° C durante aproximadamente 3 horas. La mezcla se acidifica con HCl 2N y se agita a 45° C durante 30 min. La solución se enfría a temperatura ambiente, se filtra y se evapora. El residuo se toma con NaOH 2N y se extrae con éter, se seca sobre MgSO4, se filtra y se evapora para dar 1.51 g de (R)-1-metoxi-4-metilpentan-2-amina. Rendimiento 77 %. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.91 (m, 6H); 1.17 (m, 2H); 1.58 (s, 2H); 1.71 (m, 1H); 3.02 (m, 1H); 3.10 (m, 1H); 3.32 (m, 1H); 3.35 (s, 3H).

b. (R)-2-(1-metoxi-4-metilpentan-2-il)isoindolin-1,3-diona

(R)-2-(1-hidroxi-4-metilpentan-2-il)isoindolin-1,3-diona (ejemplo 9c) (5.88 g, 23.87 mmol) se disuelve en THF seco (25 mL) y hexametil-fosforamida (30 mL) y la solución se enfría a 0° C. Se agrega hidruro de sodio (60 % en aceite mineral, 1.15 g, 28.65 mmol) y después de 10 minutos se agrega en forma de gota yodometano (7.43 ml, 119.35 mmol) y la solución se calienta lentamente a temperatura ambiente y se agita durante la noche. La mezcla de reacción se vierte en hielo/agua, se extrae con EtOAC, se lava con solución salina, se seca sobre MgSO4, se filtra y se evapora. El residuo se purifica sobre gel de sílice (20% de EtOAC en Hexano) para dar 3.92 g de (R)-2-(1-metoxi-4-metilpentan-2-il)isoindoin-1,3-diona (63 %).

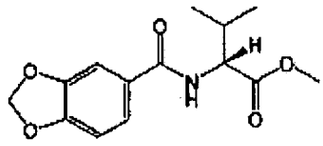
c. (R)-2-(1-hidroxi-4-metilpentan-2-il)isoindolin-1,3-diona:

Se mezclan anhídrido ftálico (10.30 g, 69.55 mmol) y D-Leucinol (8.15 g, 69.55 mmol) en THF (100 mL), la mezcla de reacción se calienta a 85° C y se refluye durante 18 horas. Después de enfriar a temperatura ambiente, se agrega agua y la solución se extrae con EtOAC, los extractos se lavan con HCl 1 N, agua, $NaHCO_3$ ac., agua y solución salina, se secan sobre $MgSO_4$, se filtran y se evaporan para dar 8.1 g de (R)-2-(1-hidroxi-4- metilpentan-2-il)isoindolin-1,3-diona (47 %). ^1H RMN (500 MHz, $CDCl_3$): δ 0.94 (m, 6H); 1.54 (m, 2H); 1.99 (m, 1H); 3.86 (m, 1H); 4.04 (m, 1H); 4.47 (m, 1H); 7.72 (m, 2H); 7.83 (m, 2H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 3.5 μM.

Ejemplo 10

(R)-metilo 2-(benzo[d][1,3]dioxol-6-carboxamido)-3-metilbutanoato

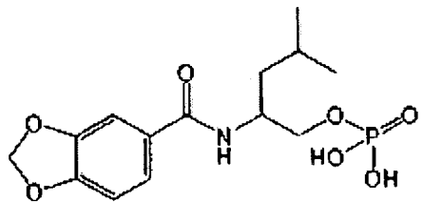


Se prepara de una forma similar al ejemplo 4 utilizando ácido benzo[d][1,3]dioxol-5-carboxílico y (R)-metilo 2-amino-3-metilbutanoato. Rendimiento: 50%. MS (M+H; 280.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.16 µM.

Ejemplo 11

2-(benzo[d][1,3]dioxol-6-carboxamido)-4-metilpentilo dihidrogen fosfato



N-(1-hidroxi-4-metilpentan-2-il)benzo[d][1,3]dioxol-5-carboxamida (ejemplo IIa) (0.57 mmol, 151 mg) se disuelve en acetonitrilo anhidro (2 ml) y 1 ml de 0.45 M de solución de tetrazol en acetonitrilo se agrega bajo nitrógeno y se agita durante 5 min. Luego se agrega en forma de gota 0.627 (1.1 eq, 207 µl) de fosforoamidita diisopropil dibencilo bajo nitrógeno. La mezcla se agita durante 1h. El disolvente se evapora y in intermediario crudo se disuelve en DCM y se lava dos veces con 2% de carbonato de potasio y solución salina y se seca con sulfato de sodio. El

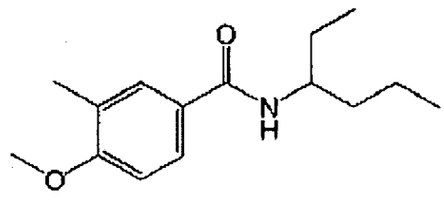
material se seca y se oxida con 5 ml de tert.butilhidroperóxido (4 M de solución en nonano) durante 30 min. El disolvente se evapora y el intermediario dibenciléster se purifica (TLC preparativo). Los grupos bencilo se hidrolizan utilizando ácido trifluoroacético (3 ml de una mezcla de 95% de TFA y 5% de agua, 1.5 h, ta). El producto final se seca suministrando 69 mg (35%) de material puro. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.88-0.90 (t, 6H), 1.23-1.27 (m, 2H), 1.36-1.37 (m, 1H), 1.53-1.62 (m, 2H), 3.93 (s, 1H), 3.98 (s, 1H), 4.32 (s, 1H), 5.90 (s, 2H), 6.66-6.67 (d, 1H), 6.98-6.99 (b, 2H), 7.14 (s, 2H); ^{31}P: δ 0.5 l(s). MS (M+H, 346.0).

a. N-(1-hidroxi-4-metilpentan-2-il)benzo[d][1,3]dioxol-5-carboxamida se prepara de una forma similar al ejemplo 4 a partir de ácido piperonílico y 2-amino-4-metil- pentan-1-ol.

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 10.9 μM.

Ejemplo 12

N-(hexan-3-il)-4-metoxi-3-metilbenzamida

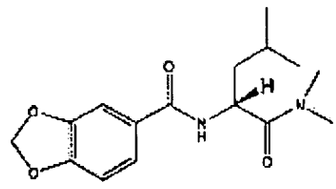


Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-metoxi-3-metilbenzoico y hexan-3-amina (ejemplo 28a). ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.94 (m, 6H); 1.41 (m, 4H); 1.46 (m, 1H); 1.64 (m, 1H); 2.24 (s, 3H); 3.87(s, 3H); 4.08 (m, 1H); 5.69 (d, 1H); 6.83 (d, 1H); 7.54 (s, 1H); 7.62 (d, 1H). MS (M+H, 250).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.12 μM.

Ejemplo 13

(R)-N-(1-(dimetilamino)-4-metil-1-oxopentan-2-il) benzo[d][1,3]dioxol-5-carboxamida



Ácido (R)-2-(benzo[d][1,3]dioxol-6-carboxamido)-4-metilpentanoico (ejemplo 13a) (52 mg, 0.19 mmol) en DMF (4 mL) y dimetil amina (2M en Metanol, 36 μL, 2 eq) se condensan en la presencia de HOBt (26 mg, leq) y de clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (44 mg,1.2 eq) a temperatura ambiente durante la noche. La mezcla de reacción se evapora y el residuo se disuelve en acetato de etilo y se lava sucesivamente con $NaHCO_3$ saturado y agua, se seca sobre $MgSO_4$ se filtra y se evapora para dar 48.6 mg del producto (84%). El material se purifica adicionalmente utilizando RPHPLC. ^1H RMN (500 MHz, $CDCl_3$): δ 0.93-0.94 (d, 3H), 1.03-1.05 (d, 3H), 1.48-1.52 (m, 1H), 1.59-1.63 (m,1H), 2.98 (s, 3H), 3.14 (s, 3H), 5.17-5.21 (m, 1H), 6.01 (s, 2H), 6.80-6.82 (d, 1H), 6.89-6.91 (d, 1H), 7.29-3.30 (d, 1H), 7.33-7.35 (dd, 1H). MS (M+H; 307.2).

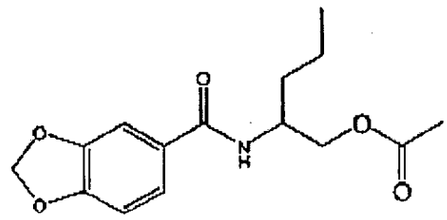
a. ácido (R)-2-(benzo[d][1,3]dioxol-6-carboxamido)-4-metilpentanoico:

Se prepara de una forma similar al ejemplo 1 utilizando cloruro de benzo[d][1,3]dioxol-5-carbonilo y D-Leucina. Rendimiento: 55%. MS (M+H, 280.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.06 μM.

Ejemplo 14

Acetato de 2-(benzo[d][1,3]dioxol-6-carboxamido)pentilo



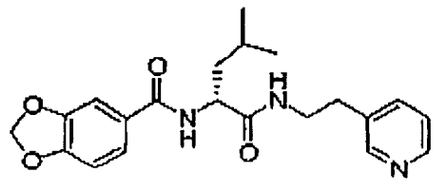
A una solución de N-(1-hidroxipentan-2-il)benzo[d][1,3]dioxol-5-carboxamida (ejemplo 14a) (59.8 mg, 0.238 mmol) en diclorometano (5 mL) se agrega trietilamina (166 mL, 1.19 mmol). Se agrega lentamente anhídrido de acetilo (112.5mL, 1.19mmol) y la mezcla se agita bajo argón a temperatura ambiente durante la noche. La solución se lava sucesivamente con una solución saturada de bicarbonato de sodio, agua y solución salina. La capa orgánica se seca sobre sulfato de sodio anhidro. La filtración seguida por remoción del disolvente bajo presión reducida proporciona 50.8 mg de acetato de 2-(benzo[d][1,3]dioxol-6-carboxamido)pentilo (73%). ^{1}H RMN ($CDCl_3$): □0.95 (t, 3H, *J*= 7.2 Hz), 1.43(m, 2H), 1.57(m, 2H), 2.1 (s, 3H), 4.11(dd, 1H, *J*= 3.5 Hz, *J*= 11.5 Hz), 4.27(dd, 1H, *J*= 3.5 Hz, *J*= 11.4 Hz), 4.29 (m, 1H), 6.02 (s, 2H), 6.1 (m, 1H), 6.82 (d, 1H, J = 8.4 Hz), 7.27 (m, 2H). MS (M+H, 294).

a. N-(1-hidroxipentan-2-il)benzo[d][1,3]dioxol-5-carboxamida se prepara de una forma similar al ejemplo 4 utilizando ácido benzo[d][1,3]dioxol-5-carboxílico y 2- aminopentan-1-ol. Rendimiento: 76%. MS (M+H, 252).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 11.9 μM, y cuando está presente en 3 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 4.1.

Ejemplo 15

(R)-N-(4-metil-1-oxo-1-(2-(piridin-3-il)etilamino)pentan-2-il) benzo[d][1,3]dioxol-5-carboxamida

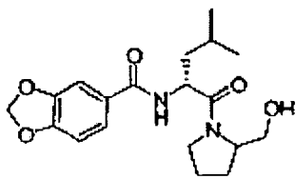


Se prepara de una forma similar al ejemplo 13 utilizando 2-(3-piridil)etilamina y ácido (R)- 2-(benzo[d][1,3]dioxol-6-carboxamido)-4-metilpentanoico (ejemplo 13a). (MS M+ 384.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.7 μM.

Ejemplo 16

N-((R)-1-(2-(hidroximatil)pirrolidin-1-il)-4-metil-1-oxopentan-2-il)benzo[d][1,3]dioxol-5-carboxamida

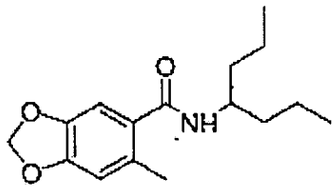


Se prepara de una forma similar al ejemplo 13 utilizando R/S propinol y ácido (R)-2- (benzo[d][1,3]dioxol-6-carboxamido)-4-metilpentanoico (ejemplo 13a). (MS M+ 363.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 3 μM.

Ejemplo 17

N-(heptan-4-il)-6-metilbenzo[d][1,3]dioxol-5-carboxamida

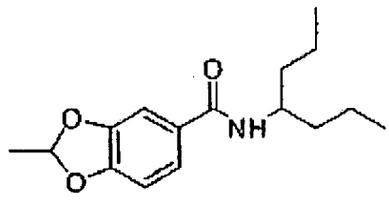


Se prepara de una forma similar al ejemplo 4 utilizando ácido 6-metilbenzo[d][1,3]dioxol-5- carboxílico y heptan-4-amina. MS (M+H, 278.67).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.11 μM.

Ejemplo 18

N-(heptan-4-il)-2-metilbenzo[d][1,3]dioxol-5-carboxamida



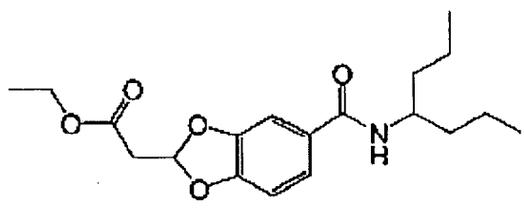
N-(heptan-4-il)-3,4-dihidroxibenzamida (ejemplo 18a) (0.5 mmol) se disuelve en tolueno (1.6 mL). Se agrega monohidrato de ácido p-toluenosulfónico (0.3eq) a la reacción, seguido por adición de acetaldehído (2eq). La reacción se desarrolla utilizando microonda (180C, 300W) y se corre durante 10 minutos. El disolvente se evapora. El residuo se disuelve en metanol (1 ML) y se purifica por HPLC. Rendimiento 20%, MS (M+H 278.10).

a. N-(heptan-4-il)-3,4-dihidroxibenzamida se prepara de una forma similar al ejemplo 4 utilizando ácido 3,4-dihidroxibenzoico y heptan-4-amina. Rendimiento: 25%. MS (M+H, 252.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.1 μM, y cuando está presente en 0.03 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 3.68.

Ejemplo 19

2-(5-(heptan-4-ilcarbamoil)benzo[d][1,3]dioxol-2-il)acetato de etilo

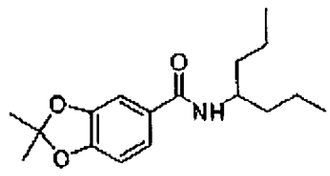


N-(heptan-4-il)-3,4-dihidroxibenzamida (ejemplo 18a) (0.29 mmol, 75 mg) se disuelve en acetona seca con exceso 6 eq (242 mg) de carbonato de potasio luego se agrega exceso de 1.2 eq (36 µl) de éster de etilo de ácido propiónico y una mezcla se refluye durante 24 h. El disolvente se evapora y un sólido se disuelve en diclorometano y se extrae con 10% de $NaHCO_3$ y agua. El producto crudo se purifica por cromatografía sobre gel de sílice para dar 72 mg del producto deseado (71%). ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.91-0.94 (t, 6H), 1.23-1.30 (m, 4H), 1.37-1.41 (4H), 2.97-2.98 (d, 2H), 3.70-3.74 (dd, 2H), 4.12-4.17 (m, 1H), 4.2-4.24 (m, 3H), 5.61-5.64 (d, 1H), 6.58-6.60 (t, 1H), 6.79-6.81 (d, 1H), 7.23 (s, 1H), 7.60-7.85 (b, 1H). MS (M+ H, 350.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 14 µM, y cuando está presente en 3 µM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 2.5.

Ejemplo 20

N-(heptan-4-il)-2,2-dimetilbenzo[d][1,3]dioxol-5-carboxamida



Se prepara de una forma similar al ejemplo 4 utilizando 2,2-dimetilbenzo[d][1,3]dioxol-5-carboxilato de sodio y 4-heptilamina (ejemplo 20a). Rendimiento 30%. ^{1}H RMN: □ 0.92 (t, 6H, *J*= 7.2 Hz), 1.42 (m, 6H), 1.53 (m, 2H),

1.68 (s, 6H), 4.12 (m, 1H), 5.61(d, 1H, J = 8.9 Hz), 6.72 (d, 1H, J= 8Hz), 7.16 (d, 1H, *J*= 1.5 Hz), 7.22 (dd, 1H, *J*= 1.5 Hz, *J*= 17 Hz). MS (M+H, 292).

a. 2,2- dimetilbenzo[d][1,3]dioxol-5-carboxilato de sodio y 4-heptilamina:

2,2-dimetilbenzo[d][1,3]dioxol-5-carboxilato de etilo (ejemplo 20b) (461mg, 2.08 mmol) se agita en dioxano (16mL) y NaOH acuoso 1.0 N (4.16 mL) durante 20 horas a temperatura ambiente. El disolvente se remueve bajo presión reducida para proporcionar el producto deseado (449mg). (M-H, 193).

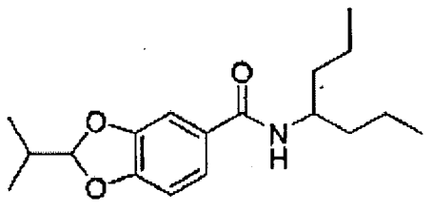
b. 2,2-dimetilbenzo[d][1,3]dioxol-5-carboxilato de etilo:

3,4-dihidroxibenzoato de etilo (910.9 mg, 5mmol) se combina con 2,2-dimetoxipropano (1.23 mL, 10 mmol) y una cantidad catalítica de ácido p-tolueno sulfónico en tolueno. La mezcla se calienta a reflujo utilizando una trampa Dean-Stark durante 20 horas. Después el disolvente se remueve bajo presión reducida, el crudo se disuelve en acetato de etilo y se lava sucesivamente con una solución acuosa saturada de bicarbonato de sodio, agua, y solución salina. La capa orgánica se seca sobre sulfato de sodio anhidro. La purificación por cromatografía sobre gel de sílice utilizando un gradiente Hexano:acetato de etilo, 90:10 a 75:25, proporciona un polvo blanco (539.1 mg, 49%). ^{1}H RMN($CDCl_3$): □ 1.36 (t, 3H, *J*= 7.2Hz), 1.69 (s, 6H), 4.32 (q, 2H, *J*= 7.1 Hz, *J*= 14.2 Hz), 6.74 (d, 1H, d, *J*= 8.2Hz), 7.38 (d, Ih, *J*= 1.7 Hz), 7.61 (dd, 1H, *J*= 1.8 Hz, *J*= 8.3 Hz).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 2.7 μM.

Ejemplo 21

N-(heptan-4-il)-2-isopropilbenzo[d][1,3]dioxol-5-carboxamida



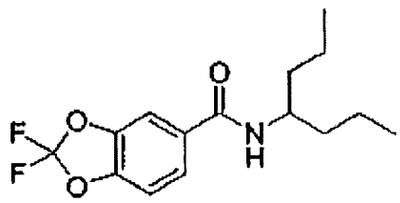
Se prepara de una forma similar al ejemplo 4 utilizando ácido 2-isopropilbenzo[d][1,3]dioxol-5-carboxílico (ejemplo 21a) y 4-heptilamina. Rendimiento: 34%. ^{1}H RMN($CDCl_3$): □ 0.92 (t, 6H, *J*= 7.2Hz), 1.04 (d, 6H, *J* = 6.9 Hz), 1.40 (m, 6H), 1.43 (m, 2H), 2.15 (m, 1H), 4.11 (m, 1H), 5.62 (d, 1H, *J*= 8.9Hz), 5.96 (d, 1H, *J*= 4.4 Hz), 6.75 (d, 1H, *J*= 8.0 Hz), 7.19 (d, 1H, J = 1.8 Hz), 7.22 (d, 1H, *J*= 1.9 Hz), 7.23 (d, 1H, J = 1.6 Hz). MS (M+H, 291).

a. ácido 2-isopropilbenzo[d][1,3]dioxol-5-carboxílico: ácido 3,4-dihidrobenzoico (154.12 mg, 1 mmol) y isobutiraldehído (182 µL, 2 mmoles) se combinan en tolueno (3mL) y se agrega cantidades catalíticas de ácido p-tolueno sulfónico. La mezcla se somete a el microondas durante 10 minutos a 180° C con un sistema de poder a 275. La solución se filtra y se evapora para proporcionar 100 mg del producto deseado (48%). MS (M-H, 207).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 11.5 µM, y cuando está presente en 3 µM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 2.2.

Ejemplo 22

2,2-difluoro-N-(heptan-4-il)benzo[d][1,3]dioxol-5-carboxamida

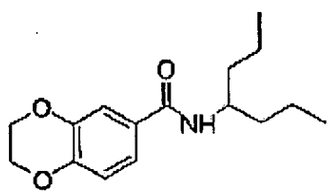


Se prepara de una forma similar al ejemplo 4 utilizando ácido 2,2-difluorobenzo[d][1,3]dioxol-5-carboxílico y 4-heptilamina. (M+H, 300.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.51 μM, y cuando está presente en 1 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 2.87.

Ejemplo 23

(1-propil-butil)-amida de ácido 2,3-Dihidro-benzo[1,4]dioxin-6-carboxílico

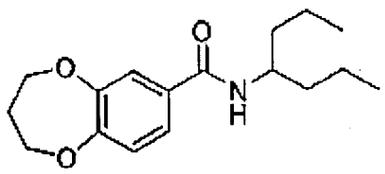


Se prepara de una forma similar al ejemplo 4 utilizando ácido 2,3-Dihidro-benzo[1,4]dioxin-6-carboxílicoy heptan-4-amina. MS (M+H, 278.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.49 μM.

Ejemplo 24

N-(heptan-4-il)-3,4-dihidro-2H-benzo[b][1,4]dioxepin-7-carboxamida

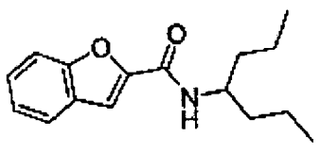


Se prepara de una forma similar al ejemplo 4 utilizando ácido 2,3-Dihidro-benzo[1,4]dioxin-6-carboxílico y heptan-4-amina. MS (M+H, 292.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 6.4 μM.

Ejemplo 25

(1-propilbuti)amida de benzofurano-2-carboxílico



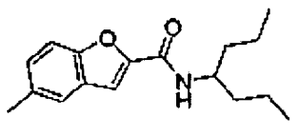
Se prepara de una forma similar al ejemplo 1 utilizando cloruri de benzofurano-2-carbonilo y heptan-4-amina. Rendimiento: 73%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93 (t, 6H, *J*= 7.2 Hz), 1.41 (m, 8H), 3.01 (s, 3H), 4.18 (m, 1H), 6.29 (d, 1H, *J*= 9.94 Hz), 7.20 (d, 1H, *J*= 8.62 Hz), 7.37 (m, 2H), 7.44 (s, 1H). MS (M+H, 260)

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.88 μM, y cuando

está presente en 0.3 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 2.6.

Ejemplo 26

N-(heptan-4-il)-5-metilbenzofurano-2-carboxamida



Se prepara de una forma similar al ejemplo 4 utilizando ácido 5-metilbenzofurano-2-carboxílico (ejemplo 26a) y heptan-4-amina. Rendimiento: 46%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.94 (t, 6H, *J*= 7.2 Hz), 1.41 (m, 10H), 2.44 (s, 1H), 4.18 (m, 1H), 6.29 (d, 1H, *J*= 8.6 Hz), 7.21 (d, 1H, *J*= 8.4 Hz), 7.37(m, 2H), 7.44 (s, 1H). MS (M+H, 274).

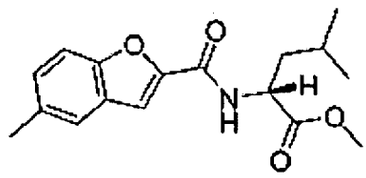
a. ácido 5-metilbenzofurano-2-carboxílico: 2-Hidroxi-5-metilbenzaldehído (544.2 mg, 4 mmol) se combina con dietilbromomalonato (1 mL, 6 mmol) y carbonato de potasio (1.1 g, 8 mmol) en metil etil cetona (5 mL) y la mezcla se calienta a reflujo durante la noche. El disolvente se remueve por evaporación rotativa para proporcionar un aceite crudo. El aceite luego se toma en una solución al 10% de hidróxido de potasio en etanol (10 mL) y se calienta a reflujo durante 45 minutos. El disolvente se remueve bajo presión reducida y el residuo luego se trata con una solución 2.0 N de H_2SO_4. El ácido libre luego se extrae con cantidades copiosas de acetato de etilo. La capa orgánica se seca sobre sulfato de sodio anhidro. El acetato de etilo removido proporciona 566 mg de 5-Metil-2-carboxibenzofurano (80%) como un polvo amarillento. ^{1}H RMN (500 MHz,

CD_3OD): □2.44 (s, 3H), 7.30 (d, 1H, *J*= 8.7 Hz), 7.45 (d, 1H, *J*= 8.5 Hz), 7.51 (d, 2H, *J*= 7.5 Hz).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.94 μM.

Ejemplo 27

(R)-metil 4-metil-2-(5-metilbenzofurano-2-carboxamido)pentanoato

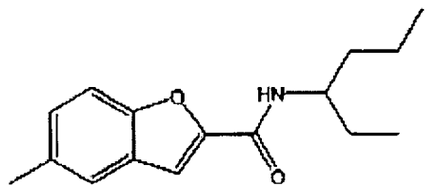


Se prepara de una forma similar al ejemplo 4 utilizando ácido 5-metilbenzofurano-2-carboxílico (ejemplo 26a) y éster de metil D-leucina. ^{1}H RMN (500 MHz, $CDCl_3$): □ 0.98 (d, 3H, *J*= 6.26 Hz), 1.00 (d, 3H, *J*= 6.17 Hz), 1.56 (s, 3H), 1.76 (m, 3H), 2.48 (s, 3H), 3.78 (s, 3H), 4.86 (m, 1H), 6.95 (m, 1H), 7.23 (dd, 1H, *J*= 8.54 Hz, *J*= 1.55 Hz), 7.40 (m, 2H). 7.44 (dd, 1H, *J*= 1.72, *J*= 0.9 Hz). MS 304 (M+H, 304).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.11 μM.

Ejemplo 28

N-(hexan-3-il)-5-metilbenzofuan-2-carboxamida



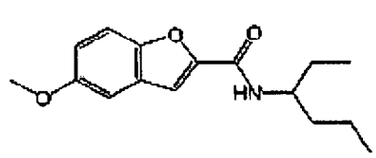
Se prepara de una forma similar al ejemplo 4 utilizando 5-metilbenzofurano-2-carboxílico (ejemplo 26a) y hexan-3-amina (ejemplo 28a).Rendimiento: 49%. ^{1}H RMN (500 MHz, $CDCl_3$): □0.94 (m, 6H), 1.40-1.68 (m, 6H), 2.36 (s, 3H), 4.07 (m, 1H), 5.74 (d, 1H, *J*= 8.97 Hz), 7.16 (d, 1H, *J*= 7.80 Hz), 7.31 (dd, 1H, *J*= 1.73 Hz, *J*= 1.73 Hz), 7.66 (d, 1H, *J*= 1.72 Hz). MS (M+H, 260).

a. Hexan-3-amina se prepara utilizando el mismo procedimiento descrito en el ejemplo 2a partiendo de hexan-3-ona. Rendimiento: 58 %. ^{1}H RMN (500 MHz, $CDCl_3$): □ 0.94 (m, 6H); 1.36-1.58 (m, 6H); 2.83 (m, 1H); 3.12 (s, 2H). MS: (102, M+H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.74 μM.

Ejemplo 29

N-(hexan-3-il)-5-metoxibenzofurano-2-carboxamida



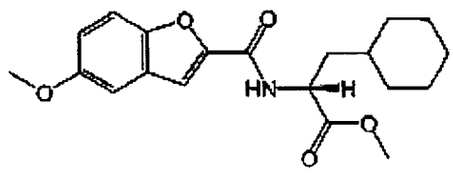
Se prepara de una forma similar al ejemplo 4 utilizando ácido 5-metoxibenzofurano-2-carboxílico y hexan-3-amina (ejemplo 28a). Rendimiento: 32%. ^{1}H RMN (500 MHz, $CDCl_3$): □ 0.96 (m, 6H); 1.40-1.67 (m, 6H); 3.85 (s, 3H);

4.09 (m, 1H); 6.28 (d, 1H); 7.01 (dd, 1H); 7.08 (d, 1H); 7.38 (m, 2H). MS (276, M+H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.4 μM.

Ejemplo 30

3-ciclohexil-2-(5-metoxibenzofurano-2-carboxamido) propanoato de (R)-metilo

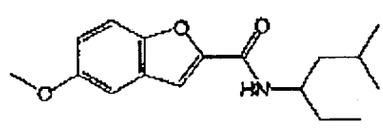


Se prepara de una forma similar al ejemplo 4 utilizando ácido 5-metoxibenzofurano-2-carboxílico y 2-amino-3-ciclohexilpropanoato de (R)-metilo. Rendimiento: 45%. MS (M+H, 260.3).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.14 μM.

Ejemplo 31

5-metoxi-N-(5-metilhexan-3-il)benzofurano-2-carboxamida

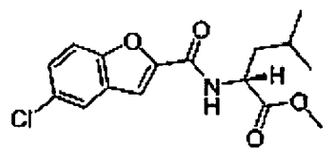


Se prepara de una forma similar al ejemplo 4 utilizando ácido 5-metoxibenzofurano-2-carboxílico y 5-metilhexan-3-amina (ejemplo 5a). Rendimiento: 67%. ^{1}H RMN (500 MHz, $CDCl_3$): □ 0.96 (m, 9H); 1.39-1.52 (m, 3H); 1.66 (m, 2H); 3.85 (s, 3H); 4.17 (m, 1H); 6.24 (d, 1H); 7.01 (dd, 1H); 7.08 (d, 1H); 7.38 (m, 2H). MS (290, M+H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.04 μM.

Ejemplo 32

Preparación de 4-cloro-2-(5-metilbenzofurano-2-carboxamido)pentanoato de (R)-metilo

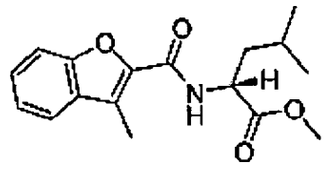


Se prepara de una forma similar al ejemplo 4 utilizando ácido 5-clorobenzofurano-2-carboxílico y éster de metil D-leucina. MS (M+H, 324).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.82 μM.

Ejemplo 33

4-metil-2-(3-metilbenzofurano-2-carboxamido)pentanoato de (R)-metilo

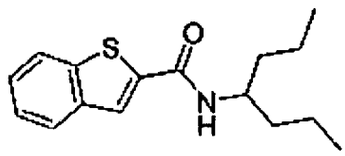


Se prepara de una forma similar al ejemplo 4 utilizando ácido 3-metilbenzofurano-2-carboxílico y éster de metil D-leucina. MS (M+H, 304).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.18 μM.

Ejemplo 34

N-(heptan-4-il)benzo[b]tiofeno-2-carboxamida

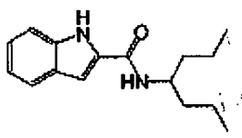


Se prepara de una forma similar al ejemplo 4 utilizando ácido benzo[b]tiofeno-2-carboxílico y 4-heptilamina. MS (M+H, 276).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.21 μM.

Ejemplo 35

N-(heptan-4-il)-1H-indol-2-carboxamida

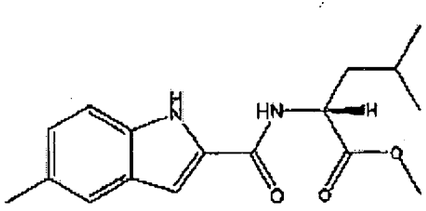


Se prepara de una forma similar al ejemplo 4 utilizando ácido 1H-indol-2-carboxílico y 4-heptilamina. MS (M+H, 259).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 6.8 μM.

Ejemplo 36

4-metil-2-(5-metil-1H-indol-2-carboxamido)pentanoato de (R)-metilo

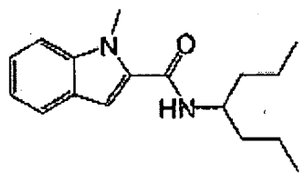


Se prepara de una forma similar al ejemplo 4 utilizando ácido 5-Metil-1H-indol-2-carboxílico y éster de metil D-leucina. Rendimiento: 50%. ^{1}H RMN (500 MHz, $CDCl_3$): □0.98(d, 3H, *J*= 6.3Hz), 1.00(d, 3H, *J*= 6.1 Hz), 2.44 (s, 3H), 3.784(s, 3H), 4.87(m, 1H), 6.56 (d, 1H, *J*= 8.39 Hz), 6.85 (dd, 1H, J =1.94 Hz, *J*= 0.68 Hz), 7.12 (dd, 1H, *J*= 8.46 Hz, *J*= 1.55 Hz), 7.31(d, 1H, *J*= 8.45 Hz), 7.42 (s, 1H).. MS (MH+, 303).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 6.6 μM.

Ejemplo 37

N-(heptan-4-il)-1-metil-1H-indol-2-carboxamida

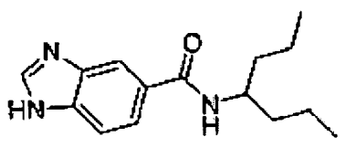


Se prepara de una forma similar al ejemplo 4 utilizando ácido 1-metil-1H-indol-2-carboxílico y 4-heptilamina. Rendimiento 45%. ^{1}H RMN (500 MHz, $CDCl_3$): □0.95 (t, 6H, *J*= 12 Hz), 1.46 (m, 4H), 1.57 (m, 4H), 4.05 (s, 3H), 4.15 (m, 1H), 5.85 (d, 1H), 6.80 (s, 1H), 7.14 (t, 1H, *J*= 7.4 Hz), 7.31 (t, 1H, *J*= 7.5 Hz), 7.38 (d, 1H, *J*= 8.4 Hz), 7.62 (d, 1H, *J*= 8 Hz). MS (M+H, 273).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.79 μM.

Ejemplo 38

N-(heptan-4-il)-1H-benzo[d]imidazol-5-carboxamida

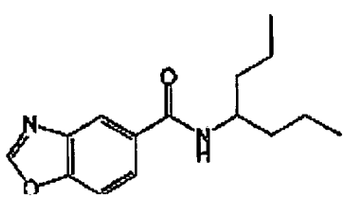


Se prepara de una forma similar al ejemplo 4 utilizando ácido 1H-benzo[d]imidazol-5-carboxílico y 4-heptilamina. Rendimiento: 80%. ^{1}H RMN (500 MHz, $CDCl_3$): □ 0.94 (t, 6H, *J*= 7.2 Hz), 1.42 (m, 6H), 1.57 (m, 2H), 4.21 (m, 1H), 6.18 (m, 1H), 7.64 (m, 2H), 8.16 (m, 1H), 8.28 (s, 1H). MS (M+H, 260).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 18.6 μM.

Ejemplo 39

(1-propilbutil)amida de ácido benzooxazol-5-carboxílico



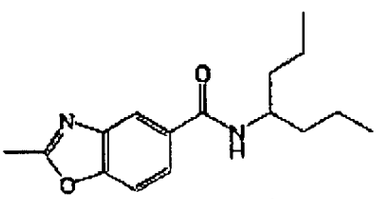
Se prepara de una forma similar al ejemplo 4 utilizando ácido benzooxazol-5-carboxílico (Ejemplo 39a) y 4-heptilamina. ^{1}H RMN (500 MHz, $CDCl_3$): □ 8.16 (d, *J*= 5.4 Hz, 1H), 7.89 (d, *J*= 8.6 Hz, 1H), 7.64 (d, *J*= 8.6 Hz, 1H),5.82 (d, *J*= 8.6 Hz, 1H) 4.10-4.22 (m, 1H), 1.58-1.62 (m, 4H), 1.40-1.49 (m, 4H), 0.95 (t, *J*= 7.2 Hz, 6H); ESIMS: 261 (M^+H).

a. ácido benzooxazol-5-carboxílico: Una mezcla de ácido 3-amino-4-hidroxibenzoico (500 mg, 3.26 mmol) y ortoformato de trimetilo(5 mL) se calienta a 65° C durante 2 h bajo argón. La mezcla de reacción se enfría a temperatura ambiente, se filtra y se lava con Hexanos. El filtrado se concentra en vacío para proporcionar el producto como un sólido blanco (78 mg, 15%): ^{1}H RMN (500 MHz, $CDCl_3$): □ 8.57 (d, *J*= 1.5 Hz, 1H), 8.20 (dd, *J*= 8.4, 1.8 Hz, 1H), 8.20 (s, 1H), 7.67 (d, *J*= 9.0 Hz, 1H). MS (M+H, 164).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.91 μM.

Ejemplo 40

(1-propil-butil)-amida de ácido 2-Metil-benzooxazol-S-carboxílico



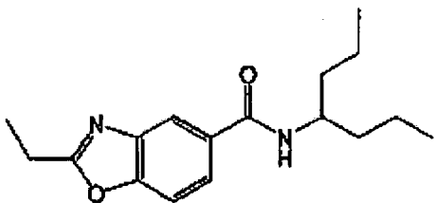
Se prepara de una forma similar al ejemplo 4 partiendo de ácido 2-metilo benzooxazol-5-carboxílico (ejemplo 40) y 4-heptilamina. ^{1}H RMN (500 MHz, $CDCl_3$) δ 8.00 (d, J = 1.6 Hz, 1H), 7.77 (d, *J*= 8.5, 1.6 Hz, 1H), 7.50 (d, *J*= 8.5 Hz, 1H),5.79 (d, *J*= 8.9 Hz, 1H para NH) 4.10-4.22 (m, 1H), 2.66 (s, 3H), 1.58-1.65 (m, 4H), 1.38-1.55 (m, 4H), 0.94 (t, *J*= 7.2 Hz, 6H); MS(APCI, M+1): 275.2.

a. ácido 2-metilo benzooxazol-5-carboxílico: Una mezcla de ácido 3-amino-4-hidroxibenzoico (1.5 g, 9.79 mmol) y ortoacetato de trimetilo (15 mL, exceso mayor) se calienta a 65° C durante 5 hrs bajo argón. La mezcla de reacción se enfría a temperatura ambiente, se filtra, se lava con Hexanos. El filtrado se concentra en vacío para proporcionar el producto como un sólido amarillo (1.4 g, 80%): ^{1}H RMN (500 MHz, CD_3OD) δ 8.26 (d, *J*= 1.7 Hz, 1H), 8.07 (dd, *J*= 8.5, 1.6 Hz, 1H), 7.67 (d, *J*= 8.2 Hz, 1H), 2.67 (s, 1H); MS(APCI, M+1): 178.10.

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.33 μM.

Ejemplo 41

(1-propil-butil)-amida de ácido 2-etil-benzooxazol-5-carboxílico



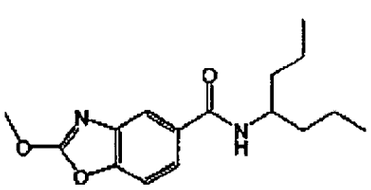
Una mezcla de 3-amino-4-hidroxi-N-(1-propilbutil)benzamida (ejemplo 41a) y orthopropirato de trimetilo se calienta a 65° C durante 5 hr bajo N_2. La mezcla de reacción se enfría a temperatura ambiente y se concentra en vacío. El residuo resultante se purifica sobre gel de sílice por vía de TLC preparativo (3% de MeOH en CH_2Cl_2) para proporcionar el producto como un sólido blanco (42 mg, 73%): pf 107-108° C; MS(APCI, M+1): 289.10.

a. 3-amino-4-hidroxi-N-(1-propilbutil)benzamida se prepara de una forma similar al ejemplo 4 utilizando ácido 3-amino-4-hidroxibenzoico y 4-heptilamina. Rendimiento 57%.^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93 (t, 6H); 1.26-1.51 (m, 8H); 4.09 (m, 1H); 6.74 (m, 1H); 7.05 (s, 1H); 7.43 (m, 2H); 7.77 (m, 2H).MS: (251, M+H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.68 μM.

Ejemplo 42

(1-propil-butil)-amida de ácido 2-Metoxi-benzooxazol-5-carboxílico

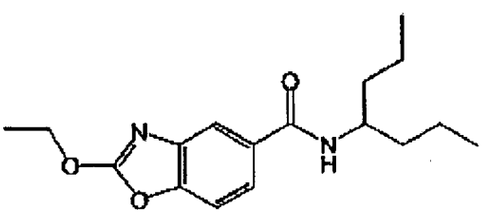


Se prepara de una forma similar al ejemplo 41 utilizando 3-amino-4-hidroxi-N-(1-propilbutil)benzamida (ejemplo 4aa) y tetrametilortocarbonato. Rendimiento: 60%. pf 137-138° C; MS (M+H, 291.10).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.69 µM.

Ejemplo 43

(1-propil-butil)-amida ácido 2-Etoxi-benzooxazol-5-carboxílico

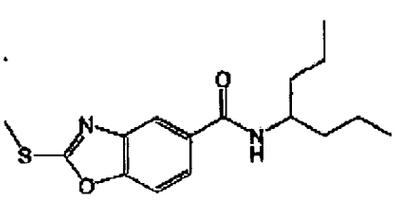


Se prepara de una forma similar al ejemplo 41 utilizando 3-amino-4-hidroxi-N-(1-propilbutil)benzamida (ejemplo 41a) y tetraetoximatano: pf 128-129° C; MS (M+H, 305.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 5 µM.

Ejemplo 44

N-(heptan-4-il)-2-(metiltio)benzo[d]oxazol-5-carboxamida



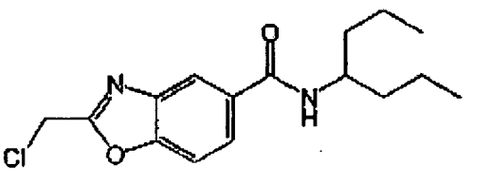
A una solución de N-(Heptan-4-il)-2-(mercapto)benzo[d]oxazol-5-carboxamida (ejemplo 44a) (50 mg, 0.17 mmol) en DMF (3 mL) a 0° C se agrega K_2CO_3 (29 mg, 0.17 mmol) y MeI (29 mg, 0.20). La mezcla de reacción resultante se calienta a 80° C durante la noche. El disolvente se remueve bajo presión reducida. El residuo se diluye con diclorometano y se lava con agua, se seca (Na_2SO_4), se filtra, se concentra en vacío, se purifica por vía de PTLC (15% de EtOAc en Hexanos) para proporcionar el producto como un sólido blanco (50 mg, 96%): pf 113-114° C; ^{1}H RMN (500 MHz, $CDCl_3$) δ 7.94 (d, *J*=1.8 Hz, 1H), 7.73 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.46 (d, *J*= 8.4 Hz, 1H), 5.76 (d, *J*= 8.4 Hz, 1H), 4.15-4.25 (m, 1H), 2.77 (s, 3H), 1.58-1.65 (m, 2H), 1.1.38-1.55 (m, 6H), 0.94 (t, *J*= 7.2 Hz, 6H); MS(APCI, M+): 307.2.

a. N-(Heptan-4-il)-2-(mercapto)benzo[*d*]oxazol-5-carboxamida: A una solución de 3-amino-4-hidroxi-N-(1-propilbutil)benzamida (ejemplo 41a) (250 mg, 1.0 mmol) en EtOH se agrega KSCSOEt (160 mg, 1.0 mmol). La mezcla de reacción resultante se calienta a 80° C durante la noche. El disolvente se remueve bajo presión reducida. y el residuo se toma en agua. La mezcla resultante se acidifica con HOAc a pH ~ 5 y luego se filtra. El residuo se lava con agua para proporcionar el producto como un sólido blanco (160 mg, 55%). MS (M+H, 293.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 3.1 μM.

Ejemplo 45

(1-propil-butil)amida clorometilo de ácido benzooxazol-5-carboxílico

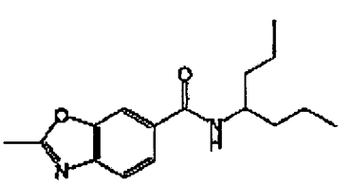


Se prepara de una forma similar al ejemplo 41 utilizando 3-amino-4-hidroxi-N-(1-propilbutil)benzamida (ejemplo 41a) y cloro-ortoacetato de trimetilo. Rendimiento: 65%. Pf 108.5-109° C. MS (M+H, 309.05).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.23 µM.

Ejemplo 46

(1-propil-butiD-amida de ácido 2-Metil-benzooxazol-6-carboxílico



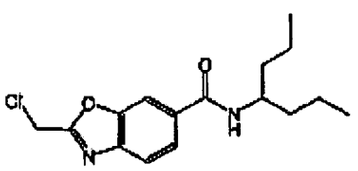
Se prepara de una forma similar al ejemplo 4 utilizando ácido 2-metilo benzooxazol-6-carboxílico (ejemplo 46a) y 4-heptilamina Re ndimiento 50%: ^{1}H RMN (500 MHz, CD_3OD) δ 8.19 (d, *J*= 1.4 Hz, 1H), 8.05 (dd, *J*= 8.3, 1.5 Hz, 1H), 7.63 (d, *J*= 8.2 Hz, 1H), 2.68 (s, 1H); MS (M+1, 178.10).

a. ácido 2-metilo benzooxazol-6-carboxílico se prepara de una forma similar al ejemplo 40a a partir de ácido 4-amino-3-hidroxibenzoico (50%): ^{1}H RMN (500 MHz, CD_3OD) δ 8.19 (d, *J*= 1.4 Hz, 1H), 8.05 (dd, *J*= 8.3, 1.5 Hz, 1H), 7.63 (d, *J*= 8.2 Hz, 1H), 2.68 (s, 1H); MS (M+H, 178.10).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 2.1μM.

Ejemplo 47

(1-propil-butil)-amida de ácido 2-clorometil-benzooxazol-6-carboxílico



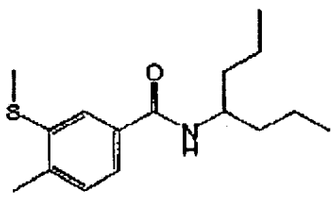
Se prepara de una forma similar al ejemplo 41 utilizando 3-amino-4-hidroxi-N-(1-propilbutil)benzamida (ejemplo 47a) y cloro-ortoacetato de trimetilo. El producto se obtiene como un sólido blanco (45 mg, 73%): pf 137.0-137.5° C; MS (M+H, 309.05.

a. 3-amino-4-hidroxi-N-(1-propilbutil)benzamida se prepara de una forma similar al ejemplo 41a a partir de ácido 4-amino-3-hidroxibenzoico. Rendimiento: 50%. ^1H RMN (500 MHz, $CDCl_3$): δ 0.91 (t, 6H); 1.41 (m, 6H); 1.54 (m, 2H); 4.13 (m, 1H); 5.81 (d, 1H); 6.63 (d, 1H), 6.95 (d, 1H); 7.82 (s, 1H). MS: (251, M+H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.45 μM.

Ejemplo 48

4-metil-3-metilsulfanil-N-(1-propilbutil)benzamida



Se prepara en forma similar como en el ejemplo 4 utilizando ácido 4-metil-3-(metiltio)benzoico (ejemplo 48a) y 4-heptilamina. Rendimiento: 50%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93 (t, 6H, *J*= 7.2 Hz), 1.40-1.41 (m, 8H), 2.35 (s, 3H), 2.51 (s, 1H), 4.15 (m, 1H), 5.75 (d, 1H, J = 8.5 Hz), 7.15 (d, 1H, *J*= 7.8 Hz), 7.31 (d, 1H, *J*= 7.8 Hz), 7.65 (d, 1H, *J*= 1.5 Hz). MS (M+H, 280).

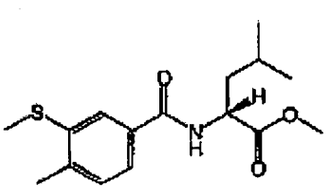
a. ácido 4-metil-3-(metiltio)benzoico: se suspende ácido 3-Amino-4-metilbenzoico en agua helada (55 mL), y se agrega lentamente HCl concentrado (8.56 mL). Una solución acuosa de nitrito de sodio (2.4 g en 5.5 mL) se agrega a la suspensión durante un periodo de 15 minutos y la mezcla se agita durante otros 15 minutos. Luego se agrega en forma de gota una solución acuosa de acetato de sodio (9.31 g en 18 mL). La reacción se le permite proceder durante 45 min. Un precipitado naranja pesado se obtiene. El precipitado se filtra y se lava con porciones pequeñas de agua enfriada con huelo. El sólido se combina con una solución de xantogenato de potasio (11.93 g) y carbonato de potasio (8.22 g) en 250 mL de agua. El recipastelnte de reacción se coloca en un baño de aceite precalentado a 70° C y la mezcla se agita durante 25 minutos. La solución rojiza se saca del baño y se agita durante 15 minutos o hasta que la temperatura alcance 30° C. Se agrega hidróxido de sodio (0.782 g) y se agita hasta disolución. se agrega dimetilsulfato (5.70 mL). La mezcla se agita durante 1 hora a temperatura ambiente luego se refluye brevemente. El disolvente removido bajo presión reducida produce un sólido naranja. El sólido se trata con una solución 2.0 N de H_2SO_4 y se extrae con EtOAc. Los extractos se lavan con agua luego se

secan sobre $MgSO_4$ anhidro. El disolvente se remueve bajo presión reducida para dar un sólido crudo rojizo. El sólido se adsorbe en gel de sílice y se purifica por cromatografía de columna (gradiente 5 a 50% de acetato de etilo en Hexano) para dar ácido 4-metil-3-(metiltio)benzoico como un polvo amarillo pálido (2 g). ^{1}H RMN (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.54 (s, 3H), 7.24 (d, 1H, *J*= 7.8 Hz), 7.79 (d, 1H, *J*= 7.8 Hz), 7.86 (d, 1H, *J*= 1.5 Hz).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.21 μM.

Ejemplo 49

4-metil-2-(4-metil-3-(metiltio)benzamido)pentanoato de (R)-metilo

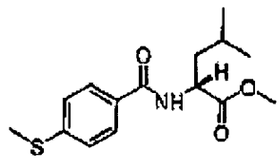


Se prepara de una forma similar al ejemplo 4 utilizando ácido 3-metil-4-(metiltio)benzoico (ejemplo 48a) y éster de metil D-Leucina. Rendimiento: 45%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.97 (d, 3H, *J*= 6.36Hz), 0.99 (d, 3H, *J*= 6.1 Hz), 1.64-1.77 (m, 2H), 2.36 (s, 3H), 2.51(s, 3H), 3.77 (s, 3H), 4.85(m, 1H), 6.50 (d, 1H, *J*= 8.10 Hz), 7.18 (d, 1H, J=7.83 Hz), 7.38 (dd, 1H, *J*= 7.77 Hz, *J*= 1.78Hz), 7.65 (d, 1H, *J*= 1.65 Hz). MS (M+H, 310).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.1 μM.

Ejemplo 50

4-metil-2-(4-(metiltio)benzamido)pentanoato de (R)-metilo

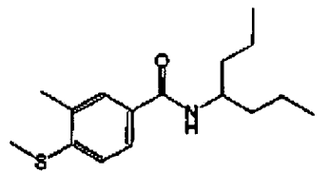


Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-(metiltio)benzoico y éster de metil D-Leucina. MS (M+H, 296).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.16 μM.

Ejemplo 51

N-(heptan-4-il)-3-metil-4-(metiltio)benzamida



Se prepara de una forma similar al ejemplo 4 utilizando ácido 3-metil-4-(metiltio)benzoico (ejemplo 51a) y 4-heptilamina. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93 (t, 6H); 1.37-1.46 (m, 6H); 1.54-1.56 (m, 2H); 2.35 (s, 3H); 2.49 (s, 3H); 4.17 (m, 1H); 5.73 (d, 1H); 7.14 (d, 1H); 7.52 (s, 1H); 7.58 (d, 1H). MS (280, M+H) p.f.: 129-131° C.

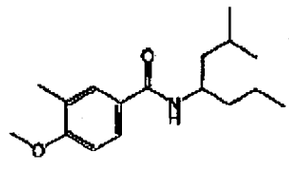
a. ácido 3-metil-4-(metiltio)benzoico se prepara utilizando el mismo procedimiento descrito en el ejemplo 48a partiendo de ácido 3-Amino-4-

metilbenzoico. Rendimiento 30 %. ^{1}H RMN (500 MHz, $CDCl_3$): δ 2.36 (s, 3H); 2.53 (s, 3H); 7.17 (d, 1H); 7.85 (s, 1H); 7.93 (d, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.12 μM.

Ejemplo 52

4-metoxi-3-metil-N-(2-metilheptan-4-il)benzamida

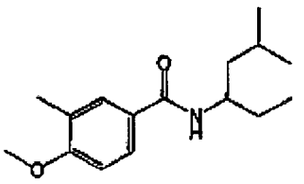


Se prepara en una forma similar como se describe en el ejemplo 4 utilizandoácido 4-metoxi-3-metilbenzoico y 2-metil-4-heptanamina (ejemplo 2a). Rendimiento: 45%.^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93 (m, 9H); 1.39 (m, 5H); 1.53 (m, 1H); 1.67 (m, 1H); 2.24 (s, 3H); 3.86 (s, 3H); 4.23 (m, 1H); 5.64 (d, 1H); 6.82 (d, 1H); 7.54 (s, 1H); 7.61 (d, 1H). MS (278, M+H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.1 μM.

Ejemplo 53

4-metoxi-3-metil-N-(5-metilhexan-3-il)benzamida

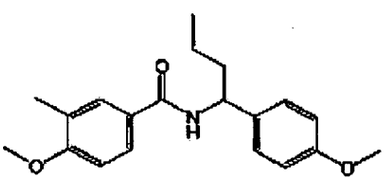


Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-metoxi-3-metilbenzoico y 5-metilhexan-3-amina (ejemplo 5a). ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.94 (m, 9H); 1.38 (m, 2H); 1.47 (m, 1H); 1.65 (m, 2H); 2.24 (s, 3H); 3.86 (s, 3H); 4.16 (m, 1H); 5.65 (d, 1H); 6.83 (d, 1H); 7.54 (s, 1H); 7.61 (d, 1H). MS (264, M+H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.09 μM.

Ejemplo 54

4-metoxi-N-(1-(4-metoxifenil)butil)-3-metilbenzamida



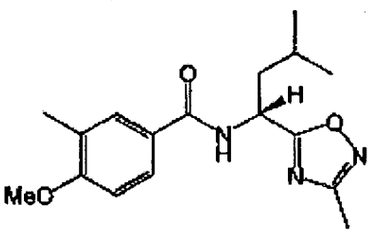
Se prepara de una forma similar al ejemplo 4 utilizando ácido 3-metil-4-metoxi-benzoico y 1-(4-metoxifenil)butan-1-amina (ejemplo 54a). Rendimiento 52%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.94 (t, 3H); 1.31-1.41 (m, 2H); 1.82-1.92 (m, 2H); 2.22 (s, 3H); 3.79 (s, 3H); 3.86 (s, 3H); 5.11 (m, 1H); 6.14 (d, 1H); 6.81 (d, 1H); 6.88 (d, 2H). 7.28 (d, 2H); 7.53 (s, 1H); 7.61 (d, 1H). MS (328, M+H).

a. 1-(4-metoxifenil)butan-1-amina se prepara como se describe en el ejemplo 2a a partir de 1-(4-metoxifenil)butan-1-ona. Rendimiento 90%. MS (M+H, 180).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 3.14 μM.

Ejemplo 55

(R)-4-metoxi-3-metil-N-(3-metil-1-(3-metil-1,2,4-oxadiazol-5-il)butil)benzamida



Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-metoxi-3-metilbenzoico y 3-metil-1-(3-metil-[1,2,4]oxadiazol-5-il)-butilamina (Ejemplo 55a). MS (M+H, 318).

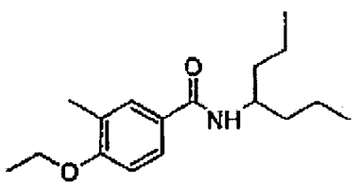
a. (R)-3-metil-1-(3-metil-1,2,4-oxadiazol-5-il)butan-1-amina: Boc-D-Leu-OH (0.23 g, 1 mmol) se trata con N-hidroxiacetamidina (74 mg, 1 eq) y DIC (155 μL, 1 eq) en dioxano (2 mL) a temperatura ambiente durante la noche. Se agrega otra porción de DIC (1 equiv) y la mezcla de reacción se calienta a 110° C durante 4 horas. Después de remoción del disolvente, el residuo se trata con 50% de TFA/DCM (2 mL) durante 1 h y luego el disolvente se evapora. La mezcla cruda se purifica por HPLC preparativo (columna C-18, MeOH-H_2O fase móvil y ácido fórmico como modificador) para dar 75 mg de la amina (45% de rendimiento). ^1H

RMN (500 MHz, $CDCl_3$): δ 0.95 (d, 3H), 0.99 (d, 3H), 1.70-1.78 (m, 1H), 1.92-1.98 (m, 2H), 2.39 (s, 3H), 3.50 (b, 2H, NH_2), 4.65 (t, 1H). MS (M+H, 170).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 5.4 μM.

Ejemplo 56

4-etoxi-N-(heptan-4-il)-3-metilbenzamida



Se prepara en una forma similar como en el ejemplo 4 utilizando ácido 4-etoxi-3-metilo benzoico (ejemplo 56a) y 4-heptilamina. Rendimiento: 75%. ^1H RMN (500 MHz, $CDCl_3$): δ 0.93 (t, 6H); 1.37-1.45 (m, 6H); 1.53-1.59 (m, 2H); 2.24 (s, 3H); 4.07 (q, 2H); 4.15 (m, 1H); 5.67 (d, 1H); 6.80 (d, 1H); 7.54 (s, 1H); 7.58 (d, 1H). MS (278, M+H).

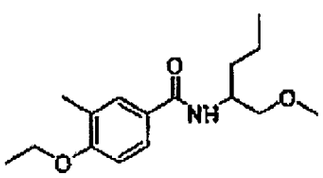
a. ácido 4-etoxi-3-metilo benzoico: ácido 4-hidroxi-3 -metilo benzoico (10 g) se disuelve en DMF (400 mL) seguido por la adición de carbonato de sodio (3eq). Yoduro de etilo (3eq) se disuelve en DMF (50 mL) se agrega en forma de gota a la mezcla de reacción y la solución se agita durante la noche. Después que la reacción se completa, el disolvente se evapora. El residuo se disuelve en acetato de etilo y se lava con agua. La capa orgánica se aísla y se evapora. El residuo se disuelve en 200 mL de metanol/agua (3:1). Se agrega hidróxido de litio (3eq) y se le permite agitar durante la noche. Hasta que se completa la hidrólisis, el

disolvente se remueve y el producto se cristaliza utilizando mezcla de acetato de etilo/Hexano para dar 8.2 g de ácido 4-etoxi-3 -metilo benzoico. Rendimiento: 70%, MS (M-H, 179.20).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.17 μM.

Ejemplo 57

4-etoxi-N-(1-metoxipentan-2-il)-3-metilbenzamida



Se prepara en una forma similar como en el ejemplo 4 utilizando ácido 4-etoxi-3 -metilo benzoico (ejemplo 56a) y 1-metoxipentan-2-amina (ejemplo 57a). Rendimiento: 33%. MS (M+H, 280.1).

a. 1-metoxipentan-2-amina se prepara de una forma similar al ejemplo 9a a partir de 2-(1-metoxipentan-2-il)isoindolin-1,3-diona (ejemplo 57b). Rendimiento 67%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.91 (t, 3H); 1.24 -1.45 (m, 4H); 1.52 (s, 2H); 2.94 (m, 1H); 3.12 (t, 1H); 3.33 (m, 1H); 3.35 (s, 3H).

b. 2-(1-metoxipentan-2-il)isoindolin-1,3-diona se prepara de una forma similar al ejemplo 9b a partir de 2-(1-hidroxipentan-2-il)isoindolin-1,3-diona (ejemplo 57c). Rendimiento: 82%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.91 (t, 3H); 1.32

491

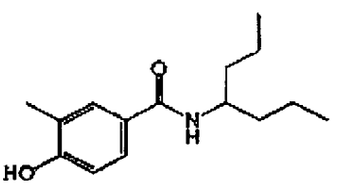
(m, 2H); 1.64 (m, 1H); 2.03 (m, 1H); 3.31 (s, 3H); 3.54 (m, 1H); 3.98 (t, 1H); 4.50 (m, 1H); 7.70 (m, 2H); 7.82 (m, 2H).

c. 2-(1-hidroxipentan-2-il)isoindolin-1,3-diona se prepara de una forma similar al ejemplo 9c utilizando isobenzofurano-1,3-diona y 2-aminopentan-1-ol. Rendimiento 62%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.92 (t, 3H); 1.33 (m, 2H); 1.76 (m, 1H); 1.95 (m, 1H); 3.88 (m, 1H); 4.06 (m, 1H); 4.39 (m, 1H); 7.72 (m, 2H); 7.83 (m, 2H).

El compuesto tiene una activación para EC_{50}, de un receptor umami hT1R1/hTIR3 receptor umami que se expresa en una línea celular HEK293 de 0.69 μM.

Ejemplo 58

4-hidroxi-3-metil-N-(1-propil-butil)-benzamida



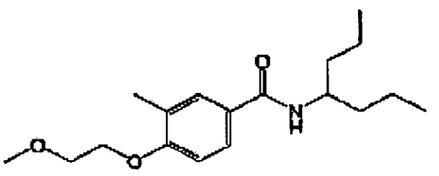
Se prepara en una forma similar como se describe en el ejemplo 4 utilizando ácido 4-hidroxi-3 -metilo benzoico y 4-heptilamina. MS (M+H, 250.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.92 μM.

Ejemplo 59

492

N-(heptan-4-il)-4-(2-metoxietoxi)-3-metilbenzamida

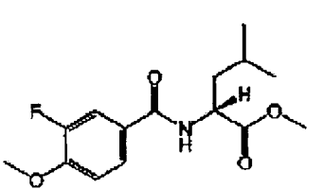


Se disuelve hidróxido de potasio (4 mmol) en etanol (5 mL) y se calienta a 80° C. Se agrega 4-hidroxi-3-metil-N-(1-propil-butil)-benzamida (ejemplo 58) (1 mmol) dentro de la solución seguido por cloroetanol (3 mmol). La reacción se agita durante la noche a 80° C. La mezcla de reacción se concentra y se disuelve en 5% de ácido cítrico, la mezcla se agita durante 1 hora. La mezcla acuosa se extrae tres veces con acetato de etilo. El acetato de etilo combinado se lava con agua y se seca sobre sulfato de sodio. La capa orgánica se concentra y se purifica por HPLC para producir 39% de N-(heptan-4-il)-4-(2-metoxietoxi)-3-metilbenzamida. MS (M+H, 308.25).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.21 μM.

Ejemplo 60

2-(3-fluoro-4-metoxibenzamido)-4-metilpentanoato de (R)-metilo

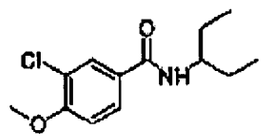


Se prepara de una forma similar al ejemplo 4 utilizando ácido 3-fluoro-4-metoxibenzoico y éster de metil D-leucina. MS (M+H, 298).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.3 μM.

Ejemplo 61

3-cloro-4-metoxi-N-(pentan-3-il)benzamida

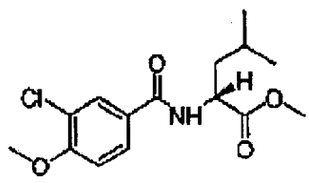


Se prepara de una forma similar al ejemplo 4 utilizando 3-pentilamina y ácido 3-cloro-4-metoxi benzoico. Rendimiento 40%. MS (M+H, 256.20).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.56 μM, y cuando está presente en 0.3 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 6.28.

Ejemplo 62

2-(3-cloro-4-metoxibenzamido)-4-metilpentanoato de (R)-metilo

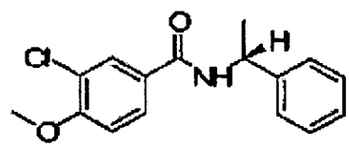


Se prepara de una forma similar al ejemplo 4 utilizando ácido 3-cloro-4-metoxi benzoico y clorhidrato de éster de metilo D-leucina. MS (M+H, 314.10).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.08 μM, y cuando está presente en 0.01 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 13.18.

Ejemplo 63

(R)-3-cloro-4-metoxi-N-(1-feniletil)benzamida

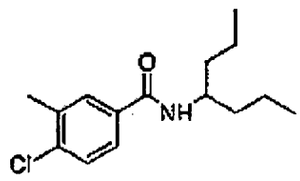


Se prepara en una forma similar al ejemplo 4 utilizando (R)-1-feniletanamina y ácido 3-cloro-4-metoxi benzoico. MS (M+H, 290.0).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 2.5 μM, y cuando está presente en 0.3 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 2.7.

Ejemplo 64

4-cloro-3-metil-N-(1-propil-butil)-benzamida

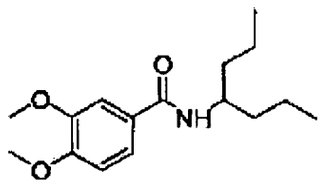


Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-cloro-3-metilo benzoico y heptan-4-amina. MS (M+H, 268).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.8 μM.

Ejemplo 65

3,4-Dimetoxi-N-(1-propil-butil)-benzamida

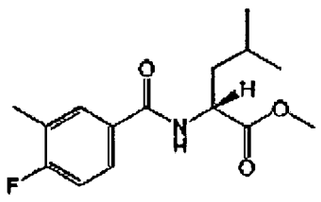


Se prepara de una forma similar al ejemplo 4 utilizando ácido 3,4dimetoxi benzoico y heptan-4-amina. MS (M+H, 279.37).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.36 μM.

Ejemplo 66

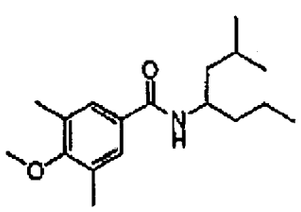
2-(4-fluoro-3-metilbenzamido)-4-metilpentanoato de (R)-metilo



Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-fluoro-3-metilbenzoico y éster de metil D-leucina. MS (M+H, 282). El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.32 μM.

Ejemplo 67

4-metoxi-3,5-dimetil-N-(2-metilheptan-4-il)benzamida

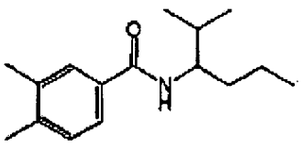


Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-metoxi-3,5-dimetilbenzoico y 2-metilheptan-4-amina (ejemplo 2a). MS (M+H, 292.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.85 μM.

Ejemplo 68

3,4-dimetil-N-(2-metilhexan-3-il)benzamida

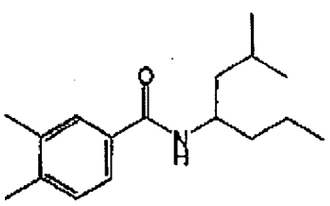


Se prepara de una forma similar al ejemplo 4 utilizando ácido 3,4-dimetilbenzoico y hexan-3-amina (ejemplo 3a). ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.94 (m, 9H); 1.39 (m, 3H); 1.56 (m, 1H); 1.84 (m, 1H); 2.30 (s, 3H); 2.31 (s, 3H); 4.04 (m, 1H); 5.76 (d, 1H); 7.18 (d, 1H); 7.46 (d, 1H); 7.55 (s, 1H); MS (248, M+H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.11 μM.

Ejemplo 69

3,4-dimetil-N-(2-metilheptan-4-il)benzamida

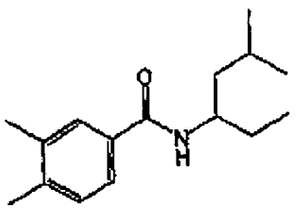


Se prepara de una forma similar al ejemplo 4 utilizando ácido 3,4-dimetilbenzoico y 2-metilheptan-4-amina (ejemplo 2a). ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.94 (m, 9H); 1.40 (m, 5H); 1.53 (m, 1H); 1.68 (m, 1H); 2.29 (s, 3H); 2.30 (s, 3H); 4.24 (m, 1H); 5.69 (d, 1H); 7.17 (d, 1H); 7.46 (d, 1H); 7.54 (s, 1H). MS (262, M+H).

El compuesto tiene una activación para EC_{50} de ahT1R1/hT1R3 receptor umami que se expresa en una línea celular HEK293 de 0.13 μM.

Ejemplo 70

3,4-dimetil-N-(5-metilhexan-3-il)benzamida

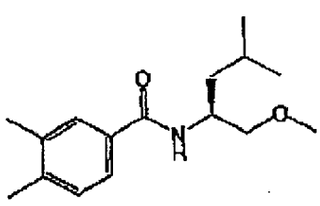


Se prepara de una forma similar al ejemplo 4 utilizando ácido 3,4-dimetilbenzoico y 5-metilhexan-3-amina (ejemplo 5a). ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.94 (m, 9H); 1.38 (m, 2H); 1.46 (m, 1H); 1.65 (m, 2H); 2.29 (s, 3H); 2.30 (s, 3H); 4.18 (m, 1H); 5.70 (d, 1H); 7.17 (d, 1H); 7.46 (d, 1H); 7.55 (s, 1H). MS (248, M+H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.17 μM.

Ejemplo 71

(R)-N-(1-metoxi-4-metilpentan-2-il)-3,4-dimetilbenzamida



A una solución de (R)-N-(1-hidroxi-4-metilpentan-2-il)-3,4-dimetilbenzamida (1.59 g, 6.39 mmol) (ejemplo 71a) en DMF seco (20 mL) se agrega NaOH en polvo (281 mg, 7 mmol) la solución se agita a 0° C durante 2 hrs. Se agrega en forma de gota yodometano (1 eq, 6.39 mmol) en DMF (10 ml) durante un periodo de 1 hr. La temperatura se mantiene a 0° C y la mezcla se agita durante 1 hr. La

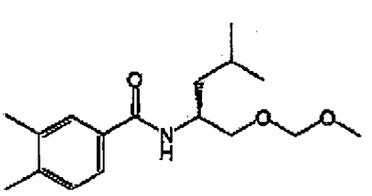
reacción se apaga por la adición de 300 ml de agua. La capa acuosa se extrae con diclorometano, se seca sobre $MgSO_4$ y se evapora. El residuo se purifica por cromatografía flash sobre gel de sílice (tolueno-acetato de etilo; 5-20% de gradiente) para dar 1.23 g de (R)-N-(1-metoxi-4-metilpentan-2-il)-3,4-dimetilbenzamida (73%). ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.94-0.97 (t, 6H), 1.41-1.47 (M, 1H), 1.54-1.60 (m, 1H), 1.64-1.68 (m, 1H), 2.29 (d, 6H), 3.36 (s, 3H), 3.45-3.50 (m, 2H), 4.34-4.39 (m, 1H), 6.23-6.25 (d, 1H), 7.16-7.17 (d, 1H), 7.47-7.49 (dd, 1H), 7.56 (s, 1H). MS (M+H, 264.3).

a. (R)-N-(1-hidroxi-4-metilpentan-2-il)-3,4-dimetilbenzamida se prepara en una forma similar como se describe en el ejemplo 4 utilizando ácido 3,4-dimetilbenzoico y con (R)-aminoleucinol. Rendimiento: 75%. MS (M+H, 250.3).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.2 μM.

Ejemplo 72

(R)-N-(1-metoximatoxi)-4-metilpentan-2-il)-3,4-dimetilbenzamida



A una solución de (R)-N-(1-hidroxi-4-metilpentan-2-il)-3,4-dimetilbenzamida (Ejemplo 71a) (0.24 mmol) disuelta en DMF seco (2mL) se agrega a 0° C NaOH en polvo (0.36 mmol, 14.5 mg, 1.5 eq) y la mezcla se agita durante 1 hr a 0° C. Luego se agrega cloro-metoxi-metano (19.3μl, 1 eq) y la reacción se agita a 0° C

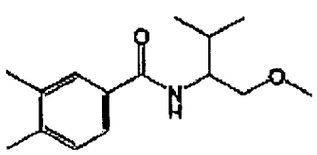
500

durante 1 hora. La reacción se apaga con agua (30 mL) y la mezcla se extrae con diclorometano. La fase orgánica se seca sobre $MgSO_4$ y se evapora. El producto crudo se purifica por TLC preparativo (20% de acetato de etilo/Hexanos) para dar 37.7 mg de (R)-N-(1-(metoximatoxi)-4-metilpentan-2-il)-3,4-dimetilbenzamida (53%). ^1H RMN (500 MHz, $CDCl_3$): δ 0.98-1.00 (t, 6H), 1.49-1.53 (m, 1H), 1.58-1.64 (m, 1H), 1.69-1.73 (m, 2H), 2.32-2.33 (d, 6H), 3.38-3.39 (t, 3H), 3.64-3.72 (ddd, 2H), 4.41-4.44 (m, 1H), 4.65-4.69 (dd, 2H), 6.37-6.39 (d, 1H), 7.19-7.21 (d, 1H), 7.50-7.52 (dd, 1H), 7.60 (sb, 1H). MS (M+H, 294.3).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.06 μM.

Ejemplo 73

N-(1-Metoximatil-2-metil-propil)-3,4-dimetil-benzamida



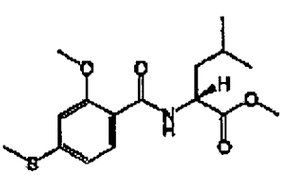
Se prepara de una forma similar al ejemplo 71 utilizando N-(1-hidroxi-3-metilbutan-2-il)-3,4-dimetilbenzamida (ejemplo 73a) y yoduro de metilo. Rendimiento 87%. ^1H RMN (500 MHz, $CDCl_3$): δ 0.97-1.00 (dt, 6H), 1.96-2.00 (m, 1H), 2.29 (s, 3H), 2.30 (s, 3H), 3.35 (s, 3H), 3.42-3.45 (dd, 1H), 3.60-3.62 (dd,1H), 4.01-4.05 (m, 1H), 6.31-6.33 (d, 1H), 7.16-7.18 (d, 1H), 7.48-7.50 (dd, 1H), 7.56-7.57 (d, 1H). MS (M+H, 250).

a. N-(1-hidroxi-3-metilbutan-2-il)-3,4-dimetilbenzamida se prepara de una forma similar al ejemplo 71a utilizando ácido 3,4-dimetoxibenzoico y 2-amino-3-metilbutan-1-ol. Rendimiento 75%. MS (M+H, 236.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.87 μM.

Ejemplo 74

2-(2-metoxi-4-(metiltio)benzamido)-4-inetilpentanoato de (R)-metilo

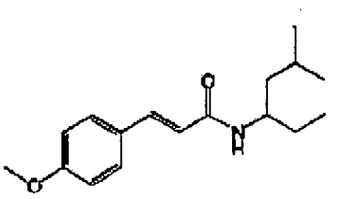


Se prepara de una forma similar al ejemplo 4 utilizando ácido 2-metoxi-4-(metiltio)benzoico y éster de metil D-leucina. MS (M+H, 326).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 15.8 μM.

Ejemplo 75

N-(2-metilheptan-4-il)benzo[d][1,3]dioxol-5-carboxamida

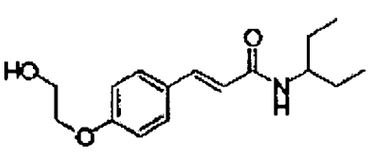


Se prepara de una forma similar al ejemplo 4 utilizando ácido 3-(4-Metoxi-fenil)-acrílico y 5-metilhexan-3 -amina (ejemplo 5a). Rendimiento: 59%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93 (m, 9H); 1.33 (t, 2H); 1.43 (m, 1H); 1.58-1.67 (m, 2H); 3.83 (s, 3H); 4.11 (m, 1H); 5.19 (d, 1H); 6.25 (d, 1H); 6.88 (d, 2H);7.44 (d, 2H); 7.58 (d, 1H). MS (276, M+H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.24 μM.

Ejemplo 76

N-(1-Etil-propil)-3-[4-(2-hidroxi-etoxi)-fenil]-acrilamida



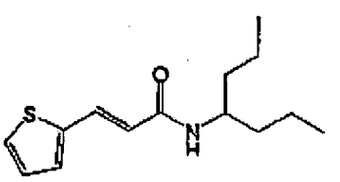
N-(1-Etil-propil)-3-(4-hidroxi-fenil)-acrilamida (ejemplo 76a) (0.44 mmol, 103 mg) se disuelve en etanol absoluto con KOH (0.7 mmol, 37 mg). La mezcla se agita a 80° C durante 1 hr. Luego se agrega en forma de gota 2-cloro-etanol (1.76 mmol, 118 μL) y la mezcla se refluye durante la noche. Luego de la evaporación el producto crudo se disuelve en diclorometano y se lava con agua y 5% de ácido cítrico. La fase orgánica se evapora y el residuo se purifica por cromatografía sobre gel de sílice para dar 73 mg del producto deseado (60%). ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.92-0.95 (t, 6H), 1.25 (s, 1H),1.40-1.46 (m, 2H), 1.59-1.64 (m, 2H), 3.93-3.94 (m, 1H), 3.95-3.98 (m, 2H), 4.09-4.11 (m, 2H), 5.28-5.30 (d, 1H), 6.26-6.29 (d, 1H), 6.88-6.90 (d, 2H), 7.43-7.45 (d, 2H), 7.56-7.59 (d, 1H). MS (M+H, 278.1).

a. N-(1-Etil-propil)-3-(4-hidroxi-fenil)-acrilamida se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido 4-hidroxi-cinnámico y 3-pentilamina. MS (M+H, 234.10).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 5.8 μM.

Ejemplo 77

(E)-N-(heptan-4-il)-3-(tiofen-2-il)acrilamida

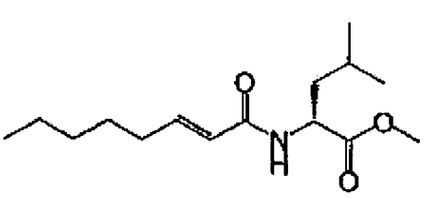


Se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido (E)-3-(tiofen-2-il)acrílico y 4-heptilamina. MS (M+H, 252).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.44 μM.

Ejemplo 78

4-metil-2-oct-2-enamidopentanoato de (R,E)-metilo

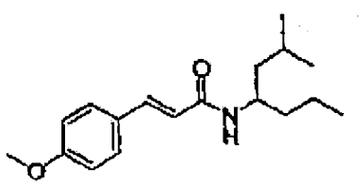


Se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido (E)-oct-2-enoico y éster de metil D-leucina. MS (M+H, 270).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.92 μM.

Ejemplo 79

3-(4-Metoxi-fenil)-N-(3-metil-1-propil-butil)-acrilamida



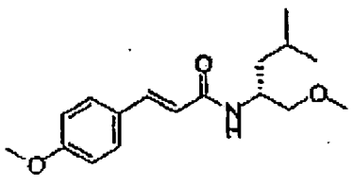
Se prepara de una forma similar al ejemplo 4 utilizando ácido 3-(4-metoxi-fenil)-acrílico y 3-metil-1-propil-butilamina (ejemplo 2a). Rendimiento: 65%. ^1H RMN (500 MHz, $CDCl_3$): δ 0.90-0.95 (m, 9H), 1.30-1.39 (m, 5H), 1.49-1.50 (m, 1H), 1.64-1.67 (m, 1H), 3.82 (s, 3H), 4.17-4.18 (m, 1H), 5.18-5.20 (d, 1H), 6.22-6.26 (d, 1H), 6.86-6.89 (d, 2H), 7.42-7.45 (d, 2H), 7.56-7.59 (d, 1H). MS (M+H, 290.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.84 μM.

Ejemplo 80

N-(1-Metoximatil-3-metil-butil)-3-(4-metoxi-fenil)-acrilamida

505

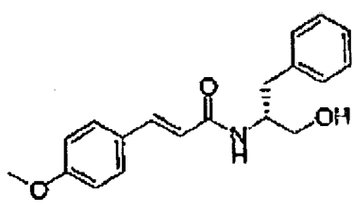


Se prepara en una forma similar como se describe en el ejemplo 71 a partir de ácido 3-(4-Metoxi-fenil)-acrílico y D-leucinol. Rendimiento: 41%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93-0.96 (t, 6H), 1.38-1.42 (m, 1H), 1.48-1.54 (m, 1H), 1.63-1.66 (m, 1H), 3.36 (s, 3H), 3.41-3.46 (m, 2H), 3.82-3.83 (s, 3H), 4.29-4.31 (m, 1H), 5.69-5.71 (d, 1H), 6.24-6.27 (d, 1H), 6.87-6.89 (d, 2H), 7.43 (s, 1H), 7.44 (s, 1H), 7.56-7.59 (d, 1H). MS (M+H, 292.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.90 μM.

Ejemplo 81

N-(1-Bencil-2-hidroxi-etil)-3-(4-metoxi-fenil)-acrilamida



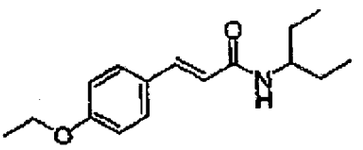
Se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido 3-(4-Metoxi-fenil)-acrílico y D-fenilalaninol. MS (M+H, 312.3).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.1 μM.

S66

Ejemplo 82

3-(4-Etoxi-fenil)-N-(1-etil-propil)-acrilamida

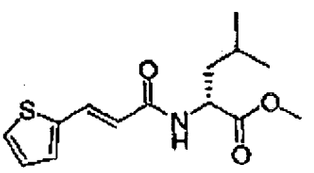


Se prepara de una forma similar al ejemplo 4 utilizando ácido 3-(4-etoxi-fenil)-acrílico y 3-pentilamina.MS (M+H, 262.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.35 μM.

Ejemplo 83

Éster de metilo de ácido 4-Metil-2-(3-tiofen-2-il-acriloulamino)-pentanoico

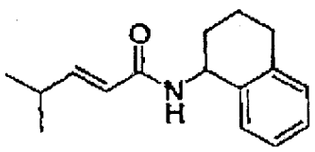


Se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido 3 -tiofen-2-il-acrílico y éster de metil D-leucina. MS (M+H, 282.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.59 μM.

Ejemplo 84

(1,2,3,4-tetrahidro-naftalen-1-il)-amida de ácido 4-Metil-pent-2-enoico

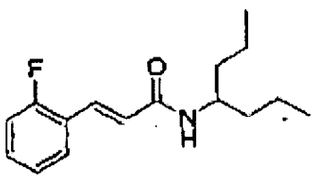


Se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido 4-metil-pent-2-enoico y 1,2,3,4-tetrahidro-naftalen-1-ilamina. MS (M+H, 244.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.5 μM.

Ejemplo 85

3-(2-Fluoro-fenil)-N-(1-propil-butil)-acrilamida

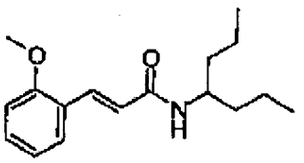


Se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido 3-(2-fluoro-fenil)-acrílico y 4-heptilamina. MS (M+H, 264.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.16 μM.

Ejemplo 86

3-(2-Metoxi-fenil)-N-(1-propil-butil)-acrilamida

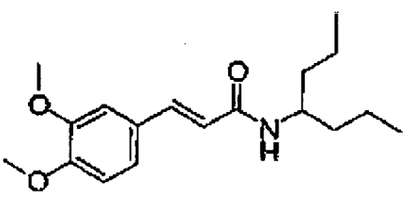


Se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido 3-(2-metoxi-fenil)-acrílico y 4-heptilamina. MS (M+H, 276.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.90 μM.

Ejemplo 87

3-(3,4-Dimetoxi-fenil)-N-(1-propil-butil)-acrilamida



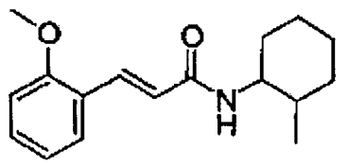
Se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido 3-(3,4-dimetoxi-fenil)-acrílico y 4-heptilamina. MS (M+H, 306.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.97 μM, y cuando está presente en 0.3 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 2.4.

Ejemplo 89

S69

3-(2-Metoxi-fenil)-N-(2-metil-ciclohexil)-acrilamida

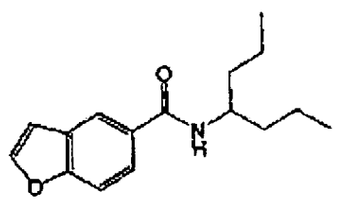


Se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido 3-(2-metoxi-fenil)-acrílico y 2-metil-ciclohexilamina. MS (M+H, 274.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 3.4 μM.

Ejemplo 90

N-(heptan-4-il)benzofurano-5-carboxamida

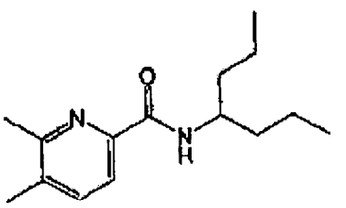


Se prepara de una forma similar al ejemplo 4 utilizando ácido benzofurano-5-carboxílico y heptan-4-amina. Rendimiento 41%. MS (M+H, 260.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.19 μM.

Ejemplo 91

N-(heptan-4-il)-5,6-dimetilpicolin amida



Se prepara de una forma similar al ejemplo 4 utilizando ácido 5,6-Dimetilpicolínico (Ejemplo 91a) y 4-heptilamina. Rendimiento: 49%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.91-0.94 (t, 6H), 1.38-1.48 (m, 4H), 1.49-1.61 (m, 4H), 2.32 (s, 3H), 2.52 (s, 3H), 4.11-4.13 (m, 1H), 7.52-7.53 (d, 1H), 7.93-7.94 (d, 1H). MS (M+H, 249.1).

a. ácido 5,6-Dimetilpicolínico: 5,6-dimetilpicolinonitrilo (ejemplo 91b) se refluye en HCl concentrado (15 mL) durante la noche. El disolvente se evapora y el residuo sólido se co-evapora varias veces con EtOH. El secado suministra 453 mg de ácido 5,6-Dimetilpicolínico (80%) como un sólido blanco. MS (M+H, 152.1).

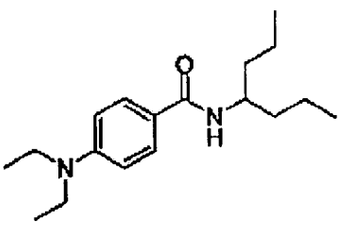
b. 5,6-dimetilpicolinonitrilo: 2,3-lutidina (13.25 mmol) se refluye durante la noche con 18 ml de AcOH glacial y 6 ml de hidrógeno peróxido. El disolvente se evapora y el residuo se co-evapora dos veces con agua, se basifica con Na_2CO_3 y se extrae con cloroformo. La capa orgánica se seca sobre Na_2SO_4 y se evapora para dar 1.45 g de un producto cristalino. El producto (615 mg, 5 mmol) se hace reaccionar con trimetilsilano carbonitrilo (5.5 mmol) en diclorometano (10 mL) a temperatura ambiente durante 5 min seguido por adición de cloruro de dimetilcarbarnoilo (5 mmol) y la solución se agita a temperatura ambiente durante 3 días. La mezcla de reacción se trata con 10% de carbonato de potasio (10 mL), la capa orgánica se separa y la capa acuosa se extrae 2 veces con diclorometano. La fase orgánica se seca sobre Na_2SO_4 y se evapora para dar 495 mg de 5,6-

dimetilpicolinonitrilo (75%). ^{1}H RMN (500 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.53 (s, 3H), 7.43-7.45 (d, 1H), 7.51-7.52 (d, 1H); ^{13}C: δ 19.71, 22.80, 117.87, 126.36, 130.60, 136.58, 137.66, 159.84). MS (M+H, 133.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 2.8 μM.

Ejemplo 92

4-(dietilamino)-N-(heptan-4-il)benzamida

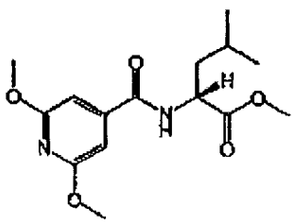


Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-dietilamino benzoico y 4-heptilamina. (31% %). ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.92(t, 6H, J = 7.17 Hz), 1.18 (t, 6H, *J*= 7.04 Hz), 1.41(m, 4H), 1.55(m, 4H), 3.39 (m, 4H), 4.15 (m, 1H), 5.62 (m, 1H), 6.64 (d, 2H, *J*= 10.26Hz), 7.64 (d, 2H, *J*= 10.26 Hz). MS (M+H, 291).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 7.6 μM.

Ejemplo 93

2-(2,6-dimetoxiisonicotinamido)-4-metilpentanoato(R)-metilo

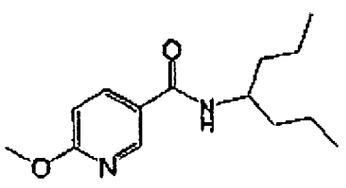


Se prepara de una forma similar al ejemplo 4 utilizando ácido 2,6-Dimetoxi-isonicotínico y éster de metil D-leucina. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.92 (d, 3H, J=7.27 Hz), 0.93 (d, 3H, *J*= 7.26 Hz), 1.41-1.58 (m, 8H), 3.95 (s, 3H), 4.08 (s, 3H), 4.15 (m, 1H), 6.43 (d, 1H, *J*= 8.32 Hz), 7.47 (m, amplio, 1H), 8.41 (d, 1H, *J*= 8.34 Hz). MS (M+H; 311).

El compuesto tiene una activación para EC_{50} de ahT1R1/hT1R3 receptor umami que se expresa en una línea celular HEK293 de 1.91 μM.

Ejemplo 94

N-(heptan-4-il)-6-metoxinicotinamida



Se prepara de una forma similar al ejemplo 4 utilizando T6-metlioxinicotinato de sodio (ejemplo 94a) y 4-heptilamina. Rendimiento: 44%. MS (M+H, 251).

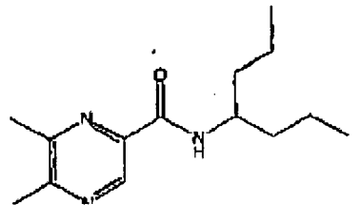
a. 6-metoxinicotinato de metilo (2.097g, 12.56mmol) se disuelve en dioxano (30 mL). Una solución acuosa de NaOH (1.0N, 25mL) se agrega a la solución y la

S13

mezcla se agita a temperatura ambiente durante la noche. El disolvente se remueve bajo presión reducida 2.2 g de sodio 6-metoxinicotinate. El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 2.66 μM.

Ejemplo 95

(1-propilbutil)amida de ácido 5,6-dimetilpirazin-2-carboxílico



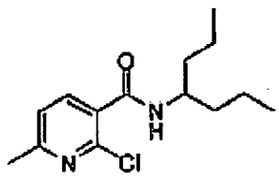
Se prepara de una forma similar al ejemplo 4 utilizando ácido 5,6-dimetil-pirazin-2-carboxílico (ejemplo 95a) y 4-heptilamina. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.91-0.94 (t, 6H), 1.35-1.42 (m, 4H), 1.48-1.51 (m, 2H), 1.55-1.60 (m, 2H), 2.57-2.60 (d, 6H), 4.13-4.16 (m, 1H), 7.52-7.53 (d, 1H), 9.09 (s, 1H); MS (M+H, 250).

a. ácido 5,6-dimetil-pirazin-2-carboxílico: A una solución de ácido 2,3-diaminopropiónico (1.0 g, 9.6 mmol) en metanol (20 mL) se agrega butano-2,3-diona (728 μL; 11.5 mmol) y NaOH (1.4 g; 56.6 mmol). La mezcla se refluye durante 2 h y luego se enfría a temperatura ambiente mientras que se burbujea aire durante 1 hora. El precipitado blanco se filtra y el producto gelatinaoso se concentra bajo vacío. El producto crudo se toma en diclorometano, se lava con 10% de ácido cítrico, se seca sobre $MgSO_4$ y se filtra. El disolvente se remueve bajo presión reducida para dar ácido 5,6-dimetil-pirazina-2-carboxílico como un sólido volátil. El compuesto se utiliza como está en la próxima etapa.

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.01 μM.

Ejemplo 96

2-cloro-N-(heptan-4-il)-6-metilnicotinamida

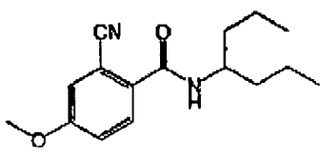


Se prepara de una forma similar al ejemplo 4 utilizando ácido 2-cloro-6-metilnicotínico y 4-Heptilamina. MS (M+H, 269).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 3.9 μM.

Ejemplo 97

2-ciano-N-(heptan-4-il)-4-metoxibenzamida

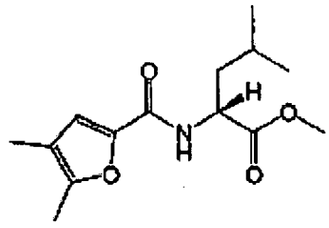


Se prepara de una forma similar al ejemplo 4 utilizando ácido 2-ciano-4-metoxibenzoico y 4-Heptilamina. Rendimiento: 73%. ^{1}H RMN (CD_3OD): □0.94 (t, 6H, *J*= 7.3 Hz), 1.38 (m, 4H), 1.53 (m, 4H), 4.02 (s, 3H),4.12 (m, 1H), 7.27 (d, 1H, *J*= 9.40 Hz), 8.11 (d, 2H, *J*= 2.21 Hz). MS (M+H, 275).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.39 μM, y cuando está presente en 1 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 4.52.

Ejemplo 98

2-(2,3-dimetilfiiran-5-carboxamido)-4-metilpentanoato de (R)-metilo

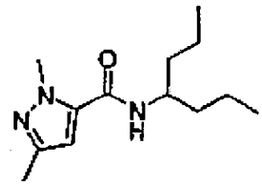


Se prepara de una forma similar al ejemplo 4 utilizando ácido 4,5-dimetil-furano-2-carboxílico y éster de metil D-leucina. Rendimiento: 27 %. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.96 (t, 6H), 1.66 (m, 3H), 1.96 (s, 3H), 2.26 (s, 3H), 3.75 (s, 3H), 4.78 (m, 1H), 6.51 (d, 1H), 6.89 (s, 1H). MS (M+H, 268).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.59 μM.

Ejemplo 99

N-(heptan-4-il)-1,3-dimetil-1H-pirazol-5-carboxamida

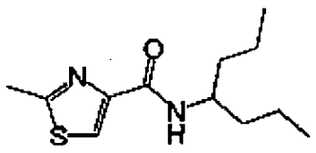


Se prepara de una forma similar al ejemplo 4 utilizando ácido 1,3-dimetil-1H-pirazol-5-carboxílico y 4-heptilamina. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.90 (t, 6H, *J*= 12 Hz), 1.41 (m, 4H), 1.50 (m, 4H), 2.27 (s, 3H), 3.77 (s, 3H), 4.09 (m, 1H), 6.49 (d, 1H), 6.53 (s, 1H). MS (M+H, 238).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 7.8 μM.

Ejemplo 100

N-(heptan-4-il)-2-metiltiazol-4-carboxamida

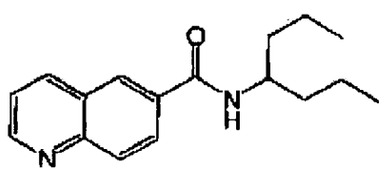


Se prepara de una forma similar al ejemplo 4 utilizando ácido 1,3-dimetil-1H-pirazol-5-carboxílico y 4-heptilamina. MS (M+H, 241).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 7.2 μM.

Ejemplo 101

N-(heptan-4-il)quinolin-6-carboxamida

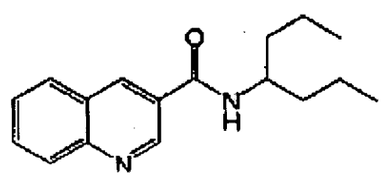


Se prepara de una forma similar al ejemplo 4 utilizando ácido quinolin-6-carboxílico y 4-heptilamina. ^{1}H RMN (500 MHz, $CDCl_3$) δ 0.96 (t, *J*= 7.2 Hz, 6H), 1.42-1.58 (m, 6H), 1.62-1.70 (m, 2H), 4.18-4.20 (m, 1H), 5.95 (d, *J*= 9.0 Hz, 1H), 7.49 (br s, 1H), 8.04 (dd, *J*= 8.5, 1.5 Hz, 1H), 8.17 (d, *J*= 8.5 Hz, 1H), 8.27 (d, *J*= 8.2 Hz, 1H), 8.30 (s, 1H), 8.99 (br s, 1H); MS (M+H, 271.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 3.2 μM.

Ejemplo 102

N-(heptan-4-il)quinolin-3-carboxamida

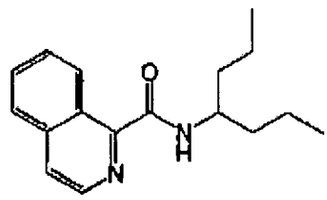


Se prepara de una forma similar al ejemplo 4 utilizando ácido quinolin-3-carboxílico y heptilamina: ^{1}H RMN (500 MHz, $CDCl_3$) δ 0.96 (t, *J*= 7.3 Hz, 6H), 1.40-1.58 (m, 6H), 1.60-1.67 (m, 2H), 4.20-4.30 (m, 1H), 6.01 (d, *J*= 8.8 Hz, 1H), 7.61 (t, *J*= 7.5, 1H), 7.80 (t, *J*= 7.6 Hz, 1H), 7.90 (d, *J*= 8.1 Hz, 1H), 8.15 (d, *J*= 8.5 Hz, 1H), 8.57 (d, *J*= 1.2 Hz, 1H), 9.26 (br s, 1H); MS (M+H, 271.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 15.8 μM.

Ejemplo 103

N-(heptan-4-il)isoquinolin-1-carboxamida

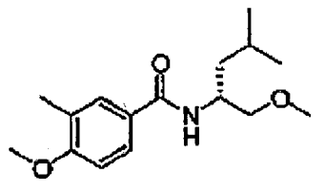


Se prepara de una forma similar al ejemplo 4 utilizando ácido isoquinolin-1-carboxílico y heptamina: ^{1}H RMN (500 MHz, $CDCl_3$) δ 0.98 (t, *J*= 7.05 Hz, 6H), 1.42-1.56 (m, 6H), 1.58-1.66 (m, 2H), 4.20-4.32 (m, 1H), 5.83 (d, *J*= 9.1 Hz, 1H), 7.36 (d, *J*= 4.2, 1H), 7.60 (t, *J*= 7.7 Hz, 1H), 7.75 (t, *J*= 7.7 Hz, 1H), 8.11 (d, *J*= 8.5 Hz, 1H), 8.18 (d, *J*= 8.4 Hz, 1H), 8.88 (d, *J*= 4.9, 1H); MS(APCI, M+): 271.2.

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 14.2 μM.

Ejemplo 104

4-Metoxi-N-(1-metoximatil-3-metil-butil)-3-metil-benzamida



Se prepara en una forma similar como se describe en el ejemplo 71 a partir de ácido 4-metoxi-3-metil-benzoico y D-leucinol. Rendimiento: 86%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.94—0.97 (t, 6H), 1.42-1.47 (m, 1H), 1.54-1.60 (m, 1H), 1.64-1.68 (m, 2H), 2.24 (s, 3H), 3.37 (s, 3H), 3.46-3.48 (m, 2H), 3.87 (s, 3H), 4.35-4.38 (m,

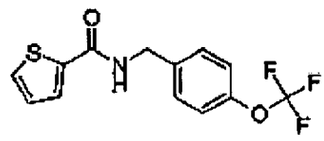
S19

1H), 6.14-6.16 (d, 1H), 6.82-6.84 (d, 1H), 7.56 (d, 1H), 7.61-7.63 (dd, 1H). MS (M+H, 280.3).

El compuesto tiene una activación para EC_{50} de a hT1R1/liT1R3 receptor umami que se expresa en una línea celular HEK293 de 0.24 μM.

Ejemplo 105

N-(4-(trifluorometoxi)Bencil)tiofeno-2-carboxamida

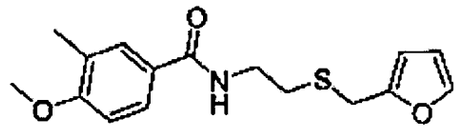


Se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido tiofeno-2-carboxílico y (4-(trifluorometoxi)fenil)metanamina. MS (M+H, 303).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 2.4 μM.

Ejemplo 106

N-(2-(furano-2-ilmetiltio)etil)-4-metoxi-3-metilbenzamida



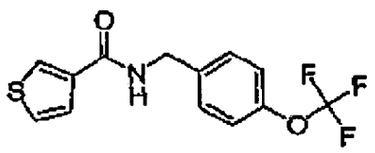
S20

Se prepara en una forma similar como se describe en el ejemplo 4 de ácido 4-metoxi-3-metilbenzoico y 2-(furano-2-ilmetiltio)etanamina. Rendimiento 58%. ^{1}H RMN (500 MHz, $CDCl_3$) 2.23 (s, 3H), 2.76 (t, 2H, *J*= 6.37 Hz), 3.59 (q, 2H, *J*= 12.2 Hz), 3.76 (s, 2H), 3.86 (s, 3H), 6.22 (dd, 1H, *J*= 3.49 Hz, *J*= 2.67 Hz), 6.30 (dd, 1H, *J*= 3.04 Hz, *J*= 1.78 Hz), 6.46 (m, 1H, amplio), 6.83 (d, 1H, *J*= 8.51 Hz), 7.34(dd, 1H, *J*= 1.97 Hz, *J*= 1 Hz), 7.56 (d, 1H, J = 1.72 Hz), 7.61(dd, 1H, *J*= 8.53 Hz, *J*= 2.25 Hz). MS (M+H, 306).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 5.6 µM.

Ejemplo 107

Ácido Tiofeno-3-carboxílico 4-trifluorometoxi-bencilamida

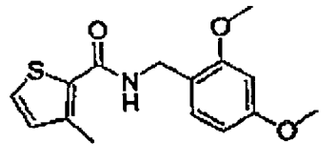


Se prepara de una forma similar al ejemplo 4 utilizando ácido tiofeno-3-carboxílico y 4-trifluorometoxi-bencilamina. MS (M+H, 302.0).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 2.2 µM, y cuando está presente en 3 µM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 8.5.

Ejemplo 108

Ácido 3-Metil-tiofeno-1-carboxílico 2,4-dimetoxi-bencilamida

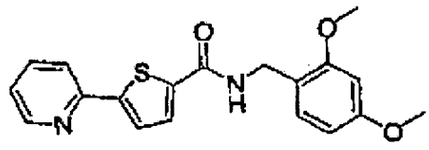


Se prepara de una forma similar al ejemplo 4 utilizando ácido 3-metil-tiofeno-2-carboxílico y 2,4-dimetoxi-bencilamina. MS (M+H, 292.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 5.6 μM, y cuando está presente en 3 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 5.8.

Ejemplo 109

Ácido 5-Piridin-2-il-tiofeno-2-carboxílico 2,4-dimetoxi-bencilamida

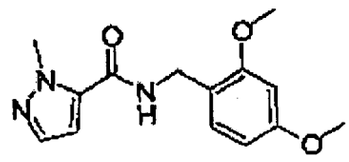


Se prepara de una forma similar al ejemplo 4 utilizando ácido 5-piridin-2-il-tiofeno-2-carboxílico y 2,4-dimetoxi-bencilamina. MS (M+H, 355.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 2.86 μM, y cuando está presente en 3 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 8.

Ejemplo 110

Ácido 2-Metil-2H-pirazol-3-carboxílico 2,4-dimetoxi-bencilamida

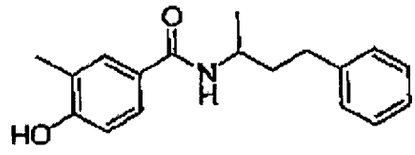


Se prepara de una forma similar al ejemplo 4 utilizando 2-metil-2H~pirazol-3-carboxílicoand 2,4-dimetoxi-bencilamina. MS (M+H, 276.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 6 µM, y cuando está presente en 3 µM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 7.9.

Ejemplo 111

4-Hidroxi-3-metil-N-(1-metil-3-fenil-propil)-benzamida



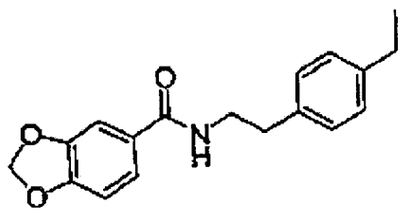
Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-hidroxi-3-metil-benzoico y 1-metil-3-fenil-propilamina. MS (M+H, 284.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 2.7 µM, y cuando está presente en 03 µM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 7.

523.

Ejemplo 112

Ácido Benzo[1,3] dioxol-5-carboxílico [2-(4-etil-fenil)-etil]-amida

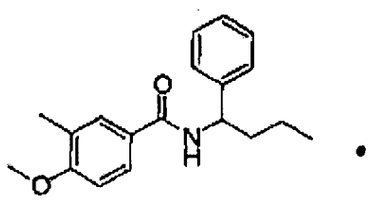


Se prepara de una forma similar al ejemplo 4 utilizando ácido benzo[1,3] dioxol-5-carboxílico y 2-(4-etil-fenil)-etilamina. MS (M+H, 298.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 3.86 μM.

Ejemplo 113

4-Metoxi-3-metil-N-(1-fenil-butil)-benzamida



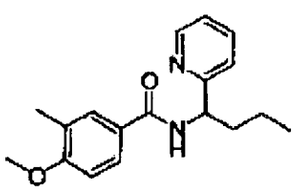
Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-metoxi-3-metil-benzoico y 1-fenil-butilamina. MS (M+H, 298.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 2.5 μM.

S24

Ejemplo 114

4-Metoxi-3-metil-N-ri-Piridin-2-il-butil)-benzamida

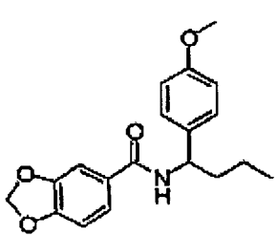


Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-metoxi-3-metil-benzoico y 1-piridin-2-il-butilamme. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.91-0.92 (t, 3H), 1.25-1.3 (m, 2H, 1.85-1.9 (m, 2H), 3.86 (s, 3H), 5.25-5.3 (m, 1H), 6.80-6.82 (d, 1H), 7.2-7.3 (m, 2H), 7.42-7.44 (d, 1H), 7.6-7.7 (m, 3H), 8.6 (d, 1H). MS (M+H, 299.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.54 μM.

Ejemplo 115

Ácido Benzo[1,,3]dioxol-5-carboxílico [1-(4-metoxi-fenil)-butill-amida



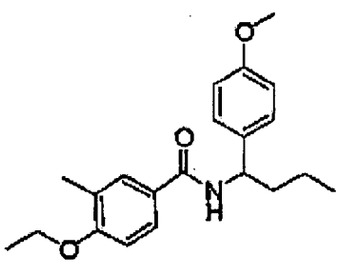
Se prepara de una forma similar al ejemplo 4 utilizando ácido benzo[1,3]dioxol-5-carboxílico y 1-(4-metoxi-fenil)-butilamina ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93-0.95 (t, 3H), 1.30-1.39 (m, 2H), 1.80-1.90 (m, 2H), 3.79 (s, 3H),

5.08-5.09 (dd, 1H), 6.00 (s, 2H), 6.10-6.12 (d, 1H), 6.79-6.80 (d, 1H), 6.87(s, 1H), 6,88 (s, 1H), 7.25-7.28 (m, 4H). MS (M+H, 328.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 4.12 μM.

Ejemplo 116

4-Etoxi-N-[l-(4-metoxi-fenil)-butill-3-metil-benzamida



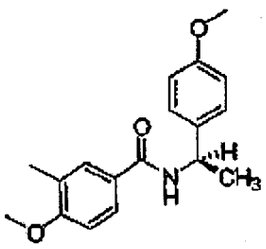
Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-etoxi-3-metil-benzoico y 1-(4-metoxi-fenil)-butilamina. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93-0.96 (t, 3H), 1.31-1.41 (m, 2H), 1.41-1.45 (t, 3H), 1.82-1.92 (m, 2H), 2.28 (s, 3H), 3.79 (s, 3H), 4.04-4.08 (q, 2H), 5.10-5.12 (d, 1H), 6.12-6.14 (d, 1H), 6.78-6.80 (d, 1H), 6.87 (s, 1H), 6.88 (s, 1H), 7.26-7.29 (m, 2H), 7.52-7.53 (d, 1H), 7.57-7.59 (d, 1H). MS (M+H, 342.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 3.9 μM.

Ejemplo 117

4-Metoxi-N-[1-(R)-(4-metoxi-fenil)-etil)-3-metil-benzamida

S 26

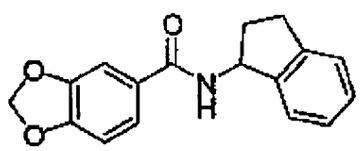


Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-metoxi-3-metil-benzoico y 1-(R)-(4-metoxi-fenil)-etilamina. MS (M+H, 300.1).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 2.8 μM.

Ejemplo 118

Benzo[1,3]dioxol-5-carboxílico indan-1-ilamida



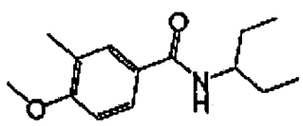
Se prepara de una forma similar al ejemplo 4 utilizando ácido benzo[1,3]dioxol-5-carboxílico y indan-1-ilamina. MS (M+H, 282.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.2 μM, y cuando está presente en 0.3 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 5.33.

Ejemplo 119

527

4-metoxi-3-metil-N-(pentan-3-il)benzamida

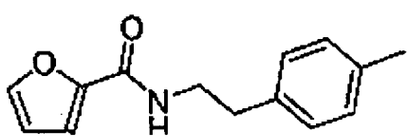


Se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido 4-metoxi-3-metilbenzoico y pentan-3-amina. MS (M+H, 236)

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.4 μM.

Ejemplo 120

3-metil-N-(p-toliletil)furano-2-carboxamida

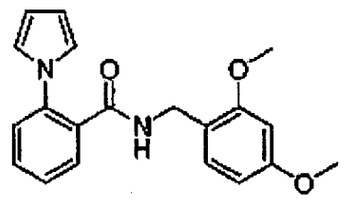


Se prepara en una forma similar como se describe en el ejemplo 4 a partir de ácido 3-metilfurano-2-carboxílico y 2-p-toliletanamina. MS (M+H, 244).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 6 μM, y cuando está presente en 1 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 3.3.

Ejemplo 121

N-(2,4-dimetoxiBencil)-2-(1H-pirrol-1-il)benzamida

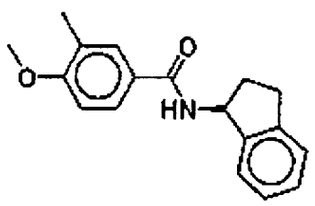


Se prepara de una forma similar al ejemplo 4 utilizando 1-(2-(1H-pirrol-1-il)fenil)etanona y 2,4-dimetoxi-bencilamina. MS (M+H, 337.2).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.66 µM, y cuando está presente en 1 µM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 11.

Ejemplo 121-1

(S)-N-(2,3-Dihidro-1H-inden-1-il)-4-metoxi-3-metilbenzamida



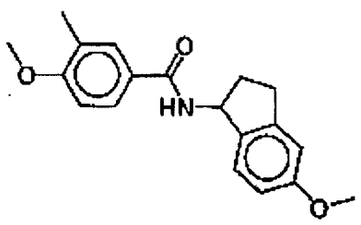
Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-metoxi-3-metilbenzoico y (S)-2,3-dihidro-1H-inden-1-amina. Rendimiento 63% ^{1}H RMN (500 MHz, *d*MSO): δ 1.94-1.99 (m, 1H), 2.17 (s, 3H), 2.41-2.46 (m, 1H), 2.82-2.87 (m, 1H), 2.96-3.01 (m, 1H), 3.83 (s, 3H), 5.53-5.57 (dd, 1H), 6.98-6.99 (d, 1H), 7.16-7.23 (m, 3H), 7.26-7.27 (m,1H), 7.75-7.80 (m, 2H), 8.54-8.55 (d, 1H). MS (M+H, 282).

529

El compuesto tiene activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.08 μM.

Ejemplo121-2

(R/S)-4-Metoxi-N-(5-metoxi-2,3-dihidro-1H-inden-1-il)-3-metilbenzamida



Se prepara de una forma similar al ejemplo 4 utilizando ácido 4-metoxi-3-metilbenzoico y 5-metoxi-2,3-dihidro-1H-inden-1-amina (Ejemplo 121-2a)(47%). MS (M+H, 312).

El compuesto tiene activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.08 μM.

Ejemplo 121-2a: 5-metoxi-2,3-dihidro-1H-inden-1-amina

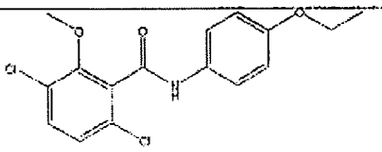
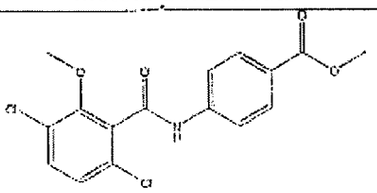
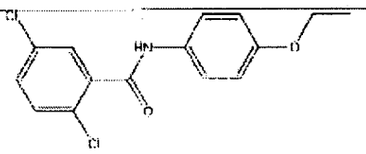
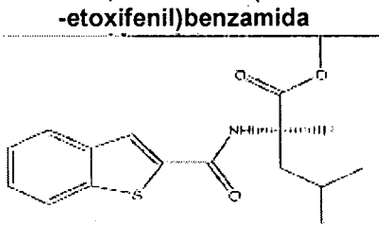
Se agrega 5-Metoxi-2,3-dihidroinden-1-ona (lg, 6.17mmol) a una solución de hidroxilamina HCl (730mg, 10.5mmol) en 10 ml de agua. La mezcla se conduce hasta 70° C y se agrega una solución de acetato de sodio (1.4g, 16.7mmol) en 7mL de H_20, 14ml de MeOH, 3ml de THF. Después de agitación durante 1.5 h a 70°C, se agrega 10ml de H_2O para producir un precipitado y la suspensión se le permite agitar durante 2 h. El precipitado se recolecta por filtración para dar 5-metoxi-2,3-dihidroinden-1-ona oxima siempre cuantitativamente y se utiliza en la

S30

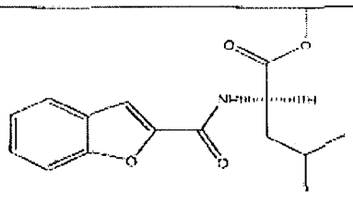
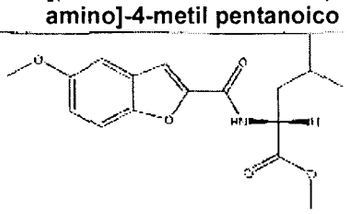
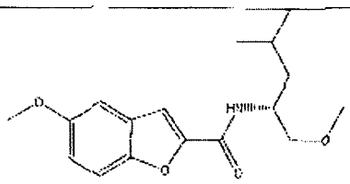
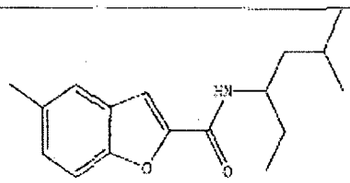
siguiente etapa sin purificación adicional. La oxima (0.5g, 2.82mmol) se disuelve en MeOH y una cantidad catalítica de niquel Raney y se agrega 25mL de solución de amoniaco en MeOH (7N). La reacción se agita a t.a. durante la noche bajo H_2. se filtra la suspensión sobre celita y se concentra en vacío, con EtOAc, se lava con agua y solución salina, se seca sobre $MgSO_4$, se filtra, y se concentra en vacío para dar la amina cruda del título (rendimiento, 45%). El crudo amina se utiliza sin purificación adicional.

Compuestos de "amida" adicional que se sintetizan y se ensayan experimentalmente y se ha encontrado que tienen un nivel relativamente alto de eficacia como un activador de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK 293. Los resultados de tales ensayos se muestran adelante en la Tabla A.

531

Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A1	 3,6-Dicloro-N-(4-etoxi-fenil)-2-metoxi-benzamida	0.22	2.74	1
A2	 éster de metilo de ácido 4-(3,6-Dicloro-2-metoxi-benzoilamino) benzoico	0.93	6.98	0.01
A3	 2,5-dicloro-N-(4 -etoxifenil)benzamida	1.08	6.14	0.03
A4	 éster de metilo de ácido [(benzo[b]tiofeno-2-carbonilo)-amino]-4-metil pentanoico	0.4		

532

Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (µM)	Proporción Ec50(Vs.MSG)	@(µM)
A5	 éster de metilo de ácido [(benzofurano-2-carbonil)-amino]-4-metil pentanoico	0.31		
A6	 éster de metilo de ácido 2-[(5-Metoxi-benzofurano-2-carbonil)-amino]-4-metil-pentanoico	0.32	2.86	1
A7	 (R)-5-metoxi-N-(1-metoxi-4-metilpentan-2-il)benzofuran-2-carboxamida	0.46		
A8	 5-metil-N-(5-metilhexan-3-il) benzofuran-2-carboxamida	0.5		

533

Tabla A - Amidas Umami

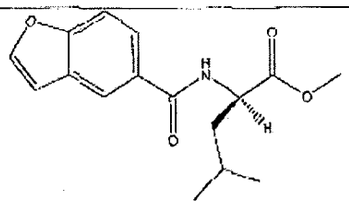
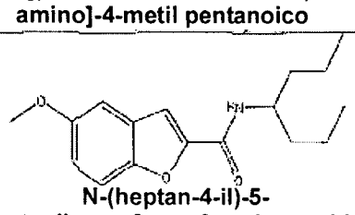
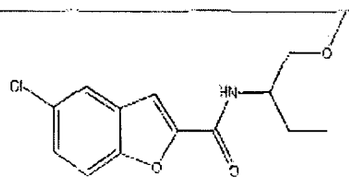
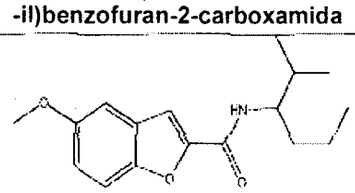
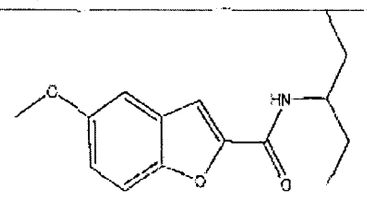
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A9	 (R)-metil 2-(benzofuran-5-carboxamido)-4-metilpentanoato de éster de metilo de ácido 2-[(benzofurano-5-carbonil)-amino]-4-metil pentanoico	0.71		
A10	 N-(heptan-4-il)-5-metoxibenzofuran-2-carboxamida	0.91	4.51	1
A11	 5-cloro-N-(1-metoxibutan-2-il)benzofuran-2-carboxamida	1.05	6.5	0.3
A12	 5-metoxi-N-(2-metilhexan-3-il)benzofuran-2-carboxamida	1.13		
A13	 5-metoxi-N-(pentan-3-il)benzofuran-2-carboxamida	1.14	4.46	1

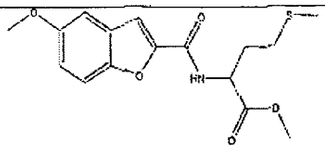
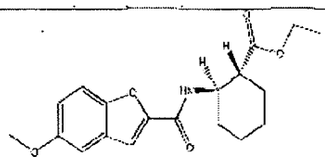
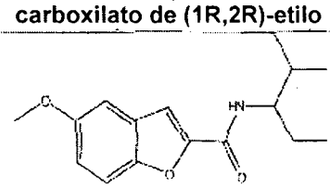
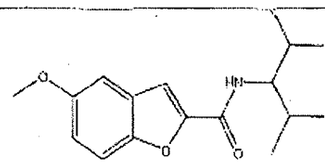
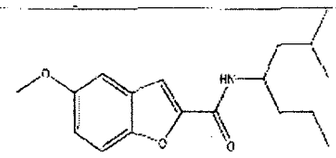
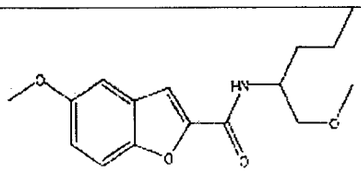
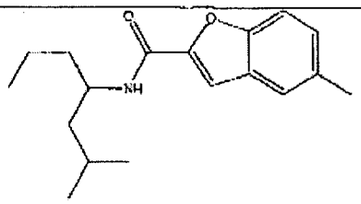
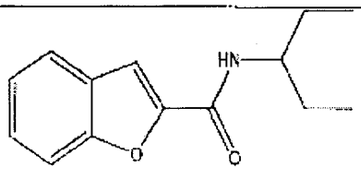
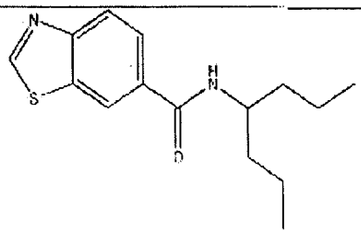
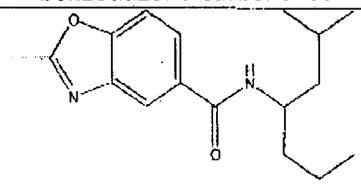
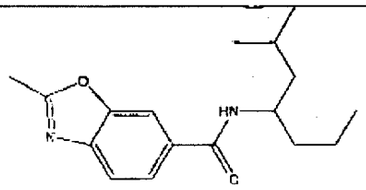
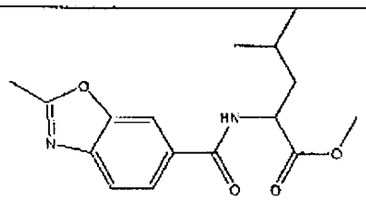
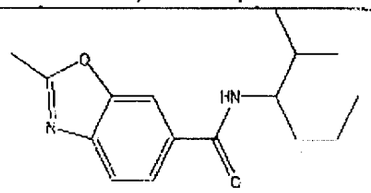
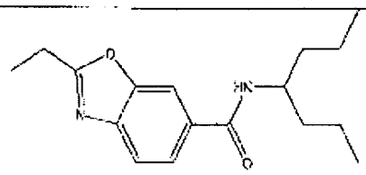
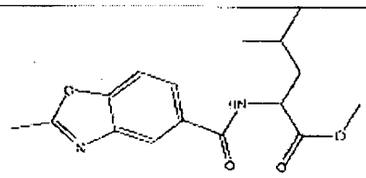
Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A14	 metil 2-(5-metoxibenzofuran-2-carboxamido)-4-(metiltio)butanoato de éster de metilo de ácido 2-[(5-Metoxi-benzofuran-2-carbonil)-amino]-4-metilsulfanil-butírico	1.14		
A15	 2-(5-metoxibenzofuran-2-carboxamido)ciclohexano carboxilato de (1R,2R)-etilo	1.14		
A16	 5-metoxi-N-(2-metilpentan-3-il)benzofuran-2-carboxamida	1.18		
A17	 N-(2,4-dimetilpentan-3-il)-5-metoxibenzofuran-2-carboxamida	1.2		
A18	 5-metoxi-N-(2-metilheptan-4-il)benzofuran-2-carboxamida	1.27		

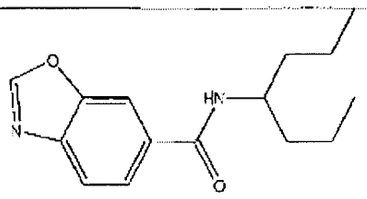
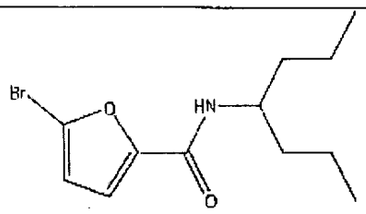
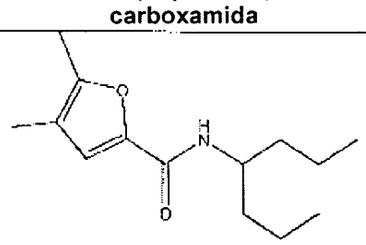
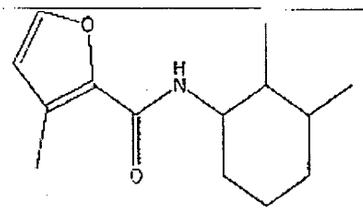
Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A19	 5-metoxi-N-(1-metoxipentan-2-il) benzofuran-2-carboxamida	1.3		
A20	 5-metil-N-(2-metilheptan-4-il) benzofuran-2-carboxamida	1.32		
A21	 N-(pentan-3-il) benzofuran-2-carboxamida	1.52	3.74	1
A22	 (1-propil-butil)amida de ácido benzotiazol-6-carboxólico	1.58		
A23	 2-metil-N-(2-metilheptan-4-il)benzo[d]oxazol-5-carboxamida	0.38		

536

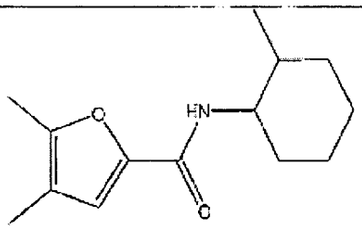
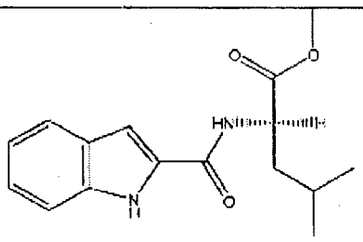
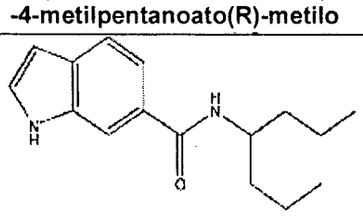
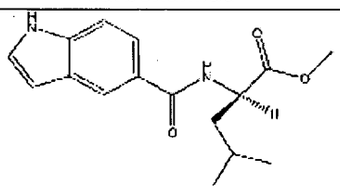
Tabla A - Amidas Umami

Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A24	 2-metil-N-(2-metilheptan-4-il)benzo[d]oxazol-6-carboxamida	1.12		
A25	 metiléster de ácido (R)-4-metil-2-[(2-metil-benzooxazol-6-carbonil)-amino]pentanoico	1.48		
A26	 2-metil-N-(2-metilhexan-3-il)benzo[d]oxazol-6-carboxamida	1.6		
A27	 2-etil-N-(2-heptan-4-il)benzo[d]oxazol-6-carboxamida	1.61		
A28	 metiléster de ácido (R)-4-metil-2-[(2-metil-benzooxazol-5-carbonil)-amino]pentanoico	1.69		

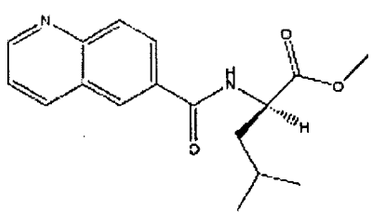
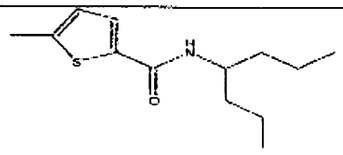
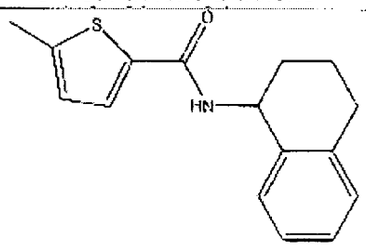
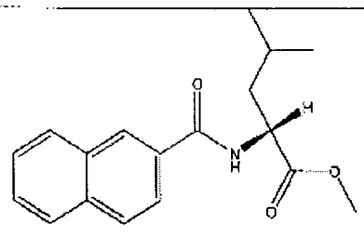
537.

Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A29	 N-(heptan-4-il)benzo[d]oxazol-6-carboxamida	1.91		
A30	 5-bromo-N-(heptan-4-il)furan-2-carboxamida	0.49	12.6	1
A31	 N-(heptan-4-il)-4,5-dimetilfuran-2-carboxamida	0.62	10.04	1
A32	 N-(2,3-dimetilciclohexil)-3-metilfuran-2-carboxamida	1.15		

538.

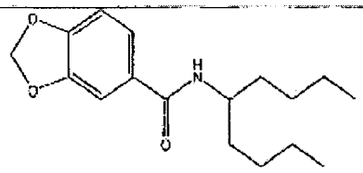
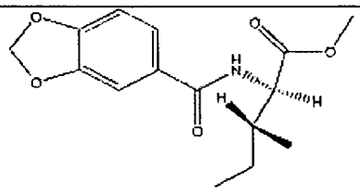
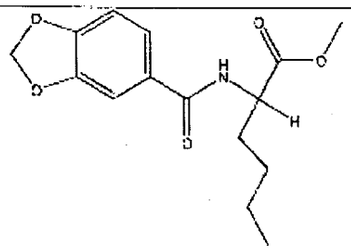
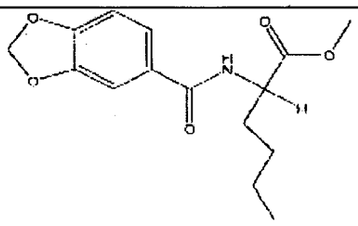
Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A33	 4,5dimetil-N-(2-metilciclohexil) furan-2-carboxamida	1.33		
A34	 2-(1H-indol-2-carbixamido) -4-metilpentanoato(R)-metilo	0.53		
A35	 N-(heptan-4-il)-1H-indol-6-carboxamida	0.82	8.81	1
A36	 2-(1H-indole-5-carboxamido)-4-metilpentanoato (R)-metilo	1.01		

539.

Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A37	 4-metil-2-(quinolino-6-carboxamido) pentanoato (R)-metilo	1.5		
A38	 (1-propil-butil)-amida de ácido 5-metil-tiofeno-2-tiofeno	1.22	6.54	1
A39	 (1,2,3,4-tetrahidro-naftalen-1-il)-amida de ácido 5-metil-tiofeno-2-carboxílico	1.31	2.3	1
A40	 2-(2-naftamido)-4-metilpentanoato de (R)-metilo	0.37		

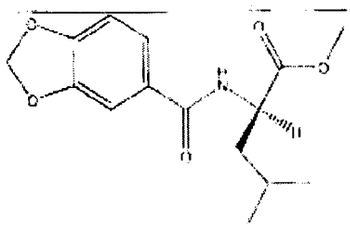
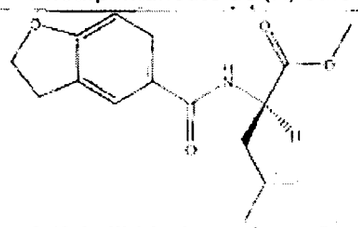
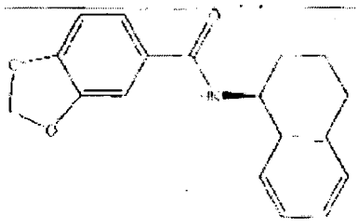
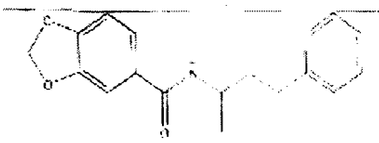
S40

Tabla A - Amidas Umami

Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A41	 N-(nonan-5-il)benzo[d][1,3]dioxol-5-xarboxamida	0.7	2.14	3
A42	 2-(benzo[d][1,3]dioxol-5-carboxamido)-3-metilpentanoato de (2R,3R)-metilo	0.35		
A43	 metiléster de ácido 2-(benzo[d][1,3]dioxol-5-carbonil)-amino]hexamoico	0.49		
A44	 metiléster de ácido (R)-2-[1,3]dioxol-5-carbonil) -amino]hexanoico	0.61		

 S 41

Tabla A - Amidas Umami

Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A45	 2-(benzo[d][1,3]diozol-5-carboxamido)-4-netilpentanoato de (R)-etilo	0.88		
A46	 2-(2,3-dihidrobenzofuran-5-carboxamido)-4-metilpentanoato de (R)-metilo	1.32		
A47	 (S)-N-(1,2,3,4-tetrahidronaftalen-1-il) benzo[d][1,3]dioxol-5-carboxamida	1.33	6.42	0.1
A48	 n-(4-fenilbutan-2-il)benzo[d][1,3]dioxol-5-carboxamida	1.51	9.27	1

S42

Tabla A - Amidas Umami

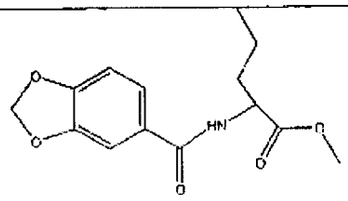
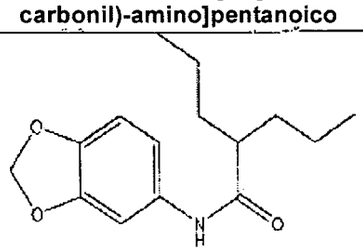
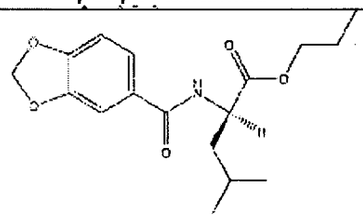
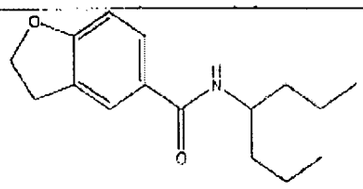
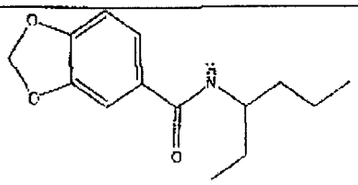
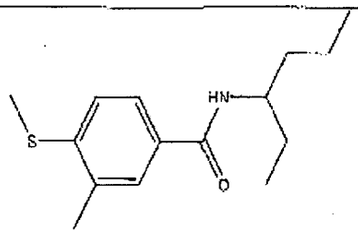
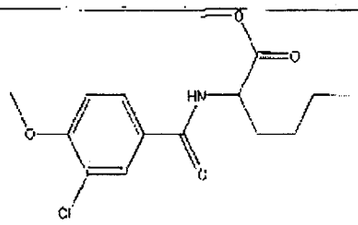
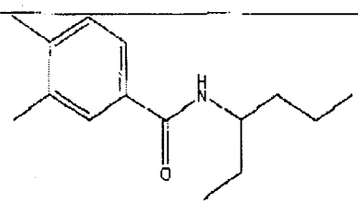
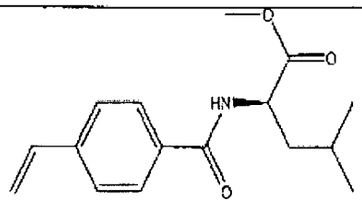
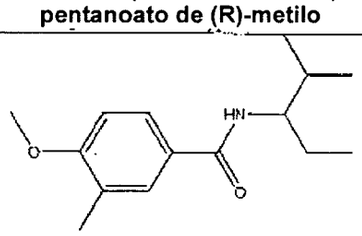
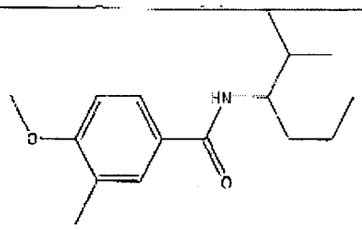
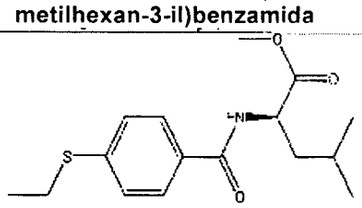
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A49	 metiléster de ácido 2-[1,3]dioxazol-5-carbonil)-amino]pentanoico	1.54	9.53	1
A50	 N-benzo[d]1,3]dioxo-5-il)-2-polipentanamida	1.57		
A51	 2-(benzo[d][1,3]dioxol-5-carboxamido de (R)propilo	1.58		
A52	 N-(heptan-4-il)-2,3-dihidrobenzofuran -5-carboxamida	1.65		

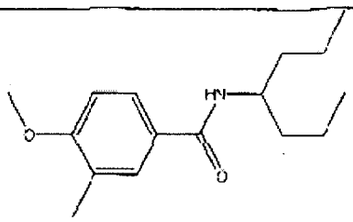
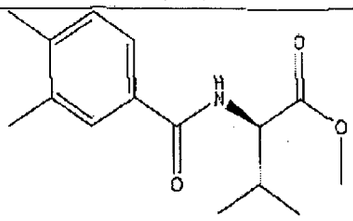
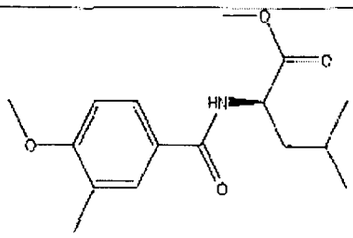
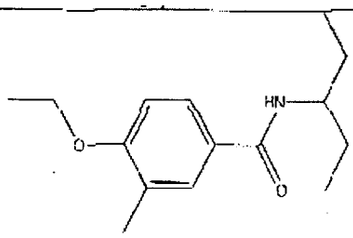
Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A53	 N-(hexan-3-il)benzo[d] [1,3]dioxol-5-carboxamida	1.83		
A54	 N-(hexan-3-il)-3-metil-4-(metiltio)benzamida	0.12		
A55	 2-(3-cloro-4-metoxibenzamido) hexanoato de metilo	0.12		
A56	 N-(hexan-3-il)-3,4-ilmetilbenzamida	0.14		

544

Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A57	 4-metil-2-(4-vinilbenzamido) pentanoato de (R)-metilo	0.18		
A58	 4-metoxi-3-metil-N-(2-metilpentan-3-il)benzamida	0.2		
A59	 4-metoxi-3-metil-N-(2-metilhexan-3-il)benzamida	0.2		
A60	 2-(4-(etiltio)benzamido)-4-metil pentanoato de (R)-metilo	0.2		

545

Tabla A - Amidas Umami

Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A61	 N-heptan-4-il)-4-metoxi-3-metilbenzamida	0.22		
A62	 2-(3,4-dimetilbenzamido) -3-metilbutanoato de (R)-metilo	0.25		
A63	 2-(4-metoxi-3-metilbenzamido)-4-metilpentanoato de (R)-metilo	0.25		
A64	 4-etoxi-3-metil-N-(pentan-3-ilbenzamida	0.26		

546

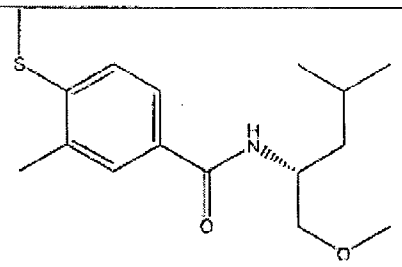
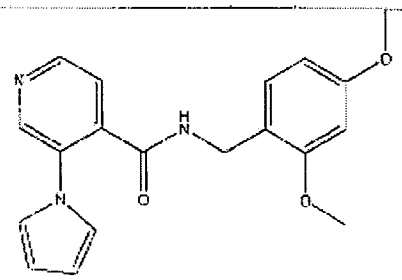
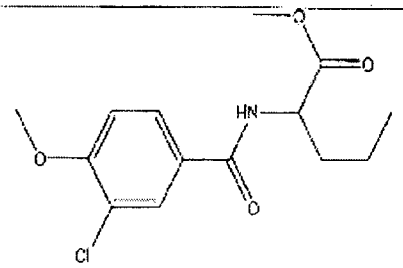
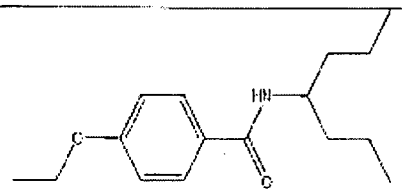
Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A65	 (R)-N-(1-metoxi-4-metilpentan-2-il-3-metil-4-(metiltio)benzamida	0.29		
A66	 N-(2,4-dimetoxibenzil)-3-(1H-pirrol-1-il)isonicotinamida	0.29		
A67	 2-(3-cloro-4-metoxibenzamido) pentanoato de metilo	0.29	10.75	1
A68	 4-etoxi-N-(heptan-4-il)benzamida	0.32	2.62	0.3

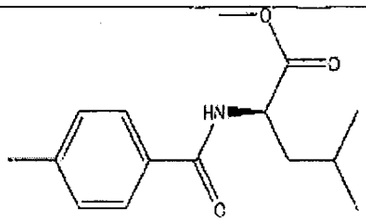
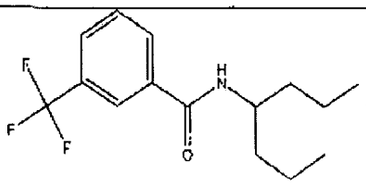
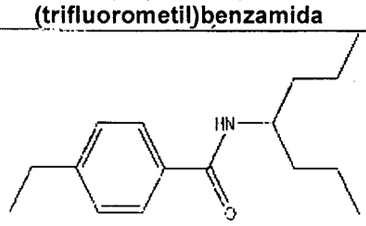
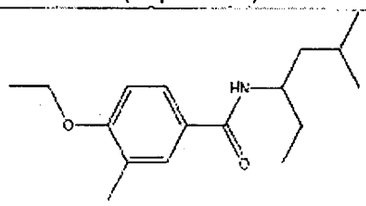
Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A69	 4-metil-2-(4-metilbenzamido) pentanoato de (R)-metilo	0.32		
A70	 N-(heptan-4-il)-3-(trifluorometil)benzamida	0.33		
A71	 4-etil-etil-N-(heptan-4-il)benzamida	0.34		
A72	 4-etoxi-3-metil-N-)5-metilhexan-3-il) benzamida	0.34		

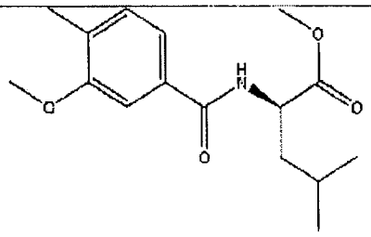
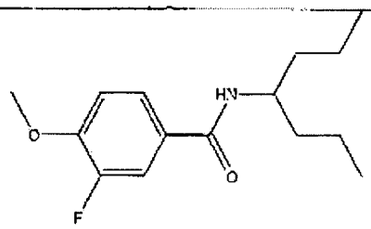
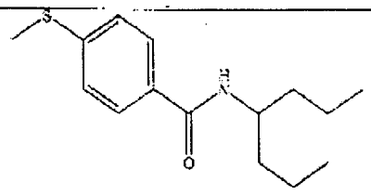
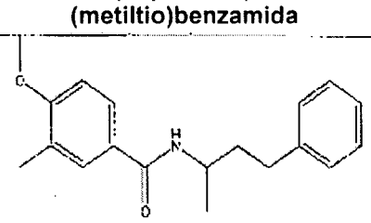
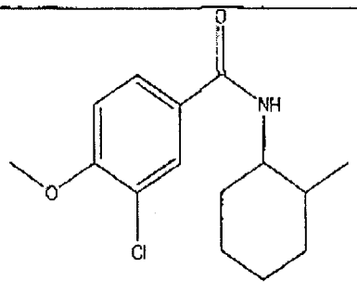
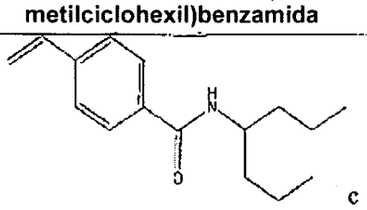
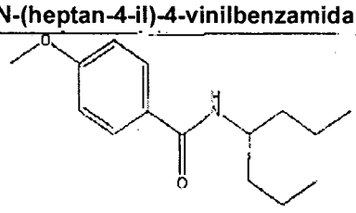
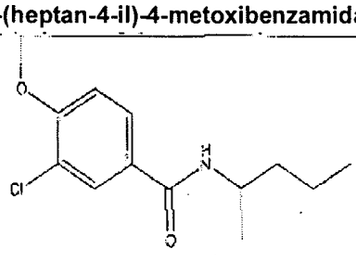
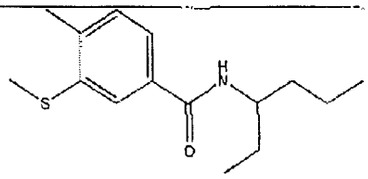
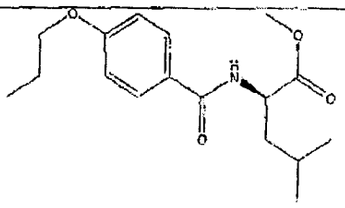
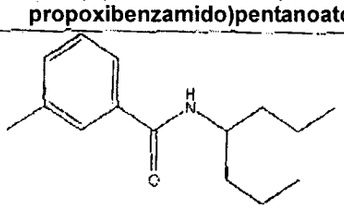
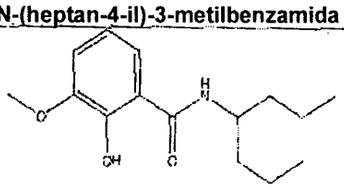
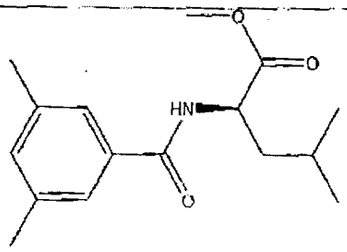
Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A73	 2-(3-metoxi-4-metilbenzamido)-4-metilpentanoato (R)-metilo	0.34		
A74	 3-fluoro-N- (heptan-4-il)-4-metoxibenzamida	0.35	4.98	0.3
A75	 N-(heptan-4-il)-4-(metiltio)benzamida	0.39		
A76	 4-metil-3-metilo-N-(4-fenilbutan-2-il)benzamida	0.4		

Tabla A - Amidas Umami

Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A77	 3-cloro-4-metoxi-N-(2-metilciclohexil)benzamida	0.44		
A78	 N-(heptan-4-il)-4-vinilbenzamida	0.46	10.22	0.3
A79	 N-(heptan-4-il)-4-metoxibenzamida	0.46		
A80	 3-cloro-4-metoxi-N-(pentan-2-il) benzamida	0.47	5.12	0.1
A81	 N-(hexan-3-il)-4-metil-3-(metiltio)benzamida	0.5		

550.

Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A82	 (R)-metil-4-metil-2-(4-propoxibenzamido)pentanoato	0.51		
A83	 N-(heptan-4-il)-3-metilbenzamida	0.52		
A84	 N-(heptan-4-il)-2-hidroxi-3-metoxibenzamida	0.53		
A85	 (R)-metil-2-(3,5-dimetilbenzamido)-4-metilpentanoato	0.53		

551

Tabla A - Amidas Umami

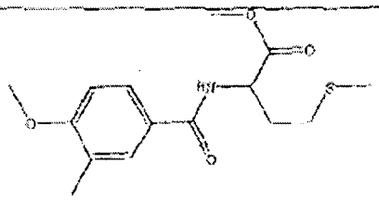
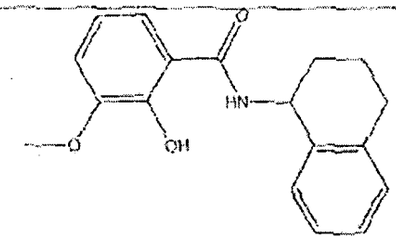
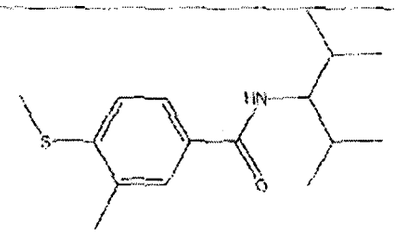
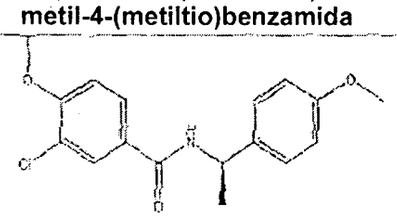
Compuesto No.	Compuesto	*Umami* EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A86	 metil 2-(4-metoxi-3-metilbenzamido)-4-(metiltio)butanoato	0.53		
A87	 2-hidroxi-3-metoxi-N-(,3,4-tetrahidronaftalen-1-il)benzamida	0.54	3.8	1
A88	 N-(2,4dimetilpentan-3-il)-3-metil-4-(metiltio)benzamida	0.55		
A89	 (R)-3-cloro-4-metoxi-N-(1-(4-metoxifenil)etil)benzamida	0.6	2.85	1

Tabla A - Amidas Umami

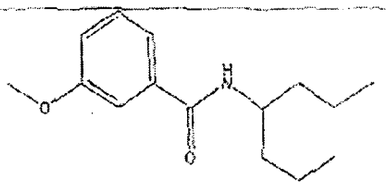
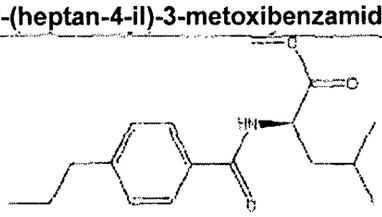
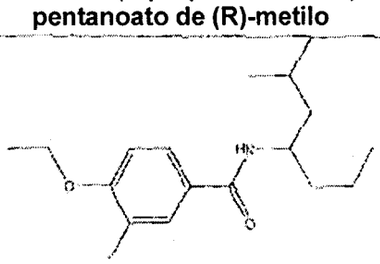
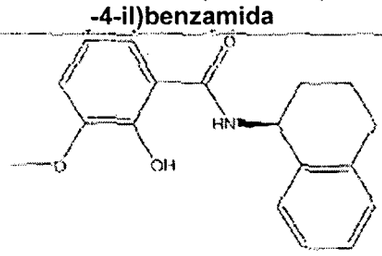
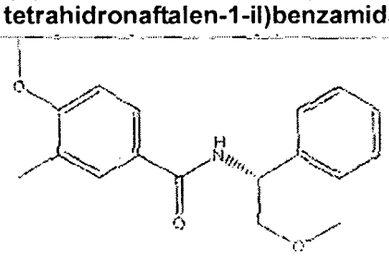
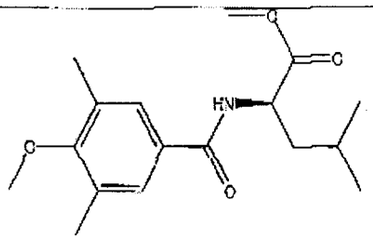
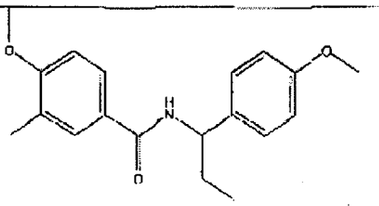
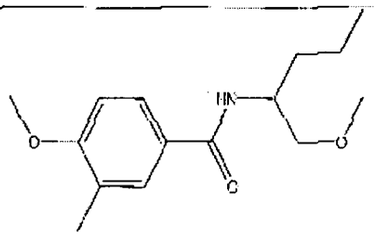
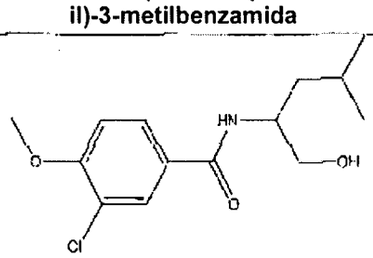
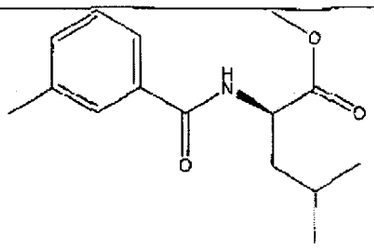
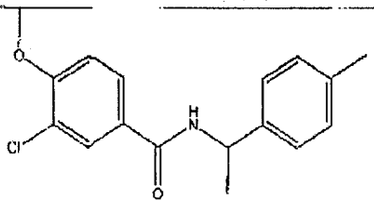
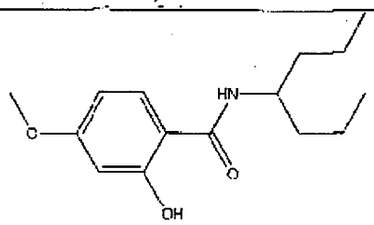
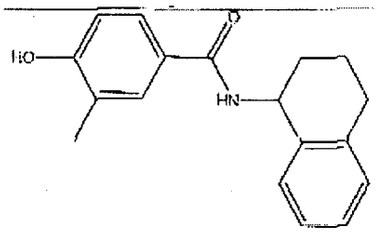
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A90	 N-(heptan-4-il)-3-metoxibenzamida	0.61		
A91	 4-metil-2-(4-propilbenzamido) pentanoato de (R)-metilo	0.62		
A92	 4-etoxi-3-metil-N-(2-metilheptan -4-il)benzamida	0.65		
A93	 (S)-2-hidroxi-3-metoxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	0.7	5.7	1
A94	 (R)-4-metoxi-N-(2-metoxi-1-feniletil)-3-metilbenzamida	0.72		

Tabla A - Amidas Umami

Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A95	 2-(4-metoxi-3,5-dimetilbenzamido) -4-metilpentanoato de (R)-metilo	0.74		
A96	 4-metoxi-N-(1-(4-metoxifenil)propil)-3-metilbenzamida	0.76		
A97	 4-metoxi-N-(1-metoxipentan-2-il)-3-metilbenzamida	0.85		
A98	 3-cloro-N-(1-hidroxi-4-metilpentan-2-il)-4-metoxibenzamida	0.88		

554

Tabla A - Amidas Umami

Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A99	 4-metilo-2-(3-metilbenzamido) pentanoato de (R)-metilo	0.89		
A100	 3-cloro-4-metoxi-N-(1-p-toliletil)benzamida	1.1		
A101	 N-heptan-4-il)-2-hidroxi-4-metoxibenzamida	1.16	7.62	I
A102	 4-hidroxi-3-metil-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	1.32	9.49	I

555

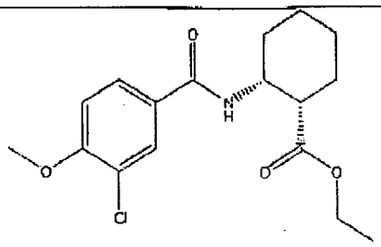
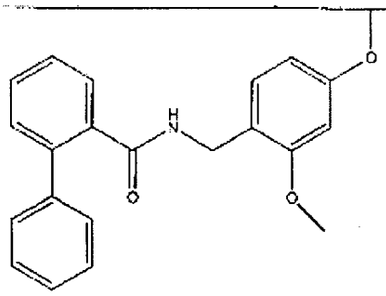
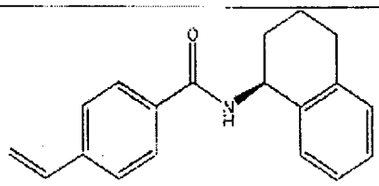
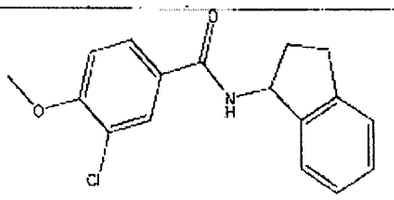
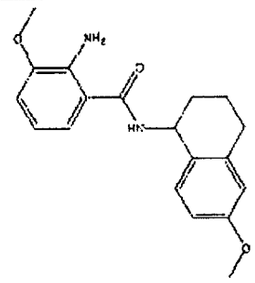
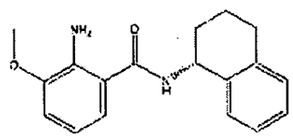
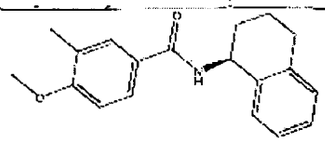
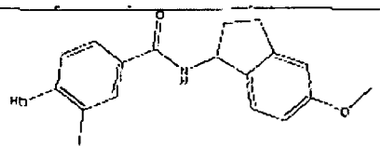
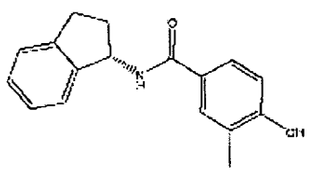
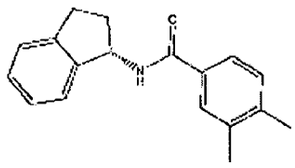
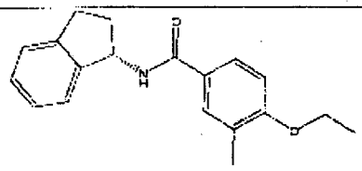
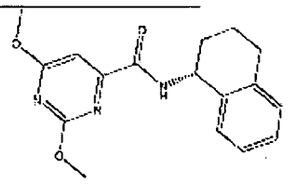
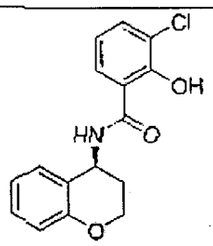
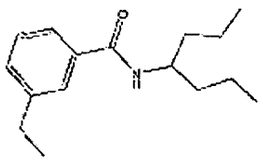
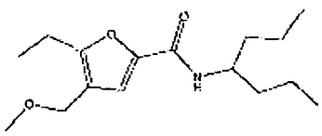
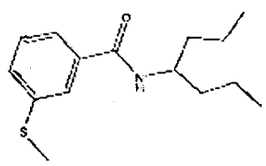
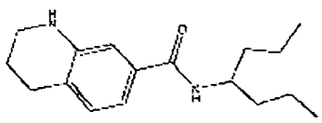
Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A103	 2-(3-cloro-4-metoxibenzamida) de (1S,2R)-etilo ciclohexanoocarboxilato	1.36		
A104	 2,4-dimetoxi-benzilamida de ácido bifenil-2-carboxílico	1.37		
A105	 (S)-N-(1,2,3,4-tetrahidronaftalen-1-il) vinilbenzamida	1.38	2.79	1
A106	 3-cloro-N-(2,3-dihidro-1H-inden-1-il-4-metoxibenzamida	1.39	4.01	0.3

Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A107	 2-amino-3-metoxi-N-(6-metoxi 1,2,3,4-tetrahidronaftalen-1-il)benzamida	0.07		
A108	 (R)-2-amino-3-metoxi-N-(1,2,3,4-tetrahidronaftalen-1-)benzamida	0.09		
A109	 (S)-4-metoxi-3-metil-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	0.08		
A110	 4-hidroxi-N-(5-metoxi-2,3-dihidro-1H-inden-1-il)-3-metilbenzamida	0.3		

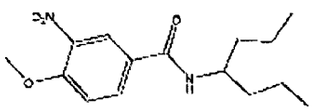
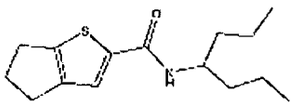
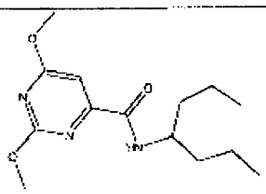
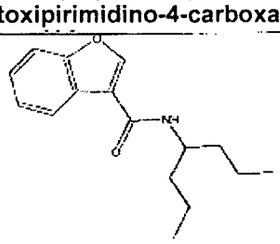
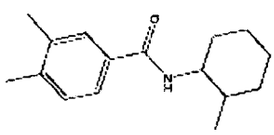
557

Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A111	 (S)-N-(2,3-dihidro-1H-inden-1-il)-4-hidroxi-3-metilbenzamida	0.66		
A112	 (S)-N-(2,3-dihidro-1H-inden-1-il)-3,4-dimetilbenzamida	0.79		
A113	 (S)-N-(2,3-dihidro-1H-inden-1-il)-4-etoxi-3-metilbenzamida	0.85		
A114	 (R)-2,6-dimetoxi-N-(1,2,3,4-tetrahidronaftalen-1-il)pirimidino-4-varboxçilico	2.35		

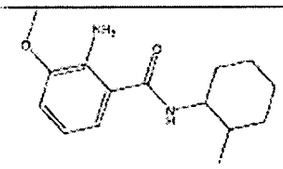
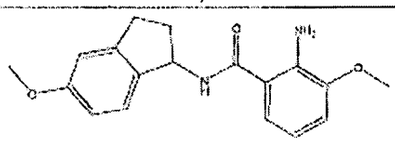
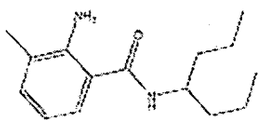
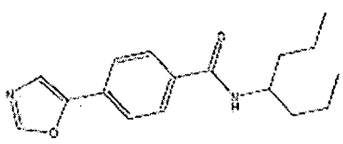
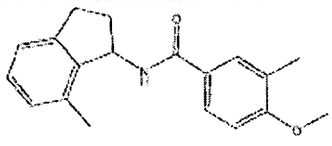
5582

Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A115	 (s)-3-cloro-N-(croman-4-il)-2-hidroxibenzamida	5.0		
A116	 3-etil-N-(heptan-4-il)benzamida	0.01		
A117	 5-etil-N-(heptan-4-il)-4-(metoximetil)furan-2-carboxamida	0.03		
A118	 N-(heptan-4-il)-3-(metiltio)benzamida	0.03		
A119	 N-(heptan-4-il)-1,2,3,4-tetrahidroquinolino-7-carboxamida	0.05		

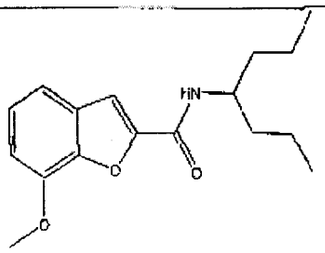
559

Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A120	 N-(heptan-4-il)-4-metoxi-3-nitrobenzamida	0.08		
A121	 N-(heptan-4-il)-5,6-dihidro-4H-ciclopenta[b]tiofeno-2-carboxamida	0.15		
A122	 N-(heptan-4-il)-2,6-dimetoxipirimidino-4-carboxamida	0.22		
A123	 N-(hepetan-4-il)benzofuran-3-carboxamida	0.51		
A124	 3,4-dimetil-N-(2-metilciclohexil)benzamida	0.01		

S60

Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A125	 2-amino-3-metoxi-N-(2-metoxiciclohexil)benzamida	0.02		
A126	 2-amino-3-metoxi-N-(5-metoxi 2,3-dihidro-1H-inden-1-il)benzamida	0.04		
A127	 2-amino-N-(heptar-4-il)-3-metilbenzamida	0.14		
A128	 N-(heptar-4-il)-4-(oxazol-5-il)benzamida	0.4		
A129	 4-metoxi-3-metil-N-(7-metil-2,3-dihidro-1H-inden-1-il)benzamida	1.03		

561

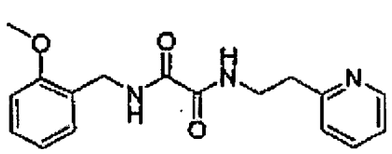
Tabla A - Amidas Umami				
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@(μM)
A130	 N-(heptan-4-il)-7-metoxibenzofuran-2-carboxamida	0.16		

Numerosos compuestos de amida de Fórmula (I) que caen dentro del alcance de compuestos de "oxalamida " compuestos descritos en cualquier parte aquí también se sintetizan y se ensayan experimentalmente para eficacia como activadores de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293

Ejemplo 122

Procedimiento general A para la preparación de una oxalamida

Síntesis de N-(2-Metoxi-bencil)-N'-(2-piridin-2-il-etil)-oxalamida



Se mezcla 2-Metoxibencilo amina (5 mmol) con trietilamina (2 equiv.) dioxano anhidro. Se agrega cloruro oxalilo de etilo (1 equiv.) y la mezcla se agita a temperatura ambiente durante 0.5-2 horas. Luego se agrega 2-(2-piridinil)etilo amina (1 equiv.) y la suspensión se calienta a 80° C durante la noche. La solución

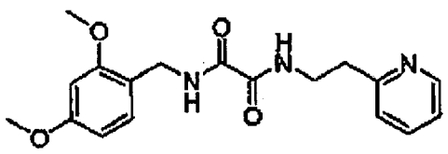
S62

se concentra y el residuo se disuelve en acetato de etilo y se lava con agua. La capa orgánica se seca por sulfato de sodio y el disolvente se evapora para dar el producto crudo, que se purifica por cromatografía de columna flash para proporcionar el compuesto del título: rendimiento 70%, p.f. 118-119° C; *m/e* = 314 [M+1]; 1H RMN ($CDCl_3$): □ 3.02 (t, 2H), 3.76 (dt, 2H), 3.86 (s, 3H), 4.47 (d, 2H), 6.80-6.90 (m, 2H), 7.14-7.18 (m, 2H), 7.20-7.30 (m, 2H), 7.55-7.62 (m, 1H), 7.75-7.83 (m, 1H), 8.05-8.12 (m, 1H), 8.55-8.63 (m, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.34 μM, y cuando está presente en 0.3 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 18.85.

Ejemplo 123

N-(2,4-Dimetoxi-bencil)-N>-(2-piridin-2-il-etil)-oxalamida

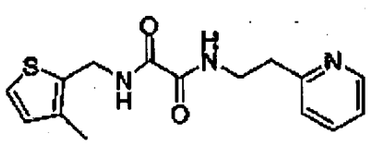


Se prepara de una forma similar al ejemplo 122 utilizando 2,4-dimetoxibencilo amina, cloruro oxalilo de etilo y 2-(2-piridinil)etilo amina. Rendimiento 72%, p.f. 123-124° C; *m/e* = 344 [M+1]; ^{1}H RMN ($CDCl_3$): δ 3.02 (t, 2H); 3.73 (dd, 2H); 3.78 (s, 3H); 3.82 (s, 3H); 4.38 (d, 2H) 6.40 (dd, 1H); 6.44 (d, 1H); 7.14 (m, 3H); 7.59 (m, 1H); 7.82 (t, 1H); 8.11 (t, 1H); 8.56 (d, 1H); ^{13}C RMN: δ 36.9, 38.9, 39.4, 55.6, 55.6, 98.8, 104.1, 117.8, 121.9, 123.5, 130.7, 136.8, 149.6, 158.8, 158.8, 159.6, 160.1, 161.0.

El compuesto tiene una activación para EC_{50} de a hT1R1/hT1R3 uniami receptor que se expresa en una línea celular HEK293 de 0.09 µM, y cuando está presente en 0.3 µM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 6.51.

Ejemplo 124

N-(3-Metil-tiofen-2-ilmetil)-N'-(2-piridin-2-il-etil)-oxalamida

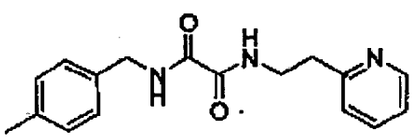


Se prepara de una forma similar al ejemplo 122 utilizando (3-metil-tiofen-2-il)-metilamina, cloruro oxalilo de etilo y 2-(2-piridinil)etilo amina. Rendimiento 40%; p.f. 122-124° C; *m/e* -304 [M+1]; ^{1}H RMN (*DMSO*-d_6): δ 2.19 (s, 3H), 2.92-2.95 (t, 2H), 3.48-3.52 (dd, 2H), 4.37-4.38 (d, 2H), 6.79-6.80 (d, 1H), 7.20-7.27 (m, 3H), 7.67-7.71 (dt, 1H), 8.48-8.49 (d, 1H), 8.87-8.89 (t, 1H), 9.25-9.28 (t, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.37 µM.

Ejemplo 125

Procedimiento general B para la séntesis de una Oxalamida N-(4-metil-Bencil)-N'-(2-piridm-2-il-etil)-oxalamida

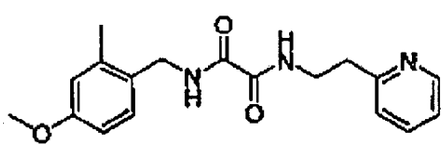


4-Metilbencilo amina (1 mmol) se le permite reaccionar con cloruro oxalilo de etilo (1 equiv.) en la presencia de trietil amina (2 equiv.) en acetonitrilo a temperatura ambiente durante 0.5 -1 hora. Luego se agrega 2-(2-piridinil)etilo amina (1 equiv.) y la suspensión se calienta a 160° C en un reactor de microondas durante 5 minutos. La mezcla de reacción se somete a HPLC preparativo para dar la oxalamida del título pura: rendimiento 60%; p.f. 152-154° C; *m/e* = 298 [M+1]; ^{1}H RMN ($CDCl_3$): δ 2.33 (s, 3H), 3.10 (t, 2H), 3.75 (dt, 2H), 4.43 (d, 2H), 7.10-7015 (m, 4H), 7.18-7.22 (m, 2H), 7.65-7.73 (m, 2H), 8.12 (b, 1H), 8.60 (d, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.41 μM.

Ejemplo 126

N-(2-Metil-4-metoxibencil)-N'-(2-piridin-2-il-etil)-oxalamida

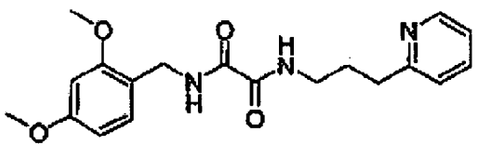


Se prepara de una forma similar al ejemplo 122 utilizando 2-metil-4-metoxibencilo amina, cloruro oxalilo de etilo y 2-(2-piridinil)etilo amina. Rendimiento 51%; p.f. 133-134° C; *m/e* = 328 [M+1]; ^{1}H RMN ($CDCl_3$): δ 2.29 (s, 3H); 3.04 (t, 2H); 3.74-3.77 (m, 2H); 3.78 (s, 3H); 4.40 (d, 2H); 6.69-6.73 (m, 2H); 7.13-7.18 (m, 3H); 7.51 (t, 1H); 7.60-7.63 (m, 1H); 8.17 (t, 1H); 8.58 (d, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.11 μM.

Ejemplo 127

N-(2,4-Dimetoxi-bencil)-N'-(3-piridin-2-il-propil)-oxalamida

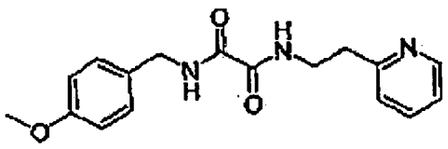


Se prepara de una forma similar al ejemplo 125 utilizando 2,4-dimetoxibencilo amina, cloruro oxalilo de etilo y 3-(2-piridinil)propilo amina. Rendimiento 60%; *m/e* = 358 [M+1]; ^{1}H RMN ($CDCl_3$): δ 1.99-2.04 (m, 2H); 2.84 (t, 2H); 3.36 (dd, 2H); 3.79 (s, 3H); 3.82 (s, 3H) 4.60 (d, 2H); 6.41-6.45 (m, 2H); 7.10-7.17 (m, 3H); 7.57-7.60 (m, 1H); 7.81 (t, 1H); 7.89 (t, 1H); 8.54 (d, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.84 μM.

Ejemplo 128

N-(4-Metoxibencil)-N'-(2-piridin-2-il-etil)-oxalamida

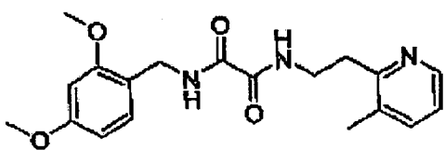


Se prepara de una forma similar al ejemplo 125 utilizando 4-metoxibencilo amina, cloruro oxalilo de etilo y 2-(2-piridinil)etilo amina. Rendimiento 50%; p.f. 156-158° C; ^{1}H RMN: 3.05 (t, 3H), 3.72-3.77 (m, 2H), 3.79 (s, 3H), 4.40 (d, 2H), 6.86 (d, 2H), 7.16-7.22 (m, 4H), 7.65-7.69 (m, 3H), 8.15 (b, 1H), 8.62 (d, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.75 µM.

Ejemplo 129

N-(2,4-Dimetoxibencil)-N'-(2-(3-metilpiridin-2-il)etil)oxalamida



Se prepara de una forma similar al ejemplo 125 utilizando 2,4-dimetoxibencilo amina, cloruro oxalilo de etilo y 2-(3-metilpiridin-2-il)etilo amina (ejemplo 129a). Rendimiento 10%; *m/e* = 358 [M+1]; ^{1}H RMN ($CDCl_3$): δ 2.28 (s, 3H), 3.01 (t, 2H), 3.75-3.82 (m, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 4.39 (d, 2H), 6.41 (dd, 1H), 6.44 (d, 1H), 7.10 (t, 1H), 7.15 (d, 1H), 7.45 (d, 1H), 7.81 (bs, 1H), 8.28 (bs, 1H), 8.40 (d, 1H).

a. 2-(3-Metilpiridin-2-il)etilo amina: A una solución de 2-(3-metilpiridina-2-il)acetonitrilo (ejemplo 129b) (95 mg, 0.72 mmol) en THF (0.5 mL) se agrega 1 M de BH_3-THF (2.2 mL, 2.2 mmol) en forma de gota a temperatura ambiente. La mezcla resultante se calienta en un reactor de microondas a 130° C durante 7 min. Luego, se agrega en forma de gota HCl acuoso 6 N (1 mL) a temperatura ambiente. La mezcla resultante se calienta en un reactor de microondas a 120° C

567

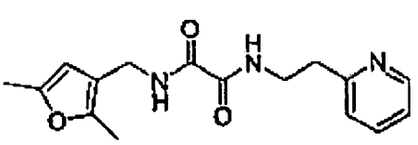
durante 4 min. La mezcla de reacción se lava con Et_2O (3x3 mL), luego se enfría a 0° C y se agrega NaOH acuoso 10 N (0.8 mL). La solución acuosa se satura con K_2CO_3. El producto se extrae con $CHCl_3$ (6x5 mL). Los extractos orgánicos se secan (1:1 K_2CO_3/Na_2SO_4), se filtran, se concentran en vacío para proporcionar un aceite (85 mg, 86%), que se utiliza directamente en el Ejemplo 8. *m/e* = 137 [M+1].

b. 2-(3-Metilpiridin-2-il)acetonitrilo: A una solución de n-BuLi (2.5 N en Hexanos, 7.92 mL, 19.8 mmol) a -78° C bajo N_2 se agrega THF seco (75 mL), seguido inmediatamente por una solución de MeCN seco (1.15 mL, 21.78 mmol) en THF anhidro (30 mL) durante un periodo de 5 min. La mezcla de reacción resultante se agita continuamente a -78° C durante 1 h. Luego se agrega.2-bromo-3-metilpiridina (516 mg, 3 mmol) La mezcla de reacción resultante se agita a -78° C durante 1 h, luego se calienta a temperatura ambiente, y se apaga con agua. El disolvente orgánico se evapora en vacío, disuelto en CH_2Cl_2. La capa orgánica se lava con solución salina, se seca ($MgSO_4$), se concentra, se purifica por vía de cromatografía de columna (20% de EtOAc en Hexanos) para proporcionar el producto cuantitativamente: *m/e* = 133 [M+1].

El compuesto tiene una activación para EC_{50} de a hT1R1/hT1R3 uniami receptor que se expresa en una línea celular HEK293 de 1.64 µM.

Ejemplo 130

N-(2,5-Dimetil-furano-3-ilmetil)-N'-(2-piridin-2-il-etil)-oxalamida

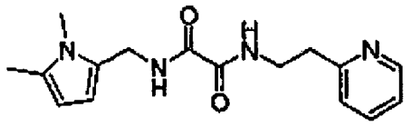


Se prepara de una forma similar al ejemplo 122 utilizando 2,5-dimetil-furano-3-ilmetilamina, cloruro oxalilo de etilo y 2-(2-piridinil)etilo amina. Rendimiento 51%; p.f. 112-115° C; *m/e* = 302 [M+1]; ^{1}H RMN (*DMSO-d*$_6$): δ 2.14 (s, 3H), 2.18 (s, 3H), 2.91-2.94 (t, 2H), 3.47-3.51 (dd, 2H), 3.98-3.99 (d, 2H), 5.89 (s, 1H), 7.20-7.25 (m, 2H), 7.68-7.71 (dt, 1H), 8,48-8.49 (d, 1H), 8.81-8.84 (t, 1H), 8.97-9.00 (t, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.01 μM.

Ejemplo 131

N-(1,5-Dimetil-1H-pirrol-2-ilmetil)-N'-(2-piridin-2-il-etil)-oxalamida

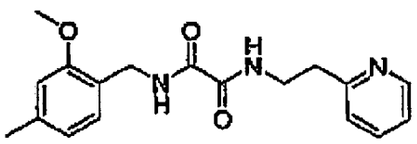


Se prepara de una forma similar al ejemplo 122. utilizando 1,5 -dimetil-1H-pirrol-2-ilmetilo amina, cloruro oxalilo de etilo y 2-(2-piridinil)etilo amina. Rendimiento 25%; p.f. 147-149° C; *m/e* = 301 [M+1]; ^{1}H RMN (*DMSO-d*$_6$): δ 2.11 (s, 3H), 2.92-2.95 (t, 2H), 3.38 (s, 3H), 3.48-3.52 (q, 2H), 4.24-4.25 (d, 2H), 5.64-5.65 (d, 1H), 5.79-5.65 (d, 1H), 7.20-7.25 (m, 2H), 7.68-7.71 (dt, 1H), 8.48-8.49 (d, 1H), 8.82-8.86 (m, 2H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 2.3 μM.

Ejemplo 132

N-(2-metoxi-4-metilbencil)-N'-(2-(piridin-2-il)etil)oxalamida



Se prepara de una forma similar al ejemplo 125 utilizando (2-metoxi-4-metilfenil)metanamina (ejemplo 132a), cloruro de oxalilo etilo, y 2-(2-piridinil)etilo amina, rendimiento 20%. p.f.: 128-131° C; *m/e* = 328 [M+1]; ^{1}H RMN($CDCl_3$): 2.33 (s, 3H); 3.02 (t, 2H); 3.73 (m, 2H); 3.84 (s, 3H); 4.42(d, 2H); 6.70 (m, 2H); 7.14 (m, 3H); 7.60 (m, 1H); 7.86 (s, 1H); 8.09 (s, 1H); 8.56 (d, 1H).

a. (2-metoxi-4-metilfenil)metanamina: A una solución de 2-metoxi-4-metilbenzamida (ejemplo 132b) (200 mg, 1.21 mmol) en THF (0.5 mL) se agrega lentamente 1 M BH_3 THF (2.4 ml, 2.42 mmol) a temperatura ambiente. La mezcla resultante se calienta en un reactor de microondas a 130° C durante 7 min. Luego HCl acuoso 6 N (1 mL) se agrega en forma de gota a temperatura ambiente. La mezcla resultante se calienta en un reactor de microondas a 120° C durante 4 min. La mezcla de reacción se lava con Et_2O (3x3 mL), luego se enfría a 0° C y se agrega NaOH acuoso 10 N (0.8 mL). La solución acuosa se satura con K_2CO_3. El producto se extrae con $CHCl_3$ (6x5 mL). Los extractos orgánicos se secan (1:1 K_2CO_3/Na_2SO_4), se filtran, se concentran en vacío para proporcionar 180 mg de (2-metoxi-4-metilfenil)metanamina que se utiliza directamente en el Ejemplo 11.

b. 2-metoxi-4-metilbenzamida: ácido 2-metoxi-4-metilbenzoico (500 mg, 3.01 mmol) se mezcla con clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (577 mg, 3.01 mmol) y 1-hidroxibenzotriazol (407 mg, 3.01 mmol) en 25 ml de diclorometano a t.a. y se agita durante 5 min. Se

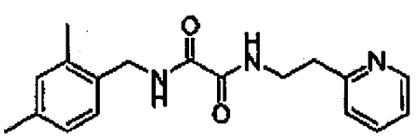
S70.

agrega solución de amoniaco en 2M metanol (4.5 ml, 9.03 mmol), la mezcla de reacción se agita a t.a. durante aproximadamente 5 hr. luego se diluye con diclorometano, se lava con HCl 1N, $NaHCO_3$ sat , agua y solución salina, se seca sobre $MgSO_4$, se filtra y se evapora para dar 440 mg de 2-metoxi-4-metilbenzamida, rendimiento 88%.

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.04 uM.

Ejemplo 133

N-(2,4-dimetilbencil)-N'-(2-(piridin-2-il)etil)oxalamida



Se prepara de una forma similar al ejemplo 125 utilizando (2,4-dimetilfenil)metanamina (ejemplo 133a), cloruro de oxalilo etilo, y 2-(2-piridinil)etilo amina, rendimiento 60%; p.f. 148-149° C; m/e= 312 [M+1]; ^{1}H RMN ($CDCl_3$): 2.28 (s, 3H); 2.30 (s, 3H); 3.05 (t, 2H); 3.76 (dd, 2H); 4.43 (d, 2H); 6.99 (m, 2H); 7.11 (d, 1H); 7.17 (m, 2H); 7.54 (s, 1H); 7.62 (m, 1H); 8.17 (s, 1H); 8.58 (d, 1H).

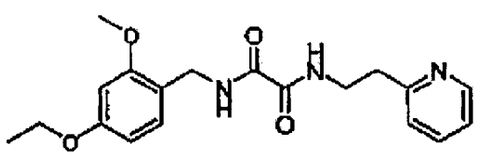
a. (2,4-Dimetilfenil)metanamina: solución de hidruro de aluminio litio 1M en THF (15.2 ml, 15.2 mmol) se coloca en un frasco pre-secado bajo argón a 0° C; se agrega en forma de gota una solución de 2,4-dimetilbenzonitrilo (1.0 g, 7.6 mmol) en 15 ml de éter anhidro. Despúes de la adición, la mezcla de reacción se calienta lentamente a t.a. y se agita durante 3 hr. luego se enfría a 0° C, se agrega sulfato anhidro de sodio, y se agrega en forma de gota 1 ml de agua. La mezcla se diluye

con acetato de etilo, la materia insoluble se filtra, el filtrado se lava con agua y solución salina, se seca sobre $MgSO_4$, se filtra y se evapora para dar 1.03 g de (2,4-dimetilfenil)metanamina pura en rendimiento cuantitativo sin purificación.

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.07 μM.

Ejemplo 134

N-(4-etoxi-2-metoxibencil)-N'-(2-(piridin-2-il)etil)oxalamida



Se prepara de una forma similar al ejemplo 125 utilizando (4-etoxi-2-metoxifenil)metanamina (ejemplo 134a), cloruro de oxalilo etilo, y 2-(2-piridinil)etilo amina; rendimiento 10%; p.f. 117-118° C; *m/e* -358 [M+1]; ^{1}H RMN ($CDCl_3$): 1.40 (t, 3H); 3.03 (t, 2H); 3.74 (dd, 2H); 3.82 (s, 3H); 4.01 (dd, 2H); 4.39 (d, 2H); 6.39 (d, 1H); 6.44 (s, 1H); 7.15 (m, 3H), 7.61 (m, 1H); 7.81 (s, 1H); 8.10 (s, 1H); 8.56 (d, 1H).

a. (4-etoxi-2-metoxifenil)memanamina: A una solución de 4-etoxi-2-metoxibenzaldehído (ejemplo 134b) (880 mg, 4.88 mmol) en 50 ml de metanol ahidro, se agregan acetato de amonio (7.5 g, 97.60 mmol) y cianoborohidruro de sodio (613 mg, 9.76 mmol). La mezcla de reacción se agita a t.a. durante aproximadamente 4 hr. Luego se concentra en un evaporador rotatorio, el residuo se diluye con agua y se basifica con 15 % de NaOH acuoso, se extrae con acetato de etilo, se lava con agua y solución salina, se seca sobre $MgSO_4$, se filtra y el disolvente se evapora, el residuo se cromatografía en columna de gel de sílice

572

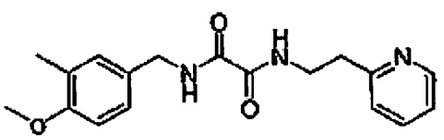
(DCM/MeOH 9:1) para proporcionar 150 mg del producto; rendimiento 17 % (El método no se puede optimizar).

b. 4-Etoxi-2-metoxibenzaldehído: A una solución de 4-hidroxi-2-metoxibenzaldehído (1.0 g, 6.57 mmol) en 10 ml de acetona, se agrega carbonato de potasio (0.91 g, 6.57 mmol) y yodoetano (1.6 ml, 19.71 mmol), la mezcla de reacción se agita a t.a. durante la noche. La acetona se remueve en un evaporador rotatorio; el residuo se diluye con agua y acetato de etilo; se extrae con acetato de etilo, se lava con solución salina, se seca sobre $MgSO_4$, se filtra y se evapora para dar el producto crudo, que se cromatografía en columna de gel de sílice (acetato de etilo/Hexano = 1:4) para dar 943 mg del producto; rendimiento 80%.

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.1 μM.

Ejemplo 135

N-(4-Metoxi-3-metilbencil)-N'-(2-(piridm-2-il)etil)oxalamida



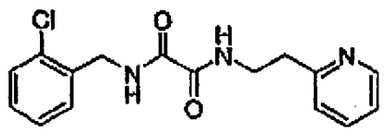
Se prepara de una forma similar al ejemplo 125 utilizando (4-metoxi-3-metilfenil)-metanamina (ejemplo 135a), cloruro de oxalilo etilo, y 2-(2-piridinil)etilo amina, rendimiento 12%; p.f. 145-147° C; m/e= 328 [M+1]; ^1H RMN ($CDCl_3$): 2.19 (s, 3H); 3.04 (t, 2H); 3.76 (dd, 2H); 3.81 (s, 3H); 4.37 (d, 2H); 6.76 (d, 1H); 7.06 (m, 2H); 7.16 (m, 2H); 7.61 (m, 1H); 7.66 (s, 1H); 8.18 (s, 1H); 8.58 (d, 1H).

a. 4-Metoxi-3-metilfenil)metanamina: Se prepara de una forma similar al ejemplo 134a utilizando 4-metoxi-3-metilbenzaldehído, acetato de amonio, y cianoborohidruro de sodio en MeOH; rendimiento 22% (110 mg).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 se expresa en una línea celular HEK293 de 1.04 μM.

Ejemplo 136

N-(2-clorobencil)-N'-(2-(piridin-2-il)etil)oxalamida:

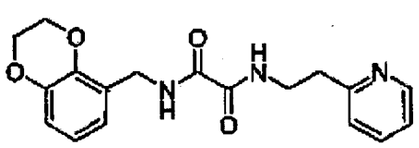


Se prepara de una forma similar al ejemplo 125 utilizando (2-clorofenil)metanamina, cloruro de oxalilo etilo, y 2-(2-piridinil)etilo amina; rendimiento 45%; *m/e* = 318 [M+1].

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.01 μM.

Ejemplo 137

N-((2,3-dihidrobenzo[b][1,4]dioxin-5-il)metil)-N'-(2-(piridin-2-il)etil) oxalamida

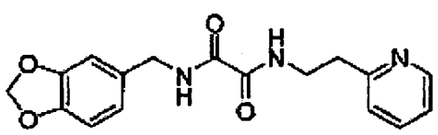


Se prepara de una forma similar al ejemplo 122 utilizando (2,3-dihidrobenzo[b][1,4] dioxin-5-il)metanamina, cloruro de oxalilo etilo, y 2-(2-piridinil)etilo amina; rendimiento 50%; *m/e* = 342 [M+1].

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.3 μM.

Ejemplo 138

N-(benzo[d][1,3]dioxol-5-ilmetil)-N'-(2-(piridin-2-il)etil)oxalamida

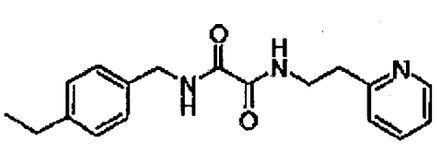


Se prepara de una forma similar al ejemplo 125 utilizando benzo[d][1,3]dioxol-5-ilmetanamina, cloruro de oxalilo etilo, y 2-(2-piridinil)etilo amina; rendimiento 35%; *m/e* = 328 [M+1].

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en en una línea celular HEK293 de 0.5 μM.

Ejemplo 139

N-(4-Etilbencil)-N'-(2-(piridin-2-il)etil)oxalamida



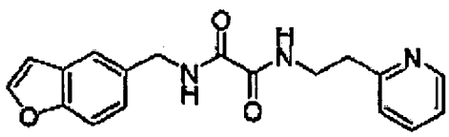
575

Se prepara de una forma similar al ejemplo 125 utilizando 4-etilbencilamina, cloruro de oxalilo etilo, y 2-(2-piridinil)etilo amina; rendimiento 38%; *m/e* = 312 [M+1].

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.79 μM.

Ejemplo 140

N-(Benzofurano-5-ilmetil)-N'-(2-(piridin-2-il)etil)oxalamida

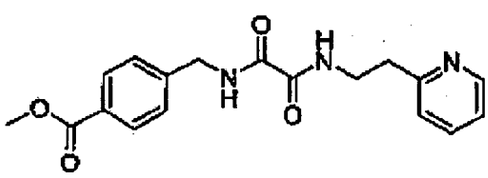


Se prepara de una forma similar al ejemplo 125 utilizando benzofurano-5-ilmetilamina, cloruro de oxalilo etilo, y 2-(2-piridinil)etilo amina; rendimiento 64%; *m/e* = 324 [M+1].

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.78 μM.

Ejemplo 141

N-((4-Metoxicarbonilfenil)metil)-N'-(2-(piridin-2-il)etil)oxalamida



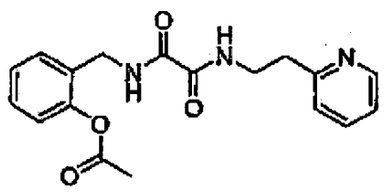
576

Se prepara de una forma similar al ejemplo 122 utilizando 4-metoxicarbonilfenilo metilamina, cloruro de oxalilo etilo, y 2-(2-piridinil)etilo amina; rendimiento 52%; *m/e* = 342 [M+1].

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 3.63 μM.

Ejemplo 142

N-((2-Carbamoilfenil)metil)-N'-(2-(piridin-2-il)etil)oxalamida

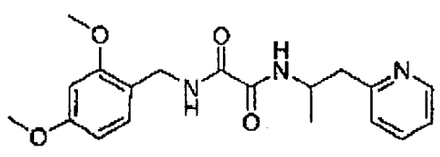


Se prepara de una forma similar al ejemplo 122 utilizando 2-Carbamoilfenilo metilamina, cloruro de oxalilo etilo, y 2-(2-piridinil)etilo amina; rendimiento 48%; *m/e* = 342 [M+1].

El compuesto tiene una activación para EC50 de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 8.5 μM.

Ejemplo 143

N-(2,4-Dimetoxibencil)-N'-(1-(piridin-2-il)propan-2-il)oxalamida



Se prepara de una forma similar al ejemplo 125 utilizando 2,4-dimetoxibencilamina, cloruro de oxalilo etilo, y 1-(piridin-2-il)propan-2-ilo amina (ejemplo 143a); rendimiento 34%; *m/e* = 357 [M+1].

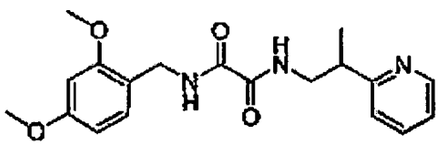
a. 1-(Piridin-2-il)propan-2-ilo amina: Se prepara de una forma similar al ejemplo 129a utilizando 2-(piridin-2-il)propanonitrilo (ejemplo 143b); el producto crudo se utiliza directamente en el ejemplo 143; rendimiento 53%; *m/e* = 137 [M+1].

b. 2-(piridin-2-il)propanonitrilo: 5 mmol de 2-(piridin-2-il)acetonitrilo se disuelve en 8 ml THF anhidro y se coloca en baño de hielo. Se agrega t-butóxido de potasio (1 equiv) y la reacción se agita durante 30 minutos. Yoduro de metilo (1 equiv) se disuelve en 5 mL THF anhidro y se agrega lentamente durante 30 minutos. La reacción se agita durante la noche a temperatura ambiente. El disolvente se evapora y la mezcla cruda se disuelve en acetato de etilo y se lava con agua. La capa de acetato de vinilo se evapora y el producto se purifica por TLC preparativo (30% de acetato de etilo/Hexano); rendimiento 71%; *m/e* = 133 [M+1].

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.4 μM.

Ejemplo 144

N-(2,4-DimetoxiBencil)-N'-(2-(piridin-2-il)propil)oxalamida



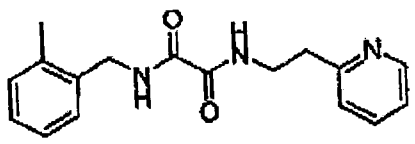
Se prepara de una forma similar al ejemplo 125 utilizando 2,4-dimetoxibencilamina, cloruro de oxalilo etilo, y 2-(piridin-2-il)propilamina (ejemplo 144a); rendimiento 35%; *m/e* = 357 [M+1].

a. 2-(piridin-2-il)propilamina: 10 mmol de 2-metilpiridina se disuelve en THF anhidro y se mantiene bajo condición inerte a 0° C. Se agrega en forma de gota butil litio (1.2 equiv) y se agita durante 15 minutos adicionales a 0° C mientras la temperatura regresa a temperatura ambiente. Después de agitación a temperatura ambiente durante 1 hora, la mezcla de reacción se enfría otra vez con 0° C y se agrega en forma de gota acetonitrilo (2 equiv). La reacción se agita durante la noche a temperatura ambiente. Después de enfriamiento la reacción a 0° C, se agrega 30 mL de metanol en la mezcla de reacción. Se agrega en porción lentamente borohidruro de sodio (3 equiv) a 0° C. La reacción se agita durante otra hora para elevar a temperatura ambiente. La mezcla de reacción se diluye con agua y se extrae exhaustivamente con acetato de etilo. Los extractos combinados se lavan con agua, solución salina y se secan sobre sulfato de sodio. Se concentra la solución y se disuelve en éter. El producto se extrae con HCl acuoso 3 N, y el extracto acídico se lava con éter y se hace básico con NaOH. El producto se extrae exhaustivamente con éter. Los extractos de éter combinados se lavan con agua y se secan sobre sulfato de sodio. El disolvente se evapora para producir producto puro suficiente; rendimiento 47%; *m/e* = 137 [M+1].

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.07 μM.

Ejemplo 145

N-(2-Metoxibencil)-N'-(2-(piridin-2-il)etil)oxalamida

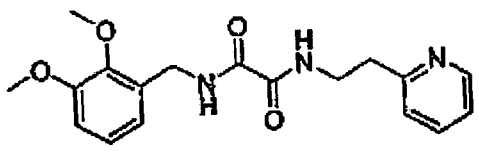


Se prepara de una forma similar al ejemplo 125 utilizando 2-metilbencilamina, cloruro de oxalilo etilo, y 2-(piridin-2-il)etilamina; *m/e* = 298 [M+1]; ^{1}H RMN ($CDCl_3$) δ 2.32 (s, 3H), 3.11 (t, 2H), 3.78 (dt, 2H), 4.46 (d, 2H), 7.15-7.26 (m, 6H), 7.50-7.55 (m, 1H), 7.62-7.67 (m, 1H), 8.12-8.15 (m, 1H), 8.60 (d, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.59 μM.

Ejemplo 146

N-(2,3-Dimetoxibencil)-N'-(2-(piridin-2-il)etil)oxalamida

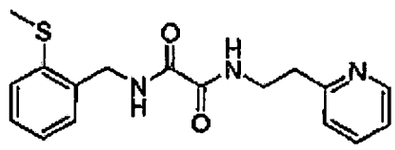


Se prepara de una forma similar al ejemplo 125 utilizando 2,3-dimetoxibencilamina, cloruro de oxalilo etilo, y 2-(piridin-2-il)etilamina; *m/e* = 343 [M+1].

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.69 μM.

Ejemplo 147

N-(2-(Metiltio)bencil)-N'-(2-(piridin-2-il)etil)oxalamida

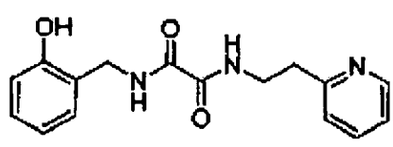


Se prepara de una forma similar al ejemplo 125 utilizando 2-metiltiobencilamina, cloruro de oxalilo etilo, y 2-(piridin-2-il)etilamina; *m/e* = 330 [M+1]; ^{1}H RMN ($CDCl_3$) δ 2.49 (s, 3H), 3.08 (t, 2H), 3.77 (dt, 2H), 4.55 (d, 2H), 7.11-7.14 (m, 1H), 7.15-7.20 (m, 2H), 7.22-7.27 (m, 3H), 7.62 (t, 1H), 7.78-7.83 (m, 1H), 8.08-8.11 (m, 1H), 8.56 (d, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.96 μM.

Ejemplo 148

N-(2-HidroxiBencil)-N'-(2-(piridin-2-il)etil)oxalamida

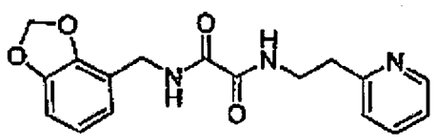


Se prepara de una forma similar al ejemplo 125 utilizando 2-hidroxibencilamina, cloruro de oxalilo etilo, y 2-(piridin-2-il)etilamina; *m/e* = 300 [M+1].

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 3.11 μM.

Ejemplo 149

N-(Benzo[d][1,3]dioxol-4-ilmetil)-N'-(2-(piridin-2-il)etil)oxalamida



Se prepara de una forma similar al ejemplo 125 utilizando benzo[d][1,3]dioxol-4-ilmetilo amina (ejemplo 149a), cloruro de oxalilo etilo, y 2-(piridin-2-il)etilo amina; rendimiento 12%; *m/e* = 328 [M+1]; ^{1}H RMN ($CDCl_3$): δ 3.12 (m, 2H), 3.77-3.80 (m, 2H), 4.46-4.47 (d, 2H), 5.98 (s, 2H), 6.74-6.79 (m, 3H), 7.24 (m, 1H), 7.7-7.8 (m, 3H), 8.10-8.15 (m, 1H), 8.58-8.59 (m, 1H).

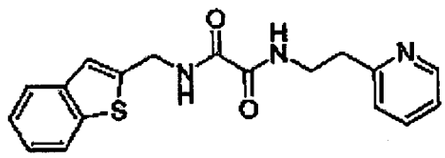
a. Benzo[d][1,3]dioxol-4-ilmetilo amina: Se prepara de una forma similar al ejemplo 134a a partir de benzo[d][1,3]dioxol-4-carbaldehído y acetato de amonio. El crudo material contiene aproximadamente. 20 % del producto (m/e = 152.2 [M+1]) y se utiliza directamente en ejemplo 149.

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.17 μM.

Ejemplo 150

S82

N-(Benzo[b]tiofen-2-ilmetil)-N'-(2-(piridin-1-il)etil)oxalamida

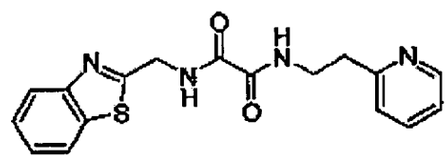


Se prepara de una forma similar al ejemplo 125 utilizando benzo[b]tiofen-2-ilmetanamina, cloruro de oxalilo etilo, y 2-(piridin-2-il)etilo amina; rendimiento 32%; *m/e* = 240 [M+1]; ^{1}H RMN (DMSO-d_6): δ 2.92-2.95 (t, 2H), 3.48-3.53 (m, 2H), 4.55-4.56 (d, 2H), 7.20-7.25 (m, 2H), 7.38-7.41 (m, 2H), 7.50 (s, 1H), 7.66-7.70 (m, 1H), 7.95-7.99 (m, 2H), 8.47-8.49 (d, 1H), 8.88-8.90 (t, 1H), 9.29-9.31 (t, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.74 μM.

Ejemplo 151

N-(Benzo[d]tiazol-2-ilmetil)-N'-(2-(piridin-2-il)etil)oxalamida

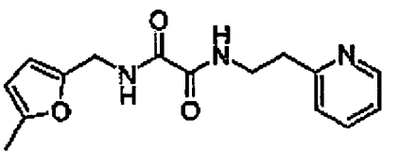


Se prepara de una forma similar al ejemplo 125 utilizando benzo[d]tiazol-2-ilmetanamina, cloruro de oxalilo etilo, y 2-(piridin-2-il)etilo amina; rendimiento 33%; *m/e*= 341 [M+1]; ^{1}H RMN (DMSO-d_6): δ 2.95-2.98 (t, 2H), 3.52-3.57 (m, 2H), 4.72-4.73 (d, 2H), 7.22-7.24 (m, 1H), 7.25-7.27 (d, 1H), 7.40-7.44 (t, 1H), 7.48-7.51 (t, 1H), 7.69-7.72 (dt, 1H), 7.95-7.96 (d, 1H), 8.05-8.07 (d, 1H), 8.49-8.50 (d, 1H), 8.96-8.98 (t, 1H), 9.67-9.70 (t, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 4.4 μM.

Ejemplo 152

N-((5-Metilfurano-2-il)metil)-N2-(2-(piridin-2-il)etil)oxalamida

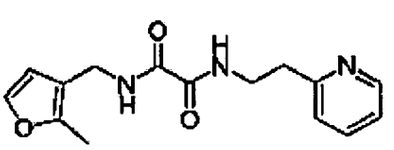


Se prepara de una forma similar al ejemplo 125 utilizando (5-metilfurano-2-il)metanamina, cloruro de oxalilo etilo, y 2-(piridin-2-il)etilo amina; rendimiento 38%; *m/e* = 288 [M+1]; ^{1}H RMN (DMSO-d_6): δ 2.20 (s, 3H), 2.92-2.95 (t, 2H), 3.48-3.52 (m, 2H), 4.23-4.24 (d, 2H),5.96-5.97 (d, 1H), 6.06-6.07 (d, 1H), 7.20-7.25 (m, 2H), 7.68-7.71 (t, 1H), 8.48-8.49 (d, 1H), 8.85-8.87 (t, 1H), 9.04-9.07 (t, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 4.9 μM.

Ejemplo 153

N-((2-Metilfurano-3-il)metil)-N'-α-(piridin-2-il)etil)oxalamida



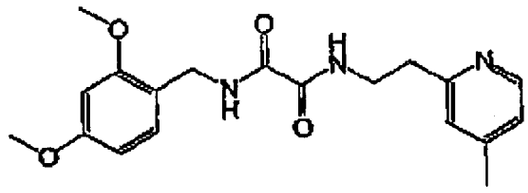
Se prepara de una forma similar al ejemplo 125 utilizando (2-metilfurano-3-il)metanamina (ejemplo 153a), cloruro de oxalilo etilo, y 2-(piridin-2-il)etilo amina; rendimiento 50%; *m/e* = 288 [M+1]; ^{1}H RMN (DMSO-d_6): δ 2.23 (s, 3H), 2.91-2.94 (t, 2H), 3.48-3.52 (q, 2H), 4.05-4.06 (d, 2H), 6.30-6.31 (d, 1H), 7.20-7.25 (m, 2H), 7.38-7.39 (d, 1H), 7.67-7.71 (dt, 1H), 8.48-8.49 (d, 1H), 8.83-8.86 (t, 1H), 9.04-9.07 (t, 1H).

a. (2-Metilfurano-3-il)metanamina: Una solución de 10 mmol (1.256 ml) de metilo 2-metilfurano-3-carboxilatoy 38.9 mmol (2.1 g) de NaOMe en 20 ml de formamida se agita a 100° C durante 30 min. La mezcla de reacción se vierte en agua helada (20 ml) y se extrae con acetato de etilo (3x). El extracto se seca sobre MgSO4 y se concentra para dar 1.05 g (83%) de 2-metilfurano-3-carboxamida como un aceite (m/e = 126.2 [M+1]). La amida se disuelve en THF seco (10 ml) y en forma de gota se agrega a 15 ml de $LiAlH_4$ 1M con 15 ml de THF a 0° C bajo argón. Luego la mezcla se agita durante 5 hrs a 60° C. Seguido por enfriamiento, 50% de THF acuoso (30 ml) se agrega a la mezcla a 5-10° C. El precipitado resiltante se remueve por filtración y la solición filtrada se seca y se concentra para dar un producto aceitoso (0.93 g, 84%).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.82 μM.

Ejemplo 154

N-(2,4-Dimetoxibencil)-N'-(2-(4-metilpiridin-2-il)etil)oxalamida



Se prepara de una forma similar al ejemplo 122 utilizando 2,4-dimetoxibencilamina, cloruro de oxalilo etilo, y 2-(4-nietilpiridin-2-il) etil o amina (ejemplo 154a); rendimiento 11%; *m/e* = 358 [M+1]; p.f. 144-145° C; ^{1} HRMN ($CDCl_3$): δ 2.31 (s, 3H), 2.97 (t, 2H), 3.71 (q, 2H), 3.79 (s, 3H), 3.83 (s, 3H), 4.39 (d, 2H), 6.40 (dd, 1H), 6.44 (d, 1H), 6.97 (s, 1H), 6.98 (d, 1H), 7.15 (d, 1H), 7.81 (br s, 1H), 8.08 (br s, 1H), 8.41 (d, 1H).

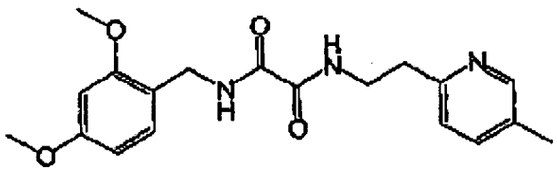
a. 2-(4-Metilpiridin-2-il) etilo amina: Se prepara de una forma similar al ejemplo 129 utilizando 2-(4-metilpiridin-2-il)acetonitrilo (ejemplo 154b); rendimiento 83%; *m/e* = 137 [M+1].

b. 2-(4-Metilpiridin-2-il)acetonitrilo: Se prepara de una forma similar al ejemplo 129b utilizando 2-bromo-4-metilpiridina, acetonitrilo y n-BuLi; rendimiento 88%; *m/e* = 133 [M+1].

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 1.64 μM

Ejemplo 155

N-(2,4-Dimetoxibencil)-N'-(2-(5-metilpiridin-2-il)etil)oxalamida



Se prepara de una forma similar al ejemplo 122 utilizando 2,4-dimetoxibencilamina, cloruro de oxalilo etilo, y 2-(5-metilpiridin-2-il)etilo amina (ejemplo 155a); rendimiento 9%; *m/e* = 358 [M+1]; p.f. 124-125° C; ^{1}H RMN ($CDCl_3$): δ 2.30 (s, 3H), 2.97 (t, 2H), 3.70 (q, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 4.38 (d, 2H), 6.40 (dd, 1H), 6.44 (d, 1H), 7.03 (d, 1H), 7.14 (d, 1H), 7.40 (dd, 1H), 7.81 (br s, 1H), 8.08 (br S, 1H), 8.38 (d, 1H).

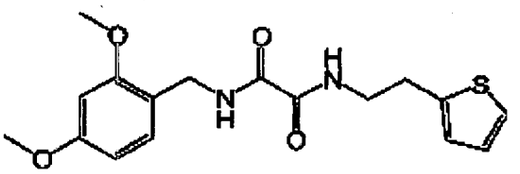
a. 2-(5-Metilpiridin-2-il)etilo amina: Se prepara en forma similar a 129a utilizando 2-(5-metilpiridin-2-il)acetonitrilo (155b); rendimiento 40%; *m/e* = 137 [M+1].

b. 2-(5-Metilpiridin-2-il)acetonitrilo: Se prepara en forma similar a 129b utilizando 2-bromo-5-metilpiridina, acetonitrilo y n-BuLi; rendimiento 68%; *m/e* = 133 [M+1].

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.07 μM.

Ejemplo 156

N-(2,4-DimetoxiBencil)-N'-(2-(tiofen-2-il)etil)oxalamida

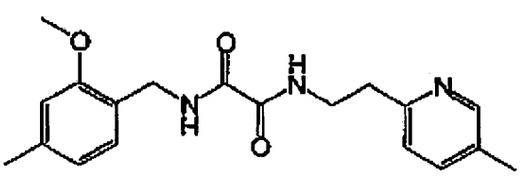


Se prepara de una forma similar al ejemplo 122 utilizando 2,4-dimetoxibencilamina, cloruro oxalilo de etilo y 2-(tiofen-2-il)etilo amina; rendimiento 72%; *m/e* = 349 [M+1]; p.f. 146-147° C; ^{1}H RMN ($CDCl_3$): δ 3.06 (t, 2H), 3.58 (q, 2H), 3.80 (s, 3H), 3.83 (s, 3H), 4.40 (d, 2H), 6.41 (dd, 1H), 6.45 (d, 1H), 6.84 (dd, 1H), 6.93 (dd, 1H), 7.15 (d, 1H), 7.16 (d, 1H), 7.61 (br s, 1H), 7.81 (br s, 1H).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 4.87 μM.

Ejemplo 157

N'-(2-metoxi-4-metilbencil)-N^2-(2-(5-metilpiridin-2-il)etil)oxalamida



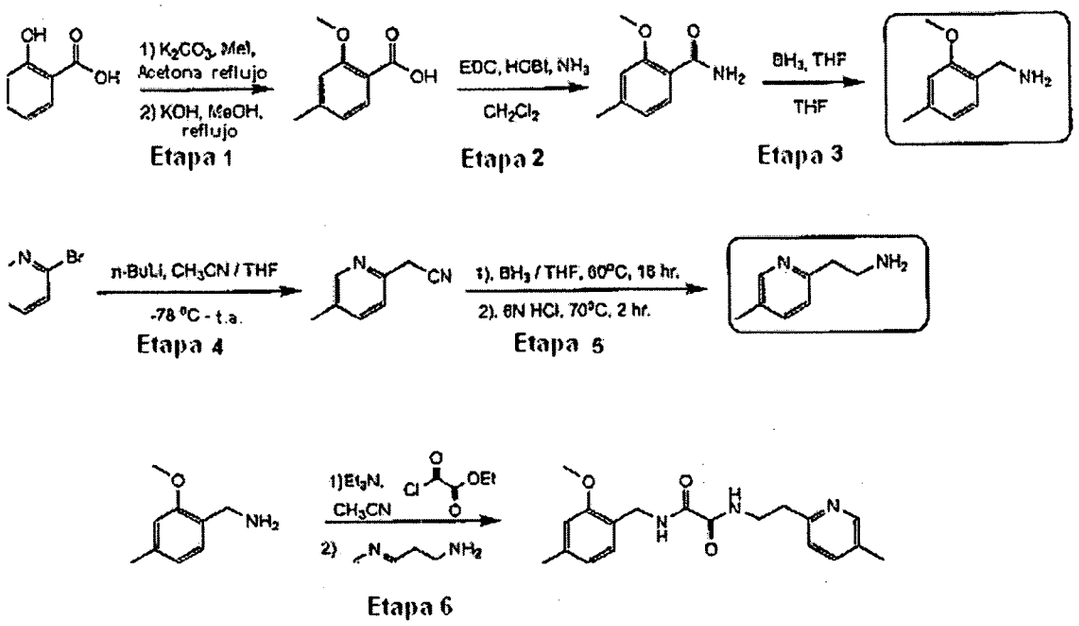
^{1}H RMN ($CDCl_3$, 500 MHz): δ 2.29 (3H, s); 2.33 (3H, s); 2.97 (2H, t, *J*= 6.5 Hz); 3.71 (2H, q, *J*= 6.5 Hz); 3.83 (3H, s); 4.40 (2H, d, *J*= 6.2 Hz); 6.68 (1H, s); 6.69 (1H, d, J = 7.7 Hz); 7.02 (1H, d, *J*= 7.9 Hz); 7.09 (1H, d, *J*= 7.5 Hz); 7.40 (1H, dd, J_1= 1.8 Hz, J_2= 7.8 Hz); 7.85 (1H, br t); 8.06 (1H, br t); 8.38 (1H, s, *J*= 7.5 Hz).

13C RMN ($CDCl_3$, 500 MHz): 18.3, 21.8, 36.5, 39.1, 39.6, 55.5, 111.5, 121.3, 122.3, 123.0, 129.9, 131.3, 137.4, 139.6, 150.0, 155.7, 157.7, 159.7, 160.1.

Análisis elemental: calculado para $C_{18}H_{21}N_3O_3.1l/4\ H_2O$: C, 65.97; H, 6.85; N, 12.15. Encontrado: C, 66.10; H, 7.34; N, 12.17. MS (342, M+1). Polvo blanco, punto de ebullición= 133.5-134 °C

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.03 μM.

El compuesto se sintetiza por vía de la secuencia de reacción en el diagrama de adelante, y y los detalles de cada una de las seis etapas que se suministran posteriormente adelante



Etapa 1: A una solución de ácido 2-hidroxi-4-metilbenzoico (25g, 0.164 mol) en acetona (350 mL) se agrega K_2CO_3 (68 g, 0.492 mmol) seguido por MeI (41 mL, 0.656 mmol) y la mezcla de reacción se calienta a reflujo durante 48 hrs. Después de enfriar a t.a. la mezcla de reacción se filtra y el filtrado se evapora

para dar el metilo 2-metoxi-4-metilbenzoato crudo. KOH (11.3 g, 1.2 eq) se disuelve en MeOH (300 mL) y el éster crudo se agrega a la mezcla y la solución se calienta a reflujo 48hrs. Después de enfriamiento la mezcla de reacción se acidifica con HCl (1N) ac. y se extrae con acetato de etilo. La capa orgánica se lava con solución salina, se seca sobre $MgSO_4$, se filtra y se evapora. El residuo se tritura con acetato de etilo/Hexano para dar 20 g de ácido 2-metoxi-4-metilbenzoico como un sólido blanco crema 85% de rendimiento)

Etapa 2: A una mezcla de ácido 2-metoxi-4-metilbenzoico (20 g, 120.4 mmol), EDC (23.1 g, 120.4 mmol) y HOBt (16.3 g, 120.4 mmol) en diclorometano (1 L) se agrega NH_3 (7N en MeOH, 52 mL, 3 eq) en forma de gota. La mezcla de reacción se agita a temperatura ambiente durante la noche luego se lava sucesivamente con HCl (1N), $NaHCO_3$ saturado ac., agua y solución salina, se seca sobre $MgSO_4$, se filtra y se evapora. El residuo se recristaliza de acetato de etilo/ Hexano para dar 16.5 gr de 2-metoxi-4-metilbenzamida (83% de rendimiento).

Etapa 3: A una solución de 2-metoxi-4-metilbenzamida (14.55 g, 88.08 mmol) en THF seco (50 mL) se agrega en forma de gota complejo de Borano-tetrahidrofurano (1.0 M en THF, 220 mL, 2.5 eq) a 0° C bajo atmósfera N_2. La mezcla de reacción luego se calienta a 60° C durante la noche. La reacción se enfría a temperatura ambiente, se agrega cuidadosamente HCl ac. (6 N, 37 mL) y la mezcla de reacción luego se calienta a 70° C durante 2 hrs. Después de enfriar, se agrega agua y la solución resultante se lava con éter. La capa acuosa se basifica con NaOH ac. (10 N) a 0° C y se satura con K_2CO_3 luego se extrae con acetato de etilo. La capa orgánica se lava con solución salina, se seca sobre

$MgSO_4$, se filtra y se evapora para dar 8.5 g de (2-metoxi-4-metilfenil)metanamina. (64% de rendimiento).

Etapa 4: A una solución de acetonitrilo anhidro (10.1 mL, 191.83 mmol, 3.3 eq) en THF seco (500 mL) se agrega en forma de gota n-BuLi (2.5 M en Hexano, 69.8 mL, 174.39 mmol, 3 eq) a -78° C bajo atmósfera N_2. La suspensión blanca resultante se agita a -78° C durante 1 hr, y luego se agrega una solución de 2-bromo-5-metilpiridina (10.0 g, 58.13 mmol, leq) en THF seco (30 mL). La mezcla de reacción se mantiene a -78° C durante 1 hr luego se calienta lentamente a t.a y se agita durante 1 hr. Se agrega hielo/agua y la capa se separa. La capa orgánica se lava con agua y solución salina, se seca sobre $MgSO_4$, se filtra y se evapora para dar 18 g de 2-(5-metilpiridin-2-il)acetonitrilo crudo. Después el producto es muy volátil, este no seca bajo alto vacío y todavía contiene algunos disolventes.

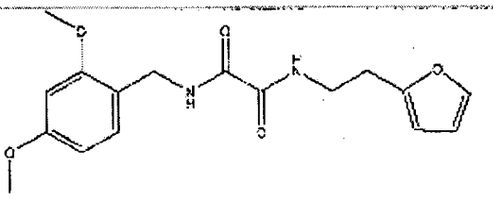
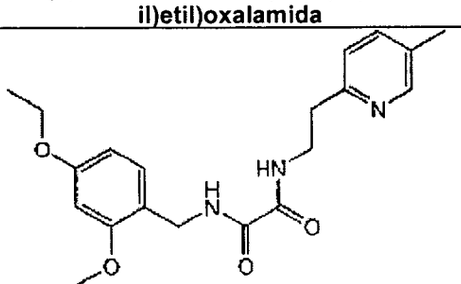
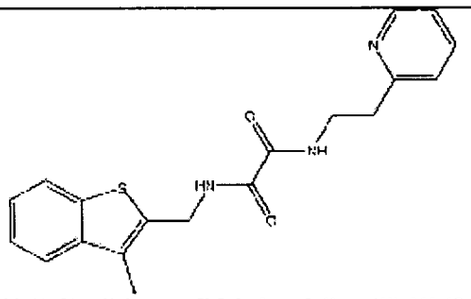
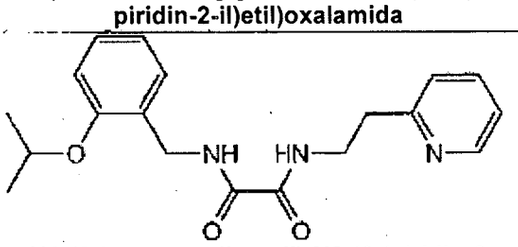
Etapa 5: A una solución de 18 g de 2-(5-metilpiridin-2-il)acetonitrilo crudo en THF seco (100 mL) se agrega en forma de gota complejo de Borano-tetrahidrofurano (1.0 M en THF, 232 mL, 232.5 mmol, 4 eq) a 0° C bajo atmósfera N_2. La mezcla de reacción luego se calienta a 60° C durante la noche. La reacción se enfría a temperatura ambiente, HCl ac. (6 N, 40 mL) se agrega cuidadosamente y la mezcla de reacción luego se calienta a 70° C durante 2 hrs. Después de enfriar, se agrega agua y la solución resultante se lava con éter. La capa acuosa se basifica con NaOH ac. (10 N) a 0° C y se satura con K_2CO_3 luego se extrae con éter (5 x 100 mL). La capa orgánica se seca sobre $MgSO_4$, se filtra y se evapora para dar 7.6 g de 2-(5-metilpiridin-2-il)etanamina. Cruda (96% rendimiento crudo)

Cuando se evapora el éter, la temperatura de baño de agua se mantiene 25° C después el punto de ebullición de la amina es probablemente alrededor de 100 °C.

Etapa 6: Una mezcla de 2g de (2-metoxi-4-metilfenil)metanamina (de la etapa 3) y Et_3N (3.7 mL, 2eq) en CH_3CN seco (45 mL) se enfría a 0° C bajo atmósfera N_2 y se agrega en forma de gota 2-cloro-2-oxoacetato de etilo (1.47 mL, 1 eq). Después de que la adición se completa, la mezcla de reacción se agita a temperatura ambiente durante 4 horas y se agrega 2-(5-metilpiridin-2-il)etanamina (2.52 g, 1.4 eq, from etapa 5). La reacción se calienta a reflujo durante 24 horas. Después de enfriamiento el disolvente se remueve bajo presión reducida y el residuo se disuelve en acetato de etilo y se lava sucesivamente con agua y solución salina, se seca sobre $MgSO_4$, se filtra y se evapora. El residuo se cromatografía sobre gel de sílice (eluyente: 25-35% acetona en Hexano) y se recristaliza de acetato de etilo /hexane y etanol/agua para dar 650 mg de N'-(2-metoxi-4-metilbencil)-N^2-(2-(5-metilpiridin-2-il)etil)oxalamida (15%).

Compuestos de "oxalamida" adicionales se sintetizan y se ensayan experimentalmente y se ha encontrado que tienen un nivel relativamente alto de eficacia como un activador de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK 293. Los resultados de tales ensayos se muestran en la Tabla B.

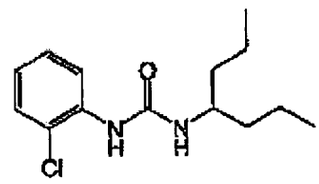
S92

Tabla B - Oxalamidas Umami			
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)
B1	 N1-(2,4-dimetoxibencil)-N2-(2-(furan-2-il)etil)oxalamida	0.18	
B2	 N1-(4-etoxi-2-metoxibencil)-N2-(2-(5-metilpiridin-2-il)etil)oxalamida	0.19	
B3	 N-(3-Metil-benzo[b]tiofen-2-ilmetil)-N´-(2-piridin-2-il)etil)oxalamida	0.81	
B4	 N1-(2-isoporpoxibencil)-N2-(2-(piridin-2--il)etil)oxalamida	1.22	

Numerosos compuestos de amida de Fórmula (I) que caen dentro del alcance de compuestos "urea" descritos en cualquier parte aquí como Fórmula (IV) también se sintetizan y se ensayan experimentalmente para eficacia como activadores de receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293.

Ejemplo 158

1-(4-clorofenil)-3-(heptan-4-il)urea

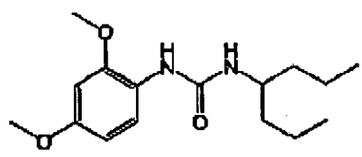


A una solución de heptan-4-amina (0.18 mL, 1 mmol) en CH_2Cl_2 (5 mL) se agrega 1-cloro-2-isocianatobenceno (0.12 mL, 1 mmol) a temperatura ambiente. La mezcla de reacción se agita durante 2 h. Se precipita un sólido blanco. La mezcla de reacción se filtra. El sólido se lava con CH_2Cl_2 para proporcionar 1-(4-clorofenil)-3-(heptan-4-il)urea (180 mg, 67%) como un sólido blanco, pf: 135-136° C. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93 (t, 6H), 1.45 (m, 6H), 1.53 (m, 2H), 3.80 (br s, 1H), 4.33 (d, 1H), 6.00 (s, 1H), 6.95 (td, 1H), 7.23 (dt, 1H), 7.33 (dd, 1H), 8.13 (dd, 1H). MS(M+H, 269).

El compuesto tiene una activación para EC_{50} de ahT1R1/hT1R3 receptor umami que se expresa en una línea celular HEK293 de 0.37 μM, y cuando está presente en 1 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 4.95.

Ejemplo 159

1-(2,4-dimetoxifenil)-3-(heptan-4-il)urea

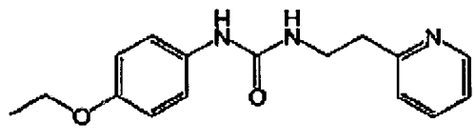


Se prepara de una forma similar al ejemplo 158 utilizando heptan-4-amina y 1-isocianato-2,4-dimetoxibenceno. Rendimiento: 88%. pf: 172-173° C. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.93 (t, 6H), 1.45 (m, 8H), 3.82 (s, 3H), 3.83 (m, 1H), 3.84 (s, 1H), 4.32 (br s, 1H), 6.34 (br s, 1H), 6.49 (d, 1H), 6.50 (s, 1H), 7.71 (d, 1H). MS (M+H, 295).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.98 μM, y cuando está presente en 0.3 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 7.61.

Ejemplo 160

1-(4-etoxifenil)-3-(2-(piridin-2-il)etil)urea



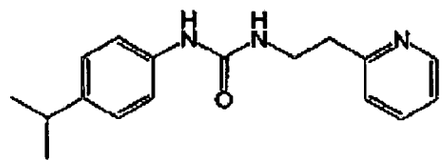
Se prepara de una forma similar al ejemplo 158 utilizando 2-(piridin-2-il)etanamina y 1-etoxi-4-isocianatobenceno. Rendimiento: 95%. pf: 163-164° C ^{1}H RMN (500 MHZ, $CDCl_3$): δ 1.43 (t, 3H), 3.03 (t, 2H), 3.68 (t, 2H), 4.03 (q, 2H), 5.69 (br s, 1H), 6.45 (br s, 1H), 6.84 (m, 2H), 7.14 (m, 3H), 7.20 (d, 1H), 7.64 (dt, 1H), 8.43 (dd, 1H). MS (M+H,286).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 4.1 μM, y cuando está presente en 1 μM mejora la eficacia de glutamato monosódico con una proporción EC_{50} de 4.2.

595

Ejemplo 161

1-(4-isopropilfenil)-3-(2-(piridin-2-il)etil)urea



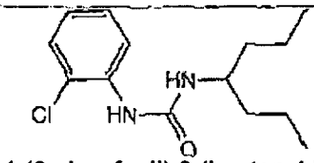
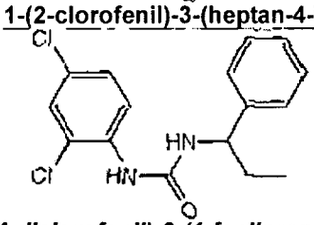
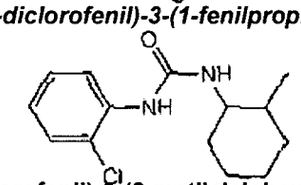
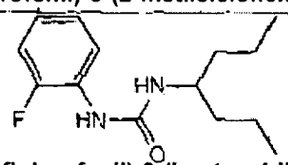
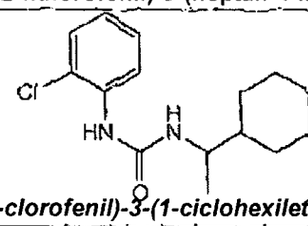
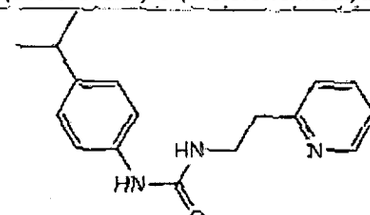
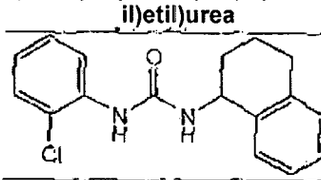
Se prepara de una forma similar al ejemplo 158 utilizando 2-(piridin-2-il)etanamina y 1-isocianato-4-isopropilbenceno. Se purifica por vía de cromatografía de columna (1% de MeOH en CH_2Cl_2 a 3% de MeOH en CH_2Cl_2) para proporcionar 1-(4-isopropilfenil)-3-(2-(piridin-2-il)etil)urea (130 mg, 50%) como un sólido blanco, pf: 72-73° C. ^{1}H RMN (500 MHz, $CDCl_3$): δ 1.25 (d, 6H), 2.89 (m, 1H), 3.06 (t, 2H), 3.70 (t, 2H), 5.80 (br s, 1H), 6.55 (br s, 1H), 7.19 (m, 5H), 7.24 (d, 1H), 7.68 (dt, 1H), 8.46 (d, 1H). MS (M+H, 284).

El compuesto tiene una activación para EC_{50} de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK293 de 0.98 μM.

Compuestos "urea" adicionales se sintetizan y se ensayan experimentalmente y se ha encontrado que tienen un nivel relativamente alto de eficacia como un activador de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK 293. Los resultados de tales ensayos se muestran adelante en la Tabla C.

596.

Tabla C - Ureas Umami

Compuesto No.	Nombre IUPAC	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)	Con. (µM)
C1	 1-(2-clorofenil)-3-(heptan-4-il)urea	0.37	4.95	1
C2	 *1-(2,4-diclorofenil)-3-(1-fenilpropil)urea*	0.49	4.52	1
C3	 1-(2-clorofenil)-3-(2-metilciclohexil)urea	0.52	3.24	3
C4	 1-(2-flulorofenil)-3-(heptan-4-il)urea	0.79	12.15	3
C5	 *1-(2-clorofenil)-3-(1-ciclohexiletil)urea*	0.84	9.08	1
C6	 1-(4-isopropilfenil)-3-(2-piridin-2-il)etil)urea	0.98		
C7		0.99	3.68	1

597

Tabla C - Ureas Umami

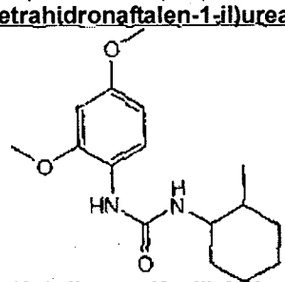
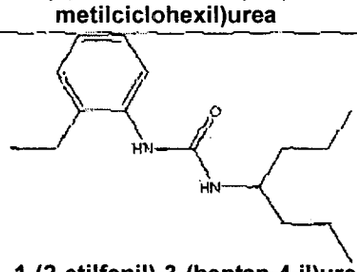
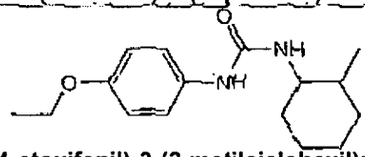
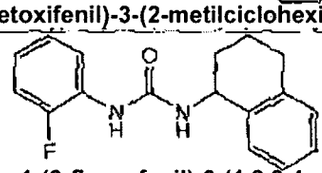
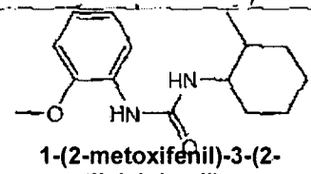
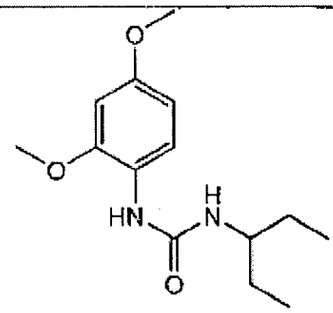
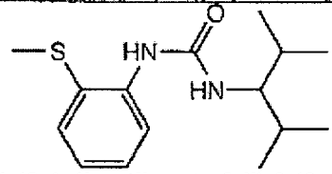
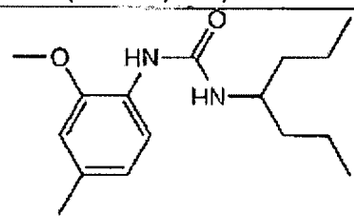
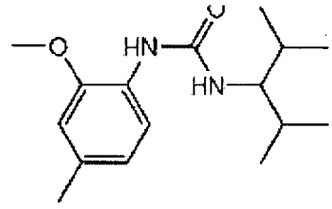
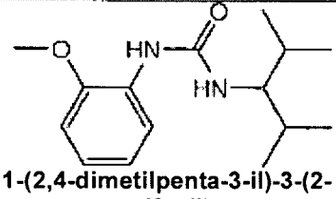
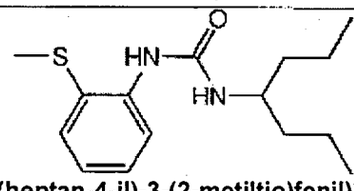
Compuesto No.	Nombre IUPAC	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)	Con. (µM)
	1-(2-clorofenil)-3-(1,2,3,4 tetrahidronaftalen-1-il)urea			
C8	 1-(2,4-dimetoxifenil)-3-(2-metilciclohexil)urea	1.41	2.62	0.3
C9	 1-(2-etilfenil)-3-(heptan-4-il)urea	1.42		
C10	 1-(4-etoxifenil)-3-(2-metilciclohexil)urea	1.51	2.1	0.3
C11	 1-(2-fluorofenil)-3-(1,2,3,4 tetrahidronaftalen-1-il)urea	1.65	4.49	1
C12	 1-(2-metoxifenil)-3-(2-metilciclohexil)urea	1.67		

Tabla C - Ureas Umami

Compuesto No.	Nombre IUPAC	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)	Con. (µM)
C13	 1-(2,4-dimetilfenil)-3-(pentan-3-il)urea	1.72	11.87	1
C14	 1-(2,4-dimetilpenta-3-il)-3-(2-(metiltio)fenil)urea	0.14		
C15	 1-(heptan-4-il)-3-(2-metoxi-4-metilfenil)urea	0.16		
C16	 1-(2,4-dimetilpenta-3-il)-3-(2-metoxi-4-(metilfenil)urea	0.21		
C17	 1-(2,4-dimetilpenta-3-il)-3-(2-metoxifenil)urea	0.24		
C18	 1-(heptan-4-il)-3-(2-metiltio)fenil)urea	0.26		

599

Tabla C - Ureas Umami

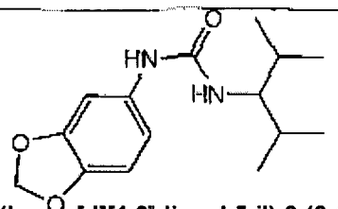
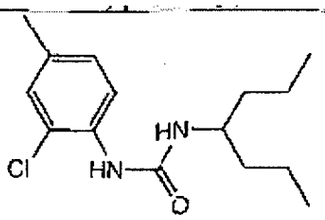
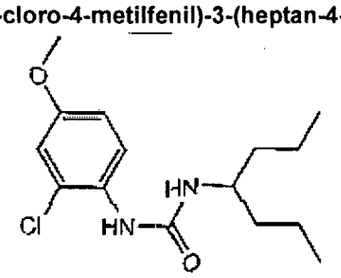
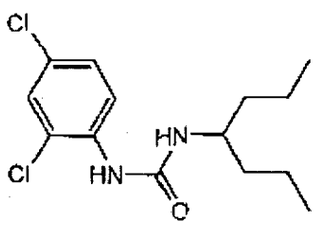
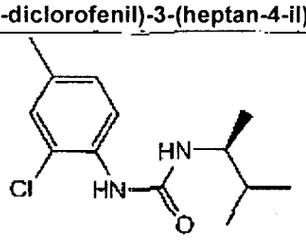
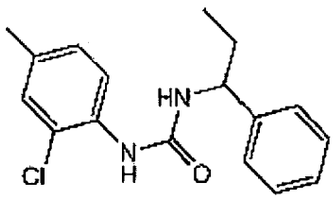
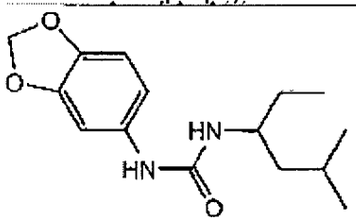
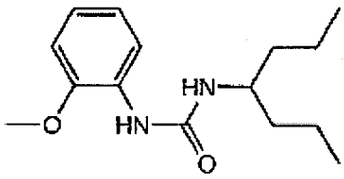
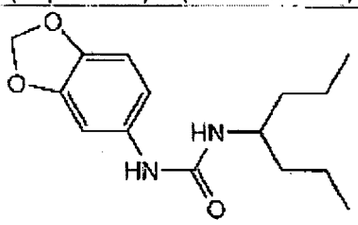
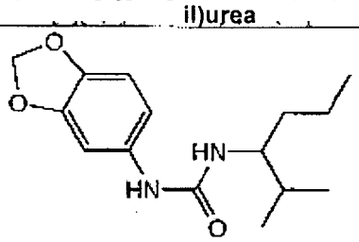
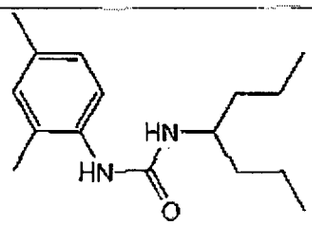
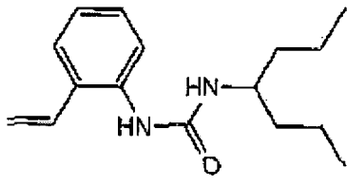
Compuesto No.	Nombre IUPAC	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)	Con. (µM)
C19	 1-((benzo[d][1,3]dioxol-5-il)-3-(2,4-dimetilpentan-3-il)urea	0.32		
C20	 1-(2-cloro-4-metilfenil)-3-(heptan-4-il)urea	0.09		
C21	 1-(2-cloro-metoxifenil)-3-(heptan-4-il)urea	0.11		
C22	 1-(2,4-diclorofenil)-3-(heptan-4-il)urea	0.18		
C23	 (S)-1-(2-cloro-metilfenil)-3-(3-metilbutan-2-il)urea	0.38		

Tabla 3 - Umami

Compuesto No.	Nombre IUPAC	Umami EC_{50} µM	Proporción Ed_{50} (VMHG)	Con. (µM)
C24	 1-(2-cloro-4-metilfenil)-3-(1-fenilpropil)urea	0.48		
C25	 1-(benzo[d][1,3]dioxol-5-il)-3-(5-metilhexan-3-il)urea	0.48		
C26	 1-(heptan-4-il)-3-(2-metoxilfenil)urea	0.49		
C27	 1-(benzo[d][1,3]dioxol-5-il)-3-(heptan-4-il)urea	0.54		
C28	 1-(benzo[d][1,3]dioxol-5-il)-3-(2-metilhexan-3-il)urea	0.57		

601

Tabla C - Ureas Umami

Compuesto No.	Nombre IUPAC	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)	Con. (µM)
C29	 1(2,4-dimetilfenil)-3--(heptan-4-il)urea	0.79		
C30	 1-(heptan-4-il)-3-(2-vinilfenil)urea	0.79		

Numerosos compuestos de amida de Fórmula (I) que caen dentro del alcance de compuestos "acrilamida" descritos en cualquier parte aquí también se sintetizan y se ensayan experimentalmente para eficacia como activadores de un receptor umami hT1R1/hT1R3 que se expresa en una línea celular HEK 293. Los resultados de tales ensayos se muestran adelante en la Tabla D.

Tabla D - Acrilamidas Umami

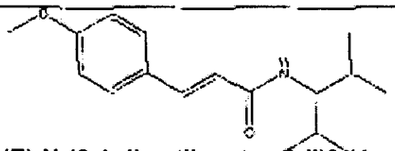
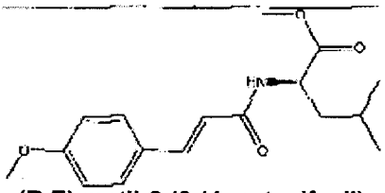
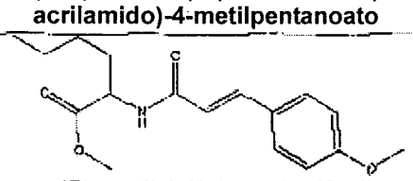
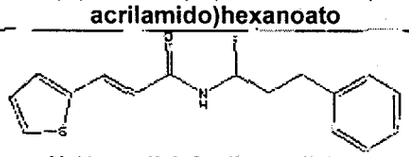
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@ (μM)
D1	 (E)-N-(2,4-dimetilpentan-3-il)3-(4-metoxifenil)acrilamida	0.29	3.46	1
D2	 (R,E)-metil-2-(3-(4-metoxifenil) acrilamido)-4-metilpentanoato	0.32		
D3	 (E)-metil-2-(3-(4-metoxifenil) acrilamido)hexanoato	0.63		
D4	 N-(1-metil-3-fenil-propil-3-	0.69	9.73	1

Tabla D - Acrilamidas Umami

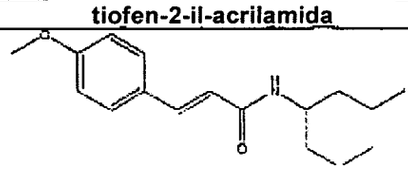
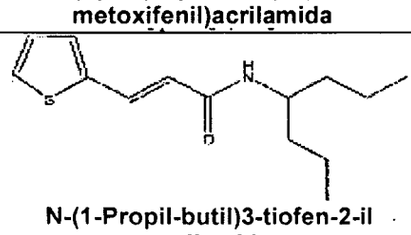
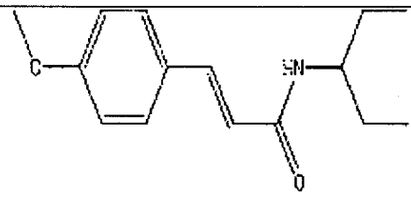
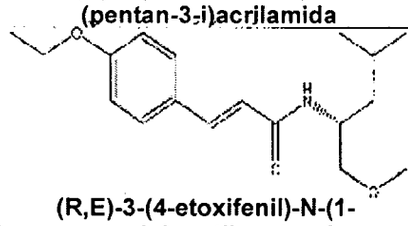
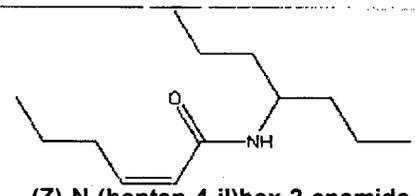
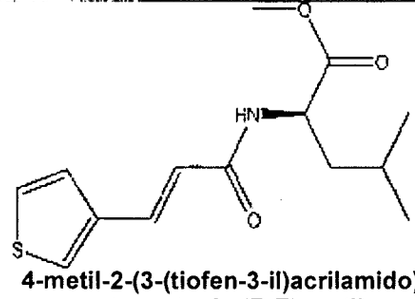
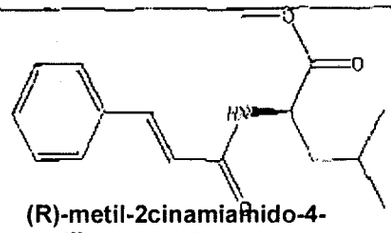
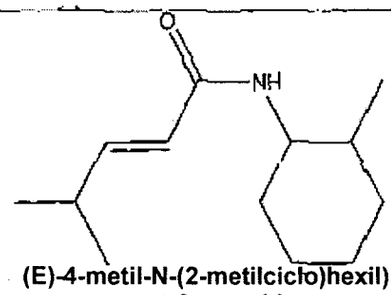
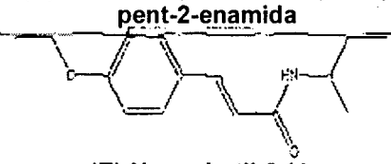
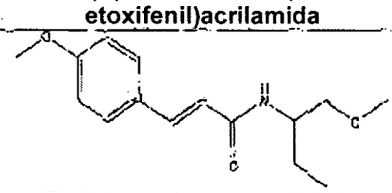
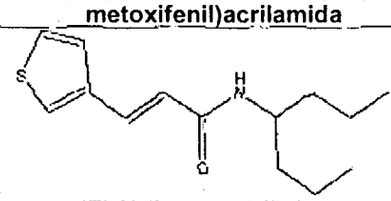
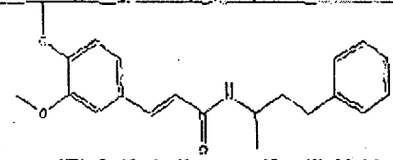
Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@ (μM)
	tiofen-2-il-acrilamida			
D5	 (E)-N-(heptan-4-il)3-(4-metoxifenil)acrilamida	0.72	3.48	0.3
D6	 N-(1-Propil-butil)3-tiofen-2-il acrilamida	0.75	6.3	1
D7	 (E)-3-(4-metoxifenil)-N-(pentan-3-i)acrilamida	0.82	9.62	1
D8	 (R,E)-3-(4-etoxifenil)-N-(1-metoxi-4-metilpentan-2-il)acrilamida	0.94		
D9	 (Z)-N-(heptan-4-il)hex-2-enamida	0.98		
D10	 4-metil-2-(3-(tiofen-3-il)acrilamido) pentanoato de (R,E)-metilo	1.09		

Tabla D - Acrilamidas Umami

Compuesto No.	Compuesto	Umami EC_{50} (μM)	Proporción Ec50(Vs.MSG)	@ (μM)
D11	 (R)-metil-2cinamiamido-4-metilpentanoato	1.17		
D12	 (E)-4-metil-N-(2-metilciclo)hexil) pent-2-enamida	1.28		
D13	 (E)-N-sec-butil-3-(4-etoxifenil)acrilamida	1.31	2.7	0.3
D14	 (E)-N-(1-*metoxibutan*-2-il)-3-(4-metoxifenil)acrilamida	1.43	8.48	1
D15	 (E)-N-(heptan-4-il)-3-(tiofen-3-il)acrilamida	1.54	2.22	0.3
D16	 (E)-3-(3,4-dimetoxifenil)-N-(4 fenilbutan-2-il)acrilamida	1.56	3.13	1

Experimentos de sabor umami es la compuestos salados o picantes utilizando panelistas humanos

Selección de panelista general: selección básica de probadores sensoriales de sabor. Se ensayan panelistas potenciales para la capacidad de numerar y

clasificar la intensidad de las soluciones que representan los cinco sabores básicos. Los panelistas numeran y clasifican la intensidad de cinco concentraciones diferentes de cada uno de los cinco siguientes compuestos: sacarosa (dulces), cloruro de sodio (salado), ácido cítrico (amargo), cafeína (agrio) , y glutamato monosódico (dulce o salado). Con el fin de ser seleccionado para anticipar en las pruebas, los panelistas necesitan clasificar y numerar correctamente las muestras por intensidad, por un número razonable de errores.

Ensayos preliminares de sabor: los panelistas seleccionados en el anterior procedimiento se consideraron calificados para desarrollar procedimientos de pruebas de sabor preliminares. Las pruebas de sabor preliminares se utilizan para evaluar nuevos compuestos para intensidad de sabores básicos y sin sabor. Un grupo pequeño de panelistas (n=5) prueban aproximadamente 5 concentraciones del compuesto (rangos típicamente entre 1-100μM, en ciclos de mitas – log, por ejemplo,1,3,10,30, y 100μM)en agua y en una solución de 12 mM de MSG para evaluar la mejora. Los panelistas clasifican los cinco sabores básicos (dulce, salado, amargo, agrio, y umami) así como también sin sabor (tal como químicos, metálicos, azufres) en una escala de magnitud marcada. Las muestras se sirven en porciones de 10mL a temperatura ambiente. En el propósito del ensayo es determinar la mayor concentración en la que no hay sin sabor objecionable, y determinar si el sabor salado o picante obvio o mejora del sabor salado o picante existe en alguna concentración ensayada.

Si el compuesto es efectivo y no tiene sin sabor objecionable, se prueba con un (panel experto)entrenados en un estudio mayor.

Selecciones de panelistas entrenados: se utiliza un panel de expertos entrenados para evaluar adicionalmente los compuestos que se han probado con la prueba de sabor preliminar.

Los panelistas para el panel entrenado se seleccionan a partir de un grupo grande de panelistas de sabor calificados. Los panelistas se entrenan adicionalmente en sabor salado o picante al clasificar y enumerar experimentos que utilizan combinaciones MSG e IMP. Los panelistas completan una serie de clasificación, numeración y diferencia de pruebas de referencia con soluciones de sabor dulce o salado. En experimentos de clasificación y numeración los panelistas evalúan fácilmente concentraciones MSG (0,6,18,36mM) y concentraciones mas difíciles de MSG (3,6,12,18mM MSG)en agua.

Panel entrenado con compuesto de ensayo: los compuestos probados por el panel entrenado se evalúan en diferencia a partir de experimentos de referencia. A los panelistas se les da una muestra de referencia (12mM de MSG + 100μM IMP)y se les solicitas clasificar las muestras en una escala de -5 +5 en términos de diferencia en sabor salado o picante partir de la referencia (clasificación: -5= mucho menor sabor salado o picante que la referencia; 0= el mismo sabor salado o picante como la referencia; +5= mucho mas sabor salado o picante que la referencia). Las muestras de ensayo son soluciones con cantidades variantes de MSG y IMP, y el compuesto, típicamente cada sesión compara la muestra de referencia con numerosas muestras de ensayo. Las pruebas incluyen típicamente varias muestras con varias concentraciones de MSG, IMP, así como también una muestra ciega de la referencia en si misma para evaluar la exactitud del panel. Los resultado de los ensayos de sabor se describen en la tabla 3 y muestran que los compuestos de la invención sean encontrado que suministra sabor salado o picante o mejora del sabor salado o picante en 1μM + MSG cuando se comparan con 100μM IMP + MSG. Los compuestos se prueban contra la referencia en muestras con y sin 12mM de MSG. Todas las muestras se presentan en

607

volúmenes de 10mL a temperatura ambiente. Se contemplan 2 sesiones para cada compuesto ensayado para evaluar la reproductividad del panel.

Prueba de sabor en prototipo de producto: se puede hacer de forma similar como se describió anteriormente.

Tabla 3. Resultados de Ensayo de Sabor salado o picante

Compuesto No.	Nombre químico	Datos de Ensayo
Ejemplo 1	N-(heptan-4-il)benzo[d][1,3]dioxol-5-carboxamida	12 mM MSG + 3 μM cpd tan fuerte como 12 mM MSG + 100 μM IMP
Ejemplo 6	(R)-metil 2-(benzo[d][1,3]dioxol-6-carboxamido)-4-metilpentanoato	12 mM MSG + 10 μM cpd tan fuerte como 12mM MSG+ 100 μM IMP
Ejemplo 71	(R)-N-(1-metoxi-4-metilpentan-2-il)-3,4-dimetilbenzamida	12 mM MSG + 3 μM cpd tan fuerte como 12Mm MSG+ 100 μM IMP
Ejemplo 98	(R)-metil-2-(2,3-dimetilfuran-5-carboxamido)-4-metilpentanoato	12 mM MSG + 10 μM cpd tan fuerte como 12mM MSG + 100 μM IMP
Ejemplo 104	4-Metoxi-N-(1-metoximetil-3-metil- butil)-3-metil-benzamida	12 mM MSG + 3 μM cpd tan fuerte como 12mM MSG + 100 μM IMP
Ejemplo 123	N-(2,4-Dimetoxi-bencil)-N'- (2-piridin- 2-il-etil)- oxalamida	12 mM MSG + 1 μM cpd tan fuerte como 12mM MSG + 100 μM IMP 1 μM cpd tan fuerte como 12mM MSG
Ejemplo 132	N-(2metoxi-4-metilbencil)- N'-(2(5-metilpiridin-2-il)etil)oxalamida	12 mM MSG + 1 μM cpd tan fuerte como 12mM MSG + 100 μM IMP 1 μM cpd tan fuerte como 12mM MSG
Ejemplo 157	N'-(2-metoxi-4-metilbencil)-N^2-(2-(5-metilpiridin-2-il)etil)oxalamida	12 mM MSG + 0.3 μM cpd tan fuerte como 12mM MSG + 100 μM IMP 0.3 μM cpd tan fuerte como 12mM MSG
Ejemplo 121-1	(S)-N-(2,3-Dihidro-1H-inden-1-il)-4-metoxi-3-metilbenzamida	12 mM MSG + 1 μM cpd tan fuerte como 12mM MSG + 100 μM IMP 1 μM cpd tan fuerte como 12mM MSG

Ejemplos de Amida Dulce

Numerosos compuestos de amida de Fórmula (I) se sintetizan y se ensayan experimentalmente para eficacia como activadores de un receptor "dulce"

608

hT1R2/hT1R3 "que se expresa en una línea celular HEK 293. Ejemplos de la síntesis y ensayos biológicos eficaces en términos de medidas de dulce EC_{50} para tales compuestos dulces se listan adelante. Más aún, muchas de las amidas "dulces" de Fórmula (I) también se exhiben para actividad en los ensayos de proporción EC_{50} y EC_{50} umami, y como se ilustra adelante, algunos de los compuestos de amida de Fórmula (I) tienen actividad significante y potencial para servir simultáneamente como mejoradores de sabor dulce y salado o picante para el uso en productos comestible y medicinales y composiciones.

Ejemplo 162

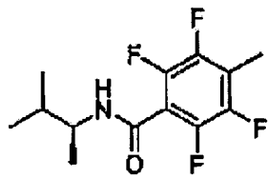
2,3,5,6-tetrafluoro-4-metil-N-(2-metilciclohexil)benzamida

Ácido 2,3,5,6 -tetrafluoro-p-toluico (4.00 g, 19.22 mmol), HOBt (5.19 g, 38.44 mmol) y EDCI (4.42 g 23.06 mmol) se mezclan en 200 ml de DCM anhidro y 30 ml de DMF anhidro. La mezcla se enfría a 0° C y se le permite agitar bajo Ar durante 15 minutos. A la mezcla se agrega 2-metilciclohexanamina (3.05 mL, 23.06 mmol) y la mezcla de reacción se le permite calentar lentamente a temperatura ambiente y se agita durante la noche. La mezcla de reacción se diluye con DCM, se lava con HCl 1N, agua, $NaHCO_3$ acuoso, agua y solución salina, se seca sobre $MgSO_4$, la filtración y remoción del disolvente en vacío, proporciona el producto crudo como un sólido amarillo pálido La recristalización ($EtOH/H_2O$) y secado en vacío da 5.23 g del compuesto del título como un sólido blanco (mezcla de 2 diastereómeros, 90%). ^1H RMN ($CDCl_3$) δ 0.95, 1.01 (d, *J*= 7.0, 6,6 Hz, 3H) 1.1-2.1 (m, 9H), 2.29 (m, 3H), 3.70, 4.29 (m, 1H), 5.65, 5.92 (m, 1H). MS (304.1, M+H). p.f. 202-204° C.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.39 μM.

Ejemplo 163

(S)-2,3,5,6-tetrafluoro-4-metil-N-(3-metilbutan-2-il)benzamida

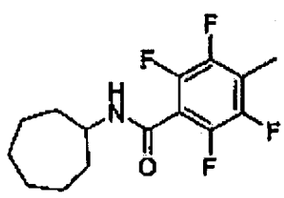


Se prepara de una forma similar al ejemplo 162 utilizando (S)-3-metilbutan-2-amina y ácido 2,3,5,6 -tetrafluoro-p-toluico (93%). ^{1}H RMN ($CDCl_3$) δ 0.98 (d, *J*= 6.9 Hz, 6H) 1.18 (d, *J*= 6.8 Hz, 3H), 2.29 (m, 3H), 4.09 (m, 1H), 5.72 (bs, 1H).MS (304.1, M+H) p.f. 146-147° C.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.6 μM.

Ejemplo 164

N-cicloheptil-2,3,5,6-tetrafluoro-4-metilbenzamida



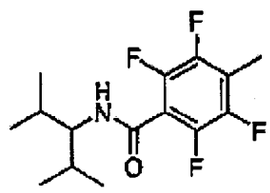
Se prepara de una forma similar al ejemplo 162 utilizando cicloheptilamina y ácido 2,3,5,6 -tetrafluoro-p-toluico (94%). ^{1}H RMN ($CDCl_3$) δ 1.53 (m, 6H), 1.57 (m,

4H), 2.03 (m, 2H) 2.28 (m, 3H), 4.17 (m, 1H), 5.85 (bs, 1H)JMS (304.1, M+H) p.f. 164-165° C.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 1.85 µM.

Ejemplo 165

N-(2,4-dimetilpentan-3-il)-2,3,5,6-tetrafluoro-4-metilbenzamida

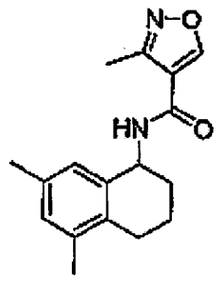


Se prepara de una forma similar al ejemplo 162 utilizando 2,4-dimetilpentan-3 -amina y ácido 2,3,5,6 -tetrafluoro-p-toluico (90%). ^{1}H RMN ($CDCl_3$) δ 0.91 (d, J = 6.7 Hz, 6H), 1.00 (d, J = 6.8 Hz, 6H), 1.85 (m, 2H), 2.29 (m, 3H), 3.82 (m, 1H), 5.52 (bd, 1H).MS (306.1, M+H) p.f. 184-187° C.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.81 µM.

Ejemplo 166

N-(5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-il)-3-metilisoxazol-4-carboxamida



A una solución de ácido 3-metilisoxazol-4-carboxílico (83 mg, 0.0.67 mmol), HOBt (100 mg, 0.74 mmol) y EDCI-HCl (142 mg, 0.74 mmol) en DMF (4 mL), se agrega 5,7-dimetil-1,2,3, 4-tetrahidronaftil-1-amina (ejemplo 166a) (130 mg, 0.74 mmol). La mezcla de reacción se agita durante 24h a t.a., en cuyo tiempo el disolvente se remueve bajo presión reducida y el residuo se purifica por cromatografía de columna flash (10:1 Hex:EtOAc) para proporcionar 134 mg de N-(5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-il)-3-metilisoxazol-4-carboxamida (70 %) como un sólido espumoso blanco. ^{1}H RMN (500 MHz, DMSO-d_6): δ 1.74 (m, 2H), 1.86 (m, 2H), 2.16 (s, 3H), 2.19 (s, 3H), 2.43 (s, 3H), 2.55 (m, 2H), 5.10 (m, 1H), 6.86 (s, 1H), 6.89 (s, 1H), 8.60 (d, 1H, *J*= 8.40 Hz), 9.27 (s, 1H). ^{13}C RMN (125 MHz, DMSO-d_6): δ 10.6, 19.1, 19.6, 20.6, 25.8, 29.4, 46.9, 115.4, 126.4, 129.1, 132.6, 134.1, 135.8, 136.6, 158.5, 159.6, 159.9. MS(M+H, 285). Pf 57-58° C.

a. 5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-amina: una cantidad catalítica de Níquel Raney (suspensión en agua) se lava con MeOH seco bajo argón en un frasco de fondo redondo. A una solución del Ni Raney lavada en amoniaco metanólico (25 mL, 7N), se agrega 5,7-dimetil-3,4-dihidronaftalen-1(2H)-ona oxima (ejemplo 166b) (420 mg, 2.22 mmol), y la mezcla se agita bajo un balón de H_2 durante 20 hr. Luego de completar , la reacción se filtra a través de celita, el filtrado se concentra en vacío, se diluye con EtOAC, se lava con agua y solución salina, se seca sobre $MgSO_4$, se filtra y el disolvente se remueve bajo presión reducida para proporcionar 360 mg de 5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-

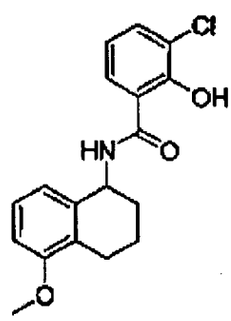
amina (93 %). ^{1}H RMN (500 MHz, $CDCl_3$): δ 1.66-1.83 (m, 4H), 1.96 (m, 2H), 2.19 (s, 3H), 2.28 (s, 3H), 2.55 (m, 1H), 2.66 (m, 1H), 3.97 (m, 1H), 6.88 (s, 1H), 7.09 (s, 1H).

b. Preparación de 5,7-dimetil-3,4-dihidronaftalen-1(2H)-ona oxima: A una mezcla de 5,7-dimetil-3,4-dihidronaftalen-1(2H)-ona (2.0 g, 11.48 mmol) y clorhidrato de hidroxilamina (1.6 g, 19.73 mmol) en 10 ml de agua a 70° C, se agregan MeOH (14 mL), THF (3 mL) y una solución de acetato de sodio (2.53 g, 30.83 mmol, en 7 mL de H_2O). La agitación se continúa durante 85 min a 70° C, en cuyo tiempo un precipitado se forma y se agregan 10 ml de agua. La mezcla resultante se agita a temperatura ambiente durante 2 hr. Luego de completar, el producto se recolecta por filtración para proporcionar 2.12 g de 5,7-dimetil-3,4-dihidronaftalen-1(2H)-ona oxima (98 %). MS (M+H, 190).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.76 μM.

Ejemplo 167

3-cloro-2-hidroxi-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il) benzamida



613

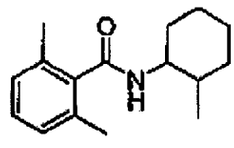
Se prepara en la forma similar al Ejemplo 166 utilizando 5-metoxi-1,2,3,4-tetrahidronaftalen-1 -amina (Ejemplo 167a). Rendimiento 40 %. ^{1}H RMN (500 MHz, DMSO-d_6): δ 1.73 (m, 1H), 1.83 (m, 1H), 1.96 (m, 2H), 2.61 (m, 2H), 3.78 (s, 3H), 5.27 (m, 1H), 6.78 (d, 1H, *J*= 7.82 Hz), 6.86 (m, 2H), 7.14 (t, 1H, *J*= 7.98 Hz), 7.60 (dd, 1H, *J*= 7.88, 1.30 Hz), 7.94 (dd, 1H, *J*= 8.03, 1.39 Hz), 9.30 (d, 1H, *J*= 8.06 Hz), 13.80 (s, 1H). ^{13}C RMN (125 MHz, DMSO-d_6): δ 19.5, 22.7, 28.9, 47.4, 55.3, 108.6, 115.8, 118.7, 119.8, 121.1, 125.9, 126.2, 126.4, 133.8, 137.3, 156.7, 156.8, 168.7. MS(M+H, 332). Pf 175-176° C.

a. 5-metoxi-1,2,3,4-tetrahidronaftalen-1-amina: Se prepara de una forma similar al ejemplo 166a utilizando 5-metoxi-3,4-dihidronaftalen-1(2H)-ona. Rendimiento 94 %. ^{1}H RMN (500 MHz, $CDCl_3$): δ 1.63-1.79 (m, 4H), 1.94 (m, 2H), 2.60 (m, 1H), 2.71 (m, 1H), 3.82 (s, 3H), 3.97 (m, 1H), 6.71 (d, 1H), 7.02 (d, 1H), 7.17 (t, 1H).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.21 μM.

Ejemplo 168

2,6-dimetil-N-(2-metilciclohexil)benzamida



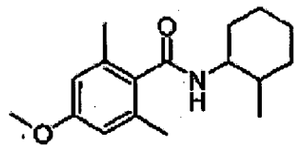
Se prepara de una forma similar al ejemplo 162 utilizando ácido 2,6-dimetilbenzoico y 2-metilciclohexilamina. Rendimiento: 59%. ^{1}H RMN (500 MHz,

$CDCl_3$): δ 0.88-0.94 (3H, dd), 1.14-1.89 (9H, m), 2.21-2.22 (6H, d), 3.39-3,45 (1H, m), 7.02-7.03 (2H,d), 7.12-7.15 (1H, t), 8.11-8.13 (1H, d). MS(M+H, 246.2).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 1.88 μM.

Ejemplo 169

4-metoxi-2,6-dimetil-N-(2-metilciclohexil)benzamida



Se prepara de una forma similar al ejemplo 166 utilizando ácido 4-metoxi-2,6-dimetilbenzoico (ejemplo 169a) y 2-metilciclohexilamina. ^1H RMN (500 MHz, $CDCl_3$): δ 0.86-0.92 (3H, dd), 1.00-1.85 (m, 9H), 2.18-2.19 (6H, d), 3.33-3.45 (1H, m), 3.71-3.72 (3H, d), 6.59 (2H, s), 7.98-8.05 (1H, m). MS (276.2, M+H).

a. ácido 4-metoxi-2,6-dimetilbenzoico: 2-Bromo-5-metoxi-1,3-dimetilbenceno (ejemplo 169b) (3.38 g, 15.79 mmol) sin purificación adicional se disuelve en 100 ml de THF seco. La mezcla se enfría a -78° C y bajo argón se agrega en forma de gotas n-butillitio (1.6 M de solución en Hexanos, 9.9 ml, 15,8 mmol) durante 15 min y la mezcla se agita durante 15 min más a -78° C. Luego las piezas pequeñas de hielo seco se agregan y la mezcla se agita 20 min a -78° C. Luego el enfriado se remueve y la mezcla se agita mientras continúa la evolución de dióxido de carbono. Luego la mezcla se vierte sobre hielo (100 ml) y se acidifica utilizando HCl 6N. La capa orgánica se separa y la fase de agua se extrae con EtOAc. Los extractos orgánicos se combinan, se lavan con solución salina,

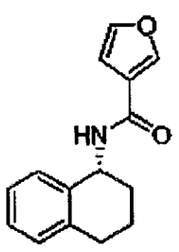
agua, se secan sobre $MgSO_4$ y se concentran bajo vacío. El producto ácido 4-metoxi-2,6-dimetilbenzoico se obtiene como un sólido blanco (2.7 g, 95%). (M+H, 181).

b. 2-Bromo-5-metoxi-1,3-dimetilbenceno: 20 mmol de 1-metoxi-3,5-dimetilbenceno (2.82 ml) se disuelve en 100 ml de acetonitrilo seco seguido por 22 mmol (3.56 g) de N-bromosuccinimida. La mezcla se agita a temperatura ambiente durante la noche. Luego el disolvente se evapora bajo presión reducida y un sólido se filtra y se lava con Hexanos suministrando 2-bromo-5-metoxi-1,3-dimetilbenceno (3.9 g, 92%) como un sólido blanco. ^1H RMN (500 MHz, $CDCl_3$): δ 2.41 (6H, s), 3.78 (3H, s), 6.67 (2H, s).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 2.1 μM.

Ejemplo 170

(R)-N-(1,2,3,4-tetrahidronaftalen-1-il)furano-3-carboxamida



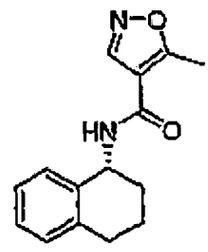
A una solución de ácido furano-3-carboxílico (100 mg, 0.68 mmol), HOBt (240 mg, 1.78 mmol) y EDCI-HCl (196 mg, 1.03 mmol) en CH_2Cl_2 (8 mL) y DMF (1.5 mL) a 0° C, se agrega (R)-1,2,3,4-tetrahidronaftalen-1-amina (160 μL, 1.06 mmol). La reacción se agita a t.a. durante 24h, después de lo cual se agrega

CH_2Cl_2. La solución resultante se lava con $NaHCO_3$ saturado, H_2O, solución salina, se seca sobre $MgSO_4$ y se concentra en vacío. La recristalización de $EtOH/H_2O$ proporciona (*R*)-*N*-(1,2,3,4-tetrahidronaftalen-1-il)-2,5-dihidrofurano-3-carboxamida. ^1H RMN (500 MHz, $CDCl_3$): δ 1.89 (m, 3H), 2.12 (m, 1H), 2.84 (m, 2H), 5.35 (m, 1H), 5.96 (br d, 1H, *J*= 7.75 Hz), 6.59 (dd, 1H, *J*= 1.90, 0.86 Hz), 7.13 (m, 1H), 7.19 (m, 2H), 7.32 (m, 1H), 7.43 (t, 1H, *J*= 1.73 Hz), 7.93 (m, 1H). MS(M+H, 242).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 6.6 μM.

Ejemplo 171

(*R*)-5-metil-*N*-(1,2,3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida

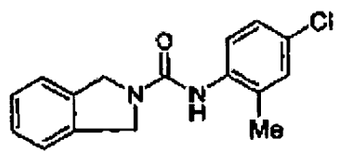


Se prepara de una forma similar al ejemplo 170 utilizando ácido 5-metilisoxazol-4-carboxílico. Se purifica por TLC preparativo (5:1 Hex:EtOAc). ^1H RMN (500 MHz, $CDCl_3$): δ 1.80 (m, 3H), 2.12 (m, 1H), 2.74 (s, 3H), 2.85 (m, 2H), 5.35 (m, 1H), 5.89 (br d, 1H, *J*= 7.75 Hz), 7.10 (m, 1H), 7.18 (m, 2H), 7.32 (m, 1H), 8.26 (s, 1H). MS(M+H, 257).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 8.1 μM.

Ejemplo 172

N-(4-cloro-2-metilfenil)isoindolin-2-carboxamida

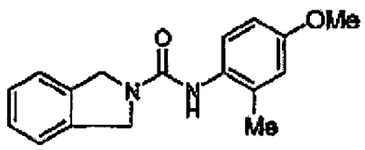


A una solución de isoindolina (238 mg, 2.0 mmol) en 1,4-dioxano seco (10 mL) se agrega 4-cloro-2-metilfenilo isoccianato (335 mg, 2.0 mmol) bajo argón a temperatura ambiente. La mezcla de reacción luego se agita a t.a. durante la noche. El disolvente se evapora bajo presión reducida, y el residuo se purifica por la recristalización a partir de etanol para dar el compuesto del título (540 mg, 94 %) como un sólido blanco. ^{1}H RMN (500 MHz, DMSO-d_6): δ 2.24 (s, 2H), 4.76 (s, 4H), 7.20 (dd, J = 2.5, 8.5 Hz, 1H), 7.27 (d, J = 2.5 Hz, 1H), 7.30-7.32 (m, 2H), 7.34-7.37 (m, 2H), 7.42 (d, J = 8.5 Hz, 1H), 7.84 (s, 1H); ^{13}C RMN (DMSO-d_6): δ 17.7, 51.9, 122.8, 125.6, 126.8, 127.3, 128.1, 129.5, 134.7, 136.8, 154.2; MS(MH^+, 287); EA calculado para $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.27; N, 9.77; Encontrado C, 66.82; H, 5.41; N, 9.92.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.89 μM.

Ejemplo 173

N-(4-metoxi-2-metilfenil)isoindolin-2-carboxamida

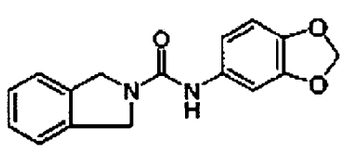


A una solución de isoindolina (576 mg, 4.0 mmol) en 1,4-dioxano seco (20 mL) se agrega 4-metoxi-2-metilfenilo isoccianato (815 mg, 5.0 mmol) bajo argón a temperatura ambiente. La mezcla de reacción luego se agita a t.a. durante la noche. El disolvente se evapora bajo presión reducida, y el residuo se purifica por cromatografía sobre gel de sílice (TBtO Ac/Hexanos: 1:1) para dar el compuesto del título (1.18 g, 84 %) como un sólido blanco. ^{1}H RMN (500 MHz, DMSO-d_6): δ 2.19 (s, 3H), 3.72 (s, 3H), 4.73 (s, 4H), 6.72 (dd, J = 2.5 Hz, 8.5 Hz, 1H), 6.78 (d, J = 2.5 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.30-7.32 (m, 2H), 7.34-7.36 (m, 2H), 7.74 (s, 1H), ^{13}C RMN (DMSO-d_6): δ 18.2, 51.9, 55.1, 110.9, 115.1, 122.8, 127.2, 127.8, 130.6, 135.1, 137.0, 154.9, 156.5; MS(MH^+, 283); EA calculado para $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92; Encontrado C, 72.16; H, 6.82; N, 9.98.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 4.5 μM.

Ejemplo 174

N-(3,4-metilenodioxifenil)isoindolin-2-carboxamida



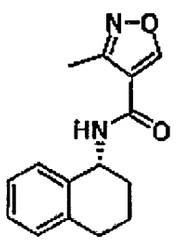
A una solución de 3,4-(metilenodioxi)anilina (150 mg, 1.09 mmol) en DCM seco (4 mL) se agrega en forma de gota cloroformato de fenilo (0.138 ml, 1.09

mmol) y trietilamina (0.153 ml, 1.09 mmol). Después la mezcla de reacción se agita a t.a durante 8 hr., se agregan isoindolina (0.123 ml, 1.09 mmol) y trietilamina (0.153 ml, 1.09 mmo), y la mezcla de reacción se agita durante la noche. El disolvente luego se remueve bajo presión reducida, y el residuo se purifica por cromatografía sobre gel de sílice (EtOAC/Hexano: 1:3) para dar el compuesto del título (185 mg, 60%) como un sólido blanco: pf:165-166° C. ^{1}H RMN ($CDCl_3$, 500 MHz): 4.82 (s, 4H); 5.93 (s, 2H); 6.20 (s, 1H); 6.73 (s, 2H); 7.17 (s, 1H); 7.30 (m, 4H). MS (MH^+, 283).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 1.05 μM.

Ejemplo 175

(1,2,3,4-tetrahidro-naftalen-1-il)-amida de ácido 3-Metil-isoxazol-4-carboxílico



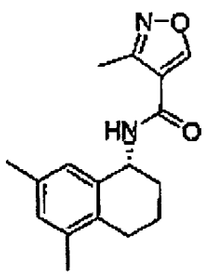
A una solución de ácido 3-Metil-isoxazol-4-carboxílico (0.52 g, 4.06 mmol) en DCM (15 mL) y DMF (2 mL), se agrega HOBt (1.1 g, 8.14 mmol) y EDCI (0.896 g 4.67 mmol). La solución amarilla clara se enfría a 0 C y se le permite agitar bajo Ar durante 15 minutos. Se agrega a la solución (R)-1-Amino-1,2,3,4-tetrahidronaftaleno (0.73 mL, 5.04 mmol y la mezcla de reacción se le permite calentar lentamente a temperatura ambiente y se agita durante la noche. La dilución con DCM (50 mL) se sigue por extracción acuosa ($NaHCO_3$ agua, solución

salina (50 mL), se seca sobre $MgSO_4$, la filtración y remoción del disolvente en vacío. La cromatografía de gel de sílice (0 -25% Hexano:EtOAc) proporciona el compuesto del título (650 mg; 62.5 %) como un sólido pegajoso. ^1H RMN ($CDCl_3$) δ 1.88 (m, 3H), 2.12 (m, 1H), 2.51 (s, 3H), 2.81 (m, 2H), 5.32 (m, 1H), 5.99 (bd, 1H), 7.13 (m, 1H), 7.20 (m, 2H) 7.20 (m, 2H); ^{13}C RMN ($CDCl_3$) δ 11.22, 20.15, 29.41, 30.35, 47.93, 116.73, 126.72, 127.88, 128.88, 129.65, 136.25, 138.00, 158.45, 160.28. ESIMS: 257 (M^+H) EA calculado para $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93; encontrado C, 70.61; H, 6.11; N, 11.09.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 5.8μM.

Ejemplo 176

(*R*)-*N*-(5,7-Pimetil-1,2,3,4-tetrahidronaftalen-1-il)-3-metilisoxazol-4-carboxamida



A una solución de ácido 3-metilisoxazol-4-carboxílico (41.7 mg, 0.339 mmol) en 3 mL DMF se agregan EDCI·HCl (71 mg, 0.373 mmol) y HOBt (50 mg, 0.373 mmol). La mezcla se agita a t.a. durante 20 min, en cuyo tiempo se agrega (R)-5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-amina (ejemplo a) (65 mg, 0.37 mmol). La mezcla de reacción se agita a t.a. durante la noche, se diluye con EtOAc, se lava sucesivamente con HCl 1 N, H_2O, $NaHCO_3$ saturado, H_2O y solución salina. La

solución resultante se seca sobre $MgSO_4$, se filtra, se concentra en vacío y se cromatografía en columna flash (15-20 % de EtOAc en Hexano) para producir (*R*)-*N*-(5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-il)-3-metilisoxazol-4-carboxamida (55 mg, 57% de (*S*)-2-((*R*)-5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-ilamino)-2-feniletanol (ejemplo b). ^{1}H RMN (500 MHz, DMSO-d_6): δ 1.74 (m, 2H), 1.86 (m, 2H), 2.16 (s, 3H), 2.19 (s, 3H), 2.43 (s, 3H), 2.55 (m, 2H), 5.10 (m, 1H), 6.86 (s, 1H), 6.89 (s, 1H), 8.60 (d, 1H, *J*= 8.40 Hz), 9.27 (s, 1H). ^{13}C RMN (125 MHz, DMSO-d_6): δ 10.6, 19.1, 19.6, 20.6, 25.8, 29.4, 46.9, 115.4, 126.4, 129.1, 132.6, 134.1, 135.8, 136.6, 158.5, 159.6, 159.9. MS(M+H, 285). Pf = 124-125° C.

a. Preparación de (*R*)-5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-amina: A una solución de (*S*)-2-((*R*)-5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-ilamino)-2-feniletanol (ejemplo b) (100 mg, 0.339 mmol) en 2.5 mL de MeOH a t.a. se agregan metilamina (1.4 mL, 2 M de solución en MeOH) y ácido peryódico (200 mg, 0.880 mmol, en 2 mL H_2O). La mezcla de reacción se agita a t.a. durante 4 h, en cuyo tiempo se extrae con éter. A los extractos de éter combinados se agrega 2 mL de HCl 2N, y la mezcla bifásica se agita durante 30 min, se concentra en vacío, y la fase acuosa restante se lava con éter, se basifica con solución de NaOH 6 N a 0° C, se extrae con éter, se seca sobre K_2CO_3, se filtra y se concentra en vacío para producir 65 mg de (R)-5,7-dimetil-1, 2,3,4-tetrahidronaftalen-1 –amina cruda, llevada a la siguiente etapa sin purificación adicional.

b. Preparación de (*S*)-2-((*R*)-5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-ilamino)-2-feniletanol: A una solución de (*S*)-2-(5,7-dimetil-3,4-dihidronaftalen-l(2H)-ilideneamino)-2-feniletanol (ejemplo c) (908 mg, 3.10 mmol) disuelto en 15 mL de TNF anhidro se agrega ácido acético glacial . La mezcla se enfría a 0° C, en cuyo tiempo se agrega lentamente $NaBH_4$. La reacción se agita bajo Ar a 0° C

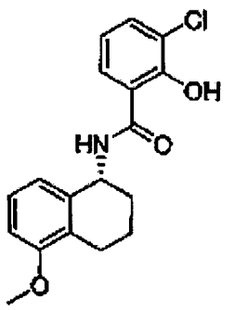
durante 2h, en cuyo tiempo se agregan 15 mL de CH_2Cl_2 seguido por 10 mL $NaHCO_3$ saturado. La capa orgánica se separa y se lava sucesivamente con $NaHCO_3$ saturado (4 x 20 mL) y solución salina (1x). La solución se seca sobre $MgSO_4$, se filtra, se concentra en vacío y se purifica por cromatografía de columna flash (4:1 Hex:EtOAc) para producir (*S*)-2-((*R*)-5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-ilamino)-2-feniletanol como un sólido ceroso blanco (30 % de tetralona). ^{1}H RMN (500 MHz, $CDCl_3$): δ 1.42 (m, 1H), 1.55 (m, 2H), 1.90 (m, 1H), 2.11 (s, 3H), 2.22 (s, 3H), 2.35 (ddd, 1H, *J*= 17.32, 10.84, 6.47 Hz), 2.57 (m, 1H), 3.25 (ddd, 1H, *J*= 10.63, 8.90, 6.01 Hz), 3.41 (dt, 1H, *J*= 10.70, 4.65 Hz), 3.50 (bs, 1H), 3.86 (dd, 1H, *J*= 8.70, 4.23 Hz), 4.93 (t, 1H, *J*= 5.44 Hz), 6.82 (s, 1H), 6.85 (s, 1H), 7.24 (td, 1H, *J*= 7.22, 1.22 Hz), 7.34 (t, 2H, *J*= 7.42 Hz), 7.42 (dd, 2H, *J*= 7.08, 1.28 Hz). MS(M+H, 296).

c. Preparación de (*S*)-2-(5,7-dimetil-3,4-dihidronaftalen-1(2*H*)-ilideneamino)-2-feniletanol: A un frasco de fondo redondo de 50 mL equipado con una trampa Dean-Stark y condensador de reflujo se agregan 5, 7-dimetil tetralona (540 mg, 3.10 mmol), (S)-fenilglicinol (468 mg, 3.40 mmol), monohidrato de ácido toluenosulfónico (30 mg, 0.16 mmol) y xilenos (30 mL). La reacción se refluye durante 8h, se enfría a t.a., se diluye con tolueno y se lava sucesivamente con $NaHCO_3$ saturado (1x), H_2O (5x) y solución salina (Ix). La solución resultante se seca sobre $MgSO_4$, se filtra, se concentra en vacío y se lleva a la siguiente etapa sin purificación adicional.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.52 μM.

Ejemplo 177

(*R*)-3-Cloro-2-hidroxi-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il) benzamida

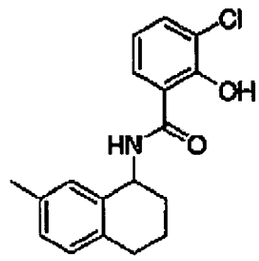


Se prepara de una forma similar al ejemplo 176 partiendo de 5-metoxi-3,4-dihidronaftalen-1(2H)-ona. El acoplamiento de amida se desarrolla utilizando ácido 3-clorosalicílico. Rendimiento 27 % general. ^{1}H RMN (500 MHz, DMSO-d_6): δ 1.73 (m, 1H), 1.83 (m, 1H), 1.96 (m, 2H), 2.61 (m, 2H), 3.78 (s, 3H), 5.27 (m, 1H), 6.78 (d, 1H, *J*= 7.82 Hz), 6.86 (m, 2H), 7.14 (t, 1H, *J*= 7.98 Hz), 7.60 (dd, 1H, *J*= 7.88, 1.30 Hz), 7.94 (dd, 1H, *J*= 8.03, 1.39 Hz), 9.30 (d, 1H, *J*= 8.06 Hz), 13.80 (s, 1H). ^{13}C RMN (125 MHz, DMSO-d_6): δ 19.5, 22.7, 28.9, 47.4, 55.3, 108.6, 115.8, 118.7, 119.8, 121.1, 125.9, 126.2, 126.4, 133.8, 137.3, 156.7, 156.8, 168.7. MS(M+H, 332). Pf 175-176° C.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.18 μM.

Ejemplo 178

3-Cloro-2-hidroxi-N-(7-metil-1,2,3,4-tetrahidronaftalen-1-il)benzamida



A una solución de ácido 3-clorosalicílico (33 mg, 0.19 mmol), HOBt (28 mg, 0.21 mmol) y EDCI -HCl (40 mg, 0.21 mmol) disuelto en 1 mL DMF se agrega una solución de 7-metil-1,2,3, 4-tetrahidronaftalen-1-amina (ejemplo a) (33 mg, 0.20 mmol) en 1 mL DMF. La mezcla resultante se agita a t.a. durante 24 h, en cuyo tiempo se concentra en vacío y se purifica por LCMS preparativo para producir 3-cloro-2-hidroxi-N-(7-metil-1,2,3,4-tetrahidronaftalen-1-il)benzamida como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 1.74 (m, 1H), 1.82 (m, 1H), 1.97 (m, 2H), 2.21 (s, 3H), 2.73 (m, 2H), 5.26 (m, 1H), 6.89 (m, 1H), 6.98 (s, 1H), 7.02 (t, 2H, *J*= 8.32 Hz), 7.60 (m, 1H), 7.95 (m, 1H), 9.32 (m, 1H), 13.83 (s, 1H). MS(M+H, 316).

a. Preparación de 7-metil-1,2,3,4-tetrahidronaftalen-1-amina: una cantidad catalítica de Níquel Raney (suspensión en agua) se lava con MeOH seco bajo argón en un frasco de fondo redondo. A una solución del Ni Raney lavada en amoniaco metanólico (15 mL, 7N), se agrega 7-metil-3,4-dihidronaftalen-1(2H)-ona oxima (ejemplo b) (218 mg, 1.24 mmol), y la mezcla se agita bajo un balón de H_2 durante 20 h. Luego de completar, la reacción se filtra a través de celita, el filtrado se concentra en vacío, se diluye con EtOAc, se lava con agua y solución salina, se seca sobre $MgSO_4$, se filtra y el disolvente se remueve bajo presión reducida para proporcionar 7-metil-1,2,3,4-tetrahidronaftalen-1-amina as un jarabe café, se lleva a la siguiente etapa sin purificación adicional. MS(M+H, 161).

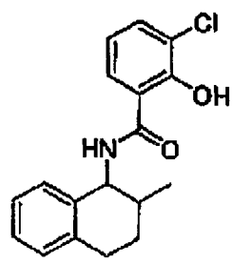
625

b. A una solución de 7-metil-3,4-dihidronaftalen-1(2H)-ona (200 mg, 1.24 mmol) y clorhidrato de hidroxilamina (148 mg, 2.12 mmol) en 1.08 mL de H_2O, 1.52 mL MeOH y 320 µL de THF, se agrega una solución de acetato de sodio (274 mg, 3.34 mmol) disuelto en 760 µL de H_2O. La mezcla se agita a 70° C durante 2 h, se enfría a t.a. y se diluye con 2 mL de H_2O. La mezcla resultante se agita durante 9.6 h, el agua se pipetea hacia afuera del jarabe resultante y H_2O residual se azeotropiza con tolueno para producir un jarabe café, que se lleva a la siguiente etapa sin purificación adicional.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 1.48 µM.

Ejemplo 179

3-cloro-2-hidroxi-N-(2-metil-1,2,3,4-tetrahidronaftalen-1-il)benzamida



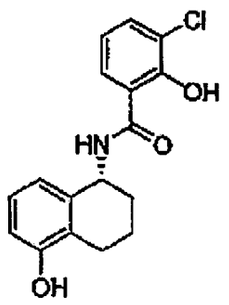
Se prepara de una forma similar al ejemplo 178 partiendo de 2-metil-3,4-dihidronaftalen-1(2H)-ona para producir dos mezclas de productos isoméricos (170 mg, 49 %). MS(M+H, 316). Pf de mezcla 161-162° C. El producto A: ^{1}H RMN (500 MHz, DMSO-d_6): δ 1.00 (d, 3H, *J*= 6.80 Hz), 1.64 (qd, 1H, *J*= 11.47, 5.90 Hz), 2.09 (m, 1H), 5.39 (dd, 1H, *J*= 9.08, 4.77 Hz), 6.89 (t, 1H, *J*= 7.94 Hz), 7.17 (m, 4H), 7.59 (dd, 1H, *J*= 7.88, 1.38 Hz), 8.00 (dd, 1H, *J*= 8.17, 1.42 Hz), 8.96 (d, 1H, *J*= 9.07 Hz), 13.70 (s, 1H).). ^{13}C RMN (125 MHz, DMSO-d_6): δ 17.0, 25.5, 28.4, 32.6,

39.0, 49.9, 115.9, 118.6, 121.1, 125.9, 126.5, 127.2, 128.8, 129.5, 133.8, 133.9, 136.3, 137.0, 156.6, 168.8. El producto B: ^{1}H RMN (500 MHz, DMSO-d_6): δ 1.00 (d, 3H, *J*= 6.80 Hz), 1.64 (qd, 1H, *J*= 11.47, 5.90 Hz), 2.09 (m, 1H), 5.39 (dd, 1H, *J*= 9.08, 4.77 Hz), 6.89 (t, 1H, *J*= 7.94 Hz), 7.17 (m, 4H), 7.59 (dd, 1H, *J*= 7.88, 1.38 Hz), 8.00 (dd, 1H, *J*= 8.17, 1.42 Hz), 8.96 (d, 1H, *J*= 8.92 Hz), 13.85 (s, 1H).). ^{13}C RMN (125 MHz, DMSO-d_6): δ 19.0, 28.4, 29.7, 34.4, 54.2, 115.7, 118.8, 121.2, 125.9, 126.0, 126.7, 127.2, 128.6, 133.9, 136.6, 137.0, 156.9, 169.6.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.38 μM.'

Ejemplo 180

3-cloro-2-hidroxi-N-(5-hidroxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida

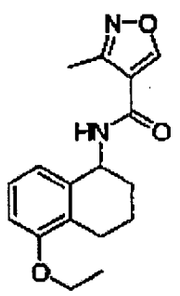


Se prepara de una forma similar al ejemplo 178 partiendo de 5-hidroxi-3,4-dihidronaftalen-1(2H)-ona, y el enantiómero puro se aísla utilizando purificación HPLC quiral. MS(M+H, 318). Pf 148-151° C.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 1.17 μM.

Ejemplo 181

3-Cloro-*N*-(5-etoxi-1,2,3,4-tetrahidronaftalen-1-il)-2-hidroxibenzamida



Se prepara de una forma similar al ejemplo 178 partiendo de 5-etoxi-3,4-dihidronaftalen-1(2H)-ona (ejemplo a). El acoplamiento de amida se desarrolla utilizando ácido 3-metilisoxazol-4-carboxílico. ^{1}H RMN (500 MHz, DMSO-d_6): δ 1.33 (t, 3H, *J*= 6.98 Hz), 1.73 (m, 2H), 1.89 (m, 2H), 2.42 (s, 3H), 2.60 (m, 2H), 4.01 (m, 2H), 5.12 (m, 1H), 6.81 (t, 2H, *J*= 8.65 Hz), 7.11 (t, 1H, *J*= 7.94 Hz), 8.62 (d, 1H, *J*= 8.51 Hz), 9.26 (s, 1H). MS(M+H, 301).

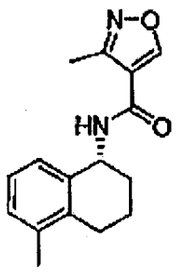
a. Preparación de 5 -etoxi-3,4-dihidronaftalen-1 (2H)-ona: A una solución de 5-hidroxi-3,4-dihidronaftalen-1(2H)-ona (600 mg, 3.70 mmol) y K_2CO_3 (2.56 g, 18.5 mmol) en 18 mL de DMF, se agrega yoduro de etilo (1.48 mL, 18.5 mmol). La reacción se calienta a 180° C durante 20 min en un reactor de microondas. Luego de completar, la reacción se diluye con EtOAc, se lava con en HCl (2x), solución salina, se seca sobre $MgSO_4$, se filtra y se concentra en vacío. Los cristales rojos resultantes se purifican por cromatografía de columna flash (2:1 Hex:EtOAc) para obtener 5-etoxi-3,4-dihidronaftalen-1(2H)-ona como un sólido amarillo claro (490 mg, 70 %). ^{1}H RMN (500 MHz, DMSO-d_6): δ 1.36 (t, 3H, *J*= 6.95 Hz), 2.01 (quint, 2H, *J*= 6.48 Hz), 2.54 (m, 2H), 2.81 (t, 2H, *J*= 6.12 Hz), 4.07 (q, 2H, *J*= 7.00 Hz),

7.19 (dd, 1H, *J*= 8.02, 0.80 Hz), 7.28 (t, 1H, *J*= 8.02 Hz), 7.46 (dd, 1H, *J*= 7.72, 0.96 Hz).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 4.5 μM.

Ejemplo 182

(*R*)-3-Metil-N-(5-metil-1,2,3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida



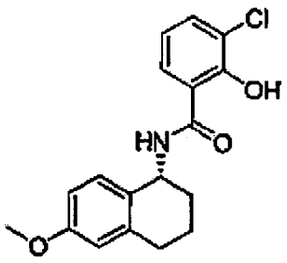
Se prepara en forma similar al Ejemplo 178 partiendo de 5-metil-3,4-dihidronaftalen-1 (2H)-ona[1]. El acoplamiento de amida se desarrolla utilizando ácido 3-metilisoxazol-4-carboxílico. El enantiómero puro se aísla utilizando purificación HPLC quiral . ^{1}HRMN (500 MHz, DMSO-d_6): δ 1.75 (m, 2H), 1.91 (m, 2H), 2.19 (s, 3H), 2.42 (s, 3H), 2.61 (m, 2H), 5.13 (m, 1H), 7.06 (m, 3H), 8.62 (d, 1H, *J*= 8.51 Hz), 9.25 (s, 1H). MS(M+H, 271).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 2.80μM.

[1] Zhang, X.; De Los Angeles, J. E.; He, M.-Y.; Dalton, J. T.; Shams, G.; Lei, L.; Patil, P. N.; Feller, D. R.; Miller, D. D.; Hsu, F.-L. *J. Med. Chem.* 1997, 40, 3014-3024.

Ejemplo 183

(*R*)-3-Cloro-1-hidroxi-N-(6-metoxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida

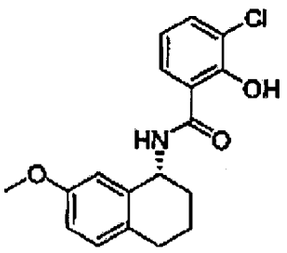


Se prepara de una forma similar al ejemplo 178 partiendo de 6-metoxi-3,4-dihidronaftalen-1(2H)-ona. El enantiómero puro se aísla utilizando purificación HPLC quiral . ^{1}H RMN (500 MHz, DMSO-d_6): δ 1.74 (m, 1H), 1.83 (m, 1H), 1.97 (m, 2H), 2.77 (m, 2H), 3.72 (s, 3H), 5.23 (m, 1H), 6.70 (d, 1H, *J*= 2.60 Hz), 6.74 (dd, 1H, *J*= 8.60, 2.78 Hz), 6.87 (t, 1H, *J*= 8.03 Hz), 7.08 (d, 1H, *J*= 8.52 Hz), 7.60 (dd, 1H, *J*= 7.88, 1.38 Hz), 7.94 (dd, 1H, *J*= 8.13, 1.43 Hz), 9.25 (d, 1H, *J*= 8.34 Hz), 13.83 (s, 1H). ^{13}C RMN (125 MHz, DMSO-d_6): δ 20.1, 29.1, 29.6, 46.9, 55.0, 112.5, 113.1, 115.8, 118.6, 121.1, 126.2, 128.4, 129.2, 133.8, 138.7, 156.8, 158.2, 168.7. MS(M+H, 332). Pf 111-113° C.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.85μM.

Ejemplo 184

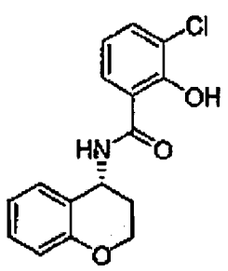
(*R*)-3-Cloro-2-hidroxi-N-(7-metoxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida



Se prepara de una forma similar al ejemplo 178 partiendo de 7-metoxi-3,4-dihidronaftalen-1(2H)-ona. El enantiómero puro se aísla utilizando purificación HPLC quiral. ^{1}H RMN (500 MHz, DMSO-d_6): δ 1.74 (m, 1H), 1.82 (m, 1H), 1.97 (m, 2H), 2.71 (m, 2H), 3.66 (s, 3H), 5.24 (m, 1H), 6.70 (d, 1H, *J*= 2.69 Hz), 6.79 (dd, 1H, *J*= 8.44, 2.78 Hz), 6.87 (t, 1H, *J*= 7.96 Hz), 7.06 (d, 1H, *J*= 8.46 Hz), 7.60 (dd, 1H, *J*= 7.88, 1.28 Hz), 7.95 (dd, 1H, *J*= 8.01, 2.60 Hz), 9.33 (m, 1H), 13.75 (s, 1H). MS(M+H, 332). El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.26μM.

Ejemplo 185

(R)-3-Cloro-N-(3,4-dihidro-2H-cromen-4-il)-2-hidroxibenzamida



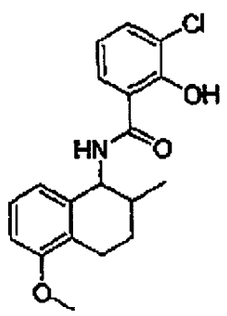
Se prepara de una forma similar al ejemplo 178 partiendo de 2,3-dihidrocromen-4-ona. El enantiómero puro se aísla utilizando purificación HPLC quiral. ^{1}H RMN (500 MHz, DMSO-d_6): δ 2.12 (m, 2H), 4.27 (m, 2H), 5.33 (m, 1H), 6.81 (d, 1H, *J*= 8.27 Hz), 6.89 (td, 2H, *J*= 7.49, 0.72 Hz), 7.17 (d, 2H, *J*= 7.40 Hz),

7.60 (d, 1H, *J*= 7.32 Hz), 7.93 (d, 1H, *J*= 8.03 Hz), 9.40 (br. s, 1H), 13.65 (s, 1H). MS(M+H, 304).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 1.03μM.

Ejemplo 186

3-Cloro-2-hidroxi-*N*-(5-metoxi-2-metil-1,2,3,4-tetrahidronaftalen-1-il)benzamida



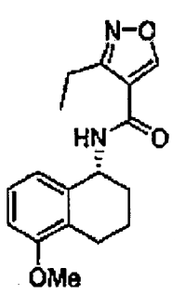
Se prepara de una forma similar al ejemplo 178 partiendo de 5-metoxi-2-metil-3,4-dihidronaftalen-1(2H)-ona (ejemplo a) para suministrar una mezcla de dos series de enantiómeros. El par enantiomérico A: ^{1}H RMN (500 MHz, DMSO-d_6): δ 0.92 (d, 3H, *J*= 6.78 Hz), 1.67 (m, 1H), 1.76 (m, 1H), 2.02 (m, 2H), 2.80 (m, 1H), 3.79 (s, 3H), 5.34 (m, 1H), 6.79 (d, 1H, *J*= 7.69), 6.84 (d, 1H, *J*= 7.82 Hz), 7.13 (t, 1H, *J*= 7.90 Hz), 7.56 (m, 1H), 7.93 (m, 1H), 8.90 (br. s, 1H). MS(M+H, 346). Par enantiomérico B: ^{1}H RMN (500 MHz, DMSO-d_6): δ 0.99 (d, 3H, *J*= 6.47 Hz), 1.55 (m, 1H), 1.67 (m, 1H), 1.76 (m, 1H), 2.02 (m, 2H), 2.80 (m, 1H), 3.78 (s, 3H), 4.92 (m, 1H), 6.72 (d, 1H, *J*= 7.85 Hz), 6.84 (m, 1H), 7.13 (m, 1H), 7.56 (m, 1H), 7.93 (m, 1H), 9.25 (br. s, 1H). MS(M+H, 346).

a. Preparación de 5-metoxi-2-metil-3,4-dihidronaftalen-1(2H)-ona: A una solución de LDA (2.85 mL, 2.0 M de solución en heptano/THF/etilbenceno) en 2 mL de THF a -78° C se agrega una solución de 5-metoxi-3,4-dihidronaftalen-1(2*H*)-ona (1.00 g, 5.70 mmol) en 2 mL de THF. La mezcla se agita a -78° C durante 20 min, en cuyo tiempo se agrega en forma de gota MeI. La reacción se calienta a t.a. durante 17 h y se apaga con NH_4Cl saturado. La suspensión se extrae con Et_2O, se seca sobre $MgSO_4$, se filtra, se concentra en vacío y se cromatografía en columna flash (9:1 Hex:EtOAc) para producir 5-metoxi-2-metil-3,4-dihidronaftalen-1(2H)-ona como un aceite claro (374 mg, 35 %). ^{1}H RMN (500 MHz, $CDCl_3$): δ 1.24 (d, 3H, *J*= 6.72 Hz), 1.83 (m, 1H), 2.20 (dq, 1H, *J*= 13.32, 4.50 Hz), 2.58 (m, 1H), 2.74 (ddd, 1H, *J*= 16.66, 11.35, 4.92 Hz), 3.08 (dt, 1H, *J*= 17.80, 4.32 Hz), 3.86 (s, 3H), 7.00 (dd, 1H, *J*= 7.90, 0.70 Hz), 7.26 (t, 1H, *J*= 7.82 Hz), 7.64 (dd, 1H, *J*= 7.86, 0.72 Hz).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.50μM.

Ejemplo 187

(*R*)-3-Etil-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida



A una solución de ácido 3-etilisoxazol-4-carboxílico (ejemplo a) (30 mg, 0.21 mmol), HOBt (41 mg, 0.30 mmol) y EDCI-HCl (58 mg, 0.30 mmol) disuelto en 2 mL

633

DMF, se agrega (R)-5-metoxi-1,2,3,4-tetrahidronaftalen-1-amina (ejemplo c) (53 mg, 0.30 mmol). La reacción se agita a t.a. durante 24 h, en cuyo tiempo se concentra en vacío y se purifica por TLC preparativo (10:1 Hex:EtOAc) para suministrar (*R*)-3-Etil-*N*-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida como un sólido blanco. ^{1}H RMN (400 MHz, CD_3OD): δ 1.30 (t, 3H, *J*= 7.20 Hz), 1.84 (m, 2H), 1.97 (m, 2H), 2.68 (m, 2H), 2.96 (q, 2H, *J*= 7.60 Hz), 3.81 (s, 3H), 5.21 (m, 1H), 6.80 (d, 1H, *J*= 7.60 Hz), 6.85 (d, 1H, *J*= 7.60 Hz), 7.14 (d, 1H, *J*= 8.00 Hz), 8.98 (s, 1H). MS(M+H, 301).

a. Preparación de ácido 3-etilisoxazol-4-carboxílico: A una solución de 3-etilisoxazol-4-carboxilato de etilo (ejemplo b) (422 mg, 2.49 mmol) en 2 mL de 1:1 EtOH:H_2O, se agrega NaOH (110 mg, 2.74 mmol). La reacción se agita a t.a. durante 24 h, en cuyo tiempo se neutraliza con HCl 1N, se extrae con EtOAc, se seca sobre $MgSO_4$, se filtra y se concentra en vacío para producir un sólido blanco se lleva a la siguiente etapa sin purificación adicional.

b. Preparación de 3-etilisoxazol-4-carboxilato de etilo: A una solución preparada por el método de McMurry, J. E.; *Org. Syn. Coll.* Vol. 6, 781, de 3-(pirrolidin-1-il)acrilato de etilo (2.0 g, 11.8 mmol), Et_3N (4.7 mL) y nitropropano (1.38 mL, 15.4 mmol) en 12 mL de $CHCl_3$ a 0º C, se agrega una solución de $POCl_3$ (1.21 mL, 13.00 mmol) en 2.5 mL de $CHCl_3$ por vía de un embudo de adición durante 3 h. Hasta completar la adición de la mezcla $POCl_3$, la reacción se calienta a t.a., se agita durante 20 h y se apaga con H_2O. La capa orgánica se separa y se lava sucesivamente con HCl 1N, 5 % de NaOH y solución salina. La solución resultante se seca sobre $MgSO_4$, se filtra, se concentra en vacío y se purifica por cromatografía de columna flash (4:1 Hex:EtOAc) para producir 3-etilisoxazol-4-carboxilato de etilo como un sólido blanco (1.43 g, 72 %). ^{1}H RMN (500 MHz,

DMSO-d_6): δ 1.21 (t, 3H, *J*= 7.62 Hz), 1.28 (t, 3H, *J*= 7.30 Hz), 2.85 (q, 2H, *J*= 7.47 Hz), 4.26 (q, 2H, *J*= 6.98 Hz), 9.51 (s, 1H). ^{13}C RMN (125 MHz, DMSO-d_6): δ 11.9, 14.0, 18.5, 60.5, 79.1, 160.8, 162.7, 164.7, 164.8.

c. Preparación de (*R*)-5-metoxi-1,2,3,4-tetrahidronaftalen-1-amina: A una solución de (*S*)-2-((*R*)-5-metoxi-1,2,3,4-tetrahidronaftalen-1-ilamino)-2-feniletanol (ejemplo d) (3.22 g, 10.83 mmol) en 70 mL de MeOH a 0° C se agregan metilamina (7.5 mL, 40 % de solución en H_2O) y ácido peryódico (6.4 g, 28.15 mmol, en 50 mL H_2O). La mezcla de reacción se agita a t.a. durante 4 h, en cuyo tiempo se extrae con éter. A los extractos de éter combinados se agrega 30 mL de HCl 2N, y la mezcla bifásica se agita durante 30 min, se concentra en vacío, y la fase acuosa restante se lava con éter, se basifica con solución de NaOH bisásica a 0° C, se extrae con éter, se seca sobre K_2CO_3, se filtra y se concentra en vacío para producir 1.72 g de (*R*)-5-metoxi-1, 2,3,4-tetrahidronaftalen-1 -amina crudo (90 %), que se lleva a la siguiente etapa sin purificación adicional.

d. Preparación de (*S*)-2-((*R*)-5-metoxi-1,2,3,4-tetrahidronaftalen-1-ilamino)-2-feniletanol: A una solución de $NaBH_4$ (781 mg, 20.63 mmol), disuelto en 40 mL de THF anhidro bajo Ar a 0° C, se agrega ácido acético glacial (3.48 mL, 60.10 mmol) en forma de gotas. La mezcla se agita a 0° C durante 15 min o hasta que la evolución del gas se completa. Una solución de (*S*)-2-(5-metoxi-3,4-dihidronaftalen-1(2*H*)-ilideneamino)-2-feniletanol (ejemplo e) (5.3 g, 17.94 mmol) disuelta en 25mL de THF anhidro se agrega a la mezcla $NaBH(OAc)_3$, y la reacción se agita durante 3 h a 0° C. Luego de completar , la reacción se apaga por por adición de K2CO3 saturado, se diluye con EtOAc, y la capa orgánica se seca sobre MgSO4, se filtra, se concentra en vacío y se purifica por cromatografía de columna flash (15-25 % de EtOAc en Hex) para producir (*S*)-2-((*R*)-5,7-dimetil-

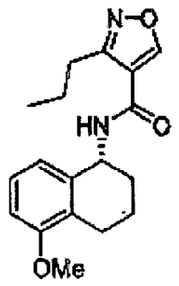
1,2,3,4-tetrahidronaftalen-1-ilamino)-2-feniletanol como un sólido ceroso blanco (3.22 g, 60 % de tetralona). ^{1}H RMN (500 MHz, $CDCl_3$): δ 1.70 (m, 3H), 1.84 (m, 1H), 2.51 (m, 1H), 2.74 (m, 1H), 3.50 (dd, 1H, *J*= 10.73, 7.95 Hz), 3.71 (dd, 1H, *J*= 10.76, 4.67 Hz), 3.77 (m, 1H), 3.81 (s, 3H), 3.99 (dd, 1H, *J*= 7.95, 4.60 Hz), 6.72 (d, 1H, *J*= 7.98 Hz), 6.96 (d, 1H, *J*= 7.70 Hz), 7.15 (t, 1H, *J*= 7.90 Hz), 7.29 (m, 1H), 7.36 (m, 4H). MS(M+H, 298).

e. Preparación de (*S*)-2-(5-metoxi-3,4-dihidronaftalen-1(2*H*)-ilideneamino)-2-feniletanol: A un frasco de fondo redondo de 50 mL equipado con una trampa Dean-Stark y condensador de reflujo se agregan 5-metoxi tetralona (3.7 g, 21.0 mmol), (*S*)-fenilglicinol (3.17 g, 23.1 mmol), monohidrato de ácido toluenosulfónico (200 mg, 1.05 mmol) y xilenos (40 mL). La reacción se refluye durante la noche, se enfría a t.a., se diluye con tolueno y se lava sucesivamente con $NaHCO_3$ saturado (1x), H_2O (5x) y solución salina (1x). La solución resultante se seca sobre $MgSO_4$, se filtra, se concentra en vacío y se lleva a la siguiente etapa sin purificación adicional.

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.40 μM.

Ejemplo 188

(*R*)-3-Propil-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida

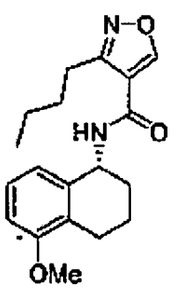


Se prepara de una forma similar al ejemplo 187 utilizando ácido 3-propilisoxazol-4-carboxílico. ^{1}H RMN (400 MHz, CD_3OD): δ 1.01 (t, 3H, *J*= 7.60 Hz), 1.74 (sext, 2H, *J*= 8.00 Hz), 1.83 (m, 2H), 1.96 (m, 2H), 2.67 (m, 2H), 2.90 (t, 2H, *J*= 7.20 Hz), 3.80 (s, 3H), 5.20 (m, 1H), 6.80 (d, 1H, *J*= 7.60 Hz), 6.85 (d, 1H, *J*= 7.60 Hz), 7.14 (d, 1H, *J*= 8.00 Hz), 8.98 (s, 1H). MS(M+H, 315).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.24 μM.

Ejemplo 189

(*R*)-3-Butil-N-(5-metlioxi-l,2,3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida



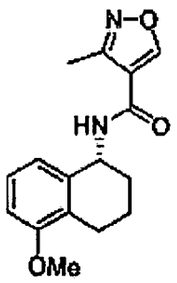
Se prepara de una forma similar al ejemplo 187 utilizando ácido 3-butilisoxazol-4-carboxílico. ^{1}H RMN (400 MHz, CD_3OD): δ 0.96 (t, 3H, *J*= 7.20 Hz), 1.40 (sext, 2H, *J*= 6.80 Hz), 1.69 (quint, 2H, *J*= 7.60 Hz), 1.84 (m, 2H), 1.97 (m, 2H), 2.67 (m, 2H), 2.92 (t, 2H, J = 7.20 Hz), 3.80 (s, 3H), 5.20 (m, 1H), 6.80 (d, 1H,

J= 7.60 Hz), 6.85 (d, 1H, *J*= 7.60 Hz), 7.14 (d, 1H, *J*= 8.00 Hz), 8.98 (s, 1H). MS(M+H, 329).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.36 μM.

Ejemplo 190

(*R*)-3-metil-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida

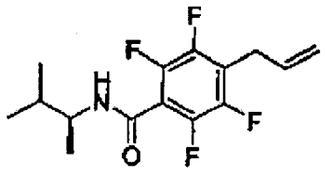


Se prepara de una forma similar al ejemplo 187 utilizando ácido 3-metilisoxazol-4-carboxílico. ^{1}H RMN (400 MHz, CD_3OD): δ 1.84 (m, 3H), 1.97 (m, 3H), 2.48 (s, 3H), 3.80 (s, 3H), 5.21 (m, 1H), 6.80 (d, 1H, *J*= 7.60 Hz), 6.85 (d, 1H, *J*= 7.60 Hz), 7.14 (d, 1H, *J*= 8.00 Hz), 8.98 (s, 1H). MS(M+H, 287).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.95 μM.

Ejemplo 191

(*S*)-4-alil-2,3,5,6-tetrafluoro-N-(3-metilbutan-2-il)benzamida

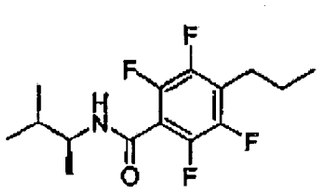


En un frasco de proceso Smith se agrega ácido 2,3,5,6 -tetrafluoro-4-alilbenzoico (238 mg, 1.02 mmol), HOBt (260 mg, 2.13 mmol), EDCI (225 mg 1.18 mmol), trietilamina (0.160 mL, 1.15 mmol), ACN (2.5 mL) y DMF (0.5 mL). a la solución se agrega (S)-3-metilbutan-2-amina (163.3 uL, 1.24 mmol) y la solución se sella y se transfiere a el microondas. Después de calentar en el microondas (150° C, 5 min del tiempo mantenido fijo), la mezcla de reacción se diluye con DCM, se lava con en HCl, agua, $NaHCO_3$ acuoso, agua y solución salina, se seca sobre MgSO4, se filtra y el disolvente se remueve en vacío, para dar el producto crudo como un sólido amarillo pálido. La recristalización de $EtOH/H_2O$ da el compuesto del título como agujas blancas (105 mg, 34%). ^1H RMN (DMSO-d6) δ 0.88 (d, J = 6.8 Hz, 6H) 1.07 (d, J = 6.8 Hz, 3H), 1.70 (m, 1H), 3.50 (d, J = 6 Hz, 2H), 3.83 (m, 1H), 5.02 (d, J = 17 Hz, 1H), 5.10 (dd, J = 1.3, 10.1 Hz, 1H), 5.94 (m, 1H), 8.64 (d, J = 8.6 Hz, 1H). MS (304.1, M + H).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.14 μM.

Ejemplo 192

(*S*)-2,3,5,6-tetrafluoro-N-(3-metilbutan-2-il)-4-propilbenzamida

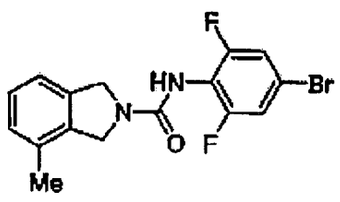


En un frasco de proceso Smith se agrega (*S*)-4-alil-2,3,5,6-tetrafluoro-N-(3-metilbutan-2-il)benzamida (ver Ejemplo 191) (80.3 mg, 0.26 mmol), formato de amonio (86 mg, 5 eq), Pd/C (10%, 9.2 mg) y EtOH (2.5 mL). La solución se sella y se transfiere al microondas. Después de calentar en el microondas (140° C, 6 min se mantiene el tiempo fijo), la mezcla de reacción se diluye con acetonitrilo (2 mL), se filtra a través de Celita, y los disolventes volátiles se remueven en vacío, para dar el producto crudo como un sólido amarillo pálido (93 mg). La recristalización de EtOH/agua da el compuesto del título como cristales frágiles blancos (45 mg, 56%). 1H RMN (DMSO-d6) δ 0.88 (s, 9H), 0.90 (m, 9H), 1.05 (d, J = 6.8 Hz, 3 H), 1.60 (m, 2 H), 1.70 (m, 1H), 2.71 (t, J = 7. 5 Hz, 2H), 3.80 (m, 1H), 8.64 (d, *J*= 8.8 Hz, 1H). MS (306.3, M+H).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.14 μM.

Ejemplo 193

N-(4-bromo-2,6-difluorofenil)-4-metilisoindolin-2-carboxamida



Se prepara de una forma similar al ejemplo 172 utilizando 2,6-difluoro-4-bromofenilo isoccianato y 4-metilisoindolina (**Ejemplo 193a**). ^{1}H RMN (500 MHz, DMSO-d_6): δ 2.25 (s, 3H), 4.65 (s, 2H), 4.71 (s, 2H), 7.10 (d, J = 7.4 Hz, 1H), 7.16

(d, J = 7.4 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.52 (d, J = 7.1 Hz, 2H), 8.29 (s, 1H). MS (MH^+, 369, 367).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.02 µM.

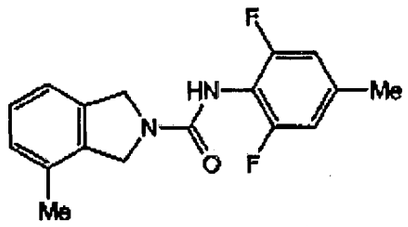
Ejemplo 193a: 4-Metilisoindolina: Una solución de 3-metilftalimida (1.61 g, 10.0 mmol; **Ejemplo 193b**) y complejo sulfuro de metil borano (2.0 M de solución en THF, 20 mL, 40.0 mmol) en THF seco (20 mL) se refluye bajo argón durante 48 h. Después se enfría por debajo de 0° C, la mezcla de reacción cuidadosamente se apaga con MeOH (10 mL), y luego con HCl 3 N (10 mL). La solución luego se refluye durante otras 2 h, y se enfría por debajo de 0° C otra vez con un baño de hielo, y se neutraliza con NaOH 3 N. La mezcla se extrae con Et_2O (3X), y las capas orgánicas combinadas se lavan con solución salina, se secan sobre NaOH sólido. La evaporación del disolvente da la 4-metilisoindolina cruda como aceite café el cual se utiliza directamente en la síntesis de urea sin purificación adicional. MS (MH^+, 134).

Ejemplo 193b: 3-Metilftalimida: Un polvo agitado de anhídrido 3-metilftálico (3.24 g, 20.0 mmol) se trata con solución de amoniaco concentrada (~ 28 %, 10 mL). La solución se calienta gradualmente a 250° C hasta que la mezcla esté en un estado de fusión quieta. Se requiere de aproximadamente una hora antes que toda el agua se haya ido y aproximadamente otra hora antes que la temperatura de la mezcla de reacción alcance 250° C y la mezcla se funda homogéneamente. La mezcla de reacción caliente se enfría por debajo de y se solidifica para dar 3-metilftalimida como un sólido blancuzco que es prácticamente puro Sin tratamiento adicional. La muestra analítica se purifica por sublimación

para dar 3-metilftalimida como un sólido blanco. ^{1}H RMN (500 MHz, DMSO-d_6): δ 2.59 (s, 3H), 7.59 (d, J = 7.4 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.67 (t, J = 7.4 Hz, 1H), 10.35 (b, 1H). MS (MH^+, 162).

Ejemplo 194

N-(2,6-difluoro-4-metilfenil)-4-metilisoindolin-2-carboxamida



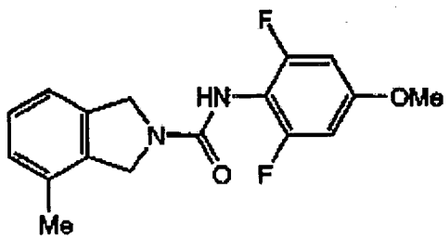
Se agrega cloruro de metilmagnesio (3.0 M en THF, 0.1 mL, 0.3 mmol) lentamente a $ZnCl_2$ anhidro (68 mg, 0.3 mmol) en THF seco (1 mL) bajo argón. La suspensión blanca resultante se agita a 50° C durante 3 h. en un frasco separador una solución de N-(4-bromo-2,6-difluorofenil)-4-metilisoindolin-2-carboxamida (ejemplo 192) (37 mg, 0.1 mmol) en THF seco (2 mL) se trata secuencialmente con $PdCl_2$(dppf) (8 mg, 0.01 mmol) y CuI (9 mg, 0.05 mmol) bajo argón. La suspensión de zinc alquilo que se ha agitado a 50° C durante 3 h se agrega lentamente a la anterior solución. La mezcla de reacción luego se agita a 65° C durante la noche. Después se enfría por debajo de temperatura ambiente, la solución de reacción se apaga con solución de NH_4Cl acuosa, y se extrae con cloruro de metileno (2X). Las capas orgánicas combinadas se lavan con solución salina, y se secan sobre Na_2SO_4. Después de la evaporación del disolvente , el residuo se purifica por cromatografía sobre sílice (EtOAc/Hexano: 2:8) para dar el compuesto del título (24 mg, 79 %) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 2.30 (s, 3H), 4.66 (s, 2H), 4.70 (s, 2H), 6.95 (d, J = 8.6

Hz, 2H), 7.08 (d, J = 7.4 Hz, 1H), 7.13 (d, J = 7.4 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 8.09 (s, 1H). MS (MH^+, 303).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 of.060 µM.

Ejemplo 195

N-(2,6-difluoro-4-metoxifenil)-4-metilisoindolin-2-carboxamida

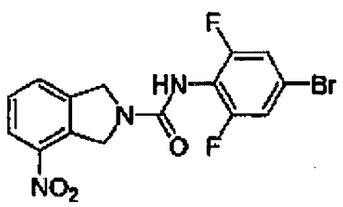


Una solución de N-(4-bromo-2,6-difluorofenil)-4-metilisoindolin-2-carboxamida (ejemplo 192) (22 mg, 0.06 mmol) en DMF seco (2 mL) se trata secuencialmente con CuBr (6 mg, 0.04 mmol) y MeONa (25 % de solución en MeOH, 5.0 equiv.) bajo argón. La mezcla de reacción luego se agita a 110° C durante 1 h bajo argón. Después se enfría por debajo de temperatura ambiente, la mezcla de reacción se neutraliza con HCl 1 N, y se extrae con EtOAc (2X). Las capas orgánicas combinadas se lavan con solución salina, y se secan sobre Na_2SO_4. Después de la evaporación del disolvente , el residuo se purifica por cromatografía sobre sílice eluyendo primero con 20 % de EtOAc en Hexano para dar el compuesto del título (7 mg, 37 %) como un sólido blanco: ^1H RMN (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 3.76 (s, 3H), 4.65 (s, 2H), 4.70 (s, 2H), 6.76 (d, J = 9.4 Hz, 2H), 7.08 (d, J = 7.4 Hz, 1H), 7.13 (d, J = 7.4 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.98 (s, 1H). MS (MH^+, 319).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 of.067 μM.

Ejemplo 196

N-(4-Bromo-2,6-difluorofenil)-4-nitroisoindolin-2-carboxamida



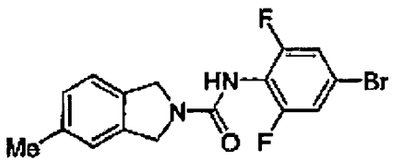
Se prepara de una forma similar al ejemplo 172 utilizando 2,6-difluoro-4-bromofenilo isoccianato y 4-nitroisoindolina (**Ejemplo 196a**). MS (MH^+, 398, 400).

Ejemplo 196a: 4-Nitroisoindolina: Una solución de 3-nitroftalimida (1.95 g, 10.0 mmol) y complejo sulfuro de metil borano (2.0 M de solución en THF, 20 mL, 20.0 mmol) en THF seco (20 mL) se refluye bajo argón durante 48 h. Después se enfría por debajo de 0° C, la mezcla de reacción se apaga cuidadosamente con MeOH (10 mL), y luego con HCl 3 N (10 mL). La solución luego se refluye durante otras 3 h, y se enfría por debajo de 0° C otra vez con un baño de hielo, y se neutraliza con solución de amoniaco concentrada. La mezcla se extrae con Et_2O (3X), y las capas orgánicas combinadas se lavan con solución salina, se secan sobre Na_2SO_4 sólido. La evaporación del disolvente da la 4-nitroisoindolina cruda como aceite café la cual se utiliza directamente en la síntesis de urea sin tratamiento adicional. MS (MH^+, 165).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 1.07 μM.

Ejemplo 197

N-(4-Bromo-2,6-difluorofenil)-5-metilisoindolin-2-carboxamida



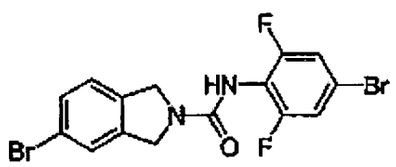
Se prepara de una forma similar al ejemplo 172 utilizando 2,6-difluoro-4-bromofenilo isoccianato y 5-metilisoindolina **(Ejemplo 197a)**. ^{1}H RMN (500 MHz, DMSO-d_6): δ 2.32 (s, 3H), 4.69 (b, 4H), 7.12 (d, J = 7.8 Hz, 1H), 7.16 (s, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.1 Hz, 2H), 8.25 (s, 1H). MS (MH^+, 369, 367).

Ejemplo 197a: 5-Metilisoindolina: Una solución de 4-metilftalimida (1.61 g, 10.0 mmol) y complejo sulfuro de metil borano (2.0 M de solución en THF, 15 mL, 30.0 mmol) en THF seco (10 mL) se refluye bajo argón durante 3 días. Después se enfría por debajo de 0° C, la mezcla de reacción se apaga cuidadosamente con MeOH (5 mL), y luego con HCl 3 N (10 mL). La solución luego se refluye durante otras 2 h, y se enfría por debajo de 0° C otra vez con un baño de hielo, y finalmente se neutraliza con NaOH 3 N. La mezcla de reacción se extrae con Et_2O (3X), y las capas orgánicas combinadas se lavan con solución salina, se secan sobre NaOH sólido. La evaporación del disolvente bajo vacío da la 5-metilisoindolina cruda como aceite café la cual se utiliza directamente en la síntesis de urea sin purificación adicional. MS (MH^+, 134).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.52 μM.

Ejemplo 198

5-Bromo-N-(4-bromo-2,6-difluorofenil)isoindolin-2-carboxamida



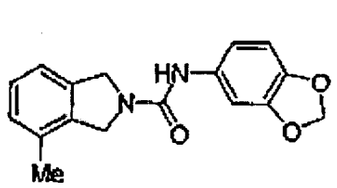
Se prepara de una forma similar al ejemplo 172 utilizando 2,6-difluoro-4-bromofenilo isoccianato y 5-bromoisoindolina (**Ejemplo 198a**). ^{1}H RMN (500 MHz, DMSO-d_6): δ 4.69 (bs, 2H), 4.73 (bs, 2H), 7.33 (d, J -8.2 Hz, 1H), 7.50 (dd, J = 8.2 Hz, 1.7 Hz, 1H), 7.52 (d, J = 7.2 Hz, 2H), 7.59 (s, 1H), 8.31 (s, 1H). MS (MH^+, 433, 431, 435).

Ejemplo 198a: 5-Bromoisoindolina: Se prepara de una forma similar al ejemplo 192a utilizando 4-bromoftalimida. MS (MH^+, 198, 200).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.42 μM.

Ejemplo 199

N-(3,4-(metilenodioxi)fenil)-4-metilisoindolin-2-carboxamida

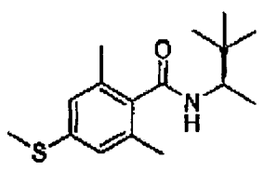


Se prepara de una forma similar al ejemplo 172 utilizando 3,4-(metilenodioxi)fenilo isoccianato y 4-metilisoindolina (ejemplo 197a). ^{1}H RMN (500 MHz, DMSO-d_6): δ 2.26 (s, 3H), 4.68 (s, 2H), 4.73 (s, 2H), 5.95 (s, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 7.09-7.22 (m, 3H), 7.25 (d, J = 2.1 Hz, 1H), 8.25 (s, 1H). MS (MH^+, 297).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 0.95 μM.

Ejemplo 200

(R)-N-(3,3-dimetilbutan-2-il)-2,6-dimetil-4-(metiltio)benzamida



Se prepara de una forma similar al ejemplo 13 utilizando (R)-3,3-dimetilbutan-2-amina y ácido 2,6-dimetil-4-(metiltio)benzoico (ejemplo 200a). Rendimiento 23%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.90 (s, 9H), 1.03-1.05 (s, 3H), 2.19 (s, 6H), 2.45 (s, 3H), 3.87-3.90 (m, 1H), 6.93 (s, 1H), 7.99-8.00 (d, 1H). MS (MH-H, 280).

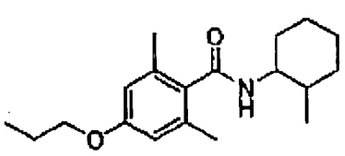
Ejemplo 200a: ácido 2,6-dimetil-4-(metiltio)benzoico:_3,5-Dimetiltioanisol (6.6 mmol) en 100 ml de acetonitrilo seco se mezcla con N-bromosuccmimida (6.6 mmol) y se agita durante la noche a t.a. El disolvente se remueve en vacío y el residuo sólido se trata con Hexanos. Un sólido se filtra, se lava con Hexanos y las

fracciones de hexano se combinan y se concentran bajo presión reducida suministrando aceite amarillo (99%). El bromuro crudo se seca en vacío y luego se diluye con 75 ml de THF seco. La solución se enfría a -78° C bajo argón y se agrega en forma de gota de solución de n-BuLi 2.5 M en Hexanos (6.7 mmol) durante un periodo de 30 min. Luego la mezcla se agita durante 30 min adicionales y las piezas pequeñas de hielo seco se sumergen en la solución. Después de 30 min el baño frío se remueve y la mezcla se dejan calentar a t.a. y se agitan durante 2 h. La mezcla la mezcla se vierte sobre 100 ml de hielo aplastado y se acidifica utilizando HCl 6N a pH 1. La fase orgánica se separa y la fase de agua se extrae con acetato de etilo. Los extractos orgánicos se combinan y se lavan con solución salina y agua, se secan sobre $MgSO_4$ y se concentran en vacío, suministrando un sólido blanco (98%). ^{1}H RMN (500 MHz, cMSO): δ 2.23 (s, 6H), 2.46 (s, 3H), 6.96 (s, 2H), 13.0 (bs, 1H).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 1.02 μM.

Ejemplo 201

2,6-dimetil-N-(2-metilciclohexil)-4-propoxibenzamida



4-Hidroxi-2,6-dimetil-N-(2-metilciclohexil)benzamida (ejemplo 201a) (0.38 mmol) se disuelve en 2 ml de una solución de EtOH absoluto y 50 mg de KOH. La mezcla se agita a 80° C durante 1 h y luego se agrega en forma de gotas yoduro de propilo (1.5 mmol) ta la mezcla caliente. La mezcla se agita a 80° C durante la

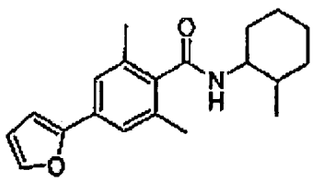
noche. El disolvente se evapora y el material se purifica sobre gel de sílice. Rendimiento 57%. ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.91-0.97 (m, 6H), 1.03-1.04 (m, 1H), 1.14-1.18 (m, 2H), 1.24-1.26 (m, 1H), 1.35-1.36 (m, 1H), 1.55-1.6 (m, 1H), 1.67-1.73 (m, 4H), 1.84-1.86 (m, 1H), 2.18 (s, 6H), 3.32 (s, 3H), 3.36-3.42 (m, 1H), 3.88-3.90 (t, 2H), 6.58 (s, 2H), 7.98-8.00 (d, 1H). MS (M+H, 304).

Ejemplo 201a: 4-hidroxi-2,6-dimetil-N-(2-metilciclohexil)benzamida: 4-Metoxi-2,6-dimetil-N-(2-metilciclohexil)benzamida (ejemplo 69) (3 mmol) se disuelve en 30 ml de DCM seco y se enfría a -78° C bajo argón. Se agrega en forma de gota solución 1M de BBr_3 en DCM (3.3 mmol) y el baño frío se remueve. La mezcla se agita a t.a. durante 34 h y luego se concentra en vacío. El residuo se disuelve en acetato de etilo y se lava con $NaHCO_3$ saturado, agua y solución salina. La fase orgánica se seca sobre $MgSO_4$ y se concentra en vacío para suministrar el producto como una espuma blanca (95%). ^{1}H RMN (500 MHz, $CDCl_3$): δ 0.90-0.91 (s, 3H), 1.03-1.05 (s, 3H), 1.00-1.03 (m, 1H), 1.13-1.17 (m, 2H), 1.25-1.27 (m, 1H), 1.35-1.37 (m, 1H), 1.60-1.62 (d, 1H), 1.62-1.72 (m, 2H), 1.83-1.85 (m, 1H), 2.13 (s, 6H), 3.36-3.42 (m, 1H), 6.40 (s, 2H), 7.93-7.95 (d, 2H). MS (M+H, 262).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en en una línea celular HEK293 de 0.69 μM.

Ejemplo 202

4-(furano-2-il)-2,6-dimetil-N-(2-metilciclohexil)benzamida



Trifluorometanosulfonato de 3,5-dimetil-4-(2-metilciclohexilCarbamoil)fenilo (ejemplo 202a) (0.25 mmol) se disuelve en 10 ml de tolueno, 2 ml de EtOH y 1.5 ml de agua. Se agrega ácido furano-2-ilborónico (0.25 mmol) y K_2CO_3 (0.5 mmol) y la mezcla se desgasifica utilizando una corriente de argón (20 min). Luego se agrega un catalizador, $Pd(PPh_3)_4$ y la mezcla se refluye durante la noche a 80° C. los disolventes se evaporan y el residuo se disuelve en acetato de etilo y se lava con agua. Los extractos orgánicos se combinan, se secan sobre $MgSO_4$ y se evaporan bajo presión reducida. El material crudo se purifica sobre placa TLC preparativa para suministrar el producto como un sólido blanco (40%). ^1H RMN (500 MHz, $CDCl_3$): δ 1.04-1.06 (s, 3H), 1.13-1.80 (m, 8H), 2.15-2.23 (m, 1H), 2.36 (s, 6H), 3.70-3.73 (m, 1H), 5.43-5.45 (d, 1H), 6.46-6.47 (m, 1H), 6.62-6.63 (d, 1H), 7.32 (s, 2H), 7.45-7.46 (d, 1H). MS (M+H, 312).

Ejemplo 202a: trifluorometanosulfonato de 3,5-dimetil-4-(2-metilciclohexilCarbamoil)fenilo: A una solución de 4-Hidroxi-2,6-dimetil-N-(2-metilciclohexil)benzamida (ejemplo 200a) (7.65 mmol) en DCM (50 ml) se agrega piridina (9.18 mmol). La solución se enfría a 0° C y se agrega en forma de gota anhídrido tríflico (9.18 mmol). Luego la mezcla de reacción se calienta lentamente a t.a. y se agita durante la noche. La mezcla se diluye con DCM, se lava con HCl 1N ac., $NaHCO_3$ sat., solución salina y la fase orgánica se seca sobre $MgSO_4$. El disolvente se remueve bajo presión reducida suministrar el producto como un sólido blanco (20%).

El compuesto tiene una activación para EC_{50} de un receptor dulce hT1R2/hT1R3 que se expresa en una línea celular HEK293 de 1.02 μM.

Numerosos compuestos de amida de Fórmula (I) también se sintetizan y se ensayan experimentalmente para eficacia como activadores de in receptor "dulce" hT1R2/hT1R3 que se expresa en una línea celular HEK293.

Los resultados de tales ensayos se muestran adelante en la Tabla E.

Tabla E - Amidas Mejoradoras de Dulce

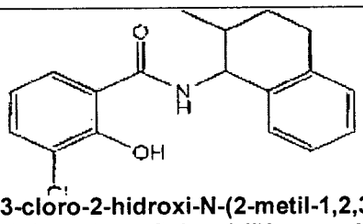
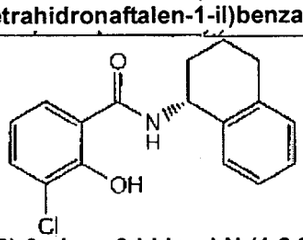
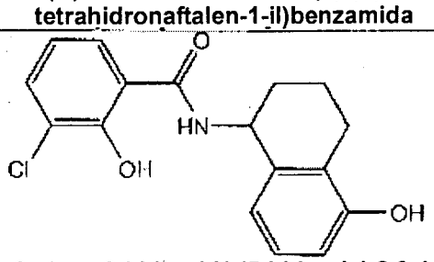
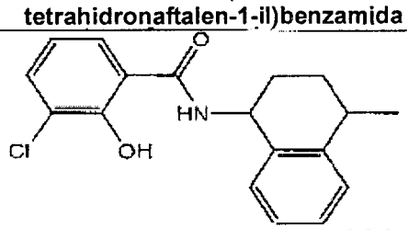
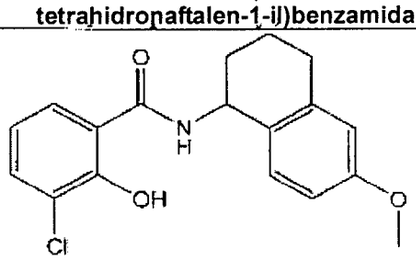
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)
E1	 3-cloro-2-hidroxi-N-(2-metil-1,2,3,4-tetrahidronaftalen-1-il)benzamida	0.19		
E2	 (R)-3-cloro-2-hidroxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	0.65		
E3	 3-cloro-2-hidroxi-N-(5-hidroxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida	1.03		
E4	 3-cloro-2-hidroxi-N-(4-metil-1,2,3,4-tetrahidronaftalen-1-il)benzamida	1.61		
E5	 3-cloro-2-hidroxi-N-(6-metoxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida	1.61		

Tabla E - Amidas Mejoradoras de Dulce

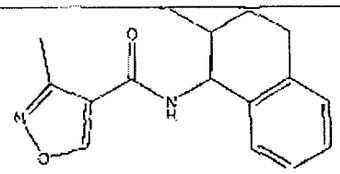
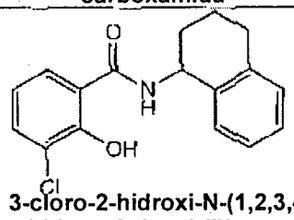
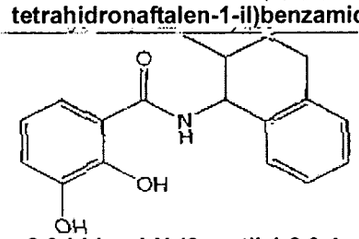
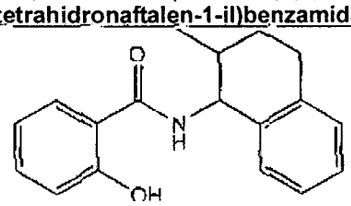
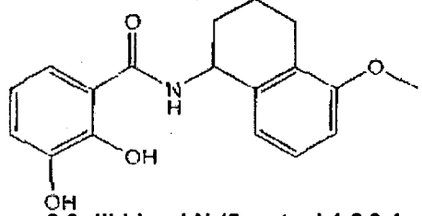
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)
E6	 **3-metil-N-(2-metil-1,2,3,4-*tetrahidronaftalen*-1-il)*isoxazol*-4-carboxamida**	1.48		
E7	 **3-cloro-2-hidroxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida**	1.81		4.04
E8	 **2,3-hidroxi-N-(2-metil-1,2,3,4-tetrahidronaftalen-1-il)benzamida**	1.98		
E9	 **2-hidroxi-N-(2-metil-1,2,3,4-tetrahidronaftalen-1-il)benzamida**	2.36		
E10	 **2,3-dihidroxi-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida**	2.44		

Tabla E - Amidas Mejoradoras de Dulce

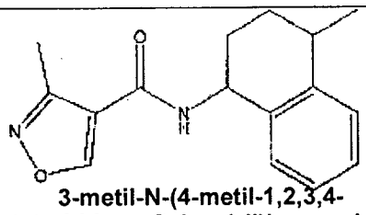
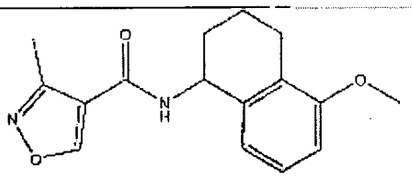
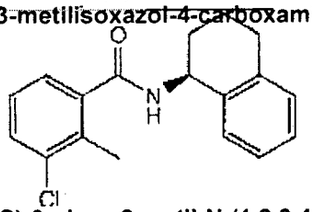
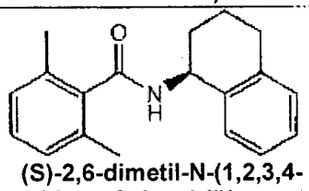
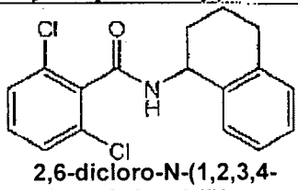
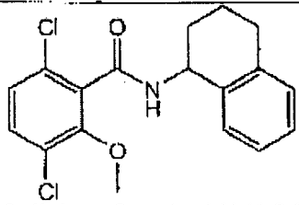
Compuesto No.	Compuesto	Sweet EC_{50} Dulce μM	Umami EC_{50} μM	Proporción Ec50(Vs.MSG)
E11	 3-metil-N-(4-metil-1,2,3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida	2.46		
E12	 N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)-3-metilisoxazol-4-carboxamida	2.85		
E13	 (S)-3-cloro-2-metil-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	2.91		
E14	 (S)-2,6-dimetil-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	2.91		
E15	 2,6-dicloro-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	3.02		
E16	 3,6-dicloro-2-metoxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	3.04		

Tabla E - Amidas Mejoradoras de Dulce

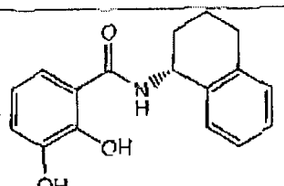
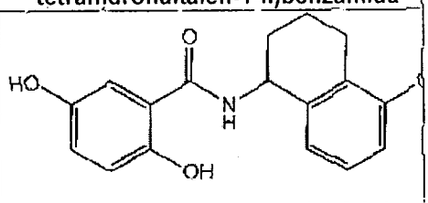
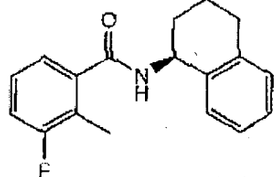
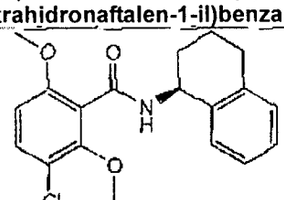
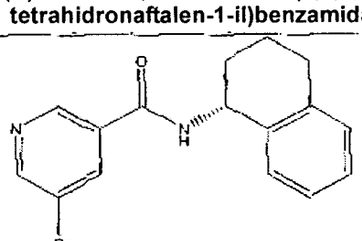
Compuesto No.	Compuesto	Dulce EC_{50} μM	Umami EC_{50} μM	Proporción Ec50(Vs.MSG)
E17	 (R)-2,3-dihidroxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	3.13		
E18	 2,3-dihidroxi-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida	3.38		
E19	 (S)-3-fluoro-2-metil-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	3.57		
E20	 (S)-3-cloro-2,6-dimetoxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	4.13		
E21	 (R)-5-bromo-N-(1,2,3,4-tetrahidronaftalen-1-il)nicotinamida	4.19		

Tabla E - Amidas Mejoradoras de Dulce

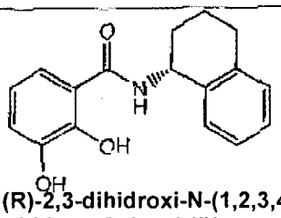
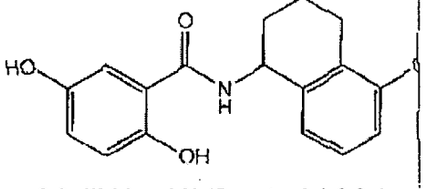
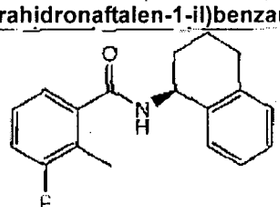
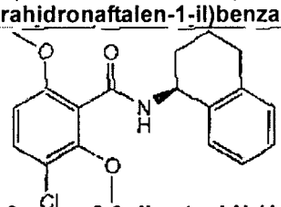
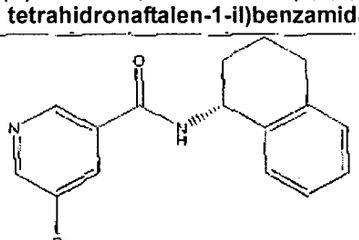
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporcion Ec50(Vs.MSG)
E17	 (R)-2,3-dihidroxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	3.13		
E18	 2,3-dihidroxi-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida	3.38		
E19	 (S)-3-fluoro-2-metil-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	3.57		
E20	 (S)-3-cloro-2,6-dimetoxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	4.13		
E21	 (R)-5-bromo-N-(1,2,3,4-tetrahidronaftalen-1-il)nicotinamida	4.19		

Tabla E - Amidas Mejoradoras de Dulce

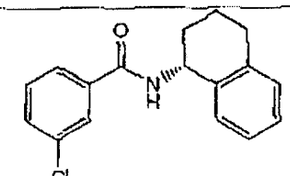
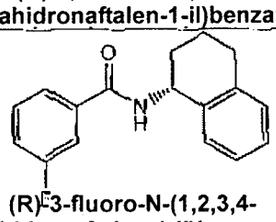
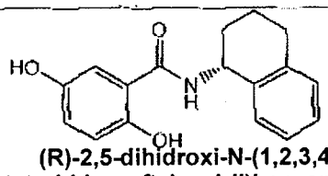
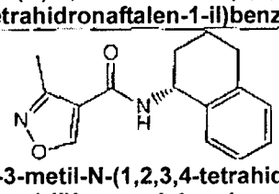
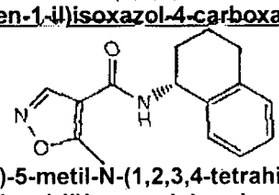
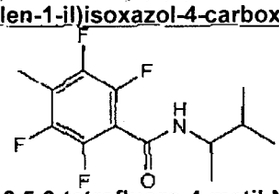
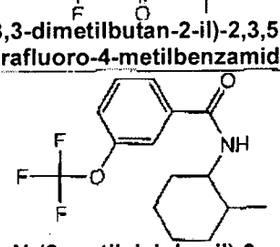
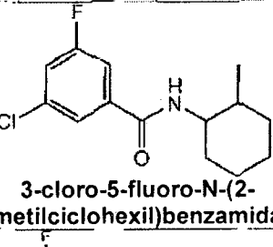
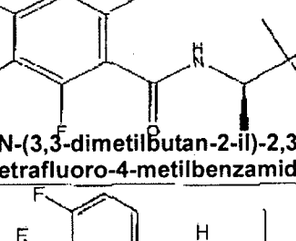
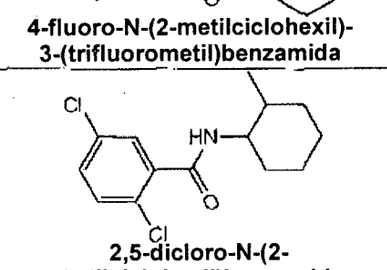
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)
E22	 (R)-2,3-cloro-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	4.52		
E23	 (R)-3-fluoro-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	4.86		
E24	 (R)-2,5-dihidroxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida	6.04		
E25	 (R)-3-metil-N-(1,2,3,4-tetrahidro naftalen-1-il)isoxazol-4-carboxamida	7.79		
E26	 (R)-5-metil-N-(1,2,3,4-tetrahidro naftalen-1-il)isoxazol-4-carboxamida	8.09		
E27	 2,3,5,6-tetrafluoro-4-metil-N-(3-metilbutan-2-il)benzamida	0.14		

Tabla E - Amidas Mejoradoras de Dulce

Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)
E28	 N-(3,3-dimetilbutan-2-il)-2,3,5,6-tetrafluoro-4-metilbenzamida	0.21		
E29	 N-(2-metilciclohexil)-3-(trifluorometoxi)benzamida	0.42		
E30	 3-cloro-5-fluoro-N-(2-metilciclohexil)benzamida	0.45		
E31	 (R)-N-(3,3-dimetilbutan-2-il)-2,3,5,6-tetrafluoro-4-metilbenzamida	0.49		
E32	4-fluoro-N-(2-metilciclohexil)-3-(trifluorometil)benzamida	0.51		
E33	2,5-dicloro-N-(2-metilciclohexil)benzamida	0.63		

658

Tabla E - Amidas Mejoradoras de Dulce

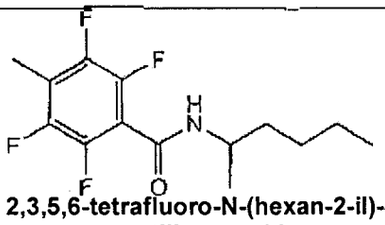
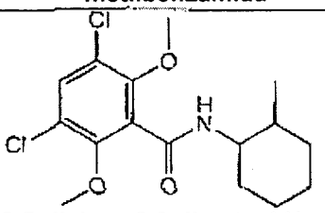
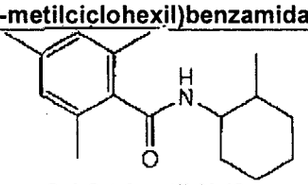
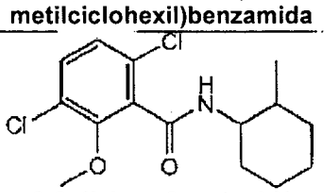
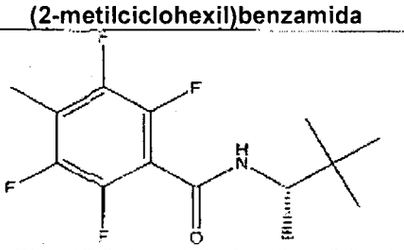
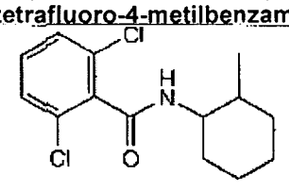
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)
E34	 2,3,5,6-tetrafluoro-N-(hexan-2-il)-4-metilbenzamida	0.71		
E35	 3,5-dicloro-2,6-dimetoxi-N-(2-metilciclohexil)benzamida	0.71		
E36	 2,4,6-trimetil-N-(2-metilciclohexil)benzamida	0.72		
E37	 3,6-dicloro-2-metoxi-N-(2-metilciclohexil)benzamida	0.77		
E38	 (S)-N-(3,3-dimetilbutan-2-il)-2,3,5,6-tetrafluoro-4-metilbenzamida	0.9		
E39	 2,6-dicloro-N-(2-metilciclohexil)benzamida	0.91		

Tabla E - Amidas Mejoradoras de Dulce

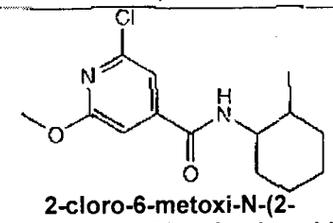
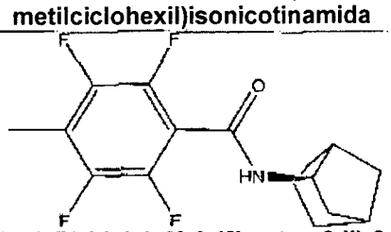
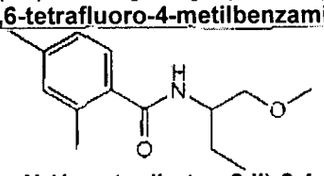
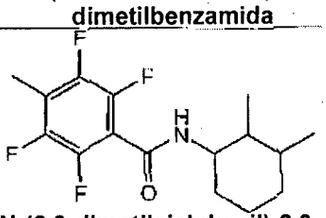
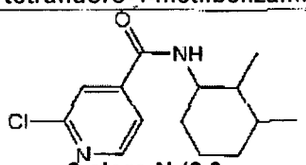
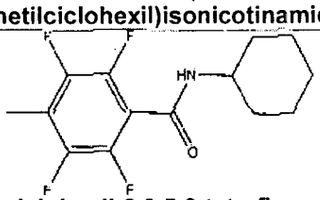
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)
E40	 2-cloro-6-metoxi-N-(2-metilciclohexil)isonicotinamida	0.95		9.77
E41	 N-((2R)-biciclo[2.2.1]heptan-2-il)-2,3,5,6-tetrafluoro-4-metilbenzamida	1.02		
E42	 N-(1-metoxibutan-2-il)-2,4-dimetilbenzamida	1.06		
E43	 N-(2,3-dimetilciclohexil)-2,3,5,6-tetrafluoro-4-metilbenzamida	1.08		
E44	 2-cloro-N-(2,3-dimetilciclohexil)isonicotinamida	1.08		
E45	 N-ciclohexil-2,3,5,6-tetrafluoro-4-metilbenzamida	1.13		

Tabla E - Amidas Mejoradoras de Dulce

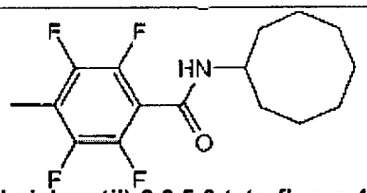
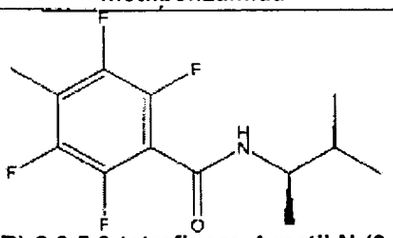
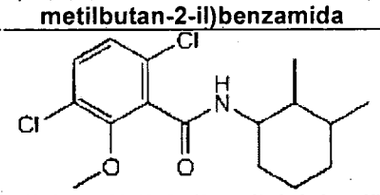
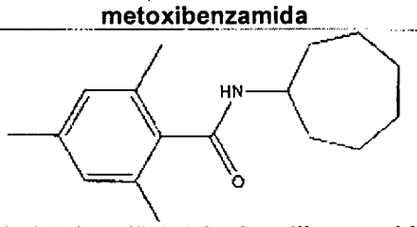
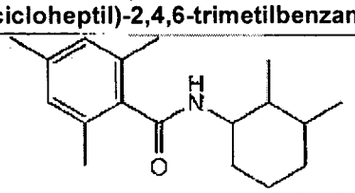
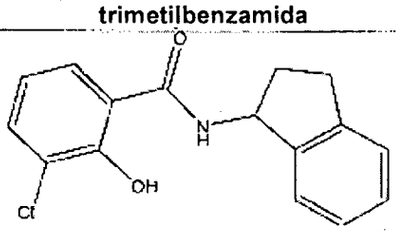
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)
E46	 N-ciclooctil)-2,3,5,6-tetrafluoro-4-metilbenzamida	1.25		
E47	 (R)-2,3,5,6-tetrafluoro-4-metil-N-(3-metilbutan-2-il)benzamida	1.25		
E48	 3,6-dicloro-N-(2,3-dimetilciclohexil)-2-metoxibenzamida	1.29		
E49	 N-cicloheptil)-2,4,6-trimetilbenzamida	1.39		
E50	 N-(2,3-dimetilciclohexil)-2,4,6-trimetilbenzamida	1.41		
E51	 2-cloro-N-(2,3-dihidro-1H-inden-1-il)-2-hidroxiamida	1.49		

Tabla E - Amidas Mejoradoras de Dulce

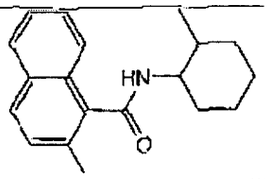
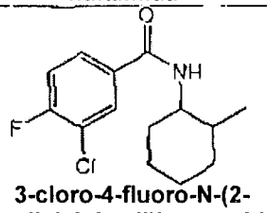
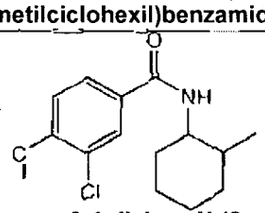
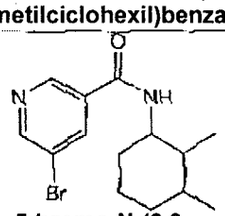
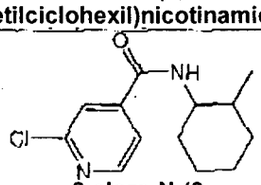
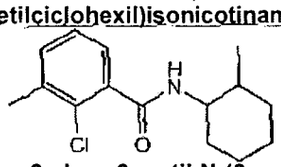
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)
E52	 2-metil-N-(2-metilciclohexil)-1-naftamida	1.52		
E53	 3-cloro-4-fluoro-N-(2-metilciclohexil)benzamida	1.7		
E54	 3,4-dicloro-N-(2-metilciclohexil)benzamida	1.83		10.66
E55	 5-bromo-N-(2,3-dimetilciclohexil)nicotinamida	1.89		
E56	 2-cloro-N-(2-imetilciclohexil)isonicotinamida	1.92		2.08
E57	 2-cloro-3-metil-N-(2-metilciclohexil)benzamida	1.95		

Tabla E - Amidas Mejoradoras de Dulce

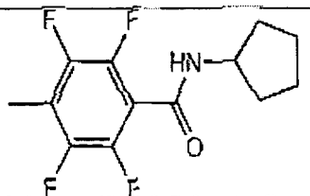
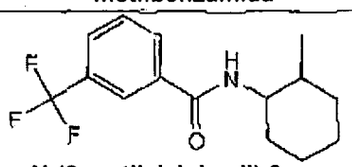
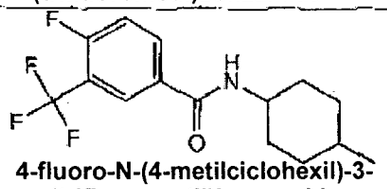
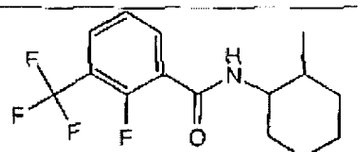
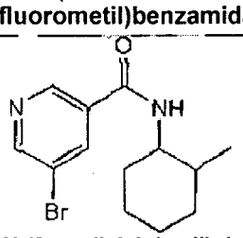
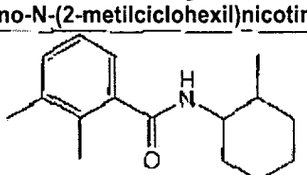
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)
E58	 N-ciclopentil)-2,3,5,6-tetrafluoro-4-metilbenzamida	2.23		
E59	 N-(2-metilciclohexil)-3-(trifluorometil)benzamida	2.34		2.07
E60	 4-fluoro-N-(4-metilciclohexil)-3-(trifluorometil)benzamida	2.37		
E61	 2-fluoro-N-(2-metilciclohexil)-3-(trifluorometil)benzamida	2.4		
E62	 5-bromo-N-(2-metilciclohexil)nicotinamida	2.47		
E63	 2,3-dimetil-N-(2-metilciclohexil)benzamida	2.6		

Tabla E - Amidas Mejoradoras de Dulce

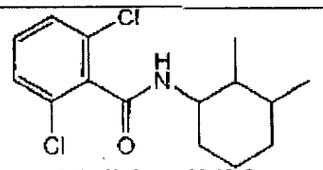
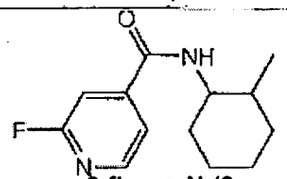
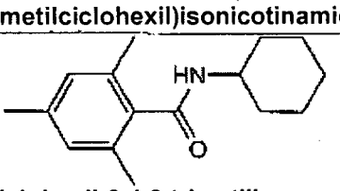
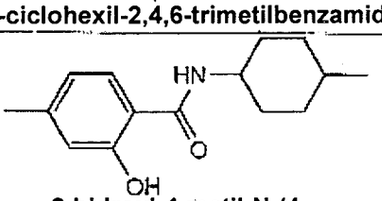
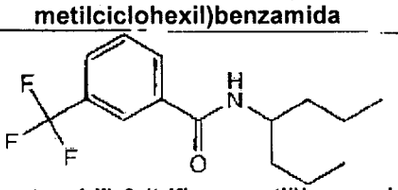
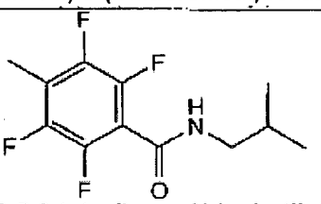
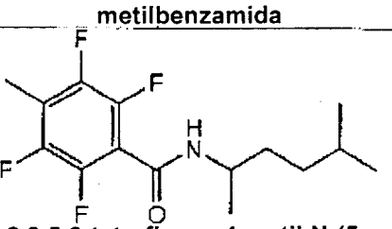
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)
E64	 2,6-dicloro-N-(2,3-dimetilciclohexil)benzamida	2.77		
E65	 2-fluoro-N-(2-metilciclohexil)isonicotinamida	2.83		
E66	 N-ciclohexil-2,4,6-trimetilbenzamida	2.86		
E67	 2-hidroxi-4-metil-N-(4-metilciclohexil)benzamida	2.98		
E68	 N-(heptan-4-il)-3-(trifluorometil)benzamida	3.03	0.33	
E69	 2,3,5,6-tetrafluoro-N-isobutil-4-metilbenzamida	3.19		
E70	 2,3,5,6-tetrafluoro-4-metil-N-(5-metilhexan-2-il)benzamida	3.2		

Tabla E - Amidas Mejoradoras de Dulce

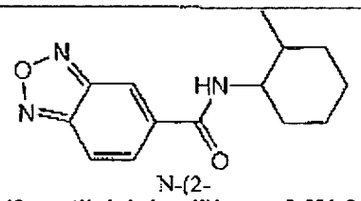
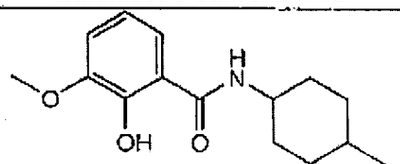
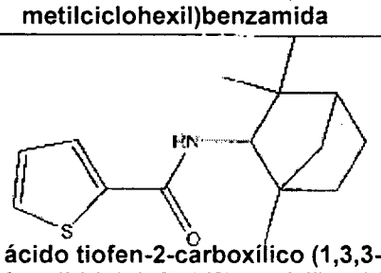
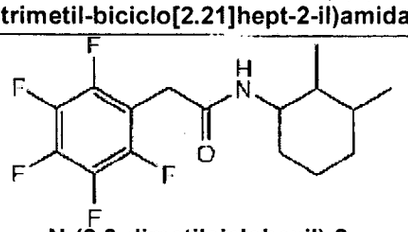
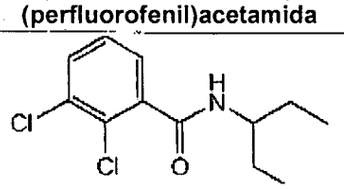
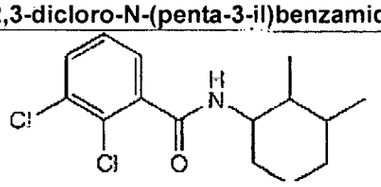
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50(Vs.MSG)
E71	 N-(2-metilciclohexil)benzo[c][1,2,5]oxadiazol-5-carboxamida	3.33		
E72	 2-hidroxi-3-metoxi-N-(4-metilciclohexil)benzamida	3.35		
E73	 ácido tiofen-2-carboxílico (1,3,3-trimetil-biciclo[2.21]hept-2-il)amida	3.36		
E74	 N-(2,3-dimetilciclohexil)-2-(perfluorofenil)acetamida	3.62		
E75	 2,3-dicloro-N-(penta-3-il)benzamida	3.78		
E76	 2,3-dicloro-N-(2,3-dimetilciclohexil)benzamida	3.99		

Tabla E - Amidas Mejoradoras de Dulce

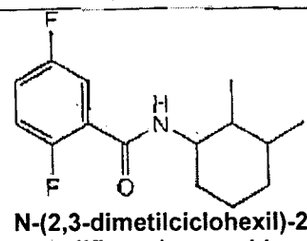
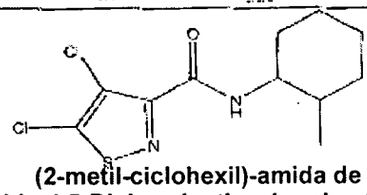
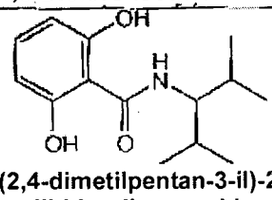
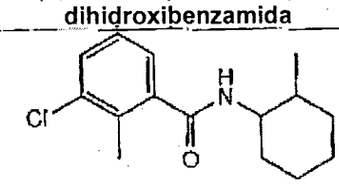
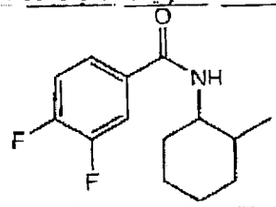
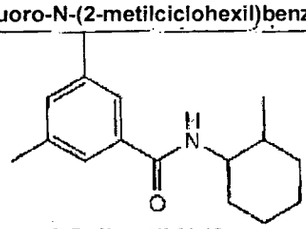
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50 Umami
E77	 N-(2,3-dimetilciclohexil)-2,5-difluorobenzamida	4.11		
E78	 (2-metil-ciclohexil)-amida de acido 4,5-Dicloro-isotiazol-carboxílico	4.24	8.51	
E79	 N-(2,4-dimetilpentan-3-il)-2,6-dihidroxibenzamida	4.28		
E80	 3-cloro-2-metil-N-(2-metilciclohexil)benzamida	4.29		
E81	 3,4-difluoro-N-(2-metilciclohexil)benzamida	4.37		6.98
E82	 3,5-dimetil-N-(2-metilciclohexil)benzamida	4.48		

Tabla E - Amidas Mejoradoras de Dulce

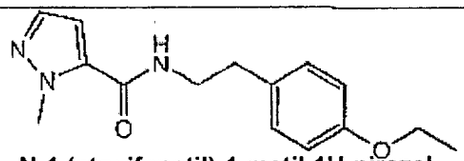
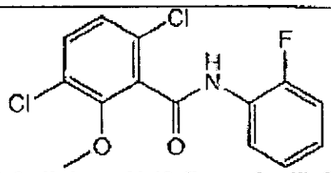
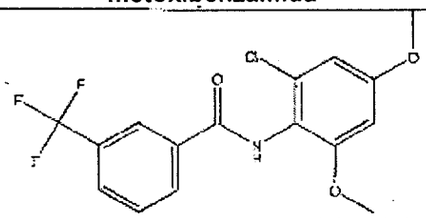
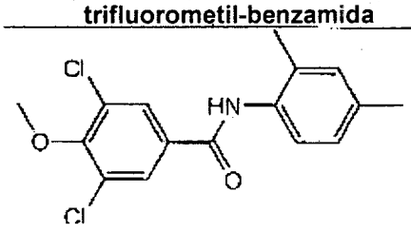
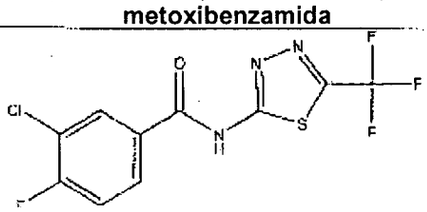
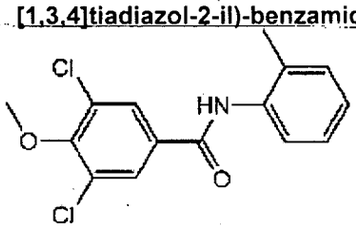
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50 Umami
E83	 N-1 (etoxifenetil)-1-metil-1H-pirazol-5-carbozamida	4.68		
E84	 3,6-dicloro-N-(2-fluorofenil)-2 metoxibenzamida	0.83		16.51
E85	 N-(2-Cloro-4,6-dimetoxi-fenil)-3-trifluorometil-benzamida	1.42		
E86	 3,5-dicloro-N-(2,4-dimetilfenil)-4-metoxibenzamida	1.48		
E87	 3-Cloro-4-fluoro-N-(5-trifluorometil-[1,3,4]tiadiazol-2-il)-benzamida	1.55		
E88	 3,5-dicloro-4-metoxj-N-o-tolibenzamida	1.84		

Tabla E - Amidas Mejoradoras de Dulce

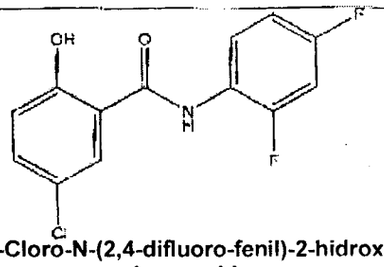
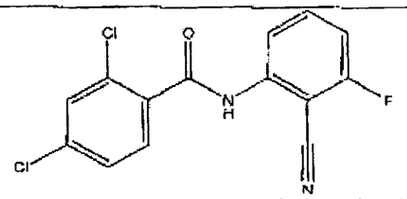
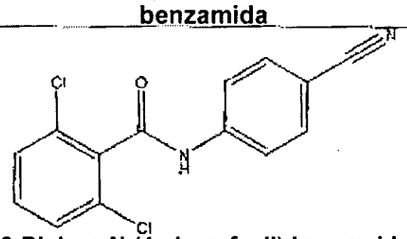
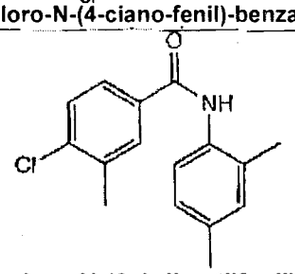
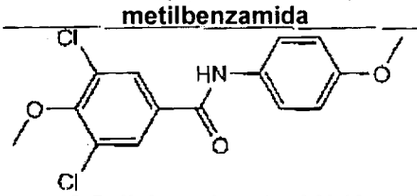
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50 Umami
E89	 5-Cloro-N-(2,4-difluoro-fenil)-2-hidroxi-benzamida	2.56		
E90	 2,4-Dicloro-N-(2-ciano-3-fluoro-fenil)-benzamida	2.71		
E91	 2,6-Dicloro-N-(4-ciano-fenil)-benzamida	2.74		
E92	 4-cloro-N-(2,4-dimetilfenil)-3-metilbenzamida	2.74		
E93	 3,5-dicloro-4-metoxi-N-(4-metoxifenil)benzamida	3.24		

Tabla E - Amidas Mejoradoras de Dulce

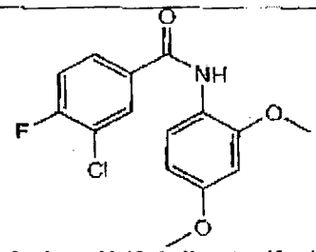
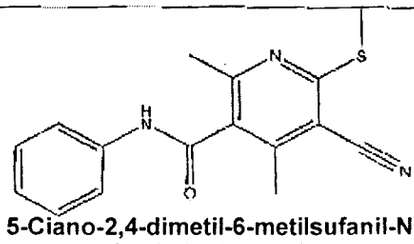
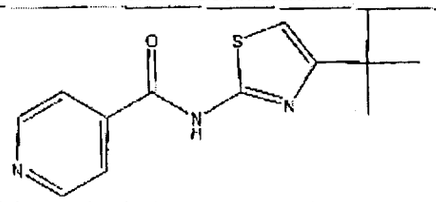
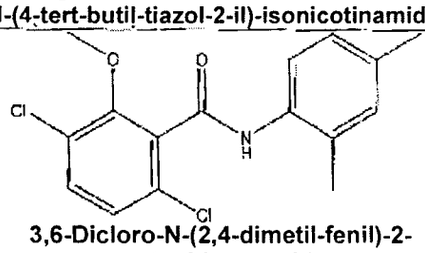
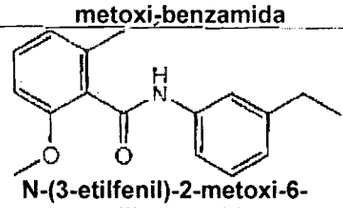
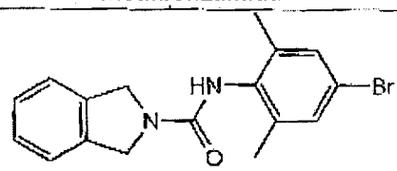
Compuesto No.	Compuesto	Dulce EC_{50} μM	Umami EC_{50} μM	Proporción Ec50 Umami)
E94	 3-cloro-N-(2,4-dimetoxifenil)-4-fluorobenzamida	3.56		
E95	 5-Ciano-2,4-dimetil-6-metilsufanil-N-fenil-nicotinamida	3.58		
E96	 N-(4-tert-butil-tiazol-2-il)-isonicotinamida	3.73		
E97	 3,6-Dicloro-N-(2,4-dimetil-fenil)-2-metoxi-benzamida	4.25		
E98	 N-(3-etilfenil)-2-metoxi-6-metilbenzamida	4.63		
E99	 N-(4-bromo-2,6-dimetilfenil)isoindolina-2-carboxamida	0.93		

Tabla E - Amidas Mejoradoras de Dulce

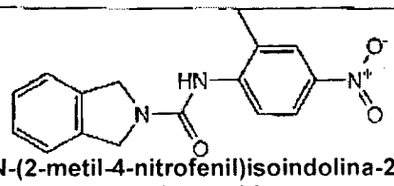
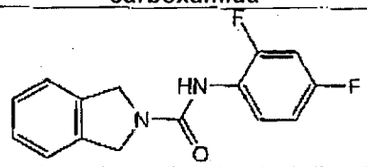
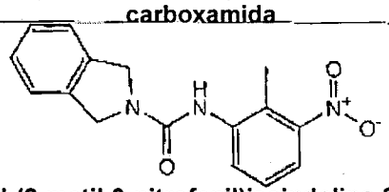
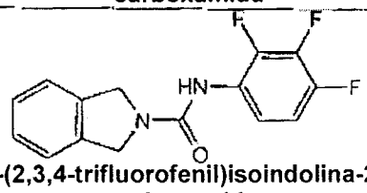
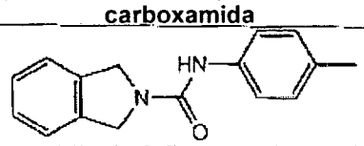
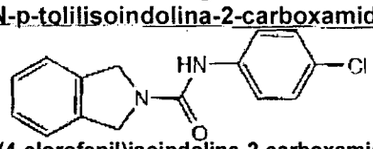
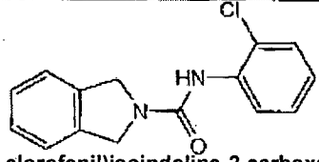
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50 Umami
E100	 N-(2-metil-4-nitrofenil)isoindolina-2-carboxamida	1.3		
E101	 N-(2,4-difluorofenil)isoindolina-2-carboxamida	1.37		
E102	 N-(2-metil-3-nitrofenil)isoindolina-2-carboxamida	2.01		
E103	 N-(2,3,4-trifluorofenil)isoindolina-2-carboxamida	2.58		
E104	 N-p-tolilisoindolina-2-carboxamida	3.05		
E105	 N-(4-clorofenil)isoindolina-2-carboxamida	3.4		
E106	 N-(2-clorofenil)isoindolina-2-carboxamida	3.85		

Tabla E - Amidas Mejoradoras de Dulce

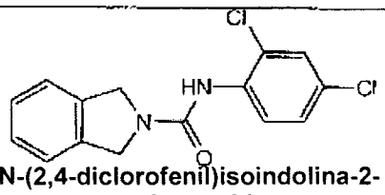
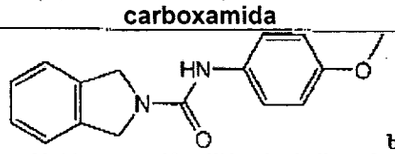
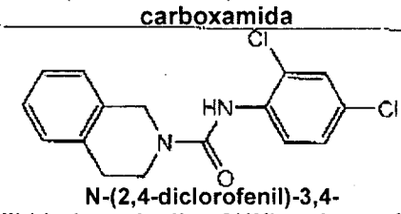
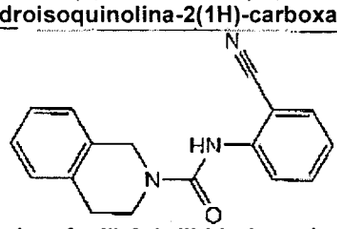
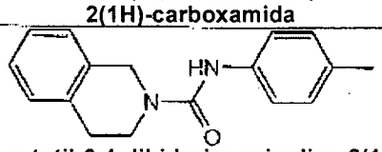
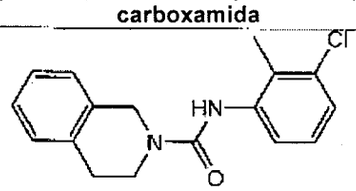
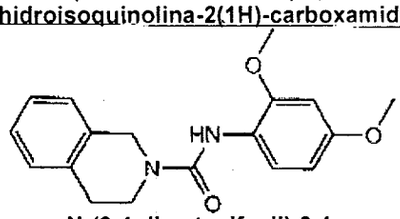
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50 Umami
E107	 N-(2,4-diclorofenil)isoindolina-2-carboxamida	4.15		
E108	 N-(4-metoxifenil)isoindolina-2-carboxamida	4.99		
E109	 N-(2,4-diclorofenil)-3,4-dihidroisoquinolina-2(1H)-carboxamida	2.34		
E110	 N-(2-cianofenil)-3,4-dihidroisoquinolina-2(1H)-carboxamida	2.5		
E111	 N-p-totil-3,4-dihidroisoquinolina-2(1H)-carboxamida	4.27		
E112	 N-(3-cloro-2-metilfenil)-3,4-dihidroisoquinolina-2(1H)-carboxamida	4.33		
E113	 N-(2,4-dimetoxifenil)-3,4-dihidroisoquinolina-2(1H)-carboxamida	4.44		

Tabla E - Amidas Mejoradoras de Dulce

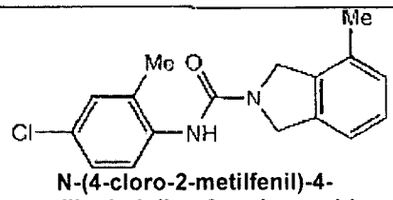
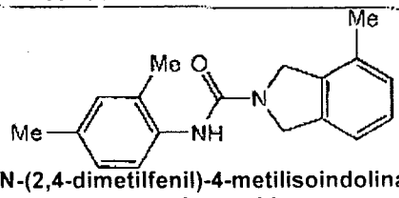
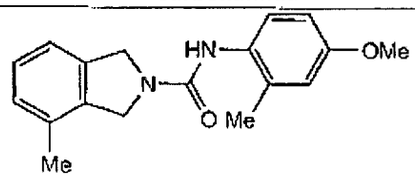
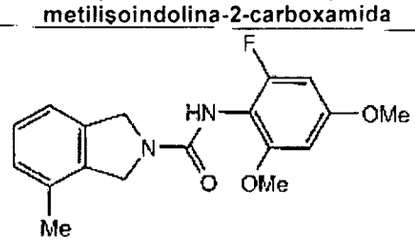
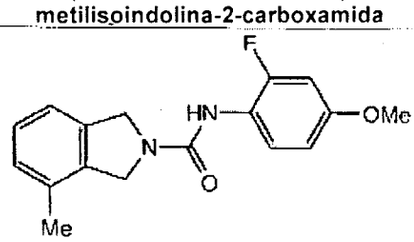
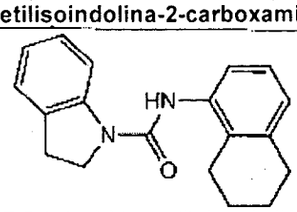
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50 Umami
E114	 N-(4-cloro-2-metilfenil)-4-metilisoindolina-2-carboxamida	0.19		
E115	 N-(2,4-dimetilfenil)-4-metilisoindolina-2-carboxamida	0.25		
E116	 N-(4-metoxi-2-metilfenil)-4-metilisoindolina-2-carboxamida	0.71		
E117	 N-(2-fluro-4,6-dimetoxifenil)-4-metilisoindolina-2-carboxamida	0.09		
E118	 N-(2-fluoro-4-metoxifenil)-4-metilisoindolina-2-carboxamida	0.1		
E119	 N-(5,6,7,8-tetrahidronaftalen-1-il)indolina-1-carboxamida	1.06		

Tabla E - Amidas Mejoradoras de Dulce

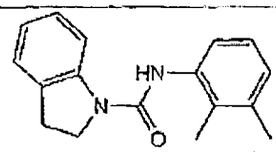
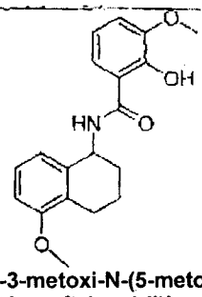
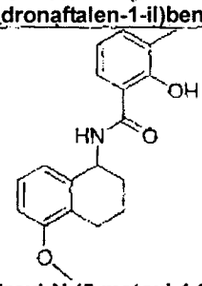
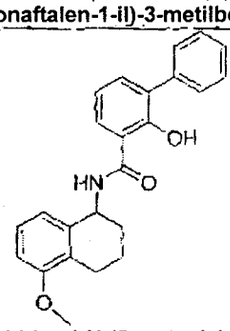
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50 Umami
E120	 N-(2,3-dimetilfenil)indolina-1-carboxamida	2.38		
E121	 2-hidroxi-3-metoxi-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida	1.61		
E122	 2-hidroxi-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)-3-metilbenzamida	1.95		
E123	 2-hidroxi-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)-3-fenilbenzamida	2.56		

Tabla E - Amidas Mejoradoras de Dulce

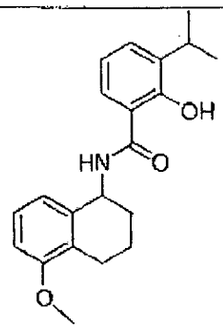
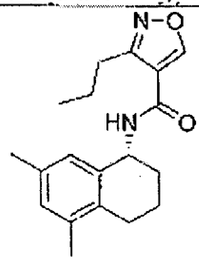
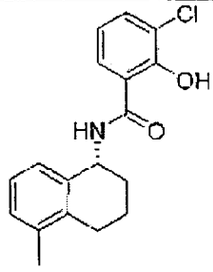
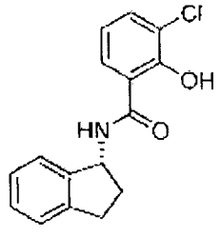
Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50 Umami
E124	 2-hidroxi-3-isopropil-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida	2.64		
E125	 (R)-N-(5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-il)-3-propilisoxazol-4-carboxamida	0.62		
E126	 (R)-3-cloro-2-hidroxi-N-(5-metil-1,2,3,4-tetrahidronaftalen-1-il)benzamida	0.89		
E127	 (R)-3-cloro-N-(2,3-dihidro-1H-inden-1-il)-2-hidroxibezamida	0.95		2.81 (10 M cpd)

Tabla E - Amidas Mejoradoras de Dulce

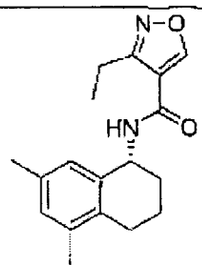
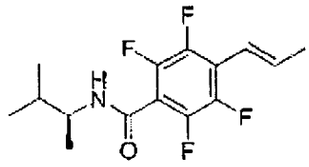
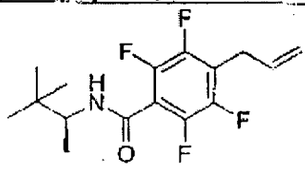
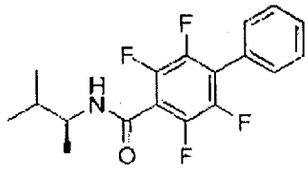
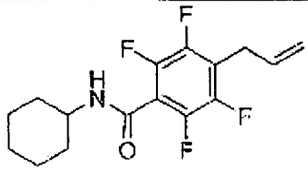
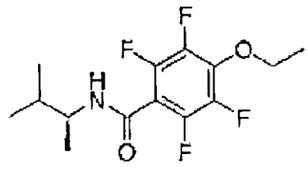
Compuesto No.	Compuesto	Dulce EC_{50} μM	Umami EC_{50} μM	Proporción Ec50 Umami
E128	 **(R)-N-(5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-il)-3-etilisoxazol-4-carbozamida**	1.24		
E129	 **(S,E)-2,3,5,6-tetrafluoro-N-(3-metilbutan-2-il)-4-(prop-1-enil)benzamida**	0.41		
E130	 **(S)-4-alil-N-(3,3-deimetilbutan-2-il)-2,3,5,6-tetrafluorobenzamida**	0.43		
E131	 **(S)-2,3,5,6-tetrafluoro-N-(3-metilbutan-2-il)-4-(fenil benzamida**	0.44		
E132	 **4-alil-N-ciclohexil-2,3,5,6-tetrafluorobenzamida**	0.55		

Tabla E - Amidas Mejoradoras de Dulce

Compuesto No.	Compuesto	Dulce EC_{50} µM	Umami EC_{50} µM	Proporción Ec50 Umami
E133	 (S)-4-etoxi-2,3,5,6-tetrafluoro-N-(3-metilbutan-2-il)benzamida	0.6		

Medición del sabor Dulce y de la Mejora del Sabor Dulce Utilizando Panelistas Humanos

Propósito: Investigar la intensidad de varios sabores y no sabores de un compuesto experimental. Determinar la concentración máxima del compuesto experimental que no es licita una característica indeseable o sin sabor.

Repaso: Varias concentraciones del compuesto experimental (normalmente soluciones acuosas que contienen 1, 3, 10, y 30µM de concentraciones del compuesto experimental; y opcionalmente concentraciones de 50uM y/o 100uM) se prueban individualmente por sujetos humanos entrenados y clasificados por intensidad de varios atributos de sabor. El compuesto experimental también se puede probar cuando se disuelve en una solución "de sabor clave".

Procedimiento: Una cantidad apropiada del compuesto experimental se disuelve en agua típicamente también contiene 0.1% de etanol, que se utiliza para ayudar en la dispersión inicial del compuesto en la solución madre acuosa. Cuando es apropiado, el compuesto experimental se puede disolver en soluciones acuosas de "un gusto clave" (por ejemplo, 4% de sacarosa, 6% de sacarosa, 6% de fructosa/glucosa, o 7% fructosa/glucosa, en un pH de 7.1 o 2.8).

Se utilizan cinco sujetos humanos para pruebas de gusto preliminar. Los sujetos tienen una capacidad demostrada de probar los atributos de gusto deseados, y se entrenan para utilizar una Escala de Magnitud Etiquetada (LMS) de 0 (Endulzantes Detectables) a 100 (Endulzantes más Fuertes Imaginables). Los sujetos que se abstienen de comer o beber (excepto agua) durante al menos 1 hora antes de la prueba. Los sujetos comen una galleta y se enjuagan la boca con agua cuatro veces para limpiarla antes de las pruebas de ensayo.

Las soluciones acuosa se dispensan en volúmenes de 10 ml en tazas de 1 oz. de muestra y sirven para los sujetos a temperatura ambiente. Las muestras del compuesto experimental disueltas en un saborizante clave apropiado (por ejemplo, 4% sacarosa, 6% fructosa, o 6% fructosa/glucosa, típicamente un pH de 7.1) en varias concentraciones del compuesto experimental también pueden servir a los sujetos. Los sujetos también reciben una muestra de referencia de el saborizante clave (por ejemplo, sacarosa, fructosa, o fructosa/glucosa, típicamente en pH 7.1) en diferentes concentraciones para comparación.

Los sujetos prueban las soluciones, partiendo con la concentración más baja, y la taza de intensidad de los siguientes atributos en la Escala de Magnitud Etiquetada (LMS) para endulzantes, salinidad, agrio, amargo, salado o picante (umami), y otros (sin sabor). Los sujetos se enjuagan tres veces con agua entre saborizantes. Si una concentración particular elicita una característica indeseable o son sabor, las pruebas de saborizantes de concentraciones mayores se eliminan. Después de un descanso, los sujetos prueban una solución de saborizante clave (por ejemplo, 4% sacarosa, 6% fructosa, o 6% fructosa/glucosa, típicamente en pH 7.1) sin el compuesto experimental. Luego las soluciones del saborizante clave más el compuesto más el compuesto experimental se prueban

en orden incrementado de concentración. La solución de saborizante clave se puede probar nuevamente para comparación con un saborizante clave más soluciones de compuestos experimentales si es necesario. La discusión entre los panelistas esta permitida.

La concentración máxima de un compuesto experimental que no elicita una característica objecionable o sin sabor es la más alta concentración que un compuesto particular se probara en experimentos sensoriales posteriores. Para confirmar los resultados de pruebas preliminares, la prueba se puede repetir con otro grupo pequeño de panelistas.

La prueba de perfil preliminar siempre es la primer prueba desarrollada en un nuevo compuesto experimental. Dependiendo de los resultados de la prueba de perfil preliminar, pruebas adicionales más cuantitativas sen pueden desarrollar para caracterizar adicionalmente el compuesto experimental.

"Diferencia de Referencia" de Procedimientos de Prueba de Gusto Humanos

Propósito: Determinar como la intensidad de una muestra de ensayo de un compuesto experimental difiere de aquella de una muestra de referencia en términos de endulzantes. Este tipo de estudio requiere un panel mayor (típicamente 15-20 sujetos) con el fin de obtener datos estadísticamente significativos.

Repaso: Un grupo de 10 o más pares de panelistas para sabor de soluciones en donde una de las muestras es la "referencia" (que típicamente no incluye un compuesto experimental y es una sustancia aprobada o sustancia

reconocida generalmente como segura (GRAS), es decir, un endulzante) y la otra muestra es el "Ensayo" (que puede o no incluir un compuesto experimental) los sujetos tasan la diferencia en intensidad e la muestra de ensayo comparada con la muestra de referencia para un atributo clave en una escala de -5 (mucho menor dulce que la referencia a +5 (muchos más dulce que la referencia). Una clasificación de cero indica que la muestra de ensayo es igualmente tan dulce como al referencia.

Procedimiento:

Se utilizan 10 o más sujetos para la prueba de "diferencia de referencia". Los sujetos se han familiarizado previamente con el gusto de gusto de atributo clave y se entrenan para utilizar la escala -5 a +5. Los sujetos se abstienen de comer o beber (excepto agua) durante al menos 1 hora antes de la pruieba. Los sujetos comen galletas y se enjuagan con agua cuatro veces para limpiar la boca.

Las soluciones de ensayo pueden incluir el compuesto experimental en agua, el compuesto experimental más un saborizante clave (por ejemplo, 4% de sacarosa, 6% de sacarosa, 6% de fructosa, 6% de fructosa/glucosa, o 7% fructosa/glucosa, en pH 7.1 o 2.8), y un rango de saborizante clave solo como soluciones de referencia.

Las muestras del saborizante clave sin el compuesto experimental se utilizan para determinar si el panel esta clasificando exactamente; es decir la referencia sen prueba contra si misma (ciego) para determinar que exactamente el panel esta clasificando en un día de prueba dado. Las soluciones se dispensan en

volúmenes de 10 ml en tasas de muestra de 1 oz. Y sirven a los sujetos a temperatura ambiente.

Los sujetos primero prueban la muestra de referencia inmediatamente luego prueban la muestra de ensayo y clasifican la muestra en intensidad del atributo clave en al escala de Referencia de Diferencia (- 5 a +5). Todas la muestras se expectoran. Los sujetos pueden volver a probar las muestras pero solo pueden utilizar el volumen de muestra dado. Los sujetos deben enjuagar al menos dos veces la boca con agua antes de utilizar los pares de muestras. Comer una galleta entre pares de muestra se puede requerir dependiendo de las muestras ensayadas.

La clasificación para cada prueba se promedia a través de los sujetos y se calcula el error estándar. La exactitud del panel se puede determinar utilizando la clasificación de la prueba de referencia ciega. Las pruebas de comparación ANOVA y múltiple (tal como la prueba de Diferencia Significativa Honesta de Tukey) se pueden utilizar para determinar diferencias entre pares, dada que la muestra de referencia es la misma entre todas las pruebas. Si el par de prueba idéntico se prueba en otra sección, se pueden un ensayo t de Student (pareado, de dos colas; alfa = 0.05) determinar si existe cualquier diferencian entre las clasificaciones de secciones.

Se ha utilizado un número diferente de referencia de endulzantes para la medición de la mejora del sabor dulce. Por ejemplo, para probar (R)-3-metil-N-(1,2,3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida, una muestra de referencia que consiste de 4% de sacarosa se utiliza, que tiene más del nivel de umbral de endulzante (es decir, 2% de sacarosa), y un endulzante en la región de percepción

del sabor dulce en donde los sujetos humanos son más sensibles a pequeños cambios en la percepción del sabor dulce. Para la prueba 2,3,5,6-tetrafluoro-4-metil-N-(2-metilciclohexil)benzamida, una mezcla a-50:50 de fructosa:glucosa se utiliza para modelos mejores de soluciones de jarabe de maíz de alta fructosa utilizados comúnmente en la industria de bebidas. Se demuestra que una mezcla de fructosa/glucosa del 6% es aproximadamente igual en la percepción del sabor dulce como 6% de sacarosa, que esta dentro del rango de los panelistas que son sensibles a pequeños cambios en la percepción del sabor dulce. Después de estudios iniciales en 6% de fructosa/glucosa en pH 7.1, los estudios de cambio para evaluar el desempeño del compuesto en un producto prototipo mas similar a una bebida cola, es decir concentraciones mayores de endulzante y un pH bajo.

Los resultados de algunas muestras de gusto humano del compuesto amida dulce de la invención en composiciones acuosas están destinadas al modelo de composición de una bebida carbonatada y se muestran adelante en la tabla F.

Tabla F. Resultados de Prueba de Sabor dulce

Compuesto No	Contenido de la solución	pH	Solución Dulce Equivalente Percibida
175	50 μM Compuesto 175 + 4% sacarosa	*	6% Sacarosa
171	30 μM Compuesto 171 + 6% fructosa/glucosa	*	Mas del 6% pero menos del 8% de fructosa/glucosa
170	30 μM Compuesto 170 + 6% fructosa/glucosa	pH 7.1	Mas del 6% pero menos del 8% de fructosa/glucosa
162	10 μM Compuesto 162 + 6% fructosa/glucosa	pH 7.1	Mas de o igual 8% de fructosa/glucosa
162	10 μM Compuesto 162 + 7%	pH 2.8	Mas de o igual 9% de

	fructosa/glucosa		fructosa/glucosa
168	30 μM Compuesto 168 + 6% fructosa/glucosa	pH 7.1	Igual 8% fructosa/glucosa
163	10 μM Compuesto 163 + 6% fructosa/glucosa	pH 7.1	Mas del 6% pero menos del 8% de fructosa/glucosa
191	5 μM Compuesto 191 + 6% fructosa/glucosa	pH 7.1	Mas del 6% pero menos del 8% de fructosa/glucosa
192	3 μM Compuesto 192 + 6% fructosa/glucosa	pH 7.1	Mas del 6% pero menos del 8% de fructosa/glucosa
176	10 μM Compuesto 176 + 6% fructosa/glucosa	pH 2.8	Igual 10.5% fructosa/glucosa
176	10 μM Compuesto 176 + 7% fructosa/glucosa	pH 7.1	Igual 10% fructosa/glucosa
177	3 μM Compuesto 177 + 6% fructosa/glucosa	pH 7.1	Igual 10% fructosa/glucosa

*el pH de estas soluciones acuosas no se mide ni controla.

Ejemplo 203

Preparación de Sopa Utilizando una Solución Madre de etanol

Se diluye un compuesto de la invención utilizando etanol 200 proof a 1000x la concentración deseada en sopa. El compuesto se puede sonicar y calentar (si esta estable) para asegurar la solubilidad completa en etanol. La sopa de base de caldo se hace al agregar 6 g de base de caldo vegetal en 500 ml de agua caliente en un tazón de vidrio o gres. El agua se calienta a 80°C. La concentración de MSG en el caldo disuelto es 2.2 g/L y no se agrega IMP. Después la base de caldo se disuelve, la solución madre de etanol se agrega a la base de sopa. Para 500 mL de sopa, 0.5 mL de solución madre de etanol 1000x se agrega para una concentración de etanol final de 0.1%. Si el etanol interfiere con sabor de la sopa,

una concentración mayor de solución madre de etanol se puede preparar dado que el compuesto es soluble.

Ejemplo 204

Preparación de piezas

Una mezcla de sal de un compuesto de la invención se prepara al mezclar con sal de tal manera que 1.4% de la mezcla de sal se agrega p/p a las piezas que podría resultar en la concentración deseada del compuesto. Para 1 ppm final del compuesto en las piezas, 7 mg del compuesto se mezcla con 10 g de sal. El compuesto se muele utilizando un mortero y pistillo con la sal y el compuesto y la sal se mezcla bien. Las piezas se rompen en piezas pequeñas uniformes al utilizar un mezclador. Para cada 98.6 g de piezas, 1.4 g de la mezcla de sal se pesa. Los trozos de piezas se calientan primero en un microondas durante 50 segundos hasta que se calientas. Los trozos se esparcen sobre una pastelza grande de lámina de aluminio. La mezcla de sal se esparce uniformemente sobre las piezas. Las piezas luego se colocan en una bolsa plástica para asegurar que toda la sal esta en el lugar en la bolsa también. La mezcla se sal y los trozos luego se agitan para asegurar que la sal se esparza uniformemente sobre las piezas.

Ejemplo 205

Preparación de Galleta

Una composición de la invención se diluye utilizando etanol de graduación normal 200 para 1000x loa concentración deseada en producto final. El compuesto

se puede sonicar y calentar (si es est6able) para asegurar la solubilidad completa en etanol. La solución que contiene el compuesto de la invención se mezcla luego con otros ingredientes líquidos (es decir, agua, huevos líquidos y saborizantes) hasta que se mezcla bien. La solución se mezcla con un emulsificador seco tal como lecitina y se mezcla adicionalmente con manteca vegetal. La manteca vegetal se mezcla con componentes secos (es decir, harina, azúcar, sal, cacao) que se han mezclado bien. La masa se particiona en una lámina de panadería, y se hornea en una temperatura deseada.

Ejemplo 206

Preparación de Jugo

Se diluye un compuesto de la invención utilizando etanol de graduación normal 200 para 1000x la concentración deseada en jugo. El compuesto se mezcla adicionalmente con un componente alcohol de sabores naturales y/o artificiales para elaborar una "clave". El sabor clave se mezcla con una porción de concentrado de jugo para asegurar homogeneidad. El restante concentrado de jugo se diluye con agua y se mezcla. Endulzantes, tal como HFCS (jarabe de maíz de alta fructosa), aspartame, o sucralosa, se mezclan. La porción de sabor/compuesto se agrega como una etapa final y se mezcla.

Ejemplo 207

Jugo de Tomate Condimentosado o Mezcla Bloody Mary

Un compuesto de la invención se agrega como un ingrediente seco a una mezcla de condimentos, que puede incluir opcionalmente glutamato monosódico, y mezclada vigorosamente. La mezcla de condimentos se dispersa en una porción de la pasta de tomate, se mezcla, y la pasta mezclada se mezcla adicionalmente en la pasta restante. La pasta se diluye luego con agua para hacer jugo de tomate condimentosado una alta temperatura durante un corto periodo de tiempo.

Ejemplo 208

Pruebas de Gusto Humano de Jugo de Tomate Bajo en sodio

Se conducen pruebas de gusto humano con el fin de evaluar la capacidad de los compuestos de la invención para mejorar el sabor salado o picante del jugo de tomate bajo en sodio (que comprende naturalmente algún glutamato monosódico).

Procedimiento de Preparación de la Muestra

Las muestras de jugo de tomate finales para ensayar el sabor se preparan de tal manera que comprenden 90% (por volumen) preelaboradas de solución madre de jugo de tomate bajo en sodio (pH 4.2, 80~100mg Na/8 oz, 16mM de MSG de ocurrencia natural), 5% (por volumen) de soluciones madre formuladas para producir los niveles finales seleccionados de sodio de jugo final y 5% (por volumen) de una solución madre del compuesto de la invención. Los compuesto de oxalamida seleccionados de la invención se disuelven en LSB (amortiguador de fosfato bajo en sodio), para suministrar una solución madre en 20 veces la concentración final deseada en el jugo de tomate final. La concentración de sodio

final deseada del jugo de tomate experimenta casi 73.6 mM (400 mg de sodio en 8 oz. De jugo), por lo tanto una solución madre de NaCl se hace en 1.48 M NaCl. El pH de la solución madre se ajusta a 4.2 utilizando una solución de ácido cítrico 1 M, y la solución madre se sonica para asegurar los compuesto aditivos que se disuelven completamente. Para producir una muestra final de 1,000 mL de muestra de jugo de tomate para ensayar sabor, 50 mL de solución madre de compuesto de ensayo, y 50 mL de cloruro de sodio se agregan a 900 mL de solución madre de jugo de tomate baja en sodio.

Pruebas de Gusto Humano

Se utilizan 16 sujetos humanos en prueba de gusto. Los sujetos se abstienen de comer o beber (excepto agua) durante al menos 1 hora antes de la prueba. Los sujetos comen una galleta y se enjuagan con agua para limpiar la boca antes de iniciar la prueba. Se sirven muestras de 15mL en tasas de muestra de 2oz. A temperatura ambiente. Los panelistas se enjuagan con agua entre las muestras, y se animan a comer una galleta para remover todos los sabores antes de pasar a la siguiente muestra. Las muestras se presentan en orden aleatorizado contrabalanceado dentro de cada cesión de prueba (con diferentes códigos de mezcla). Se le pregunta a los panelistas para evaluar los comentarios hechos sobre el umami (nivel de sal o picante) en las muestras en una escala de línea no estructurada (clasificación 0-10), en cesiones en duplicado. Hubo 5 interrupciones entre las cesiones de prueba, y un total de 4 cesiones durante un periodo de 2 días. Las muestras probadas se dan adelante.

Muestras Ensayadas
400 mg Na / 8 oz de jugo de tomate
400 mg Na + 3uM Compuesto 123 / 8 oz jugo de tomate
400 mg Na + 3uM Compuesto 157 / 8 oz jugo de tomate

Las clasificaciones se promedian a través de panelistas y cesiones, y se evalúan utilizando un ensayo ANOVA de 2 vías (factores: panelistas y muestras) y un ensayo de comparación múltiple de Duncan (alfa = 0.05) para determinar la diferencia significativa en tasa de intensidad los resultados se resuelven adelante.

Tabla G. Resultado de Pruebas de Sabor de Jugos de Tomate

Compuesto	Nombre Químico	Datos de Sabor
123	N1-(2,4-dimetoxibencil)N2-(2-(piridin-2-il)etil)oxalamida	3 μM cpd mejora el sabor salado o picante de 16 mM de glutamato (de existencia natural) en jugo de tomate bajo en sodio por 1.4 a 1.5 veces
157	N1-(2-metoxi-4-metilbencil)-N2-(2-(5-metilpiridin-2-il)etil)oxalamida	3 μM cpd mejora el sabor salado o picante de 16 mM de glutamato (de existencia natural) en jugo de tomate bajo en sodio por 1.8 a 1.9 veces

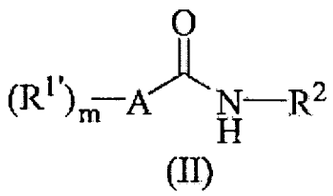
Será evidente para aquellos expertos en la técnica que varias modificaciones y variaciones se pueden hacer en la presente invención sin apartarse del alcance o espíritu de la invención. Otras modalidades de la invención serán evidentes para aquellos expertos en la técnica a partir de la consideración de la especificación y practica de la invención descrita aquí. Se pretende que la especificación y ejemplo se consideren como ejemplos, con un alcance y espíritu verdadero de la invención que se indica por las siguientes reivindicaciones.

REIVINDICACIONES

1. Un método para incrementar el sabor dulce de un producto comestible o medicinal que comprende:

a) suministrar al menos un producto comestible o medicinal, o uno o más precursores de estos, y

b) combinar el producto comestible o medicinal o uno o más precursores de estos con al menos un compuesto amida aromático o heteroaromático, o una sal comestiblemente aceptable de este, para formar un producto comestible o medicinal modificado que comprende al menos aproximadamente 0.001 ppm del compuesto amida; en donde el compuesto amida tiene la estructura:



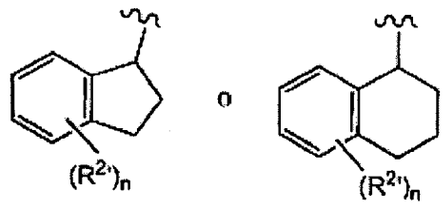
(II)

en donde A es un anillo arilo o heteroarilo de cinco o seis miembros;

m es 1, 2, o 3;

cada R^1 se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, un radical orgánico C_1-C_8;

R^2 es un radical que tiene la estructura:



en donde R^2 comprende la configuración óptica indicada en exceso enantiomérico,

n es 1, 2, o 3, cada $R^{2'}$ pueden estar unidos a el anillo aromático o no aromático de R^2, y cada $R^{2'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4, y

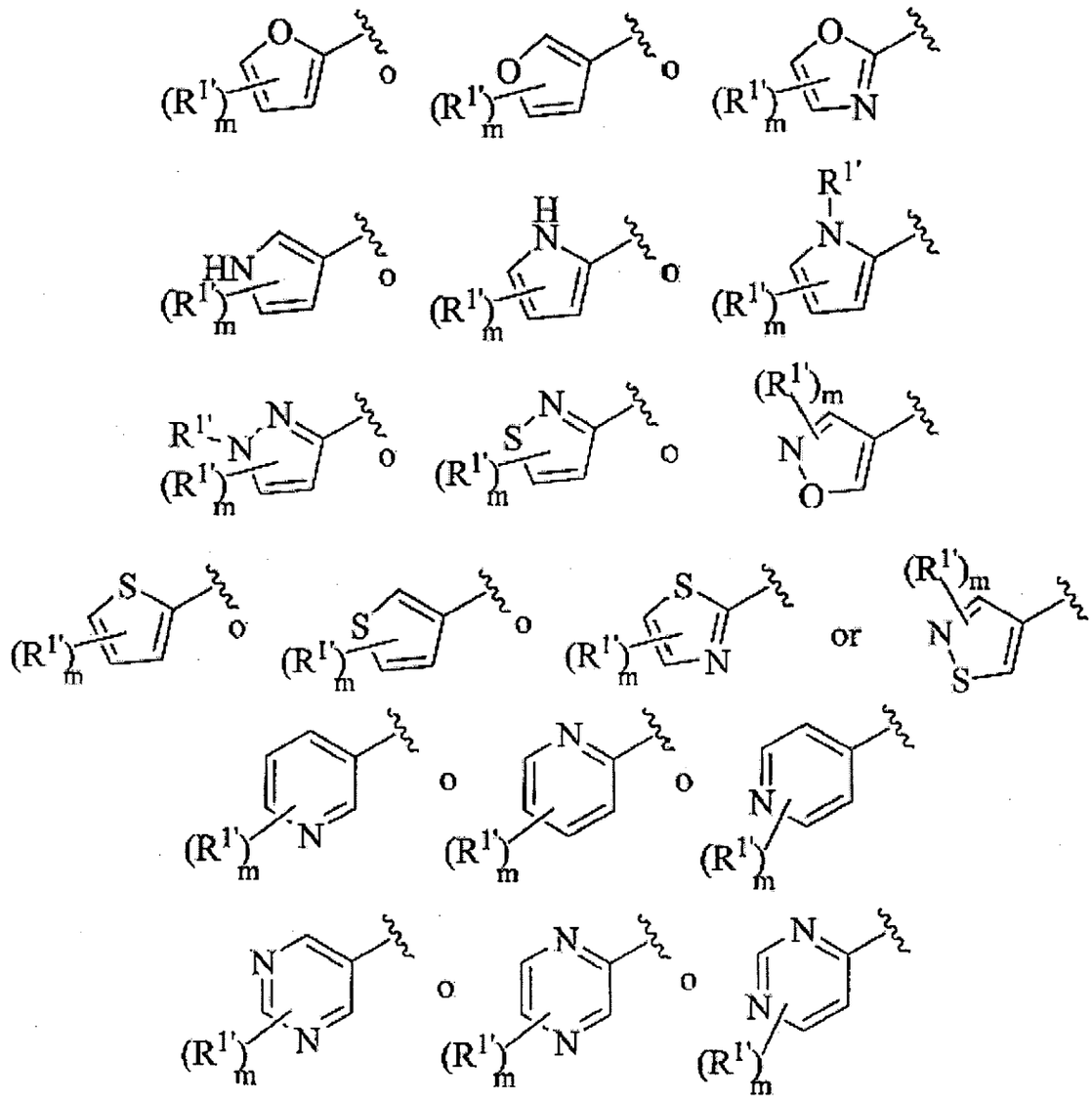
en donde el producto comestible o medicinal modificado comprende adicionalmente al menos una cantidad de agente saborizante dulce de uno o más agentes saborizantes de dulces naturales, semi-sintéticos, o sintéticos, o una mezcla de estos.

2. El método de la reivindicación 1 en donde el radical R_2 tiene la configuración óptica indicada en al menos 90% de exceso enanatiomérico.

3. El método de la reivindicación 1 en donde cada $R^{1'}$ y cada $R^{2'}$ se seleccionan independientemente del grupo que consiste de grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, SEt, metilo, etilo, isopropilo, n-propilo, n-butilo, 1-metil-propilo, isobutilo, t-butilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

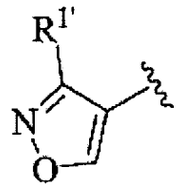
4. El método de la reivindicación 1 en donde A es un anillo fenilo.

5. El método de la reivindicación 1 en donde el radical A tiene una de las siguientes fórmulas:



6. El método de la reivindicación 5 en donde m es 1 o 2, y cada $R^{1'}$ se selecciona independientemente de hidrógeno, grupos hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, SEt, metilo, etilo, isopropilo, n-propilo, n-butilo, 1-metil-propilo, isobutilo, t-butilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

7. El método de la reivindicación 1 en donde el radical A tiene la estructura:



en donde $R^{1'}$ es hidrógeno, hidroxilo, NH_2, SH, halógeno, alquilo C_1-C_8, haloalquilo C_1-C_8, haloalcoxi C_1-C_8, alcoxilo C_1-C_8, alcoxi-alquilo C_1-C_8, hidroxi-alquilo C_1-C_8, OH, NH_2, NHR^6, $NR^6{}_2$, CN, CO_2H, CO_2R^6, CHO, COR^6, SH, SR^6, $S(O)R^6$, $S(O)_2R^6$, y halógeno, en donde R^6 es alquilo C_1-C_4.

8. El método de la reivindicación 7 en donde $R^{1'}$ es un alquilo C_1-C_8.

9. El método de la reivindicación 7 en donde $R^{1'}$ es grupo hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, SEt, metilo, etilo, isopropilo, n-propilo, n-butilo, 1-metil-propilo, isobutilo, t-butilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, trifluorometoxi, CH_2OCH_3, CH_2OH, CH_2NH_2, CH_2NHCH_3, o $CH_2N(CH_3)_2$.

10. El método de la reivindicación 1 en donde el compuesto amida tiene una de las siguientes fórmulas:

(R)-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)-3-propilisoxazol-4-carboxamida;
(R)-3-butil-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida;
(R)-3-etil-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida;
(R)-N-(5,7-Dimetil-1,2,3,4-tetrahidronaftalen-1-il)-3-metilisoxazol-4-carboxamida;
(R)-3-Cloro-2-hidroxi-N-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il) benzamida; o
(R)-3-Cloro-2-hidroxi-*N*-(7-metoxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida.

11. El método de una cualquiera de las reivindicaciones 1-10 en donde los agentes saborizantes dulces naturales, semi-sintéticos, o sintéticos se seleccionan del grupo que consiste de sacarosa, fructosa, glucosa, eritritol, isomaltosa, lactitol, manitol, sorbitol, xilitol, aspartamo, sacarina, acesulfamo-K, ciclamato, sucralosa, y alitamo, o una mezcla de estos.

12. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado tiene un sabor más dulce que un producto comestible o medicinal de control que no comprende el compuesto amida, como es juzgado por la mayoría de un panel de al menos ocho probadores de sabores humanos.

13. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado se selecciona del grupo que consiste de confiterías, productos de panadería, helados, productos lácteos, pasabocas salado o picante y dulce, pasabocas en barra, productos que reemplazan comida, cómidas rápidas, sopas, pastas, fideos, alimentos conservados, alimentos congelados, alimentos secos, alimentos enfriados, aceites y grasas, alimentos para bebés, y productos para untar.

14. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado comprende uno o más carnes, pollo, pescados, vegetales, granos, o frutas.

15. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado es un alimento congelado, un alimento crudo, o un alimento parcial o completamente cocinado.

16. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado es una sopa, una sopa concentrada o deshidratada, o una sopa seca.

17. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado es un alimento de pasaboca.

18. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado es un producto auxiliar de cocción, un producto de solución de comida, un producto mejorador de comida, un condimento, o una mezcla de condimentos.

19. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado es una torta, galleta, pastel, bombones, chicles, gelatina, helado, sorbete, pudín, mermelada, jalea, aliño, condimentos, cereales, frutas en conserva, o salsas de frutas.

20. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado es una bebida, una mezcla de bebidas, o una bebida concentrada.

21. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado es un soda, o jugo.

22. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado es una bebida alcohólica.

23. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado es un producto de higiene oral.

24. El método de una cualquiera de las reivindicaciones 1-10 en donde el compuesto amida est á presente en el producto comestible o medicinal modificado en una concentración de aproximadamente 0.01 ppm a aproximadamente 30 ppm.

25. El método de una cualquiera de las reivindicaciones 1-10 en donde el producto comestible o medicinal modificado tiene un sabor dulce que un producto comestible o medicinal de control que no comprende el compuesto, como es juzgado por la mayoría de un panel de al menos ocho probadores de sabores humanos.

26. El método de una cualquiera de las reivindicaciones 1-10 en donde el compuesto amida tiene un EC_{50} para unir un receptor hT1R2/hT1R3 que se expresa en una línea celular HEK293-Gα15 de menos de aproximadamente 2 μM.

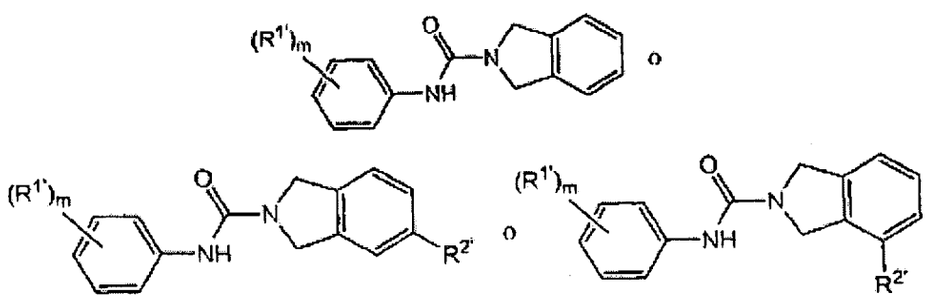
27. Un producto comestible o medicinal elaborado por el proceso de una cualquiera de las reivindicaciones 1 -26.

28. Un método para mejorar el sabor dulce de un producto comestible o medicinal que comprende:

a) suministrar al menos un producto comestible o medicinal, o uno o más precursores de estos, y

b) combinar el producto comestible o medicinal o uno o más precursores de estos con al menos un compuesto de urea, o una sal comestiblemente aceptable de este, para formar un producto comestible o medicinal modificado que comprende al menos aproximadamente 0.001 ppm del compuesto de urea;

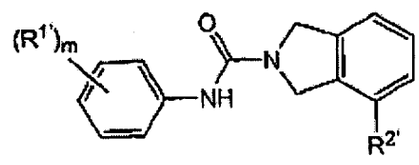
c) en donde el producto comestible o medicinal modificado comprende adicionalmente un endulzante artificial o natural conocido, en donde el compuesto de urea tiene la fórmula:



en donde m es 1, 2, o 3, y cada $R^{1'}$ y $R^{2'}$ se selecciona independientemente de flúor, cloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, SEt, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, metilo, etilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, o dos grupos $R^{1'}$ juntos forman un anillo metilenodioxi.

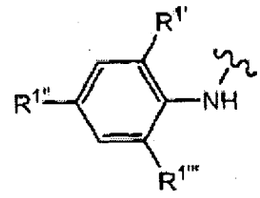
29. El método de la reivindicación 28 en donde el compuesto de urea tiene la fórmula:

695



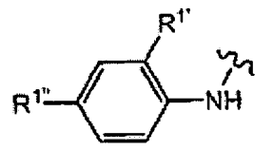
30. El método de la reivindicación 29 en donde R^2 es metilo o metoxi.

31. El método de la reivindicación 28 en donde el radical anilina tiene la fórmula:



en donde $R^{1'}$, $R^{1''}$ y $R^{1'''}$ se seleccionan independientemente de hidrógeno, flúor, cloro, bromo, metilo, y metoxi.

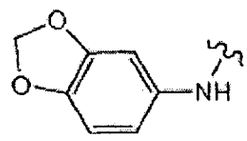
32. El método de la reivindicación 28 en donde el radical anilina tiene la fórmula:



en donde $R^{1'}$ y $R^{1''}$ se seleccionan independientemente de flúor, cloro, bromo, metilo, y metoxi.

696

33. El método de la reivindicación 28 en donde los grupos $R^{1'}$ juntos forman un radical anillo metilenodioxi que tienen la fórmula:



34. El método de la reivindicación 28 en donde el compuesto de urea comprende de aproximadamente 0.1 ppm a aproximadamente 100 ppm del producto comestible o medicinal modificado, y en donde el producto comestible o medicinal modificado tiene un sabor más dulce que un producto comestible o medicinal de control que no comprende el compuesto de urea, como es juzgado por la mayoría de un panel de al menos ocho probadores de sabores humanos.

35. El método de una cualquiera de las reivindicaciones 28-34 en donde los agentes saborizantes dulces naturales, semi-sintéticos, o sintéticos se seleccionan del grupo que consiste de sacarosa, fructosa, glucosa, eritritol, isomaltosa, lactitol, manitol, sorbitol, xilitol, aspartamo, sacarina, acesulfamo-K, ciclamato, sucralosa, y alitamo, o una mezcla de estos.

36. El método de una cualquiera de las reivindicaciones 28-34 en donde el producto comestible o medicinal modificado modifica un producto comestible o medicinal que tiene un sabor dulce que un producto comestible o medicinal de control que no comprende el compuesto amida, como es juzgado por la mayoría de un panel de al menos ocho probadores de sabores humanos.

37. El método de una cualquiera de las reivindicaciones 28-34 en donde el producto comestible o medicinal modificado se selecciona del grupo que consiste de confiterías, productos de panadería, helados, productos lácteos, pasabocas salado o picante y dulce, pasabocas en barra, productos que reemplazan comida, comidas rápidas, sopas, pastas, fideos, alimentos conservados, alimentos congelados, alimentos secos, alimentos enfriados, aceites y grasas, alimentos para bebés, y productos para untar.

38. El método de una cualquiera de las reivindicaciones 28-34 en donde el producto comestible o medicinal modificado comprende uno o más de carnes, pollo, pescados, vegetales, granos, o frutas.

39. El método de una cualquiera de las reivindicaciones 28-34 en donde el producto comestible o medicinal modificado es un alimento congelado, un alimento crudo, o un alimento parcial o completamente cocinado.

40. El método de una cualquiera de las reivindicaciones 28-34 en donde el producto comestible o medicinal modificado es una sopa, una sopa concentrada o deshidratada, o una sopa seca.

41. El método de una cualquiera de las reivindicaciones 28-34 en donde el producto comestible o medicinal modificado es un alimento de pasaboca.

42. El método de una cualquiera de las reivindicaciones 28-34 en donde el producto comestible o medicinal modificado es un producto auxiliar de cocción, un producto de solución de comida, un producto mejorador de comida, un condimento, o una mezcla de condimentos

43. El método de una cualquiera de las reivindicaciones 28-34 en donde el producto comestible o medicinal modificado es un torta, galleta, pastel, bombones, chicles, gelatina, helado, sorbete, pudín, mermelada, jalea, aliño, condimentos, cereales, frutas en conserva, o salsas de frutas.

44. El método de una cualquiera de las reivindicaciones 28-34 en donde el producto comestible o medicinal modificado es una bebida, una mezcla de bebidas, o una bebida concentrada.

45. El método de una cualquiera de las reivindicaciones 28-34 en donde el producto comestible o medicinal modificado es un soda, o jugo.

46. El método de una cualquiera de las reivindicaciones 28-34 en donde el producto comestible o medicinal modificado es una bebida alcohólica.

47. El método de una cualquiera de las reivindicaciones 28-34 en donde el producto comestible o medicinal modificado es un producto de higiene oral.

48. Un producto comestible o medicinal elaborado por el proceso de una cualquiera de las reivindicaciones28-47.

49. Una composición que comprende más de aproximadamente 0.001 ppm de uno o más de los compuestos:

3-etil-N-(heptan-4-il)benzamida;

5-etil-N-(heptan-4-il)-4-(metoximatil)furano-2-carboxamida;

3,4-dimetil-N-(2-metilciclohexil)benzamida;

2-amino-3-metoxi-N-(2-metilciclohexil)benzamida;

N-(heptan-4-il)-3-(metiltio)benzamida; o

N-(heptan-4-il)-1,2,3,4-tetrahidroquinolin-7-carboxamida; o una sal comestiblemente aceptable de estos, o una mezcla de estos.

50. Una composición que comprende más de aproximadamente 0.001 ppm de uno o más de los compuestos:

(S)-N-(2,3-Dihidro-1H-inden-1-il)-4-metoxi-3-metilbenzamida;

4-Metoxi-N-(5-metoxi-2,3-dihidro-1H-inden-1-il)-3-metilbenzamida;

(S)-4-Metoxi-N-(5-metoxi-2,3-dihidro-1H-inden-1-il)-3-metilbenzamida;

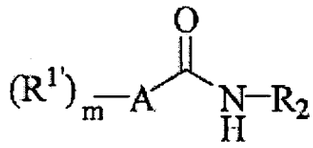
2-Amino-3-metoxi-N-(5-metoxi-2,3-dihidro-1H-inden-1-il)benzamida

2-amino-3-metoxi-N-(6-metoxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida;

(S)-2-amino-3-metoxi-N-(6-metoxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida;

(S)-2-amino-3-metoxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida; o una sal comestiblemente aceptable de estos, o una mezcla de estos.

51. Una composición comestible o medicinal que comprende de un producto comestible o medicinal o uno o más precursores de estos, y al menos aproximadamente 0.0001 ppm de un compuesto amida que tiene la estructura:

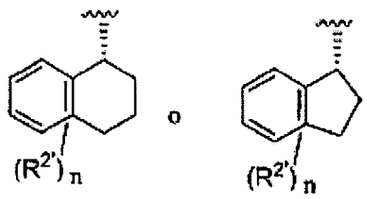


en donde A es un anillo arilo o heteroarilo de cinco o seis miembros;

m es 1, 2, o 3;

cada $R^{1'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, un radical orgánico C_1-C_8;

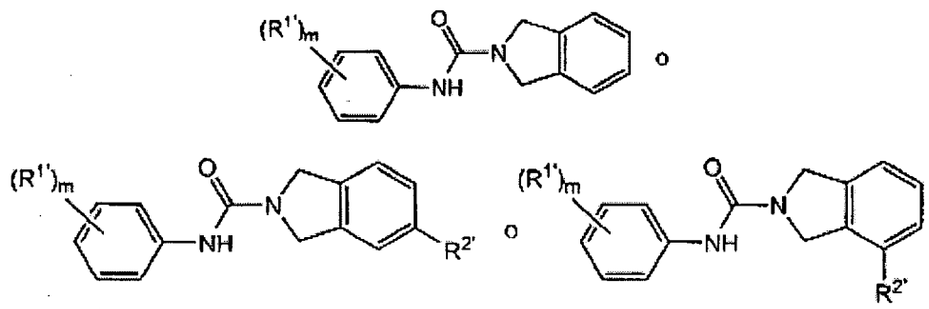
R^2 es un radical que tiene la estructura:



en donde R^2 comprende la configuración óptica indicada en exceso enantiomérico, n es 1, 2, o 3, cada $R^{2'}$ puede estar unidos a el anillo aromático o no aromático de R^2, y cada $R^{2'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4; o una sal comestiblemente aceptable de este;

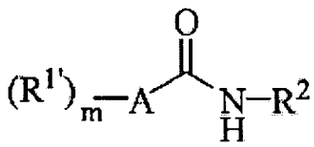
en donde el producto comestible o medicinal modificado comprende adicionalmente al menos una cantidad de agente saborizante dulce de uno o más agentes saborizantes dulces naturales, semi-sintéticos, o sintéticos, o una mezcla de estos.

52. Un producto comestible o medicinal modificado que comprende al menos un producto comestible o medicinal, o uno o más precursores de estos, y al menos aproximadamente 0.001 ppm de al menos un compuesto de urea que tiene la fórmula:



en donde m es 1, 2, o 3, y cada $R^{1'}$ y $R^{2'}$ se selecciona independientemente de flúor, cloro, bromo, NH_2, $NHCH_3$, $N(CH_3)_2$, SEt, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, metilo, etilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi, o dos grupos $R^{1'}$ juntos forman un anillo metilenodioxi: o una sal comestiblemente aceptable de este.

53. Un producto comestible o medicinal modificado que comprende al menos un producto comestible o medicinal, o uno o más precursores de estos, y al menos aproximadamente 0.001 ppm de al menos un compuesto que tiene la estructura:



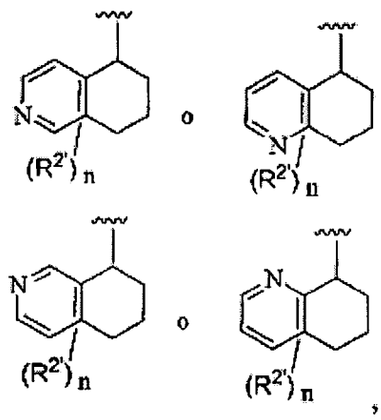
en donde A es un anillo arilo o heteroarilo de cinco o seis miembros;

m es 0, 1, 2, 3, o 4;

cada $R^{1'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, un radical orgánico C_1-C_8;

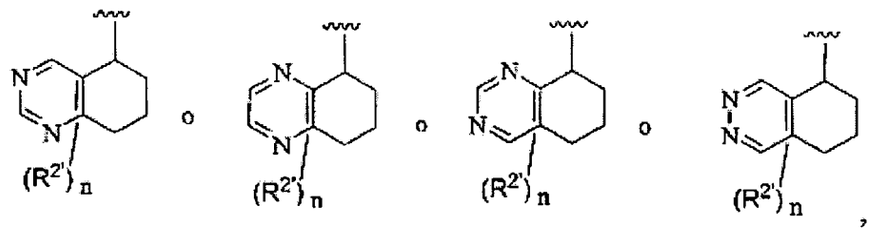
R^2 comprende un anillo tetrahidronaftaleno o indano modificado que comprende uno o más heteroátomos o grupos heteroatómicos independientemente seleccionados de oxígeno, nitrógeno, o azufre.

54. El producto comestible o medicinal modificado de la reivindicación 53, en donde R^2 tiene la estructura:



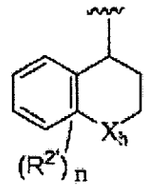
en donde n es 1, 2, o 3, cada $R^{2'}$ puede estar unido a el anillo aromático o no aromático de R^2, y cada $R^{2'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4.

55. El producto comestible o medicinal modificado de la reivindicación 53, en donde R^2 tiene una de las estructuras:



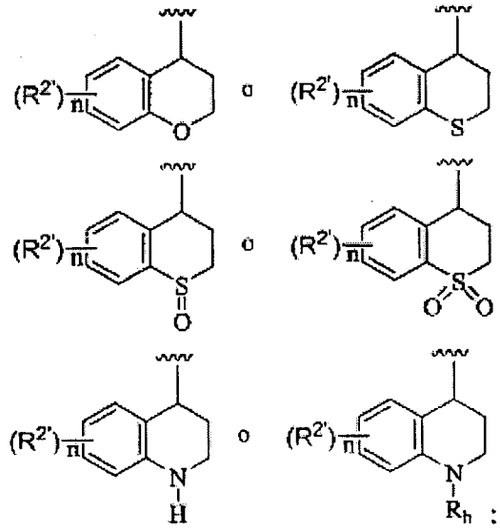
en donde n es 1, 2, o 3, cada R^2 pueden estar unidos a el anillo aromático o no aromático de R^2, y cada $R^{2'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4.

56. El producto comestible o medicinal modificado de la reivindicación 53, en donde R^2 tiene la estructura



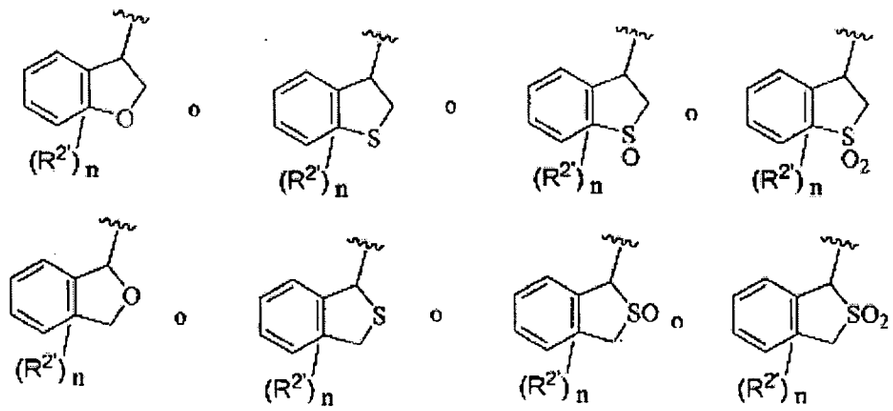
en donde n es 0, 1, 2, o 3; X_h es O, S, SO, SO_2, NH, o NR_h, en donde R_h es un radical orgánico C_1-C_4; cada $R^{2'}$ puede estar unido a el anillo aromático o no aromático de R^2;y cada $R^{2'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4.

57. El producto comestible o medicinal modificado de la reivindicación 53, en donde R^2 tiene la estructura:



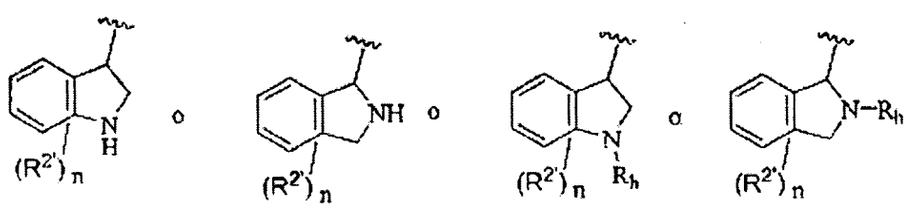
en donde n es 0, 1, 2, o 3; en donde R_h es un radical orgánico C_1-C_4; y cada $R^{2'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4

58. El producto comestible o medicinal modificado de la reivindicación 53, en donde R^2 tiene la estructura:



en donde n es 1, 2, o 3, cada $R^{2'}$ pueden estar unidos a el anillo aromático o no aromático de R^2, y cada $R^{2'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4.

59. El producto comestible o medicinal modificado de la reivindicación 53, en donde R^2 tiene la estructura:



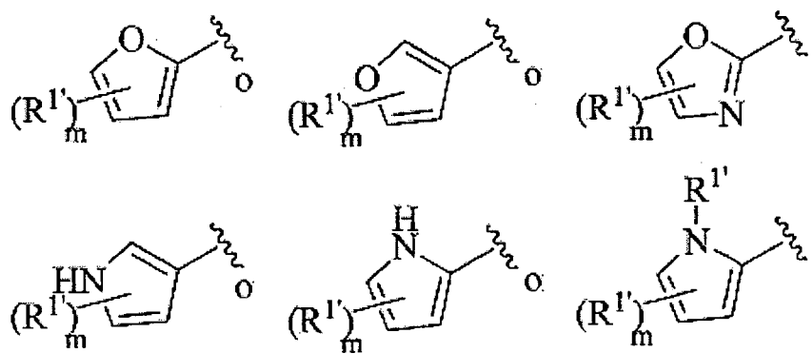
en donde n es 1, 2, o 3, cada $R^{2'}$ puede estar unido a el anillo aromático o no aromático de R^2, y cada $R^{2'}$ se selecciona independientemente del grupo que consiste de hidroxilo, NH_2, SH, halógeno, o un radical orgánico C_1-C_4.

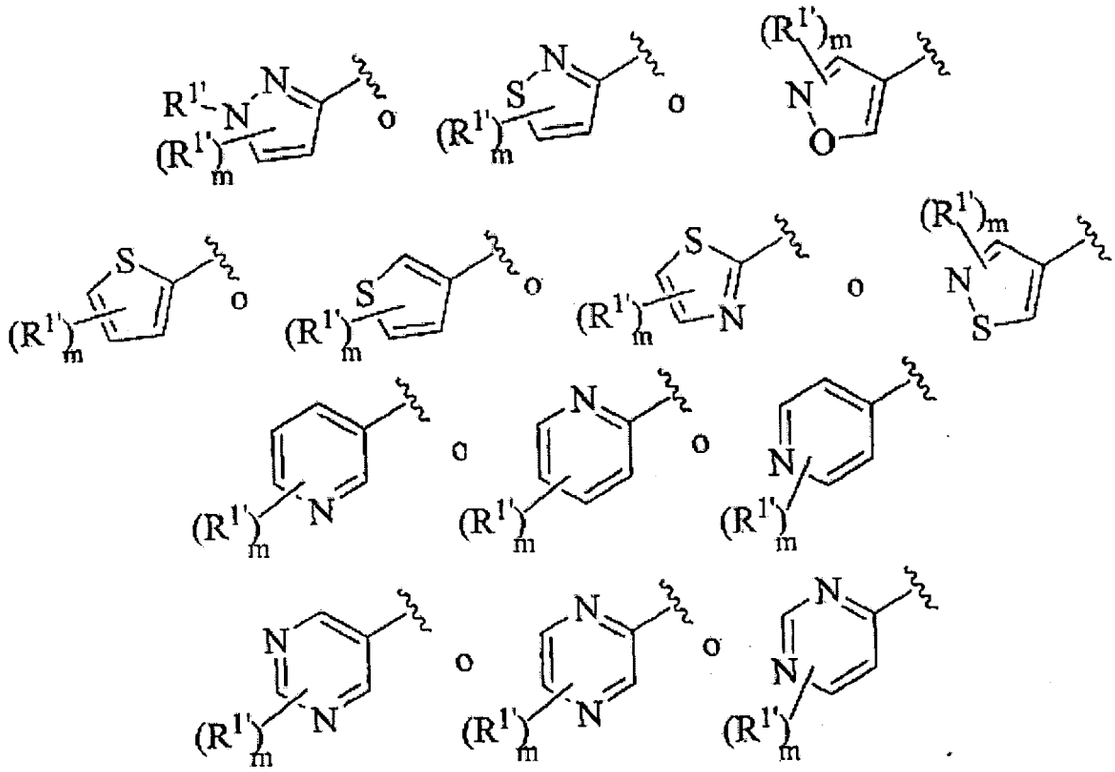
60. El producto comestible o medicinal modificado de cada una de las reivindicaciones 54-59 en donde el radical orgánico C_1-C_4 se selecciona independientemente del grupo que consiste de hidrógeno, hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometlioxi.

61. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-60 en donde A es un anillo fenilo.

62. El producto comestible o medicinal modificado de la reivindicación 53 en donde el radical orgánico C_1-C_8 se selecciona independientemente del grupo que consiste de hidrógeno, hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

63. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-60 en donde el radical A tiene una de las siguientes fórmulas:





64. El producto comestible o medicinal modificado de la reivindicación 63 en donde el radical orgánico C_1-C_8 se selecciona independientemente del grupo que consiste de hidrógeno, hidroxi, flúor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi.

65. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-64 en donde el producto comestible o medicinal modificado comprende adicionalmente al menos una cantidad de agente saborizante dulce de uno o más agentes saborizantes dulces naturales, semi-sintéticos, o sintéticos, o una mezcla de estos.

66. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-64 en donde los agentes saborizantes dulces naturales, semi-sintéticos, o sintéticos comprenden sacarosa, fructosa, glucosa,

eritritol, isomaltosa, lactitol, manitol, sorbitol, xilitol, aspartamo, sacarina, acesulfamo-K, ciclamato, sucralosa, y alitamo, o una mezcla de estos.

67. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-64 en donde el producto comestible o medicinal modificado comprende uno o más de carnes, pollo, pescados, vegetales, granos, o frutas.

68. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-64 en donde el producto comestible o medicinal modificado es un alimento congelado, un alimento crudo, o un alimento parcial o completamente cocinado.

69. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-64 en donde el producto comestible o medicinal modificado es una sopa, una sopa concentrada o deshidratada, o una sopa seca.

70. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-64 en donde el producto comestible o medicinal modificado es un alimento de pasaboca.

71. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-64 en donde el producto comestible o medicinal modificado es un producto auxiliar de cocción, un producto de solución de comida, un producto mejorador de comida, un condimento, o una mezcla de condimentos.

72. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-64 en donde el producto comestible o medicinal modificado es un torta, galleta, pastel, bombones, chicles, gelatina, helado, sorbete, pudín, mermelada, jalea, aliño, condimentos, cereales, frutas en conserva, o salsas de frutas.

73. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-64 en donde el producto comestible o medicinal modificado es una bebida, una mezcla de bebidas, o una bebida concentrada.

74. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-64 en donde el producto comestible o medicinal modificado es un soda, o jugo.

75. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-64 en donde el producto comestible o medicinal modificado es una bebida alcohólica.

76. El producto comestible o medicinal modificado de una cualquiera de las reivindicaciones 53-64 en donde el producto comestible o medicinal modificado es un producto de higiene oral.

709

RESUMEN

La invención descrita aquí se relaciona con compuestos de amida de ocurrencia no natural que son capaces, cuando se ponen en contacto con alimento comestible o bebidas o composiciones farmacéuticas en concentraciones preferiblemente en el orden de 100 ppm o menos, de servir como modificadores de sabor dulce o ("umami") salado o picante, agentes saborizantes de dulce o salado o picante y mejoradores de sabor de dulce o salado o picante, para el uso en alimentos, bebidas, y otros comestible o productos medicinales de administración oral o composiciones, opcionalmente en la presencia de o en mezclas con agentes saborizantes tales como glutamato monosódico o endulzantes artificiales y naturales conocidos.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/004132

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005041684 A	12-05-2005	AU 2004263871 A1	17-02-2005
		AU 2004285410 A1	12-05-2005
		CA 2535036 A1	12-05-2005
		CA 2535045 A1	17-02-2005
		EP 1660859 A2	31-05-2006
		EP 1659881 A2	31-05-2006
		WO 2005015158 A2	17-02-2005
EP 1205116 A	15-05-2002	US 6365215 B1	02-04-2002
EP 0055689 A	07-07-1982	CA 1175059 A1	25-09-1984
		DK 572481 A	23-06-1982
		IE 52496 B1	25-11-1987
		NO 814365 A	23-06-1982
		US 4429152 A	31-01-1984
		US 4522839 A	11-06-1985
		US 4869913 A	26-09-1989
WO 9907235 A	18-02-1999	AT 253836 T	15-11-2003
		AU 745909 B2	11-04-2002
		AU 8776998 A	01-03-1999
		BR 9811888 A	22-08-2000
		CA 2293349 A1	18-02-1999
		CN 1265563 A	06-09-2000
		DE 69819737 D1	18-12-2003
		DE 69819737 T2	23-09-2004
		DK 1003383 T3	22-03-2004
		EA 2803 B1	31-10-2002
		EP 1003383 A1	31-05-2000
		ES 2207852 T3	01-06-2004
		HK 1029497 A1	07-03-2003
		JP 2001513330 T	04-09-2001
		NZ 502654 A	28-03-2002
		PL 338547 A1	06-11-2000
		PT 1003383 T	31-03-2004
WO 03070713 A	28-08-2003	US 2003161860 A1	28-08-2003
WO 2004026840 A	01-04-2004	AU 2003266321 A1	08-04-2004
		BR 0314447 A	19-07-2005
		CN 1694872 A	09-11-2005
		EP 1546114 A1	29-06-2005
		JP 2006512294 T	13-04-2006
		US 2006106217 A1	18-05-2006
		US 2004067970 A1	08-04-2004
GB 1489359 A	19-10-1977	NONE	
US 4136163 A	23-01-1979	NONE	
US 4150052 A	17-04-1979	NONE	
GB 1502680 A	01-03-1978	AU 1446876 A	08-12-1977
		AU 503510 B2	06-09-1979
		AU 1446976 A	08-12-1977
		BE 842516 A1	03-12-1976
		BE 842517 A1	03-12-1976
		BR 7603484 A	04-01-1977

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/004132

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1502680 A		CA 1054441 A1	15-05-1979
		DE 2623868 A1	16-12-1976
		DE 2624504 A1	23-12-1976
		DK 242776 A	04-12-1976
		DK 242876 A	04-12-1976
		FR 2391722 A1	22-12-1978
		FR 2312971 A1	31-12-1976
		IE 43232 B1	14-01-1981
		IT 1060764 B	30-09-1982
		IT 1060882 B	30-09-1982
		JP 51148074 A	18-12-1976
		JP 51148040 A	18-12-1976
		LU 75061 A1	21-01-1977
		LU 75062 A1	21-01-1977
		NL 7605913 A	07-12-1976
		NL 7605914 A	07-12-1976
		ZA 7603155 A	27-04-1977
		ZA 7603156 A	27-04-1977
WO 02064139 A	22-08-2002	EP 1361878 A1	19-11-2003
		JP 2004523543 T	05-08-2004
		US 2004063742 A1	01-04-2004
WO 2004113304 A	29-12-2004	AU 2004249675 A1	29-12-2004
		BR PI0410745 A	27-06-2006
		CA 2526430 A1	29-12-2004
		EP 1638941 A1	29-03-2006
		MX PA05012596 A	22-02-2006
WO 9832733 A	30-07-1998	AP 929 A	18-01-2001
		AT 270285 T	15-07-2004
		AT 242208 T	15-06-2003
		AU 723895 B2	07-09-2000
		AU 5234098 A	18-08-1998
		BG 103597 A	29-02-2000
		BR 9714328 A	21-03-2000
		CA 2279186 A1	30-07-1998
		CN 1245490 A	23-02-2000
		CZ 9902575 A3	13-09-2000
		DE 69722663 D1	10-07-2003
		DE 69722663 T2	29-04-2004
		DE 69729762 D1	05-08-2004
		DE 69729762 T2	14-07-2005
		DK 1270565 T3	04-10-2004
		DK 964849 T3	25-08-2003
		DZ 2407 A1	04-01-2003
		EA 1803 B1	27-08-2001
		EP 0964849 A1	22-12-1999
		ES 2222426 T3	01-02-2005
		ES 2198598 T3	01-02-2004
		HR 980045 A2	30-06-1999
		HU 0000567 A2	28-10-2000
		ID 22223 A	16-09-1999
		JP 3573757 B2	06-10-2004
		JP 2000511200 T	29-08-2000
		MA 26468 A1	20-12-2004
		NO 993658 A	28-09-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/004132

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
		NZ 336248 A		27-10-2000
WO 9832733	A	OA 11079 A		14-03-2002
		PL 335052 A1		27-03-2000
		PT 1270565 T		30-09-2004
		PT 964849 T		29-08-2003
		SK 98299 A3		08-10-2001
		TR 9901816 T2		22-11-1999
		TW 515788 B		01-01-2003
		ZA 9800685 A		29-07-1999
US 4177279	A	04-12-1979	NONE	
EP 0656350	A	07-06-1995	AU 690133 B2	23-04-1998
		AU 7446394 A		27-04-1995
		CA 2132771 A1		08-04-1995
		JP 7188151 A		25-07-1995
		US 5547966 A		20-08-1996
US 3535335	A	20-10-1970	AT 278847 B	10-02-1970
		BE 718257 A		20-01-1969
		DE 1770915 A1		24-02-1972
		ES 356776 A2		01-02-1970
		FR 342 F		11-01-1971
		FR 95283 E		06-07-1970
		GB 1193289 A		28-05-1970
US 3503962	A	31-03-1970	AT 263800 B	12-08-1968
		BE 683614 A		04-01-1967
		CH 461500 A		31-08-1968
		DE 1620393 A1		02-04-1970
		DK 118505 B		31-08-1970
		FR 5836 M		04-03-1968
		GB 1146979 A		26-03-1969
		NL 129208 C		
		NL 6608786 A		16-01-1967
		NO 119800 B		06-07-1970
		SE 303294 B		26-08-1968
US 3294544	A	27-12-1966	DE 1517109 A1	18-12-1969
		GB 1072029 A		14-06-1967
		SE 331223 B		14-12-1970

714

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 64,952
FECHA : AGOSTO 13 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-090851- -00000-0000

Fecha: 2007-09-04 16:48:47 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 714

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	63769917	13/08/2007	39,640,000.00

***** C O N C E P T O *****

[redacted]	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

[redacted]

RDO 15159-841-003-9

215

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-090851- -00000-0000

Fecha: 2007-09-04 16:48:47 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 714

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Claudia M Nevao

Firma Responsable

Fecha_____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia